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CHEMISTRY
OF THE
STEROIDS

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PREFACE

ALTHOUGH interest and activity in the steroid field has been maintained, and even increased, during the last few years, no book on the chemistry of the steroids has appeared since the masterly monograph by Louis and Mary Fieser (*Natural Products Related to Phenanthrene*, 3rd ed.) in 1949, and the extensive text edited by Sir Robert Robinson, O.M., and E. H. Rodd (*Chemistry of the Carbon Compounds*, Volume IIB) in 1953.

This book, therefore, sets out to present as concisely as possible the present state of knowledge. Accordingly, earlier structural investigations on the sterols and bile acids are given only in brief outline, but later structural investigations dealing with the sex hormones, the adrenocortical hormones, the cardiac glycosides and aglycones, and the sapogenins, are presented in full; stereochemistry, partial syntheses, and total syntheses are also described as fully as is consistent with brevity. An attempt has been made to cover the more important papers in the literature up to the end of 1955, and to include a few of the most important papers appearing in 1956.

Some idea of the immense amount of work carried out on steroid chemistry in a period of five years is conveyed by the number of references cited for the period 1951–55; in Chapters I, II, III, IV, V and VI the percentage of references relating to this period are 16, 35, 26, 57, 32, and 45, respectively; my perpetual problem has been to decide not what to include, but what to omit.

I wish to take this opportunity to acknowledge my indebtedness to my former teachers, and present colleagues and friends—C. K. Ingold, F.R.S., who taught me to appreciate the relation between structure and mechanism in organic chemistry, and T. Reichstein, Nobel Laureate, For.Mem.R.S., who guided my first steps in the field of natural products. I should like to thank my wife for assistance in reading the proofs, Miss P. Sims, my secretary, for help in checking the references, and the staff of Messrs. Butterworths, the publishers, for the beautiful drawings of complex formulae and for their continuous assistance at all stages of the production.

C. W. SHOPPEE

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Australia.

July, 1957.

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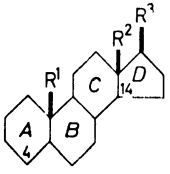
I

INTRODUCTION

THE steroids are a widely occurring group of colourless and, for the most part, saturated natural products possessing the tetracyclic carbon skeleton (1). Apart from minor differences due to the presence of nuclear substituents and sometimes the degree of unsaturation, the diverse types of compound comprised by the group arise mainly from variation in the entities R^1, R^2, and R^3.



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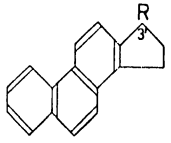

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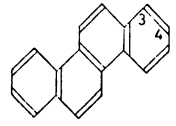


(3)

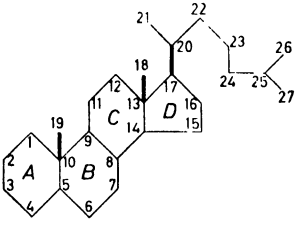
R^1 may be absent, as when ring *A* and/or ring *B* is aromatic, but R^1 and R^2 are generally methyl groups, although incompletely reduced residues such as primary alcohol and aldehyde groups are sometimes encountered [$-CH_2OH$: strophanthidol, *iso*rubijervine; $-CH{=}O$: strophanthidin, aldosterone]. The side chain R^3 may be absent, or may comprise two, four, five, eight, nine, or ten carbon atoms; in the steroid alkaloids eight carbon atoms are associated with an atom of nitrogen, as in solanidine and conessine. Substitution of the two hydrogen atoms at position 4 and of that at position 14 by methyl groups leads to a group of compounds [lanosterol, *cyclo*artenol, euphadienol], which may be regarded as 4 : 4 : 14ξ-trimethyl-steroids or as triterpenoids.

Some representative of nearly all the types mentioned above has been converted by dehydrogenation with selenium into 1 : 2-*cyclo*pentenophenanthrene [(2): R = H] [for syntheses *see* reference 1] or 3′-methyl-1 : 2-*cyclo*pentenophenanthrene [(2): R = Me] [for syntheses *see* reference 2]; thus (+)-oestrone and *iso*rubijervine give the former, whilst cholesterol, cholesteryl chloride, ergosterol, cholic acid, and solanidine give the latter, accompanied by other products such as fluorene, chrysene (3), and picene [≡ 3 : 4-benzchrysene]. It should, however, be noted that lanosterol yields

1 : 2 : 8-trimethylnaphthalene, and so behaves like other tetracyclic triterpenoids.

Nomenclature

The carbon skeleton of the hydrocarbons cholestane and coprostane [rings *A* and *B* of which are related at $C_{(5)}$ as the *trans*- and *cis*-decalins] is given in formula (4), which shows the correct numbering

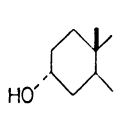


(4)

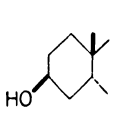
of the system and the alphabetical designation of the four rings. The extra carbon atom in ergostane [$C_{(28)}$] is present as a $C_{(24)}$-methyl group, whilst the two extra carbon atoms in sitostane [=stigmastane] [$C_{(29)}$] form a $C_{(24)}$-ethyl group. The convention adopted for the description and representation of steroids is that originally proposed by L. F. Fieser [*The Chemistry of Natural Products Related to Phenanthrene*, 2nd ed., New York (1937)], extended by T. Reichstein and C. W. Shoppee [*Vitamins and Hormones*, New York (1943)], and later modified by L. F. Fieser and Mary Fieser [op. cit., 3rd ed., New York (1949)] with a view to international adoption. Arbitrary trivial indices are indicated by use of 'α' and 'β'. At nuclear centres of asymmetry, position is specified by the number of the carbon atom in question and configuration by the suffixes α or β. If the orientation of the hydrogen atom or a substituent corresponds to that of the two angular carbon atoms $C_{(18)}$ and $C_{(19)}$ lying *above* the general plane of the ring system, then the atom or group possesses the β-configuration and this is represented by a heavy full-line bond. Conversely, an atom or group, lying *below* the general plane of the ring system, is said to possess the α-configuration and this is represented by a broken-line bond. If the configuration of an atom or group is not known, this may be specified by the Greek letter ξ and a wavy-line bond. The Greek letters are written without parentheses.

The angular methyl group [$C_{(19)}$] attached to $C_{(10)}$ was assumed by convention to be β-orientated, and this is now known to be the correct absolute configuration; it can be shown that the angular methyl group [$C_{(18)}$] attached to $C_{(13)}$ is also β-orientated. It may

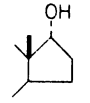
be noted that any other arrangement raises difficulty from the crystallographic standpoint in relation to the packing of steroid molecules into unit cells. Methyl groups are commonly represented in formulae by strokes.



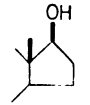
3α-Hydroxy



3β-Hydroxy



17α-Hydroxy

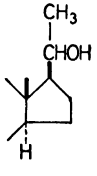


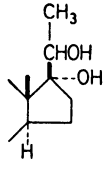
17β-Hydroxy

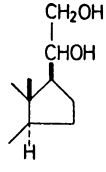
A substance differing from a natural or typical steroid in the configuration at a nuclear asymmetry centre other than $C_{(5)}$ and involving inversion of the orientation of a C—C or C—H linkage is termed an *iso*-compound. Configuration at $C_{(5)}$ may be indicated either by classical names [cholestane, coprostane, *allo*pregnane, and pregnane], or by use of the prefixes α and β [coprostane = 5β-cholestane, aetiocholane = 5β-androstane]; the prefix *allo* is reserved solely to indicate α-orientation of the hydrogen atom at $C_{(5)}$. A substance differing from a natural or typical steroid with respect to the orientation of a hydroxyl group is described as an *epi*-compound.

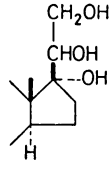
For asymmetric centres in a side chain, position is specified by the number of the carbon atom bearing the substituent, but since stereoisomerism is now no longer geometrical in character but of the tartaric acid type ['free' rotation], a definite spatial orientation cannot in general be assigned. In the case of configuration at $C_{(20)}$, when this can be related to that at $C_{(17)}$ and the whole ring system, the suffixes α and β are employed according to the convention, proposed by Fieser and Fieser [loc. cit.], shown to correspond to the absolute configuration by PRELOG and TSATSAS[3], and supported experimentally by KLYNE[4] and JEGER *et al.*[5].

All 20-hydroxy-steroids should be capable of description using the indices 20α and 20β; the solution of this problem is mainly due to SARETT[6], who has correlated the four structural types of naturally occurring 20-hydroxy-steroids:



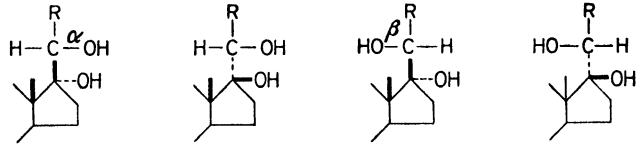






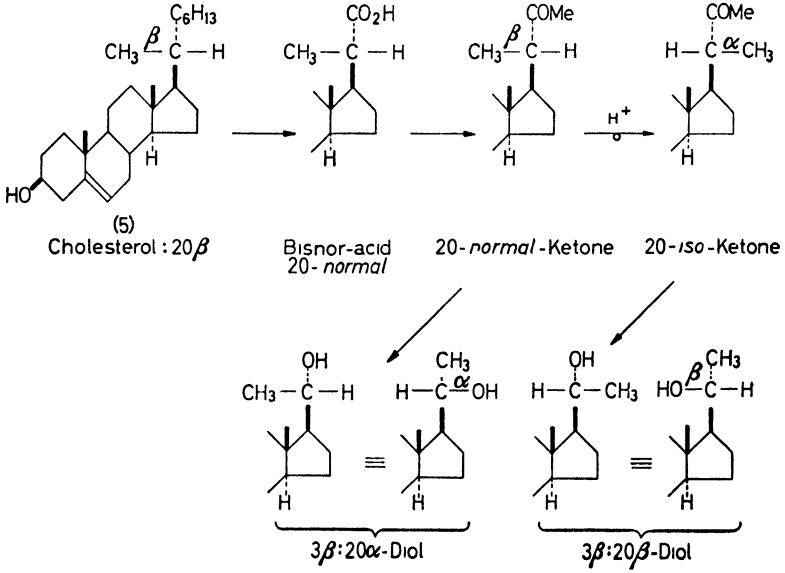
20-Hydroxy-steroids conform to two generalizations: (i) the acetates of the 20β-series are always more dextrorotatory than their

epimerides; (ii) acetylation of a 20α-hydroxyl group decreases the molecular rotation, whilst acetylation of a 20β-hydroxyl group increases it. It has thus been found that the prefixes α and β, which had previously been assigned independently and arbitrarily[7] to 20-hydroxy-steroids of different types, are fortuitously in agreement with the convention of Fieser and Fieser and with the absolute configuration.



17α 20α-Dihydroxy 17β 20α-Dihydroxy 17α:20β-Dihydroxy 17β 20β-Dihydroxy

All natural steroids containing 24 or more carbon atoms have a methyl group attached to $C_{(20)}$; x-ray analysis of cholesteryl iodide indicates that cholesterol has the 20β-configuration (5), which has been correlated with 20α-hydroxy-steroids by WIELAND and MIESCHER[8]. Oxidation of cholesterol (5) affords the bisnor acid, converted to the 20-*normal*-ketone, which could be isomerized by acid to the 20-*iso*-ketone; perbenzoic acid oxidation [with temporary protection of the double bond], and alkaline hydrolysis gave respectively pregn-5-ene-3β : 20α-diol and pregn-5-ene-3β : 20β-diol:



(5)
Cholesterol : 20β

Bisnor-acid
20-*normal*

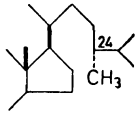
20-*normal*-Ketone

20-*iso*-Ketone

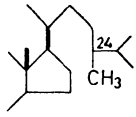
3β:20α-Diol

3β:20β-Diol

For configuration at $C_{(20)}$ non-relative to $C_{(17)}$, and at $C_{(24)}$, the suffixes a and b are employed but *n* and *iso* have also been used. These suffixes serve to distinguish stereoisomerides without any spatial implication, and since suffix assignment is arbitrary, designations applied provisionally in one series imply no correspondence to those in another. Typographically such stereoisomerides may be distinguished by reversal of position or by use of full-line and broken-line bonds.

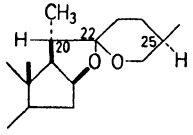


24a-Methyl

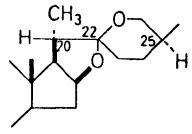


24b-Methyl

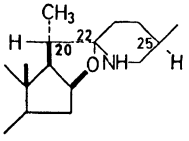
When the side chain becomes involved in heterocyclic structures [spirostans, alkaloids], geometrical isomerism may appear at $C_{(20)}$, $C_{(22)}$, and $C_{(25)}$.



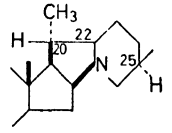
22a-or 22-*iso*Spirostan



22b-or 22-*n*-Spirostan



Solasodine or
tomatidine



Solanidine

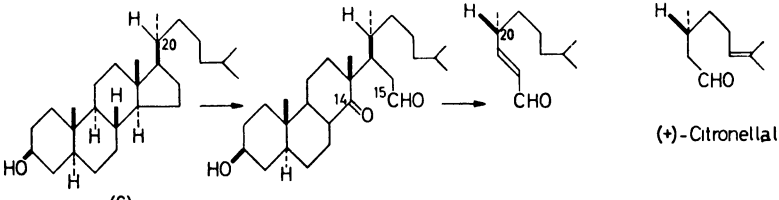
In principle, it should ultimately be possible to relate configuration at other asymmetry centres in the side chain to configuration at $C_{(17)}$; for an attempt to do this, and for proposed rules for steroid nomenclature, *see Chem. & Ind.* (1951) 930, and the Appendix thereto, by Plattner.

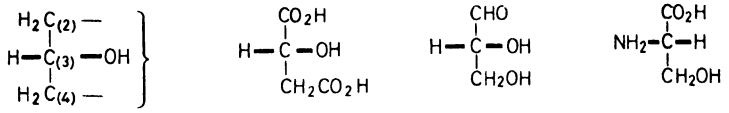
In the older literature, cholesterol (5) is described as a 4-hydroxy compound [cf. (5a)], and deoxycholic acid, properly described as a 3 : 12-dihydroxycholanic acid (7), is described as 3 : 7-dihydroxycholanic acid [cf. (7a)]. In the literature of the period 1939–1946 there is much confusion with respect to configuration at positions 11, 12, and 17; thus deoxycholic acid (7) was successively assigned the 3α : 12β : 17β-configuration (1939–1943), the

3α : 12β : 17α-configuration (1943–1946), and the present correct 3α : 12α : 17β-configuration (7).

Absolute Configuration

The absolute configuration of the steroid asymmetry centre at $C_{(3)}$ has been determined by Prelog *et al.*[9], by argument based on asymmetric syntheses; the 3-hydroxyl group in cholestanol (6), as also the hydroxyl groups in dihydrolanosterol and the triterpene α-amyrin, possess the same β-configuration which corresponds to that of D(+)-malic acid and of D(+)-glyceraldehyde. The tentative and opposite conclusion of Reichstein *et al.*, who degraded the methyl ether of vitamin D_2 to a (−)-3-methoxyadipic acid, appears to be due to assignment of the wrong configuration to the latter substance, and has been rectified[10].





Cholestanol viewed from the left in the general plane of the ring system

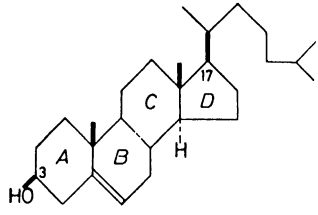
D(+)-Malic acid D(+)-Glyceraldehyde L(-)-Serine

Direct correlation of the configuration at $C_{(20)}$ in cholestanol (6), through the Δ^{14}-derivative by the reaction sequence shown above, with (+)-citronellal of known absolute configuration by Cornforth *et al.*[11] and by Jeger *et al.*[12], confirms the absolute configuration of the steroid molecule. The conventional formulae of all steroids are therefore correct and may be correlated with the usual convention for the representation of the absolute configurations of D(+)-glyceraldehyde and of natural L(−)-serine.

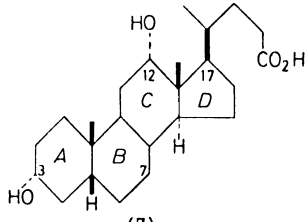
Historical Development

Early structural investigations were concerned principally with the nature of the nucleus, and carried out mainly with cholesterol (5)

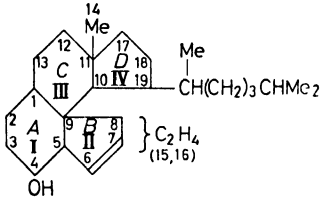
and the bile acids cholic, deoxycholic (7), 'α'-hyodeoxycholic, and lithocholic acid. Cholesterol, $C_{27}H_{46}O$, was shown to be a monohydric secondary alcohol with one double bond and a C_8-side chain: $-CHMe(CH_2)_3 \cdot CHMe_2$. The bile acids were recognized as hydroxy-derivatives of cholanic acid, $C_{24}H_{40}O_2$, which contained the same C_{19}-skeleton as cholesterol and a C_5-side chain: $-CHMe \cdot (CH_2)_2 \cdot CO_2H$. The empirical formula of cholestane, $C_{27}H_{48}$, the parent hydrocarbon of cholesterol, by comparison with that of the paraffin, $C_{27}H_{56}$, indicated a tetracyclic structure, the character of which was determined by systematic oxidative degradation.



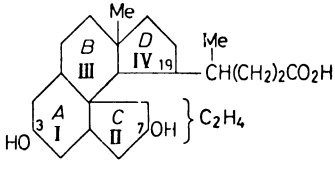
(5)
Cholesterol



(7)
Deoxycholic acid



(5a)



(7a)

In 1928, A. Windaus and H. Wieland surveyed in Nobel Prize Addresses the results of their respective investigations on cholesterol and the bile acids. These had followed parallel but independent paths; a combination of correct and [as is now known] mistaken evidence had led to the structures (5a) for cholesterol and (7a) for deoxycholic acid, which appeared to be established in all details except for two carbon atoms [$C_{(15)}$ and $C_{(16)}$] assumed to be present as an ethyl group at $C_{(10)}$. The four rings were indicated by Roman numerals; their identities in relation to those of the correct formulae are shown by italic letters. It should be noted that, because of failure of the Blanc rule [*see* p. 19], ring II in cholesterol was thought to be five-membered and identical with ring II in the bile acids, whereas in fact both rings are six-membered and non-identical [*B* and *C*, respectively].

In 1930, WIELAND and VOCKE[13] proved that there was no ethyl group at $C_{(10)}$, and attempts to insert the two carbon atoms as a >CHMe group into ring III to give a seven-ring were unsatisfactory. In 1932, ROSENHEIM and KING[14] suggested that chrysene (3), obtained by DIELS, GÄDKE, and KORDING[15] by dehydrogenation of cholesterol with palladium-charcoal at 500°, is a normal degradation product; on the basis of this fact, and of x-ray crystallographic measurements of ergosterol by BERNAL[16], which indicated a thin lath-like molecule [7·2 × 5 × 17–20 Å] whereas the Wieland–Windaus formulae, (5a) and (7a), with three rings meeting at a point required a rather thick molecule [8·5 × 7 × 18 Å], Rosenheim and King proposed that the nuclear skeleton of the steroids was that of chrysene (3). [On this basis ergosterol should measure 7·5 × 4·5 × 20 Å.] Subsequently and almost simultaneously, ROSENHEIM and KING[17] and WIELAND and DANE[18] modified the nuclear structure from that of chrysene (3) to that of 1 : 2-*cyclo*pentenophenanthrene [(2): R = H]. This structure readily accommodated all the available experimental evidence, and continues to do so. Final proof of its correctness is supplied by the total syntheses of equilenin, oestrone, *epi*androsterone, cortisone, and cholesterol.

STRUCTURE AND GEOMETRY

Stereochemistry

THE NUCLEUS

There are seven asymmetry centres [$C_{(5)}$, $C_{(8)}$, $C_{(9)}$, $C_{(10)}$, $C_{(13)}$, $C_{(14)}$, $C_{(17)}$] giving a total of 128 possible stereoisomerides.

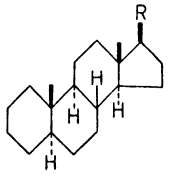
A/B

Fusion of rings *A* and *B* may be either *trans* or *cis* to give two isomeric [*allo* and *normal*] C_{27}-hydrocarbons (8) and (9), and, by progressive shortening of the side chain, three similar pairs of isomeric hydrocarbons:

Table I

allo-Series *A/B* : *trans* (8)				*normal*-Series *A/B* : *cis* (9)		
		m.p.°	$[\alpha]_D$°		m.p.°	$[\alpha]_D$°
$C_{27}H_{48}$	Cholestane	80	+24	Coprostane	70	+25
$C_{24}H_{42}$	*allo*Cholane	—	—	Cholane	90	—
$C_{21}H_{36}$	*allo*Pregnane	84	+13	Pregnane	83	+20
$C_{19}H_{32}$	Androstane	49	+ 1	Aetiocholane*	78	+ 3

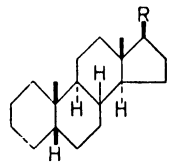
* The Greek prefix aetio signifies complete removal of the side chain. To avoid using the names aetiocholane and aetiocholanic [or aetio*allo*cholanic] acid for compounds with C_{19} and C_{20}, respectively, the names etianic acid and *allo*etianic acid have been suggested.



(8)
allo-Series

A/B trans
B/C trans
C/D trans

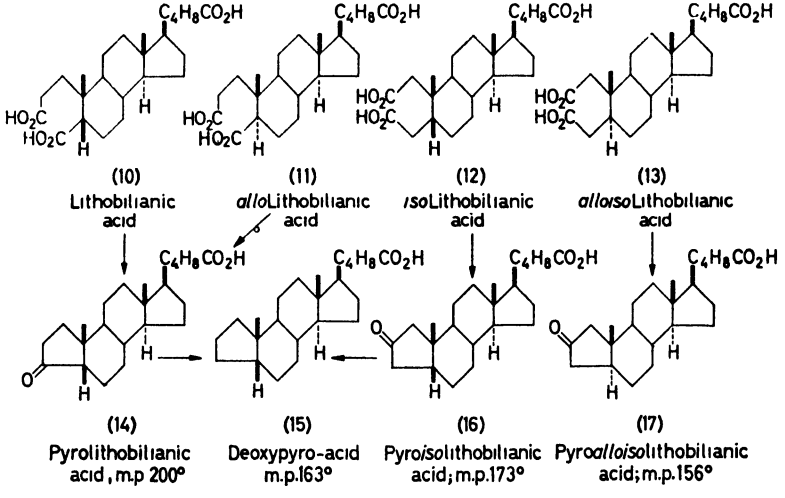
A/B cis
B/C trans
C/D trans



(9)
normal-Series

R = C_8H_{17}, C_5H_{11}, C_2H_5, or H

The work of WINDAUS[19] on 3α : 6α-dihydroxycholanic acid ['α'-hyodeoxycholic acid] established the steric relationship of rings *A*/*B* in the *allo*cholane and cholane series; he prepared and studied the pyrolytic behaviour of the four isomeric lithobilianic acids. Lithobilianic acid (10) and *allo*lithobilianic acid (11) both yield the same pyro-acid (14); *iso*lithobilianic acid (12) and *alloiso*lithobilianic acid [Staden's acid] (13) give different pyro-acids, (16) and (17). Clemmensen reduction of pyrolithobilianic acid (14) and pyro*iso*-lithobilianic acid (16) give the same deoxypyro-acid (15). The pyro-acid (14) must have the more easily formed *cis*-configuration[20], and its formation from *allo*lithobilianic acid involves inversion of configuration at $C_{(5)}$ [$C_{(5)}$—H is α to CO_2H]; *iso*lithobilianic acid (12) and *alloiso*lithobilianic acid (13) are not susceptible to inversion [$C_{(5)}$—H is β to CO_2H] and yield stereoisomeric pyro-acids with retention of configuration at $C_{(5)}$. Lithobilianic and *iso*lithobilianic acids, being both obtained from the natural bile acid, lithocholic acid [*see* p. 82], must possess the same *A*/*B* ring-fusion :



they are degradation products of cholane [(9): *A/B cis*], whilst the *allo*lithobilianic acids, although prepared from natural 3α: 6α-dihydroxycholanic acid ['α'-hyodeoxycholic acid], are derived from the synthetic 3α-hydroxy*allo*cholanic acid [*see* p. 80] and are degradation products of *allo*cholane [(8): *A/B trans*].

Similar results have been obtained with the corresponding dicarboxylic acids from cholestan-3β-ol and coprostan-3β-ol [21], and show that, apart from the *A/B* ring-junction, the spatial configuration of the nucleus is the same in (8) and (9).

Cholestane has a lower density, higher molecular refraction, and higher melting point than coprostane[22], which suggests by analogy with the decalins that cholestane has structure (8) and coprostane has structure (9). There are also chemical dissimilarities; thus bromination, enolization, and oxidation of 3-ketones of cholestane type gives respectively 2α-bromoketones, 3-ethoxy-Δ^2-compounds, and mainly 2 : 3-*seco*-diacids, whereas 3-ketones of coprostane type give respectively 4β-bromoketones, 3-ethoxy-Δ^3-compounds, and, mainly, 3 : 4-*seco*-diacids.

It is only possible to pass from one series to the 5-epimeric series by conversion to a 4 : 5- or 5 : 6-unsaturated compound and hydrogenation, or from the *cis*-series to the *trans*-series by 'allomerization' i.e. enolization, of a 4- or 6-keto group[23].

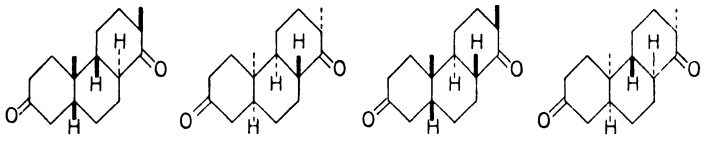
B/C

X-ray crystallographic evidence adduced by BERNAL *et al.*[24], indicates that this ring-union is a *trans*-fusion; Bernal states that 'to keep the molecule flat, the $C_{(10)}$-angular methyl group [formerly by convention and now by absolute configuration β-orientated] must be *trans* to the $C_{(9)}$-hydrogen atom' as in (8). This determines that, of the two possible modes of *trans-B/C*-fusion [cf. (18Aa) and (18Ba)], that one involving the arrangement 8β-H/9α-H is correct, as is confirmed by the complete x-ray crystallographic analysis of cholesteryl iodide[25].

The stability to hydroxyl ions of 7- and 11-ketosteroids, regarded as 'α'-decalones, also indicates a *trans-B/C*-fusion. Similar indications are derived from ionic elimination reactions of 7- and 11-substituted steroids; thus 11β-hydroxy- and 11β-bromo-steroids [9α-H (axial)/11β-OH (Br) (axial): *trans*] readily undergo ionic dehydration or dehydrobromination but 11α-hydroxy- and 11α-bromo-steroids [9α-H (axial)/11α-OH (Br) (equatorial): *cis*] are resistant; again 7α-hydroxy-steroids, e.g. cholic acid (35) [7α-OH (axial)/8β-H (axial): *trans*], readily undergo ionic dehydration, but 7β-hydroxy-steroids [7β-OH (equatorial)/8β-H (axial): *cis*] are resistant.

It is very probable that all natural steroids have the *B/C-trans*

arrangement; this conclusion is supported, in general by the various steroid total syntheses, and in particular by the total synthesis of the four diketones (18) by CORNFORTH and ROBINSON[26]. Starting from 1 : 6-dihydroxynaphthalene, the two pairs of enantiomorphs, (18Aa and Ab) and (18Ba and Bb), were obtained, of which (18Ba) was identical with the diketone obtained from cholesterol[27] and from deoxycholic acid[28].



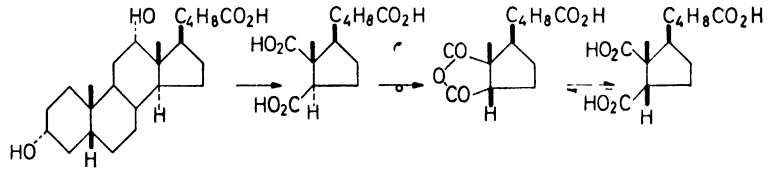
(18Aa) (18Ab) (18Ba) (18Bb)

mp.141°, $[\alpha]_D \pm 20°$ mp 141°, $[\alpha]_D \pm 20°$ mp 117°, $[\alpha]_D$ +25° mp 117°, $[\alpha]_D$ -25°

Synthetic steroids with both the possible *B/C-cis* arrangements [8α-H/9α-H and 8β-H/9β-H] have been prepared [*see* pp. 60 and 61].

C/D

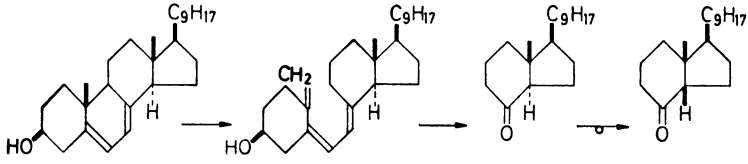
The complete x-ray crystallographic analysis of cholesteryl iodide carried out by CARLISLE and CROWFOOT[25] shows that this ring-union is *trans* in the sterols, the bile acids, and related steroids, and confirms the earlier chemical evidence. Thus WIELAND and DANE[29], by degradation of deoxycholic acid (7) [*see* p. 21], obtained the *trans*-acid $C_{13}H_{20}O_6$ (19), which gives no anhydride but by heating undergoes inversion at $C_{(14)}$ to afford the *cis*-anhydride (20) which is readily hydrolysed to the *cis*-acid (21).



(7) (19) (20) (21)

Deoxycholic acid

Similarly, DIMROTH and JONSSON[30] obtained from ergosterol via vitamin D_2 [*see* p. 57] the *trans*-ketone (22), which with acid or alkali is converted irreversibly into the *cis*-ketone (23) [cf. *trans*-'α'-hydrindanones→*cis*-'α'-hydrindanones].



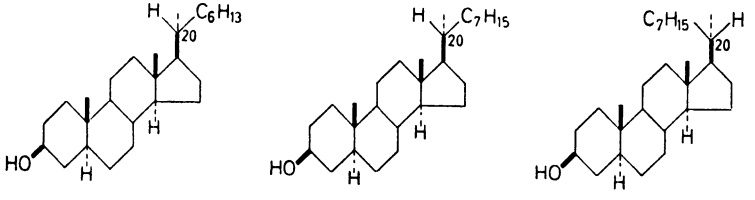
Ergosterol Vitamin D_2 (22) (23)

The *C/D*-ring fusion is, on the contrary, *cis* in (i) the cardiac glycosides and aglycones, and (ii) the toad poisons. In these compounds, formation of 14 : 21-oxides [*iso*-compounds, *see* pp. 234 and 235] requires a *cis*-relationship of the $C_{(14)}$-hydroxyl group and the $C_{(17)}$-side chain. The established β-configuration of the side chain [*see* p. 28] requires β-orientation of the $C_{(14)}$-hydroxyl group; this is proved for (i) by degradation of digitoxigenin to methyl 3β-acetoxy-14β-hydroxy-14-*iso*aetiocholanate[31,32], and for (ii) by degradation of bufalin to methyl 3β-acetoxy-14β-hydroxy-14-*iso*aetiocholanate, of telocinobufagin to methyl 3β-acetoxy-5β : 14β-dihydroxy-14-*iso*aetiocholanate, of gamabufotalin to methyl 3β : 11α-diacetoxy-14β-hydroxy-14-*iso*aetiocholanate, and of bufotalin to methyl 3β : 16β-diacetoxy-14β-hydroxy-14-*iso*aetiocholanate[33].

The Side Chain

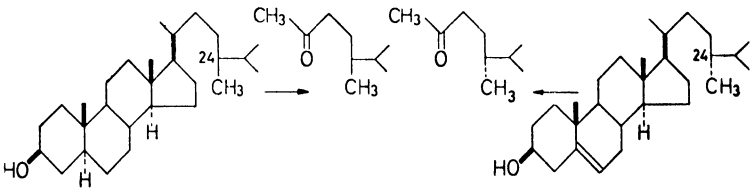
As already mentioned [p. 5], if the side chain becomes involved in heterocyclic structures, geometrical isomerism may appear at $C_{(20)}$, $C_{(22)}$, and $C_{(25)}$. Stereoisomerism of the classical tartaric acid type involving 'free' rotation, however, occurs generally at the asymmetry centre at $C_{(20)}$, and may occur at $C_{(24)}$ when substitution of hydrogen by a methyl or ethyl group leads to asymmetry.

Many natural steroids have a methyl group attached to $C_{(20)}$; cholesterol, cholestanol, ergosterol, stigmasterol, campesterol, campestanol, and the bile acids correspond in configuration at $C_{(20)}$ and are 20β-compounds, whilst stellasterol and stellastanol appear to belong to the 20α-series. Steroids with other substituents at $C_{(20)}$ [e.g. OH, Br, CO_2H] are known in two forms, which arise from stereoisomerism at $C_{(20)}$.



(6)
Cholestanol Campestanol Stellastanol

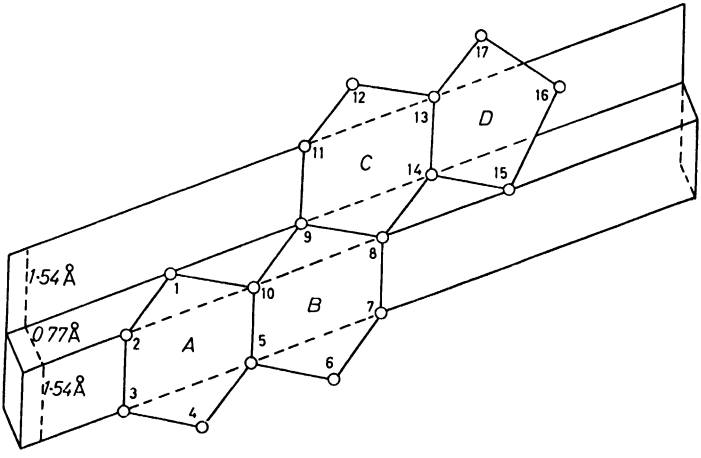
Stereoisomerism at $C_{(24)}$ is encountered among the higher sterols and the derived stanols. Ergosterol, brassicasterol, 'β'-sitosterol, stigmasterol, and 'α'-spinasterol all belong to the series described as 24b, whilst campesterol, stellasterol, and poriferasterol belong to the 24a series; thus ergostanol by oxidation gives (—) 5 : 6-dimethylheptan-2-one (24)[34], whilst campesterol affords (+) 5 : 6-dimethylheptan-2-one (25)[35].



Ergostanol (24) (25) Campesterol

Molecular Geometry of the Nucleus

The *cyclo*hexane ring can exist theoretically in two strainless conformations—the chair, which is rigid, and the boat, which is mobile[36,37,38]. The chair conformation is more thermodynamically stable than the boat conformation, but can undergo conversion into



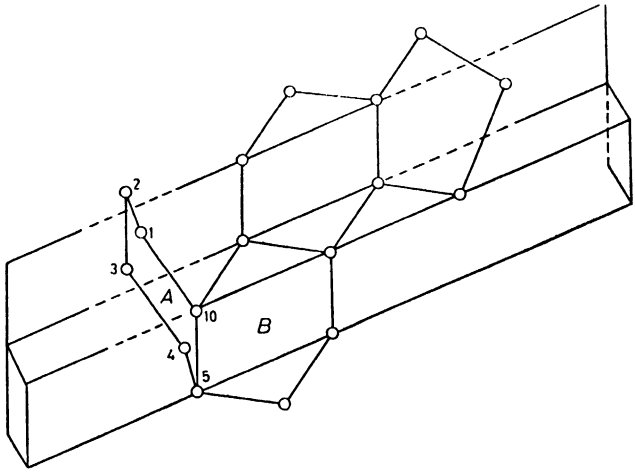
(26)

Carbon skeleton of androstane with rings *A* and *B* as chair-forms

(*By Courtesy of The Chemical Society.*)

the boat conformation by passage over a small energy barrier[39,40,41]; the most stable conformation of a fused *cyclo*hexane ring system will,

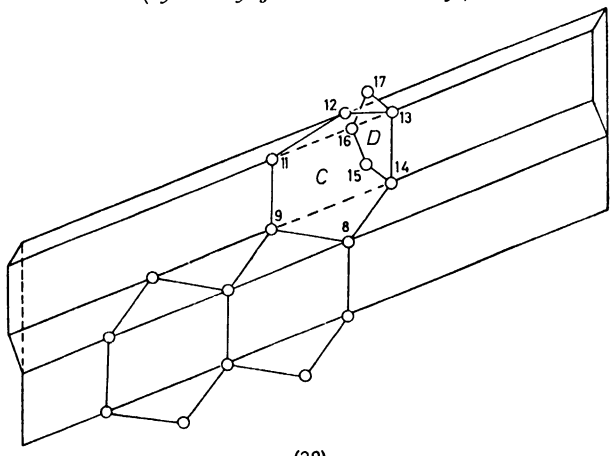
in general, be that conformation with the maximum number of chairs. In the steroid nucleus there is present a set of three fused



(27)

Carbon skeleton of aetiocholane (=5β-androstane) with rings *A* and *B* as chair-forms

(*By Courtesy of The Chemical Society.*)



(28)

Carbon skeleton of 14β-androstane with rings *A* and *B* as chair-forms, *C* as a boat-form and rings *C* and *D* *cis*-united

*cyclo*hexane rings [*A*, *B*, *C*]. When the *C*/*D* ring-fusion is *trans*, because the $C_{(13)}$ angular methyl group has the β-configuration,

ring *C* is a chair-form, as in (26) or (27), and is completely rigid due to the double locking by rings *B* and *D*. When the *C*/*D* ring-union is *cis*, ring *C* can be a boat-form with ends at $C_{(8)}$ and $C_{(12)}$, ring *D* planar, and the molecule L-shaped (28). Rings *A* and *B* as chair-forms are capable both of *trans*- union (26), and of *cis*-union leading to the L-shaped structure (27), which has been shown to be the correct representation for *cis*-decalin by electron diffraction and x-ray crystallographic studies[42,43]. Mixed types are also possible, e.g. ring *A* in (26), (27), and (28) can become a boat-form with ends at $C_{(3)}$ and $C_{(10)}$[39].

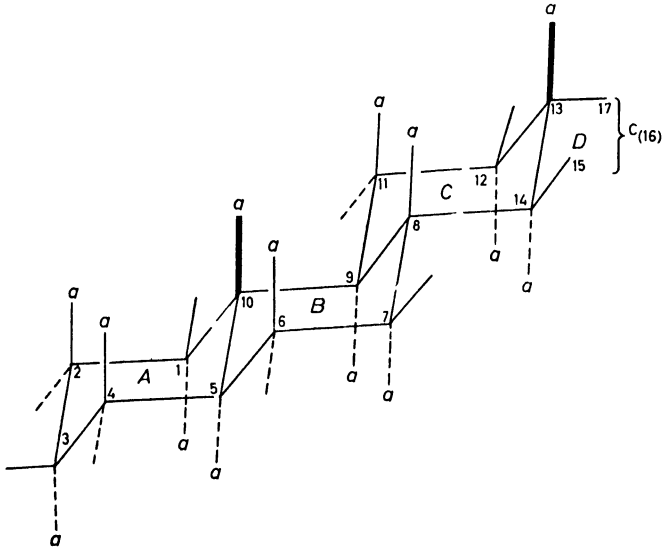
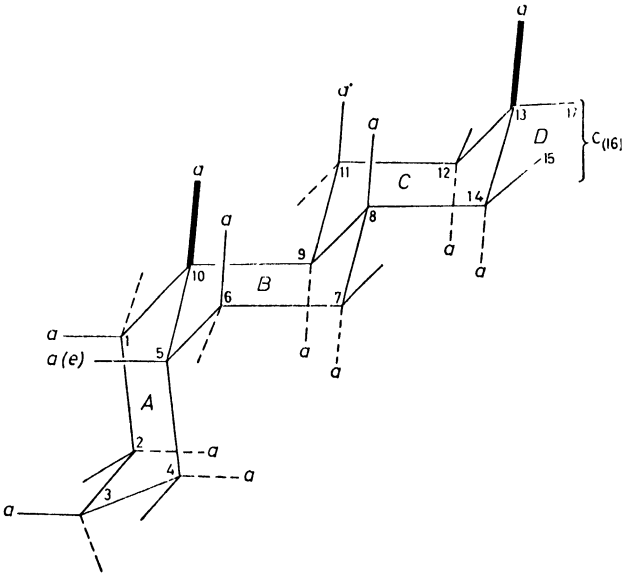


Figure 1. Conformation of androstane:
a = axial bonds
(*By Courtesy of The Chemical Society.*)

Because of the rigidity of the chair conformation of *cyclo*hexane, the 12 C—H bonds may be divided into two sets of 6 bonds distinguished by horizontality [equatorial] and verticality [axial] to the three-fold axis of symmetry of the ring system[44,45,46]. In the steroid nucleus: (i) a substituent linked by an equatorial bond is thermodynamically more stable than the same substituent linked to the same carbon atom by an axial bond; (ii) ionic elimination reactions involving *trans*-substituents on adjacent carbon atoms proceed most readily between axial bonds because the four centres are then in one plane [e.g. 3α-X : 2β-Y in *Figure 1*, 3β-X : 2α-Y in *Figure 2*, or 11β-X : 12α-Y in both *Figure 1* and *Figure 2*]; (iii) a substituent

linked by an equatorial bond is less sterically hindered than the same substituent linked to the same carbon atom by an axial bond, and is liable to become involved in pinacolic rearrangement with ring-decrease because the four participating centres [e.g. 12β-X, $C_{(12)}$, $C_{(13)}$, $C_{(14)}$ in *Figures 1* or *2*] are coplanar.

The energies involved in the transformations of different geometrical conformations are small [~ 5–10 kcals] compared with the activation energies of most chemical reactions; so long as these


a
a
a

Determination of Structure

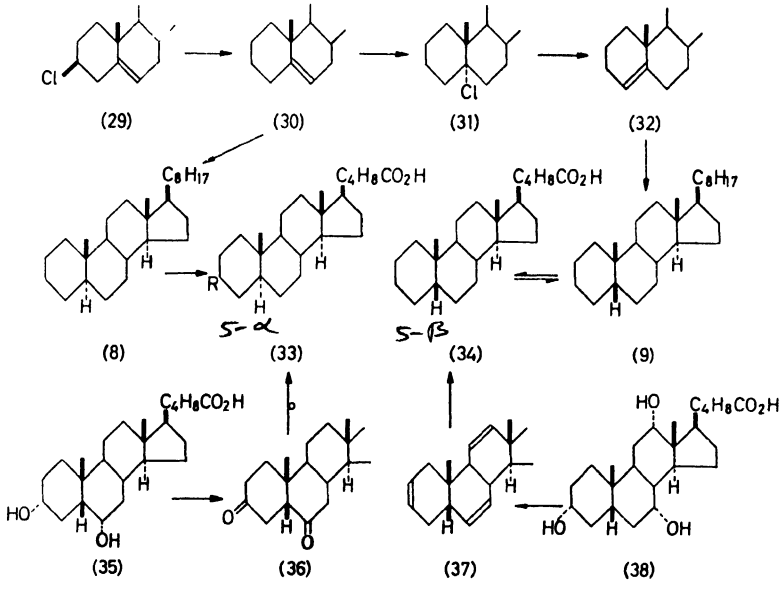
THE NUCLEUS

Investigations were carried out almost exclusively with the sterols and bile acids, and mainly by oxidative degradation. This work, largely by Windaus and Wieland over a period of 30 years, is given here in summary only; for a detailed exposition the monograph by Fieser and Fieser [*Natural Products Related to Phenanthrene*, 3rd ed., Reinhold Publishing Corp., New York (1949)] or the author's text edited by Robinson and Rodd [*Chemistry of Carbon Compounds*, Vol. IIB, Elsevier Publishing Co., Amsterdam (1953)] may be consulted.

The Common Nuclear Skeleton

It was suspected [cf., however, (5a) and (7a)] that the nuclear carbon skeleton is identical in the sterols and bile acids; this was finally proved by Windaus and confirmed by Wieland.

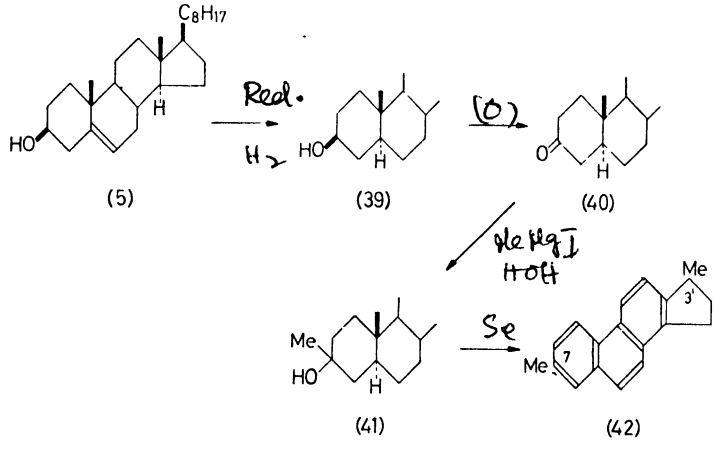
Cholesterol (5) with phosphorus pentachloride[47] or thionyl chloride[48] gives cholesteryl chloride (29), which may be reduced to



cholest-5-ene (30) and hydrogenated to cholestane (8); the order of these operations may be reversed[49, 50]. Addition of hydrogen chloride to cholest-5-ene gives 5-chlorocholestane (31), dehydrochlorinated with potassium acetate to cholest-4-ene [formerly

called pseudocholestene] (32)[51], which by hydrogenation in neutral solvents gives coprostane [formerly called pseudocholestane] (9)[52]; hydrogenation in an acidic medium gives cholestane. Oxidation of cholestane and coprostane with chromium trioxide affords, amongst other products, *allo*cholanic acid [(33): R = H] and cholanic acid (34), respectively[53]. These two acids can also be obtained from 'α'-hyodeoxycholic acid (35) by way of 3 : 6-dioxocholanic acid [= 'β'-dehydrohyodeoxycholic acid] (36), which undergoes allomerization and reduction[23, 54], and from cholic acid (38) by way of cholatrienic acid (37)[55]; finally, cholanic acid as ethyl ester may be converted by the action of magnesium *iso*propyl bromide to a carbinol, oxidized to a ketone which by Clemmensen reduction affords coprostane (9)[56].

A direct proof that the hydroxyl group of cholesterol (5) is at $C_{(3)}$ is furnished by its hydrogenation to cholestanol (39 ≡ 6), oxidized to cholestan-3-one (40); this with methyl magnesium iodide gives the methylcarbinol (41), dehydrogenated by selenium to 3' : 7-dimethyl-1 : 2-*cyclo*pentenophenanthrene (42)[57].



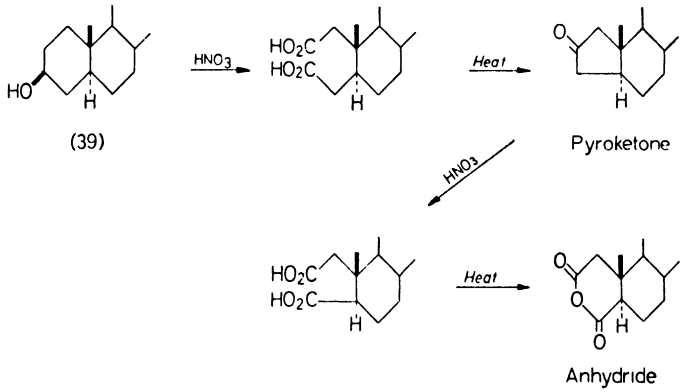
(5) (39) (40)

(41) (42)

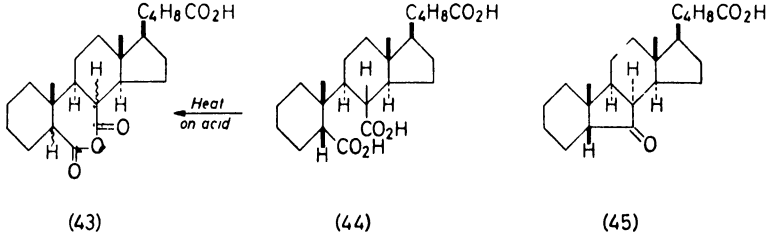
This transformation also proves that the hydroxyl group in lithocholic acid [*see* p. 82] and the bile acids is at $C_{(3)}$ because cholesterol and lithocholic acid can both be converted into 3α-hydroxy*allo*cholanic acid [(33): R = OH][58, 59].

RING *A*. Ring *A* in both the sterol[60, 61] and bile-acid series[19] was proved to be six-membered by application of the Blanc rule [dicarboxylic acids, heated with acetic anhydride and distilled, or simply pyrolysed, give anhydrides when the carboxyl groups are separated by one, two, or three carbon atoms, but give cyclic

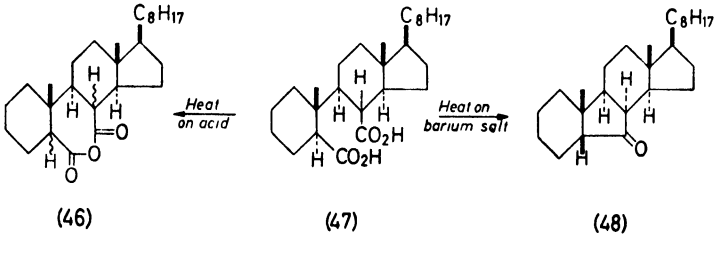
ketones when the intervening chain is longer]. Thus cholestan-3β-ol (39) gives a dicarboxylic acid which yields a pyroketone, in turn oxidized to a nordiacid, which affords an anhydride.



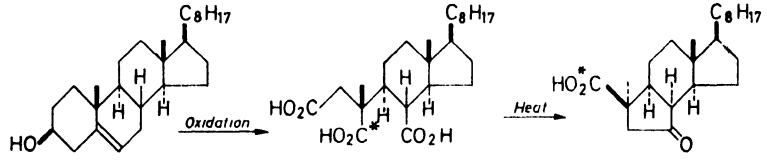
RING *B*. Ring *B* is six-membered in both series but recognition of this fact was delayed by failure of the Blanc rule, which applies only to dicarboxylic acids in which the two carboxyl groups are attached to the *same* ring[62]. The failure was discovered in the case of thilobilianic acid (44), a derivative of cholic acid (51), which gave the seven-ring anhydride (43) and not the ketone (45)[62].



Similarly, the 6:7-*seco*diacid (47) from cholestan-6-one [*see* pp. 48 and 69] gave an anhydride (46) and not the ketone (48)[63]; subsequently it has been found that pyrolysis of the barium salt affords the ketone (48)[64].

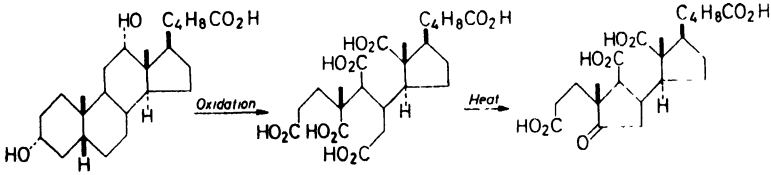


Ring *B* [and ring *A*] in cholesterol (5) is six-membered because the tricarboxylic acid (49) obtained by successive oxidations with loss of three carbon atoms gives a pyroketone (50)[65].



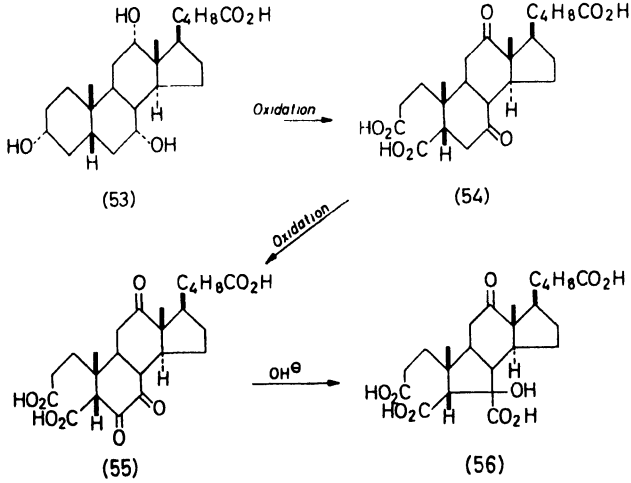
(5) (49) (50)

Similarly, ring *B* in deoxycholic acid (7) is six-membered because progressive oxidation gives the 5 : 6-11 : 12-bis*seco*hexa-acid solannellic acid (51) [*solus annellus* = one ring], which by pyrolysis affords the ketone pyrosolannelic acid (52)[66, 67].



(7) (51) (52)

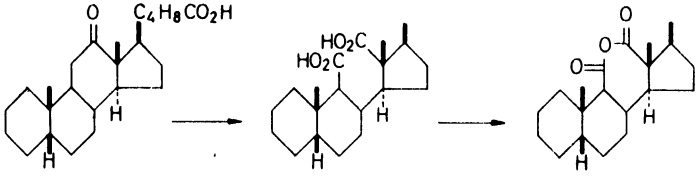
Ring *B* in cholic acid (53) is six-membered because progressive oxidation gives the 3 : 4-*seco*triacid bilianic acid (54), which with alkaline permanganate affords, via the 6 : 7 : 12-triketone (55) by



(53) (54) (55) (56)

a benzil–benzilic acid change[68], cilianic acid (56), which is an α-hydroxyacid and loses carbon monoxide with warm sulphuric acid[69].

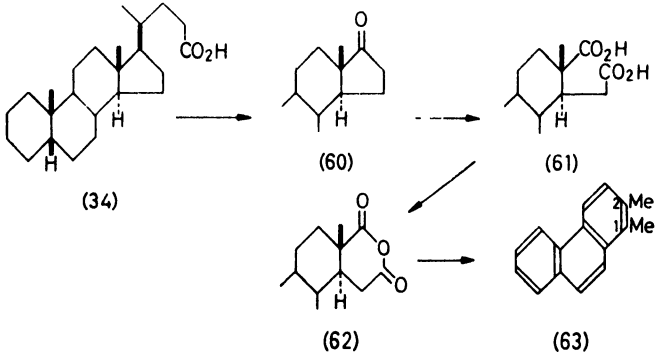
RING *C*. Investigation was not possible in the sterol series because no sterol was available with an oxidizable group in this ring. In the bile-acid series, deoxycholic acid (7), by mild oxidation to 3 : 12-dioxocholanic acid and Clemmensen reduction, gave 12-oxocholanic acid (57), which by oxidation with nitric acid yielded the 11 : 12-*seco*triacid (58), affording by pyrolysis an anhydride (59)[70].



(57) (58) (59)

This originally was interpreted to mean that ring *C* was five-membered, but the failure of the Blanc rule for ring *B* [*vide supra*] invalidated this evidence, and ring *C* is six-membered.

RING *D*. Direct investigation was not possible because no sterol or bile acid possessing an oxidizable group in ring *D* was available. WIELAND[71] successfully destroyed rings *A*, *B*, and *C* of deoxycholic acid (7) by oxidation and isolated a C_{13}-tricarboxylic acid [(19), *see* p. 11], but the yield was so small [0·5%] that he was compelled to introduce a keto-group into ring *D* by complete removal of the side chain. Cholic acid (38) was converted to cholanic acid (34), which by repeated Barbier-Wieland degradation [*see* p. 25] gave the C_{19}-ketone (60); this by oxidation afforded the 16 : 17-*seco*diacid aetiobilianic acid (61), pyrolysed to an anhydride (62)[72].

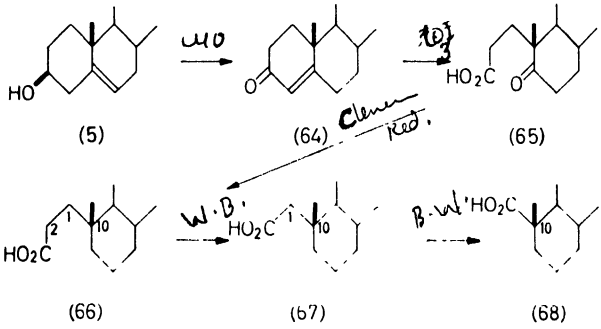


(34) (60) (61) (62) (63)

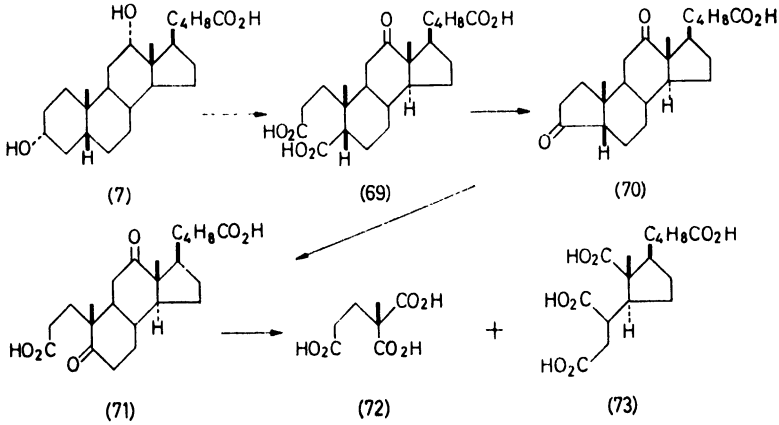
Ring *D* is thus five-membered; dehydrogenation of aetiobilianic acid (61) with selenium to 1 : 2-dimethylphenanthrene (63)[73] proves that rings *A*, *B*, and *C* are six-membered and form a perhydrophenanthrene system.

Position and Configuration of the Angular Methyl Groups

$C_{(19)}$: Position. Cholesterol (5) by oxidation gives successively cholest-4-en-3-one (64) [*see* p. 38] and the Windaus keto-acid (65)[74]; Clemmensen reduction affords the acid (66), which can be subjected twice only to Wieland-Barbier degradation [*see* p. 25] to give successively the noracid (67) and the bisnoracid (68). The latter is a tertiary carboxylic acid, difficult to esterify and readily losing carbon monoxide by treatment with warm concentrated sulphuric acid[75]. A methyl group must therefore be attached to $C_{(10)}$.



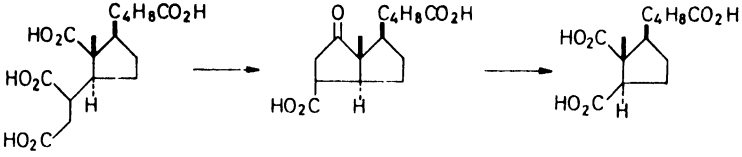
Alternatively, deoxycholic acid (7) by mild oxidation to 3 : 12-dioxocholanic acid and more vigorous oxidation with cleavage of ring *A* gives deoxybilianic acid (69); pyrolysis then affords the



pyro-acid (70), oxidized to the 5 : 12-dioxoacid (71)[76], which by drastic oxidation yields 1-methyl-1-carboxyglutaric acid (72) and a tetracarboxylic acid (73)[77].

$C_{(19)}$: CONFIGURATION. The absolute β-configuration of the 3-hydroxyl group in cholestanol (6) has been proved [*see* p. 6]; since the 3-hydroxyl group and the $C_{(10)}$-angular methyl group have been shown to possess the same orientation[78], the latter must have the β-configuration.

$C_{(18)}$: POSITION. The tetracarboxylic acid (73) gives the pyro-acid (74) by interaction of the carboxyl groups, and further oxidative degradation yields the C_{13}-tricarboxylic acid (19) [*see* p. 21][79] also obtained more directly by repeated bromination, hydrolysis, and oxidation of 12-ketocholanic acid[80].

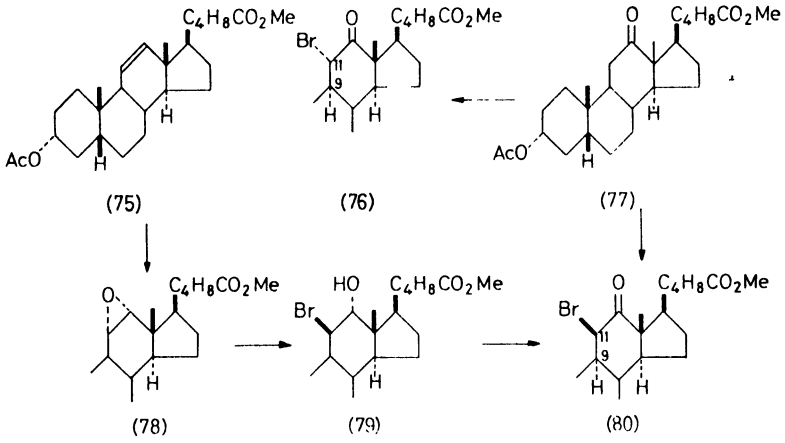


The C_5-bile-acid side chain [*see* p. 25], the five-membered ring *D*, and the two carboxyl groups account for C_{12} in the acid (19); the thirteenth carbon atom is a methyl group. One of the carboxyl groups can be esterified with diazomethane, but not by the Fischer-Speier method, and is tertiary and so adjacent to the methyl group. The acid (19) is a *trans*-$C_{(13)}/C_{(14)}$-diacid [p. 11], and the precursor (74) is a strained *trans*-α-hydrindanone, whose rearrangement to a strainless *cis*-α-hydrindanone by enolization is prevented by the angular methyl group at the adjacent $C_{(13)}$-bridge-head[81].

The production of 1 : 2-dimethylphenanthrene (63) and not 1-methyl-phenanthrene from aetiobilianic acid (61) [*see* p. 22] is also evidence for an angular methyl group at $C_{(13)}$.

$C_{(18)}$: CONFIGURATION. Methyl 3α-acetoxychol-11-enate (75) with perbenzoic acid gives an 11α : 12α-oxide (78)[82, 83, 84], converted by hydrogen bromide to the 11β-bromo-12α-hydrin (79), which by catalytic hydrogenation gives the methyl ester 3-acetate of deoxycholic acid (7)[82, 84], and by oxidation gives the 11β-bromo-12-ketone (80)[83]. This is the minor product of the bromination of methyl 3α-acetoxy-12-oxocholanate (77), and its reactivity to

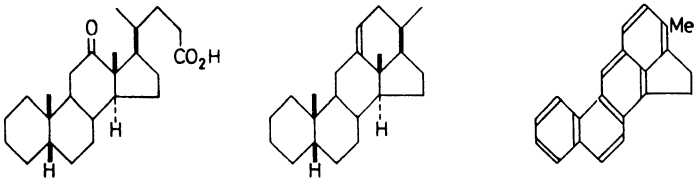
dehydrobromination is greater than that of the epimeric 11α-bromo-12-ketone (76) [*compare* p. 10][85].



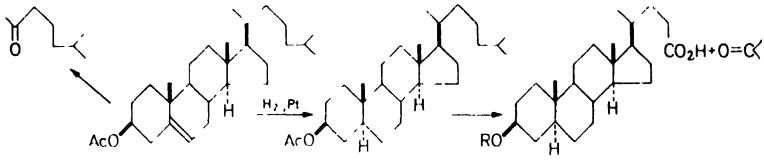
The oxide, the bromhydrin, and deoxycholic acid thus possess the same α-configuration at $C_{(12)}$ by reference to the centre of asymmetry at $C_{(9)}$, the stereochemical relationship of which to the $C_{(10)}$-angular methyl group [9α-H/10β-Me: *trans*] is established [*see* p. 10]. Since it is known that the $C_{(12)}$-hydroxyl group in deoxycholic acid is *trans* to the $C_{(13)}$-angular methyl group[86] [*see* p. 28], the latter is *cis* to the $C_{(10)}$-angular methyl group, and so has the β-configuration.

The Side Chain

Position. The side chain is attached to ring *D* at $C_{(17)}$; this follows from degradation of various bile acids [e.g. cholanic acid (*see* p. 21)], but the most direct evidence is the conversion of 12-oxocholanic acid (81) by pyrolysis to dehydronorcholene (82), which is dehydrogenated with selenium to the carcinogen 20-methylcholanthrene (83)[87, 88] whose structure has been established by synthesis[89].



STRUCTURE. The *iso*propyl group eliminated as acetone in the oxidation of cholestane and coprostane to *allo*cholanic and cholanic acid, respectively [*see* p. 17], forms part of the cholesterol side chain, the structure of which is disclosed by the vigorous oxidation of cholesteryl acetate (85) with chromium trioxide to methyl *iso*hexyl ketone (84)[90]; enzymic oxidation of cholesterol gives *iso*caproic acid[91]. Oxidation of cholestan-3β-yl acetate (86) with chromium trioxide gives 3β-acetoxy*allo*cholanic acid [(87): R = Ac] and acetone[92].



(84) (85) (86) (87)

The Wieland-Barbier degradation[72, 93] permits the bile-acid side chain progressively to be shortened by use of alternate Grignard reactions and oxidations of the olefins resulting from the tertiary carbinols:

(i) $\mathrm{R\cdot\overset{\overset{\mathrm{Me}}{|}}{\underset{20}{C}}HCH_2CH_2\underset{24}{CO_2}\underset{23}{Me}} \xrightarrow{\mathrm{MeMgBr}} \mathrm{R\cdot\overset{\overset{\mathrm{Me}}{|}}{\underset{20}{C}}HCH_2CH_2\underset{24}{CMe_2}\underset{23}{OH}} \xrightarrow{CrO_3}$

METHYL CHOLANATE

$\mathrm{R\cdot\overset{\overset{\mathrm{Me}}{|}}{\underset{20}{C}}HCH_2\underset{23}{CO_2}H}$

NORCHOLANIC ACID

(ii) $\mathrm{R\cdot\overset{\overset{\mathrm{Me}}{|}}{\underset{20}{C}}HCH_2\underset{23}{CO_2}Me} \xrightarrow{\mathrm{MeMgBr}} \mathrm{R\cdot\overset{\overset{\mathrm{Me}}{|}}{\underset{20}{C}}HCH_2\underset{23}{CMe_2}OH} \xrightarrow{CrO_3} \mathrm{R\cdot\overset{\overset{\mathrm{Me}}{|}}{\underset{20}{C}}H\underset{22}{CO_2}H}$

BISNORCHOLANIC ACID

(iii) $\mathrm{R\cdot\overset{\overset{\mathrm{Me}}{|}}{\underset{20}{C}}H\underset{22}{CO_2}Me} \xrightarrow{\mathrm{PhMgBr}} \mathrm{R\cdot\overset{\overset{\mathrm{Me}}{|}}{\underset{20}{C}}H\underset{22}{CPh_2}OH} \xrightarrow{-H_2O} \mathrm{R\cdot\overset{\overset{\mathrm{Me}}{|}}{\underset{20}{C}}=\underset{22}{CPh_2}} \xrightarrow{CrO_3}$

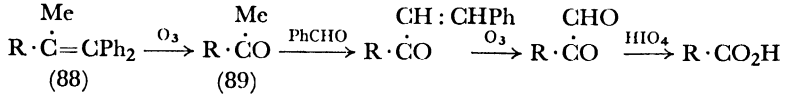
(88)

$\mathrm{R\cdot\underset{20}{CO_2}H}$

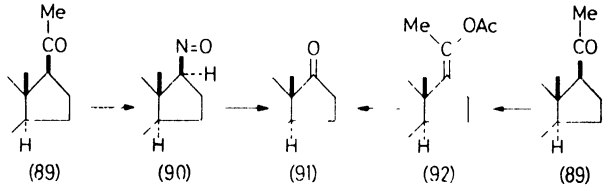
AETIOCHOLANIC ACID
= ETIANIC ACID

Elimination of a single carbon atom in steps (i) and (ii) reveals two methylene groups adjacent to the carboxyl group; in step (iii) elimination of two carbon atoms discloses the position of the branching methyl group. The overall yield varies from 3–7%.

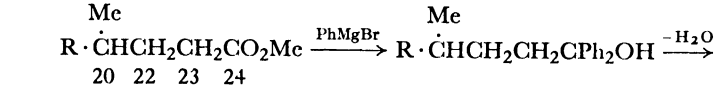
A variation in step (iii) proceeds from the ethylene (88) through the 20-ketone (89) to the aetioacid[94].



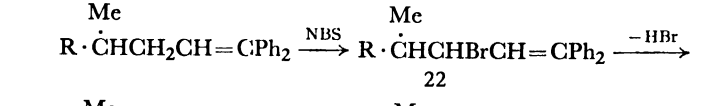
Numerous methods for the conversion of 20-ketones (89) to 17-ketones (91), and so effecting the complete removal of the side chain, have been described; the best are (i) cleavage with ethyl nitrite–sodium ethoxide and hydrolysis [without isolation of the *iso*nitroso = oximino intermediate (90)][95], and (ii) conversion with acetic anhydride in presence of toluene-*p*-sulphonic acid to the enol-acetate (92) and ozonolysis[96].

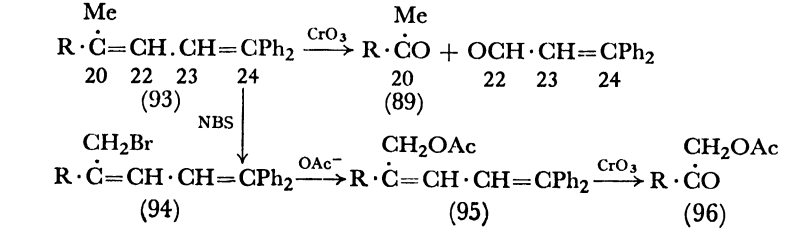


The elegant Miescher-Wettstein degradation[97] eliminates three side-chain carbon atoms at one time and permits overall yields of 20–30%; as in the Wieland-Barbier degradation an initial Grignard reaction gives a tertiary carbinol, which is dehydrated, and the resulting allylic system brominated at $C_{(22)}$ with N-bromsuccinimide; dehydrobromination with boiling dimethylaniline gives a 20 : 23-diene (93), oxidized by chromium trioxide at 0° to the 20-ketone (89) and diphenylacraldehyde:



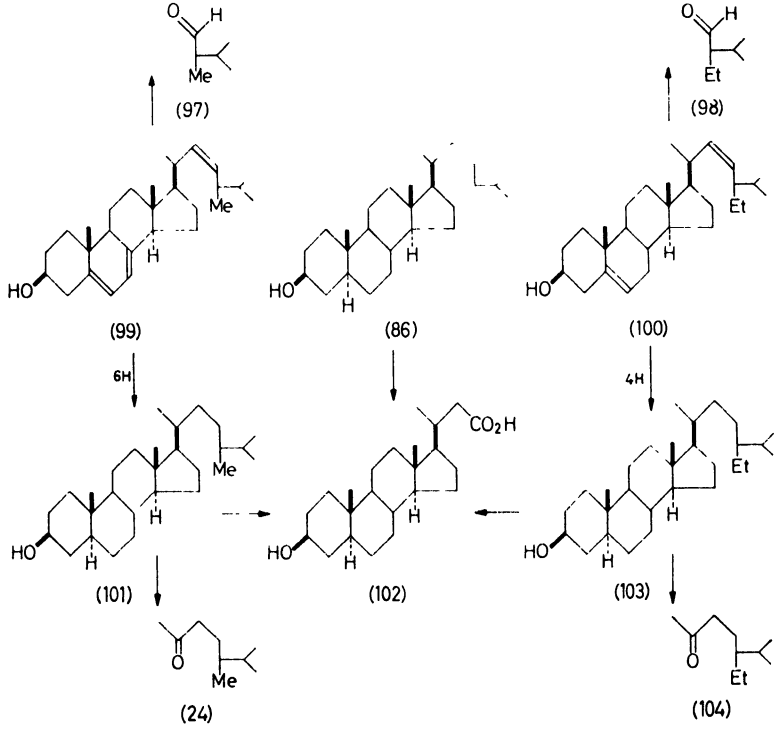
METHYL CHOLANATE





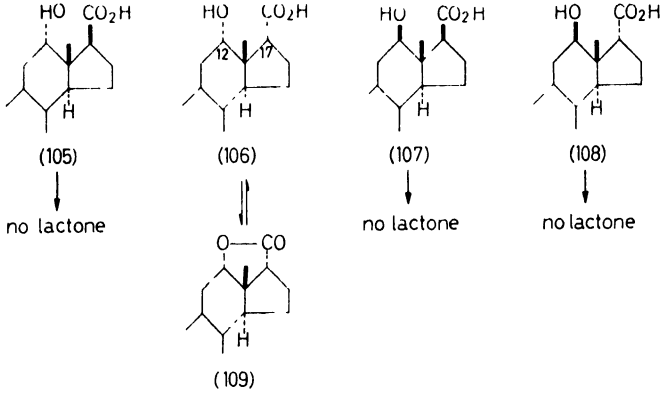
The methyl group of the diene (93) forms part of an allylic system, and may be brominated with N-bromosuccinimide alone[98] or in the presence of allyl bromide[99] to give a 21-bromodiene (94) yielding by acetolysis a 21-acetoxydiene (95), oxidized to a 21-acetoxy-20-ketone (96). These results afford further evidence of the structure of the bile-acid side chain.

The chief variations from the *iso*octyl side chain of cholesterol are unsaturation, generally at the 22 : 23-position, and alkylation at $C_{(24)}$. Ergosterol (99) by ozonolysis gives methyl*iso*propylacetaldehyde (97)[100,101], whilst stigmasterol (100) gives ethyl*iso*propylacetaldehyde (98)[102]. Hydrogenation of these sterols gives ergostanol (101) and stigmastanol (103), which by oxidation [after protection of the 3β-hydroxyl groups by acetylation] yield by fission at the tertiary carbon atom $C_{(24)}$ 3β-hydroxynor*allo*cholanic acid (102)[103], also obtained from cholesterol by the reaction sequence [(85)⟶(86)⟶(87) : p. 25] and subsequent Wiel ınd-Barbier degradation of the acid (87); other products of these oxidations are (—) 5 : 6-dimethylheptan-2-one (24)[34] and (+) 5-ethyl-6-methylheptan-2-one (104)[104], which despite their different signs of rotation have the same configuration[105].



These results demonstrate the structure of the side chains of ergosterol and stigmasterol and relate them to that of the bile acids. The structures of the side chains of the adreno-corticoids, cardiac aglycones, toad poisons, and sapogenins, are dealt with in the appropriate chapters.

CONFIGURATION. As originally suggested by RUZICKA *et al.*[106], and verified by CARLISLE and CROWFOOT[107] by complete x-ray crystallographic analysis of cholesteryl iodide, the $C_{(17)}$-side chain has the β-configuration. Further proof was adduced by Reichstein and M. Sorkin[86], who prepared the four aetiodeoxycholic acids [(105), (106), (107), (108)] differing in configuration at $C_{(12)}$ and $C_{(17)}$:

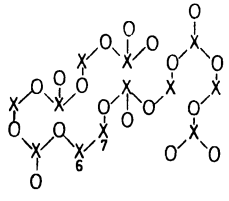


Three of these acids cannot be lactonized under drastic conditions, but the fourth acid gives a γ-lactone (109) with great ease. This acid is 17-*iso*aetiodeoxycholic acid (106); it corresponds in configuration at $C_{(12)}$ with natural deoxycholic acid but is inverted at $C_{(17)}$. Natural deoxycholic acid is therefore 3α: 12α-dihydroxy-(17*n*)-cholanic acid (7), a configuration which has also been established by Gallagher and Long[83], and by KENDALL *et al.*[108], by reference the asymmetry centre $C_{(9)}$. The steroid side chain is therefore β-orientated, and the previously designated 17β-hydroxy-steroids [e.g. 17-hydroxyprogesterone, 17-hydroxycorticosterone (*see* p. 169)] are actually 17α-hydroxy-compounds. Apart from very numerous synthetic 17-*iso*-steroids, the only naturally occurring steroids in which the side chain is known to possess the α-configuration are the so-called '*allo*' cardiac glycosides and aglycones; these 17-*iso*-compounds are derived from the natural 17-*n*-epimerides by the action of enzymes which cause inversion of configuration at $C_{(17)}$. The 22 : 23-double bond in ergosterol (99) and stigmasterol (100) has been shown by infra-red spectroscopy to have the *trans*-configuration[109].

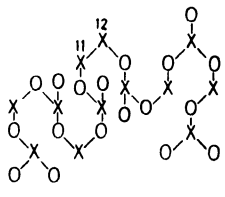
It should be noted that optical rotation[110], ultra-violet[111], and infra-red spectroscopy[112, 113] furnish valuable and detailed information about structure and configuration for which the appropriate literature should be consulted.

Biogenesis

Theories of steroid biogenesis have been advanced by REICHSTEIN[114], ROBINSON[115], MIESCHER[116], and WOODWARD and BLOCH[117]. By use of tracer techniques BLOCH *et al.*[118] have shown that cholesterol is derived biologically, at least in part, from acetic acid units, and undergoes degradation in the organism to cholic acid and progesterone. The theories of Robinson (A) and of Woodward and Bloch (B) involve two sesquiterpene units [each consisting of three head-to-tail isoprene units] joined head-to-tail at $C_{(6)}$–$C_{(7)}$ (A) or $C_{(11)}$–$C_{(12)}$ (B) to give the triterpene squalene (110):

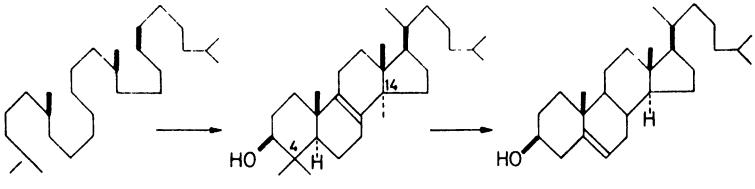


(A)



(B)

CORNFORTH *et al.*[119] have shown that $C_{(6)}$ of cholesterol is derived from the carboxyl group of acetic acid, which is consistent with both schemes; DAUBEN and TAKEMURA[120] have, however, shown that $C_{(7)}$ of cholesterol is derived from the methyl group of acetic acid, which disproves scheme (A) for direct implication of squalene in the biosynthesis of cholesterol. Scheme (B) has now been proved by BLOCH[121] by (i) synthesis from labelled acetic acid of the 4 : 4 : 14-trimethyl-steroid lanosterol (111), and (ii) transformation of squalene (110) to lanosterol (111) and demethylation of this to cholesterol (5) by enzyme systems present in rat-liver homogenates.



(110) (111) (5)

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II

STEROLS, BILE ACIDS, AND RELATED COMPOUNDS

THE sterols [Gr. *stereos*, solid] are steroid alcohols containing an aliphatic side chain; they are crystalline, widely distributed in nature, occurring both free and as esters of higher aliphatic acids, and may be classified on the basis of occurrence as zoosterols [animals], phytosterols [plants], mycosterols [yeast and fungi], and marine sterols [sponges]. All possess Δ^5-unsaturation and are often referred to as stenols whilst their saturated derivatives are called stanols [*see Table II*].

Table II

THE COMMONER STEROLS AND RELATED STANOLS

Name	Structure	Formula	m.p.°	$[\alpha]_D^\circ$
Cholesterol	Cholest-5-en-3β-ol	$C_{27}H_{46}O$	149	−39
*epi*Cholesterol	Cholest-5-en-3α-ol	$C_{27}H_{46}O$	141	−25
3 : 5-*cyclo*Cholestanol	3 : 5-*cyclo*Cholestan-6β-ol	$C_{27}H_{46}O$	75	+24
Cholestanol	Cholestan-3β-ol	$C_{27}H_{48}O$	142	+24
*epi*Cholestanol	Cholestan-3α-ol	$C_{27}H_{48}O$	182	+28
Coprostanol*	Coprostan-3β-ol	$C_{27}H_{48}O$	101	+28
*epi*Coprostanol	Coprostan-3α-ol	$C_{27}H_{48}O$	118	+32
Ergosterol	24b-Methylcholesta-5 : 7 : 22-trien-3β-ol	$C_{28}H_{44}O$	165	−130
Dehydroergosterol	24b-Methylcholesta-5 : 7 : 9(11) 22-tetraen-3β-ol	$C_{28}H_{42}O$	146	+149
Ergostanol	24b-Methylcholestan-3β-ol	$C_{28}H_{50}O$	150	+16
*epi*Ergostanol	24b-Methylcholestan-3α-ol	$C_{28}H_{50}O$	207	+14
Stigmasterol	24b-Ethylcholesta-5 : 22-dien-3β-ol	$C_{29}H_{48}O$	170	−49
Stigmastanol	24b-Ethylcholestan-3β-ol	$C_{29}H_{52}O$	138	+25
*epi*Stigmastanol	24b-Ethylcholestan-3α-ol	$C_{29}H_{52}O$	200	+25

* Formerly called coprosterol

Sterols are isolated from the unsaponifiable fraction of neutral fats, and whilst the product may crystallize readily it is liable to be a mixture of closely related compounds. The sterols are notable for their ability to form molecular compounds and mixed crystals. 3β-Hydroxysteroids, but not 3α-hydroxysteroids, usually give insoluble complexes with digitonin, whilst compound formation occurs between cholestanol [3β-OH] and *epi*coprostanol [3α-OH], coprostanol [3β-OH] and *epi*cholestanol [3α-OH], cholestanol [3β-OH] and *epi*cholest-4-enol [3α-OH], and cholest-4-enol [3β-OH] and *epi*cholest-4-enol [3α-OH]; the configuration of the hydroxyl groups appears to be determinant since acetylation prevents compound formation, and one component of a compound may be replaced by a stereochemically similar substance, e.g. cholestanol may be replaced by ergostanol. Mixed crystals are formed by sterols and 5 : 6-dihydrosterols, e.g. by cholesterol and cholestanol or by ergosterol and 5 : 6-dihydroergosterol; acetylation, or methylation, does not interfere with mixed crystal formation, but elimination of the hydroxyl group prevents it. Occurrence of molecular compounds and mixed crystals often renders purification by fractional crystallization impracticable or impossible, and m.p. is an unreliable guide to purity; differential solubilities of derivatives, e.g. acetates, benzoates, digitonides, or chromatography, are generally used for separation, and optical rotations, ultra-violet and infra-red absorption spectra are employed to supplement m.p. in checking purity.

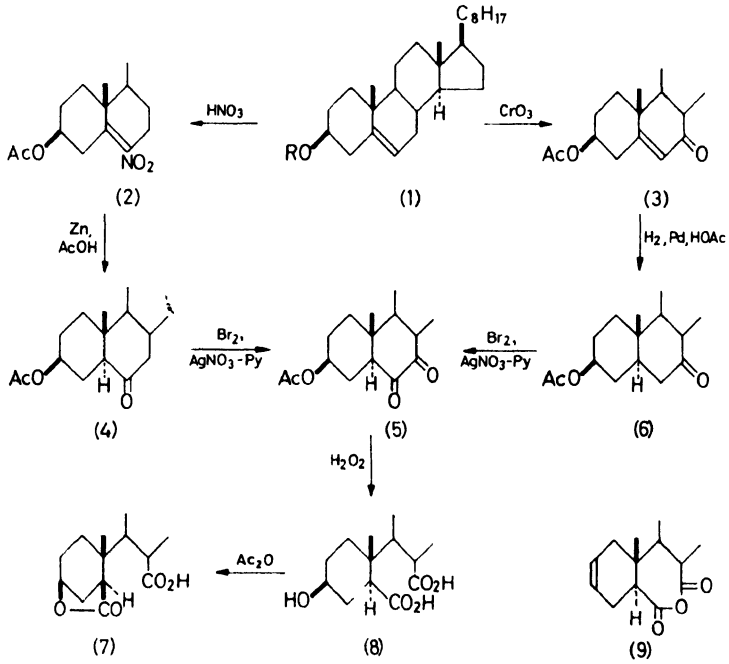
The Commoner Sterols and Related Compounds

Cholesterol (1)

Cholesterol, $C_{27}H_{46}O$, [Gr. *chole*, bile] is the characteristic sterol of higher animals, and is present [0·05–5%] in all tissues; free cholesterol forms 17% of the solid matter of the human brain and is the chief constituent of gall-stones. Commercial cholesterol is obtained from spinal chord of cattle by solvent extraction with or without saponification; purification[1,2] is achieved by recrystallization of the 5 : 6-dibromide which is debrominated with zinc–acetic acid or with sodium iodide–ethanol. Cholesterol preparations derived from tissues contain 1–2% of cholestanol[3]; traces of ergosterol and of cholest-7-en-3β-ol [lathosterol][4] are also present. No specific biological function can be assigned to cholesterol. Its biosynthesis and metabolism have been investigated using deuterium as a tracer; it appears to arise, at least in part, from acetic acid units, and to undergo degradation in the organism to cholic acid and the steroid hormones.

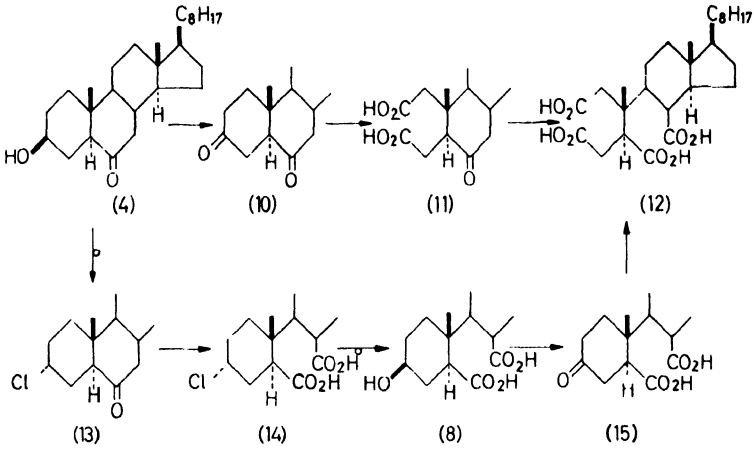
The structural relationship of cholesterol [(1): R = H)] to the

parent hydrocarbons cholestane and coprostane, has been discussed [p. 17], and proofs of the position, structure, and configuration of the side chain given [pp. 24–28]. The position at $C_{(3)}$ of the hydroxyl group has been established [p. 18]; its β-configuration has been proved by SHOPPEE[5] as follows. Cholesteryl acetate [(1): R = Ac] can be converted via (2) and (3) by the oxidation and reduction procedures indicated into 6-oxocholestanyl acetate (4) and 7-oxocholestanyl acetate (6); these by monobromination[6, 7, 8, 9] and subsequent oxidative hydrolysis give the same 6 : 7-dioxocholestanyl acetate (5). Alkaline hydrolysis and oxidation with hydrogen peroxide affords the 6 : 7-*seco*acid (8), which readily gives a γ-lactonic acid (7); since the 5-carboxyl group is β-orientated, the 3-hydroxyl group must possess the β-configuration. The 3α-epimeride of (8), in which the hydroxyl and carboxyl group lie on opposite sides of ring *A*, does not form a γ-lactone but yields an unsaturated anhydride (9). This proof is valid for all 3-hydroxy compounds which have been correlated with cholesterol.



