THESIS

submitted to

THE UNIVERSITY OF GLASGOW

in fulfilment of the

requirements for the

DEGREE OF DOCTOR OF PHILOSOPHY

by

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SEPTEMBER, 1958

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ACKNOWLEDGEMENT

The author desires to record to Professor F. S. Spring, F.R.S., F.R.S.E., his sincere thanks for his keen interest and helpful guidance during the course of this work.

THE CHEMISTRY OF SOME TETRACYCLIC TRITERPENOIDS.

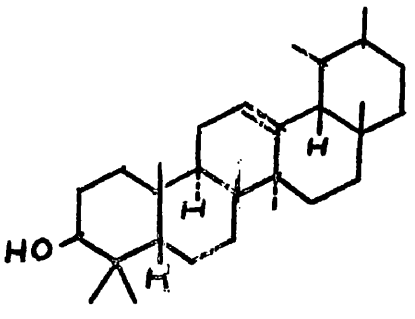
C O N T E N T S

HISTORICAL

INTRODUCTION

The triterpenoids were originally defined as a group of naturally occurring compounds containing thirty carbon atoms, the molecules of which may be considered to be formed from six isoprene units linked in a regular or irregular arrangement. The triterpenoid class of compounds may conveniently be divided into groups according to the number of rings contained in their carbocyclic structures.

(1) The pentacyclic triterpenoid group, comprising over fifty compounds all of which are of vegetable origin, is by far the largest of the groups. Five sub-groups, represented by α-amyrin (I), β-amyrin (II), lupeol (III), taraxasterol (IV) and hydroxyhopanone (V), accommodate the members of this class which conform to the classical isoprene rule. Phyllanthol (VI), a



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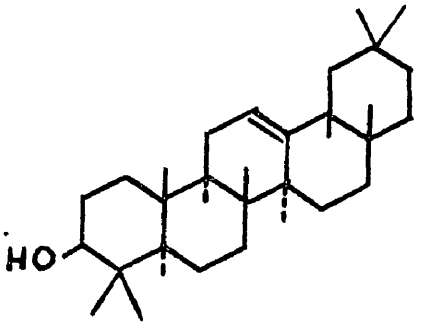

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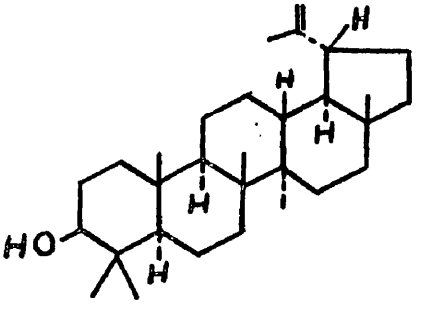

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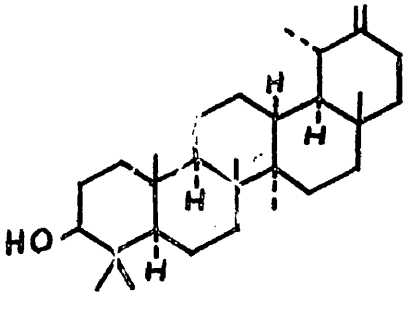

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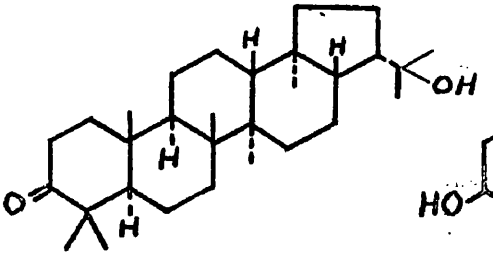

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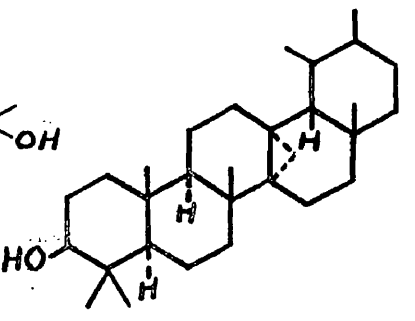
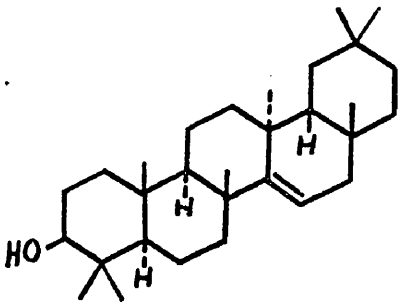


(VI)

hexacyclic triterpenoid containing a cyclopropane ring, can be classified as a member of the α-amyrin sub-group. Further sub-groups which include members clearly related in a biogenetic sense to the β-amyrin sub-group are exemplified by taraxerol (VII), glutinone (alnusenone) (VIII) and friedelin (IX).



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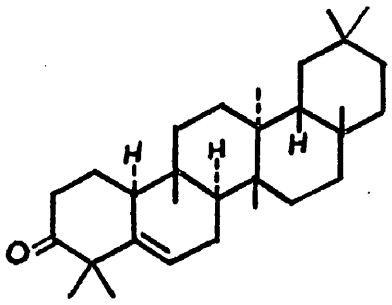

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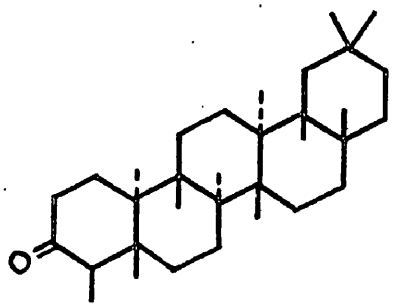
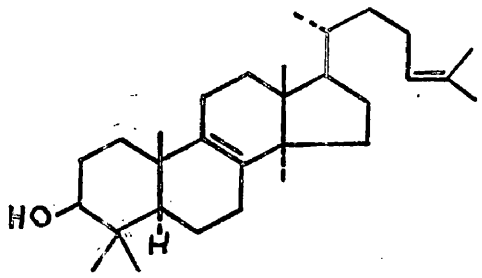
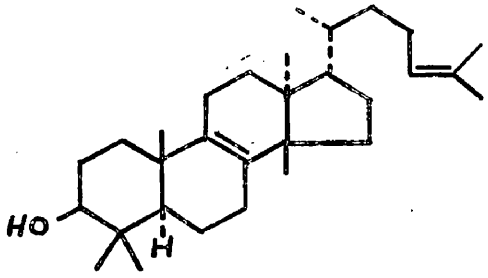


(IX)

(2) Members of the smaller tetracyclic group of triterpenoids are found in plants, wood-rotting fungi and in sheep wool-wax, the only known animal source. The tetracyclic triterpenoids possess the perhydro-1:2-cyclopentenophenanthrene ring system of the steroids and may be regarded as tri- or tetramethyl steroids. Members of this group can be further classified into two sub-groups typified by lanosterol (X) and euphol (XI). Although the compounds in this group do not obey the isoprene rule, it is now known that they obey the "biogenetic isoprene rule"[1].



(X)



(XI)

cycloArtenol, cyclolaudenol, cyclocrysterol and cycloeucalenol, pentacyclic triterpenoids containing a cyclopropane ring, may also be included in the lanosterol sub-group.

(3) Ambrein, a tricyclic alcohol, squalene, an acyclic hydrocarbon, and the diol, onocerin, can be included in the "squalenoid" group of triterpenoids.

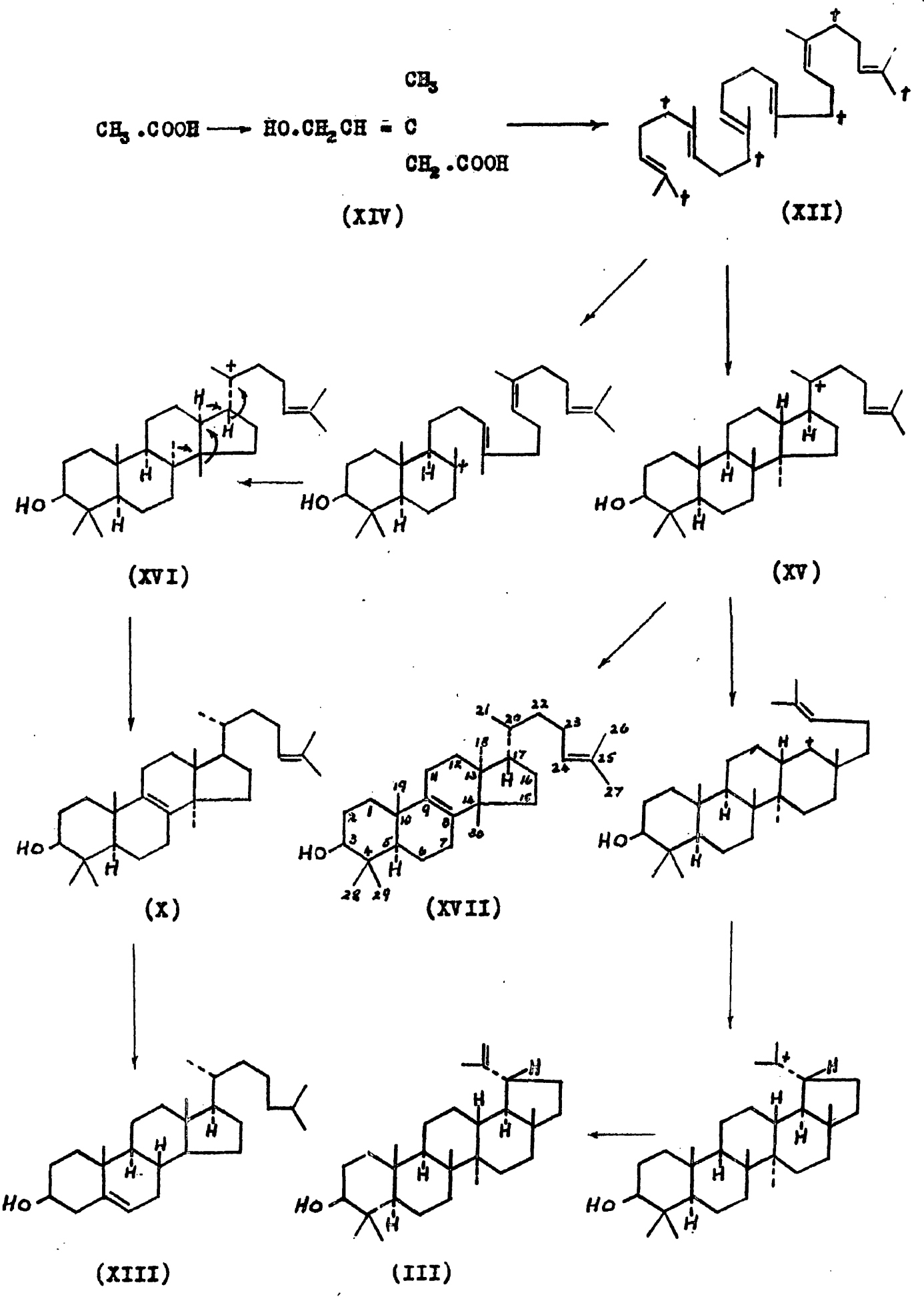
The triterpenoids and steroids are now believed to originate by cyclisation processes from squalene (XII) which has been shown[2] to possess the fully transoid arrangement necessary for the biosynthesis of the steroids and triterpenoids with their particular stereochemistry. It was first shown[4-8] that acetic acid is the precursor of squalene and hence of lanosterol and cholesterol (XIII). In 1956, Skeggs, et al.[3] isolated the lactone of mevalonic acid (XIV) from the incubation mixture for the growth of Lactobacillus acidophilus and showed that this lactone could replace acetic acid as a growth factor. Tavormina, et al.[12(b)] and Cornforth, et al.[12(a)] subsequently found that DL-mevalonic acid was a precursor in the biogenesis of squalene, lanosterol and cholesterol and by using DL-mevalonic acid labelled with ^{14}C at position $C_{(2)}$, they found that 42% of the isotopic carbon was incorporated into the squalene and the cholesterol. By means of degradation experiments on cholesterol[12(c)] and squalene[12(d)], biosynthetically prepared from ^{14}C-labelled mevalonic acid, six ^{14}C-carbon atoms were detected (at the positions marked + in

squalene (XII)], so that six mevalonic acid units must be utilisted in the biosynthesis of one molecule of squalene. The six-carbon molecule of mevalonic acid must therefore in the process of its self condensation, lose one carbon atom to give an intermediate isoprenoid unit. The high efficiency of the conversion of DL-mevalonic acid to squalene (42%) and the observation that about 10% carbon dioxide originally present as the $C_{(1)}$-carboxyl group, is liberated during the process, support the intermediation of an isoprenoid unit.

The cyclisation of squalene takes place by a synchronous process[9,10] which is considered to be motivated by the attack of a cation, for example OH^+, derived from molecular oxygen[9,10], at position $C_{(3)}$[1,9,10,11a-d]. Two different paths are then followed. In the first, the carbonium ion (XV), which is considered to be the precursor of the pentacyclic triterpenoids and of the euphol-tirucallol group at tetracyclic triterpenoids, is formed, while in the second, the isomeric carbonium ion (XVI) which leads to the formation of members of the steroid and lanosterol groups, is produced. These reactions are formulated below and they illustrate the biogenesis of lanosterol (X) cholesterol (XIII), tirucallol (XVII) and lupeol (III) from acetic acid.

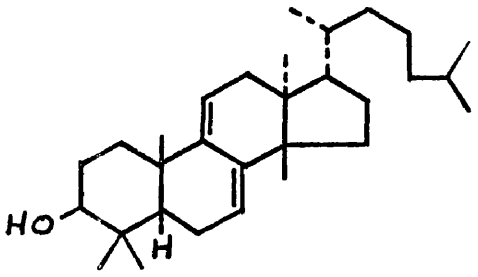
The additional carbon atom at $C_{(24)}$ in eburicoic acid[13] and in ergosterol[14] has been shown to be derived from formate.

Since this work is concerned only with compounds of the tetracyclic group of triterpenoids, a historical review of the pentacyclic triterpenoids is excluded.

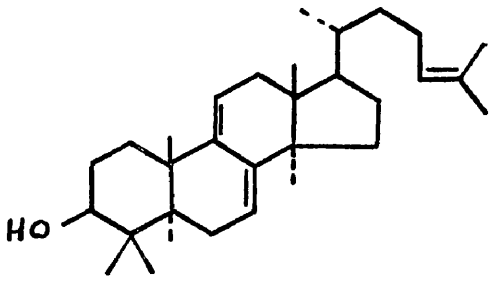

CH3 .COOH ⟶ HO.CH2CH = C
CH3
CH2 .COOH
(XIV)
(XII)
(XVI)
(XV)
(X)
(XVII)
(XIII)
(III)

THE CLASSIFICATION OF THE TETRACYCLIC TRITERPENOIDS.

The members of the tetracyclic group of triterpenoids may be sub-divided into two series typified by lanosterol (X) and euphol (XI)[15]. Members of each of these series undergo reactions characteristic of their particular sub-group. Thus, in the euphol series, the formation of the conjugated $\Delta^{7:9(11)}$-diene (XVIII) from a Δ^{8}-ene parent is accompanied by a very large negative change in molecular rotation, while in the lanosterol series the same conversion results in a positive change. The conjugated $\Delta^{7:9(11)}$-dienes of the two series also exhibit differences in their light absorption. In the euphol group, the heteroannular dienes have typical maxima at ca. 2320, 2390 and 2470 Å., whereas in the lanosterol series these maxima are at ca. 2370, 2440 and 2510 Å. The influence of mineral acid



(XVIII)



(XIX)

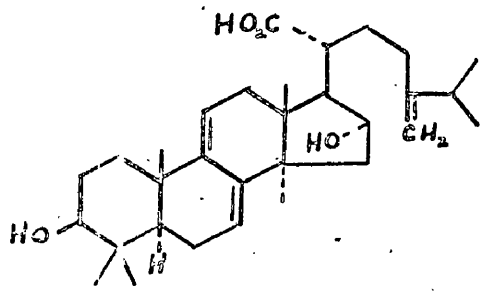
on the Δ^{8}-double bond is equally characteristic for each series. Acid isomerisation of euph-8-enol results in a molecular rearrangement in which the double bond migrates to the $\Delta^{13(17)}$-position, whereas similar treatment of lanost-8-enol produces an equilibrium mixture of the Δ^{7}- and Δ^{8}-isomers.

THE LANOSTEROL GROUP.

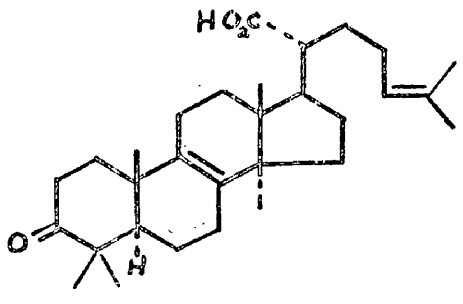
The following naturally occurring compounds are members of the lanosterol series: lanosterol, lanostenol, agnosterol, dihydroagnosterol, eburicoic acid, polyporenic acids A and C, tumulosic acid, pinicolic acid A, cycloartenol, cyclolaudenol, cycloorysterol, cycloeucalenol and parkeol.

Lanosterol [Lanosta-8:24-dien-3β-ol, (X)] and agnosterol [lanosta-7:9(11):24-trien-3β-ol, (XIX)] were first isolated by Windaus and Tschesche[16] from the "isocholesterol" mixture obtained from sheep wool wax. The corresponding dihydro derivatives, lanostenol and dihydroagnosterol (X and XIX with the side-chain double bond reduced) were subsequently obtained from the same source by Ruzicka.[17] Lanosterol itself has also been isolated from yeast sterols[18] and from one plant source.[19]

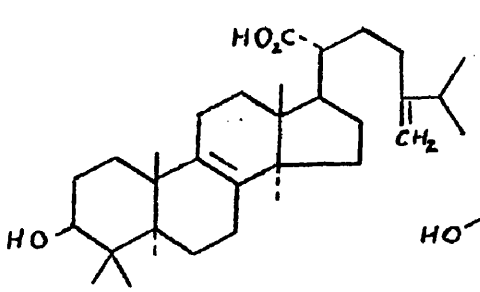
The acid members of this group are produced by the metabolism of wood-rotting fungi, in particular those of the Basidiomycetes and Polyporus classes. The structures of those fungal acids which have been fully elucidated are formulated below. Tumulosic acid and eburicoic acid occurs in certain instances together with their corresponding dehydroderivatives which are related to them in the same way as agnosterol is to lanosterol.



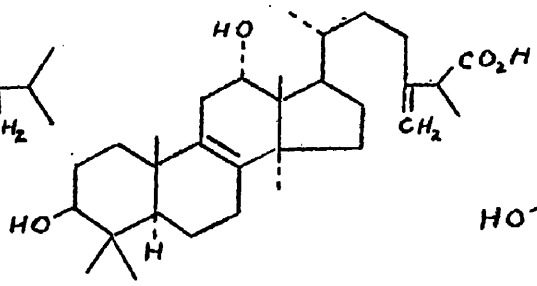
Polyporenic acid C[22,26,27]



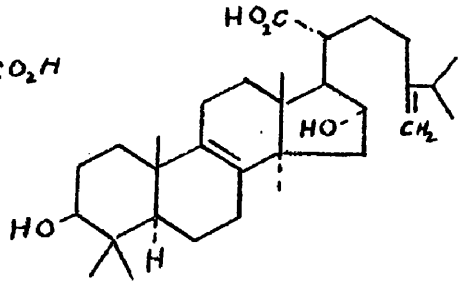
Pinicolic acid A[28]



Eburicoic acid[20,21]



Polyporenic acid A[22,23]



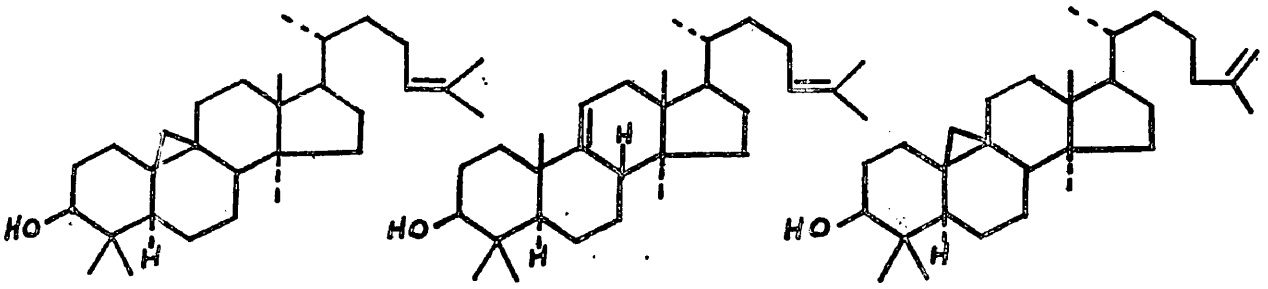
Tumulosic acid[22,24,25]

Parkeol, a minor constituent of the non-saponifiable matter of shea-nut fat from the tree Butyrospermum parkii[29a,29b], has been identified as lanosta-9(11):24-dien-3β-ol (XX)[30].

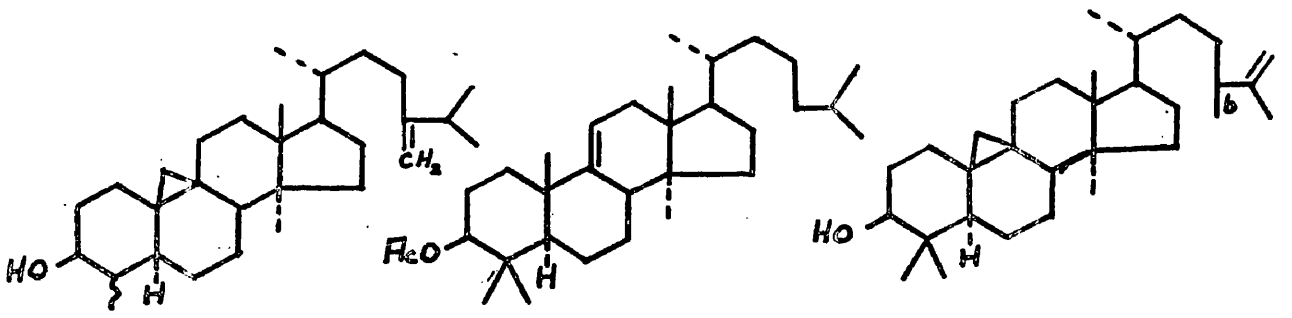
The remaining members of this series have all been shown to possess a 9:19-cyclopropane ring on the basis of chemical and spectroscopic evidence.

cycloArtenol (XXI), and the corresponding ketone, cycloartenone, can be isolated from the fruits of Artocarpus integrifolia[31]. The alcohol has subsequently been obtained from Euphorbia balsamifera[32], S. nux vomica seed fat[33], and as its ferulic acid ester from Japanese rice-bran oil[34]. Handianol,[35] an alcohol isolated from Euphorbia handiensis is identical with cycloartenol. Barton[31] demonstrated the presence of a cyclopropane ring and an isopropylidene group in cycloartenol. Spring[33] found that lanost-9(11)-enyl acetate (XXV) is the main product of the acid isomerisation of cycloartanyl acetate and later concluded,[36] on the basis of experiments in which deuterium

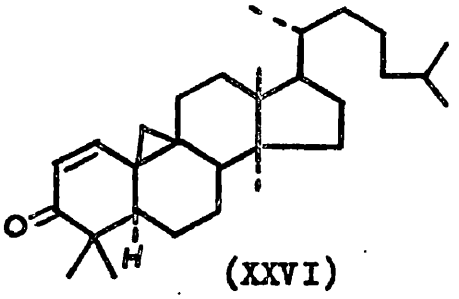
chloride was employed, that the cyclopropane bridge extends from $C_{(9)}$ to $C_{(19)}$. Structure (XXI) was confirmed by the preparation of the conjugated cycloart-1-en-3-one (XXVI)[36], the ultraviolet absorption of which (λ = 2060 and 2690 Å) is characteristic of



(XXI) (XX) (XXII)



(XXIV) (XXV) (XXIII)



(XXVI)

the chromophore. The same conclusion as to the structure of cycloartenol was reached by Barton[37].

cycloOrysterol (XXII), originally named β-tritisterol and β-orysterol, has been isolated as its ferulate from rice-bran oil by Japanese workers[34,38] and shown to be 9:19-cyclolanost-25--en-3β-ol (XXII), a double bond isomer of cycloartenol.

cycloLaudenol (XXIII) was isolated by Spring and his co-workers[39] in 1955 from opium marc. It was shown to differ from cycloartenol only in the constitution of the side-chain which possessed an extra carbon atom in a methyl group at $C_{(24)}$. From a study of molecular rotation data this methyl group was shown to have the same configuration as that found in ergostane and eburicane, and cyclolaudenol was thus formulated as 24b-methyl-9:19-cyclolanost-25-en-3β-ol (XXIII).

cycloEucalenol was isolated by King from tallow wood, Eucalyptus microcorys,[40] and has subsequently been isolated in these laboratories from the timber known as Borneo White Seraya. King[41] has shown that cycloeucalenol has the structure (XXIV).

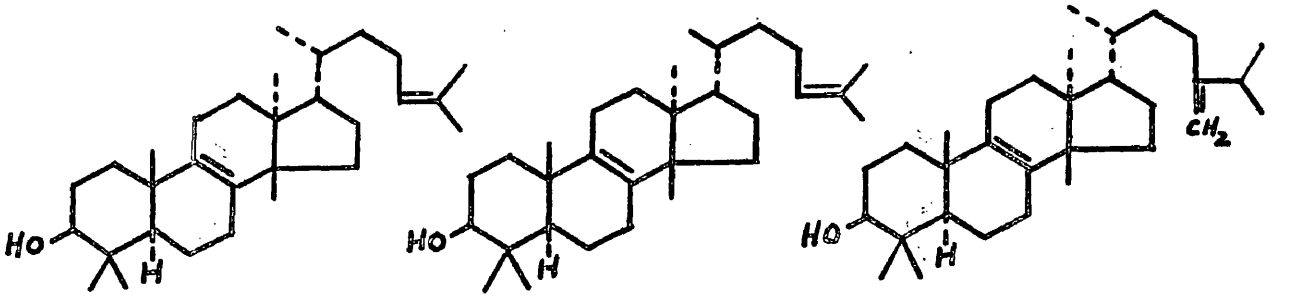
THE EUPHOL GROUP

The following natural products are members of this group: Euphol, tirucallol, euphorbol, butyrospermol, elemadienolic acid, elemadienonic acid, masticadienonic acid and the dammar resin triterpenoids.

Euphol (Eupha-8:24-dien-3β-ol, XI) was isolated by Newbold and Spring[42] from a Euphorbia resin and has since been found to occur in many plants of this species. The complete structure and stereochemistry of euphol was shown by Barton and his colleagues[43] to be as represented by (XI).

Tirucallol was isolated from Euphorbia tirucalli L. by Haines and Warren[44], and has subsequently been obtained from E. triangularis[45] and gum mastic[46]. Various oxidative and

degradative reactions have shown that it is 20-isoeuphol (XVII)[47-54, 104].



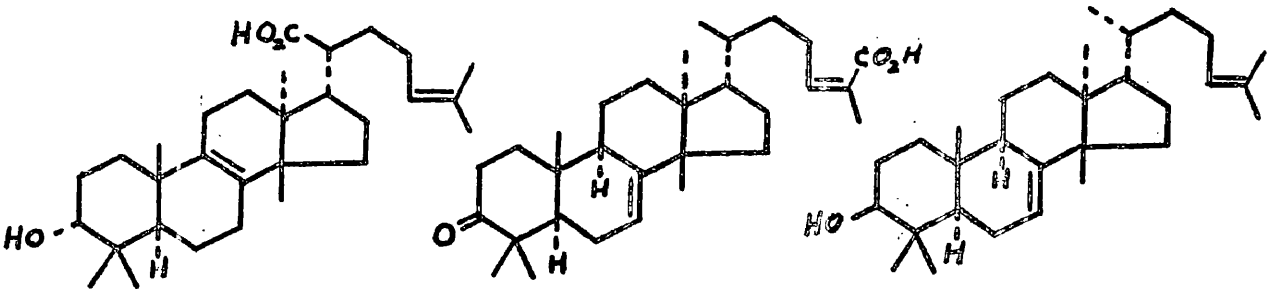
(XI) (XVII) (XXVII)

Euphorbol (XXVII), a C-31 triterpenoid occurring in various Euphorbaciae[42], was related to dihydrotirucallol by elimination of the additional methylene group at $C_{(24)}$[50,51,55].

Elemadienolic acid (XXVIII) and its corresponding 3-ketone Elemadienonic acid, occur together in Manila elemi resin[56]. The conversion of both these acids into tirucallenol[50] led to the formulation of elemadienolic acid as (XXVIII)[51].

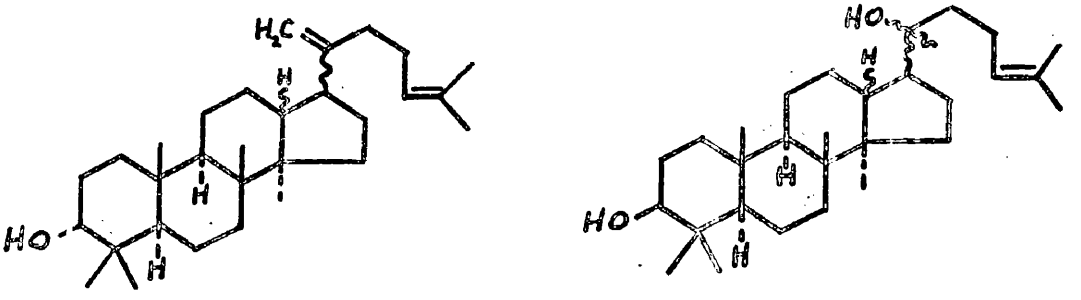
Masticadienonic acid was isolated by Barton[46] from gum mastic and by virtue of its relationship to tirucallol, formulated as (XXIX). The $C_{(9)}$ hydrogen atom is shown, from a study of molecular rotation data, to have the same configuration[57] (α) as in butyrospermol[58] (XXX). isoMasticadienonic acid, also occurring in gum mastic, has been identified as the Δ^{8}-isomer of (XXIX)[59].

Butyrospermol a minor constituent of shea-nut fat, has been identified by the author as 9α-eupha-7:24-dien-3β-ol (XXX). An account of this, and earlier work, is given in the theoretical section.



(XXVIII) (XXIX) (XXX)

Dammadienol (XXXI) and the corresponding 3-ketone, dammadienone, the dammarenediols I and II (XXXII), which differ only in the configuration of the $C_{(20)}$ hydroxyl group, and their 3-ketones, dammarenones I and II, have been isolated from dammar resin by Mills and Werner[60].



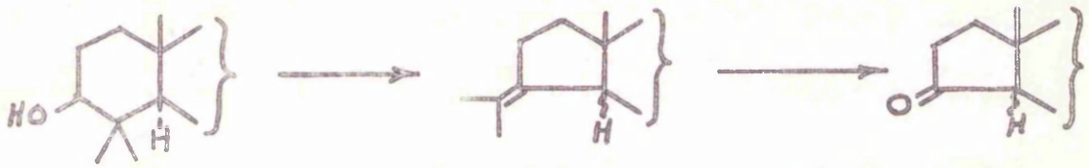
(XXXI) (XXXII)

It is of interest to note that these compounds possess the same carbon skeleton configuration as the carbonium ion (XV) postulated as an intermediate in the biosynthesis of lupeol and euphol from squalene.

THE CONSTITUTION OF LANOSTEROL.

Early work established that lanosterol, $C_{30}H_{50}O$, is a tetracyclic, diethenoid, secondary alcohol the readily reducible bond being incorporated in an isopropylidene group.[16,17,61-63]

RING A The nature of ring A in lanosterol was determined from two series of reactions. In one[64, 65] lanosterol (XXXIII) was shown to undergo a retropinacoline rearrangement on treatment with phosphorus pentachloride to yield the product (XXXIV),



(XXXIII) (XXXIV) (XXXV)

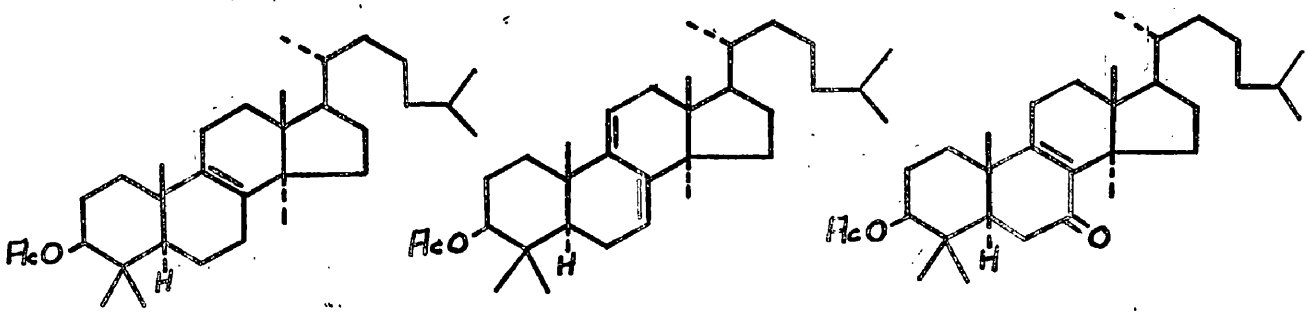
oxidation of which with osmium tetroxide followed by treatment with lead tetra-acetate gave the trisnorketone (XXXV). This ketone was also obtained by ozonolysis of the diene (XXXIV)[68, 66]. In the other series, lanostenone (XXXVI) was converted into the hydroxymethylene derivative (XXXVII) which on oxidation with alkaline hydrogen peroxide afforded the dicarboxylic acid (XXXVIII). Pyrolysis of this dicarboxylic acid gave the norlanostenone (XXXIX). These sequences of reactions show

(XXXVI) (XXXVII) (XXXVIII) (XXXIX)

that the terminal, hydroxyl-bearing ring is at least six-membered. Thus by comparison with earlier studies of the same nature in the pentacyclic series,[67] ring A of lanosterol can be provisionally formulated as in (XXXIII).

