THE TETRACYCLIC TRITERPENES

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Introduction

THE triterpenes [1] can be conveniently divided into groups according to the number of rings contained in their structures. The pentacyclic triterpenes, which are of plant origin, form the largest and best known of these groups and include about fifty compounds of known structure. These structures all contain one of the five carbon skeletons exemplified in β-amyrin (Ia), α-amyrin (Ib),[2] lupeol (Ic), taraxasterol (Id),[2] and taraxerol (Ie).[2] With the exception of taraxerol these carbon skeletons differ only in the structure and configuration of ring E. The tetracyclic group is smaller and has been closely investigated only in the last few years. Some members of this group occur in higher plants, others occur in fungi, and the most important member, lanosterol, is obtainable in quantity from an animal source. There is also one tricyclic triterpene, ambrein (If), and one acyclic triterpene, squalene (Ig), both of which are of animal origin.

Intensive investigations in triterpene chemistry began about 1930, and until 1950 were concerned mainly with establishing the structures and relations of members of the pentacyclic group. During this period little correlation was possible with the other major class of naturally-occurring multi-ring alicyclic compounds, the steroids. The chemistry of the steroids has always been well in advance of that of the triterpenes mainly because of the importance of many steroids in animal metabolism. In general the two fields were regarded as distinct: the triterpenes then known contained thirty carbon atoms and their structures conformed to the isoprene rule whereas the steroids contain varying numbers of carbon atoms and do not conform to this rule.

Since 1950 it has become apparent that the two fields are closely related in some fundamental respects.* Three factors which have contributed to this development may be distinguished:

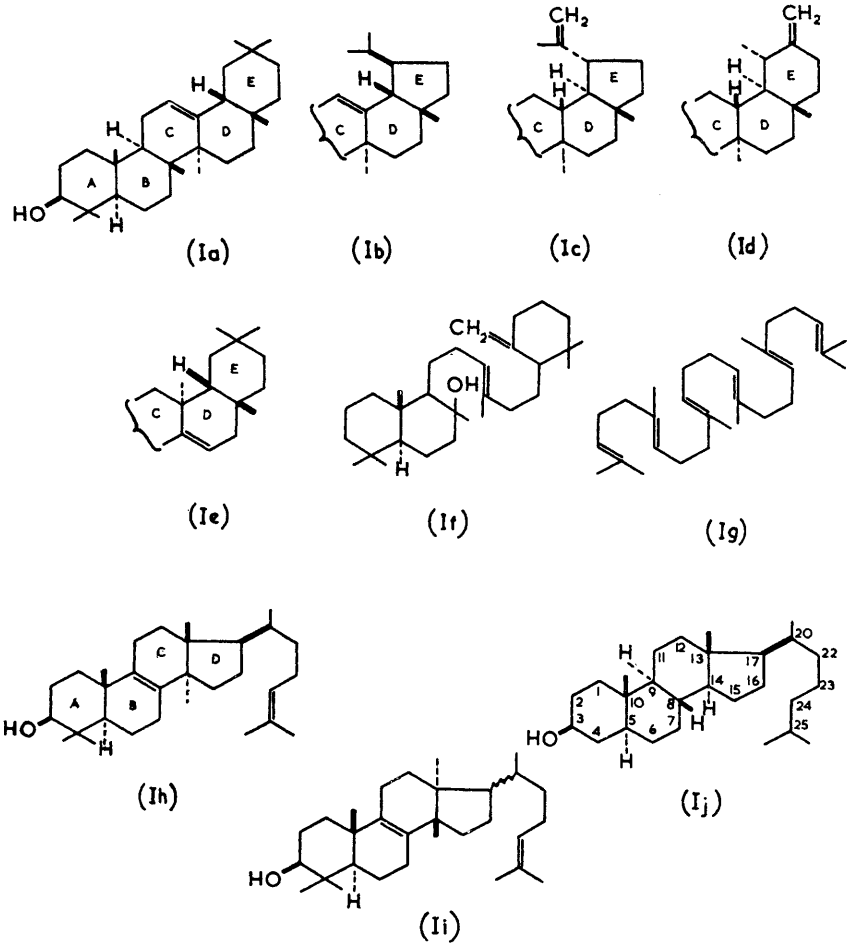
(i) The structure of lanosterol (Ih), the key member of the tetracyclic group, was elucidated in 1952 after a comparatively brief but intensive period of investigation. Lanosterol has obvious structural relations with

[1] Recent reviews: Jeger, *Fortschr. Chem. org. Naturstoffe*, 1950, **7**, 1; Barton, *Prog. Org. Chem.*, 1953, **2**, 67; "Chemistry of Carbon Compounds" (Ed. Rodd), Elsevier, London, 1953, Vol. IIB, 726.

[2] Structures (Ib), (Id), and (Ie) have recently been proposed by Spring *et al.*, *J.*, 1955, 2610; Ames, Beton, Bowers, Halsall, and Jones, *J.*, 1954, 1905, and Spring *et al.*, *J.*, 1955, 2131, respectively. Structure (Ib) for α-myrin has been questioned by Meisels, Rüegg, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1955, **38**, 1298.

* As a result the method of writing the structural formulae of triterpenes and their numbering have been altered to conform to the steroid system; cf. Halsall, Jones and Meakins, *J.*, 1952, 2862; Nomenclature Report, *J.*, 1953, 4203.

both the steroids and the triterpenes and could be regarded as intermediate between the two classes. Also other members of the tetracyclic group whose structures were subsequently deduced have additional structural



(Ia) *β-Amyrin.* (Ib) *α-Amyrin.* (Ic) *Lupeol.*
(Id) *Taraxasterol.* (Ie) *Taraxerol.* (If) *Ambrein.*
(Ig) *Squalene.* (Ih) *Lanosterol.* (Ii) *Euphol.*
(Ij) *Cholestanol.*

Note : Throughout this Review methyl groups are indicated only by the bonds to them but hydrogen atoms, when included at ring junctions, are indicated by the bond and the symbol H.—Ed.

features, in some cases reminiscent of the steroids and, in other cases, of terpenes. The group can be divided into two sub-groups represented by lanosterol and euphol. Euphol (Ii) is a stereoisomer of lanosterol and differs from it in the configuration of the C/D ring junction and possibly

also in the attachment of the side chain. Both sub-groups include C_{31}-compounds which have an extra carbon atom attached to position 24. Several acids isolated from fungi are of this type and their carbon skeleton has the same relation to lanosterol as ergosterol (the common sterol of fungi) has to cholesterol. Other structural variations include the presence of a *cyclo*propane ring in the lanosterol skeleton and stereoisomerism at $C_{(20)}$. In contrast to other terpenes the tetracyclic triterpenes do not conform to the " empirical " isoprene rule ; they do however conform to the " biogenetic " isoprene rule.[3]

(ii) The main features of the stereochemistry of the pentacyclic triterpenes [1–3] (see structures Ia, b, c, d, and e) and the complete stereochemistry of lanosterol (Ih) have now been established. Wherever comparisons are applicable the stereochemistry of the triterpenes is, in general, the same as that of the 5α-steroids.[4] Thus the configurations of the asymmetric carbon atoms at the A/B, B/C, and C/D ring junctions are the same in most triterpenes as in cholestanol (Ij). (Taraxerol and euphol differ from the steroids at the C/D ring junction.) The deduction of the structural and stereochemical similarities of lanosterol to the steroids has received striking confirmation from the recent conversion of cholesterol into dihydrolanosterol.[5] The absolute configuration of the steroids, and consequently of the triterpenes, is now known.[6]

(iii) Knowledge of the biosynthesis of the steroids is now accumulating,[7] and it appears that biosynthetically the steroids and the triterpenes may be closely connected. Bloch [8] has shown that cholesterol is synthesised *in vivo* from acetic acid and that squalene (Ig) is probably an intermediate in the synthesis. Subsequent evidence has led to the hypothesis that squalene may undergo cyclisation in such a way as to form lanosterol which may then, by loss of three carbon atoms, be converted into cholesterol.[9] Ruzicka[3] has suggested that the cyclisation of squalene could give rise to an intermediate related to lanosterol from which, by various pathways, the tetracyclic and pentacyclic triterpenes and the steroids could be derived.

For the reasons indicated above the tetracyclic triterpenes are now of considerable interest. This Review traces the main outlines of their chemistry and indicates the methods by which their structures were deduced. The term " triterpene " is used here in a general sense to include C_{30} and C_{31} compounds whether or not they conform to the empirical isoprene rule.

[3] Ruzicka, *Experientia*, 1953, **9**, 357.

[4] Cf. Mills and Klyne, *Progr. Stereochem.*, 1954, **1**, 177.

[5] Barton, Ives, Kelly, Woodward, and Patchett, *J. Amer. Chem. Soc.*, 1954, **76**, 2852 ; *Chem. and Ind.*, 1954, 605.

[6] Cornforth, Youhotsky, and Popják, *Nature*, 1954, **173**, 536 ; Riniker, Arigoni, and Jeger, *Helv. Chim. Acta*, 1954, **37**, 546 ; cf. also ref. 4.

[7] Recently reviewed by Cornforth, *Rev. Pure Appl. Chem.* (*Australia*), 1954, **4**, 275, and by Popják, *Lectures Roy. Inst. Chem.*, 1955, No. 2.

[8] Bloch, *Recent Progr. Hormone Res.*, 1951, **6**, 111 ; Langdon and Bloch, *J. Biol. Chem.*, 1953, **200**, 129, 135.

[9] Woodward and Bloch, *J. Amer. Chem. Soc.*, 1953, **75**, 2023 ; Dauben *et al.*, *ibid.*, pp. 3038, 6302 ; *Chem. and Ind.*, 1955, 94 ; Bloch, *Helv. Chim. Acta*, 1953, **36**, 1611.

The tetracyclic triterpenes, at least those of the lanosterol sub-group, are sometimes referred to as the " trimethyl-steroids ".

Lanosterol

Occurrence.—The only practical source of lanosterol is the " *iso*-cholesterol " mixture from wool wax.[10, 11] This mixture consists of approximately equal proportions of lanosterol and dihydrolanosterol together with smaller proportions of the related compounds, agnosterol and dihydro-agnosterol. Traces of lanosterol also occur in some other animal products and in the minor sterols of yeast.[12] It has been isolated from the latex of *Euphorbia balsamifera*,[13] apparently the only known case of its occurrence in a higher plant. The " *iso*cholesterol " mixture has been found in the hair fat of some other ruminants besides the sheep ; evidently it is synthesised in the sebaceous glands of the skin.[10]

Lanosterol and its dihydro-compound form mixed crystals and are virtually inseparable. It was not until 1945 that pure lanosterol was obtained from the mixture by an indirect method of separation [14] and found to be identical with the material from yeast, hitherto called cryptosterol. Although pure lanosterol is very difficult to obtain, the pure dihydro-compound can be obtained readily by hydrogenation of the mixture, and has consequently been the starting point for most of the investigations into the chemistry of lanosterol.

Since wool wax contains about 10% of the lanosterol–dihydrolanosterol mixture (the cholesterol content is about the same [11]) and since wool wax is produced in large amounts by the wool-scouring industry, lanosterol, or rather dihydrolanosterol, is probably more readily available than any other triterpene or steroid, except cholesterol. Some of the work on the chemistry of lanosterol has been inspired by the aim of using it as a chemical raw material.

Elucidation of Structure.—The elucidation of the structure of lanosterol has been briefly surveyed by Halsall [15] and by Barton.[16] The early work [12, 17] established *inter al.* the presence of the secondary alcoholic group and the two double bonds, only one of which could be hydrogenated. Oxidative fission at the reducible double bond yielded acetone, thus establishing the presence of the *iso*propylidene group. Ruzicka and Jeger and their co-workers began work on the problem in 1944 ; they found that the

[10] Lederer and his co-workers, *Bull. Soc. Chim. biol.*, 1945, **27**, 211, 218, 419 ; *Biochim. Biophys. Acta*, 1948, **2**, 91.

[11] Truter, *Quart. Rev.*, 1951, **5**, 390.

[12] Wieland and his co-workers, *Annalen*, 1937, **529**, 68 ; 1941, **546**, 103 ; *Z. physiol. Chem.*, 1942, **274**, 215.

[13] Gonzalez and his co-workers, *Anales Fís. Quím.*, 1952, **48**, *B*, 475, 487.

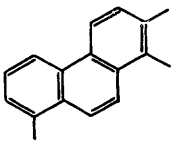
[14] Ruzicka, Denss, and Jeger, *Helv. Chim. Acta*, 1945, **28**, 759.

[15] *Ann. Reports*, 1952, **49**, 184.

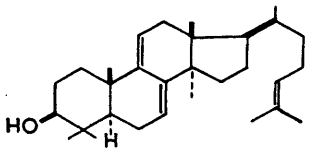
[16] Ref. 1, also *Ciba Foundation Colloquia Endocrinol.*, 1953, **7**, 27.

[17] Windaus and Tschesche, *Z. physiol. Chem.*, 1930, **190**, 51 ; Schulze, *ibid.*, 1936, **238**, 35 ; Marker and his co-workers, *J. Amer. Chem. Soc.*, 1937, **59**, 1368, 2289 ; Dorée and his co-workers, *J.*, 1941, 176, and earlier papers.