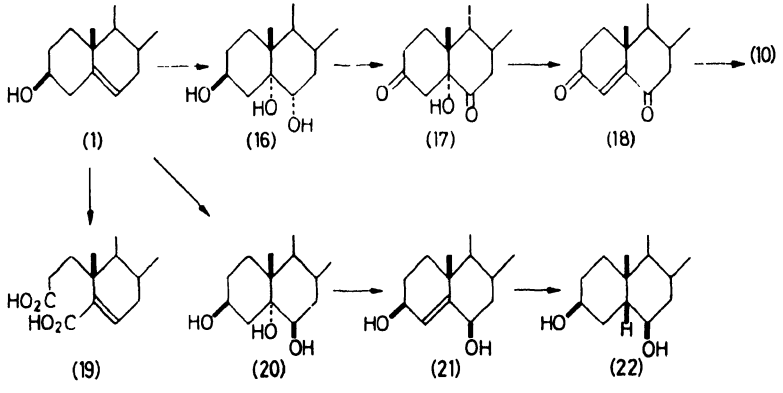
Cholesterol contains one double bond which is situated in ring *B* adjacent to the hydroxylated ring *A*. 6-Oxocholestan-3β-ol (4) by oxidation with chromium trioxide at 20° gives 3 : 6-dioxocholestane (10), cleaved by more vigorous oxidation to

6-oxo-2 : 3-*seco*cholestane-2 : 3-dioic acid (11) and 2 : 3–6 : 7-*seco*-cholestane-2 : 3 : 6 : 7-tetroic acid (12)[10].



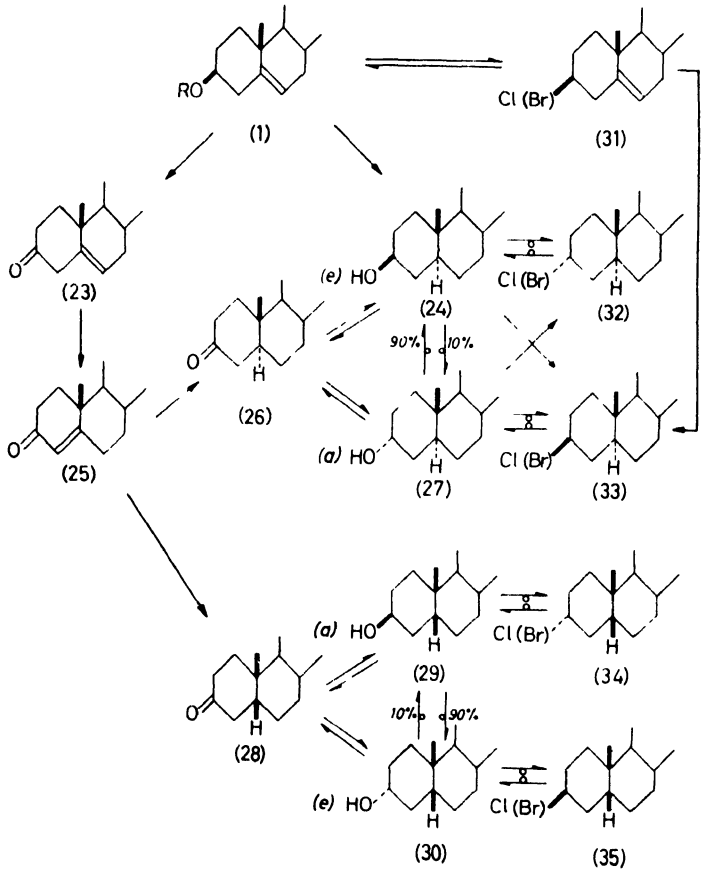
Alternatively, the ketol (4) with phosphorous pentachloride yields 3α-chlorocholestan-6-one (13), oxidized to the 3α-chloro-6 : 7-*seco*-diacid (14); alkaline hydrolysis affords the 3β-hydroxy-6 : 7-*seco*-diacid (8)[5, 11], successively oxidized by chromium trioxide to 3-oxo-6 : 7-*seco*cholestane-6 : 7-dioic acid (15) and the tetracarboxylic acid (12)[12].

Cholesterol (1) with alkaline permanganate[13] or osmium tetroxide[14] gives cholestane-3β : 5α : 6α-triol (16), whilst use of hydrogen peroxide[15] yields cholestane-3β : 5α : 6β-triol (20); these triols are both oxidized to 3 : 6-dioxocholestan-5-ol (17)[16], dehydrated to 3 : 6-dioxocholest-4-ene (18), which by reduction with zinc–acetic acid gives 3 : 6-dioxocholestane (10). Dehydration of the triol (20)



gives cholest-4-ene-3β : 6β-diol (21), which by catalytic reduction to coprostane-3β : 6β-diol (22)[16] provides one of the few good routes to the coprostane series.

Cholesterol (1) is oxidized by hypobromite to the unsaturated 3 : 4-*seco*diacid [Diels' acid] (19)[17]; oxidation of free cholesterol with chromium trioxide gives *epi*cholesterol[18], but use of cholesterol dibromide gives, after debromination with zinc–acetic acid, cholest-4-en-3-one (25)[19,20], which can be obtained directly from cholesterol by oxidation with aluminium *tert.*-butoxide and acetone[21]. The initial product is cholest-5-en-3-one (23), which can be isolated by debromination with zinc–methanol[22,23], and is converted by acid[22] or alkali[22] or by alkaline, but not neutral, aluminium oxide[24] to the conjugated isomeride (25). For peroxidation of cholesterol, *see* pp. 37 and 40. Cholesterol with molecular oxygen at 20° affords 7α- and 7β-hydroxycholesterol together with 7-oxocholesterol (3)[25,26];

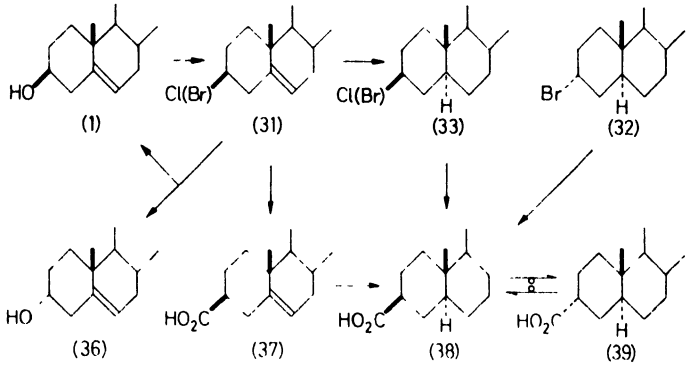


irradiation with x-rays in an aqueous medium gives cholestane-3β : 5α : 6β-triol (20) and 7-oxocholesterol[27]. Cholesterol with selenium dioxide–acetic acid at 90° yields cholest-5-ene-3β : 4β-diol, which at higher temperatures rearranges to cholest-4-ene-3β : 6β-diol (21)[28, 29, 30, 31]; alkaline permanganate gives, as stated, cholestane-3β : 5α : 6α-triol (16), but acid permanganate appears initially to yield the 5α : 6α-epoxide [*see* p. 40], converted to cholestane-3β : 5α : 6β-triol (20) and further oxidized to 3 : 6-dioxocholestan-5-ol (17)[32, 33]. Cholesteryl acetate [(1): R = Ac] by oxidation with chromium trioxide–acetic acid or permanganate–acetic acid gives mainly 7-oxocholesteryl acetate (3)[34, 35, 36].

Cholesterol [(1) : R = H] by catalytic hydrogenation with platinum–acetic acid and a trace of perchloric acid gives cholestanol (24) [with 3·5% of coprostanol (29)][37, 38], oxidized to cholestan-3-one (26). Cholesterol, by conversion to cholest-4-en-3-one (25) and partial hydrogenation with platinum in acid solution, gives mainly cholestan-3-one[20], but partial hydrogenation with palladium in neutral solution gives mainly coprostan-3-one (28)[39]. Catalytic hydrogenation of cholestan-3-one (26) and of coprostan-3-one (28) in *neutral* solvents gives respectively cholestanol (24)[40] and *epi*-coprostanol (30)[20], but in *acidic* media yields respectively *epi*cholestanol (27)[41] and coprostanol (29)[42]. The cholestanols (24) and (27) and the coprostanols (29) and (30) yield equilibrium mixtures with sodium ethoxide at 180°[43] or with aluminium *iso*propoxide[44]; the proportions of the alcohols at equilibrium and the rates of alkaline hydrolysis of their acetates[45] [(24) > (27); (30) > (29)] are consistent with the equatorial character of the hydroxyl group in cholestanol (24) and *epi*coprostanol (30), and the axial character of the hydroxyl group in *epi*cholestanol (27) and coprostanol (29)[46].

Cholesterol [(1): R = H] with phosphorus pentachloride[47] or thionyl chloride[48, 49], or as the chloroformate by pyrolysis[50] gives cholesteryl chloride (31). Cholesteryl bromide (31) is obtained by use of phosphorus tribromide in benzene[51, 52], or thionyl bromide[53]; cholesteryl iodide [as (31)] is obtained from cholesteryl methane- or toluene-*p*-sulphonate with sodium iodide in acetone[54], or by rearrangement with hydrogen iodide in acetic acid at 15° of 6β-methoxy-3 : 5-*cyclo*cholestane [*see* p. 48][55]. Cholesteryl chloride (31) or bromide by catalytic hydrogenation yields 3β-chlorocholestane (33)[56] or 3β-bromocholestane[57], also obtained from *epi*cholestanol (27) with phosphorus pentachloride[58] or phosphorus tribromide[57], and from cholestanol (24) with thionyl chloride or bromide[56]; 3α-chlorocholestane (32) and 3α-bromocholestane are obtained from cholestanol (24) with phosphorus pentachloride[58, 59, 60] or phosphorus tribromide[57, 61], and from *epi*cholestanol (27) with thionyl chloride or bromide[56]. Cholesteryl chloride by acetolysis

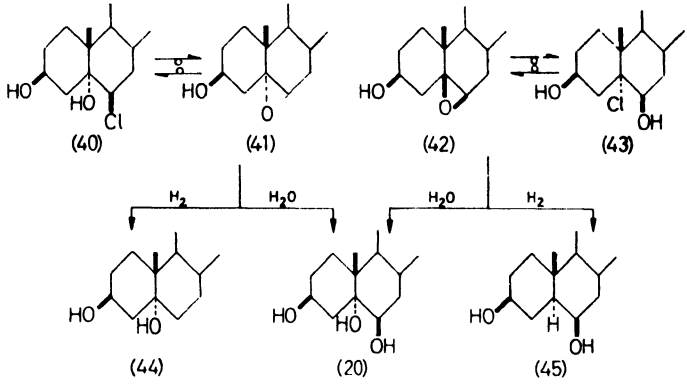
and alkaline hydrolysis gives only cholesterol with retention of configuration[62], whilst 3α-chlorocholestane (32) and 3β-chlorocholestane (33) give mainly cholestanol (24) and *epi*cholestanol (27), respectively, with inversion of configuration, and much cholest-2-ene by elimination[63]. Coprostanol (29) and *epi*coprostanol (30) with phosphorus pentachloride or bromide yield 3α-chloro- and 3α-bromocoprostane (34) and 3β-chloro- and 3β-bromocoprostane (35), respectively, which by acetolysis and alkaline hydrolysis undergo inversion to regenerate coprostanol (29) and *epi*coprostanol (30) accompanied by coprost-2-ene[64].



Cholesteryl chloride or bromide (31) with magnesium yields a Grignard complex giving with oxygen approximately equal proportions of cholesterol (1) and *epi*cholesterol (36)[65, 66], but with carbon dioxide a single acid [Marker's acid] (37)[57, 65, 67]. 3β-Bromocholestane (33) and 3α-bromocholestane (32) with magnesium and then oxygen yield approximately equal proportions of cholestanol (24) and *epi*cholestanol (27)[66], but by carbonation afford a *single* acid (38), also prepared by hydrogenation of the acid (37)[57, 68]. Epimerization of the acid (38) with sodium–diethylene glycol at 235° gives 5% of cholest-5-ene-3α-carboxylic acid (39)[57].

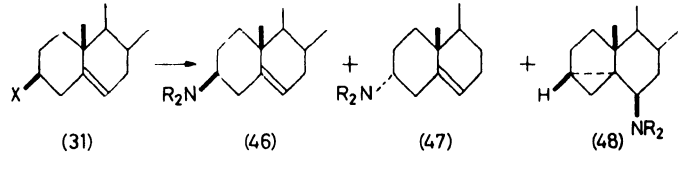
Cholesterol with perbenzoic acid[23, 69] gives mainly the 5α : 6α-epoxide (41), m.p. 142°, $[\alpha]_D$ — 46°, accompanied by some of the 5β : 6β-epoxide (42), m.p. 132°, $[\alpha]_D$ + 10°; the substances formerly regarded as the 5β : 6β-epoxide and its acetate are molecular [αβ]-compounds of the epoxides or their acetates[70, 71], and can be separated into their components by repeated fractional crystallization[71] or by chromatography[72]. Cholesteryl acetate with perbenzoic acid gives the αβ-epoxide acetate[23] and cholesteryl benzoate with monoperphthalic acid yields the αβ-epoxide benzoate[73]. The 5α : 6α-epoxide (41) with hydrogen chloride gives the 6β-chloro-3β : 5α-diol (40) which forms a monoacetate and is easily dehydrated[74],

whilst the 5β : 6β-epoxide (42) gives the 5α-chloro-3β : 6β-diol (43), which forms a diacetate; the chlorodiols with potassium hydroxide yield the respective epoxides, this method being used[70] to prepare the pure 5β : 6β-epoxide for the first time.



The 5α : 6α-epoxide (41) as the acetate is hydrogenated with platinum–acetic acid to give after hydrolysis cholestane-3β : 5α-diol (44) which by oxidation with chromium trioxide yields the 3-keto-5α-ol, dehydrated with characteristic ease to cholest-4-en-3-one (25), and which affords a diacetate only under forcing conditions[75]. Hydrogenation of the 5β : 6β-epoxide (42) as the acetate gives, after hydrolysis, cholestane-3β : 6β-diol (45)[75], also obtained together with the 3β : 6α-diol by reduction of 6-oxocholestanyl acetate (4) and hydrolysis[28, 75, 76, 77, 78]. Hydrolysis of either epoxide, (41) or (42), in dioxan at 160° gives, after hydrolysis, cholestane-3β : 5α : 6β-triol (20)[75].

Cholesteryl chloride and toluene-*p*-sulphonate [(31): X = Cl, TsO] react with ammonia[79, 80, 81], benzylamine[80, 82, 83], and dimethylamine[81, 84] to give 3β-aminocholest-5-ene (46) and its substitution products, accompanied by the appropriate 3α-aminocholest-5-ene (47)[83, 84] and 6β-amino-3 : 5-*cyclo*cholestane (48)[80, 83, 84].



Cholesteryl bromide, iodide, and toluene-*p*-sulphonate [(31) : X = Br, I, TsO] react with pyridine to give, by substitution, the quaternary salt [(31): X = $C_5H_5N^+$} *p*-TsO^-] and 21% of cholesta-3 : 5-diene

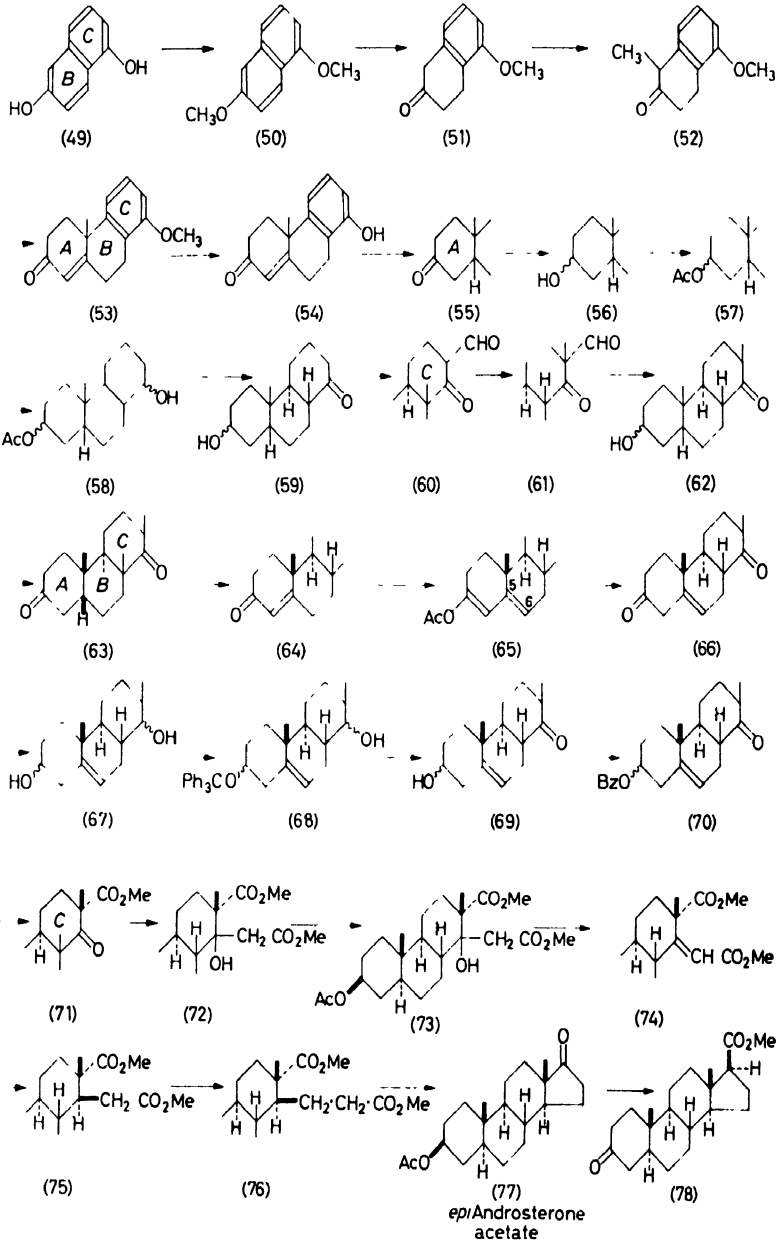
by elimination of HX. The epimeric cholestan-3-yl halides (32) and (33) and toluene-*p*-sulphonates[81, 83, 86, 87] and the epimeric coprostan-3-yl halides (34) and (35) and toluene-*p*-sulphonates[88] react with ammonia, pyridine, and piperidine with inversion of configuration.

Cholesterol [(1): OH, equatorial] is dehydrated only with difficulty to cholesta-3 : 5-diene, e.g. by anhydrous copper sulphate at 140–200°[89, 90], concentrated phosphoric acid at 137°[91], aqueous perchloric acid at 100°[92], potassium hydrogen sulphate at 215°[93, 94] copper sulphide or chloride or silver chloride at 250°[95]. Cholesta-3 : 5-diene is also formed by pyrolysis of cholesteryl acetate[96], methylxanthate[97, 98], oleate[99], phenylcarbamate[100], or of potassium cholesteryl sulphate with sodium octyloxide[101]. Similarly, cholesteryl chloride [(31): Cl, equatorial] yields cholesta-3 : 5-diene with quinoline only at 230°[102], by distillation with lime[102], with zinc oxide at 135–200°[103], with hot ethanolic sodium ethoxide[89, 102, 104], with hot ethanolic ammonia[104], or with sodium iodide in acetone at 180°[105]; cholesteryl bromide gives cholesta-3 : 5-diene with sodium iodide in acetone at 100°[106], and by acetolysis gives cholesteryl acetate with first order kinetics[107].

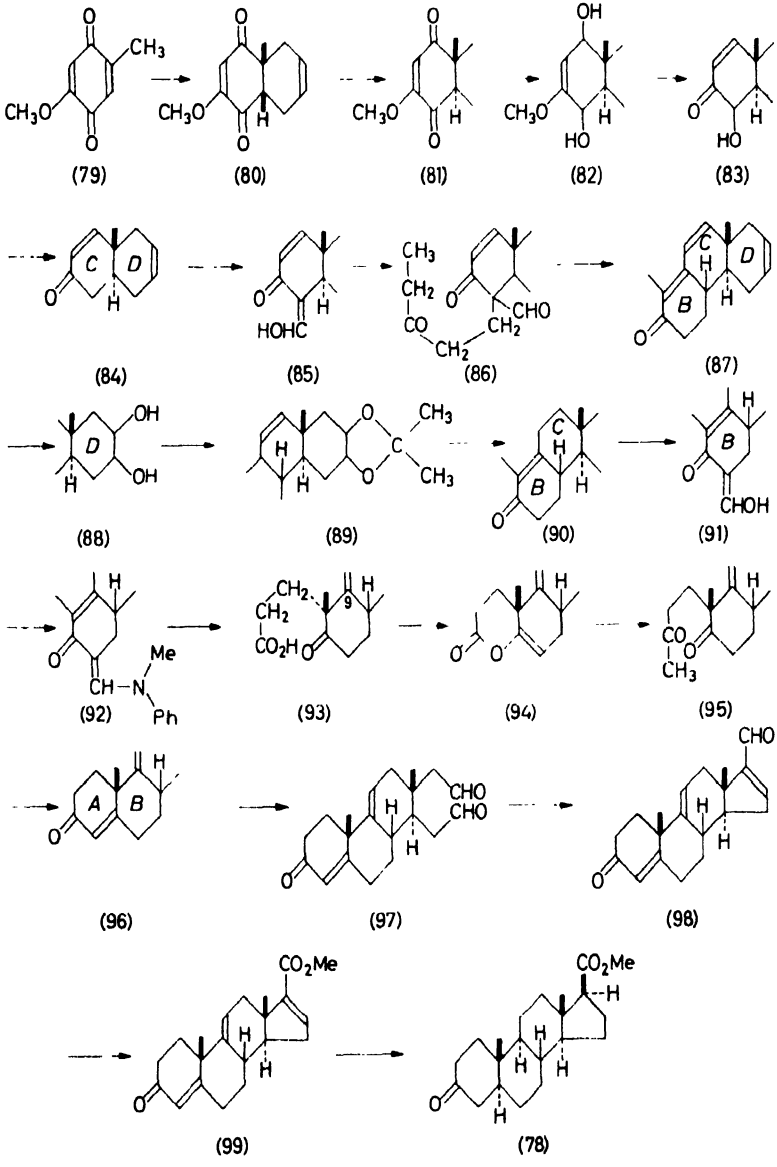
The oxidation of the side chain of cholesterol has been discussed in Chapter I [p. 25]; the numerous products isolated from oxidation of cholesteryl acetate dibromide with chromium trioxide have been summarized[108].

The structure of cholesterol receives final confirmation by two total syntheses reported simultaneously from the Oxford and Harvard Laboratories; the following brief accounts cannot do justice to the elegance and ingenuity of the work.

The *A*←*BC*→*D* synthesis (*see* Figure on p. 43) by CORNFORTH and ROBINSON[109] starts from 1 : 6-dihydroxynaphthalene (49) which as the dimethyl ether (50) was converted into 5-methoxy-1-methyl-β-tetralone (52), transformed by the Robinson-Mannich base methiodide method into the unsaturated ketone (53), demethylated to (54) which was hydrogenated through (55) to the diol (56), which was shown to possess *A*/*B*-*cis*-fusion and was transformed by standard methods into two tricyclic hydroxy-ketones [as (59)]; since these are α-decalones and have been subjected to treatment with OH^-, they represent the two possible modes of *B*/*C*-*trans*-fusion. They were resolved and the four enantiomorphs separately transformed by successive formylation, methylation, hydrolysis, and oxidation to four diketones, one of which (63) was identical with the compound previously obtained from deoxycholic acid and cholesterol. The derived $\alpha\beta$-unsatured diketone (64), as the enol-acetate (65) with potassium amide gave the $\beta\gamma$-unsaturated diketone (66), reduced with lithium aluminium hydride to the 1 : 7-diol (67). This was



Cornforth and Robinson synthesis



Woodward synthesis

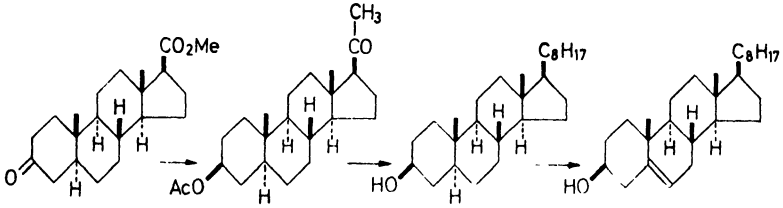
oxidized as the 7-trityl ether to the hydroxy ketone (69), which was carbonated as the benzoate (70) to give after esterification with diazomethane a mixture of two isomeric esters. One of these (71) by the Reformatsky reaction sequence gave the diester (75), which as the half-ester by the Arndt-Eistert reaction gave the homologue (76), cyclized by the Dieckmann reaction to furnish after decarboxylation the male sex hormone *epi*androsterone (77); this is convertible by known reactions into methyl 3-oxoaetio*allo*cholanate (78).

The second synthesis, of $A \leftarrow B \leftarrow C \rightarrow D$ type (*see* Figure on p. 44), is due to R. B. WOODWARD[110]. 4-Methoxy-2 : 5-toluquinone (79), which eventually formed ring *C*, was converted by the Diels-Alder reaction with butadiene to the *cis*-α-hexalone (80), readily isomerized to the *trans*-compound (81). Reduction with lithium aluminium hydride gave the diol (82), hydrolysed by mineral acid to a β-hydroxy-ketone spontaneously dehydrated to give (83), from which the remaining hydroxyl group was eliminated by a new reduction procedure using zinc–acetic anhydride to furnish the *trans*-bicyclic ketone (84). Formylation, addition of ethyl vinyl ketone catalysed by *tert.*-butoxide ion, and dehydration gave a single *B/C-anti-C/D-trans*-tricyclic ketone (87). Preparations to modify ring *D* were made by hydroxylation with osmium tetroxide to two isomeric *cis*-diols [as (88)], and conversion to the isomeric acetonides represented by (89), one of which by dehydrogenation with palladium in a non-polar medium gave the ketone (90). This was converted through the hydroxymethylene derivative (91) to the methylanilinomethylene ketone (92), which was condensed with acrylonitrile to give after hydrolysis two isomeric keto-acids, one of which (93) was converted by standard procedures into the αβ-unsaturated ketone (96). After hydrolysis of the acetonide, fission of the *D*-homo-ring with periodic acid to the dialdehyde (97), cyclization to the aldehyde (98), oxidation, and esterification gave (±)-methyl 3-oxoaetiochola-4 : 9(11) : 16-trienate (99); this was resolved by reduction with sodium borohydride to a mixture of (±)-3α-hydroxy- and (±)-3β-hydroxy-$\Delta^{4:9(11):16}$-esters, from which the (+)-form of the 3β-alcohol was precipitated preferentially by digitonin. Oppenauer oxidation regenerated the (+)-3-oxo-ester (99), identical with that prepared from cortisol [*see* p. 212] by J. VON EUW and T. REICHSTEIN[111], and hydrogenated to a mixture of 5-epimerides from which methyl 3-oxoaetio*allo*cholanate (78) was isolated.

Both groups of workers converted the ester (78) by standard methods into 3β-acetoxy*allo*pregnan-20-one (100), which by the Grignard reaction with *iso*hexylmagnesium bromide, dehydration, hydrogenation, and hydrolysis gave cholestanol (24); the route from this via cholestan-3-one (26), cholest-4-en-3-one (25), and cholest-5-en-3-one (23) to cholesterol is established [*see* p. 76].

The ester (78) can also be converted by known stages into androsterone [*see* p. 184], testosterone [p. 141], progesterone [p. 127], deoxycorticosterone [p. 183], and cortisone [p. 177], so that the total syntheses outlined above are also total syntheses of these hormones.

Cholesterol dichloride from cholesterol and chlorine is 5α : 6β-dichlorocholestan-3β-ol, m.p. 144°, $[\alpha]_D$ — 27°, whilst the isomeride obtained by use of iodobenzene dichloride is 5α : 6α-dichlorocholestan-3β-ol, m.p. 172°, $[\alpha]_D$ + 2° [112,113]. Cholesterol dibromide is 5α : 6β-dibromocholestan-3β-ol, m.p. 114°, $[\alpha]_D$ — 44°



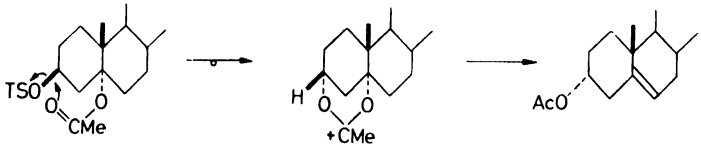
and changes slowly in chloroform solution into 5β : 6α-dibromocoprostan-3β-ol, m.p. 143°, $[\alpha]_D$ + 47° [113,114,115]. Cholesterol hydrochloride, m.p. 158° [95], is 5α-chlorocholestan-3β-ol. Cholesteryl acetate has m.p. 115°, $[\alpha]_D$ + 43° [5α : 6β-dibromide, m.p. 112°, $[\alpha]_D$ — 46°], cholesteryl benzoate has m.p. 145°, $[\alpha]_D$ — 14° [5α : 6β-dibromide, m.p. 135°, $[\alpha]_D$ — 33°; 5β : 6α-dibromide, m.p. 163°, $[\alpha]_D$ + 82°]; cholesteryl toluene-*p*-sulphonate has m.p. 131°, $[\alpha]_D$ — 39°; the urethane and phenylurethane of cholesterol have m.p. 217° and 168°, respectively. Cholesterol digitonide, $C_{27}H_{47}OH \cdot C_{56}H_{92}O_{29}$, has no m.p. and is soluble to the extent of only 0·14 mg/cc. in 95% ethanol at 18°. Radiocholesterol [4-^{14}C] has been prepared[116,117].

Cholestanyl acetate has m.p. 110°, $[\alpha]_D$ + 14°, + 16° and *epi*-cholestanyl acetate has m.p. 95°, $[\alpha]_D$ + 30°; coprostanyl acetate has m.p. 91°, $[\alpha]_D$ + 14° and *epi*coprostanyl acetate has m.p. 89°, $[\alpha]_D$ + 42°.

*epi*CHOLESTEROL (36)

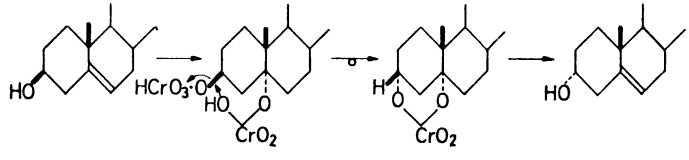
A mixture of cholesterol (1) and *epi*cholesterol (36) is produced by epimerization of cholesterol[44], by oxygenation of cholesteryl magnesium chloride [*see* p. 40][65,66], by hydrogenation with nickel in a neutral medium[118] or reduction with lithium aluminium hydride[119,120] of cholest-5-en-3-one (23)[118], and by reduction with lithium aluminium hydride[121] or sodium borohydride[122,123] of the enol-acetate of cholest-4-en-3-one (25). The mixture may be separated with digitonin, which does not form an insoluble

digitonide with *epi*cholesterol, or by successive fractional crystallization of the mixed acetates and benzoates[65]. The only satisfactory preparative methods are from cholestane-3β:5α-diol (44) [p. 41], which as the 3-toluene -(or methane)-sulphonate-5-acetate (44) by treatment with boiling pyridine gives, via the intermediate cation (101), *epi*cholesteryl acetate, m.p. 85°, $[\alpha]_D$ — 10° (36)[75,124],



(44) (101) (36)

or from cholesterol (1) which, by oxidation in warm benzene with a hot solution in acetic acid of two oxygen equivalents of dichromate by way of the chromic ester (102) and the 3α : 5α-cyclic ester (103), affords a molecular compound of 6-oxocholest-4-en-3β-ol and *epi*cholesterol, from which the latter is readily separated by chromatography[125]:



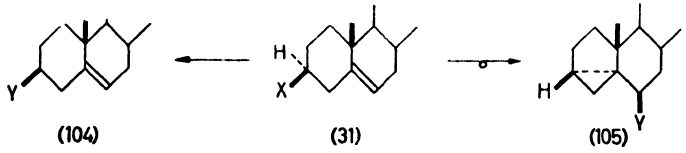
(1) (102) (103) (36)

Oxidation of *epi*cholesteryl acetate with chromium trioxide gives 3 : 6-dioxocholestan-5-yl acetate[126]. Catalytic hydrogenation of *epi*cholesterol gives both *epi*cholestanol (27) and *epi*coprostanol (30), but *epi*cholesteryl acetate and methyl ether yield only the appropriate coprostane derivative[127]. *epi*Cholesteryl toluene-*p*-sulphonate by reduction with lithium aluminium hydride gives cholest-5-ene and cholesta-3 : 5-diene[128,129]; methanolysis[128,129,130] gives cholesta-3 : 5-diene, 4β-methoxycholest-5-ene, and 6β-methoxycholest-4-ene, whilst acetolysis[131] gives cholesta-3 : 5-diene, 4β-acetoxycholest-5-ene, and 6β-acetoxycholest-4-ene, and shows first order kinetics[132].

*epi*Cholesteryl chloride and bromide cannot be prepared from *epi*cholesterol, but are obtained, analogously to the 3β-halides [(31): X = F, Cl, Br, I], by dehydration of 3α-chloro [bromo] cholestan-6β-ol[133].

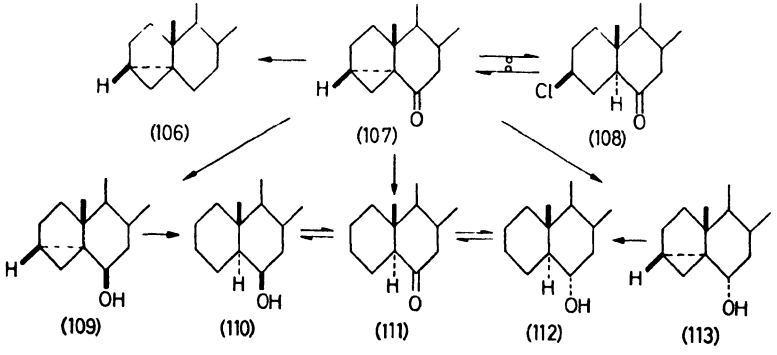
3 : 5-*cyclo*CHOLESTAN-6β-OL (109)

3 : 5-*cyclo*Cholestan-6β-ol [≡ '*i*-cholesterol']. Cholesteryl chloride and toluene-*p*-sulphonate [(31): X = Cl or TsO] undergo normal methanolysis to give 3β-methoxycholest-5-ene[48,134] [(104): Y = OMe], m.p. 84°, $[\alpha]_D$ − 42°, but in presence of potassium acetate undergo molecular rearrangement to afford 6β-methoxy-3 : 5-*cyclo*cholestane[134] [(105): Y = OMe], m.p. 79°, $[\alpha]_D$ + 52°.



(104) (31) (105)

Similarly, acetolysis[135] of (31) [X = TsO] with acetic anhydride in presence or absence of potassium acetate gives cholesteryl acetate [(104): Y = AcO] and 3 : 5-*cyclo*cholestan-6β-yl acetate [(105): Y = OAc], m.p. 73°, $[\alpha]_D$ + 48°, converted by alkaline hydrolysis to 3 : 5-*cyclo*cholestan-6β-ol [(104): Y = OH]. Hydrolysis[136] of (31) [X = TsO] with aqueous acetone in presence or absence of potassium acetate affords cholesterol [(104): Y = HO] accompanied by 3 : 5-*cyclo*cholestan-6β-ol [(105): Y = OH], m.p. 74°, $[\alpha]_D$ + 50°. Reduction of (31) [X = TsO] with lithium aluminium hydride[137] gives cholest-5-ene and 3 : 5-*cyclo*cholestane[128] (106), m.p. 78, $[\alpha]_D$ + 80°, also prepared by Wolff–Kishner reduction[138] of 3 : 5-*cyclo*cholestan-6-one (107), which is readily obtained from and reconverted to 3β-chlorocholestan-6-one (108) by elimination or



(106) (107) (108)

(109) (110) (111) (112) (113)

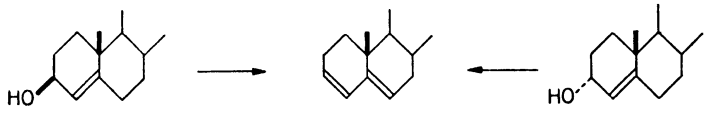
addition of hydrogen chloride[135,136]. Hydrogenation of 3 : 5-*cyclo*cholestan-6-one (107) with palladium in acetic acid[139] gives cholestan-6-one (111), but reduction with aluminium *iso*propoxide-*iso*propanol[136] yields 3 : 5-*cyclo*cholestan-6β-ol (109) accompanied by 3 : 5-*cyclo*cholestan-6α-ol (113), whilst use of lithium aluminium

hydride[138,140] or sodium-ethanol[138] affords mainly 3 : 5-*cyclo*-cholestan-6α-ol [≡ '*epi-i*-cholesterol'] (113). Hydrogenation of the epimeric 3 : 5-*cyclo*-6-ols (109) and (113) with palladium in dioxan[138] gives respectively cholestan-6β-ol (110) and cholestan-6α-ol (112), both converted by oxidation to cholestan-6-one (111), which is hydrogenated[138] to cholestan-6β-ol (110) and reduced by sodium-ethanol[138,141] to cholestan-6α-ol (112).

3 : 5-*cyclo*Cholestane derivatives are sensitive to acids[142]; thus with dilute sulphuric acid both the 3 : 5-*cyclo*-6-ols, (109) and (113), rearrange to cholesterol[135,138,140], and with the halogen acids in acetic acid at 15° afford cholesteryl fluoride[143], chloride, bromide, and iodide[136] [(31): X = F, Cl, Br, I]. 3 : 5-*cyclo*Cholestane derivatives are indifferent to perbenzoic acid and ozone, but react readily with bromine[136,144]; they are optically transparent in the 200 mμ. region, and give faint yellow colours with tetranitromethane–chloroform[138,145].

CHOLEST-4-EN-3-OLS (114) *and* (116)

The name '*allo*cholesterol' for cholest-4-en-3β-ol (114), m.p. 132°, $[\alpha]_D$ + 44°, is misleading and should disappear; a mixture of this compound and cholesterol is produced when 5α-chlorocholestan-3β-ol [≡ 'cholesterol hydrochloride'] is dehydrochlorinated with potassium acetate[146]. A molecular compound of the two cholest-4-en-3-ols, (114) and (116), is obtained from cholest-4-en-3-one (25) by Meerwein-Poundorf reduction[147], or with lithium aluminium hydride[148,149,150], and is resolved by treatment with digitonin with which cholest-4-en-3α-ol (116), m.p. 84°, $[\alpha]_D$ + 121° does not form an insoluble digitonide; reduction of cholest-4-en-3-one with sodium-ethanol gives a molecular compound of cholestanol (24) and cholest-4-en-3α-ol (116)[59,151].



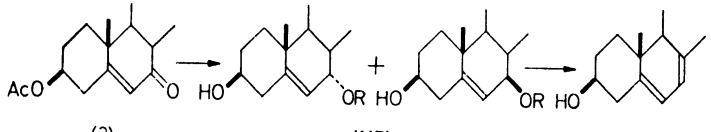
(114) (115) (116)

Both epimerides are rapidly dehydrated by N/30 ethanolic hydrogen chloride to cholesta-3 : 5-diene (115) [*see* p. 68]. Catalytic hydrogenation[147] of the 3β-ol (114) gives coprostanol (29), whereas the 3α-ol (116) yields *epi*cholestanol (27) and *epi*coprostanol (30). Oxidation of the 3β-ol (114) with chromium trioxide[152] furnishes cholest-4-en-3-one (25) and cholest-4-en-3 : 6-dione (18),

whilst use of manganese dioxide[153] in benzene, chloroform, or ethylene dichloride at 20° affords successively cholest-4-en-3-one (25) and cholesta-4 : 6-dien-3-one.

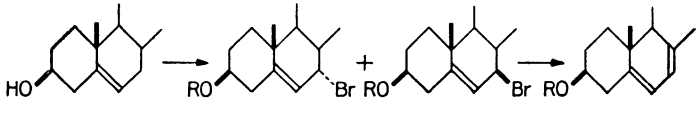
CHOLESTA-5 : 7-DIEN-3β-OL, 7-DEHYDROCHOLESTEROL (118)

This substance has been identified as the precursor of cholecalciferol [≡ natural vitamin D_3] [*see* p. 59]. 7-Oxocholesteryl acetate (3) [*see* p. 36] by Meerwein-Poundorf reduction[154] gives a mixture of 7α- and 7β-hydroxycholesterols [as (117): R = H]; use of lithium aluminium hydride[155] gives mainly the 7β-ol, whilst cholesteryl hydrogen phthalate by oxidation with permanganate[156] gives the 7α-ol. Pyrolysis of the benzoates [as (117): R = Bz], or, better, heating with dimethylaniline[155,157,158,159] yields 7-dehydrocholesteryl esters hydrolysed to 7-dehydrocholesterol (118), m.p. 145–147°, $[\alpha]_D$ −120°.



(3) (117) (118)

Alternatively, cholesterol (1) by bromination as the acetate or benzoate with N-bromosuccinimide[53,160,161,162] gives 7α- or 7β-bromocholesteryl acetate or benzoate [(119) or (120): R = Ac or Bz], dehydrobrominated with tertiary bases or alkaline reagents to 7-dehydrocholesterol acetate or benzoate [(118): R = Ac or Bz][53,160,161,162,163,164,165].

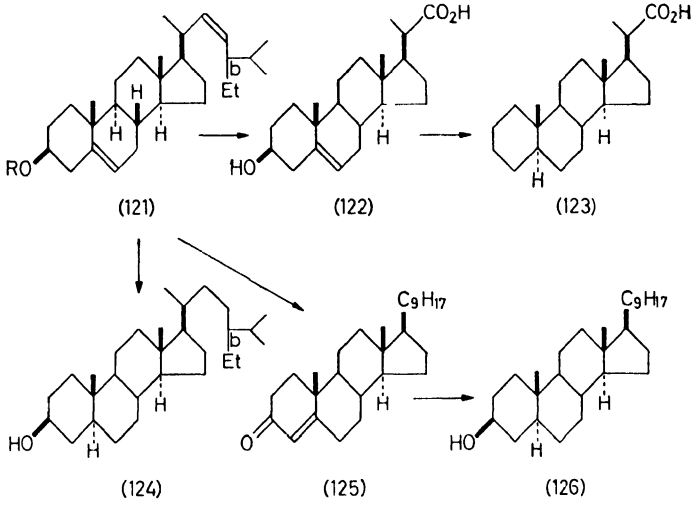


(1) (119) (120) (118)

Stigmasterol (121)

Stigmasterol, $C_{29}H_{48}O$, is widely distributed in plants, but only calabar bean and soya bean contain sufficient to serve as sources. The sterol is readily isolated as the sparingly soluble acetate tetrabromide, m.p. 211°, $[\alpha]_D$ − 40°. Stigmasterol [(121): R = H] contains two carbon atoms more than cholesterol[166,167], and ozonolysis[168] to give ethyl*iso*propylacetaldehyde proves the presence of a $C_{(24)}$-ethyl group, provisionally described as possessing the b-configuration (Chapter I, pp. 13 and 27), and Δ^{22}-unsaturation. Stigmasteryl acetate

[(121): R = Ac] reacts with one molecule of bromine to give the 5 : 6-dibromide, m.p. 132°; this by ozonolysis and debromination gives 3β-hydroxybisnorchol-5-enic acid (122), converted by hydrogenation, oxidation to the saturated 3-keto acid, and Clemmensen reduction to bisnor*allo*cholanic acid (123)[169]. The position and configuration of the hydroxyl group are established by hydrogenation to stigmastanol (124), which by oxidation as the acetate with chromium trioxide yields 3β-hydroxynor*allo*cholanic acid[169]. The position of the nuclear double bond follows from the conversion of stigmasterol to a 3 : 6-diketone analogous to 3 : 6-dioxocholestane[170], and to 3-oxostigmasta-4 : 22-diene (125)[171]. Reduction of (125)



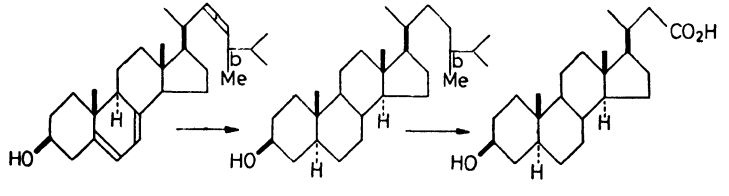
yields a molecular compound of 5 : 6-dihydrostigmasterol (126), m.p. 159°, $[\alpha]_D$ + 2°, and the 3α-*cis*-*A*/*B*-isomeride[171,172]; the isomeric 22 : 23-dihydrostigmasterol is identical with 'β'-sitosterol. Stigmasterol [(121): R = H] undergoes the 3 : 5-*cyclo*steroid rearrangement to give 3 : 5-*cyclo*stigmastan-6β-ol, whilst 3 : 5-*cyclo*stigmastan-6α-ol has been prepared[173]. Δ^7-Stigmasterol, the higher homologue of ergosterol, has been isolated from rye-germ oil[174].

Stigmasteryl acetate has m.p. 144°, $[\alpha]_D$ − 56°; benzoate, m.p. 160°; *p*-nitrobenzoate, m.p. 203°, $[\alpha]_D$ − 13°.

Ergosterol (127)

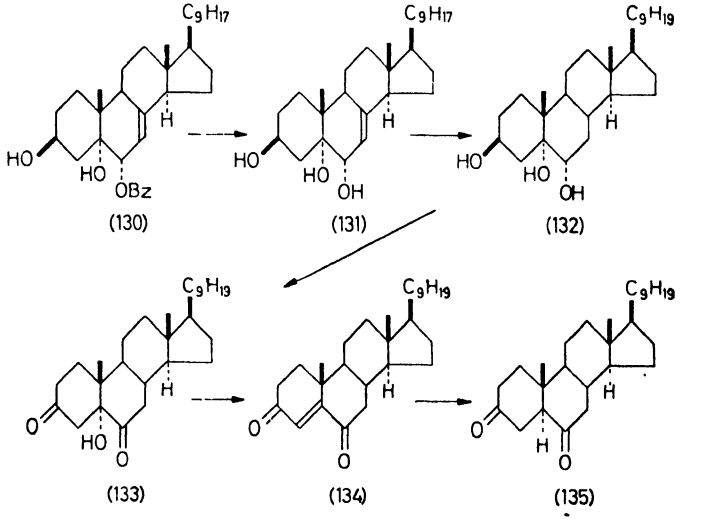
Ergosterol, $C_{28}H_{44}O$, (127), the commonest of the mycosterols, occurs in yeast together with 5 : 6-dihydroergosterol, and was isolated by TANRET[175]. Ergosterol possesses one more carbon atom

than cholesterol[176]; ozonolysis gives methyl*iso*propylacetaldehyde[168], which proves the presence of a 24b-methyl group [Chapter I, pp. 13 and 27], and Δ^{22}-unsaturation. The nuclear skeleton is disclosed by oxidation of the parent saturated hydrocarbon ergostane to nor*allo*-cholanic acid[177], whilst the position and configuration of the hydroxyl group follow from the oxidation of ergostanol (128), m.p. 150°, $[\alpha]_D$ + 16°, as the acetate to 3β-hydroxynor*allo*cholanic acid (129)[169]; this confirmed views based on study of dicarboxylic acids obtained by fission of ring *A*[178]. For partial hydrogenation of ergosterol, *see* p. 67; complete hydrogenation gives ergostanol (128).



(127) (128) (129)

Ergosterol reacts with 1 mol. perbenzoic acid[179] (or monoperphthalic acid[180]) to give a doubly unsaturated 3β : 5α : 6α-triol monobenzoate (130), hydrolysed by alkali to ergosta-7 : 22-diene-3β : 5α : 6α-triol (131), which forms only a diacetate, hydrogenated



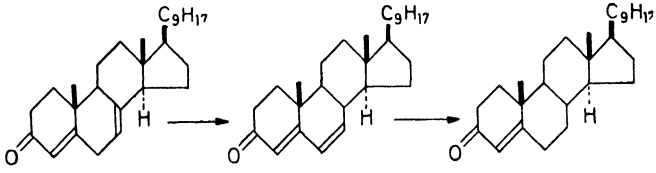
(130) (131) (132)

(133) (134) (135)

and hydrolysed to ergostane-3β : 5α : 6α-triol (132)[181]. This, with chromium trioxide, affords 3 : 6-dioxoergostan-5α-ol (133), dehy-

drated by hydrogen chloride in chloroform to 3 : 6-dioxoergost-4-ene (134), reduced by zinc–acetic acid to 3 : 6-dioxoergostane (135)[182]. This sequence is analogous to that [(1)→(16)→(17)→(18)→(10): p. 37] for cholesterol and proves the presence of Δ^5-unsaturation.

The ultra-violet absorption spectrum[183,184] of ergosterol indicates that the two nuclear double bonds are conjugated, and with maleic anhydride an adduct is formed[185], which by ozonolysis gives methyl*iso*propylacetaldehyde and by partial reduction affords a dihydro-derivative[186]; this by vacuum sublimation gives 22 : 23-dihydroergosterol. Further, ergosterol by oxidation with aluminium *tert.*-butoxide-*cyclo*hexanone gives 3-oxoergosta-4 : 7 : 22-triene ['ergosterone'] (136)[187,188], rearranged by hydrogen chloride in chloroform to the conjugated 3-oxoergosta-4 : 6 : 22-triene ['*iso*ergosterone'] (137)[187,188,189], partially hydrogenated with palladium to 3-oxoergosta-4 : 22-diene (138)[188].



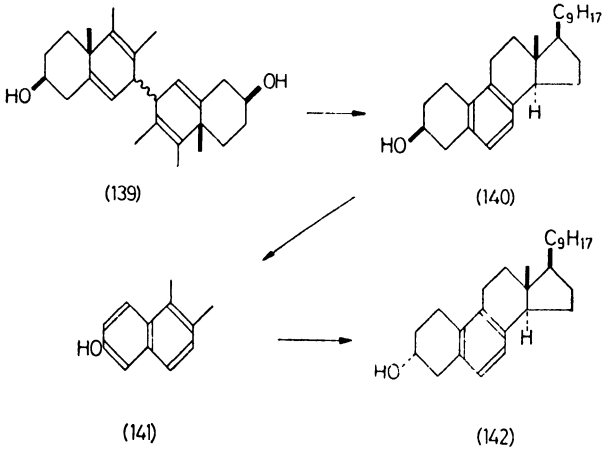
(136) (137) (138)

Ergosterol by oxidation with chromium trioxide gives 3 : 6-dioxoergosta-7 : 22-dien-5α-ol [cf. (133)][190], also obtained by oxidation of the triol (131)[191]. Use of nitric acid gives toluene-2 : 3 : 5 : 6-tetracarboxylic acid by rearrangement of the steroid phenanthrene skeleton to that of anthracene during oxidation[192,193,194,195]. Ergosterol by oxidation with permanganate yields ergosta-7 : 14 : 22-triene-3β : 5α : 6α-triol and an unidentified O_5-compound[196].

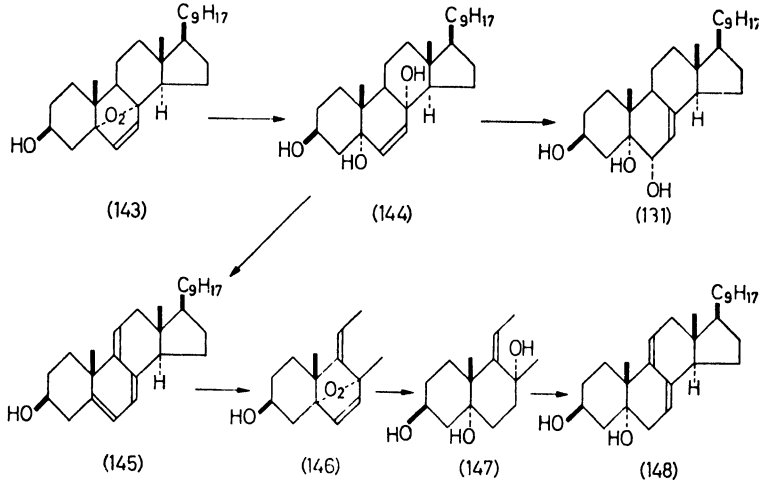
Dehydration of ergosterol with phosphorus oxychloride or toluene-*p*-sulphonyl chloride in pyridine furnishes 3 : 5-*cyclo*ergosta-6 : 8(14): 22-triene[197,198], and ergosta-4 : 6 : 8 (14) : 22-tetraene[197,198,199].

Ergosterol by irradiation with visible light in the presence of a sensitizing dye, e.g. eosin, and in absence of oxygen gives a bisergostadienol ('ergopinacol'), $C_{56}H_{86}O_2$, (139)[200], which by pyrolysis yields methane and neoergosterol, $C_{26}H_{40}O$ (140)[201]. Neoergosterol gives no sterol colour reactions but contains four double bonds; only one is reactive and is in the side chain since ozonolysis affords methyl*iso*propylacetaldehyde. This suggests that by loss of methane, the $\Delta^{5:7}$-diene system becomes aromatic, which is proved by oxidation with fuming nitric acid to benzene-1 : 2 : 3 : 4-tetracarboxylic acid[202] and by catalytic dehydrogenation with platinum

black to dehydroneoergosterol (141), which is a naphthol[203], and is reduced by sodium-amyl alcohol to *epi*neoergosterol (142)[204].



Irradiation with visible light in presence of eosin and oxygen yields ergosterol peroxide (143)[205,206]; reduction with zinc–potassium hydroxide gives ergosta-6 : 22-diene-3β : 5α : 8α-triol (144)[207], which forms only a monoacetate and readily rearranges to the 3β : 5α : 6α-triol (131); both triols (131) and (144) by

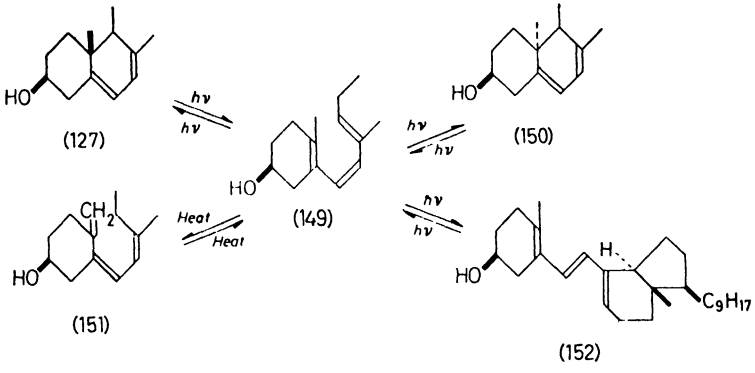


oxidation with chromium trioxide give 3 : 6-dioxoergosta-7 : 22-dien-5α-ol[181,208]. The 3β : 5α : 8α-triol (144) by pyrolysis eliminates the two tertiary hydroxyl groups to give dehydroergosterol

(145)[209], m.p. 146°, $[\alpha]_D$ + 149°, also obtained from ergosteryl acetate by oxidation with mercuric acetate[210,211,212]. Dehydroergosterol forms a peroxide (146)[209], which by partial hydrogenation[213] with palladium or nickel yields ergosta-9(11) : 22-diene-3β : 5α : 8α-triol (147)[214], readily dehydrated by acid to the cortisone intermediate, ergosta-7 : 9(11) : 22-triene-3β : 5α-diol (148)[213,214].

Dehydroergosterol (145) by treatment with toluene-*p*-sulphonyl chloride in pyridine gives 3 : 5-*cyclo*ergosta-6 : 8(14) : 9(11) : 22-tetraene[215]; dehydroergosteryl toluene-*p*-sulphonate by methanolysis in the presence of potassium acetate gives 6β-methoxy-3 : 5-*cyclo*ergosta-7 : 9(11) : 22-triene[216]; buffered hydrolysis affords 3 : 5-*cyclo*ergosta-7 : 9(11) : 22-trien-6β-ol [≡ '*i*-dehydroergosterol'] and a hydrocarbon regarded as 3 : 5-*cyclo*ergosta-6 : 8(14) : 9(11) : 22-tetraene[216], but different from that prepared from dehydroergosterol[215].

Ergosterol by irradiation with ultra-violet light affords various isomerides regarded by WINDAUS[217] as forming a linear series: ergosterol (127) $\xrightarrow{h\nu}$ lumisterol (150) $\xrightarrow{h\nu}$ tachysterol (152) $\xrightarrow{h\nu}$ ergocalciferol [≡ vitamin D_2] (151) $\xrightarrow{heat}$ pyroergocalciferol (154) and *iso*-pyroergocalciferol (157) $\underset{heat}{\overset{h\nu}{\rightleftharpoons}}$ photopyroergocalciferol and *iso*photopyroergocalciferol. Recently, another isomeride preergocalciferol (149) has been isolated by VELLUZ[218] and shown to be reversibly related photochemically to ergosterol (127), lumisterol (150), and tachysterol (152), and reversibly isomerized by gentle thermal treatment, but not ultra-violet light, to ergocalciferol [≡ vitamin D_2] (151); this has been confirmed by INHOFFEN[219].



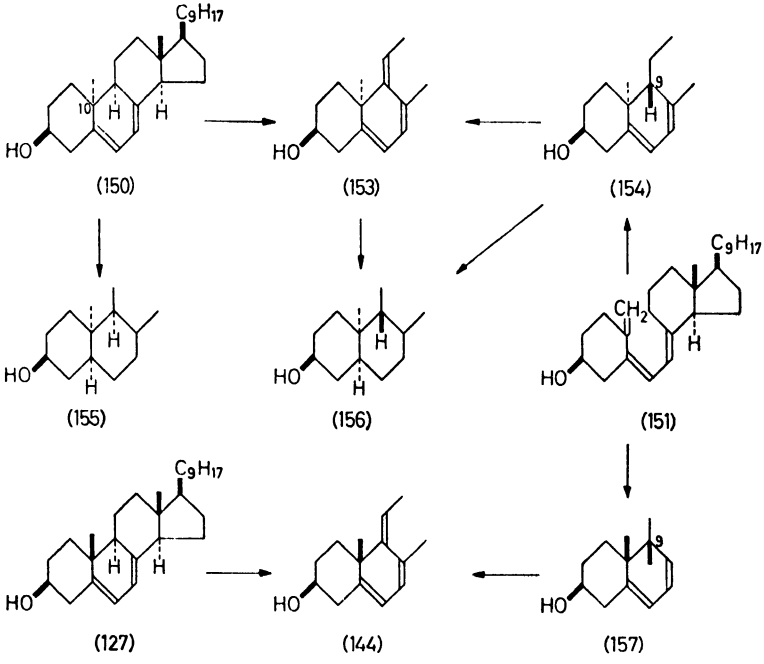
All the foregoing isomerides by ozonolysis[168] give methyl*iso*propylacetaldehyde and so possess the same side chain as ergosterol.

PREERGOCALCIFEROL (149)

Preergocalciferol is a 9 : 10-*seco*-5(10) : 6 : 8 : 22-ergostatetraen-3β-ol taking up four mols. of hydrogen by catalytic hydrogenation and four atoms of oxygen with perbenzoic acid; ozonolysis gives little or no formaldehyde[218]. Treatment with monoperphthalic acid at 20° gives a monoepoxide hydrolysed by acid with anionotropic rearrangement to a 5 : 7 : 22-triene-3β : 9ξ : 10ξ-triol[218]. The ultra-violet absorption spectrum suggests that preergocalciferol has the *cis-cis-cis*-triene structure (149), but it does not react with maleic anhydride at 20°[218].

LUMISTEROL [≡ 10α-ERGOSTEROL] (150)

Lumisterol contains the same system of conjugated double bonds as ergosterol and the ultra-violet absorption spectrum is similar; although lumisterol affords no 'pinacol' [cf. (139)], it is converted through a peroxide into two lumistadientriols[220,221] [cf. (143)→(144)→(131)], oxidized to the same 3 : 6-dioxolumista-7 : 22-dien-



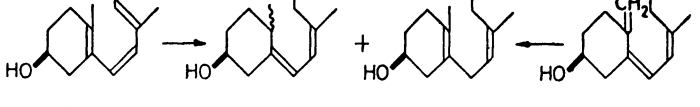
5α-ol[222]. Dehydrogenation with selenium gives the Diels hydrocarbon[223,224]. Oxidation with nitric acid gives toluene-2 : 3 : 5 : 6-tetracarboxylic acid[193], whilst oxidation with mercuric acetate

yields dehydrolumisterol [≡ 10α-dehydroergosterol] (153)[220]. Hydrogenation of lumisterol (150) gives lumistanol (155)[222,225], whilst hydrogenation of dehydrolumisterol (153) gives perhydropyroergocalciferol [≡ 9β-lumistanol] (156)[221], also obtained from ergocalciferol [≡ vitamin D_2] (151) by pyrolysis at 180° to pyroergocalciferol [≡ 9β-lumisterol ≡ 9β : 10α-ergosterol] (154) and catalytic hydrogenation[226]. *iso*Pyroergocalciferol [≡ 9β-ergosterol] (157) is also formed by pyrolysis of ergocalciferol (151), and by oxidation with mercuric acetate gives dehydroergosterol (145)[227], whilst pyroergocalciferol (154) similarly affords dehydrolumisterol (153)[227].

The infra-red spectrum of lumistanol has been examined and its conformation inferred[228].

TACHYSTEROL (152)

Tachysterol has not been obtained in crystalline form, although pure samples have been prepared[229]. The ultra-violet absorption spectrum shows the presence of three conjugated double bonds; two of these react so readily [Gr. *tachys*, swift] with maleic anhydride that ALDER[230] assigns a *cis-trans-cis*-arrangement [(152), p. 55], and various model substances have been prepared for comparison[231]. Ozonolysis[232] gives no formaldehyde, whilst reduction [as the 3-ester] with sodium-propanol[233] affords dihydrotachysterol [1 : 6-addition] (158) and dihydroergocalciferol [1 : 4-addition] (159)[234], also obtained from ergocalciferol (151) by reduction with sodium-propanol. The ultra-violet absorption spectrum[235,236] of dihydrotachysterol (158) indicates the presence of two conjugated double bonds although no adduct is formed with maleic anhydride; oxidation with chromium trioxide gives the C_{19}-ketone (163) [*see* p. 58] and locates a double bond at the Δ^7-position. An *iso*tachysterol has been obtained from ergocalciferol with boron trifluoride[237].



(152) (158) (159) (151)

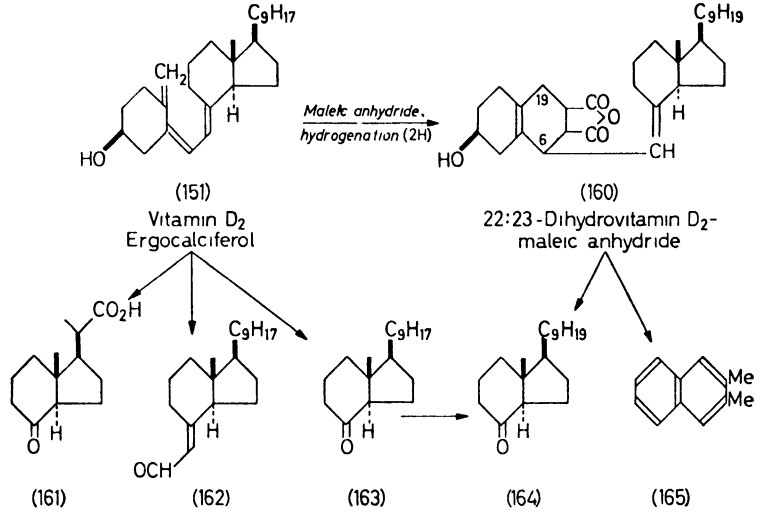
ERGOCALCIFEROL, VITAMIN D_2 (151)

In 1924 it was observed that ultra-violet irradiation of foodstuffs produced antirachitic properties; fats were later studied and it was also found that irradiation of sterols gave very potent preparations. At first cholesterol was regarded as the provitamin D, but in 1926 it was shown[238,239,240] that the biological activity of the irradiated product depended upon the content in the cholesterol of an impurity

possessing the absorption spectrum of ergosterol. Ergosterol thus appeared to be the provitamin D, and in 1930–1931 potent crystalline preparations, called vitamin D_1[241] and 'calciferol'[242], were isolated from the irradiation products of ergosterol. The pure vitamin was fully described in 1932 as vitamin D_2[234,243], or calciferol[244]; the earlier preparation, vitamin D_1, is a molecular compound of vitamin D_2 and lumisterol[245].

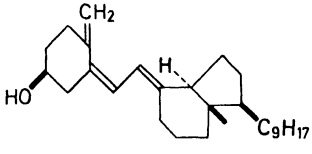
Vitamin D_2 has antirachitic potency of 40,000 international units (I.U.) per mg; the pure vitamin is stable for months at 37°, but oil solutions in contact with air deteriorate and the 'half-life' of an olive-oil solution under these conditions is about three years[246]. Vitamin D_2 and its analogues regulate phosphate and calcium metabolism in the organism by some unknown mechanism.

The structure of vitamin D_2 (151) rests on the following evidence[247,248,249]. Microcatalytic hydrogenation discloses four double bonds, three of which react with perbenzoic acid, whilst reduction with sodium-propanol gives dihydroergocalciferol (159), shown to have three double bonds by titration with perbenzoic



acid[234]; of these, two are in the nucleus and are not conjugated[233]. Ozonolysis of vitamin D_2 gave a keto-acid, $C_{13}H_{20}O_3$ (161), and formaldehyde, isolated as the dimedon derivative, in 30% of the yield expected; careful oxidation with cold chromium trioxide or permanganate gave the aldehyde, $C_{21}H_{34}O$ (162), shown to be $\alpha\beta$-unsaturated by the absorption spectrum of its semicarbazone; a ketone, $C_{19}H_{32}O$ (163), was also isolated.

These products locate the positions of the three nuclear double bonds, whilst the irreversible conversion of the *trans*-'a'-hydrindanone (163) by hydroxyl ions into the *cis*-isomeride shows the *trans* character of the *C/D*-ring-union[250]. Vitamin D_2 readily gives two isomeric maleic anhydride adducts, from which dihydro-derivatives [represented by (160)] are obtained by reduction of the side-chain double bond; ozonolysis of the dihydro-adducts gave a saturated ketone, $C_{19}H_{34}O$ (164), also obtained by hydrogenation of (163)[248]. Selenium dehydrogenation of (160) gave 2 : 3-dimethylnaphthalene (165) and palladium dehydrogenation gave β-naphthoic acid and naphthalene; these products originate from the ring system produced by adduct-formation and show that this occurs at $C_{(6)}$ and $C_{(19)}$. Analogies for the reduction of anhydride carbonyl groups to the methyl groups in 2 : 3-dimethylnaphthalene have been found[251]. X-ray analysis[252] of the 4-iodo-5-nitrobenzoate of vitamin D_2 confirms formula (151) showing that the molecule has an extended *trans*-orientation (151a), whilst the *C/D*-ring-union is a *trans*-fusion and the 3-hydroxyl group and the $C_{(17)}$-side chain have the β-configuration, although the ultra-violet absorption spectrum suggests that in solution the molecule has the completely *cis*-orientation (151b)[253].



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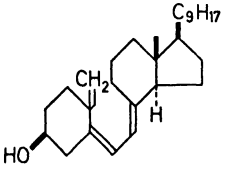
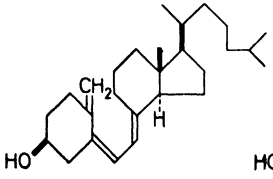


(151b)

CHOLECALCIFEROL, VITAMIN D_3 (166)

This, the natural vitamin D of fish liver-oils, is closely similar to ergocalciferol (151), and is derived from 7-dehydrocholesterol



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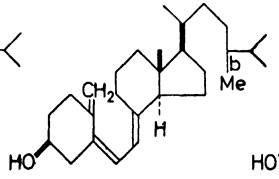


(167)

(118)[254,255]. Irradiation with ultra-violet lig[1] been isolated from calciferol[218] converted by gentle heating into

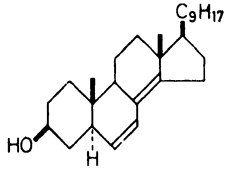
m.p. 82–85°, $[\alpha]_D$ + 83°, potency/mg = 40,000 I.U., identical with the product isolated from concentrates of tuna liver-oil and halibut liver-oil by chromatography and subsequent fractional crystallization and chromatography of the crude 3 : 5-dinitrobenzoate[256].

22 : 23-Dihydroergocalciferol, Vitamin D_4 (167)

Ultra-violet irradiation of 22 : 23-dihydroergosterol leads to 22 : 23-dihydroergocalciferol (167), m.p. 107°, $[\alpha]_D$ + 89°, potency/mg = 30,000 I.U.[257,258]. The product (168) from 7-dehydrositosterol has some antirachitic activity[259] but that from 7-dehydrostigmasterol is inactive[260].

Ergosterol-B_1, B_2, B_3, *and* D

Ergosterol (127) as the acetate with dry hydrogen chloride gives successively ergosterol-B_2 (169), m.p. 126°, $[\alpha]_D$ − 88°, ergosterol-B_1 (170), m.p. 148°, $[\alpha]_D$ − 40°, and ergosterol-B_3 (171)[198,261,262,263], m.p. 136°, $[\alpha]_D$ − 207°.



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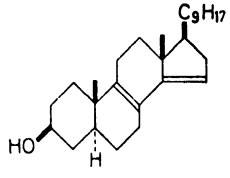

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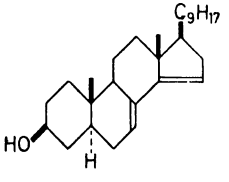

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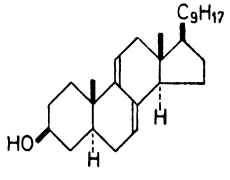


(172)

The important cortisone intermediate ergosterol D (172), m.p. [illegible]°, $[\alpha]_D$ + 25°, is obtained from 5 : 6-dihydroergosterol by [illegible]tion with mercuric acetate[264,265], perbenzoic acid[179], selenium [illegible][266], and bromine[267]; hydrogenation with nickel in ethyl acid[234] [illegible]f ergosteryl-D acetate gives ergost-7-en-3β-yl acetate[268].

Ozonoly[illegible]
formaldehyd[illegible]F Stereoisomeric Ergostanes

yield expected [illegible]lumisterol [= 10α-ergosterol] (150), *iso*pyroergo-permanganate g[illegible]osterol] (157), and pyroergocalciferol [= 10α : $\alpha\beta$-unsaturated by there have recently been described numerous a ketone, $C_{19}H_{32}O$ ([illegible]n ergostanes in which one or more of the

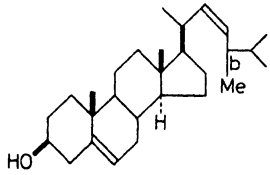
natural bridge-head configurations 9α, 8β, and 14α is inverted, with resultant alteration of molecular conformation. These compounds may result from reduction of carbonyl-activated 8 : 9-double bonds, whereby chemical reduction [Li–liquid NH_3] affords the natural 8β : 9α-epimer whilst catalytic hydrogenation by *cis*-addition yields the unnatural 8α : 9α-epimer[269]; under appropriate conditions a carbonyl group at $C_{(7)}$ or $C_{(11)}$ facilitates inversion 9β → 9α[270] and 8α → 8β[271] to furnish a *trans-B/C*-fusion. Among such compounds are 9β-ergostanols[270,272,273], 8α-ergostanols[270,271,274,275], 14β-ergostanols[272,276], 9β : 14β-ergostanols[277], and 8α : 14β-ergostanols[272].

Less Common Sterols

Phytosterols

Brassicasterol (173)

Brassicasterol, $C_{28}H_{46}O$ (173), m.p. 148°, $[\alpha]_D$ — 64°, occurs in rape-seed oil, and is isolated as the acetate-tetrabromide[278]; ozonolysis gives methyl*iso*propylacetaldehyde and 3β-hydroxybisnorchol-5-enic acid, whilst hydrogenation gives ergostanol (128)[279]. Brassicasterol is thus 24b-methylcholesta-5 : 22-dien-3β-ol (173).



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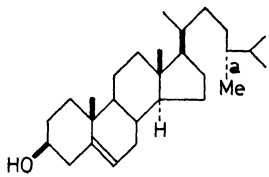


(174)

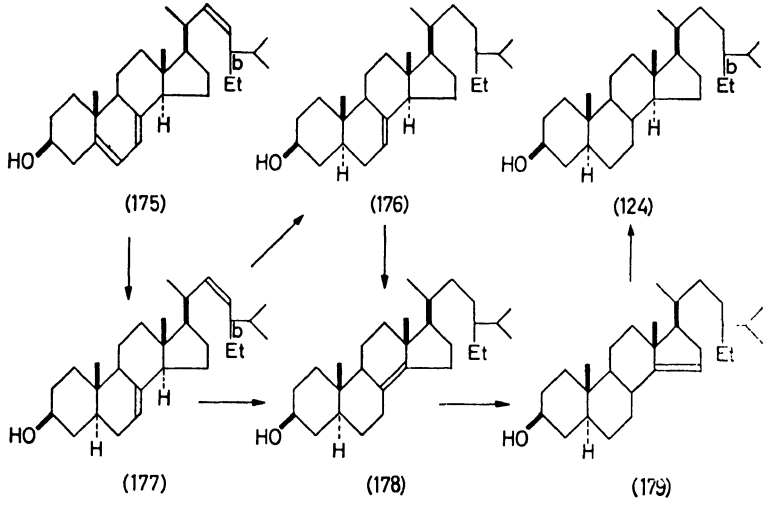
Campesterol (174)

Campesterol, $C_{28}H_{48}O$, m.p. 158°, $[\alpha]_D$ — 33°, has been obtained from rape-seed oil, soya-bean oil, wheat-germ oil[280], and from molluscs[281]. Perbenzoic acid titration indicates one double bond, which is at the 5 : 6-position since rearrangement affords derivatives of 3 : 5-*cyclo*campestane[282]. Hydrogenation of the acetate gives campestanyl acetate [*see* p. 12][282], oxidized by chromium trioxide to 3β-hydroxynor*allo*cholanic acid[282]. Similar oxidation of campesteryl acetate gives (+)-5 : 6-dimethylheptan-2-one[282] [*see* p. 13]; campesterol is a 24-isomeride of 22 : 23-dihydrobrassicasterol and is 24a-methylcholest-5-en-3β-ol (174)[284].

Spinasterols

Four isomeric spinasterols, $C_{29}H_{48}O$, have been isolated from spinach or alfalfa.

'α'-Spinasterol (177), m.p. 172°, $[\alpha]_D$ — 4°, is a 7 : 22-diene[285]; ozonolysis[286] gives ethyl*iso*propylacetaldehyde, whilst hydrogenation[286,287] with palladium in ether or platinum in acetic acid saturates the side chain but causes migration of the nuclear double bond to give stigmast-8(14)-enol (178); this resists hydrogenation, but is isomerized by hydrogen chloride to stigmast-14-enol (179), readily hydrogenated to stigmastanol (124). 'α'-Spinasterol (177) by hydrogenation with *platinum* in *ether* gives stigmast-7-enol (176) rearranged by platinum in acetic acid in presence of hydrogen to stigmast-8(14)-enol (178)[288]. 'α'-Spinasterol (177) has been synthesized from 7-dehydrostigmasterol (175) by partial hydrogenation under non-isomerizing conditions using *platinum* in *ether*[36].



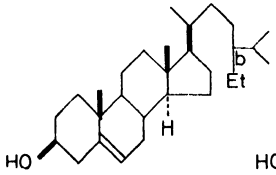
'β'-, 'γ'-, and 'δ'-Spinasterol all give stigmast-8(14)-enol (178) by hydrogenation under isomerizing conditions; they are probably Δ^7-compounds differing in the position of the side-chain double bond[285].

Sitosterols

The five sitosterols (Gr. *sito*, grain) are the most widely distributed plant sterols; they occur as mixtures with stigmastanol [= 22 : 23-dihydro-'β'-sitosterol] (124) and are unusually difficult to purify and identify[289].

'α'$_1$-, 'α'$_2$-, and 'α'$_3$-Sitosterol. Crystallization of the *m*-dinitrobenzoates of the 'α'-sitosterol fraction gives 'α'$_1$-, 'α'$_2$-, and 'α'$_3$-sitosterol, $C_{29}H_{50}O$; all are precipitated by digitonin, appear to contain two non-conjugated double bonds, and are claimed to be

homogeneous. A new sterol, ergosta-7 : 22-dien-3β-ol, which is the lower homologue of 'α'-spinasterol, has been obtained from the 'α'$_3$-sitosterol fraction[290].



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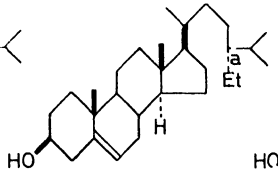

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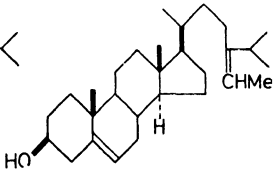

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'β'-*Sitosterol* [= *Cinchol*] (180), $C_{29}H_{50}O$, m.p. 140°, $[\alpha]_D$ − 36° is the principal sterol of cottonseed oil, calycanthus oil, and soya-bean oil; it has been obtained from wheat-germ oil, corn oil, rye-germ oil, cinchona wax, and crepe rubber.

Oxidation (as the acetate) with chromium trioxide gives 3β-hydroxynor*allo*cholanic acid (129), dehydro*epi*androsterone[291], and (+)-5-ethyl-6-methylheptan-2-one[292]. Hydrogenation gives stigmastanol (124)[293,294]; conversely, selective side-chain hydrogenation of stigmasterol [(121) : R = H] gives 'β'-sitosterol which is thus 22 : 23-dihydrostigmasterol[295] or 24b-ethylcholest-5-en-3β-ol (180).

'γ'-*Sitosterol* (181), $C_{29}H_{50}O$, m.p. 148°, $[\alpha]_D$ − 43° occurs in soya-bean oil[293,296]. It has the nuclear structure of 'β'-sitosterol (180) because oxidation (as the acetate) with chromium trioxide gives dehydro*epi*androsterone[297] and (−)-5-ethyl-6-methylheptan-2-one[292], so that 'γ'-sitosterol is the 24-epimer of 'β'-sitosterol, viz. 24a-ethyl-cholest-5-en-3β-ol[284] (181) and identical with clionasterol [*see* p. 66].

FUCOSTEROL (182)

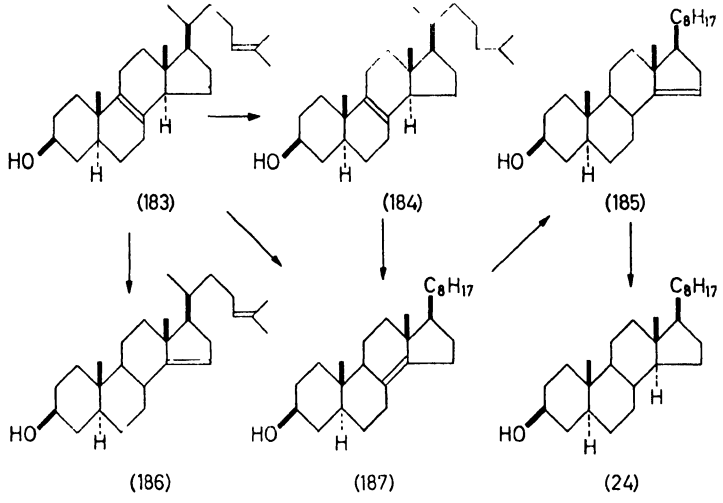
Freshwater green algae furnish the usual phytosterol mixture of higher plants, but marine brown algae yield fucosterol (182), m.p. 124°, $[\alpha]_D$ − 38°[298], which contains two isolated double bonds. Oppenauer oxidation gives an αβ-unsaturated ketone fucostadienone[299], whilst ozonolysis gives acetaldehyde[300]. Complete hydrogenation gives stigmastanol (124), whilst partial hydrogenation affords 'β'-sitosterol [= 22 : 23-dihydrostigmasterol] (180)[298]. Fucosterol, $C_{29}H_{48}O$, is thus 24-ethylidenecholest-5-en-3β-ol (182).

Mycosterols

ZYMOSTEROL (183)

Zymosterol, $C_{27}H_{44}O$, m.p. 110°, $[\alpha]_D$ + 49°, occurs in yeast[301, 302], and is shown by perbenzoic acid titration to possess two double bonds[303], but forms only a dibromide[304]. One double bond is

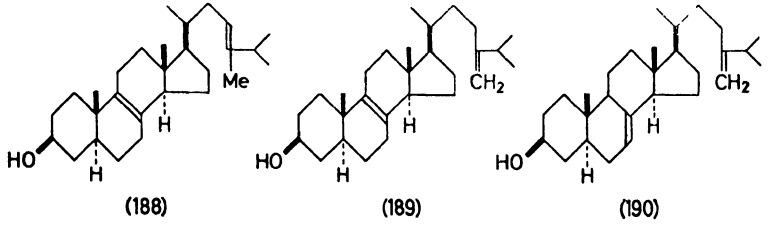
readily hydrogenated[303] and is part of an *iso*propylidene group since ozonolysis yields acetone[304,305]. The nuclear double bond resists hydrogenation[303] and was originally placed at the 8 : 14-position[304] and the 9 : 11-position[305], but is actually at the 8 : 9-position (183)[306]. Hydrogenation with platinum in ethyl acetate gives cholest-8-enol (184)[305], isomerized by platinum and hydrogen in acetic acid or by hydrogen chloride to cholest-8(14)-enol (187), which with hydrogen chloride gives cholest-14-enol (185)[307], readily



reduced to cholestanol (24). Hydrogenation with platinum in acetic acid reduces the side chain and isomerizes the nuclear double bond to give cholest-8(14)-enol (187)[304]. Zymosterol is cholesta-8 : 24-dien-3β-ol (183) and is isomerized by hydrogen chloride to cholesta-8(14) : 24-dien-3β-ol [= 'β'-zymosterol] (186)[305].

ASCOSTEROL (188) *and* FECOSTEROL (189)

Ascosterol, m.p. 142°, $[\alpha]_D$ + 45°, and fecosterol, m.p. 162°, $[\alpha]_D$ + 42°, are minor sterols, $C_{28}H_{46}O$, from yeast containing two double bonds[299,302,308,309]. Ascosterol (188) when shaken with platinum



in acetic acid and nitrogen gives fecosterol (189), whilst both by hydrogenation with platinum in acetic acid yield ergost-8(14)-enol[309]. Both sterols appear to have the nuclear double bond at the 8 : 9-position[306], and the formulae (188) and (189) have been suggested[310].

EPISTEROL (190)

Episterol, $C_{28}H_{46}O$, m.p. 151°, $[\alpha]_D$ − 5° from yeast[311], gives by hydrogenation ergost-8(14)-enol, but is unchanged by platinum in nitrogen in ethyl acetate[309]; it affords formaldehyde by ozonolysis[309], whilst the nuclear double bond is at the 7 : 8-position (190)[285]. A new ergosta-5 : 7 : 22 : 24(28)-tetraen-3β-ol has been isolated from yeast[312].

Marine Sterols

Whilst the principal sterol of gastropods is cholesterol, pelecypods [bivalves] furnish a complex mixture of C_{28}- and C_{29}-sterols, which is very difficult to separate.

CHALINASTEROL (191)

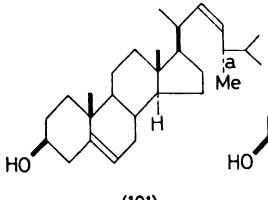
Chalinasterol [= Ostreasterol], $C_{28}H_{46}O$, m.p. 144°, $[\alpha]_D$ − 42°, from sponge, oyster, and clams[282,313], is 24a-methylcholesta-5 : 22-dien-3β-ol since partial hydrogenation gives campesterol (174)[284].

STELLASTEROL (192)

Stellasterol, $C_{28}H_{46}O$, and its 22 : 23-dihydro-derivative, stellastenol, from starfish, have not been completely separated; ozonolysis of the mixture gives (+)-methyl*iso*propylacetaldehyde, whilst hydrogenation of the 22 : 23-double bond is accompanied by migration of the nuclear double bond to give homogeneous 'α'-stellastenol, which is an 8(14)-stenol, isomerized by hydrogen chloride to 'β'-stellastenol, a 14-stenol, readily hydrogenated to stellastanol, which differs from campestanol owing to stereoisomerism at $C_{(20)}$ [*see* p. 12][314].

NEOSPONGOSTEROL (193)

Neospongosterol, $C_{28}H_{48}O$, m.p. 153°, $[\alpha]_D$ + 10°, by ozonolysis gives (+)-methyl*iso*propylacetaldehyde and 3β-hydroxybisnor*allo*-cholanic acid and by hydrogenation yields campestanol[315].



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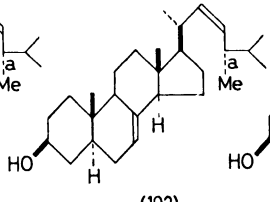

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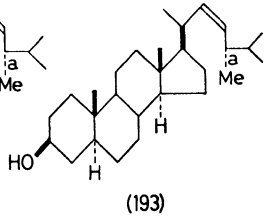

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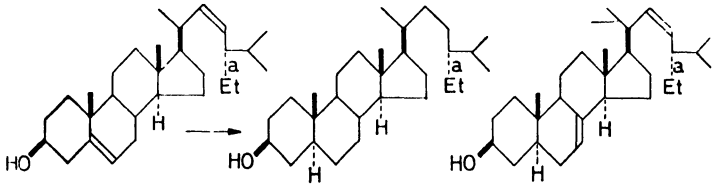
PORIFERASTEROL (194) *and* CLIONASTEROL (181)

Poriferasterol, $C_{29}H_{48}O$, m.p. 156°, $[\alpha]_D$ — 49°, and clionasterol [≡ 'γ'-sitosterol] (181) have been isolated from sponges; poriferasterol by hydrogenation gives 'γ'-sitostanol [≡ 24a-ethylcholestanol] (195), and by ozonolysis affords (+)-ethyl*iso*propylacetaldehyde and 3β-hydroxybisnorchol-5-enic acid. Poriferasterol (194) is thus the 24a-epimer of stigmasterol (121)[316,317,318,319].

CHONDRILLASTEROL (196)

Chondrillasterol, $C_{29}H_{48}O$, m.p. 169°, $[\alpha]_D$ — 1°, is the 24a-epimer of 'α'-spinasterol (177)[320].



