T H E S I S

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A C K N O W L E D G E M E N T

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STUDIES IN THE TETRACYCLIC GROUP OF TRITERPENOIDS

CONTENTS

HISTORICAL

Introduction

The triterpenes were originally defined as a series of naturally occurring compounds, the molecules of which contain thirty carbon atoms arranged so that six isoprene units linked together regularly or irregularly could be recognised as components of the structure. However, the more comprehensive term triterpenoid has now been adopted to describe members of this class since it is now known that a number of compounds exist which are clearly related to the triterpenes proper and which contain not thirty but thirty-one carbon atoms.

The triterpenoids may be initially classified in three main groups according to the nature of their carbon skeletons:

(i) The largest and most abundant group consists of the pentacyclic triterpenoids all of which are of vegetable origin. Although there are over fifty compounds of known constitution in this group, their structures all contain one of the five carbon skeletons typified by those of α-amyrin, β-amyrin, lupeol, taraxasterol, and taraxerol and conform to the classical isoprene rule. The hexacyclic triterpenoid, phyllanthol, which contains a cyclopropane ring and is closely related to α-amyrin, may also be included in this group.

(ii) The tetracyclic group of triterpenoids is smaller but members of this group are fairly widely distributed in Nature, being found in plants, in fungi, and in one animal source, sheep

wool-fat, from which lanosterol, one of the most important members of the group, is obtained in quantity. The compounds of this group possess the tetracyclic nucleus typical of the steroids and from a structural point of view are at present considered to occupy an intermediate position between the triterpenoids and the steroids. The group also includes the pentacyclic compounds, cycloartenol and cycloläudenol, both of which are closely related to lanosterol.

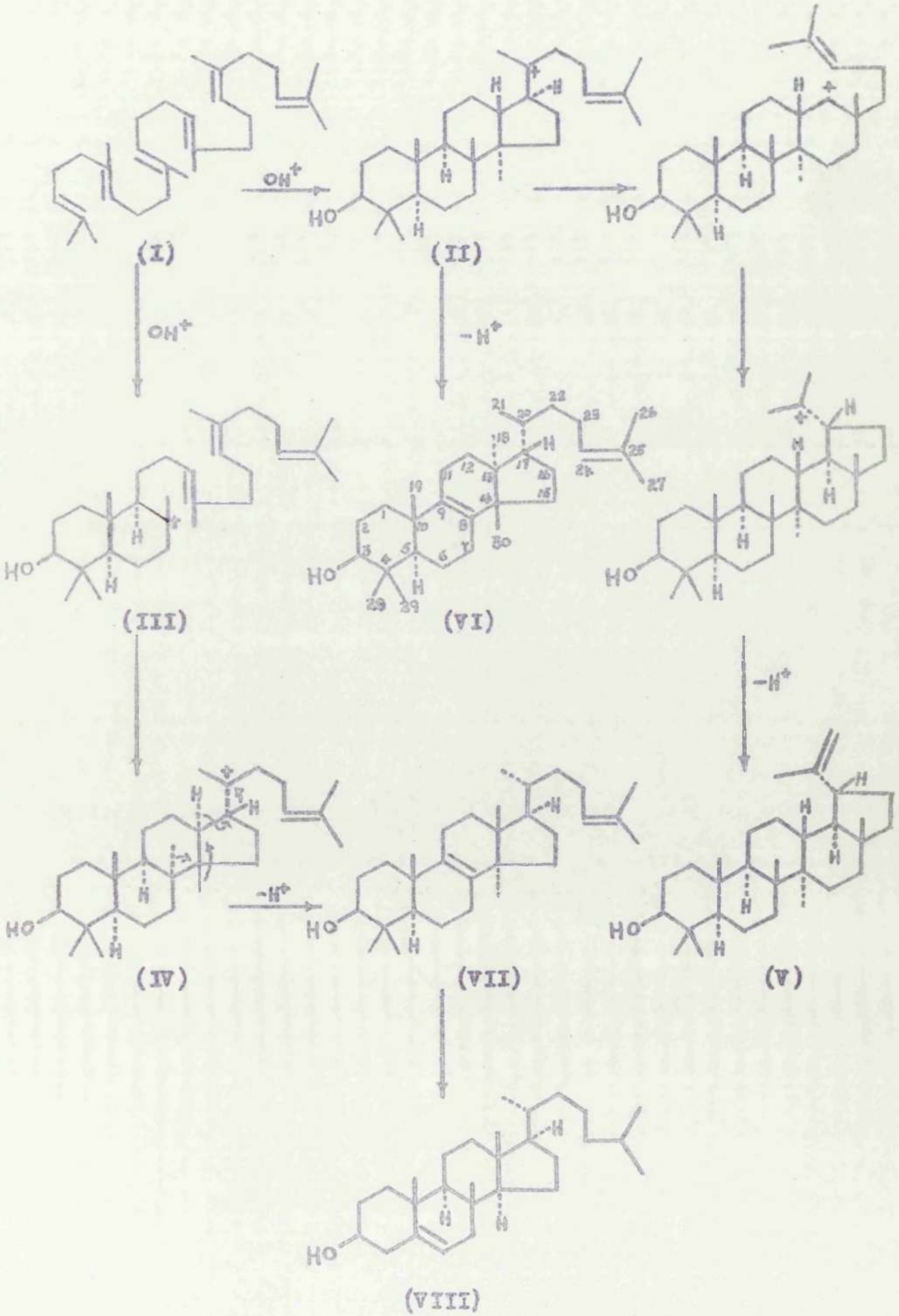
(iii) The tricyclic alcohol, ambrein and the acyclic hydrocarbon, squalene, both of which are of animal origin, are best classified together as members of the "squalenoid" group of triterpenoids along with the diol onocerin which is of vegetable origin and which has recently been shown to possess a new type of tetracyclic structure.

Unlike the other triterpenoids, those of the tetracyclic group do not conform to the classical isoprene rule and it has been suggested that it may be more correct to regard them as trimethyl-steroids. This non-conformity with the isoprene rule does not, however, disprove their origin from isoprene units since it is now considered that the tetracyclic triterpenoids obey the "biogenetic isoprene rule"[1] and that their structures are produced biogenetically from a conforming intermediate by molecular rearrangement involving Wagner-Meerwein type migrations of angular methyl groups.

The theory of steroid and triterpenoid biogenesis has advanced considerably in recent years. Bloch[2a-d] has shown experimentally that squalene (I) is an intermediate in the biosynthesis of lanosterol and thence cholesterol from acetic acid and at the present time it is considered to be the precursor from which, by slight variations in its cyclisation, all the triterpenoids and steroids are derived. The molecule of natural squalene is now known to have a fully transoid arrangement throughout[3]. This is of considerable importance since, if the cyclisation is fully concerted, only this conformation can give rise to the stereochemistry found in the triterpenoids and steroids[4-8]. Evidence that the cyclisation of squalene does in fact take place by a synchronous, non-stop process, without the formation of any stabilised intermediates has recently been obtained by Bloch.[6,7] In the case of the cyclic triterpenoids of the "squalenoid" group, this cyclisation must start simultaneously at both ends of the squalene molecule, while in the biosynthesis of the tetracyclic and pentacyclic triterpenoids, the cyclisation is considered to be motivated by the attack of a cation, for example OH^+ derived from molecular oxygen,[6,7] at the double bond at one end only of the squalene chain (I)[1,4-8]. The cyclisation then proceeds synchronously by two different paths: In the first, the concerted closure of four rings leads to the formation of the

carbonium ion (II) which is considered to be the precursor of the pentacyclic triterpenoids and of the euphol-tirucallol group of tetracyclic triterpenoids. The second path leads to the formation of the isomeric ion (IV), the precursor of the lanosterol group and thence of the steroids. It has been suggested[8a] that the ion (IV) is produced from squalene (I) by the concerted formation of the first two rings (III) immediately followed by the concerted closure of the last two. The formation of lupeol (V) and tirucallol (VI) from the carbonium ion (II) and of lanosterol (VII) and cholesterol (VIII) from the ion (IV) is illustrated below. It is now known that in the formation of cholesterol (VIII) from lanosterol (VII), the methyl groups at $C_{(4)}$ and $C_{(14)}$ in the lanosterol molecule are eliminated as carbon dioxide.[9]

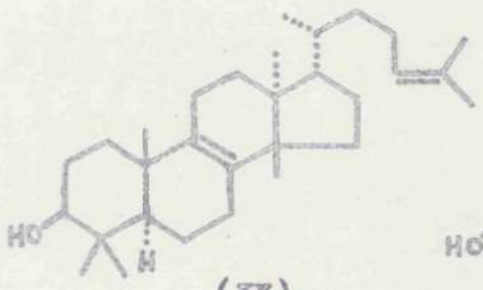
These mechanisms account for the formation of triterpenoids and steroids containing up to thirty carbon atoms all of which are known to have been derived from acetate.[2] They do not, however, explain why a number of tetracyclic triterpenoids and steroids contain an additional carbon atom attached to the side chain at $C_{(24)}$. Previously the source of this carbon atom was also considered to be acetate but recently it has been shown that formate is in fact the precursor of the carbon atom attached to $C_{(24)}$ in eburicoic acid[10] and in ergosterol[11].


(I)
(II)
(III)
(VI)
(IV)
(VII)
(V)
(VIII)

As the work described in the theoretical sections of this thesis is concerned only with compounds of the tetracyclic group which are shown experimentally to be related to lanosterol or euphol, it is not proposed to include in this historical review a summary of the chemistry of the pentacyclic triterpenoids.

Classification of the Tetracyclic Triterpenoids.

All members of the tetracyclic group of triterpenoids, whose basic structures are known, are at present generally classified in two principal sub-groups, typified by lanosterol (VII) and euphol (IX)[12]. For compounds of the lanosterol



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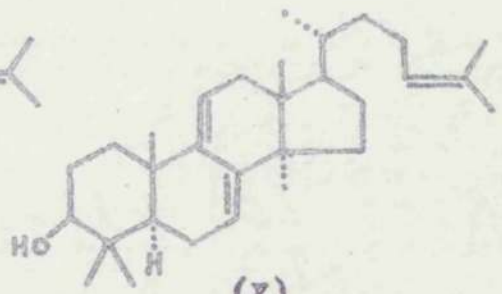


(X)

series, conversion into the conjugated $\Delta^{7:9(11)}$-diene (X) results in a moderate positive change in molecular rotation, whereas a similar conversion in the euphol series produces a very large negative change. In addition, the $\Delta^{7:9(11)}$-dienes of the two series show characteristic differences in their ultraviolet spectra: In the lanosterol series, as in the steroids, the heteroannular dienes exhibit three

characteristic maxima at ca., 2370, 2440, and 2510 Å. while in the euphol series these maxima occur at distinctly shorter wavelengths (ca., 2320, 2390, and 2470 Å.). The effect of mineral acid on the Δ^8-double bond is also a distinguishing feature in each series. Acid isomerisation of lanost-8-enol gives an equilibrium mixture of Δ^7- and Δ^9-isomers, whereas similar treatment of euph-8-enol causes movement of the double bond from the Δ^8- to the $\Delta^{13(17)}$-position, a rearrangement involving a concerted double methyl group migration. These characteristic differences between compounds of the two series arise from a difference in the orientation of certain methyl groups in the nuclei, the stereochemistry in the lanosterol series corresponding in general with that of the steroids while in compounds belonging to the euphol series, the configuration of the methyl groups attached to $C_{(13)}$ and $C_{(14)}$ and of the side chain attached to $C_{(17)}$ is reversed.

The Lanosterol Series.

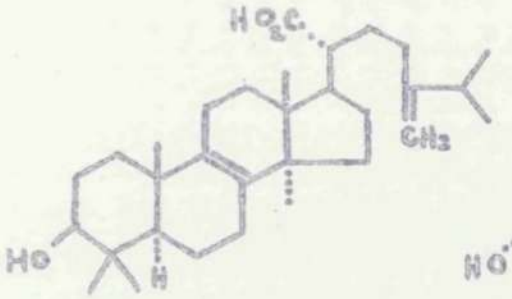
The following naturally occurring compounds are members of the lanosterol series: lanosterol, dihydrolanosterol, agnosterol, dihydroagnosterol, eburicoic acid, the polyporenic acids A, and C, tumulosic acid, pinicolic acid A, cycloartenol, cycloläudenol, cycloeucalenol, cyclo-orysterol, and parkeol.

Lanosterol (lanosta-8:24-dien-3β-ol, VII) and agnosterol (lanosta-7:9(11):24-trien-3β-ol, X) were first recognised by

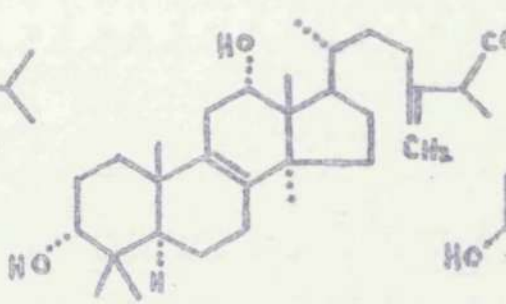
Windaus and Tschesche in 1930[13] as components of "isocholesterol", a fraction obtained from the non-saponifiable matter of sheep wool wax and which, until that time was believed to be a pure compound. The corresponding dihydro-compounds (VII and X with the side-chain double bond reduced) were later obtained from the same source by Ruzicka[14]. Lanosterol also occurs in the minor sterols of yeast[15] and in only one plant source[16]. The chemistry of lanosterol is briefly discussed in a later part of this section.