RINGS B and C. The structure of rings B and C and the environment of the less reactive double bond in lanostenol,

were deduced from the results of oxidative and degradative experiments. The tetrasubstituted nature of this double bond was indicated on the basis of the infrared[68] and ultraviolet[67] absorption of lanostene. Mild chromic acid oxidation of lanostenyl acetate (XL) or dihydroagnosteryl acetate (lanosta--7:9(11)-dienyl acetate) (XLI), which is formed by dehydrogenation of (XL) with selenium dioxide in acetic acid[69-71], yielded the αβ-unsaturated ketone (XLII). Further oxidation of (XLII), or more vigorous oxidation of (XL) or (XLI) with chromic acid gave a yellow, unsaturated diketone (XLIII)[17,70,72] the



(XL) (XLI) (XLII)

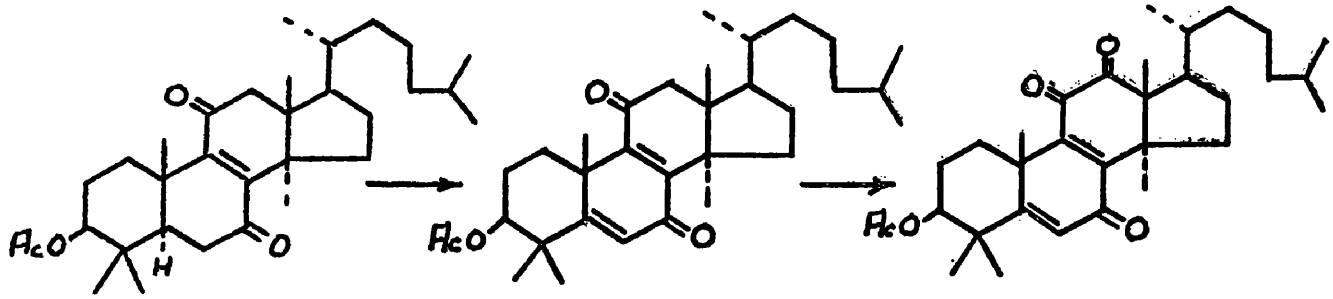
light absorption of which[17,73] showed it to possess a fully transoid structure. The double bond in lanostenyl acetate (XL) is therefore flanked by two methylene groups[17]. Reduction of the ene-dione (XLIII) with zinc in acetic acid, hydrogen and platinum or by the method of Clemmenson, gave[74] the saturated diketone (XLIV, R = Ac), the infrared spectrum of which showed that the carbonyl groups are each present in six-membered rings[73]. These deductions were confirmed by the preparation of further oxidation products. Treatment of the ene-dione (XLIII) with

selenium dioxide in acetic acid gave the compound (XLV) which possesses the extended diene-dione chromophore[70,73] and which on further treatment with the same reagent yielded the diene-trione (XLVI, R = Ac). The diene-trione is also formed by chromic acid oxidation of the conjugated triene-one[70] (XLVII), which is itself prepared by selenium dioxide oxidation of 7-oxolanost-8-enyl acetate (XLII)[70,73,75]. The position of the nuclear double bond of lanosterol was related to that of the hydroxyl group by the conversion of the diene-trione (XLVI, R = H) by means of a retropinacoline rearrangement, into 7:11:12-trioxo<u>iso</u>lanosta-3:5:8-triene (XLVIII) in which the conjugated system has been extended to ring A.[67] This relationship is confirmed by the conversion of (XLVIII), by treatment with alkaline hydrogen peroxide, into the dicarboxylic acid (IL) and this shows that the α-diketone grouping is in ring C. The fact that further oxidation products of the diene-trione (XLVI, R = Ac) could not be obtained indicated that all the carbon atoms adjacent to the chromophore were fully substituted, and supported the view that the nuclear double bond is between $C_{(8)}$ and $C_{(9)}$.

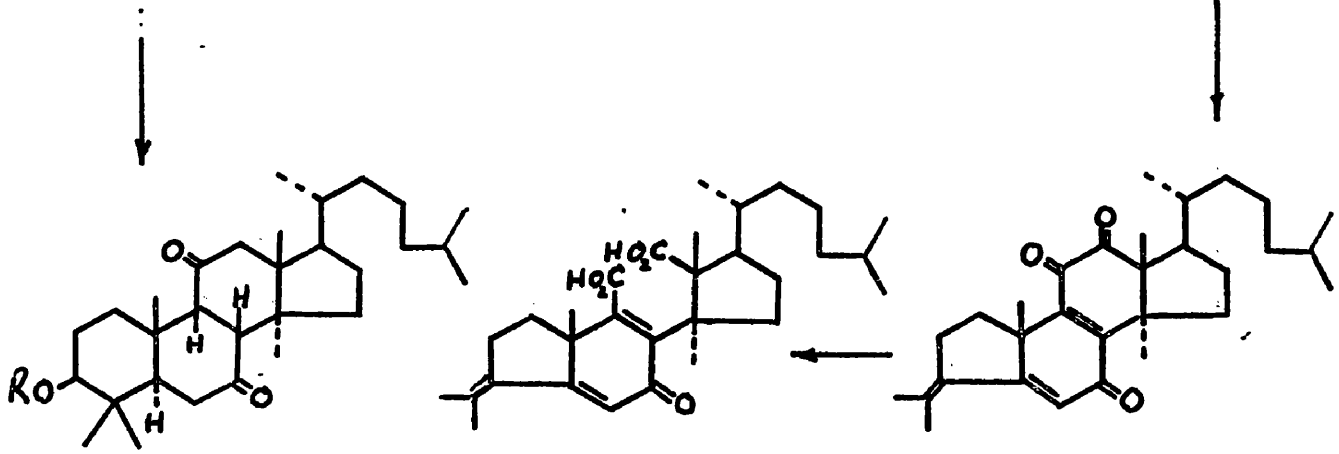
An equilibrium mixture of lanost-8-enyl acetate (XL) and its Δ^{7}-isomer is obtained when either is treated with mineral acid[71,76-77]. In the analogous Δ^{8}-steroid compounds, acid isomerisation moves the double bond to the $\Delta^{8(14)}$-position. This difference is explained by Barton's suggestion that the attachment of angular methyl groups at $C_{(13)}$ and $C_{(14)}$ in

lanosterol effectively block those positions. This was confirmed by the isolation of 1:2:8-trimethylphenanthrene (L) from the complex mixture obtained on selenium dehydrogenation.[17,63]

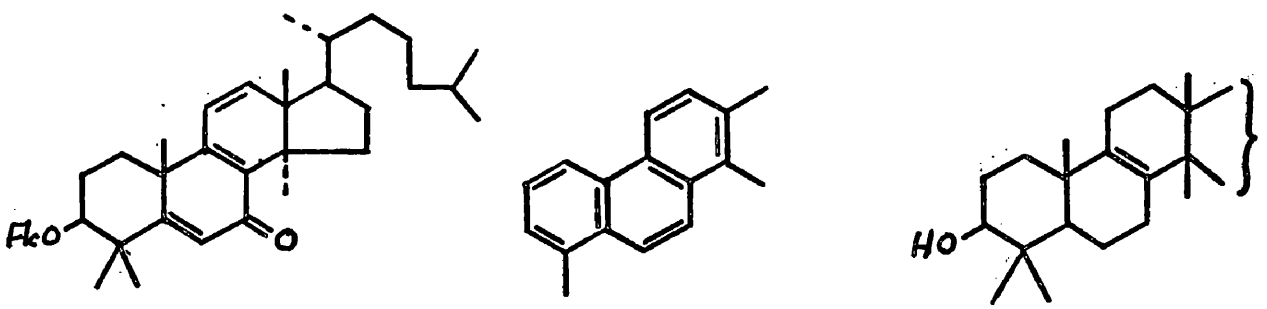
At this stage, lanosterol could be represented by the partial formula (LI).



(XLIII) (XLV) (XLVI)

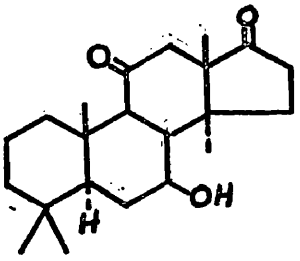


(XLIV) (IL) (XLVIII)

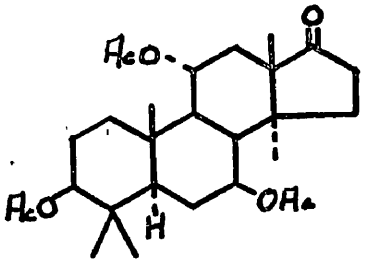


(XLVII) (L) (LI)

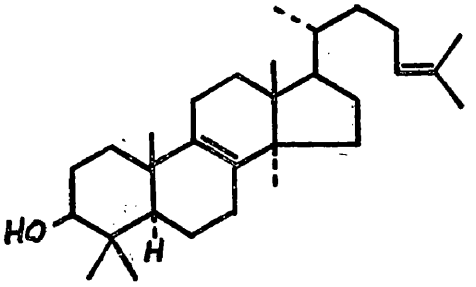
RING D AND THE SIDE-CHAIN. The presence of an isopropylidene group in the side-chain was ascertained by the isolation of acetone from lanosteryl acetate by vigorous chromic acid oxidation[78] or on treatment with osmic acid followed by reaction of the product with lead tetra-acetate.[61] The side-chain was shown to be iso-octenyl in nature by the isolation of 6-methylheptan-2-one on vigorous chromic acid treatment of lanost-8-enyl acetate.[79,80] This was confirmed by a step-wise degradation of the side-chain by Ruzicka,[81] which led to the dioxoalcohol (LII). The presence of a five-membered ring carbonyl group in this dioxo-alcohol followed from its infrared absorption spectrum.[82] It was also



(LII)



(LIII)



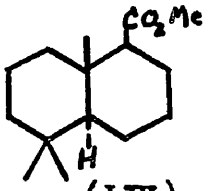
(X)

shown that the carbonyl group in the related degradation product (LIII) has but one α-methylene group[83]. It follows that the point of attachment of the side-chain must be either $C_{(15)}$ or $C_{(17)}$. Ruzicka[84] showed by a series of oxidative reactions that the side-chain must be attached to the carbon atom β- to $C_{(13)}$; hence the side-chain is attached to $C_{(17)}$. Thus apart from its stereochemistry, lanosterol must be represented by formula (X).

STEREOCHEMISTRY OF LANOSTEROL

The stereochemistry of lanosterol (X) was revealed by a study of the X-ray diffraction spectra of lanostenyl iodoacetate[85,86] and

was confirmed by chemical means[84,87-89]. The β-(equatorial) nature of the $C_{(3)}$-hydroxyl group was deduced from its stability towards sodium alkoxide[18] and from the fact that it is regenerated by reduction of the corresponding 3-ketone with sodium in alcohol[77]. This view was confirmed by the observation that on dehydration with phosphorus pentachloride[64,65], ring A undergoes a retropinacoline rearrangement, a reaction which is known to be specific for 3β-(equatorial) hydroxyl groups where rings A and B are trans-fused.[90] The trans-fusion of rings A and B, where the $C_{(5)}$ hydrogen is α, was established from a study of molecular rotation data[91] and from the fact that the same, known degradation product (LIV) was obtained from both lanosterol and manool.[92]



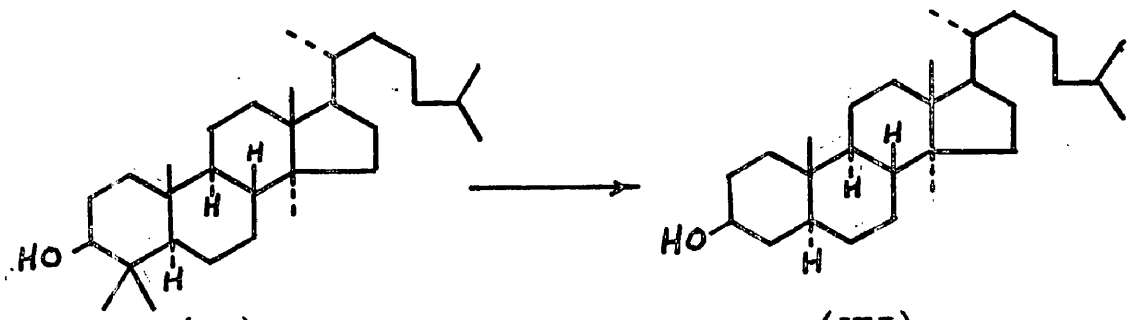
(LIV)

To account for the hindered nature of the $C_{(11)}$-carbonyl group in 11-oxo derivatives of lanosterol, the $C_{(13)}$- methyl group was assigned[67] the β-configuration as in the steroids. Molecular rotation evidence showed that rings C and D were trans-fused[89,91] and that the configurations of the $C_{(17)}$-side-chain and the $C_{(20)}$-methyl group were the same as in cholesterol[89]. Further confirmation that the stereochemistry of lanosterol is as formulated in (X) was obtained from biogenetic evidence[92].

The stability of 7:11-dioxolanostanol (XLIV, R = H) to strong alkali treatment led Barton[89] to conclude that the $C_{(8)}$ and

$C_{(9)}$ hydrogen atoms have the thermodynamically more stable configurations, being mutually trans-relative and anti-relative to the $C_{(10)}$ and $C_{(14)}$ methyl groups.

Conformation of the stereochemistry of lanosterol as outlined above, was obtained by the preparation, from lanostanol (LV) of 14α-methylcholestanol (LVI) which has subsequently been prepared[94] from cholesterol. A total synthesis of lanost-8-enol and lanosterol has been described[95,96] which confirms the constitution and stereochemistry already proposed for these compounds.



(LV) (LVI)

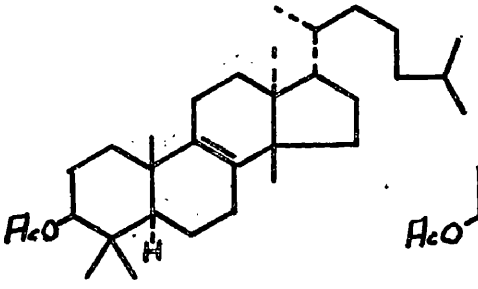
THE CONSTITUTION OF EUPHOL

Euphol, $C_{30}H_{50}O$, was first isolated in a pure state, together with euphorbol, by Newbold and Spring[42]. These workers showed that euphol is a tetracyclic triterpenoid containing a secondary hydroxyl group and two isolated double bonds, one of which is readily reducible and was later shown to be present in an isopropylidene group,[97,98] which terminates a lanosterol or cholesterol type of side-chain.[99]

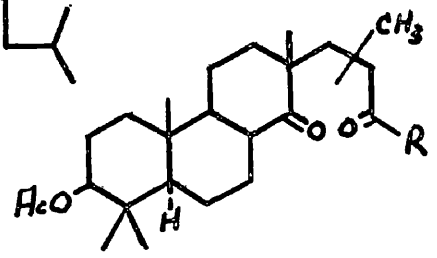
The elucidation of the structure of euphol was based on experiments similar to those employed in connection with lanosterol which established that the hydroxyl group is at $C_{(3)}$ and has the β-(equatorial) configuration[100]. Dehydrogenation of euphol with selenium gave 1:2:8-trimethylphenanthrene[100] and euphenyl acetate was shown to undergo oxidation reactions very similar to those of lanostenyl acetate[44,68,98,100]. These observations led Jeger to propose that rings A, B and C of euphol are the same as those of lanosterol and that they can be represented by the same partial formula (LI). Ring D was shown to be five-membered by Barton[43] from a study of the infrared absorption spectra of euph-8-ene and lanost-8-ene which indicated that both these compounds have the same number of methyl groups. Allowing for the isooctenyl side-chain and rings A, B and C, only three carbon atoms were available so that ring D must be five-membered.

In contrast with the analogous reaction of lanost-8-enyl acetate, Vilkas[101] showed that treatment of euph-8-enyl acetate (LVII) with mineral acid moves the double bond from the Δ^{8}-position to another fully substituted position, the product being isoeuphenyl acetate. Since isoeuphenyl acetate is oxidised to a diketone, then formulated as (LVIII), Jeger[100] proposed the structures (LIX) and (LX) for euphol and isoeuphol respectively. Since structure (LIX) did not account for the formation of 1:2:8-trimethylphenanthrene from euphol Ruzicka suggested that euphol might be (LXI) (isolanosterol) in which rings C and D are cis-fused. The formation of 1:2:5-trimethylnaphthalene by selenium

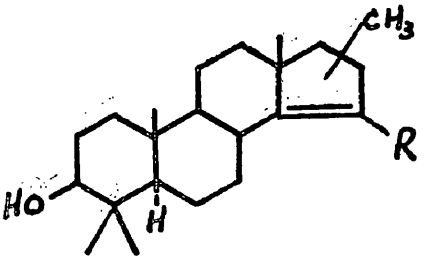
dehydrogenation of isoeuphadiene led Barton[43] to conclude that the latter compound must possess a methyl group at $C_{(8)}$ which was originally at $C_{(14)}$ in euphadiene. isoEuphenol was thus formulated as (LXII) or (LXIII), the corresponding diketone being then represented as (LXIV) or (LXV) rather than (LVIII). Since



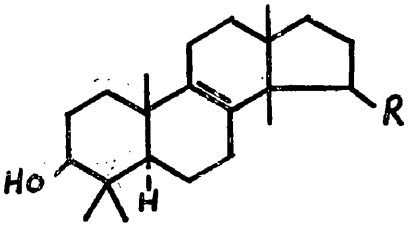
(LVII)



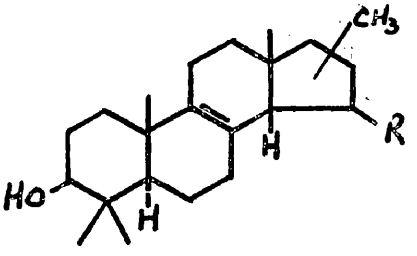
(LVIII)



(LX)

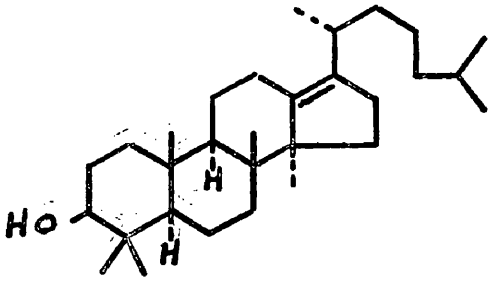


(LXI)

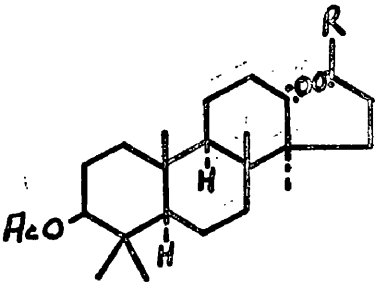


(LIX)

it was found that this diketone absorbed five moles of bromine, Barton[43] concluded that its structure can only be represented by (LXIV) and hence isoeuphenol must be (LXII) and euphol must be (XI).

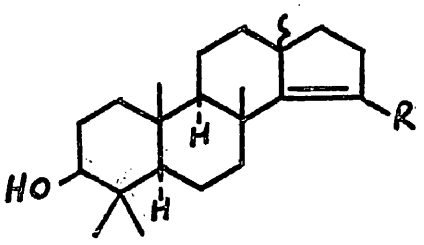


(LXII)

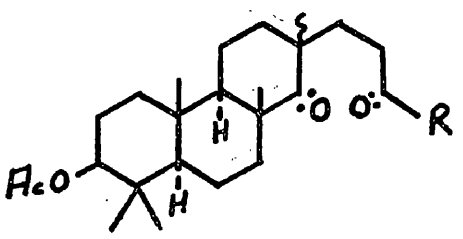


(LXIV)

R = isooctyl

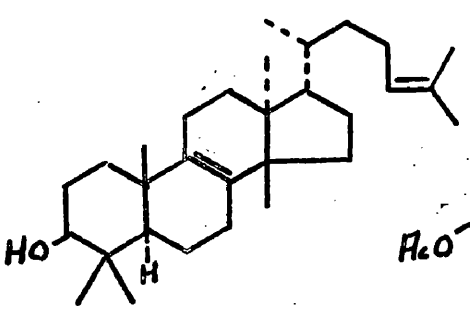


(LXIII)

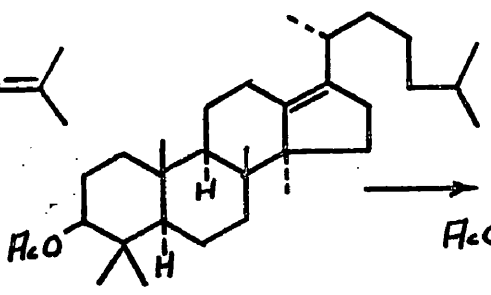


(LXV)

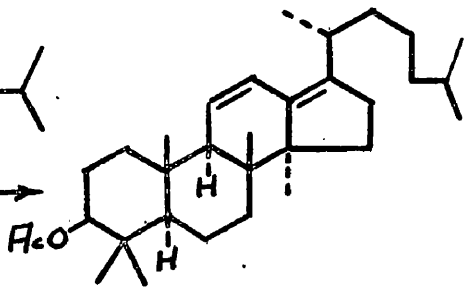
Confirmation of this view was obtained from a study of the infrared absorption of isoeuphenol and from the observation that the light absorption of the conjugated dienyl acetate (LXVII), formed by oxidation of isoeuphenyl acetate (LXVI) with selenium dioxide, is very similar to that of oleana-11:13(18)-dienyl acetate (LXVIII).[43]



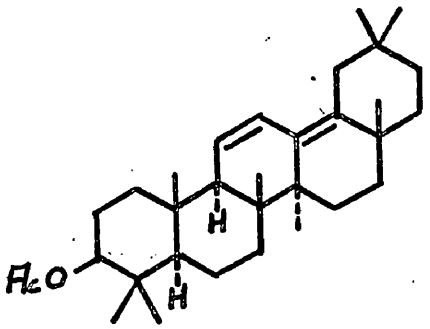
(XI)



(LXVI)



(LXVII)



(LXVIII)

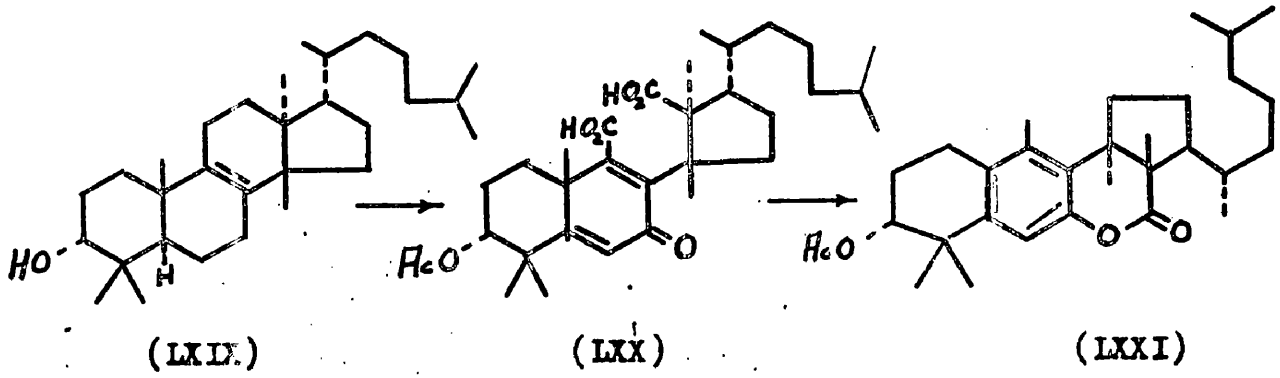
The same conclusions as to the nature of ring D, the position of attachment of the side-chain and the acid-induced isomerisation of euphenol to isoeuphenol were reached independently by Jeger and Ruzicka[103].

THE STEREOCHEMISTRY OF EUPHOL.

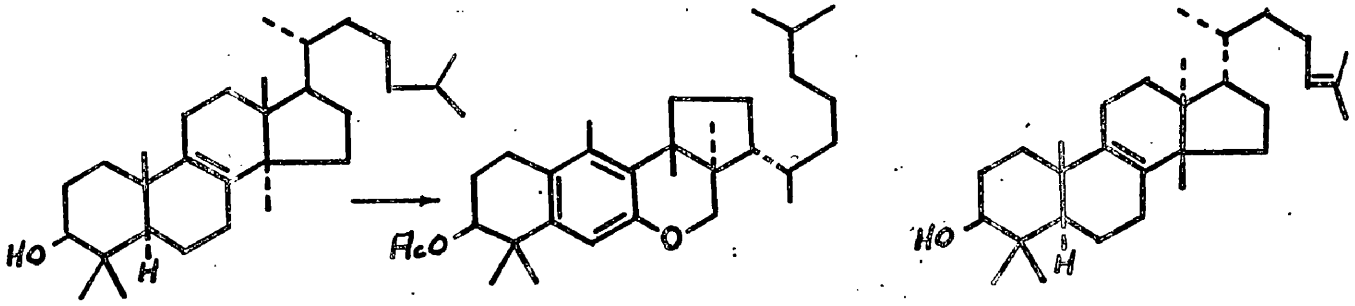
On the evidence of molecular rotation data, the configuration of the groups at $C_{(3)}$, $C_{(5)}$ and $C_{(10)}$ were deduced to be as in a normal triterpenoid ring A. The angular methyl groups at $C_{(13)}$ and $C_{(14)}$ were assigned the α- and β- configurations respectively since Barton[43] claimed that, in this configuration, these groups cause the molecule to assume an unfavourable conformation which provides the driving force necessary for the double methyl group migration involved in the euphenol-isoeuphenol rearrangement, the latter compound adopting the more stable, all-chair conformation. In addition, if this rearrangement can be considered to be fully synchronous, then the side-chain at $C_{(17)}$ must have the same configuration (α-) as the $C_{(13)}$-methyl group. From a comparison of molecular rotations in the euphol and lanosterol series, Barton concluded that the configurations at $C_{(17)}$ and $C_{(20)}$ were the opposite from those in lanosterol. More positive chemical evidence from which it was concluded that the configuration at $C_{(20)}$ in euphol is the same (α-) as in lanosterol, was shortly afterwards obtained by the Swiss workers.[103]

Final confirmation of the configuration at $C_{(17)}$ and $C_{(20)}$ in euphol was obtained when it was shown[83] that euphol and tirucallol differ only in configuration at $C_{(20)}$ and that lanosterol is

epimeric with tirucallol at $C_{(13)}$, $C_{(14)}$, $C_{(17)}$ and $C_{(20)}$. Warren[84] arrived at the same conclusion by the preparation of a degradation product common to both euphol and tirucallol and in which the asymmetry at $C_{(20)}$ was removed. Conclusive proof that euphol is correctly represented by (XI) came by the correlation of tirucallol with lanosterol. epiTirucallenol (tirucall-8-en-3α-ol, LXIX) was converted via the dicarboxylic acid (LXX) into the acetoxy-phenol lactone (LXXI) which was found to be the optical enantiomer of the corresponding compound (LXXIII) prepared from lanost-8-enol (LXXII).[89] Thus euphol may be formulated as 13-iso:14-iso:17-iso-lanosterol (XI). A recent communication by Warren and Watling[104] confirms that euphol is 20-isotirucallol.



(LXIX) (LXX) (LXXI)



(LXXII) (LXXIII) (XI)

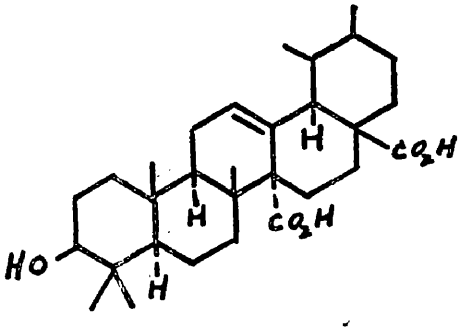
THEORETICAL

CHAPTER I

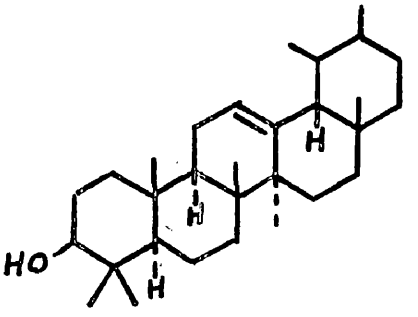
Attempts to introduce a 9:19-cyclopropane bridge into a lanosterol derivative

Starting from various derivatives of lanosterol, reactions are described which it was considered would result in the formation of a cyclopropane bridge between $C_{(9)}$ and $C_{(19)}$ in the tetracyclic nucleus. In the course of this work, the stereochemistry at position $C_{(8)}$ and $C_{(9)}$ in saturated lanostane derivatives was investigated.

In recent years, phyllanthol (VI, R = H), a hexacyclic triterpenoid from the root bark of Phyllanthus angleri (Pax), has been partially synthesised from the pentacyclic triterpenoids quinovic acid (LXXIV)[109a] and α-amyrin (I)[109b]. These conversions represent the first, and so far the only, instances of the preparation of a naturally occurring triterpenoid containing a cyclopropane ring. The method employed in the latter case



(LXXIV)

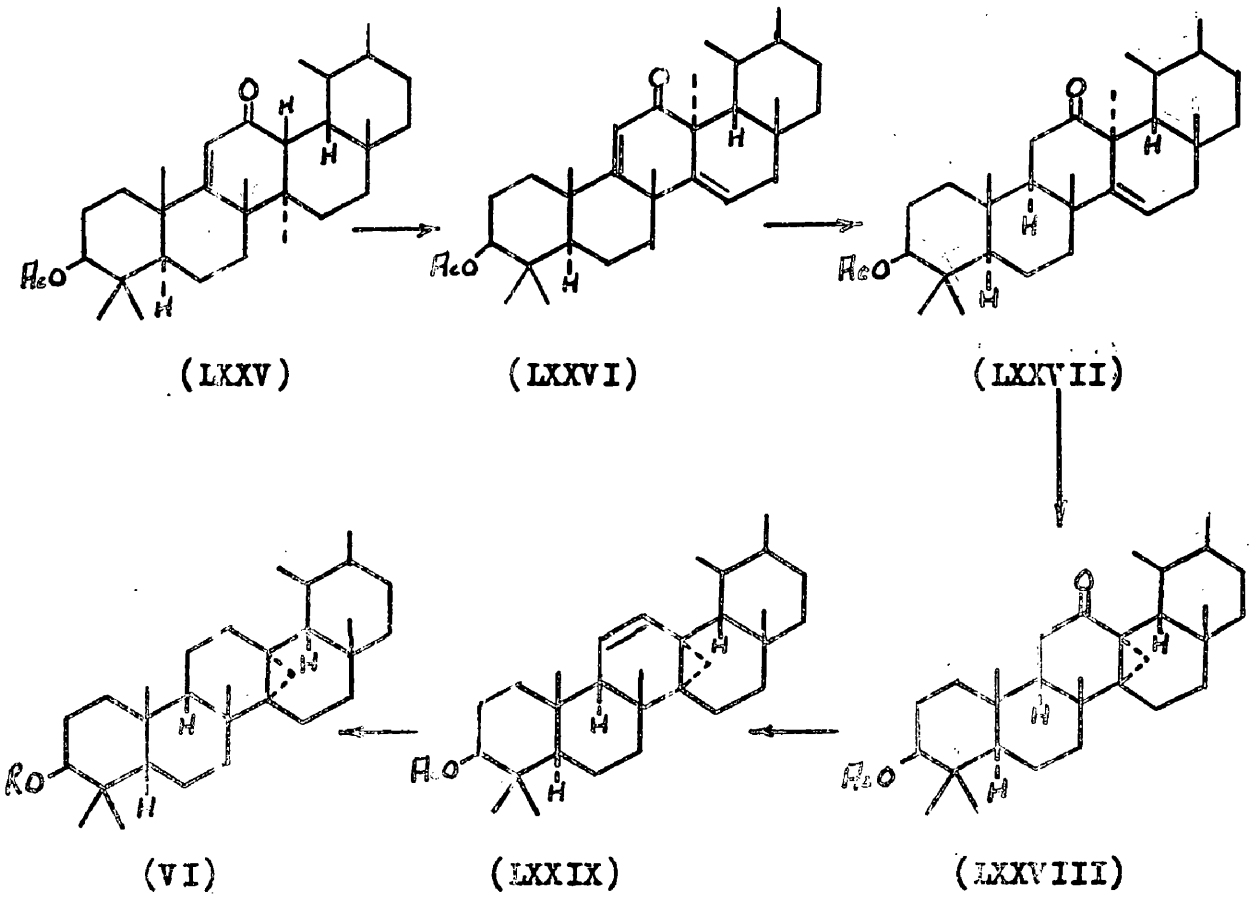


(I)

involved the oxidation of 12-oxoisours-9(11)-enyl acetate (LXXV) with selenium dioxide in acetic acid to give the doubly unsaturated ketone, 12-oxoisoursa-9(11):14-dienyl acetate (LXXVI) which on reduction with lithium in liquid ammonia yielded 12-oxoisours-14--enyl acetate (LXXVII).[109b] This non-conjugated unsaturated ketone was found to be isomerised by mineral acid at room temperature to the 12-oxo-13:27-cyclopropane derivative (LXXVIII) which on reduction with lithium aluminium hydride followed by acetylation of the product yielded 13:27-cyclours-11-enyl acetate (LXXIX). Catalytic hydrogenation of this acetate gave phyllanthyl acetate (VI, R = Ac).

The formation of a cyclopropanoid compound in the tetracyclic series has not so far been achieved although there

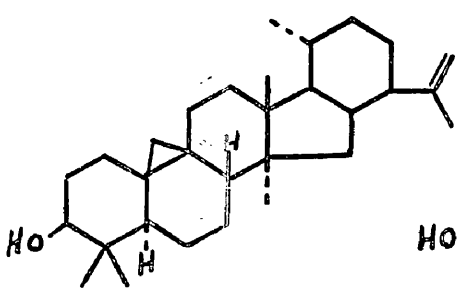
are four naturally occurring tetracyclic triterpenoids at present known, which contain in addition a cyclopropane ring



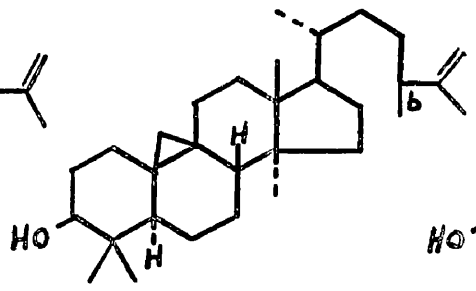
(LXXV) (LXXVI) (LXXVII)

(VI) (LXXIX) (LXXVIII)

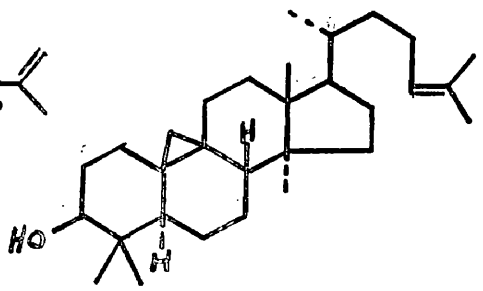
bridging carbon atoms $C_{(9)}$ and $C_{(10)}$. These compounds are cycloartenol (XXI)[33,36], cyclolaudenol (XXIII),[39] cycloorysterol (XXII)[38] and cycloeucalenol (XXIV)[41], all of which are members of the lanosterol series. On treatment with mineral acid the cyclopropane bridge is broken to give a mixture of double bond isomers. Thus for example, cycloartanyl acetate (LXXX) yields a mixture of Δ^{7}-, Δ^{8}- and $\Delta^{9(11)}$-lanostenyl acetates. Lanost-9(11)-enyl acetate (XXV), the most stable component, can be separated from the mixture by selective oxidation of the Δ^{7}- and Δ^{8}-isomers[33].