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RELATED COMPOUNDS AND GENERAL REACTIONS

Cholestenes, Cholesten-3β-ols, Ergosten-3β-ols, and Stigmasten-3β-ols

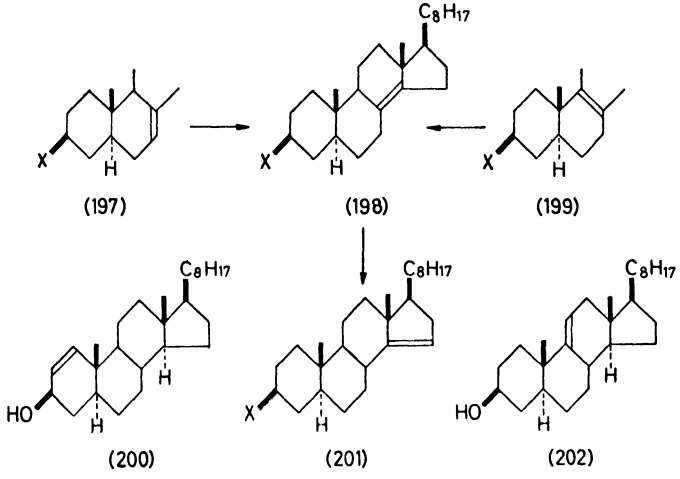
A nearly complete set of cholestenes is known; their properties are given in *Table III*, but for their methods of preparation and literature references, and those of cholestenols, ergostenols, and stigmastenols, Elsevier's *Encyclopaedia*, Vol. 14 and *Supplements* should be consulted.

Table III

Structure	m.p.°	$[\alpha]_D$°	Hydrogenation product
Cholest-2-ene*	75	+67	Cholestane
Cholest-3-ene	72	+57	Cholestane
Cholest-4-ene**	83	+76	Cholestane (acid) Coprostane (neutral)
Cholest-5-ene	91	−56	Cholestane
Cholest-6-ene	86	−88	Cholestane
Cholest-7-ene	86	+11	Cholest-8(14)-ene
Cholest-8-ene	93	+56	Cholest-8(14)-ene
Cholest-8(14)-ene	53	+21	unchanged
Cholest-14-ene	73	+27	Cholestane

* Formerly neocholestene. ** Formerly pseudocholestene.

Cholest-7-ene [(197): X = H] resists hydrogenation but like cholest-8-ene [(199): X = H] is isomerized by platinum saturated with hydrogen in acetic acid or by palladium saturated with hydrogen in either ethyl acetate or acetic acid to cholest-8(14)-ene [(198): X = H], which resists hydrogenation but is isomerized by hydrogen chloride to cholest-14-ene [(201): X = H].



Similar relationships exist between cholest-7-enol [≡ 'γ'-cholestenol], [(197): X = OH]; cholest-8-enol [≡ 'δ'-cholestenol] [(184) and (199): X = OH]; cholest-8(14)-enol [≡ 'α'-cholestenol] [(187) and (198): X = OH]; and cholest-14-enol [≡ 'β'-cholestenol] [(185) and (201): X = OH]. Cholest-1-enol (200)[321], cholest-9(11)-enol (202)[322], and cholest-20(22)-enol have recently been prepared[322]. Ergost-7-enol [≡ 'γ'-ergostenol], ergost-8-enol [≡ 'δ'-ergostenol], ergost-8(14)-enol [≡ 'α'-ergostenol], and ergost-14-enol [≡ 'β'-ergostenol] are similarly related; hydrogenation of ergosterol (127) or of 22 : 23-dihydroergosterol with platinum in ether or nickel in ethyl acetate or reduction with sodium in ethanol, gives ergost-7-enol [(197): X = OH], but hydrogenation with palladium in ethyl acetate or platinum in acetic acid affords ergost-8(14)-enol [(198): X = OH]. Again, stigmast-7-enol [(176) and (197): X = OH], stigma-8(14)-enol [(178) and (198): X = OH], and stigmast-14-enol [(179) and (201): X = OH] exhibit similar relationships.

Cholestadienes

Homoannular dienes [conjugated system in one ring only] have ultra-violet absorption maxima in the region 260–280 mμ, form peroxides, are reduced by sodium in amyl alcohol, add maleic

anhydride, and are isomerized by heat or mineral acid to hetero-annular dienes [conjugated system distributed between two rings], which absorb in the region 235–250 mμ, are not reduced by sodium-amyl alcohol, and with the exception of cholesta-7 : 14-diene do not add maleic anhydride. The properties of the various cholestadienes are given in *Table IV*.

Table IV

Structure	m.p.°	$[\alpha]_D$°	λ_{max} mμ	Product of hydrogenation
Cholesta-2 : 4-diene	68	+ 168	275	Coprostane
Cholesta-2 : 5-diene	73	− 25		
Cholesta-3 : 5-diene*	80	− 123	234	Cholestane + Coprostane
Cholesta-4 : 6-diene	91	+ 4	238	Cholestane + Coprostane
Cholesta-5 : 7-diene	89	− 127	273, 280	
Cholesta-7 : 9(11)-diene	84	+ 32	213	
Cholesta-7 : 14-diene	83	− 93	242, 250	
Cholesta-8 : 14-diene	84	23	245	Cholest-8(14)-ene

* Formerly called cholesterylene

The products of the direct dehydration of cholesterol (1) are cholesta-2 : 5-diene and cholesta-3 : 5-diene [*see* p. 42], but refluxing with activated aluminium oxide in xylene at 140° [90] or vacuum distillation with aluminium oxide gives cholesta-2 : 4-diene[323,324], converted by heat or acid to cholesta-3 : 5-diene (115) [*see* p. 49]. Dehydration of cholest-5-en-7α-ol with acetic anhydride gives cholesta-4 : 6-diene, whilst pyrolysis of the benzoate at 125° yields cholesta-5 : 7-diene[184,323]; at higher temperatures this is converted to cholesta-4 : 6-diene which is isomerized by dry hydrogen chloride in chloroform to cholesta-3 : 5-diene[325]. Cholesta-7 : 9(11)-diene is obtained from cholest-7-ene by oxidation with mercuric acetate or bromine, whilst use of perbenzoic acid affords cholesta-7 : 14-diene; similarly, oxidation of cholest-8(14)-ene gives cholesta-8 : 14-diene, hydrogenated to regenerate cholest-8(14)-ene[326]. Various nuclear dienes derived from ergost-22-ene, ergostane, stigmast-22-ene, and stigmastane have been described.

Ketones and Alcohols

A nearly complete set of cholestanones is known; in the other *A/B-trans* series [*allo*cholane, *allo*pregnane, androstane] and in the *A/B-cis* series [coprostane, cholane, pregnane, aetiocholane] generally only the 3- and 6-ketones are known [*see Table V*].

Table V

Ketone	m.p.°	$[\alpha]_D^c$	Alcohol α	m.p.°	$[\alpha]_D^\circ$	Alcohol β	m.p.°	$[\alpha]_D^\circ$	References
Cholestan-1-one	86	+112	α-1-ol (*a*)	105	+34	β-1-ol (*e*)	98	+20	327, 328
Cholestan-2-one	130	+ 51	α-2-ol (*e*)	181	+27	β-2-ol (*a*)	154	+33	329, 330
Cholestan-3-one	129	+ 44	α-3-ol (*a*)	184	+26	β-3-ol (*e*)	142	+23	—
Cholestan-4-one	96	+ 25	α-4-ol (*e*)	188	− 5	β-4-ol (*a*)	131	+29	331, 332, 333
Cholestan-6-one	96	+ 5	α-6-ol (*e*)	130	+35	β-6-ol (*a*)	82	+ 8	138, 141, 334
Cholestan-7-one	118	− 47	α-7-ol (*a*)	98	+11	β-7-ol (*e*)	113	+52	335, 336
Coprostan-3-one	62	+ 37	α-3-ol (*e*)	116	+32	β-3-ol (*a*)	102	+28	—
Coprostan-6-one	133	− 44	α-6-ol (*e*)	liq	+18	β-6-ol (*a*)	liq	−21	130

(*a*) = axial (*e*) = equatorial

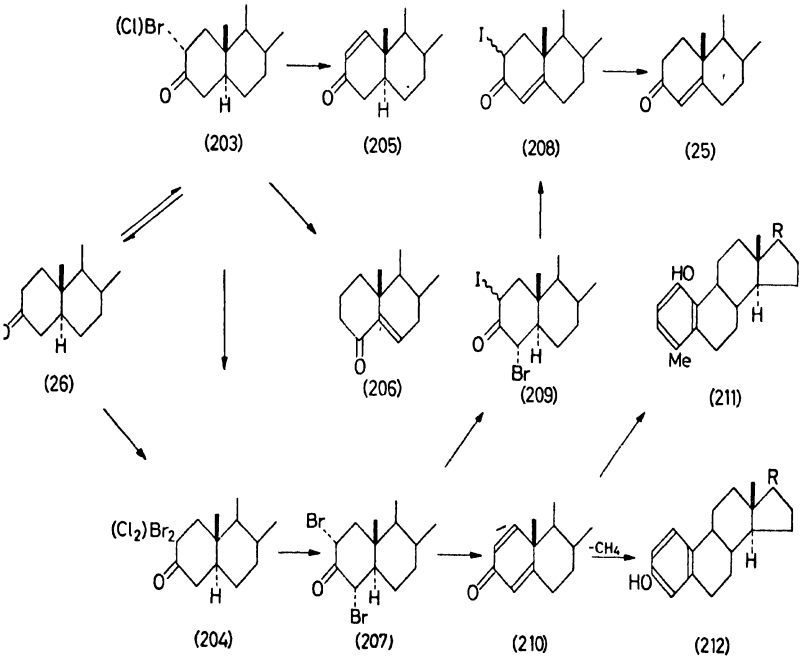
Reduction of a ketone with sodium and an alcohol affords the epimeric alcohols in their equilibrium proportions, the more thermodynamically stable equatorial epimer exceeding the less stable axial epimer. Reduction products given by other reagents depend on the degree of steric hindrance of the ketone grouping, which in the cholestane series follows the order: 3 < 2 < 7 < 4, 6 < 1, 12 < 11[337]. Lithium aluminium hydride and sodium borohydride afford the equatorial alcohol if the keto-group is not hindered, the axial alcohol if the keto-group is strongly hindered; reduction with *iso*propoxide ions present affords both epimers although use of ethoxide ions gives the axial alcohol[338], whilst rapid catalytic hydrogenation [acid media] generally gives the axial alcohol whereas slow hydrogenation [neutral media] yields the equatorial alcohol if the keto-group is not hindered, and the axial alcohol if the keto-group is strongly hindered.

Equatorial alcohol groups are less hindered than their axial epimers, and are more readily acylated and their esters more readily hydrolysed, e.g. cholestan-2α-yl acetate > cholestan-2β-yl acetate[330]; cholestan-3β-yl acetate > cholestan-3α-yl acetate[45]; cholestan-4α-yl benzoate > cholestan-4β-yl benzoate[333]; cholestan-7β-yl benzoate > cholestan-7α-yl benzoate[336]; coprostan-3α-yl acetate > coprostan-3β-yl acetate[45]. In chromium trioxide oxidation, the situation is reversed because the rate determining step is not formation of the chromate ester but attack on the oppositely orientated carbon—hydrogen bond, and cholestan-3α-ol is more rapidly oxidized than cholestan-3β-ol to give cholestan-3-one[41]. Axial alcohols are more rapidly dehydrated than their equatorial epimers, e.g. *epi*cholesterol > cholesterol, because of the geometric condition that the four centres of importance in the reaction should be coplanar for ready elimination; this condition is satisfied by 1 : 2-*trans*-groups when both are axial, but not by 1 : 2-*trans*-groups when both are equatorial, or by 1 : 2-*cis*-groups since then one is axial and the other equatorial. The axial and equatorial character of steroid alcoholic groups has been related to the frequency of the C–O stretching vibration in their infra-red absorption spectra [axial OH: 1000–1010 cm^{-1}; equatorial OH: 1030–1040 cm^{-1}] and to the complexity of the band at 1240 cm^{-1} in their acetates[339,340,341]. In adsorption chromatography, the axial alcohols are generally eluted more easily than the equatorial alcohols; this also applies to their esters.

The reactions of steroid ketones often depend on the direction of enolization, which appears to be controlled by the stereochemical configuration of the nearest bridge-head[342]. Thus cholestan-3-one (26) enolizes to give 3-ethoxy- and 3-acetoxy-cholest-2-ene, but coprostan-3-one (28) enolizes to give 3-ethoxy- and 3-acetoxy-coprost-3-ene[343,344], whilst *A/B-trans*-3-ketones by oxidation yield

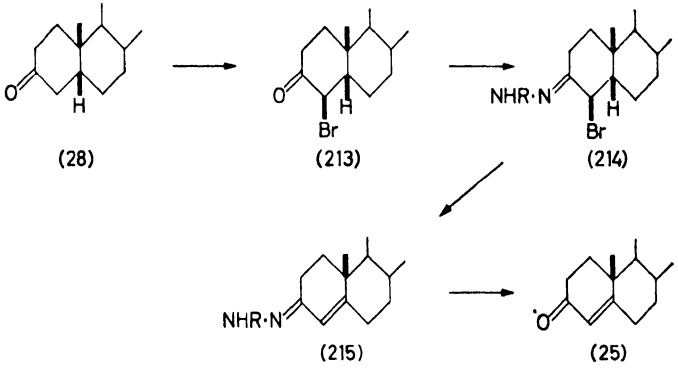
mainly 2 : 3-*seco*-2 : 3-dioic acids and *A/B-cis*-3-ketones yield mainly 3 : 4-*seco*-3 : 4-dioic acids[345], but peroxidation affords lactones in both stereochemical serics[346,347].

A/B-trans-3-Ketones by bromination with bromine or N-bromosuccinimide give 2α-bromo- and 2 : 2-dibromoketones. Cholestan-3-one (26) gives 2α-bromocholestan-3-one (203)[348] converted by hot pyridine into a salt[348] pyrolysed with rearrangement to give cholest-4-en-3-one (25)[349]. Dehydrobromination of (203) with hot collidine[350] or by brief treatment with hydrazines[351,352] yields cholest-1-en-3-one (205), whilst use of sodium iodide in acetone regenerates (26)[353]; potassium acetate in acetic acid at 200° causes rearrangement of (203) to cholest-5-en-4-one (206)[348,354]. The first product of dibromination of cholestan-3-one (26) or of bromination of the 2α-bromoketone (203) is 2 : 2-dibromocholestan-3-one (204)[355], which rearranges in the presence of dry hydrogen bromide to 2α : 4α-dibromocholestan-3-one (207)[356,357]; the rearrangement is inhibited by traces of water[358]. *A/B-trans*-Stan-3-ols with *tert.* butyl hypochlorite give 2α-chloro-3-ketones [as (203)] chlorinated to 2 : 2-dichloro-3-ketones [as (204)][359], which do not rearrange to 2 : 4-dichloroketones[360]. Brief treatment of the 2α : 4α-dibromoketone (207) with sodium iodide in acetone gives the 2ξ-iodo-4α-bromo-ketone (209), whilst extended treatment affords the 2ξ-iodo-Δ⁴-ketone (208)



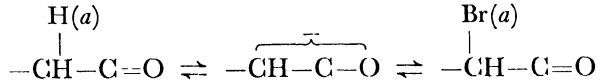
readily reduced with chromous chloride to cholest-4-en-3-one (25)[353]. Dehydrobromination of 2α : 4α-dibromoketones [as (207)] with hot collidine affords dienones [as (210)], transformed by treatment with acetic anhydride–sulphuric acid into phenols, and by pyrolysis with loss of methane into oestrogens; thus cholesta-1 : 4-dien-3-one (210) gives sterophenol [(211): R = C_8H_{17}][361,362], whose structure has been proved by conversion to 3 : 8-dimethyl*cyclo*pentenophenanthrene[363], and by pyrolysis gives 3-hydroxy-19-nor-cholesta-1 : 3 : 5(10)-triene [(212): R = C_8H_{17}]. 17-Oxo- and 17β-hydroxyandrosta-1 : 4-dien-3-one [as (210)] yield the phenols [(211): R = O and R = OH][356,364], and (+)-oestrone-b and oestradiol-17β [(212): R = O and R = OH].

A/B-cis-3-Ketones by bromination with bromine or N-bromosuccinimide give 4β-bromo-[348] and 4 : 4-dibromoketones[365], which do not react with sodium iodide in acetone[353]. Thus coprostan-3-one (28) gives 4β-bromocoprostan-3-one (213), also obtained by bromination of 3-acetoxy-[366] and 3-methoxycoprost-3-ene[367], and directly from the *cis-A/B*-stan-3α-ol by treatment with N-bromoacetamide, N-bromosuccinimide, hypochlorous acid, or *tert.*-butyl hypochlorite[368]. 4β-Bromoketones are dehydrobrominated in poor yield by hot pyridine to Δ4-3-ketones; thus 4β-bromocoprostan-3-one (213) gives cholest-4-en-3-one (25). Improved procedures include treatment with lithium chloride in dimethylformamide[369], and with hydrazines which give 4β-bromo-3-ketone hydrazones [as (214)], rapidly dehydrobrominated in 90% yield to Δ4-3-ketone hydrazones [as (215)], cleaved by exchange with pyruvic acid to Δ4-3-ketones [as (25)][351,352]. 4 : 4-Dibromoketones rearrange to 2β : 4β-dibromoketones[365]; 4 : 4-dichloroketones do not rearrange.



Recent work on the infra-red absorption spectra of cyclic α-halogeno-ketones has enabled prediction of the configuration of the halogen atom. The effects of vicinal bromination on the carbonyl stretching vibration in the spectra of keto-steroids indicate that a

coplanar arrangement of the C–Br and C=O bonds is associated with an increase of 15–20 cm^{-1} in the frequency of the carbonyl band, but that when the C—Br and C=O bonds are mutually perpendicular bromination does not change the frequency of the carbonyl band[370]. This hypothesis has been confirmed, rationalized, and generalized[371]; the most thermodynamically stable conformation of 2-bromo*cyclo*hexanone is that chair-form in which the bromine atom is axial [dipole-dipole interaction > steric interaction], whereas the most thermodynamically stable conformation of 2-bromo-4 : 4-dimethyl*cyclo*hexanone is that chair-form in which the bromine atom is equatorial [steric interaction > dipole interaction]. From the preferred conformations of α-bromo*cyclo*hexanones the relative stabilities of the epimeric bromination products of any keto-steroid with a ketonic function in ring *A*, *B*, or *C* can be deduced. When bromination of a *cyclo*hexanone is kinetically controlled the axial epimer is produced because it is formed faster; the energy of the transition state for enolization is minimized by the maximum overlap between the *p* orbital made available by the departing axial [as opposed to equatorial] proton, and it follows from the principle of microscopic reversibility that in ketonization of the enol the incoming group [Br^+ or H^+] adopts the axial orientation



When bromination of a *cyclo*hexanone is thermodynamically controlled, the more stable epimer predominates [*see Table VI*].

These predictions have been verified by infra-red spectroscopy or by chemical methods for *A/B-trans*-3-ones[372,373,374], -6-ones[371,375], and -7-ones[9], and for *A/B-cis*-3-ones[376], -7-ones[371], -11-ones[377,378], and -12-ones[371,379]. Epimerization of the less stable to the more stable α-bromoketone in presence of hydrogen bromide may occur, not by acid-catalysed enolization, but by reduction of the α-bromoketone and rebromination[8].

The effect of equatorial and axial α-halogen substitution on the ultra-violet absorption spectra of ketones enables an assignment of configuration to the halogen atom in α-halogeno-ketones to be made. The change in the position and intensity of λ_{max} of a ketone produced by α-halogen substitution is a function of the angle between the C—Hal bond and the C=O bond; the change ($\Delta\lambda_e$) in position of $\lambda_{max.}$ produced by introduction of an equatorial α-halogen atom is of average value −5 mμ, whereas the corresponding change ($\Delta\lambda_a$) for axial substitution is of average value +28 mμ; the change ($\Delta \log\epsilon$) in intensity for an equatorial α-halogen atom is 0 to +0·3, but about +0·6 for an axial α-halogen atom[8].

Table VI

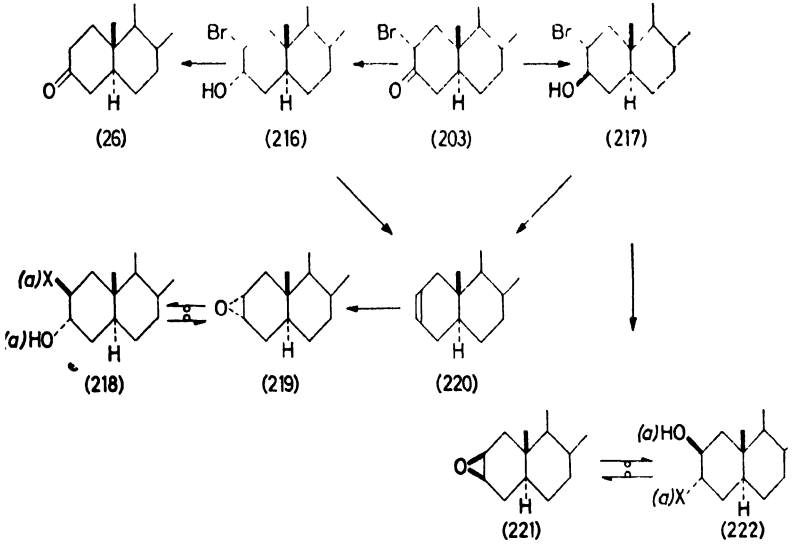
STABILITIES OF EPIMERIC α-BROMOKETO-STEROIDS

A/B-trans- Ketones	1-one	2-one	3-one	4-one	6-one	7-one	11-one	12-one
Configuration of stable epimer	2α-Br(*e*)	1α-Br(*a*) 3α-Br(*a*)	2α-Br(*e*) 4α-Br(*e*)	3α-Br(*a*) 5α-Br(*a*)	5α-Br(*a*) 7α-Br(*a*)	6α-Br(*e*) 8β-Br(*a*)	9α-Br(*a*) 12α-Br(*a*)	11α-Br(*e*)
A/B-cis- Ketones	1-one	2-one	3-one	4-one	6-one	7-one	11-one	12-one
Configuration of stable epimer	2β-Br(*e*)	1β-Br(*a*) 3β-Br(*a*)	2β-Br(*e*) 4β-Br(*e*)	3β-Br(*a*) 5β-Br(*a*)*	5β-Br(*e*)* 7β-Br(*e*)	6α-Br(*e*) 8β-Br(*a*)	9α-Br(*a*) 12α-Br(*a*)	11α-Br(*e*)

(*a*) = axial (*e*) = equatorial.

* Axial to ring A equatorial to ring B

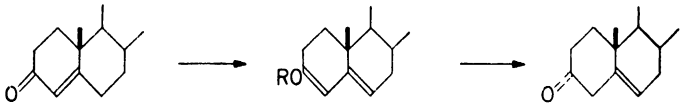
α-Bromoketones of either stereochemical series give *vic.*-bromhydrins by reduction with lithium aluminium hydride or sodium borohydride[380]. Thus 2α-bromocholestan-3-one (203) gives 2α-bromocholestan-3α-ol (216) and -3β-ol (217), which are converted with equal ease by zinc in acetic acid or in ethanol into cholest-2-ene (220)[372,373]. The 2α-bromo-3α-hydrin (216) with potassium hydroxide by *trans*-elimination of hydrogen bromide affords cholestan-3-one (26), whilst the 2α-bromo-3β-hydrin (217) loses hydrogen bromide to give, with inversion of configuration, the 2β : 3β-epoxide (221). The 2β : 3β-epoxide (221), by fission with hydrogen bromide, gives with inversion at $C_{(3)}$ the 3α-bromo-2β-hydrin [(222): X = Br]. The 2α : 3α-epoxide is obtained from cholest-2-ene (220) with perbenzoic acid, and by fission with hydrogen bromide yields, with inversion at $C_{(2)}$, the isomeric 2β-bromo-3α-hydrin [(218): X = Br][381]. Similar relationships hold for *A/B-trans*-6-ones[375,381] and 7-ones[9], for *A/B-cis*-3-ones[373,376] and 11-ones[382,383], and for *A/B-trans*-3α : 4α-, -3β : 4β-, -5α : 6α-, -6α : 7α-, -6β : 7β-, -8α : 9α-, -16α : 17α-epoxides, and *A/B-cis*-3α : 4α-, -3β : 4β-, -5β : 6β-, -11α : 12α-, -11β : 12β-epoxides[337].



When a *cyclo*hexene epoxide, (219) and (221), is cleaved, the C—OH bond and the newly-formed inverted C—X bond in the adducts, (218) and (222), are always both axial[384]. In reductions with lithium aluminium hydride, to give [(218) and (222): X = H], the nucleophilic reagent H^-, the displaced group $-O^-$, and the appropriate carbon atom [$C_{(2)}$ or $C_{(3)}$] form an approximately linear transition state of minimum energy when the entering group and

the displaced group are becoming axial, and similar considerations apply to other fission reactions.

Steroid Δ^4-3-ketones, e.g. cholest-4-en-3-one (25), show a characteristic absorption band in the ultra-violet at λ_{max} 240 mμ, log ε 4·2–4·3. Oxidation of Δ^4-3-ketones leads to fission of ring *A*; thus cholest-4-en-3-one (25) with permanganate affords a 4 : 5-*seco*-5-oxo-4-oic acid. Catalytic hydrogenation of Δ^4-3-ketones generally affords mixtures of the saturated *A/B-trans*- and *A/B-cis*-ketones[385]; the proportion of the products varies with the conditions and with the structure of remote parts of the molecule, and 11β-hydroxyl groups lead to exclusive production of the saturated *A/B-trans*-ketones[385,386], whilst 11α-hydroxyl groups lead to formation of saturated *A/B-cis*-ketones[387]. The catalytic reduction of cholest-4-en-3-one has been discussed [*see* p. 39]. In the presence of acidic or alkaline catalysts, Δ^4-3-ketones [as (25)] are in equilibrium with the corresponding Δ^5-3-ketones [as (23)], but the equilibrium is greatly in favour of the former.

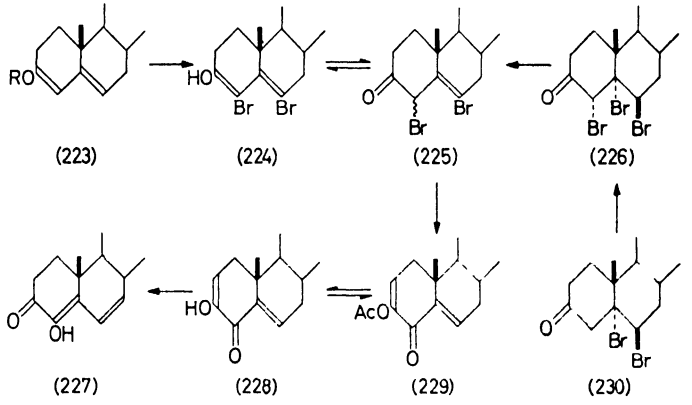


(25) (223) (23)

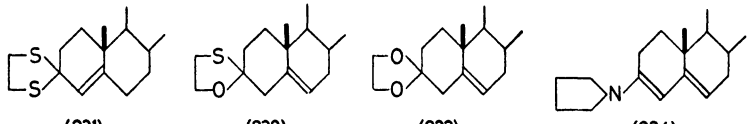
Treatment of cholest-4-en-3-one (25) as the enol-acetate [(223): R = Ac] with potassium amide in liquid ammonia followed by water gives cholest-5-en-3-one (23)[388], reduced by lithium aluminium hydride to cholesterol (1)[24]; reduction of the enol-acetate (223) with lithium aluminium hydride or sodium borohydride gives a mixture of cholesterol (1) and *epi*cholesterol (36) [*see* p. 46].

Bromination of Δ^4-3-ketones may take place by addition or substitution; ordinary bromination requires the presence of hydrogen bromide since it is prevented by presence of potassium acetate, and takes place through an enol which has the $\Delta^{3:5}$-structure[389]. The result is bromination at an unexpected position; thus cholest-4-en-3-one (25) via the enol [(223): R = H] finally gives 4 : 6-dibromocholest-4-en-3-one (224) or (225)[390]. This substance can be obtained from 5α : 6β-dibromocholestan-3-one (230), the oxidation product of cholesterol dibromide. Bromination in acetic acid or in ether or with N-bromosuccinimide gives first 6-bromo-Δ^4-3-ketones[359,391] and then probably 2 : 6-dibromo-Δ^4-3-ketones[392], whilst further bromination appears to be preceded by migration of bromine from $C_{(2)}$ to $C_{(4)}$ and to give 4-epimeric tribromocholestan-3-ones, m.p. 106° and 138°, of which the latter (226) is converted by potassium acetate into (224) or (225). Further action of potassium acetate on (224) $\rightleftharpoons$ (225) leads with rearrangement to

an enol acetate (229) hydrolysed to diosterol-II (228), also obtained by oxidation and subsequent debromination of the dibromide of cholest-5-en-3β : 4β-diol[393]. The name diosterol is applied to the two enolic forms of cholest-5-ene-3 : 4-dione; the diosterols have reducing properties [cf. diosphenol], and diosterol-II (228) is isomerized by acid to diosterol-I (227), which is also obtained by various processes that probably all proceed through (224) $\rightleftharpoons$ (225)[390, 394]. The above structures, which modify those originally assigned, are based on spectrographic evidence[395].

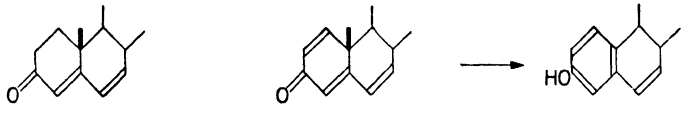


Removal of carbonyl groups from saturated ketones may be achieved by Wolff-Kishner reduction[396, 397, 398, 399], or by conversion to the ethylene thioketal and desulphurization with nickel[400]. Removal of the carbonyl group from cholest-4-en-3-one (25) by Wolff-Kishner reduction affords cholest-3-ene, this method leading to migration of the double bond to the adjacent position[401]. This may be avoided by reduction with nickel of the ethylene thioketal (231)[400, 402]; hemithioketals (232)[403] and ketals [$\equiv$ dioxolanes] (233)[404, 405, 406, 407] with nickel regenerate the parent Δ^4-3-ketones, whilst pyrrolidine derivatives (234)[408] also form useful protective devices.

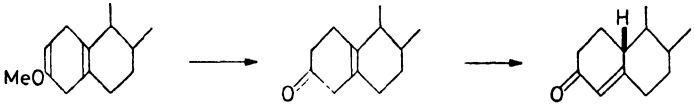


Steroid $\Delta^{4:6}$-diene-3-ketones (235) are obtained from Δ^4-3-ketones by oxidation with manganese dioxide[153], or by oxidation with monoperphthalic acid to 6-hydroxy-Δ^4-3-ketones and dehydration[409].

Steroid $\Delta^{1:4:6}$-trienc-3-ketones (236) arc prepared by bromination of Δ^4-3-ketones or of $\Delta^{1:4}$-diene-3-ketones (210) with N-bromosuccinimide and treatment with hot collidine; by pyrolysis at 600° they lose methane to give Δ^6-oestrogens (237)[392, 409a].



(235) (236) (237)



(238) (239) (240)

Steroid phenols, as the methyl ethers, by reduction with sodium[388] or lithium[410] in liquid ammonia give enol-ethers (238), which by hydrolysis give the 19-nor-$\Delta^{5(10)}$-3-ketones (239) rearranged to the 19-nor-Δ^4-3-ketones (240).

Colour Reactions

Colourless sterols by treatment with strong acids under dehydrating conditions give numerous colour reactions, which are useful for preliminary identification and for quantitative analysis although not completely specific.

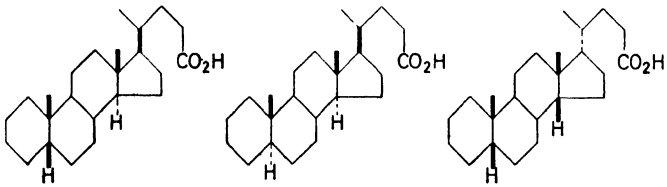
The Liebermann–Burchard reaction[411] is carried out by treating the sterol, dissolved in chloroform, with sulphuric acid–acetic anhydride; the test is positive with stenols, negative with stanols, and a mechanism involving bicholestadiene has been suggested[412]. The Salkowski reaction[413] is similar but omits the use of acetic anhydride. The Rosenheim test[414] involves treatment of a chloroform solution of a sterol with 90% trichloroacetic acid; a blue or pink colour indicates an actual or potential [dehydration] diene system. In the Tschugaev reaction[415] a glacial acetic acid solution of the sterol is heated with zinc chloride and acetyl chloride. In the Lifschütz test the sterol and perbenzoic acid are heated together in glacial acetic acid and sulphuric acid added[416]. The Tortelli-Jaffe test[417] is carried out by layering a 2% bromine–chloroform solution with an acetic acid solution of a sterol; a green coloration produced at the interface indicates the presence or potential presence [isomerization] of a ditertiary double bond between bridge-heads.

The Zimmermann reaction[418] depends on the presence of the group —CO—CH_2—, and is carried out by treatment of an alcoholic solution of a keto-steroid with *m*-dinitrobenzene and potassium hydroxide; it is used for quantitative estimation of 17-ketosteroids, and, because the absorption maximum of the coloured complex varies with the position of the keto group, has diagnostic value.

By underlayering an alcoholic solution of a steroid with sulphuric acid alone[419] or in the presence of benzaldehyde[420] or furfuraldehyde[419] characteristic colours are produced which may indicate the stereochemical configuration of a hydroxyl group. A diazo-coupling test [421] may be used to characterize non-ketonic steroids containing a conjugated system of double bonds in one ring or distributed between two rings.

The Bile Acids

The natural bile acids are generally hydroxy-derivatives of cholanic acid (241). They are produced in the liver, either synthetically or by degradation of cholesterol, and occur in bile as water-soluble sodium salts of peptide conjugates with glycine or taurine. These conjugates promote the resorption of fats and water-insoluble substances, e.g. β-carotene and vitamin K_1, in the intestinal tract by acting as emulsifying agents and by facilitation of enzymatic hydrolysis and re-esterification. The conjugates may be synthesized by coupling the azide of a bile acid[422] with the appropriate amino-acid in an alkaline medium. The nature of the conjugation varies with the species; human and ox bile contain more glyco-acids than tauro-acids whilst hog bile contains mainly glyco-acids and codfish bile is rich in tauro-acids. Hydrolysis affords the free bile acids; thus ox bile furnishes cholic and deoxycholic acid with traces of chenodeoxycholic and lithocholic acid, whereas pig bile readily furnishes 'α'-hyodeoxycholic acid.



(241) (242) (243)

The bile acids obtained by degradation of steroids are generally derivatives of cholanic acid (241) or *allo*cholanic acid (242). The names, structures, properties, and sources of natural and synthetic bile acids are listed in *Table VII*; the methyl ester-acetates are useful for characterization.

Table VII

NATURAL AND DERIVED BILE ACIDS

Name	Hydroxyl groups	m.p.°	$[\alpha]_D°$	Source
Monohydroxy-acids $C_{24}H_{40}O_3$				
Lithocholic acid	3α	184–186	+32	Man, ox, rabbit
3β-Hydroxycholanic acid	3β	176–177	+26	—
3α-Hydroxy*allo*cholanic acid	3α	208–210	+29	—
3β-Hydroxy*allo*cholanic acid	3β	218	+17	—
6α-Hydroxycholanic acid	6α	221–222	+8	—
7α-Hydroxycholanic acid	7α	96–102	—	—
11β-Hydroxycholanic acid (methyl ester)	11β	85–86	+50	—
12α-Hydroxycholanic acid	12α	90–95	+43	—
12β-Hydroxycholanic acid	12β	110–116	+38	—
Dihydroxy-acids $C_{24}H_{40}O_4$				
'α'-Hyodeoxycholic acid	3α : 6α	196–197	+8	Pig (G), boar
3α : 6β-Dihydroxycholanic acid	3α : 6β	205	+37	—
'β'-Hyodeoxycholic acid	3β : 6α	189–190	+5	Hog
3β : 6β-Dihydroxycholanic acid	3β : 6β	258	+15	—
Chenodeoxycholic acid	3α : 7α	110	+11	Man, ox, bear, hen, guinea pig, goose (T)
Ursodeoxycholic acid	3α : 7β	203	+57	Bear (T)
3α : 11α-Dihydroxycholanic acid	3α : 11α	147	+22	—
3α : 11β-Dihydroxycholanic acid	3α : 11β	201	+55	—
3β : 11β-Dihydroxycholanic acid (methyl ester 3-acetate)	3β : 11β	140	+50	—
Deoxycholic acid	3α : 12α	176–177	+53	Man (G, T), ox (G), deer, dog, sheep, goat (G, T), antelope, rabbit (G)
12-*epi*Deoxycholic acid	3α : 12β	186	+38	—
*iso*Deoxycholic	7α : 12α	210–211	+27	—
7 : 12-Dihydroxycholanic acid	7? : 12?	226–227	—	—
11α : 12α-Dihydroxycholanic	11α : 12α	211–214	—	—
11β : 12β-Dihydroxycholanic acid	11β : 12β	170–174	—	—

Conjugate acid: G=glycine, S=sulphuric acid, T=taurine.

Table VII

NATURAL AND DERIVED BILE ACIDS—*cont.*

Name	Hydroxyl groups	m.p.°	$[\alpha]_D°$	Source
		Dihydroxy-acids $C_{24}H_{40}O_4$—*cont.*		
Bufodeoxycholic acid	3 : x	—	—	Toad (T)
'α'-Lagodeoxycholic acid	—	156–157	+80	Rabbit (G)
'β'-Lagodeoxycholic acid	—	213	+37	Rabbit (G)
		Trihydroxy-acids $C_{24}H_{40}O_5$		
Cholic acid	3α : 7α : 12α	196–198	+37	Man (G, T), ox (G, T), sheep, dog (T), goat, snake (T), fish (T)
3 : 11 : 12-Trihydroxycholanic acids	3α : 11α : 12α	173–175	+31	—
	3α : 11α : 12β	161–166	+45	—
	3α : 11β : 12α	145–147	+54	—
	3α : 11β : 12β	177	+43	—
'β'-Phocaecholic acid	3 : 7 : 23	222–223	+27	Walrus (T), seal (T)
Pythocholic acid	3α : 12α : 16α	—	—	African python
		Acids containing more than twenty-four carbon atoms		
'β'-Trihydroxybisnorstero-cholanic acid $C_{26}H_{46}O_5$	3α : 7α : 12α : 25 *L*	194–196	—	Frog (S)
Trihydroxycoprostanoic acid $C_{27}H_{46}O_5$ [formerly 'α'-Trihydroxybisnorstero-cholanic acid]	3α : 7α : 12α : 25 *D*	180–182	+27	Frog, alligator, cayman, crocodile
Varanic acid [hydrate] $C_{27}H_{46}O_6$	—	120	—	Lizard
Tetrahydroxynorsterocholanic acid $C_{27}H_{46}O_6$	3α : 6α : 12 : 24	217	—	Teleost fish
Acid $C_{27\text{-}28}H_{46\text{-}48}O_6$	—	255	—	Shark
Tetrahydroxysterocholanic acid $C_{27\text{-}28}H_{46\text{-}48}O_6$	3α : 7α : 12α : ?	150	—	Turtle, tortoise
Tetrahydroxy*iso*sterocholanic acid $C_{27\text{-}28}H_{46\text{-}48}O_6$	—	205	—	Japanese turtle
Sterocholic acid $C_{28}H_{46}O_4$	—	256	—	Ox, turtle
Trihydroxybufosterocholenic acid $C_{28}H_{46}O_5$	3α : 7α : 12α	160	—	Japanese toad
Trihydroxy*iso*sterocholenic acid $C_{28}H_{46}O_5$	3α : 7α : 12α	227	—	Japanese toad

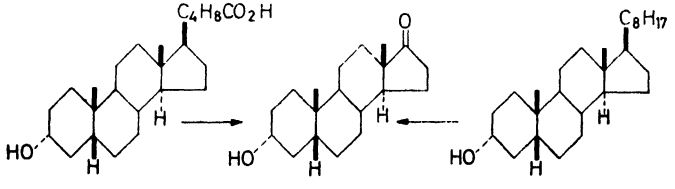
Conjugate acid: G=glycine, S=sulphuric acid, T=taurine.

3 : 4-*seco*-3 : 4-Dioic acids are bilianic acids, whilst 2 : 3-*seco*-2 : 3-dioic acids are *iso*bilianic acids; 6 : 7-*seco*-6 : 7-dioic acids obtained by fission of ring *B* are thilobilianic acids, and 16 : 17-*seco*-16 : 17-dioic acids obtained by fission of ring *D* after complete removal of the $C_{(17)}$-side chain are aetiobilianic acids [cf. pp. 9, 19–21].

Hydroxycholanic Acids

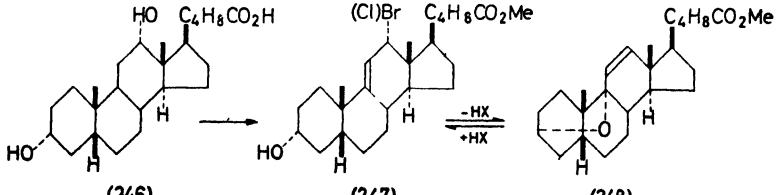
Natural bile acids may possess hydroxyl groups at $C_{(3)}$, $C_{(6)}$, $C_{(7)}$, $C_{(12)}$, and $C_{(23)}$; nearly all have been dehydrated and subsequently hydrogenated to saturated acids; cholic, deoxycholic, chenodeoxycholic, ursodeoxycholic, and lithocholic acids all give cholanic acid, $C_{24}H_{40}O_2$ (241), m.p. 164°, $[\alpha]_D$ + 22°; 'α'-hyodeoxycholic acid undergoes allomerization during degradation and gives *allo*cholanic acid, $C_{24}H_{40}O_2$ (242), m.p. 170°, $[\alpha]_D$ + 22°. Bufodeoxycholic acid gives by oxidation a dehydro-acid which also undergoes allomerization, but Clemmensen-reduction of the dehydro-acid gives bufocholanic acid, $C_{24}H_{40}O_2$, m.p. 236°, $[\alpha]_D$ − 20°; the toad poison bufotalin [*see* p. 263] by degradation gives *iso*bufocholanic acid, m.p. 179°, $[\alpha]_D$ + 50°, now known to be 14-*iso*-17-*iso*cholanic acid (243).

With the exception of 'β'-hyodeoxycholic acid the 3-hydroxyl group always has the α-configuration. Thus lithocholic acid (244) [as the acetate] is oxidized by chromium trioxide to 3α-hydroxyaetiocholan-17-one (245)[423], which is also obtained from *epi*coprostanol (30) by oxidation [as the acetate] with chromium trioxide[20].



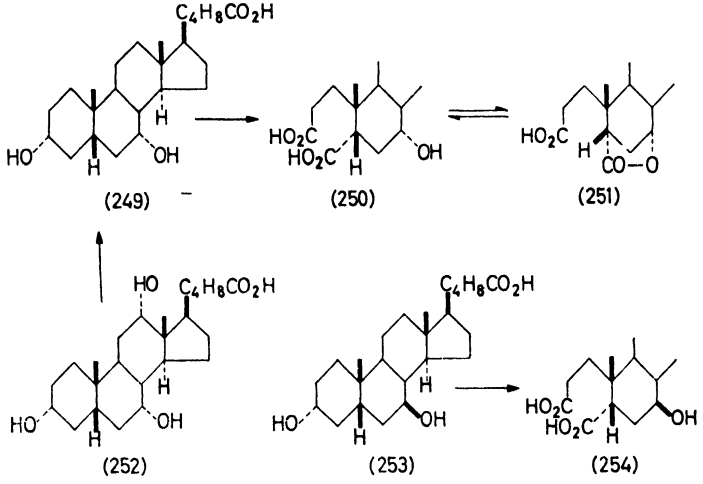
(244) (245) (30)

Deoxycholic acid (246) can be converted into methyl 3α-hydroxy-12α-chloro(bromo)chol-9(11)-enate (247), which by washing with water at 20° is rapidly transformed into the 3α : 9α-epoxide (248)[424]. The structure (248) is strainless only if ring *A* is a boat-form with ends at $C_{(3)}$ and $C_{(10)}$ and rings *A*/*B* are *cis*-fused.

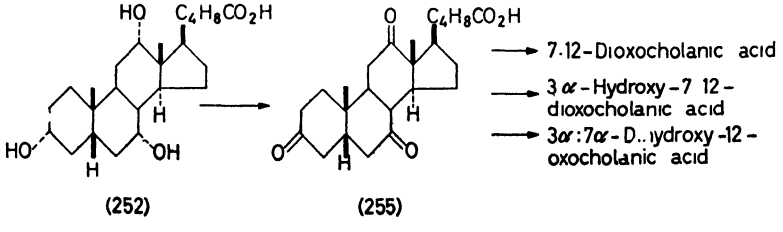


(246) (247) (248)

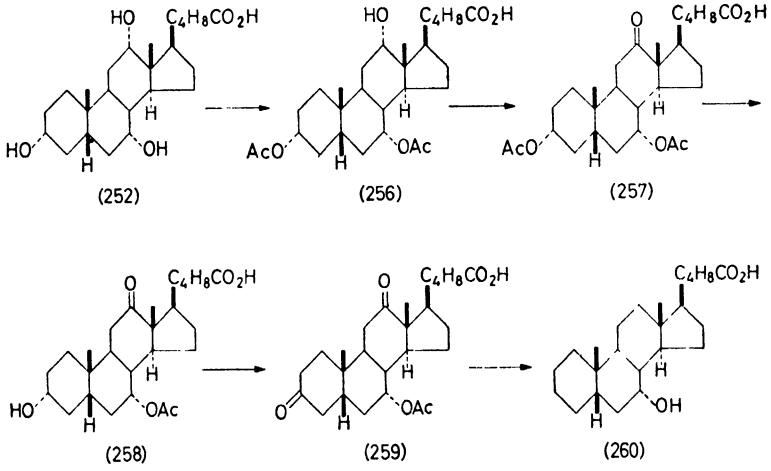
The 7-hydroxyl group in cholic acid (252) is α-orientated. Cholic acid can be converted into chenodeoxycholic acid (249)[425], oxidized by hypobromite to the 3 : 4-*seco*-3 : 4-dioic acid (250), which gives the 5α → 7α-lactonic acid (251)[426]. Since chenodeoxycholic acid is a coprostane derivative[427], the 5-carboxyl group in (250) must be α-orientated, from which it follows that the 7-hydroxyl must also be α-orientated. Ursodeoxycholic acid (253) by oxidation with hypobromite gives the 7β-hydroxy acid (254) which does not yield a lactonic acid[428]. The relationship 7α-OH(axial)/8β-H (axial): *trans* in (252) is consistent with the ready ionic dehydration of cholic acid derivatives to chol-7-enes[429].



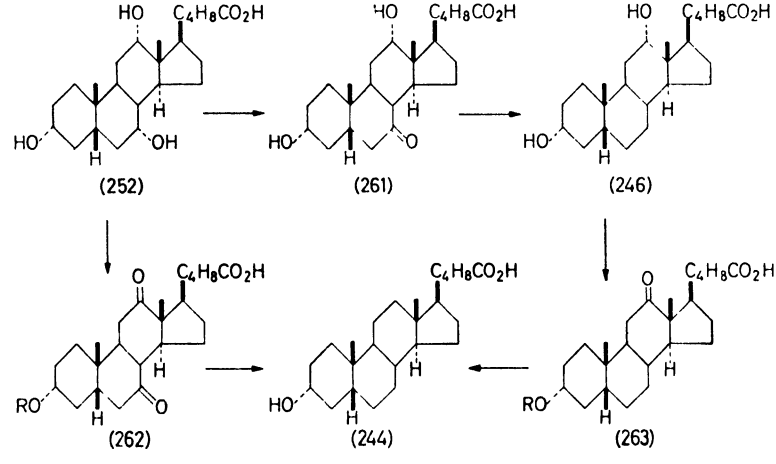
Hydroxycholanic acids are smoothly oxidized to keto-acids by chromium trioxide in acetic acid; cholic acid (252) gives 3 : 7 : 12-trioxocholanic acid [dehydrocholic acid] (255). The rate determining step is attack on the C—H bonds, and the order of reactivity is $C_{(7)} > C_{(12)} > C_{(3)}$, whilst $C_{(6)} > C_{(3)}$. Thus 7α : 12α-dihydroxycholanic acid gives the 7-oxo-12α-hydroxy acid, chenodeoxycholic acid (249) and ursodeoxycholic acid (253) give the 3α-hydroxy-7-oxo acid, and deoxycholic acid (246) affords the 3α-hydroxy-12-oxo



acid, whilst 'α'-hyodeoxycholic acid furnishes the 3α-hydroxy-6-oxo acid. For reduction, hydrogenation, acylation, and hydrolysis the order of reactivity is: $C_{(3)} > C_{(7)} > C_{(12)}$. Thus dehydrocholic acid (255) by mild Clemmensen reduction, by use of sodium amalgam, and by partial hydrogenation respectively gives 7 : 12-dioxocholanic acid, m.p. 176°, and 3α-hydroxy-7 : 12-dioxocholanic acid, m.p. 186°, reduced by the Wolff-Kishner method to lithocholic acid, and 3α : 7α-di-hydroxy-12-oxocholanic acid, m.p. 219°, $[\alpha]_D$ + 74°.



Again, cholic acid (252) by partial acetylation gives first the 3α-monoacetate and then the 3α : 7α-diacetate (256), m.p. 257°, oxidized to the 12-oxo-acid (257), m.p. 221°; partial hydrolysis

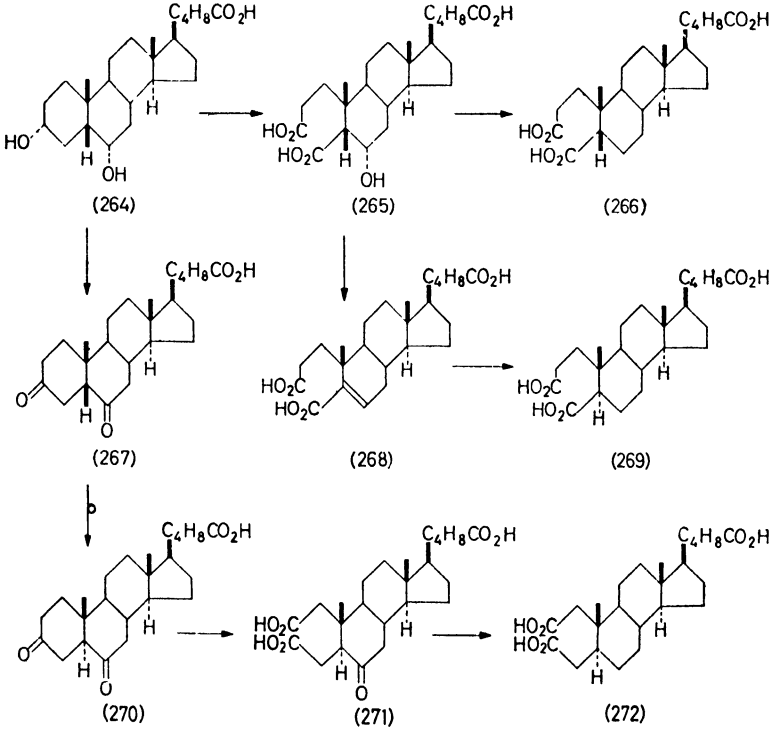


furnishes the 3α-hydroxy-7α-acetoxy-12-oxo-acid (258), m.p. 239°, oxidized to the 3 : 12-dioxo-7α-acetoxy acid (259), m.p. 190°, which by Wolff-Kishner reduction affords 7α-hydroxycholanic acid (260).

The above transformations provide routes from cholic acid to the 3-, 7-, 12-hydroxy or -oxocholanic acids; cholic acid (252) may also be converted in 88% yield via the 3-succinate to lithocholic acid (244) by oxidation to the 7 : 12-dioxo-3-succinate (262) and Wolff-Kishner reduction of the latter[430]. Deoxycholic acid (246) may be converted to lithocholic acid (244) in 81% yield via the 3-succinate by an analogous process[429,431]; similarly, deoxycholic acid affords 84% of the 3α-tosyloxy-12α-hydroxycholanic acid, which with pyridine gives 12α-hydroxychol-2(or 3)-enic acid hydrogenated smoothly to 12α-hydroxycholanic acid[432].

By selective oxidation of cholic acid (252) with N-bromosuccinimide to 3α : 12α-dihydroxy-7-oxocholanic acid (261), m.p. 199°, $[\alpha]_D$ + 1°, followed by Wolff-Kishner reduction, deoxycholic acid (246) is obtained in 70% yield[433]; other procedures also involving selective oxidation at $C_{(7)}$ have been described.

Oxidation of 'α'-hyodeoxycholic acid (264) with cold chromium



trioxide gives 3 : 6-dioxocholanic acid ['α'-dehydrohyodeoxycholic acid] (267), allomerized by warming with acid or alkali to 3 : 6-dioxo*allo*cholanic acid ['β'-dehydrohyodeoxycholic acid] (270)[434]. By use of hypobromite, 'α'-hyodeoxycholic acid gives the 6α-hydroxy-3 : 4-*seco*-3 : 4 : 24-trioic acid (265), reduced by hydriodic acid to lithobilianic acid (266). Dehydration of the hydroxy-acid (265) with sodium ethoxide at 195° affords lithobilienic acid (268), hydrogenated to *allo*lithobilianic acid (269)[434]. The isomeric *allo-iso*lithobilianic acid (272) is obtained from the dioxo acid (270) by oxidation with permanganate or hypobromite to the 6-oxo-2 : 3-*seco*-2 : 3 : 24-trioic acid (271), and Clemmensen reduction[434]. The isomeric bilianic acids played an important part in the elucidation of the steric relationship of rings *A*/*B* [*see* p. 9]; the fourth isomeride, *iso*lithobilianic acid, is obtained together with (266) by oxidation of lithocholic acid (244), and together with (272) by Wolff-Kishner reduction of (271)[434].

Hydrogenation of 3-oxocholanic acid [≡ dehydrolithocholic acid] gives mainly the 3α-hydroxy acid in presence of sodium hydroxide, and the 3β-hydroxy acid in acidic media[435]; sodium borohydride gives mainly the 3α-hydroxy acid. Hydrogenation of 7-oxocholanic acid in acetic acid gives the 7α-hydroxy acid[436], whilst use of sodium borohydride affords both epimers[437]. Hydrogenation of 11-oxocholanic acids with platinum or nickel under pressure gives the 11β-hydroxy acids[438], also obtained almost exclusively by use of lithium aluminium hydride[439], sodium borohydride[440], or lithium borohydride[441]; reduction with sodium in propanol[442,443], or lithium in liquid ammonia and ethanol furnishes the 11α-hydroxy acids[444]. Hydrogenation of 12-oxocholanic acids with platinum in acetic acid gives mainly the 12α-hydroxy acids, but use of nickel in presence of sodium hydroxide affords preferentially the 12β-hydroxy acids[445]. The enol acetates derived from 3-oxo-, 7-oxo-, and 11-oxocholanic acids have the double bond in the 3 : 4-, 6 : 7-, and 9 : 11-positions, respectively[446].

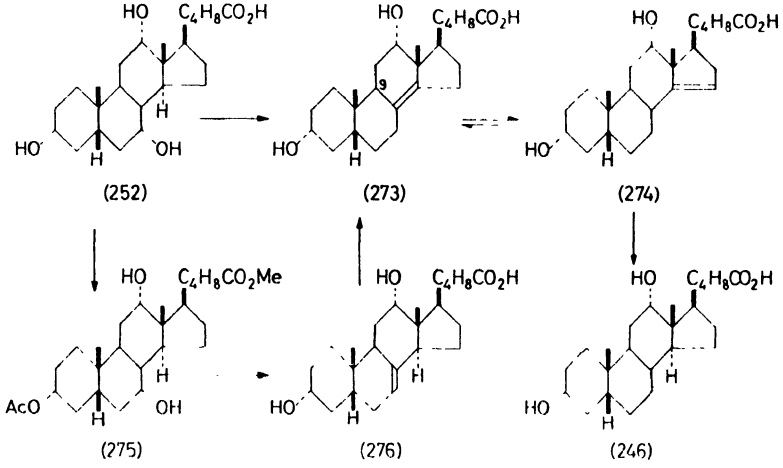
Deoxycholic acid (246) as the ethyl ester-12-acetate has been converted into the 19-nor-1-hydroxy-4-methyl aromatic compound analogous to (211), and into the 19-nor-1-methyl-4-hydroxy isomeride [409a].

Unsaturated Bile Acids

Apocholic Acid

Dehydration of bile acids by heating in a vacuum leads to unsaturated acids. Lithocholic acid (244) gives a mixture in the ratio of 1 : 9 of 'α'-lithochol-2(?)-enic and 'β'-lithochol-3(?)-enic acids, separated through the dibromides[447]; cholic acid (252) gives

chola-2 : 6 : 11-trienic acid[448,449]. With mild dehydrating agents, e.g. zinc chloride, cholic acid (246) loses the 7α-hydroxyl group to give mixtures of 3α : 12α-dihydroxychol-8(14)-enic acid [apocholic acid] (273), $C_{28}H_{38}O_4$, m.p. 176°, $[\alpha]_D$ + 50°, 3α : 12α-dihydroxychol-14-enic acid (274), and an unidentified *iso*dihydroxy-acid. The acid (274) can be hydrogenated to deoxycholic acid (246), but apocholic acid (273) is completely resistant[429,450,451].



Dehydration of methyl cholate 3-acetate (275), m.p. 149°, $[\alpha]_D$ + 48°, with phosphorus oxychloride–pyridine gives [after hydrolysis] 3α : 12α-dihydroxychol-7-enic acid (276), which is isomerized by shaking with platinum in hydrogen to apocholic acid[429]; the relationship of the acids (276), (273), and (274) is analogous to that of the γ-, α-, and β-stenols [*see* p. 67].

Dehydrogenation of apocholic acid with perbenzoic acid or selenium dioxide affords two isomerides, $C_{28}H_{36}O_4$, of uncertain structure; 'α'-dihydroxycholadienic acid, m.p. 248°, $[\alpha]_D$ − 60°, regenerates apocholic acid by hydrogenation, whilst 'β'-dihydroxycholadienic acid, m.p. 251°, $[\alpha]_D$ + 71°, furnishes 'β'-apocholic acid, m.p. 165°, $[\alpha]_D$ + 79°, which may differ from apocholic acid (273) in configuration at $C_{(9)}$[450,451,452].

7-Dehydro-bile acids [analogues of 7-dehydrosterols], e.g. 3β-hydroxychola-5 : 7-dienic acid, by irradiation give products with only feeble antirachitic activity[453,454]. Numerous chol-9(11)-enic acids and chola-7 : 9(11)-dienic acids[455] have been prepared for use in the synthesis of cortisone [*see* p. 194]. 3β-Hydroxychol-5-enic acid is available as a by-product of the oxidation of cholesterol in the industrial production of testosterone.

The Side Chain

The position, structure, and configuration of the bile-acid chain has already been discussed [*see* Chapter I, pp. 24–28].

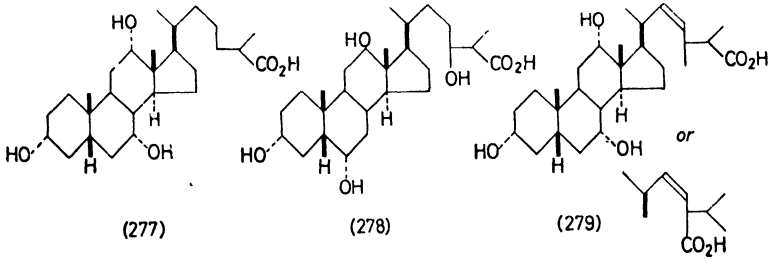
Other Acids from Bile

'Weyland's acid' from ox bile is a molecular compound of chenodeoxycholic acid and 3α-hydroxy-12-oxocholanic acid; 3α-hydroxy-7-oxocholanic acid [guinea pig] and 3α-hydroxy-6-oxo*allo*-cholanic acid [pig] have been isolated, but the latter may be an artefact arising by allomerization. Traces of 3α : 12α-dihydroxy-7-oxocholanic and 7 : 12-dihydroxy-3-oxocholanic acids have been obtained from cow bile. Rabbit bile contains mainly deoxycholic acid and small amounts of the isomeric acids, 'α'-lagodeoxycholic acid and 'β'-lagodeoxycholic acid of unknown structure[456]. Chicken bile contains 3α-hydroxychol-8(14)-enic [deoxyapocholic] acid. Nutriacholic acid, which occurs conjugated with glycine in beaver and coypu bile, is 3α-hydroxy-7-oxocholanic acid[457].

Pythocholic acid, $C_{24}H_{40}O_5$, from various species of African python, is probably 3α : 12α : 16α-trihydroxycholanic acid[458]; optical rotatory data suggest the 16-position for the third hydroxyl group, but do not completely exclude the 15-position. Pythocholic acid has been converted into deoxycholic acid (246)[459].

Several $C_{(27)}$-bile acids [coprostanoic acids] have been isolated. 3α : 7α : 12α : 25*L*-Trihydroxycoprostan-26-oic acid (277)[459a], $C_{27}H_{46}O_5$, from the gall-bladders of three species of crocodile [alligator, cayman, and the Nile crocodile][460], is identical with 'α'-trihydroxybisnorsterocholic acid[461]. It has been converted into coprostan-26-oic acid[460], which has been obtained synthetically from cholanic acid (241)[462]. The 3α : 7α : 12α : 25*D*-isomeride is identical with 'β'-trihydroxybisnorsterocholic acid[459a]. Other coprostanoic acids have been described[463, 464, 465].

A similar acid, tetrahydroxynorsterocholanic acid (278), $C_{27}H_{46}O_6$, isolated from bile of gigi fish, has been converted into 'α'-hyodeoxycholic acid, 12-oxocholanic acid, and *allo*cholanic acid (242)[466, 467].



Several C_{28}-bile acids have been isolated. Sterocholic acid, $C_{28}H_{46}O_4$, is present in ox bile[468] and turtle bile[469,470]. From toad bile are obtained trihydroxybufosterocholenic acid, $C_{28}H_{46}O_5$ (279?) and trihydroxy*iso*sterocholenic acid, $C_{28}H_{46}O_5$ (279?), which both, by ozonolysis, give bisnorcholic acid and thus differ only in the terminal portion of the side chain[471].

Choleic Acids

Bile acids tend to form molecular compounds, and generally contain a molecule of solvent of crystallization. Cholic acid forms a remarkable blue compound $(C_{24}H_{40}O_5 \cdot I)_4 \cdot K \cdot IH_2O$, but molecular complex formation is strongly exhibited by apocholic and 'β'-apocholic acid and especially by deoxycholic acid.

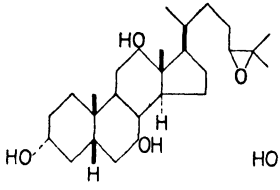
Deoxycholic acid forms a series of remarkably stable molecular compounds, known collectively as choleic acids, with aliphatic hydrocarbons, acids, esters, alcohols, ethers, and with aromatic hydrocarbons, phenols, and alkaloids. Formic acid alone of the monobasic aliphatic acids fails to form a compound; the compound with acetic acid is a 1 : 1-molecular compound, that from propionic acid contains 1 mol. $Et \cdot CO_2H$ to 3 mols. deoxycholic acid. Normal acids with C_4–C_8 form 1 : 4-compounds, those with C_9–C_{14} give 1 : 6-compounds, and higher acids yield 1 : 8-compounds. The numer of molecules of combined deoxycholic acid conforms to the coordination-number series, 1, 2, 3, 4, 6, 8, but the significance of this is unknown[472]. X-ray diagrams of the choleic acids from propionic acid up to cerotic acid show identical interference and intensity patterns[473]. Acylation or esterification prevents choleic acid formation, but since functional groups are not required in the addendum choleic acids have been suggested as a means for resolution of chemically inert substances, e.g. hydrocarbons[474]. The choleic acids differ greatly in solubility in organic solvents and degree of dissociation in solution; xylene displaces ethanol from the ethanol–choleic acid even in alcoholic solution, whilst recrystallization of the xylene–choleic acid from acetic acid affords the acetic–choleic acid.

Doubt has been cast on the real existence of the choleic acids because all such compounds have previously been prepared only by use of specimens of deoxycholic acid now known to be seriously impure; it is stated[475] that a mixture of pure deoxycholic acid with xylene [or oleic acid] can be separated completely by two crystallizations from ethanol.

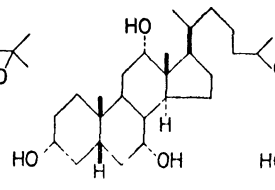
The Bile Alcohols

The bile of sharks, frogs, and toads contains polyhydric steroid alcohols usually present as sodium salts of the sulphuric acid esters.

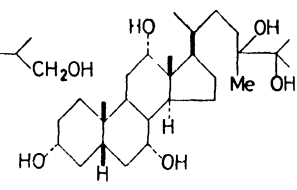
Shark bile contains scymnol (280), $C_{27}H_{48}O_5$, m.p. 187°[476,477]; three secondary hydroxyl groups and one primary group are present since oxidation with chromium trioxide gives a trioxo-acid, $C_{27}H_{40}O_6$, further oxidized to dehydrocholic acid (255). The fifth oxygen atom is probably oxidic, because scymnol with hydrogen chloride forms a chlorohydrin from which it can be regenerated; scymnol may contain a $C_{(24)}$: $C_{(25)}$-ethylene oxide or a $C_{(24)}$: $C_{(27)}$-trimethylene oxide system[478].



(280)



(281)



(282)

Allied to scymnol are the compounds 3α : 7α : 14 : 22-tetrahydroxycholane, $C_{24}H_{42}O_4$, present as a $C_{(14)}$-sulphuric acid ester in frog bile[461], tetrahydroxynorbufostane (281?)[479], $C_{27}H_{48}O_4$, and pentahydroxybufostane (282?), $C_{28}H_{50}O_5$, from toad bile[480].

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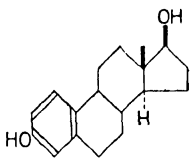
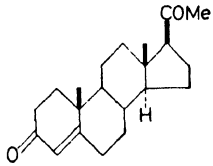
III

SEX HORMONES

THE glands of the genital system elaborate specific chemical compounds which control the sexual processes; the compounds are called hormones because they produce their effects at a site other than that of their origin. Production of the sex hormones is regulated by the gonadotropic hormones, which are protein in character and secreted by the anterior lobe of the pituitary; partial or total removal of the anterior lobe [hypophysectomy] arrests or inhibits sexual activity, which can be restored by implantation of pituitary tissue or injection of cell-free pituitary extracts. There are three types of sex hormones, or sexogens; the oestrogens, the gestogens, and the androgens. Oestradiol-17β (1), formerly called 'α'-oestradiol, is the ovarian hormone that produces oestrus; progesterone (2), produced by the corpus luteum is essential for



(1)



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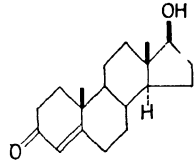


(3)

successful pregnancy; testosterone (3) is elaborated in the testes: these appear to be the true sex hormones, whilst other compounds of related physiological function [oestrone, oestriol (oestrogens); androsterone, dehydro*epi*androsterone (androgens)] are metabolic transformation products. The distinction between male and female sex hormones is convenient chemically, but its physiological significance is doubtful; thus androst-4-ene-3 : 17-dione is a potent androgen, but has some oestrogenic activity and also slight progestational activity.

THE OESTROGENS

Occurrence

The female sex organs undergo a periodic change; this uterine cycle is controlled by the oestrogens in conjunction with progesterone. Oestrogen produced in the ovary passes to the uterus and the vagina, and in animals produces the condition of oestrus

[sexual heat]; rats, mice, and guinea pigs show characteristic changes in the tissues of the vagina, accompanied by a vaginal discharge, which has a typical cornified appearance easily recognizable by microscopic examination. The bioassay of oestrogenic activity[1] is carried out by subcutaneous injection of a compound at several concentrations into a group of five or more spayed mice [or rats], whilst a group of control animals is simultaneously injected with a standard oestrogen; the relative potency is then determined by comparison of the concentrations necessary to produce oestrus in more than 50% of the animals. The results are generally expressed in mouse units [M.U.]; by international agreement, one mouse unit is defined as the effect produced by 0·1 γ [1 γ = 0·001 mg] of pure oestrone administered in sesame oil by subcutaneous injection. The ratio of the mouse unit to the rat unit (R.U.) varies from 1 : 5 to 1 : 8.

Oestrogens are present in low concentrations in tissue extracts prepared from the gonads, and mammalian placenta, in follicular fluid, in blood, and in the urine of both sexes. Human pregnancy urine is rich in oestrogen[2], and pregnant mares' urine is even richer[3] [*see Table VIII*]. Oestrogenic hormones have been found in lower animals and in plants; oestrone has been isolated from palm-kernel extract[4] and oestriol from pussy-willow[5].

Table VIII

OESTROGEN CONTENT OF URINES

	Per litre [M.U.]	Per day [M.U.]
Man	160	240
Sexually mature woman	200	300
Pregnant woman	10,000	20,000
Mare	200	2,000
Pregnant mare	100,000	1,000,000

Isolation

Pregnancy urine of women or of mares is the usual source; the hormones are present partly in the free state and partly as non-extractable glycuronides, from which they are liberated by hydrolysis with hydrochloric acid. The hormones are extracted with suitable solvents, e.g. *n*-butanol, freed from acidic material, and purified by partition between various solvents. Alternatively, the

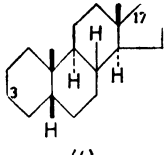
ketonic hormones, after extraction, may be separated by Girard's reagents which afford water-soluble derivatives. Further purification is achieved by high vacuum distillation, chromatography, and crystallization. Molecular compounds such as that of oestrone with quinoline, or of oestradiol-17β with urea can be utilized for final purification.

Colorimetric Determination

The oestrogens give a number of colour reactions that are useful for quantitative estimation. In the *Kober test*, oestradiol, oestrone, or oestriol give a pink colour when heated with phenolsulphonic acid and sulphuric acid followed by addition of water; this reaction has been used to determine urinary oestrogens. The test is more sensitive using guiacolsulphonic acid, when oestrone and oestradiol-17β are positive, but oestriol is essentially negative. In the *diazo-coupling test*, the oestrogens as phenols develop orange or red colours by coupling with diazotized *p*-nitroaniline, sulphanilic acid, and other aromatic amino-compounds. In the *David test* a blue colour is given with sulphuric and arsenic acids, whilst in the *Bachmann test*, a stable violet-pink colour is produced with sodium toluene-*p*-sulphonate and phosphoric acid; these tests are specific for oestriol. In the *benzoyl chloride test*, oestrone and oestradiol-17β by treatment in chloroform with benzoyl chloride and a solution of zinc chloride in acetic acid, form complexes which absorb at 502 mμ, but with oestriol the test is negative. The *Zimmermann test* [*see* p. 79] can be used for determination of oestrone, whilst the *Girard test*, whereby the Girard derivative gives an insoluble coloured complex with potassium mercuric iodide, can be used for its gravimetric estimation.

Structure

The natural oestrogenic hormones may be regarded as derivatives of the hypothetical saturated hydrocarbon oestrane (4). Ring *A*, or rings *A* and *B* are aromatic, so that the $C_{(3)}$-hydroxyl group is phenolic and there is strong absorption in the ultra-violet at 260–280 mμ. In ring *D* at $C_{(17)}$, there is either a carbonyl group or a hydroxyl group. Their physical and physiological properties are collected in *Table IX*.



(4)

Table IX

PROPERTIES OF OESTROGENS

Compound	Structure	Formula	m.p.°	$[\alpha]_D°$	Physiol. activity γ per R.U.
(+)-Oestrone (6)	3-Hydroxy-17-oxooestra-1 : 3 : 5(10)-triene	$C_{18}H_{22}O_2$	259	+170	0·8
Oestradiol-17β (1)	3 : 17β-Dihydroxyoestra-1 : 3 : 5(10)-triene	$C_{18}H_{24}O_2$	178	+ 81	0·1
Oestradiol-17α (39)	3 : 17α-Dihydroxyoestra-1 : 3 : 5(10)-triene	$C_{18}H_{24}O_2$	222	+ 54	4
Oestriol (5)	3 : 16α : 17β-Trihydroxyoestra-1 : 3 : 5(10)-triene	$C_{18}H_{24}O_3$	280	+ 61	10
Equilin (48)	3-Hydroxy-17-oxooestra-1 : 3 : 5(10) : 7-tetraene	$C_{18}H_{20}O_2$	240	+308	1–1·5
(+)-Equilenin (47a)	3-Hydroxy-17-oxooestra-1 : 3 : 5(10) : 6 : 8-pentaene	$C_{18}H_{18}O_2$	259	+ 87	15–20
(−)-Equilenin (47b)			259	− 87	400
(—)-14-*iso*Equilenin (27a)	3-Hydroxy-17-oxo-14-*iso*oestra-1 : 3 : 5(10) : 6 : 8-pentaene	$C_{18}H_{18}O_2$	258	+147	>500
(−)-14-*iso*Equilenin (27b)			258	−147	>500
Dihydroequilenin-17β	3 : 17β-Dihydroxyoestra-1 : 3 : 5(10) : 6 : 8-pentaene	$C_{18}H_{20}O_2$	248	− 60	12
Dihydroequilenin-17α	3 : 17α-Dihydroxyoestra-1 : 3 : 5(10) : 6 : 8-pentaene	$C_{18}H_{20}O_2$	222	− 5	25–30
Dihydroequilin-17β (28)	3 : 17β-Dihydroxyoestra-1 : 3 : 5(10) : 7-tetraene	$C_{18}H_{22}O_2$	175	−207	—
Dihydroequilin-17α	3 : 17α-Dihydroxyoestra-1 : 3 : 5(10) : 7-tetraene	$C_{18}H_{22}O_2$	206	+213	40
17α-Ethinyloestradiol-17β (46)	17α-Ethinyl-3 : 17β-dihydroxyoestra-1 : 3 : 5(10)-triene	$C_{20}H_{24}O_2$	146	+ 1	0·1

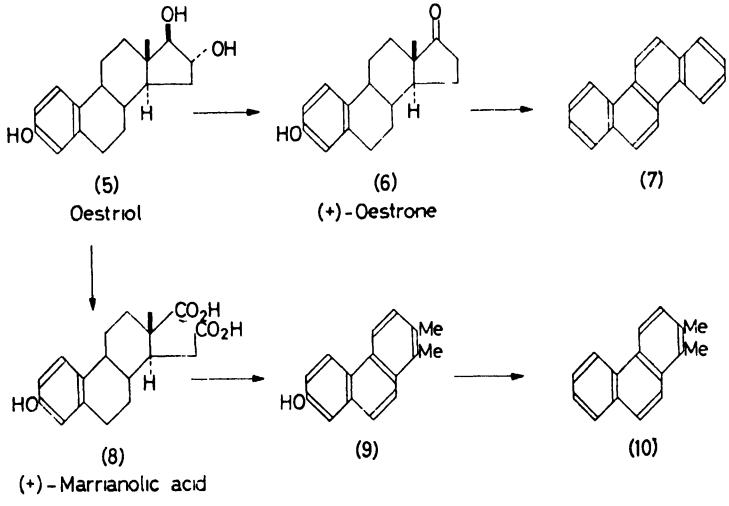
Oestrone, Oestriol, and Oestradiols

OESTRONE (6)

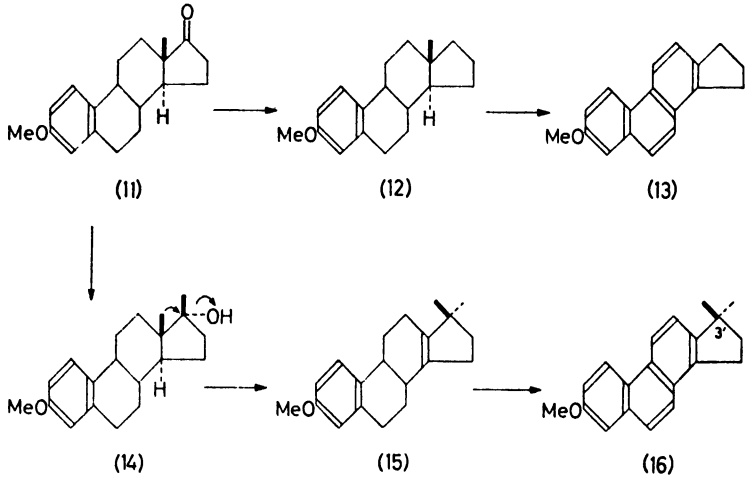
Oestrone, the first oestrogenic hormone to be isolated, was reported simultaneously by E. A. DOISY *et al.*[6], and by A. BUTENANDT[7], whilst a year later oestriol (5) was isolated by G. F. MARRIAN[8]; in each case the source was human pregnancy urine. X-ray and surface film measurements suggested a steroid-ring structure with the chemically active groups at opposite ends of the molecule[9,10]. Butenandt and Marrian each showed the hydroxyl group to be phenolic; Butenandt obtained an oxime, and by catalytic hydrogenation and molecular refraction showed the presence of only three double bonds, thereby indicating a tetracyclic system.

In 1932, Butenandt and Marrian independently suggested the correct formula for oestrone. It had been found that oestriol (5) was converted by dehydration to oestrone (6)[11,12], and although this, by distillation with zinc, underwent rearrangement to chrysene (7), a successful degradation was achieved by potash-fusion of oestriol to (+)-*trans*-marrianolic acid (8)[13], which gives an anhydride and not a ketone by distillation with acetic anhydride, and is dehydrogenated by selenium to 1 : 2-dimethylphenanthr-7-ol (9), reduced by distillation with zinc to 1 : 2-dimethylphenanthrene (10)[14]; the structure (9) was subsequently confirmed by synthesis[15].

Proof of the location of the phenolic hydroxyl group at $C_{(3)}$ was obtained by reduction of oestrone methyl ether (11) to the deoxo-ether (12), and dehydrogenation of this with selenium to 7-methoxy-1 : 2-*cyclo*pentenophenanthrene (13), the structure of which was established by synthesis[16].



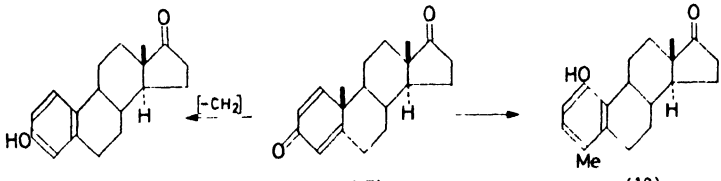
The position of the carbonyl group and of the angular methyl group at $C_{(13)}$ was established by marking the former with a methyl group by reaction with magnesium iodide, dehydration of the resulting carbinol (14) with pinacolic rearrangement to the olefin (15), which by reduction and subsequent dehydrogenation with selenium gave 7-methoxy-3′ : 3′-dimethyl-1 : 2-*cyclo*pentenophenanthrene (16)[17].



Oestrone, by fusion with potassium hydroxide at 275°, gives (+)-*trans*-doisynolic acid [*see* p. 124]; dehydrogenation with palladium at 270° gives (+)-14-*iso*equilenin with inversion at $C_{(14)}$ [*see* p. 114], whilst oxidation with hydrogen peroxide or performic acid leads to lactones by fission of ring *D* [*see* p. 126]. Reduction yields the 17-epimeric oestradiols [*see* p. 115], but hydrogenation in an acid medium leads to reduction of the aromatic nucleus[18].

Partial Synthesis of Oestrone

The partial synthesis of oestrone by reduction of dehydroneoergosterol [p. 54] with sodium-amyl alcohol and oxidative removal of the side chain, and by similar reduction of ring *B* of equilenin has been claimed[19,20], but not confirmed. No phenolic product is produced from dehydroneoergosterol by reduction with sodium-amyl alcohol[21], whilst only traces of phenolic material are obtained by similar reduction of equilenin[22,22a]. Later, (+)-oestrone was obtained from dehydro*epi*androsterone, and so effectively from cholesterol, by aromatization of androsta-1 : 4-diene-3 : 17-dione (17)[23,24], together with a rearrangement product, m.p. 253°, $[\alpha]_D$ + 348° [at one time regarded as 1-methyloestrone], which can be readily obtained from androsta-1 : 4-diene-3 : 17-dione (17) by treatment

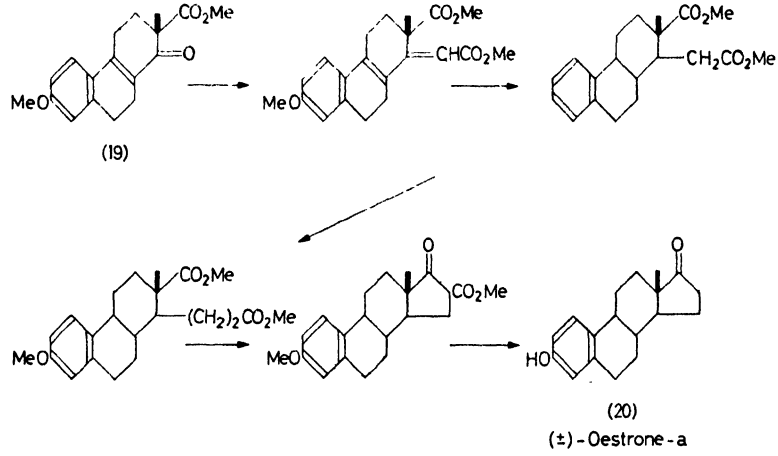


(6)
(+)-Oestrone

(17)

(18)
1-Hydroxy-4-methyl-3-deoxyoestrone

with acetic anhydride–sulphuric acid at 25°. This product, originally termed 'x-methyl-hetero-oestrone', has no oestrogenic activity[25], and is 1-hydroxy-4-methyl-3-deoxyoestrone (18)[26,27]. The true 1-methyloestrone, m.p. 252°, $[\alpha]_D$ + 257°, has been prepared from androsta-1 : 4 : 6-triene-3 : 17-dione[28], and its structure proved by dehydrogenation to 1-ethyl-2 : 5-dimethyl-7-methoxyphenanthrene[29].



(19)

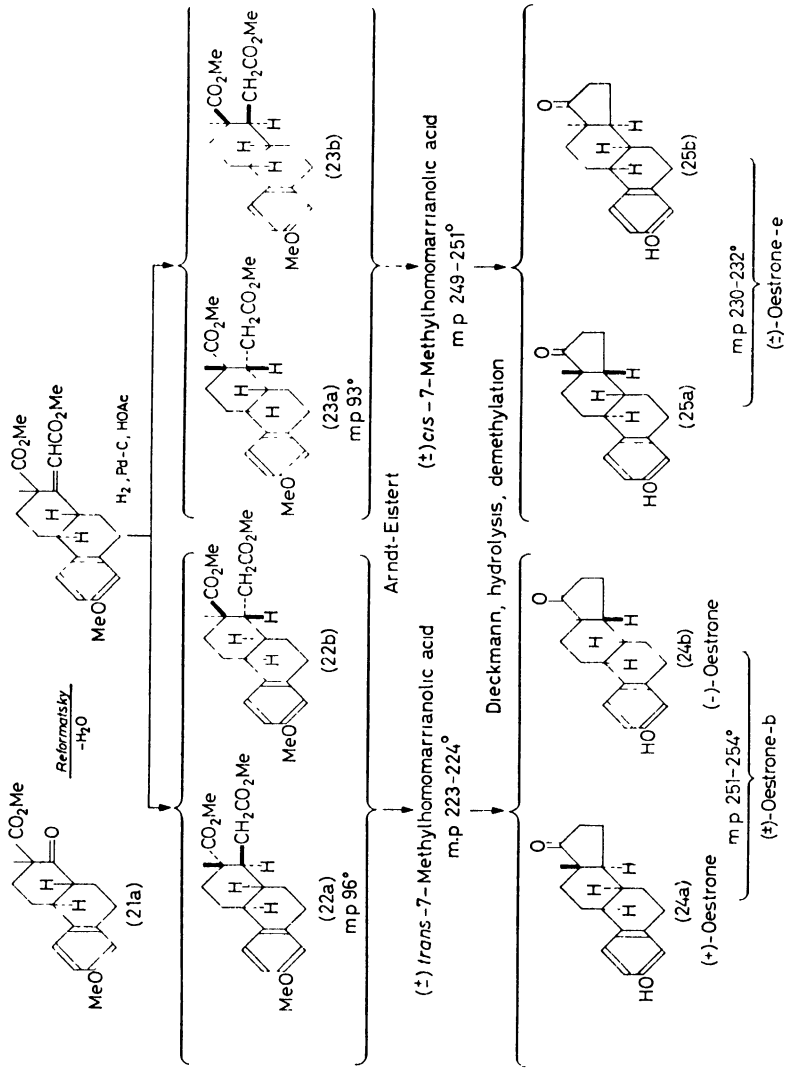
(20)
(±)-Oestrone-a

Total Synthesis of Oestrone

The first synthetic substance possessing the oestrone skeleton was oestrone-a[30]; the unsaturated keto-ester (19) by successive Reformatsky reaction with methyl bromoacetate, dehydration of the resulting carbinol, and hydrogenation gave a mixture of stereoisomerides, which by the Arndt–Eistert reaction, cyclization, hydrolysis, and demethylation gave a product from which (±)-oestrone-a (20) was isolated.

The total synthesis of ANNER and MIESCHER[31] [*see* scheme, p. 112] starts from the saturated keto-ester (21)[30,32]. Three of the four possible racemic modifications have been obtained crystalline; one ester [(21A), m.p. 133°] by the Reformatsky reaction with ethyl

bromoacetate, dehydration of the resulting hydroxy-ester, and hydrogenation affords two (±)-dimethyl 7-methylmarrianolates [(22a) plus (22b)] and [(23a) plus (23b)]. The higher melting



Total synthesis of oestrone (Anner and Miescher)

ester gives no m.p. depression with the methyl ether dimethyl ester of 'natural' (+)-*trans*-marrianolic acid (8) [*see* p. 109]; by hydrolysis of the primary carbomethoxy group, the Arndt–Eistert reaction, and

hydrolysis, it is converted into (±)-7-methylhomomarrianolic acid, which is cyclized by the Dieckmann procedure to give after hydrolysis and demethylation (±)-oestrone-b [(24a) plus (24b)] [*compare* the total synthesis of equilenin, p. 120]. Resolution via the (−)-menthoxyacetates furnished (+)-oestrone-b (24a), chemically, physically, and physiologically identical with the natural hormone. The lower melting (±)-ester [(23a) plus (23b)] is similarly transformed into (±)-oestrone-e [(25a) plus (25b)]. By analogous treatment of the racemic keto-esters [(21B), m.p. 127–128°] and [(21C), m.p. 87–89°], (±)-oestrone-a, which appears to be identical with the oestrone-a of Bachmann [*see* (20)], (±)-oestrone-d, (±)-oestrone-e, and (±)-oestrone-f are obtained[33,34]. A new synthesis by Johnson starting from *m*-methoxyphenylacetylene and decalin-1 : 5-dione leads to (±)-oestrone-b, (±)-oestrone-d, and two new stereo-isomerides, (±)-oestrone-g [(±)-lumioestrone] and (±)-oestrone-h[35]. Another new synthesis by Johnson involves the preparation of 1-keto-8-methoxydodecahydrochrysene in two stereoisomeric forms converted by fission of ring *D* and closure with ring-decrease into (±)-oestrone-b and (±)-oestrone-g and into (±)-oestrone-c and (±)-oestrone-h, respectively[36]. The eight possible stereoisomeric racemic forms of oestrone are all known, and their properties are given in *Table X*.