The acids listed above are generally classified together as members of the Fungal acid sub-group of the lanosterol series being produced by the metabolism of various wood-rotting fungi, notably those of the Polyporus and Basidiomycetes classes. In certain fungi, eburicoic acid and tumulosic acid occur along with their corresponding dehydro-compounds and the difficultly separable mixture of the latter with its dehydro-compound was, for a time, known as polyporenic acid B. The structures of the fungal acids have been elucidated mainly by the work of Halsall and Jones and are formulated below. It will be noted that all except pinicolic acid A contain thirty-one carbon atoms.

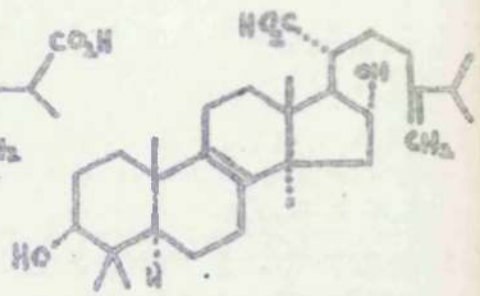
cycloArtenol (XI) was first isolated by Barton, along with the corresponding ketone, cycloartenone, from the fruits of Artocarpus integrifolia[38]. Handianol[36], an alcohol isolated earlier from Euphorbia handiensis has been shown to be identical



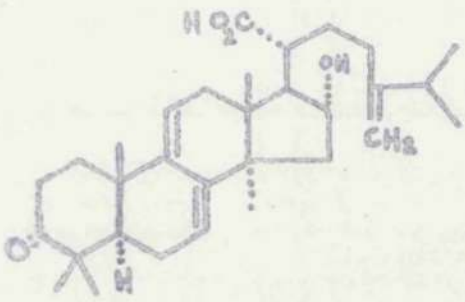
Eburicoic Acid[17-22]



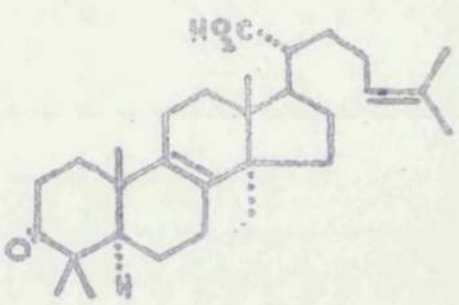
Polyporenic Acid A[23-30]



Tumulosic Acid[23,28,31,32]



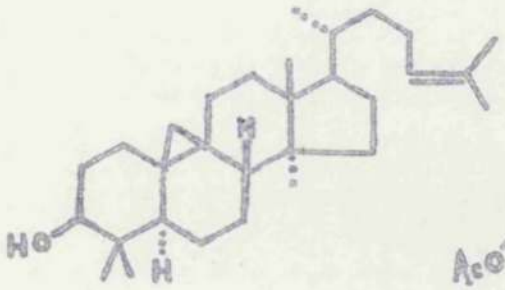
Polyporenic Acid C[23,31,33]



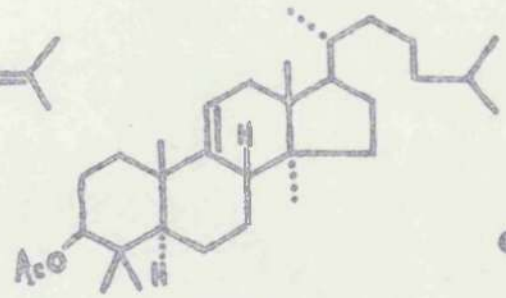
Pinicolic Acid A.[34]

with cycloartenol which has also been obtained from Euphorbia balsamifera[37], from the seed fat of Strychnos nux-vomica L.,[38] and more recently, as its ferulic acid ester from Japanese rice-bran oil[39]. The presence of a cyclopropane ring and an isolated double bond in an isopropylidene group in cycloartenol were first recognised by Barton[35] from both spectroscopic and chemical studies. Its relationship with lanosterol was discovered by Spring[36] who found that, when cycloartanyl acetate is treated with mineral acid, the cyclopropane ring is opened and the main product is lanost-9(11)-enyl acetate (XII). From a study of the infrared spectrum of cycloartenol, Cole[40] deduced

that the cyclopropane ring contains a methylene group and as a result of experiments in which deuterium chloride was used, Spring[41] was able to conclude that it extends from $C_{(9)}$ to $C_{(10)}$ and that cycloartenol is, therefore, 9:19-cyclolanost-24-en-3β-ol (XI), the configuration at $C_{(8)}$ being β as in lanost-9(11)-enyl acetate (XII). The structure (XI) was confirmed by the preparation of cycloart-1-en-3-one (XIII) which showed the ultraviolet absorption characteristics of an αβ-unsaturated ketone in conjugation with the cyclopropane ring[41]. Independent evidence for the structure (XI) was published simultaneously by Barton[42].



(XI)



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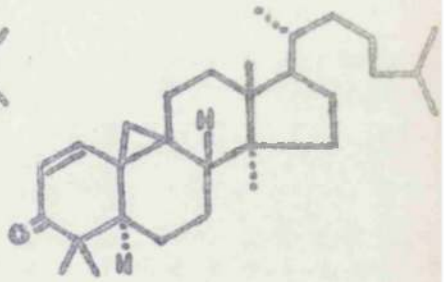
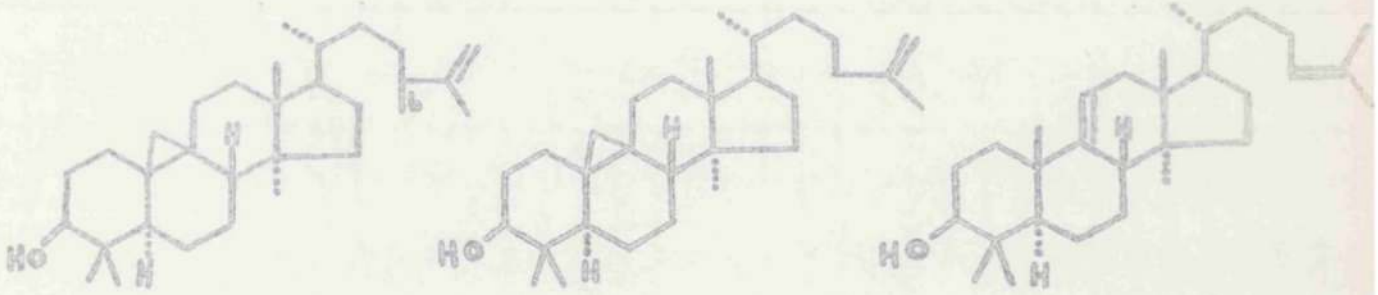


(XIII)

cycloLaudenol (XIV): Shortly after the elucidation of the structure of cycloartenol, Spring and his associates isolated a similar compound, which also contained a cyclopropane ring , from opium marc.[43]. The compound which was named cyclolaudenol, contained thirty-one carbon atoms and was shown to differ from cycloartenol only in the constitution of the side-chain. cycloLaudenol was eventually related to

cycloartenol by the partial degradation of the side-chains of both compounds to a common derivative[44]. This allowed the former to be formulated as 24b-methyl-9:19-cyclolanost-25-en--3β-ol (XIV); the configuration of the methyl group attached to $C_{(24)}$ being shown, by molecular rotation differences, to be the same as that in eburicane and ergostane.



(XIV) (XV) (XVI)

cycloOrysterol (XV), a simple double bond isomer of cycloartenol (XI), was originally called β-orysterol and β-tritisterol before the presence of the cyclopropane ring was recognised. It was recently obtained as its ferulate (orizanol B) from rice bran oil by two groups of Japanese workers[39, 45] and identified as 9:19-cyclolanost-25-en-3β-ol (XV) by direct comparison with cycloartanol derivatives[45].

cycloEucalenol, a new triterpenoid containing a cyclopropane ring has recently been isolated by King[46] from the heartwood of Eucalyptus microcorys. It has also been obtained

in this laboratory by Dr. J. McLean from the commercial timber known as white seraya imported from Borneo.

Parkeol, a minor constituent of the non-saponifiable fraction of shea-nut fat from the West African tree Butyrospermum parkii,[47,48] has been identified as lanosta-9(11):24-dien-3β-ol (XVI) by the author. The earlier investigations and details of its characterisation are discussed in the theoretical section.

The Euphol Series.

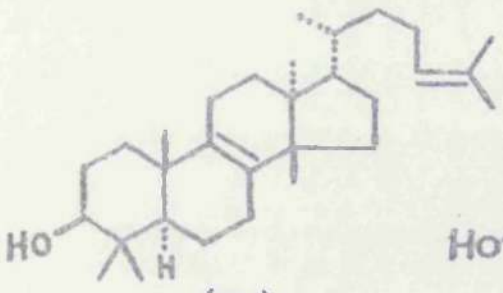
The following tetracyclic triterpenoids are members of the euphol series: euphol, tirucallol, euphorbol, elemadienolic acid, elemadienonic acid, masticadienonic acid, butyrospermol, and the triterpenoids of dammar resin.

Euphol (eupha-8:24-dien-3β-ol, IX) was first isolated in a pure state from an unidentified Euphorbia resin by Newbold and Spring in 1944.[49] It has since been found in the latex of many other plants of the Euphorbia species. After a period of intensive research, particularly by the schools of Barton and Ruzicka, its structure and stereochemistry was shown to be as in (IX). A brief review of the chemistry of euphol is included in this section.

Tirucallol was first obtained along with euphol and taraxasterol from Euphorbia tirucalli L. by Haines and Warren.[50] It has since been found in E. triangularis[51] and more recently

in gum mastic.[52] It was shown to be 20-isoeuphol (XVII) by various oxidative and degradative studies in which it was related to both lanosterol and euphol[53-60].

Euphorbol, a $C_{(31)}$-triterpenoid which often occurs along with euphol in the resins of the Euphorbia species,[49] was related to dihydrotirucallol by the elimination of the additional methylene group located in the side-chain at $C_{(24)}$[49] so that it may be formulated as (XVIII).[51, 55-61]



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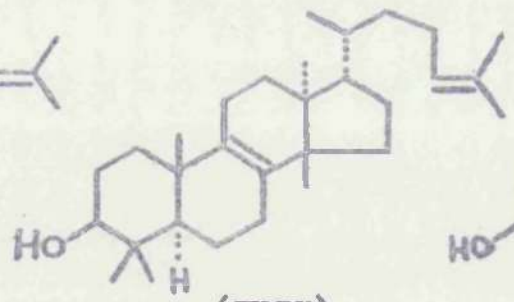
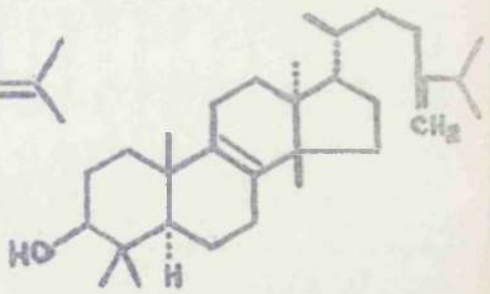


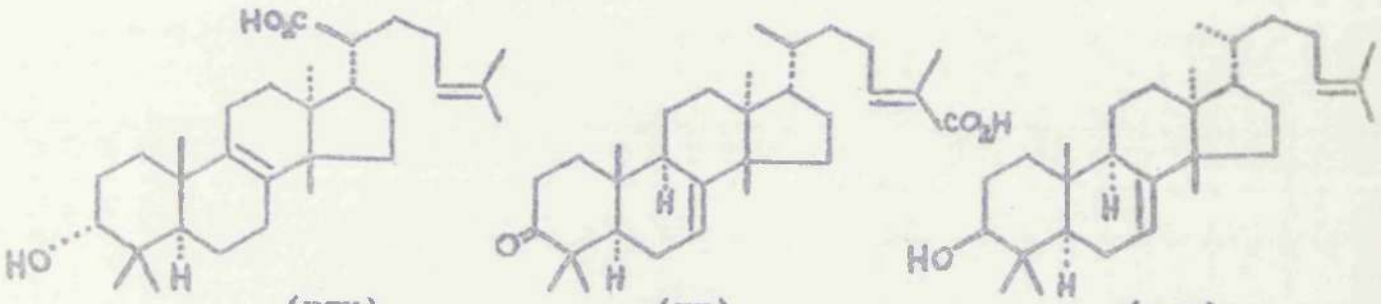
(XVII)



(XVIII)

Elemadienolic acid (XIX), a 3α-hydroxy-acid and elemadienonic acid, the corresponding 3-ketone, are constituents of Manila elemi resin[62]. The conversion of elemadienolic acid into epielemenol[63] which was eventually recognised as being identical with tirucallenol,[56] led to its structure being formulated as (XIX).[57] This was confirmed by its partial conversion into euph-8-enol.[59] The stereochemistry assigned to positions 3, 13, 14, 17, and 20 was further confirmed by the degradation of elemadienolic acid and lanosterol to

enantiomeric derivatives in which the asymmetry at $C_{(8)}$ and $C_{(10)}$ had been destroyed.[59]

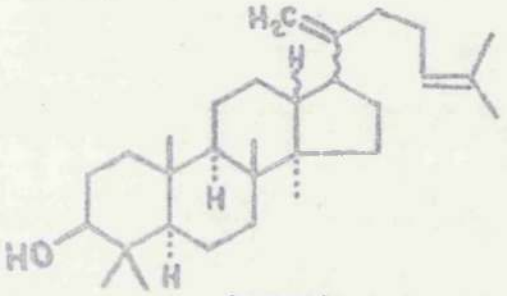


Masticadienonic Acid, a new tetracyclic triterpenoid, was recently isolated from gum mastic by Barton,[52] who has related it to tirucallol and formulated its structure as (XX). A study of molecular rotation data reveals that the configuration of the 9-hydrogen atom, which is not specified in the original paper,[52] is α[64] as in butyrospermol (XXI).[65] Another component of gum mastic, isomasticadienonic acid, has been identified as the corresponding Δ^{6}-isomer of (XX).[66]

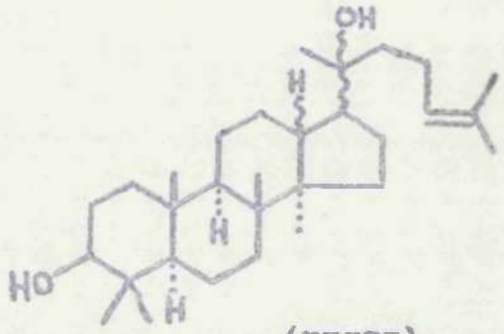
Butyrospermol, like parkeol, is a minor constituent of shea-nut fat. As a result of experiments described in this thesis, it has been identified as 9α-eupha-7:24-dien-3β-ol (XXI). Details of the earlier investigations are discussed in the theoretical section.