"*iso*cholesterol" mixture of lanosterol and its dihydro- and dehydro-derivatives yielded 1 : 2 : 8-trimethylphenanthrene (IIa) as the main product of selenium dehydrogenation.[18] The formation of this hydrocarbon, previously observed by Schulze,[17] is in contrast to the formation of naphthalene and picene derivatives in the dehydrogenation of pentacyclic triterpenes. Dehydrogenation to 1 : 2 : 8-trimethylphenanthrene was subsequently found to be characteristic of the tetracyclic triterpenes and provided valuable evidence for the ring structure of lanosterol and other members of the group.



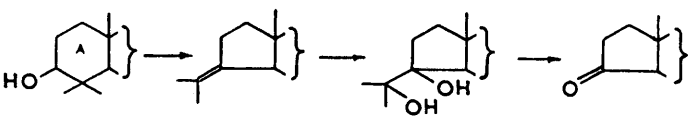
(IIa)



(IIb)

The close relation of agnosterol (IIb) to lanosterol (Ih) was revealed by the oxidation of dihydrolanosterol to dihydroagnosterol [17, 19] (initially called γ-lanosterol). Both agnosterol and its dihydro-compound exhibit ultraviolet absorption with $\lambda_{max.}$ 243 mμ, indicating the presence of a hetero-annular conjugated diene system. Also agnosterol, like lanosterol, yields acetone on oxidative fission of the reducible double bond.[19]

The location of the hydroxyl group of lanosterol in a terminal ring adjacent to a carbon atom carrying a *gem*-dimethyl group was shown [20] by the application of a standard reaction sequence previously applied to pentacyclic triterpenes. Dehydration of dihydrolanosterol (IIIa) with phosphorus pentachloride is accompanied by a retropinacolin rearrangement resulting in the contraction of ring A to a five-membered ring (IIIb).

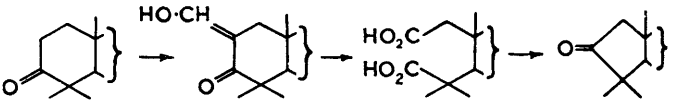


(IIIa) (IIIb) (IIIc) (IIId)

Oxidation with osmium tetroxide then gave two stereoisomeric glycols (IIIc) both of which on oxidation with lead tetra-acetate yielded acetone and a trisnorketone (IIId). It is now known that the above rearrangement requires an equatorial configuration of the hydroxyl group.[21] Evidence that the hydroxyl group is also adjacent to a methylene group and is in a

[18] Ruzicka, Rey, and Muhr, *Helv. Chim. Acta*, 1944, **27**, 472.
[19] Ruzicka, Denss, and Jeger, *ibid.*, 1946, **29**, 204.
[20] Ruzicka, Montavon, and Jeger, *ibid.*, 1948, **31**, 818; Dorée, McGhie, and Kurzer, *J.*, 1949, S167.
[21] Barton, *J.*, 1953, 1027.

six-membered ring was provided by the observation that lanostenone * (IVa) condenses with ethyl formate to form a hydroxymethylene derivative (IVb). Oxidation of the latter yielded a dicarboxylic acid (IVc) which, when heated, formed a norketone (IVd).[18]



(IVa) (IVb) (IVc) (IVd)

In an outstanding paper by Ruzicka and his collaborators [22] the structure of rings A, B, and C and the location of the double bonds in dihydrolanosterol and dihydroagnosterol were deduced from the dehydrogenation evidence and from a study of the spectroscopic and chemical properties of a series of oxidation products. Most of these oxidation products had been prepared in the exploratory work of Dorée, McGhie, and their co-workers.[23] The absence of olefin absorption in the infrared spectrum of dihydrolanosterol indicated that the inert double bond present is tetrasubstituted. The infrared spectrum of dihydroagnosterol on the other hand contained absorption characteristic of trisubstituted double bonds. In view of these facts and the other above-mentioned evidence, the partial structures (Va) and (Vb) were proposed for dihydrolanosteryl and dihydroagnosteryl acetates. Apparently the oxidation (Va → Vb), which can be effected by a variety of mild oxidising agents,[23] involves an allyl rearrangement. [On the evidence then available the Δ^8-position of the double bond in (Va) was not the only position possible.] The presence of a methyl group at position 10 was assumed by analogy with other triterpenes and was confirmed by later evidence outlined below.

Oxidation of either acetate (Va) or (Vb) by chromic acid yielded a yellow unsaturated diketone (Vd). [In mild conditions the intermediate $\alpha\beta$-unsaturated ketone (Vc) can also be obtained.[23]] Such diketones are characteristic oxidation products of all the well-known tetracyclic triterpenes and are not normally formed by pentacyclic triterpenes. The ultraviolet absorption ($\lambda_{max.}$ 275 mμ) of compound (Vd) indicated the presence of the O:C·Ċ=Ċ·CO chromophore and from the infrared absorption, particularly in view of the absence of olefin absorption, the Zurich workers deduced the centrosymmetrical or transoid arrangement of this chromophore which is represented in the assigned partial structure (Vd).

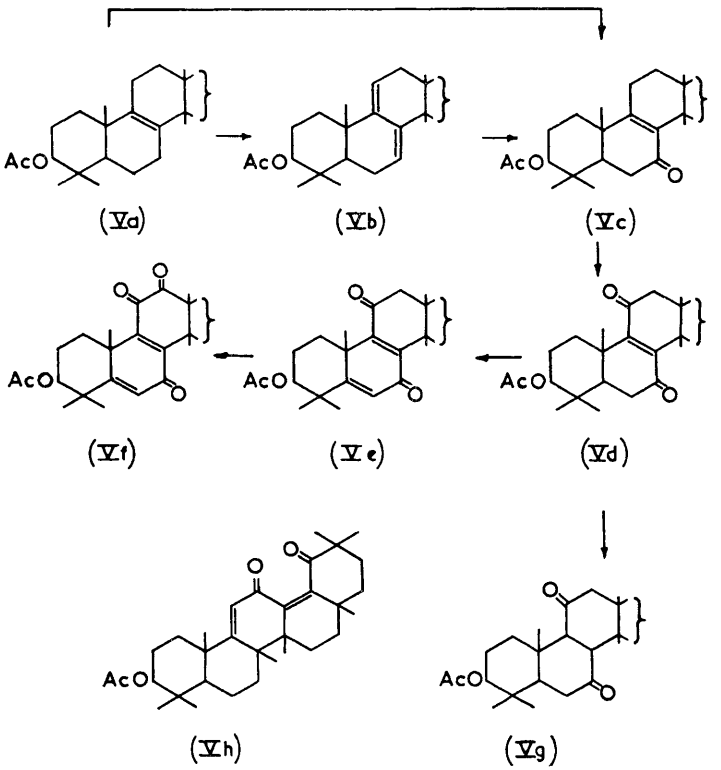
Oxidation of the enedione (Vd) with selenium dioxide yielded a dienedione (Ve) the transoid structure of which was deduced from spectroscopic evidence and from the fact that it did not react with hydrazine to form a

[22] Voser, Montavon, Günthard, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1950, **33**, 1893.

[23] Dorée, McGhie, and their co-workers, *J.*, 1953, 305, and earlier papers.

* The systematic nomenclature is based on the name lanostane for the parent saturated hydrocarbon. Thus dihydrolanosterol becomes lanostenol.

pyridazine, in contrast to the dienediones (*e.g.*, Vh) which are readily obtained from many pentacyclic triterpenes. Further oxidation of the dione (Vd) or (Ve) with selenium dioxide yielded a dienetrione (Vf) which was shown to contain an α-diketone system by formation of a dicarboxylic acid without loss of carbon on oxidative fission. Treatment of the enedione (Vd) with zinc and acetic acid [23] brought about a ready reduction of the tetrasubstituted double bond yielding the saturated diketone (Vg). One of the carbonyl groups in this (now known to be the sterically hindered 11-oxo-group) is

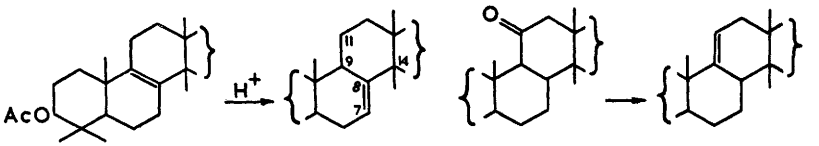


unreactive. The properties of this group and of the derived hydroxyl group, together with the presence of an *iso*propylidene group in the structure, led to the first suggestion of the steroid-like nature of lanosterol.[22]

The conclusions summarised in formulae (Va)—(Vg) were confirmed by McGhie and by Barton and their co-workers [24, 25] who provided further evidence for structures (Vc), (Vf), and (Vg) and established the Δ^8-location of the double bond. Barton *et al.*[25] also gave evidence for an important feature of the lanosterol structure, namely the attachment of an angular methyl group at $C_{(14)}$ as well as at $C_{(13)}$. On treatment with acid, lanostenyl

[24] Cavalla, McGhie, and Pradhan, *J.*, 1951, 3142.
[25] Barton, Fawcett, and Thomas, *J.*, 1951, 3147.

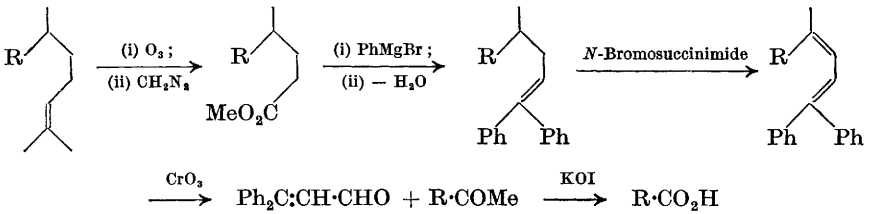
acetate (VIa) is isomerised to the Δ^7-isomer * (VIb).[24, 25] Thus the double bond of lanostenol migrates to the Δ^7- rather than to the $\Delta^{8(14)}$-position as in the case of the " classical " steroids.[26] Hence it appeared that the



(VIa) (VIb) (VIc) (VId)

14-position is blocked by the attachment of an angular methyl group. In support of this it was pointed out [25] that it had not been possible to extend unsaturation or substitution beyond the system represented in structure (Vf). Also the dehydrogenation evidence confirmed [25, 27] the presence of an angular methyl group at $C_{(14)}$.

The structure of the side chain was established by both the Zurich and the London workers. The latter, in an experiment reminiscent of Windaus's original proof of the side chain of cholesterol,[28] isolated a small yield of 6-methylheptan-2-one by vigorous oxidation of lanostenyl acetate.[29] Both Ruzicka and his co-workers [27] and McGhie and his co-workers [30] used a degradation of the Meystre–Miescher type starting from derivatives of the trisnor-acid obtained by ozonolysis of lanosterol :



Derivatives of the above methyl ketone were used [31] as the starting point in the next phase of the problem, namely the elucidation of the size

[26] Fieser and Fieser, " Natural Products Related to Phenanthrene ", Reinhold, New York, 3rd Edn., 1949, pp. 240, 290.

[27] Voser, Mijović, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1951, **34**, 1585.

[28] Ref. 26, p. 122.

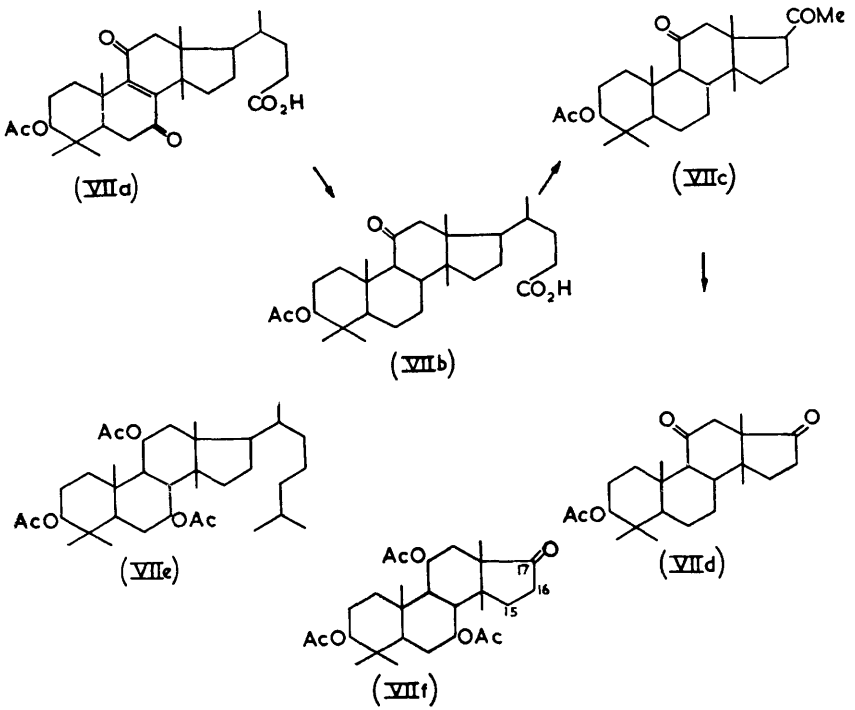
[29] Barnes, Barton, Fawcett, Knight, McGhie, Pradhan, and Thomas, *Chem. and Ind.*, 1951, 1067.