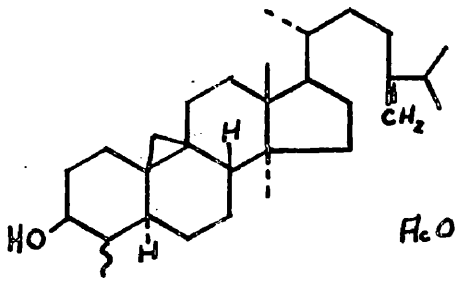
(XXII)



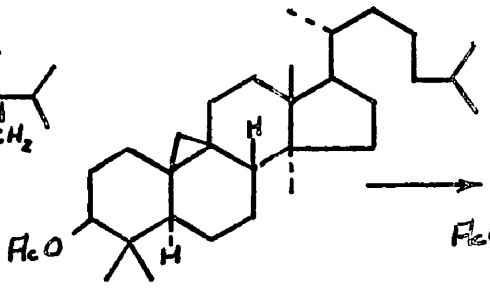
(XXIII)



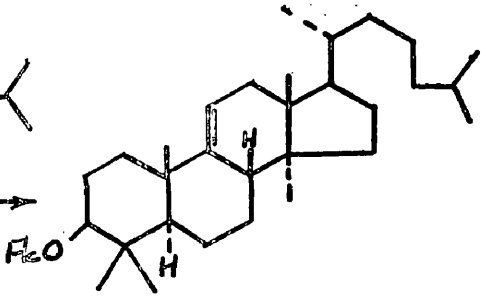
(XXI)



(XXIV)



(LXXX)

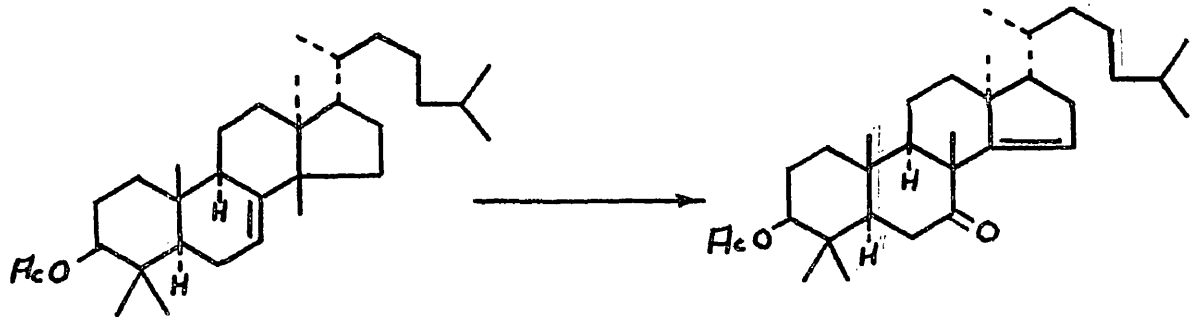


(XXV)

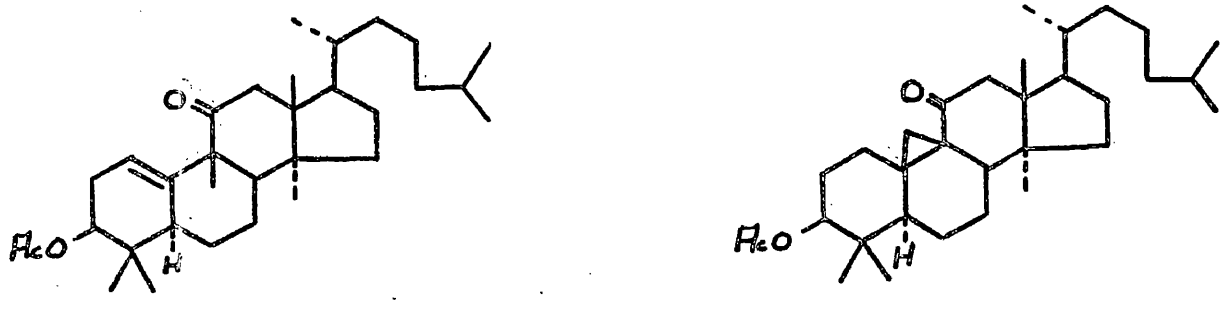
The present investigation is concerned with possible methods for the introduction of a cyclopropane ring into the tetracyclic nucleus and the partial synthesis of a cycloartanyl derivative from lanosterol was attempted.

Lanost-9(11)-enyl acetate (XXV) was the starting material for the first series of reactions, the proposed method being based on a rearrangement encountered earlier in this laboratory during studies on the structure of butyrospermol, the chemistry of which is discussed in a later section. Mild oxidation of dihydrobutyrospermyl acetate (LXXXI) with chromic--acetic acid gives a new $\beta\gamma$-unsaturated ketone, 7-oxoapoeuph-14--enyl acetate (LXXXII). In the course of this reaction, the

$C_{(14)}$-methyl group migrates to $C_{(8)}$ and the reaction terminates in the loss of a proton from $C_{(15)}$ with the formation of a double bond. By analogy, it was considered possible that similar oxidation of lanost-9(11)-enyl acetate (XXV) might give rise to the $\beta\gamma$ -unsaturated ketone (LXXXIII) which under acid isomerisation conditions as in the partial synthesis of phyllanthol, may yield the cyclopropanoid ketone (LXXXIV).



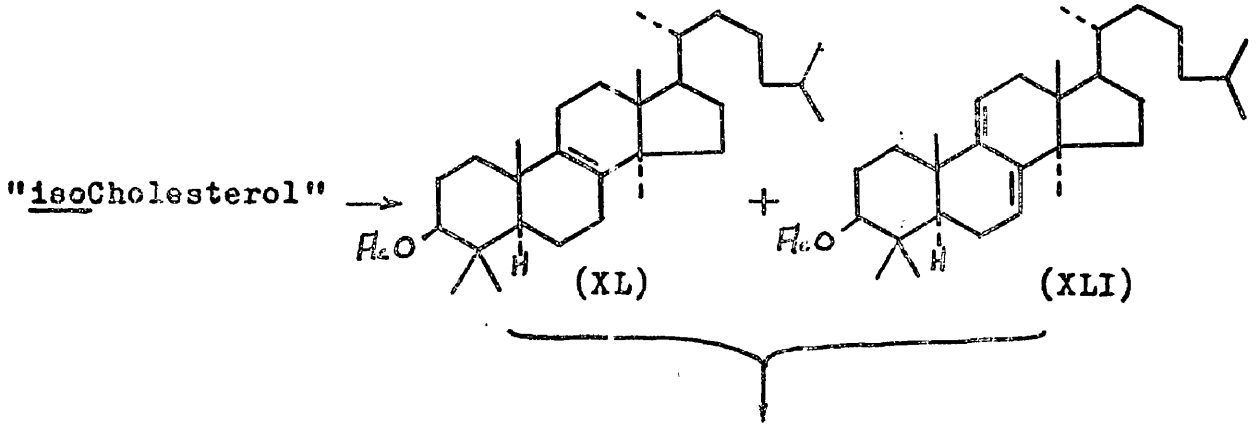
(LXXXI) (LXXXII)

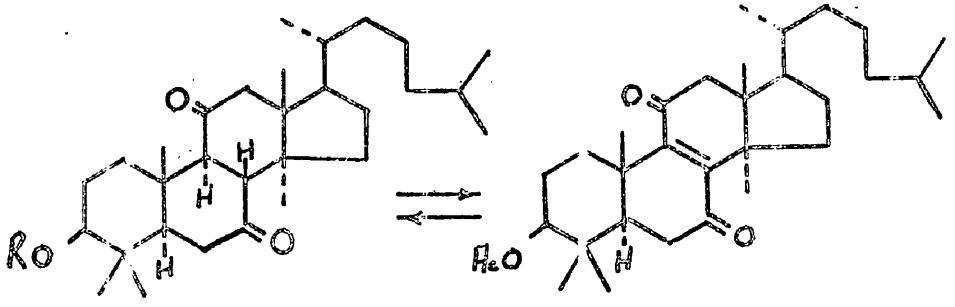


(LXXXIII) (LXXXIV)

The starting material, lanost-9(11)-enyl acetate, was prepared from "isocholesterol", acetylation and catalytic hydrogenation of which gave a mixture of lanost-8-enyl acetate

(XL) and lanosta-7:9(11)-dienyl acetate (XLI). Oxidation of this mixture with chromic-acetic acid and chromatography of the resulting crude product yielded 7:11-dioxolanost-8-enyl acetate (XLIII), reduction of which with zinc in acetic acid followed by extensive crystallisation from chloroform-methanol gave 7:11--dioxolanostanyl acetate (XLIV, R = Ac), m.p. 223-223.5, $[\alpha]_D$ + 62°. Dorée, et al.[74] and Cavalla and McGhie[70] have reported values of + 55° for the specific rotation of this compound and it is believed that they were dealing with an impure sample since a recent communication by Milburn, et al.[102] records a value for the specific rotation in agreement with that found by the present author.

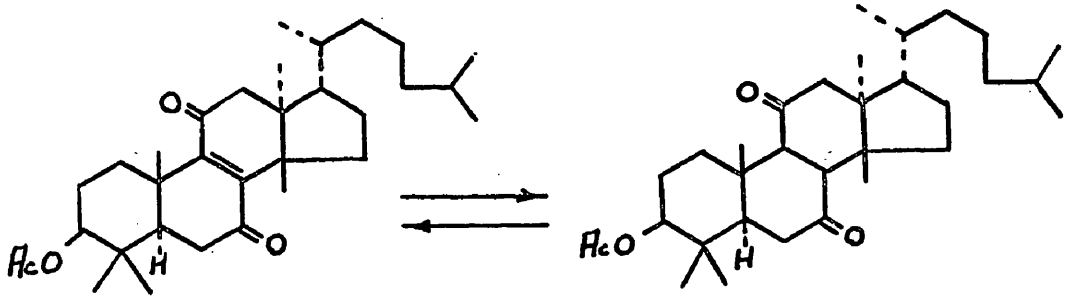




(XLIV) (XLIII)

It was observed also, that in both the lanosterol and the euphol series, the saturated 7:11-dioxoacetates (XLIV) and (LXXXVI)

can be formed from their corresponding 7:11-dioxo-8-enyl acetates (XLIII) and (LXXXV), by reduction with zinc in boiling methanol. This reduction has only previously been accomplished in the lanosterol series[74] by hydrogenation over platinum, by treatment with zinc in acetic acid and by the Clemmenson method. Doree, et al.[74] also claim that the saturated diketone (XLIV) is obtained from 7:11-dioxolanost-8-enyl acetate (XLIII) by reduction with sodium in propanol, but this is remarkable in view of experience

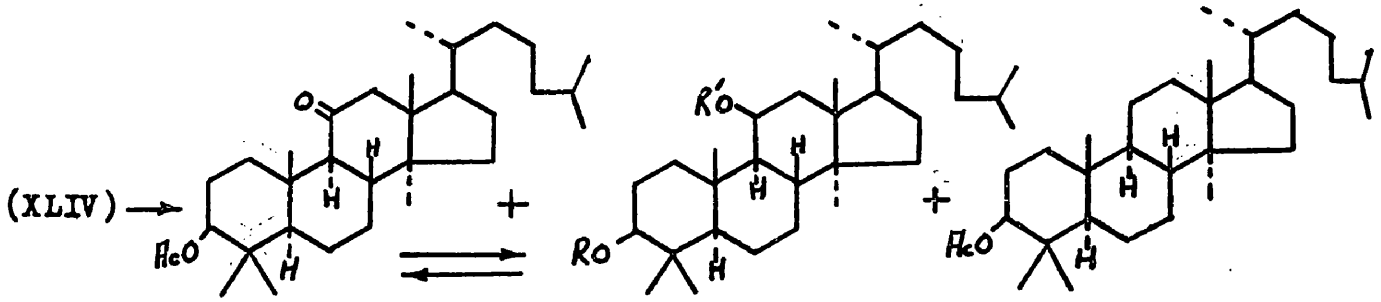


(LXXXV) (LXXXVI)

to be described later.

Wolff-Kishner reduction of 7:11-dioxolanostanyl acetate (XLIV, R = Ac) gave a mixture which after acetylation at 100° and chromatography yielded lanostanyl acetate (LXXXVII), 11-oxo-lanostanyl acetate (LXXXVIII) and a white crystalline material later identified by means of mixed melting point determination, specific rotation and infrared absorption, as 11β-hydroxylanostanyl acetate (LXXXIX, R = Ac, R' = H). Barnes and Palmer[107] have reported the isolation of lanostanyl acetate, 3β:7β- and 3β:7α--diacetoxylanostanes, and 3β:7-diacetoxylanostan-11-ol from a similar reaction mixture. This is the first report however, of

the isolation of 11β-hydroxylanostan-3β-yl acetate (LXXXIX, R = Ac, R' = H) from this source.



(LXXXVIII) (LXXXIX) (LXXXVII)

Reduction of 11-oxolanostanyl acetate (LXXXVIII) with lithium aluminium hydride in ether according to the method of Voser, et al.[73], gave a diol, $C_{30}H_{54}O_2$, the specific rotation of which (+54°) was considerably greater than that observed by the previous workers[73,110] (+29°, + 28.4°) for lanostane-diol, although the melting point (193-194°) was in good agreement (190-191°). The specific rotation was unchanged by repeated crystallisation and by acetylation followed by hydrolysis. Acetylation of the diol (+54°) with acetic anhydride and pyridine either at room temperature for 24 hours or at 100° for 2 hours, gave a diol monoacetate, $C_{32}H_{56}O_3$, which differed markedly in specific rotation from the lanostane-diol monoacetate (acetoxy-lanostanol) described by Voser, et al.[73] and by McGhie, et al.[110] A comparison of the physical constants of the diol and monoacetate is shown in Table I.

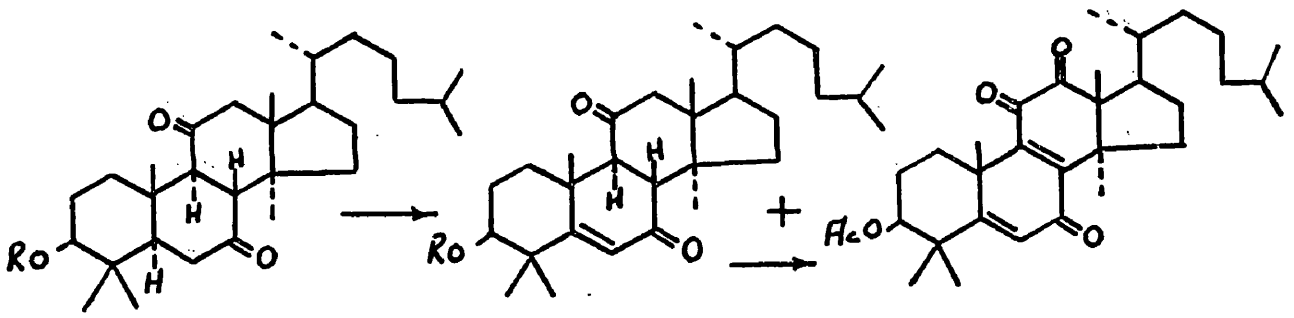
TABLE I

	Lanostanediol (11β-Hydroxylanostanol)		Acetoxylanostanol (11β-Hydroxylanostanyl acetate)	
	m.p.	$[\alpha]_D$	m.p.	$[\alpha]_D$
This work	193-194°	+ 54°	210-211°	+ 62.8°
Voser, et al.[73,88]	190-191°	+ 29°	219-220°	+ 23°
McGhie, et al.[110]	190-191°	+ 28.4°	215-216°	+ 22.8°

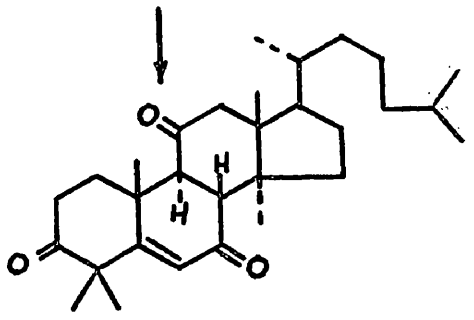
These discrepancies were disturbing and it was at first considered that they were due to differences in configuration at $C_{(8)}$, $C_{(9)}$ or $C_{(11)}$. Since it was believed that the introduction of the 9:19-cyclopropane bridge might be dependant upon the stereochemistry, particularly of the $C_{(9)}$-hydrogen atom, it was decided at this stage to establish beyond doubt that the generally accepted configurations at $C_{(8)}$ and $C_{(9)}$ in the lanostane series are in fact correct.

The hydrogen atoms attached to $C_{(8)}$ and $C_{(9)}$ in 7:11-dioxo--lanostanyl acetate (XLIV, R = Ac) have been assigned the β- and α- configurations respectively on the basis of experiments carried out by Barton and his colleagues[43,89,106,108,119] and by McGhie and Knight[121]. These workers have observed that in the euphol series, treatment of 7:11-dioxoeuphanyl acetate (LXXXVI) with alkali followed by acetylation gives 7:11-dioxoeuph-8-enyl acetate (LXXXV), whereas in the lanosterol series, 7:11-dioxolanostanyl acetate (XLIV, R = Ac) even under vigorous conditions is simply hydrolysed to the corresponding saturated dioxo-alcohol (XLIV, R = H) the $C_{(8)}$ and the $C_{(9)}$ hydrogen atoms remaining intact. Furthermore, they have stated that selenium dioxide oxidation of 7:11-dioxo-euphanyl acetate also gives the corresponding 7:11-dioxoeuph-8-enyl

acetate while 7:11-dioxolanostanyl acetate gives 7:11-dioxolanost--5-enyl acetate (XC, R = Ac). From these observations Barton has concluded that in the euphanyl series the hydrogen atoms at $C_{(8)}$ and $C_{(9)}$ are mutually <u>cis</u> relative, having either the α- or the β- configuration, while in 7:11-dioxolanostanyl acetate these hydrogen atoms are mutually <u>trans</u> relative but <u>anti</u> relative to $C_{(10)}$ and $C_{(14)}$ so that the molecule has the thermodynamically more stable all-chair conformation.



(XLIV) (XC) (XLVI)



(XCI)

These experiments have been repeated by the author. In the first case, contrary to the observations of Barton, it was found that prolonged treatment of 7:11-dioxolanostanyl acetate (XLIV, R = Ac) with methanolic potassium hydroxide and acetylation of the product yielded 7:11-dioxolanost-8-enyl acetate (XLIII). It was further noted that in addition to alkali treatment, treatment with mineral acid also converted 7:11-dioxoeuphanyl

acetate into the corresponding 7:11-dioxoeuph-8-enyl acetate (LXXXV).

On repeating the second experiment on which Barton's argument regarding the stereochemistry of the hydrogen atoms at $C_{(8)}$ and $C_{(9)}$ is based, oxidation of 7:11-dioxolanostanyl acetate (XLIV, R = Ac) with selenium dioxide in acetic acid gave a mixture from which 7:11-dioxolanost-5-enyl acetate (XC, R = Ac) and 7:11:12-trioxolanosta-5:8-dienyl acetate (XLVI) were isolated by chromatography. The formation of the former but not of the latter compound is in agreement with the work of Barton. The earlier workers[74,76,82] have also stated that the acetate (XC, R = Ac) is resistant to hydrolysis with either 15% methanolic potassium hydroxide or ethanolic hydrogen chloride. If this unsaturated dioxo-acetate does have the structure (XC, R = Ac) assigned to it, there is no apparent reason for its failure to hydrolyse. A further attempt was therefore made by the author to effect hydrolysis by boiling the unsaturated dioxo-acetate (XC, R = Ac) under reflux for two hours with 5% methanolic potassium hydroxide. On crystallisation of the product from methanol, a compound, m.p. 178-179°, $[\alpha]_D$ + 6.0°, unchanged by further purification, was obtained. On admixture with starting material (m.p. 178-179°, $[\alpha]_D$ + 5.1°) a depression of 20° in melting point was observed. The infrared absorption spectrum of this compound, in contrast to that of the starting material, did not possess bands at 1739 and 1243 $cm.^{-1}$ characteristic of an acetate grouping, but did exhibit a hydroxyl band in the 3500-3600 $cm.^{-1}$ region. The infrared

absorption spectra were identical in all other respects. The analysis supported the molecular formula $C_{30}H_{48}O_3$ which is that required by the corresponding 3β-alcohol. It is therefore concluded that the earlier reports[74,76,82] of the inability of 7:11-dioxolanost-5-enyl acetate (XC, R = Ac) to undergo hydrolysis are in error and that the hydrolysis product is in fact 7:11--dioxolanost-5-en-3β-ol (XC, R = H). Reacetylation of this alcohol regenerated the original acetate (XC, R = Ac) while oxidation with the Kiliani reagent yielded the corresponding triketone, 3:7:11-trioxolanost-5-ene (XCI), m.p. 167-168°, $[\alpha]_D$ + 58.8°. Further oxidation of 7:11-dioxolanost-5-enyl acetate (XC, R = Ac) with selenium dioxide in boiling acetic acid gave the fully conjugated trioxodienyl acetate (XLVI) obtained as described above by similar oxidation of 7:11-dioxolanostanyl acetate (XLIV, R = Ac), thus confirming that the double bond in (XC) is between $C_{(8)}$ and $C_{(9)}$.

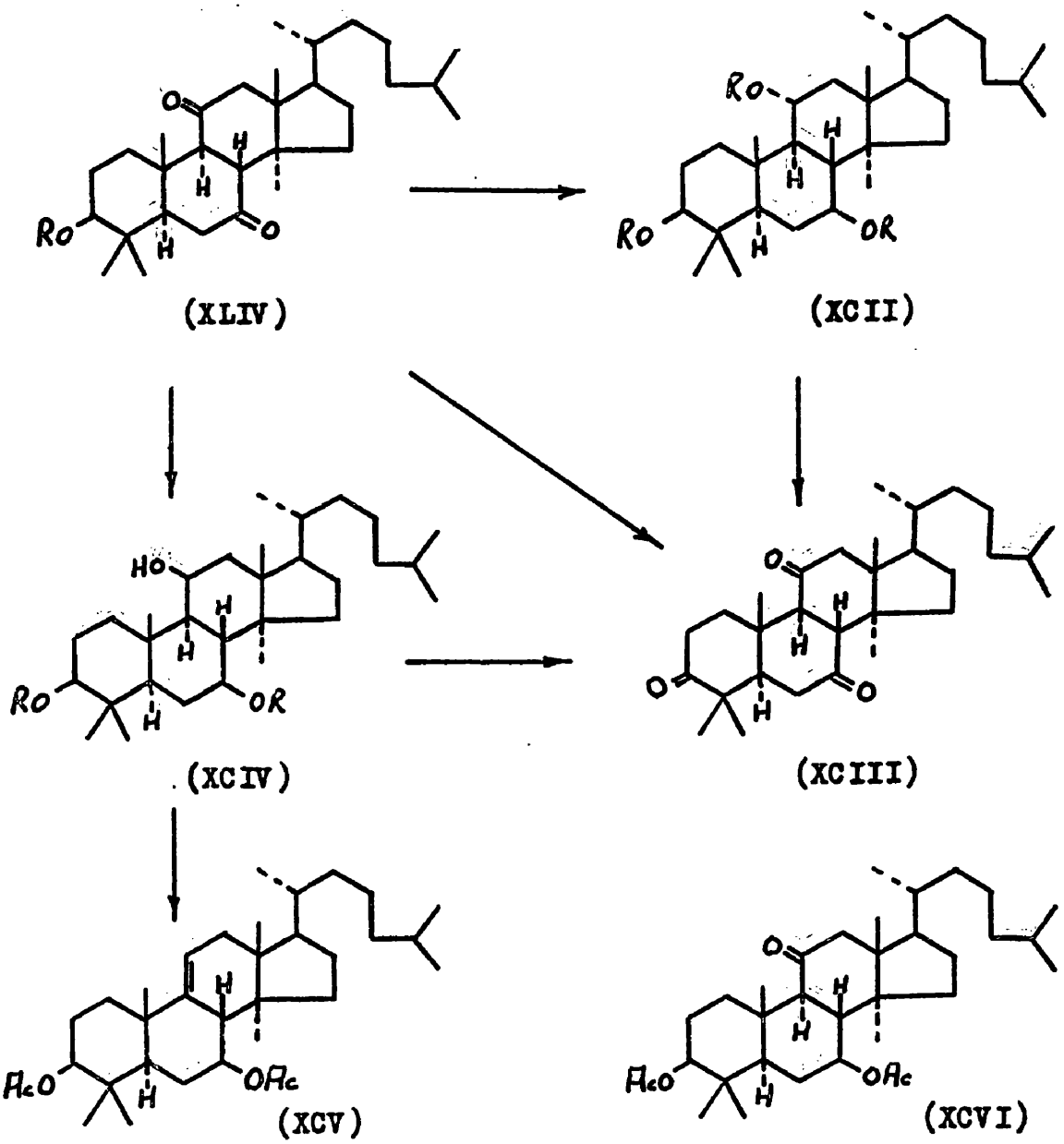
In view of the differences encountered above, it was considered desirable at this stage to re-examine several other lanostane derivatives.

As previously mentioned, Doree, et al.[74] have reported that reduction of 7:11-dioxolanost-8-enyl acetate (XLIII) with sodium in boiling propanol followed by acetylation, gives the saturated dioxo-acetate (XLIV, R = Ac). This is unlikely, however, since similar treatment of this saturated acetate (XLIV, R = Ac) results in the reduction of the carbonyl groups and gives a triol, m.p. 207-208°, $[\alpha]_D$ + 3°[199]. The author has repeated this reduction

and obtained a triol having m.p. 215-216° and $[\alpha]_D$ + 26.3°, using the same method. Acetylation of the triol, m.p. 215-216°, $[\alpha]_D$ + 26.3°, under normal conditions gave a triacetate, m.p. 155-156°, $[\alpha]_D$ + 30°, the constants of which are in excellent agreement with those reported by Barnes, et al.[107,108] (m.p. 156°, $[\alpha]_D$ + 29°) for the triacetate prepared from the triol, m.p. 207-208°, $[\alpha]_D$ + 3°. The author believes that the constants of the triol reported by Barnes et al. are in error.

Alkaline hydrolysis of the triacetate (m.p. 155-156°, $[\alpha]_D$ + 30°) regenerated the original triol, m.p. 215-216°, $[\alpha]_D$ + 26°. The triacetate was shown to have the thermodynamically more stable conformation when it was recovered unchanged after treatment under equilibrating conditions with sodium propoxide, followed by reacetylation. That is, the triol is 3β:7β:11α-trihydroxylanostane (XCII, R = H) and the triacetate, 3β:7β:11α-triacetoxylanostane (XCII, R = Ac) in which the hydrogen atoms at $C_{(8)}$ and $C_{(9)}$ have the β- and α- configurations respectively, giving the stable trans-anti-trans-arrangement throughout.

Oxidation of the triol (XCII, R = H) with the kiliani reagent gave the corresponding trione, 3:7:11-trioxolanostane (XCIII) which must also have 8β-, 9α-substituents by virtue of its preparation from the triol of established stereochemistry and by the observation that it is recovered unchanged after prolonged treatment with hydrochloric-acetic acid at 100°. The trione (XCIII) had m.p. 167-168°, $[\alpha]_D$ + 48°, whereas that prepared by



Doree, et al.[74] by oxidation of 7:11-dioxolanostanol (XLIV, R = H) had m.p. 166-167°, $[\alpha]_D$ + 121.1°. The large difference in specific rotation suggested that the two compounds were again distinct and to establish if this was in fact the case, the experiment of Doree was repeated. It was found that similar oxidation of 7:11-dioxolanostanol (XLIV, R = H) obtained by mild alkaline hydrolysis of the corresponding acetate, gave the trione (XCIII) m.p. 166-167°, $[\alpha]_D$

+ 48.5°, as obtained above by the author, and it is concluded that the specific rotation given by Doree for this compound is incorrect. That no inversion of configuration had occurred during hydrolysis or oxidation was demonstrated when 7:11-dioxolanostanyl acetate (XLIV, R = Ac) was regenerated by acetylation of the dioxo alcohol (XLIV, R = H) and by the fact that the dioxo acetate was recovered unchanged after similar treatment with the kiliani reagent.

This evidence proves that the $C_{(8)}$- and $C_{(9)}$- hydrogen atoms in 7:11-dioxolanostanyl acetate (XLIV, R = Ac) have the same configurations as those in 3:7:11-trioxolanostane (XCIII) which has been shown to have the stable 8β-, 9α- arrangement. Thus, although 7:11-dioxolanostanol (XLIV, R = H) is not in fact stable to vigorous treatment with alkali but is thereby converted into 7:11-dioxolanost--8-enol, the final conclusion of Barnes and Barton regarding the orientation of these hydrogen atoms is correct.

The diol obtained by reduction of 11-oxolanostanyl acetate with lithium aluminium hydride in ether was next considered. It has already been noted that the physical constants of this diol and of its monoacetate differ very markedly from the previously recorded values[73,110] (Table I). Similar reduction of the saturated dioxo acetate (XLIV, R = Ac) gave an uncrystallisable triol which on acetylation with acetic anhydride in pyridine at 100° gave 3β:7β-diacetoxylanostan-11β-ol (XCIV, R = Ac), m.p. 239.5-240°, $[\alpha]_D$ + 59°. Both Voser, et al.[73] and Cavalla and McGhie[70] give m.p. 239°, $[\alpha]_D$ + 70°, + 73° for this compound. Later, Bentley, et al.[33] recorded the value + 58° for its specific rotation, in good agreement with that

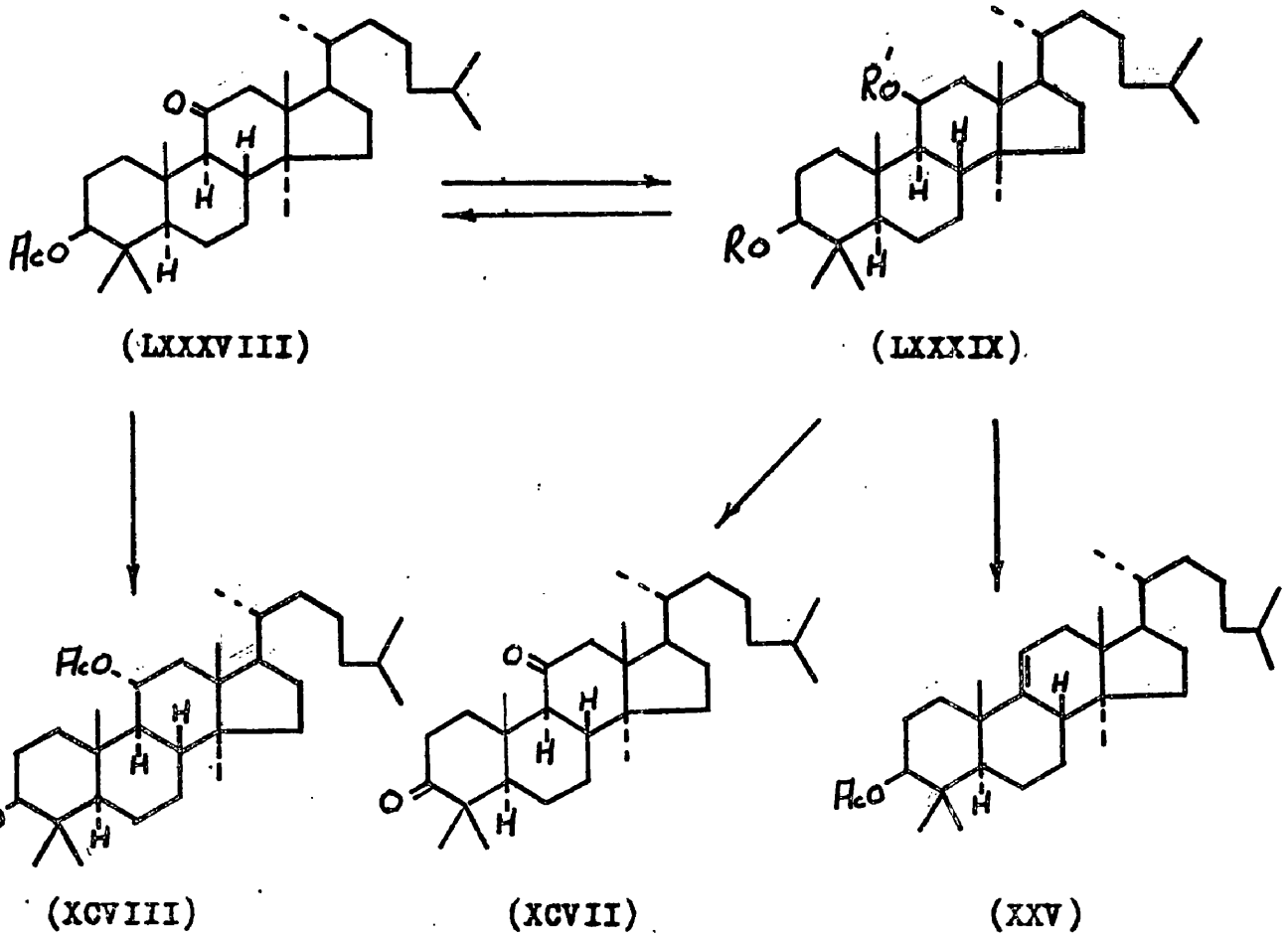
found by the present author. Since this section of the work was completed, Barnes and Palmer[107] have drawn attention to the discrepancy between the value for the specific rotation found by them (+ 57°) for the triol-diacetate, and those previously observed by Voser, et al.[73] and Cavalla and McGhie.[70] Barnes and Palmer have apparently overlooked the work of Bentley, et al.[33] That the compounds are the same was demonstrated when oxidation of the triol-diacetate (+ 58°) gave 3β:7β-diacetoxylanostan-11-one (XCVI), m.p. 171°, $[\alpha]_D$ + 58°, these values being in agreement with those reported by Cavalla and McGhie[70] and subsequently by Barnes and Palmer.[107] On dehydration with phosphorus oxychloride, the triol--diacetate (XCIV, R = Ac) gave an olefin, 3β:7β-diacetoxylanost--9(11)-ene (XCV), m.p. 213-213.5°, $[\alpha]_D$ + 77.4°. Cavalla and McGhie reported + 83° to 84° for the specific rotation of this compound and Barnes and Palmer have subsequently quoted + 58°. This dehydration reaction shows that the 11-hydroxyl group and the $C_{(9)}$-hydrogen atom must be axial and antiparallel. Hydrolysis with lithium aluminium hydride in ether and subsequent oxidation of the triol-diacetate (XCIV, R = Ac) gave the corresponding trione identical with 3:7:11-trioxolanostane (XCIII) prepared by the two methods outlined above. The $C_{(8)}$- and the $C_{(9)}$- hydrogen atoms in the triol-diacetate (XCIV, R = Ac) therefore have the β- and α- configurations respectively and hence the 11-hydroxyl group must be β-(axial). Thus, by analogy, the 3:11-diol and the corresponding monoacetate prepared by reduction of 11-oxolanostanyl acetate with lithium aluminium hydride

in ether, should similarly have the 11-hydroxyl group in the β-(axial) configuration, the hydrogen atoms being 8β and 9α. The following considerations show that this is the case and that these compounds are identical with those obtained by Voser, et al.[73,88] and by McGhie, et al.[110], the discrepancies in the physical constants being due to error either in the recording or in the reporting of the earlier values.