Table X

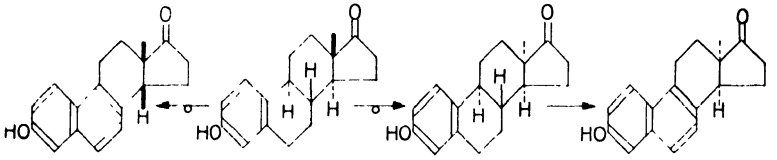
STEREOISOMERIC RACEMIC OESTRONES

	(±)-Oestrone m.p.°	Methyl ether m.p.°	Benzoate m.p.°	Oestrogenic activity γ per R.U. [subcut.]
a	214–216	114–116	175–176	1,000
b	251–254	143–144	184–186	2.0
c	181	115–116	149–151	—
d	184–186	oil	150–152	1,000
e	230–232	162–164	134–136	7–10
f	188–190	oil	161–163	1,000
g	238–240	109–110	158	—
h	197–198	67–68	160	—

Other Isomerides of Oestrone

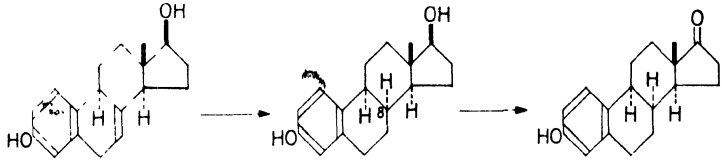
Irradiation of (+)-oestrone with ultra-violet light of wave-length 313 mμ gives the physiologically inactive (−)-lumioestrone, which is 13-*iso*oestrone (26) and by dehydrogenation with palladium at 270° affords (−)-14-*iso*equilenin (27b) with retention of configuration at

$C_{(14)}$[37]. (+)-Oestrone, by dehydrogenation with palladium, however, undergoes inversion at $C_{(14)}$ to give (+)-14-*iso*equilenin (27a).



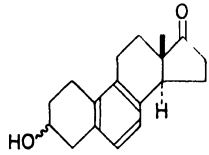
(27a) (+)-14-*iso*Equilenin | (6) (+)-Oestrone | (26) (-)-Lumioestrone | (27b) (-)-14-*iso*Equilenin

Dihydrocquilin-17β [*see* p. 120] (28) is hydrogenated with nickel to give 8-*iso*oestradiol-17β (29), oxidized to 8-*iso*oestrone (30), which has about one-third of the activity in rats of natural (+)-oestrone[38].



(28) Dihydroequilin | (29) 8-*iso*Oestradiol-17β | (30) 8-*iso*Oestrone

The isomeric 3-hydroxyoestra-5(10) : 6 : 8-triene-17-one (31), has been isolated from the non-phenolic fraction of equine pregnancy urine[39,40]. The same structure is claimed for 'folliculosterone', a



(31)

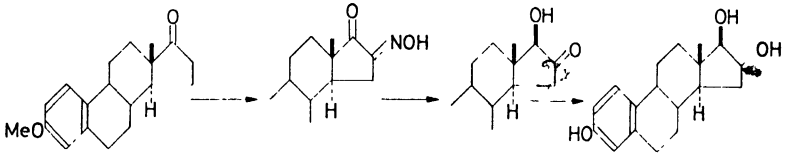
reputed substance obtained by an incompletely described oxidation of neoergosterol[41,42].

OESTRIOL (5)

Oestriol was isolated from human pregnancy urine by MARRIAN[43]. Although (+)-oestrone and oestriol differ only slightly in acid strength, oestriol alone is extracted from ether with 0·1 N-NaOH, oestrone requiring N-NaOH. Oestriol is less potent than (+)-oestrone by subcutaneous injection, but more active when given orally.

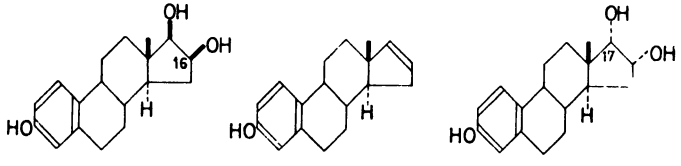
Oestriol forms a triacetate, and the secondary hydroxyl groups are at $C_{(16)}$ and $C_{(17)}$ since dehydration yields (+)-oestrone (6); fusion with potassium hydroxide gives (+)-*trans*-marrianolic acid (8),

reconverted to oestriol by treatment as the methyl ether dimethyl ester with sodium to afford the acyloin (33), and reduction of this with lithium aluminium hydride[44]. Oestriol fails to form an acetonide[45], and the 16α : 17β-configuration is deduced from partial syntheses. (+)-Oestrone (6) as methyl ether by treatment with amyl nitrite–potassium *tert.*-butoxide gives the 16-oximino derivative (32), reduced by zinc-acetic acid to the acyloin (33); further reduction of this with sodium-*iso*propanol, or aluminium amalgam, gives, after demethylation, oestriol (5)[46,47]. Another partial synthesis of oestriol has been reported[48].



(6) (+)-Oestrone methyl ether — (32) — (33) — (5) Oestriol

Hydrogenation of the α-ketol (33) with platinum in an alkaline medium[47,49], or reduction with lithium aluminium hydride[44] gives 16-*epi*oestriol [$\equiv$ '*iso*oestriol-A'] (34), which forms an acetonide. 17-*epi*Oestriol (36) is obtained by hydroxylation with osmium tetroxide of the 16-olefin (35), prepared by pyrolysis of oestradiol-17β 3 : 17β-dibenzoate[50]. Both these epimerides are less active than oestriol in rats; 16-*epi*oestriol (34) has been isolated from human pregnancy urine[50a].



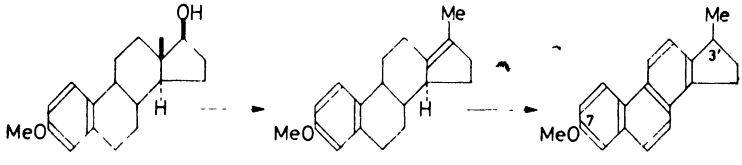
(34) 16-*epi*Oestriol — (35) — (36) 17-*epi*Oestriol

'α'- *and* 'β'-OESTRADIOL

These trivial names are not related to configuration; the natural ovarian hormone 'α'-oestradiol is oestradiol-17β (1), whilst the 17-epimeride 'β'-oestradiol is oestradiol-17α (39). Oestradiol-17β [12 mg] was isolated from sows' ovaries [4 tons] by DOISY, MACCORQUODALE, and THAYER[51]. It had previously been prepared from (+)-oestrone and used therapeutically and it has also been obtained from mares' pregnancy urine, human pregnancy urine, from stallions' urine, and from horse testes. Oestradiol-17α has

also been isolated from mares' pregnancy urine. The mixed oestradiols may be separated as the dipropionates[52].

Oestradiol-17β (1) is the almost exclusive product of hydrogenation of (+)-oestrone in a neutral or alkaline medium[53,54,55], or of reduction with sodium-ethanol[56], or lithium aluminium hydride[57], or of biological reduction[58]. It can be prepared from the α-ketol (33) by elimination of the 16-carbonyl group by the thiol-Raney nickel procedure[44]. Oestradiol-17β [and also its 3-benzoate] forms an insoluble digitonide[55]; it gives an insoluble complex with urea in methanol which is cleaved by warm water. By fusion with potassium hydroxide, oestriol-17β affords (+)-*trans*-doisynolic acid (85) [*see* p. 124], and as the 3-methyl ether is dehydrated with pinacolic change to give the 13(17)-olefin (37), dehydrogenated by selenium to 7-methoxy-3′-methyl-1 : 2-*cyclo*pentenophenanthrene (38)[59].



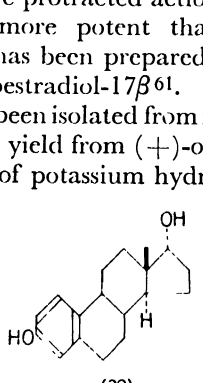
(1)
Oestradiol-17β-3-methyl ether

(37)

(38)

Oestradiol-17β is used therapeutically by injection as the 3-benzoate, and has a more protracted action than the free hormone, which is 8–10 times more potent than (+)-oestrone. Radio oestradiol-17β-[16-^{14}C] has been prepared[60]. Δ^6-Oestradiol-17β is about half as potent as oestradiol-17β[61].

Oestradiol-17α (39) has been isolated from mares' pregnancy urine[62]; it is obtained in 10–20% yield from (+)-oestrone by hydrogenation with nickel in presence of potassium hydroxide[54,63], and by *in vivo*

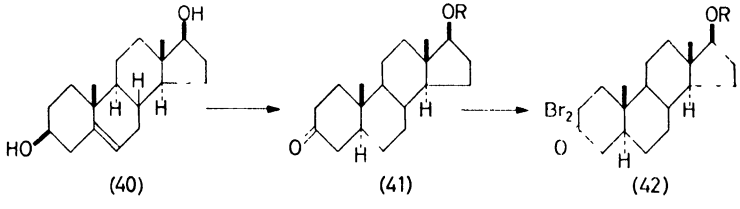


(39)
Oestradiol-17α

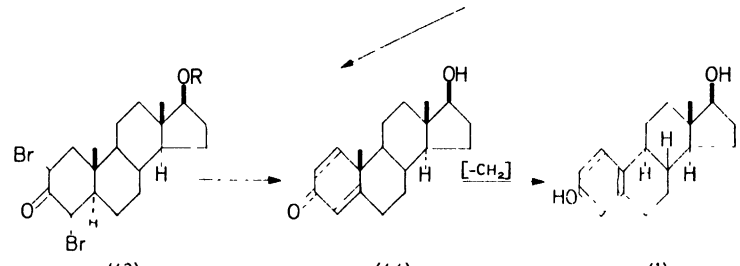
reduction in rabbits. Oestradiol-17α [in which the 17α-OH may be regarded as axial] is more readily dehydrated than oestradiol-17β [in which the 17β-OH may be regarded as equatorial], a difference which can be used for recognition[64,65,66]. Oestradiol-17α is some forty times less potent than oestradiol-17β.

Partial Synthesis

A partial synthesis of oestradiol-17β was reported in 1940 by INHOFFEN[67]; a rearrangement product was also obtained. WILDS and DJERASSI[68], repeated the work and defined the various stages. Androst-5-ene-3β : 17β-diol (40) in four steps afforded dihydrotestosterone benzoate (41) [*see* p. 142], which by dibromination gave (43); dehydrobromination and hydrolysis gave the dienone (44), pyrolysed at 280° to yield 10% of oestradiol-17β (1).



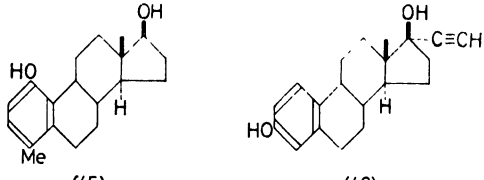
(40) (41) (42)



(43) (44) (i)

[R=·COPh or ·COC_6H_{11}] Oestradiol-17β

The rearrangement product, 1-hydroxy-4-methyl-3-deoxyoestradiol-17β (45), m.p. 232°, $[\alpha]_D$ + 180°, is readily obtained from 3-oxoandrosta-1 : 4-dien-17β-ol (44) by treatment with acetic anhydride–sulphuric acid, or by reduction of 1-hydroxy-4-methyl-3-deoxyoestrone (18) [p. 111] with lithium aluminium hydride[26,27,69,70]; it has no oestrogenic activity. 1-Methyloestradiol-17β, m.p. 116°, $[\alpha]_D$ + 146°, has been prepared from 3-oxoandrosta-1 : 4 : 6-triene-17β-yl acetate; its dipropionate is four times as potent as (+)-oestrone[70].



(45) 1-Hydroxy-4-methyl-3-desoxyoestradiol-17β

(46) 17α-Ethinyloestradiol-17β

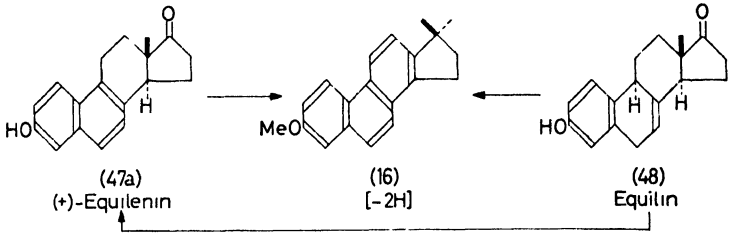
17α-Ethinyloestradiol-17β (46) is obtained almost exclusively by treatment of (+)-oestrone with potassium acetylide in liquid ammonia[71]. In rats it is as active as oestradiol-17β by subcutaneous injection and considerably more active orally; in human subjects the compound is also extremely active by oral administration.

Equilenin, Equilin, and Dihydroequilenins

Very large quantities of mares' pregnancy urine processed by GIRARD[72] using his reagent T furnished the equine oestrogens (+)-equilenin and equilin possessing activities of 1/25 and 1/120, respectively, of that of (+)-oestrone; the isolation of a third substance 'hippulin' has not been confirmed. The epimeric 17-dihydroequilenins have been obtained from mares' pregnancy urine, whilst (+)-3-deoxyequilenin has also been isolated[73]. These substances have not been detected in human pregnancy urine.

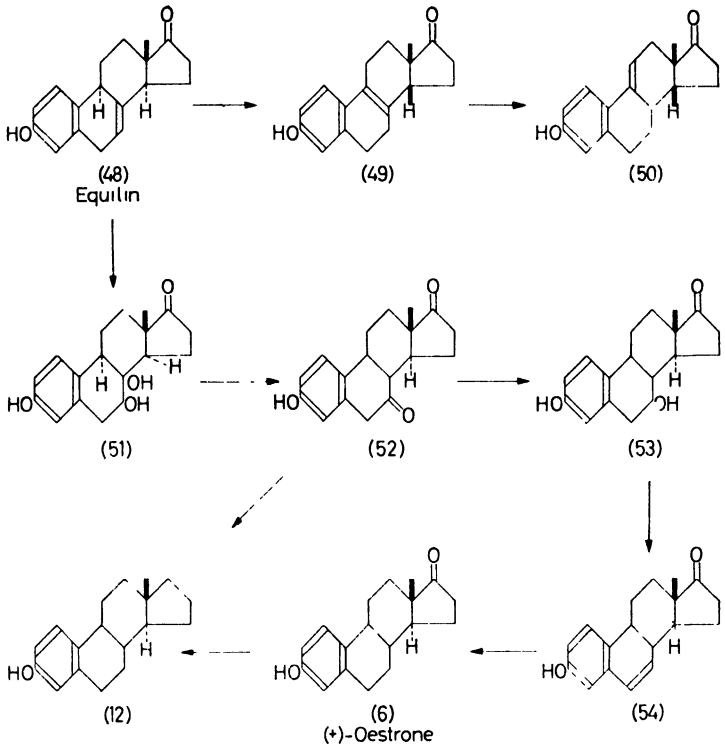
(+)-EQUILENIN (47a) *and* EQUILIN (48)

These are bisdehydro- and monodehydro-derivatives of (+)-oestrone (6). (+)-Equilenin is readily recognized by formation of an amorphous red compound on heating in air; it gives a stable picrate and shows the ultra-violet absorption spectrum of a naphthalene derivative. Both (+)-equilenin and equilin have been degraded by way of the 3-methyl ether 17-methyl-carbinols to 7-methoxy-3′ : 3′-dimethyl*cyclo*pentenophenanthrene (16), which establishes the location of the phenolic hydroxyl, angular methyl, and carbonyl groups[74]. (+)-Equilenin by oxidation with potassium nitrosodisulphonate yields a red 3 : 4-quinone[75]; oxidation with hypoiodite [*see* p. 124] or with hydrogen peroxide or performic acid [*see* p. 126] leads to fission of ring *D*. (+)-Equilenin acetate by oxidation with chromium trioxide gives the 11-oxo-derivative[76] and 14ξ-hydroxy-derivative, dehydrated to Δ^{14}-equilenin acetate (72) [*see* p. 122][77].



Equilin [= Δ^{7}-oestrone] absorbs 1 mol. of bromine, and by dehydrogenation with palladium-ethanol at 80° gives (+)-equilenin[78]. It is isomerized by hydrogen chloride in hot acetic

acid to Δ^{8}-14-*iso*oestrone (49) and $\Delta^{9(11)}$-14-*iso*oestrone (50), also isolated by partition chromatography from equine pregnancy urine[79].



Equilin by hydroxylation with osmium tetroxide gives the glycol (51)[80], which gives only a 3 : 7-diacetate, and by distillation in a high vacuum yields 7-oxo-oestrone (52); this as the Δ^{6}-enol acetate by hydrogenation with palladium gives 7-hydroxyoestrone (53), converted by successive treatment with phosphorus pentachloride and sodium iodide–pyridine to Δ^{6}-oestrone (54), which has one-third the activity of (+)-oestrone in rats, and is hydrogenated with palladium to (+)-oestrone (6). Both (+)-oestrone and 7-oxo-oestrone by Wolff-Kishner reduction give 17-deoxo-oestrone (12)[83]. These transformations show that (+)-oestrone, (+)-equilenin, and equilin have the same configuration at both $C_{(13)}$ and $C_{(14)}$.

'*α*'- *and* '*β*'-Dihydroequilenin

(+)-Equilenin (47a) by reduction with aluminium *iso*propoxide–*iso*-propanol or hydrogenation with platinum-acetic acid gives 17-dihydroequilenin-17*β* ['*α*'-dihydroequilenin], accompanied by

17-dihydroequilenin-17*a* ['*β*'-dihydroequilenin]; hydrogenation in ethanol–ether gives only the 17*β*-epimeride[84, 85, 86, 87]. More vigorous catalytic hydrogenation leads to reduction of ring *A* and to hydrogenolysis of the 3-hydroxyl group. 1-Methyl-17-dihydroequilenin-17*β* has been prepared[70].

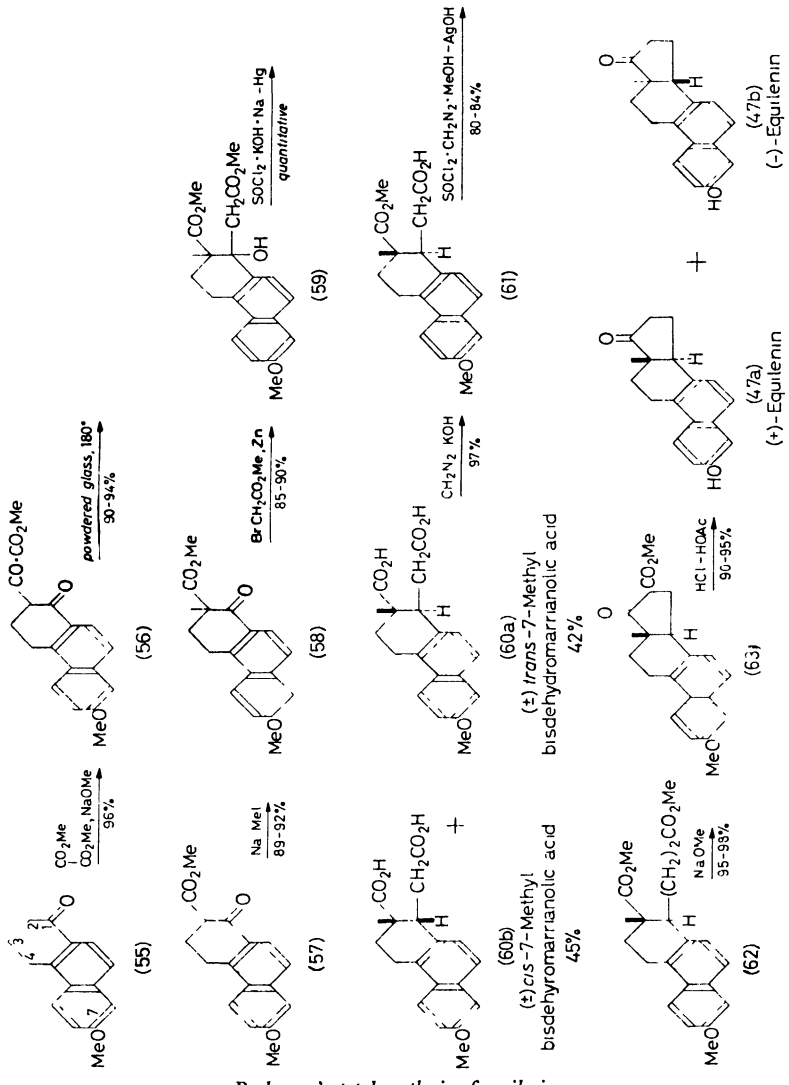
DIHYDROEQUILINS

Equilin by reduction with lithium aluminium hydride gives dihydroequilin-17*β* [$= \Delta^7$-oestradiol-17*β*] (28); use of sodium-ethanol or aluminium *iso*propoxide–*iso*propanol gives a mixture of this with dihydroequilin-17*a* separated by partition chromatography[79].

Total Synthesis of Equilenin

The first total synthesis of a natural oestrogenic hormone was accomplished in 1939–1940 by BACHMANN, COLE, and WILDS[88]. The synthesis starts from 7-methoxy-1-oxo-1 : 2 : 3 : 4-tetrahydrophenanthrene (55), which by condensation with dimethyl oxalate in presence of sodium methoxide in nitrogen gives the glyoxalate (56), which is refractory to elimination of carbon monoxide by pyrolysis[89] but is smoothly converted to (57) by use of powdered soft glass at 180°. The sodium-derivative of the ketonic ester (57) is methylated and the C-methyl ketonic ester (58) condensed with methyl bromoacetate. The hydroxy-ester (59) is converted, through the chloride and the unsaturated ester, by reduction and, finally, hydrolysis, into two stereoisomeric (±)-*cis*- and (±)-*trans*-7-methyl-bisdehydromarrianolic acids [(60a) *trans*: m.p. 213–214°; (60b) *cis*: m.p. 222–225°] [*see* p. 124] in about equal amounts. The *trans*-acid via the dimethyl ester and partial hydrolysis furnished the methyl hydrogen ester (61), converted by the Arndt-Eistert procedure into the dimethyl homo-ester (62), cyclized by heating with sodium methoxide in nitrogen to (±)-16-carbomethoxyequilenin (63). Hydrolysis followed by decarboxylation and demethylation gave (±)-equilenin (47), m.p. 278°, resolved through the (−)-menthoxyacetate to give (+)-equilenin (47a), identical with the natural hormone. (−)-Equilenin (47b), isolated through the (+)-menthoxyacetate, has about 1/13 of the oestrogenic activity of (+)-equilenin. The racemic *cis*-acid (60b) by a similar series of reactions gave (±)-14-*iso*equilenin (27), m.p. 223°, which could not be resolved; the racemic *cis*-acid was therefore resolved and the synthesis carried through on both the (−)-*cis*-acid (91b) and the (+)-*cis*-acid (91a) [p. 121], to give respectively (+)-14-*iso*-equilenin (27a) and (−)-14-*iso*equilenin (27b) [p. 114]. From 10 g of the ketone (55) about 2·5 g of (±)-equilenin and 2·5 g of (±)-14-*iso*equilenin were obtained. Analogous syntheses of related compounds have been recorded by BACHMANN[90].

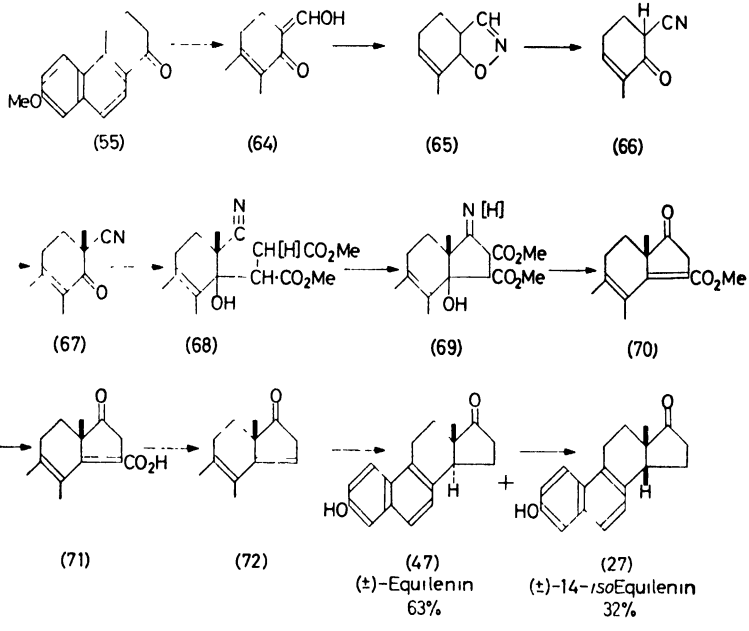
A second total synthesis of equilenin by W. S. JOHNSON[91] is based upon the Thorpe reaction. 7-Methoxy-1-oxo-1 : 2 : 3 : 4-tetrahydrophenanthrene (55) with ethyl formate furnishes the formyl-



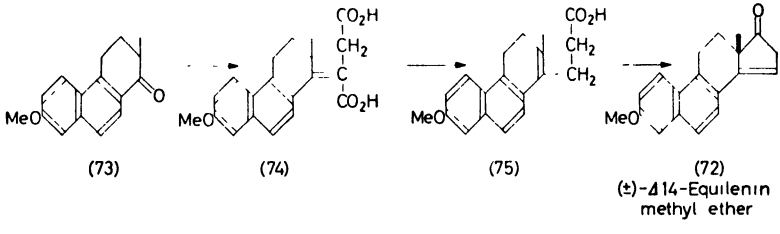
Bachmann's total synthesis of equilenin

derivative (64) converted by hydroxylamine acetate into the isoxazole (65), which with potassium *tert.*-butoxide gives the potassium derivative of the oxo-nitrile (66) methylated to afford (67). Stobbe condensation of (67) with dimethyl succinate gave (68)

which undergoes a Thorpe reaction to give the imino-ester (69), converted by dehydration, hydrolysis, and decarboxylation into the unsaturated oxo-ester (70). Further hydrolysis at $C_{(15)}$ to the carboxylic acid (71), and decarboxylation with baryta yielded Δ^{14}-equilenin methyl ether (72); pyrolytic decarboxylation gave on the contrary Δ^{15}-14-*iso*equilenin methyl ether. Hydrogenation of (72) gave a readily separable mixture of (±)-equilenin methyl ether [as (47)] and (±)-14-*iso*-equilenin methyl ether [as (27)]; hydrogenation of the Δ^{15}-14-*iso*-isomeride gave only (27). Demethylation gave (±)-equilenin, converted into (+)-equilenin by resolution; from 10 g of the ketone (55), about 3·3 g of (±)-equilenin may be obtained in seven operations.

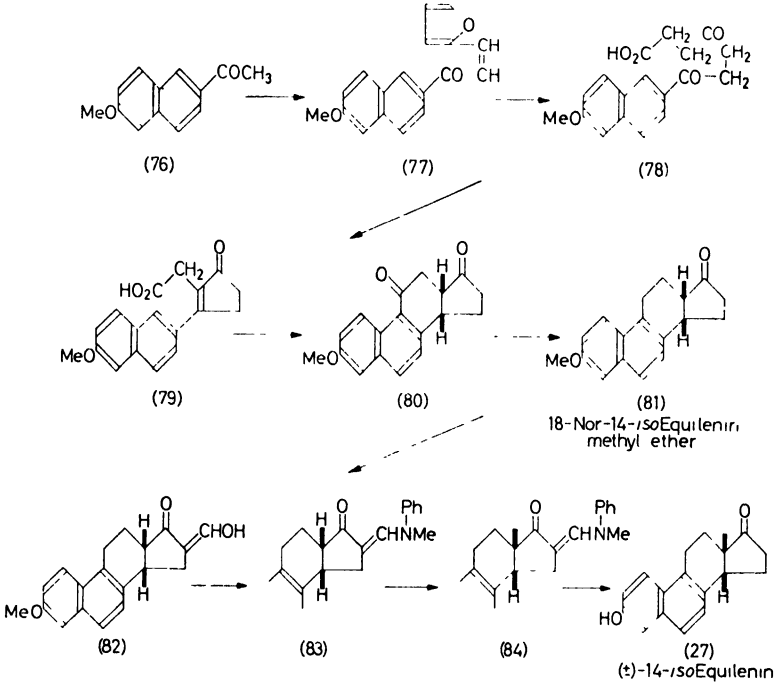


A third total synthesis[92] of (±)-equilenin starts from 2-methyl-7-methoxy-1-oxo-1 : 2 : 3 : 4-tetrahydrophenanthrene (73), m.p. 110°, which by Stobbe condensation with dimethyl succinate yields



[after hydrolysis] two stereoisomeric dibasic acids (74), both decarboxylated to the acid (75), which by cyclization affords (±)-Δ^{14}-equilenin methyl ether (72)[92].

The total synthesis of (±)-14-*iso*equilenin has been achieved by BIRCH, JAEGER, and ROBINSON[93]. 6-Methoxy-2-naphthyl methyl ketone (76) is condensed with furfural and the product (77) hydrolysed to the dioxo-acid (78), readily cyclized to (79); hydrogenation and further cyclization gives the diketone (80). The 11-carbonyl group is inert to ketonic reagents, but because of conjugation with the aromatic system is removed by hydrogenation to give the 18-nor-14-*iso*equilenin methyl ether (81). By blocking the 16-position

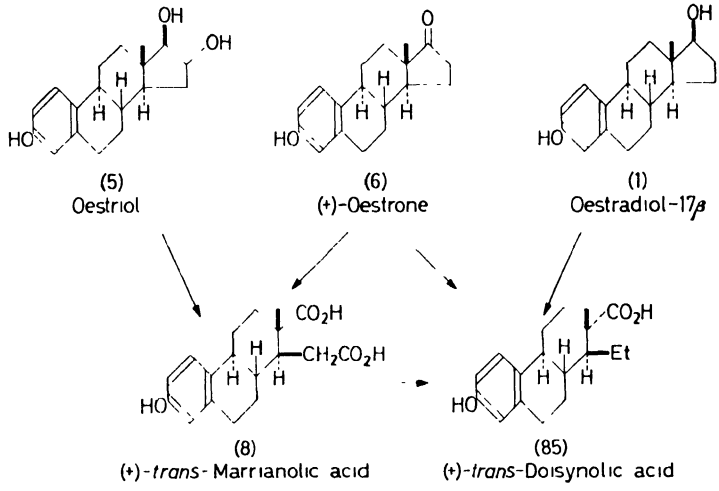


by formylation (82), and condensation to the methylanilinomethylene derivative (83), methylation yields (84), hydrolysed and demethylated to (±)-14-*iso*equilenin [as (27)]. 18-Nor-14-*iso*equilenin (81) has also been synthesized by BACHMANN[94]; other noroestrane derivatives have been prepared by ROBINSON and RYDON[95] and by GOLDBERG and MÜLLER[96].

Oestrogenolic Acids

Oestriol (5) by fusion with potassium hydroxide gives (+)-*trans*-marrianolic acid (8) [*see* p. 109], also obtained by permanganate

oxidation of oestriol 3-methyl ether[97] or via its 16-oximino-derivative[98], but more readily prepared from (+)-oestrone (6) as benzyl ether by oxidation with hypoiodite followed by hydrogenolysis of the benzyl group[99]. (+)-Oestrone or oestradiol-17β (1) by fusion with potash gives (+)-*trans*-doisynolic acid (85), also obtainable by reduction of the primary carboxyl group from (+)-*trans*-marrianolic acid; the structure of (85) follows from catalytic dehydrogenation with palladium-charcoal to 1-ethyl-2-methylphenanthr-7-ol, reduced by zinc-dust distillation to 1-ethyl-2-methylphenanthrene[99,100].

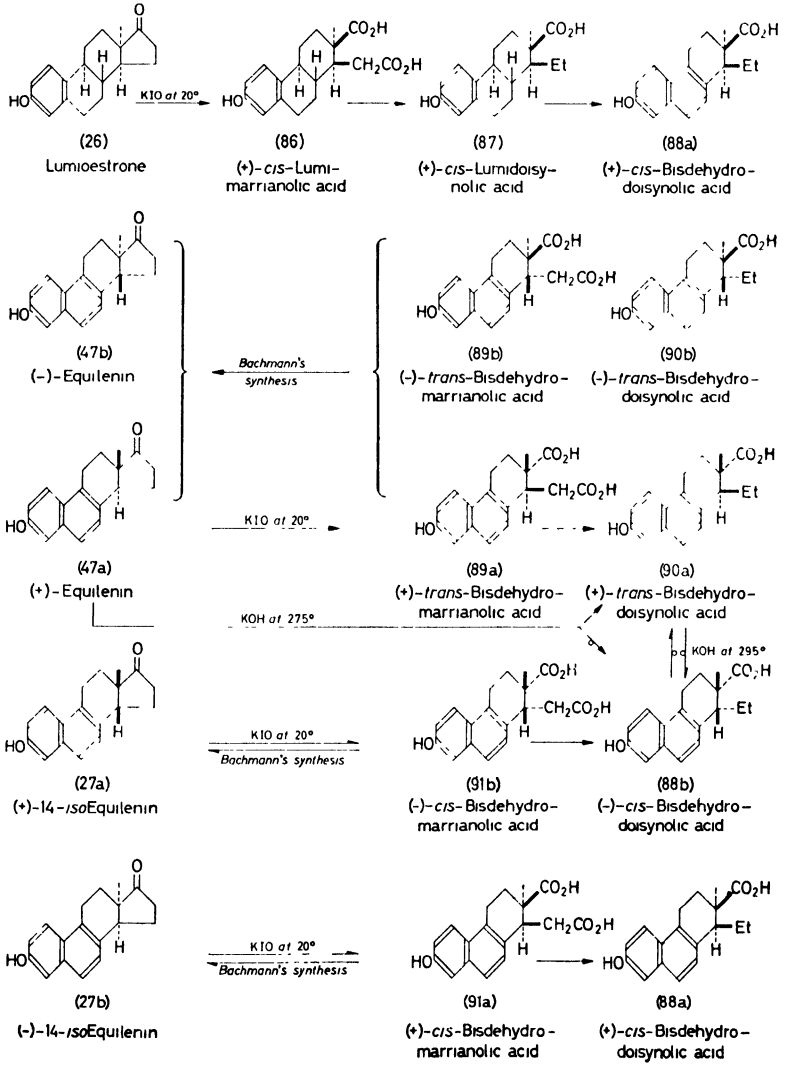


Lumiocstrone [13-*iso*-oestrone] (26) as the methyl or benzyl ether by hypoiodite oxidation similarly affords (+)-*cis*-lumimarrianolic acid (86), converted into (+)-*cis*-lumidoisynolic acid (87), dehydrogenated to (+)-*cis*-bisdehydrodoisynolic acid (88a)[101,102,103].

(+)-Equilenin (47a) by oxidation with hypoiodite yields (+)-*trans*-bisdehydromarrianolic acid (89a), the methyl ether of which, (+)-*trans*-7-methylbisdehydromarrianolic acid, is the (+)-enantiomorph of the racemic acid, m.p. 213°, used by Bachmann for the total synthesis of (±)-equilenin; (+)-equilenin or 17-dihydroequilenin-17β by fusion with potash at 275° give a mixture of (+)-*trans*-bisdehydrodoisynolic acid (90a) and (−)-*cis*-bisdehydrodoisynolic acid (88b), the latter being formed from the former by inversion at $C_{(14)}$[101,102,103]. (+)-14-*iso*Equilenin (27a) by hypoiodite oxidation gives (−)-*cis*-bisdehydromarrianolic acid (91b), the methyl ether of which is identical with the (−)-*cis*-acid used by Bachmann for the total synthesis of (+)-14-*iso*equilenin [*see* p. 114],

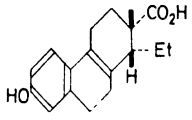
converted into (—)-*cis*-bisdehydrodoisynolic acid (88b); since (±)-14-*iso*equilenin has been converted via (±)-*cis*-bisdehydromarrianolic acid into (±)-*cis*-bisdehydrodoisynolic acid, in effect it is known that (—)-14-*iso*equilenin (27b) gives (+)-*cis*-bisdehydromarrianolic acid (91a) and (+)-*cis*-bisdehydrodoisynolic acid (88a)[103]. [The set of formulae below gives a complete and consistent picture of these transformations[104].]

(+)-*trans*-Bisdehydrodoisynolic acid (90a) is inactive in the oestrus test in rats in doses of 200–300 γ, but (—)-*cis*-bisdehydro-

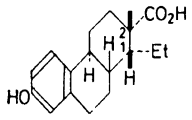


doisynolic acid (88b) and its methyl ether are fully active at 0·05 γ; this acid, the most potent oestrogen known, is inactive in man.

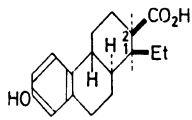
The various marrianolic acids and bisdehydromarrianolic acids are devoid of oestrogenic activity. (+)-*trans*-Doisynolic acid (85) is as active as oestrone. Various doisynolic, monodehydrodoisynolic [as



(92)
(±)-*cis*-Monodehydrodoisynolic acid



(93a)



(93b)

(±)-*cis*-Doisynolic acid-A

(92)], and bisdehydrodoisynolic acids have been synthesized[105, 106, 107]; one of these, (±)-*cis*-doisynolic acid-A, (93a) and (93b), m.p. 182°, is active at a level of 0·05 γ in rats.

The physical and physiological properties of some oestrogenolic acids are collected in *Table XI.*

Table XI

OESTROGENOLIC ACIDS*

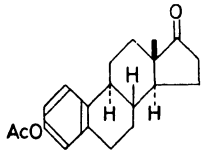
Compound	m.p.°	$[\alpha]_D^{\circ}$	Physiol. activity γ per R.U.	
			γ[subcut.]	γ[oral]
(+)-*cis*-Bisdehydrodoisynolic acid (88a) . .	160	+ 115	10	10
(−)-*cis*-Bisdehydrodoisynolic acid (88b) . .	160	− 116	0·05	0·05
(+)-*trans*-Bisdehydrodoisynolic acid (90a) .	256	+ 27	200-300	—
(+)-*cis*-Bisdehydrodoisynolic acid . . .	204	-	0·1	0·1
(±)-*trans*-Bisdehydrodoisynolic acid .	238	—	100	500
(+)-*cis*-7-Methylbisdehydrodoisynolic acid .	221	+ 100	15	15
(−)-*cis*-7-Methylbisdehydrodoisynolic acid	221	−100	0·05	0·05
(±)-*cis*-7-Methylmonodehydrodoisynolic acid (92)	170	—	- -	0·1
(±)-*trans*-7-Methylmonodehydrodoisynolic acid .	171	—	- -	3
(+)-*trans*-Doisynolic acid (85) . . .	200	+ 102	0·7-1·0	1·5
(+)-*cis*-Lumidoisynolic acid (87) . . .	154	+ 70	250	—
(±)-*cis*-7-Methyldoisynolic acid-A (93) . .	182	—	0·05	0·05

* Originally, stereoisomeric oestrogenolic acids were distinguished by the prefixes *normal* and *iso* because it was thought that, despite contrary rotatory powers, biologically active acids corresponded with biologically active equilenin and biologically inactive acids with biologically inactive 11-isoequilenin. Later, it was shown that this assumption was untenable, the formulae employed were interchanged, and trivial indices α [= *n*] and β [= *iso*] were introduced, since the configurations are now known, the prefixes *cis* [= α] and *trans* [= β] relative to the $C_{(1)}$-ethyl group and the $C_{(2)}$-carboxyl group are employed here.

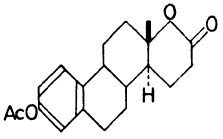
Many compounds structurally related to bisdehydrodoisynolic acids have been prepared[108]; high activity appears to depend on *cis*-orientation of $C_{(1)}$-Et/$C_{(2)}$-CO_2H, but these groups must be α-orientated as in (93a) and not β-orientated as in (93b).

Oestrogenolic Lactones

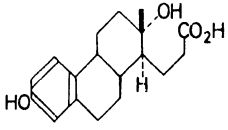
Oxidation of (+)-oestrone acetate (6a) with hydrogen peroxide or peracetic acid gives the lactone (94), hydrolysed by alkali to the sodium salt of a 3-hydroxy-acid, oestrolic acid (95), which is liberated at pH_5; oestrolic acid (95) with excess of acid gives the



(6a)



(94)



(95)
Oestrolic acid

3-hydroxy-lactone [as (94)], and yields a methyl ester which is easily hydrolysed by sodium hydrogen carbonate[109,110]. The same lactone is formed by the action of x-rays on (+)-oestrone in aqueous media[111]. Bisdehydro-oestrolic acids and lactones have been prepared from (+)-equilenin acetate[110], and from (±)-14-*iso*equilenin acetate[112].

Oestrogens and Carcinogenesis

Every oestrogen in certain conditions can produce tumours of organs concerned with reproduction and also at other sites; mammary cancer in mice has been induced by oestrone, oestradiol-17β, and by equilin and equilenin.

The Gestogens

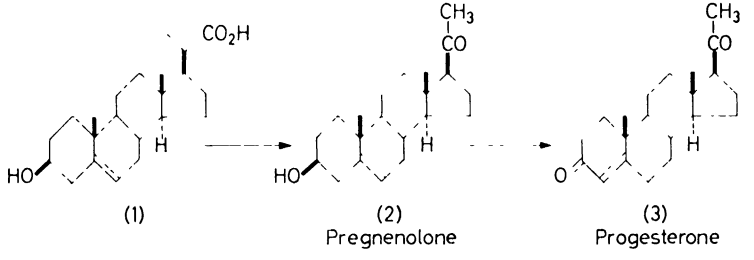
Progesterone

Crude, potent fractions from corpora lutea of pregnant sows were obtained by Allen[113], but the pure hormone was first isolated in 1934 by Butenandt[114] working in Berlin; shortly afterwards Slotta, Rushig, and Fels[115], working at the University of Breslau, Allen and Wintersteiner[116] in the U.S.A., and Hartmann and Wettstein[117] in Switzerland also described pure preparations. Minced ovaries or corpora lutea are extracted with ethanol, and the residue obtained by evaporation dissolved in ether: phospholipids are

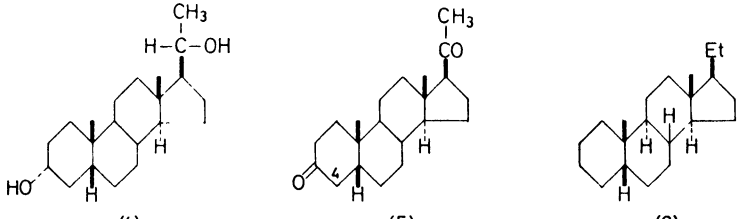
precipitated with acetone, whilst cholesterol and fats are frozen out from methanol and acidic material removed with sodium hydrogen carbonate. On distribution between petrol and 33% ethanol, progesterone goes into the former and oestrogens into the latter; precipitation of the semicarbazone, hydrolysis of this, high vacuum sublimation, chromatography, and crystallization afford progesterone together with 3β-hydroxy*allo*pregnan-20-one. Improved procedures afford 50 mg of progesterone from 100 kg of sows' ovaries = 25 kg of corpora lutea.

Structure and Synthesis

Progesterone (3) is dimorphous forming prisms, m.p. 128°, and needles, m.p. 121°, $[\alpha]_D$ + 192°; it is an αβ-unsaturated ketone, $\lambda_{max.}$ 240 mμ. The correct structure was first suggested by SLOTTA[118], and proved by BUTENANDT[119].



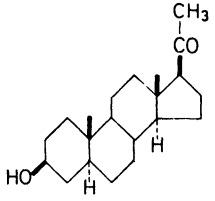
(1) (2) Pregnenolone (3) Progesterone



(4) (5) (6)

Stigmasterol [p. 50] was degraded via 3β-hydroxybisnorchol-5-enic acid (1) to 3β-hydroxypregn-5-en-20-one [pregnenolone] (2), m.p. 190°, $[\alpha]_D$ + 28°; originally this was converted into progesterone (3) by direct oxidation with chromium trioxide or copper oxide[120]; subsequently, the change was accomplished by addition of bromine, oxidation, and debromination[121] and by dehydrogenation with aluminium *iso*propoxide[122] or platinum black[123]. Progesterone was also obtained from pregnane-3α : 20α-diol (4), m.p. 242°, $[\alpha]_D$ + 27°, of pregnancy urine by oxidation to pregnane-3 : 20-dione (5), bromination at $C_{(4)}$, and dehydrobromination with

pyridine; Clemmensen reduction of the diketone (5) furnished pregnane (6)[124]. Similarly, oxidation of *allo*pregnanolone (7), m.p. 194°, $[\alpha]_D$ + 91°, gave *allo*pregnane-3 : 20-dione (8) reduced to



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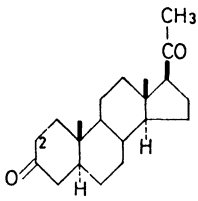

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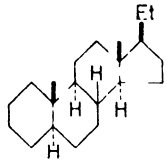
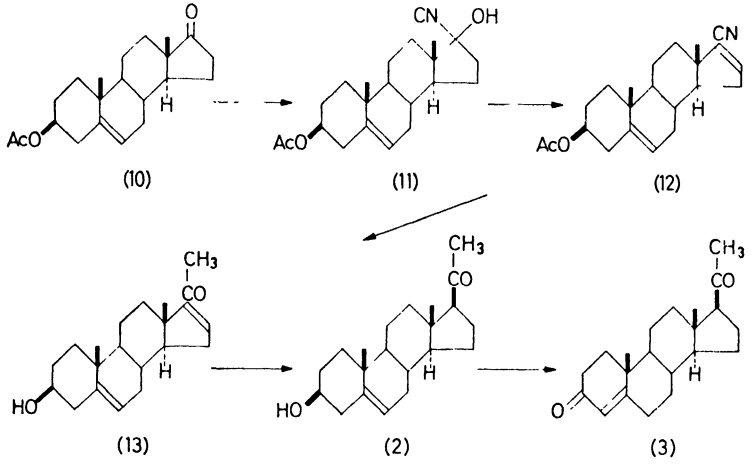


(9)

*allo*pregnane (9)[125]. Progesterone has also been obtained by direct oxidation of cholesterol in 0·3% yield[126], by oxidation of cholest-4-en-3-one[127], and from deoxycorticosterone [= 21-hydroxyprogesterone][128]. A commercial process has been based on the following synthesis by BUTENANDT *et al.*[129]; dehydro*epi*androsterone acetate (10) [*see* p. 140] is converted through the 17-epimeric cyanohydrins (11) to the unsaturated nitrile (12), which with methyl magnesium bromide gives 3β-hydroxypregna-5 : 16-dien-17-one (13), the activated Δ^{16}-linkage being selectively hydrogenated with nickel in alkaline solution to give pregnenolone (2), oxidized to progesterone (3).

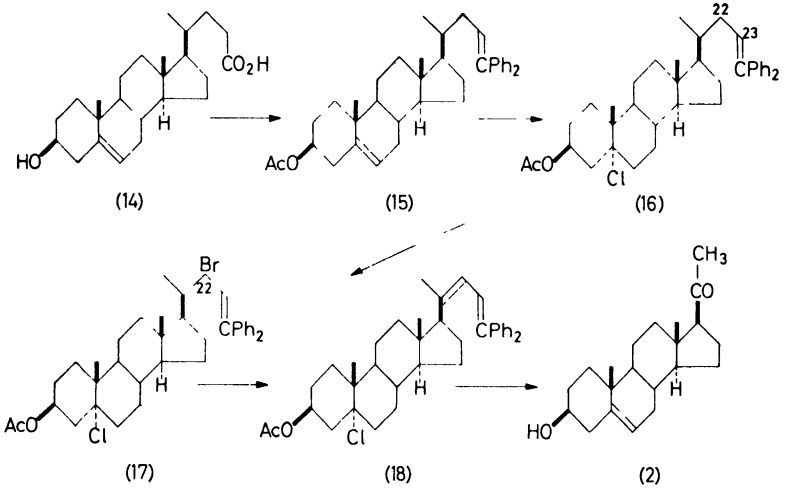


(10) (11) (12)

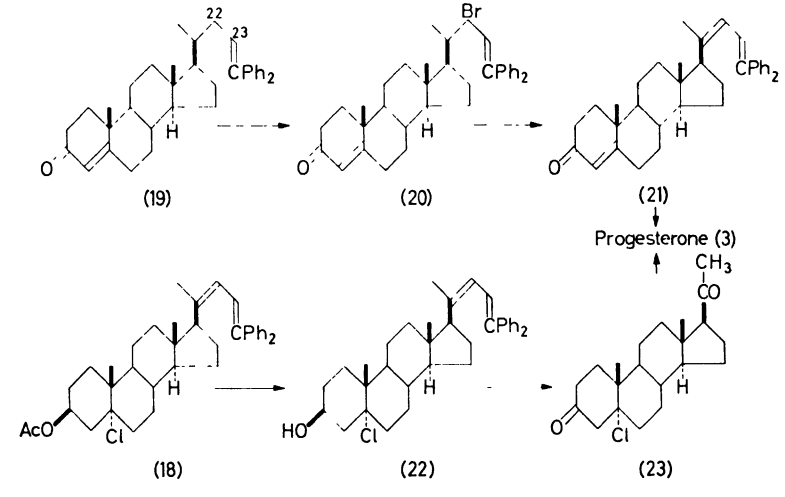
(13) (2) (3)

In 1944 MIESCHER and WETTSTEIN[130] employed their side-chain degradation procedure [p. 26] to convert 3β-hydroxychol-5-enic acid (14), a by-product of the manufacture of dehydro*epi*androsterone from cholesterol, into pregnenolone (2) and thence into

progesterone (3) by three different routes, one of which is shown below:



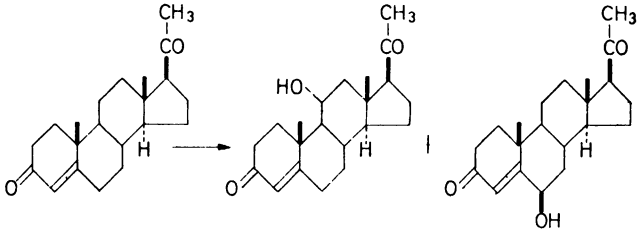
If N-bromosuccinimide is used with irradiation, bromination at $C_{(22)}$ of 24 : 24-diphenylchol-23-enes [cf. (16) → (17)] proceeds so rapidly that 3-ketones and Δ^4-3-ketones can be employed. This observation affords a fourth route to progesterone; Oppenauer oxidation of (15) gives the Δ^4-3-ketone (19), which yields the 22-bromo-compound (20), dehydrobrominated by boiling dimethylaniline to the 20(22) : 23-diene (21), which by oxidation with chromium trioxide at 0° gives progesterone. Alternatively, the acetoxychlorodiene (18) may be hydrolysed with hydrogen chloride



to the hydroxychlorodene (22) and oxidized with chromium trioxide at 0° to the 5α-chloro-3 : 20-diketone (23) [fifth route], or the sequence may be reversed [sixth route]; the chlorodiketone (23) with potassium carbonate gives progesterone[131].

The preparation of progesterone from ergosterol and stigmasterol has been reported[132], and its preparation from sapogenins is described later [p. 291]; the total synthesis has already been given [p. 46]. Radioprogesterone-[4-^{14}C] has been prepared[133].

Progesterone, by fermentation with *Rhizopus* strains, undergoes hydroxylation to give 11α-hydroxyprogesterone (24) and 6β : 11α-dihydroxyprogesterone (25)[134, 135, 136, 137].



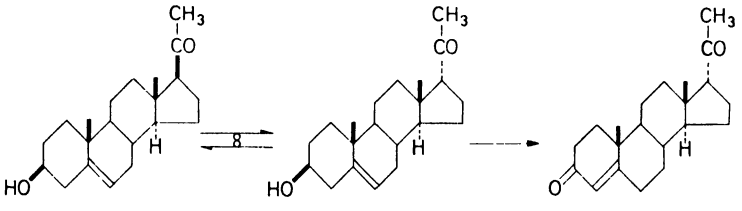
(3) (24) (25)

17α-Hydroxyprogesterone similarly gives 11α : 17α-dihydroxyprogesterone[138, 139] and 6β : 17α-dihydroxyprogesterone[137, 138]; Δ^6-progesterone, pregnane-3 : 20-dione (5), and *allo*pregnane-3 : 20-dione (8) afford the 11α-hydroxy derivatives[138], but with strains of *Gliocladium*, *Penicillium*, and *Aspergillus* microbiological degradation of the side chain to C_{19}-ketones occurs[140]. The production of 11α-hydroxyprogesterone (24) in 95% yield permits an eight-stage synthesis of cortisone [= 11-oxo-17α : 21-dihydroxyprogesterone][141], and the preparation of cortisol [= 11β : 17α : 21-trihydroxyprogesterone][142]. The adreno-cortical hormones are hydroxylated progesterones and numerous analogues including 2α-hydroxyprogesterone[143], 6β-hydroxyprogesterone[144], 11β-hydroxyprogesterone[145, 146, 147], 12α-hydroxyprogesterone[148], 14β-hydroxyprogesterone[149], 16α-hydroxyprogesterone[150], 17α-hydroxyprogesterone [*see* p. 183], 19-hydroxyprogesterone[151, 152], and 21-hydroxyprogesterone [= DOCA; *see* p. 183] have been described. Oxidation of those compounds containing secondary hydroxyl groups affords the related triketones, e.g. 11-ketoprogesterone[145, 146, 153].

Isomerides of Progesterone

Pregnenolone (2) by treatment with hot methanolic potassium hydroxide gives an equilibrium mixture of pregnenolone [(2) : ~70%] and 17-*iso*pregnenolone [(26) : ~ 30%], m.p. 173°, $[\alpha]_D$ — 140°, oxidized by the Oppenauer method to 17-*iso*progesterone (27), m.p.

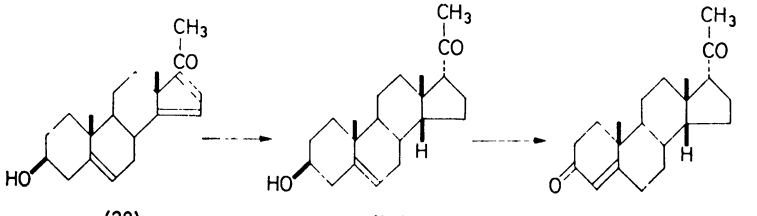
145°, $[\alpha]_D$ 0°, which is isomerized to progesterone by alcoholic hydrogen chloride[154, 155]; similarly, *allo*pregnanolone (7) gives 17-*isoallo*pregnanolone, pregnane-3 : 20-dione (5) gives 17-*iso*pregnane-3 : 20-dione, and *allo*pregnane-3 : 20-dione (8) gives 17-*isoallo*pregnane-3 : 20-dione[156, 157, 158]. Δ^{16}-Progesterone is converted by *Rhizopus* to 11α-hydroxy-17-*iso*progesterone[159]. 14-*n*-17-*iso*- and Δ^{14}-17-*iso*-Steroids[149, 160] are more laevorotatory and less stable than their 14-*n*-17-*n*- and Δ^{14}-17-*n*-isomerides. 17-*iso*Pregnenolone (26) and 17-*isoallo*pregnenolone, despite possession of a 3β-hydroxyl group, do not form insoluble digitonides, and this enables their preparation in a pure state[159].



(2) (26) (27)

17-*iso*Progesterone

Hydrogenation of Δ^{14}- or Δ^{16}-steroids leads to saturated compounds of the 14-*n*-17-*n*-series, but $\Delta^{14:16}$-dienes yield 14-*iso*-17-*iso*-steroids[161, 162]; thus hydrogenation with palladium of the $\Delta^{14:16}$-ketol (28) gives 14-*iso*-17-*iso*pregnenolone (29), m.p. 205°, $[\alpha]_D$ − 14°, converted by Oppenauer oxidation into 14-*iso*-17-*iso*progesterone (30), m.p. 107°, $[\alpha]_D$ + 39°[163, 164]. In the 14-*iso*-series, the 17-*iso*-ketone is more stable than the 17-*n*-ketone[149, 165].



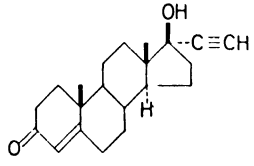
(28) (29) (30)

14-*iso*-17-*iso* Progesterone

Progestational Activity and Structure

Progesterone is distinguished from other sex hormones by the relatively enormous dose required [the international rabbit unit = 1 mg] and by structural specificity. The Δ^4-3-keto grouping in ring *A* is essential and *allo*pregn-1-ene-3 : 20-dione[166], and pregn-5-ene-3 : 20-dione[167] are inactive. Additional double bonds may

increase or decrease activity; Δ^6-progesterone[168] has one-third, $\Delta^{9(11)}$-progesterone[148, 169, 170] has one-half, Δ^{11}-progesterone[171] has thrice, whilst Δ^{16}-progesterone[172, 173] has one-hundredth the activity of progesterone. 6β-Acetoxyprogesterone[144] is one-third, 19-hydroxyprogesterone[151, 152] is one-fiftieth, and 21-hydroxyprogesterone [= deoxycorticosterone] is one-tenth as active, but 14β-hydroxyprogesterone[149] and 17α-hydroxyprogesterone are inactive. 19-nor-Progesterone[174] is four to eight times as active, and 21-norprogesterone[175] is one-tenth as active, whilst 17α-methylprogesterone[176] is twice as active but 21-methylprogesterone[177] is only about one-tenth as active as progesterone, and 21-ethylprogesterone[178] is inactive; both the 20-epimerides of norchol-4-ene-3 : 22-dione[179, 180] are inactive. Reduction of the 20-keto group of progesterone to pregn-4-en-20α-ol-3-one decreases the activity[166, 181]. 17α-Ethinyltestosterone[182, 183] [= 17-*iso*pregnenynolone] (31), readily obtained from dehydro*epi*androsterone (10) by addition of acetylene and Oppenauer oxidation of the product, its Δ^{11}-analogue[184], and its partial reduction product 17α-vinyltestosterone[185, 186] (32), are somewhat less active than progesterone by subcutaneous injection, but much more active by oral administration[187]; 19-nor-17α-ethinyltestosterone (33) is the most active oral gestogen[188]. Several androgens, e.g. androst-4-en-3 : 17-dione and 17α-methyltestosterone, are active as gestogens.



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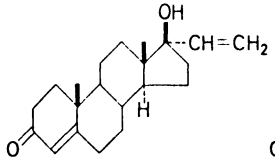

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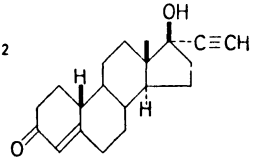


(33)

Progesterone Metabolism

Progesterone in the organism is derived, at least in part, from cholesterol[189]; pregnane-3α : 20α-diol (4), excreted as the 3-glucuronide in pregnancy urine, and *allo*pregnanolone (7), found in ovarian extracts, are biological reduction products.

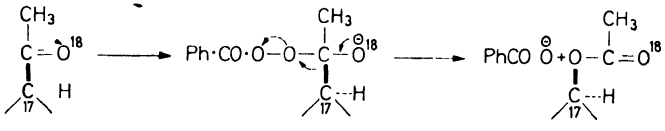
Pregnane and allo*Pregnane Derivatives*

Progesterone is one member of a large group of compounds, derived from pregnane (6) or *allo*pregnane (9), which includes the adrenocortical substances [*see* p. 168]. For preparation of *allo*pregnane derivatives, the usual starting material is 3β-hydroxypregn-5-en-20-one (2), which is available commercially, whilst hydrogenation with platinum in presence of strong acids [$HClO_4$, HBr] of

3α-substituted pregn-5-enes leads to pregnane derivatives[190]. ψ-Sapogenins may be oxidized to pregn-16-en-3-ol-20-ones or *allo*pregn-16-en-3-ol-20-ones [*see* p. 290], from which various pregnane and *allo*pregnane derivatives may be prepared.

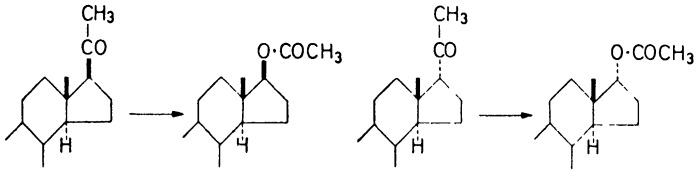
Pregnane-3α : 20α-diol (4) cannot be prepared by hydrogenation of pregnane-3 : 20-dione (5), and is obtained by reduction with sodium-ethanol of pregn-16-en-3α-ol-20-one, available from ψ-*epi*-sarsasapogenin; pregnane-3β : 20α-diol is obtained by sodium-ethanol reduction of pregn-16-en-3β-ol-20-one, available from ψ-sarsasapogenin. Such Δ^{16}-pregnen-20-ones of the *n*- or *allo*-series are preferentially hydrogenated at the Δ^{16}-double bond by palladium, or by nickel in an alkaline medium; thus pregna-5 : 16-dien-3β-ol-20-one from ψ-diosgenin gives pregnenolone (2). Hydrogenation of pregnane-3 : 20-dione (5) gives pregnane-3α : 20β-diol in acidic media and pregnane-3β : 20β-diol in neutral media; the 3-keto-group is reduced first, and pregnan-3α-ol-20-one, also available by Miescher-Wettstein degradation of lithocholic acid[191], and pregnan-3β-ol-20-one are readily obtained by partial hydrogenation. Reduction of pregnan-3α-ol-20-one with sodium-ethanol or nickel-hydrogen gives both pregnane-3α : 20α-diol (4) and pregnane-3α : 20β-diol, whilst use of platinum hydrogen–acetic acid gives mainly the latter[191, 192]; the supposition of MARKER[193] that hydrogenation of 20-ketosteroids in neutral media gives only a single 20-hydroxy-steroid is incorrect. By analogous methods the *allo*pregnane-3 : 20-diols and *allo*pregnanolones have been obtained from *allo*pregnane-3 : 20-dione and from ψ-tigogenin and ψ-*epi*tigogenin. 3α- and 3β-Hydroxyl groups are more reactive than 20α- or 20β-hydroxyl groups, so that preferential acetylation at $C_{(3)}$, or partial hydrolysis at $C_{(3)}$ of a 3 : 20-diacetate, can be accomplished and permits the preparation of 3-substituted or 20-substituted derivatives; 20-hydroxyl groups cannot be epimerized[193]. Pregnane- or *allo*pregnane-3 : 16β : 20α-triols can be obtained by peroxidation of sapogenins, whilst ψ-sapogenins by oxidative fission and subsequent reduction afford epimeric 3 : 16β : 20β triols[194].

Pregnan- or *allo*pregnan-20-ones are oxidized by persulphuric acid[195], performic acid[196], and other peracids to 17-acyloxysteroids with retention of configuration at $C_{(17)}$[197, 198] by the following mechanism[199, 200]:



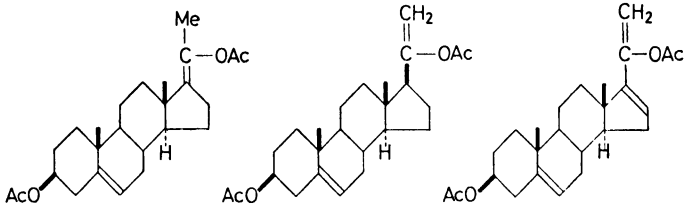
17-*n*-20-Ketones of the pregnane or *allo*pregnane series [as (34)] give androstan-17β-yl or aetiocholan-17β-yl acetates [as (35)],

whilst the 17-*iso*-20-ketones [as (36)] give the epimeric 17α-yl acetates [as (37)]; the appropriate 21-acetoxy-20-ketones and the corresponding aetio-acids are also formed.



(34) (35) (36) (37)

17-*n*-20-Ketones of the pregnane, *allo*pregnane, and pregn-5-ene series [as (34)] afford two types of enol acetates. Thus pregnanolone[201], *allo*pregnanolone (7)[201,202], and pregnenolone (2)[203,204] heated with acetic anhydride and an acidic catalyst [toluene-*p*-sulphonic, sulphosalicyclic, or perchloric acid] give $\Delta^{17(20)}$-enol diacetates [as (38)], which give yellow colours with tetranitromethane and 17-ketones by ozonolysis. Although it has been reported[205] that in benzene solution *iso*propenyl acetate and toluene-*p*-sulphonic acid do not react with 20-keto-steroids, pregnenolone (2) by distillation with *iso*propenyl acetate and toluene-*p*-sulphonic acid or heating with *iso*propenyl acetate and sulphuric acid gives the Δ^{20}-enol diacetate (39)[206,207]; *allo*pregnanolone (7) by heating with *iso*propenyl acetate and sulphuric acid likewise gives the Δ^{20}-enol diacetate[207]. These Δ^{20}-enol acetates give no colour with tetranitromethane and by ozonolysis yield the aetio-acids.



(38) (39) (40)

$\Delta^{17(20)}$-Enol acetates (38) react with N-bromosuccinimide by a radical mechanism to give Δ^{16}-20-ketones[208]; Δ^{20}-enol acetates (39) react with N-iodosuccinimide by an ionic mechanism to give 21-iodo-20-ketones, whilst $\Delta^{16:20}$-dienol acetates (40) yield Δ^{16}-21-iodo-20-ketones[209]. 17-*n*-Ketones [as (34)] by heating with ethanolic ethyl orthoformate and a trace of sulphuric acid give a mixture of $\Delta^{17(20)}$- and Δ^{20}-enol ethers[210].

Pregnene derivatives are available by use of the usual methods for introducing unsaturation [*see* pp. 71 and 72]; thus pregnane-3 : 20-dione (5) gives the 4β-bromo-compound dehydrobrominated with

pyridine or collidine to pregn-4-ene-3 : 20-dione [= progesterone] [*see* p. 128]. *allo*Pregnane-3 : 20-dione (8) gives the 2α-bromo-derivative, converted by dehydrobromination with pyridine or collidine to *allo*pregn-1-ene-3 : 20-dione[166], and by potassium acetate–acetic acid to pregn-5-en-4 : 20-dione[211]. The best method for conversion of 3-hydroxypregn-5-enes to Δ^4-3-ketones is the Oppenauer method with acetone or *cyclo*hexanone, whilst use of quinone as hydrogen acceptor leads to $\Delta^{4:6}$-3-ketones[212]. Pregn-11-enes are obtained by elimination reactions from 12α-toluene-*p*-sulphonates[213] and from 12-triakylammonium salts[214]; pregn-9-enes have been prepared by elimination reactions from both 11β- and 11α-hydroxy-derivatives[170, 215-220]. Other reactions leading to pregnenes are dealt with in connection with the androgens and with the adreno-cortical hormones [*see* p. 184].

Urinary C_{21}-Steroids

The following forty-five C_{21}-steroids have been isolated from urines[272, 273]; pregnane-3α : 20α-diol, *allo*pregnane-3α : 20α-diol, and -3β : 20α-diol probably arise by metabolic reduction of progesterone, whilst the compounds with an 11-oxygen substituent are almost certainly derived from the adreno-cortical substances [*see* Chapter IV]:

*allo*Pregn-2-en-20-one
3α-Hydroxypregn-16-en-20-one
*allo*Pregnane-3 : 20-dione (8)
Pregnane-3 : 20-dione (5)
3α-Hydroxy*allo*pregnan-20-one
3β-Hydroxy*allo*pregnan-20-one (7)
3α-Hydroxypregnan-20-one
3α-Hydroxy-17-*iso*pregnan-20-one
*allo*Pregnane-3α : 20α-diol diacetate
*allo*Pregnane-3β : 20α-diol diacetate
Pregnane-3α : 20α-diol (4)
Pregnane-3α : 20α-diol diacetate
Pregnane-3β : 20α-diol diacetate
17a-Methyl-*D*-homoandrostane-3β : 17aα-diol diacetate
3β : 17α-Dihydroxypregn-5-en-20-one [acetate]
3β : 21-Dihydroxypregn-5-en-20-one
3α-Hydroxypregnane-11 : 20-dione
3α : 20α-Diacetoxypregnan-11-one
3α : 6α-Dihydroxy*allo*pregnan-20-one
3β : 6α-Dihydroxy*allo*pregnan-20-one
3α : 6α-Dihydroxypregnan-20-one
3α : 11β-Dihydroxypregnan-20-one
3α : 17α-Dihydroxy*allo*pregnan-20-one
3α : 17α-Dihydroxypregnan-20-one
3β : 17α-Dihydroxypregnan-20-one
3α : 17aα-Dihydroxy-17aβ-methyl-*D*-homoaetiocholan-17-one
3α : 17aβ-Dihydroxy-17aα-methyl-*D*-homoaetiocholan-17-one
3α : 17α-Dihydroxy-17β-methyl-*D*-homoaetiocholan-17α-one
Pregnane-3α : 11β : 20α-triol 3 : 20-diacetate
*allo*Pregnane-3β : 16α : 20α-triol triacetate
Pregnane-3α : 17α : 20α-triol 3 : 20-diacetate
3α : 17α-Dihydroxypregnane-11 : 20-dione
3α : 20α-Diacetoxy-17α-hydroxypregnan-11-one
3α : 11β : 21-Trihydroxy*allo*pregnan-20-one

3α : 11β : 21-TRIHYDROXYPREGNAN-20-ONE
PREGNANE-3α : 11β : 17α : 20α-TETROL 3 : 20-DIACETATE
CORTISONE ACETATE
CORTISOL ACETATE
3α : 21-DIACETOXY-17α-HYDROXYPREGNANE-11 : 20-DIONE
3α : 21-DIACETOXY-11β : 17α-DIHYDROXYPREGNAN-20-ONE
3α : 20α : 21-TRIACETOXY-17α-HYDROXYPREGNAN-11-ONE
3α : 20β : 21-TRIACETOXY-17α-HYDROXYPREGNAN-11-ONE
PREGNANE-3α : 11β : 17α : 20α : 21-PENTOL
PREGNANE-3α : 11β : 17α : 20β : 21-PENTOL

THE ANDROGENS

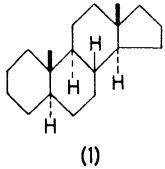
Compounds have been isolated from the urine of males, females, and eunuchs, and from testicular extracts, which by injection into castrated or immature males cause restoration or development, respectively, of the male genital organs [seminal vesicles, penis, vas deferens, prostate, Cowper glands] and secondary sexual characteristics. These are the so-called male hormones or androgens [Gr. *andro*, male] of which testosterone, androsterone, and dehydro*epi*-androsterone are the most important.

For bioassay, the effect of the hormone in promoting comb-growth in capons may be used[221]; the capon unit is defined as the amount of compound which, administered to each of three capons on two successive days, produces during the course of the third and fourth days an average increase of 20% in comb-area measured on a shadow-graph with a planimeter[222, 223]. The international unit [I.U.] is the androgenic activity of 0·1 mg [= 100γ] of androsterone. Alternatively, the effect on the growth of the accessory sex organs in castrated and in immature rats [or mice] may be used.

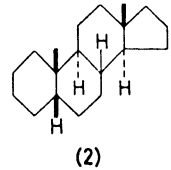
Isolation of Urinary Androgens

Male urine is extracted with chloroform, acidic and phenolic compounds removed with dilute alkali, and the neutral fraction hydrolysed with hot hydrochloric acid. The unhydrolysed fraction is dissolved in benzene, the solution diluted largely with petrol, and the active material extracted with 60% ethanol. Further purification is achieved by high vacuum sublimation, conversion to ketonic derivatives [e.g. oxime], crystallization thereof, and regeneration by hydrolysis[222].

The natural androgens and their transformation products are derivatives of androstane (1) and aetiocholane [5-*iso*androstane] (2).



(1)

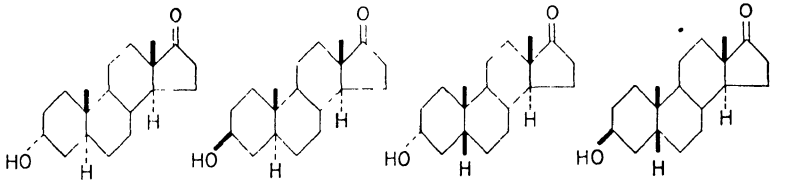


(2)

Androsterone

Androsterone, $C_{19}H_{30}O_2$, was isolated in 1931 by BUTENANDT[224]; 15,000 litres of normal male urine gave 15 mg of crystalline androsterone, although bioassay indicates a content of 1 mg/litre, of which some 25% can now be isolated. The hormone was characterized as a hydroxyketone [acetate, oxime, semicarbazone] and on the basis of the molecular formula, which indicates the presence of four reduced rings, Butenandt, in 1932, suggested the correct formula (3), apart from stereochemical detail, when only 25 mg of the hormone had been obtained.

In 1934 Ruzicka converted cholestanyl acetate by oxidative removal of the side chain into a ketone of the structure suggested by Butenandt; the product was *epi*androsterone [formerly called *iso*androsterone] (4), m.p. 174°, $[\alpha]_D$ + 88°, one-seventh as active as androsterone[225]. Androsterone (3) was similarly obtained from *epi*cholestanyl acetate[226,227], and 3α-hydroxyaetiocholan-17-one (5) and 3β-hydroxyaetiocholan-17-one (6) from coprostanyl and *epi*coprostanyl acetate, respectively[226]. Despite poor yields these degradations establish the structures of androsterone, *epi*androsterone, and their isomerides.



(3) Androsterone — m.p. 183°, $[\alpha]_D$ +94°, I.U. 100

(4) *epi*Androsterone — m.p. 174°, $[\alpha]_D$ +88°, I.U. 700

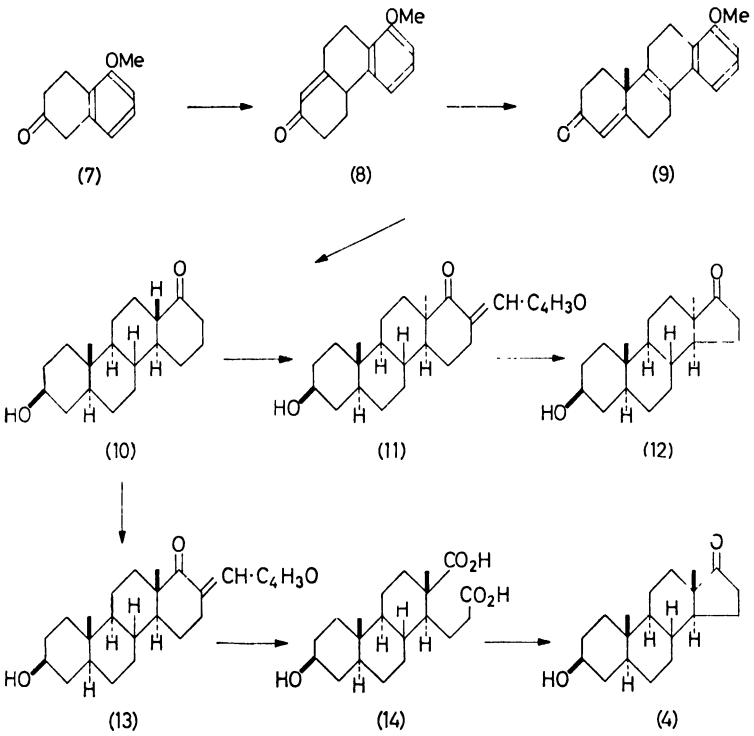
(5) 3α-Hydroxyaetiocholan-17-one — m.p. 151°, $[\alpha]_D$ +105°, inactive

(6) 3β-Hydroxyaetiocholan-17-one — m.p. 152°, $[\alpha]_D$ +89°, inactive

As an alternative to the route: cholesterol —○→ *epi*cholestanol —→ androsterone, Ruzicka has described the sequence: cholesterol —○→ *epi*cholestanol —○→ 3β-chlorocholestane —○→ androsterone[228], and Marker the route: cholesterol —→ cholesteryl chloride —→ 3β-chlorocholestane —○→ androsterone[229]. Other partial syntheses involve degradation of 3β-hydroxy*allo*cholanic acid[230] and *epi*stigmastanol[231]. The best method of preparation is from dehydro*epi*androsterone (15), an intermediate in the commercial production of testosterone, which is converted by treatment with phosphorus pentachloride with retention of configuration at $C_{(3)}$ into 3β-chloroandrost-5-en-17-one (16)[232,233]; hydrogenation with palladium gives 3β-chloroandrostan-17-one (17), which undergoes acetolysis

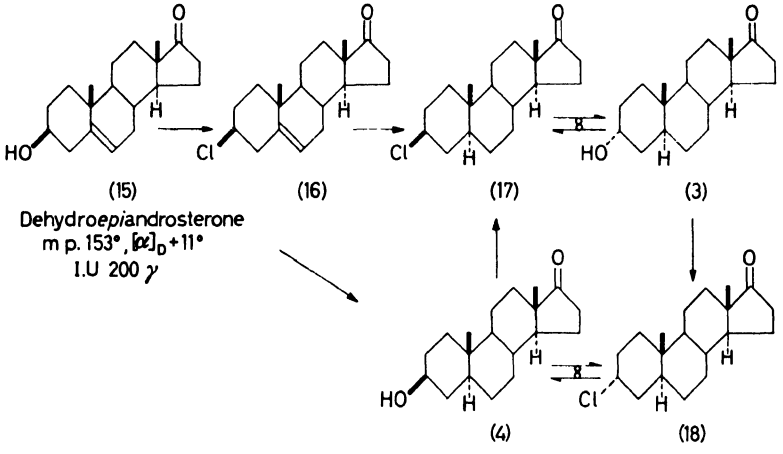
with inve sion to give [after alkaline hydrolysis] androsterone (3)[234]. Alternatively, *epi*androsterone (4) can be converted into androsterone in 61% yield[234a].

The total synthesis of androsterone has been described by WOODWARD[235], and that of *epi*androsterone by CORNFORTH and ROBINSON[236] [*see* pp. 45 and 46]. A total synthesis of (±)-*epi*androsterone of striking simplicity has been given by JOHNSON[237].



5-Methoxy-2-tetralone (7) by successive condensation with 1-dimethylaminopentan-3-one methiodide and methyl vinyl ketone gave the tricyclic ketone (8) and the tetracyclic D-homoketone (9); reduction with lithium and ethanol in liquid ammonia and hydrogenation introduced six new centres of asymmetry to furnish a single product (±)-18-nor-D-homo*epi*androsterone [as (10)]. Methylation of the furfurylidene derivative introduced the $C_{(13)}$-methyl group to give the racemates represented by (11) and (13); thereafter ozonolysis of (13) furnished the dicarboxylic acid [as (14)], cyclized, hydrolysed, and decarboxylated to (±)-*epi*androsterone [as (4)]; the racemate represented by (11) similarly afforded (±)-lumi*epi*androsterone [as (12)].

3α-Hydroxyaetiocholan-17-one (5) has also been obtained by oxidation of 3α-acetoxycholanic acid [= lithocholic acid acetate] with chromium trioxide[238,239].

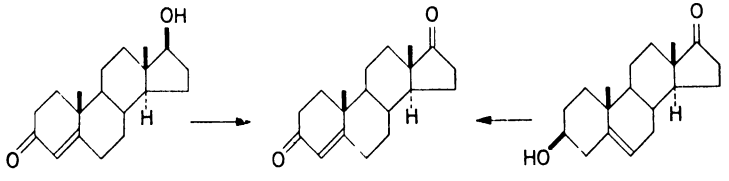


*Dehydro*epi*androsterone*

Dehydro*epi*androsterone, $C_{19}H_{28}O_2$ (15), an unsaturated hydroxyketone, and the related chloride, 3β-chloroandrost-5-en-17-one (16), were isolated in 1934 from male urine by BUTENANDT[224]. The chloride is formed by esterification during hydrochloric acid hydrolysis of the urine, and regenerates dehydro*epi*androsterone by treatment with benzoate ions in molten benzoic acid, and subsequent alkaline hydrolysis; hydrogenation of the chloroketone (16) with palladium in ethanol or acetic acid yields 3β-chloroandrostan-17-one (17), which by acetolysis undergoes substitution with inversion to give, after alkaline hydrolysis, androsterone (3)[234,240]. The 3β-chloroketone (17) is obtained by treatment of androsterone (3) with phosphorus pentachloride and from *epi*androsterone (4) with thionyl chloride. The 3α-chloroketone (18) is obtained from androsterone (3) using thionyl chloride, or from *epi*androsterone (4) with phosphorus pentachloride, and acetolysis and subsequent alkaline hydrolysis regenerates *epi*androsterone (4)[228,240,241,242]. Dehydro*epi*androsterone has a 3β-hydroxyl group, and is the 5 : 6-dehydro-derivative, not of androsterone (3), but of *epi*androsterone (4). Its structure is confirmed by partial synthesis of its acetate from cholesteryl acetate dibromide[243,244], and from sitosteryl acetate dibromide[245], and by hydrogenation to *epi*androsterone (4) accompanied by 10% of 3β-hydroxyaetiocholan-17-one (6)[246]. The 3α-hydroxy-epimeride of (15) is known[247].

Testosterone

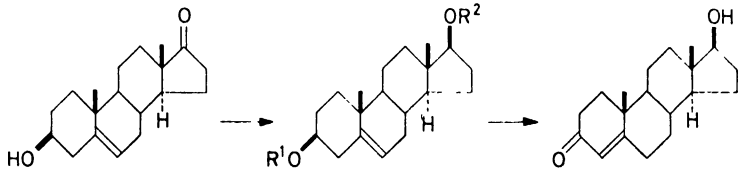
Testosterone, $C_{19}H_{28}O_2$, was isolated in 1935 by LAQUEUR[248] from testis tissue. The testicular hormone is an $\alpha\beta$-unsaturated hydroxyketone [acetate, oxime] with $\lambda_{max.}$ 240 mμ, some 10 times as potent as androsterone; its structural formula (19) was established by DAVID[249] by oxidation with chromium trioxide to androst-4-en-3 : 17-dione (20), which is readily obtained from dehydro*epi*androsterone (15) by Oppenauer oxidation, and which can be reconverted to testosterone[250, 251, 252, 252a].



(19) (20) (15)

Testosterone
m p 155°; $[\alpha]_D$ +109°
IU 10-15 γ

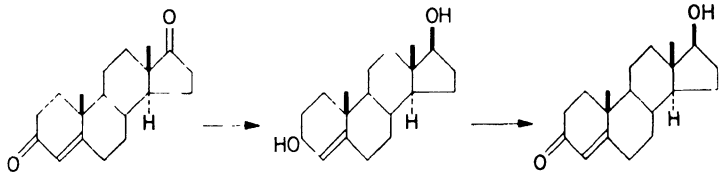
Testosterone was prepared simultaneously, independently, and by the same method in 1935 by BUTENANDT[253] and by RUZICKA[254]. Dehydro*epi*androsterone (15) was reduced with sodium-propanol to androst-5-ene-3β : 17β-diol [(21): R^1 = R^2 = H], converted by partial hydrolysis of the diacetate to the 17-monoacetate [(21): R^1 = H; R^2 = Ac]; this was originally oxidized as the 5α : 6β-dibromide with chromium trioxide, and subsequently with aluminium *tert.*-butoxide–acetone[255], to testosterone (19).



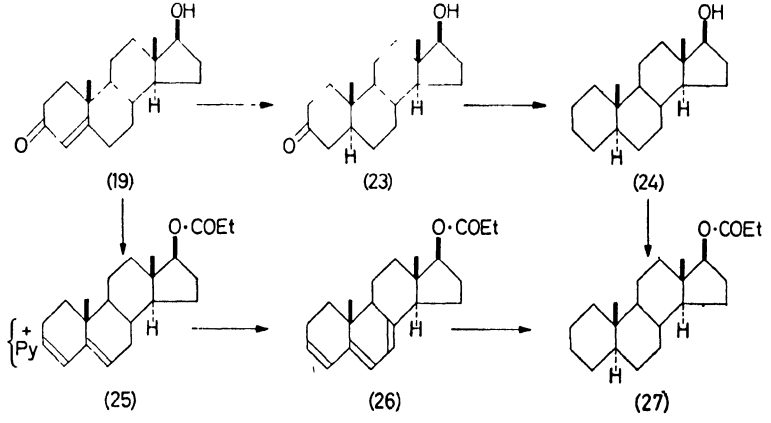
(15) (21) (19)

The transformation [(15) → (19)] can be achieved in 81% yield microbiologically, but proceeds via androst-4-ene-3 : 17-dione (20)[256]. Improved partial syntheses of testosterone have been described[257, 258], and the simplest partial synthesis is probably that of ROSENKRANZ[259] from androst-4-ene-3 : 17-dione by reduction with lithium aluminium hydride to the mixture of 3-epimerides represented by (22), which by oxidation with manganese dioxide in chloroform at 20° gives a 90% overall yield of testosterone (19).

The total synthesis of testosterone has been accomplished by W. S. JOHNSON[259a] and testosterone has been obtained from sarsasapogenin and diosgenin[260]; radiotestosterone-[4-^{14}C] has been prepared[261].