[30] McGhie, Pradhan, Cavalla, and Knight, *Chem. and Ind.*, 1951, 1165. Cf. Curtis and Silberman, *J.*, 1952, 1187 ; *Austral. J. Chem.*, 1953, **6**, 421.

[31] Voser, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1952, **35**, 497.

* The $\Delta^{9(11)}$-isomer (VId), which is important in connection with the structure of *cyclo*artenol, had previously been prepared [22] by a sequence of reactions involving removal of the reactive 7-oxo-group of (Vg) to yield the 11-ketone (VIc). This was reduced to the alcohol which was dehydrated to give (VId).

of ring D and the position of attachment of the side chain. In practice the 11-ketone (VIIc) was the most suitable starting point and was obtained *via* the above degradation from the oxo-trisnor-acid (VIIb) which in turn was prepared in good yield from the dioxo-trisnor-acid (VIIa), obtainable in relatively large quantities from oxidation of the " *iso*cholesterol " mixture. Degradation of the 11-ketone (VIIc) yielded the ring-D ketone (VIId), an analogue of which (the 3-deoxy-7-hydroxy-compound, prepared in a similar manner) had infrared absorption characteristic of a five-membered, as well as a six-membered, ring. From this it was deduced that ring D is five-membered.[32]



Barton and his co-workers attacked the problem of the structure of ring D by a different route.[33] From oxidation of 3 : 7 : 11-triacetoxylanostane [(VIIe) ; prepared by reduction of the diketone (Vg) and subsequent acetylation] they isolated *inter al.* the ring-D ketone (VIIf). Derivatives of this ketone had infrared absorption characteristic of a five-membered ring ketone. Furthermore, the infrared absorption of the ring-D ketone (VIIf), its degree of steric hindrance, and the extent of its reaction with

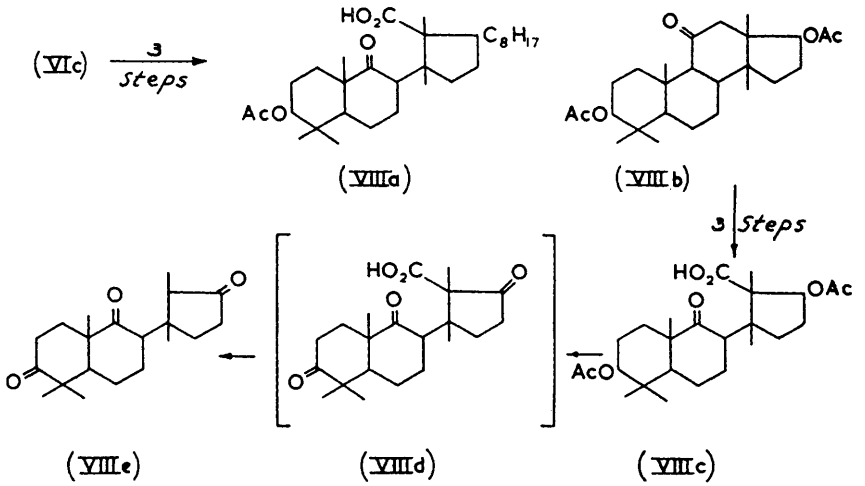
[32] Voser, Günthard, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1952, **35**, 66 ; Voser, Jeger, and Ruzicka, *ibid.*, p. 503.

[33] Barnes, Barton, Cole, Fawcett, and Thomas, *Chem. and Ind.*, 1952, 426 ; *J.*, 1953, 571.

bromine showed that the carbonyl group is flanked by only one methylene group. Consequently $C_{(16)}$ was eliminated as the position of the carbonyl group, and hence of the side chain, leaving positions 15 and 17 for consideration. Attachment of the side chain at $C_{(15)}$ would give a structure which conformed to the isoprene rule whereas attachment at $C_{(17)}$, as in the " classical " steroids, would mean a violation of this rule.

At this point the results of the *X*-ray analysis of lanostenyl iodoacetate were published [34] giving a complete description of the structure and configuration of lanostenol. The results agreed with the structure deduced from the chemical work and furthermore located the side chain at $C_{(17)}$.

An ingenious chemical proof of the location of the side chain was published simultaneously by Ruzicka and his co-workers.[35] In model experiments [36] a method for the oxidative fission of ring C had been devised whereby 11-oxolanostanyl acetate (VIc) was converted into the tricyclic compound (VIIIa). The same method was applied to the diacetoxy-ketone



[(VIIIb); conveniently prepared by oxidation of (VIIc) with monopersulphuric acid] yielding the analogous tricyclic compound (VIIIc). Deacetylation of the diacetoxy-acid (VIIIc) followed by oxidation with chromic acid led directly to the triketone (VIIIe). The intermediate keto-acid (VIIId) could not be isolated. Since the model compound (VIIIa) was quite stable, the spontaneous decarboxylation of (VIIId) must have been due to the presence of a β-keto-acid grouping. Hence the ring-D carbonyl group, and consequently the side chain, must be located at $C_{(17)}$.

[34] Curtis, Fridrichsons, and Mathieson, *Nature*, 1952, **170**, 321; Fridrichsons and Mathieson, *J.*, 1953, 2159.

[35] Voser, Mijović, Heusser, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1952, **35**, 2414.

[36] Voser, Günthard, Heusser, Jeger, and Ruzicka, *ibid.*, p. 2065.

Stereochemistry and Relation to the Steroids and Other Classes of Terpenes.—The stereochemistry of lanosterol has been deduced by several methods. The *X*-ray analysis of lanostenyl iodoacetate [34] gave a complete description of the configuration of lanostenol independently of the chemical evidence. The main features found were *trans*-fusion at the A/B and C/D ring junctions and β-orientation of the hydroxyl group, the side chain, and the $C_{(10)}$- and $C_{(13)}$-methyl groups; the $C_{(14)}$-methyl group, necessarily, is α-oriented. Lanostenol, therefore, has the same configuration as the steroids of the cholestane series [37] and consequently is 4 : 4 : 14-trimethylcholest-8-en-3β-ol (cf. Ih and Ij).* (The presence of the double bond at the B/C ring junction of course removes the possibility of stereoisomerism at this junction.)

Evidence from molecular-rotation differences indicated the same configuration. In correlating the stereochemistry of the triterpenes with that of the steroids by this method, Klyne [38] had shown that in lanosterol and in the pentacyclic triterpenes the A/B ring junction is *trans* and the orientation of the angular methyl group at $C_{(10)}$ is the same as in the steroids. By further application of the method, together with conformational evidence, it was deduced [35, 39] that the other configurational features of lanosterol are the same as in the cholestane series. Similarly, application of Prelog's asymmetric synthesis method [40] showed that the configuration (and conformation) of ring A is the same in lanosterol, euphol, and α-amyrin as in cholestan-3β-ol.

The hydrocarbon lanostane and a number of its derivatives are known. Such compounds have a single bond at the B/C ring junction thus permitting stereoisomerism at this junction. These compounds are invariably prepared from 7 : 11-dioxolanostanyl acetate (Vg) and conformational arguments indicate that the steric arrangement at the B/C ring junction in this diketone is the same as in cholestane, *i.e.*, *anti-trans*.[39]

Another line of evidence bearing on the stereochemistry of lanosterol was biological. By methods which are described below, lanosterol has been converted into 14-methyl-11-oxoprogesterone (Xb) which was as active physiologically as 11-oxoprogesterone.[41] The physiological activity of the progestational hormones is very dependent on their structure and configuration, small variations in which can lead to loss of activity. Consequently the activity of 14-methyl-11-oxoprogesterone is a strong indication that its configuration is the same as that of 11-oxoprogesterone.

The conclusive chemical proof of the structure and configuration of lanosterol came from the conversion of cholesterol into lanostenol.[5] This involved, essentially, the introduction of the *gem*-dimethyl grouping at

[37] Cf. ref. 26, Ch. X. [38] Klyne, *J.*, 1952, 2916; cf. ref. 4
[39] Barnes, Barton, Fawcett, and Thomas, *J.*, 1953, 576.
[40] Dauben, Dickel, Jeger, and Prelog, *Helv. Chim. Acta*, 1953, **36**, 325; cf. ref. 4
[41] Kyburz, Riniker, Schenk, Heusser, and Jeger, *Helv. Chim. Acta*, 1953, **36** 1891.

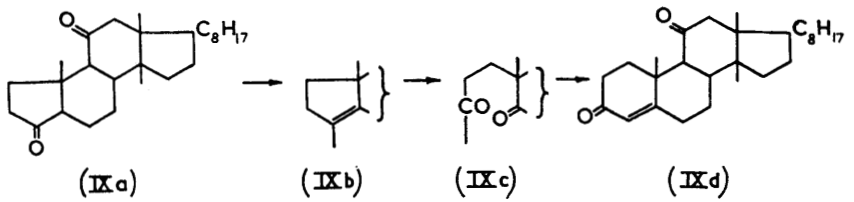
* It was not explicit that the configuration of $C_{(20)}$, the asymmetric centre of th side chain, is the same as in cholesterol; this follows, however, from the conversio of cholesterol into lanostenol.[5]

position 4 in ring A and then the more difficult introduction of the methyl group at position 14. This conversion, incidentally, represents the first total synthesis of a cyclic triterpene.

Since lanosterol has thus been directly and completely related to the steroids its relation to other classes of terpene compounds is of considerable interest. Direct inter-relation of the structure and configuration of rings A and B of lanosterol, the pentacyclic triterpenes, ambrein, and the di- and tri-cyclic diterpenes has been achieved ;[42] these inter-relations have been reviewed by Ruzicka.[3]

Conversion into Analogues of Steroid Hormones, etc.—The availability of lanosterol and the conclusion that it is a 4 : 4 : 14-trimethyl-steroid have prompted efforts to convert it into methyl derivatives of physiologically important steroids. An important feature of the chemistry of lanosterol in this connection is the ease of introduction of the 11-oxo-group. Introduction of this group has been one of the major problems in the conversion of steroid raw materials, such as diosgenin, stigmasterol, ergosterol, etc., into important adrenocortical hormones such as cortisone.[43] It is of interest that one of the main methods of introducing the 11-oxo-group in steroids, namely from 7 : 9(11)-dienes, was originally suggested in at least one research centre [44] by the conversion of dihydroagnosterol into 11-oxolanostanol (Vb → Vd → Vg → VIc).

Conversion of lanosterol into true steroidal compounds would involve *inter al.* removal of the extra methyl groups at $C_{(4)}$ and $C_{(14)}$. Removal of the $C_{(14)}$-methyl group presents a difficulty which, it appears, can fortunately be avoided. Removal of the *gem*-dimethyl group at $C_{(4)}$, with simultaneous introduction of the biologically important Δ^4-3-one system, was achieved by Ruzicka and his collaborators [45] in model experiments



(IXa) (IXb) (IXc) (IXd)

starting from 11-oxolanostanol (VIc). Application to the latter of the reaction sequence (IIIa → IIId), described on p. 332, afforded the C_{27} diketone (IXa). Methylmagnesium iodide reacted selectively with the carbonyl

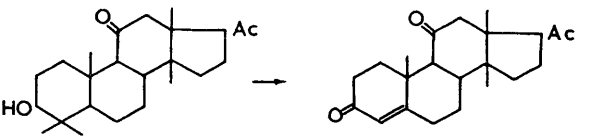
[42] Heusser, Jeger, Ruzicka, and their co-workers, *Helv. Chim. Acta*, 1952, **35**, 2073 ; 1953, **36**, 1891.

[43] Cf. Peterson, *Research*, 1953, **6**, 309 ; Djerassi, *Vitamins and Hormones*, 1953, **11**, 205 ; Rosenkranz and Sondheimer, *Progr. Chem. of Org. Natural Products*, 1953, **10**, 274 ; Spring, *Progr. Org. Chem.*, 1953, **2**, 104 ; Cornforth, *Ann. Reports*, 1952, **49**, 193 ; 1953, **50**, 222.

[44] Jeger, Heusser, and their co-workers, *Helv. Chim. Acta*, 1951, **34**, 2106 ; 1952, **35**, 295, 936, 964.

[45] Voser, White, Heusser, Jeger, and Ruzicka, *ibid.*, p. 830.

group in ring A of the diketone (IXa) yielding the unsaturated C_{28} ketone (IXb). Oxidative fission of the double bond of the latter led to the tricyclic triketone (IXc) which underwent ring closure forming 14-methyl-3 : 11-dioxocholest-4-ene (IXd). Subsequently [46] this reaction sequence was applied to the intermediate (Xa ; cf. VIIc) yielding 14-methyl-11-oxoprogesterone (Xb). (The carbonyl group at $C_{(20)}$ was protected during the



(Xa) (Xb)

process by reduction to the alcohol which was acetylated.) The fact that 14-methyl-11-oxoprogesterone is biologically as active as 11-oxoprogesterone [41] has no doubt stimulated further conversions of lanosterol into 14-methyl-steroidal hormones.