Voser and his colleagues[88] deduced from the inability of the lanostane-3:11-diol to undergo complete acetylation at room temperature, that the 11-hydroxyl group is sterically hindered and assigned to this compound the structure represented by (LXXXIX, R = Ac; R' = H) in which this group has the β-(axial) configuration. By analogy, since acetylation of the diol obtained in this work gives only a monoacetate even at 100°, the 11-hydroxyl group in this compound must also be sterically hindered and provided that the molecule retains its all-chair conformation as in the saturated dioxo-acetate (XLIV), the hindered 11-hydroxyl group must also be assigned the β-(axial) configuration. Oxidation of the diol--monoacetate (+62°) by the kiliani method at room temperature gave 11-oxolanostanyl acetate (LXXXVIII) identical in all respects with the original ketone. Thus both the diol and its monoacetate have the same basic stereochemistry as 11-oxolanostanyl acetate; that is, the $C_{(9)}$-hydrogen atom is in each case α-(axial) and they can be represented by the structure (LXXXIX).

Similar oxidation of the diol (+ 54°) gave 3:11-dioxolanostane

(XCVII) having physical constants in close agreement with those reported by Voser, et al.[73,88] for the dione they obtained by chromic acid oxidation of 11-oxolanostanol[73], of the 3β:11β-diol (LXXXIX, R = R' = H)[88] and of the 3β:11α-diol[88]. It is evident therefore



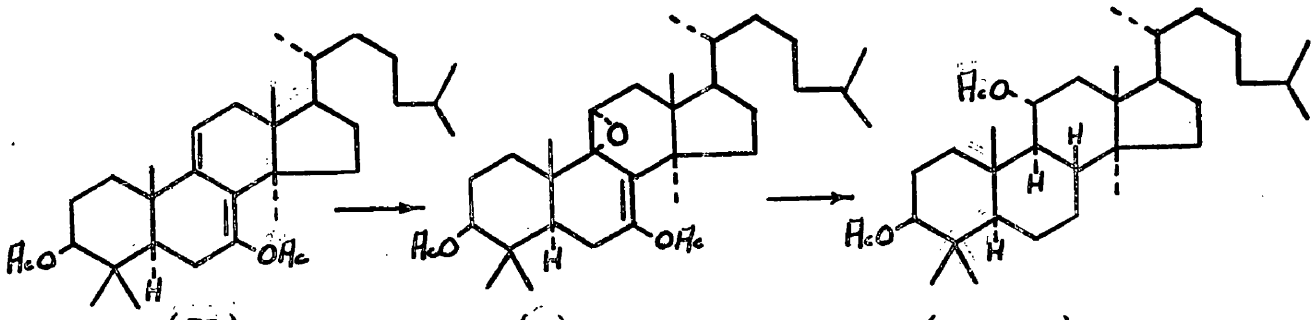
(LXXXVIII) (LXXXIX)

(XCVIII) (XCVII) (XXV)

that the diol (+ 29°) obtained by Voser has the $C_{(9)}$-hydrogen atom in the same configuration (α) as the diol (+ 54°) obtained in this work. The compounds are thus identical and it appears that the earlier values for the specific rotation of both the diol (LXXXIX, R = R' = H) and of its monoacetate (LXXXIX, R = Ac, R' = H) are in error.

During the course of the above investigation, the hitherto unknown 3β:11β-diacetoxylanostane (LXXXIX, R = R' = Ac) was prepared

by treatment of the diol-monoacetate (LXXXIX, R = Ac, R' = H) under reflux in chloroform solution with acetyl chloride and dimethylaniline[111]. The product, $C_{34}H_{56}O_4$, m.p. 182°, $[\alpha]_D$ + 71°, which from the absence of a band in the 3300-3600 $cm.^{-1}$ region of its infrared absorption spectrum, did not contain a hydroxyl group, is the required 3β:11β--diacetate (LXXXIX, R = R' = Ac). It is distinct from the isomeric 3β:11α-diacetate (XCVIII) which was prepared in this instance by acetylation at room temperature of the diol obtained by reduction of 11-oxolanostanyl acetate with sodium in propanol. 3β:11α-Diacetoxylanostane (XCVIII) was first prepared by Mijovic, et al.[89] from the enol-diacetate (IC) via the 9α:11α-epoxide (C). A summary of the



(IC) (C) (XCVIII)

discrepancies in the physical constants of compounds encountered in this section is given in table II.

TABLE II.

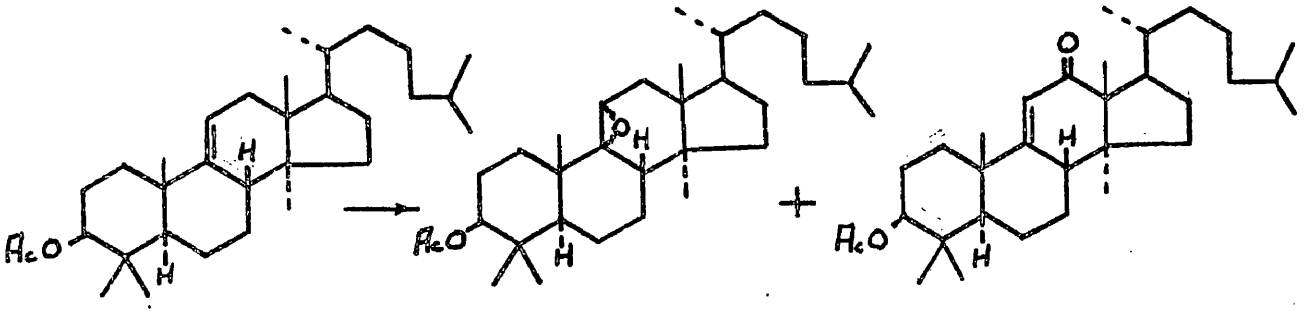
Compound	m.p.	$[\alpha]_D$
7:11-Dioxolanostan-3β-yl acetate		
This work	223-224°	+ 62°
Vorser, et al.[73,98]	222-224°	+ 55°
McGhie, et al.[110]	222-224°	+ 55°
Milburn, et al.[102]	223°	+ 65°

Compound	m.p.	$[\alpha]_D$
3β:11β-Dihydroxylanostane.		
This work	192-193°	+ 53.3°
Voser, et al.[73,88]	190-191°	+ 29°
McGhie, et al.[110]	190-191°	+ 28.2°
11β-Hydroxylanostan-3β-yl acetate		
This work	210-212°	+ 62°
Voser, et al.[73,88]	219-220°	+ 23°
McGhie, et al.[110]	219-220°	+ 22.8°
3β:7β:11α-Trihydroxylanostane		
This work	215-216°	+ 26.3°
Barnes, et al.[108]	207-208°	+ 3°
3:7:11-Trioxolanostane		
This work	167-168°	+ 48.2°
Doree, et al.[74]	165-167°	+ 121.1°
3β:7β-Diacetoxylanostan-11β-ol		
This work	238-239°	+ 58.6°
Voser, et al.[73]	239°	+ 73°
Cavalla, et al.[70]	239°	+ 70°
Bentley, et al.[33]	236-237°	+ 58°
Barnes, et al.[107]	234-236°	+ 56°
3β:7β-Diacetoxylanost-9(11)-ene.		
This work	213-213.5°	+ 77.4°
Cavalla, et al.[70,76]	213-214°	+ 83, + 84°
Barnes, et al.[107]	212-214°	+ 58°
3β:11α-Diacetoxylanostane		
This work	120-122°	+ 24.1°
Mijovic, et al.[88]	127-128°	+ 13°

Having thus confirmed the absolute configurations of the intermediate compounds, the attempted synthesis of a 9:19-cyclopropanoid derivative of lanostanol was continued. Dehydration of

11β-hydroxylanostanyl acetate (LXXXIX, R = Ac, R' = H) with phosphorus oxychloride in pyridine at 100° for three hours gave lanost-9(11)-enyl acetate (XXV), m.p. 173-174°, $[\alpha]_D$ + 90°, in good yield.

The first attempt involved the oxidation of lanost-9(11)-enyl acetate (XXV) under conditions identical with those used in the preparation of 7-oxoapoeuph-14-enyl acetate (LXXXII) from dihydrobutyrospermyl acetate (LXXXI). Purification of the resulting mixture by chromatography yielded unchanged lanost-9(11)-enyl acetate (75%), 9β:11-epoxy-lanostanyl acetate (CI)[33] and 12-oxolanost-9(11)-enyl acetate (CII)[33]. Further oxidation of the 9:11-epoxide (CI) gave only unchanged starting material.

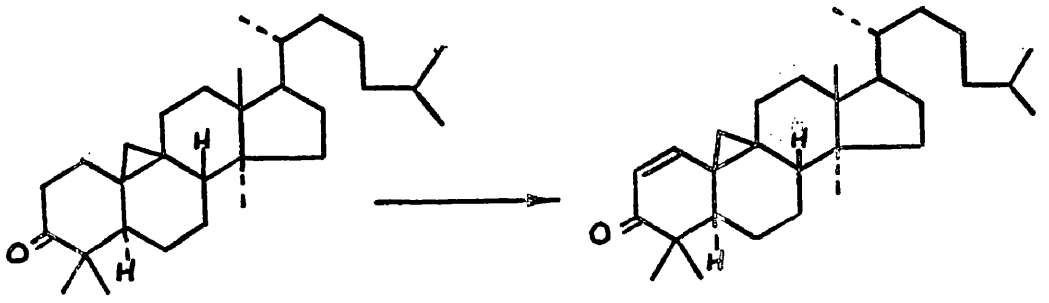


(XXV) (CI) (CII)

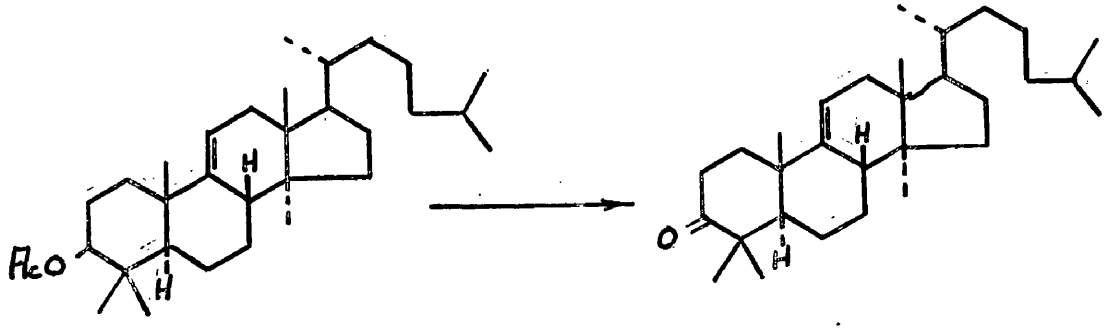
When lanost-9(11)-enyl acetate was treated under more vigorous conditions with chromium trioxide in acetic acid under reflux for 1 hour, 12-oxolanost-9(11)-enyl acetate (CII) was isolated in good yield as the sole product. No cyclopropanoid derivative or intermediate compound, could be detected among the products in any of these oxidation reactions.

Henry, et al.[36] have shown that bromination of cycloartanone (CIII) with N-bromosuccinimide in carbon tetrachloride, followed by dehydrobromination with collidine, gives the fully conjugated

cycloart-1-en-3-one (CIV). It was therefore considered possible that a similar series of reactions on lanost-9(11)-en-3-one (CV) would lead to the introduction of a double bond between $C_{(1)}$ and $C_{(2)}$. Treatment of the product with mineral acid might be expected to bring the 9(11)-double bond into conjugation with the α:β-unsaturated carbonyl system as a 9:19-cyclopropane ring to give cycloart-1-en-3-one (CIV).



(CIII) (CIV)



(XXV) (CV)

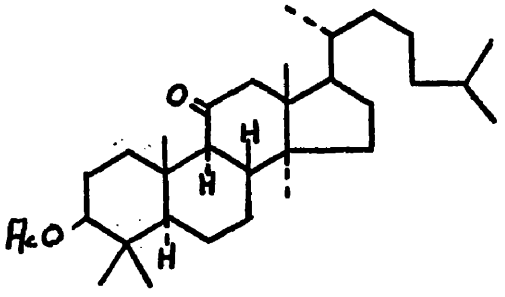
Lanost-9(11)-enyl acetate (XXV) was hydrolysed with lithium aluminium hydride in ether and the corresponding 3β-alcohol oxidised with the chromium trioxide-pyridine complex to give lanost-9(11)-en-3-one, (CV), m.p. 113.5-114°, $[\alpha]_D$ + 66.4°. Photobromination of lanost-9(11)-en-3-one under conditions

identical with those employed in the preparation of the conjugated cycloartenone (CIV),[36] gave an uncrystallisable gum the ultraviolet absorption of which exhibited high intensity bands at 2060, 2300 and 2400 Å., suggestive of a highly conjugated aromatic system. No trace of the expected $\Delta^{1,9(11)}$-ketone or of cycloart-1-en-3-one (λ= 2690 Å.) was detected even after dehydrobromination. It was found that a side reaction due to the effect of bromine on the 9(11)-double bond occurs since bromination of lanost-9(11)-enyl acetate itself gives a gum with the same light absorption characteristics.

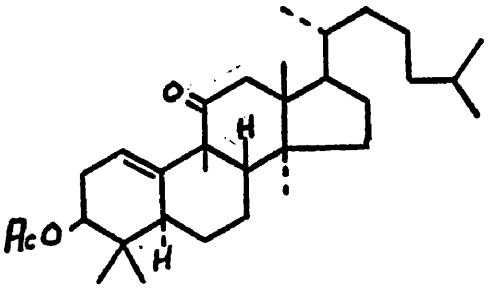
Since in a test experiment it was shown that lanost-9(11)-enyl acetate (XXV) is recovered unchanged after prolonged treatment with selenium dioxide in boiling glacial acetic acid, lanost-9(11)-en-3-one (CV) was refluxed with this reagent for periods up to 2 days in an attempt to introduce a double bond between $C_{(1)}$ and $C_{(2)}$, but again only unchanged starting material was recovered in quantitative yield.

The failure of these methods to form a 9:19-cyclopropanoid derivative led us to employ the technique used in the phyllanthol synthesis[109b,112] and which was discussed earlier. The comparable starting material in this instance is 11-oxolanostanyl acetate (LXXXVIII) which on treatment with selenium dioxide under the same conditions[112] might be expected to give rise to the intermediate unsaturated ketone (CVI). With this object in view, a solution of 11-oxolanostanyl acetate in glacial acetic acid was

boiled under reflux for 24 hours with dry selenium dioxide and the neutral fraction separated by chromatography to give unchanged 11-oxo acetate (LXXXVIII) and a colourless crystalline compound, m.p. 200-202°, $[\alpha]_D$ - 16.5°, -17° in 50% yield. In subsequent experiments the same yield of this compound was obtained after only 3-6 hours reaction time. The analysis corresponded to an emperical formula $C_8H_{12}O$, and a molecular weight estimation showed that the molecular formula is $C_{32}H_{48}O_4$. Its ultraviolet spectrum shows peaks at 2160 Å. (ε; 29,400), 2600 Å. (12,000) and 3120 Å. (1,950). By analogy with that of 12-oxo-13:27-cycloursanyl acetate (LXXVIII) (λ = 2140 Å., ε; 5,500)



(LXXXVIII)



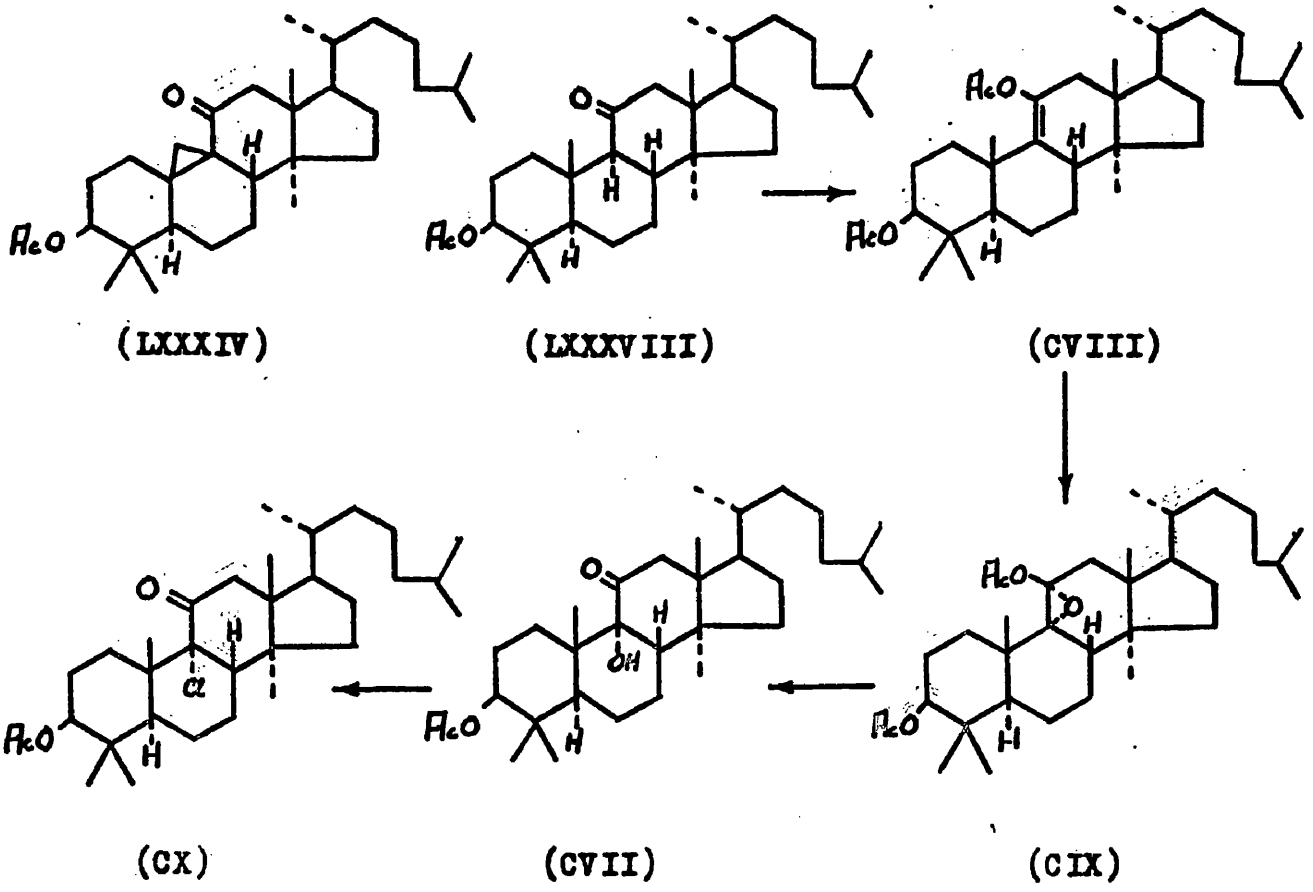
(CVI)

this compound does not contain the expected cyclopropanoid chromophore. Its infrared absorption spectrum showed the presence of acetoxy (1739 and 1243 $cm.^{-1}$), hydroxyl (3584 $cm.^{-1}$) and carbonyl (1724 $cm.^{-1}$) functional groups, while bands at 1580, 1480 and 867 $cm.^{-1}$ suggested the presence of a benzene ring. The compound is recovered unchanged after treatment with dry hydrogen chloride in acetic acid at room temperature for 3 days, conditions which isomerise 12-oxoisours-14-enyl acetate (LXXVII)

to the cyclopropanoid derivative, 12-oxo-13:27-cycloursanyl acetate (LXXVIII).

The chemistry of this new aromatic derivative from 11-oxolanostanyl acetate will be discussed in detail later.

A final attempt was made to form a 9:19-cyclopropane derivative using as starting material in this instance, 9α-hydroxy-11-oxolanostanyl acetate (CVII). It was hoped that under acid conditions this compound would dehydrate to give 11-oxocycloartanyl acetate (LXXXIV).



(LXXXIV) (LXXXVIII) (CVIII)

(CX) (CVII) (CIX)

11-Oxolanostanyl acetate (LXXXVIII) was heated under reflux with p-toluene sulphonic acid in acetic anhydride for 5 hours. Chromatography of the resultant product gave unchanged starting material and a compound, $C_{34}H_{58}O_4 \cdot \frac{1}{2}CH_3OH$, which crystallised as stout needles, m.p. 114-115°, $[\alpha]_D$ + 83.5°, from methanol. Its

infrared spectrum shows bands at 1739 and 1240 cm.$^{-1}$ (acetate) and 1764 and 1220 cm.$^{-1}$ (enol acetate), and it is considered that this is the required 3:11-diacetoxylanost-9(11)-ene (CVIII). In the steroid field[146] epoxidation of the enol acetate is carried out with ethereal monoperphthalic acid and the resultant 3β:11β--diacetoxy-9α:11α-epoxide then converted to the hydroxy ketone by treatment with methanolic potassium hydroxide followed by reacetylation. In the present instance, epoxidation of the enol acetate (CVIII) was carried out with hydrogen peroxide in acetic acid at 100°. The product crystallised from methanol to give, in 70% yield, a compound m.p. 183-184°, $[\alpha]_D$ + 66°. Its infrared spectrum shows bands at 3520 cm.$^{-1}$ (hydroxyl), 1739 and 1243 cm.$^{-1}$ (acetate) and 1720 cm.$^{-1}$ (carbonyl) and thus it cannot be the expected epoxide (CIX). The analysis supports the formula $C_{32}H_{54}O_4$ which is that required for 11-oxo-9α-hydroxy--lanostanyl acetate (CVII). The mother liquors of this compound failed to crystallise and were given a brief treatment with methanolic potassium hydroxide and reacetylated at 100°. The product readily crystallised from methanol as small prisms, m.p. 182-184°, $[\alpha]_D$ + 68°, undepressed in mixed melting point determination with the above compound. Moreover, their infrared spectra were identical and it is concluded that the compound is 9α--hydroxy-11-oxolanostanyl acetate. It appears that the epoxidation conditions used in the present work (hydrogen peroxide -acetic acid) are sufficient not only to form the epoxide (CIX) but to cause in the main, its fission to the hydroxyketone (CVII).

The uncrystallisable gum from the mother liquors, since it yields the hydroxy ketone on treatment with alkali, must consist mainly of the intermediate epoxide. When perbenzoic acid was used for the epoxidation, the product was a gum which also yielded the hydroxyketone (CVII) when treated as above.

9α-Hydroxy-11-oxolanostanyl acetate (CVII) was treated with hydrochloric-acetic acid (1:20) for 4 hours at 100°. Chromatography of the product gave a compound which crystallised from methanol as needles, m.p. 165-167°, $[\alpha]_D$ + 27.9°. It is transparent to ultraviolet light and its infrared spectrum shows bands corresponding to acetate (1739 and 1243 $cm.^{-1}$) and carbonyl (1714 $cm.^{-1}$) groups. A Beilstein test is positive for halogen and its analysis supports the formula $C_{32}H_{53}O_3Cl$. It is tentatively suggested that this compound is 9α-chloro-11-oxolanostanyl acetate (CX).

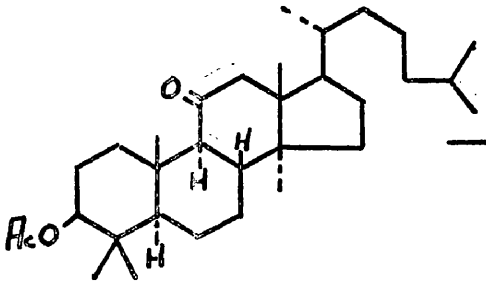
CHAPTER II

The Conversion of Lanosterol into an Aromatic Derivative.

The reaction of 11-oxolanostanyl acetate with selenium dioxide is shown to give rise to a new compound having aromatic properties. This compound has been examined in some detail and is considered to be 9β-methyl-10ξ-hydroxy-11-oxo-C-nor-D--homolanosta-12:14:16-trien-3β-yl acetate.

The aromatic acetate (m.p. 200-202°, $[\alpha]_D$ - 17°)[p.47], obtained by selenium dioxide oxidation of 11-oxolanostanyl acetate in acetic acid solution was examined in more detail with a view to ascertaining its structure.

Hydrolysis of this compound with 5% methanolic potassium hydroxide gave an amorphous white solid acetylation of which at 100° regenerates the parent acetate. The ultraviolet absorption spectrum of the amorphous solid is similar to that of the parent acetate with maxima at λ = 2160, 2600 and 3100 Å. The infrared spectrum of the amorphous solid is also identical with that of the parent acetate in all points except for the absence of the characteristic acetate bands at 1739 and 1243 $cm.^{-1}$, and it is concluded that the amorphous solid is the corresponding oxodiol. For the purpose of illustration, this oxodiol is represented by the partial formula (CXII) and the parent acetate, m.p. 200-202°, by (CXI).



$C_{30}H_{44}$ { -OH, = O, -O.CO.CH_3 } ⇌ $C_{30}H_{44}$ { -OH, = O, - OH }

(CXI) (CXII)

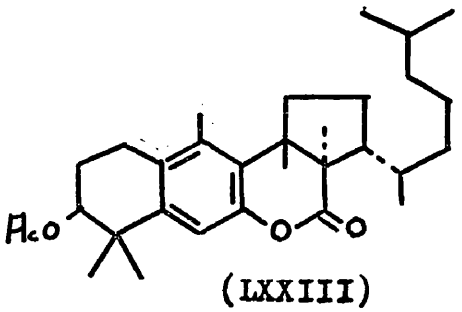
$C_{30}H_{44}$ { -O.CO.CH_3, = O, -O.CO.CH_3 } (CXXXII)

$C_{30}H_{44}$ { -OH, -OH, -O.CO.CH_3 } (CXXX)

$C_{30}H_{43}$ { -OH, = O, = O } (CXIV)

The acetate (CXI) is recovered unchanged after shaking with hydrogen over platinum in either ethyl acetate or acetic acid at room temperature. If the compound is still tetracyclic, it can be seen from its molecular formula that it must possess three double bonds. This observation together with the fact that it gives a yellow colour with tetranitromethane in chloroform yet is resistant to isomerisation or catalytic hydrogenation, further suggests the presence of an aromatic ring.

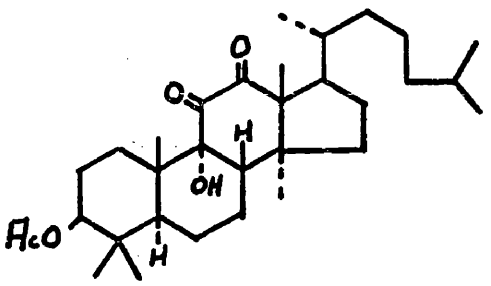
The only known aromatic compound in the lanosterol series is the phenol-lactone (LXXIII) first prepared by Barton[113] and subsequently by Menard, et al.[114] A comparison of physical constants and light absorption characteristics, shows that the aromatic acetate, m.p. 200-202° is not identical with the phenol-lactone (LXXIII).



(LXXIII)

Treatment of 11-oxolanostanyl acetate (LXXXVIII) with selenium dioxide has been described by Jeger and his colleagues[34] who used the non-polar dioxan as solvent in a sealed tube at 180°. On chromatography of the reaction product they obtained a yellow, crystalline compound, m.p. 211-212°, $[\alpha]_D$ + 140°, to which they assigned the structure represented by (CXIII). This compound, 11:12-dioxo-9α-hydroxylanostanyl acetate has again been prepared by

the author using the method of Jeger[84]. Since selenium dioxide oxidation of 11-oxolanostanyl acetate under acid conditions gives rise to the aromatic compound (CXI), it was thought possible that the hydroxydione (CXIII) was an intermediate in the formation of (CXI).



(CXIII)

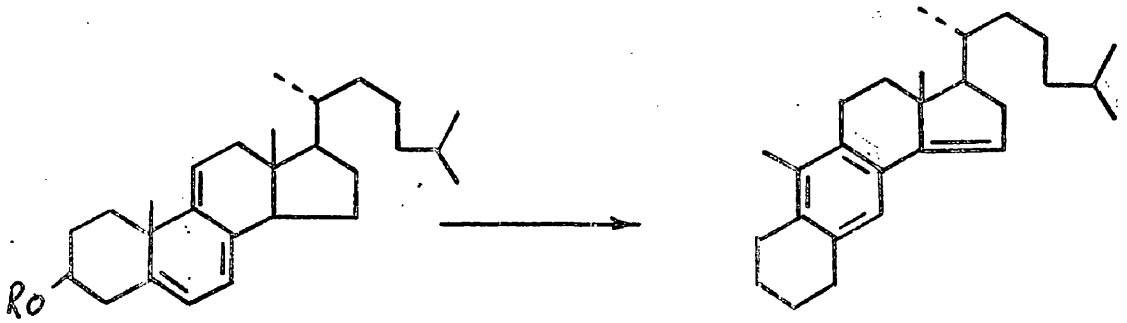
This was disproved however, since treatment of the hydroxydione (CXIII) with selenium dioxide in acetic acid resulted in the recovery of only unchanged starting material in almost quantitative yield.

The chemistry of this aromatic acetate (CXI) was studied in more detail with a view to determining (i) the position of the benzene ring and (ii) the position and nature of the hydroxyl group.

Oxidation with the chromium trioxide-pyridine complex of the oxodiol (CXII) gave a crystalline product, $C_{30}H_{44}O_3$. Its ultraviolet absorption spectrum (maxima at λ = 2160, 2620 and 3140 Å) is almost identical with that of the acetate (CXI) and with that of the corresponding oxodiol (CXII). The infrared spectrum still shows a band at 3585 $cm.^{-1}$ indicating that the hydroxyl group present in the acetate m.p. 200-202° (CXI) has not been oxidised. That is, only the hydroxyl group in the oxodiol (CXII) corresponding to the 3-acetoxy group in the parent acetate (CXI) has been attacked and the compound can be represented by the partial formula (CXIV).

From the close similarity of the ultraviolet absorption spectra of (CXI) and (CXIV), it is concluded that this new oxo-group is not in conjugation with the original chromophore. It then follows that since this oxo-group is derived from the acetoxy group at $C_{(3)}$, the original ring A has not been aromatised. Furthermore, if we concede that the carbonyl group in the aromatic acetate (CXI) is derived from the $C_{(11)}$-carbonyl group of 11-oxolanostanyl acetate, the original ring C has not been aromatised.

The possibility of aromatisation of ring B was then considered. In the steroids, aromatisation of ring B can be brought about by means of the "anthrasteroid" rearrangement. The $\Delta^{5,7,9(11)}$-trienes (CXV) on treatment with mineral acid yield the fully conjugated tetraenes (CXVI).[118] If a comparable reaction has occurred in the reaction

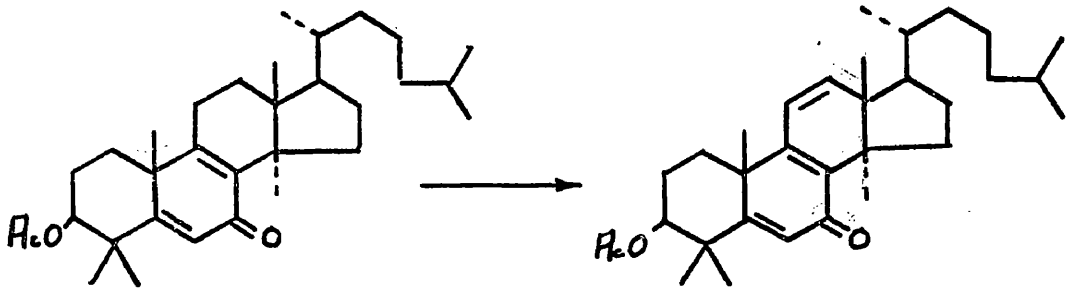


(CXV) (CXVI)

under discussion, then the $\Delta^{5,7,9(11)}$-triene system is a necessary intermediate. At an early stage it was thought that this may be the case since a product (CXVII) containing an aromatic ring, an acetoxy, a hydroxyl and a carbonyl group, could be obtained from 11-oxolanostanyl acetate.

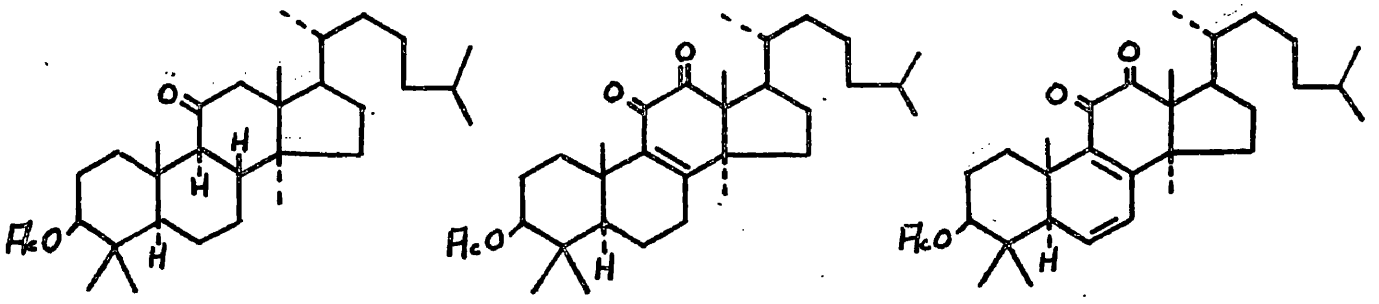
The first step in the oxidation was considered to be the introduction of a carbonyl group at $C_{(12)}$ followed by the formation

of the Δ^{8-} and then the Δ^{6-} double bonds to give 11:12-dioxolanost--8-enyl acetate (CXVIII) and the dioxodienyl acetate (CXIX) respectively, this series of reactions being comparable with the

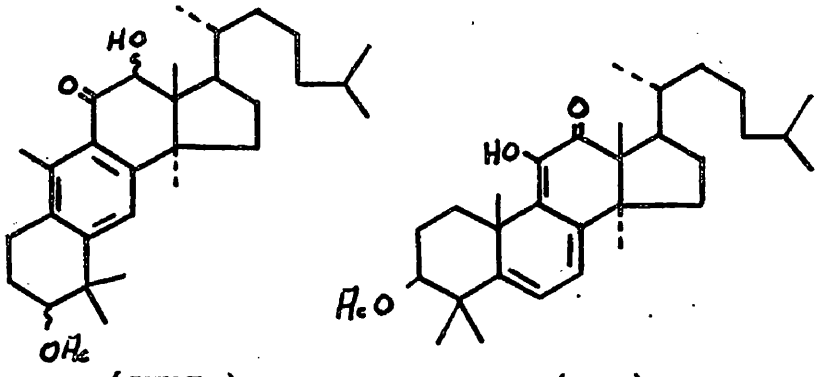


(CXXI) (CXXII)

selenium dioxide oxidation of 7-oxolanosta-5:8-dienyl acetate (CXXI) to 7-oxolanosta-5:8:11-trienyl acetate (CXXII). Enolisation of compound (CXIX) would lead to the formation of the required $\Delta^{5,7,9(11)}$ triene system in (CXX) which by means of the anthrasteroid rearrangement could yield the ring B aromatic compound (CXVII).