There remains to be mentioned the small group of tetracyclic triterpenoids which have recently been isolated from Dammar resin.[67] They are dammadienol (XXII) and the corresponding 3-ketone, dammadienone, the dammarenediols I and

II (XXIII), which differ only in the configuration at $C_{(20)}$, and the corresponding 3-ketones, hydroxydammarenones I and II.



(XXII)



(XXIII)

The dammar triterpenoids were identified as members of the euphol series when acid-catalysed dehydration of dihydrodammarenediols I and II gave a mixture of iso-euphenol and isotirucallenol.[68] The compounds are of interest because they all have the same carbon skeleton as the first tetracyclic carbonium ion (II) postulated in the cyclisation of squalene to euphol and to lupeol.

The Constitution of Lanosterol.

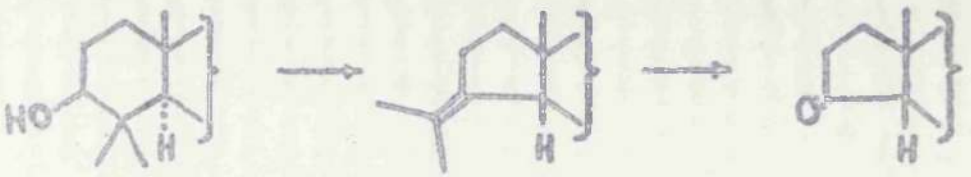
The initial investigations established that lanosterol, $C_{30}H_{50}O$, is a tetracyclic secondary alcohol containing two double bonds one of which is present in an isopropylidene group and and is readily reduced.[13,14,69,70,71]

Ring A: The constitution of the ring carrying the hydroxyl group in lanosterol was deduced from two separate series of degradations. In the first,[14] lanostenone (XXIV) was converted into the hydroxymethylene derivative (XXV) which on oxidation

with alkaline hydrogen peroxide gave the dicarboxylic acid (XXVI). Pyrolysis of (XXVI) yielded a nor-ketone (XXVII) indicating that the hydroxyl group is adjacent to an unsubstituted methylene group in a terminal ring which is at least six-membered. In the second series,[72,73] lanostenol (XXVIII) was shown to undergo a retropinacoline rearrangement

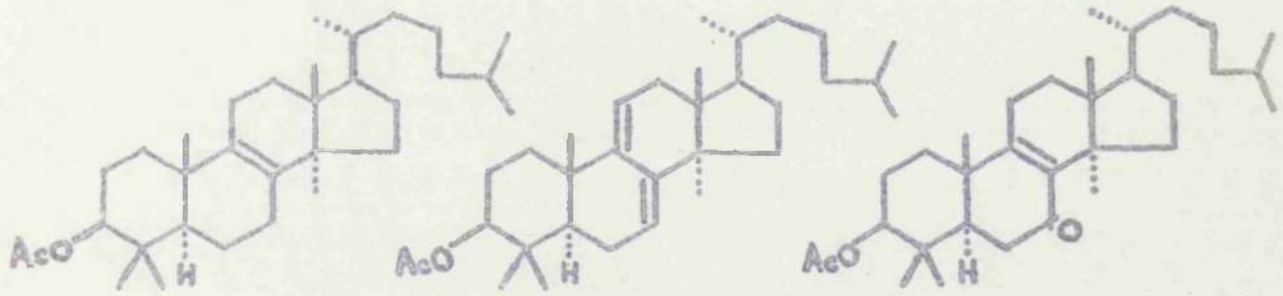
(XXIV) (XXV) (XXVI) (XXVII)

on treatment with phosphorus pentachloride. Treatment of the product (XXIX) with osmium tetroxide followed by lead tetra-acetate led to the five-membered ring ketone (XXX). This reaction sequence had previously been applied with similar results to a number of pentacyclic triterpenoids[73] and enabled ring A of lanosterol to be formulated as (XXVIII).



(XXVIII) (XXIX) (XXX)

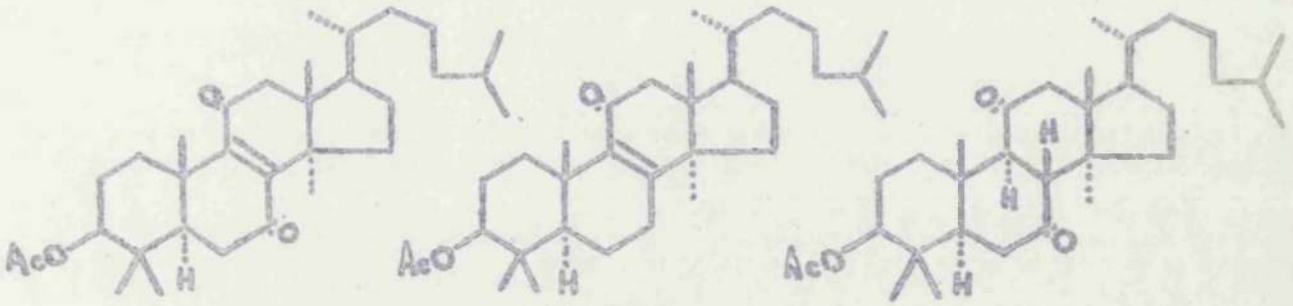
Rings B and C: The structures of rings B and C and the environment of the nuclear double bond, which was shown to be tetrasubstituted,[74,75] were largely deduced from a study of the physical and chemical properties of a series of oxidation products: Treatment of lanostenyl acetate (XXXI) with selenium dioxide in boiling acetic acid gave dihydroagnosteryl acetate (lanosta-7:9(11)-dienyl acetate, XXXII) in which the double bonds were deduced to be trisubstituted.[76-78] The diene (XXXII) was also obtained from (XXXI) using other reagents.[79,80] Mild chromic acid oxidation of either (XXXI) or (XXXII) yielded



(XXXI) (XXXII) (XXXIII)

the αβ-unsaturated ketone (XXXIII) which, on further oxidation, gave a yellow unsaturated diketone.[14,77,82] From its ultraviolet[14] and infrared spectra[81] it was shown to have the fully transoid structure (XXXIV), which indicated that the double bond in lanost-8-enyl acetate (XXXI) is flanked by two methylene groups.

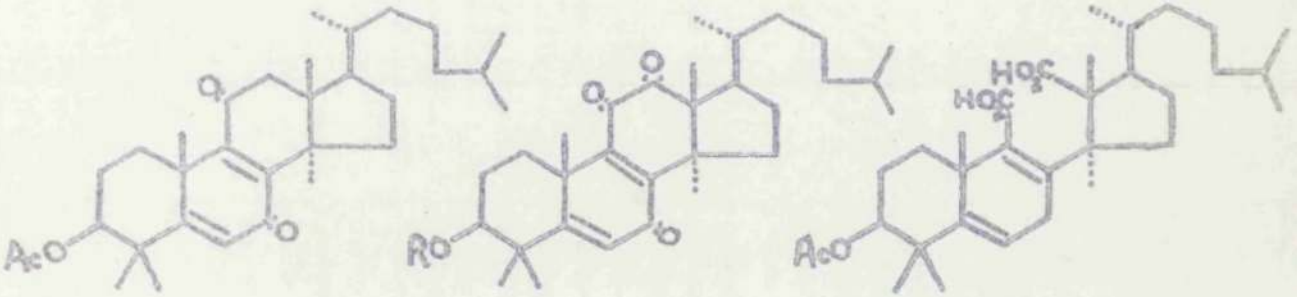
The diketone (XXXIV) was also obtained direct from either (XXXI) or (XXXII) by more vigorous treatment with chromic acid,[14,38] and from (XXXI) by treatment with hydrogen peroxide in acetic acid.[81] Of the two ketone groups in (XXXIV), that at $C_{(7)}$ is the more reactive and is removed by Wolff-Kishner reduction, the product being 11-oxolanost-8-~~onyl~~ acetate (XXXV).[83] Reduction of (XXXIV) with zinc in acetic acid or with hydrogen over platinum gave the saturated diketone (XXXVI),[79] the infrared absorption of which indicated that the carbonyl groups are present in six-membered rings.[81]



(XXXIV) (XXXV) (XXXVI)

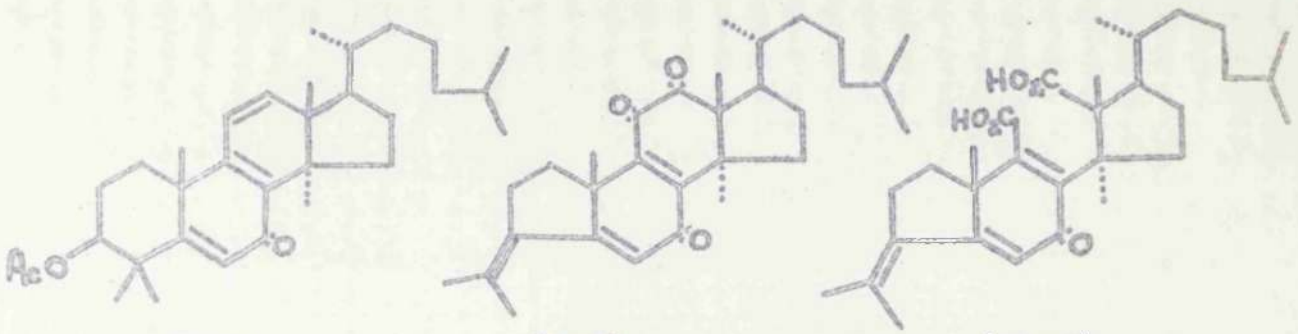
Oxidation of the ene-dione (XXXIV) with selenium dioxide introduced a trisubstituted double bond in conjugation with the system and gave the doubly-unsaturated diketone (XXXVII).[77,81] Further treatment of the latter with selenium dioxide yielded the diene-trione (XXXVIII, R = Ac), the α-diketone system of which was readily split with alkaline hydrogen peroxide to give the dicarboxylic acid (XXXIX) without loss of carbon.[78,77,79,81]

The diene-trione (XXXVIII, R = Ac) was also obtained by chromic acid oxidation of 7-oxolanosta-5:8:11-trienyl acetate (XL) which is itself formed by oxidation of lanost-8-enyl acetate (XXXI) or 7-oxolanost-8-enyl acetate (XXXIII) with selenium dioxide.[77,80,81] Dehydration of (XXXVIII, R = H) with phosphorus pentachloride caused a retropinacoline rearrangement with the formation of



(XXXVII) (XXXVIII) (XXXIX)

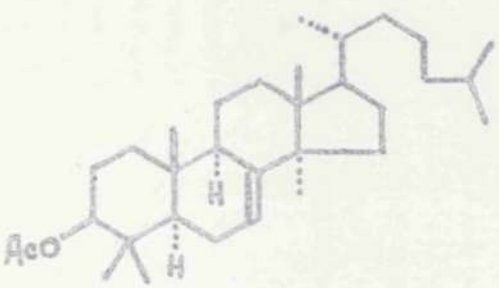
7:11:12-trioxoisolanosta-3:5:8-triene (XLI) in which the conjugated system has been extended to ring A and the position of the hydroxyl group related to that of the double bond.[76] Also, the formation of the dicarboxylic acid (XLII) by the action of alkaline hydrogen peroxide on (XLI) established that the α-diketone grouping is in ring C since an extended conjugated system is still present. Further the non-enolisation of the



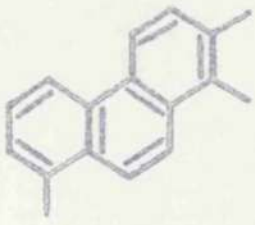
(XL) (XLI) (XLII)

α-diketone system in (XXXVIII) and the inability to form more complex oxidation products indicated that all the carbon atoms adjacent to the diene-trione and trione-ketone systems in (XXXVIII) and (XL) were fully substituted and confirmed the view that the nuclear double bond of lanosterol is in the fully substituted position between rings B and C rather than between rings C and D.