Lanosterol has been converted into an analogue of a valuable steroid, provitamin D_3 (7-dehydrocholesterol), without removal of the three extra methyl groups, by Barton and Thomas.[47]

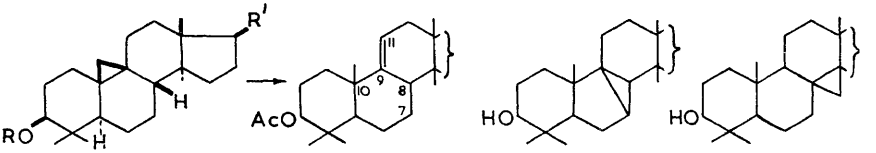
*cyclo*Artenol

*cyclo*Artenol (XIa) was the first triterpene found to contain a *cyclo*propane ring ; strictly, it is a pentacyclic triterpene. It has been isolated from several plant sources. The presence of the *cyclo*propane ring was deduced by Barton [48] from spectroscopic evidence and from the formation of a double bond by the action of acid on *cyclo*artanyl (dihydro*cyclo*artenyl) acetate. The formation of acetone on oxidative fission of *cyclo*artenyl derivatives indicated the presence of an *iso*propylidene group. The nature of the carbon skeleton was directly established by the observation by Bentley, Henry, Irvine, and Spring [49] that the product obtained by the action of acid on *cyclo*artanyl acetate (XIb) consisted mainly of lanost-9(11)-enyl acetate (XIc ; cf. footnote p. 335). Clearly this compound is formed by the acid-catalysed fission of the *cyclo*propane ring.

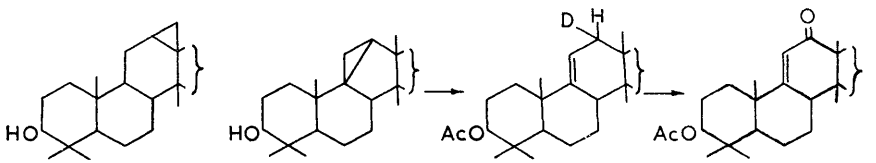
It remained solely to locate the position of the *cyclo*propane ring, a formidable problem for the classical methods of organic chemistry. This problem was, however, soon solved by ingenious application of modern techniques. Following its conversion into lanost-9(11)-enol, several formulae could be suggested for *cyclo*artenol. Some of these, *e.g.* (XId), were shown to be untenable by Cole's observation that *cyclo*artenol has an infrared band near 3045 cm.$^{-1}$ characteristic of a methylene group included in a

[46] Voser, Heusser, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1953, **36**, 299.
[47] Barton and Thomas, *J.*, 1953, 1842.
[48] Barton, *J.*, 1951, 1444.
[49] Bentley, Henry, Irvine, and Spring, *J.*, 1953, 3673.

*cyclo*propane ring.[50] Irvine, Henry, and Spring,[51] by eliminating other possibilities on chemical grounds, were able to conclude that formula (XIa) is correct. Some formulae, *e.g.* (XIe) and (XIf), were eliminated by the following facts : acid treatment of *cyclo*artanol gives mainly lanost-9(11)-enol together with a small amount of an equilibrium mixture of the Δ^8- and the Δ^7-isomer ; lanost-9(11)-enol is not isomerised by acid ; neither the Δ^7- nor the Δ^8-isomer is converted by acid into lanost-9(11)-enol. The exclusion of formula (XIg) utilised an ingenious method originally developed by Barton and de Mayo in the similar problem of phyllanthol.[52] By treatment of *cyclo*artanyl acetate with deuterium chloride, Irvine, Henry, and Spring [51] obtained a deuterolanost-9(11)-enyl acetate which on oxidation with chromic acid gave a 12-oxo-compound still containing deuterium. If *cyclo*artenol had the formula (XIg) then the product of the reaction with deuterium chloride would be 12-deuterolanost-9(11)-enyl acetate (XIh) which on oxidation would yield the undeuterated 12-oxo-compound (XIi).



(XIa ; R = H, R' = C_8H_{15}) (XIc) (XId) (XIe)
(XIb : R = Ac, R' = C_8H_{17})



(XIf) (XIg) (XIh) (XIi)

It follows that *cyclo*artenol cannot be formulated as (XIg). Direct evidence for formula (XIa) was obtained by bromination of *cyclo*artanone (in conditions which prevented the formation of hydrogen bromide) to give the 2-bromo-compound which on dehydrobromination yielded *cyclo*art-1-en-3-one. This compound had an ultraviolet absorption maximum at 269 mμ indicating that the $\alpha\beta$-unsaturated carbonyl group is conjugated with the *cyclo*propane ring.[51]

Evidence for formula (XIa) was also advanced simultaneously by

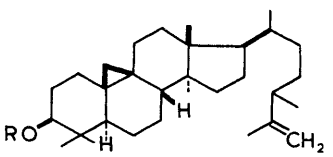
[50] Cole, *Chem. and Ind.*, 1953, 946 ; *J.*, 1954, 3810.
[51] Irvine, Henry, and Spring, *Chem. and Ind.*, 1954, 189 ; *J.*, 1955, 1316.
[52] Barton and de Mayo, *J.*, 1953, 2178.

Barton, Page, and Warnhoff [53] from a spectroscopic study of the products of reaction of deuterium chloride with derivatives of *cyclo*artanol. Methyl groups have infrared absorption (CH bending) at about 1380 cm.$^{-1}$, but the deuteromethyl group does not absorb at this wavelength; when the absorption of the products from the reaction of *cyclo*propane compounds with hydrogen chloride and deuterium chloride are compared it is therefore found that the absorption at 1380 cm.$^{-1}$ is less intense if a deuteromethyl group has been formed. This diminished intensity was observed when the deuterated lanost-9(11)-ene, prepared from *cyclo*artane by the action of deuterium chloride, was compared with lanost-9(11)-ene. Hence a deuteromethyl group must have been formed in the reaction; formula (XIa) could give rise to such a group.

The establishment of structure (XIa) for *cyclo*artenol implies a difference in configuration between it and the saturated hydrocarbon lanostane. The latter has the same configuration as cholestane; in particular the B/C ring junction is *trans* and the $C_{(9)}$-hydrogen atom is α-oriented. In *cyclo*artenol $C_{(9)}$ is linked in the *cyclo*propane ring to the β-oriented carbon atom attached to $C_{(10)}$. Consequently the configuration of this $C_{(9)}$-linkage must be β. Furthermore, the configuration of $C_{(8)}$ must be the same in *cyclo*artenol as in lanost-9(11)-enol, *i.e.*, with the attached hydrogen atom β; hence the B/C ring junction in *cyclo*artenol must be *cis*.

*cyclo*Laudenol

Shortly after the structure of *cyclo*artenol was established a closely related C_{31} compound, *cyclo*laudenol, was isolated from opium and shown to have the structure (XIIa; R = H) by Spring and his co-workers.[54] The presence of the *cyclo*propane ring was deduced spectroscopically and



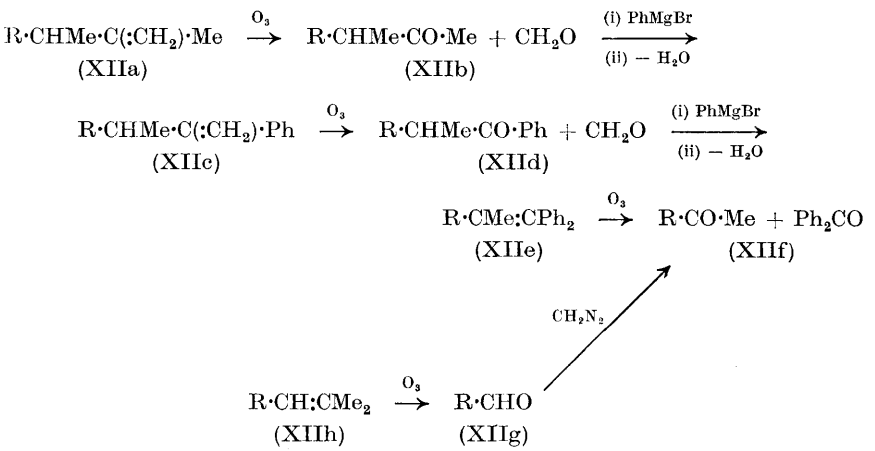
(XIIa)

by the formation of an unsaturated compound, laudenol, on treatment of *cyclo*laudanol with acid. The chemical properties and molecular-rotation differences of *cyclo*laudanol were very similar to those of *cyclo*artanol.

The structure of the side chain was established by an oxidative degradation which left the *cyclo*propane ring intact and so made possible a direct correlation with *cyclo*artenol. Ozonolysis of *cyclo*laudenyl acetate (XIIa) yielded formaldehyde and a nor-ketone (XIIb), which was shown to be a methyl ketone by hypobromite oxidation to an acid. Barbier–Wieland degradation of the nor-ketone (XIIb) led to the ketone (XIIf). From this

[53] Barton, Page, and Warnhoff, *Chem. and Ind.*, 1954, 220; *J.*, 1954, 2715.
[54] Spring and his co-workers, *J.*, 1955, 596, 1607.

sequence it could be deduced that the side chain terminates in an *iso*propenyl group and that an alkyl group is attached to $C_{(24)}$. Conversion of *cyclo*artenyl acetate (XIIh) into the ketone (XIIf), by reaction of its ozonolysis



product (XIIg) with diazomethane, established that the alkyl group is a methyl group and provided final proof for the structure of *cyclo*laudenol.

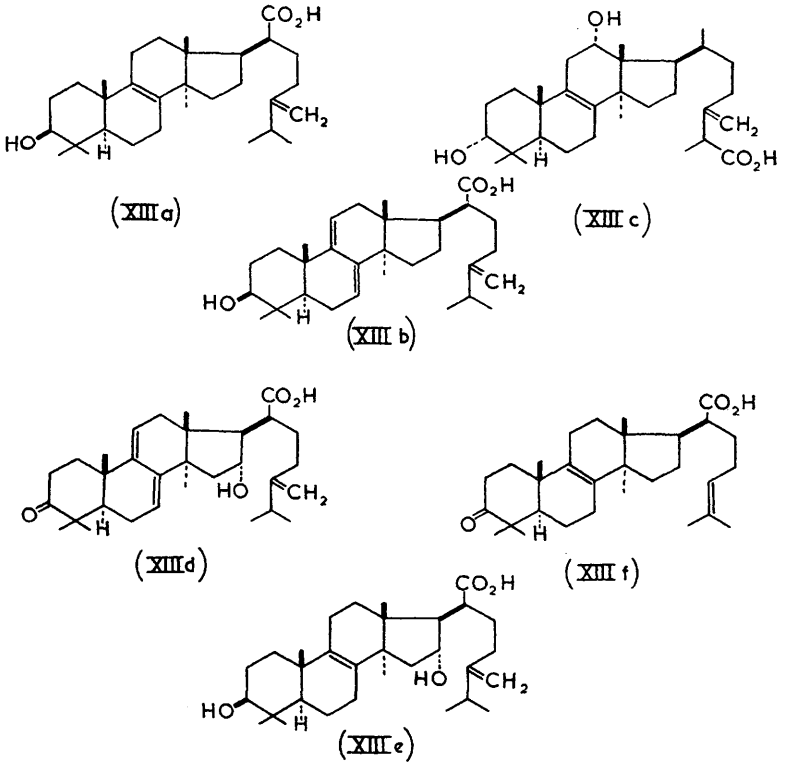
The configuration of $C_{(24)}$, to which the extra carbon atom is attached, was shown by molecular-rotation differences to be the same as in eburicane (p. 346) and ergostane.

The Fungal Acids

Introduction.—A number of wood-rotting fungi of the Basidiomycete class contain acidic tetracyclic triterpenes. The first representatives of this group of compounds whose structures were established, namely eburicoic acid (XIIIa), dehydroeburicoic acid (XIIIb), polyporenic acid A (XIIIc), polyporenic acid C (XIIId), and tumulosic acid (XIIIe), are C_{31} compounds closely related to lanosterol. The extra carbon atom in all cases is attached to position 24. Recently the C_{30} compounds, pinicolic acid A (XIIIf) and trametenolic acid B (the corresponding 3β-hydroxy-compound), have been discovered. A number of hydroxy-dicarboxylic acids have also been isolated.

The fungal acids are obtained from naturally grown fungi and also from fungi grown on a synthetic medium containing glucose as sole carbon source. In either case they are frequently accompanied by varying amounts of closely related compounds which have ultraviolet absorption with $\lambda_{max.}$ 243 mμ, indicating the presence of a heteroannular conjugated diene system. The compound of this type which accompanies eburicoic acid has been shown to be dehydroeburicoic acid (XIIIb), which bears the same relation to eburicoic acid as agnosterol does to lanosterol. The fungal acids are thus often accompanied by their corresponding dehydro-compounds.