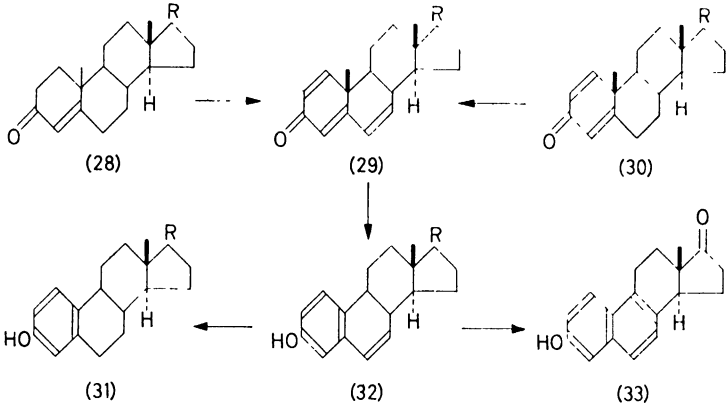


The $C_{(17)}$-hydroxyl group in testosterone was originally assigned the α-configuration by RUZICKA[262] because esters of testosterone are more rapidly hydrolysed than those of 17-*epi*testosterone (34), m.p. 220°, $[\alpha]_D$ + 71°, which was obtained from the androst-5-ene-3β : 17α-diol isolated from residues of large-scale preparations of androst-5-ene-3β : 17β-diol [(21): $R^1 = R^2$ -H][263]. This assignment has been invalidated by studies of the rates of hydrolysis of 17-epimeric aetiocarboxylic acid methyl esters[264 265]; in conformity with the molecular rotations of the two compounds PLATTNER [266] suggested that testosterone is a 17β-hydroxy-compound whilst *epi*testosterone is a 17α-hydroxy-compound, and this has been shown to be correct. Testosterone (19) by hydrogenation with palladium[257, 267] gives dihydrotestosterone (23), m.p. 181°, $[\alpha]_D$ + 32°, converted by Clemmensen reduction into androstan-17β-ol (24)[267]; alternatively, testosterone as the propionate by treatment with phosphorus oxychloride–pyridine gives the enol pyridinium chloride (25), pyrolysed at 50–150°/0·001 mm to androsta-3 : 5 : 7-trien-17β-yl propionate (26), which by hydrogenation with platinum-acetic acid gives androstan-17β-yl propionate (27)[268]. The configuration of androstan-17β-ol follows from its production



from *allo*pregnan-20-one by oxidation with peracetic acid[260] [*see* p. 134], and is confirmed by comparison of its molecular rotation with that of androstan-17α-ol[269].

Testosterone has been transformed into the natural oestrogenic hormones oestradiol-17β, (+)-oestrone, and (+)-equilenin[270]. Testosterone acetate [(28): R = OAc] with N-bromosuccinimide gives the 2 : 2-dibromo-compound dehydrobrominated with collidine to androsta-1 : 4 : 6-trien-3-on-17β-yl acetate [(29): R = OAc], also obtained from androsta-1 : 4-dien-3-on-17β-yl acetate [(30): R = OAc] by conversion with N-bromosuccinimide to the 6-bromide and dehydrobromination with collidine. Androst-4-ene-3 : 17-dione [(28): R = : O] similarly affords androsta-1 : 4 : 6-triene-3 : 17-dione [(29): R = : O].

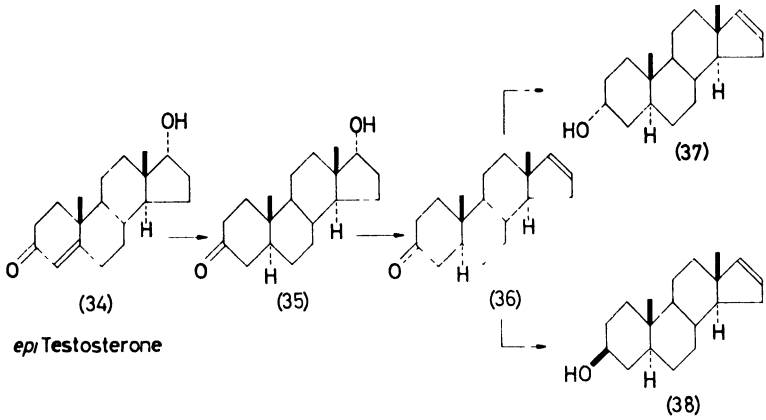


Aromatization of these trienes in mineral oil at 600° gives 40% of Δ⁶-oestradiol-17β 17-monoacetate [(32): R = OAc], easily hydrogenated with palladium and hydrolysed to oestradiol-17β [(31): R = OH], or of Δ⁶-oestrone [(32): R = : O], smoothly hydrogenated with palladium to (+)-oestrone [(31): R = : O] and readily dehydrogenated as the 3-acetate by selenium dioxide in acetic acid to (+)-equilenin acetate, hydrolysed to (+)-equilenin [(33): R = O].

Other Constituents of Testicular Extracts and Urine

Numerous other compounds have been isolated from testicular extracts: cholest-4-en-3-one, cholesta-4 : 6-dien-3-one, 3β-hydroxy-*allo*pregnan-20-one, 3β-hydroxypregn-4-en-20-one, 3α-hydroxy-androst-16-ene (37), and 3β-hydroxyandrost-16-ene (38). The last named two compounds have a musk-like odour and have been prepared from *epi*testosterone (34) via dihydro*epi*testosterone (35), m.p. 180°, $[\alpha]_D$ + 5°; this as the hexahydrobenzoate by pyrolysis gives androst-16-en-3-one (36) which possesses a penetrating

'urine' smell and by Meerwein-Ponndorf reduction and digitonin separation gives (37) and (38). These compounds bear a curious formal resemblance to the 17-membered ring ketone, civetone, but the two *cis-A/B*-epimerides of (37) and (38) are odourless[271].



Systematic chromatographic separation of urinary steroids[272] has furnished eighty-four substances, of which the following thirty-nine are C_{19}-compounds[272 273]:

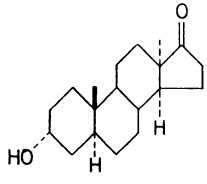
ANDROST-2-EN-17-ONE
ANDROSTA-3 : 5-DIEN-17-ONE
ANDROST-16-EN-3α-OL
ANDROST-1-ENE-3 : 17-DIONE
ANDROST-4-ENE-3 : 17-DIONE (20)
ANDROSTA-4 : 6-DIENE-3 : 17-DIONE
17α-HYDROXYANDROST-4-EN-3-ONE (34)
17β-HYDROXYANDROST-4-EN-3-ONE (19)
3β-HYDROXYANDROST-5-EN-17-ONE (15)
3β-CHLOROANDROST-5-EN-17-ONE (16)
3α-HYDROXYANDROST-9(11)-EN-17-ONE
3β-HYDROXYANDROST-9(11)-EN-17-ONE
3α-HYDROXYAETIOCHOL-9(11)-EN-17-ONE
3β-HYDROXYAETIOCHOL-9(11)-EN-17-ONE
ANDROSTANE-3 : 17-DIONE
AETIOCHOLANE-3 : 17-DIONE
3α-HYDROXYANDROSTAN-17-ONE (3)
3β-HYDROXYANDROSTAN-17-ONE (4)
3α-HYDROXYAETIOCHOLAN-17-ONE (5)
3β-HYDROXYAETIOCHOLAN-17-ONE (6)
ANDROSTANE-3α : 17β-DIOL DIACETATE
ANDROSTANE-3β : 17β-DIOL DIACETATE
AETIOCHOLANE-3α : 17α-DIOL [DIACETATE]
AETIOCHOLANE-3α : 17β-DIOL DIACETATE
11α-HYDROXYANDROST-4-ENE-3 : 17-DIONE
3β-HYDROXYANDROST-5-ENE-7 : 17-DIONE
AETIOCHOLANE-3 : 11 : 17-TRIONE
11β-HYDROXYANDROSTANE-3 : 17-DIONE
11β-HYDROXYAETIOCHOLANE-3 : 17-DIONE
3α-HYDROXYANDROSTANE-11 : 17-DIONE

3α-HYDROXYAETIOCHOLANE - 11 : 17-DIONE
3β-HYDROXYAETIOCHOLANE - 11 : 17-DIONE
3α : 11β-DIHYDROXYANDROSTAN-17-ONE
3β : 11β-DIHYDROXYANDROSTAN-17-ONE
3α : 11β-DIHYDROXYAETIOCHOLAN-17-ONE
3β : 11β-DIHYDROXYAETIOCHOLAN-17-ONE
3α : 17β-DIACETOXYAETIOCHOLAN-11-ONE
ANDROSTANE-3α : 16α : 17β-TRIOL TRIACETATE
AETIOCHOLANE-3α : 16α : 17β-TRIOL TRIACETATE

For determination of urinary 17-ketosteroids the Zimmermann reaction [*see* p. 79] is used[274]. The principal 17-ketosteroids excreted in normal human urine are androsterone (3), aetiocholanolone (5), and dehydro*epi*androsterone (15); these are derived from the adrenal cortex in women, and from the testes and the adrenal cortex in men.

Isomerides and Derivatives of Androsterone, epi*Androsterone, and Testosterone*

Lumiandrosterone [= 13-*iso*androsterone] (39), m.p. 146°, $[\alpha]_D$ — 100°, is obtained by irradiation of androsterone (3) with ultraviolet light[275]; 14-*iso*-17-*epi*testosterone (40) has been prepared[276]. The Δ^1-isomeride (41) of testosterone is obtained from the 2α-bromo-derivative of dihydrotesterone (23) by dehydrobromination with collidine, whilst use of potassium acetate in acetic acid gives the isomeric 17β-hydroxyandrost-5-en-4-one (42)[277].



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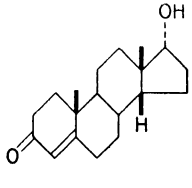

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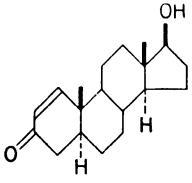

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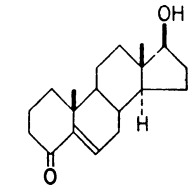
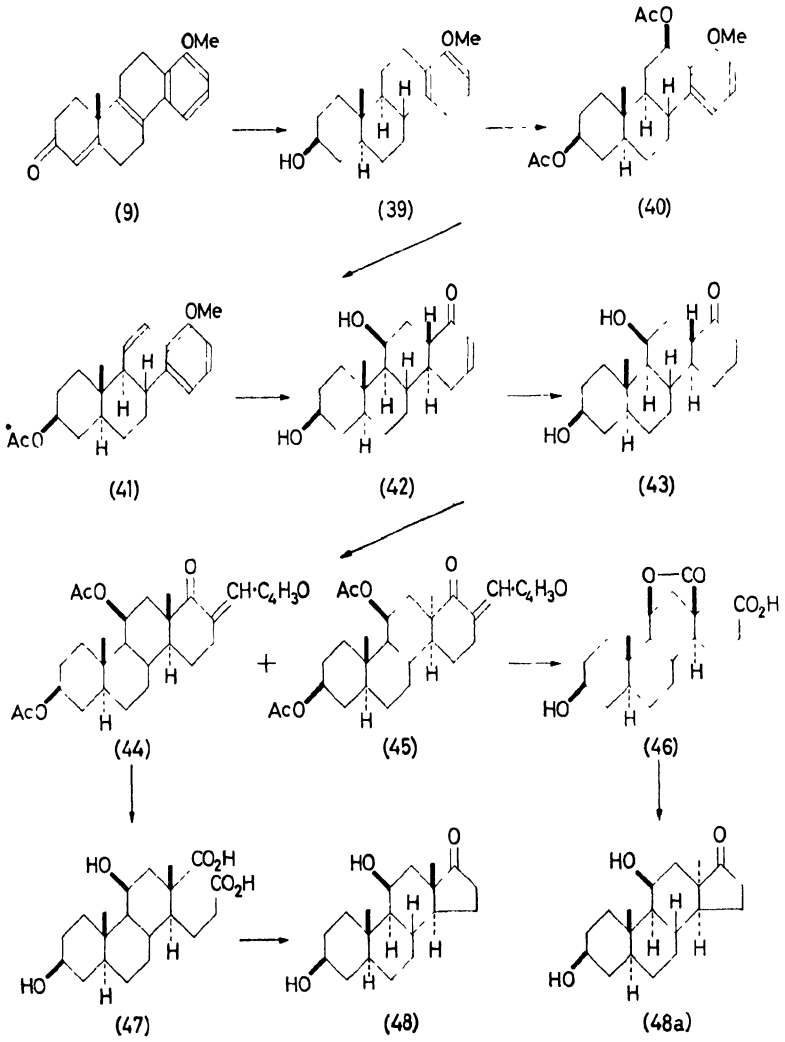


(42)

$\Delta^{9(11)}$- and Δ^{11}-Androst-4-ene-3 : 17-dione have been prepared[278], and 11β-hydroxy- and 11-oxoandrost-4-ene-3 : 17-dione [= adrenosterone] have been obtained by partial synthesis[278, 279, 280]. The total synthesis of (±)-lumi*epi*androsterone [as 12] has been described [*see* p. 139]. The total synthesis of (±)-11β-hydroxy*epi*androsterone has been achieved by JOHNSON[281] as follows. The tetracyclic ketone (9) by reduction with lithium–ethanol in ammonia gave the alcohol (39), which as the acetate by treatment with lead tetracetate gave the 3β : 12β-diacetate (40), converted by heating in acetic acid to the Δ^{11}-compound (41); this by hydroxylation

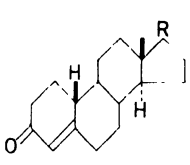
with performic acid gave a mixture of stereoisomeric 3β : 11 : 12-triols, converted by lithium-ethanol in ammonia with simultaneous hydrogenolysis at $C_{(12)}$ and aromatic reduction, after acid hydrolysis of the enol methyl ether group at $C_{(17a)}$, to the racemic



ketone [as (42)], hydrogenated with palladium in alkaline solution to a single product (±)-18-nor-D-homo-11β-hydroxy*epi*androsterone [as (43)]. Methylation of the furfurylidene derivative, and acetylation gave the racemates represented by (44) and (45); ozonolysis of (44) and hydrolysis gave the dicarboxylic acid [as

(47)], cyclized, hydrolysed, and decarboxylated to (±)-11β-hydroxy*epi*androsterone [as (48)]. Ozonolysis of (45) and hydrolysis gave the racemic γ-lactonic acid [as (46)], convertible into (±)-11β-hydroxylumi*epi*androsterone [as (48a)].

2β- and 2α-Hydroxytestosterone[282] and 6-oxotestosterone[283] are known. 11β-Hydroxy- and 11-oxotestosterone[278, 279, 280] have been prepared, whilst 11β-hydroxytestosterone has also been obtained by biosynthesis[280, 284] and has been converted into $\Delta^{9(11)}$-testosterone[285], whilst Δ^{11}-testosterone has also been made[286]. 16β-Hydroxy- and 16-oxotestosterone have been prepared[287]. 19-nor-Androst-4-en-3 : 17-dione [(49): R = O] and 19-nor-testosterone [(49): R = OH] have been prepared from (+)-oestrone[288]; 19-nor-17α-ethinyltestosterone (50) is the most potent gestogen by oral administration[289], whilst 19-nor-17α-methyltestosterone[289] (51), 17α-methyltestosterone[290], and its dihydro-[291] and Δ^{11}-derivatives[286] have been prepared.



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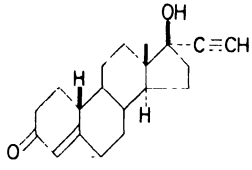

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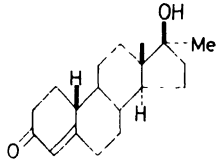
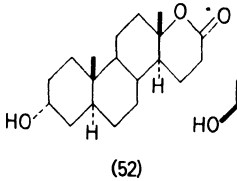


(51)

Androgenolic Lactones

Oxidative fission of ring *D* with peracids leads to lactones. Androsterone (3) and *epi*androsterone (4) with peracetic acid afford androlololactone (52) and *epi*androlololactone (53)[110], also obtained from 3β : 17α-dihydroxy*allo*pregnan-20-one [Reichstein's substance L, *see* Chapter V, p. 175] with perbenzoic acid [cf. p. 134][292]. Similarly, testosterone (19) gives testololactone (54)[110], which has also been obtained from progesterone and 17α-hydroxyprogesterone by microbiological oxidation with *Aspergillus flavus* and *Penicillia*[293]; Δ^{11}-testololactone has been described[134].



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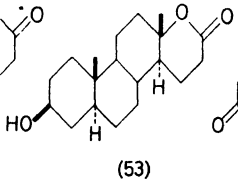

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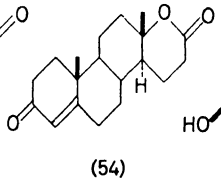

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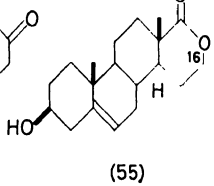


(55)

Dehydro*epi*androsterone (15) has been transformed by oxidation with potassium hypoiodite to 3β-hydroxy-16 : 17-*seco*androst-5-en-16 : 17-dioic acid, conversion of the 16-acid chloride-17-methyl

ester and 17-acid chloride-16-methyl ester to the benzylthiol-methyl esters, and treatment of these with Raney nickel, into the dehydro-*epi*andrololactone (55) and the isomeride in which the carbonyl group is at $C_{(16)}$[294].

Derivatives of Androstane and Aetiocholane

Following elucidation of the structures of the natural androgens, very numerous derivatives of androstane and aetiocholane bearing oxygen at $C_{(3)}$ and/or $C_{(17)}$ have been prepared from the commercially available dehydro*epi*androsterone (15), or its reduction products *epi*androsterone (4) and 3β-hydroxyaetiocholan-17-one (6). For details of such derivatives, a larger work, e.g. Elsevier's *Encyclopaedia of Organic Chemistry*, Vol. 14 and *Supplements*, should be consulted. Compounds with oxygen substituted at positions 2, 3, 4, 6, 7, 11, 12, 16, 17 providing reactive nuclear centres are known; in particular, 17-ketosteroids permit elaboration of a $C_{(17)}$-side chain, but this generally has the unnatural 17α-configuration[295] although the sequence 17α-ethinyl[296] $\rightarrow$ 17α-vinyl[297] $\rightarrow$ 17(20)-olefin[298] allows access to compounds with 17β-side chains. Only in the case of cyanohydrins are isomerides produced in roughly equal quantity[299]; the 17α-hydroxyepimeride is unaffected by acetic anhydride–pyridine at 20°, whereas the 17β-hydroxyepimeride is acetylated and so readily separated[300].

Physiological Activity and Structure

Testosterone (19) has the highest comb-growth activity, and is clinically the most important androgen; it is usually administered as the propionate, which has a protracted action[301], although some alkoxy and alkylthio esters surpass it[302]. 19-nor-Testosterone[288] (49), and 19-nor-17α-methyltestosterone[289] (51) are nearly as active as testosterone. *Table XII* shows some activities in the comb-growth test taking testosterone as the standard.

The 17-hydroxyl group must possess the β-configuration and the 17α-hydrogen atom can be replaced by a methyl group, whilst supplementary double bonds other than Δ^{11} decrease activity. It is remarkable that Δ^4-unsaturation is not essential [cf. progesterone, corticosterone, aldosterone], for dihydrotestosterone (23) and 17α-methyldihydrotestosterone are, respectively, two-thirds as active and equally as active as testosterone, whilst dihydro*epi*testosterone (35) is only one-twentieth as active. These points are illustrated in *Table XII*, which also shows that in saturated compounds an *A/B-trans*-union is essential and that the 3α : 17β-dihydroxy combination is highly effective; thus 17α-methylandrostane-3α : 17β-diol is one-third as active as testosterone. Androstane-3 : 17-dione, androst-4-ene-3 : 17-dione (20), and androsta-4 : 11-diene-3 : 17-dione are all

Table XII

COMB-GROWTH ACTIVITY

17-Hydroxy-3-Ketones			
Δ4-17β-ol* (19) 1	Δ4 11-17β-ol $\frac{1}{2}$	Δ1-17β-ol $\frac{1}{13}$	Δ6-17β-ol $\frac{1}{16}$
Δ4-17α-ol (34) $\frac{1}{300}$			
Δ4-17α-Me $\frac{2}{3}$	Δ4:11-17α-Me $\frac{2}{3}$		
Δ4-17β-Me inact.			

* = Testosterone.

3-Hydroxy-17-Ketones			
A/B-trans	Δ4	Δ5	*A/B-cis*
3α-ol* (3) $\frac{1}{8}$	3α-ol —	3α-ol $\frac{1}{8}$	3α-ol (5) inact.
3β-ol** (4) $\frac{1}{600}$	3β-ol $\frac{1}{10}$	3β-ol† (15) $\frac{1}{10}$	3β-ol (6) inact.

* = Androsterone
** = *epi*Androsterone
† = Dehydro*epi*androsterone.

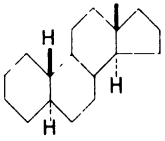
3 : 17-Diols [*A/B-trans*]		3 : 17-Diols [Δ5]	
3α : 17β-diol	$\frac{1}{2}$	3α : 17β-diol	$\frac{1}{3}$
3α : 17α-diol	$\frac{1}{270}$	3α : 17α-diol	—
3β : 17β-diol	$\frac{1}{400}$	3β : 17β-diol (21)	$\frac{1}{400}$
3β : 17α-diol	$\frac{1}{700}$	3β : 17α-diol	$\frac{1}{700}$

about one-tenth as active as testosterone; androst-4-ene-3 : 17-dione is remarkable as also possessing weak oestrogenic and progestational activity, whilst 14-*iso*-17-*iso*progesterone[276] is one-third as active as androsterone and so about one-sixth as active as testosterone. *D*-Homoandrostane derivatives [*vide infra*] are also highly active as androgens.

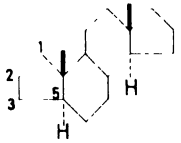
norSteroids and Homosteroids

The omission of angular methyl groups or alteration of ring-size leads to steroid analogues. Elimination of an angular methyl group or ring-decrease is indicated by the prefix 'nor' preceded

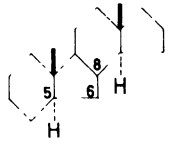
by the appropriate number [(18) or (19)] or letter [*A*, *B*, *C*, *D*], whilst replacement of an angular methyl group by an ethyl group or ring-increase is similarly indicated by the prefix 'homo'[303]. In ring-contraction the highest-numbered carbon atom in the ring disappears, whilst in ring-increase the new carbon atom receives the highest number of the ring in question coupled with the suffix 'a'.



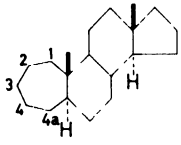
19-norAndrostane



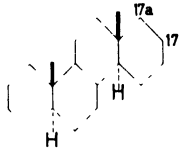
A-norAndrostane



B-norAndrostane



A-homoAndrostane



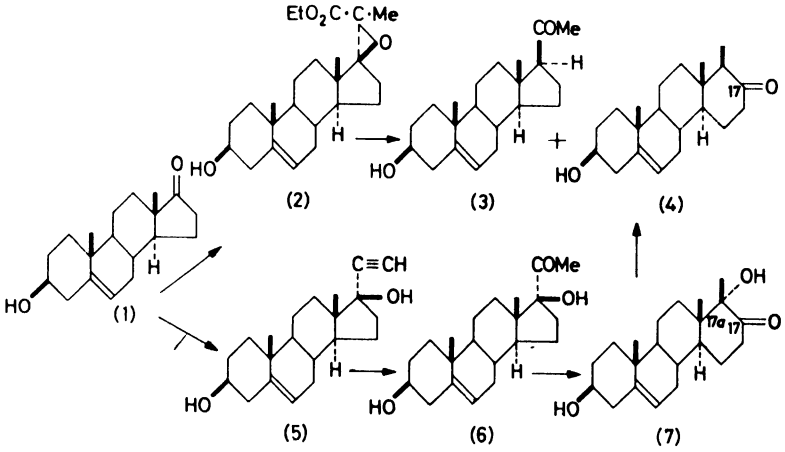
D-homoAndrostane

Attention has recently been focussed on 19-norsteroids by the unexpectedly high biological activities of 19-norprogesterone[174], 19-nortestosterone[288], 19-nor-17α-methyltestosterone[289], 19-nor-17α-ethinyltestosterone[289], 19-norandrost-4-ene-3 : 17-dione[288], 19-nordeoxycorticosterone[304], 19-norcorticosterone, 19-norcortisol, and 19-norcortisone[304a].

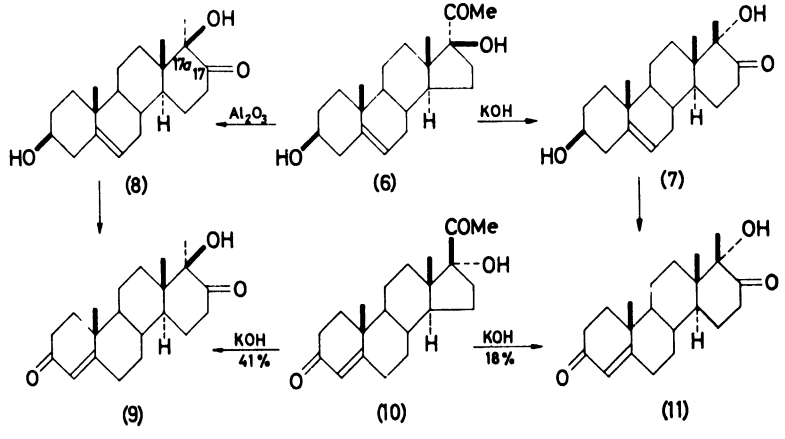
Derivatives of *A*-norandrostane and *A*-noraetiocholane are known, apart from the numerous pyroketones prepared by Wieland and Windaus [*see* Chapter I, p. 9], whilst examples of *B*-nor- and *C*-nor-structures have been reported [*see* Elsevier, Vol. 14, *Supplement* 1]. *D*-Homosteroids are known in considerable numbers.

Dehydro*epi*androsterone (1), as the acetate, by Darzens condensation with ethyl αα-dichloropropionate gives the ester (2), which by hydrolysis and decarboxylation rearranges to give pregnenolone (3) and 17aβ-methyl-*D*-homoandrost-5-en-3β-ol-17-one (4) [originally called 'neopregnenolone'][305, 306]. Hydration of the 17α-ethinyl derivative (5) of dehydro*epi*androsterone (1) with mercuric oxide–boron trifluoride–acetic acid gives 17-*iso*pregn-5-ene-3β : 17β-diol-20-one (6), which rearranges with potassium hydroxide to the 17aβ-methyl-*D*-homo-17aα-hydroxy-17-ketone (7) convertible into the *D*-homo-17-ketone (4)[307], in which the presence of a six-

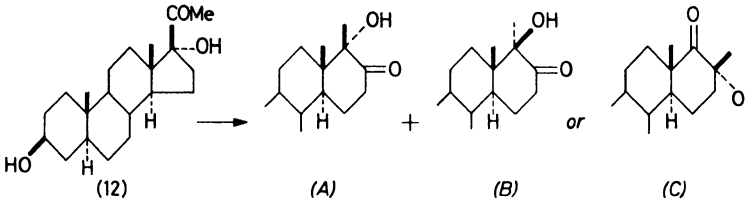
membered *D*-ring was established by selenium dehydrogenation to 1-methylchrysene[308].



Some of the primary hydration product (6) can be isolated by hydration of (5) with mercuric chloride–aniline[309], whilst rearrangement can completely be prevented by use of the 17β-monoacetate or 3β : 17β-diacetate of (5)[310]. The 17-*iso*-α-ketol (6) readily rearranges in the presence of boron trifluoride or of moist alkaline aluminium oxide to the 17aα-methyl-*D*-homo-17aβ-hydroxyketone (8)[310]. Ring-enlargement is not determined by the original configuration at $C_{(17)}$ since 17α-hydroxyprogesterone (10) with hot potassium hydroxide gives the 17a-epimerides (9) and (11), which are obtained by Oppenauer oxidation of the epimerides (8) and (7), respectively[309, 310, 311, 312].

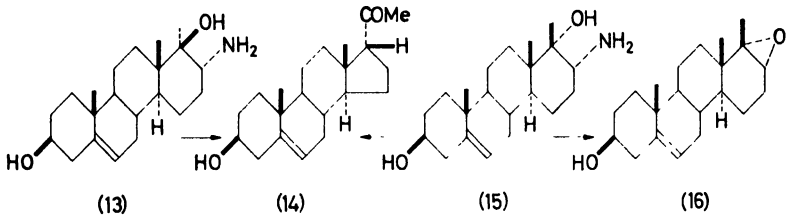


The stereochemical course of *D*-homo-annulation has been considered[313, 314], and it has been shown that 17a-ketones may be formed[315]. This has been proved in a refined investigation, in which chromatography was controlled by infra-red spectrometry[315a]; *allo*pregnane-3β : 17α-diol-20-one (12) with potassium hydroxide gives the 17aα-hydroxy-17-ketone [*A*: 13%] and the epimeric 17aβ-hydroxy-17-ketone [*B*: 67%], but with Lewis acids [e.g. boron trifluoride, aluminium *tert.*-butoxide] affords the 17aα-hydroxy-17-ketone [*A*:15%] accompanied by the isomeric 17α-hydroxy-17a-ketone [*C*: 52%], whilst heating at the m.p. also furnishes both [*A*: 15%] and [*C*: 15%], together with much unchanged starting material.



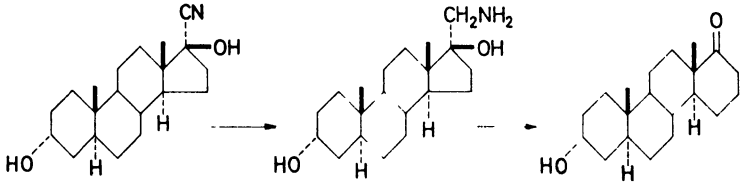
The original configurations at $C_{(17a)}$ assigned by Shoppee and Prins[310] are thus confirmed. Similar results have been obtained using pregnane-3α : 17α-diol-20-one[315a].

Conversion of a *D*-homosteroid to a normal steroid with ring-decrease can be accomplished only under favourable stereoelectronic circumstances; thus the 17a-epimeric 17α-amin-17a-ols (13) and (15) [by contrast with the 17β-amin-17aβ-ol (44), *vide infra*] with nitrous acid give 17-*iso*pregnenolone (14), accompanied in the case of (15) by the 17α : 17aα-oxide (16)[316]. In general, ring-fission and cyclization are necessary[317, 318, 319].



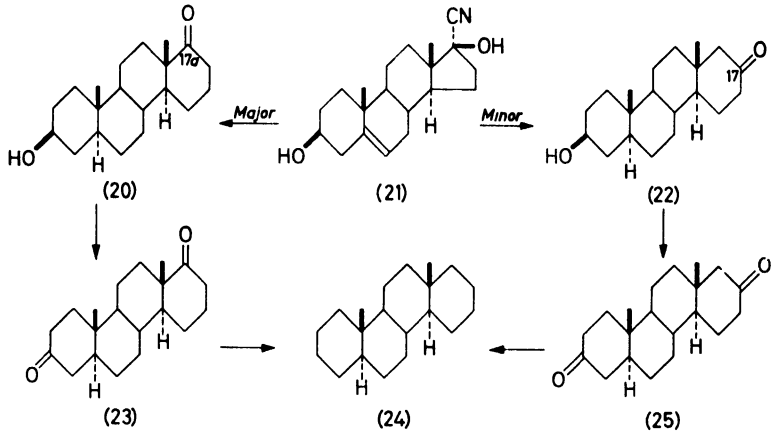
A route to *D*-homo-sex hormones utilizes pinacolic deamination. Androsterone cyanhydrin (17) by hydrogenation with platinum-acetic acid gives the α-aminol (18), which by deamination with nitrous acid gives *D*-homoandrosterone (19) which is nearly as potent as androsterone[320].

D-Homo*epi*androster-17a-one (20), prepared similarly from dehydro*epi*androsterone cyanhydrin (21), equals androsterone in



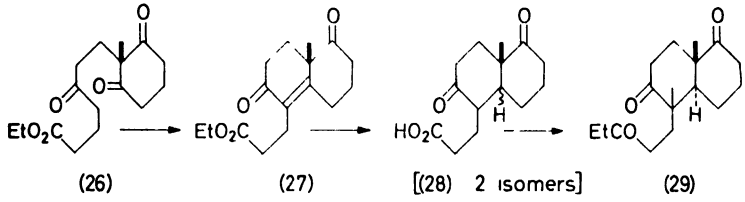
(17) (18) (19)

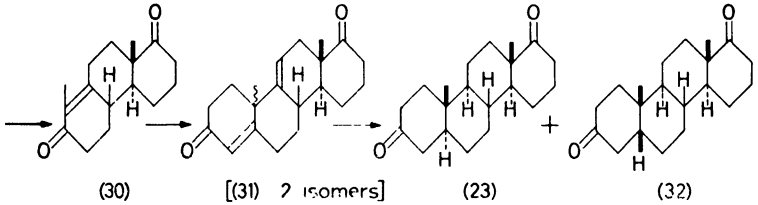
potency, and is accompanied by *D*-homo*epi*androster-17-one (22); oxidation with chromium trioxide gives respectively *D*-homoandrostane-3 : 17a-dione (23) and *D*-homoandrostane-3 : 17-dione (25), both converted by Wolff-Kishner reduction to *D*-homoandrostane (24)[321].



The total synthesis of (±)-*D*-homoandrostane-3 : 17a-dione (23) has been reported. MIESCHER and co-workers[322] condensed 2-methyl*cyclo*hexane-1 : 3-dione and ethyl 7-chloro-5-oxoheptanoate with trimethylamine to give the trioxoester (26), cyclized by trimethylamine benzoate in boiling xylene to the dioxoester (27). Hydrogenation and alkaline hydrolysis then gave two racemic acids (28), which were separated. The more abundant isomeride (as the bisethylene ketal) was converted by treatment as the dimethylamide with ethylmagnesium bromide into the ethyl ketone (29), which by hydrolysis of the ketal groups and alkaline cyclization gave the racemic $\alpha\beta$-unsaturated tricyclic diketone [as (30)], whose configuration was established by correlation with an intermediate in Woodward's total synthesis of cholestanol [*see* Chapter II, p. 45].

Reaction with methyl vinyl ketone then gave two racemic tetracyclic diketones (31), one of which by hydroxylation gave (±)-*D*-homoandrostane-3 : 17a-dione [as (23)] accompanied by (±)-*D*-homoaetiocholane-3 : 17a-dione [as (32)].

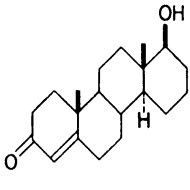




(±)-18-nor-*D*-Homoandrostane-3 : 17a-dione (34) has been totally synthesized by JOHNSON and co-workers[323] from (±)-18-nor-*D*-homo*epi*androsterone (33), an intermediate in the total synthesis of (±)-*epi*androsterone [*see* p. 134]; the racemic compound (34) was at least one-tenth as active as testosterone, which suggests that 18-nor hormones may be expected to exhibit biological activity provided the *C*/*D*-rings are *trans*-fused.

D-Homotestosterone (35) has been prepared, and has two-thirds of the activity of testosterone[266]; *D*-homo*epi*androsterone (20) has been converted into *D*-homodihydrotestosterone, which is almost as androgenic as dihydrotestosterone[324]; dihydrotestosterone cyanhydrin by reduction and deamination gives an *A*-homodihydrotestosterone [(36) or the 3-oxoisomeride][325]. The total synthesis of 18 : 19-bisnor-*D*-homotestosterone [(37): R = H] has been reported by WILDS and NELSON[326].

17aα-Methyl-*D*-homotestosterone [(37): R = Me] and its 17aβ-epimeride have been prepared; the former is as active as testosterone, but the latter is relatively inactive[327].



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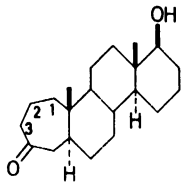

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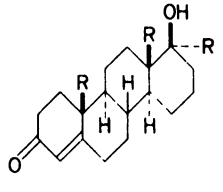
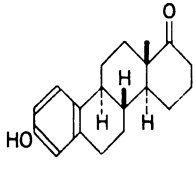


(37)

D-Ring-increase does not materially affect androgenic activity; by contrast progestational, cortical, or oestrogenic activity is largely or completely destroyed. (+)-Oestrone acetate cyanhydrin by reduction and deamination yields *D*-homo-oestrone (38)[328], reduced to *D*-homo-oestradiol-17aβ (39)[328], and converted through its cyanhydrin by reduction and deamination into *D*-bishomo-oestrone (40)[328].



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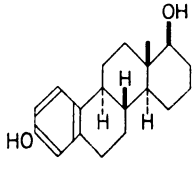

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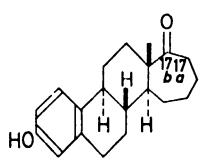
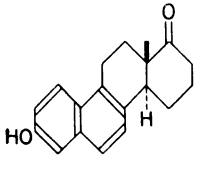


(40)

The *D*-homo-oestrogens (38) and (39) are only one-thirtieth as active as (+)-oestrone; on the other hand totally synthetic (+)-*D*-homoequilenin (41)[329] is almost as potent as natural (+)-equilenin, although (±)-14-*iso*-*D*-homoequilenin [as (42)][330] is inactive like totally synthetic (±)-14-*iso*equilenin. *D*-Homoprogesterone [(43): R = H][331] has been prepared but not compared with progesterone, whilst *D*-homodeoxycorticosterone acetate [(43): R = OAc][331] is about one-tenth as active as deoxycorticosterone acetate.



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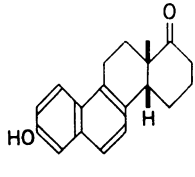

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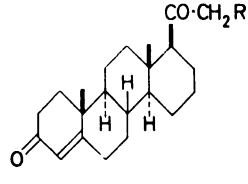
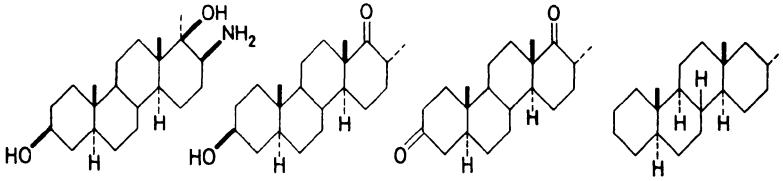


(43)

The compounds 'uranediol' and 'uranetriol' isolated from mares' pregnancy urine[332, 333] are *D*-homoandrostane derivatives. Although

the diol and triol from a diacetate and triacetate, the related diketone and triketone possess one hindered carbonyl group. The oxime of 17aα-methyl-*D*-homoandrost-5-ene-3β : 17aβ-diol-17-one (8) by catalytic reduction gives the 17β-amin-17aβ-ol (44), deaminated with nitrous acid to a substance which was regarded as a 17 : 17a-oxide because it exhibited no ketonic activity[334], but which is 17α-methyl-*D*-homoandrostan-3β-ol-17a-one (45)[335, 336] and identical with 'uranolone'; oxidation affords 17α-methyl-*D*-homoandrostane-3 : 17a-dione (46), identical with 'uranedione', which furnishes the corresponding hydrocarbon 'uranc', which is 17α-methyl-*D*-homoandrostane (47).



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IV

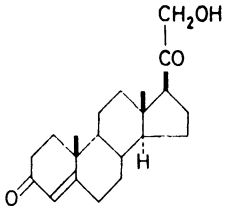
THE ADRENOCORTICAL HORMONES

THE adrenal glands of mammals comprise two sharply differentiated regions, the medulla producing (—)-adrenaline, and the cortex elaborating one or more hormones essential to life. Absence of these hormones, following destruction of the glands by tubercular infection, or bilateral adrenalectomy, was shown by Addison (1855) and Brown-Sequard (1856), respectively, to lead to multiple insufficiency symptoms and to death. Production of the adrenocortical hormones is controlled by the adrenocorticotrophic hormone [ACTH], which is a polypeptide of the anterior lobe of the pituitary.

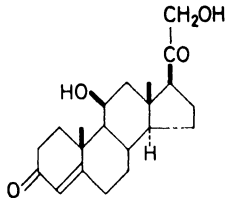
About 1930, adreno-cortical extracts were prepared, which by daily injection were capable of maintaining Addisonian patients and adrenalectomized animals alive for practically unlimited periods. It was at first thought that the biological activity of such extracts was due to a single substance, but during the period 1935–1957 forty-one compounds have been isolated, of which eight [(1)–(8)] are highly active.

Isolation. The mixture of substances is separated by use of Girard's reagent T into ketonic and non-ketonic fractions, and the water-soluble hydrazones fractionally hydrolysed at varying pH. Further separation is achieved by careful chromatography of the acetates on neutralized aluminium oxide, or by partition chromatography using Kieselguhr and water as the stationary phase and hexane with increasing proportions of benzene and chloroform as the mobile phase. Four groups of workers were engaged in the isolation of individual compounds, which they designated initially by letters, some of which subsequently gave place to trivial names. The letter designations employed here are those of Reichstein [University of Basle], who isolated thirty-one of the substances shown in *Table XIII* and classified on the basis of oxygen content; Kendall and Mason [The Mayo Clinic, U.S.A.] isolated eight of these compounds, Pfiffner and Wintersteiner [Columbia University] four of these compounds, whilst Kuizenga and Cartland [The Upjohn Co., Kalamazoo, Mich., U.S.A.] obtained five of these compounds. Recently Wettstein [CIBA, Basle] has isolated ten compounds.

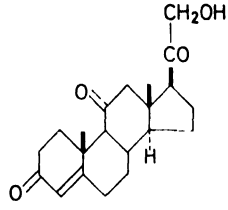
Cortisol is probably the primary product of the adrenal cortex, but glands exposed to minimal enzymatic change yield cortisol, cortisone, dehydrocorticosterone, substance S, and corticosterone in decreasing quantity.



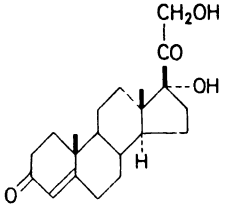
(1)
Substance Q
11-Deoxycorticosterone
[Cortexone]



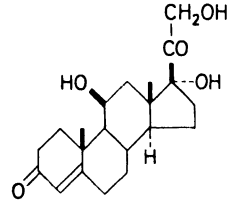
(2)
Substance H
Corticosterone



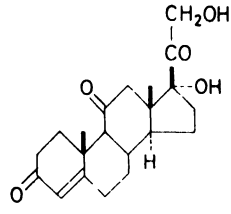
(3)
Kendall's Compound A
11-Dehydrocorticosterone



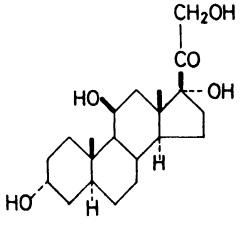
(4)
Substance S
17α-Hydroxy-11-deoxycorticosterone



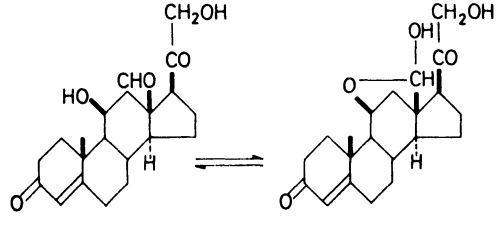
(5)
Substance M
17α-Hydroxycorticosterone
[Cortisol]



(6)
Substance F
Kendall's Compound E
17α-Hydroxy-11-dehydrocorticosterone
[Cortisone]



(7)
Substance C



(8)
Aldosterone

Except in substance C, when the hydroxyl group at $C_{(3)}$ is α-orientated, the configuration of hydroxyl groups at $C_{(3)}$ is β; the 3β-hydroxy compounds are precipitated by digitonin. The β-configuration of hydroxyl groups at $C_{(11)}$ is proved and is invariable. All the substances have β-orientated side chains so that a hydroxyl group at $C_{(17)}$ must be α-orientated. Of the eight

Table XIII

ADRENOCORTICAL STEROIDS

Compound	Substance: Reichstein	Substance: Kendall	Substance: Wintersteiner	Formula	m.p.°	$[\alpha]_D°$	Acetate: m.p.°	Acetate: $[\alpha]_D°$
*allo*Pregnane-3β : 11β : 17α : 20β : 21-pentol	A	D	A	$C_{21}H_{36}O_5$	222	+ 16	220	+ 74
*allo*Pregnane-3α : 11β : 17α : 21-tetrol-20-one	C	C	D	$C_{21}H_{34}O_5$	276	+ 73	205	+ 74
*allo*Pregnane-3β : 11β : 17α : 21-tetrol-20-one	V	—	—	$C_{21}H_{34}O_5$	225	+ 51	227	+ 63
*allo*Pregnane-3β : 17α : 21-triol-11 : 20-dione	D	G	B	$C_{21}H_{32}O_5$	242	+ 62	224	+ 72
*allo*Pregnane-11β : 17α : 21-triol-3 : 20-dione	—	—	—	$C_{21}H_{32}O_5$	—	—	212	+ 69
Pregn-4-ene-11β : 17α : 20β : 21-tetrol-3-one	E	—	—	$C_{21}H_{32}O_5$	125*	+ 87*	230	+ 163
Pregn-4-ene-17α : 20β : 21-triol-3 : 11-dione	U	—	—	$C_{21}H_{30}O_5$	208	—	253	+ 178
Pregn-4-ene-17α : 20α : 21-triol-3 : 11-dione	20-*epi*-U	—	—	$C_{21}H_{30}O_5$	243	+ 141	280	+ 99
Pregn-4-ene-6β : 17α : 21-triol-3 : 20-dione	—	—	—	$C_{21}H_{30}O_5$	234	+ 59	—	—
Pregn-4-ene-17α : 19 : 21-triol-3 : 20-dione	—	—	—	$C_{21}H_{30}O_5$	241	+ 119	232	—
Pregn-4-ene-6β : 11β : 21-triol-3 : 20-dione	—	—	—	$C_{21}H_{30}O_5$	227	+ 118	188	—
Pregn-4-ene-11β : 19 : 21-triol-3 : 20-dione	—	—	—	$C_{21}H_{30}O_5$	192	—	amorph.	—
Pregn-4-ene-11β : 17α : 21-triol-3 : 20-dione [17α-Hydroxycorticosterone; CORTISOL]	M	F	—	$C_{21}H_{30}O_5$	220	+ 167	225	+ 157
Pregn-4-ene-17α : 21-diol-3 : 11 : 20-trione [17α-Hydroxy-11-dehydrocorticosterone; CORTISONE]	F	E	F	$C_{21}H_{28}O_5$	215	+ 209	241	+ 164
Pregn-4-ene-6β : 21-diol-3 : 11 : 20-trione	—	—	—	$C_{21}H_{28}O_5$	208	—	183	—
18-Carboxypregn-4-ene-21-ol-3 : 20-dione	—	—	—	$C_{21}H_{28}O_5$	219	+ 88	—	—
*allo*Pregnane-3β : 17α : 20β : 21-tetrol	K	—	—	$C_{21}H_{36}O_4$	200	— 1	179	+ 53
*allo*Pregnane-3β : 17α : 21-triol-20-one	P	—	—	$C_{21}H_{34}O_4$	239	+ 48	209	+ 38

* Hydrate

Compound	Substance			Formula	m.p.°	$[\alpha]_D$°	Acetate	
							m.p.°	$[\alpha]_D$°
*allo*Pregnane-3β : 11β : 21-triol-20-one	R	—	—	$C_{21}H_{34}O_4$	204	—	174	+ 92
*allo*Pregnane-3β : 21-diol-11 : 20-dione	N	H	—	$C_{21}H_{32}O_4$	191	+ 94	145	+ 77
Pregn-4-ene-17α : 21-diol-3 : 20-dione [17α-HYDROXY-11-DEOXYCORTICOSTERONE]	S	—	—	$C_{21}H_{30}O_4$	205	+ 132	241	+ 116
Pregn-4-ene-20β : 21-diol-3 : 11-dione	T	—	—	$C_{21}H_{30}O_4$	224	+ 176	208	+ 170
Pregn-4-ene-11β : 21-diol-3 : 20-dione [CORTICOSTERONE]	H	B	—	$C_{21}H_{30}O_4$	182	+ 223	145/153	+ 200
Pregn-4-en-21-ol-3 : 11 : 20-trione [11-DEHYDROCORTICOSTERONE]	—	A	—	$C_{21}H_{28}O_4$	180	+ 229	181	+ 234
Pregn-4-ene-19 : 21-diol-3 : 20-dione	—	—	—	$C_{21}H_{28}O_4$	165	+ 180	127	+ 210
$\alpha\beta$-Unsaturated ketone: structure uncertain	—	—	—	$C_{21}H_{28-30}O$	264	+ 133	210	—
*allo*Pregnane-3β : 17α : 20β-triol	J	—	—	$C_{21}H_{36}O_3$	217	− 8	160	+ 25
*allo*Pregnane-3β : 17α : 20α-triol	O	—	—	$C_{21}H_{36}O_3$	223	− 13	250	− 30
*allo*Pregnane-3β : 17α-diol-20-one	L	—	G	$C_{21}H_{34}O_3$	264	+ 38	192	+ 15
Pregn-4-en-21-ol-3 : 20-dione [11-DEOXYCORTICOSTERONE, CORTEXONE]	Q	—	—	$C_{21}H_{30}O_3$	142	+ 178	159	+ 174
Pregn-4-en-17α-ol-3 : 20-dione [17α-HYDROXYPROGESTERONE]	—	—	—	$C_{21}H_{30}O_3$	223	+ 105	179†	—
*allo*Pregnan-3β-ol-20-one	—	—	—	$C_{21}H_{34}O_2$	194	+ 91	144	+ 77
Pregn-4-ene-3 : 20-dione [PROGESTERONE]	—	—	—	$C_{21}H_{30}O_2$	121/128	+ 192	—	—
Androstane-3β : 11β-diol-17-one	—	—	—	$C_{19}H_{30}O_3$	235	+ 84	229	+ 70
Androst-4-en-11β-ol-3 : 17-dione	—	—	—	$C_{19}H_{26}O_3$	199	+ 203	—	—
Androst-4-ene-3 : 11 : 17-trione [ADRENOSTERONE]	—	—	—	$C_{19}H_{24}O_3$	224	+ 262	—	—
Androst-4-ene-3 : 17-dione	—	—	—	$C_{19}H_{26}O_2$	174	+ 190	—	—
(+)-Oestrone	—	—	—	$C_{18}H_{24}O_2$	260	+ 165	125	—

†$\Delta^{2:4}$-Enol-3 : 17α- diacetate

substances possessing a hydroxyl group at $C_{(20)}$, seven possess the 20β-configuration whilst Substances O and 20-*epi*-U are 20α-hydroxy compounds. The single compound of unknown structure is probably a *D*-homosteroid; one compound has a $C_{(13)}$-carboxyl group.

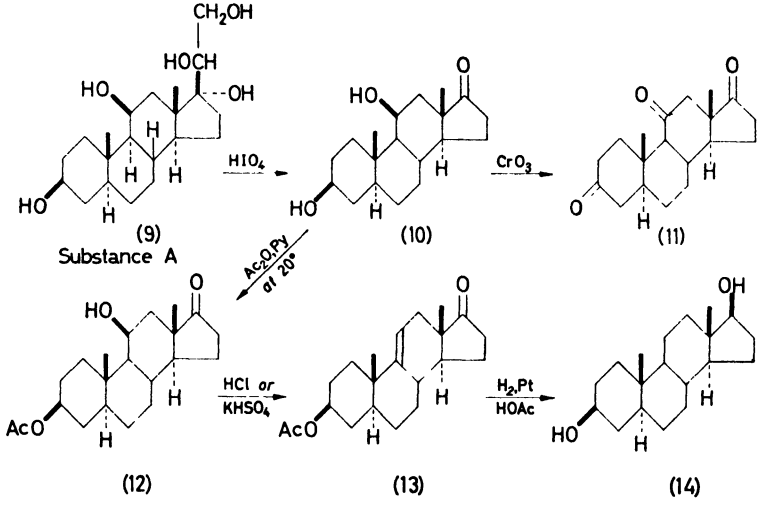
Five non-steroidal compounds have been isolated and comprise leucylproline, $\beta\beta$-dihydroxydiethylsulphoxide, dimethylsulphone, a base $C_{12}H_{12}O_2N_2$, and an acid $C_{12}H_{20}O_3N_2$.

Structure

allo*Pregnane Compounds*

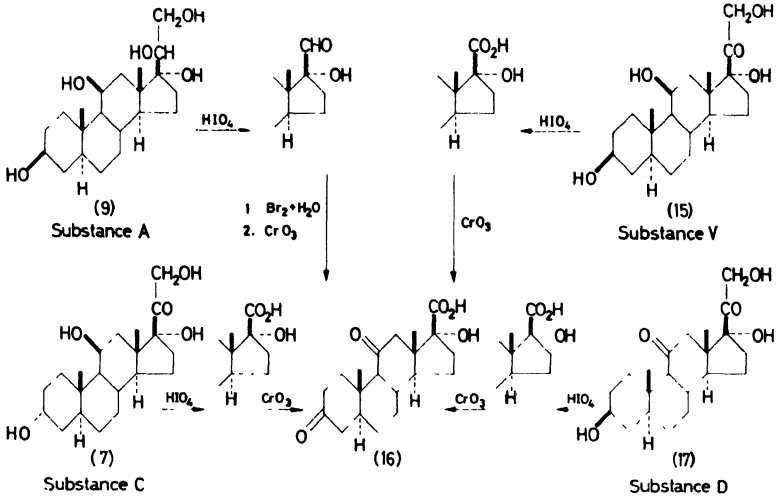
$C_{21}O_5$-Group: Substances A, C, D, *and* V

The first adrenal compound to be characterized was Substance A (9)[1,2,3]; it readily yields a 3 : 20 : 21-triacetate, and under forcing conditions a 3 : 17 : 20 : 21-tetracetate and a 3 : 11 : 17 : 20 : 21-pentacetate. Of the five hydroxyl groups, two furnish a mono-acetone derivative and are attached to adjacent carbon atoms. With excess periodic acid two equivalents of oxygen are consumed to give formaldehyde and androstane-3β : 11β-diol-17-one (10); use of chromium trioxide gives androstane-3 : 11 : 17-trione (11), converted by Clemmensen reduction into a mixture of androstane-17β-ol and androstane[2]. The presence of a 3β-hydroxyl group in Substance A was proved by Shoppee[4]; dehydration of the acetate (12) of the diolone (10) gave a 95% yield of $\Delta^{9(11)}$-*epi*androsterone acetate (13) converted by hydrogenation and hydrolysis to androstane-3β : 17β-diol (14).



Combination of this proof of an oxygen atom at $C_{(3)}$ with that, disclosed by production of androstan-17β-ol, of another oxygen atom at $C_{(17)}$ in the triketone (11), limits the position of the third oxygen atom in this compound to $C_{(11)}$ or $C_{(12)}$ because the triketone (11) is not soluble in alkali and one of the carbonyl groups is inert to ketonic reagents. Positions $C_{(1)}$, $C_{(2)}$, $C_{(4)}$, $C_{(15)}$, and $C_{(16)}$ are excluded because (11) is neither an α-diketone nor an alkali-soluble β-diketone; positions $C_{(6)}$ and $C_{(7)}$ are eliminated because 6- and 7-keto-compounds are not sterically hindered and are available for comparison. Position $C_{(12)}$ is improbable because introduction here of a carbonyl group would lead to manifestation of some of the properties of a β-diketone; position $C_{(11)}$ alone remains and has been proved correct by synthesis.

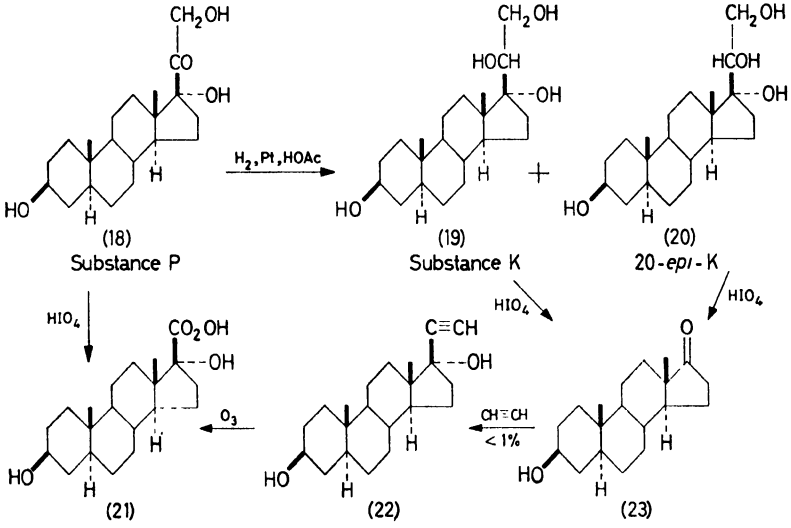
Like Substance A, Substance C [= 3-*epi*V] (7)[2,3,5], Substance D (17)[1,2,3,5], and Substance V (15)[2,6,7] by oxidation with chromium trioxide all give the triketone (11). By cautious oxidation with chromium trioxide V-diacetate yields D-diacetate, and



the four substances are correlated by conversion into the same 17α-hydroxy-3 : 11-dioxo*allo*etianic acid (16)[7,8]. Substance A does not reduce alkaline silver solution at 20°, and the presence of the glycerol-type side chain is shown by oxidation with periodic acid to an α-hydroxyaldehyde. Substances C, D, and V with the dihydroxyacetone side chain reduce alkaline silver solution rapidly at 20° and by oxidation with periodic acid give α-hydroxy acids. Only Substance D has been obtained synthetically[9].

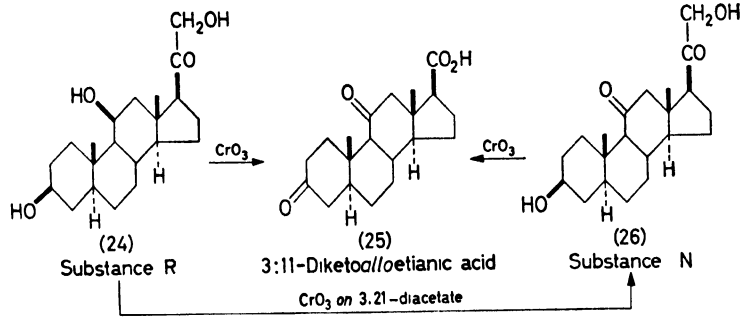
$C_{21}O_4$-Group: Substances P, K, R, *and* N

Substances P (18)[10,11] and K (19)[10] by oxidation with chromium trioxide give androstane-3 : 17-dione, whilst hydrogenation of P yields a mixture of K and 20-*epi*-K (20); both K and 20-*epi*-K by

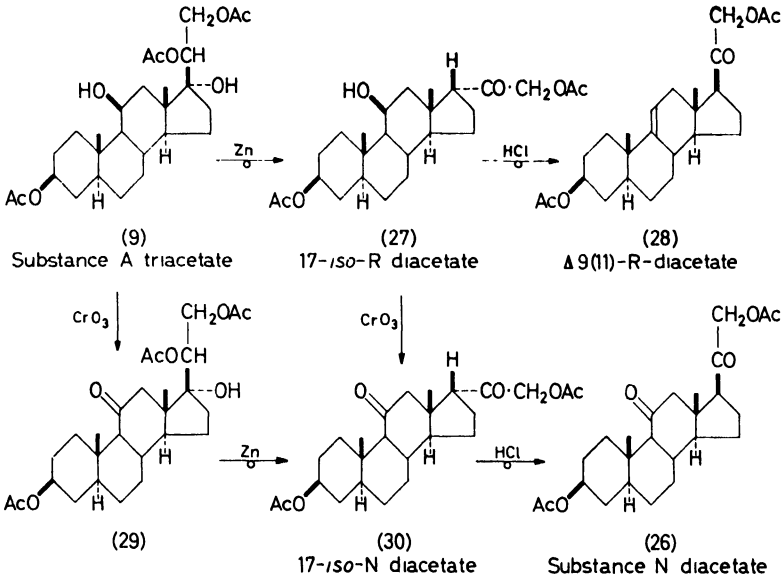


oxidation with excess periodic acid furnish *epi*androsterone (23). Oxidation of P with periodic acid affords 3β : 17α-dihydroxy*allo*etianic acid (21), also obtained from the 17β-ethinyl derivative (22) of *epi*androsterone[12]. Substance P, but not Substance K, reduces alkaline silver solution at 20°. The two compounds have been prepared by partial syntheses[13,14,15,16]; because the side chain is β-orientated they are 17α-hydroxy compounds. The 20β-hydroxy configuration of Substance K has been deduced from molecular rotation differences.

Substance R (24)[17] and Substance N (26)[10,18] by oxidation with chromium trioxide at 20° both give 3 : 11-dioxo*allo*etianic acid (25),



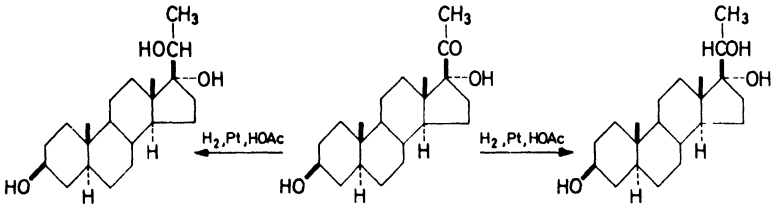
which has one inert carbonyl group; oxidation of R-diacetate gives N-diacetate. Both substances reduce alkaline silver solution rapidly at 20°. The structure of Substance N follows from its preparation from Substance A by SHOPPEE and REICHSTEIN[19]. When Substance A triacetate (9) is heated with zinc dust in toluene, one molecule of acetic acid is eliminated with inversion of configuration at $C_{(17)}$ [Serini reaction] to give 17-*iso*-R-diacetate (27); acidic rearrangement at $C_{(17)}$ of this leads also to dehydration with production of (28), but oxidation furnishes 17-*iso*-N-diacetate (30) also obtained by the Serini reaction from the oxo-triacetate (29) formed by oxidation of A triacetate. Brief treatment of 17-*iso*-N-diacetate (30) with ethanolic hydrogen chloride yields Substance N diacetate (26). Configuration at $C_{(3)}$ in Substances R and N is proved by this transformation; configuration at $C_{(11)}$ in Substance R has also been proved[20]. Substance R and, in principle, Substance N have been synthesized[21,22].



$C_{21}O_3$-GROUP: SUBSTANCES J, O, *and* L

Substance J (31)[23], Substance O (33)[10], and Substance L (32)[23] afford the common degradation product *epi*androsterone (23). Substance L is a ketone [monoxime] and by hydrogenation gives a mixture of J and O, which are 20-epimeric secondary alcohols, and are both oxidized by periodic acid to acetaldehyde and *epi*androsterone (23); substance L by oxidation with perbenzoic acid

also gives *epi*androsterone[24]. These substances have been obtained by partial syntheses[15,25-32]; they possess a 17α-hydroxyl group which

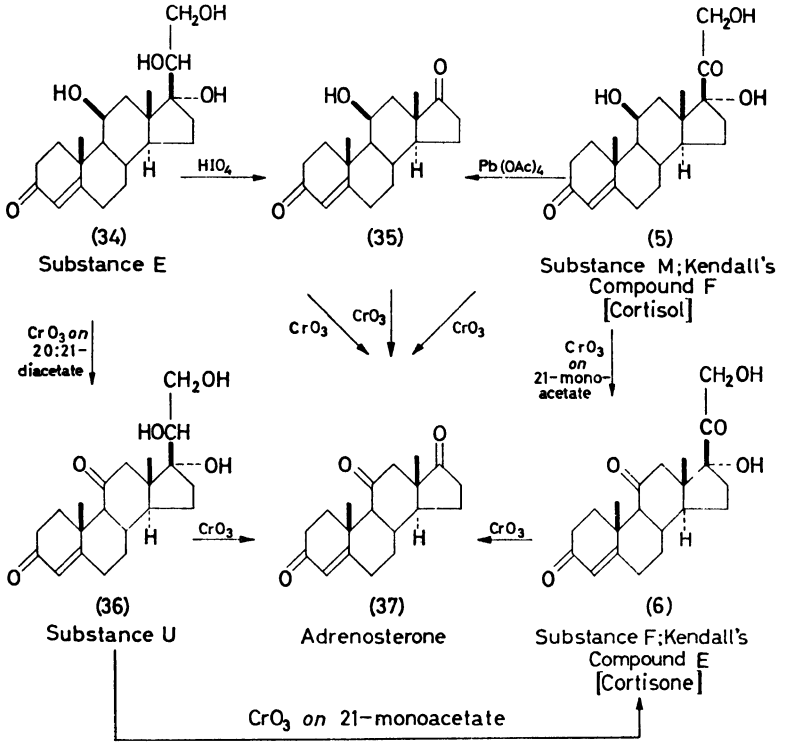


can be acetylated with acetic anhydride in the presence of toluene-*p*-sulphonic acid[33,34]. The configurations at $C_{(20)}$ are established.

Δ4-Pregnene Compounds

$C_{21}O_5$-Group: Substances E, F, M, *and* U, *and* Aldosterone

Substance E (34)[2,6,8], Substance U (36)[7,8], Substance M ≡ Kendall's Compound F ≡ 17α-hydroxycorticosterone ≡ cortisol (5)[3,5,6], and Substance F ≡ Kendall's Compound E ≡ 17α-hydroxy-11-dehydrocorticosterone ≡ cortisone (6)[3,5,21,35,36] are αβ-unsaturated ketones and all by oxidation with chromium trioxide afford adrenosterone (37). This αβ-unsaturated triketone has one inert carbonyl group [dioxime], and has been prepared by partial synthesis [*see* Chapter III, p. 145]; by hydrogenation it gives androstane-3 : 11 : 17-trione (11). The presence of the $C_{(17)}$-hydroxyl group in Substances E and cortisol is shown by their oxidation by periodic acid and lead tetracetate, respectively, to androst-4-en-11β-ol-3 : 17-dione (35), oxidized by chromium trioxide to adrenosterone (37)[37]. E-Diacetate by cautious oxidation gives U-diacetate, and cortisol monoacetate likewise gives cortisone monoacetate, whilst U-21-monoacetate affords cortisone monoacetate in poor yield in addition to adrenosterone[38]. Cortisone with acetic anhydride–toluene-*p*-sulphonic acid gives a 17α : 21-diacetate[34]. The structure of the side chain in Substances E, U, cortisol, and cortisone follows from the observations that E and U do not reduce alkaline silver solution at 20°, whereas cortisol and cortisone do so immediately and are oxidized by periodic acid to 11β : 17α-dihydroxy-3-oxoeti-4-enic acid and 17α-hydroxy-3 : 11-dioxoeti-4-enic acid, respectively. The $C_{(20)}$-hydroxyl group in Substances E and U has the β-configuration since these substances are obtained by stereospecific reduction with sodium borohydride of cortisol 21-monoacetate and cortisone 21-monoacetate, respectively[39]; 20-*epi*-U has been described[68a].



The constitution and configuration of Substance E also follow from its direct conversion into Substance A (9) by hydrogenation[8].

With concentrated sulphuric acid, Substances E and U and their diacetates give orange solutions showing a green fluorescence when viewed on a dark background. Most natural specimens of cortisone and its acetate give a similar orange solution with a green fluorescence; pure cortisone acetate, chromatographically purified, does not give this colour reaction which is probably due to traces of cortisol, which gives an orange solution with a very vivid green fluorescence. A quantitative colorimetric estimation of cortisone has been described[40].

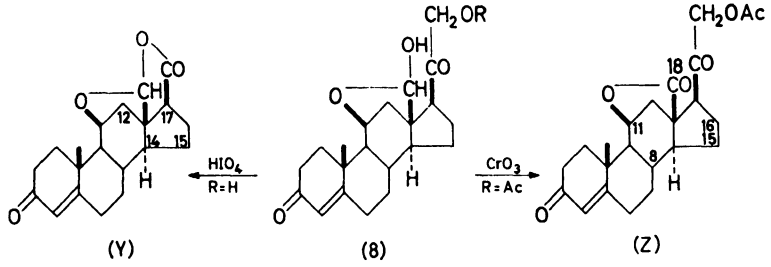
Cortisone (6)

Cortisone, Substance F, Kendall's Compound E, on account of its dramatic influence on chronic rheumatoid arthritis and acute rheumatic fever[41], is produced commercially. Numerous partial and total syntheses have been effected by chemical and microbiological methods [*see* pp. 198 and 205 et seq.]. Partial syntheses of cortisol and Substances E and U have also been achieved [*see* p. 210].

Aldosterone [= electrocortin] (8)

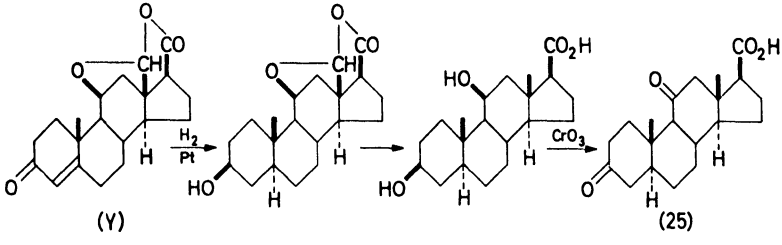
Aldosterone, the substance responsible for the high biological activity of the 'amorphous fraction' remaining after separation of the various crystalline adreno-cortical substances, was isolated in pure crystalline form in 1953[42,43], following its detection by a microbioassay method based on the urinary Na^{24}/K^{42}-ratio in adrenalectomized rats[44]. It is an $\alpha\beta$-unsaturated ketone, and it readily forms a monoacetate and a diacetate so that it contains two primary or secondary hydroxyl groups. It reduces alkaline silver solution at once at 20°, gives 1 mol. of formaldehyde by oxidation with sodium bismuthate and is thus an α-ketol.

Aldosterone [(8): R = H] by oxidation with potassium periodate gives a crystalline compound of high m.p. shown by its infra-red spectrum to be a γ-lactone (Y)[43]. The only γ-positions relative to a 17β-carboxyl group are $C_{(12)}$, $C_{(14)}$, $C_{(15)}$, and $C_{(18)}$; a hydroxyl group at $C_{(12)}$ cannot lactonize owing to the presence of the β-orientated angular methyl group at $C_{(13)}$, whilst a hydroxyl group at $C_{(14)}$ would be tertiary, so that aldosterone must possess a hydroxyl group at $C_{(15)}$ or $C_{(18)}$.



Aldosterone [lactol form]

Aldosterone monoacetate [(8): R = Ac] by oxidation with chromium trioxide at 20° gives a second γ-lactone (Z)[43]. The carbonyl group of this lactone represents one of the original hydroxyl groups, and can only be at $C_{(18)}$ to yield a γ-lactone by interaction with the original second hydroxyl group placed at $C_{(8)}$, $C_{(11)}$, $C_{(15)}$,

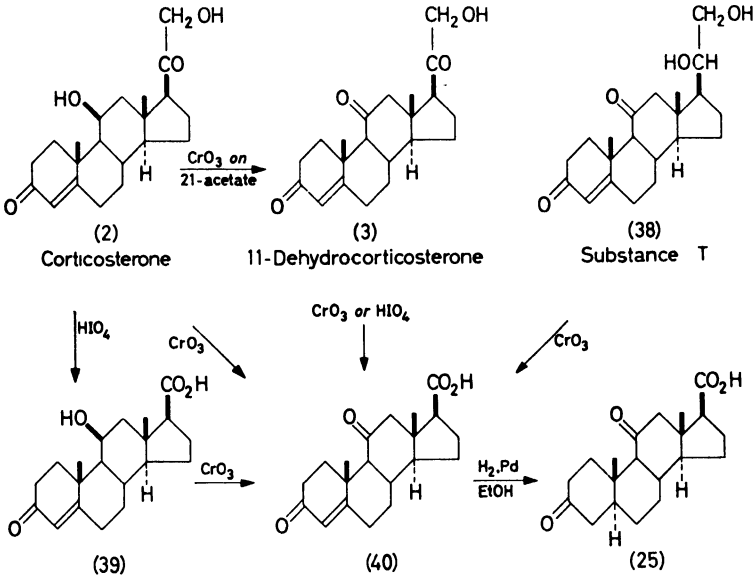


or $C_{(16)}$. Aldosterone is an 11β-hydroxy-compound since hydrogenation of (Y) and subsequent Wolff-Kishner reduction gives 3β : 11β-dihydroxy*allo*etianic acid, oxidized to 3 : 11-dioxo*allo*etianic acid (25)[43]. In solution aldosterone exists as an equilibrium mixture of aldo and lactol forms; it is 18-oxocorticosterone, and has recently been totally synthesized [*see* p. 213].

$C_{21}O_4$-Group: Corticosterone, 11-Dehydrocorticosterone, Substances T *and* S

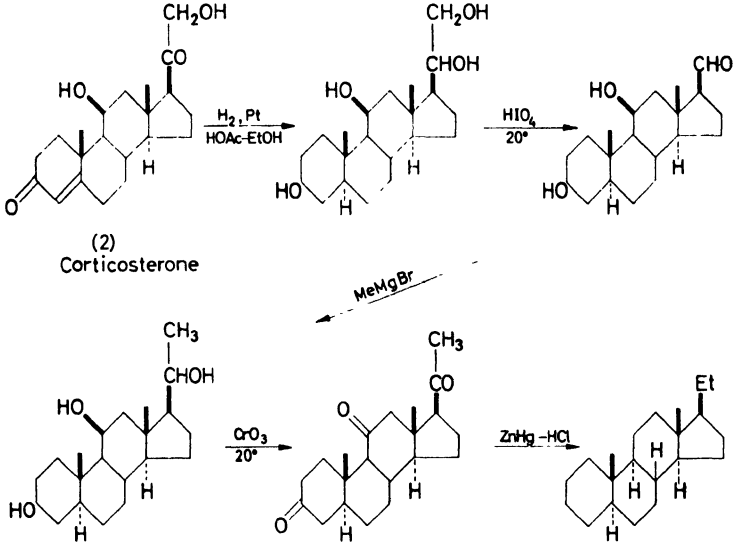
Corticosterone [originally called Substance H] (2)

Corticosterone was the first biologically active compound to be isolated from the adrenal gland[6,8,45]. 11-Dehydrocorticosterone ≡ Kendall's Compound A, (3)[3,5,17] and Substance T (38)[46], like corticosterone, are $\alpha\beta$-unsaturated ketones and by oxidation with chromium trioxide at 20° all three compounds yield 3 : 11-dioxoeti-4-enic acid (40)[47]; by hydrogenation with palladium–ethanol this gives 3 : 11-dioxo*allo*etianic acid (25), which provides a correlation with the *allo*pregnane-$C_{21}O_4$-group, whilst use of platinum in a neutral medium gives 3β-hydroxy-11-oxo*allo*etianic acid. Corticosterone gives only a 21-monoacetate, which by cautious oxidation with chromium trioxide gives 11-dehydrocorticosterone (3) as the 21-monoacetate; Substance T 20 : 21-diacetate is stable to chromium trioxide at 20°.

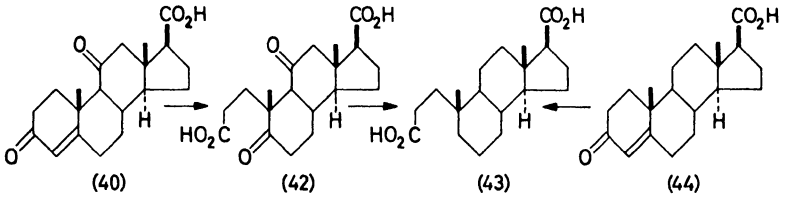


Corticosterone, 11-dehydrocorticosterone, and their esters, but not Substance T, reduce alkaline silver solution at 20° immediately; the α-ketol side chain is also disclosed by oxidation with periodic acid when corticosterone yields formaldehyde [1 mol.] and the acid (39), whilst 11-dehydrocorticosterone gives formaldehyde [1 mol.] and the dioxo acid (40). The conversion of the acid (39) by oxidation with chromium trioxide into the dioxo acid (40) provided the first evidence of a strongly hindered secondary hydroxyl group in corticosterone.

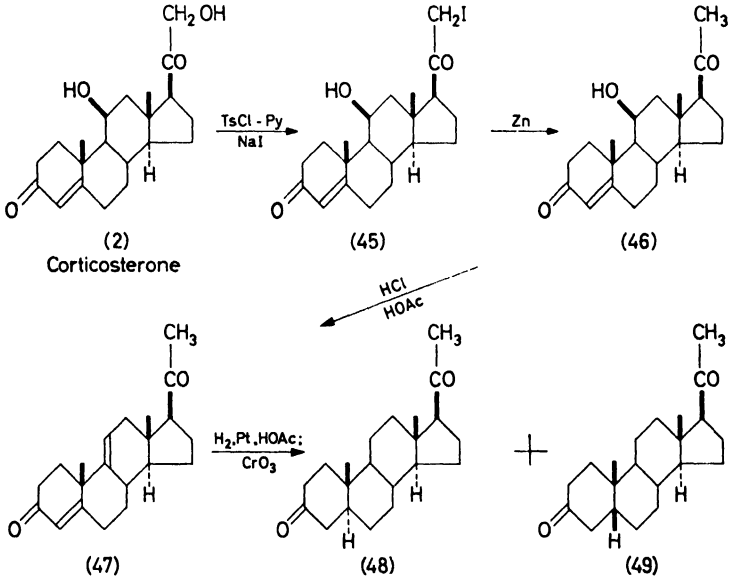
The carbon skeleton of corticosterone (2) was established by conversion to *allo*pregnane (41)[48]: the transformation involves a successful Clemmensen reduction of the $C_{(11)}$-carbonyl group, and proves the attachment of the side chain at $C_{(17)}$.



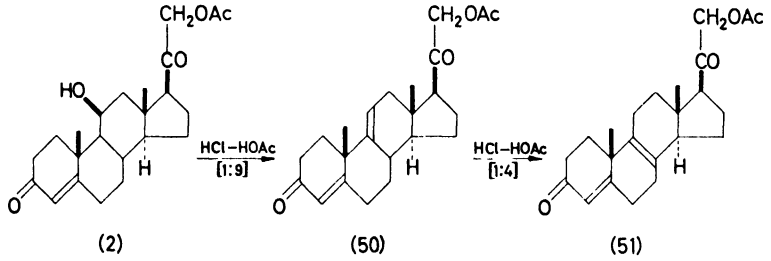
The presence of an oxygen atom at $C_{(3)}$ in corticosterone was first proved by the demonstration of a 3β-hydroxyl group in Substance A by SHOPPEE[4]; this had been correlated by SHOPPEE and REICHSTEIN[19] with Substances R and N, which are converted by oxidation with chromium trioxide into 3 : 11-dioxo*allo*etianic acid (25). A direct proof, somewhat vitiated by a yield of 0·5%, was obtained by degradation of 3 : 11-dioxoeti-4-enic acid (40) as methyl ester with ozone and Clemmensen reduction of the resulting dioxodicarboxylic acid (42) to the dicarboxylic acid (43) identical with the acid obtained by similar treatment from 3-oxoeti-4-enic acid (44) or progesterone[49].



A direct and satisfactory proof of the presence of an oxygen atom at $C_{(3)}$ and simultaneously of the position of the double bond at $C_{(4)} : C_{(5)}$ was adduced by SHOPPEE and REICHSTEIN[50] by transformation of corticosterone (2) through the 21-iodoketone (45) into 11β-hydroxyprogesterone (46), readily dehydrated to $\Delta^{9(11)}$-progesterone (47), which by complete hydrogenation and oxidation of the product to regenerate the two carbonyl groups afforded *allo*-pregnane-3 : 20-dione (48) and a little pregnane-3 : 20-dione (49).



Corticosterone and 11-dehydrocorticosterone are rather rapidly decomposed by hydroxyl ions at 20°; 11-dehydrocorticosterone is stable to hot dilute mineral acid, but corticosterone acetate is converted[51] partly into 9 : 11-anhydrocorticosterone acetate (50)[52] and an isomeride, originally regarded as the 11 : 12-anhydro-compound, which is probably Δ^8-11-deoxycorticosterone acetate (51)[51]; 11 : 12-anhydrocorticosterone acetate was subsequently obtained by partial synthesis[53,54], and is different from both (50) and (51).



(2) (50) (51)

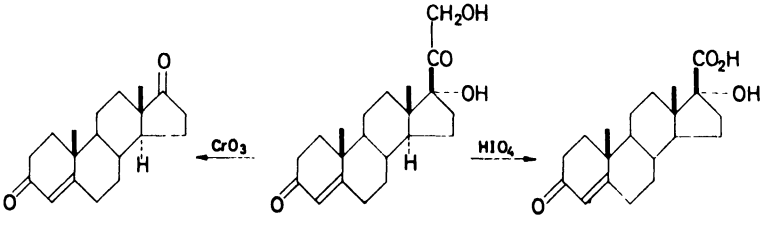
Corticosterone acetate

Corticosterone and its various esters yield orange solutions in concentrated sulphuric acid which show an intense green fluorescence when viewed above a dark surface; 11-dehydrocorticosterone gives an orange solution but no green fluorescence with concentrated sulphuric acid.

The partial synthesis of corticosterone was achieved by Reichstein in 1943; cortisone and cortisol have been converted into corticosterone[55]. 11-Dehydrocorticosterone has since been synthesized by numerous routes, whilst Substance T and 20-*epi*-T have also been obtained [*see* p. 202].

Substance S (53)

Substance S[17] is an $\alpha\beta$-unsaturated ketone; it reduces alkaline silver solution at once at 20°. By oxidation with chromium trioxide it gives androst-4-ene-3 : 17-dione (52), whilst use of periodic acid yields formaldehyde [1 mol.] and 17α-hydroxy-3-oxoeti-4-enic acid (54). Substance S with acetic anhydride–pyridine at 20° gives a 21-monoacetate and with acetic anhydride–toluene-*p*-sulphonic acid at 20° gives the 17α : 21-diacetate[33,34].



(52) (53) (54)

Substance S

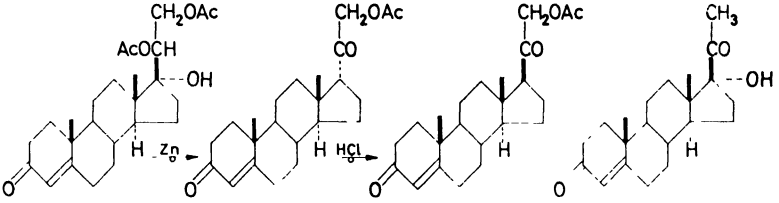
Substance S and its acetate melt at the same temperature as cortisone and its acetate, respectively, and give no mixed m.p. depression; apart from analysis and optical rotatory power, the reaction with concentrated sulphuric acid, whereby Substance S

and its acetate give a pure red colour, serves for differentiation. The partial synthesis has been accomplished by several routes.

$C_{21}O_3$-Group: 11-Deoxycorticosterone, 17α-Hydroxyprogesterone

11-Deoxycorticosterone, cortexone [Substance Q] (1)

11-Deoxycorticosterone was obtained by partial synthesis [*see* p. 199] about a year prior to its isolation in 1938 from adrenal extracts[17] and is a commercial product. It is an αβ-unsaturated ketone with an α-ketol side chain; it reduces alkaline silver solution immediately at 20° whilst periodic acid oxidation gives 3-oxoeti-4-enic acid. The 21-acetate [= DOCA] (57) and a large number of esters have been described; both parent substance and esters are sensitive to hydroxyl ions, but relatively stable to acids. The conversion to progesterone by the reaction sequence: $-CO-CH_2OH \rightarrow -CO-CH_2OTosyl \rightarrow -CO-CH_2I \rightarrow -CO-CH_3$, has been described[56,57]; conversely, 11-deoxycorticosterone may be obtained in poor yield by the action of lead tetraacetate on progesterone[58,59]. 17-*iso*-11-Deoxycorticosterone and its acetate (56), which are physiologically inactive, have been prepared by the Serini reaction from pregn-4-ene-17α : 20β : 21-triol-3-one diacetate (55); brief treatment of (56) with acid causes isomerization to 11-deoxycorticosterone acetate (57)[60].



(55) (56) (57) (58)

17-*iso*-11-Deoxycorticosterone acetate — 11-Deoxycorticosterone acetate [DOCA]

17α-Hydroxyprogesterone (58)

17α-Hydroxyprogesterone[61,62], an αβ-unsaturated ketone, gives a dioxime and disemicarbazone, and is unaffected by acetic anhydride–pyridine at 20°, but with refluxing *iso*propenyl acetate–toluene-*p*-sulphonic acid gives the $\Delta^{3,5}$-enol-3 : 17α-diacetate[63]. Oxidation with chromium trioxide yields androst-4-ene-3 : 17-dione (52); biochemical oxidation with *Rhizopus* yields 6β : 17α- and 11α : 17α-dihydroxyprogesterone[64]. On slow heating at 220° molecular rearrangement occurs to afford a *D*-homoandrostane derivative [*see* Chapter III, p. 151].

Numerous syntheses have been recorded[15,26,28,29,32,65,122a], and 9α-fluoro-17α-hydroxyprogesterone has been prepared[66]. 17α-Hydroxyprogesterone is not a gestogen, but possesses androgenic activity of the same order as androsterone[61,62].

Androstane Compounds

ANDROSTANE-3β : 11β-DIOL-17-ONE (10)

First obtained by degradation of Substance A, androstane-3β : 11β-diol-17-one was later isolated from adrenal extracts[17]; it gives a 3β-monoacetate, and with great difficulty a 3β : 11β-diacetate[67], and is androgenic[2].

ADRENOSTERONE, androst-4-ene-3 : 11 : 17-trione (37)

Adrenosterone was isolated from adrenal extracts[62], and is obtained by degradation of the Δ^4-unsaturated members of the $C_{21}O_5$-group. It has been synthesized [*see* p. 205; *also* Chapter III, p. 145], and converted into 11-oxotestosterone and 11β-hydroxyandrost-4-ene-3 : 17-dione[37,68], which has recently been isolated from hog adrenals[68a].

ANDROST-4-ENE-3 : 17-DIONE (52)

Androst-4-ene-3 : 17-dione was already well known [*see* Chapter III, p. 141] when it was isolated from adrenal extracts[62].

Cholesterol occurs in the adrenal gland, whilst *allo*pregnan-3β-ol-20-one[69], progesterone[69], and (+)-oestrone[70] have been isolated from adrenal extracts.

PARTIAL SYNTHESES

The major difficulties in the synthesis of adrenocortical steroids are (i) introduction of the Δ^4-3-keto-grouping, (ii) elaboration of the 17β-orientated α-ketol [$>CH\cdot CO\cdot CH_2OH$], hydroxyacetone [$>C(OH)\cdot CO\cdot CH_3$], and dihydroxyacetone [$>C(OH)\cdot CO\cdot CH_2OH$] side chains, and (iii) introduction of an oxygen atom at $C_{(11)}$. The principal methods for producing these molecular features are summarized, and syntheses of the physiologically active compounds [(1)–(6)] are outlined; for further detail, and for information relating to syntheses of the physiologically inactive adrenocortical substances, various reviews may be consulted[71–74].