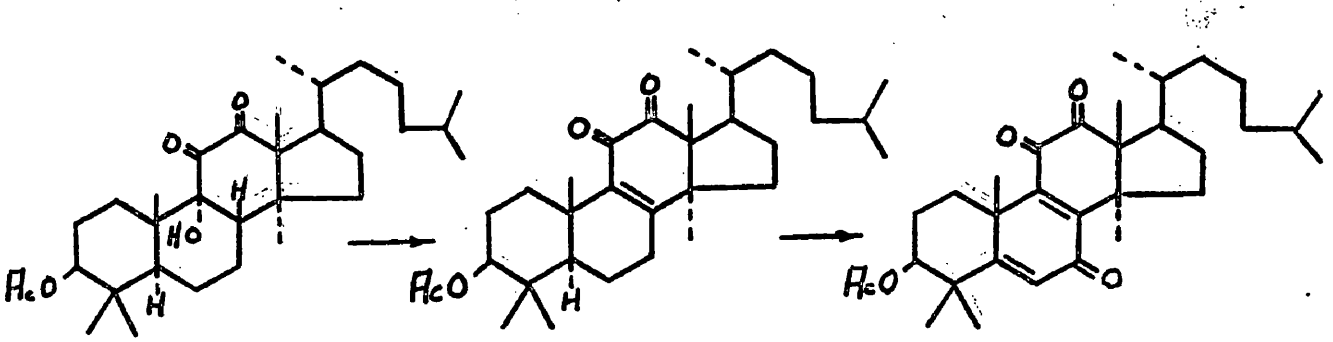


(LXXXVIII) (CXVIII) (CXIX)



(CXVII) (CXX)

In order to test this hypothesis, the preparation of the postulated intermediate, 11:12-dioxolanost-8-enyl acetate (CXVIII), was undertaken. Dehydration of 9α-hydroxy-11:12-dioxolanostanyl acetate (CXIII) was not effected by boiling acetic acid or phosphorus oxychloride in pyridine at 100°. Under vigorous conditions however, using thionyl chloride in pyridine at room temperature, a yellow, crystalline product, $C_{32}H_{50}O_4$, was obtained. The ultraviolet absorption spectrum of this compound has maxima at λ = 2100 Å. and 2800 Å. (ε; 3,900; 5,500) which together with a band at 1675 $cm.^{-1}$ in its infrared absorption spectrum, is attributed to a 3:4-unsaturated-1:2-diketone chromophore. This compound is therefore 11:12-dioxolanost-8-enyl acetate (CXVIII). Treatment



(CXIII) (CXVIII) (XLVI)

of this unsaturated diketone (CXVIII) with selenium dioxide in acetic acid and chromatography of the crude product gave 7:11:12-trioxolanosta-5:8-dienyl acetate (XLVI) identified by its optical and physical characteristics and by direct comparison with an authentic specimen.[P.34] No trace of the aromatic acetate was detected. The isolation of the trioxodienyl acetate (XLVI) shows that not only is 11:12-dioxolanost-8-enyl (CXVIII) excluded as a possible intermediate, but also that the $\Delta^{8,7,9(11)}$-triene system necessary for

aromatisation of ring B by means of the anthrasteroid rearrangement, is not formed.

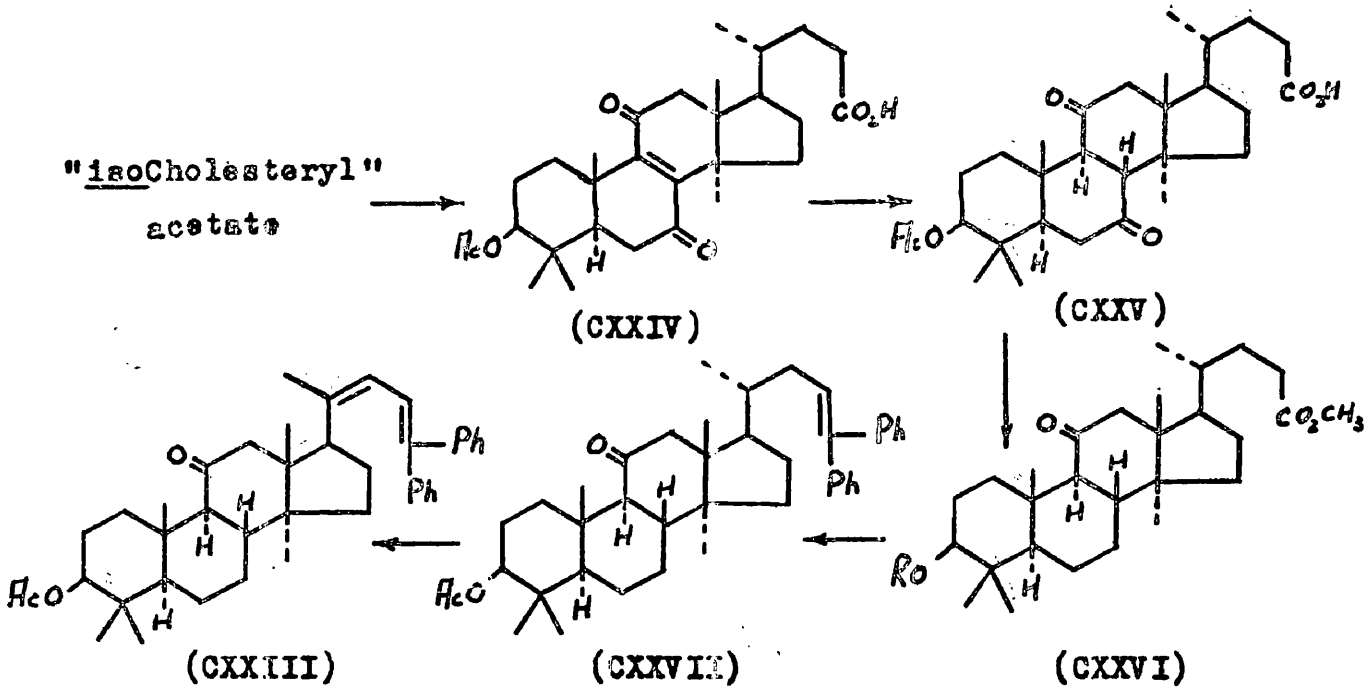
The conclusion that the aromatic centre is not situated in rings A, B, or C, suggested that the formation of the acetate, m.p. 200-202°, from 11-oxolanostanyl acetate involves aromatisation of ring D. This was supported when it was discovered that oxidation of 24:24-diphenyltrisnor-11-oxolanosta-20(22):23-dienyl acetate (CXXIII) with selenium dioxide in acetic acid yielded a yellow, amorphous solid the ultraviolet absorption spectrum of which (λ = 2070, 2400, 2650 and 3750 Å) showed that the diphenylbutadiene chromophore of (CXXIII) had been extended through another aromatic centre.

The diphenylbutadiene derivative (CXXIII) was prepared from "isocholesteryl" acetate using, in part, the methods of Ruzicka et al.[82] Oxidation of "isocholesteryl" acetate with chromium trioxide in acetic acid at 95° and crystallisation of the acid fraction from methanol gave trisnor-7:11-dioxo-3-acetoxylanost-8-en-24-oic acid (CXXIV) as yellow needles. Reduction of this dioxo-acid with zinc in acetic acid gave the saturated dioxo acid (CXXV) which on Wolff-Kishner reduction followed by esterification with ethereal diazomethane and acetylation, gave, after chromatography, trisnor--11-oxo-3-acetoxylanostan-24-oic acid methyl ester (CXXVI, R = Ac).

Treatment of the corresponding alcohol (CXXVI, R = H) with phenylmagnesium bromide in benzene-ether solution followed by dehydration and acetylation of the resultant product with acetic anhydride and potassium acetate, gave the diphenylethylene derivative

(CXXVII). Photobromination of this compound with N-bromosuccinimide in dry carbon tetrachloride followed by dehydrobromination with acetic acid and acetic anhydride in boiling carbon tetrachloride, gave the required diphenylbutadiene derivative (CXXIII), (λmax. = 3080 Å.; ε ; 27,800).

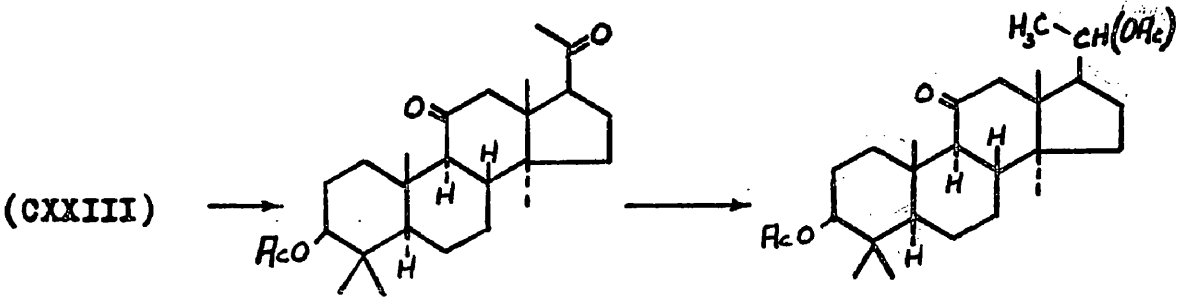
With a view to obtaining a crystalline compound exhibiting conjugation between the side chain and the aromatic ring D, the



diphenylbutadiene (CXXIII) was oxidised with chromic-acetic acid at 0°-18° to yield the 17-acetyl derivative (CXXVIII). Treatment of this diketone with selenium dioxide in acetic acid gave an uncrystallisable gum which did not exhibit any significant light absorption.

Reduction of the 17-acetyl derivative (CXXVIII) with lithium aluminium hydride in ether followed by acetylation at 100° gave the 3:20-diacetoxy-11-hydroxy derivative (not isolated) which on oxidation with the kiliani reagent gave the hitherto unknown 3:20-diacetoxy-11--oxo-derivative (CXXIX), m.p. 213-215°, $[\alpha]_D$ + 54.7°. Similar

oxidation of this oxodiacetate (CXXIX) with selenium dioxide in acetic acid failed to yield any trace of an aromatic derivative



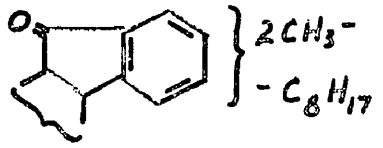
(CXXVIII) (CXXIX)

and so further conjugation with the side-chain and ring D could not be effected. It is concluded that the side-chain in compounds (CXXVIII) and (CXXIX) are susceptible to attack by selenium dioxide, hence their failure to yield any of the expected aromatic products.

Further evidence for the expansion and aromatisation of ring D was obtained when it was demonstrated that the $C_{(11)}$--carbonyl group in the aromatic acetate (CXI) is in conjugation with the benzene ring. Reduction of the acetate (CXI) with lithium aluminium hydride in ether followed by acetylation of the product at room temperature for 18 hours, gave a triol--monoacetate (CXXX), $C_{32}H_{50}O_4$, the ultraviolet spectrum of which ($\varepsilon_{2060} = 50{,}000$; $\varepsilon_{2200} = 12{,}000$; $\varepsilon_{2260} = 11{,}000$; $\varepsilon_{2720} = \varepsilon_{2800} = 687$) is markedly distinct from that of the parent compound (CXI) and typical of a non-conjugated, substituted benzene ring[118]. The infrared spectrum of the triol monoacetate (CXXX) shows in addition to acetate bands (1739 and 1243 $cm.^{-1}$), bands due to hydroxyl (3610 and 3500 $cm.^{-1}$) and benzene ring (868 and 1480 $cm.^{-1}$) absorption.

It is significant that the band at 1580 cm.$^{-1}$, which is characteristic of a conjugated phenyl group such as Ph.Co.R[116] and which is present in the infrared spectra of all the other derivatives of this aromatic acetate (CXI), is not present in the spectrum of the triol monoacetate. The triol monoacetate (CXXX) is inert to the 1:2-glycol-splitting reagent, lead tetra-acetate, starting material being recovered almost quantitatively.

The position of the carbonyl band in the infrared spectrum of the aromatic acetate (CXI), 1724 cm.$^{-1}$, is indicative of a five-membered ring ketone in conjugation with a benzene ring (which point will be dealt with fully in the subsequent discussion) and it is considered that the aromatisation of ring D is coincident with the contraction of ring C to give a C-nor-D-homo system as in (CXXXI).



(CXXXI)

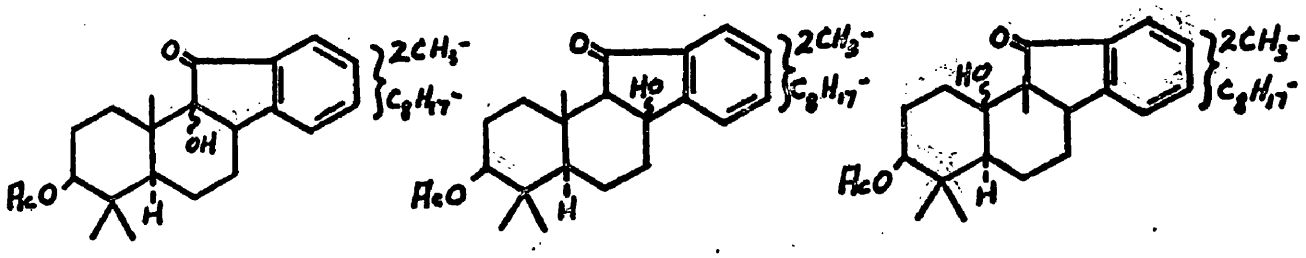
The nature and the probable position of the hydroxyl group in the aromatic acetate (CXI) were next considered. Since this compound is non-acidic and does not colour ferric trichloride solution, the hydroxyl group cannot be phenolic in nature. Attempted oxidation of this compound (CXI) with the chromium trioxide-pyridine complex, Kiliani solution or chromic-acetic acid at room temperature or at 35°, reagents which would convert a primary or a secondary hydroxyl group to an aldehyde or a ketone respectively, was unsuccessful, unchanged starting material being

recovered in good yield. More vigorous oxidation of (CXI) using chromic-acetic acid at 95°, however, gave an acidic product which could not be crystallised. It is thus concluded that the hydroxyl group is tertiary and, since the hydroxyl (3585 $cm.^{-1}$) and carbonyl (1724 $cm.^{-1}$) bands in its infrared spectrum are indicative of hydrogen bonding, that it is positioned α- or β- to the $C_{(11)}$-carbonyl group. The tertiary nature of the hydroxyl group was confirmed by the fact that it did not acetylate under the normal conditions of heating with acetic anhydride and pyridine at 100° for 2-3 hours, but did acetylate under vigorous conditions using acetyl chloride and dimethylaniline in boiling chloroform solution for 20 hours, to give the corresponding oxodiacetate (CXXXIX), $C_{34}H_{50}O_5$, m.p. 165-166°, $[\alpha]_D$ - 49°. The absence of a band at 1770 $cm.^{-1}$ in its infrared spectrum which is typical of phenolic esters[116], confirms that the hydroxyl group is not directly attached to the benzene ring. This evidence excludes the possibility of the aromatisation occurring by means of the dienone-phenol rearrangement since the product would in that case necessarily be phenolic.

The only position for this tertiary hydroxyl group α- or β- to the $C_{(11)}$-carbonyl group is $C_{(8)}$, $C_{(9)}$ or $C_{(10)}$, the latter being permissible only if the $C_{(10)}$-methyl group has migrated to, say, $C_{(9)}$. That is, formula (CXI) can be extended to (CXIa), (CXIb) or (CXIc).

Formula (CXIa) is excluded on the following considerations. Firstly, the corresponding triol monoacetate (CXXX) does not appear

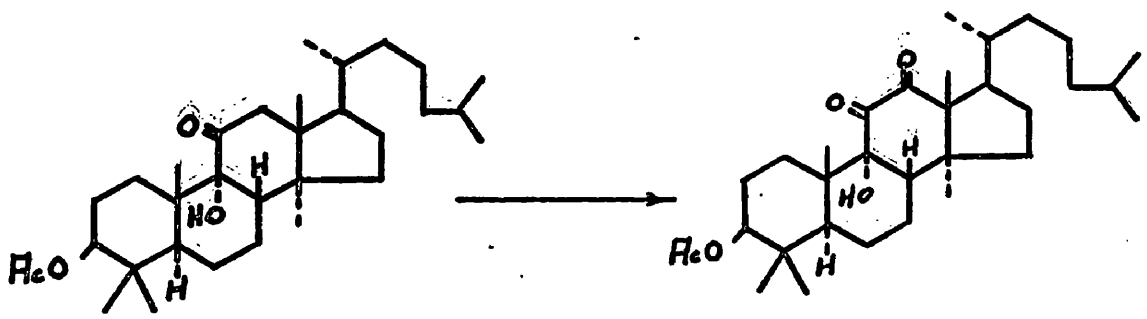
to possess a 1:2-glycol system, since it is stable to treatment with lead tetra-acetate. Secondly, if (CXIa) is correct, 11-oxo-9-hydroxylanostanyl acetate (CVII) would be an intermediate



(CXIa) (CXIb) (CXIc)

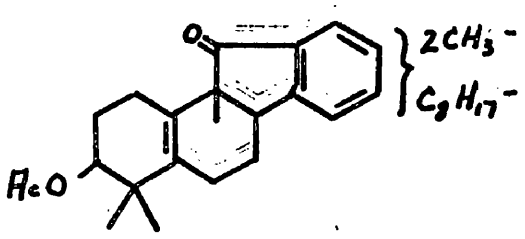
in its formation from 11-oxolanostanyl acetate.

To test this possibility, 11-oxo-9-hydroxylanostanyl acetate (CVII) was treated with selenium dioxide in acetic acid and the neutral fraction chromatographed over alumina to give as the sole product, 11:12-dioxo-9α-hydroxylanostanyl acetate (CXIII), identical in all respects with an authentic specimen. No trace of the aromatic derivative (CXI) was detected. The possibility that the hydroxyl group is introduced at $C_{(9)}$ <u>after</u> aromatisation has taken place is discounted on the basis of the following consideration.

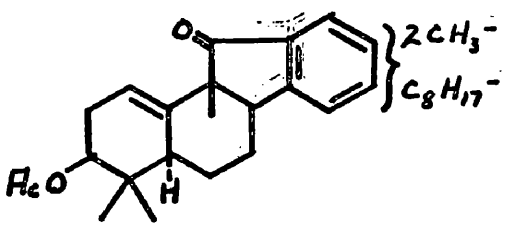


(CVII) (CXIII)

Dehydration of the aromatic acetate (CXI) with phosphorus oxychloride in pyridine at 100° for 3 hours gave an uncrystallisable gum. The ultraviolet spectrum of this gum differed only from that of the parent compound (CXI) in that it had a shoulder at 2080-2100 Å. typical of an isolated double bond. The presence of an isolated double bond is also inferred from its infrared spectrum which includes sharp bands at 1630 and 890 $cm.^{-1}$ but does not include hydroxyl absorption in the 3300-3600 $cm.^{-1}$ region. The Ph.CO-R system absorbs at 875, 1480 and 1580 $cm.^{-1}$, and the carbonyl absorption, now free of hydrogen bonding, has decreased to 1710 $cm.^{-1}$ as in the α-indanones.[116] These considerations indicate that dehydration of compound (CXI) has occurred to yield a compound containing a non-conjugated double bond. This evidence eliminates formula (CXIa) which would give rise to the conjugated Δ^{8}- double bond, and formula (CXIb) which would give either a Δ^{6}- or a Δ^{7}- double bond, both of which would be conjugated with the original chromophore. This allows only formula (CXIc) in which the hydroxyl group at $C_{(10)}$ is separated from the $C_{(11)}$-carbonyl group by the fully substituted carbon atom, $C_{(9)}$. The dehydration product is thus either (CXXXIII) or (CXXXIV).



(CXXXIII)



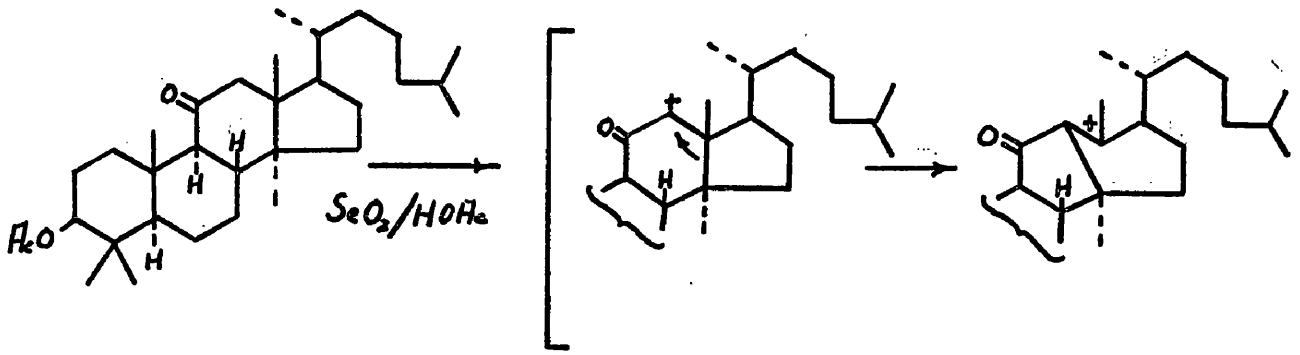
(CXXXIV)

Although a decision between formulae (CXXXIII) and (CXXXIV) is not pertinent to the argument, the latter is preferred on account of the position of the bands at 1630 and 890 cm.$^{-1}$ in its infrared spectrum which suggest the presence of a trisubstituted or a disubstituted double bond in preference to a tetrasubstituted double bond. In any case, the hydroxy group must be attached to $C_{(10)}$. This is supported by the fact that the two hydroxyl bands at 3610 and 3500 cm.$^{-1}$ in the infrared spectrum of the triol monoacetate (CXXX) are in a similar position to the bands exhibited by cyclohexane-1:3-diol (3620 and 3540 cm.$^{-1}$) where the hydroxyl groups are both cis- and axial.[116] They are quite distinct from those of the other possible cyclohexane-diol isomers, and it is concluded that the hydroxyl groups in the triol monoacetate (CXXX) are attached to $C_{(11)}$ and $C_{(10)}$, being cis- and axial.

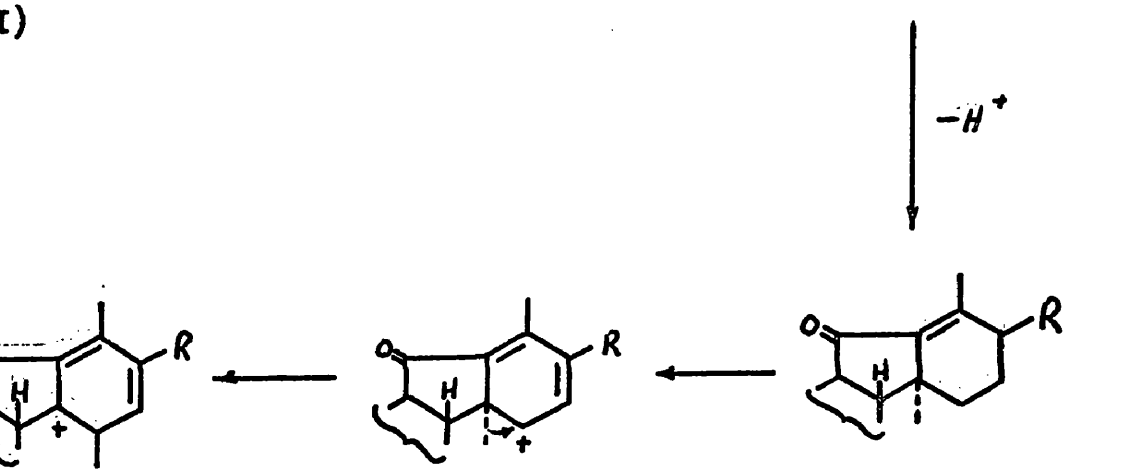
The mechanism proposed for the formation of the aromatic acetate (CXI) and (CXIc) from 11-oxolanostanyl acetate (LXXXVIII) is formulated below, these partial formulae being thus extended to (CXXXV). This compound is named 9β-methyl-10ʃ-hydroxy-11-oxo-C-nor-D-homolanosta-12:14:16-trienyl acetate.

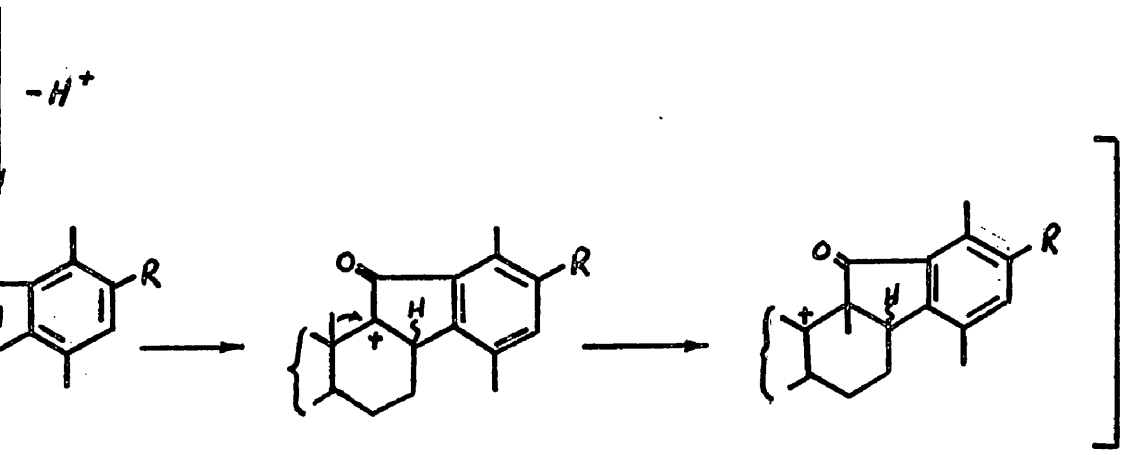
In the course of the reaction, the configuration of the hydrogen atom attached to $C_{(8)}$ can be inverted and if this is the case this inversion to the 8α- form may provide the driving force for the methyl group migration from $C_{(10)}$ to $C_{(9)}$.

The partial formulae (CXII), (CXIV), (CXXX) and (CXXXII) can thus be extended to (CXXXVI), (CXXXVII), (CXXXVIII) and (CXXXIX) respectively.

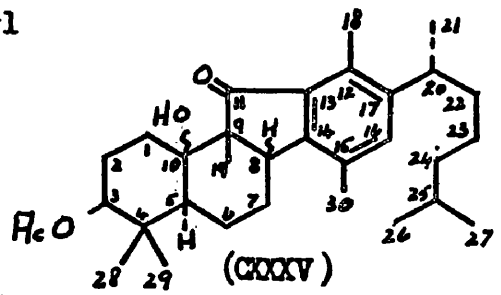


(LXXXVIII)





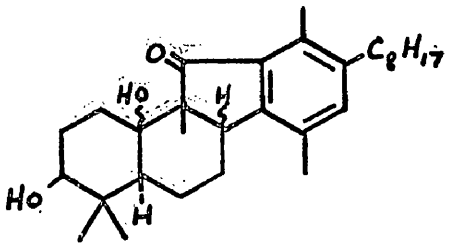
R = isoOctyl



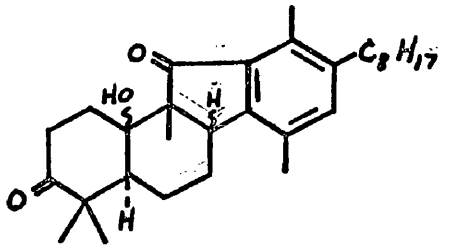
(CXXXV)

The following points already referred to briefly in the text, require further elaboration and discussion.

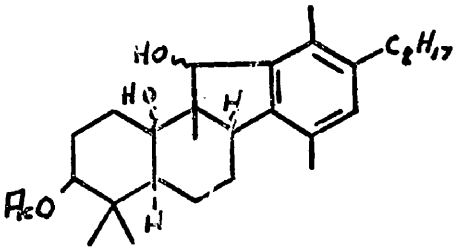
The infrared absorption spectra of the aromatic acetate (CXXXV) and of the corresponding alcohol (CXXXVI) exhibit



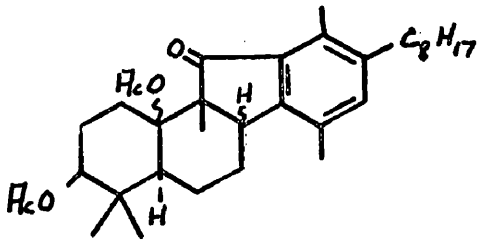
(CXXXVI)



(CXXXVII)

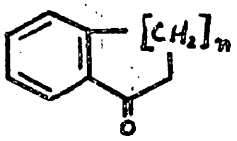


(CXXXVIII)

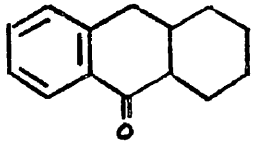


(CXXXIX)

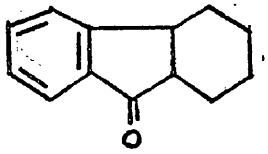
carbonyl absorption at 1722-1724 cm.$^{-1}$. Considering compounds represented by (CXL), when $n = 1$ as in the α-indanones, the wave number of its carbonyl absorption is 1709 cm.$^{-1}$. In the α-tetralones ($n = 2$) the average value[116] is 1703 cm.$^{-1}$, and as n increases the wave number of its carbonyl absorption decreases to 1660-1680 cm.$^{-1}$. In the case of the simple Ph.Co.R type, the value[116] is in the 1690 cm.$^{-1}$ region. Thus, the greater the strain imposed on the carbonyl group by virtue of ring contraction, the greater is the wavenumber of its absorption, and it is this effect which is in part responsible for the large value of 1724 cm.$^{-1}$ encountered in this instance.



(CXL)



(CXLI)



(CXLII)

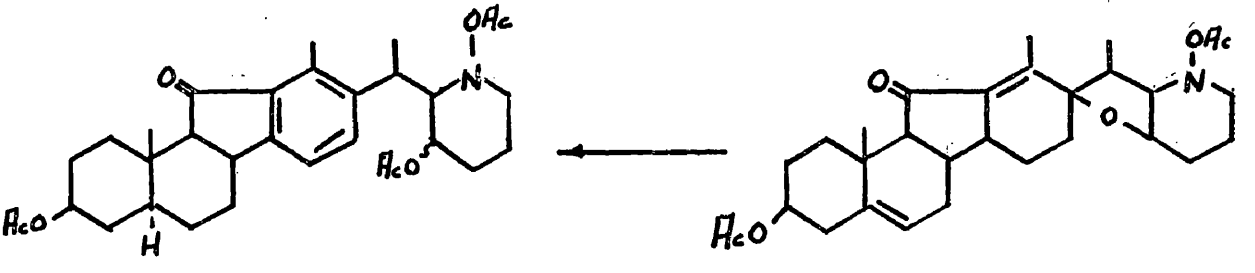
A second determining factor is the effect of substitution. The 2:3-cyclopentanotetralone (CXLI) shows absorption at 1680-1686 cm.$^{-1}$, whereas the corresponding indanone derivative (CXLII) absorbs at 1715 cm.$^{-1}$. In the former case where the carbonyl--bearing ring is six-membered, increased substitution has led to a decrease in the wavenumber from 1703 cm.$^{-1}$ as in α-tetralone (CXL, n = 2). In the latter case, the value has <u>increased</u> from 1709 cm.$^{-1}$ to 1715 cm.$^{-1}$. This observation lends further support for the C-nor-D-homo system of the aromatic acetate (CXXXV). It is also noted that the same relationship between ring size and wavenumber as already observed for the compounds (CXL), is also evident in the case of the corresponding substituted derivatives (CXLI, 1680-6 cm.$^{-1}$) and (CXLII, 1715 cm.$^{-1}$).

A further factor to be considered is the effect of the hydroxyl group on the carbonyl absorption. Present data for α-hydroxy-ketones[116] shows that the wavenumber in the case of the latter compounds is somewhat lower than for the free, non-bonded ketone. It is observed by the author, however, that while 11-oxolanostanyl acetate exhibits carbonyl absorption at 1707-1710 cm.$^{-1}$, 9α-hydroxy-11-oxolanostanyl acetate shows

absorption at 1715-1720 cm.$^{-1}$, an <u>increase</u> of <u>ca.</u> 7-10 mu.$^{-1}$ It is thus concluded that the value of 1724 cm.$^{-1}$ observed for compounds (CXXXV) and (CXXXVI) is due also in part to this hydrogen bonding effect and in part to the effect of ring size and substitution.

As would be expected if the above argument is valid, the hydrogen bonding effect is partly removed in the case of the oxodiacetate (CXXXIX) (1718 cm.$^{-1}$) and completely in the case of the dehydration product (CXXXIV) (1711 cm.$^{-1}$).

The structure (CXXXV) proposed for the aromatic acetate is similar in many respects to 11-oxotriacetylveratramine (CXLIII) which structure was assigned to it by Tamm and Wintersteiner[120]. This compound is identical with the dihydroderivative of the product of acetolysis of O,N-diacetyljervine (CXLIV)[122]. The



(CXLIII) (CXLIV)

ultraviolet absorption spectrum of the aromatic ketone(CXLIII) shows maxima at λ = 2510 Å. (10,700) and 3,000 Å. (2,000) similar to that of the α-tetralones and α-indanones. In the present case, the aromatic acetate (CXXXV) has maxima at λ= 2600 Å. (11,000) and 3100 Å. (2,000). The bathochromic displacement from the expected 2500 Å. to 2600 Å. is believed to be due in part to the effect of the 9β-methyl and 10β-hydroxy substituents in the close

proximity of the $C_{(11)}$-carbonyl. The value of 2650 Å. observed in an 11-oxoveratramine derivative is explained by Wintersteiner[117] as being due to a hydrogen bonding effect.

The ultraviolet absorption of the triol monoacetate (CXXXVIII) with peaks at λ = 2720 Å. and 2800 Å (ε;678:678) corresponds with that of the 11-hydroxyveratramine derivative (λ = 2660 Å. and 2770 Å.) formed by reduction of ketoveratramine (CXLIII) with zinc in acetic acid.

It is of interest to note that the C-D ring system of O,N-diacetyljervine (CXLIV) and which so readily aromatises on acetolysis to that in ketoveratramine (CXLIII), has been postulated as being intermediate in the formation of the aromatic acetate (CXXXV) from 11-oxolanostanyl acetate.

CHAPTER III

The Constitution of Butyrospermol

Butyrospermol, a tetracyclic triterpenoid from the non-saponifiable fraction of shea-nut fat, is shown to be 9α-eupha-7:24-dien-3β-ol. Experiments which led to the complete elucidation of the structure and stereochemistry of butyrospermol are described.