Eburicoic Acid.—The initial investigations [55, 56] into the structure of eburicoic acid established the presence of the carboxyl group, the secondary hydroxyl group, and the two double bonds only one of which could be hydrogenated. Oxidative fission of the reducible double bond yielded formaldehyde thus revealing the presence of a vinylidene group. The



(XIIIa) *Eburicoic acid.*
(XIIIb) *Dehydroeburicoic acid.*
(XIIIc) *Polyporenic acid A.*
(XIIId) *Polyporenic acid C.*
(XIIIe) *Tumulosic acid.*
(XIIIf) *Pinicolic acid A.*

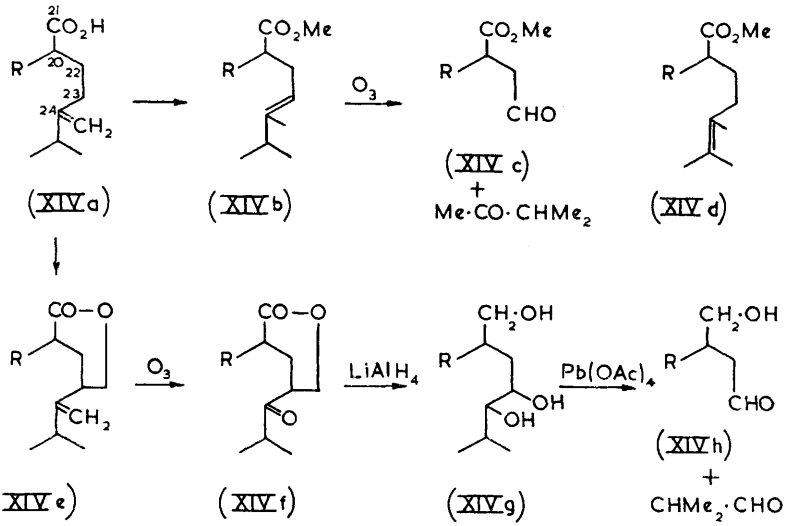
equatorial configuration of the hydroxyl group and its location in a si membered ring adjacent to a *gem*-dimethyl group and a methylene grou were established [56, 57] by means of the standard procedures which had be used with lanosterol.

The structure of rings A, B, and C and the location of the inert doul bond were indicated [57, 58] by a number of reactions analogous to thc described for lanosterol. Thus a series of oxidation products was obtain

[55] Lahey and Strasser, *J.*, 1951, 873.
[56] Gascoigne, Holker, Ralph, and Robertson, *J.*, 1951, 2346.
[57] Holker, Powell, Robertson, Simes, and Wright, *J.*, 1953, 2414.
[58] Gascoigne, Robertson, and Simes, *J.*, 1953, 1830.

corresponding in detail to those represented in the formulæ series (V). Furthermore, the action of acid on derivatives of dihydroeburicoic acid caused migration of the inert double bond from the Δ^8- to the Δ^7-position (see VIa → VIb).

The structure of the terminal portion of the side chain followed from the action of hydrogen chloride on derivatives of eburicoic acid.[59] This caused not only the migration of the inert double bond already mentioned but also the addition of hydrogen chloride to the vinylidene group ; dehydrochlorination then yielded the isomer (XIVb).* Ozonolysis of the isomer (XIVb) yielded an aldehyde (XIVc) and methyl *iso*propyl ketone.



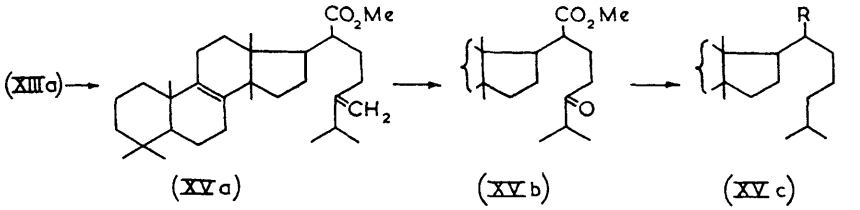
Attachment of the carboxyl group to $C_{(20)}$ was deduced from the formation of a lactone (XIVe) by the mild oxidation of acetyleburicoic acid with selenium dioxide. The structure of this lactone followed from the indication of a five-membered ring (infrared evidence), and by conversion into the trihydroxy-derivative (XIVg) which on oxidative fission yielded *iso*butyraldehyde. The carboxyl group was shown to be secondary by use of a method which had previously been applied to elemolic acid (see p. 356).

The similarity of eburicoic acid to lanosterol in rings A, B, and C, together with the structure (XIVa) of the side chain, suggested the structure (XIIIa). This was confirmed by the conversion of eburicoic acid into lanost-8-ene.[59]

[59] Holker, Powell, Robertson, Simes, Wright, and Gascoigne, *J.*, 1953, 2422.

* Some of the compound with the reducible double bond in its original position, as in (XIVa), was also obtained. The formation of another isomer (XIVd) is to be expected in this reaction but it was not found. When *cyclo*laudenol (XIIa), which has the vinylidene group at the end of the chain, was similarly treated, the only product isolated contained the re-formed double bond in the original position.[54] However, in different experimental conditions, an isomer of the type (XIVd) was formed by acid treatment of methyl polyporenate C (p. 349) which has the same side chain as eburicoic acid.

Ozonolysis of methyl 3-deoxyeburicoate (XVa) removed the extra carbon atom of the vinylidene group yielding the keto-ester (XVb) which was



(XVa) (XVb) (XVc)

reduced to the ester (XVc; R = CO_2Me). This was converted into lanost-8-ene (XVc; R = Me) by a standard reaction sequence involving reduction of the ester to a primary alcohol by means of lithium aluminium hydride, oxidation of the alcohol to an aldehyde, and Wolff–Kishner reduction of the aldehyde group to a methyl group.

This conversion, together with previous evidence, established not only the structure of eburicoic acid but also, very probably, its stereochemistry. On the assumption that no configurational changes took place during the conversion of eburicoic acid into lanost-8-ene the configuration of eburicoic acid is the same as that of lanosterol. This is supported by molecular-rotation evidence;[58] also, the only likely configurational change in the conversion is an inversion, in the hot alkaline conditions of the Wolff–Kishner reductions, at $C_{(20)}$, the position adjacent to the ester group. It has been shown, however, that derivatives of eburicoic acid do not undergo any stereochemical changes under these conditions.[57] It follows incidentally that $C_{(20)}$ must be in the more stable configuration; this has also been found to be so with polyporenic acid C, pinicolic acid A, and elemolic acid.

The systematic nomenclature of eburicoic acid and the other C_{31} fungal acids is based on the name eburicane for the (unknown) saturated hydrocarbon.* The numbering [59, 60] follows steroid principles. Thus eburicoic acid becomes 3β-hydroxyeburico-8 : 24(28)-dien-21-oic acid. Eburicane can be named 4 : 4 : 14-trimethylergostane since molecular-rotation differences indicate that the configuration of $C_{(24)}$ in dihydroeburicoic acid is the same as in ergostane [54, 61] and since the configuration of eburicoic acid has been correlated, *via* lanost-8-ene, with that of cholestane.

Dehydroeburicoic Acid.—Dehydroeburicoic acid (XIIIb) accompanies eburicoic acid in several fungi. Its relation to eburicoic acid was partly established by selenium dioxide oxidation of dihydroeburicoic acid to the dihydro-derivative of dehydroeburicoic acid (cf. the oxidation of dihydrolanosterol to dihydroagnosterol), and completely established by the conversion of eburicoic acid into dehydroeburicoic acid, by a necessarily less direct method.[58]

[60] Nomenclature Report, *J.*, 1953, 4203.

[61] Guider, Halsall, and Jones, *J.*, 1954, 4471.

* By definition, eburicane is taken to have the *anti-trans* configuration at the B/C ring junction as in lanostane and cholestane. The saturated hydrocarbon, laudane, has recently been prepared from *cyclo*laudenol and should be identical with eburicane.[54]

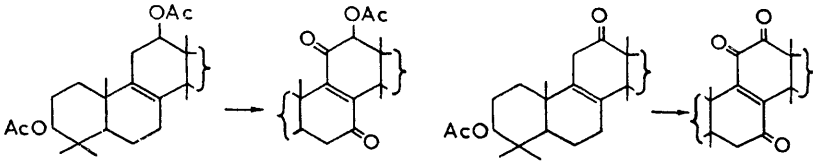
Polyporenic Acid A.—The preliminary characterisation [62] of polyporenic acid A showed the presence of a carboxyl group, two hydroxyl groups, and two double bonds. One of the double bonds was inert to hydrogenation and the other was present in a vinylidene group. The hydroxyl groups are both secondary but have considerably different reactivities, and were therefore designated *a* and *b* ; [63] subsequently they were shown to be at $C_{(3)}$ and $C_{(12)}$, respectively. The $C_{(12)}$-hydroxyl group was acylated less readily than that at $C_{(3)}$ and on oxidation yielded a carbonyl group which did not react with the usual carbonyl reagents and was not reducible by the Wolff–Kishner method. The lack of reactivity of this carbonyl group prevented the preparation of the parent mono-olefinic hydrocarbon and thus prevented an early correlation of eburicoic acid and polyporenic acid A. Such lack of reactivity can be ascribed to steric hindrance ; it is noteworthy that the $C_{(12)}$-position in polyporenic acid A appears to be considerably more hindered than the $C_{(12)}$-position in steroids. This has been attributed [64] to the presence in polyporenic acid A of the α-oriented methyl group at $C_{(14)}$.

In contrast to most triterpenes and steroids the $C_{(3)}$-hydroxyl group has the less usual axial (3α) configuration.[65] Thus oxidation of a polyporenic acid A derivative and reduction of the resulting 3-oxo-compound with lithium aluminium hydride or sodium borohydride yielded an epimer of the original derivative. This epimer had the equatorial configuration since on dehydration and ozonolysis it yielded acetone (and so the dehydration must have been of the retropinacolin type ; cf. formulae III). On the other hand, dehydration of the original derivative and ozonolysis did not give acetone. These conclusions are in accord with current views concerning the dehydration of 3β- and 3α-hydroxy-triterpenes.[21] The $C_{(12)}$-hydroxyl group is also considered to be axial (12α) particularly from its ease of dehydration.[64]

Evidence that the structure of rings A, B, and C and the location of the inert double bond in polyporenic acid A are the same as in lanosterol was obtained [64] by dehydrogenation to 1 : 2 : 8-trimethylphenanthrene and by formation of a series of oxidation products corresponding in general to those represented in the formulae series (V). These oxidation reactions also provided evidence for the location of the second ($C_{(12)}$) hydroxyl group. In the first place, oxidation with chromic acid of methyl diacetyldihydropolyporenate A (XVIa) yielded the ene-1 : 4-dione (XVIb) whose formation and ultraviolet absorption properties were analogous to those of the products obtained on oxidation of lanosterol and other tetracyclic triterpenes. However, oxidation of methyl *a*-acetyl-*b*-oxo-(*i.e.*, 3-acetyl-12-oxo-)polyporenate A (XVIc) yielded a compound (XVId) whose ultraviolet absorption was different from that of the ene-1 : 4-dione (XVIb). The structure (XVId) assigned to this compound was deduced from its ultraviolet absorption and from the fact that oxidation with alkaline hydrogen peroxide

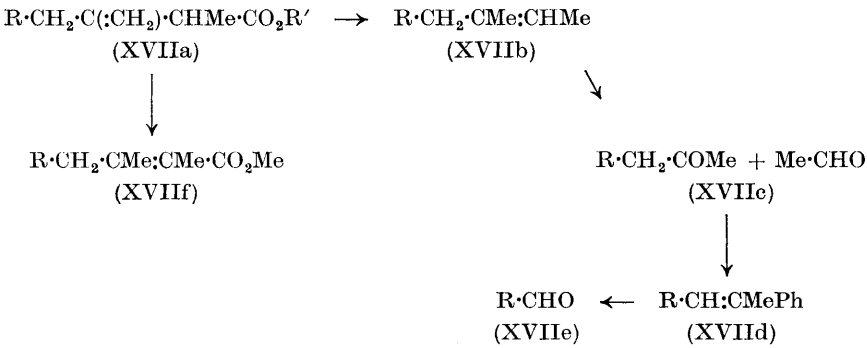
[62] Cross, Eliot, Heilbron, and Jones, *J.*, 1940, 632 ; Cross and Jones, *J.*, 1940, 1491.
[63] Curtis, Heilbron, Jones, and Woods, *J.*, 1953, 457.
[64] Halsall, Jones, and Lemin, *J.*, 1953, 468.
[65] Halsall, Hodges, and Jones, *J.*, 1953, 3019.

yielded a dicarboxylic acid without loss of carbon. The establishment of structure (XVId) leads to the location of the second (*b*) hydroxyl group at $C_{(12)}$; the alternative possibility, that it could be located at $C_{(6)}$, was eliminated.[64]



(XVIa) (XVIb) (XVIc) (XVId)

The investigations into the structure of the side chain [65] utilised the fact that polyporenic acid A (XVIIa; R′ = H) is readily decarboxylated on melting. Since this property was not exhibited by the dihydro-derivatives and since the decarboxy-compound (XVIIb) no longer had infrared absorption typical of the original vinylidene group it was concluded that polyporenic acid A contains the vinylidene double bond in a position $\beta\gamma$ to the carboxyl group.[66] (The absence of selective absorption in the ultraviolet region eliminated the possibility of an $\alpha\beta$-unsaturated acid. $\beta\gamma$-Unsaturated acids in general undergo decarboxylation accompanied by migration of the



double bond.) This conclusion was substantiated by partial isomerisation of the methyl ester (XVIIa; R′ = Me) to an $\alpha\beta$-unsaturated ester (XVIIf) on treatment with alkali. Ozonolysis of the decarboxy-compound (XVIIb) yielded acetaldehyde and the methyl ketone (XVIIc) which was also obtained by ozonolysis of the *iso*-ester (XVIIf). Reaction of the methyl ketone (XVIIc) with phenylmagnesium bromide gave the olefin (XVIId) which on ozonolysis gave acetophenone and the aldehyde (XVIIe), characterised by oxidation to an acid. These reactions establish the partial structure (XVIIa; R′ = H) for the terminal portion of the side chain.