Introduction of the Δ^4-3-Keto-Grouping

3-Ketones of the *A/B-cis*-series by bromination in acetic acid or with N-bromosuccinimide in carbon tetrachloride give 4β-bromo-3-ketones, dehydrobrominated with hot pyridine or collidine to Δ^4-3-ketones. Improved yields are obtained by the general method

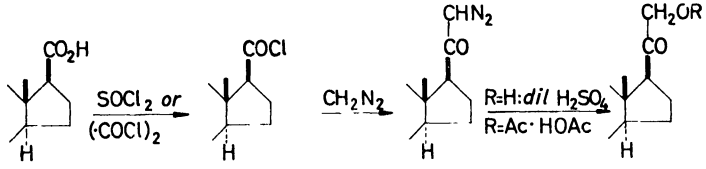
of MATTOX and KENDALL[75], whereby 4β-bromo-3-ketones undergo facile spontaneous dehydrobromination in polar solvents with 2 : 4-dinitrophenylhydrazine or semicarbazide, and the resulting Δ4-3-ketone hydrazone is cleaved by exchange with pyruvic acid. A recent development is the use of *tert.*-butyl hypochlorite simultaneously to produce the 3-ketone and convert it to the 4β-chloro-3-ketone[76].

3-Ketones of the *A/B-trans*-series by bromination in acetic acid or with N-bromosuccinimide in carbon tetrachloride give first the 2α-bromo-3-ketones, then the 2 : 2-dibromo-3-ketones, which in the presence of hydrogen bromide rearrange to 2α : 4α-dibromo-3-ketones[77]. These with sodium iodide in acetone or methyl ethyl ketone give 2α-iodo-4α-bromo-3-ketones, or by extended treatment, 2α-iodo-Δ4-3-ketones, which are readily reduced by chromous chloride to Δ4-3-ketones[78].

5α- or 5β-Hydroxy-3-ketones very readily give Δ4-3-ketones by treatment with acid[79,80,81], alkali[82], or by high vacuum pyrolysis[83,84]. 3α- or 3β-Hydroxy-Δ4-steroids are specifically oxidized by manganese dioxide in chloroform at 20° to Δ4-3-ketones[85].

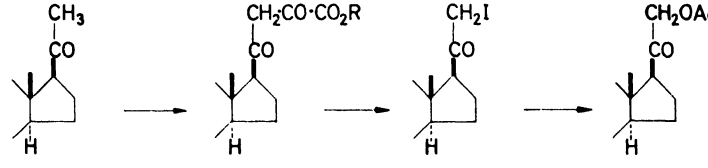
Elaboration of the 17β-[$>$CH·CO·CH$_2$OH] *Side Chain*

The diazoketone synthesis, developed by Reichstein for the synthesis of 11-deoxycorticosterone, has been extended by use of oxalyl chloride[86], and can now be applied to 11β-hydroxy compounds as the 11β-formates or 11β-trifluoroacetates[87]:

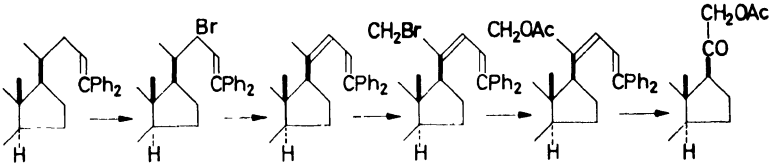


Formerly, oxidation of a methyl 20-ketone with lead tetracetate, $>$CH·CO·CH$_3$ → $>$CH·CO·CH$_2$OAc, had to be used for 11-hydroxy compounds[88]. The diazoketone synthesis cannot be applied to 16-dehydrosteroid acids[89].

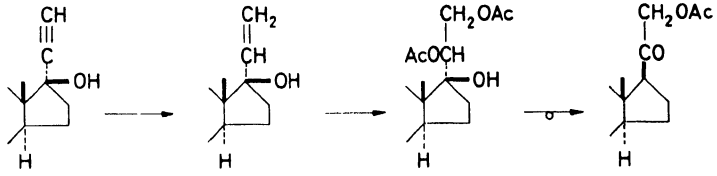
Another method introduced by RUSHIG[90] involves condensation of a methyl 20-ketone with an oxalic ester, iodination at C$_{(21)}$, and acetolysis.



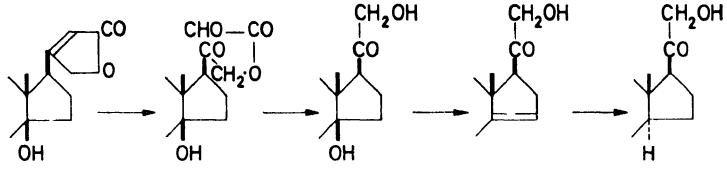
Alternatively, the modified Miescher-Wettstein degradation [*see* Chapter I, p. 26] may be employed and has been simplified by use of 2 mols. of N-bromosuccinimide in the presence of allyl bromide, whereby the first three steps are combined in one stage[91].



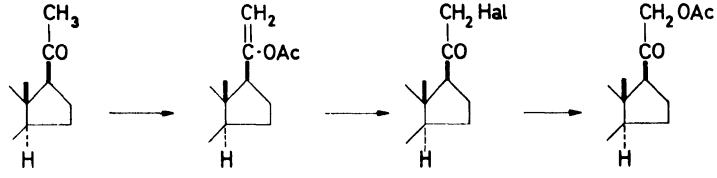
Steroid 17-ketones give 17α-ethinyl derivatives hydrogenated by palladium in pyridine to 17α-vinyl compounds; these with osmium tetroxide give 17β : 20β : 21-triols, which as the diacetates by treatment with zinc undergo the Serini reaction to give the α-ketol acetates[60, 92, 93, 100].



Cardiac aglycones can be degraded by ozonolysis at — 80° to glyoxylic esters, which are hydrolysed with potassium bicarbonate to 14β : 21-dihydroxy-20-ketones, convertible by dehydration and hydrogenation to the α-ketols[94, 95].



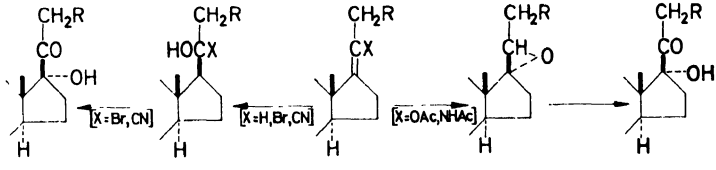
A new approach is provided by conversion of methyl 20-ketones with *iso*propenyl acetate to 20 : 21-enol acetates[96], which react with bromine or N-iodosuccinimide[97] to give 21-halogeno-20-ketones, acetolysed to the α-ketol acetates which are also obtained from the 20 : 21-enol acetates by oxidation with perbenzoic acid and rearrangement[98, 99].



Elaboration of the 17β-[>C(OH)·CO·CH_2R] *Side Chain* [R = H *or* OH]

The only efficient routes to 17α-hydroxy-steroids are from $\Delta^{17(20)}$-steroids or from Δ^{16}-steroids. $\Delta^{17(20)}$-Steroids are available by dehydration of 17β-hydroxy-steroids[100], by anionotropic change of 17α-vinyl-17β-hydroxy-compounds[92, 101], by Wolff-Kishner reduction of Δ^{16}-20-ketone semicarbazones[102], by the Favorski reaction on 17 : 21 : 21-tribromo-20-ketones and subsequent reduction of the resulting 20-bromo-acids with lithium aluminium hydride[103], from 17α-ethoxyethinyl compounds by hydration and lithium aluminium hydride reduction[104], or as the 17 : 20-enol acetates of 20-ketones[105]. Δ^{16}-Steroids are available by standard methods[65,106–108], and, notably, by treatment of 17 : 20-enol acetates of 20-ketones with N-bromosuccinimide[109], and by bromination of 20-ketones in presence of hydrogen bromide[110]; commercially they are obtained by degradation of ψ-sapogenins [*see* Chapter VI, p. 290].

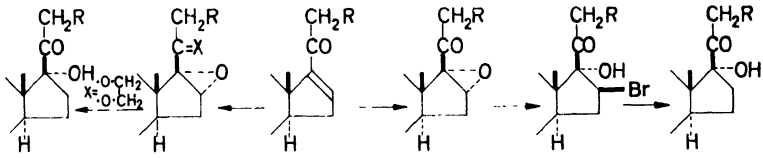
Hydroxylation of $\Delta^{17(20)}$-steroids with osmium tetroxide gives almost exclusively 17α : 20β-dihydroxy-compounds[12,16,111,112]; alternatively, hydroxylation of 20-bromo-[113] or 20-cyano-17(20)-ethylenes[114] leads by elimination of hydrogen bromide or hydrogen cyanide on hydrolysis of the intermediate osmic esters to the 17α-hydroxy-20-ketones. Hydroxylation of unsubstituted ethylenes can be achieved by use of hydrogen peroxide in presence of 5% of osmium tetroxide and combined with oxidation at $C_{(20)}$ to give the 17α-hydroxy-20-ketone in a single stage[115], whilst the use of osmium tetroxide can be eliminated by oxidation of 20-cyanoethylenes with permanganate[116] to give 90% yields of 17α-hydroxy-20-ketones[117].



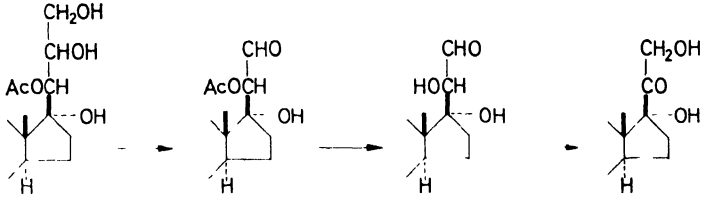
When the $\Delta^{17(20)}$-steroid is a 17 : 20-enol acetate, GALLAGHER's excellent method of conversion with perbenzoic acid to the 17α : 20α-epoxide and alkaline hydrolysis readily gives 17α-hydroxy-20-ketones in > 70% yield[32,118,119]. This method also permits preparation of 17 : 20-monoenol acetates from 11 : 20-diketones[120, 121], but has, so far, only been used for side chains with 21-methyl groups [R = H]. Alternatively, the $\Delta^{17(20)}$-steroid may be a 17 : 20-enamine acetate[121a].

Δ^{16}-Steroids with perbenzoic acid or with alkaline hydrogen peroxide afford 16α : 17α-epoxides, which by reduction with lithium aluminium hydride give 17α : 20-diols[65, 122]; if keto

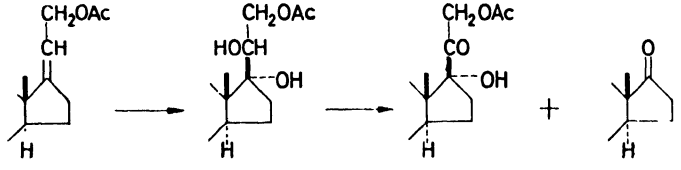
groups are protected by conversion to the ketals[30,65,76,123,124,125], hemithioketals[126], or thioketals[127], this route can yield 17α-hydroxy-20-ketones after removal of the protecting group(s) by mild acid hydrolysis or with Raney nickel; alternatively, the 16α : 17α-epoxide may be cleaved with hydrogen bromide and the resulting 16β-bromo-17α-hydrin reduced with nickel in ethanol[30,128] or by hydrogenolysis with palladium[110].



Previously, 17α : 20β : 21 : 22-tetrols had been converted as the 21 : 22-acetonides into the 20β-monoacetates, oxidized by periodic acid to the 20β-acetoxy-21-aldehydes, hydrolysed with potassium bicarbonate to the 20β-hydroxy-21-aldehydes, and rearranged by boiling pyridine[13,129,130].

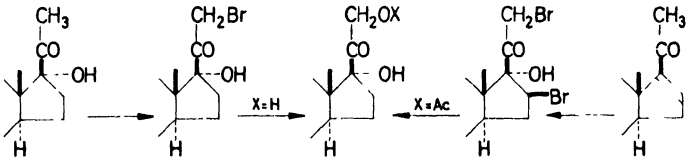


Subsequently, despite statements in the literature that chromium trioxide oxidation of 17α : 20 : 21-triol 21-monoacetates, readily prepared from 21-acetoxy-Δ^{17}-steroids, leads to complete loss of the side chain, SARETT[38] has shown that at low temperatures small yields of 17α : 21-dihydroxy-20-ketone 21-monoacetates are produced.



The 17α-hydroxyl group may be introduced prior to that at $C_{(21)}$ by hydroxylation of a 20-cyano-17(20)-ethylene[114] [R = H], or most conveniently by Gallagher's enol–acetate method[131]; thereafter

bromination of the 17α-hydroxy-20-ketone gives the 21-bromide, which by mild alkaline hydrolysis yields the 17α : 21-dihydroxy-20-ketone[118], or the 21-bromide may be transformed into the 21-iodide and subjected to acetolysis[132].



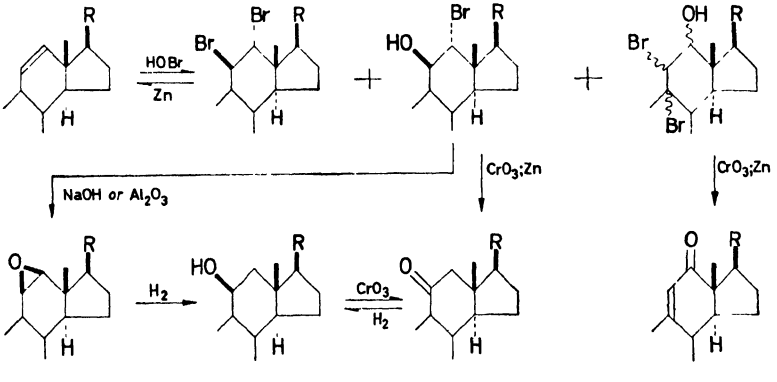
Alternatively, Δ^{16}-steroids may be converted via 16α : 17α-epoxides to 16β-bromo-17α-hydroxy-20-ketones, which may be brominated at $C_{(21)}$, converted to 21-acetates, and the 16β-bromine atom removed[128]. A specific paper-chromatographic test for distinguishing the side chain $>C(OH)\cdot CO\cdot CH_2OH$ from $>CH\cdot CO\cdot CH_2OH$ has been described[128a].

Introduction of Oxygen at $C_{(11)}$

The more abundant plant steroids ergosterol, stigmasterol, and diosgenin have no substituent in ring *C*, whilst the bile acids possess a hydroxyl group at $C_{(12)}$; methods have therefore been developed for the chemical or biochemical introduction of oxygen at $C_{(11)}$, and for the chemical transference of oxygen from $C_{(12)}$ to $C_{(11)}$.

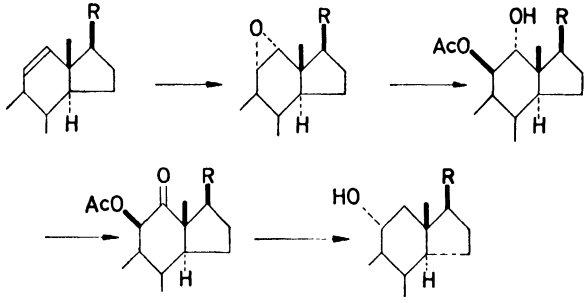
Oxygenation of Δ^{11}-Steroids [Reichstein, Gallagher, Kendall]

Δ^{11}-Steroids, obtainable by pyrolysis of 12-hydroxysteroids, e.g. 12α-hydroxycholanic acid[133], or their benzoates[134,135], anthraquinone-β-carboxylates[136], or from their toluene-*p*-sulphonates[137], by treatment with hypobromous acid, especially in the presence of traces of sulphuric or perchloric acid, give a difficultly separable

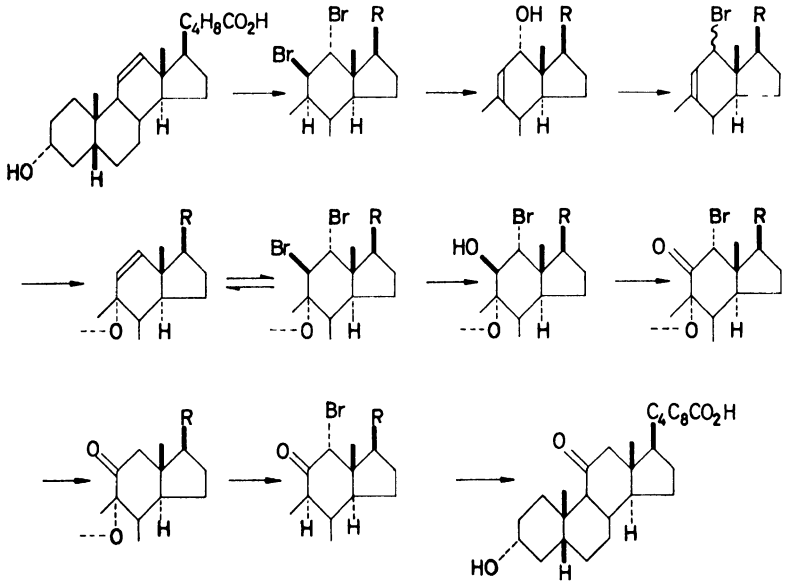


mixture of 11β : 12α-dibromide, 12α-bromo-11β-hydrin, and 9 : 11-dibromo-12-hydrin; oxidation of this mixture with chromium trioxide, followed by debromination with zinc gives starting material, 11-oxo-steroid, and $\Delta^{9(11)}$-12-oxo-steroid, which are readily separated chromatographically. This process, by which 11-oxygenated steroids were first prepared by REICHSTEIN, has been applied to the methyl esters of chol-11-enic acid[138], 3-oxo-, 3α-, and 3β-acetoxychol-11-enic acids[139], 3-oxo-, 3α-, and 3β-acetoxybisnorchol-11-enic acids[140], 3-oxo-, 3α-, and 3β-acetoxyeti-11-enic acids[141], and other compounds[142,143]. Alternatively, the 12α-bromo-11β-hydrins with alkali or by filtration through aluminium oxide give 11β : 12β-epoxides hydrogenated to 11β-hydroxysteroids[144].

Δ^{11}-Steroids with perbenzoic acid were found by GALLAGHER[145] to give 11α : 12α-epoxides, which undergo acetolysis with acetic–sulphuric acid at 20° to yield 11β-acetoxy-12α-hydroxy-steroids; these are oxidized to 11β-acetoxy-12-ketones, which by Wolff-Kishner reduction undergo inversion to give 11α-hydroxy-steroids readily oxidized to 11-oxo-steroids.

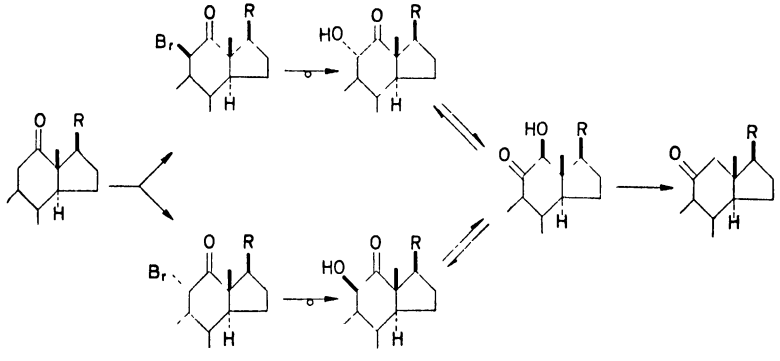


In 1946 KENDALL[146] found that 3α-hydroxychol-11-enic acid by bromine addition and dehydrobromination with aqueous sodium hydroxide gave 3α : 12α-dihydroxychol-9(11)-enic acid, readily converted by hydrogen bromide in chloroform to the 12ξ-bromide, which by washing with water gives quantiatively the Δ^{11}-3α : 9α-epoxide. This affords two isomeric *trans*-dibromides[147]. In the 11β : 12α-dibromide [diaxial] the 11β-bromine atom is labile and undergoes substitution by anions such as OH^-, OAc^- with retention of configuration; both lability and preservation of configuration are due to participation of the neighbouring bromine atom at $C_{(12)}$ in a linear transition state. Oxidation at $C_{(11)}$, reduction of the 12α-bromine atom, fission of the 3α : 9α-epoxide with hydrogen bromide, and removal of the resulting 12α-bromine atom gave 3α-hydroxy-11-oxocholanic acid.



TRANSFERENCE OF OXYGEN FROM $C_{(12)}$ TO $C_{(11)}$ [Gallagher, Cornforth, Hems, Wettstein]

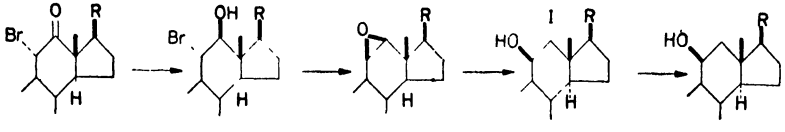
Bromination of methyl 3α-acetoxy-12-oxocholanate[148,149] gives a little of the 11β-bromide and much of the 11α-bromide[150]. GALLAGHER found that these epimeric bromides undergo bimolecular hydrolysis [S_N2] with 0·5N-potassium hydroxide at 20°; steric retardation operates and there is inversion, so that the 11β-bromide reacts rapidly to give the 11α-hydroxy-12-oxoacid, whilst the 11α-bromide reacts slowly to give the 11β-hydroxy-12-oxoacid[145,151]. Either ketol by Wolf-Kishner reduction gives the same 11α-hydroxy-acid; either ketol when heated with 4N-potassium hydroxide gives



an equilibrium mixture of 3α : 12β-dihydroxy-11-oxocholanic acid [the Marker-Lawson acid] [63%], its 12α-epimeride [1%], the 11α-ketol [30%], and the 11β-ketol [trace][152]. Conversion of the Marker-Lawson acid, which resists Wolff-Kishner reduction, to the methyl 3α-succinate, replacement of the 12β-hydroxyl group by bromine[153], and reduction with zinc or chromous chloride affords 3α-hydroxy-11-oxocholanic acid[154,155].

Similar reactions have been carried out in the norcholanic acid[156], bisnorcholanic acid[156], and etianic acid series[153,156,157]. In the hecogenin series, replacement of the 12β-hydroxyl group leads to attack in the side chain[156], but elimination of the 12-oxygen function may be achieved by oxidation with bismuth oxide to the 11 : 12-diketone, and Wolff-Kishner reduction of the 12-oxo group[159], or, more simply, in 80% yield by treatment of the 12β-acetate with calcium in liquid ammonia[160].

A new method, discovered simultaneously and independently by groups associated with CORNFORTH[161], HEMS[162], and WETTSTEIN[163], involves reduction of 11α-bromo-12-ketones with alkali borohydrides in good yield to 11α-bromo-12β-hydrins converted almost quantitatively by alkali or by silver oxide in pyridine to 11β : 12β-epoxides. These with halogen acids give 12α-halogeno-11β-hydrins, which in the case of the iodo-compounds are dehalogenated directly in quantitative yield to 11β-hydroxy-steroids.

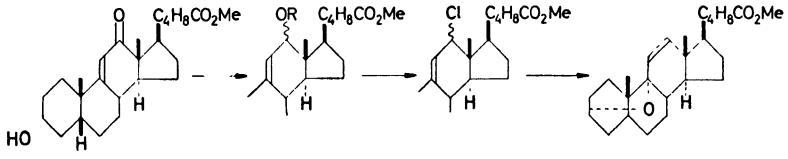


OXYGENATION OF $\Delta^{9(11)}$-STEROIDS [Kendall, Wallis, Sarett, Fieser]

$\Delta^{9(11)}$-Steroids may be obtained from $\Delta^{9(11)}$-12-oxosteroids; thus deoxycholic acid gives methyl 3α-benzoyloxy-12-oxocholanate, dehydrogenated by selenium dioxide in chlorobenzene–acetic acid, and hydrolysed to 3α-hydroxy-12-oxochol-9(11)-enic acid[164], which by the HUANG-MINLON[165] modification of the Wolff-Kishner reduction gives 50% of 3α-hydroxychol-9(11)-enic acid[166].

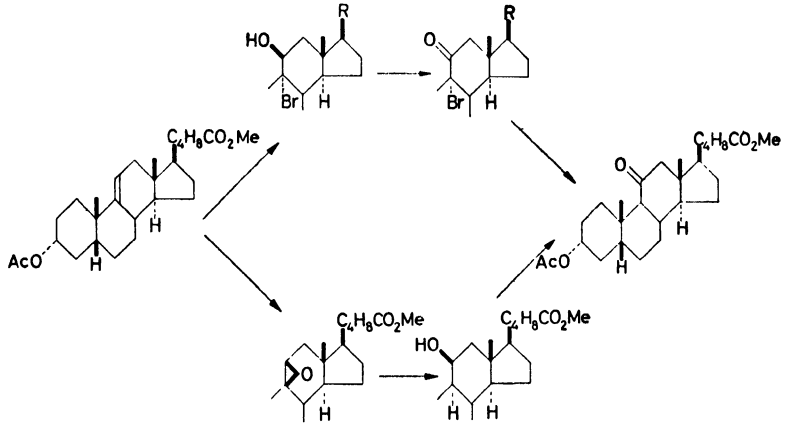
Since Kendall's 1946 method [*see* above] involves a $\Delta^{9(11)}$-intermediate, KENDALL[164] in 1948 introduced an improved procedure employing a $\Delta^{9(11)}$-steroid as starting material, thereby eliminating the wasteful prior pyrolytic preparation of a Δ^{11}-steroid. Methyl 3α-hydroxy-12-oxochol-9(11)-enate by hydrogenation yields a mixture of epimeric $\Delta^{9(11)}$-12-ols, converted by methanol–hydrochloric acid into a $\Delta^{9(11)}$-12ξ-methoxy-compound; when this is shaken in chloroform with concentrated hydrochloric acid, and the

$\Delta^{9(11)}$-12ξ-chloride washed with sodium hydrogen carbonate, the Δ^{11}-3α : 9α-epoxide is produced in 91% yield.



The whole reaction sequence proceeds smoothly with an overall yield of 60% and is of permanent synthetic value.

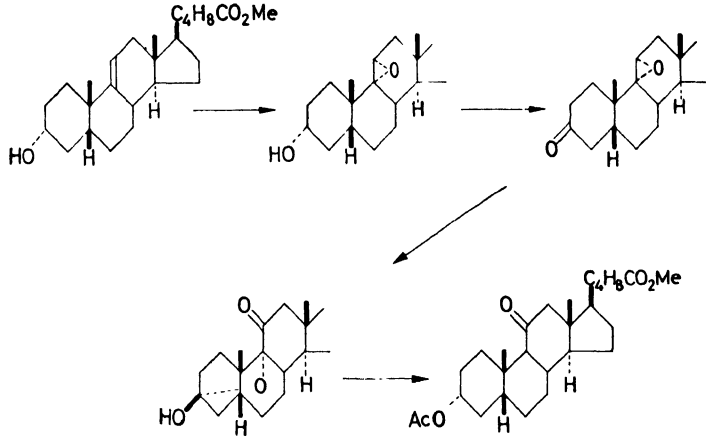
The simplest method is due to WALLIS[167]; methyl 3α-acetoxychol-9(11)-enate with hypobromous acid gives the 9α-bromo-11β-hydrin, oxidized with chromium trioxide, and debrominated with zinc to methyl 3α-acetoxy-11-oxocholanate, but in $\sim$ 8% yield only.



Another simple route, which proceeds in rather poor yield, has been described by SARETT[168]; methyl 3α-acetoxychol-9(11)-enate by oxidation with permanganate in aqueous acetic acid[169] gives 30% of the 9β : 11β-epoxide, hydrogenated in 25% yield by platinum–acetic acid to the 11β-ol, which by oxidation with chromium trioxide give methyl 3α-acetoxy-11-oxocholanate.

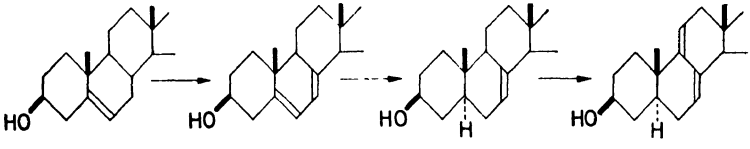
A more complex method is due to FIESER[170,171]; methyl 3α-hydroxy-chol-9(11)-enate with perbenzoic or perphthalic acid gives the 3α-hydroxy-9α : 11α-epoxide, which is extremely inert. Oxidation with chromium trioxide–acetic acid affords the 3-oxo-9α : 11α-epoxide, which shows remarkable reactivity in solvolytic reactions, and is further oxidized by chromium trioxide to methyl 3β-hydroxy-11-oxo-3α : 9α-epoxycholanate [= the hemiketal form of methyl

9α-hydroxy-3 : 11-dioxocholanate], which may be converted to methyl 3α-acetoxy-11-oxocholanate in numerous ways.

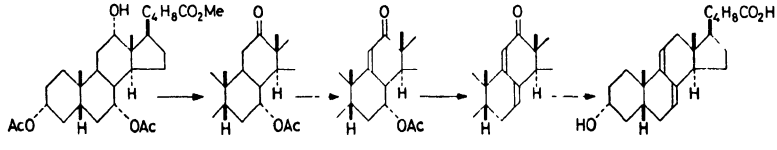


OXYGENATION OF $\Delta^{7\,9(11)}$-STEROIDS [Fieser, Djerassi, and Rosenkranz; Heusser and Jeger; Spring; Tishler]

$\Delta^{7\cdot 9(11)}$-Steroids are obtained by dehydrogenation of Δ^7-steroids with mercuric acetate[172,173,174,175,176] or with bromine[174, 177]. A $\Delta^{5:7}$-system is present in ergosterol, whilst Δ^5-steroids with bromine[178] or, preferably, with N-bromosuccinimide[179,180,181,182], are readily converted into $\Delta^{5:7}$-steroids; quantitative reduction of $\Delta^{5:7}$-steroids to Δ^7-steroids is readily carried out[177,182,183,184,185].



Cholic acid is readily converted as the methyl ester 3α : 7α-diacetate to the 12-ketone, dehydrogenated by selenium dioxide to the $\Delta^{9(11)}$-12-ketone; this by treatment with hydroxyl ions gives the $\Delta^{7:9(11)}$-12-ketone, which by Wolff-Kishner reduction affords 3α-hydroxychola-7 : 9(11)-dienic acid[183,186].

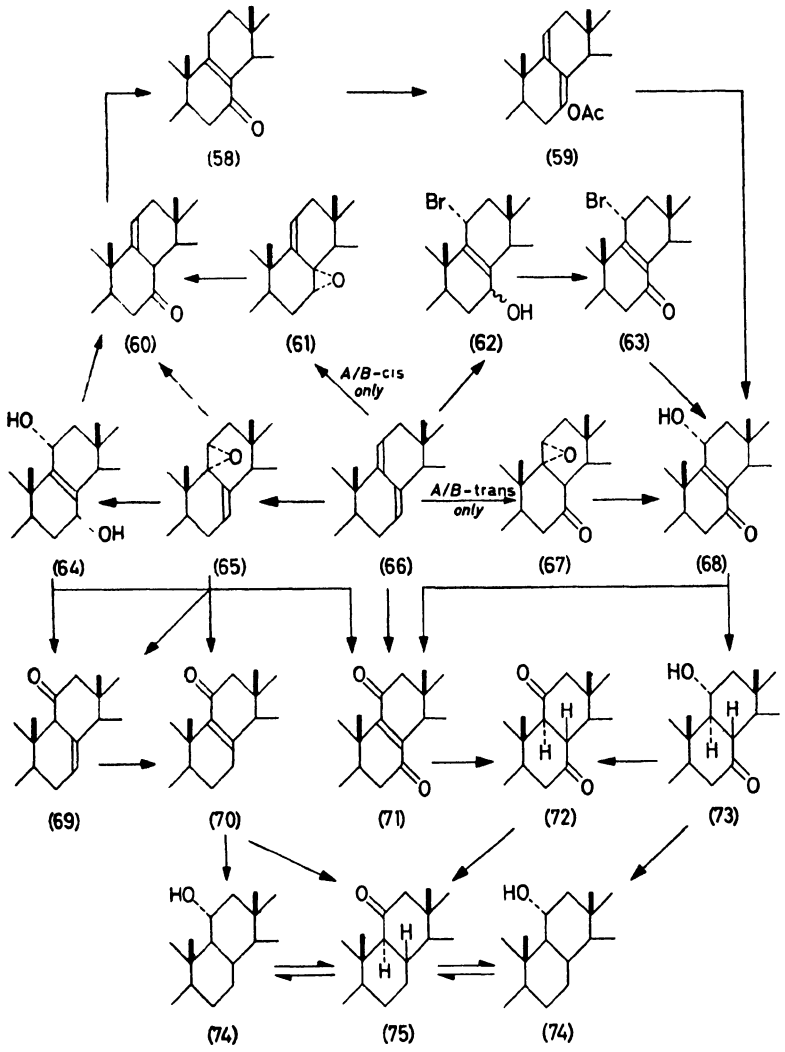


$\Delta^{7:9(11)}$-Steroids (66) of either the *A/B-cis*-series [e.g. methyl 3α-hydroxychola-7 : 9(11)-dienate] or the *A/B-trans*-series [e.g. ergosterol D] by oxidation with sodium dichromate dihydrate–acetic acid according to FIESER[187] yield Δ^{8}-7 : 11-diketones (71), readily reduced by zinc–acetic acid to 7 : 11-diketones (72), which by removal [Wolff-Kishner, or thioketal-nickel] of the more reactive 7-oxo-group give 11-oxosteroids (75); alternatively, dienes of either series with N-bromosuccinimide in aqueous *tert.*-butanol give Δ^{8}-11α-bromo-7ξ-hydrins (62), oxidized by excess of the reagent to Δ^{8}-11α-bromo-7-ketones (63), which may be converted by silver nitrate followed by chromic acid to Δ^{8}-11α-hydroxy-7-ketones (68)[188].

$\Delta^{7:9(11)}$-Steroids of the *A/B-trans*-series only [as (66)] with performic or peracetic acid were found by Rosenkranz and Djerassi to give 9α : 11α-epoxy-7-ketones (67), hydrolysed under mild alkaline conditions to Δ^{8}-11α-hydroxy-7-ketones (68)[177,189]; these can be converted with hydroxyl[177] or *tert.*-butoxide[190] ions, by triad prototropy and ketonization, directly to 7 : 11-diketones (72), or by selective hydrogenation with palladium–charcoal in ethanol or platinum in ethanolic potassium hydroxide to 11α-hydroxy-7-ketones (73) from which 11α-hydroxy-steroids (74) can be obtained[191,192].

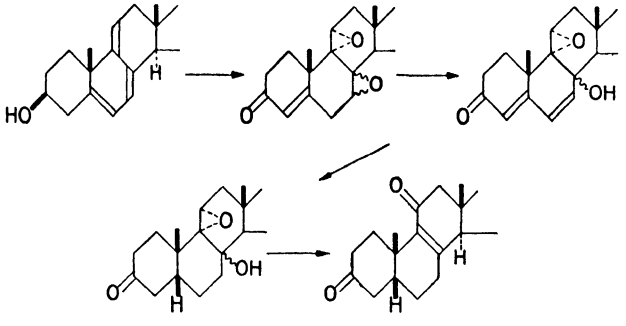
$\Delta^{7:9(11)}$-Steroids (66) of either stereochemical series with perbenzoic or permonophthalic acid were found by HEUSSER and JEGER[192], and by TISHLER[193], to yield mainly Δ^{7}-9α : 11α-epoxides (65), converted by acidic aluminium oxide[194] to Δ^{8}-7α : 11α-diols (64); these by oxidation give Δ^{8}-7 : 11-diketones (71)[187,192,194], or, by further peroxidation, hydrolysis, and dehydration, 9α : 11α-dihydroxy-7-ketones, further dehydrated to Δ^{8}-11α-hydroxy-7-ketones (68)[192,195]. Δ^{7}-9α : 11α-Epoxides (65) may be converted by boron trifluoride or ferric chloride[192] to Δ^{7}-11-ketones (69), isomerized in 85% yield by sulphuric acid in ether to Δ^{8}-11-ketones (70)[196], which are reduced by lithium in liquid ammonia to 11-oxo-steroids (75) and in presence of ethanol to 11α-hydroxy-steroids (74)[192,197,198,199]; alternatively, Δ^{7}-9α : 11α-epoxides (65) and Δ^{8}-7α : 11α-diols (64) may be transformed by brief treatment with acid to $\Delta^{9(11)}$-7-ketones (60)[192,197,198], which, together with $\Delta^{9(11)}$-7α : 8α-epoxides (61), are by-products in the peroxidation of *A/B-trans*-7 : 9(11)-dienes and the dichromate oxidation of dienes of both stereochemical series. Such $\Delta^{9(11)}$-7α : 8α-epoxides (61) and $\Delta^{9(11)}$-7-ketones (60) are readily rearranged to Δ^{8}-7-ketones (58) [also obtained by debromination of the 11α-bromo-Δ^{8}-7-ketones (63)[188]], which are the exclusive products of performic acid oxidation of $\Delta^{7:9(11)}$-steroids of the *A/B-cis*-series[177,187,188,200]. A Δ^{8}-7-ketone [as (58)] has been obtained by HEUSSER and JEGER[201] from ergosteryl acetate by oxidation with *tert.*-butyl chromate, and

reduction of the resulting 8α : 9α-epoxy-7-ketone with zinc–acetic acid. DJERASSI and ROSENKRANZ[191,200] discovered that Δ^8-7-ketones (58) of either the *A/B-cis-* or the *A/B-trans*-series by heating



with *iso*propenyl acetate and toluene-*p*-sulphonic acid give enol acetates (59), which when treated with perbenzoic acid or perphthalic acid give directly Δ^8-11α-hydroxy-7-ketones (68). Recently, a 5 : 7 : 9(11)-triene has been converted to the 7ξ : 8ξ-9α : 11α-diepoxide, which may be successively rearranged by hydroxide ions,

hydrogenated with palladium, and again rearranged to the 5β-Δ⁸-11-ketone (70)[202]. For a more detailed account of these transformations see ROSENKRANZ and SONDHEIMER[72].

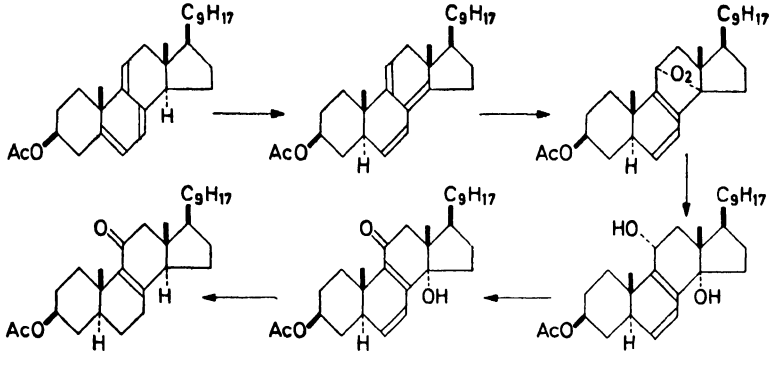


(70)

The use by JONES[203], INHOFFEN[204], HEUSSER and JEGER[205], and DJERASSI and ROSENKRANZ[206], of 5α-hydroxy-Δ$^{7:9(11)}$-steroids for some of the above reactions should be noted, since these 5α-hydroxy-compounds contain a potential Δ⁴-double bond.

BY FISSION OF A 11α : 14α-PEROXIDE [Laubach and Brunings]

Dehydroergosteryl acetate is catalytically isomerized in liquid sulphur dioxide to 3β-acetoxyergosta-6 : 8(14) : 9(11) : 22-tetraene, photoperoxidized to the 11α : 14α-peroxide; hydrogenolysis of this gives a 11α : 14α-diol, and base-catalysed rearrangement yields 3β-acetoxy-14α-hydroxyergosta-6 : 8 : 22-trien-11-one, dehydrated and then hydrogenated with nickel to 3β-acetoxyergosta-8 : 22-dien-11-one [cf. (70)][207].

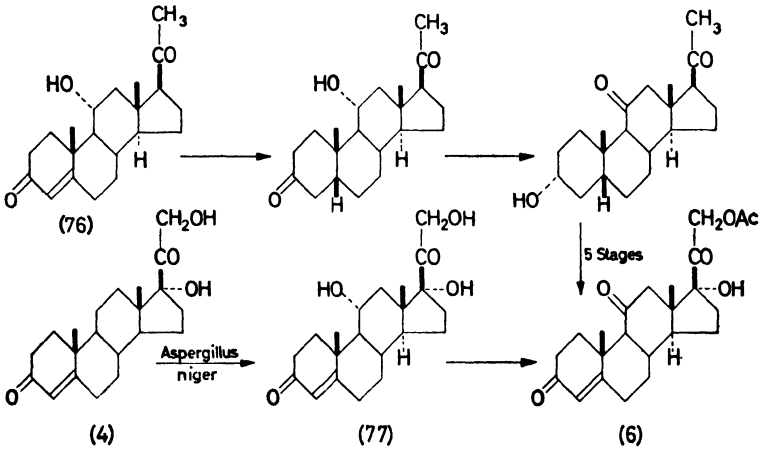


The extraordinarily unreactive 11β-hydroxyl group is sterically hindered by *both* angular methyl groups; this hindrance extends to

the 11-oxo group[165], which can however be removed by Clemmensen reduction[48], or by Wolff-Kishner reduction under special conditions[208]. 11β-Hydroxysteroids [OH: axial] are acylated with difficulty[67,87,209], but undergo ionic dehydration with ease [11β-OH/9α-H: *trans*][4,51,138,139]; 11α-hydroxysteroids [OH: equatorial] are readily acylated and resist ionic dehydration [11α-OH/9α-H: *cis*][145,151]. Recently, eliminations of *both* 11α- and 11β-substituents to yield $\Delta^{9(11)}$-steroids have been reported[52,211,212,213,214]. 11-Oxosteroids give 11β-hydroxy-steroids by catalytic hydrogenation[20], and by reduction with lithium aluminium hydride[215,216,217,218,219], sodium borohydride[220,221], lithium borohydride[222], and potassium borohydride[221]; the more thermodynamically stable 11α-hydroxy-steroids are obtained by reduction with sodium–propanol [198,218,223,224,225,226], or with lithium in liquid ammonia in presence of ethanol[219,227].

By Biochemical Oxygenation [Pincus, Peterson, Fried, Haines, and Wettstein]

The original demonstration of hydroxylation of deoxycorticosterone (1) to corticosterone (2) and of Substance S (4) to cortisol (5) by enzyme systems associated with adrenal gland tissue by Pincus[228] was followed by the fundamental work on hydroxylation with micro-organisms of Peterson and Murray[229] who discovered that *Rhizopus* species converted progesterone to 11α-hydroxyprogesterone (76). The yield in this hydroxylation has been raised to 45%[230,231], and finally to 95%[232]; this allows cortisone (6) to be obtained in eight steps from progesterone or twelve steps from diosgenin[233].



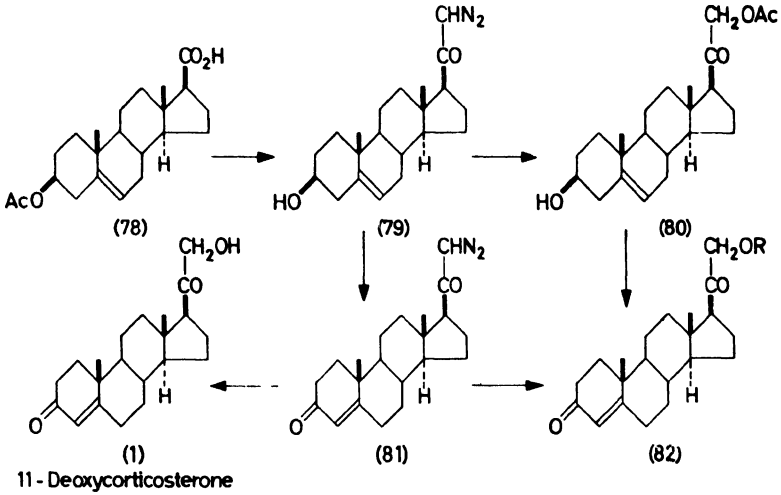
Similarly, 11-deoxycorticosterone[230,232,234] gives the 11α-hydroxy-derivative and Substance S (4)[230,232,234,235] gives 11-*epi*cortisol (77), converted by acetylation and oxidation in 70% yield to cortisone acetate (6).

Enzyme systems associated with adrenal tissue can cause hydroxylation at the 6β, 11β, 17α, 18, 19, and 21 positions, whereas appropriate micro-organisms can effect hydroxylation at the 6β, 7α, 7β, 8, 11α, 11β, 14α, 15β, 16α, 17α, and 21 positions[236,237].

Partial Syntheses of 11-*Deoxycorticosterone and Substance S*

11-Deoxycorticosterone (1)

3β-Acetoxyeti-5-enic acid (78) as the chloride with diazomethane gives the 3β-acetoxy-21-diazoketone, hydrolysed by alkali to the 3β-hydroxydiazoketone (79); this with acetic acid gives the 21-acetoxyketone (80) converted to 11-deoxycorticosterone acetate [(82): R = Ac] by oxidation as the dibromide[238]. The diazoketone (79) is sufficiently stable to give by Oppenauer oxidation [$Al(OBu^t)_3$—Me_2CO, 20°, 2–3 weeks] 21-diazoprogesterone (81), which can be converted into 11-deoxycorticosterone (1) with dilute sulphuric acid, or into its acetate [(82): R = Ac] with dilute acetic acid[239], whilst *p*-toluenesulphonic acid gives the 21-toluene-*p*-sulphonate [(82): R = Ts] which is otherwise inaccessible[240].



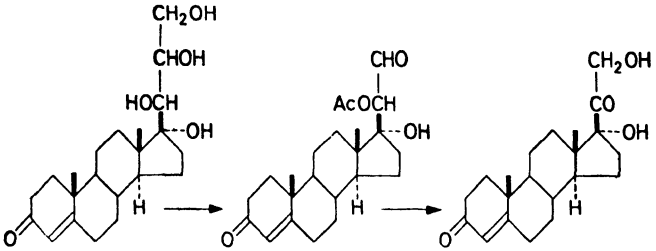
11-Deoxycorticosterone has also been prepared from 3α- and 3β-hydroxyeti-5-enic acid[241,242], from 17-*iso*pregn-4-ene-17β : 20β-21-triol diacetate by the Serini reaction[92], from progesterone in 3% yield[243,244], from pregn-5-en-3β-ol-20-one by condensation with

oxaloacetic ester, iodination at $C_{(21)}$, hydrolysis and oxidation[90], from 3-oxoeti-4-enic acid[86], from lithocholic acid[245], from pregn-5-en-3β-ol-20-one by oxidation with lead tetraacetate[246], from digitoxigenin[94], and from certain ψ-sapogenins[247].

Numerous substitution products of 11-deoxycorticosterone and/or its acetate have been described including 2α-acetoxy-[248], 6α-hydroxy-[249], 6β-hydroxy-[229,250], 7α-hydroxy-[237], 9α-fluoro-[251], 11α-hydroxy-[229,230,232,234], 11β-hydroxy- [= corticosterone], 12α-hydroxy-[252], 14β-hydroxy-[94,253], 16α-hydroxy-[254], 17α-hydroxy- [= substance S], 19-hydroxy-[68a, 255, 256, 257], 19-oxo-[258], and 18-carboxy-11-deoxycorticosterone[68a], and the 21-thiol[259]. 1 : 2-Dehydro-[260], 9 : 11-dehydro-[51,52], 11-dehydro-[53,54], and 16-dehydro-11-deoxycorticosterone acetate[261] are known, whilst 19-nor-11-deoxycorticosterone acetate[262,263] and 17α-methyl-11-deoxycorticosterone acetate[264,265], are remarkable for their biological activities, which exceed that of the parent compound; 17-*iso*-11-deoxycorticosterone acetate is inactive[60].

Substance S, 17α-Hydroxy-11-deoxycorticosterone (4)

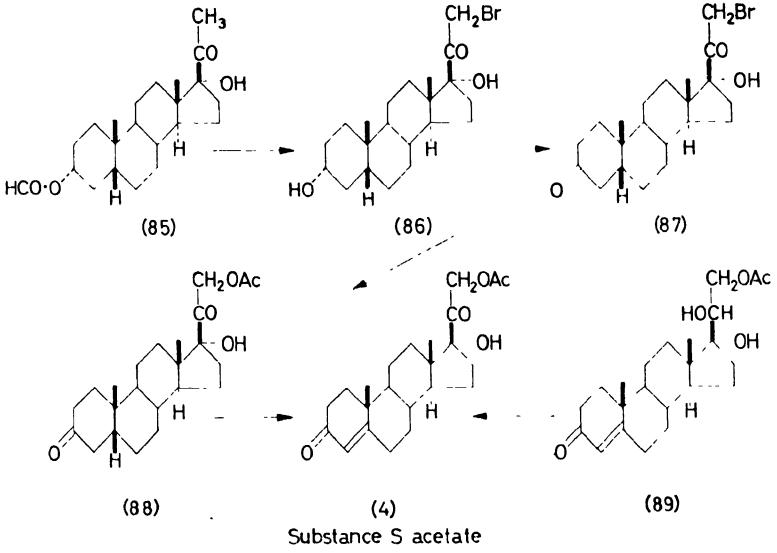
Substance S was originally synthesized by Reichstein[266]; the tetrol (83) was converted to the 20β-acetoxy-21-aldehyde (84), hydrolysed and then rearranged in hot pyridine to Substance S (4). A simpler route[267] involves periodic acid oxidation of the tetrol (83) to the 20β-hydroxy-21-aldehyde analogous to (84), and rearrangement of this.



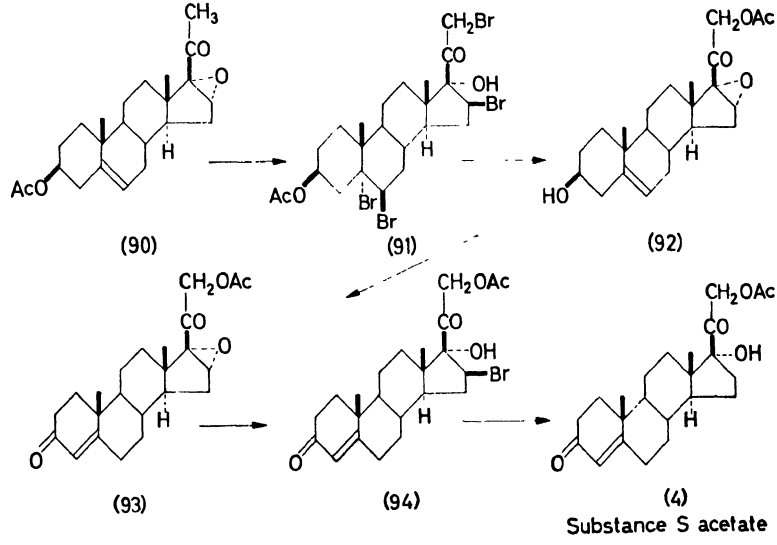
(83) (84) (4)
Substance S

A later synthesis by Gallagher[14] starts from 3α-formoxy-17α-hydroxypregnan-20-one (85), which is brominated and then hydrolysed to give 3α : 17α-dihydroxy-21-bromopregnan-20-one (86); this is oxidized with N-bromoacetamide to the 21-bromo-3 : 20-diketone (87), which after hydrolysis with 0·05N-sodium hydroxide and acetylation gives 21-acetoxy-17α-hydroxypregnane-3 : 20-dione (88), brominated at $C_{(4)}$ and dehydrobrominated by the Mattox-Kendall arylhydrazone method to Substance S monoacetate (4). Sarett[38] has shown that oxidation with chromium

trioxide–acetic acid at 11° of 17α : 20β : 21-trihydroxypregn-4-en-3-one 21-acetate (89) gives some Substance S monoacetate (4).



Another synthesis by JULIAN[128] uses 16α : 17α-epoxy-3β-acetoxypregn-5-en-20-one (90), which, as the 5 : 6-dibromide, is cleaved with hydrogen bromide and brominated to give the 16β : 21-dibromo-17α-hydrin (91); this by hydrolysis at $C_{(3)}$ with methanolic



hydrogen bromide, simultaneous debromination and conversion to the 21-iodide with sodium iodide, acetolysis, and regeneration of the oxide ring with potassium acetate, yields the 16α : 17α-epoxide (92). Oppenauer oxidation affords 16α : 17α-epoxy-21-acetoxy-progesterone (93), which is cleaved by hydrogen bromide to the 16β-bromo-17α-hydrin (94), reduced by Raney nickel in ethanol to Substance S monoacetate (4). Other syntheses have been described by MIESCHER[115,116] and by ROSENKRANZ and DJERASSI[268].

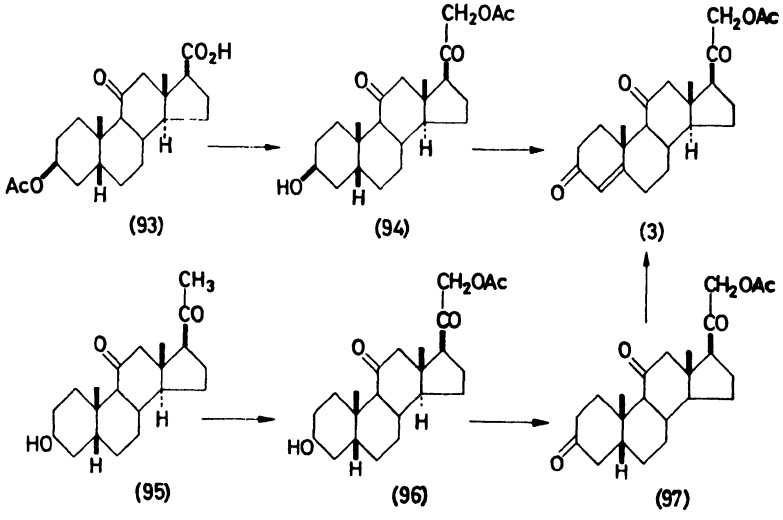
Derivatives of Substance S acetate that have been described include the 2α-hydroxy-[269], 6β-hydroxy-[68a,229,250,270,271], 11α-hydroxy- [≡ 11-*epi*cortisol (77)][198,218,229,230,232,234,235,272,273,274], 11β-hydroxy-compound [≡ cortisol], the 21-thiol[259], the 1 : 2-dehydro-[260], and the 9 : 11-dehydro-compound[275,276].

Partial Syntheses of 11-*Dehydrocorticosterone* (3) *and Corticosterone* (2)

11-DEHYDROCORTICOSTERONE (3)

The first 11-oxygenated adreno-cortical hormone, to be obtained by partial synthesis, was prepared by REICHSTEIN and LARDON[277] from 3β-acetoxy-11-oxoetianic acid (93) by the diazo-ketone synthesis. The acid by successive treatment with thionyl chloride, diazomethane, potassium hydroxide, and acetic acid gives 21-acetoxy-3β-hydroxypregnane-11 : 20-dione (94), quantitatively oxidized by chromium trioxide to the 3 : 11 : 20-trione, which by bromination and dehydrobromination with pyridine affords the acetate of 11-dehydrocorticosterone (3).

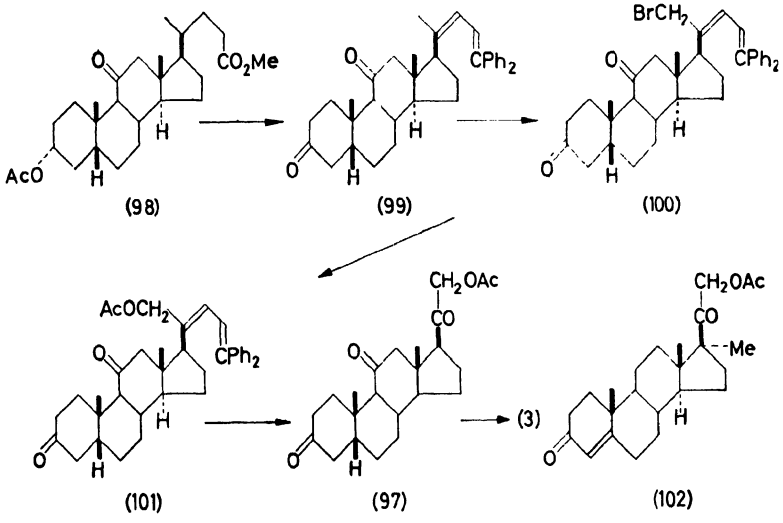
A second synthesis by REICHSTEIN, VON EUW, and LARDON[278]



employs the 3-epimeric pregnan-3-ol-11 : 20-diones represented by (95) and obtained from pregnane-3α : 12α-diol-20-one or from bisnordeoxycholic acid. Acetoxylation with lead tetraacetate gives the 3-epimerides represented by (96), which by modified Oppenauer oxidation with aluminium phenoxide–acetone afford 21-acetoxypregnane-3 : 11 : 20-trione (97), converted by bromination and dehydrobromination to 11-dehydrocorticosterone acetate (3).

A third synthesis by Reichstein arises from that of corticosterone [*see* p. 204], and a fourth synthesis has been described by Reichstein and von Euw[279], and a fifth synthesis by Sarett[38,280].

A sixth partial synthesis by Wettstein and Meystre[281] starts from methyl 3α-acetoxy-11-oxocholanate (98) and utilizes these authors' modification of the Miescher-Wettstein degradation [*see* p. 26]. The diene (99) with N-bromosuccinimide affords the 21-bromide (100) which yields the 21-acetate (101); oxidation eliminates the side chain to give the 21-acetoxypregnane-3 : 11 : 20-trione (97), brominated and dehydrobrominated to furnish the acetate of 11-dehydrocorticosterone (3).

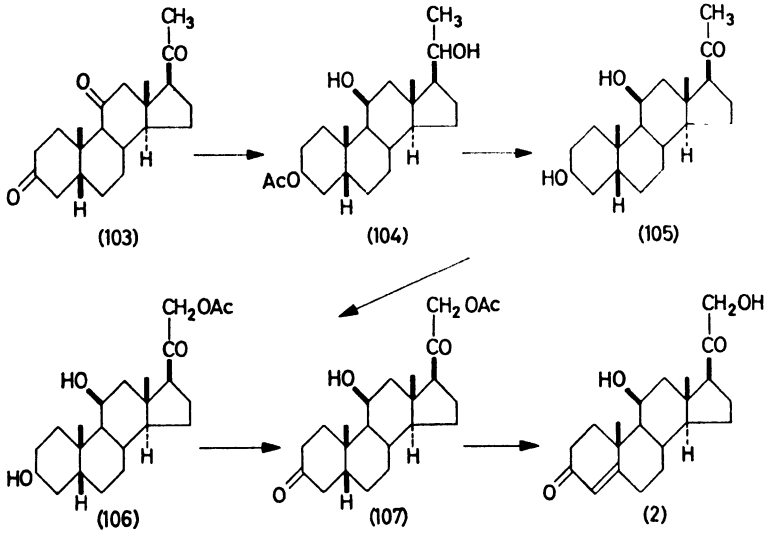


The 6β-hydroxy derivative[68a,250] and 17α-methyl-11-dehydrocorticosterone acetate (102)[282] have been prepared.

Corticosterone (2)

Corticosterone was obtained by Reichstein, von Euw, and Lardon[278]; in 1944 the diazoketone synthesis could not be used because an 11β-hydroxyl group cannot be acetylated, and has only recently been found capable of protection as the formate or the

trifluoroacetate [*see* p. 185]. Pregnane-3 : 11 : 20-trione (103), obtained from deoxycholic acid via pregnane-3α : 12α-diol-20-one, is partially hydrogenated and acetylated at $C_{(3)}$ and then completely hydrogenated to yield the epimeric 3 : 11β : 20-triol 3-monoacetates represented by (104); modified Oppenauer oxidation using aluminium phenoxide–acetone gives after hydrolysis the epimeric 3 : 11β-diol-20-ones, represented by (105), also obtained from bisnordeoxycholic acid. These after separation with digitonin are separately converted by treatment with lead tetraacetate to the epimeric 3 : 11β : 21-triol-20-one 21-monoacetates represented by (106); both by modified Oppenauer oxidation with aluminium phenoxide–acetone give the same pregnane-11β : 21-diol-3 : 20-dione 21-acetate (107). This by bromination and dehydrobromination yields corticosterone acetate, hydrolysed by potassium bicarbonate to corticosterone (2). From deoxycholic acid a total of forty-four stages is required.

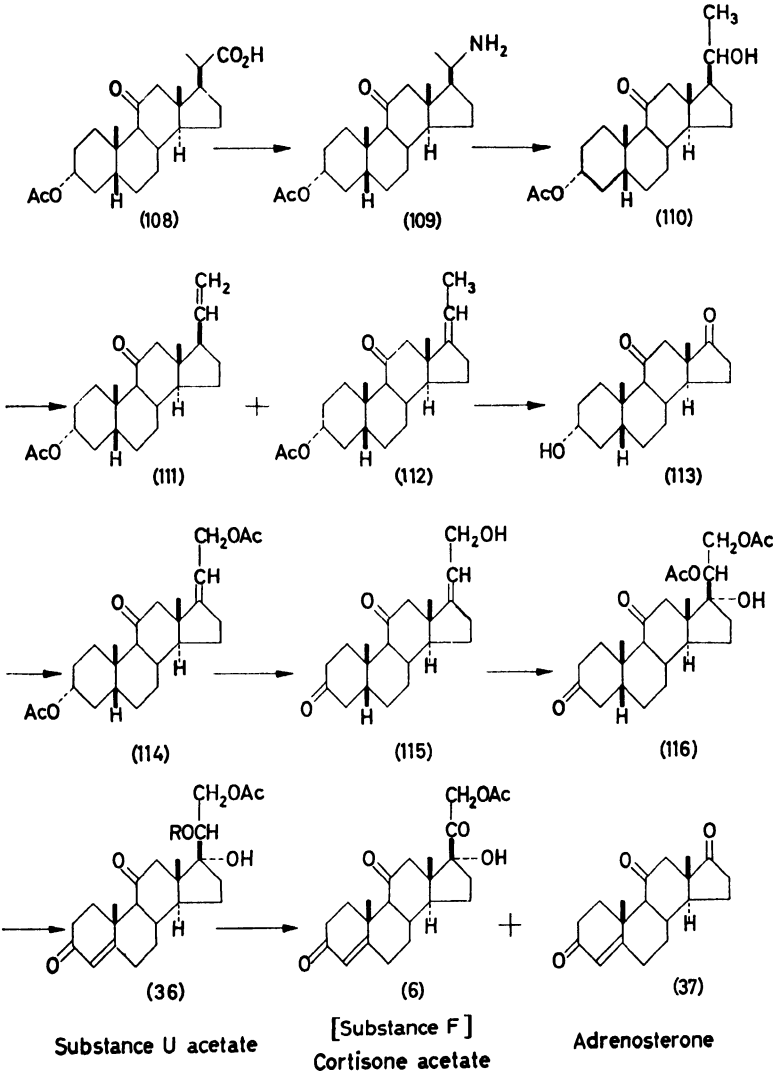


Alternatively, the hydroxydiketone (107) may be oxidized to the 21-acetoxypregnane-3 : 11 : 20-trione (97), whence bromination and dehydrobromination gives 11-dehydrocorticosterone acetate (3) [*see* p. 203]. Corticosterone acetate (2) by cautious oxidation with chromium trioxide gives 11-dehydrocorticosterone acetate (3), whilst conversely, 11-dehydrocorticosterone (3), as the 3 : 20-disemicarbazone, is reduced by lithium borohydride to corticosterone (2)[283]. The 6β-hydroxy and 19-hydroxy-derivatives[68a] have been described. 19-norCorticosterone has been prepared by

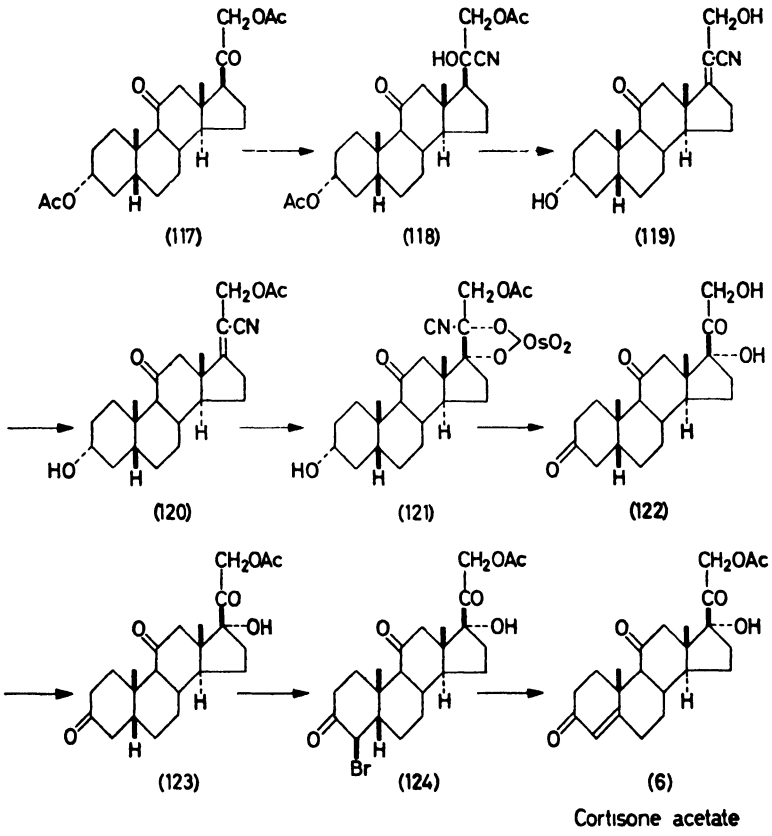
incubation of 19-norprogesterone or 19-nordeoxycorticosterone with adrenal homogenates[290].

Substance F, Kendall's Compound E, Cortisone (6)

The original partial synthesis by SARETT[38] of this compound starts from 3α-acetoxy-11-oxobisnorcholanic acid (108) which is degraded by the Curtius rearrangement to the 20-amino-pregnane (109), deaminated by nitrous acid in aqueous pyridine to the epimeric



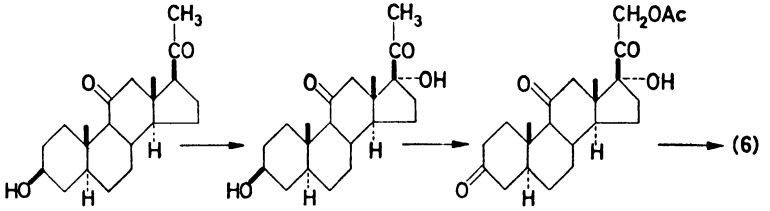
20-hydroxypregnanes represented by (110), accompanied by the $\Delta^{17(20)}$-pregnene (112) and the Δ^{20}-pregnene (111). The product is treated successively with tosyl chloride and hot collidine, and the resulting mixture of (111) and (112) ozonized to give 3α-acetoxy-11-oxoetianic acid and, after hydrolysis, 3α-hydroxyaetiocholane-11 : 17-dione (113). This hydroxy-ketone by condensation with acetylene [which adds at $C_{(17)}$ only], partial hydrogenation, acetylation, bromination, and anionotropic change, yields with potassium acetate 3α : 21-diacetoxypregn-17(20)-en-11-one (114); after hydrolysis and selective succinoylation of the 21-hydroxyl group, the 3α-hydroxyl group is oxidized to give, after removal of the protective succinoyl group, 21-hydroxypregn-17(20)-ene-3 : 11-dione (115). Acetylation and hydroxylation [OsO_4] then affords the saturated 17α : 20β : 21-triol-3 : 11-dione 20 : 21-diacetate (116) brominated and dehydrobrominated to furnish Substance U diacetate [(36): R = Ac]; this by hydrolysis affords Substance U, which by partial



acetylation gives the 21-monoacetate [(36): R = H] converted by cautious oxidation into the acetate of cortisone (6) [18%] and adrenosterone (37) [28%].

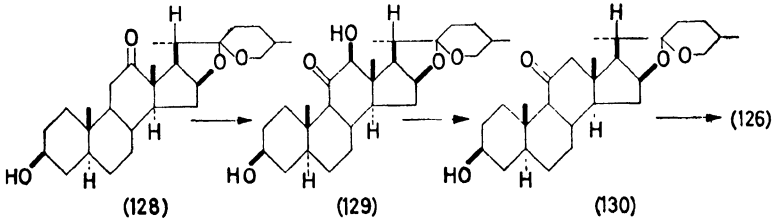
An improved partial synthesis [No. 2] by SARETT[114] sets out from 3α : 21-diacetoxypregnane-11 : 20-dione (117), which is converted by dehydration of the cyanohydrin (118) into the 20-cyanopregn-17(20)-ene (119). Partial acetylation gives the 21-mono-acetate (120), hydroxylated to afford the osmic ester (121), which is oxidized at $C_{(3)}$ and then cleaved with sodium sulphite to 17α : 21-dihydroxypregnane-3 : 11 : 20-trione (122). The 21-acetate (123) by bromination gives the 4β-bromoketone (124) which by dehydrobromination affords cortisone acetate (6).

Another partial synthesis [No. 3][284] uses 3β-hydroxy*allo*pregnane-11 : 20-dione (125), obtained from cholesterol, ergosterol, stigmasterol, and diosgenin [*see* p. 286] by the 7 : 9(11)-diene-perbenzoic acid method [*see* p. 194], which was converted by the enol-acetate–perbenzoic acid procedure of Gallagher [*see* p. 187] into 3β : 17α-dihydroxy*allo*pregnane-11 : 20-dione (126); this by bromination at $C_{(21)}$, acetolysis, and oxidation with N-bromoacetamide gave 21-acetoxy-17α-hydroxy*allo*pregnane-3 : 11 : 20-trione (127), converted by bromination-dehydrobromination into cortisone acetate (6). An alternative route from ergosterol to 3β-hydroxy*allo*pregnane-11 : 20-dione (125) has been described[285].



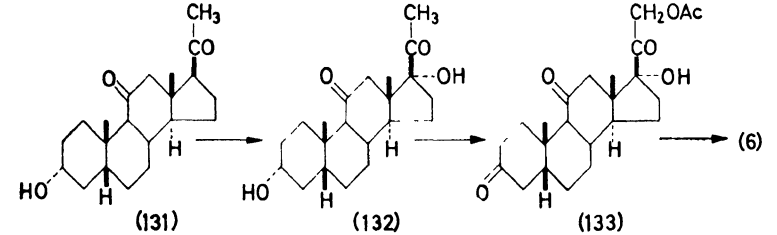
In partial synthesis [No. 4], hecogenin (128) [*see* p. 292] has been transformed by ROSENKRANZ and DJERASSI[286] using Gallagher's bromination, alkaline hydrolysis, and isomerization procedure [*see* p. 191] into 3β : 12β-dihydroxy-22a : 25a-*allo*spirostan-11-one (129). Oxidation with bismuth oxide gave the related 11 : 12-diketone, converted by removal of the 12-carbonyl group [Wolff-Kishner reduction or hydrogenolysis of the 12-thioketal] into 3β-hydroxy-22a : 25a-*allo*spirostan-11-one (130); oxidative degradation of the corresponding furost-20(22)-ene [*see* p. 290] gave 3β-hydroxy*allo*-pregnane-11 : 20-dione (125), whence the conversion to cortisone acetate proceeds as in synthesis No. 3. The ketol (129) is converted

directly into the 11-ketone (130) by treatment with calcium–liquid ammonia[287].



(128) (129) (130)

In partial synthesis No. 5, 3α-hydroxypregnane-11 : 20-dione [(131): cf. (95)] from deoxycholic acid has been converted by GALLAGHER[287], using his enol-acetate–perbenzoic acid method [*see* p. 187], into 3α : 17α-dihydroxypregnane-11 : 20-dione (132), which by bromination at $C_{(21)}$, mild alkaline hydrolysis, oxidation at $C_{(3)}$ with N-bromosuccinimide, and acetylation gave 21-acetoxy-17α-hydroxypregnane-3 : 11 : 20-trione (133), transformed by the hydrazone method [*see* p. 185] into cortisone acetate (6).

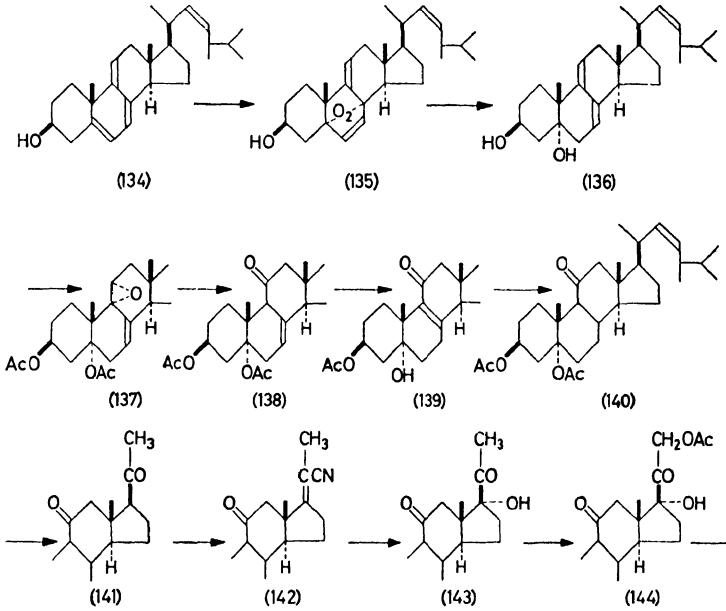


(131) (132) (133)

In partial synthesis No. 6, ROSENKRANZ and DJERASSI[231] used 11α-hydroxyprogesterone (76) obtained by biochemical oxygenation of progesterone [*see* p. 198] or from diosgenin [*see* p. 286]; in partial synthesis No. 7, Substance S (4) is biochemically hydroxylated to 11-*epi*cortisol (77), which is converted to cortisone acetate (6)[235] [*see* p. 198].

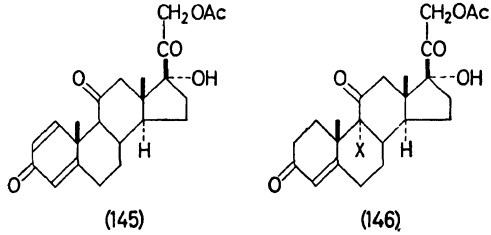
In partial synthesis No. 8, REICHSTEIN and LARDON[288] have converted sarmentogenin [*see* p. 250] into cortisone acetate. In partial synthesis No. 9 by E. R. H. JONES[203], dehydroergosterol (134) [*see* p. 54] is converted to the 5α : 8α-peroxide (135), which is selectively hydrogenated with concomitant dehydration to the 3β : 5α-dihydroxy-7 : 9(11) : 22-triene [(136): R = H]. The diacetate [(136): R = Ac] with perbenzoic acid gives the 9α : 11α-epoxide (137), converted by boron trifluoride to the Δ^7-11-ketone (138), and isomerized by acid to the Δ^8-11-ketone (139), which is reduced with lithium–liquid ammonia to the 11-ketone (140); at this stage the

side chain is degraded to 3β : 5α-diacetoxy*allo*pregnane-11 : 20-dione [(141): R = Ac]. The monoacetate [(141): R = H] is then transformed into the 20-cyano-17(20)-ethylene (142) for introduction of the 17α-hydroxyl group [*see* pp. 187 and 206] to give the 3β : 5α : 17α-triol-11 : 20-dione (143), brominated at $C_{(21)}$ and acetolysed to the 3β : 5α : 17α : 21-tetrol-11 : 20-dione 21-monoacetate (144), dehydrated with hot acetic acid to cortisone acetate (6).



A tenth partial synthesis from hecogenin (128) has been completed by HEMS, ELKS, and EVANS[160,162], although details of the last stages have not yet been published.

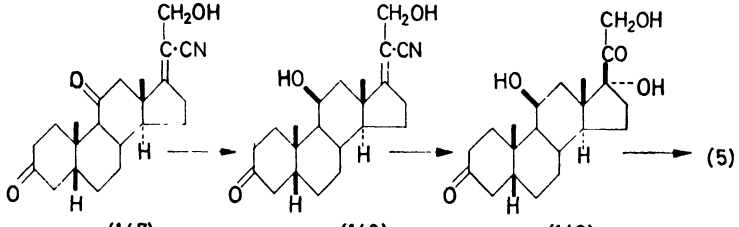
Radiocortisone containing tritium, mainly at $C_{(16)}$, has been prepared[289]; 19-norcortisone[290], 1 : 2-dehydro-[260,291], and 6 : 7-dehydro-[292], 2α-hydroxy-[269], 6β-hydroxy- and 6-oxo-[270], and 9α-fluoro, 9α-chloro- and 9α-bromocortisone acetate[293] and the



21-thiol[259] have been obtained. 1 : 2-Dehydrocortisone acetate ['prednisone', formerly 'metacortandracin'] (145), the 9α-halo cortisone acetates [(146): X = F, Cl, Br] and the 1 : 2-dehydro-9α-halocortisone acetates show not only intense mineralocorticoid physiological activity but also glucocorticoid activity exceeding that of cortisone acetate by a factor of ten. The Δ^1-5α-isomeride of cortisone acetate has been made and has one-tenth to one-fifth the activity of cortisone[294,295,296]. The 21-aldehyde corresponding to cortisone has equal physiological activity[297].

Substance M, Kendall's Compound F, Cortisol (5)

A partial synthesis by TISHLER[298], uses 21-hydroxy-20-cyanopregn-17(20)-en-3 : 11-dione (147), derived from (119), which by reduction as the 3-diethylketal with lithium borohydride gives the 11β : 21-diol (148); hydroxylation with osmium tetroxide gives the ketol (149), brominated and dehydrobrominated with semicarbazide by the hydrazone method [*see* p. 185] to cortisol acetate (5).

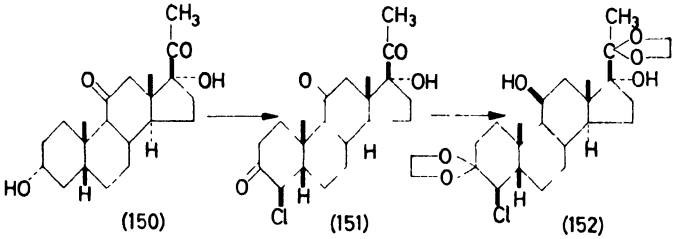


In partial synthesis No. 2, the 3 : 20-disemicarbazone of cortisone (6) with lithium borohydride gives cortisol 3 : 20-disemicarbazone, hydrolysed by exchange with pyruvic acid [*see* p. 185] to cortisol (5)[299,300].

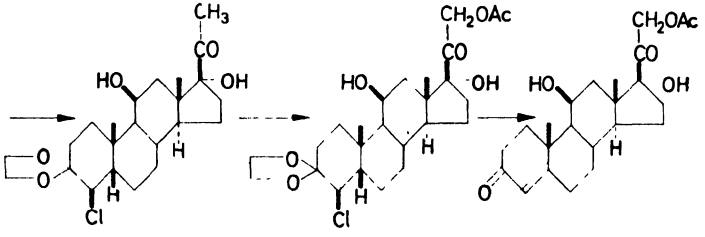
In partial synthesis No. 3, by LEVIN *et al.*[301], 3α : 11α : 17α-trihydroxypregnane-20-one or 3α : 17α-dihydroxypregnane-11 : 20-dione (150), both derived from 11α-hydroxyprogesterone (76), is converted by *tert.*-butyl hypochlorite to 4β-chloro-17α-hydroxypregnane-3 : 11 : 20-trione (151), which as the 3 : 20-bisethyleneketal is reduced by lithium aluminium hydride to the 11β-hydroxy-3 : 20-bisketal (152); selective acid hydrolysis affords the 11β-hydroxy-3-ketal (153), which by bromination at $C_{(21)}$ and acetolysis yields the 21-acetoxy-compound (154), converted by the aryl hydrazone method [*see* p. 185] into cortisol acetate (5).

In partial synthesis No. 4, FRIED and SABO[293] converted 11-*epi*-cortisol (77) as the 21-acetate-11α-tosylate with sodium acetate into the $\Delta^{9(11)}$-compound, which by addition of hypobromous acid gave 9α-bromocortisol acetate [(155): X = Br], reduced by zinc–ethanol to cortisol acetate.

Partial synthesis No. 5 has been accomplished by direct conversion of Substance S (4) to cortisol by incubation with the microorganism *Cunninghamella*[302].



(150) (151) (152)

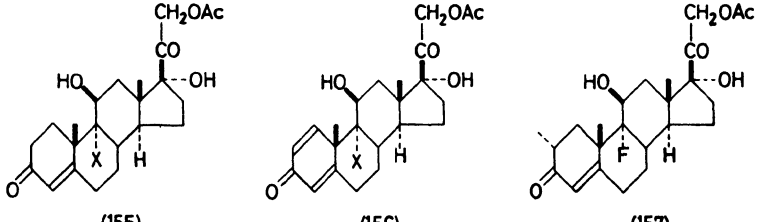


(153) (154) (5)

Cortisol acetate

In partial synthesis No. 6 by HERSHBERG[303], 3α : 11β : 17α-trihydroxypregnan-20-one or 11β : 17α-dihydroxypregnane-3 : 20-dione are transformed into cortisol acetate by several routes; thus the diketone, as the 3 : 3-dimethylacetal or 3-ethyleneketal, by bromination at $C_{(21)}$, acetolysis, and ketal hydrolysis gave 4 : 5β-dihydrocortisol acetate (149).

19-norCortisol[290], and 9α-fluoro-, chloro-, bromo-, and iodocortisol acetate[293] [(155): X = F, Cl, Br, I] have been prepared, and exhibit not only intense mineralocorticoid activity but also glucocorticoid activity exceeding that of cortisone acetate by a factor of ten. 1 : 2-Dehydrocortisol acetate[260, 291] [(156) : X = H] [= 'prednisolone', formerly 'metacortandralone'] and its 9α-halo derivatives[260, 291, 304, 305, 306] [(156) : X=F, Cl, Br] show intense mineralocorticoid activity and possess thirty times the glucocorticoid

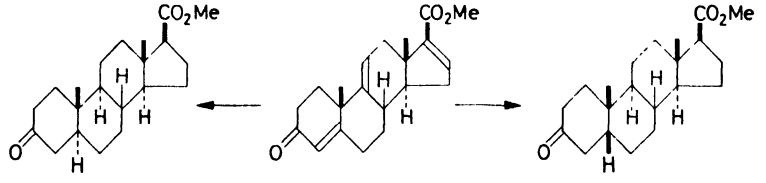


(155) (156) (157)

activity of cortisone acetate. The most potent adreno-cortical 'hormone' yet discovered is 2α-methyl-9α-flurocortisol acetate[306] (157), which has sixty to ninety times the sodium retaining activity of DOCA and forty times the activity of cortisone acetate in the liver glycogen deposition test in rats.

Total Syntheses

The *A*←*BC*→*D* total synthesis by Cornforth and Robinson[307] of *epi*androsterone and cholesterol [*see* p. 42] leads to total syntheses of 11-deoxycorticosterone (1), corticosterone (2), 11-dehydrocorticosterone (3), Substance S (4), cortisol (5), and cortisone (6), because *epi*androsterone is convertible by known reactions to methyl 3-oxo*allo*etianate (158) and thence into the hormones (1)–(6). The *A*←*B*←*CD* total syntheses of (±)-*epi*androsterone and (±)-11β-hydroxy*epi*androsterone by Johnson[308,309] [*see* pp. 139 and 146] are equivalent to total syntheses of the racemic forms of the hormones (1)–(6).



(158) (159) (160)

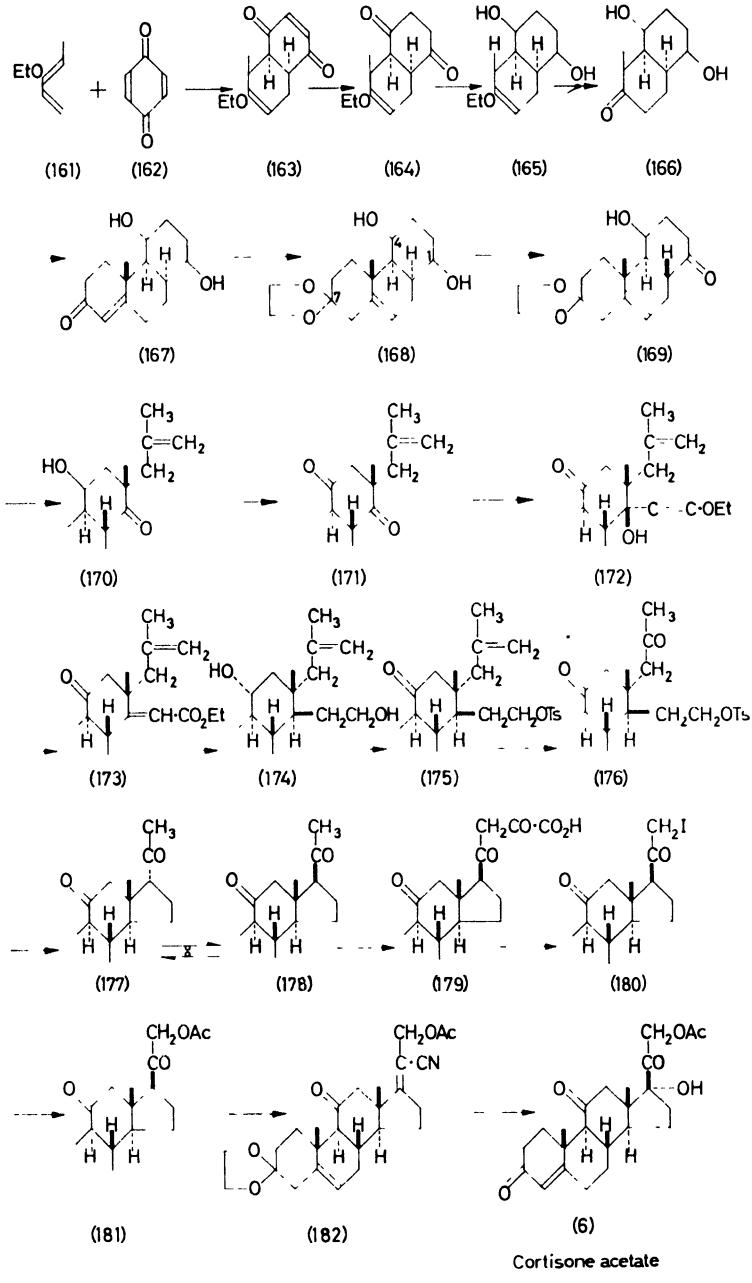
Similarly, the *A*←*B*←*CD* total synthesis by Woodward[310] [*see* p. 45] of (+)-methyl 3-oxoetia-4 : 9(11) : 16-trienate (159), which is hydrogenated to a mixture of the ester (158) and methyl 3-oxoetianate (160), is equivalent to total syntheses of the hormones (1)–(6); Woodward's synthesis has recently been carried through to natural (+)-cortisol, (+)-cortisone, and (±)-cortisone by Knowles[311]. Again, the *A*←*B*←*C*→*D* total synthesis by Wilds[312] of (±)-methyl 3-oxoetianate [as (160)] from resorcinol is equivalent to the total syntheses of the racemic forms of the hormones (1)–(6).

A stereospecific *A*←*B*←*C*→*D* total synthesis of 11-dehydrocorticosterone and cortisone has been achieved by Sarett[313]; 'stereospecific' here means that in each reaction producing a fixed centre of asymmetry the ratio, to all other isomerides, of the isomeride having the configuration of the end-product is greater than 8 : 1.