Heilbron, Moffat and Spring[123] isolated in 1934, a new triterpenoid alcohol which they named basseol, of approximate molecular formula $C_{30}H_{50}O$, from the non-saponifiable material of shea-nut fat (Butyrospermum parkii). Basseol was shown to be tetracyclic when treatment with perbenzoic acid revealed the presence of two non-conjugated double bonds, one of which was resistant to catalytic hydrogenation.[124] The same workers also deduced that the reactive double bond was present in a vinylidene group since ozonolysis of basseol acetate gave formaldehyde in 20% yield, and they claimed that on treatment with various acidic reagents it was converted to β-amyrin acetate.

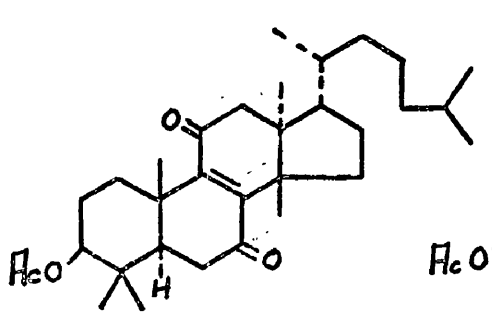
In a subsequent re-examination of shea-nut fat, Heilbron, Jones and Robins[125] again isolated an acetate, the physical constants of which (m.p. 139-141°, $[\alpha]_D$ + 23°) were in agreement with those previously recorded for basseol acetate. However, this was shown to be a mixture since on repeated recrystallisation it yielded an acetate, m.p. 146.5-147.5°, $[\alpha]_D$ + 11° which was named butyrospermyl acetate, alkaline hydrolysis of which gave butyrospermol, m.p. 111-113°, $[\alpha]_D$ - 12°. This new acetate differed markedly from basseol acetate as it was shown to possess an isopropylidene group and not a vinylidene group and failed to give any trace of β-amyrin acetate on treatment with mineral acid. Basseol acetate is now considered to be a mixture of butyrospermyl acetate together with approximately 16% of β-amyrin acetate[30,126,127]. Basseol itself, however, is a pure compound identical with butyrospermol, the

product of alkaline hydrolysis of butyrospermyl acetate.

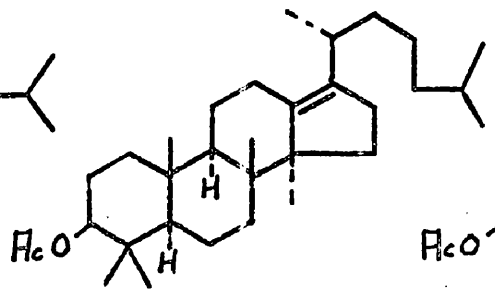
Butyrospermol has also been isolated from the fruits of Artocarpus integrifolia[31] and has recently been obtained in these laboratories from horse-chestnut fat.

Butyrospermol was characterised[125] as a tetracyclic, diethenoid alcohol, $C_{30}H_{50}O$, the reactive double bond being present in an isopropylidene group. The less reactive double bond which is not catalytically reduced but which does react with perbenzoic acid, was deduced, on the basis of the infrared spectrum of butyrospermene,[126] to be tetrasubstituted. Later, Halsall[129] stated that in addition, this double bond is endocyclic and probably in a similar position to that in lanost-8-enol. Dawson et al.,[30] showed that on treatment with mineral acid, dihydrobutyrospermyl acetate is converted to the isomeric dihydroisobutyrospermyl acetate the double bond of which was now considered to be tri-substituted. This isomerisation was thought to be analogous to the conversion of lanost-8-enyl acetate to its Δ^{7}-isomer. This conclusion was disproved however, by Spring and his co-workers[126] who showed conclusively that dihydroisobutyrospermyl acetate is identical with euph-8-enyl acetate by its conversion into 7:11-dioxoeuph-8-enyl acetate (LXXXV) on chromic-acetic acid oxidation; into isoeuph-13(17)--enyl acetate (LXVI) on isomerisation with hydrochloric-acetic acid and into 8:9-epoxyeuphanyl acetate (CXLV) on treatment with perbenzoic acid.

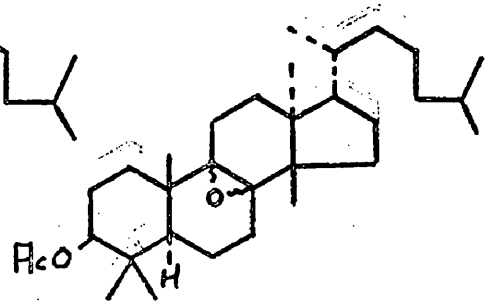
The close relationship between butyrospermol and euphol was confirmed by the conversion of the former into the latter.[126]



(LXXXV)



(LXVI)

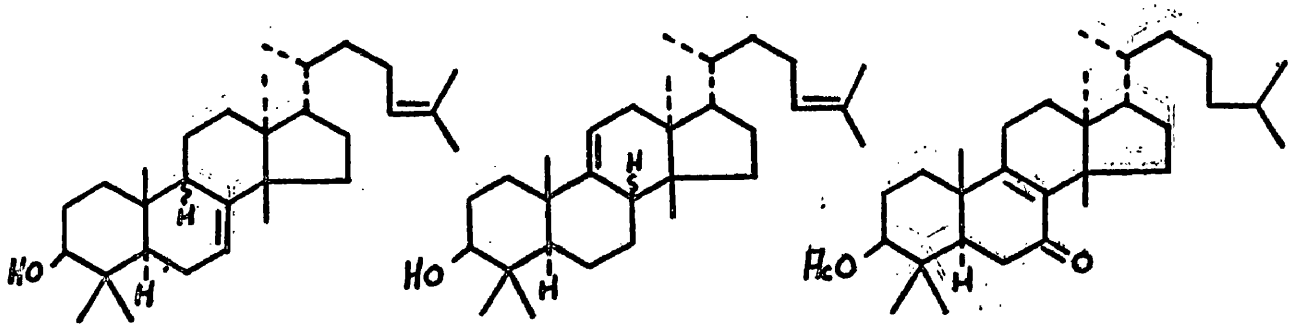


(CXLV)

Addition of bromine to the side-chain double bond in butyrospermyl acetate followed by isomerisation of the nuclear double bond with hydrogen chloride in chloroform at 0° and then regeneration of the side-chain double bond with zinc in acetic acid, gave eupha-8:24-dienyl acetate (euphyl acetate). Treatment of dihydrobutyrospermyl acetate with osmic acid, followed by acetylation gave a saturated triol-diacetate thus indicating that the nuclear double bond of butyrospermol is tri- and not tetrasubstituted. This fact, together with the observation that the triol-diacetate is converted into eupha-7:9(11)-dienyl acetate by mild heat treatment led these workers to conclude that butyrospermol is either 9β-eupha-7:24-dien-3β-ol (CXLVI) or 8β-eupha-9(11):24-dien-3β-ol (CXLVII). A similar conclusion was reached simultaneously by Jones and his colleagues[127] who stated a preference for the 9β-formulation of (CXLVI).

Jones[127] obtained 7-oxoeuph-8-enyl acetate (CXLVIII) on treatment of dihydrobutyrospermyl acetate with excess perbenzoic acid. From this and other reactions he deduced that butyrospermol

differs from euphol only in the position of the nuclear double bond which could be between $C_{(7)}$ and $C_{(8)}$ or between $C_{(9)}$ and $C_{(11)}$, since both these isomers could give rise to the αβ-unsaturated

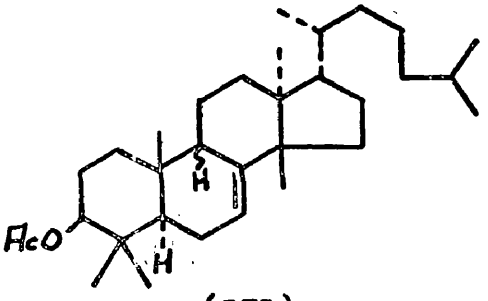


(CXLVI) (CXLVII) (CXLVIII)

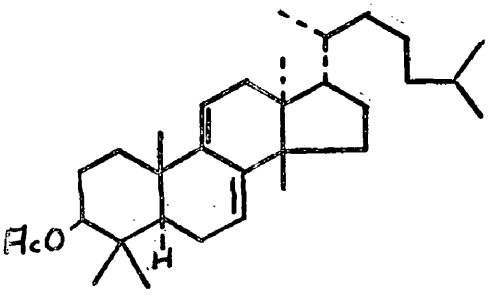
ketone (CXLVIII) if eupha-7:9(11)-dienyl acetate (XVIII) is an intermediate. Furthermore, a comparison of the behaviour of dihydrobutyrospermyl acetate with that of lanost-7-ene and lanost-8-ene derivatives on mineral acid treatment led Jones to suggest that dihydrobutyrospermyl acetate is a euph-7-enyl acetate (CIL) since, as with dihydrobutyrospermyl acetate, in lanost-7-enyl acetate the double bond is inert towards hydrogenation and is partially isomerised to the 8:9-position on treatment with mineral acid. If such is the case, there are two possible structures for butyrospermol depending on the configuration of the hydrogen atom attached to $C_{(9)}$. The euph-7-enyl acetate prepared by Barton[102] by Wolff-Kishner reduction of 7-oxoeuph-8--enyl acetate (CXLVIII) and which differs from dihydrobutyrospermyl acetate, is assumed by Jones[127] to have the $C_{(9)}$-hydrogen atom in the α-configuration. Also, in order to explain the large negative change in molecular rotation when butyrospermol and

cycloartenol (XXI) are oxidised to the corresponding 3-ketones, Jones suggested that like cycloartenol, butyrospermol has a 9β-substituent. The experiments described below, however, show that butyrospermol has the 9α-configuration and is 9α-eupha-7:24--dien-3β-ol (XXX).

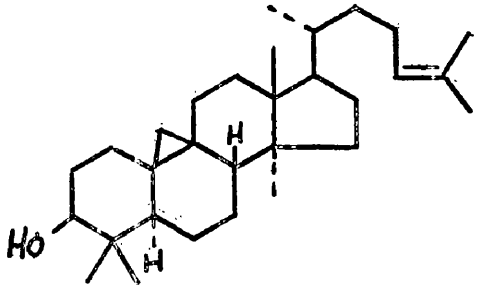
Isolation of pure butyrospermol or butyrospermyl acetate by extensive crystallisation of basseol or basseol acetate results



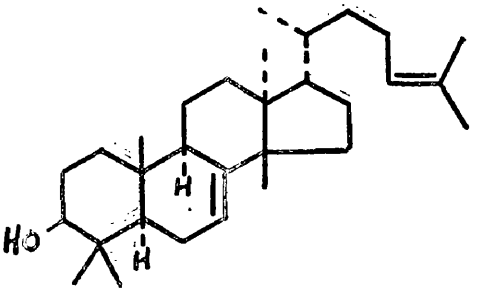
(CIL)



(XVIII)



(XXI)



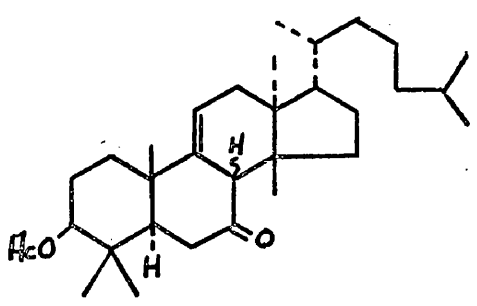
(XXX)

in very large losses of material. The starting material used in many of the following experiments, dihydrobutyrospermyl acetate, is readily separable from β-amyrin acetate by chromatography[127,130] and this technique was employed by the author.

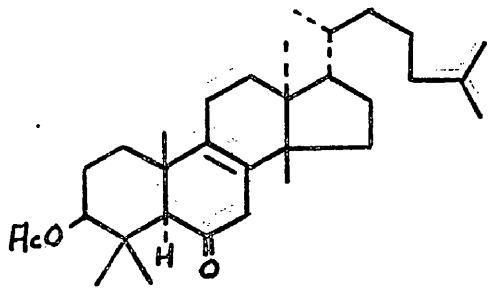
Hydrolysis of shea-nut fat with alcoholic potassium hydroxide solution gave the non-saponifiable material as a yellow resin in 3% yield. This material was refluxed in acetic anhydride for 3 hours and allowed to stand at room temperature overnight. The semi-crystalline mass which separated was removed and the filtrate kept at 0° for a further 2 days when a second crop of material separated. This product on crystallisation from ethanol-ethyl acetate gave bassool acetate as stout needles, m.p. 136-138°, $[\alpha]_D$ + 23°. Catalytic hydrogenation of this material in ethyl acetate solution and filtration of the product in light petroleum through alumina, gave fractions which consisted of pure dihydrobutyrospermyl acetate, m.p. 135-136°, $[\alpha]_D$ + 10.8°. Subsequent fractions were found to be mainly β-amyrenyl acetate and lupanyl acetate.

During the present investigation, it was found in these laboratories by Dr. W. Lawrie that mild chromic acid oxidation of dihydrobutyrospermyl acetate, followed by careful chromatography of the product, gave a new compound $C_{32}H_{52}O_3$. From a study of its light absorption spectra, this acetate was shown to possess a carbonyl group in a six-membered ring and an isolated double bond, and was named oxo<u>apo</u>euphenyl acetate, a non-conjugated, unsaturated ketone. After treatment with dry hydrogen chloride in chloroform at 0°, conditions which isomerise dihydrobutyrospermyl acetate to euph-8-enyl acetate, oxo<u>apo</u>euphenyl acetate was recovered unchanged. However, by using hydrochloric acid in acetic acid at 100° conditions which convert euph-8-enyl acetate into <u>iso</u>euph-

-13(17)-enyl acetate (LXVI), oxoapoeuphenyl acetate is converted into an isomeric non-conjugated unsaturated ketone which on reduction by the forcing method of the Wolff-Kishner reaction[131] and reacetylation, gave isoeuph-13(17)-enyl acetate, identical with an authentic specimen prepared from euph-8-enyl acetate. This isomeric ketone is thus an oxoisoeuph-13(17)-enyl acetate in which the carbonyl group is not at $C_{(12)}$ since the compound does not exhibit the ultraviolet absorption typical of an α:β-unsaturated ketone. That the carbonyl group in oxoisoeuph-13(17)-enyl acetate does not include $C_{(11)}$ was shown by the preparation of an oxoisoeupha-11:13(17)-dienyl acetate by selenium dioxide oxidation of oxoisoeuph-13(17)- enyl acetate. Hence since the carbonyl group in oxoisoeuph-13(17)-enyl acetate and therefore in oxoapoeuphenyl acetate is neither at $C_{(11)}$ or $C_{(12)}$, it must be at either $C_{(8)}$ or $C_{(7)}$.



(CL)



(CLI)

If oxoapoeuphenyl acetate has been formed from dihydrobutyrospermyl acetate without any molecular rearrangement, then it must be represented by structures (CL) or (CLI), and the

reaction would have to proceed *via* eupha-7:9(11)-dienyl acetate (XVIII) since a double bond will not move out of conjugation with a carbonyl group under the reaction conditions. In order to prove or disprove this hypothesis, the diene (XVIII) was oxidised with chromic-acetic acid under conditions identical with those used in the preparation of oxo*apo*euphenyl acetate from dihydrobutyrospermyl acetate. Careful chromatography of the resultant product did not however, reveal any trace of oxo*apo*euphenyl acetate; only 7-oxoeuph-8-enyl acetate (CXLVIII) and 7:11-dioxoeuph-8-enyl acetate (LXXXV) were obtained in low yield together with starting material. Thus since eupha-7:9(11)-dienyl acetate is not an intermediate in the formation of oxo*apo*euphenyl acetate from dihydrobutyrospermyl acetate, oxo*apo*euphenyl acetate cannot be represented by formula (CL). This decision, together with the exclusion of formulae for oxo*apo*euphenyl acetate in which the carbonyl group is at $C_{(11)}$ or $C_{(12)}$, shows that butyrospermol is not a eupha-9(11):24-dienol (CXLVII) and is thus a eupha-7:24--dienol (CXLVI) in which only the configuration of the $C_{(9)}$-hydrogen atom remains to be determined. Similar oxidation of euph-8-enyl acetate gave a mixture which failed to disclose any trace of oxo*apo*euphenyl acetate, showing that the latter compound is not formed from dihydrobutyrospermyl acetate *via* euph-8-enyl acetate.

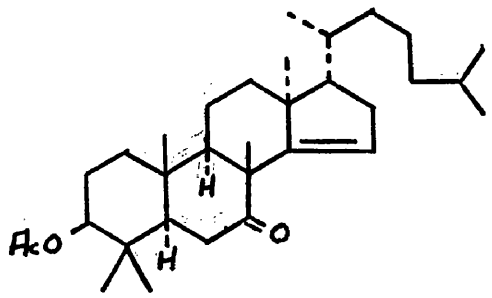
The alternative formula (CLI) for oxo*apo*euphenyl acetate was also excluded since on reduction with the forcing conditions of the Wolff-Kishner reaction it gives *apo*euphenyl acetate which

is not identical with euph-8-enyl acetate. From a consideration of its light absorption spectra, the double bond in oxoapoeuphenyl acetate is deduced to be trisubstituted. The decision that oxoapoeuphenyl acetate is neither (CL) nor (CLI) is supported by the observation mentioned earlier, that it is not isomerised by treatment with acid or alkali to an αβ-unsaturated ketone.

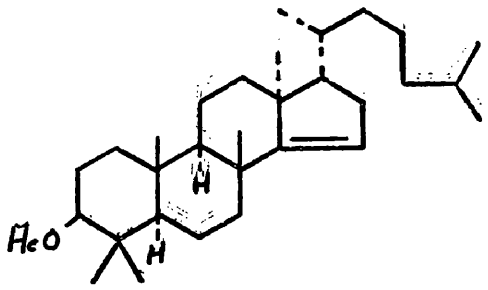
These considerations show that the formation of oxoapoeuphenyl acetate from dihydrobutyrospermyl acetate has involved a molecular rearrangement, the carbonyl group being insulated from the double bond by a fully substituted carbon atom. A further study of apoeuphenyl acetate supported this decision. Treatment of this acetate with dry hydrogen chloride in chloroform at 0° converts it into isoeuph-13(17)-enyl acetate (LXVI). Under the same condition euph-8-enyl acetate is unchanged and dihydrobutyrospermyl acetate is isomerised to euph-8-enyl acetate.

Thus the formation of oxoapoeuphenyl acetate from dihydrobutyrospermyl acetate (a euph-7-enyl acetate) involves a synchronous reaction in which oxidation of the Δ^7-double bond is accompanied by the migration of the 14β-methyl group to $C_{(8)}$, thereafter one of two possible paths being followed. In the first, the reaction terminates in the loss of a proton from $C_{(15)}$. In the second, the movement of the 14β-methyl group to $C_{(8)}$ is accompanied by the migration of the 13α-methyl group to $C_{(14)}$ and the loss of a proton from $C_{(12)}$. In either case, the carbonyl group is at $C_{(7)}$ and 7-oxoapoeuphenyl acetate is thus

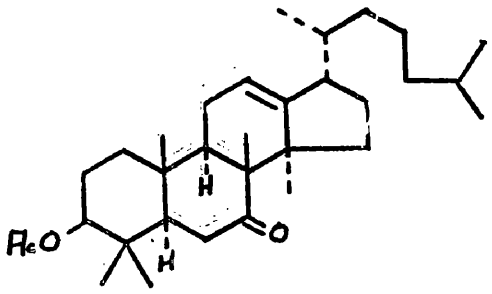
(CLII) or (CLIV), and apoeuphenyl is consequently (CLIII) or (CLV).



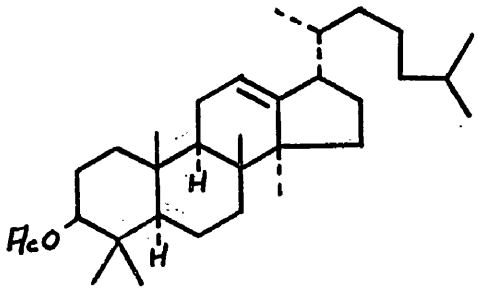
(CLII)



(CLIII)



(CLIV)

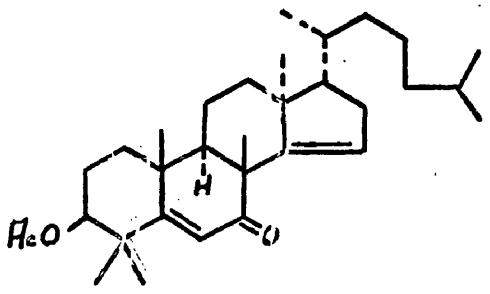


(CLV)

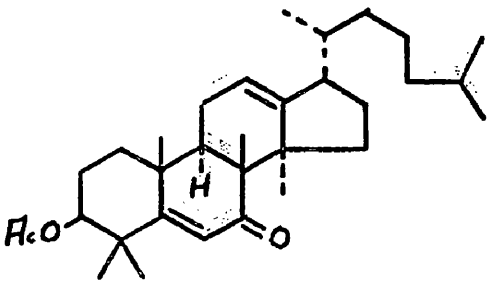
It is a fundament of these mechanisms that the $C_{(9)}$-hydrogen atom in dihydrobutyrospermyl acetate is not involved in its oxidation to 7-oxoapoeuphenyl acetate, and this is substantiated by the observation recorded above that neither eupha-7:9(11)-dienyl acetate nor euph-8-enyl acetate are intermediates in the formation of this oxo-acetate. Consequently, the configuration of the $C_{(9)}$-hydrogen atom in dihydrobutyrospermyl acetate must be the same (α) as that in isoeuph-13(17)-enyl acetate (LXVI). It

is concluded then that butyrospermol is 9α-eupha-7:24-dien-3β-ol (CIL).

Although a decision between formulae (CLII) and (CLIV) for 7-oxo<u>apo</u>euphenyl acetate is not pertinent to the argument regarding the structure and stereochemistry of butyrospermol, the former structure is preferred for the following reasons. Firstly, Lawrie has shown that selenium dioxide oxidation of 7-oxo<u>apo</u>euphenyl acetate gives an αβ-unsaturated ketone, $C_{32}H_{50}O_3$, which on the basis of its light absorption characteristics has this additional conjugated double bond in the 5:6-position, and is either (CLVI) or (CLVII). The fact that the double bond in

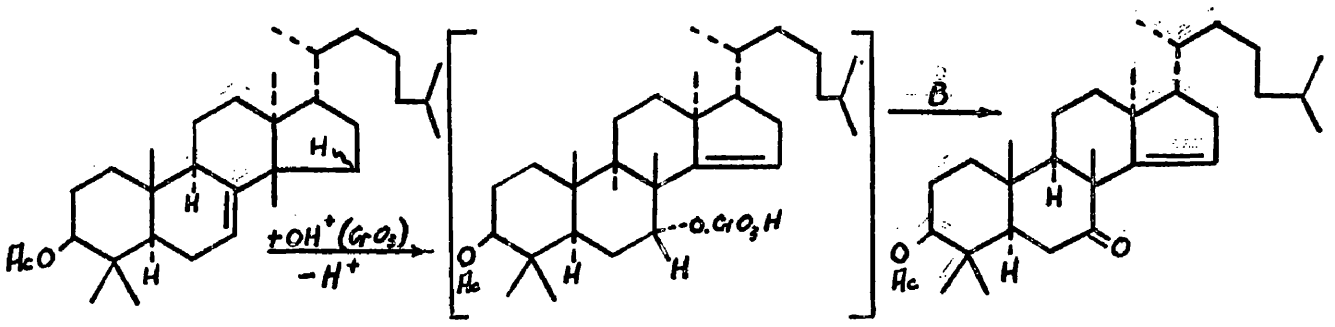


(CLVI)



(CLVII)

7-oxo<u>apo</u>euphenyl acetate is unattacked by selenium dioxide supports the view that this compound is (CLII) and not (CLIV). <u>apo</u>Euphenyl acetate is thus correctly represented by formula (CLIII). The formation of 7-oxo<u>apo</u>euph-14-enyl acetate from dihydrobutyrospermyl acetate is represented as attack at the Δ^7-double bond from the rear (α) side as shown.



(LXXXI) (CLII)

The fact that apoeuphenyl acetate (CLIII), a compound containing a relatively stable double bond in a position intermediate between euph-8-enyl acetate and isoeuph-13(17)-enyl acetate has been obtained as outlined above, suggested that it may also be a stable intermediate in this isomerisation. In attempts to isolate this possible intermediate, euph-8-enyl acetate in acetic acid was treated with trichloracetic acid at room temperature overnight, at 100° for 3 hours and under reflux for 3 hours. In each case starting material was recovered in quantitative yield, the iso derivative only being obtained when the normal method of treatment with hydrochloric-acetic acid at 100° was employed. The isomerisation was then followed polarimetrically for 400 hours using a solution of dry hydrogen chloride in chloroform. A plot of the rotation against time was a straight line indicating that the reaction is indeed fully synchronous. When formula (CLV) was still under consideration for apoeuphenyl acetate, it was thought that it might be identical with the γ-euphenyl acetate reported by Vilkas, et al.[139] and Christen, et al.[140]

who obtained it by hydrogenation of isoeupha-11:13(17)-dienyl acetate. This experiment was repeated and the product which was isolated in almost quantitative yield was identical with isoeuph-13(17)-enyl acetate. Barton[43] had also previously failed to obtain δ-euphenyl acetate.

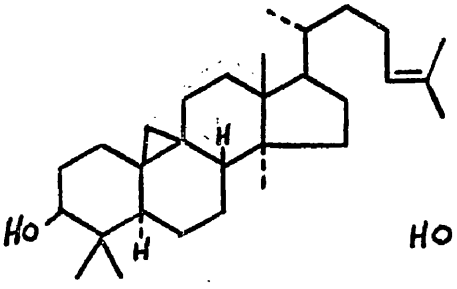
Secondly, it will be noted that in the conversion of 7-oxoapoeuph-14-enyl acetate (CLII) to the corresponding $\Delta^{13(17)}$ isomer, the reaction only proceeds when the compound is refluxed with hydrochloric-acetic acid, whereas, in contrast, apoeuph-14-enyl acetate (CLIII) is readily isomerised to isoeuph-13(17)-enyl acetate using the less vigorous conditions of dry hydrogen chloride in chloroform at 0°. Hence, the ketone group at $C_{(7)}$ must to some extent stabilise the double bond which in that instance requires the more vigorous isomerisation conditions. This fact indicates that the double bond must not be far removed from the 7-carbonyl group and supports the decision that 7-oxoapoeuphenyl acetate is (CLII) and not (CLIV).

It follows that since the euph-8-enyl - isoeuph-13(17)-enyl acetate rearrangement requires more vigorous conditions than the parallel isomerisation of apoeuph-14-enyl acetate, the movement of the $C_{(14)}$-methyl group to $C_{(8)}$ must require more energy than the migration of the 13α-methyl group to $C_{(14)}$. This explains the synchronous nature of the euphenyl - isoeuphenyl rearrangement and accounts for the ease of conversion of apoeuphenyl acetate to isoeuphenyl acetate.

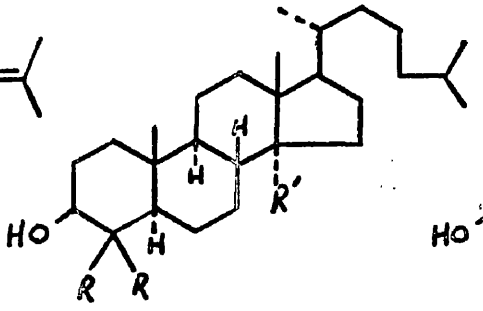
Final confirmation that the hydrogen atom attached to $C_{(9)}$ in butyrospermol has the α-configuration, was obtained from a consideration of molecular rotation data. Barton[31] had previously observed that the change in molecular rotation (Δ_3) on converting butyrospermol and cycloartenol to the corresponding 3-ketones, is in each case negative (Table VI). This is in contrast to the majority of 3β-hydroxy-5α-steroids and 3β-hydroxy-triterpenoids in which this change is positive. From this observation he suggested that the two alcohols may be related and following the structural and stereochemical elucidation of cycloartenol (XXI)[33,36,37], Jones and his colleagues[127,132] deduced that butyrospermol, like cycloartenol, has a 9β-substituent and tentatively suggested that the former was 9β-eupha-7:24-dien-3β-ol. This argument is believed to be invalid.

A generally accepted principle in applying molecular relations to structural and stereochemical analysis is that terminal rings of the same type make contributions to the molecular rotation which are very approximately independent of the nature of the rest of the molecule, provided that the adjacent ring is a saturated unsubstituted cyclohexane ring[91]. Another widely accepted principle is that non-angular methyl groups have little effect on the contribution of a terminal ring to the molecular rotation[91]. Thus the molecular rotation change (Δ_{co}) accompanying the introduction of a 3-carbonyl group into most 5α-steroids and 5α-triterpenoids is positive while that (Δ_3) accompanying the oxidation of a

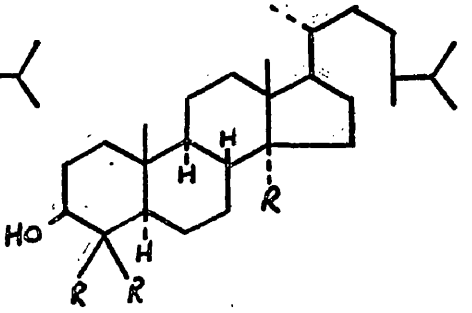
3β-hydroxy-triterpenoid or 3β-hydroxy-steroid to the corresponding 3-ketone is also positive. However it is noted (Table III) that lanostanol (CLVIII, R = R' = Me) and laudanol (CLIX, R = Me) are exceptions to the above rule, whereas their steroid analogues, cholestanol (CLVIII, R = R' = H) and ergostanol (CLIX, R = H)



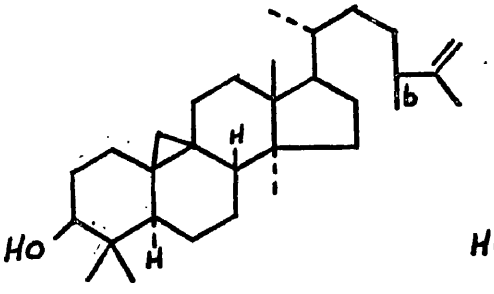
(XXI)



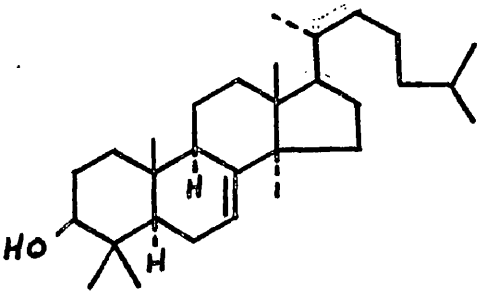
(CLVIII)



(CLIX)



(XXIII)



(CLX)

together with the methyl steroid, 14-methyl cholestanol (CLVIII, R = H, R' = Me) conform to the rule.

These figures show that the introduction of a methyl group into position 14 in cholestanol has little effect on the contribution of the terminal ring towards molecular rotation, but the introduction of two further methyl groups at $C_{(4)}$ in cholestanol and ergostanol has a profound effect.

TABLE III

	M_D			Δ_3	Δ_{3c}
	3β-alcohol	Hydrocarbon	3-ketone		
Lanostanol (CLVIII, R = R' = Me)[73]	+150	+149	+116	-34	-33
Laudanol (CLIX, R = Me)[39]	+ 93	+107	+ 62	-31	-45
Cholestanol (CLVIII, R = R' = H)[133]	+ 93	+ 91	+159	+66	+68
Ergostanol (CLIX, R = H)[134]	+ 64	+ 66	+140	+76	+74
14-Methylcholestanol (CLVIII, R = H, R' = Me)[135]	+157	-	+244	+87	-

Furthermore, from a comparison of molecular rotation differences of double bond isomers of cholestenol and ergostenol, it is possible to differentiate between compounds containing a Δ^{8-} double bond and those containing a Δ^{7-} double bond (Table IV). Cholest-7-enol and ergost-7-enol show a small negative change in molecular rotation on acetylation (Δ_1), whereas the corresponding Δ^{8-} isomers exhibit a much larger negative change.

TABLE IV.

	M_D			Δ_1	Δ_2	Δ_3
	Alcohol	Acetate	Benzoate	Ketone			
Cholest-8-enol[136]	+193	+144	+201	+227	-47	+ 8	+34
Ergost-8-enol[136]	+156	+110	+171	-	-46	+15	-
Cholest-7-enol[137]	+ 15	+ 8	+ 34	+95	- 7	+19	+84
Ergost-7-enol[138]	- 8	- 18	+ 10	+88	-10	+18	+96

The recognition of these features led us to compare the molecular rotation changes associated with reactions of dihydro-

butyrospermol with the corresponding changes for lanost-7-en-3β-ol (CLX). Although lanost-7-en-3-one had previously been prepared[79], its specific rotation was not recorded and its preparation was undertaken.

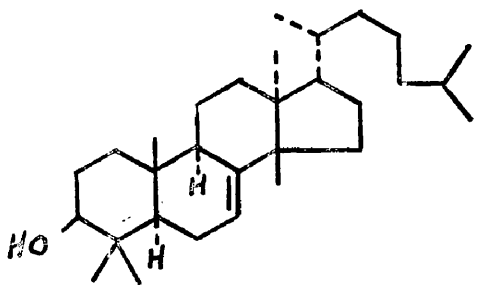
Lanost-8-enyl acetate was isomerised with dry hydrogen chloride in chloroform at 0° to a mixture consisting mainly of the Δ^7 isomer together with some starting material. The latter was selectively oxidised with chromic-acetic acid and pure lanost-7--enyl acetate obtained by chromatography of the resultant product. Reduction of this acetate with lithium aluminium hydride in ether gave lanost-7-en-3β-ol (CLX), benzoylation of which gave lanost-7--enyl benzoate. The constants of these three compounds were in good agreement with the literature values.[95] Lanost-7-en-3-one m.p. 146-147°, $[\alpha]_D$ - 20° was prepared by oxidation of the alcohol (CLX) with the chromium trioxide-pyridine complex at room temperature. The molecular rotation comparison is shown in table V.

TABLE V

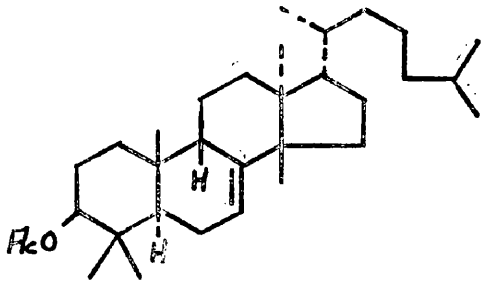
	M_D			Δ_1	Δ_2	Δ_3
	Alcohol	Acetate	Benzoate	Ketone			
Lanost-7-en-3β-ol (CLX)	+45	+156	+266	- 85	+111	+221	-130
Dihydrobutyrospermol[125]	-60	+ 56	+164	-182	+116	+224	-122

It was found that the change in molecular rotation when lanost-7-en-3β-ol is oxidised to lanost-7-en-3-one is <u>negative</u> and

almost identical with the change associated with the conversion of dihydrobutyrospermol to the corresponding 3-ketone. Further, the Δ_1 (acetylation) and Δ_2 (benzoylation) values for lanost-7-en-3β-ol are nearly identical with the related values for dihydrobutyrospermol. The close correspondence of these values indicates that the structure and stereochemistry of rings A and B is the same in both compounds. That is, dihydrobutyrospermol must possess a double bond between $C_{(7)}$ and $C_{(8)}$ and have the $C_{(9)}$-hydrogen atom in the α-configuration and is thus 9α-euph-7-en-3β-ol (LXXXI).