This evidence on the structure of rings A, B, and C and the terminal

[66] Jones and Woods, *J.*, 1953, 464.

portion of the side chain indicated a close analogy with other tetracyclic triterpenes and led to the suggestion of structure (XIIIc) for polyporenic acid A.[65] Confirmation of this structure and configuration was provided by correlation of the acid with lanosterol.[67, 68] Using essentially the same method both groups of workers converted polyporenic acid A and lanosterol into a common intermediate by oxidising the $C_{(3)}$-hydroxyl group (β in lanosterol and α in polyporenic acid A), removing the $C_{(12)}$-hydroxyl group, and converting the two side chains into a common structure. Polyporenic acid A is therefore $3\alpha : 12\alpha$-dihydroxyeburico-8 : 24(28)-dien-26-oic acid (XIIIc).

Polyporenic Acid C.—Polyporenic acid C contains a hydroxyl, a carboxyl, and a keto-group and a reducible double bond present in a vinylidene group.[62, 69, 70] Also it exhibits ultraviolet absorption with $\lambda_{max.}$ 243 mμ, characteristic of a heteroannular diene system such as is present in agnosterol and dehydroeburicoic acid.

The locations of the keto- and hydroxyl-groups were deduced in the following way.[70] Polyporenic acid C has an infrared absorption band at 1712 cm.$^{-1}$ indicating that the keto-group is present in a six-membered ring. Oxidation of the methyl ester yielded a dioxo-ester which had an additional absorption band at 1743 cm.$^{-1}$ characteristic of a keto-group in a five-membered ring. This band must have been due to the new keto-group derived from the original hydroxyl group and the latter must therefore be attached to a five-membered ring. Sodium borohydride preferentially reduced the original, and apparently less hindered, keto-group of the dioxo-ester since the spectrum of the resulting hydroxyoxo-ester (XIXa ; see later) still had the band at 1743 cm.$^{-1}$ but not the band at 1712 cm.$^{-1}$. This compound on dehydration yielded a product which gave acetone on ozonolysis ; hence the familiar retropinacolin rearrangement must have taken place in the dehydration. It follows that the original keto-group is located at $C_{(3)}$ in a typical triterpene ring A.

The structure of the terminal portion of the side chain was indicated by the observation that the action of chloroformic hydrogen chloride on methyl polyporenate C (XVIIIa) yielded an isomer (XVIIIb) which on

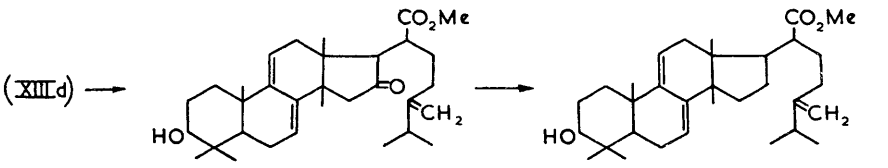
$$\underset{\text{(XVIIIa)}}{R\cdot C(:CH_2)\cdot CHMe_2} \longrightarrow \underset{\text{(XVIIIb)}}{R\cdot CMe{:}CMe_2} \longrightarrow \underset{\text{(XVIIIc)}}{R\cdot COMe + COMe_2}$$

ozonolysis gave acetone and a ketone (XVIIIc).[70] (An alternative formulation of the side chain is possible on this evidence but was eliminated by subsequent findings.)

At this stage the structure and stereochemistry of polyporenic acid C, except for the position and configuration of the hydroxyl group and the configuration of $C_{(17)}$ and $C_{(20)}$, were established by its conversion into

[67] Roth, Saucy, Anliker, Jeger, and Heusser, *Helv. Chim. Acta*, 1953, **36**, 1908.
[68] Halsall and Hodges, *J.*, 1954, 2385.
[69] Birkenshaw, Morgan, and Findlay, *Biochem. J.*, 1952, **50**, 509.
[70] Bowers, Halsall, Jones, and Lemin, *J.*, 1953, 2548.

methyl dehydroeburicoate (XIXb).[70] This was accomplished simply by Wolff–Kishner reduction of the hydroxy-keto-ester (XIXa).

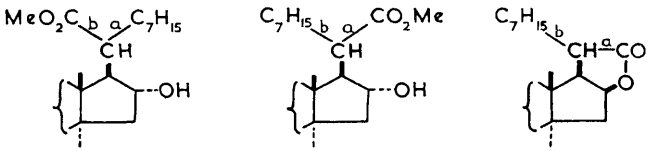


(XIXa) (XIXb)

The location of the hydroxyl group at $C_{(16)}$ was indicated by molecular-rotation differences [70] and was confirmed in several ways, particularly by the isolation of a γ-lactone (XXc) from the action of thionyl chloride on methyl dihydropolyporenate C.[71] (The formation of this lactone involves configurational inversions at $C_{(16)}$ and $C_{(20)}$.) Reduction of a 16-oxo-derivative of polyporenic acid C with lithium aluminium hydride gave two epimeric 16-hydroxy-compounds. Comparison of molecular-rotation differences for these epimers and their acetates with molecular-rotation differences for 16α- and 16β-hydroxy-steroids and their acetates showed that the 16-hydroxy-group in polyporenic acid C has the α-configuration.[71]

If no stereochemical changes occur during the conversion of polyporenic acid C into dehydroeburicoic acid the foregoing evidence establishes that polyporenic acid C has the structure and configuration represented in (XIIId) and can be named 16α-hydroxy-3-oxoeburico-7 : 9(11) : 24(28)-trien-21-oic acid. Since the conversion into dehydroeburicoic acid involved heating with alkali (Wolff–Kishner reduction) possible configurational changes would be inversion at $C_{(17)}$ and at $C_{(20)}$. Inversion at $C_{(17)}$ has been excluded but derivatives of polyporenic acid C can in fact undergo inversion at $C_{(20)}$ on treatment with alkali. However, inversion of the naturally-occurring configuration takes place only when the 16-hydroxyl group is present ; it does not occur with 16-oxo- or 16-deoxy-compounds and so does not occur during the above conversion.[71]

The occurrence of inversion at $C_{(20)}$ is shown in the Wolff–Kishner reduction of methyl dihydropolyporenate C. Of the two isomeric 3-deoxy-



(XXa) (XXb) (XXc)

compounds formed, one (XXa) has the normal $C_{(20)}$-configuration as in eburicoic acid and lanosterol, and the other (XXb) has the *iso*-configuration.

[71] Bowers, Halsall, and Sayer, *J.*, 1954, 3070.

The latter is inherently the less stable and is formed only when there is present the 16-hydroxyl group to stabilise it by hydrogen bonding with the ester group [cf. the formation of the 20-*iso*-lactone (XXc)]. In the normal $C_{(20)}$-configuration such hydrogen bonding would result in close approach of the $C_{(22)}$-methylene group and the $C_{(18)}$-methyl group and consequently does not occur.

Tumulosic Acid ("Polyporenic Acid B").—A difficultly separable mixture ("polyporenic acid B") of tumulosic acid and its dehydro-compound has been isolated from several fungi.[62, 72, 73] The presence of the dehydro-compound in the mixture was shown by its ultraviolet absorption ($\lambda_{max.}$ 243 mμ). Tumulosic acid was obtained in small amount from the mixture and characterised as a dihydroxy-acid containing a vinylidene group and an inert tetrasubstituted double bond.[73] Oxidation of methyl acetyldihydrotumulosate with selenium dioxide yielded the dihydrodehydro-compound. Since this compound could be readily obtained by similar treatment of the "polyporenic acid B" mixture it formed the starting point for further work.[72, 73]

The structures of tumulosic acid and its dehydro-compound were established by relating them, in several ways, to polyporenic acid C and to eburicoic acid. For example, dihydrodehydrotumulosic acid is identical with the 3β : 16α-dihydroxy-compound formed by reduction of dihydro-polyporenic acid C. The location of the vinylidene group was established by the method used with eburicoic acid and also by conversion of the "polyporenic acid B" mixture into a derivative of polyporenic acid C containing the vinylidene group. The evidence thus establishes that tumulosic acid is 16α-hydroxyeburicoic acid, *i.e.*, 3β : 16α-dihydroxyeburico-8 : 24(28)-dien-21-oic acid (XIIIe). The naturally occurring dehydro-compound is very probably the corresponding 7 : 9(11)-diene, *i.e.*, the 3β-hydroxy-compound corresponding to polyporenic acid C.

Pinicolic Acid A and Trametenolic Acid B.[61]—Pinicolic acid A contains a carbonyl group and a reducible double bond. Ozonolysis of its methyl ester yielded acetone and an acidic non-volatile product; therefore it was concluded that the side chain ends in the group ·CH : CMe_2 and that there is no extra carbon atom attached to $C_{(24)}$.

Reduction of the carbonyl group of methyl pinicolate A with sodium borohydride gave a hydroxy-ester, the parent acid of which was identical with trametenolic acid B [74] isolated from another fungus. Dehydration of the dihydro-hydroxy-ester yielded a product which formed acetone on ozonolysis. Hence trametenolic acid B contains a 3β-hydroxyl group in a typical triterpene ring A, and pinicolic acid A is the corresponding 3-oxo-compound. The complete structures of the two acids were established by the above evidence together with the Wolff–Kishner reduction of methyl dihydropinicolate A which yielded, after remethylation of the product, methyl 28-noreburic-8-en-21-oate (XVc; R = CO_2Me). The possibility of

[72] Guider, Halsall, Hodges, and Jones, *J.*, 1954, 3234.
[73] Cort, Gascoigne, Holker, Ralph, Robertson, and Simes, *J.*, 1954, 3713.
[74] Personal communication from Dr. T. G. Halsall.

alkali-catalysed configurational inversion at $C_{(20)}$ during this conversion is eliminated since no such inversion occurs when derivatives of methyl pinicolate A are subjected to vigorous treatment with alkali. Pinicolic acid A is therefore 3-oxolanosta-8 : 24-dien-21-oic acid (XIIIf) and trametenolic acid B is the corresponding 3β-hydroxy-compound.

Pinicolic acid A is accompanied in Nature by a number of other acids and by the corresponding $C_{(21)}$-alcohol, *i.e.*, 21-hydroxy-3-oxolanosta-8 : 24-diene.[74] The identity of the trametenolic acid isolated by Gruber and Proske [75] with the trametenolic acid B from the same fungus is uncertain.

Euphol

Euphol was first isolated pure by Newbold and Spring [76] from euphorbium resin and has since been obtained from several *Euphorbia* species. The initial investigations [76, 77] established *inter al.* that it is a tetracyclic alcohol containing two double bonds, one tetrasubstituted and inert to hydrogenation, and the other present in an *iso*propylidene group. Dehydrogenation yielded 1 : 2 : 8-trimethylphenanthrene. Application of the standard procedures illustrated in formulæ series (III) and (IV) showed that it is a 3β-hydroxy-triterpene with the usual ring A structure.[78]

Evidence that the structure of rings A, B, and C and the location of the inert double bond are the same as in lanosterol was presented by Jeger and his co-workers [78] based on their own results and on the earlier work.[77] Thus a series of oxidation products was obtained corresponding to those formed from lanosterol (formulae V). There were, however, some differences compared with the lanosterol series ; these are mentioned later in connection with the configuration of euphol.

The *iso*octenyl structure of the side chain was established [79] by the same methods as had been used with lanosterol. Ring D was shown to be five-membered by degradative studies (see later) and by an ingenious physical method due to Barton and his collaborators.[80, 53] The light-absorption maxima of euphene and lanostene in the 1380 cm.$^{-1}$ region were identical in intensity. Absorption in this region is due to methyl groups (CH bending), and the equal intensities show that euphene must have the same number (eight) of methyl groups as lanostene. This fact, together with the other structural features already established, left only three carbon atoms not accounted for. Hence ring D could not be more than five-membered.

[75] Gruber and Proske, *Monatsh.*, 1950, **81,** 837, 1024 ; 1951, **82,** 255. Cf. Schmid and Czerny, *ibid.*, 1954, **85,** 1307.

[76] Newbold and Spring, *J.*, 1944, 249.