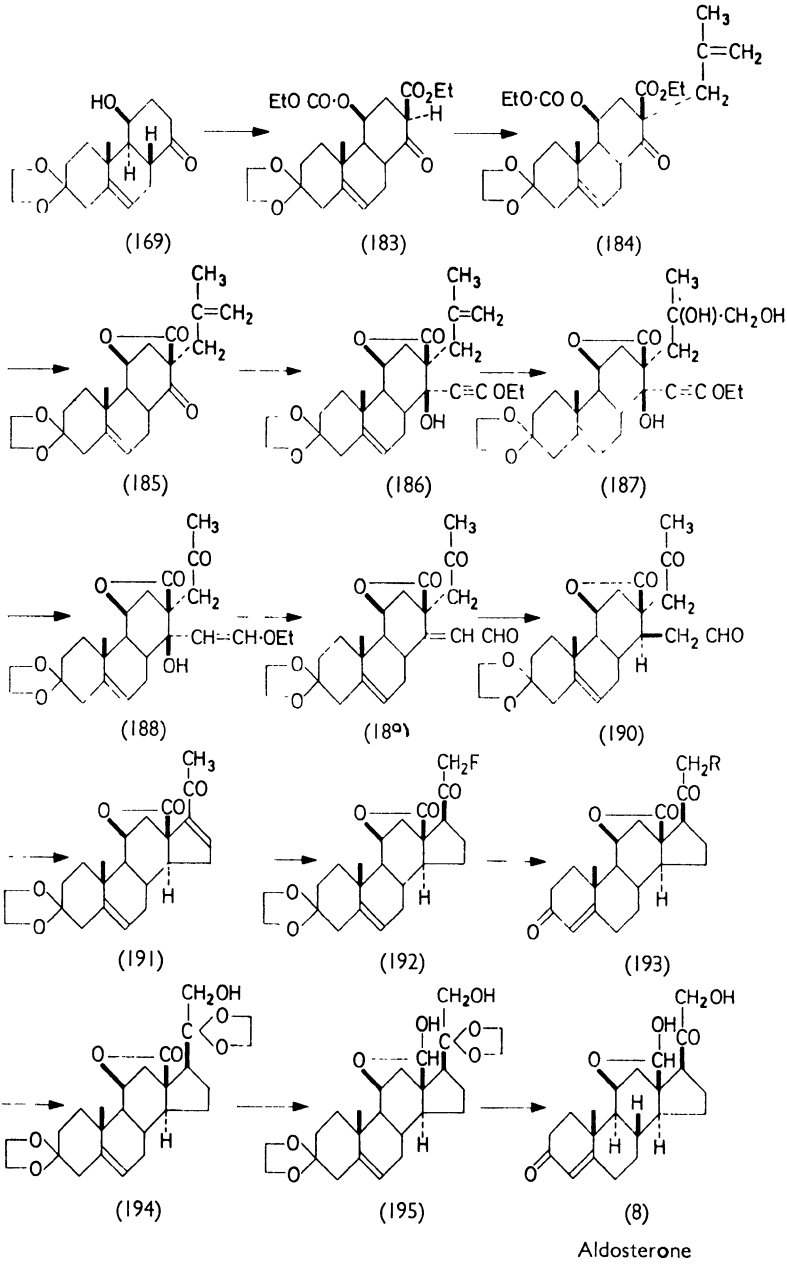
3-Ethoxypenta-1 : 3-diene (161) and benzoquinone (162), which eventually formed ring *C*, by the Diels-Alder reaction gave the adduct (163), hydrogenated with nickel to the *cis-B/C*-diketone (164), reduced by lithium aluminium hydride to the diol (165).

Hydrolysis gave the bicyclic dihydroxy-ketone (166), which by addition of methyl vinyl ketone and cyclization yielded the tricyclic dihydroxy-ketone (167); conversion to the 3-ethyleneketal (168) and selective oxidation gave the hydroxy-diketone monoketal (169) which was alkylated with methyl iodide and then with methylallyl iodide to (170). After oxidation with chromium trioxide in pyridine the resulting diketone (171) was condensed with ethoxyethinyl-magnesium bromide, and the acetylenic ether (172) rearranged with sulphuric acid to the unsaturated ester (173). This was hydrolysed to the corresponding acid, which was reduced in turn with sodium borohydride [carbonyl group], potassium-*iso*propanol in liquid ammonia [conjugated double bond], and lithium aluminium hydride [carboxyl group] to the diol (174). This was converted to the monotosylate, which was oxidized in turn with chromium trioxide in pyridine [$>CHOH \rightarrow >CO$] (175), osmium tetroxide [$>C{=}CH_2 \rightarrow >C(OH)\cdot CH_2OH$], and periodic acid [$>C(OH)\cdot CH_2OH \rightarrow >CO + CH_2O$] to the dioxo-ester (176), cyclized by sodium methoxide to the 3-ethyleneketal (177) of 17-*iso*-11-ketoprogesterone, isomerized by alkali to the 3-ethylene ketal (178) of (±)-11-ketoprogesterone. This was converted by condensation with methyl oxalate to the 21-oxalyl acid [as (179)], which was resolved with strychnine. The (+)-acid (179) with iodine gave the 21-iodide (180), acetolysed to the 21-acetate (181) [giving by hydrolysis totally synthetic 11-dehydrocorticosterone (3)], which by conversion to the 20-cyanohydrin and dehydration with phosphorus oxychloride yielded the 20-cyano-17-ethylene (182) [*see* p. 187]. This by hydroxylation with permanganate and mild acid hydrolysis of the 3-ethyleneketal group gave cortisone acetate (6).

The total synthesis of (±)-aldosterone (as 8) has been accomplished by WETTSTEIN[314] starting from Sarett's ketal (169). Carbethoxylation with diethyl carbonate gave the β-ketoester (183), alkylated with methylallyl iodide to yield (184); the carbonyl group was reduced with sodium borohydride, whereupon alkaline hydrolysis, lactonization, and oxidation with chromium trioxide in pyridine furnished the ketolactone (185). Treatment with ethoxyethinyl-magnesium bromide gave (186), converted by osmium tetroxide in pyridine to a mixture of epimeric triols represented by (187); selective reduction of the triple bond with palladium–calcium carbonate in pyridine and oxidation with periodic acid gave (188), smoothly converted by phorphorous tribromide or thionyl chloride to a mixture of *cis-trans*-isomeric aldehydes (189), hydrogenated by palladium to give mainly the aldehyde (190). Cyclization with benzoic acid and trimethylamine in hot xylene afforded the pregna-5:16-diene 18→11β-lactone (191), hydrogenated with palladium to pregn-5-ene 18→11β-lactone [(192): R = H]; this was converted



Sarett's stereospecific total synthesis of cortisone



Wettstein's total synthesis of aldosterone

by the sequence: $—CH_2—CO \cdot CO_2Me \rightarrow —CHI \cdot CO \cdot CO_2Me \rightarrow —CH_2I \rightarrow —CH_2OAc$ into [(192): R = OAc], hydrolysed by dilute acetic acid to the (±)-18→11β-lactone acetate [(193): R = Ac]. The free (±)-lactone [(193): R = H], obtained by hydrolysis with perchloric acid, was converted with ethylene glycol–toluene-*p*-sulphonic acid into the 3 : 20-bisketal (194), reduced by lithium aluminium hydride to the *cyclo*semiacetal-3 : 20-bisketal (195), hydrolysed by hydrogen chloride in tetrahydrofuran to the lactol form of (±)-aldosterone [as (8)].

Finally, microbiological resolution has furnished totally synthetic (+)-aldosterone (8)[315].

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V

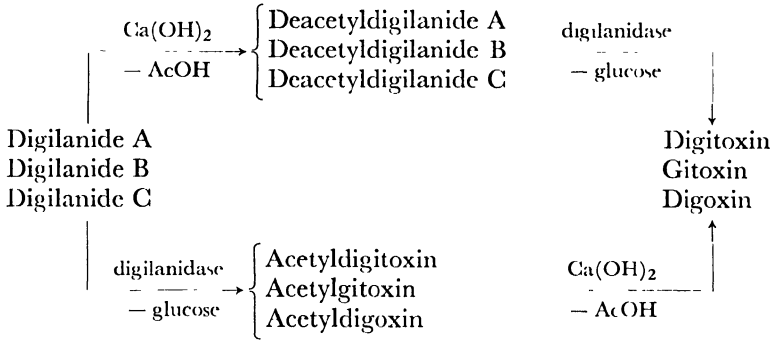
CARDIOTONIC GLYCOSIDES AND AGLYCONES

CERTAIN plant glycosides and toad venoms possess powerful cardiotonic activity. The plant heart-poisons are steroid glycosides, whilst the toad poisons are steroids conjugated with suberylarginine; acidic or enzymatic hydrolysis affords the steroid aglycones or genins [Fr. *génie*, spirit]. The cardiotonic property is associated with the special structure of the aglycone but is modified by the nature of the conjugated residue. Administration in cases of impaired heart function leads to decreased rate and increased intensity of the heart beat, whilst overdosage produces systolic stoppage of the heart. In addition to use in cardiotherapy, some glycosides have been used as drugs in trials by ordeal and as arrow poisons. The free aglycones are convulsive poisons rather than heart stimulants and are of little medicinal value.

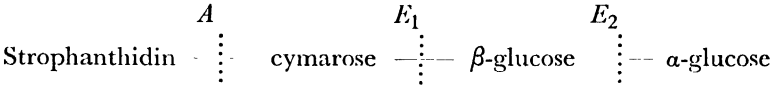
CARDENOLIDES

The main sources of the glycosides are plants of the *Apocynaceae*, *Liliaceae*, *Ranunculaceae*, and *Scrophulariaceae*; certain genera of *Digitalis* [foxglove] furnish most of the drugs of therapeutic value. The cardiac glycosides are soluble in water and ethanol, but sparingly soluble in non-hydroxylic solvents; after extraction with ether or hexane to remove fats and resins, the dried and powdered plant material [seeds, leaves, or roots] is extracted with methanol, saponins precipitated with basic lead acetate, and the products purified by partition between chloroform and water or aqueous methanol, crystallization, or chromatography of the acetates, from which the free glycosides can be regenerated by hydrolysis with potassium bicarbonate[1,2]. Isolation is difficult because of the low content in the plant tissues and the sensitivity of the glycosides to acids, bases, or enzymes occurring in the plant. Thus digitoxin, gitoxin, and digoxin, isolated from *Digitalis purpurea* and *lanata*, were regarded as the original plant glycosides, but by using a special enzyme-hindering process of extraction their precursors, the true plant glycosides digilanide A, B, and C, have been obtained, and

may be hydrolysed to their component digitoxosides, glucose, and acetic acid by successive use of the enzyme digilanidase [extracted from digitalis leaves] and dilute calcium hydroxide[3]:

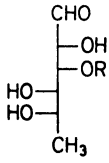


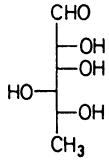
Glycosides by hydrolysis give an aglycone [or a secondary product of dehydration] and one or more sugars. Several glycosides may give the same aglycone; thus the three glycosides *k*-strophanthoside, *k*-strophanthin-β, and cymarin from *Strophanthus kombé* seed all give strophanthidin with strophanthotriose, strophanthobiose, and cymarose, respectively. *k*-Strophanthoside is a trioside:

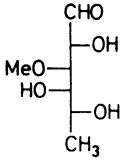


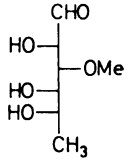
Fission with α-glucosidase at E_2 yields *k*-strophanthin-β and glucose, further split at *A* by 0·1N acid to the aglycone strophanthidin and strophanthobiose [≡ cymarose-β-glucoside]; enzymatic fission with strophanthobiase [from seed of *S. courmontii*][4] at E_1 furnishes cymarin and 2 mol. glucose; finally hydrolysis with 0·1N acid at *A* produces strophanthidin and strophanthotriose [≡ cymarose-β-glucoside-α-glucoside][5]. A very active glucosidase is obtainable from *Adenium multiflorum*[6], and differential hydrolyses using various enzymes have been accomplished[7]. Detection, separation, and estimation of glycosides and aglycones is possible chromatographically on silica-gel or on paper and the constituents of single seeds can thus be compared[8]. Natural digitaloid glycosides involving D-sugars are generally β-glycosides, whilst those involving L-sugars are α-glycosides[9].

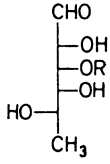
Apart from D-glucose and L-rhamnose, the sugars obtained by hydrolysis of the cardiac glycosides have not been found elsewhere in nature. L-Acofriose[10] is the 3-methyl ether of L-rhamnose (1), whilst antiarose [≡ D-6-deoxygulose][11] (2) is the 5-epimeride of L-rhamnose.

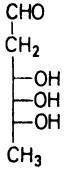

(1)
L-Rhamnose
L-Acofriose

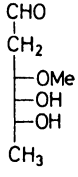

(2)
Antiarose

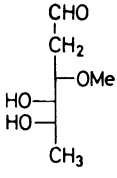

(3)
D-Digitalose

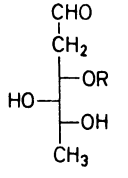

(4)
L-Thevetose

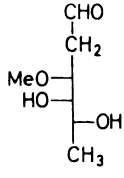

(5)
L-Talomethylose
L-Acovenose


(6)
D-Digitoxose


(7)
D-Cymarose


(8)
L-Oleandrose


(9)
D-Sarmentose
D-Boivinose

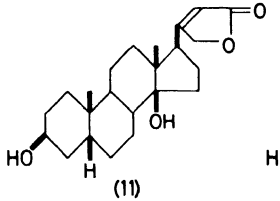

(10)
D-Diginose

Digitalose is the 3-methyl ether of the 3-epimer of antiarose and has been synthesized[12]. Thevetose, identical with cerberose[13], is the 3-methyl ether (4) of L-6-deoxyglucose[14], whilst the sugar L-6-deoxytalose (5) has been isolated several times and L-acovenose is the 3-methyl ether[15]. Digitoxose is the 2 : 6-deoxyhexose (6)[16,17]; cymarose (7) is the 3-methyl ether of digitoxose (6)[18]. Oleandrose (8) has been obtained crystalline and synthesized[19]; sarmentose [(9): R = Me] has also been synthesized[20], whilst the unmethylated compound occurs naturally as D-boivinose [(9): R = H] which has been synthesized[21,22]. D-Diginose (10) is 3-*epi*sarmentose[23] and has been obtained synthetically[24]. These 2-deoxy sugars have characteristically high reactivity; glycosides in which a 2-deoxy sugar is attached directly to the aglycone undergo mild acid hydrolysis very easily and give the Keller-Kiliani[25] reaction [formation of a blue ring at the interface of a solution in acetic acid containing Fe^{++} ions with sulphuric acid].

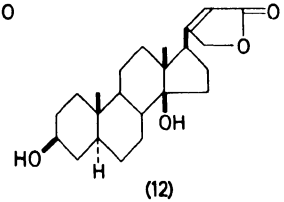
When a 2-hydroxy-sugar [e.g. glucose, rhamnose, digitalose] is attached directly to the $C_{(3)}$-hydroxyl of the aglycone, fission can only be achieved under conditions of hydrolysis so drastic as simultaneously to cause elimination of tertiary hydroxyl groups in the aglycone with production of anhydro-compounds. Alcoholysis often proceeds more rapidly and more smoothly than hydrolysis[26]. Another method much used recently by Reichstein, is that of MANNICH and SIEWERT[27], whereby a glycoside is cleaved by hydrogen chloride in acetone at 15° to the aglycone and [probably] the chloro-sugar; the method fails with polyglycosides insoluble in

acetone. Alternatively, hydrolysis-resistant glycosides may be converted (i) with alkali to the *iso*glycosides, which can be hydrolysed to the *iso*aglycones without dehydration[28], or (ii) in the case of 19-aldehydes, with sodium borohydride to the 19-alcohols, which can be hydrolysed without dehydration[29].

Early investigations by Schmiedeberg, Cloetta and Kiliani dealt mainly with problems of isolation; Windaus commenced structural studies, whilst the work of Jacobs on strophanthidin provided experimental evidence for the eventual solution of the structural problem. That the cardiac aglycones are hydroxy-steroids with a special side-chain structure was first suggested by KON[30], on the basis of x-ray measurements[31]. Interpretations of existing work in terms of the steroid structure were given in 1934 by KON[32] and in 1935 by JACOBS and ELDERFIELD[33].



(11)
Digitoxigenin



(12)
Uzarigenin

There are at present a relatively small number of aglycones [*see Table XIV*], but these can be combined with one or more sugars, which can be arranged in different sequences, to yield a large number of glycosides and polyglycosides. The simplest aglycones are the 3β : 14β-dihydroxy-5β-cardenolide digitoxigenin (11), and the 3β : 14β-dihydroxy-5α-cardenolide uzarigenin (12); the *cis*-union of rings *C* and *D* should be noted. Uzarigenin, urezigenin, corotoxigenin, and coroglaucigenin are the only cardenolides with *A/B-trans* ring-fusion, whilst urezigenin is the only natural cardenolide with a 3α-hydroxyl group.

CONSTITUTION OF THE AGLYCONES

The Nuclear Structure

Uzarin by acid hydrolysis gives D-glucose and the laevo-rotatory Δ^{14}-compound 'β'-anhydrouzarigenin (13)[34], [accompanied by a little of the dextro-rotatory $\Delta^{8(14)}$-isomeride 'α'-anhydrouzarigenin[34]]; dehydrogenation of 'β'-anhydrouzarigenin with selenium gives 3'-methyl-1 : 2-*cyclo*pentenophenanthrene [Diels' hydrocarbon][35], also obtained from strophanthidin by dehydrogenation with selenium at 320–340°[36]. Complete hydrogenation of 'β'-anhydrouzarigenin (13), followed by oxidative cleavage of the lactone ring, and

Table XIV

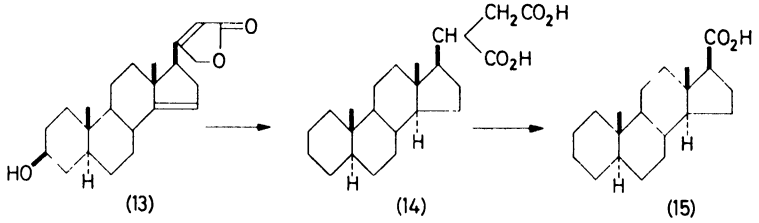
AGLYCONES

Aglycones	Formulae	Substituents	m.p.°	$[\alpha]_D°$
Diginigenin[a, e]	$C_{21}H_{28}O_4$	3β-OH	115	− 226
Strophanthidin[a]	$C_{23}H_{32}O_6$	3β : 5β : 14β-$(OH)_3$	235	+ 41*
Strophanthid-19-ol	$C_{23}H_{34}O_6$	3β : 5β : 14β : 19-$(OH)_4$	142	+ 37
Strophanthidinic acid[b]	$C_{23}H_{32}O_7$	3β : 5β : 14β-$(OH)_3$	185	+ 55
Periplogenin	$C_{23}H_{34}O_5$	3β : 5β : 14β-$(OH)_3$	185	+ 32
Digoxigenin	$C_{23}H_{34}O_5$	3β : 12β : 14β-$(OH)_3$	222	+ 18
Digitoxigenin	$C_{23}H_{34}O_4$	3β : 14β-$(OH)_2$	250	+ 18
3-*epi*Digitoxigenin	$C_{23}H_{34}O_4$	3α : 14β-$(OH)_2$	282	+ 27
Gitoxigenin	$C_{23}H_{34}O_5$	3β : 14β : 16β-$(OH)_3$	235	+ 34
Oleandrigenin [= Gitoxigenin 16-acetate]	$C_{25}H_{36}O_6$	3β : 14β-$(OH)_2$: 16β-OAc	225	− 10
Adynerigenin[c]	$C_{23}H_{32}O_4$	3β : 16β-$(OH)_2$	242	+ 18
Neriantogenin[d]	$C_{23}H_{32}O_4$	3β : 16β-$(OH)_2$	259	—
Adonitoxigenin[a] [= 19-oxogitoxigenin]	$C_{23}H_{32}O_6$	3β : 14β : 16β-$(OH)_3$	172	—
Uzarigenin*	$C_{23}H_{34}O_4$	3β : 14β-$(OH)_2$	246	+ 14
Urezigenin* [3-*epi*uzarigenin]	$C_{23}H_{34}O_4$	3α : 14β-$(OH)_2$	270	+ 4
Corotoxigenin[a]** [= 19-oxouzarigenin]	$C_{23}H_{32}O_5$	3β : 14β-$(OH)_2$	221	+ 42
Coroglaucigenin* [= uzarigen-19-ol]	$C_{23}H_{34}O_5$	3β : 14β : 19-$(OH)_3$	250	+ 23
Sarmentogenin	$C_{23}H_{34}O_5$	3β : 11α : 14β-$(OH)_3$	270	+ 21
11-*epi*Sarmentogenin	$C_{23}H_{34}O_5$	3β : 11β : 14β-$(OH)_3$	258	+ 29
11-Dehydrosarmentogenin	$C_{23}H_{32}O_5$	3β : 14β-$(OH)_2$; 12CO	252	+ 11
Sarmutogenin	$C_{23}H_{32}O_6$	3β : 12β : 14β-$(OH)_3$; 11CO	259	+ 49
Caudogenin**	$C_{23}H_{32}O_6$	3β : 12α : 14β-$(OH)_3$; 11CO	220	− 82
Decogenin	$C_{23}H_{30}O_6$	3β : 14β-$(OH)_2$; 11 : 12$(CO)_2$	235	+ 66
Sarverogenin[e]	$C_{23}H_{30}O_7$	3β : 11α : 14β-$(OH)_3$; 12CO	190	+ 45
Leptogenin[e]	$C_{23}H_{30}O_7$	3β : 12β : 14β-$(OH)_3$; 11CO	244	+ 78
Inertogenin[e]	$C_{23}H_{30}O_7$	3β : 12α : 14β-$(OH)_3$; 11CO	227	− 56
Chryseogenin[e]	$C_{23}H_{28}O_7$	3β : 14β-$(OH)_2$; 11 : 12$(CO)_2$	242	+ 40
Antiarigenin[a]	$C_{23}H_{32}O_7$	3β : 5β : 12β : 14β-$(OH)_4$	242	+ 42
Antiarigen-19-ol	$C_{23}H_{34}O_7$	3β : 5β : 12β : 14β : 19-$(OH)_5$	162	+ 37
Acovenosigenin	$C_{23}H_{34}O_5$	1β : 3β : 14β-$(OH)_3$	272	+ 2
Tanghinigenin	$C_{23}H_{32}O_5$	3β : 14β-$(OH)_2$; 7α : 15α-epoxide	187	+ 14
Ouabagenin	$C_{23}H_{34}O_8$	1β : 3β : 5β : 12β ? : 14β : 19-$(OH)_6$	255	+ 11

[a] CHO at $C_{(10)}$
[b] CO_2H at $C_{(10)}$
[c] Δ^7-ene
[d] Δ^{14}-ene
[e] One unplaced O atom, probably present as epoxide

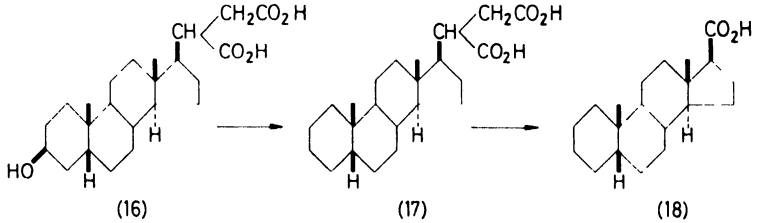
* *A/B-trans*-ring-fusion
** Substituents may be 3β 11α 11β-$(OH)_2$, 12CO

elimination of the 3β-hydroxyl group, affords the 20-epimeric dibasic acids represented by (14), both degraded by the Barbier-Wieland method to *allo*etianic acid (15)[37,38].



(13) (14) (15)

Similarly, non-pyrolytic degradation of digitoxigenin (11) by conversion to γ-digitoxanol diacid (16) gives digitoxan diacid (17), which by Wieland-Barbier degradation affords etianic acid (18)[33].



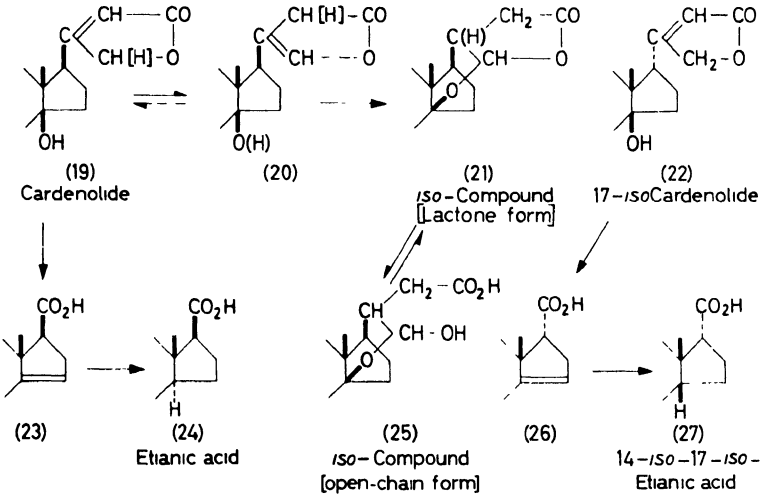
(16) (17) (18)

Neither degradation offers opportunity for change of configuration at $C_{(5)}$ or $C_{(17)}$, but both involve Δ^{14}-intermediates and so furnish no information about configuration at $C_{(14)}$.

The $\Delta^{\alpha\beta}$-γ-*Lactone Ring*

This feature, first noted in 1898 by FEIST[39], is responsible for the ultraviolet absorption maximum at 220 mμ and the characteristic reactions shown by all cardenolides in pyridine solution with (i) sodium nitroprusside–sodium hydroxide leading to a deep red colour [Legal test][40], (ii) with ammoniacal silver nitrate giving silver [Tollens test]; these reactions fail with cardanolides in which the lactone ring is saturated. JACOBS[41] suggested a $\Delta^{\beta\gamma}$-butenolide structure on the basis of experiments with the $\Delta^{\alpha\beta}$- and $\Delta^{\beta\gamma}$-angelica lactones. These are, however, γ-methylbutenolides; ELDERFIELD[42] has shown that a proper β-substituted model, β-*cyclo*hexyl-$\Delta^{\alpha\beta}$-butenolide, reproduces the typical behaviour of cardenolides in regard to the ultraviolet absorption, the Tollens and Legal test [improved modification with potassium ferricyanide], and catalytic hydrogenation to cardanolides only. The lactone ring has thus the $\Delta^{\alpha\beta}$-structure (19).

Cardenolides are cleaved by aqueous potassium hydroxide and regenerated by acidification, but in the presence of a suitably placed and correctly orientated hydroxyl group both glycosides and aglycones undergo irreversible isomeric change with alcoholic potassium hydroxide to give the so-called '*iso*-compounds'. The isomerization may occur without fission of the lactone ring by triad prototropy [(19)→(20)] followed by intramolecular electrophilic addition of the proton of the 14β-hydroxyl group to $C_{(20)}$ to give the *iso*-compound (21). This is saturated, does not give the Legal test, and by saponification yields an equilibrium mixture of lactone (21) and open-chain (25) forms[43].

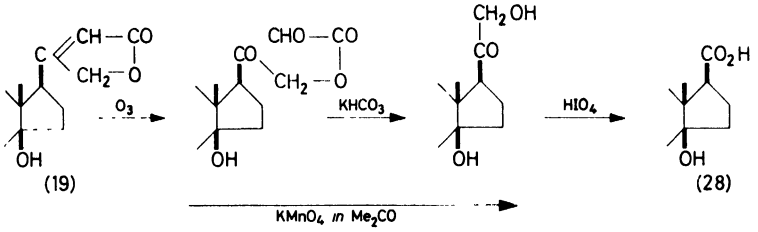


17-*iso*Cardenolides [formerly termed '*allo*glycosides' and '*allo*-aglycones'] [as (22)] give the Legal test, absorb in the ultraviolet at 220 mμ, but do not give *iso*-compounds because the lactonic side chain is α-orientated; 17-*iso*periplogenin [*see* p. 241] [as (22)] by degradation and dehydration affords 3β-hydroxy-17-*isoallo*eti-14-enic acid [as (26)], hydrogenated, like other Δ^{14}-17-*iso*-steroids and $\Delta^{14:16}$-steroids[44,45], to the *C/D-cis*-compound 3β-hydroxy-14-*iso*-17-*isoallo*etianic acid [as (27)][46].

The cis-C/D Ring-Union

Formation of 14 : 21-epoxides (21) and (25) is possible only if the $C_{(14)}$-hydroxyl group and the $C_{(17)}$-lactonic side chain are *cis* as in (19), or if a *cis*-arrangement can be achieved by inversion at $C_{(14)}$ or $C_{(17)}$. Transformation of digitoxigenin [(11), as (19)] and of *iso*digitoxigenin [as (21)] into etianic acid [(18), as (24)][33,47], by

reactions not involving the asymmetric centre at $C_{(17)}$, proves the 17β-configuration in both the cardenolide and the *iso*-compound. The $C_{(14)}$-hydroxyl group thus has the β-configuration and rings *C*/*D* are *cis*-united; this conclusion is proved by degradation of digitoxigenin to 3β : 14β-dihydroxy-14-*iso*etianic acid [as (28)][48]. Similar arguments can be advanced for other cardenolides, and the general methods of oxidative degradation of the $\Delta^{\alpha\beta}$-lactone ring introduced by Reichstein lead to other 14β-hydroxy-14-*iso*etianic acids.



The 17-*iso*cardenolides [as (22)] do not give *iso*-compounds because of the *trans*-arrangement of the 14β-hydroxyl group and the 17α-lactonic sidechain.

Structure of Individual Glycosides and Aglycones

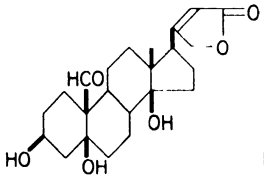
Strophanthidin

The aglycone STROPHANTHIDIN, obtainable from the glycosides of several varieties of *Strophanthus*, especially *S.kombé* [*see* p. 229], is readily available and formed the principal material for the pioneer researches of W. A. Jacobs.

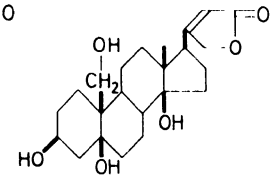
Strophanthidin (29) possesses a β-orientated secondary hydroxyl group at $C_{(3)}$ giving rise to a monobenzoate, β-orientated tertiary hydroxyl groups at $C_{(5)}$ and $C_{(14)}$, and a carbonyl group at $C_{(19)}$. The aglycone forms an oxime, does not reduce Fehling's solution[49], but is a 19-aldehyde since permanganate in acetone furnishes strophanthidinic acid (31)[50,51,52]; further oxidation of (31) as the methyl ester with chromium trioxide gives methyl strophanthidonate (33), which is a ketone and cannot be acetylated. Hydrogenation with palladium with absorption of 1 mol. of hydrogen gives dihydrostrophanthidin (32), which fails to give the Legal test and yields no *iso*-compound, and which is oxidized as the 3-acetate by permanganate to dihydrostrophanthidinic acid (34)[53]. Reduction with aluminium–amalgam or aluminium *iso*propoxide yields the primary-secondary-ditertiary tetrol strophanthid-19-ol (30)[54,55] which gives a diacetate and occurs in *S.kombé* as the 3-cymaroside cymarol [*see* p. 240]. The aldehyde group of dihydrostrophanthidin

(32) is hydrogenated with difficulty by platinum to a saturated tetrol, epimeric at $C_{(20)}$ with that obtained by hydrogenation with platinum of strophanthid-19-ol (30)[54], which has been transformed into 3β : 5β : 19-trihydroxyetianic acid[56], and into 3β : 5β : 14β : 19-tetrahydroxy-14-*iso*etianic acid, leading by dehydration [$POCl_3$—Py] and hydrogenation to 19-hydroxy*allo*etianic, 3β : 19-dihydroxyetianic and 14β : 19-dihydroxy-14-*iso*etianic acid[52,57]. These $C_{(19)}$-ols are typical *neo*pentyl alcohols and fail to react with phosphorus halides, thionyl chloride, and halogen acids, but react with organic acids[58].

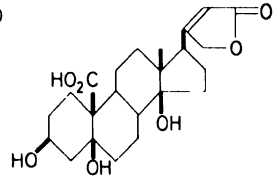
Dihydrostrophanthidin (32) by Wolff-Kishner reduction gives dihydroperiplogenin; a direct correlation with periplogenin [*see* p. 240] has been achieved by conversion of strophanthidin (29) with methylmercaptan–zinc chloride to the 19-mercaptal, which is reduced by Raney nickel to periplogenin[52,60].



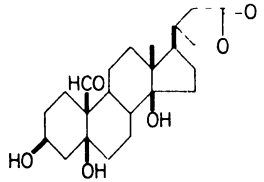
(29)
Strophanthidin



(30)
Strophanthidol



(31)



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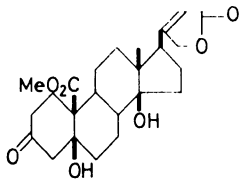

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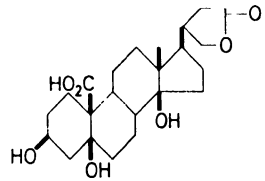
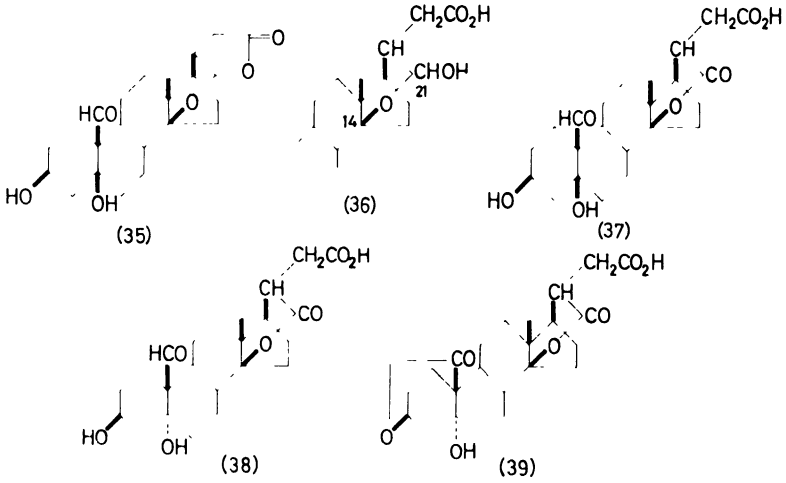


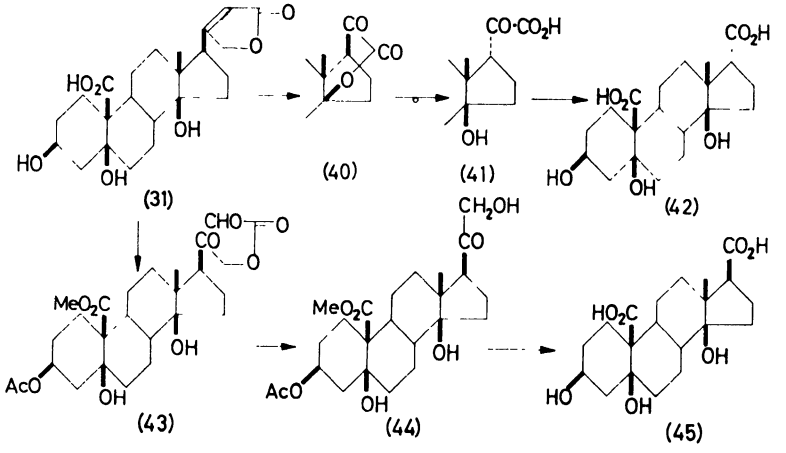
(34)

Strophanthidin (29) consumes one equivalent by titration with aqueous sodium hydroxide, but with methanolic sodium hydroxide gives irreversibly 'α'-*iso*strophanthidin (35); this dissolves in alkali to give the lactol form 'α'-*iso*strophanthidin acid (36), oxidized by potassium hypobromite to 'α'-*iso*strophanthidinic acid (37)[49,61]. Compounds of the *iso*-series [e.g. (35), (36), (37)] frequently exist in epimeric 'α' and 'β' forms; this was thought to be due to asymmetry at $C_{(20)}$[62], but has been shown to arise from inversion at $C_{(5)}$[63]. Thus, the 'α'-*iso*-acid (37) by treatment with hot potassium hydroxide yields 'β'-*iso*strophanthidinic acid (38), which forms a 3β : 19-lactol oxidized by potassium hypobromite to 'β'-*iso*strophanthic lactone acid (39)[43].

Strophanthidinic acid (31) affords an *iso*-compound [(35) with CO_2H for CHO][43]. Strophanthidinic acid (31) is oxidized by permanganate to the 20-oxo-21 → 14-lactonic acid (40)[50,64]; this

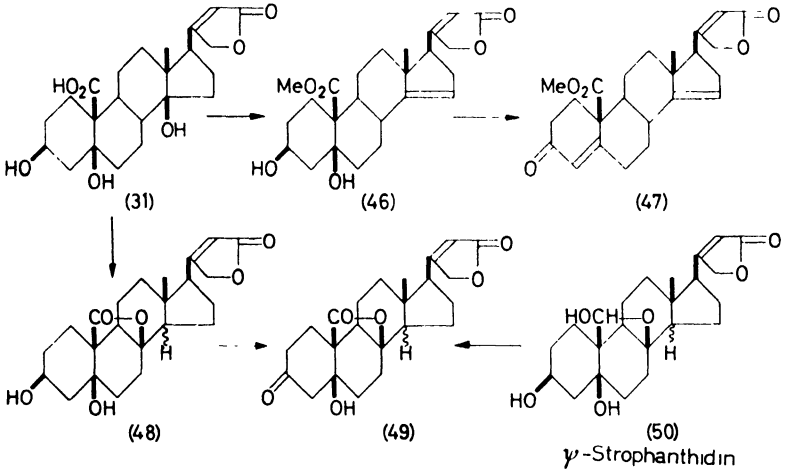


with potassium hydroxide is cleaved with inversion at $C_{(17)}$ to yield the 17-*iso*-20-oxo-acid (41), which does not lactonize[57], and is oxidized by hydrogen peroxide to the 14-*iso*-17-*iso*etianic acid (42)[57]. Strophanthidinic acid (31) [as the 3-acetate 19-methyl ester] by ozonolysis at −80° and mild hydrolysis with potassium bicarbonate of the resulting glyoxylic ester (43) gives the α-ketol (44), oxidized by periodic acid to yield [after hydrolysis] the 14-*iso*-17-*n*-epimeride (45) of the acid (42)[57].



The 14-*iso*-17-*iso*-acid (42) has been converted into a 19-nor-Δ^4-3-ketone by elimination of the 5β-, 14β-hydroxyl, and 19-carboxyl groups[65,66] and into a 19-nor-11-deoxycorticosterone and a 19-norprogesterone[67].

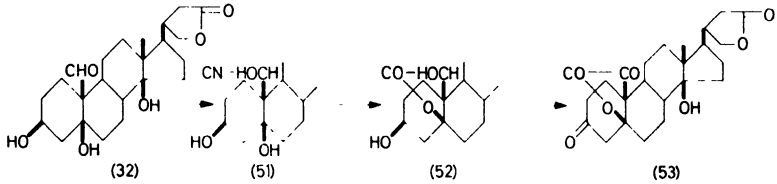
The tertiary 14β-hydroxyl group involved in the formation of *iso*strophanthidin (35) is readily eliminated by dehydration because strophanthidinic acid (31) [as methyl ester] with ethanolic hydrogen chloride gives anhydrostrophanthidinic ester (46), which yields no *iso*-compound[51]. The anhydro-ester (46) by oxidation with chromium trioxide yields a β-hydroxyketone dehydrated with great ease to the $a\beta$-unsaturated ketone dianhydrostrophanthidonic ester (47); strophanthidin therefore contains a second tertiary hydroxyl group at $C_{(5)}$[51].



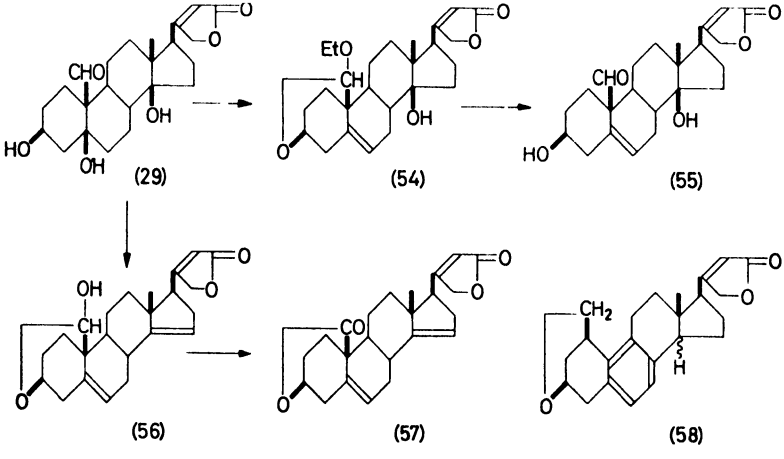
Free strophanthidinic acid (31) is dehydrated by concentrated hydrochloric acid to a very stable lactone[49,68], which was originally regarded as a 19→14β-lactone, but is more probably the 19→8β-lactone (48)[62], oxidized by chromium trioxide to the 3-oxo-19→8β-lactone (49). Strophanthidin (29) with concentrated hydrochloric acid similarly yields ψ-strophanthidin (50) which gives no *iso*-compound and is oxidized by chromium trioxide to the oxo-lactone (49)[49,68].

Interaction between the $C_{(5)}$-tertiary hydroxyl group and the aldehyde group is obtained only in the homologous $C_{(19)}$-epimeric cyanhydrins [as (51)] derived from dihydrostrophanthidin (32); the epimeric homo-acids obtained by hydrolysis give epimeric 19a→5β-homolactones [as (52)], oxidized by chromium trioxide to the same 3 : 19-dioxo-19a→5β-lactone (53)[69].

Strophanthidin (29) is converted by cold ethanolic hydrogen chloride into the cyclic ethylal (54), hydrolysed to monoanhydrostrophanthidin (55)[70]; the formerly accepted *A/B-cis*-3β : 19-epoxide



structures are stereochemically impossible, and the new structures [(54) (55)] are supported by the infra-red absorption spectra[63]. Use of hot ethanolic hydrogen chloride affords dianhydrostrophanthidin ethylal (56), also obtained from monoanhydrostrophanthidin (55) under the same conditions, oxidized by chromium trioxide to the 19→3β-lactone (57)[49,71], and further dehydrated by concentrated hydrochloric acid with molecular rearrangement to trianhydrostrophanthidin (58)[68]. This has an aromatic system [λ_{max} 279 mμ][72] located in ring *B*, since oxidation with nitric acid gives benzene-1 : 2 : 3 : 4-tetracarboxylic acid[73].



Correlation of the β-orientation of the $C_{(3)}$- and $C_{(5)}$-hydroxyl groups is achieved by conversion of strophanthidin (29) with thionyl chloride into a cyclic 3β : 5β-sulphite[59]. All the functional groups in strophanthidin have the β-configuration, although the aglycone does form an insoluble digitonide.

CONVALLATOXIN, CONVALLOSIDE, CHEIROTOXIN, and DEGLUCOCHEIROTOXIN are glycosides of strophanthidin. CONVALLATOXIN is probably the most toxic cardenolide and is obtained from leaves

and blossoms of the lily of the valley, *Convallaria majalis*[76,77]; it gives the Legal test, affords an *iso*-compound with alkali, but is resistant to acid hydrolysis finally giving monoanhydrostrophanthidin (55)[78]; use of cold methanolic hydrogen chloride yields dianhydrostrophanthidin methylal [as (57)][79]. The glycoside reacts with hydroxylamine with difficulty, and by Mannich hydrolysis with cold hydrogen chloride–acetone affords strophanthidin (29)[80]. Convallatoxin is strophanthidin-rhamnoside, and it has been synthesized from strophanthidin and 'α'-acetobromorhamnose by condensation with silver carbonate in benzene–dioxan[81,82]. Seeds of the lily of the valley contain no convallatoxin, but instead yield GLUCOCONVALLOSIDE, which is strophanthidin-rhamnoside-[glucoside][283], and CONVALLOSIDE which is strophanthidin-rhamnoside-glucoside, hydrolysed by strophanthobiase to convallatoxin and glucose[84].

Seeds of the wall flower, *Cheiranthus cheiri*, contain CHEIROTOXIN, which is strophanthidin-6-deoxyguloside-glucoside, hydrolysed by strophanthobiase to glucose and DEGLUCOCHEIROTOXIN, which is highly toxic[28,85,86].

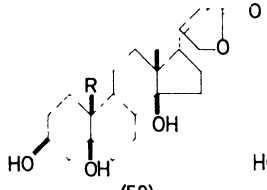
CYMAROL, which occurs in *S. kombé* seeds, is strophanthid-19-ol (30)-cymaroside, and has been obtained from cymarin by Meerwein-Ponndorf reduction[87]. CONVALLATOXOLOSIDE [≡ strophanthid-19-ol-rhamnoside-glucoside][83], and CONVALLATOXOL [≡ strophanthid-19-ol-rhamnoside] occur in lily of the valley[83]. CYMARYLIC ACID, which is strophanthidic acid (31)-cymaroside, has been synthesized by oxidation of cymarin acetate with chromium trioxide[88].

17-iso*Strophanthidin and its Glycosides*

Seeds of *Strophanthus kombé*, when ground and allowed to stand in water with the enzymes present in the seeds, afford 17-*iso*CYMARIN [formerly '*allo*cymarin'], hydrolysed by very dilute acid to 17-*iso*-STROPHANTHIDIN [as (59)][89] and cymarose.

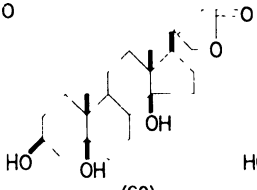
Periplogenin and its Glycosides

PERIPLOCIN, PERIPLOCYMARIN, and EMICYMARIN are the cymaroside-glucoside, the cymaroside, and the digitaloside, respectively, of PERIPLOGENIN (60), which corresponds with strophanthidin but carries the usual angular methyl group at $C_{(10)}$[90]. Periplogenin has been obtained from strophanthidin (29)[60], whilst dihydroperiplogenin has been obtained from dihydrostrophanthidin (32)[59]; it has also been correlated with digitoxigenin [*see* p. 243] and uzarigenin [*see* p. 249], and has been transformed into progesterone and 11-deoxycorticosterone[91].



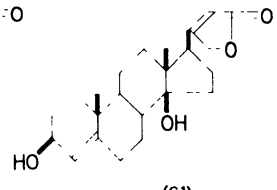
(59)

R=CHO: 17-*iso*Strophanthidin
R=Me: 17-*iso*Periplogenin



(60)

Periplogenin



(61)

Δ4-Periplogenin

ACOFRIOSIDE L is Δ4-periplogenin (61)-acofrioside, and is hydrolysed by the Mannich procedure to Δ3:5-dianhydroperiplogenin and L-acofriose[92].

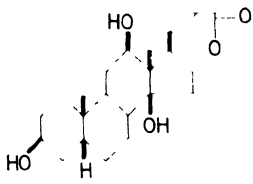
17-iso*Periplogenin and its Glycosides*

Seeds of *Strophanthus kombé* by the action of enzymes contained therein furnish not only 17-*iso*STROPHANTHIDIN[89], but also 17-*iso*EMICYMARIN [formerly '*allo*emicymarin'] and 17-*iso*PERIPLOCYMARIN [formerly '*allo*periplogenin'][93]. The former is hydrolysed by the Mannich procedure to 17-*iso*PERIPLOGENIN (59) and digitalose, whilst the latter with very dilute acid gives 17-*iso*periplogenin (59) and cymarose[93,94]. Emicymarin has also been isolated from seeds of *Strophanthus eminii*[95,96]. 17-*iso*Periplogenin (59) and periplogenin (60) afford 17-epimeric trianhydro-compounds[95,96], and 17-*iso*periplogenin has been degraded to 3β-hydroxy-14-*iso*-17-*isoallo*etianic acid [as (27)][46]. 17-*iso*Cardenolides are not isomerized by alkali[97].

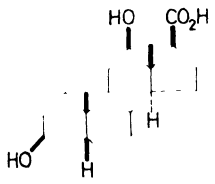
Digoxigenin and its Glycosides

DIGOXIN, 'α' and 'β'-ACETYLDIGOXIN, from *Digitalis* species, are digoxigenin-[digitoxoside]$_3$ acetates, whilst digilanide C has a fourth terminal sugar unit which is glucose. The acetyldigoxins differ in regard to the acetyl group in the trisaccharide portion of the molecule, the 'α'-compound being partly converted by hot ethanol into the more stable 'β'-isomeride[98]. DIGOXIGENIN (62) gives the Legal test, has a 14β-hydroxy group furnishing an *iso*-compound and two secondary hydroxyl groups yielding by oxidation a diketone, *digoxigenone* [(62) with 3 : 12-$(CO)_2$] which gives only a monoxime and monosemicarbazone[99]. The position and configuration of these hydroxyl groups follows from the oxidative degradation of digoxigenin diacetate to 3β : 12β-dihydroxyetianic acid (63)[100]. All four 3 : 12-dihydroxyetianic acids have been prepared[101]. Digoxigenin and its diacetate are dehydrated with some difficulty; phosphorus oxychloride–pyridine at 150° or sulphuric acid–ethanol give Δ14-anhydrodigoxigenin $[\alpha]_D$ − 16°, whilst

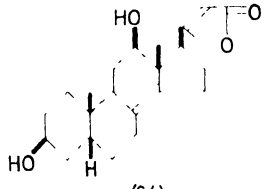
concentrated hydrochloric acid gives $\Delta^{8(14)}$-anhydrodigoxigenin, $[\alpha]_D + 46°$ (64)[102,103]; the former is converted by hydrochloric acid into the latter, which resists catalytic hydrogenation but which by bromination at $C_{(16)}$ with N-bromosuccinimide and dehydrobromination yields the $\Delta^{8(14):16}$-diene[104].



(62)
Digoxigenin



(63)



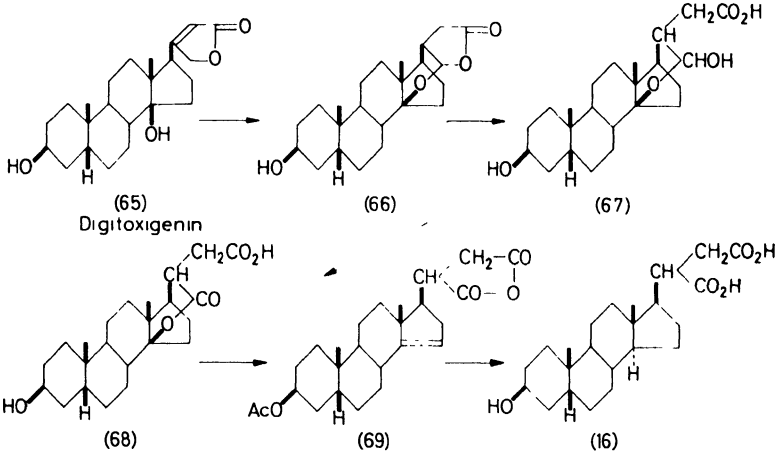
(64)

Digitoxigenin and its Glycosides

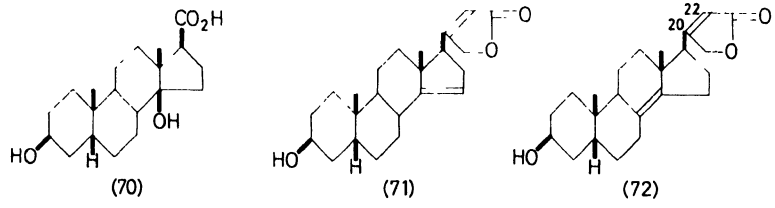
The arrow poisons ECHUJIN and ECHUBIOSIDE, from *Adenium boehmianum*, are digitoxigenin-cymaroside-[glucoside]$_2$ and digitoxigenin-cymaroside-glucoside, respectively[105,106]. SOMALIN[105-109] [≡ honghelоside G], another arrow poison from *Adenium somalense*, and ODOROSIDE A[110,111] from the oleander are respectively digitoxigenin-cymaroside and diginoside. ODOROSIDE D[112] is digitoxigenin-diginoside-glucoside, and by enzymatic hydrolysis yields odoroside A. ODOROSIDE G ACETATE[110,113] [formerly known as odoroside G] is digitoxigenin-acetyldigitaloside-[glucoside]$_2$, hydrolysed enzymatically to ODOROBIOSIDE G[110,113], which is digitoxigenin-digitaloside-2-glucoside, and ODOROSIDE H[106,113-116], which is digitoxigenin-digitaloside. GRACILOSIDE[112,114,115] [formerly odoroside F] is digitoxigenin-digitaloside-4-glucoside. DIGILANIDE A is an acetylated tetraglycoside hydrolysed to give deacetyldigilanide A, which is digitoxigenin-[digitoxoside]$_3$-glucoside; this is converted by digilanidase to digitoxin, which is digitoxigenin-[digitoxoside]$_3$ [*see* p. 229]; all these glycosides are obtained from *Digitalis* species. THEVETIN[117,118,119], isolated from be-still nuts, the fruit of *Thevetia neriifolia*, is digitoxigenin-thevetoside-[glucoside]$_2$, hydrolysed by strophanthobiase successively to THEVEBIOSIDE[118,119], with loss of 1 mol. glucose, and to NERIIFOLIN, with loss of 2 mol. glucose; use of thevetobiase gives directly neriifolin, which is digitoxigenin-thevetoside, and has been isolated from *Thevetia neriifolia*[117,118]. ACETYLNERIIFOLIN [≡ cerberin and venaniferin], isolated from the same source, is hydrolysed by potassium bicarbonate to neriifolin, which by the Mannich procedure gives the 3-methoxy-6-deoxyhexose thevetose [≡ cerberose] and 'α'-anhydrodigitoxigenin[117-120]. EVONOSIDE, from seeds of *Evonymus europaea*, is digitoxigenin-rhamnoside-[glucoside]$_2$; hydrolysis with strophanthobiase yields succes-

sively EVOBIOSIDE and EVOMONOSIDE which are digitoxigenin-rhamnoside-glucoside and digitoxigenin-rhamnoside, respectively, whilst Mannich hydrolysis gives acetone- or anhydro-derivatives of digitoxigenin together with rhamnose[121-124].

DIGITOXIGENIN (65) with alkali gives *iso*digitoxigenin (66), which as the open-chain acid (67) is oxidized by potassium hypobromite to *iso*digitoxigenic acid (68); this is converted by the successive action of hydrochloric acid and acetyl chloride into the acetyl-anhydroanhydride (69), hydrogenated and hydrolysed to γ-digitoxanoldiacid (16), which has been degraded to etianic acid (18) [*see* p. 233][33,47].



More direct evidence of structure is provided by oxidative degradation of digitoxigenin [as acetate] with permanganate in acetone to 3β : 14β-dihydroxy-14-*iso*etianic acid (70), and thence to 3β-hydroxyetianic acid[48]. Digitoxigenin has also been converted with inversion at $C_{(17)}$ into 3β-hydroxy-14-*iso*-17-*iso*etianic acid[125] and into 14-*iso*-17-*iso*pregnane[126].



Dehydration of digitoxigenin with sulphuric acid–ethanol or boron trifluoride–acetic anhydride gives a mixture of anhydro-compounds[48,127]; use of phosphorus oxychloride–pyridine gives

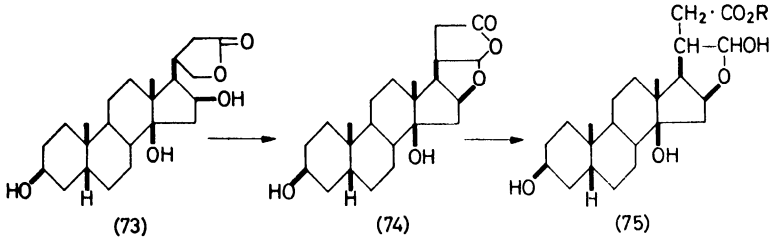
only Δ^{14}-anhydrodigitoxigenin, $[\alpha]_D$ — 13° (71)[34,127], converted by concentrated hydrochloric acid into $\Delta^{8(14)}$-anhydrodigitoxigenin, $[\alpha]_D$ + 39° (72)[34,128]. Digitoxigenin, although a 3β-hydroxy-compound, gives no insoluble digitonide; 3-*epi*digitoxigenin, prepared by reduction of digitoxigenone with sodium borohydride, is physiologically inactive[129].

Gitoxigenin, Oleandrigenin, and their Glycosides

DIGILANIDE B is gitoxigenin-[digitoxoside]$_3$-glucoside acetate and readily loses acetic acid to give DEACETYLDIGILANIDE B, converted by digilanidase to GITOXIN, which is gitoxigenin-[digitoxoside]$_3$ [*see* p. 229]; these glycosides are obtained from various *Digitalis* species. DIGITALINUM VERUM ACETATE [≡ honghelοside B], the principal glycoside of seeds of *D. purpurea* and *D. lanata*, is gitoxigenin-acetyl-digitaloside-glucoside[6,130–133]. Originally, the sugar-acetyl group was not detected and the glycoside was called 'digitalinum verum'; enzymatic hydrolysis gives the true DIGITALINUM VERUM[6,130,133], which is gitoxigenin-digitaloside-glucoside, and STROSPESIDE[130–133,134] [≡ deglucodigitalinum verum], which is gitoxigenin-digitaloside; the compound formerly called 'deglucodigitalinum verum' contains an acetyl-group in the digitalose residue. ORIDIGIN, from *D. orientalis*, consists of gitoxigenin united to glucose and an unidentified 2 : 6-deoxyhexose, hydrolysed with difficulty to dianhydrogitoxigenin (93)[98]. GITORIN, from *D. lanata*, is gitoxigenin-glucoside[135]. OLEANDRIGENIN is gitoxigenin 16-acetate; OLEANDRIN, from *Nerium oleander*, is oleandrigenin-oleandroside[136,137], HONGHELOSIDE A, from the stems of *Adenium honghel* is oleandrigenin-cymaroside[6,130,134], and CRYPTOGRANDOSIDE A, from the leaves of *Cryptostegia grandiflora*, is oleandrigenin-sarmentoside[132]. HONGHELOSIDE C is oleandrigenin-cymaroside-glucoside, converted by enzymatic hydrolysis to honghelοside A, and by long contact with aluminium oxide with loss of acetic acid to Δ^{16}-gitoxigenin-cymaroside-glucoside[130]. CRYPTOGRANDOSIDE B is oleandrigenin-sarmentoside-glucoside, converted by enzymatic hydrolysis to cryptograndoside A[132]. The 16-acetoxyl group in the foregoing glycosides is readily hydrolysed by potassium bicarbonate, whereby oleandrin, honghelοside A, and cryptograndoside A afford gitoxigenin-oleandroside, -cymaroside, and -sarmentoside, respectively[130,132]. The 16-acetoxyl group is easily eliminated as acetic acid by chromatography on aluminium oxide to give Δ^{16}-gitoxigenin-glycosides[130,132]; oleandrin by vacuum pyrolysis yields Δ^{16}-oleandrin[138].

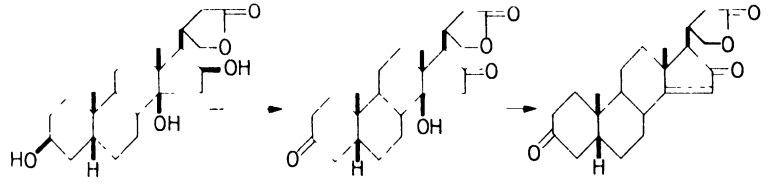
GITOXIGENIN (73) forms a dibenzoate, by oxidation gives a diketone, and with alkali gives *iso*gitoxigenin (74), which yields only a monobenzoate and a monoketone, but readily affords an anhydro-compound[139,140]. The *iso*aglycone is here a 16β : 21-epoxide (74),

hydrolysed to *iso*gitoxigeninic acid [(75): R = H], the methyl ester [(75): R = Me] of which exhibits no carbonyl reactivity and is thus not in equilibrium with a hydroxy-aldehyde form.



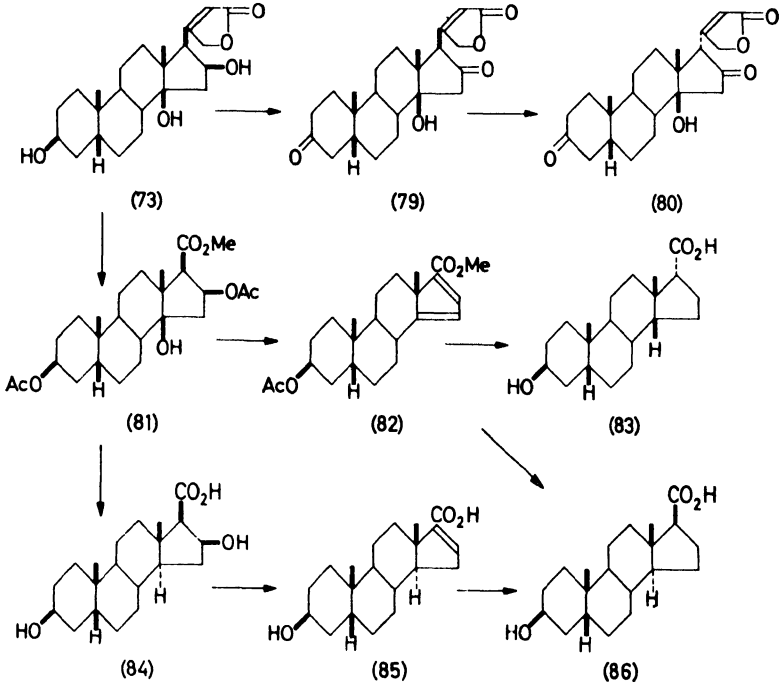
(73) (74) (75)

'α'-Dihydrogitoxigenin (76), obtained by hydrogenation of gitoxigenin with palladium, by oxidation with chromium trioxide gives dihydrogitoxigenone (77), which loses water very easily to form the αβ-unsaturated ketone (78)[141,142]. The tertiary hydroxyl group involved is at $C_{(14)}$ because oxidation of gitoxigenin (73) with chromium trioxide gives the diketone 'α'-gitoxigenone (79), converted, like other 14-*iso*-17-*n*-20-ketones[91,126,143], by alkali to the more thermodynamically stable 'β'-gitoxigenone (80) with inversion at $C_{(17)}$. These diketones give neither the Legal test nor anhydro-derivatives, but their structures are supported by their infra-red spectra[63].

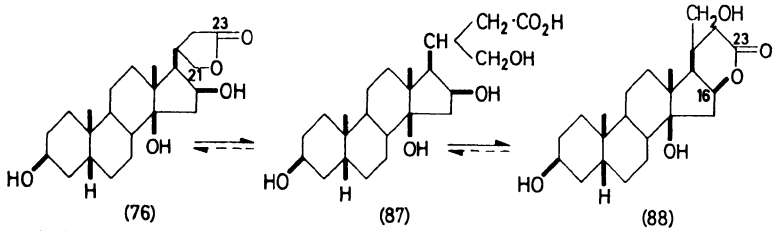


(76) (77) (78)

Gitoxigenin (73) [as diacetate] by oxidation with permanganate in acetone gives the ester-diacetate (81), dehydrated by phosphorus oxychloride–pyridine to the $\Delta^{14:16}$-ester (82) and a Δ^{14}-ester hydrogenated with platinum in acetic acid to give [after alkaline hydrolysis] 3β : 16β-dihydroxyetianic acid (84)[144], identical with synthetic material and different from the 3β : 16α-epimeride[145]. Hydrogenation of the ester (82) with platinum–acetic acid gives [after alkaline hydrolysis] a mixture of 3β-hydroxy-14-*iso*-17-*iso*-etianic acid (83) and 3β-hydroxyetianic acid (86); the acid (84) as the 3-monoacetate methyl ester [obtained from the 3 : 16-diacetate methyl ester by partial hydrolysis with potassium bicarbonate], by dehydration with phosphorus oxychloride–pyridine and alkaline



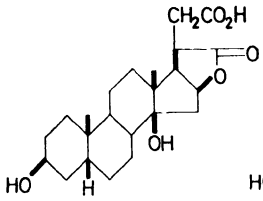
hydrolysis yields 3β-hydroxyeti-16-enic acid (85), identical with synthetic material, hydrogenated with platinum-acetic acid to 3β-hydroxyetianic acid (86)[144].



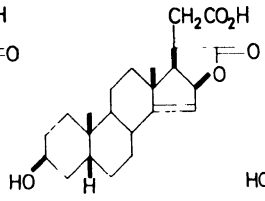
'α'-Dihydrogitoxigenin [(76): $[\alpha]_D$ + 42°] exhibits mutarotation; in aqueous solution, fission of the 23 → 21-lactone ring affords the acid (87), recyclized to the 23 → 16-lactone 'β'-dihydrogitoxigenin [(88): $[\alpha]_D$ − 55°], which by oxidation yields a 3-oxo-21-carboxylic acid[141,142,146,147].

Gitoxigenin (73) has been correlated with digitoxigenin by oxidation of *iso*gitoxigeninic acid [(75): R = H] to *iso*gitoxigenic acid (89), which is converted by concentrated hydrochloric acid through a 14α-chloro-compound into the 20-epimeric 'γ'-anhydro acid (90), hydrogenated [as methyl ester] with platinum–acetic acid to 'γ'-digitoxanoldiacid (16)[139].

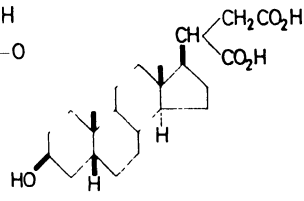
OLEANDRIGENIN [≡ gitoxigenin 16-acetate] (91) is obtained from oleandrin, honghelosides A, and cryptograndoside A by hydrolysis with 0·05N mineral acid[130,132,136,137]. It is further hydrolysed to



(89)

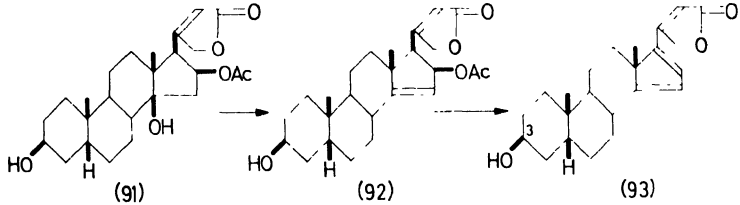


(90)



(16)

gitoxigenin (73), and has been prepared therefrom by partial acetylation [Ac_2O–Py][148]; acetylation of gitoxigenin [Ac_2O—NaOAc] gives the 3 : 16-diacetate, which by partial hydrolysis gives gitoxigenin 3-acetate. The acetyl in oleandrigenin group is located at $C_{(16)}$ and not $C_{(3)}$ since oxidation with chromium trioxide gives oleandrigenone, dehydrated by cold concentrated hydrochloric acid to dianhydrogitoxigenone [(93) with O= at $C_{(3)}$]. Hydrolysis of oleandrigenin with 1N acid gives Δ^{14}-anhydro-oleandrigenin (92) and dianhydrogitoxigenin [(93): $[\alpha]_D$ + 454°], which is the sole product with ethanolic hydrogen chloride[140].



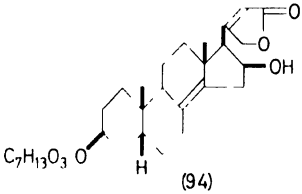
(91) (92) (93)

Oleandrigenin

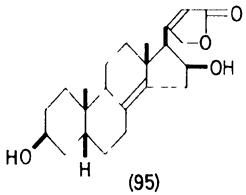
Adynerigenin, Neriantogenin, Adonitoxigenin

ADYNERIN (94)[137], isolated from oleander leaves, is stated[34] to be 8(14)-anhydro-oleandrin [= $\Delta^{8(14)}$-gitoxigenin 16-acetate oleandroside], but gentle hydrolysis gives diginose[149], not oleandrose as originally reported[137], and ADYNERIGENIN (95). Adynerigenin affords an *iso*-compound, and with dilute mineral acid yields 15-anhydroadynerigenin [=8(14) : 15-dianhydrogitoxigenin] (96), converted by concentrated hydrochloric acid to 16-anhydroadynerigenin [= 8(14) : 16-dianhydrogitoxigenin][34, 133, 137, 148] and hydrogenated to 20 : 22-dihydro-8(14)-anhydrodigitoxigenin [i.e. (20 : 22-dihydro-72)][34]. An alternative formulation of adynerin as a 3α-glycosidoxy-Δ^8-compound and of adynerigenin as a 3α-hydroxy-Δ^7-compound proposed by Tschesche and Grimmer[149] appears untenable.

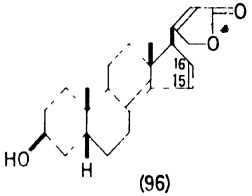
NERIANTIN[137], from oleander leaves, is neriantogenin-glucoside; hydrolysis yields neriantogenin (97) [≡ Δ^{14}-anhydrogitoxigenin], giving a diacetate, and converted by concentrated hydrochloric acid to dianhydrogitoxigenin (93)[63,133,137,148].



(94)
Adynerin

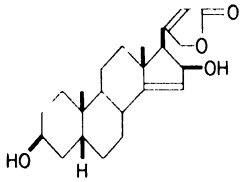


(95)
Adynerigenin

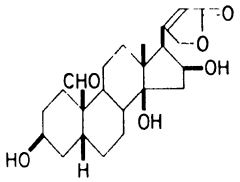


(96)

ADONITOXIN[2], from *Adonis vernalis*, is an aldehyde forming an oxime, and giving an acid by oxidation; it is 19-oxogitoxigenin-rhamnoside since Mannich hydrolysis yields rhamnose and ADONITOXIGENIN (98)[150], which has been shown to be 19-oxogitoxigenin[151].



(97)
Neriantogenin



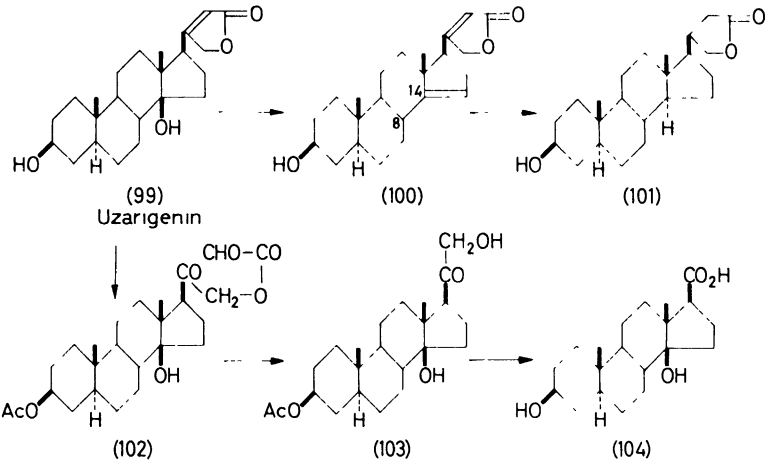
(98)
Adonitoxigenin

Uzarigenin, 3-epiUzarigenin, Corotoxigenin, Coroglaucigenin, and Related Glycosides

UZAROSIDE[152] and UZARIN[153], from uzara root, are uzarigenin-[glucoside]$_3$ and uzarigenin-[glucoside]$_2$, respectively; ODOROSIDE[114,154] and ODOROBIOSIDE K[114,154], from *Nerium odorum*, are uzarigenin-[glucoside]$_2$-diginoside and uzarigenin-glucoside-diginoside, respectively, whilst CHEIROSIDE A[86,110,111,155,156] has been found to be identical with CHEIROSIDE H and is uzarigenin-fucoside-glucoside[86]. All these glycosides require drastic acid hydrolysis which leads to a mixture of anhydrouzarigenins[37,74,153,156]. ODOROSIDE B[110,111] is uzarigenin-diginoside and is readily hydrolysed by 0·1N acid to diginose and UZARIGENIN.

UZARIGENIN[110,111] [≡ odorigenin B] (99) has the *A/B-trans*-configuration[37,38]; it has a secondary hydroxyl group [monoacetate] and a tertiary hydroxyl group readily lost to give $\Delta^{8(14)}$-anhydrouzarigenin [$[\alpha]_D$ + 5°] and Δ^{14}-anhydrouzarigenin [(100): $[\alpha]_D$

— 30°][34,37,74,153,156]. The tertiary hydroxyl group is at $C_{(14)}$ since uzarin and odoroside B with alkali give respectively *iso*uzarin and *iso*odoroside B, which is readily hydrolysed by dilute acid to *iso*-uzarigenin[156]. The structure (99) is proved by degradation [as



the acetate] with ozone at — 80° to the glyoxylic ester (102), hydrolysed by potassium bicarbonate to the α-ketol (103), which with periodic acid gives 3β : 14β-dihydroxy-14-*isoallo*etianic acid (104)[110,111], identical with synthetic material[157].

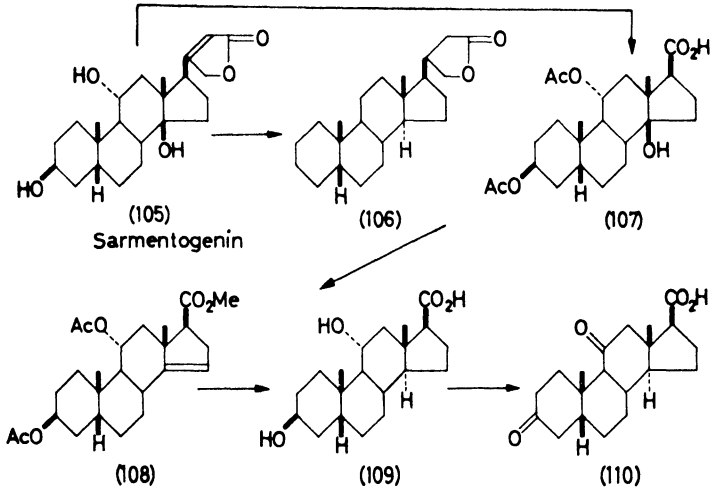
Hydrogenation of Δ^{14}-anhydrouzarigenin (100) yields two 20-epimeric tetrahydrides [as (101)][37], whose synthesis from 3β : 21-diacetoxypregn-5-en-20-one [*see* p. 246] provides further proof of structure. A correlation with periplogenin (60) has been achieved[37,38].

UREZIN[152] is 3-*epi*uzarigenin-[glucoside]$_2$; urezigenin [≡ 3-*epi*-uzarigenin] is the only natural aglycone with a 3α-hydroxyl group.

MILLOSIDE[158], PAULIOSIDE[158], STROBOSIDE[158], BOISTROSIDE[158], and CHRISTYOSIDE[158,159] are respectively the cymaroside, sarmentoside, boivinoside, digitoxoside, and digitaloside of COROTOXIGENIN, which is 19-oxouzarigenin since Wolff-Kishner reduction of its 20 : 22-dihydro-derivative gives 20 : 22-dihydrouzarigenin[158,159,160]. GOFRUSIDE[160,161,163], from seeds of *Gomphocarpus fructicosus*, is corotoxigenin-D-6-deoxyalloside. FRUGOSIDE[160,162,163,164], from seeds of *G. fructicosus* and roots of *Xysmalobium undulatum*, is coroglaucigenin-D-allomethyloside; gofruside by reduction with sodium borohydride gives frugoside, so that COROGLAUCIGENIN is uzarigen-19-ol. Christyoside and gofruside undergo auto-oxidation[165].

Sarmentogenin and its Glycosides

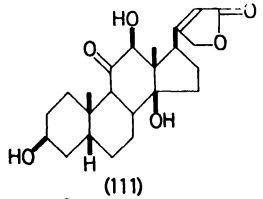
SARMENTOCYMARIN is sarmentogenin-sarmentoside, and was isolated from seeds described as *Strophanthus hispidus*[166,167]; subsequent botanical examination has suggested that the material may have consisted of seeds of *S. sarmentosus*[166] and a mixture of seeds of *S. preussii* and *barteri*[167]. Sarmentocymarin has been obtained [yield 0·45%][168] from seeds regarded as *S. sarmentosus* but now thought to be derived from some other species, because seeds of genuine *S. sarmentosus* contain only traces [0·0045%][169]. Sarmentocymarin has been isolated from seeds of *S. gerrardii* [0·134%], *S. courmontii* [0·30%], *S. petersianus* [0·1%], and *S. grandiflorus* [0·1%][170]; *S. sarmentosus glabriflorus* seeds are very rich in glycosides[171]. Seeds of *S. nicholsonii, hypoleucus, eminii, mirabilis,* and *hispidus* contain no sarmentocymarin, but yield cymarin, cymarol, periplocymarin, and emicymarin[172,173]. From seeds of various *Strophanthus* species are isolated SARGENOSIDE[32,175,176], SARNOVIDE[177,178,179,203], DIVARICOSIDE[180–183,195], and KWANGOSIDE[184], which are the digitaloside-glucoside, digitaloside, oleandroside, and diginoside, respectively, of SARMENTOGENIN (105). Sarnovide by oxidation with chromium trioxide gives DESAROSIDE[179], which also occurs naturally and is reduced by sodium borohydride to 11-*epi*-SARNOVIDE[179], which is less toxic than sarnovide. Divaricoside by oxidation with chromium trioxide gives 11-DEHYDRODIVARICOSIDE[183]. The substance formerly called 'SARMENTOSIDE B' is sargenoside diacetate, i.e. sarmentogenin-11-acetate-acetyldigitaloside-glucoside, and the former 'SARMENTOSIGENIN' is sarmentogenin 11-acetate[174,176,178].

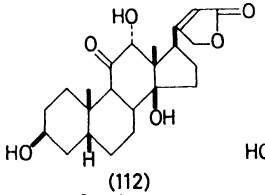


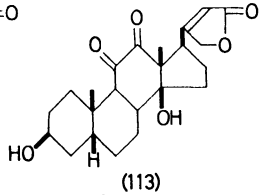
SARMENTOGENIN (105) contains two secondary hydroxyl groups [3β : 11α-dibenzoate], and a tertiary hydroxyl group at $C_{(14)}$ affording with alkali *iso*sarmentogenin and by dehydration $\Delta^{8(14)}$- and Δ^{14}-anhydrosarmentogenin[63,178]; oxidation with chromium trioxide yields a 3 : 11-diketone sarmentogenone giving only a 3-monosemicarbazone[94]. Successive elimination of the three hydroxyl groups gives the deoxylactone (106)[185], also obtained from digitoxigenin[186], and digoxigenin[103]. Sarmentogenin [as 3β : 11α-diacetate] by oxidation with permanganate in acetone yields 3β : 11α-diacetoxy-14β-hydroxy-14-*iso*etianic acid (107), dehydrated as methyl ester by phosphorus oxychloride–pyridine to the Δ^{14}-ester (108), hydrogenated with platinum–acetic acid to give, after alkaline hydrolysis, 3β : 11α-dihydroxyetianic acid (109)[168], which differs from the 3β : 11β-isomeride[184] and the 3α : 11α-isomeride[188], but by oxidation affords the known 3 : 11-dioxoetianic acid (110)[189]. Although a 3β-hydroxy-compound, sarmentogenin gives no insoluble digitonide. 11-Dehydrodivaricoside by acid hydrolysis gives oleandrose and 11-DEHYDROSARMENTOGENIN[179,183], which by reduction with sodium borohydride affords 11-*epi*SARMENTOGENIN[179,183].

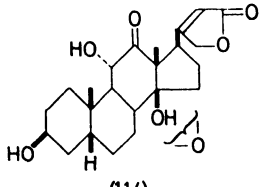
Other 11-*Oxygenated Glycosides and Aglycones*

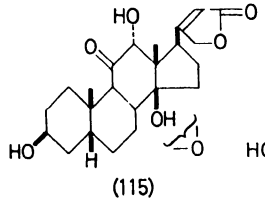
SARMUTOSIDE[182,190,191], MUSAROSIDE[182,190,191], and AMBOSIDE[184,192,193] are respectively the sarmentoside, digitaloside, and diginoside of SARMUTOGENIN (111)[194]. CAUDOSIDE[103,180,182,195] is the oleandroside of CAUDOGENIN (112), which may have the alternative 3β : 11α : 14β-trihydroxy structure, and by oxidation with chromium trioxide affords DECOSIDE[183]; this with dilute acid gives oleandrose and the 11 : 12-diketone DECOGENIN (113)[183], which is dehydrated by acetic anhydride–pyridine at 20° to the Δ^{8}-11 : 12-diketone ACETYLCAULUTOGENIN[183].

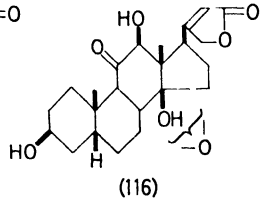

(111)
Sarmutogenin


(112)
Caudogenin


(113)
Decogenin


(114)
Sarverogenin


(115)
Inertogenin


(116)
Leptogenin

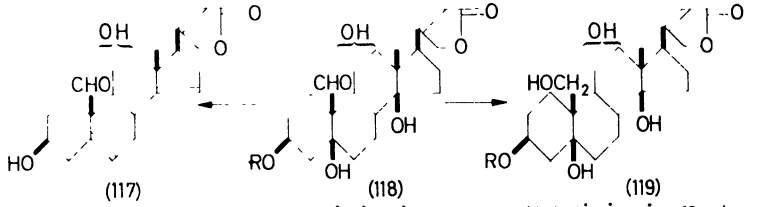
SARVEROSIDE[170,174,196,197,198], INTERMEDIOSIDE[198,199,200,201], and PANSTROSIDE[198,200,201,202,203] are the sarmentoside, diginoside, and digitaloside, respectively, of SARVEROGENIN (114), which has one unplaced oxygen atom present probably as a 7α : 15α-epoxide[194], forms a dibenzoate, and by oxidation gives the yellow 11 : 12-diketone sarverogenone[197].

INERTOSIDE[180,204,205] and LEPTOSIDE[180,204,205] are hydrolysed by dilute acid to diginose and INERTOGENIN (115)[206] and LEPTOGENIN (116)[206], respectively. By oxidation with chromium trioxide intermedioside, inertoside, and leptoside all give the same 11 : 12-diketone-diginoside, CHRYSEOSIDE[206], which by reduction with aluminium amalgam regenerates a mixture of the three glycosides; chryseoside by mild acid hydrolysis gives diginose and the 11 : 12-diketone CHRYSEOGENIN [≡ sarverogenone][206], dehydrated by acetic anhydride–pyridine at 20° to the Δ^{8}-11 : 12-diketone ACETYLFLAVOGENIN[206]. All these substances have one unplaced oxygen atom, present probably as an epoxide.

Seeds of *S. sarmentosus* appear in four 'chemical' varieties[171]; SARMENTOSIDES A, C, D, and E have been isolated[174,175,190,196,197,203,207,208], of which the first named is an aldehyde united with L-6-deoxytalose[174,207].

Antiarigenin and 'α'- and 'β'-Antiarin

The latex of the upas tree, *Antiaris toxicaria*, used as an arrow poison, yields 'α'-ANTIARIN [as (118)], which is antiarigenin-antiaroside [≡ antiarigenin-5-*epi*rhamnoside][209], and 'β'-ANTIARIN [as (118)], which is antiarigenin-rhamnoside[210]. By energetic acid hydrolysis both give the appropriate sugar and dianhydro-antiarigenin (117)[211]; this gives the Legal test, has one reactive secondary hydroxyl group and one hindered secondary hydroxyl group [monobenzoate], a carbonyl group [semicarbazone], and two non-conjugated nuclear double bonds[209,210,211]. Mannich hydrolysis of 'α'-antiarin gives antiarigenin [(118): R = H][212]. 'α'-Antiarin gives a tribenzoate [3 acyl groups in antiarose moiety], oxidized by chromium trioxide to an acid which readily lactonizes [19→11β- or 19→12β-lactone], whilst Meerwein-Ponndorf

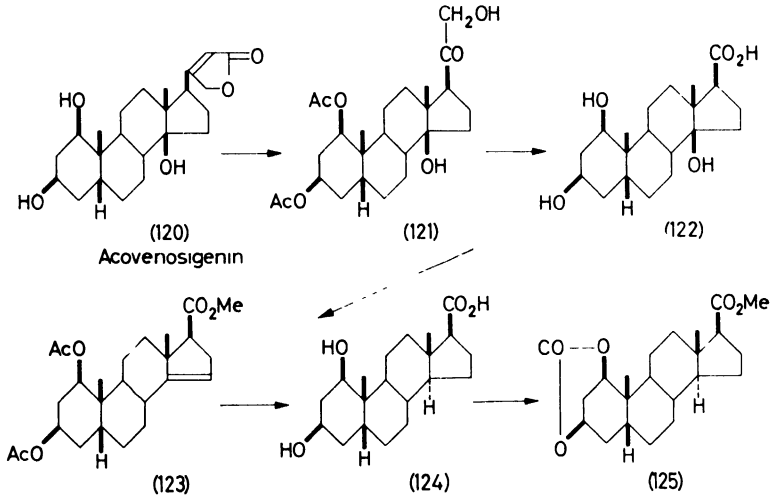


reduction of 'α'-antiarin affords 'α'-antiarol [as (119)], the tetrabenzoate of which is oxidized to a ketone[212].

'β'-Antiarin gives a tribenzoate [3 acyl groups in rhamnose residue] oxidized by chromium trioxide to a neutral compound [lactone]. Mannich hydrolysis fails, but after reduction with sodium borohydride to 'β'-antiarol [as (119)] succeeds to give rhamnose and antiarigen-19-ol [(119): R = H][213]. 'α'- and 'β'-Antiarin [as (118)] and 'α'- and 'β'-antiarol [as (119)] are about equally toxic[213].

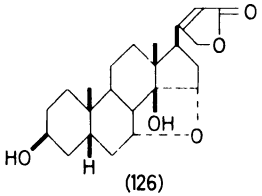
Acovenosigenin and its Glycosides

ACOVENOSIDES A[15,214,215,216], B[15], and C[217], from seeds of *Acokanthera venenata*, are acovenosigenin-acovenoside, acovenosigenin combined with an unknown sugar, and acovenosigenin-acovenoside-[glucoside]$_2$. Seeds of *Acokanthera longiflora*[215] and *friesiorum*[216,218] afford acovenoside A and the incompletely characterized *acolongiflorosides* E, G, H, J, and K[15,215]. ACOVENOSIGENIN A (120) is obtained from acovenoside A by Mannich hydrolysis[15], and by degradation with ozone, hydrolysis of the resulting glyoxylic ester to the α-ketol (121), and oxidation with periodic acid affords 1β : 3β : 14β-trihydroxy-14-*iso*ctianic acid (122); this by dehydration [as diacetate-methyl ester] with phosphorus oxychloride or thionyl chloride gives the Δ^{14}-ester (123), hydrogenated with platinum–acetic acid to yield, after hydrolysis, 1β : 3β-dihydroxyetianic acid (124), which [as methyl ester] with carbonyl chloride–pyridine gives the 1β : 3β-carbonate (125)[219]. Elimination of the 1β-hydroxyl group yields ultimately 3-oxoctianic acid[219,220].