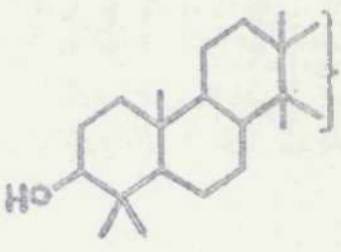
On treatment with mineral acid, lanost-8-enyl acetate (XXXI) is partially isomerised into the Δ^7-isomer (XLIII).[75,80,84,86] This is in contrast to the behaviour of the analogous steroid compounds in which the double bond moves from the Δ^8- to the $\Delta^{8(14)}$-position on acid isomerisation. To explain this, Barton suggested that both the $C_{(13)}$- and the $C_{(14)}$-positions in lanosterol are blocked by the attachment of methyl groups. This is supported by the oxidation reactions described above and confirmed by the formation of 1:2:8-trimethylphenanthrene (XLIV) on dehydrogenation with selenium.[14,71,75,86] The partial structure (XLV) was therefore, at this stage, assigned to lanosterol.



(XLIII)

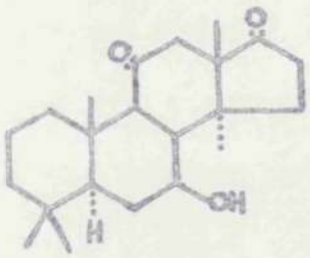


(XLIV)

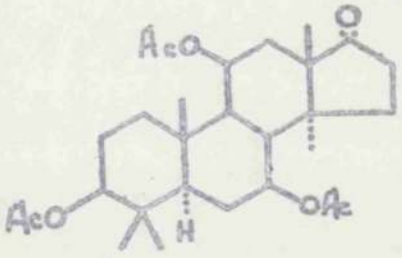


(XLV)

The Side-Chain and Ring D: By the isolation of acetone and 6-methylheptan-2-one from the vigorous chromic acid oxidation of lanost-8-enyl acetate (XXXI), Barton[87,88] was able to deduce that the lanosterol side-chain is isooctanyl in nature. The same conclusion was reached independently by Ruzicka[86] from a step-wise degradation of the side-chain. This degradation also led to the diketo-alcohol (XLVI), the infrared spectrum of which showed that one of the carbonyl groups



(XLVI)



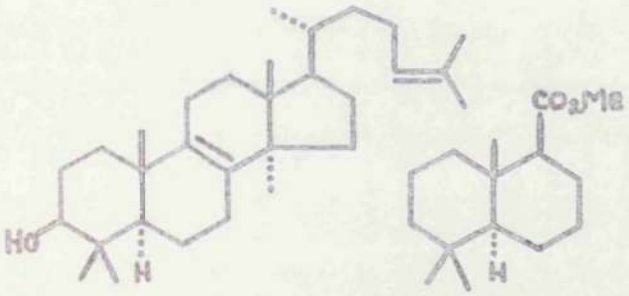
(XLVII)

was present in a five-membered ring.[89] From a study of the infrared spectrum of a similar degradation product (XLVII), Barton[90] showed that only one methylene group is adjacent to the carbonyl group so that the side-chain must be attached at either $C_{(16)}$ or $C_{(17)}$. The latter possibility was finally proved correct by Ruzicka[91] after an ingenious series of reactions involving oxidative fission of ring C. These indicated that the carbon atom to which the side chain is attached, must be β to $C_{(12)}$.

The Stereochemistry of Lanosterol: From an X-ray diffraction analysis of lanostenyl iodoacetate, a complete description (XLVIII) of the structure and stereochemistry of lanosterol was obtained.[82,93] This was quickly confirmed by chemical means.[91,94] From its stability towards epimerisation[15] and the fact that it is regenerated from the derived ketone on reduction with sodium in alcohol,[84] the 3-hydroxyl group was deduced to have the β-configuration. This was emphasised by the observation that ring A undergoes a retropinacoline rearrangement on dehydration with phosphorus pentachloride,[72,73] a reaction now known to be characteristic of a 3β-(equatorial)-hydroxyl group in a system having rings A and B trans-fused.[95] That rings A and B of lanosterol are in fact trans-fused was established by Klyne[96] from a study of molecular rotation data which showed that the methyl group at $C_{(10)}$ and the hydrogen atom at $C_{(5)}$ have the same absolute configurations as the 5α-steroids. Confirmation was obtained by Jeger who isolated the dicyclic ester (XL) corresponding to rings A and B from both lanosterol and manool (L).[97]

Shortly before the appearance of the X-ray studies, Barton,[76] to explain the hindered nature of the carbonyl group in 11-oxo derivatives of lanosterol, suggested that as in the steroids, the $C_{(13)}$-methyl group is on the same side of the molecule as the $C_{(10)}$-methyl group. The former was therefore

assigned the β-configuration. The trans-fusion of rings C and D and consequently the α-configuration of the $C_{(14)}$-methyl group was deduced from a study of the molecular rotation change which accompanies the removal of the 17-oxo group from 3β:7β:11α-triacetoxylanostan-17-one (LI).[94,96] The configurations of the side-chain attached to $C_{(17)}$ and the methyl group at $C_{(20)}$ were also determined using molecular

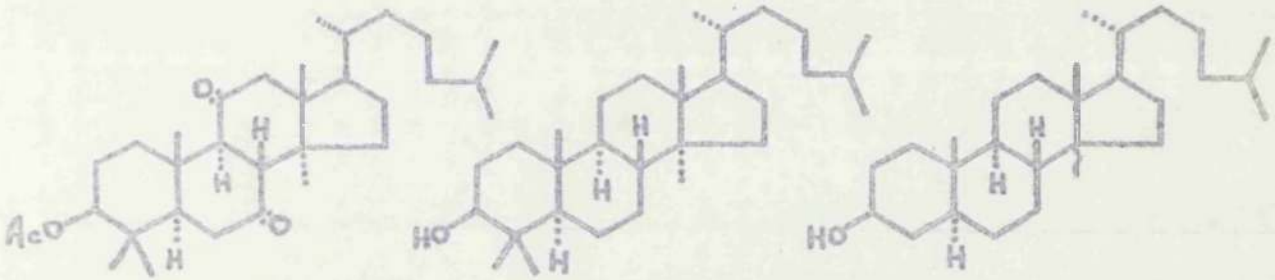


(XLVIII) (IL) (L) (LI)

rotation relations and shown to be as in cholesterol.[94] In the lanosterol series, the molecular rotation differences between compounds having the saturated isooctyl side-chain and those in which this has been replaced by $-CO_2CH_3$ were observed to be in good agreement with the differences given by the analogous 17β-steroid compounds. Further confirmation that the stereochemistry of lanosterol is the same as that in the 5α-steroids was obtained from biochemical considerations.[4,97]

The hydrogen atoms attached to $C_{(8)}$ and $C_{(9)}$ in 7:11-dioxolanostanyl acetate (XXXVI) and hence in lanostanol (LII), partly because of their stability to alkali,[94] are considered to

have the more stable trans-configuration with respect to each other and anti-relative to $C_{(14)}$ and $C_{(10)}$ giving an all-chair conformation throughout the molecule.[98]



(XXXVI) (LII) (LIII)

Confirmation of the constitution and stereochemistry (XLVIII) of lanosterol, deduced as outlined above, was obtained in 1954 when lanostanol (LII) was converted into 14-methylcholestanol (LIII)[99] which was later prepared from cholesterol.[100] Final proof was obtained the same year when the total synthesis of lanost-8-enol was achieved by Barton, Woodward and co-workers.[101] A fuller account of these researches has recently appeared.[102] This paper also describes the total synthesis of the three remaining wool-fat triterpenoids.

The Constitution of Euphol.

Euphol, $C_{30}H_{50}O$, was first isolated in a pure state by Newbold and Spring[49] who showed that it contains a secondary hydroxyl group and two isolated double bonds. It is therefore tetracyclic. Of the two double bonds, one is readily reduced and was later shown to be present in an

isopropylidene group[103,104] which terminates a side-chain identical in constitution with that of lanosterol.[105]

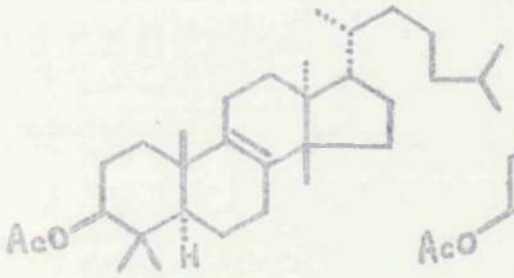
Application of the standard procedures, already mentioned in connection with lanosterol, established that the hydroxyl group has the β-configuration and is present in a normal triterpenoid ring A.[106] The close structural relationship between euphol and lanosterol became apparent when euphenyl acetate (dihydroeuphyl acetate) was shown to undergo exactly analogous oxidation reactions with the formation of derivatives closely resembling those from lanostenyl acetate.[50,74,104,106] This, together with the earlier evidence that euphol, like lanosterol, gives 1:2:8-trimethylphenanthrene on pyrolysis with selenium,[104] led Jeger to suggest that the structure of rings A, B, and C and the location of the less reactive double bond in euphol is the same as in lanosterol.[106] The dehydrogenation experiments also indicated the presence of a methyl group at both $C_{(13)}$ and $C_{(14)}$ in the euphol molecule.

The five-membered nature of ring D suggested by Jeger and Ruzicka[1,106] was eventually established by Barton.[107] From a study of the infrared spectra of lanost-8-ene and euph-8-ene, it was deduced that both compounds have the same number of methyl groups. Allowing for the C_8-side-chain and rings A, B, and C, only three carbon atoms were unaccounted for so that ring D could not be more than five-membered.

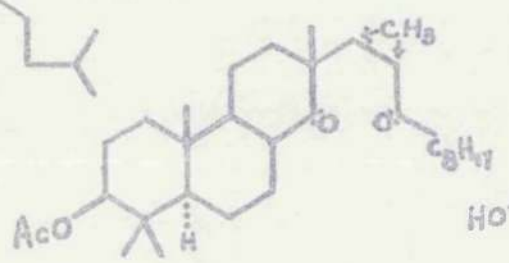
The nature of the acid catalysed isomerisation of euphenol to isoeuphenol, which was first described by Vilkas[108] and later studied in detail by Jeger,[106] was finally elucidated by Barton[107] who showed that it involved a concerted double methyl group migration. Vilkas had shown that when euphenyl acetate (LIV) is treated with mineral acid, the double bond moves from the Δ^{8}-position to another fully substituted position, the product being isoeuphenyl acetate, and after a series of degradation reactions in which the double bond of the latter was split to give a diketone formulated as (LV), Jeger[106] proposed the structures (LVI) and (LVII) for euphol and isoeuphenol. The structure (LVI) for euphol did not, however, satisfactorily explain the formation of 1:2:8-trimethylphenanthrene on dehydrogenation[104] and Ruzicka[1] from biosynthetical considerations suggested that euphol might be represented by (LVIII) or be isolanosterol with rings C and D cis-fused.