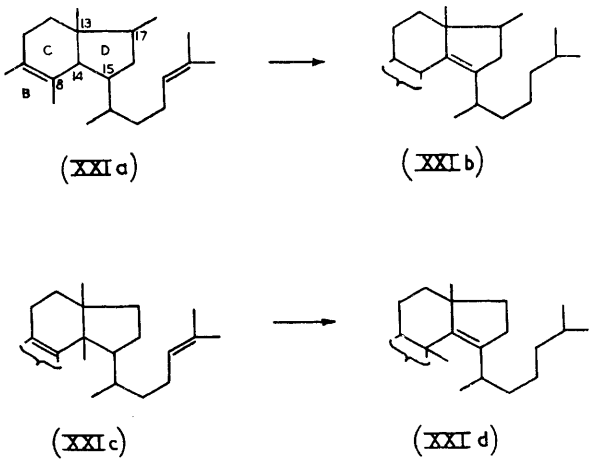
[77] Warren and his co-workers, *Chem. and Ind.*, 1952, 295 ; *J.*, 1951, 2540, and earlier papers ; Jeger and Krüsi, *Helv. Chim. Acta*, 1947, **30,** 2045 ; Roth and Jeger, *ibid.* 1949, **32,** 1620 ; Dupont, Dulou, and Vilkas, *Bull. Soc. chim. France*, 1949, 809, 813 Vilkas, *ibid.*, 1950, 582 ; *Ann. Chim.* (*France*), 1951, **6,** 325.

[78] Christen, Dünnenberger, Roth, Heusser, and Jeger, *Helv. Chim. Acta*, 1952, **35** 1756.

[79] Christen, Jeger, and Ruzicka, *ibid.*, 1951, **34,** 1675 ; Knight and McGhie, *Chem and Ind.*, 1953, 920 ; 1954, 24.

[80] Barton, McGhie, Pradhan, and Knight, *ibid.*, 1954, 1325 ; *J.*, 1955, 876.

It was evident from the foregoing conclusions that euphol differs from lanosterol only in the region of ring D. A major difference became apparent from a study of the acid isomerisation of euphenol (dihydroeuphol).[78, 81] Both lanostenol and euphenol contain a tetrasubstituted double bond at the B/C ring junction and both compounds undergo double-bond migration when they are treated with strong acids. In lanostenol the double bond migrates to the adjacent trisubstituted Δ^7-position (VIa → VIb) but euphenol forms a compound, *iso*euphenol, in which the double bond is in a new tetrasubstituted position. The structure and mode of formation of *iso*euphenol became the central feature in the final phase of the euphol problem. It was concluded that the double bond of *iso*euphenol is located in ring D ;[78, 81] consequently it seemed likely that the acid isomerisation of euphenol proceeds in the same way as with the " classical " Δ^8-steroids. These are converted into $\Delta^{8(14)}$- and Δ^{14}-isomers [26] in contrast to lanostenol in which the $C_{(14)}$-methyl group prevents double-bond migration into ring D. This consideration led to the provisional formula (XXIa) for euphol, with a hydrogen atom attached to $C_{(14)}$ (the location of the groups in ring D was suggested by the isoprene rule).[78] On this formulation *iso*euphenol would



(XXIa) (XXIb)

(XXIc) (XXId)

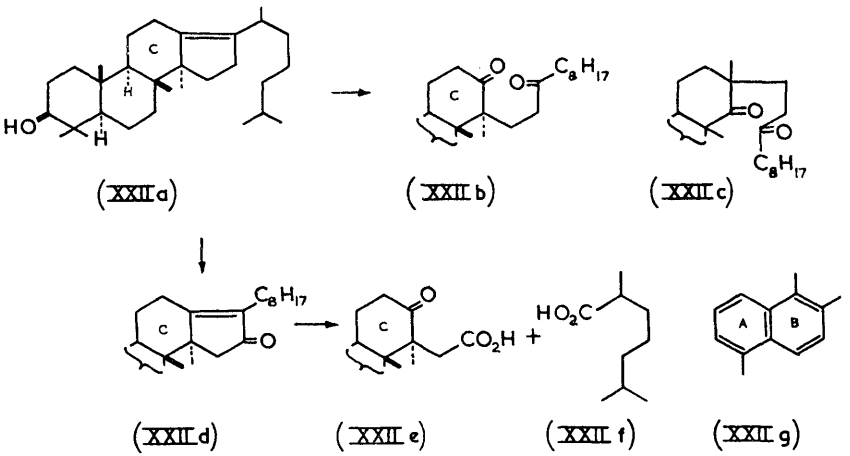
be (XXIb). Formula (XXIa) was not, however,[78] in accordance with the formation of 1 : 2 : 8-trimethylphenanthrene on dehydrogenation, which indicated that methyl groups were attached to both $C_{(13)}$ and $C_{(14)}$ and, together with biosynthetical considerations, led to the suggestion that euphol might have formula (XXIc) or be 14-*iso*lanosterol.[3] In these cases the structures postulated contain a $C_{(14)}$-methyl group and the formation of *iso*euphenol would involve migration of this methyl group ; thus if euphol were (XXIc) *iso*euphenol would be (XXId).

The conclusion [80, 82] that euphol has in fact the structure (Ii), *i.e.*,

[81] Dawson, Halsall, and Swayne, *J.*, 1953, 590.

[82] Arigoni, Viterbo, Dünnenberger, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1954, **37**, 2306.

13-*iso* : 14-*iso* : 17-*iso*(?)-lanosterol, followed from the establishment of structure (XXIIa) for *iso*euphenol. The isomerisation of euphenol thus involves the migration of two methyl groups. The structure (XXIIa) of *iso*euphenol was deduced from several lines of evidence, particularly the



(XXIIa) (XXIIb) (XXIIc)

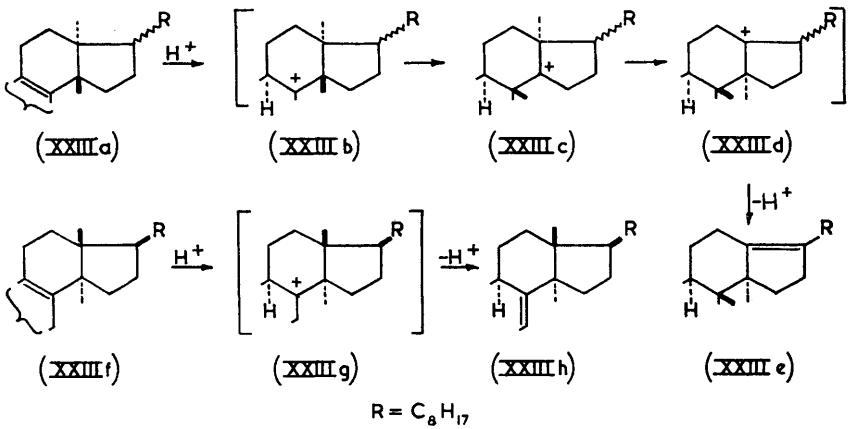
(XXIId) (XXIIe) (XXIIf) (XXIIg)

elimination of the most likely alternative (XXId). It had previously been found [78] that oxidative fission of the double bond of *iso*euphenol yields a diketone, to which the structure (XXIIb) was assigned [80] rather than the alternative structure (XXIIc ; corresponding to XXId) on the basis of the relatively unhindered nature of both carbonyl groups, reaction with five instead of three moles of bromine, and the spectroscopic detection of two $\cdot CH_2 \cdot CO \cdot$ groups. The establishment of this structure for the diketone leads to elucidation of the structure of ring D of *iso*euphenol. The same conclusion was also reached [82] from further degradative evidence, in particular from a study of the oxidation of *iso*euphenyl acetate with *tert.*-butyl chromate. This oxidation yielded *inter al.* the $\alpha\beta$-unsaturated ketone (XXIId) which on ozonolysis formed the C_{21} keto-acid (XXIIe) and optically pure D(−)-2 : 6-dimethylheptanoic acid (XXIIf). It was shown that these and other degradation products could be formed only from the structure (XXIIa) and not from (XXIb) or (XXId).

These results established the structure of ring D of *iso*euphenol and furthermore showed that the five angular methyl groups must be located in rings A, B, and C. Evidence for the presence of a methyl group at $C_{(8)}$ was provided by dehydrogenation experiments.[80] In the same conditions in which euphadiene (deoxyeuphol) yielded 1 : 2 : 8-trimethylphenanthrene, *iso*euphadiene yielded 1 : 2 : 5-trimethylnaphthalene (XXIIg). Methylnaphthalenes, originating from rings A and B, are typical products of the dehydrogenation of pentacyclic triterpenes which have a methyl group at $C_{(8)}$. (It seems likely that the fission of the molecule, with consequent formation of methylnaphthalenes, in the case of *iso*euphadiene and the pentacyclic triterpenes is due to the presence of a $C_{(8)}$-methyl group whereas

the absence of this group in the normal tetracyclic triterpenes may allow the formation of methylphenanthrenes.)

The establishment of structure (Ii) for euphol is based on the dehydrogenation evidence for the presence of the $C_{(13)}$- and $C_{(14)}$-methyl groups, the proof of the attachment of the side chain at $C_{(17)}$ (in *iso*euphenol), and the rearrangement to *iso*euphenol (XXIIIe). This rearrangement can be satisfactorily explained as a concerted double methyl-group migration, each migration being a 1 : 2-shift or Wagner–Meerwein type (XXIIIb ⟶ XXIIIc ⟶ XXIIId).[80, 82] The occurrence and nature of this rearrangement and the absence of a similar rearrangement in the lanosterol series [see XXIIIf ⟶ (lanostenol) ⟶ XXIIIg ⟶ XXIIIh (*iso*lanostenol)] gave the key to the configuration of the C/D ring junction in euphol.[80, 82] Lanostenol (XXIIIf) has an α-methyl group at $C_{(14)}$ and does not undergo the rearrangement (if it did the result would be an unfavourable configuration at the B/C ring junction). Hence it can be concluded that the $C_{(14)}$-methyl group of



euphenol (XXIIIa) must be β-oriented. Furthermore the rearrangement would be greatly facilitated (and may only occur) if the two methyl migrations are concerted. For this to be so it is probably necessary that the two methyl groups be *trans*. Hence the $C_{(13)}$-methyl group is probably α and the C/D ring junction *trans*. Barton, McGhie, Pradhan, and Knight [80] envisage a " conformational driving force " for the rearrangement, on the grounds that *iso*euphenol contains less steric strain than euphenol. The conclusions concerning the orientations of the $C_{(13)}$- and the $C_{(14)}$-methyl group are substantiated by the explanations they provide for the different course of some reactions in rings B and C of the euphol series compared with the lanosterol series.[80]

The configuration of the side chain at $C_{(17)}$ has not been proved ; Ruzicka and his co-workers [82] favour an α-configuration on the basis of the concerted mechanism for the *iso*euphenol rearrangement. The isolation of D-(—)-2 : 6-dimethylheptanoic acid (XXIIf) from degradation of *iso*euphenol establishes that $C_{(20)}$ in euphol has the same configuration as in the steroids

(and lanosterol) which have been correlated with D-glyceraldehyde.[6] The configuration of ring A (*i.e.*, of the asymmetric centres $C_{(3)}$, $C_{(5)}$, and $C_{(10)}$) is indicated to be the same as in lanosterol and cholesterol by molecular-rotation differences [78, 80] and by the asymmetric-synthesis method.[40] Thus euphol appears to be identical with lanosterol in rings A, B, and C; this has not yet been proved by any direct correlation.

The structure of *iso*euphenol and its formation by a double methyl-group migration are of considerable interest in connection with suggested schemes of biosynthesis of triterpenes and sterols from squalene.[3, 82] *iso*-Euphenol conforms to the isoprene rule and appears to have the same structure and configuration in rings A, B, and C as the pentacyclic triterpenes.

The Elemi Acids

Manila elemi resin, which is used in varnish manufacture, contains two acidic tetracyclic triterpenes, elemolic acid (hydroxyelemadienic acid, α-elemolic acid) and the corresponding keto-acid, elemonic acid (oxo-elemadienic acid, β-elemonic acid). These acids were the first tetracyclic triterpenes to be intensively studied. Nevertheless their structures were not elucidated until after the structures of most of the other tetracyclic triterpenes had been established in detail; the final clarification came from a correlation with tirucallol and thence with euphol. Earlier, much confusion was caused by the isolation of mixtures which were regarded as pure compounds, by the formation of epimers, and particularly by an apparent double-bond migration which was in fact the partial formation of conjugated dehydro-compounds during oxidation. It is now known that the elemi acids are accompanied in Nature by small amounts of their corresponding dehydro-compounds.[83]

The early work [84] established the presence of two double bonds, one in an *iso*propylidene group and the other inert to hydrogenation. Selenium dehydrogenation yielded 1 : 2 : 8-trimethylphenanthrene. Oxidation with chromic acid gave a yellow ene-1 : 4-dione and oxidation with selenium dioxide gave a dehydro-compound, with $\lambda_{max.}$ 238 mμ. Reduction of elemonic acid with sodium and alcohol yielded *epi*elemolic (β-elemolic acid). It was later found [83] that this is a 3β-hydroxy-compound and that the naturally occurring elemolic acid has a 3α-hydroxyl group.

It was concluded in the early work that the carboxyl group of elemolic acid was tertiary as in the pentacyclic triterpene acids then being investigated. Evidence for this was the hindered nature of the group, shown particularly in the difficulty of hydrolysis of the esters. However, it was later found [85] that the group is in fact secondary. The location of the carboxyl group in the side chain and the structure of the latter were indicated

[83] Halsall, Meakins, and Swayne, *J.*, 1953, 4139.