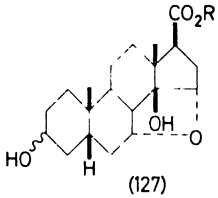


Tanghinigenin, Tanghiferigenin, and Other Glycosides

Four thevetosides have been isolated from the nut kernels of *Tanghinia venenifera*[117,119,221]; TANGHININ, which is tanghinigenin-acetylthevetoside, DEACETYLTANGHININ, TANGHIFERIN of unknown structure, and acetylnerifoliin [*see* p. 242]. Deacetyltanghinin by acid hydrolysis affords thevetose and TANGHINIGENIN[222] [(126): 3β-OH], oxidized by chromium trioxide to a 3-ketone which with sodium borohydride is reduced to 3-*epi*TANGHINIGENIN [(126): 3α-OH][222].



(126)
Tanghinigenin



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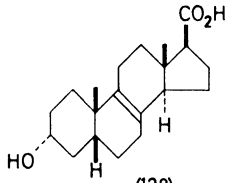


(128)

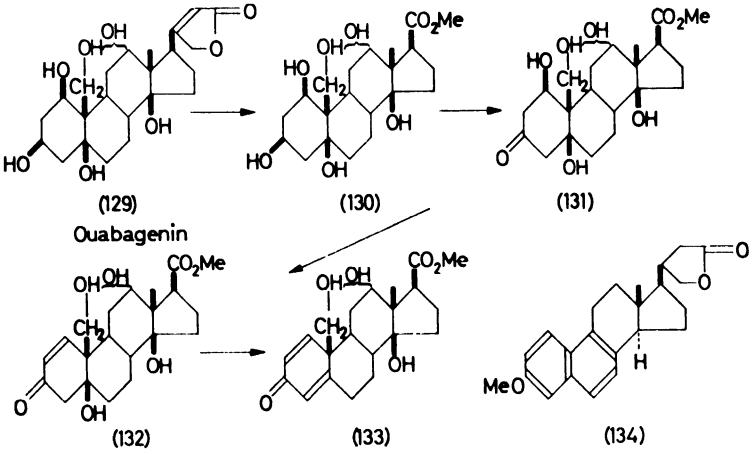
Oxidative degradation of the aglycones [as (126)] with ozone, potassium bicarbonate, and periodic acid gave respectively 3β: 14β- and 3α : 14β-dihydroxy-7α : 15α-epoxy-14-*iso*ctianic acid [as (127): R = H], yielding with chromium trioxide the same 3-oxo-acid; dehydration of the 3α : 14β-dihydroxyester [(127): 3α-OH, R = Me] with thionyl chloride–pyridine and hydrogenation of the product with platinum–acetic acid afforded 3α-hydroxyeti-8-enic acid (128), identical with synthetic material[223]. The 7α : 15α-position assigned to the epoxy ring is probable but not proved.

Ouabagenin and Ouabain

OUABAIN [≡ g-strophanthin], an arrow poison, is obtained from the bark and root of the ouabaio tree, from *Strophanthus gratus*[224], and from *Acokanthera friesiorum*[218]; it is a rhamnoside[224], gives the Legal test[225], and with alkali, *iso*ouabain[225]. Acetylation with acetic anhydride gives a hexaacetate[27], and in presence of zinc chloride a Δ^{14}-anhydroouabain heptaacetate[224]; this by hydrogenation gives a tetrahydride, which undergoes acetolysis with hydrochloric–acetic acid, with elimination of (i) rhamnose, (ii) four acetoxyl groups, and (iii) one carbon atom as formaldehyde, to give an aromatic trianhydrohydroxylactone, $\lambda_{max.}$ 270 mμ[225]. Analogous results were obtained with *iso*ouabain[225], and have been interpreted as loss of a $C_{(10)}$-CH_2OH group with aromatization of ring *B*[226] or ring *A*[227].

Ouabain by Mannich hydrolysis affords ouabagenin-acetonide[27]

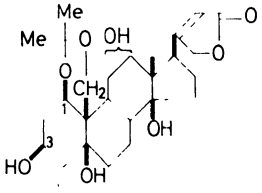
[≡ 'anhydroouabagenin'][228] reversibly converted[229] by traces of acid to OUABAGENIN (129)[27,230,231], which affords a tetraacetate A[230,231,232], a triacetate B[230,231,232] and a triacetate C[233]. Oxidative degradation of the tetraacetate A[230,231,232] and of the triacetate B[230,232] affords a tetraacetoxydihydroxy- and a triacetoxydihydroxy-14-*iso*etianic ester, both converted by sodium carbonate hydrolysis to a methyl hexahydroxy-14-*iso*etianate (130)[232,233], which affords two isomeric monoacetonides[233]. The ester (130) by oxidation with N-bromoacetamide affords a bis-β-hydroxy-ketone (131), dehydrated successively to a tetrahydroxyenone ester (132), giving a diacetate, and a trihydroxydienone ester (133), also giving a diacetate[232].



20 : 22-Dihydroouabagenin[27] has been converted by selective oxidation with platinum and oxygen and treatment with alkali with loss of formaldehyde into a phenol, which by dehydration to a Δ^{14}-anhydro-compound and rearrangement with methanolic hydrochloric acid gives the β-naphthyl methyl ether (134)[234]. These transformations permit assignment of five of the hydroxyl groups in ouabagenin, viz. 1β : 3β : 5β : 14β : 19, whilst the sixth is probably 11α[27] or 12β[230,231]; it is consistent that ouabagenin does not react with lead tetraacetate[27,229] or periodic acid[228].

Ouabagenin-acetonide has been formulated with a 1β : 3β-bridge[27,228], or more recently with a 1β : 19-bridge (135)[233]; acetylation furnishes an acetonide diacetate[27,228,229,231] converted by sulphuric acid hydrolysis into a 3β : 12β?-diacetate [≡ 'α'-ouabagenin diacetate] accompanied as the result of acyl-migration by a 3β : 19-diacetate [≡ 'β'-ouabagenin diacetate][228,229,231], oxidized to a 3 : 12?-diketone by chromium trioxide–acetic acid[233],

but to a Δ^{2}-1 : 12?-diketone (136) by chromium trioxide in pyridine and subsequent chromatography on aluminium oxide[233].



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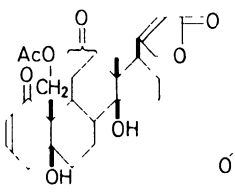

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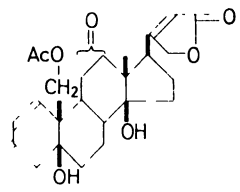


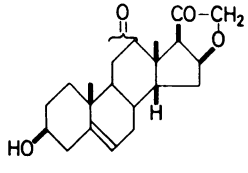
(137)

Oxidation of ouabagenin-acetonide (135) with chromium trioxide–acetic acid and subsequent chromatography on aluminium oxide gives a Δ^{1}-3 : 12?-diketone (137), converted as the 19-alcohol by hot acetic acid with loss of formaldehyde into a ring *A* phenol[233].

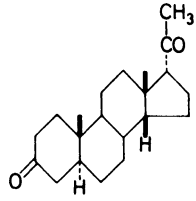
Numerous incompletely characterized glycosides and aglycones have recently been isolated by Reichstein: odorosides C, D, E, F[110]; cheirosides C, D, E, F, G[85]; abobioside, abomonoside, and abogenin[235]; courmontosides A, B, C[236]; nigrescigenin[237]; ambostroside and quilenogoside[238]; arriagoside, gossweiloside, walloside, and wallogenin[239]; bogoroside and antioside[213]; and nabogenin[240]. From the leaves, stalks, and latex of *Calotropis* varieties there have been obtained uscharin[241], uscharidin[241], calotropin[241,242], calactin[241], calotoxin[241], and, more recently, coroglaucigenin, corotoxigenin, frugoside, and other glycosides[242].

Diginigenin and Diginin

DIGININ, from leaves of *Digitalis purpurea*[243], is unique in yielding by hydrolysis with 0·1N acid diginose (10)[23] and a C_{21}-aglycone[244]. DIGINIGENIN, $C_{21}H_{28}O_4$ (138), gives the Legal test but has no lactone ring; it contains a secondary hydroxyl group [monoacetate], and two carbonyl groups one of which is hindered [monoxime] and is probably present as a $C_{(10)}$-aldehyde group[244]. The grouping $-CO\cdot CH_2-$ is present [piperonylidene derivative], and one



(138)
Diginigenin



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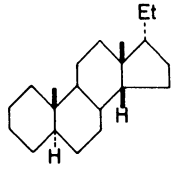


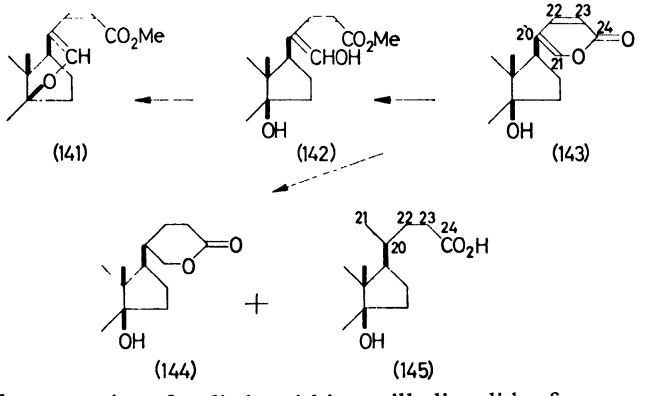
(140)

isolated double bond; the fourth oxygen atom is regarded as a 16 : 21-epoxide forming part of a β-ketotetrahydrofuran ring[245]. Diginigenin by Wolff-Kishner reduction followed by hydrogenation with platinum–acetic yields three products; one by oxidation with chromium trioxide–acetic acid gives 3 : 20-dioxo-14-*iso*-17-*iso*-pregnane (139), converted by Wolff-Kishner reduction to 14-*iso*-17-*iso*pregnane (140)[245]; these degradation products have been synthesized from 3β-hydroxy-14-*iso*-17-*iso*etianic acid[246].

Scilladienolides [≡ bufadienolides]

The scilladienolides occur conjugated with one or more sugars in plants and free or conjugated with suberylarginine as bufotoxins in the venom secreted by the skin and parotid glands of toads. They have a digitalis-like action on the heart, and extracts of squill have been used since mediaeval times, whilst the Chinese and Japanese have long employed medicinally a galenical preparation from the toad *Bufo bufo gargarizans* called Ch'an Su in China and Senso in Japan. The glycosides are beautifully crystalline substances, but the bufotoxins are difficult to purify and characterize.

In the squill glycosides and the toad poisons, the side chain is a six-membered $\Delta^{\alpha\beta\ \gamma\delta}$-lactone ring (143) with an ultraviolet absorption band at $\lambda_{max.}$ 300 mμ.; these lactones do not give the Legal test, but with methanolic potassium hydroxide yield enol-esters (142), which afford 14β : 21-epoxyesters [≡ *iso*-compounds] (141). Hydrogenation with palladium in acetic acid furnishes saturated δ-lactones (144) accompanied by 14-*iso*cholanic acids (145). Ozonolysis of the lactone ring affords formic, oxalic, and glyoxylic acids together with an etianic acid.



Colour reactions for distinguishing scilladienolides from cardenolides have been described[247]. The scilladienolide aglycones of known structure are given in *Table XV*.

Table XV

SCILLADIENOLIDE AGLYCONES

Aglycone	Formula	Substituents	m.p.°	$[\alpha]_D^\circ$
Scillarenin[a] .	$C_{24}H_{32}O_4$	3β : 14β-$(OH)_2$	238	− 17
Bufalin . .	$C_{24}H_{34}O_4$	3β : 14β-$(OH)_2$	244	− 9
Bovogenin A[b]* .	$C_{24}H_{30}O_5$	3β : 14β-$(OH)_2$	247	0
Bovogen-19-ol A*	$C_{24}H_{32}O_5$	3β : 14β : 19-$(OH)_3$	260	− 15
Telocinobufagin .	$C_{24}H_{34}O_5$	3β : 5β : 14β-$(OH)_3$	160/210	+ 4
Gamabufogenin .	$C_{24}H_{34}O_5$	3β : 11α : 14β-$(OH)_3$	263	
Hellebrigenin[b] [= Bufotalidin]	$C_{24}H_{32}O_6$	3β : 5β : 14β-$(OH)_3$	237	+ 18
Hellebrigen-19-ol	$C_{24}H_{34}O_6$	3β : 5β : 14β : 19-$(OH)_4$	257**	+ 8**
Bufotalin . .	$C_{26}H_{36}O_6$	3β : 14β-$(OH)_2$: 16β-OAc	118/222	+ 5
Bufotalinin[b] .	$C_{24}H_{30}O_6$	3β : 5β-$(OH)_2$: x-CO	201	+ 19
Marinobufagin .	$C_{24}H_{32}O_5$	3β : 5β-$(OH)_2$: x-CO	224	+ 10

[a] = Δ^1-ene
[b] = CHO at $C_{(10)}$
* = *A/B-trans*-ring-fusion
** = 3-monoacetate.

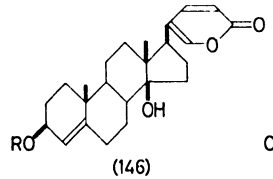
Structure of Individual Glycosides and Aglycones

Scillarenin, Proscillaridin A, Scillaren A [≡ '*Transvaalin*'], *and Glucoscillaren A; Scilliroside, Scillaren F*

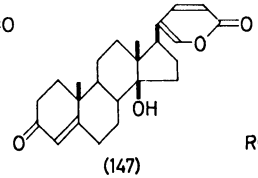
The white squill, *Scilla* [≡ *Urginea*] *maritima*, affords a remarkable series of glycosides; GLUCOSCILLAREN A, SCILLAREN A [≡ 'transvaalin'] [as (146)], and PROSCILLARIDIN A[248,249], are the rhamnoside-[glucoside]$_2$, the rhamnoside-glucoside, and rhamnoside, respectively, of scillarenin [(146): R = H] whilst GLUCOSCILLIPHAEOSIDE and SCILLIPHAEOSIDE are the rhamnoside-glucoside and glucoside, and SCILLIKRYPTOSIDE, SCILLIGLAUCOSIDE, SCILLICYANOSIDE, SCILLICOELOSIDE, and SCILLAZUROSIDE are glucosides of unknown aglycones[249,250].

Glucoscillaren A, scillaren A, and proscillaridin A are hydrolysed stepwise by appropriate enzymes finally to give SCILLARENIN [(146): R = H][251,252], which gives no insoluble digitonide. Previously, by use of hot 0·2N acid, scillaren A furnished the $\Delta^{3:5}$-diene SCILLARIDIN A (149) and various formulae were proposed for scillaren A and its then unknown aglycone[248,253]. Scillarenin by enzymatic[252] or chemical oxidation[251] gives scillarenone (147); this by Meerwein-Ponndorf reduction regenerates scillarenin[252], which proves the position of the double bond.

Hydrogenation of scillaren A [as (146)] gives a hexahydride [as (144)] and the rhamnoside-glucoside of 3β : 14β-dihydroxy-14-*iso-allo*cholanic acid [(148): R = $C_{12}H_{21}O_9$], hydrolysed at $C_{(3)}$ and dehydrated at $C_{(14)}$ with 1N methanolic hydrogen chloride to give 3β-hydroxy*allo*chol-14-enic acid, hydrogenated with platinum–acetic acid to 3β-hydroxy*allo*cholanic acid[254].



(146)
R = H Scillarenin
R = $C_{12}H_{21}O_9$ · Scillarenin A



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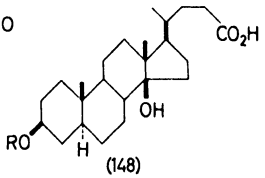

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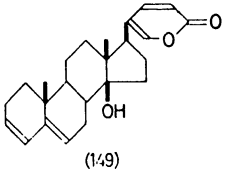

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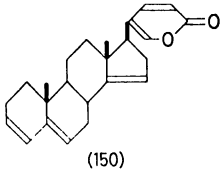

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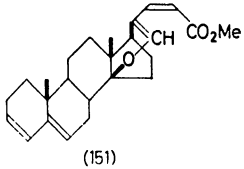


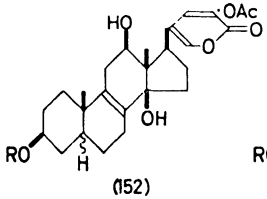
(151)

Scillaridin A (149) is dehydrated by 1N hydrochloric acid to the Δ^{14}-anhydro-compound (150) reversibly converted to an enol-ester [as (142)]; scillaridin A with methanolic potassium hydroxide gives *iso*scillaridin methyl ester (151)[248].

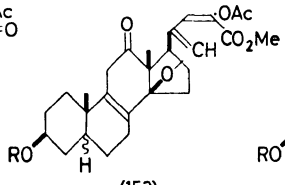
A substance called 'transvaalin', isolated from the bulbs of *Urginea burkei*[255], was originally and correctly regarded as scillaren A[256], but later as an acetylated bufalin-rhamnoside-glucoside[257]; 'transvaalin' is identical with scillaren A, and scillarenin has also been isolated from the plant[247].

SCILLIROSIDE (152)[258,259] is the chief glycoside of the red variety of *Scilla* [≡ *Urginea*] *maritima* [used from the thirteenth century as a rat poison], in which it is accompanied by scillaren A [as (146)] and SCILLAREN F[258,259], a glucoside of unknown structure, and is five hundred times more lethal to rodents than scillaren A. It is a glucoside, has $\lambda_{max.}$ 300 mμ, fails to give the Legal test, and requires two equivalents of alkali: one to open the δ-lactone ring, and one to hydrolyse an enol-acetate group, whose presence causes the 22 : 23-double bond. Scilliroside tetraacetate [four sugar acetyl groups] contains two free hydroxyl groups; one is secondary since oxidation with chromium trioxide or lead tetraacetate gives a ketone, affording by successive treatment with alkali, hydrochloric acid, and acetic anhydride, an *iso*-compound (153). A second type of *iso*-compound (154) can be obtained from scilliroside by successive treatment with alkali, hydrochloric acid, and acetic anhydride;

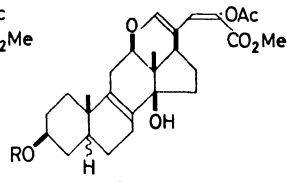
the secondary hydroxyl group is therefore placed at $C_{(12)}$, but $C_{(16)}$ has been suggested[260]. Scilliroside contains a nuclear double bond which reacts with perbenzoic acid, but resists hydrogenation and is placed at the 8 : 9-position.



(152)
R=$C_6H_{11}O_5$ Scilliroside



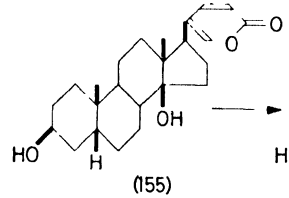
(153)
R=$C_6H_7O(OAc)_4$



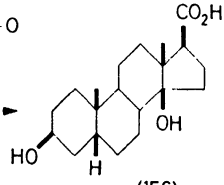
(154)
R=$C_6H_7O(OAc)_4$

Bufalin

BUFALIN (155)[261,262], from Ch'an Su [= *Bufo gargarizans*], forms a monoacetate, hydrogenated to a tetrahydride, and is oxidized with chromium trioxide to a ketone; it is dehydrated by hydrochloric acid to a Δ^{14}-anhydro-compound and by hot acetic anhydride to an acetylanhydro-compound, degraded to 3β-hydroxyetianic acid[261]. Bufalin acetate by oxidative degradation with permanganate in acetone gives 3β : 14β-dihydroxy-14-*iso*etianic acid (156)[263] and the known 21→14-lactone (157)[48].



(155)
Bufalin



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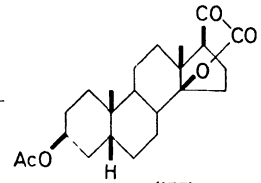


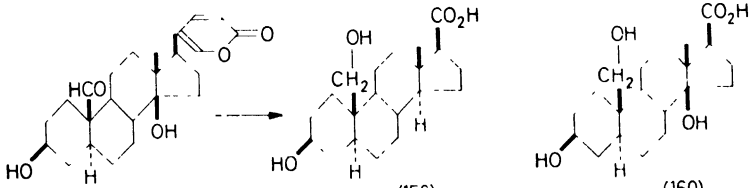
(157)

Bufalin is the lactonic homologue of digitoxigenin.

Bovogenin A, and the Bovosides A, B, C, D, and E

White and green bulbs of *Bowiea volubilis* furnish the BOVOSIDES A, B, C[264,265], and D[266,267,268], and E[266] together with bovogenin A (158)[269] [≡ bowiea-substance G]. Bovoside A is an aldehyde and undergoes autoxidation[266], especially in light, and is reduced with sodium borohydride to bovosid-19-ol A[269,271]. It is bovogenin-A-thevetoside; hydrolysis with acid gives thevetose and Δ^{14}-anhydro-bovogenin A[266]. BOVOGENIN A (158) by reduction with sodium borohydride gives BOVOGEN-19-OL-A, which by oxidative degradation, dehydration, and hydrogenation[269] yields the known 3β : 19-

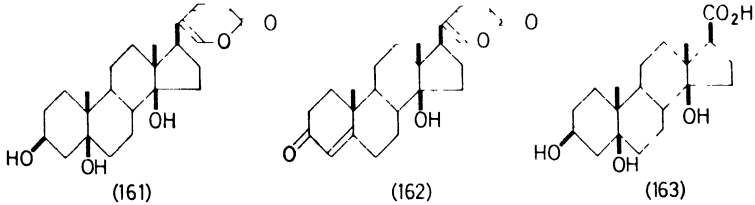
dihydroxy*allo*etianic acid (159)[163]; degradation of bovosid-19-ol-A [7·5 mg!][270] gives the known 3β : 14β : 19-trihydroxy-14-*isoallo*-etianic acid (160)[272]. Bovogenin A is the lactonic homologue of corotoxigenin.



Bovoside D is probably 16β-hydroxybovogenin-A-thevetoside[268,269].

Telocinobufagin

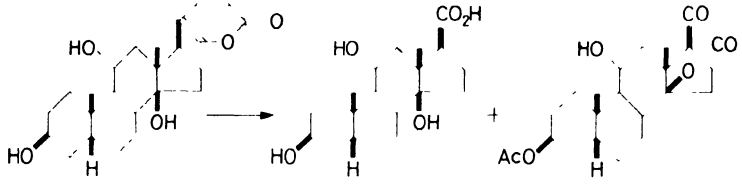
Isolated from Ch'an Su [≡ *Bufo gargarizans*][273], and from the South American toad *B. marinus*[274], and from the common European toad *B. vulgaris*[275], TELOCINOBUFAGIN (161) gives a monoacetate, and with chromium trioxide a ketone, which is readily dehydrated by hot acetic acid to an αβ-unsaturated ketone (162), which exhibits two absorption bands: (i) $\lambda_{max.}$ 240 mμ., log ε 4·23 [Δ4-3-ketone], (ii) $\lambda_{max.}$ 300 mμ., log ε 3·72 [$\Delta^{\alpha\beta\cdot\gamma\delta}$-lactone ring]. Oxidative degradation of telocinobufagin acetate with permanganate in acetone gives 3β : 5β : 14β-trihydroxy-14-*iso*etianic acid (163)[273], and the known related 21→14-lactone [as (157)][46]. Telocinobufagin is the lactonic homologue of periplogenin.



Gamabufogenin and Gamabufotoxin

GAMABUFOTOXIN, isolated from the Japanese toads *Bufo japonicus* and *B. formosus*[276], is the suberylarginine conjugate of GAMABUFOGENIN (164)[262,276–281], isolated from Ch'an Su [≡ *B. gargarizans*][282]. Gamabufogenin yields a diacetate and by oxidation a diketone; with hydrochloric acid it gives isomeric $\Delta^{8(14)}$- and Δ^{14}-anhydro-compounds, and with methanolic potassium hydroxide an *iso*-compound. Oxidative degradation of gamabufogenin diacetate

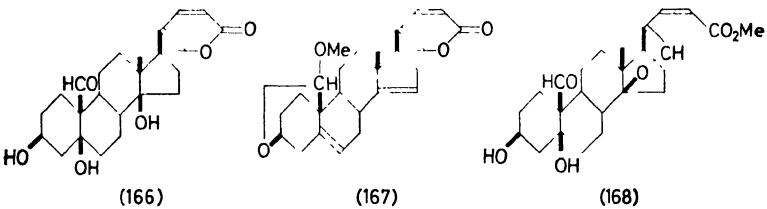
with permanganate in acetone yields 3β : 11α : 14β-trihydroxy-14-*iso*etianic acid (105)[279,282], previously obtained from sarmentogenin[168], and the related 14 $\rightarrow$21-lactone (165). Gamabufogenin is the lactonic homologue of sarmentogenin.



Hellebrigenin [≡ *Bufotalidin*], *Hellebrin*, *Deglucohellebrin*

HELLEBRIN, isolated from the Christmas rose[283], is hellebrigenin-rhamnoside-glucoside. Mannich hydrolysis fails because the glycoside is insoluble in acetone, but use of strophanthobiase affords glucose and DEGLUCOHELLEBRIN, which by Mannich hydrolysis gives rhamnose and hellebrigenin. Hellebrin is an aldehyde, yielding with methanolic hydrogen chloride dianhydrohellebrigenin methylal (167)[284,285,286].

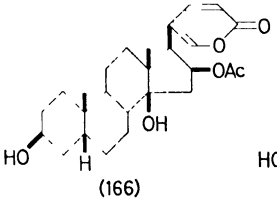
HELLEBRIGENIN [≡ BUFOTALIDIN] (166), also obtained from the venom of the common European toad *Bufo vulgaris*[275,277], has one secondary hydroxyl group [monoacetate] and two tertiary hydroxyl groups; dehydration gives a Δ^{14}-anhydro-compound, and treatment with methanolic potassium hydroxide yields the 14 : 21-epoxide *iso*hellebrinic methyl ester (168). Hellebrigenin is an aldehyde [oxime], reduced by the Meerwein-Ponndorf method to hellebrigen-19-ol, and oxidized by chromium trioxide to hellebrigenin-19-acid[284 285,286].



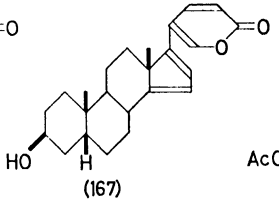
Hellebrigenin acetate by oxidative degradation with permanganate in acetone gives 10-carboxy-3β : 5β : 14β-trihydroxy-14-*iso*-19-noretianic acid (45)[286], identical with that from strophanthidin. Hellebrigenin is thus the lactonic homologue of strophanthidin.

Bufotalin and [Vulgaro]Bufotoxin

BUFOTOXIN, isolated from the common European toad *Bufo vulgaris*[275,287,288], is the most fully characterized conjugated toad poison; it is oxidized to a ketone bufotoxinone so that the suberylarginine residue is linked not at $C_{(3)}$ but at $C_{(14)}$, and acid hydrolysis gives bufotalien (167) with suberic acid and arginine. BUFOTALIN (166), which occurs free in the venom, was extensively investigated by WIELAND[277,287–289,290]; it is an acetyl-compound, which yields a monoacetate and by oxidation a ketone bufotalone, giving with 3% ethanolic-hydrogen chloride, a $\Delta^{14\ 16}$-dianhydro-derivative, and with aqueous alkali an *iso*-compound. The structure of bufotalin has been clarified by KUNO MEYER[291]. Oxidative degradation of bufotalin 3-acetate with permanganate in acetone affords the 3β : 16β-diacetoxy-14 → 21-lactone (168) and the known 3β : 14β : 16β-trihydroxy-14-*iso*ctianic acid (169) from gitoxigenin[45]. Bufotalin 3-acetate with phosphorus oxychloride–pyridine furnishes the Δ^{14}-anhydro-compound (170). The high specific rotation of bufotalien [(167): $[\alpha]_D$ + 405°] [cf. (93): $[\alpha]_D$ + 454°, p. 247], its absorption spectrum[291], and its hydrogenation by *cis*-addition to the 14 : 16-diene system[45,292] to give [after elimination of the 3β-hydroxyl group] 14-*iso*-17-*iso*cholanic acid[291] [≡ '*iso*bufocholanic' acid[289]] (171) are consistent. Bufotalin is the lactonic homologue of oleandrigenin.



(166)



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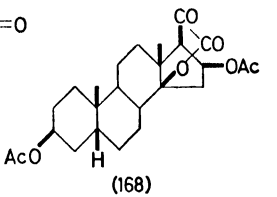
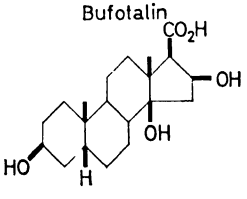


(168)

Bufotalin



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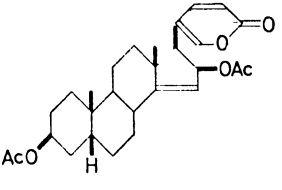

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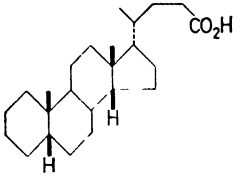
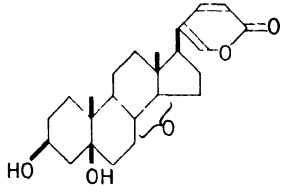


(171)

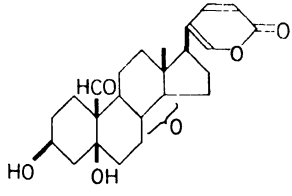
Marinobufagin, Bufotalinin, Resibufogenin, Artebufogenin

These four scilladienolides are well characterized, but their formulae are not completely established. MARINOBUFAGIN (172), the first toad poison to be isolated, has been obtained from the Central American toad *B. marinus*[274,293], the South American toad

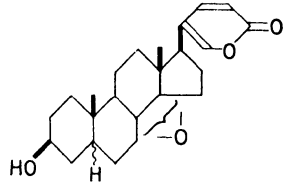
B. paracnemis[294], and the common European toad *B. vulgaris*[275]; unpublished work[295] suggests the structure (172). BUFOTALININ (173), from the common European toad *B. vulgaris*[274,289], gives a monoacetate oxidized by chromium trioxide to an acid; it is an aldehyde, but appears to possess no $C_{(14)}$-hydroxyl group as it does not undergo dehydration. It appears to be the $C_{(10)}$-aldehydo-analogue of marinobufagin. RESIBUFOGENIN [≡ '*iso*bufalin'] (174)[296], from Ch'an Su, has been degraded as the monoacetate to an unknown aetiocholanic acid, and appears to contain an epoxide ring, cleaved with hydrogen chloride in chloroform to a chlorohydrin, and regenerated from this by treatment with aluminium oxide. By use of aqueous hydrochloric acid, resibufogenin acetate undergoes rearrangement to ARTEBUFOGENIN [≡ 'anhydrobufalin'] (175), which yields two isomeric acetates, and appears to possess an unplaced hindered keto-group[296].



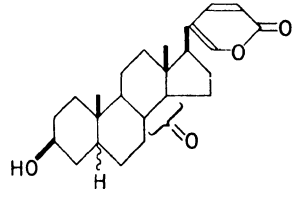
(172)
Marinobufagin



(173)
Bufotalinin



(174)
Resibufogenin

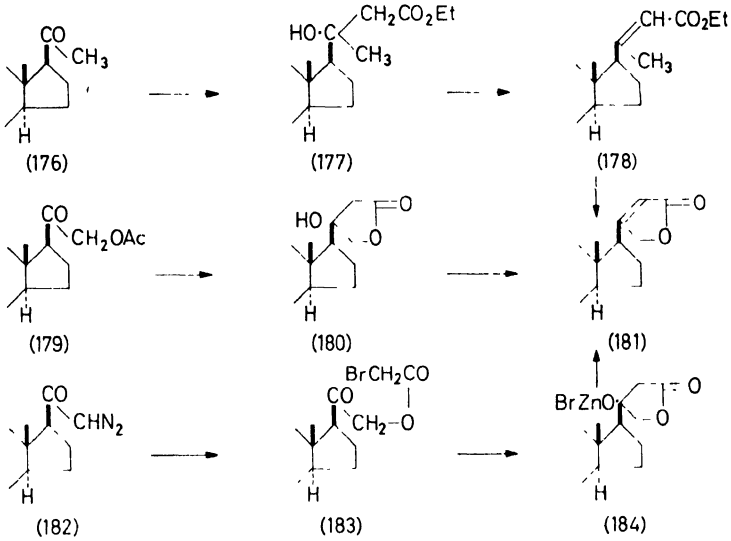


(175)
Artebufogenin

SYNTHETIC APPROACHES

A method developed by RUZICKA and REICHSTEIN[297], and by ELDERFIELD[298] utilizes the Reformatsky reaction of ethyl bromoacetate with a 21-acetoxy-20-oxo-steroid (179) to give the 20-hydroxy-21→24-lactone (180), dehydrated to the unsaturated lactone (181); by this method the 20-epimeric tetrahydroanhydrouzarigenins [p. 249] have been synthesized[299]. Alternatively, a 20-oxo-steroid (176) may be used to give the hydroxy-ester (177), which by dehydration to (178) and oxidation with selenium

dioxide affords the unsaturated lactone (181)[300,301]; oxidation with N-bromosuccinimide gives the Δ^{16}-analogue of (181)[302]. An improved procedure by condensation of a diazo-20-ketone (182)



with bromoacetic acid gives the ketol bromoacetate (183), which undergoes an internal Reformatsky reaction with zinc in presence of ethyl bromoacetate to furnish (184) and thence (181)[303].

The production of 5β- and 14β-hydroxy-compounds by reductive fission of 4β : 5β-oxides and of 14β : 15β-oxides provides in principle a route to the nuclei of the cardenolides and scilladienolides[304].

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VI

SAPONINS AND SAPOGENINS

SAPONINS are plant glycosides characterized by foaming in aqueous solution; these solutions are haemolytic when injected into the blood-stream of animals and therefore highly toxic intravenously, but comparatively harmless when ingested. They are also highly toxic to cold-blooded animals and toxicity appears to be related to their marked activity in lowering surface tension. Another characteristic is the formation of molecular compounds with cholesterol and other 3β-hydroxy steroids, which can be used both for isolation of saponins and for separation and purification of 3β-hydroxy steroids; digitonin surpasses all other saponins in yielding steroid complexes [*see* p. 35] of great insolubility, and its 1 : 1-mol. compound with amyl alcohol may be used for its purification, whilst its complexes with (±)-α-terpineol and (±)-*ac*-tetrahydro-β-naphthol have been used for resolution of these substances[1]. Saponins are commonly isolated by extraction of the plant material with hot water or ethanol followed by evaporation of the extract, usually in a vacuum; alternatively, they may be extracted with ethanol and precipitated by addition of ether.

The presence of digitonin in commercial digitalis from *Digitalis purpurea* was recognized by Schmiedeberg in 1875, and digitonin preparations were examined by Kiliani from 1890 onward, but a reputedly pure sample was shown by WINDAUS[2] in 1913 to contain $\sim$ 20% of a second saponin, gitonin. No other saponin has been isolated from digitalis, but the sapogenin tigogenin was obtained[3] from the hydrolysate of an extract of leaves of *Digitalis purpurea*, the parent saponin of which, tigonin, has been obtained[4] from leaves of *Digitalis lanata*. By hydrolysis with acid or enzymes, saponins give C_{27}-sapogenins and various sugars; the latter have been regarded as united in a straight chain with the terminal unit attached to a hydroxyl group of the sapogenin, e.g.

sarsasaponin $\equiv$ sarsapogenin-rhamnoside-glucoside-glucoside

and this view has been confirmed[5]. Some of the better characterized saponins are given in *Table XVI*; yucconin by catalytic hydrogenation yields gitonin.

Table XVI

SAPONINS

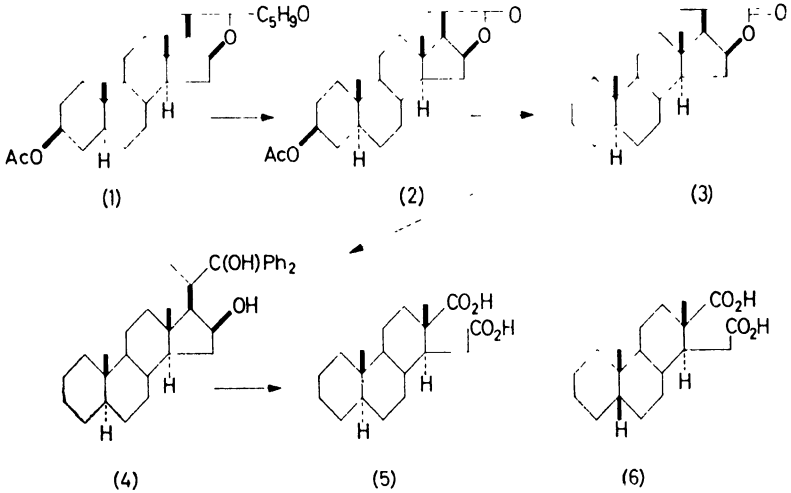
Saponin	m.p.°	$[\alpha]_D$°	Sapogenin	Sugars	Source
Amolonin	—	-- 75	Tigogenin	3 Glucose, 1 Galactose, 2 Rhamnose	*Chlorogalum pomeridianum*
Digitonin	235	— 54	Digitogenin	2 Glucose, 2 Galactose, 1 Xylose	*D. purpurea*, *D. lanata*
Dioscin	288	— 95	Diosgenin	? Rhamnose	*Dioscorea*
Dioscorea sapotoxin	220	—	Diosgenin	Glucose, Rhamnose	*Dioscorea*
Gitonin	272	-- 51	Gitogenin	3 Galactose, 1 Pentose	*D. purpurea*, *D. germanicum*
Kammonin	315	--	Kammogenin	6 sugar units	*Yucca schotii*
Nolonin	285	---	—	- -	*Beth root*
Riconin	289	—	—	---	*D. macrostachya*
Sarsasaponin (Parillin)	245	--	Sarsasapogenin	2 Glucose, 1 Rhamnose	*Radix sarsaparilla*
Smilonin	237/248	— 48	Smilagenin	5 sugar units	*Yucca schotii*, *Smilax*
Tigonin	260	—	Tigogenin	2 Glucose, 2 Galactose, 1 Xylose	*D. lanata*
Trillarin	200	—	Diosgenin	2 Glucose	*Trillium*
Trillin	275	-- 103	Diosgenin	1 Glucose	*Trillium*
Yucconin	278	---	Yuccagenin	3 Galactose, 1 Pentose	*Yucca schotii*

Saponins are difficult to purify and characterize; because of their large molecular weight, analysis gives only approximate empirical formulae and these are generally inferred from the number and nature of the sugar units. Although the sapogenins are more stable and more readily isolated in pure condition, digitogenin, gitogenin, sarsasapogenin, and tigogenin were regarded as C_{26}-compounds until 1935. The C_{27}-character of the sapogenins has been established by precision analysis of 1 g samples of sarsasapogenin and chlorogenin[6], and more generally by degradation.

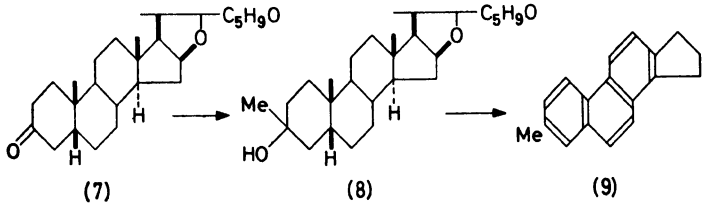
Constitution of the Sapogenins

The Nuclear Structure

The first indication of the steroid structure of the sapogenins was the isolation of 3′-methyl-1 : 2-*cyclo*pentenophenanthrene from sarsasapogenin and gitogenin by dehydrogenation with selenium[7]. The first proof of the presence of the steroid nucleus was given by the demonstration that tigogenin, gitogenin, and digitogenin are 3-, 2 : 3-, and 2 : 3 : x-hydroxy derivatives of the same ground substance, and that tigogenin acetate by non-pyrolytic degradation gives aetio*allo*bilianic acid[8,9]. Oxidation of acetyltigogenin (1) with chromium trioxide gives tigogenoic acid, $C_{27}H_{42}O_5$, and the acetate of a C_{22}-hydroxy-lactone (2), which by hydrolysis, oxidation to the ketone, and Clemmensen reduction yields the C_{22}-lactone (3); this reacts with phenylmagnesium bromide to furnish the 16β : 22-diol (4), oxidized with fission of ring *D* to aetio*allo*bilianic acid (5).



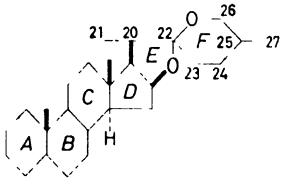
Similar degradation of sarsasapogenin acetate gives aetiobilianic acid (6)[10]; tigogenin thus belongs to the cholestane series, whilst sarsasapogenin belongs to the coprostane series. Numerous other degradations of sapogenins and their derivatives to aetiobilianic



acids have been reported. The nuclear hydroxyl group of sarsasapogenin was located at $C_{(3)}$ by conversion of sarsasapogenone (7) to the methyl carbinol (8) and dehydrogenation of this with selenium to 7-methyl-1 : 2-*cyclo*pentenophenanthrene (9)[10,11].

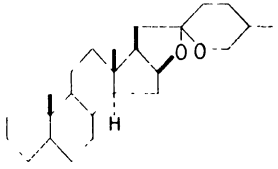
The Spiroketal Side-Chain Structure

The production of aetiobilianic acids proves that the C_8-sapogenin side chain is attached to either $C_{(16)}$ or $C_{(17)}$, and aliphatic C_8-ketones, e.g. methyl *iso*hexyl ketone, have been isolated by dehydrogenation or acetolysis of sarsasapogenin and gitogenin[12,13]. The mode of linkage of the carbon atoms composing the side chain and its 17β-configuration have been proved by conversion of diosgenin into cholesterol[14]. The formulation of the $C_8H_{14}O_2$ side chain suggested by TSCHESCHE[8] has been superseded by the spiroketal formula, (10) or (11), of MARKER[15]; this structure was established by investigations on sarsasapogenoic acid, but Marker's attribution of isomerism solely to configuration at $C_{(22)}$ is now discredited[16,17,18]. It has been suggested, however, that the designations 22a and 22b be retained until evidence is available concerning configuration at $C_{(22)}$[19].



(10)

22-*normal*-Spirostan configuration at $C_{(22)}$ unknown but designated 22b

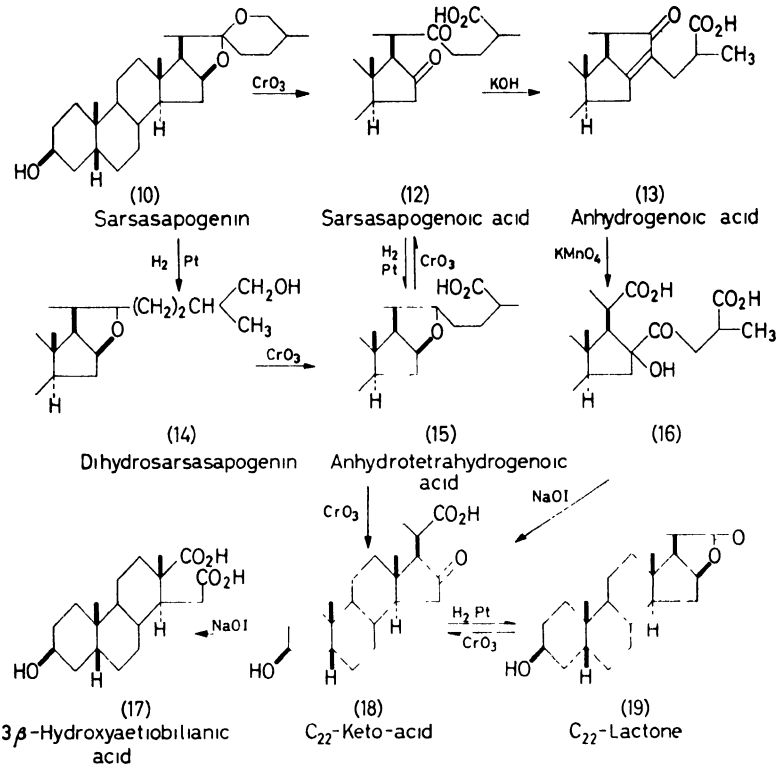


(11)

22-*iso*Spirostan configuration at $C_{(22)}$ unknown but designated 22a

Sarsasapogenin (10) as the acetate by oxidation with chromium trioxide at 60° gives sarsasapogenoic acid (12); this gives a dioxime with difficulty and undergoes internal condensation in presence of sodium hydroxide to give an $\alpha\beta$-unsaturated keto-acid (13)[20]. The anhydrogenoic acid (13) by permanganate oxidation gives the acid $C_{27}H_{42}O_7$ (16)[15], converted by hypoiodite into iodoform and 3β-hydroxyaetiobilianic acid (17)[20,21]. Anhydrosarsasapogenoic acid (13) is inert to ketonic reagents, but by ozonolysis gives the C_{22}-oxo-acid (18)[22], also obtained by oxidation of the dicarboxylic acid (16) as acetate-dimethyl ester with chromium trioxide[21]. The C_{22}-oxo-acid [3β-hydroxy-16-oxobisnorcholanic acid] (18) is readily hydrogenated to the C_{22}-lactone [(19): cf. (2)], which by oxidation [as the acetate] regenerates the C_{22}-oxo-acid[23]. Sarsasapogenoic acid (12) by hydrogenation absorbs 2 mol. of

hydrogen with loss of 1 mol. of water to give anhydrotetrahydrosarsasapogenoic acid (15)[20], reconverted to (12) by oxidation, and under more vigorous conditions oxidized to the C_{22}-oxo-acid (18)[24].

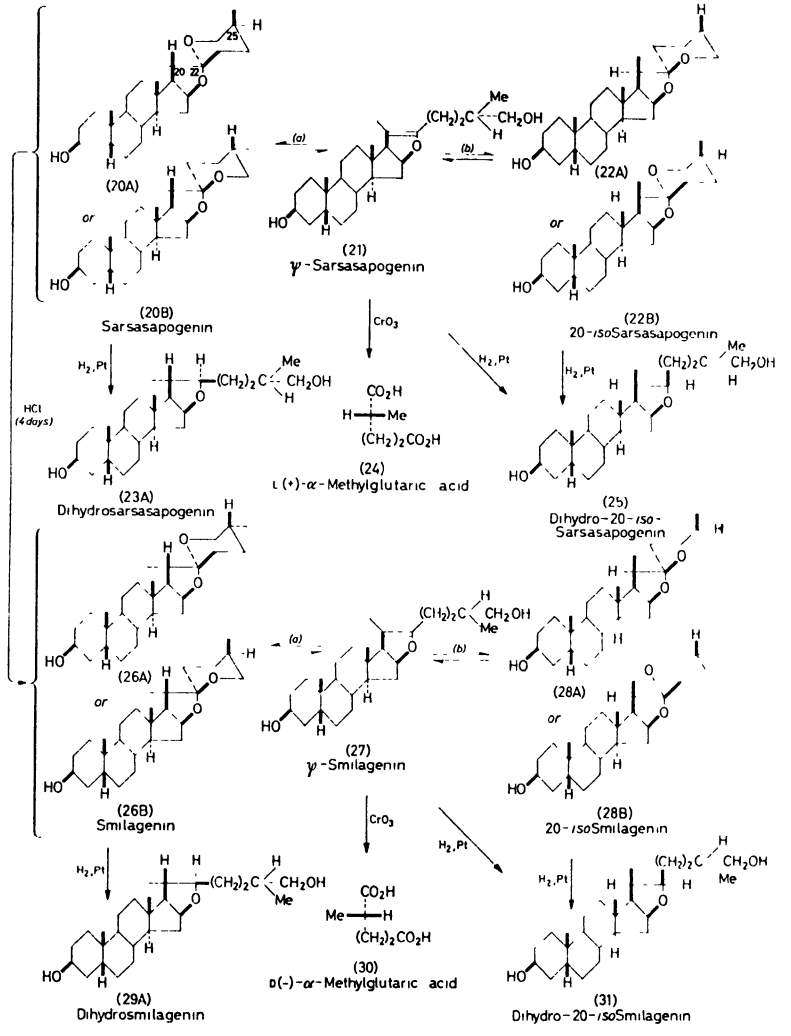


The foregoing reactions establish the structure but not the configuration of the spiroketal side chain, which contains three asymmetric carbon atoms [$C_{(20)}$, $C_{(22)}$, and $C_{(25)}$].

Stereoisomerism is now known to occur in the spiroketal side chain at $C_{(20)}$ and $C_{(25)}$; present evidence does not show whether or not stereoisomerism occurs at $C_{(22)}$[25]. Configuration at $C_{(20)}$ may be defined as α when the 20-methyl group lies behind the plane of ring E[26]; configuration at $C_{(25)}$ has been designated by use of indices 25a and 25b[19], but is best expressed in terms of the absolute configuration 25*D* and 25*L*.

Sarsasapogenin (20A) or (20B) and its side-chain isomeride smilagenin (26A) or (26B) by Clemmensen reduction both give coprostane 3β : 16β : 26-triol[27], but, *contrary* to the original statement of MARKER and ROHRMANN[27], by hydrogenation with platinum in acetic acid afford isomeric and not identical dihydrocompounds,

namely dihydrosarsasapogenin (23) and dihydrosmilagenin (29), which differ only in configuration at $C_{(25)}$ since both give 16β : 22-epoxycoprostan-3β-ol[26,28]. Again, *contrary* to the original statement of MARKER[29], sarsasapogenin and smilagenin by treatment



with acetic anhydride at 200° yield isomeric and not identical pseudo-compounds, namely, ψ-sarsasapogenin (21) and ψ-smilagenin (27)[26,28]; similarly, markogenin and its side-chain isomeride samogenin yield respectively ψ-markogenin and ψ-samogenin[30]. Oxidative degradation [*see* p. 290] of ψ-sarsasapogenin (21) gives

L(+)-α-methylglutaric acid (24) whilst ψ-smilagenin (27) gives *D*(−)-α-methylglutaric acid (30)[16,28]; similarly, neotigogenin[18] and sisalagenin[18] furnish by way of their ψ-compounds the *L*(+)-acid (24), whilst tigogenin[18], diosgenin[17], and hecogenin[17] furnish by way of their ψ-compounds the *D*(−)-acid (30). Sarsasapogenin and smilagenin, neotigogenin and tigogenin, and sisalagenin and hecogenin are $C_{(25)}$-epimers each to each; until configuration at $C_{(22)}$ is known, it is necessary to write *two* formulae for each sapogenin, i.e. for sarsasapogenin (20A) and (20B), and for smilagenin (26A) and (26B), of which either (20A) *and* (26A) must be selected, or (20B) *and* (26B) must be chosen. $C_{(25)}$-Epimerides cannot be distinguished by their infra-red absorption spectra[26,31], but are reported to give different x-ray diffraction patterns[26].

ψ-Sapogenins can be reconverted to the related sapogenins, e.g. (21)→(20A) or (20B), or (27)→(26A) or (26B), by treatment with ethanolic hydrochloric acid at 25–78°[29,32], but by very brief treatment with $< 0{\cdot}5$N ethanolic hydrochloric acid at 0°–25° or, better, with ethanol–acetic acid at 100°[26], the ψ-sapogenins rapidly afford new isomerides, variously designated as 20-*iso*sapogenins[25,26], *ana*sapogenins[33], *cyclo*-ψ-sapogenins[31,34], and neosapogenins[35,36]. MARKER and LOPEZ[37,38] probably obtained compounds of this class but failed to recognize their significance. 20-*iso*Sapogenins are unusually reactive. They are converted into the related sapogenins by relatively mild treatment with ethanolic hydrochloric acid. Nuclear hydroxyl groups are acetylated by acetic anhydride–pyridine at 100° to yield 20-*iso*sapogenin acetates, whilst acetic anhydride at 140°, and acetic anhydride–hydrogen chloride at 100° afford the ψ-sapogenin acetate and the sapogenin [acetate], respectively. 20-*iso*Sapogenins of both the 25*D*- and 25*L*-series, e.g. 20-*iso*sarsasapogenin (22A) or (22B) and 20-*iso*smilagenin (28A) or (28B), are known, and by hydrogenation with platinum–acetic acid give respectively dihydro-20-*iso*sarsasapogenin (25), identical with dihydro-ψ-sarsasapogenin, and dihydro-20-*iso*smilagenin (31), identical with dihydro-ψ-smilagenin[26]. 20-*iso*Sapogenins, like the dihydro-ψ-sapogenins but unlike the sapogenins and dihydrosapogenins, are readily oxidized by chromium trioxide–acetic acid to give after alkaline hydrolysis pregn-16-en-20-ones, accompanied in the case of 20-*iso*sapogenins of the 25*D*-series by neutral compounds provisionally regarded as 20-hydroxy-sapogenins[25]. There appears to be general agreement that in the 20-*iso*sapogenins the 20-methyl group has the β-configuration, whereas in the sapogenins the 20-methyl group has the α-configuration[26,36]. In acidic media an equilibrium probably exists:

$$\text{sapogenin} \overset{(a)}{\rightleftharpoons} \psi\text{-sapogenin} \overset{(b)}{\rightleftharpoons} \text{20-}iso\text{sapogenin}$$

in which the electrophilic cyclization reaction (*b*) is subject to kinetic control whilst, cyclization reaction (*a*) is subject to thermodynamic control. It is uncertain whether the 20-*iso*sapogenins possess the same configuration[26] as, or the opposite configuration[36] to, the sapogenins at $C_{(22)}$; the argument of WALL *et al.*[26], based on the formation by sarsasapogenin [3-acetate] of a 23 : 23-dibromo-derivative whilst smilagenin [3-acetate] forms only a 23-monobromo-derivative[39,40,41,42], is unfounded since smilagenin [3-acetate] has been shown to give a dibromo-derivative[36]. It is therefore necessary at present to envisage two formulae for 20-*iso*sarsasapogenin (22A) or (22B) and for 20-*iso*smilagenin (28A) or (28B), two formulae for dihydrosarsasapogenin (23) and for dihydrosmilagenin (29), and two formulae for dihydro-20-*iso*sarsasapogenin (25) [≡ dihydro-ψ-sarsasapogenin] and for dihydro-20-*iso*smilagenin (31) [≡ dihydro-ψ-smilagenin], each pair of formulae being related as (20A) and (20B), or as (26A) and (26B) in regard to configuration at $C_{(22)}$. For simplicity only the corresponding formula of each pair is given for the dihydrosapogenins [as (23) and (29)] and the dihydro-ψ-sapogenins [≡ dihydro-20-*iso*sapogenins] [as (25) and (31)].

The conversion of sarsasapogenin to smilagenin with inversion of configuration at $C_{(25)}$ by prolonged treatment [5 days] with ethanolic hydrochloric acid at 100°[18,26,27,36] is explicable by formulae (20A) [25Me: axial] → (26A) [(25Me: equatorial] but not by formulae (20B) and (26B)[26,36,43,44].

CORRELATIONS OF SAPOGENINS

The various sapogenins are closely related; numerous inter-conversions and correlations have been achieved by Marker and his co-workers. Variations in structure arise from (i) the number, position, and configuration of nuclear hydroxyl groups, (ii) the occasional presence of a carbonyl group at $C_{(12)}$, (iii) the mode of union, *cis*, *trans*, or involving Δ^5-unsaturation, of rings *A* and *B*, and (iv) the configuration at $C_{(20)}$, $C_{(22)}$, and $C_{(25)}$. The natural sapogenins and certain synthetic sapogenins, in all of which the $C_{(20)}$-methyl group has the α-configuration, their structures, and principal sources are given in *Table XVII*. Sapogenins possessing 3β-hydroxyl groups generally give insoluble digitonides, but contradictory results have been reported for chlorogenin, digitogenin, gitogenin, and diosgenin[8,45,46].

In addition to the sapogenins given in *Table XVII*, four compounds of closely related type have been isolated from *Beth* root; these are bethogenin (35), m.p. 191°, nologenin (32), m.p. 265°, pennogenin (33), m.p. 240°, and kryptogenin (36), m.p. 184–186°, the last of which with OH^- furnishes a synthetic compound

Table XVII

SAPOGENINS

No.	Name	Configuration			Position and configuration of nuclear substituents	m.p.°	$[\alpha]_D°$	Source
		Rings *A/B*	$C_{(22)}$	$C_{(25)}$				
1	Sarsasapogenin	*cis*	b	L	3β-OH	200	− 85	*Smilax medica, officinalis* L., and *ornata* Hook, *Radix sarsaparilla* (Vera Cruz), *Asparagus officinalis*
2	*epi*Sarsasapogenin	*cis*	b	L	3α-OH	204	—	Synthetic
3	Smilagenin	*cis*	a	D	3β-OH	188	− 74	*Smilax ornata* Hook, *Radix sarsaparilla* (Jamaica)
4	Neotigogenin	*trans*	b	L	3β-OH	202	− 75	*Chlorogalum pomeridianum* Kunth
5	Tigogenin	*trans*	a	D	3β-OH	205	− 61	*Digitalis lanata* and *purpurea*, *Chlorogalum pomeridianum* Kunth
6	*epi*Tigogenin	*trans*	a	D	3α-OH	242	—	Synthetic
7	Yamogenin	Δ^5	b	L	3β-OH	201	− 123	*Dioscoreae* (various species)

Table XVII

SAPOGENINS—*cont.*

No.	Name	Configuration			Position and configuration of nuclear substituents	m.p.°	$[\alpha]_D°$	Source
		Rings *A/B*	$C_{(22)}$	$C_{(25)}$				
8	Diosgenin	Δ^5	a	D	3β-OH	212	— 123	*Dioscoreae tokora Makino* and *villosa*, *Aletris farinosa*, *Trillium*, *Balanites aegyptica*, *Solanum xanthocapsuma*
9	Neogitogenin	*trans*	b	L	2α : 3β-$(OH)_2$	248	—	*Yucca schottii* (fruit)
10	Gitogenin	*trans*	a	D	2α : 3β-$(OH)_2$	271	— 56	*Digitalis purpurea* and *germanicum*, *Chlorogalum pomeridianum* Kunth
11	Neochlorogenin	*trans*	b	L	3β : 6α-$(OH)_2$	269	—	*Digitalis purpurea*
12	β-Neochlorogenin	*trans*	b	L	3β : 6β-$(OH)_2$	249	—	Synthetic
13	Chlorogenin	*trans*	a	D	3β : 6α-$(OH)_2$	274	— 64	*Chlorogalum pomeridianum* Kunth
14	β-Chlorogenin	*trans*	a	D	3β : 6β-$(OH)_2$	248	—	Synthetic
15	Markogenin	*cis*	b	L	2β : 3β-$(OH)_2$	256	— 70	*Yucca faxoniana*, *Y. schidigera*, *Y. baccata*
16	Samogenin	*cis*	a	D	2β : 3β-$(OH)_2$	205	— 74	*Samuela carnerosana* Trel., *Yucca schottii* Engelm.
17	*epi*Samogenin	*cis*	a	D	2β : 3α-$(OH)_2$	235	—	Synthetic

Table XVII

SAPOGENINS—*cont.*

No.	Name	Configuration			Position and configuration of nuclear substituents	m.p.°	$[\alpha]_D°$	Source
		Rings *A/B*	$C_{(22)}$	$C_{(25)}$				
18	Lilagenin	Δ^5	b	L	2α : 3β-$(OH)_2$	246	—	*Lilia Humboldtii* Roezl and Leichtl, *L. rubrum magnificum*
19	Yuccagenin	Δ^5	a	D	2α : 3β-$(OH)_2$	252	—	*Yuccae schottii* Engelm., *elata* Engelm., and *flaccida* Haw
20	Magogenin	*trans*	a	D	2ξ : 3β : 6ξ-$(OH)_3$	284	—	*Maguey cacaya*
21	Rockogenin	*trans*	a	D	3β : 12β-$(OH)_2$	210	—	*Agave gracilipes* Trel.
22	Sisalagenin*	*trans*	b	L	3β-OH : 12CO	244	− 4	*Agave sisalana* (sisal)
23	Hecogenin	*trans*	a	D	3β-OH : 12CO	268	+ 18	*Agaves deserti* Engelm., *gracilipes* Trel., and *toumeyana* Trel., *Hechtia texensis* S. Wats.; *Agave sisalana* (sisal)
24	Botogenin	Δ^5	a	D	3β-OH : 12CO	262	—	*Dioscorea mexicana*
25	Neobotogenin**	Δ^5	b	—	3β-OH : 12CO	246	—	*Dioscorea mexicana*
26	Mexogenin	*cis*	a	D	2β : 3β-$(OH)_2$: 12CO	246	—	*Samuela carnerosana* Trel., *Yucca schotii* Engelm.
27	neoMexogenin**	*cis*	b	—	2β : 3β-$(OH)_2$: 12CO	222	—	*Agave roezliana*

Table XVII

SAPOGENINS—*cont.*

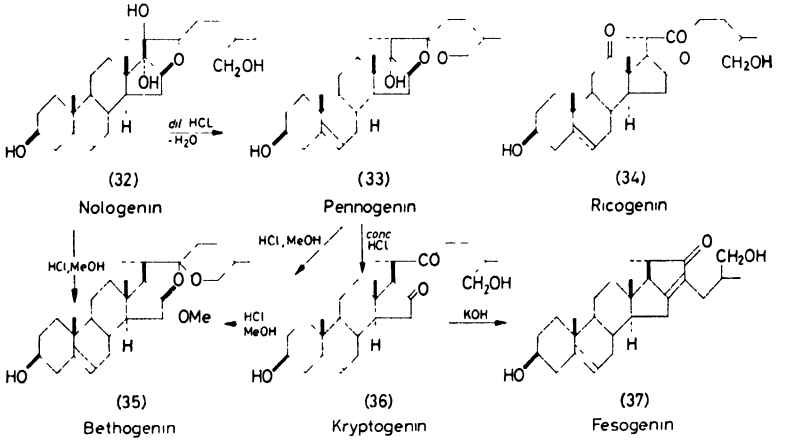
No.	Name	Configuration			Position and configuration of nuclear substituents	m.p.°	$[\alpha]_D$°	Source
		Rings *A/B*	$C_{(22)}$	$C_{(25)}$				
28	Manogenin	*trans*	a	D	2α : 3β-$(OH)_2$: 12CO	243	0	*Agaves huachucensis* Baker
29	neoManogenin**	*trans*	b	—	2α : 3β-$(OH)_2$: 12CO	242	—	*Yucca schottii* (fruit)
30	Agavogenin	*trans*	a	D	2α : 3β : 12β-$(OH)_3$	242	—	*Agave huachucensis* Baker
31	Kammogenin	Δ^5	a	D	2α : 3β-$(OH)_2$: 12CO	242	—	*Yuccae schottii* Engelm.
32	neoKammogenin**	Δ^5	b	—	2α : 3β-$(OH)_2$: 12CO	228	—	*Dioscorea mexicana*
33	Cacogenin	*trans*	a	D	2ξ : 3β : 6ξ-$(OH)_3$: 12CO	278	—	*Maguey cacaya*
34	Ruscogenin	Δ^5	—	L	3β 1ξ : $(OH)_2$	210	— 127	*Ruscus aesculatus*
35	Cholegenin	*cis*	—	—	3α : 27-$(OH)_2$	192	— 27	Ox-bile
36	*iso*Cholegenin	*cis*	—	—	3α . 27-$(OH)_2$	256	— 67	Ox-bile
37	Digitogenin	*trans*	a	D	2α : 3β : 15β-$(OH)_3$	280	— 75	*Digitalis purpurea*
38	Agapanthagenin	*trans*	a	—	2α : 3β : 5α-$(OH)_3$	285	—	*Agapanthus* sp.
39	Gentrogenin	Δ^5	a	D	3β-OH : 12-CO	215	— 57	*Dioscorea spiculiflora*
40	Correllogenin	Δ^5	a	L	3β-OH : 12-CO	209	— 69	*Dioscorea spiculiflora*

* Formerly known as *neo*hecogenin[18]

** These compounds, although obtained from plant extracts, may be 20-*iso*sapogenins formed during isolation procedures

'Furcogenin' and 'kappogenin' [MARKER *et al*, *J. Amer. chem. Soc*, 1943, **65**, 1206] are mixtures of smilagen and hecogenin and of nologenin and ψ-diosgenin, respectively [*idem*, *ibid*, 1947, **69**, 2380]

fesogenin (37), m.p. 180°[47,48,49]. These four substances result from the action of acid on nolonin, the saponin of *Beth* root; with dilute aqueous hydrochloric acid nologenin (32) gives pennogenin (33), and both compounds with methanolic hydrochloric acid yield the methoxy compound bethogenin (35). With more concentrated hydrochloric acid, pennogenin furnishes kryptogenin (36), a γ-diketone [cf. sarsasapogenoic acid (12)], cyclized by alkali to afford fesogenin (37). Ricogenin (34), m.p. 225–227°, is the 12-keto derivative of kryptogenin (36)[50]. Since the conditions for these transformations are comparable with those used in acid hydrolysis of saponins, nologenin may be the progenitor of pennogenin and kryptogenin. Kryptogenin has been converted into the alkaloid solasodine[51].



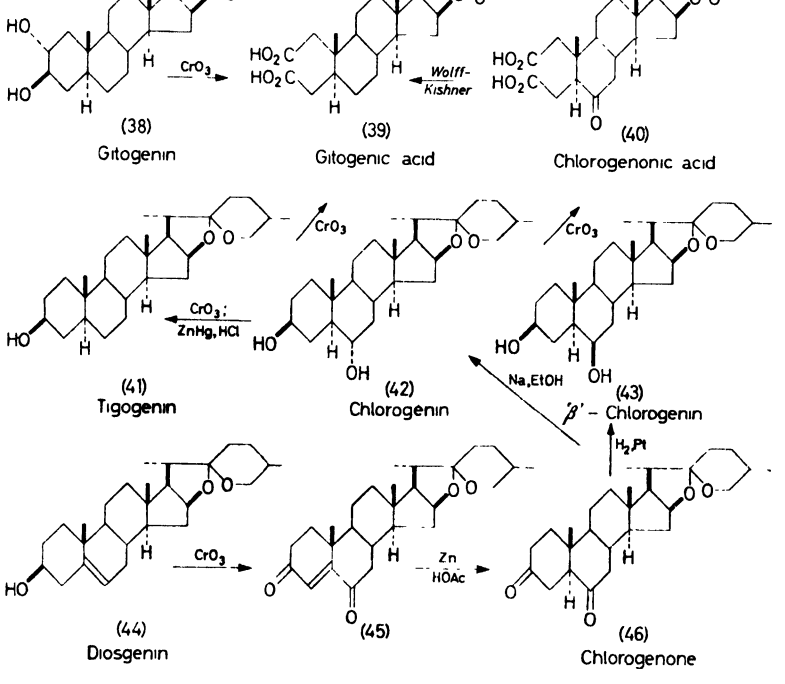
Individual Sapogenins

Sarsasapogenin (20) [*Table XVII*, No. 1], and smilagenin (26) [No. 3], neotigogenin [No. 4], and tigogenin (41) [No. 5], yamogenin [No. 7], and diosgenin (44) [No. 8], all possess a single 3β-hydroxyl group, and the first member of each pair is converted by epimerization at $C_{(25)}$ with hydrogen chloride into the second member. Sarsasapogenin [No. 1] and tigogenin [No. 5], by Oppenauer oxidation followed by Meerwin-Ponndorf reduction, or by direct epimerization at $C_{(3)}$ with sodium–amyl alcohol give respectively *epi*sarsasapogenin [No. 2] and *epi*tigogenin [No. 6][3,52,53]. The coprostane derivatives sarsasapogenin [No. 1] and smilagenin [No. 3] by oxidation to the 3-ketones, conversion to the Δ^4-3-ketones, and reduction of these, yield respectively the cholestane derivatives neotigogenin [No. 4] and tigogenin [No. 5][54]. Yamogenin [No. 7], by Oppenauer oxidation to Δ^4-neotigogenone

and reduction with sodium–ethanol, gives neotigogenin [No. 4][55], whilst diosgenin [No. 8] is converted likewise via Δ^4-tigogenone or directly by catalytic hydrogenation into tigogenin (41) [No. 5][53].

NEOGITOGENIN [No. 9] can be prepared from lilagenin [No. 18] by catalytic hydrogenation; its acid-stable 25-epimer, GITOGENIN (38) [No. 10] by oxidation gives gitogenic acid (39), also obtained by oxidation of free tigogenin (41). Since tigogenin is analogous to cholestan-3β-ol, ring-fission occurs between $C_{(2)}$ and $C_{(3)}$ [cf. pp. 10 and 70], and gitogenin is a 2α : 3β-dihydroxy compound[56], which has been partially synthesized[57,58].

CHLOROGENIN [No. 13], originally regarded as a 3α : 12-diol[46], is a 3β : 6α-diol because it can be prepared from diosgenin (44); this by oxidation gives the Δ^4-3 : 6-diketone (45), converted by zinc–acetic acid to chlorogenone (46) [cf. cholesterol (1)→(18)→(10) in Chapter II, p. 37], which by reduction with sodium–ethanol yields chlorogenin (42) whilst catalytic hydrogenation affords the synthetic sapogenin β-CHLOROGENIN (43) [No. 14]. Chlorogenin (42) by oxidation affords chlorogenonic acid (40); this 6-oxo-compound is stable to OH^- and so has a *trans-A/B*-ring-fusion, and is converted by Wolff-Kishner reduction to gitogenic



acid (39). By selective oxidation, chlorogenin (42) gives the 3β-hydroxy-6-oxo-derivative converted by Clemmensen reduction into tigogenin (41)[59]. Side-chain degradation [*see* p. 290] of chlorogenin (42) gives *allo*pregn-16-ene-3β : 6α-diol-20-one[60]. Yamogenin [No. 7], the 25-epimeride of diosgenin, is similarly related to NEOCHLOROGENIN [No. 11] and β-NEOCHLOROGENIN [No. 12][48].

MARKOGENIN [No. 15][48] is converted by hydrochloric acid into the 25-epimeride SAMOGENIN [No. 16][30]; these sapogenins by oxidation give dibasic acids analogous to gitogenic acid (39)[30] and are 2β : 3β-dihydroxy-compounds[19,61,62]. Markogenin is not identical with texogenin, which was stated to have the same structure[48], and the existence of which is doubtful[30]. Samogenin [No. 16] undergoes epimerization with sodium ethoxide at 200° to give the synthetic 2β : 3α-dihydroxysapogenin *epi*SAMOGENIN [No. 17] [cf. coprostanol ⇌ *epi*coprostanol, p. 39] and therefore possesses *cis-A/B*-ring-fusion[48]. LILAGENIN [No. 18] is transformed by hydrochloric acid into the 25-epimeride YUCCAGENIN [No. 19]; these are Δ^5-sapogenins like yamogenin [No. 7] and diosgenin [No. 8], but are 2α : 3β-diols[56,57]. Yuccagenin gives gitogenin (38) by hydrogenation with platinum–acetic acid and can be converted into 7-oxo-gitogenic acid [cf. (40)] also obtained from diosgenin[48,63]. MAGOGENIN [No. 20], a 2ξ : 3β : 6ξ-triol, by oxidation yields chlorogenonic acid (40)[64].

ROCKOGENIN [No. 21], a 3β : 12β-diol has been partially synthesized[65], and has been converted into the 11-oxo-derivative and into *C*-nor-steroids and *C*-nor-*D*-homosteroids[65,66]; it has also been obtained from manogenin [No. 28][67]. Rockogenin occurs together with HECOGENIN [No. 23], a 3β-hydroxy-12-ketone; they give the same 3 : 12-diketone by oxidation with chromium trioxide at 25°[48]. Hecogenin by reduction with sodium–ethanol, or catalytically, yields rockogenin, and by the Wolff-Kishner procedure furnishes tigogenin [No. 5][48]. It has been transformed into 11-oxygenated derivatives, e.g. 11-oxotigogenin[68,69], and so into cortisone [*see* p. 207], and is accompanied in plants by $\Delta^{9(11)}$-hecogenin, m.p. 235°, $[\alpha]_D$ − 11°, into which it has been converted[70]. Hecogenin undergoes the Stevens reaction to give a *C*-nor-*D*-homosteroid[71,72]; hecogenin acetate is reported to yield isomeric 23a- and 23b-monobromo-compounds[73]. SISALAGENIN [No. 22] is the 25-epimeride of hecogenin[18]; 3-*epi*-5β-hecogenin has been prepared[74].

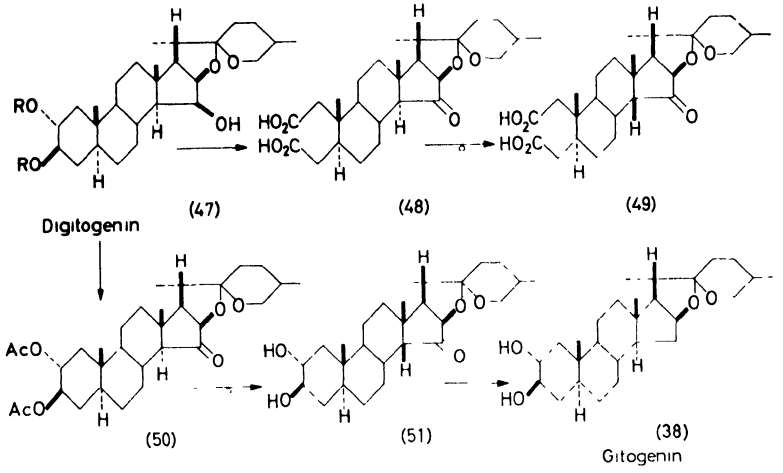
BOTOGENIN [No. 24] is the Δ^5-analogue[75] of hecogenin, and NEOBOTOGENIN [No. 25][76] may be the 20-epimeride of botogenin [≡ 20-*iso*BOTOGENIN], or the Δ^5-analogue of sisalagenin. MEXOGENIN [No. 26] and MANOGENIN [No. 28] are respectively a 2β : 3β-dihydroxy-12-ketone and a 2α : 3β-dihydroxy-12-ketone belonging to the coprostane and cholestane series and by Wolff-Kishner

reduction they yield samogenin [No. 16] and gitogenin (38) [No. 10], respectively[48,62]; manogenin by reduction with sodium–ethanol, or catalytically, yields the 2α : 3β : 12β-triol, AGAVOGENIN [No. 30][48]. NEOMEXOGENIN [No. 27], NEOMANOGENIN [No. 29], and NEOKAMMOGENIN [No. 32] are converted by hydrochloric acid into mexogenin, manogenin, and kammogenin, respectively[37], and may be their 20-epimerides. KAMMOGENIN [No. 31], the Δ^5-analogue of manogenin, has been converted into yuccagenin [No. 19] by Wolff-Kishner reduction, and correlated with agavogenin and manogenin[63]. CACOGENIN [No. 33] is 12-ketomagogenin, and affords magogenin by Wolff-Kishner reduction; oxidation yields hecogenic acid, i.e. 12-ketogitogenic acid [cf. 39][64]. RUSCOGENIN [No. 34] represents a new variation bearing a 1ξ-hydroxyl group[76a]. A further variation is exemplified by CHOLEGENIN [No. 35], which is a 22ξ-spirostan-3α : 27-diol, and by *iso*CHOLEGENIN [No. 36], its $C_{(25)}$-epimeride[76b]. AGAPANTHAGENIN [No. 38] represents another variation with a 5α-hydroxyl group[76c], whilst GENTROGENIN [No. 39] and CORRELLOGENIN [No. 40] appear to be different from botogenin [No. 24] and neobotogenin [No. 25], respectively[76d].

The carbonyl group which occurs in some sapogenins [Nos. 22–29 and 31–33], exhibits steric hindrance and the corresponding hydroxyl group in rockogenin [No. 21] and agavogenin [No. 30] is difficult to acetylate. The position of the carbonyl group at $C_{(12)}$, and the related hydroxyl group, has been proved by degradation of hecogenin [No. 23] via ψ-hecogenin [*see* p. 292] to *allo*pregn-16-ene-3 : 12 : 20-trione and *allo*pregnane-3 : 12 : 20-trione[77, 78].

DIGITOGENIN [(47): R = H] [No. 37], the earliest known and most extensively investigated of the sapogenins, is a 2α : 3β : 15β-trihydroxy compound[53, 79, 80, 81]. Oxidation of digitogenin affords digitogenic acid (48)[82,83], converted by Wolff-Kishner reduction to gitogenic acid (39)[84], and isomerized at $C_{(14)}$ by alkali to digitoic acid (49)[83,85]. Oxidation of digitogenin 2 : 3-diacetate [(47): R = Ac] affords digitogen-15-one diacetate (50), converted by alkaline hydrolysis and concomitant isomerization at $C_{(14)}$ to *iso*-digitogen-15-one (51); both (50) and (51) by Wolff-Kishner reduction give gitogenin (38)[86], but only (50) reacts if the thioketal-nickel method is used[86a].

The inversion of configuration at $C_{(14)}$ in the reactions (48 → 49) and (50 → 51) involves the unusual conversion of a *trans*- to a *cis*-'α'-hydrindanone[87], in spite of the fact that Wolff-Kishner reduction of either isomeride in each case gives the *trans*-hydrindanes (39) and (38). The 15-hydroxyl group has been shown to possess the 15β-configuration on grounds of steric hindrance[86] and on the basis of molecular-rotation comparisons[88]. The reported resistance of digitogenin to acetic anhydride at 200°[53,79] has been shown to be



incorrect and the resulting ψ-digitogenin has been degraded to 2α : 3β : 15β-triacetoxy*allo*pregn-16-en-20-one[81]; finally digitogenin (47) has been converted into *allo*pregnane-3 : 15 : 20-trione[86].

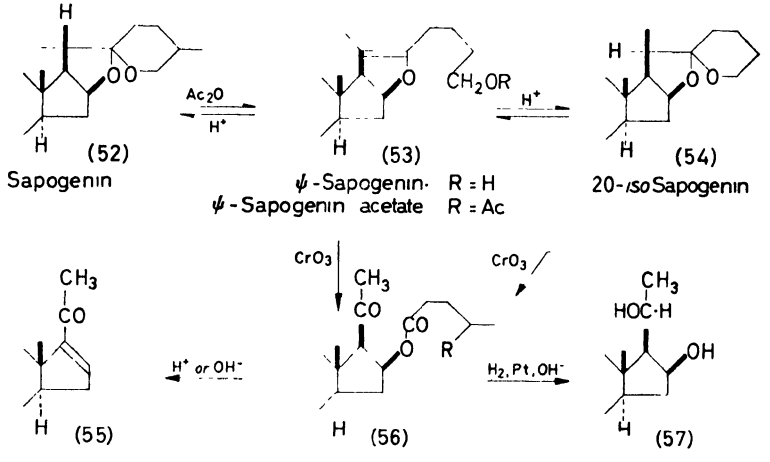
Degradation of Sapogenins

Sapogenins of both the 25*D*- and 25*L*-series [as (52)] were shown by Marker[29,48,89,99] to undergo a general reaction with acid anhydrides at 200° to give, after alkaline hydrolysis, ψ-sapogenins or furost-20(22)-en-26-ols [as (53)]. The reaction mixture corrodes stainless steel, so that special apparatus is needed for large-scale work; and much attention has been directed to finding improved conditions for the transformation[91,92]. Refluxing *n*-butyric anhydride[78,93], octanoic anhydride[94], acetic acid at 270°[94], and octanoic acid at the b.p. 237°[94] have been used. The reaction is promoted by Lewis acids; zinc acetate[94] or trichloroacetic acid[94], aluminium chloride[95], pyridine hydrochloride[96], and ammonium chloride[97] in acetic anhydride at ~140° have been employed.

ψ-Sapogenins of both the 25*D*- and the 25*L*-series [as (53): R = H] are oxidized by chromium trioxide[53,78,89,94] to ester-acids [as (56)], which by hydrolysis give *L*(+)- or *D*(−)-α-methylglutaric acid and pregn-16-en-20-ones or *allo*pregn-16-en-20-ones [as (55)], or by reduction and subsequent hydrolysis yield pregnane- or *allo*-pregnane-16β : 20β-diols [as (57)]; ψ-sapogenin acetates [as (53): R = Ac] with chromium trioxide at 30° give crystalline ester-acetates [as (56)] similarly degraded to (55) and (57)[89,98]. Similar treatment of 20-*iso*sapogenins [as (54)] or dihydro-20-*iso*sapogenins [≡ dihydro-ψ-sapogenins] affords the appropriate pregn-16-en-20-ones or *allo*pregn-16-en-20-ones [as (55)][26]. Peracetic acid has also

been employed for the oxidation[78,97], and potassium hydroxide in *tert.*-butanol has been recommended for the hydrolysis[78,97]. 16β : 20α-Diols, epimeric with the 16β : 20β-diols (57), are formed from sapogenins [as (52)] by oxidation with peracetic acid[99].

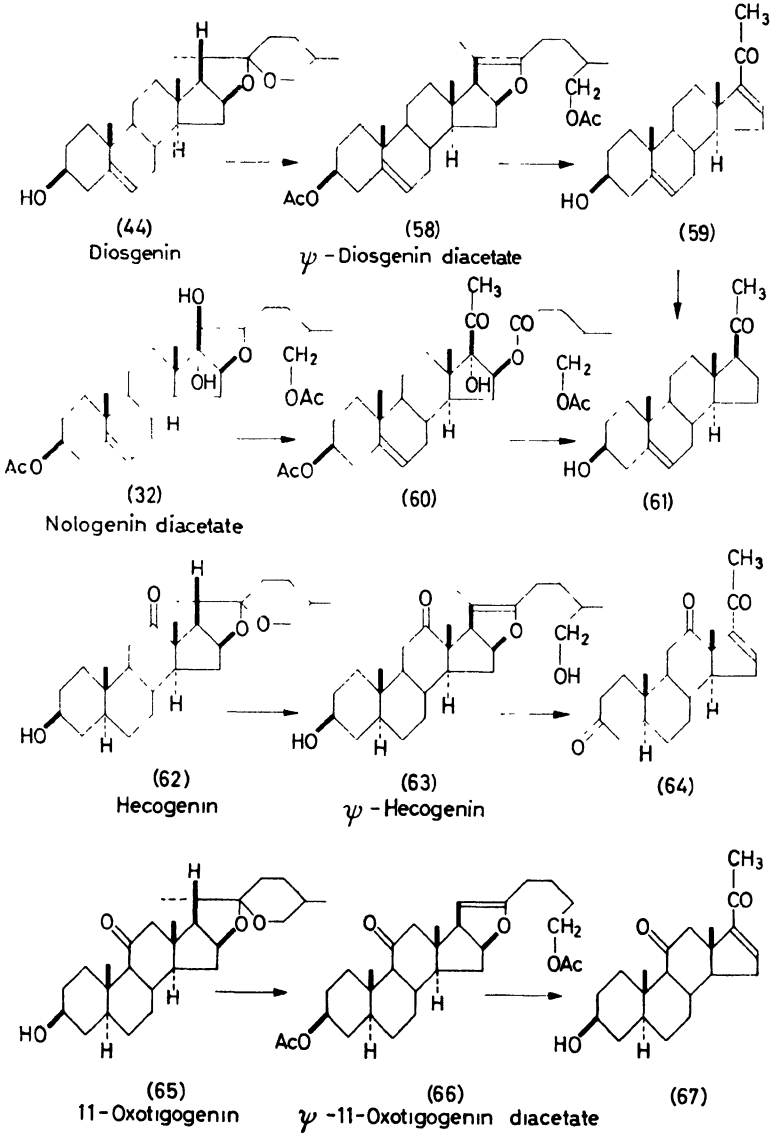
Such degradation of tigogenin (41) to 3β-hydroxy*allo*pregn-16-en-20-one [as (55)], hydrogenated to *allo*pregnane-3β : 20β-diol, furnished the first proof that this sapogenin has a 3β-hydroxyl group[100].



Oxidative degradation of ψ-sapogenins leads to sex hormones of the androstane and pregnane series. Diosgenin (44) affords ψ-diosgenin 3 : 26-diacetate (58); side-chain oxidation proceeds so rapidly that protection of the nuclear double bond is unnecessary, and yields 3β-hydroxypregna-5 : 16-dien-20-one (59), selectively hydrogenated with palladium to 3β-hydroxypregn 5-en-20-one (61) which is readily transformed into progesterone[101]. By use of nologenin 3 : 26-diacetate (32), oxidized to the diacetate-ester (60) which by Clemmensen reduction gives pregnenolone (61), the yield of progesterone may be doubled[102]. Sarsasapogenin (20A) or (20B), yields ψ-sarsasapogenin (21), which by side-chain oxidation and selective hydrogenation furnishes the progesterone intermediate pregnane-3 : 20-dione. Diosgenin (44) has also been converted into 17-dihydro*epi*androsterone[100,103], and 17-dihydroandrosterone[104]; similarly, sarsasapogenin (20A) or (20B) has been converted into testosterone and deoxycorticosterone[105].

Hecogenin (62) affords ψ-hecogenin (63), which by oxidation and subsequent hydrolysis with potassium carbonate gives *allo*pregn-16-ene-3 : 12 : 20-trione (64), selectively hydrogenated with palladium

to *allo*pregnane-3 : 12 : 20-trione[77,78]. A compound previously described as this triketone and also as 17α-hydroxy*allo*pregnane-3 : 12 : 20-trione[48,106,107], and obtained from ψ-hecogenin (63) by a



process involving hydrolysis with methanolic potassium hydroxide has been regarded as 16α-methoxy*allo*pregnane-3 : 12 : 20-trione[108,109], but may be a 20-hydroxyspirostane[25,110].

Finally, 11-oxotigogenin (65), prepared from hecogenin (62)[68,69], gives 85–90% of ψ-11-oxotigogenin (66)[94], from which 3β-acetoxy-*allo*pregn-16-en-11 : 20-dione (67) is obtained by oxidation with chromium trioxide and hydrolysis of the ester-3 : 26-diacetate with acetic acid[94]; hydrogenation of (67) with 5% palladized charcoal in ethyl acetate affords 3β-acetoxy*allo*pregnane-11 : 20-dione[94], from which cortisone can be derived[111,112].

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