In 1954, Barton isolated 1:2:5-trimethylnaphthalene (LIX) as the sole product of selenium dehydrogenation of isoeuphadiene.[107] This indicated that the latter has a methyl group at $C_{(8)}$ which must have been at $C_{(14)}$ in its precursor, euphadiene. isoEuphenol was therefore formulated as either (LX, R = H) or (LXI) depending on the position of the side-chain and on whether both or only one of the methyl groups migrate during the acid rearrangement. This led to the alternative structures (LXII)

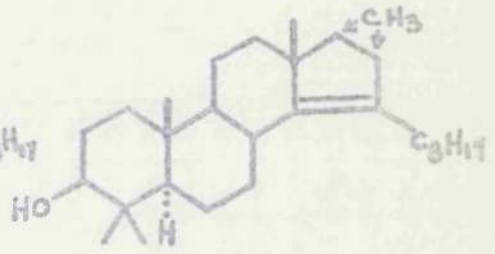
and (LXIII) for the diketone obtained by ozonolysis of isoeuphenyl acetate and previously formulated as (LV) by



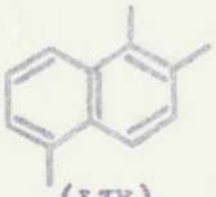
(LIV)



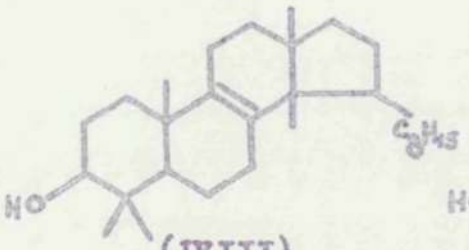
(LV)



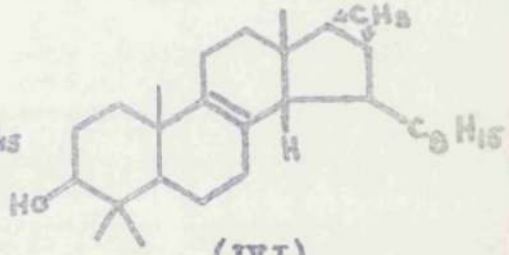
(LVII)



(LIX)

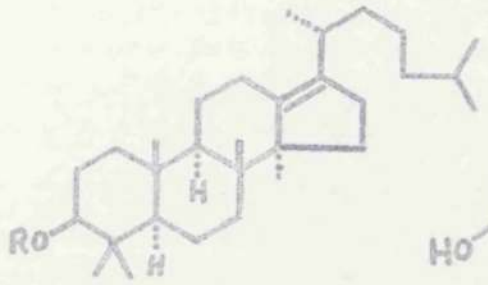


(LVIII)

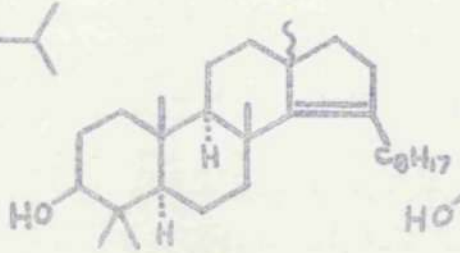


(LVI)

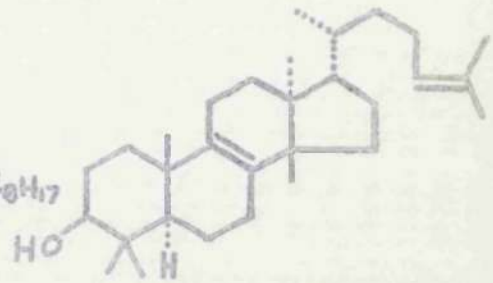
Jeger.[106] From the observation that this diketone absorbs up to five moles of bromine and that both the carbonyl groups are relatively unhindered, Barton[107] concluded that its structure can only be represented by (LXII) so that euphol is (LXIV) and isoeuphenol is (LX, R = H). This view was confirmed by a study of the infrared absorption of isoeuphenol and by the observation that the ultraviolet and infrared spectra of the conjugated diene (LXV), produced by selenium dioxide oxidation of isoeuphenyl acetate, (LX, R = Ac) closely resemble those of oleana-11:13(18)-dienyl acetate (LXVI).[107]



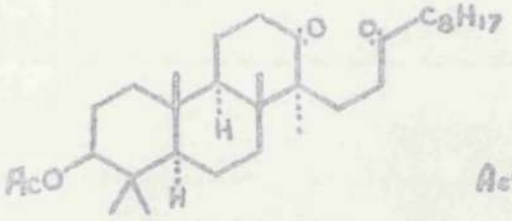
(LX)



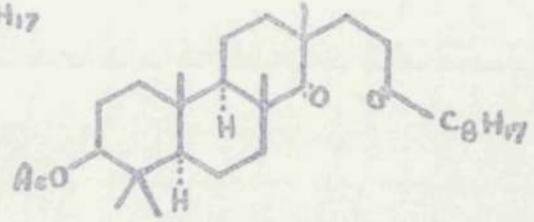
(LXI)



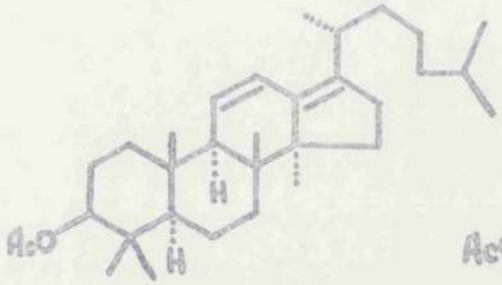
(LXIV)



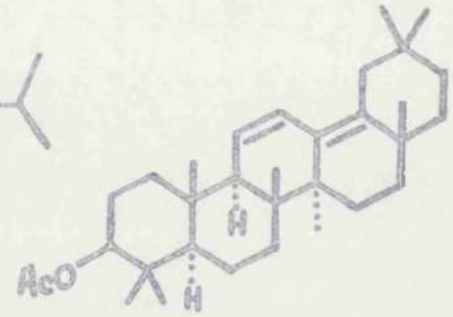
(LXII)



(LXIII)



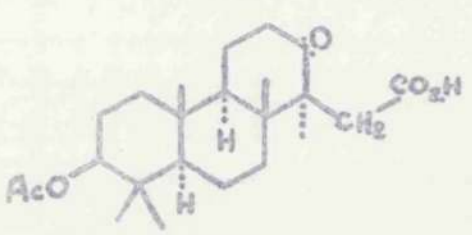
(LXV)



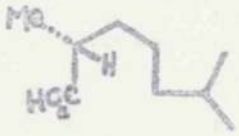
(LXVI)

The same conclusions regarding the size of ring D, the position of attachment of the side-chain and the nature of the euphenol - isoeuphenol rearrangement were reached independently by Jeger and Ruzicka.[109]

The Stereochemistry of Euphol: The configurations at $C_{(3)}$, $C_{(5)}$, and $C_{(10)}$ were deduced from the chemical evidence and molecular rotation data to be as in a normal triterpenoid ring A.[107] The methyl groups at $C_{(13)}$ and $C_{(14)}$ were assigned the α- and β-configurations respectively since with this stereochemistry the molecule is forced to adopt a strained conformation which, according to Barton,[107] provides the driving force for the concerted migration of these groups to give the more favourable all-chair conformation found in isoeuphenol (LX, R = H). Also, if the euphenol - isoeuphenol rearrangement takes place by a fully synchronous mechanism, the side chain at $C_{(17)}$ must have the same configuration (α) as the $C_{(13)}$-methyl group.[109] In support of this, Barton, from a comparison of molecular rotation differences in the lanosterol and euphol series, concluded that the configurations at $C_{(17)}$ and $C_{(20)}$ in euphol are the opposite of those in lanosterol.[107a] Shortly afterwards, Jeger and Ruzicka[109] described the degradation of isoeuphenyl acetate (LX, R = Ac) to the tricyclic acid (LXVII) and 2:6-dimethylheptanoic acid (LXVIII). This work confirmed that the side-chain is at $C_{(17)}$ and showed that the configuration at $C_{(20)}$ in euphol is the same as that at $C_{(20)}$ in lanosterol. Barton[107b] then asserted that, if the molecular rotation data are inapplicable, no definite configuration can be assigned on this basis to the side-chain at $C_{(17)}$.

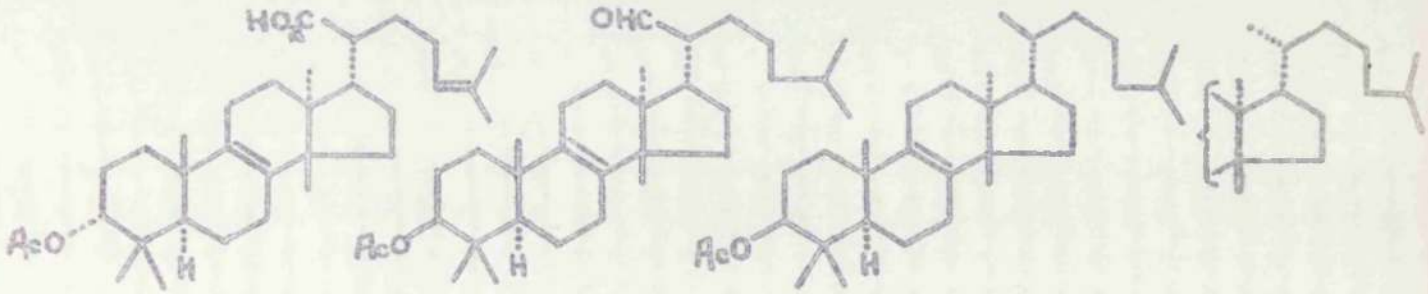


(LXVII)



(LXVIII)

Chemical proof that the configuration at $C_{(17)}$ is in fact α was obtained when it was shown by Jeger and Ruzicka[89] that euphol and tirucallol differ only in configuration at $C_{(20)}$ while lanosterol is epimeric with tirucallol at positions 13, 14, 17, and 20. The correlation of euphol with tirucallol was achieved by the conversion of elemadienolic acid (3α-hydroxytirucalla-8:24-dien-21-oic acid, XIX) into the 3β-acetoxy-21-oxo compound (LXIX) which on Wolff-Kishner reduction gave both tirucall-8-enyl acetate (LXX) and euph-8--enyl acetate (LIV). Euphol and tirucallol therefore have

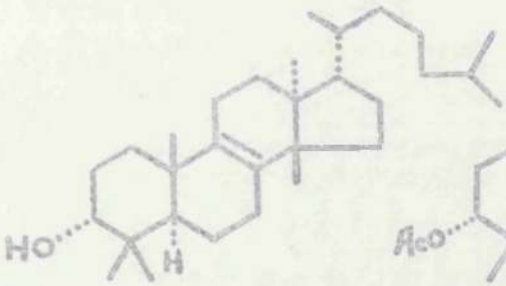


(XIX) (LXIX) (LXX) (LIV)

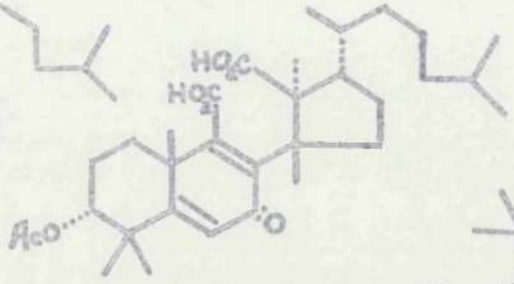
the same configuration at $C_{(17)}$ and the opposite configuration at $C_{(20)}$. This was confirmed by Warren[90] who converted eupha-8:24-diene and tirucalla-8:24-diene to the same product

by eliminating the asymmetry at $C_{(20)}$.

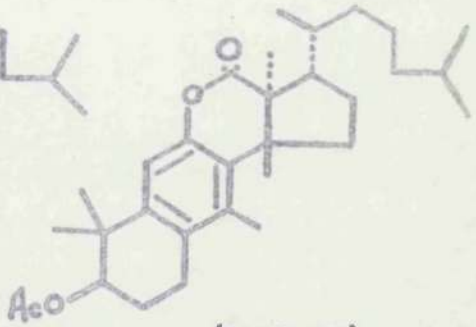
The correlation of tirucallol with lanosterol was achieved by the application[89] to both series of a sequence of reactions which had previously been carried out in the latter series by Barton.[88] epiTirucallenol (tirucall-8-en-3α-ol, LXXI) obtained from elemadienolic acid (XIX), was converted via the 7:11-dioxo-8-ene and 7:11:12-trioxo-5:8-diene derivatives into the dicarboxylic acid (LXXII). Mild heat treatment of the latter gave the acetoxyphenol lactone (LXXIII) in which the



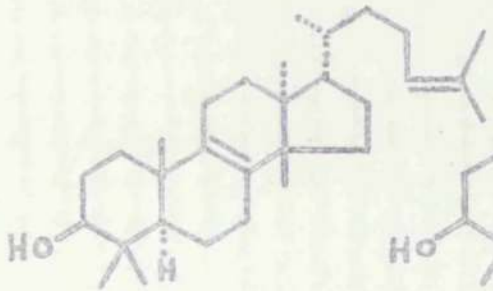
(LXXI)



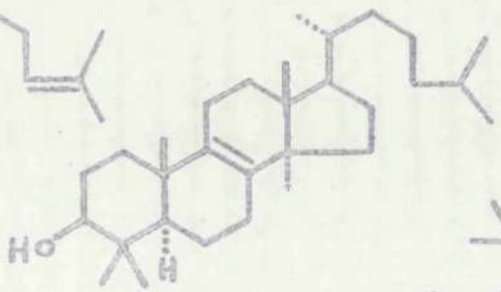
(LXXII)



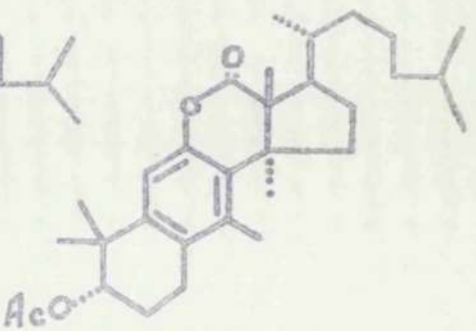
(LXXIII)



(LXIV)



(LXXV)



(LXXIV)

asymmetry at positions 5 and 10 has been destroyed in the aromatisation of ring B. This compound proved to be the optical enantiomer of the analogous derivative (LXXIV) obtained by the same route from lanost-8-enol (LXXV) showing that tirucallol has the opposite configuration from lanosterol at the four remaining asymmetric centres. Euphol has thus been indirectly related to lanosterol and can be formulated as 13-iso: 14-iso: 17-isolanosterol (LXIV).

THEORETICAL

S E C T I O N I.

The Constitution and Stereochemistry 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 have led to the complete elucidation of the structure and stereochemistry of butyrospermol are described.