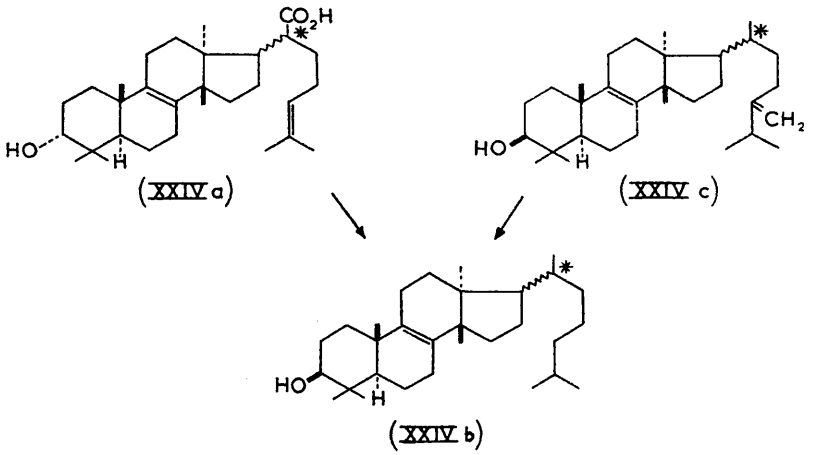
[84] Summarised by Ruzicka, Rey, Spillmann, and Baumgartner, *Helv. Chim. Acta*, 1943, **26**, 1638, and in Elsevier's "Encyclopædia of Organic Chemistry", Vol. 14, p. 598; Vol. 14S, p. 1203S.

[85] Arnold, Koller, and Jeger, *Helv. Chim. Acta*, 1951, **34**, 555; Mazur, Koller, Jeger, and Ruzicka, *ibid.*, 1952, **35**, 181.

by an oxidative fission at a position adjacent to the carboxyl group yielding 4-methylpentanoic acid.[85]

In 1953 Halsall, Meakins, and Swayne [83] put forward evidence from the early work, supplemented by spectroscopic data, that the structure of rings A, B, and C and the location of the inert double bond are the same in elemolic acid as in the other tetracyclic triterpenes. Furthermore, elemolic acid appeared to belong to the euphol group. These views were held also by Ruzicka and his co-workers.[86]

The final stage in the elucidation of the structure of elemolic acid, *i.e.*, the proof of the structure and configuration of ring D, consists of its correlation with tirucallol and the subsequent proof of the structure of that compound. Tirucallenol (dihydrotirucallol) is identical [87] with the long-known compound, *epi*elemenol, which had been prepared from *epi*elemenolic (dihydro*epi*elemolic) acid by conversion of the carboxyl into a methyl group. Tirucallenol has the structure and configuration (XXIVb); it follows from this and the conclusions described above that elemolic acid is (XXIVa). The possibility of configurational inversion at $C_{(20)}$ during the conversion of (XXIVa) into (XXIVb) has been excluded.[88]



(XXIVa) *Elemolic acid.* (XXIVb) *Tirucallenol.* (XXIVc) *Euphorbol.*

* The configuration of $C_{(20)}$ is opposite to that in euphol, lanosterol, and cholesterol. The configuration of $C_{(17)}$ has not yet been proved.

Tirucallol

Tirucallol was first isolated by Haines and Warren ;[89] it is a tetracyclic alcohol containing two double bonds, one present in an *iso*propylidene group and the other inert to hydrogenation. Subsequent work by Warren and

[86] Cf. Kyburz, Mijović, Heusser, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1952, **35**, 2073.
[87] Arigoni, Wyler, and Jeger, *ibid.*, 1954, **37**, 1553.
[88] Arigoni, Jeger, and Ruzicka, *ibid.*, 1955, **38**, 222.
[89] Haines and Warren, *J.*, 1949, 2554.

his collaborators [90] showed the similarity of tirucallol to other tetracyclic triterpenes, *e.g.*, by the formation of an ene-1 : 4-dione and a dehydro-compound.

Following the elucidation of ring D of euphol and the discovery (see earlier) that tirucallenol is identical with *epi*elemenol, the same degradation method was applied to tirucallol [88] as had been used with euphol. Treatment of tirucallenol with strong acid caused an isomerisation to *iso*tirucallenol, analogous to the isomerisation of euphenol. Oxidation of *iso*tirucallenol (stereoisomeric at $C_{(20)}$ with XXIIa) formed an $\alpha\beta$-unsaturated ketone (stereoisomeric with XXIId) which on ozonolysis yielded the keto-acid (XXIIe) identical with that obtained from euphol, and L-(+)-2 : 6-dimethylheptanoic acid, *i.e.*, the enantiomorph of the 2 : 6-dimethylheptanoic acid (XXIIf) obtained from euphol. These results clearly establish that *iso*tirucallenol differs from *iso*euphenol only in the configuration of $C_{(20)}$. Also, since the formation of *iso*tirucallenol is analogous to the formation of *iso*euphenol, there can be little doubt that the structure of tirucallol and the configuration of the C/D ring junction is the same as in euphol. On the same grounds Arigoni, Jeger and Ruzika [88] consider that the configuration of $C_{(17)}$ is the same in tirucallol as in euphol and conclude that tirucallol is 20-*iso*euphol. It has been suggested, however, that molecular-rotation differences indicate that tirucallol and euphol do differ in configuration at $C_{(17)}$.[91] Recently Arigoni *et al.*[92] have announced the conversion of *epi*elemolic acid into euphol by a method involving inversion at $C_{(20)}$. This conversion apparently establishes that elemolic acid and tirucallol both have the same configuration at $C_{(17)}$ as euphol.

At the XIVth International Congress of Pure and Applied Chemistry, held in July 1955, an ingenious correlation of tirucallol with lanosterol was described by the Zurich group. Both compounds were submitted to an identical series of reactions which destroyed the asymmetry at $C_{(3)}$, $C_{(5)}$, and $C_{(10)}$ but left intact the asymmetry at $C_{(13)}$, $C_{(14)}$, $C_{(17)}$, and $C_{(20)}$. The product obtained from tirucallol was the enantiomorph of the product from lanosterol. Hence tirucallol is 13-*iso* : 14-*iso* : 17-*iso* : 20-*iso*-lanosterol. In view of the previous work already mentioned, it appears that this result also establishes that the configuration at $C_{(17)}$ in euphol is opposite to that in lanosterol.

Euphorbol

Euphorbol has been isolated from a number of *Euphorbia* species and was first characterised as a tetracyclic alcohol by Newbold and Spring.[76] Warren and his collaborators [93] found that it resembles the other triterpenes of the euphol group in the formation of an ene-1 : 4-dione and a dehydro-compound but, by contrast, it contains the reducible double bond in a

[90] Warren and his co-workers, *J.*, 1950, 1562; 1951, 2534, 2540.

[91] Barbour, Lourens, Warren, and Watling, *Chem. and Ind.*, 1955, 226; *J.*, 1955, 2194.

[92] Ref. 88, footnote, p. 226.

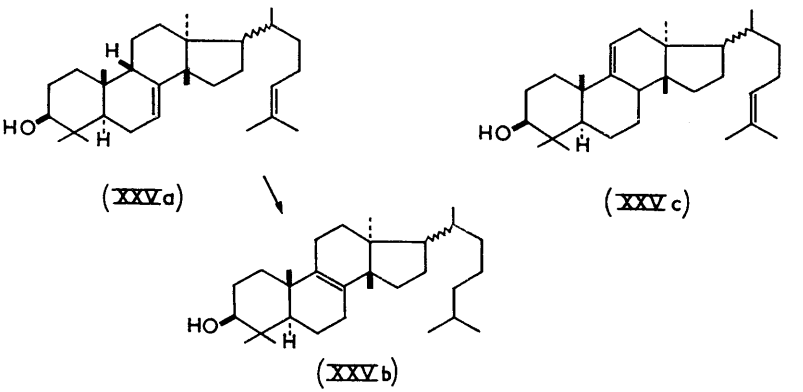
[93] Warren and his co-workers, *J.*, 1951, 2537, 2540.

vinylidene group. These observations were confirmed by Ruzicka and his co-workers [94] who subsequently found that the ketonic ozonolysis product of euphorbol yields tirucallenol (XXIVb) on Wolff–Kishner reduction.[87] This conversion revealed that euphorbol is a C_{31} compound and established the structure (XXIVc) except for the location of the extra carbon atom. By analogy with the fungal acids this is assumed to be at $C_{(24)}$ and this assumption has been shown to be correct.[91]

Butyrospermol

Butyrospermol was discovered [95] in attempts to re-isolate the presumed tetracyclic triterpene, " basseol ", from shea-nut fat. The reputed cyclisation of " basseol " to β-amyrin aroused considerable interest but it is now known [96] that " basseol " was, in fact, a mixture of butyrospermol and β-amyrin.

Butyrospermol contains a reducible double bond present in an *iso*propylidene group and an inert double bond, originally thought to be tetrasubstituted but now known to be trisubstituted.[96] Brief treatment of the dihydro-derivative with strong acid yields dihydro*iso*butyrospermol,[97] and much of the structure was established when it was found [96, 98] that



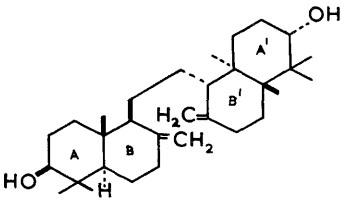
this compound is identical with dihydroeuphol (XXVb). Structures (XXVa) and (XXVc) are compatible with this and other evidence ;[96, 98] the former (XXVa), which has the $C_{(9)}$-hydrogen atom in the β-configuration, is preferred [96] because of similarities between the molecular-rotation differences of butyrospermol and those of *cyclo*artenol, which is known to have a β-substituent at $C_{(9)}$.

[94] Vogel, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1952, **35**, 510.
[95] Heilbron, Jones, and Robins, *J.*, 1949, 444 ; Seitz and Jeger, *Helv. Chim. Acta*, 1949, **32**, 1626.
[96] Dawson, Halsall, Jones, Meakins, and Phillips, *Chem. and Ind.*, 1955, 918.
[97] Dawson, Halsall, Jones, and Robins, *J.*, 1953, 586.
[98] Irvine, Lawrie, McNab, and Spring, *Chem. and Ind.*, 1955, 626.

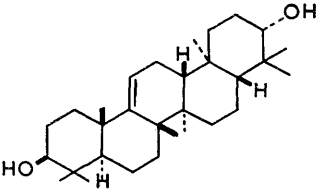
Onocerin

Recently a new type of tetracyclic structure has been discovered in the triterpene diol, onocerin, by Barton and Overton.[99] Earlier work [100] on this compound, which was first isolated a century ago, indicated that it contains two double bonds, both present in vinylidene groups. The structure (XXVIa) was established by Barton and Overton on the basis of (*a*) dehydrogenation evidence, (*b*) proof of the presence of two $\cdot CH_2 \cdot CH_2 \cdot CH(OH) \cdot CMe_2 \cdot$ groupings (in the A and the A′ ring) and two $\cdot CH_2 \cdot C(:CH_2) \cdot CH <$ groupings (in the B and B′ rings) and (*c*) proof of the equivalence of the two hydroxyl groups and the complete symmetry of the molecule. The stereochemistry was deduced from conformational and molecular-rotation evidence.

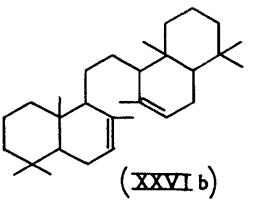
Onocerin may be included with ambrein (If) and squalene (Ig) in the "squalenoid" group of triterpenes; its structure is of great interest in connection with theories of the biosynthesis of triterpenes from squalene. Ruzicka [3] has suggested that the formation of the steroids and the usual pentacyclic and tetracyclic triterpenes involves cyclisation of squalene starting from one end only of the molecule, consequent upon the attack of an electrophilic hydroxyl group at $C_{(3)}$. On the other hand, ambrein, and now more clearly onocerin, may be formed by cyclisation proceeding from both ends of the molecule, as presumably occurs in the acid-catalysed cyclisation of squalene to tetracyclosqualene (XXVIb).



(XXVIa)



(XXVIc)



(XXVIb)

(XXVIa) *Onocerin.* (XXVIb) *Tetracyclosqualene.* (XXVIc) "*γ*"-*Onocerin.*

In the earlier work [100] onocerin was found to be isomerised by the action of concentrated acid. Barton and Overton obtained in this way a pentacyclic isomer, "*γ*"-onocerin, for which they propose the structure (XXVIc) partly on the basis of an ingenious proof of the high degree of symmetry

[99] Barton and Overton, *Chem. and Ind.*, 1955, 654; *J.*, 1955, in press.

[100] Summarised in Elsevier's "Encyclopædia of Organic Chemistry", Vol. 14, pp. 608, 1313S.

of the molecule. "γ"-Onocerin is the first known representative of a class of pentacyclic triterpenes predicted by Ruzicka.[3] Its carbon skeleton and configuration in rings A–D are the same as in the major classes of pentacyclic triterpenes ; the occurrence of an oxygenated substituent at $C_{(21)}$ is unusual, only one other example being known.[101]

[101] Djerassi and Lippman, *J. Amer. Chem. Soc.*, 1955, **77**, 1825.