(LXXXI)



(CLXI)

The molecular changes for butyrospermol, cycloartenol (XXI) and cycloläudenol (XXIII) are compared in Table VI.

TABLE VI.

	M_D				Δ_1	Δ_2	Δ_3
	Alcohol	Acetate	Benzoate	Ketone			
Butyrospermol[126]	- 51	+ 48	+159	-170	+99	+210	-119
cycloArtenol[33]	+230	+280	+400	+ 93	+50	+170	-137
cycloLaudenol[39]	+206	+265	+343	+ 83	+59	+137	-123

The euph-7-enyl acetate prepared by Barton[43] by Wolff--Kishner reduction of 7-oxoeuph-8-enyl acetate followed by reacetylation of the product can now be formulated as 9β-euph-7-enyl acetate (CLXI) and cannot be the 9α-isomer as proposed by Jones.[127] This was confirmed in these laboratories by Dr. H. S. Watson who again prepared 9β-euph-7-enyl acetate using the original method.[43] He found that this acetate was unchanged after treatment with hydrogen chloride under conditions which readily isomerise dihydrobutyrospermyl acetate to euph-8-enyl acetate. 9β-Euph-7-enyl acetate must therefore be the more stable isomer. This stereochemistry allows the molecule to adopt an all chair (or half-chair) conformation in contrast to the less stable boat (or half-boat) arrangement present in its 9α-isomer, dihydrobutyrospermyl acetate and which conformation is considered to be the driving force for its irreversible conversion into euph-8-enyl acetate which can adopt an all-chair (or half-chair) conformation throughout the molecule.

EXPERIMENTAL

Melting points are uncorrected. Specific rotations were measured at room temperature in a 1 dm. tube using chloroform as solvent. Ultraviolet absorption spectra were measured in absolute alcohol solution using a Unicam S.P.500 and a Hilger H700.307 spectrophotometer. Infrared absorption spectra were measured by Dr. G. T. Newbold and Miss N. Caramando. Grade II alumina was used for chromatography and light petroleum refers to the fraction of b.p. 60-80°. The analyses were carried out by Dr. A. C. Syme and Mr. W. McCorkindale of the Royal College of Science and Technology, Glasgow, C.1.

Acetylation of "isoCholesterol". -'isoCholesterol' (100 g.) was dissolved in a mixture of acetic anhydride (100 ml.) and pyridine (100 ml.) and the solution heated at 100° for 1 hour. The product, isolated by means of ether crystallised from chloroform-methanol as needles, m.p. 123-126° (94 g.)

Hydrogenation of "isoCholesteryl Acetate". - The above acetate (94 g.) in glacial acetic acid (800 ml.) was shaken with hydrogen for 6 hours at 70° in the presence of platinum catalyst (fr. 5 g. Platinum oxide). The filtered solution was evaporated to dryness and the product used as such for the following oxidation.

7:11-Dioxolanost-8-enyl Acetate[70,74]. - The hydrogenation product (94 g.) in stabilised acetic acid (2 l.) was treated at 100° with a solution of chromium trioxide (70 g. ≡ 5.2[O]) in water (130 ml.) added with stirring during 30 minutes. After heating at 100° for a further 1.5 hours, the excess reagent was destroyed by the addition of methanol and the solution evaporated

to near dryness under reduced pressure. The product, isolated by means of ether, was dissolved in benzene and filtered through a short column of alumina (800 g.). Crystallisation of the benzene-eluted material from methanol, gave 7:11-dioxolanost-8-enyl acetate (60 g.) as yellow plates, m.p., 156-158°, $[\alpha]_D$ + 91.5° (c,3.1).

Doree, et al.[74] quote m.p. 156-158°, for this compound.

7:11-Dioxolanostanyl Acetate. - (a)[74] Zinc dust (30 g.) was added portionwise to a solution of 7:11-dioxolanost-8-enyl acetate (25 g.) in glacial acetic acid (500 ml.) at 110° and the heating continued for 1 hour. After filtration, the solution was reduced to ca. 100 ml., poured into water and the product, isolated by means of ether, crystallised from chloroform-methanol as plates (22 g.) m.p. 221-222°, $[\alpha]_D$ + 58° (c,1.3). Five recrystallisations from the same solvent mixture gave pure 7:11-dioxolanostanyl acetate, m.p. 223-223.5°, $[\alpha]_D$ + 62.0° (c,1.9).

Doree, et al.[74] quote m.p. 222-224°, $[\alpha]_D$ + 54.6° for this compound.

(b) A solution of 7:11-dioxolanost-8-enyl acetate (200 mg.) in methanol (150 ml.) was heated under reflux with a trace of zinc bromide and activated zinc dust (2 g.) was added portionwise over 3 hours. The colourless solution was filtered, poured into water and worked up in the usual manner using ether. On crystallisation of the product from chloroform-methanol, 7:11-dioxolanostanyl acetate (180 mg.) was obtained as plates, m.p. 222-223°, $[\alpha]_D$

+ 62.0° (c,0.75), undepressed with the material prepared as above.

Treatment of 7:11-Dioxolanostanyl Acetate with Alkali. - A solution of 7:11-dioxolanostanyl acetate (250 mg.) in methanolic potassium hydroxide (10%, 125 ml.) was heated under reflux for 18 hours. The product, isolated in the usual way, was acetylated with acetic anhydride (10 ml.) and pyridine (10 ml.) at 100° for 1 hour.

Crystallisation of the product from methanol gave 7:11--dioxolanost-8-enyl acetate, m.p. and mixed melting point, 162-163°, $[\alpha]_D$ + 92.1° (c,1.4).

Euphol Derivatives. - All the euphol derivatives were prepared from euphol isolated from the commercial latex known as Gum Euphorbia, by the method of Newbold and Spring.[42] Euphol was crystallised from acetone as needles, m.p. 114-116°, $[\alpha]_D$ + 33° (c,1.7). Treatment of euphol with acetic anhydride and pyridine at 100° and crystallisation of the product from methanol-chloroform gave euphyl acetate, m.p. 106-108°, $[\alpha]_D$ + 40.5° (c,1.4). Hydrogenation of euphyl acetate in ethyl acetate over a platinum catalyst gave euph-8-enyl acetate which crystallised from methanol-chloroform as needles, m.p. 124-126°, $[\alpha]_D$ + 34° (c,1.1). Oxidation of euph-8-enyl acetate with chromic-acetic acid according to Christen et al.[100] gave 7:11-dioxoeuph-8-enyl acetate as yellow needles from methanol, m.p. 111-112°, $[\alpha]_D$ + 21° (c,1.5). Light absorption: $\lambda_{max.}$ = 2720 Å. (ε:8,750).

Christen et al.[100] give m.p. 113-114°, $[\alpha]_D$ + 20°.

7:11-Dioxoeuphanyl Acetate. - (a)[100] 7:11-Dioxoeuph-8-enyl acetate (2 g.) in acetic acid (150 ml.) heated under reflux with zinc dust (2.0 g.) added portionwise over ½ hour. The cooled solution was filtered, poured into water and the product isolated by means of ether. Crystallisation of the product from methanol gave 7:11-dioxoeuphanyl acetate, m.p. 155-156°, $[\alpha]_D$ - 120° (c,1.1). The compound was transparent to ultraviolet light. Christen

Christen et al.[100] quote m.p. 156-157°, $[\alpha]_D$ - 132° for this compound.

(b) A solution of 7:11-dioxoeuph-8-enyl acetate (100 mg.) in methanol (75 ml.) was heated under reflux for 1 hour with activated zinc dust (1.0 g.) and a trace of zinc bromide. The product, isolated in the usual manner, crystallised from methanol as colourless blades, m.p. 156-157°, $[\alpha]_D$ - 121° (c,0.6), identical with the material obtained above.

Treatment of 7:11-Dioxoeuphanyl acetate with Alkali and Acid. - (a)[141] A solution of 7:11-dioxoeuphanyl acetate (100 mg.) in methanolic potassium hydroxide (10%, 70 ml.) was heated under reflux for 3 hours. The product, isolated in the usual way, was acetylated with acetic anhydride (10 ml.) and pyridine (10 ml.) at 100° for 1 hour. Crystallisation of the product from methanol gave 7:11-dioxoeuph-8-enyl acetate, m.p. and mixed m.p. 112-113°, $[\alpha]_D$ + 21° (c,0.5).

(b) A solution of 7:11-dioxoeuphanyl acetate (110 mg.) in hydrochloric-acetic acid (1:20, 10 ml.) was heated at 100° for 3 hours. The product, isolated in the usual manner, gave

7:11-dioxoeuph-8-enyl acetate as yellow needles, m.p. and mixed m.p. 111-113°, $[\alpha]_D$ + 21° (c,1.3), on crystallisation from methanol.

7:11-Dioxolanostanol.[67,74] - 7:11-Dioxolanostanyl acetate (500 mg.) was heated under reflux for 1 hour with 3% methanolic potassium hydroxide (75 ml.). The solution was poured into water, neutralised with dilute hydrochloric acid and the product extracted with ether and crystallised from methanol to give 7:11-dioxolanostanol as needles, m.p. 189-191°, $[\alpha]_D$ + 57.8° (c,1.25). Literature values[67,74] for this compound are m.p. 183-184°, 190-191°, $[\alpha]_D$ + 58°. Reacetylation of the alcohol gave 7:11-dioxolanostanyl acetate, m.p. and mixed m.p. 222-223°, $[\alpha]_D$ + 62.1° (c,1.5).

3β,7β-Diacetoxylanostan-11β-ol. -[70,73] 7:11-Dioxolanostanyl acetate (1.6 g.) in dry ether (120 ml.) was added to a suspension of lithium aluminium hydride (1.6 g.) in dry ether (200 ml.) and the mixture refluxed for 2½ hours. The product isolated in the usual manner failed to crystallise and was acetylated with acetic anhydride (15 ml.) and pyridine (15 ml.) at 100° for 2 hours. On crystallisation of the product from methanol-chloroform, 3β,7β-diacetoxylanostan-11β-ol (1.5 g.) was obtained as needles, m.p. 239.5-240°, $[\alpha]_D$ + 58.6° (c,1.9).

Cavalla and McGhie[70] and Voser, et al.[74] give m.p. 239°, $[\alpha]_D$ + 70° to + 73° for this compound. Barnes and Palmer[107] have recently recorded m.p. 235-236°, $[\alpha]_D$ + 56°, + 57°.

3β,7β-Diacetoxylanost-9(11)-ene. -[70,107] 3β,7β-Diacetoxylanostan-11β-ol (180 mg.) in dry pyridine (11 ml.) was treated with

phosphorus oxychloride (1.5 ml.) and the solution heated at 100° for 3 hours. The cooled solution was poured into water and the product, isolated in the usual way, crystallised from methanol-chloroform to give 3β:7β-diacetoxylanost-9(11)-ene as stout needles, m.p. 213-213.5°, $[\alpha]_D$ + 77°, + 77.4° (c,1.1, 1.5). It gives a yellow colour with tetranitromethane in chloroform.

Cavalla and McGhie[70] give m.p. 213-214°, $[\alpha]_D$ + 83° to + 84° for this compound. Barnes and Palmer[107] have subsequently recorded m.p. 212-214°, $[\alpha]_D$ + 58°.

3β,7β,11α-Trihydroxylanostane. -[108] Sodium (2.0 g.) was added portionwise over 2 hours to a refluxing solution of 7:11-dioxolanostanyl acetate (2.0 g.) in n-propanol (20 ml.). The excess sodium was destroyed by the addition of ethanol-water and the solution worked up in the usual way. Crystallisation of the product from methanol-water gave 3β,7β-11α-trihydroxylanostane as needles, m.p. 215-216°, $[\alpha]_D$ + 26.3°, + 26.3° (c,1.6, 0.5). Barton[108] quotes m.p. 207-208°, $[\alpha]_D$ + 3° for this compound. Acetylation of this triol with acetic anhydride (20 ml.) and pyridine (20 ml.) at 100° for 1½ hours gave 3β,7β,11α-triacetoxylanostane, m.p. 155-156°, $[\alpha]_D$ + 30.4° (c,1.4). Barton[108] gives m.p. 156°, $[\alpha]_D$ + 29°. Hydrolysis of this triacetate with lithium aluminium hydride in ether gave the corresponding triol with the same constants as recorded above (m.p. 215-216°, $[\alpha]_D$ + 26.2° (c,1.1).

3,7,11-Trioxolanostane. - (a)[74] A solution of 7:11-dioxolanostanol (400 mg.) in pyridine (10 ml.) was added to the complex formed from chromium trioxide (400 mg.) in pyridine (4 ml.) and the

mixture allowed to stand overnight at 16°. The product, isolated in the usual manner, gave 3:7:11-trioxolanostane (350 mg.), m.p. 166-167°, $[\alpha]_D$ + 48.5° (c,1.1), on crystallisation from methanol.

Doree, et al.[74] quote m.p. 165-167°, $[\alpha]_D$ + 121.1° for this compound.

(b) A solution of the uncrystallisable triol (obtained by treatment of 3β:7β-diacetoxylanostan-11β-ol with lithium aluminium hydride in ether)(1.27 g.) in pyridine (60 ml.) was added to the complex formed from chromium trioxide (3.3 g.) and pyridine (30 ml.) and the mixture allowed to stand at 16° overnight. Crystallisation of the product from methanol gave 3:7:11-trioxolanostane, m.p. 166-167°, $[\alpha]_D$ + 48.2 (c,1.5).

(c) 3β,7β,11α-Trihydroxylanostane (1.3 g.) was dissolved in pyridine (60 ml.) and treated as in (b) to give 3:7:11-trioxolanostane m.p. 167-168°, $[\alpha]_D$ + 47.6° (c,1.5). The melting point was undepressed on admixture with the samples prepared as described under (a) and (b). The infrared absorption spectrum showed a band at 1715 $cm.^{-1}$ (carbonyl).

Treatment of 3:7:11-Trioxolanostane with Mineral Acid. - The trione (270 mg.) was dissolved in hydrochloric-acetic acid (40 ml. 1:2) and the solution kept at 100° for 3 hours. On crystallisation of the product from methanol, unchanged starting material, m.p. and mixed m.p., 166-167°, $[\alpha]_D$ + 48.0° (c,0.8), was obtained in almost quantitative yield.

Treatment of 7:11-dioxolanostanyl Acetate with Chromium Trioxide in Pyridine. - 7:11-Dioxolanostanyl acetate (100 mg.) in pyridine (5 ml.) was added to the complex formed from chromium trioxide (100 mg.) in pyridine (1 ml.) and the solution was allowed to stand at 16° overnight. The product, isolated in the usual way was crystallised from chloroform-methanol to give unchanged starting material, m.p. 222-223°, $[\alpha]_D$ + 61.9° (c,0.55), in good yield.

Treatment of 3β:7β:11α-Triacetoxylanostane under Equilibrating Conditions. - 3,7,11-Triacetoxylanostane (155 mg.) in n-propanol (10 ml.) was heated under reflux for 48 hours with sodium (2.0 g.). The product, isolated in the usual way, crystallised from methanol as needles, m.p. 215-216°, $[\alpha]_D$ + 26.3° (c,0.4), undepressed in melting point with 3β,7β,11α-trihydroxylanostane. Acetylation of the product gave 3β,7β,11α-triacetoxylanostane, m.p. and mixed m.p. 155-157°, $[\alpha]_D$ + 30.1°, (c,0.51)

11-Oxolanostanyl Acetate.[110] - A solution of 7:11-dioxolanostanyl acetate (22 g.) in redistilled diethylene glycol (730 ml.) was heated with hydrazine hydrate (100%, 11.2 ml.) at 200° for 1 hour. After cooling to 70°, the mixture was treated with a solution of sodium (22 g.) in diethylene glycol (210 ml.) and heating was continued at 220-230° for a further 6 hours. The cooled mixture was poured into water, acidified with hydrochloric acid and extracted with ether. The ethereal extract was washed, dried (Na_2SO_4) and evaporated to give a yellow gum (21 g.) which was treated with acetic anhydride in pyridine at 100° for 1½ hours. A

solution of the dry acetylated material in light petroleum (350 ml.) was chromatographed on alumina (600 g.). Elution with the same solvent (400 ml.) gave a fraction which after several crystallisations from chloroform-methanol gave lanostanyl acetate as needles, m.p. 152-154°, $[\alpha]_D$ + 41° (c,1.3). Continued elution with light petroleum (4.4 l.) and petroleum-benzene (9:1, 3.6 l.; 3:1, 1.6 l.; 1:3, 1.6 l.) gave a fraction which on crystallisation from methanol-chloroform yielded 11-oxolanostanyl acetate (8.2 g.) as needles, m.p. 144-146°. If the melted specimen was cooled until it just solidified and then remelted, the melting point was 156-157°, $[\alpha]_D$ + 62.3° (c,1.9). Sublimation of the acetate, m.p. 144-146°, $[\alpha]_D$ + 62.3° under high vacuum (0.0001 mm.) at 130-140° gave material m.p. 156-157°, $[\alpha]_D$ + 62.2° (c,3.3) which after recrystallisation from chloroform-methanol had m.p. 144-145° cf.[73]. Infrared absorption (in Nujol): bands at 1242 and 1743 cm.$^{-1}$ (acetate) and 1702 cm.$^{-1}$ (carbonyl). A further fraction (6 g.) eluted with benzene (1.6 l.) and methanol (800 ml.) crystallised from methanol to give 11β-hydroxylanostanyl acetate as fine needles, m.p. 210-211°, $[\alpha]_D$ + 62.4° (c,1.7).

3β:11β-Dihydroxylanostane. - A solution of 11-oxolanostanyl acetate (8.0 g.) in dry ether (330 ml.) was added to a suspension of lithium aluminium hydride (8.2 g.) in dry ether (500 ml.). The mixture was refluxed for 2½ hours, cooled, diluted with ether (100 ml.) and the excess hydride destroyed by the addition of crushed ice. The suspension was washed with dilute sulphuric acid (5N), water, and dried (Na_2SO_4). The product obtained by evaporation of the ether was crystallised from chloroform-methanol to give

3β:11β-dihydroxylanostane as fine needles, m.p. 193-194°, $[\alpha]_D$ + 54° (c,1.6), unchanged by further crystallisation. The infrared spectrum showed hydroxyl bands at 3642 $cm.^{-1}$ and between 3270 and 3320 $cm.^{-1}$.

[Found: C,80.9; H,12.4. Calc. for $C_{30}H_{54}O_2$: C,80.65; H,12.2%]

Voser has quoted[73] m.p. 190-191°, $[\alpha]_D$ + 29° for this compound while McGhie records the constants,[110] m.p. 190-191°, $[\alpha]_D$ + 28.4°.

11β-Hydroxylanostan-3β-yl Acetate. - A solution of the diol (7.8 g.) in pyridine (50 ml.) and acetic anhydride (50 ml.) was kept at room temperature for 15 hours. The product was isolated by means of ether and crystallised from chloroform-methanol to give 11β--hydroxylanostan-3β-yl acetate as needles, m.p. 210-211°, $[\alpha]_D$ + 62.5° (c,1.5). Its infrared spectrum (in Nujol) showed bands at 1725 and 1270 $cm.^{-1}$ (acetate) and 3600 $cm.^{-1}$ (hydroxyl).

When the experiment was repeated at 100° for 3 hours, the mono-acetate, m.p. 209-210°, $[\alpha]_D$ + 62° (c,2.0) was again isolated in high yield.

[Found: C,78.4; H,11.7. Calc. for $C_{32}H_{56}O_3$: C,78.6; H,11.55%]

Voser[73] gives m.p. 219-220°, $[\alpha]_D$ + 23° for this compound; McGhie[110] records m.p. 215-216°, $[\alpha]_D$ + 22.8°.

3β:11β-Diacetoxylanostane. - A solution of 11β-hydroxylanostan--3β-yl acetate (200 mg.) in dry chloroform (5 ml.) and redistilled dimethyl aniline (6 ml.) was treated with acetyl chloride (4 ml.) and the mixture gently refluxed for 20 hours. The product was

isolated in the usual way by means of ether and crystallised several times from methanol to give 3β:11β-diacetoxylanostane as needles m.p. 182-182.5°, $[\alpha]_D$ + 70.8° (c,2.3). A mixture with starting material had m.p. 162-180°. The compound did not colour tetranitromethane and was transparent to ultraviolet light. Infrared absorption (in Nujol): bands at 1739 $cm.^{-1}$ and between 1238 and 1253 $cm.^{-1}$.

[Found: C,77.2; H,11.23. $C_{34}H_{58}O_4$ requires C,76.9; H,11.01%].

11-Oxolanostanyl Acetate from 11β-Hydroxylanostanyl Acetate. - A solution of 11β-hydroxylanostanyl acetate (200 mg.) in acetone (20 ml.) and benzene (2 ml.) was treated at room temperature during 3 minutes with the Kiliani solution (0.176 g. sodium dichromate/c.c.; 0.30 ml.)[148]. The mixture was allowed to stand for 10 minutes before methanol (5 ml.) was added and the product isolated by means of ether. Crystallisation of the product from chloroform-methanol gave 11-oxolanostanyl acetate (135 mg.) as needles, m.p. and mixed m.p. 144-146° (remelting 156-157°), $[\alpha]_D$ + 62.6° (c,2.0).

3:11-Dioxolanostane. - A solution of 3β:11β-dihydroxylanostane (170 mg.) in stabilised acetic acid (5 ml.) was treated dropwise at room temperature with a solution of chromium trioxide (155 mg.) in acetic acid (30 ml.) and the solution kept in the cold for 18 hours. The product, isolated in the usual way, was dissolved in light petroleum (20 ml.) and filtered through a column of alumina (4 g.). Elution with petroleum-benzene (4:1, 100 ml.) gave a fraction (110 mg.) which after two crystallisations from

methanol yielded 3:11-dioxolanostane as blades, m.p. 120-121°, $[\alpha]_D$ + 66.5° (c,2.2). Voser[73,88] gives m.p. 120-123°, $[\alpha]_D$ + 61°, + 69° for this compound. Its infrared absorption (in Nujol) showed a strong band at 1710 cm.$^{-1}$ due to the carbonyl groups.

3β:11α-Diacetoxylanostane. - A solution of 11-oxolanostanyl acetate (500 mg.) in n-propanol (10 ml.) was boiled gently under reflux. Sodium metal (500 mg.) was added in small portions to the refluxing solution over 2 hours. Excess sodium was destroyed by the addition of ethanol and the product, isolated in the usual way, was treated with acetic anhydride (10 ml.) and pyridine (10 ml.) at room temperature for 18 hours. Three crystallisations of the product from methanol gave 3β:11α-diacetoxylanostane (320 mg.) as needles, m.p. 122-124°, $[\alpha]_D$ + 24° (c,3.1). The infrared spectrum (in carbon tetrachloride) showed bands at 1737 cm.$^{-1}$ and 1240-1250 cm.$^{-1}$.

Mijovic, et al.[88] give m.p. 127-128°, $[\alpha]_D$ + 13°, + 11° for this compound.

Lanost-9(11)-enyl Acetate.[73] - 11β-Hydroxylanostanyl acetate (7.5 g.) in dry pyridine (460 ml.) was treated with phosphorus oxychloride (58 ml.) and the mixture kept at 100° for 3 hours, cooled and poured into a large volume of water. The product (7.5 g.) isolated in the usual way, was dissolved in light petroleum and percolated through a column of activated alumina (230 g.). The fraction (6.91 g.) eluted with light petroleum (1.4 l.) and light petroleum-benzene (9:1, 2.1 l.) gave lanost-9(11)-enyl acetate (6.7 g.) as plates m.p. 174-176°, $[\alpha]_D$ + 91° (c,1.1) on crystallisation from

methanol-chloroform. The compound showed a yellow colour with tetranitromethane in chloroform. Light absorption: Max. at 2060 Å. (ε; 4,300).

[Found: C,81.3; H,11.6. Calc. for $C_{32}H_{54}O_2$: C,81.6; H,11.7%].

Treatment of Lanost-9(11)-enyl Acetate with Chromic-Acetic Acid. - A solution of lanost-9(11)-enyl acetate (3.0 g.) in stabilised acetic acid (385 ml.) and methylene chloride (30 ml.) was treated at room temperature with a solution of chromium trioxide (1.275 g.) in acetic acid (90%, 98 ml.) over 1½ hours. The mixture was allowed to stand at 18° for 48 hours before the excess chromium trioxide was destroyed by the addition of methanol. The product, isolated by means of ether, was dissolved in light petroleum and chromatographed on alumina (300 g.). The fraction (800 mg.) eluted with light petroleum (2.2 l.) and light petroleum-benzene (9:1, 1 l.; 4:1, 1 l.) gave starting material, m.p. and mixed m.p. 172-174°, $[\alpha]_D$ + 91° (c,1.3). Continued elution with light petroleum-benzene (1:4, 1 l.) and benzene (200 ml.) gave a second fraction (530 mg.) which crystallised from methanol-chloroform as plates m.p. 183-184°, $[\alpha]_D$ + 30° (c,0.8). It was undepressed in melting point on admixture with an authentic specimen of 9:11--epoxylanostanyl acetate [m.p. 182-183°, $[\alpha]_D$ + 30.1° (c,0.9)]. A third fraction (350 mg.) eluted with benzene (1 l.) gave on crystallisation from methanol-chloroform a mixture m.p. 146-150° which could not be purified by further crystallisation or chromatography. Elution with benzene-ether (4:1, 800 ml.) gave a final fraction (550 mg.) which on crystallisation from methanol

yielded 12-oxolanost-9(11)-enyl acetate, m.p. and mixed m.p. 180-181°, $[\alpha]_D$ + 94° (c,1.3). Light absorption: Max. at 2420 Å. (ε: 10,600).

9:11-Epoxylanostanyl Acetate. - A solution of lanost-9(11)--enyl acetate (100 mg.) in acetic acid (10 ml.) was treated with perhydrol (0.5 ml.) and the mixture heated at 100° for 2 hours. The cooled solution was diluted with water and the crystalline product collected. Recrystallisation of this material from methanol gave 9:11-epoxylanostanyl acetate as plates m.p. 182-183°, $[\alpha]_D$ + 30.1° (c,0.9).

Treatment of 9:11-Epoxylanostanyl Acetate with Chromic Acetic Acid. - A solution of 9:11-epoxylanostanyl acetate (40 mg.) in methylene chloride (0.5 ml.) and stabilised acetic acid (6 ml.) was treated as above with chromium trioxide (17 mg.) in acetic acid (90%, 1.32 ml.). The product, isolated in the usual way, gave starting material m.p. and mixed m.p. 182-183° in good yield on crystallisation from methanol.

Lanost-9(11)-en-3-one. - A solution of lanost-9(11)-enyl acetate (1 g.) in dry ether (50 ml.) was added to a suspension of lithium aluminium hydride (1 g.) in dry ether (50 ml.) and the mixture heated under reflux for 30 minutes. The product, obtained as a white solid by means of ether, was dissolved in dry pyridine (20 ml.) and added to the complex formed from chromium trioxide (1 g.) and pyridine (10 ml.). After standing at room temperature overnight, the mixture was poured into water and the product isolated in the usual way. Crystallisation of this material from methanol-chloroform

gave lanost-9(11)-en-3-one as blades (780 mg.) m.p. 113.5-114°, $[\alpha]_D$ + 66.4° (c,1.0). Infrared spectrum: band at 1710 $cm.^{-1}$ (carbonyl). Max. at 2050 Å. (ε:4,100).
[Found: C,84.20; H,11.95%. $C_{30}H_{50}O$ requires C,84.44; H,11.81%].

Bromination and Dehydrobromination of Lanost-9(11)-en-3-one. - A solution of the ketone (700 mg.) in dry carbontetrachloride (23 ml.) was boiled gently under reflux over strong illumination for 1 hour with N-bromosuccinimide (350 mg.; 1.2 moles). The solution was filtered and evaporated to dryness to give a dark brown gum which failed to crystallise from the usual solvents. The gum was treated with collidine (12 ml.) under reflux for 2 hours and the product (650 mg.) was chromatographed on alumina (17 g.). No crystalline material was obtained.

Bromination of lanost-9(11)-enyl acetate as described above also gave a gum with the same light absorption characteristics (Max. at 2060, 2300, 2400 and 2800 Å.).

Treatment of Lanost-9(11)-en-3-one with Selenium Dioxide in Acetic Acid. - Lanost-9(11)-en-3-one (100 mg.) in acetic acid (15 ml.) was boiled under reflux with selenium dioxide (100 mg.) for 50 hours. After working up in the usual way, the product was crystallised from methanol-chloroform to give unchanged starting material, m.p. and mixed m.p. 113-114°, $[\alpha]_D$ + 66.2° (c,0.6), in good yield.

Treatment of 11-Oxolanostanyl Acetate with Selenium Dioxide in Acetic Acid. cf.[109,112] (a) 11-Oxolanostanyl acetate (2.0 g.) in glacial acetic acid (65 ml.) was heated under reflux for 24 hours with dry selenium dioxide (3.0 g.). The solution was filtered and

the product, isolated in the usual way, was dissolved in light petroleum (100 ml.) and chromatographed on a column of alumina (60 g.). Elution with the same solvent (300 ml.) gave a fraction (65 mg.) which crystallised from chloroform-methanol as needles, m.p. 146-148°, undepressed in m.p. when mixed with starting material. The fraction (630 mg.) eluted with light petroleum-benzene (1:3, 1.05 l.) and benzene (600 ml.) crystallised from methanol as plates, m.p. 199-202°, $[\alpha]_D$ - 16.5° (c,1.1). Further crystallisation from the same solvent gave pure 9β-methyl-10ξ-hydroxy-11-oxo-C-nor-D--homolanosta-12:14:16-trien-3β-yl acetate as plates, m.p. 201-202° $[\alpha]_D$ - 17.2° (c,1.3). It gives a pale yellow colour with tetranitromethane in chloroform. Light absorption: Max. at 2160 Å. (ε: 70,000), 2600 Å. (ε: 11,500) and 3120 Å. (ε: 1,950). Infrared spectrum: bands at 1243 and 1736 cm.$^{-1}$ (acetate), 1724 cm.$^{-1}$ (carbonyl), 3584 cm.$^{-1}$ (hydroxyl) and 867, 1480 and 1580 cm.$^{-1}$ (benzenoid). It does not give any colour with ferric chloride. [Found: C,77.54, 77.42; H,9.81, 9.90. $C_{32}H_{48}O_4$ requires C,77.37; H,9.74%].

(b) 11-Oxolanostanyl acetate (500 mg.) in glacial acetic acid (16 ml.) was refluxed for 3 hours with dry selenium dioxide (750 mg.). Treatment as above gave 9β- methyl-10ξ-hydroxy-11-oxo-C-nor-D--homolanosta-12:14:16-trien-3β-yl acetate as plates (300 mg.), m.p. 201-203°, $[\alpha]_D$ - 17.1° (c,1.1).

Treatment of the Aromatic Acetate (CXXXV) with Mineral Acid. cf. 109 The acetate (m.p. 200-202°, 100 mg.) in acetic acid (25 ml.) was treated with a stream of dry hydrogen chloride for 40 minutes and the mixture was kept in a sealed flask for 3 days at

room temperature. The product, isolated in the usual way, gave starting material, m.p. and mixed m.p. 199-201°, $[\alpha]_D$ - 16.5° (c,0.5), on crystallisation from methanol.

Hydrolysis and Reacetylation of the Aromatic Acetate (CXXXV). - The acetate (m.p. 200-202°, 100 mg.) was heated under reflux for 2 hours with methanolic potassium hydroxide (5%, 40 ml.). The product, isolated in the usual way, was obtained as a white solid which failed to crystallise from any of the usual solvents. Light absorption: Max. at 2160 Å. (ε:30,200); 2600 Å. (ε:11,100); 3120 Å. (ε:2,200). Infrared spectrum: bands at 1722 $cm.^{-1}$ (carbonyl), 3580 $cm.^{-1}$ (hydroxyl) and 868, 1480, 1580 $cm.^{-1}$ (benzenoid). Acetylation of this material at 100° and crystallisation of the product from methanol gave the original aromatic acetate as blades, m.p. and mixed m.p., 200-201°, $[\alpha]_D$ - 17.1° (c,0.75).

3β:11-Diacetoxylanost-9(11)-ene. - cf.[146] A solution of 11-oxolanostanyl acetate (5 g.) and p-toluenesulphonic acid (1.9 g.) in acetic anhydride (350 ml.) was allowed to distil slowly during 5 hours until the volume was reduced to ca. 50 ml. The product was isolated in the usual way and chromatographed over alumina (150 g.). Elution with light petroleum benzene (4:1, 400 ml.) gave a fraction (0.7 g.) which crystallised from chloroform-methanol to yield starting material, m.p. and mixed m.p. 145-146°. Further elution with the same solvent mixture (4:1, 300 ml; 3:2, 600 ml; 2:3, 150 ml.) gave a gum (3.9 g.) which crystallised from methanol to yield the required 3β:11-diacetoxylanost-9(11)-ene as stout needles, m.p. 113-114°, $[\alpha]_D$ + 83.2°. Light absorption: Max. at 2050 Å. (ε:5,120). Infrared spectrum: bands at 1745 and 1240 $cm.^{-1}$ (3-acetate); 1764

and 1220 cm.$^{-1}$ (11-acetate); 1635 cm.$^{-1}$ ($\Delta^{9(11)}$-double bond). [Found: C,76.14; H,10.43%. $C_{34}H_{56}O_4 . \frac{1}{2}CH_3OH$ requires C,76.05; H,10.7%].

9α-Hydroxy-11-oxolanostanyl Acetate. - A solution of the enol-acetate (400 mg.) in glacial acetic acid (50 ml.) and hydrogen peroxide (30%, 2 ml.) was heated at 100° for 2 hours. Crystallisation of the product from methanol gave 9α-hydroxy-11-oxolanostanyl acetate as prisms (285 mg.), m.p. 183-184°, $[\alpha]_D$ + 66° (c,2.6). The compound is transparent to ultraviolet light. Infrared spectrum: bands at 3520 cm.$^{-1}$ (hydroxyl); 1739 and 1242 cm.$^{-1}$ (acetate); 1715 cm.$^{-1}$ (carbonyl).

[Found: C,76.52; H,10.84%. $C_{32}H_{54}O_4$ requires C,76.44; H,10.83%]

The uncrystallisable material (100 mg.) from the mother liquors of the above crystallisation was heated under reflux for 45 minutes with methanolic potassium hydroxide (5%, 10 ml.). The product was acetylated using acetic anhydride (5 ml.) and pyridine (5 ml.) at 100° for 1 hour and crystallised from methanol to yield 9α-hydroxy-11-oxolanostanyl acetate, m.p. and mixed m.p. with above material, 182-184°, $[\alpha]_D$ + 68° (c,1.6).