In 1934, Heilbron, Moffet and Spring[110] described the isolation of a new triterpenoid alcohol, later named bassool,[111] of approximate molecular formula $C_{30}H_{50}O$ from shea-nut fat from the West African tree Butyrospermum parkii. This alcohol was isolated together with the hydrocarbon illipene and the pentacyclic triterpenoids α- and β-amyrin and lupeol. Another constituent, parkeol, the chemistry of which is discussed in a later section, was isolated in a subsequent examination of shea-nut fat by Bauer and Moll.[47] Bassool acetate, obtained by acetylation and fractional crystallisation of the non-saponifiable matter, had m.p. 141°, $[\alpha]_D$ + 22.4° and on alkaline hydrolysis gave bassool m.p. 109.5°, $[\alpha]_D$ - 11.9°. The tetracyclic nature of bassool was deduced when treatment of the acetate with perbenzoic acid indicated the presence of two double bonds.

Later, Beynon, Heilbron and Spring[112] reported that the double bonds in bassool were not in conjugation and that only one was susceptible to catalytic hydrogenation. The reactive double bond was deduced to be present in a vinylidene group when ozonolysis of bassool acetate gave a 20% yield of formaldehyde. It was also claimed that treatment of bassool acetate with various acidic reagents gave the acetate of the pentacyclic triterpenoid β-amyrin in yields ranging from 13% to 90%. This apparent isomerisation of a tetracyclic to a

pentacyclic triterpenoid aroused considerable interest and would have been of great importance. Later experiments[48,113,114] were to prove, however, that bassool acetate was in fact a mixture one component of which was β-amyrin acetate.

In 1949, Heilbron, Jones and Robins[113] re-examined the acetylated non-saponifiable fraction of shea-nut fat and obtained an acetate, the physical constants of which (m.p. 139-141°, $[\alpha]_D$ + 23°) agreed with those quoted earlier for bassool acetate. This was, however, shown to be impure, when on repeated recrystallisation it gave an ester, m.p. 146.5-147.5°, $[\alpha]_D$ + 11°, isomeric with bassool acetate, and which was named butyrospermyl acetate. The latter on hydrolysis with alkali gave a new triterpenoid alcohol, butyrospermol, m.p. 111-113°, $[\alpha]_D$ - 12°. Of more importance, it was shown that the chemical properties of butyrospermyl acetate were markedly different from those reported by Beynon, Heilbron and Spring[112] for bassool acetate; in particular, no β-amyrin acetate was detected in any reaction product from pure butyrospermyl acetate, while on ozonolysis, the latter gave acetone and not formaldehyde.

It is now accepted that the original bassool acetate was an impure sample of butyrospermyl acetate containing approximately 16% of β-amyrin acetate.[48,113,114] The original bassool m.p. 109.5°, $[\alpha]_D$ - 11.9°, on the other hand is considered to have been a homogeneous compound since it has been shown[115] that alkaline hydrolysis of crude butyrospermyl acetate having $[\alpha]_D$

+ 22° ("bassool acetate") and crystallisation of the product gives pure butyrospermol, m.p. 109-110°, $[\alpha]_D$ + 12.5°, identical with a specimen prepared by hydrolysis of pure butyrospermyl acetate.

Butyrospermol also occurs in the fruits of Artocarpus integrefolia[55] and has recently been isolated from horse-chestnut fat in this laboratory.

Heilbron, Jones and Robins[115] characterised butyrospermol as a tetracyclic secondary alcohol, of approximate molecular formula $C_{30}H_{50}O$, which contains one readily reducible double bond, present in an isopropylidene group and a second, less reactive, double bond which is not reduced by hydrogen-platinum but which reacts with perbenzoic acid. These findings were confirmed by Seitz and Jeger[116] who, in addition, made a study of the infrared absorption spectrum of butyrospermene, the mono-unsaturated hydrocarbon derived from dihydrobutyrospermol, and concluded that the less reactive (nuclear) double bond of butyrospermol is tetrasubstituted. A consideration of the ultraviolet absorption of dihydrobutyrospermol led Halsall[48,117] to the same conclusion with the further limitation that the double bond is endocyclic and probably in a similar cyclic position to that in lanost-8-enol. Experiments will shortly be described, however, which establish that the less reactive double bond in butyrospermol is tri- and not tetra-substituted.

Dawson, Halsall, Jones and Robins[48] studied the effect of mineral acid on butyrospermol and showed that, when the acetate of the latter is treated in chloroform solution at 0° for a short period with dry hydrogen chloride, addition to the side chain double bond takes place while the less reactive double bond is simultaneously isomerised. Dehydrochlorination of the product yields isobutyrospermyl acetate[c.f.1146] which contains a vinylidene group in place of the original isopropylidene group. Catalytic hydrogenation of the latter gives dihydroisobutyrospermyl acetate which is also obtained by treating dihydrobutyrospermyl acetate with dry hydrogen chloride. A consideration of the reactions of this isomer, particularly of its apparent stability towards perbenzoic acid, and a careful examination of its ultraviolet absorption spectrum led to the suggestion that the conversion of dihydrobutyrospermyl acetate into dihydroisobutyrospermyl acetate is analogous to the isomerisation of lanost-8-enyl acetate to lanost-7-enyl acetate and it was concluded that the double bond in dihydroisobutyrospermyl acetate is trisubstituted.[48] It will be shown, however, that the latter compound is in fact identical with euph-8-enyl acetate (LXXVI)[89,107,108] in which the double bond is tetrasubstituted.

Butyrospermol has again been isolated from shea-nut fat by the author and it has been identified as 9α-eupha-7:24-dien-3β-ol.

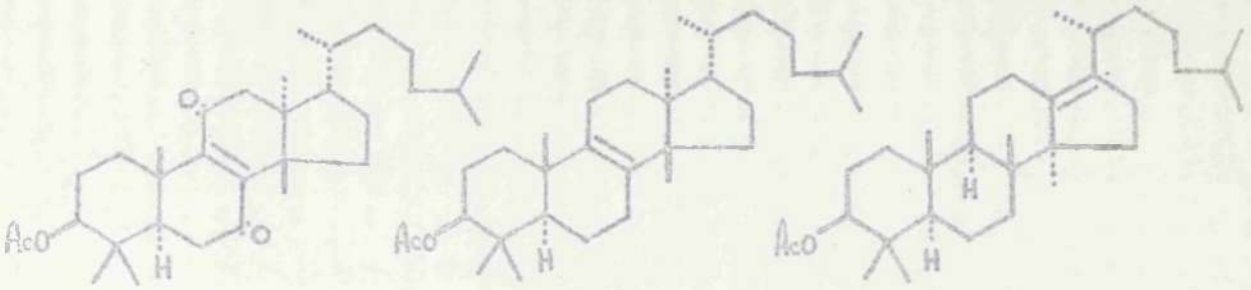
Hydrolysis of shea-nut fat with alcoholic potassium hydroxide and extraction of the resulting diluted solution with ether gave the non-saponifiable fraction as an amber-coloured resin in 3% yield. A solution of this resin in acetic anhydride was boiled under reflux for 3 hours and left overnight at room temperature. The semi-crystalline solid mass which separated was removed and the filtrate was kept at 0° for 2 days. During this interval a second crop of solid was deposited. This material was collected and crystallised from ethanol-ethyl acetate to give long stout needles the physical constants of which, (m.p. 138-139° with solid persisting in the melt above 180°, $[\alpha]_D$ + 22°), corresponded with those quoted for "bassool acetate"[110]. Repeated recrystallisation from fairly concentrated solutions in ethanol-ethyl acetate did not markedly alter the melting point or the specific rotation of the crystals and pure butyrospermyl acetate (m.p. 145°, $[\alpha]_D$ + 11°) was only obtained, in very low yield, after many recrystallisations of the material from relatively dilute solutions in the same solvent mixture.

Dihydrobutyrospermyl acetate, the starting material used in the majority of the following experiments, was obtained initially by hydrogenation of pure butyrospermyl acetate in a neutral solvent (ethyl acetate) over a platinum catalyst. A more efficient method whereby pure dihydrobutyrospermyl acetate was obtained direct from the crude "bassool acetate" mixture,

was discovered during the course of the subsequent investigations. Catalytic hydrogenation of the acetate mixture, m.p. 138-139°, $[\alpha]_D$ + 22°, in ethyl acetate solution and filtration of the product, in light petroleum, through a long column of activated alumina, gave pure dihydrobutyrospermyl acetate m.p. 135-136°, $[\alpha]_D$ + 10.8° in almost quantitative yield in the initial fractions. Later fractions consisted mainly of β-amyrenyl acetate. This technique was also discovered independently and has been recently described by Jones.[1145]

Working on the assumption that the nuclear double bond in butyrospermol is fully substituted[48,113,116] and in a similar environment to that in lanost-8-enyl acetate, a small quantity of dihydrobutyrospermyl acetate was oxidised with chromic acid, under the conditions described by McDonald, Warren and Williams[104] for the oxidation of euph-8-enyl acetate, in an attempt to prepare a 1:4-dione-ene which might be related to a tetracyclic triterpenoid of known structure. The product was an uncrystallisable gum having the ultraviolet absorption characteristics of an αβ-unsaturated ketone. The reaction was not further investigated at this stage but as will be seen, a slight modification was to prove important later. Instead the comparable oxidation of dihydroisobutyrospermyl acetate, obtained from dihydrobutyrospermyl acetate by mild treatment with mineral acid as described by Dawson, Halsall, Jones and Robins,[48]

and which was reputed to contain trisubstituted double bond, was carried out. Purification of the product by chromatography and crystallisation from methanol gave yellow needles, m.p. 110-111°, $[\alpha]_D$ + 20°, having the characteristic ultraviolet spectrum, with a maximum at 2710 Å. (ε: 8,100), of a fully transoid 1:4-dione-ene. This compound was found to be identical with 7:11-dioxoeuph-8-enyl acetate (LXXVII).[60,104,106,108] The identity of the starting material, dihydroisobutyrospermyl acetate with euph-8-enyl acetate (LXXVI), previously obtained by catalytic hydrogenation of euphyl acetate (LXXX),[69] was quickly established, a mixture of the two specimens showing no depression in melting point. This identity was at first considered remarkable since euph-8-enyl acetate (LXXVI) is itself isomerised by mineral acid to isoeuph-13(17)-enyl acetate (LXXVIII).[108] A model experiment showed, however, that the conditions, (dry hydrogen chloride in chloroform for 2 hours), which convert dihydrobutyrospermyl acetate into dihydroisobutyrospermyl acetate, leave euph-8-enyl acetate unchanged.

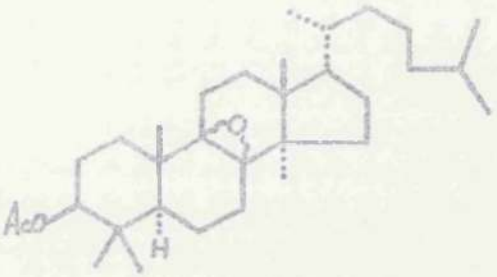


(LXXVII) (LXXVI) (LXXVIII)

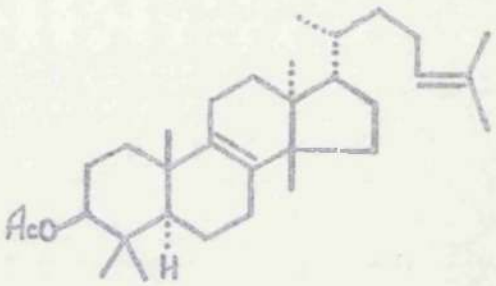
The identity of dihydroisobutyrospermyl acetate with euph-8-enyl acetate was further confirmed by the conversion of both compounds into isoeuph-13(17)-enyl acetate (LXXVIII) using more vigorous acid conditions, and also into 8β:9β-epoxy-euphanyl acetate (LXXIX) by treatment with perbenzoic acid in chloroform.[55,108] The formation of the epoxide (LXXIX) from dihydroisobutyrospermyl acetate was, at this stage, in direct contrast to the evidence of Jones and his co-workers[48] who reported that the latter compound is extremely inert towards perbenzoic acid and who, partly from this observation, concluded that its double bond is trisubstituted. These authors have since state, however, that the original report was erroneous.[1145]

Final confirmation of the close relationship between butyrospermol and euphol was obtained when butyrospermyl acetate was converted into euphyl acetate (LXXX). Addition of one molecular proportion of bromine to the former in chloroform and treatment of this solution at 0° with dry hydrogen chloride, followed by regeneration of the side-chain double bond by reaction with zinc in acetic acid gave a compound m.p. 107°, $[\alpha]_D$ + 40° identical with euphyl acetate (LXXX).[40]

The acid induced isomerisation of butyrospermol to euphol and of dihydrobutyrospermyl acetate to euph-8-enyl

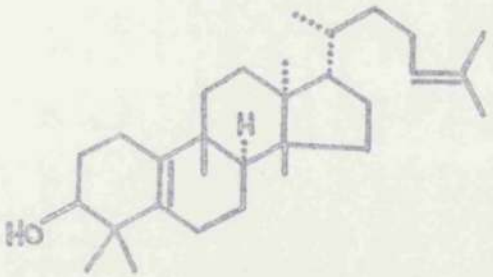


(LXXIX)



(LXXX)

acetate indicates that the isomers differ only in the position of the nuclear double bond and at this stage in the investigation it was argued that, if this less reactive double bond in butyrospermol is tetrasubstituted, the alcohol must be (LXXXI).

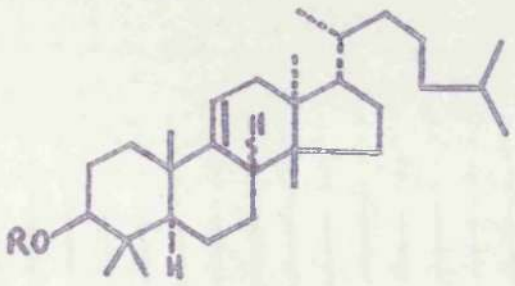


(LXXXI)

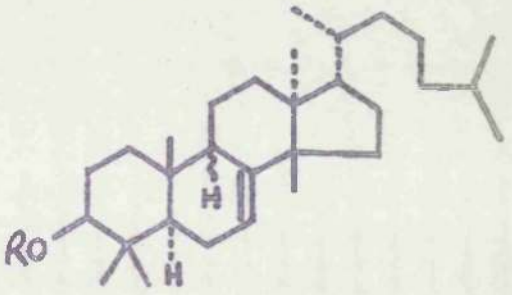
Doubt arose whether the less reactive double bond in butyrospermol is tetrasubstituted when it was found that hydrogenation of butyrospermyl acetate over platinum in acetic acid at 80° gave euph-8-enyl acetate (LXXVI), a rearrangement independently observed and recently reported by Jones and his collaborators.[11ca] A detailed examination of the infrared spectra of dihydrobutyrospermyl acetate and related compounds also led these authors to the view that the less reactive double bond in butyrospermol is tri- and not tetra-substituted as originally inferred.[48,116,117] The

relative ease with which dihydrobutyrospermyl acetate is converted into euph-8-enyl acetate and the conflicting interpretations of the spectroscopic data now led us to seek a chemical proof of the extent of substitution of this less reactive double bond of butyrospermol.

Treatment of dihydrobutyrospermyl acetate with osmic acid and acetylation of the product either at 20° or at 100° gave a crystalline compound m.p. 181-182°, which gave no colouration with tetranitromethane and which was transparent to ultraviolet light. Analysis of the compound showed it to be a triol-diacetate. From this it was concluded that the nuclear double bond is tri- and not tetrasubstituted and that dihydrobutyrospermol is either (LXXXII, R = H) or (LXXXIII, R = H). This was confirmed when, in an attempt to remove the tertiary



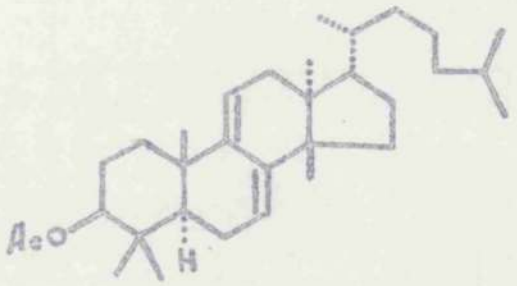
(LXXXII)



(LXXXIII)

hydroxyl group by simple dehydration with the introduction of a double bond between $C_{(8)}$ and $C_{(9)}$, the triol-diacetate was treated

with potassium acetate in acetic anhydride under reflux. The product was obtained as a white crystalline solid m.p. 111-112°, which gave a deep red colour with tetranitromethane and which showed the characteristic ultraviolet absorption, with maxima at 2320, 2400 and 2470 Å. (ε: 15,000, 17,000 and 10,500 respectively), of a heteroannular diene. This compound was quickly shown to be identical with eupha-7:9(11)-dienyl acetate (LXXXIV),[12,86] the melting point being undepressed on mixing with an authentic specimen of the latter, prepared by treating 8β:9β-epoxyeuphanyl acetate (LXXIX) with sulphuric acid in acetic acid.[85] The triol-diacetate was also very readily

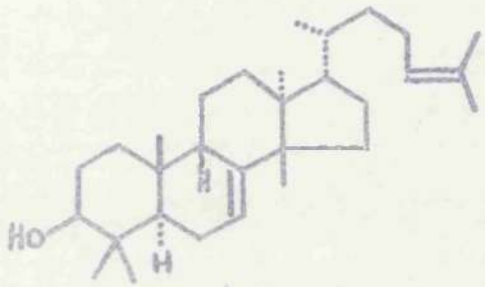


(LXXXIV)

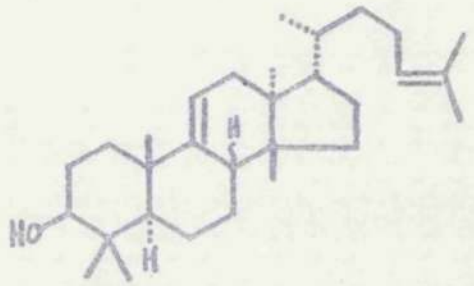
converted into eupha-7:9(11)-dienyl acetate (LXXXIV) by heating it at 100° for 2 days, by sublimation in vacuo, by treating it with zinc in acetic acid at 100°, with chromic-acetic acid at 20°, or with hydrochloric-acetic acid at 20°. Treatment with acetic acid alone had no effect even at 100° and the powerful dehydrating conditions of phosphorus oxychloride in pyridine under reflux also left the triol-diacetate unchanged.

The close relationship between dihydrobutyrospermyl acetate and euph-8-enyl acetate (LXXVI) was further emphasised when it was found that short treatment of the former in ethyl acetate at -25° with ozonised oxygen yielded an epoxide which with mineral acid was quantitatively converted into eupha--7:9(11)-dienyl acetate (LXXXIV). The latter was also obtained directly from dihydrobutyrospermyl acetate by treatment with selenium dioxide in boiling acetic acid, a reaction which, if analogy can be made with the corresponding compounds in the lanosterol series, favoured at this stage, the Δ^7-formula (LXXXIII, R=H) for dihydrobutyrospermol, since under these conditions lanost-7-enyl acetate is readily converted into the -7:9(11)--dienyl acetate[76,77] whereas lanost-9(11)-enyl acetate is not affected.

The behaviour of dihydrobutyrospermyl acetate and its derivatives in the reactions so far described proves that it is a simple double bond isomer of euph-8-enyl acetate having its unsaturated centre either between $C_{(7)}$ and $C_{(8)}$ or between $C_{(9)}$ and $C_{(11)}$. At this stage, therefore, butyrospermol may be formulated as either 9ξ-eupha-7:24-dien-3β-ol (LXXXV) or 8ξ--eupha-9(11):24-dien-3β-ol (LXXXVI). The same conclusion was reached and reported almost simultaneously by Professor Jones and his collaborators.[114a] In an attempt to prepare the corresponding heteroannular diene, these authors treated

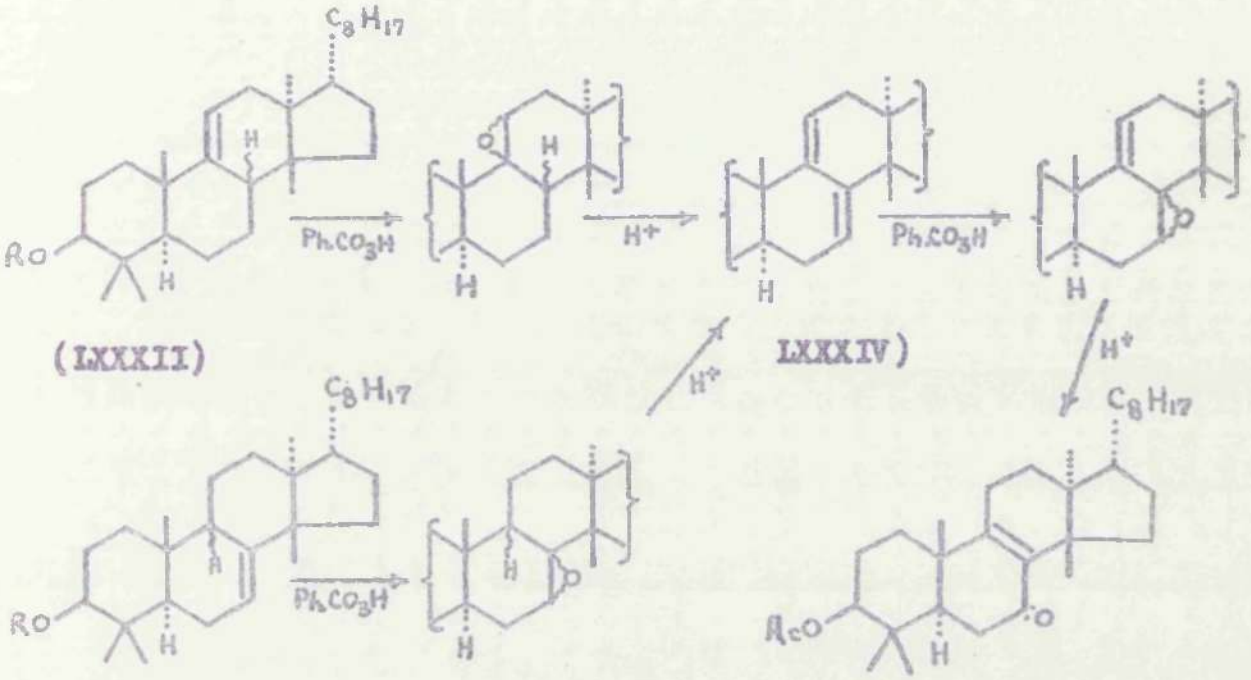


(LXXXV)



(LXXXVI)

dihydrobutyrospermyl acetate with an excess of perbenzoic acid in chloroform and found that the main product was not the expected epoxide but an αβ-unsaturated ketone which they identified as 7-oxoeuph-8-enyl acetate (LXXXVII). From this and earlier reactions they deduced that butyrospermol has a euphol-type carbon skeleton and differs from euphol only in the position of the nuclear double bond which must be either between $C_{(7)}$ and $C_{(8)}$ or between $C_{(9)}$ and $C_{(11)}$ since both isomers can give rise to 7-oxoeuph-8-enyl acetate if eupha-7:9(11)-dienyl acetate (LXXXIV) is first formed as an intermediate. Further, from a comparison of the behaviour of dihydrobutyrospermyl acetate with that of lanost-7-ene and lanost-9(11)-ene derivatives on treatment with mineral acid, Jones[114a] suggested that dihydrobutyrospermyl acetate is a euph-7-enyl acetate (LXXXIII, R = Ac) since only the double bond of lanost-7-enyl acetate and not of the $\Delta^{9(11)}$-derivative can be isomerised to the

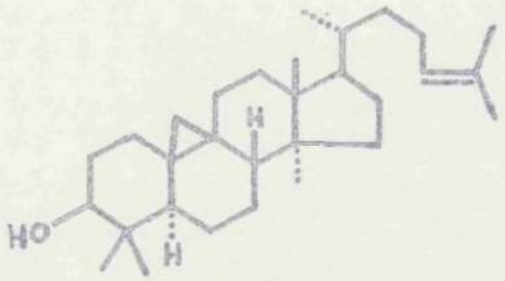


8:9-position.

[In support of this, if the argument is valid and the behaviour of corresponding compounds in the lanosterol and euphol series can be compared, it may be added that, as in the case of dihydrobutyrospermyl acetate, the double bond of lanost-7-enyl acetate is inert to catalytic hydrogenation whereas that of lanost-9(11)-enyl acetate is readily saturated.[88] The effect of selenium dioxide in acetic acid on these compounds has already been referred to.]

Thus, if dihydrobutyrospermyl acetate is a euph-7-enyl acetate there are still two possible structures depending on whether the $C_{(9)}$-hydrogen atom has the α- or the β-configuration. The euph-7-enyl acetate, prepared by Barton[107b] by Wolff-Kishner reduction of 7-oxoeuph-8-enyl acetate (LXXXVII), is assumed by

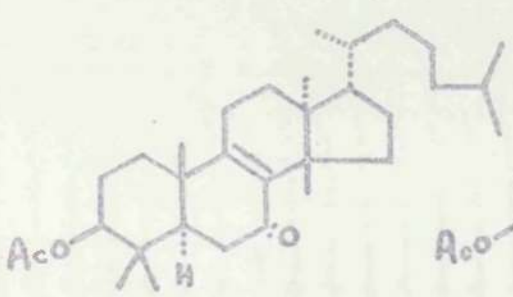
Jones[114a] to have the hydrogen atom at $C_{(9)}$ in the α-configuration and to explain the unusual negative molecular rotation changes observed when both butyrospermol and cycloartenol (LXXXVIII), which has a 9β-substituent, are oxidised to the corresponding 3-ketones, he further tentatively suggests that butyrospermol also has a 9β-substituent and that dihydrobutyrospermyl acetate is, therefore, 9β-euph-7-enyl acetate. The experiments described below, however, show that the configuration of the hydrogen atom at $C_{(9)}$ in dihydrobutyrospermyl acetate is α and that butyrospermol is, therefore, 9α-eupha-7:24-dien-3β-ol.