Treatment of 9α-Hydroxy-11-oxolanostanyl Acetate with Mineral Acid. - A solution of the hydroxy ketone (500 mg.) in hydrochloric-acetic acid mixture (1:20, 75 ml.) was heated at 100° for 4 hours and the neutral product, obtained in the usual way, was chromatographed on a column of alumina (15 g.). Elution with light petroleum (300 ml.) gave a fraction (230 mg.) which crystallised

from methanol as needles, m.p. 166-167°, $[\alpha]_D$+27.9°(c,1.25). This compound is considered to be 9β-chloro-11-oxolanostanyl acetate. It is transparent to ultraviolet light. Infrared spectrum: bands at 1739 and 1243 cm.$^{-1}$ (acetate); 1714 cm.$^{-1}$ (carbonyl). [Found: C,74.20; H,11.10; Cl,7.20%. $C_{32}H_{53}O_3Cl$ requires C,73.8; H,10.80; Cl,6.80%].

Attempted Hydrogenation of the Aromatic Acetate (CXXXV). - (a) A solution of the acetate (100 mg.) in ethyl acetate (55 ml.) was shaken with hydrogen over a platinum catalyst (from 50 mg. PtO_2) at room temperature for 30 hours. On crystallisation of the product from methanol, unchanged material was obtained as plates, m.p. and mixed m.p. 200-202°, $[\alpha]_D$ - 16.9° (c,0.84).

(b) The experiment was repeated using glacial acetic acid as solvent. Starting material, m.p. and mixed m.p. 199-201°, was again obtained in good yield.

9α-Hydroxy-11:12-dioxolanostanyl Acetate[84]. - A solution of 11-oxo-lanostanyl acetate (2 g.) in dry dioxan (25 ml.) was heated in a sealed tube at 180° for 4 hours with dry selenium dioxide (3 g.). The solution was filtered, and the product, which was isolated by means of ether, was dissolved in light petroleum and chromatographed on alumina (60 g.). The fraction (1.2 g.) eluted with benzene-ether (9:1, 450 ml.; 3:1, 300 ml.) gave 9α-hydroxy-11:12-dioxolanostanyl acetate as stout yellow needles, m.p. 211-212°, $[\alpha]_D$ + 141° (c,0.5), on crystallisation from methanol. Infrared spectrum: bands at 1243 and 1739 cm.$^{-1}$ (acetate), 1724 cm.$^{-1}$ (carbonyl) and 3425 cm.$^{-1}$ (hydroxyl).

Voser[84] gives m.p. 211-212°, $[\alpha]_D$ + 140°, for this compound.

Treatment of the Hydroxydione with Selenium Dioxide in Acetic Acid. - A solution of 9α-hydroxy-11:12-dioxolanostanyl acetate (120 mg.) in acetic acid (5 ml.) was heated under reflux for 6 hours with dry selenium dioxide (180 mg.). The filtered solution was worked up in the usual way and the product was crystallised from methanol to give unchanged starting material as yellow needles, m.p. and mixed m.p. 211-213°, in good yield.

11:12-Dioxolanost-8-enyl Acetate. - A solution of 9α-hydroxy--11:12-dioxolanostanyl acetate (760 mg.) in dry pyridine (5 ml.) was treated with redistilled thionyl chloride (5 ml.) and the mixture was allowed to stand at room temperature for 1½ hours. The solution was carefully poured into ice-water and the product, isolated by means of ether, was crystallised from methanol to give yellow needles, m.p. 176-180°. Several recrystallisations from the same solvent gave pure 11:12-dioxolanost-8-enyl acetate as yellow needles, m.p. 188-191°, $[\alpha]_D$ + 86.5° (c,1.9). Light absorption: Max. at 2100 Å. (ε:3,900) and 2800 Å. (ε:5,900). Infrared spectrum: bands at 1240 and 1739 $cm.^{-1}$ (acetate) and 1675 $cm.^{-1}$ (unsaturated diketone). [Found: C,77.42; H,10.39. $C_{32}H_{50}O_4$ requires C,77.10; H,10.10%] .

Treatment of 11:12-Dioxolanost-8-enyl Acetate with Selenium Dioxide in Acetic Acid. - A solution of 11:12-dioxolanost-8-enyl acetate (80 mg.) in glacial acetic acid (10 ml.) was heated under reflux for 5 hours with dry selenium dioxide (200 mg.). The filtered solution was worked up in the usual way and the product, in light petroleum, was chromatographed on alumina (9 g.). The fraction eluted with light petroleum-benzene (3:1, 200 ml.) gave

7:11:12-trioxolanost-5:8-dienyl acetate as orange-yellow needles, m.p. and mixed m.p. 187-189°, $[\alpha]_D$ - 66° (c,0.83).

9β-Methyl-10β-hydroxy-3:11-dioxo-C-nor-D-homolanosta-12:14:16-triene. - The uncrystallisable alcohol (300 mg.), obtained by hydrolysis of the aromatic acetate (CXXXV) as described above, was dissolved in pyridine (6 ml.) and the solution was added to the complex formed by reaction of chromium trioxide (300 mg.) with pyridine (3 ml.). The mixture was kept at room temperature overnight and worked up in the usual way by means of ether. Crystallisation of the product from methanol gave 9β-methyl-10β-hydroxy-3:11-dioxo-C-nor-D-homolanosta-12:14:16-triene as fine needles, m.p. 157-158°, $[\alpha]_D$ - 46.2°, - 45.8° (c,0.6,0.7), unchanged by further crystallisation. Light absorption: Max. at 2160 Å. (ε; 27,200), 2620 Å. (ε: 11,350) and 3140 Å. (ε: 2,380). Infrared spectrum: bands at 1714 cm.$^{-1}$ (carbonyl), 3590 cm.$^{-1}$ (hydroxyl) and 868, 1480 and 1580 cm.$^{-1}$ (benzenoid).

[Found: C,79.58; H,9.96. $C_{30}H_{44}O_3$ requires C,79.60; H,9.80%].

25:26:27-Trisnor-3β-acetoxy-7:11-dioxo-24-lanost-8-enic acid. cf.[72,83] - A solution of "isocholesteryl acetate" (150 g.) in stabilised acetic acid (2 l.) was treated at 95° with a solution of chromium trioxide (200 g.) in acetic acid (90%, 300 ml.) added over 1 hour with stirring. Heating was continued for a further 2 hours; the excess reagent was destroyed by the addition of methanol and the acid fraction isolated in the normal way. On crystallisation of this fraction from methanol the unsaturated dioxo acid was obtained as yellow needles, m.p. 191-193°, $[\alpha]_D$

+ 95.1° (c,1.75).

Voser[82] gives m.p. 192-194°, $[\alpha]_D$ + 96°, for this compound.

25:26:27-Trisnor-3β-acetoxy-7:11-dioxo-24-lanostanic Acid. cf.[84,143] The above acid (55 g.) in glacial acetic acid (1 l.) was heated under reflux for 1 hour with zinc dust (30 g.) and the solution was filtered and poured into water. After acidification with dilute hydrochloric acid, the acid fraction was isolated in the usual way and crystallised from chloroform-methanol to give the saturated dioxo-acid as fine blades m.p. 224-228°, $[\alpha]_D$ + 57.2° (c,1.4).

Voser[82] gives m.p. 223-230°, $[\alpha]_D$ + 58° for this compound.

25:26:27-Trisnor-3β-acetoxy-11-oxo-24-lanostanic Acid Methyl Ester. - A solution of the dioxo-acid (40 g.) in redistilled diethylene glycol (1.4 l.) was heated at 180° for 1 hour with hydrazine hydrate (100%, 21 ml.). After cooling to 70°, a solution of sodium (40 g.) in diethylene glycol (370 ml.) was added and the mixture heated under reflux at 220-230° for 5 hours. The cooled solution was poured into water, acidified with hydrochloric acid and the acid fraction isolated by means of chloroform. The product was esterified with an ethereal solution of diazomethane (1.3 moles) overnight at room temperature. The material obtained on evaporation of the ether was acetylated using acetic anhydride (150 ml.) and pyridine (150 ml.) at 100° for 1½ hours.

The product, isolated in the usual way, was dissolved in light petroleum and chromatographed over alumina (1,200 g.). The fraction (20 g.) eluted with light petroleum-benzene (1:3, 2 l.)

benzene (2 l.) and benzene-ether (4:1, 2 l.; 1:1, 2 l.), crystallised from methanol to give the acetate-methyl ester as needles, m.p. 174-175°, $[\alpha]_D$ + 44.6° (c,0.8).

Voser[82] gives m.p. 176-177°, $[\alpha]_D$ + 45° for this compound.

25:26:27-Trisnor-24:24-diphenyl-11-oxolanost-23-enyl Acetate cf.[82] The acetate-methyl ester (12 g.) was hydrolysed by refluxing with methanolic potassium hydroxide (5%, 250 ml.) for 3 hours. The acid fraction, isolated by means of chloroform, was treated overnight with an ethereal solution of diazomethane (1.2 moles). The solution was evaporated to dryness and the residue was dissolved in dry benzene (240 ml.) and added during 15 minutes to a solution of magnesium (12 g.) and bromobenzene (56 ml.) in dry ether (180 ml.). Ether (ca. 140 ml.) was then distilled off and the remaining solution was boiled under reflux for 7 hours before being poured over a mixture of ice (550 g.) and ammonium chloride (36 g.). The resultant liquor was steam distilled for 2½ hours to remove diphenyl and the solid remaining in the distillation flask was extracted with benzene (300 ml.) The extract was filtered and evaporated to dryness. The residue was refluxed for 1 hour with acetic anhydride (70 ml.) and then refluxed for a further 3 hours after the addition of potassium acetate (2 g.). The product, isolated in the usual way, crystallised from chloroform--methanol to give 25:26:27-trisnor-24:24-diphenyl-11-oxolanost-23-enyl acetate as needles, m.p. 187-189°, $[\alpha]_D$ + 73° (c,1.4).

Light absorption: Max. at 2520 Å. (ε:14,500).

Voser[82] gives m.p. 190-191°, $[\alpha]_D$ + 74° for this compound.

25:26:27-Trisnor-24:24-diphenyl-11-oxolanosta-20(22):23--dienyl Acetate.[82] - A solution of the diphenylethylene derivative (1 g.) in dry carbontetrachloride (28 ml.) was refluxed over strong illumination with N-bromosuccinimide (95%, ⅔ g.) for 20 minutes during which time 10 ml. of distillate were collected. The suspension was cooled and filtered, and the resulting solid was washed with dry carbontetrachloride (10 ml.). The combined filtrate and washings (28 ml.) were heated under reflux for 5 hours with acetic acid (1.8 ml.) and acetic anhydride (0.2 ml.). The product, isolated in the usual manner, crystallised from methanol-hexane to give the required diphenyl butadiene derivative as fine needles, m.p. 219-221°, $[\alpha]_D$ + 54.3° (c,0.70). Light absorption: Max. at 3080 Å. (ε: 27,800).

Voser[82] records m.p. 222-223°, $[\alpha]_D$ + 54° for this compound.

Treatment of the Diphenylbutadiene Derivative with Selenium Dioxide in Acetic Acid. - The above compound (300 mg.) was dissolved in acetic acid (10 ml.) and the solution heated under reflux for 5 hours with dry selenium dioxide (450 mg.). The product, isolated in the usual way, was dissolved in light petroleum and chromatographed on alumina (9 g.). The fraction (90 mg.) eluted with light petroleum-benzene (1:1, 300 ml.) failed to crystallise but deposited a yellow, amorphous powder from methanol. Light absorption: Max. at 2070 Å. (ε: 25,200) 2400 Å. (ε: 9,500), 2650 Å. (ε: 3,500) and 3750 Å. (ε: 14,000). Infrared spectrum: bands at 1735 and 1243 $cm.^{-1}$ (acetate), 1715 $cm.^{-1}$ (carbonyl) and 3450 $cm.^{-1}$ (hydroxyl).

20 to 27-Octakisnor-11-oxo-17-acetyl-lanostanyl Acetate.[82] - A solution of the diphenylbutadiene derivative (0.57 g.) in methylene chloride (15 ml.) and glacial acetic acid (15 ml.) was cooled to 0° - 3° and treated with stirring over 1 hour, with a solution of chromium trioxide (0.505 g.) in acetic acid (80%, 10 ml.). The mixture was kept at 0° for 2¾ hours. The temperature was then raised over a period of 30 minutes to 18° at which it was maintained for a further 2½ hours. The excess reagent was decomposed by the addition of methanol and the product, isolated in the usual way, was digested with light petroleum (2 x 10 ml.) to remove β:β-diphenylacrolein. The semi-crystalline residue gave octakisnor-11-oxo-17-acetyl-lanostanyl acetate as leaflets, m.p. 231-233°, $[\alpha]_D$ + 107.6° (c,1.95), on crystallisation from chloroform-methanol. Infrared spectrum: bands at 1735 and 1240 $cm.^{-1}$ (acetate) and 1710 $cm.^{-1}$ (carbonyl)

Voser[82] gives m.p. 232-233°, $[\alpha]_D$ + 109° for this compound.

Treatment of the Above Dioxo Acetate with Selenium Dioxide in Acetic Acid. - The dioxo acetate (200 mg.) was heated under reflux for 5 hours with selenium dioxide (300 mg.) in glacial acetic acid (10 ml.). The product was isolated by means of ether, dissolved in light petroleum, and chromatographed over alumina (6 g.). Elution with methanol gave a fraction (50 mg.) which did not crystallise and had no significant light absorption.

22 to 27-Hexanor-11-oxo-3:20-diacetoxylanostane. - A solution of octakisnor-17-acetyl-11-oxolanostanyl acetate (650 mg.) in dry ether (200 ml.) was heated under reflux for 2½ hours with lithium aluminium hydride (1.5 g.). The product was acetylated with acetic anhydride (10 ml.) and pyridine (10 ml.) at 100° for 1 hour and oxidised by treatment in acetone (15 ml.) at room temperature with Kiliani solution (0.17624 g. sodium dichromate c.c.; 0.6 ml.) for 15 minutes. On crystallisation of the product from chloroform-methanol, 22 to 27-hexanor-11-oxo-3:20-diacetoxylanostane was obtained as small needles, m.p. 210-211°, $[\alpha]_D$ + 54.7° (c,1.2). The compound is transparent to ultraviolet light. Infrared spectrum: bands at 1739 and 1240 cm.$^{-1}$ (acetate) and 1710 cm.$^{-1}$ (carbonyl).

[Found: C,72.81; H,9.90. $C_{28}H_{44}O_5$ requires C,73.00; H,9.63%].

Treatment of the Oxodiacetate with Selenium Dioxide in Acetic Acid. - A solution of the oxodiacetate (350 mg.) in glacial acetic acid (15 ml.) was heated under reflux with selenium dioxide (520 mg.) for 5 hours. The crude product, isolated in the usual way, was hydrolysed with boiling methanolic potassium hydroxide (5%, 40 ml.). A solution of the hydrolysed material in acetone (15 ml.), was oxidised with the Kiliani reagent (0.63 ml. ≡ 2.05 [o]). Chromatography of the resulting product over alumina (5 g.) failed to yield an aromatic derivative.

9β-Methyl-10:11-dihydroxy-C-nor-D-homolanosta-12:14:16-trienyl Acetate. - A solution of the aromatic acetate (m.p. 200-202°, 90 mg.) in dry ether (12 ml.) was added to a suspension of lithium

aluminium hydride (100 mg.) in dry ether (12 ml.) and the mixture was heated under reflux for 2½ hours. After dilution with ether, the excess reagent was destroyed by the careful addition of crushed ice. The ethereal solution was washed with water, dried (Na_2SO_4) and evaporated to give the triol as a white solid. Light absorption: Max. at 2080 Å., 2230 Å. and 2800 Å. Infrared spectrum: bands at 3620 $cm.^{-1}$ (hydroxyl) and 1480 and 863 $cm.^{-1}$ (benzenoid). The crude triol was dissolved in pyridine (1 ml.) and acetic anhydride (1 ml.) and the solution kept at 16° for 18 hours. The product, isolated in the usual way, crystallised from methanol as blades, m.p. 165-166°, $[\alpha]_D$ - 26.8° (c,0.40), unchanged by further crystallisation. Light absorption: Max. at 2060 Å. (49,600), 2200 Å. (ε:12,000), 2260 Å. (ε:11,000), 2720 Å. (ε:687) and 2800 Å. (ε:687). Infrared spectrum bands at 1736 and 1245 $cm.^{-1}$ (acetate), 3610 and 3450 $cm.^{-1}$ (hydroxyl) and 1480 and 863 $cm.^{-1}$ (benzenoid). This compound is 9β-methyl--10:11-dihydroxy-C-nor-D-homolanosta-12:14:16-trienyl acetate (CXXXVIII).

[Found: C,77.01; H,10.20. $C_{32}H_{50}O_4$ requires C,77.06; H,10.11%]

Oxidation of the Aromatic Acetate (CXXXV). - (a) A solution of the aromatic acetate (m.p.200-202°, 500 mg.) in pyridine (10 ml.) was added to the complex formed from chromium trioxide (500 mg.) and pyridine (5 ml.) and the mixture was allowed to stand at room temperature for 18 hours. The product, on crystallisation from methanol, gave unchanged starting material, m.p. and mixed m.p. 201-203°, in good yield.

(b) A solution of the aromatic acetate (m.p. 200-202°, 200 mg.) in stabilised acetic acid (25 ml.) was treated with a solution of chromium trioxide (60 mg.) in acetic acid (5 ml.) and the mixture was allowed to stand at room temperature for 20 hours. The excess reagent was destroyed by the addition of methanol and the product, isolated in the usual way, crystallised from methanol to give unchanged material, m.p. and mixed m.p., 200-202°.

(c) When the last experiment (b) was repeated at 25° and 50°, unchanged starting material was again recovered in good yield.

(d) A solution of the aromatic acetate (m.p. 200-202°, 100 mg.) in acetone (6 ml.) was treated with the Kiliani solution (0.176 g. sodium dichromate c.c.; 0.18 ml) added during 2-3 minutes and the mixture was allowed to stand at room temperature for a further 10 minutes. Crystallisation of the product from methanol again gave starting material, m.p. and mixed m.p. 201-203°.

(e) The above experiment (b) was repeated at 100° for 1 hour using weight for weight proportions of the aromatic acetate and chromium trioxide (= 7.5 [o]). No crystalline material was obtained from either the acidic or the neutral fractions.

9β-Methyl-3β:10ζ-diacetoxy-11-oxo-C-nor-D-homolanosta-12:14:16-triene. - A solution of the aromatic acetate (m.p. 200-202°, 100 mg.) in chloroform (2.5 ml., and dimethylaniline (3 ml.) was heated under reflux for 20 hours with acetyl chloride (2 ml.). The solution was cooled, poured into water and worked up in the usual way using ether. Crystallisation of the product from methanol gave blades, m.p. 160-163°, which on recrystallisation from

the same solvent yielded 9β-methyl-3β:10ξ-diacetoxy-11-oxo-C-nor-D-homolanosta-12:14:16-triene, as blades, m.p. 164-165°, $[\alpha]_D$ - 49° (c,0.35). Light absorption: Max. at 2150 Å. (ε: 25,500), 2600 Å. (ε:9,800) and 3100 Å. (ε:2,000). Infrared spectrum: bands at 1240 and 1740 cm.$^{-1}$ (acetate), 1718 cm.$^{-1}$ (carbonyl) and 1580, 1480 and 868 cm.$^{-1}$ (benzenoid).

[Found: C,75.54; H,9.60. $C_{34}H_{50}O_4$ requires C,75.80; H,9.40%]

Treatment of 9α-Hydroxy-11-oxolanostanyl Acetate with Selenium Dioxide in Acetic Acid. - A solution of the hydroxy ketone (230 mg.) in acetic acid (10 ml.) was heated under reflux for 5 hours with selenium dioxide (300 mg.). The product was dissolved in light petroleum and chromatographed over alumina (6 g.). The fraction (100 mg.) eluted with light petroleum-benzene (3:2, 60 ml.; 1:3, 120 ml.) and benzene (60 ml.) crystallised from methanol to give 9α-hydroxy-11:12-dioxolanostanyl acetate as yellow prisms, m.p. and mixed m.p. 210-212°, $[\alpha]_D$ + 139.2° (c,0.75).

Dehydration of the Aromatic Acetate (CXXXV). - A solution of the aromatic acetate (m.p. 200-202°, 40 mg.) in dry pyridine (4 ml.) was treated with phsophorus oxychloride (0.4 ml.) and the solution was kept at 100° for 3 hours. The product, isolated in the usual way, was obtained as an uncrystallisable gum. Light absorption: Max. at 2170 Å. (ε:30,600) with shoulder at 2100 Å.; 2600 Å. (ε:10,500) and 3100 Å. (ε:2,400). Infrared spectrum: bands at 1243 and 1739 cm.$^{-1}$ (acetate), 1710 cm.$^{-1}$ (carbonyl), 1630 and 890 cm.$^{-1}$ (double bond) and 1580, 1480 and 870 cm.$^{-1}$ (benzenoid).

Saponification of Shea-nut Fat. - A solution of shea-nut fat (5.5 Kg.) in ethanolic potassium hydroxide (10%, 15 l.) was boiled under reflux for 5 hours. Portions of the hot solution (3-4 l.) were transferred to large aspirator bottles each containing warm water (8 l.). The resulting mixture was allowed to cool to 25° before each portion was extracted with ether (2 x 6 l.). The combined ether extracts were reduced in bulk to about 4 litres, washed with aqueous alcohol (30%) and, finally, six times with water to remove soaps. The resulting ethereal solution was dried (Na_2SO_4) and evaporated to give the non-saponifiable fraction as a pale brown gum (180 g.).

Dihydrobutyrospermyl Acetate. - The non-saponifiable material (180 g.) was boiled under reflux with acetic anhydride (850 ml.) for 3 hours and the solution allowed to stand overnight at room temperature. The white semi-crystalline solid which separated (fraction A, 170 g.) was collected and the filtrate kept at 0° for 2 days, when a second crop of small crystals (fraction B, 11 g.) was deposited. Fraction A (170 g.) was boiled under reflux with acetic anhydride (580 ml.) for 1 hour and left at room temperature overnight. The solid which separated was removed by filtration and rejected. During the filtration a crop of fine granular solid separated and, after 12 hours at room temperature, was collected (fraction C, 5.3 g.). Two crystallisations of fraction B from ethanol-ethyl acetate (10:3) gave material, corresponding to "basseol acetate", as stout needles (6.9 g.), m.p. 133-135°, $[\alpha]_D$ + 24° (c,2.2), while one crystallisation of

fraction C from the same solvent mixture also gave "basseol acetate" as needles (3.5 g.), m.p. 134-136°, $[\alpha]_D$ + 23° (c,1.5). These two fractions were combined, dissolved in ethyl acetate (500 ml.)and shaken with hydrogen over a platinum catalyst (1 g.) at 20° for 9 hours. Evaporation of the filtered solution gave a semi-crystalline solid which was dissolved in light petroleum and chromatographed on a long column of alumina (500 g.). Elution with the same solvent (4 l.) gave a fraction (6 g.) which crystallised from chloroform--methanol to give dihydrobutyrospermyl acetate as prismatic needles (5.5 g.), m.p. 134-136°, $[\alpha]_D$ + 10.8° (c,2.3).

7-Oxoapoeuph-14-enyl Acetate. - Dihydrobutyrospermyl acetate (2 g.) in methylene chloride (20 ml.) and acetic acid (250 ml.) was treated dropwise during 30 minutes at room temperature with a solution of chromium trioxide in acetic acid (12 mg. ml., 70.3 ml. = 3 atoms oxygen). The mixture was kept at room temperature for 16 hours. A little methanol was then added and the mixture evaporated to dryness under reduced pressure. The product, isolated as a gum by means of ether, was dissolved in light petroleum (100 ml.) and chromatographed on alumina (60 g.). Elution with light petroleum (1,2 l.) gave fractions (442 mg.) which yielded dihydrobutyrospermyl acetate as prismatic needles m.p. and mixed m.p. 134-135°, on crystallisation from methanol. Elution with light petroleum-benzene (9:1, 1.35 l.; 4:1, 750 ml.) gave fractions (450 mg.) which on crystallisation gave 7:11-dioxoeuph-8-enyl acetate, identified by ultraviolet absorption, and 7-oxoeuph-8-enyl acetate as needles, m.p. and mixed m.p. 162-163°, $[\alpha]_D$ + 40° ± 5° (c,0.4). Continued

elution with light petroleum-benzene (1:1, 1.5 l.) gave fractions (335 mg.) which crystallised from methanol to give 7-oxoapoeuph--14-enyl acetate as stout needles m.p. 119-120°, $[\alpha]_D$ - 85° (c,1.0). Light absorption: Max. at 2060 Å., (ε: 6,500); Infrared absorption (in carbontetrachloride): bands at 1640 $cm.^{-1}$ (isolated double bond), 1710 $cm.^{-1}$ (6-membered ring-ketone), and 1735 $cm.^{-1}$ (acetate), The compound gave a bright yellow colour with tetranitromethane in chloroform.

[Found: C,79.2; H,11.1. $C_{32}H_{52}O_3$ requires C,79.3; H,10.8%]

The compound was unchanged after treatment with acetic anhydride and pyridine at 100° for 1 hour.

apoEuph-14-enyl Acetate. - 7-Oxoapoeuph-14-enyl acetate (125 mg.) in diethylene glycol (15 ml.) was mixed with a solution of sodium (375 mg.) in diethylene glycol (23 ml.) and the mixture heated to 200°. Anhydrous hydrazine, prepared by refluxing hydrazine hydrate (100%) over sodium hydroxide in an atmosphere of nitrogen for 3 hours, was distilled into the reaction mixture until it refluxed gently at 180°. After boiling at 180° for 18 hours, the mixture was distilled until the temperature reached 210°, and boiling was continued at this temperature for a further 24 hours. The cooled solution was poured into water and extracted with ether. The product, isolated in the usual way, was acetylated with acetic anhydride and pyridine at 100°. A solution of the product (130 mg.) in light petroleum was chromatographed on alumina (4 g.) Elution with light petroleum (150 ml.) gave a fraction (74 mg.) which, after two crystallisations from methanol, gave apoeuph-14-enyl acetate as needles m.p. 114-115°, $[\alpha]_D$ - 12° (c,1.1). The compound gave a

yellow colour with tetranitromethane in chloroform and showed a light absorption maximum at 2060 Å. (ε:6,400).

[Found: C,81.5; H,11.7. $C_{32}H_{54}O_2$ requires C,81.6; H,11.6%]

Oxidation of eupha-7:9(11)-dienyl Acetate with Chromium Trioxide in Acetic Acid. - Eupha-7:9(11)-dienyl (acetate (1 g.) was treated with chromic acetic acid using the method and proportions described in the preparation of 7-oxoapoeuph-14-enyl adetate (above). Chromatography of the neutral product yielded three fractions, namely starting material, 7:11-dioxoeuph-8-enyl acetate and 7-oxoeuph-8-enyl acetate. No trace of 7-oxoapoeuph-14-enyl acetate was detected.

Oxidation of Euph-8-enyl Acetate with Chromium Trioxide in Acetic Acid. - Euph-8-enyl acetate (1 g.) was oxidised with chromium trioxide (426 mg. = 3 atoms oxygen) in acetic acid - methylene chloride as described above. Chromatography of the neutral product yielded three crystalline fractions identified as euph-8-enyl acetate (m.p. and mixed m.p. 123-124°); 7:11-dioxoeuph-8-enyl acetate (m.p. and mixed m.p. 111-113°) and 7-oxoeuph-8-enyl acetate (m.p. and mixed m.p. 145°). Again no 7-oxoapoeuph-14-enyl acetate was detected.

7-Oxoisoeuph-13(17)-enyl Acetate. - A solution of 7-oxoapoeuph--14-enyl acetate (20 mg.) in a mixture of concentrated hydrochloric acid and acetic acid (1:20, 20 ml.) was kept at 100° for 3 hours. The solution was poured into water and the product, isolated by means of ether, was crystallised from methanol to yield 7-oxoisoeuph-13(17)--enyl acetate as plates, m.p. 112-113°, $[\alpha]_D$ - 50° (c,1.3). It gave a yellow colour with tetranitromethane in chloroform and showed a light absorption maximum at 2060 Å. (ε:7,600).

[Found: C,79.6; H,11.0. $C_{32}H_{52}O_3$ requires C,79.3; H,10.8%]

Treatment of 7-oxo*apo*euph-14-enyl acetate with concentrated sulphuric acid in acetic acid at 20° for 1 day or with dry hydrogen chloride in chloroform at 0° for 2 hours resulted in the recovery of starting material in good yield.

Isomerisation of apo*Euph*-14-*enyl Acetate to* iso*Euph*-13(17)--*enyl Acetate*. - *apo*Euph-14-enyl acetate (14 mg.) in dry chloroform (3 ml.) was treated at 0° with a stream of dry hydrogen chloride for 2 hours. The product was isolated in the usual way and its solution in light petroleum (20 ml.) was filtered through alumina (3 g.). Elution with the same solvent gave a fraction (11.6 mg.) which crystallised from methanol to yield *iso*euph-13(17)-enyl acetate as plates, m.p. and mixed m.p. 109-110°, $[\alpha]_D$ - 10° (*c*,0.4).

Treatment of Euph-8-*enyl Acetate with Mineral Acid*. - (a) A solution of euph-8-enyl acetate (500 mg.) in acetic acid (35 ml.) was treated with trichloro-acetic acid (1.5 g.) and the mixture was kept at room temperature for 3 hours. The product was isolated using ether and crystallised from chloroform-methanol to give unchanged euph-8-enyl acetate as needles m.p. and mixed m.p. 124-125°.

(b) The above experiment was repeated at 100° for 3 hours and (c) under reflux for 3 hours. In both cases starting material was recovered in good yield.

(d)[101] Euph-8-enyl acetate (5 g.) was dissolved in a mixture of concentrated hydrochloric acid and acetic acid (1:20, 150 ml.) and the solution was heated at 100° for 3 hours. The product, isolated in the usual way, crystallised from chloroform-methanol go give *iso*euph--13(17)-enyl acetate as plates, m.p. 109-110°, $[\alpha]_D$ -9.5° (*c*,1.0).

(c) Euph-8-enyl acetate (0.5264 g.) was dissolved in chloroform (40 ml.) which had been saturated with hydrogen chloride. The solution was transferred to a 4 dm. polarimeter tube and the reaction followed polarimetrically. Readings were taken initially every hour and as the reaction slowed down, every few hours, for a total of 379 hours. The graph of time against reading was a straight line. The product was isolated from the solution in the usual way and gave isoeuph-13(17)-enyl acetate, m.p. and mixed m.p. 110-111°, on crystallisation from chloroform-methanol.

isoEupha-11:13(17)-dienyl Acetate. - A solution of isoeuph-13(17)-enyl acetate (3 g.) in acetic acid (300 ml.) was heated under reflux for 2 hours with selenium dioxide (1.5 g.). The solution was filtered, poured into water and worked up in the usual way. Chromatography of the product over alumina and elution with light petroleum-benzene mixture and benzene gave fractions which yielded isoeupha-11:13(17)-dienyl acetate as plates, m.p. 93-94°, $[\alpha]_D$ + 20° (c,0.4), on crystallisation from methanol. Light absorption: Maxima at 2470 Å. (ε:15,200), 2550 Å. (ε:18,100) and 2640 Å. (ε: 12,400).

Hydrogenation of isoEupha-11:13(17)-dienyl Acetate. - A solution of isoeupha-11:13(17)-dienyl acetate (150 mg.) in ethyl acetate (20 ml.) was added to a suspension of platinum (from 50 mg. PtO_2) in acetic acid (20 ml.) and the mixture was shaken with hydrogen for 3 hours. The product on crystallisation from methanol gave isoeuph-13(17)-enyl acetate, m.p. and mixed m.p. 109-111°, $[\alpha]_D$ - 9.1° (c,0.5). The γ-euphenyl acetate reported by Vilkas[139] had m.p. 105-106°, $[\alpha]_D$ + 14° and by Christen[140]

had m.p. 103-104°, $[\alpha]_D$ - 6°. Barton[43] isolated only isoeuph-13(17)-enyl acetate, m.p. 110-111°, $[\alpha]_D$ - 9° from this reaction.

Lanost-7-enyl Acetate.[77] - A solution of lanost-8-enyl acetate (26 g.) in chloroform (260 ml.) was treated with a stream of dry hydrogen chloride at 0° for 2 hours and kept at room temperature for a further 2 hours. Evaporation of the solvent under reduced pressure gave a white solid. A solution of this material in acetic acid (800 ml.) was heated at 80° and a solution of chromium trioxide (7.8 g.) in acetic acid (90%, 50 ml.) was added rapidly. The solution was kept at 80° for 10 minutes and then poured into water (3 l.). The product, isolated in the usual way, was dissolved in light petroleum and filtered through a column of alumina (750 g.). Elution with light petroleum-benzene (4 :1, 5 l.) gave fraction (8.9 g.) which yielded lanost-7-enyl acetate as plates, m.p. 143-145°, $[\alpha]_D$ + 33° (c,2.9), on crystallisation from ethyl acetate-methanol. Barton[67] gives m.p. 145°, $[\alpha]_D$ + 32°.

Lanost-7-en-3β-ol. - A solution of lanost-7-enyl acetate (5 g.) in dry ether (200 ml.) was added to a suspension of lithium aluminium hydride (1 g.) in ether (300 ml.) and the mixture was heated under reflux for 1 hour. The product, isolated in the usual way, gave lanost-7-en-3β-ol as needles, m.p. 157-158°, $[\alpha]_D$ + 10.4° (c,1.5), on crystallisation from methanol-ethyl acetate. Woodward et al.,[93] give m.p. 162-163°, $[\alpha]_D$ + 10° for this compound. Re-acetylation of this alcohol gave lanost-7-enyl acetate, m.p. and mixed m.p. 143-145°, $[\alpha]_D$

+ 33.2° (c,1.7).

Lanost-7-enyl Benzoate. - Benzoylchloride (5 ml.) was added to a solution of lanost-7-enol (200 mg.) in pyridine (10 ml.) and the mixture was kept at 100° for 2 hours. On crystallisation of the product from methanol, lanost-7-enyl benzoate was obtained as needles, m.p. 207-209°, $[\alpha]_D$ + 50° (c,1.9). Woodward et al.,[95] give m.p. 207-208°, $[\alpha]_D$ + 51°.

Lanost-7-en-3-one. - A solution of lanost-7-en-3β-ol (2 g.) in pyridine (40 ml.) was kept at 16° for 24 hours with the complex formed from chromium trioxide (2 g.) and pyridine (20 ml.). The product, isolated by means of ether, was crystallised from methanol-ether to give lanost-7-en-3-one as blades, m.p. 146-147°, $[\alpha]_D$ - 20° (c,2.8). Marker[77] gives m.p. 149°, (specific rotation not recorded). Barton[142] has subsequently quoted m.p. 144-145°, $[\alpha]_D$ - 15° for this compound. [Found: C,84.7; H,12.0. $C_{30}H_{50}O$ requires C,84.4; H,11.8%].

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