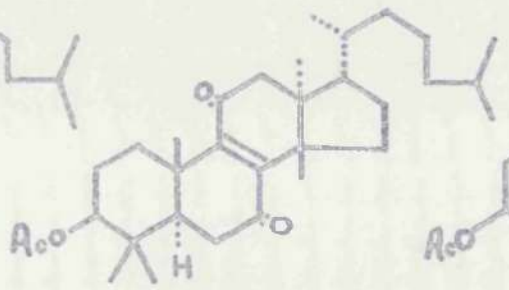
(LXXXVIII)

One of the first experiments carried out on dihydrobutyrospermyl acetate in the present investigation was its reaction with chromic acid. As has already been mentioned, the product on that occasion was an intractable gum, the ultraviolet absorption spectrum of which, with a maximum at 2480 Å., showed it to contain a small amount of an αβ-unsaturated ketone. This reaction was now re-examined in some detail using less vigorous conditions. Dihydrobutyrospermyl acetate was

oxidised with a slight excess of chromium trioxide (equivalent to 3 atoms of oxygen) in acetic acid at 16-20° for 24 hours. The yellow resinous product, which was obtained, showed selective absorption in the ultraviolet region at 2060 Å. (ε: 4,600) and between 2450 and 2700 Å. (ε: 1,500). Careful chromatography of this product gave first, a relatively large proportion (20%) of pure starting material identified by mixed melting point and specific rotation. A pale yellow semi-crystalline fraction (40%), showing λmax. 2530 Å. (ε: 7,200) was then obtained, and finally, a white crystalline solid in 17% yield. The pale yellow fraction was identified as a mixture consisting mainly of 7-oxoeuph-8-enyl acetate (LXXXVII) with a smaller proportion of 7:11-dioxoeuph-8-enyl acetate (LXXVII). The final fraction, which crystallised from methanol as fine needles m.p. 119-120°, was at first thought to be euph-8-enyl acetate (LXXVI), formed



(LXXXVII)



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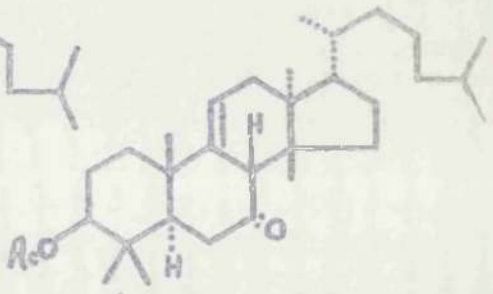


(LXXXIX)

from dihydrobutyrospermyl acetate by isomerisation of the double bond in the acidic conditions. A mixed melting point with euphenyl acetate, however, showed a large depression and when

the specific rotation of the new compound was determined it proved to be very strongly negative. The compound gave a bright yellow colour with tetranitromethane and its ultra-violet absorption spectrum showed a single maximum at 2060 Å. (ε: 4,200), indicating the presence of one isolated double bond. Analysis of the compound showed it to contain 3 oxygen atoms (i.e., one more than starting material) and indicated a molecular formula of $C_{32}H_{52-54}O_3$.

The possibility was now considered that it contained a hydroxyl group and was the product of incomplete oxidation. The compound was, however, recovered quantitatively unchanged after treatment with acetic anhydride in pyridine and was also completely stable to further treatment with chromic-acetic acid at room temperature for 24 hours.

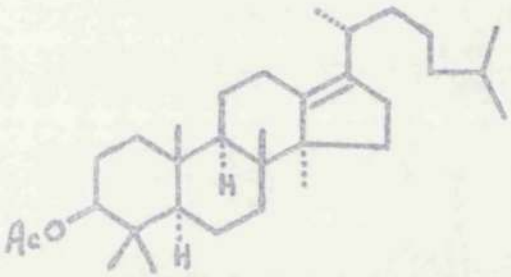
At this stage, the results of an infrared examination of the compound (in carbon tetrachloride) were received. The spectrum showed a strong band at 1710 $cm.^{-1}$, indicative of a carbonyl group in a six-membered ring, in addition to one at 1735 $cm.^{-1}$ due to the acetate group. The presence of an isolated double bond (band at 1640 $cm.^{-1}$) was also confirmed but only tentative conclusions as to its environment could be made. The compound, the molecular formula of which is now established as $C_{32}H_{52}O_3$ and which will be called oxoapoeuphenyl acetate, is therefore a non-conjugated unsaturated ketone; the presence of the ketone group is confirmed by reactions described

later. Barton[1075] had, at this time, recently prepared a similar compound by the action of perphthalic acid on eupha-7:9(11)-dienyl acetate (LXXXIV) and concluded that it was probably the βγ-unsaturated ketone (LXXXIX) since on short treatment with mineral acid it was smoothly isomerised to 7-oxoeuph-8-enyl acetate (LXXXVII). Such a βγ-unsaturated ketone could also have been formed from dihydrobutyrospermyl acetate in the present reaction provided that the diene (LXXXIV) is an intermediate. Oxoapoeuphenyl acetate was not, however, identical with the compound described by Barton, nor was it isomerised to an αβ-unsaturated ketone by either mineral acid or alkali.

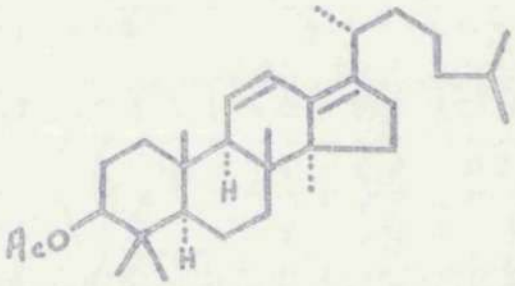
[The possibility of oxoapoeuphenyl acetate having one of the structures represented by (LXXXIX) and (XC) will be discussed in more detail at a later stage.]

After treatment with dry hydrogen chloride in chloroform at 0° or with sulphuric-acetic acid at room temperature, oxoapoeuphenyl acetate was recovered unchanged and treatment with methanolic potassium hydroxide solution under reflux followed by reacetylation of the product also failed to have any effect. Oxoapoeuphenyl acetate was next subjected to the more vigorous acid conditions (hydrochloric-acetic acid at 100°) which bring about the isomerisation of euph-8-enyl acetate (LXXVI) to iseeuph-13(17)-enyl acetate (LXXVIII). The product

proved to be an isomeric non-conjugated unsaturated ketone reduction of which by the forcing variation of the Wolff-Kishner



(LXXVIII)

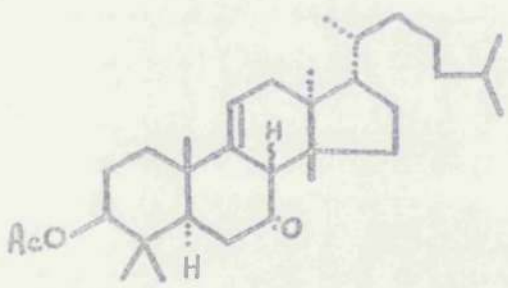


(XCI)

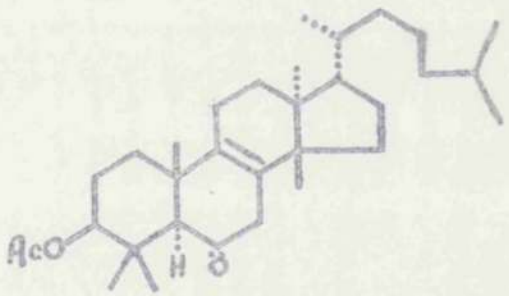
reaction[118] and reacetylation gave isoeuph-13(17)-enyl acetate (LXXVIII) identical with an authentic specimen prepared from euph-8-enyl acetate as indicated above. The isomeric non-conjugated unsaturated ketone is therefore an oxoisoeuph--13(17)-enyl acetate in which the carbonyl oxygen is not attached to $C_{(13)}$, since the compound does not show the ultraviolet absorption characteristics of an αβ-unsaturated ketone. This was confirmed when oxidation of oxoisoeuph--13(17)-enyl acetate with selenium dioxide gave an oxoisoeupha--11:13(17)-dienyl acetate which showed the same characteristic ultraviolet absorption spectrum, with maxima at 2470, 2550, and 2640 Å., (ε: 19,000, 21,000 and 14,600), as isoeupha-11:13(17)--dienyl acetate (XCI) obtained by similar treatment of isoeuph--13(17)-enyl acetate (LXXVIII) with selenium dioxide.[107b] The formation of oxoisoeupha-11:13(17)-dienyl acetate shows that the

keto-group in oxoisoeuph-13(17)-enyl acetate, and therefore in oxoapoeuphenyl acetate, does not include $C_{(11)}$ or $C_{(12)}$; consequently this group must be at either $C_{(8)}$ or at $C_{(7)}$.

If oxoapoeuphenyl acetate has been formed from dihydrobutyrospermyl acetate without molecular rearrangement only the structures represented by (LXXXIX) and (XC) qualify for consideration. To obtain a ketone (LXXXIX) from dihydrobutyrospermyl acetate [a euph-7- or euph-9(11)-enyl acetate], the



(LXXXIX)

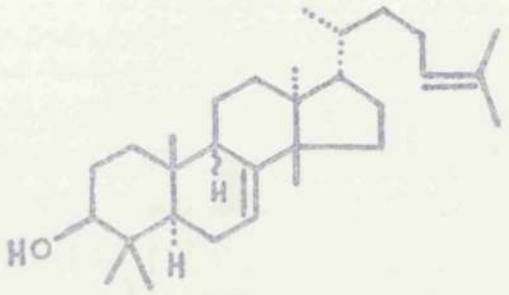


(XC)

reaction would require to proceed either through eupha-7:9(11)-dienyl acetate (LXXXIV), as already stated, or via euph-8-enyl acetate (LXXVI). Oxidation of eupha-7:9(11)-dienyl acetate with chromic acid under the conditions used for the preparation of oxoapoeuphenyl acetate from dihydrobutyrospermyl acetate and careful chromatography of the resulting mixture did not, however, yield any trace of oxoapoeuphenyl acetate; only 7:11-dioxoeuph-8-enyl acetate (LXXVII) and a little 7-oxoeuph-8-enyl acetate (LXXXVII) were obtained in poor yield in addition to some starting material. The possibility of euph-

-8-enyl acetate (LXXVI) being an intermediate in this reaction was considered less likely since a double bond will not move out of conjugation with a carbonyl group under such conditions, and, more particularly 7-oxoeuph-8-enyl acetate (LXXXVII) is stable to mineral acid.[1075] Under the conditions used for the oxidation of dihydrobutyrospermyl acetate to oxoapoeuphenyl acetate, euph-8-enyl acetate (LXXVI) also gave a mixture from which 7-oxoeuph-8-enyl acetate and 7:11-dioxoeuph-8-enyl acetate were obtained as the only identifiable products, no trace of oxoapoeuphenyl acetate was found. These experiments establish that neither eupha-7:9(11)-dienyl acetate (LXXXIV) nor euph-8--enyl acetate (LXXVI) are intermediates in the formation of oxoapoeuphenyl acetate and that the latter is not a 7-oxoeuph--9(11)-enyl acetate (LXXXIX). This decision, together with the exclusion of formulae for oxoapoeuphenyl acetate in which the carbonyl oxygen is at $C_{(11)}$ or $C_{(12)}$, shows that the double bond in dihydrobutyrospermyl acetate cannot be between $C_{(9)}$ and and $C_{(11)}$. Consequently, butyrospermol is a eupha-7:24-dien--3β-ol (LXXXV) in which only the configuration of the hydrogen atom attached to $C_{(9)}$ remains to be determined.

Formula (XC) for oxoapoeuphenyl acetate is also excluded for the following reasons. Reduction of oxoapoeuphenyl acetate, using the Wolff-Kishner technique,[113] followed by acetylation of the product, does not give euph-8-enyl acetate (LXXVI) but yields a new isomeric unsaturated acetate which will be called

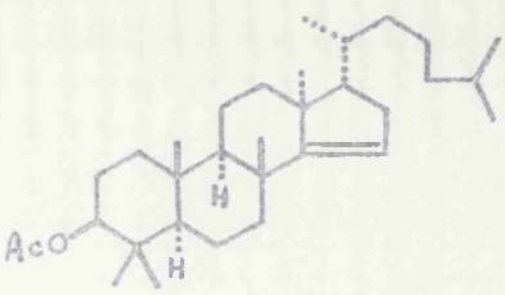


(LXXXV)

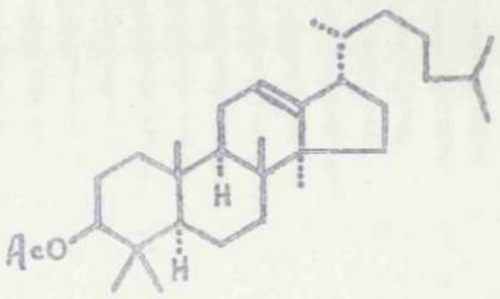
apoeuphenyl acetate. apoEuphenyl acetate also differs from dihydrobutyrospermyl acetate and from the euph-7-enyl acetate described by Barton.[107b] The infrared absorption spectrum of oxoapoeuphenyl acetate includes a band at 1640 $cm.^{-1}$ attributed to a double bond which is not fully substituted, while the ultraviolet absorption of apoeuphenyl acetate indicates that the double bond is at least trisubstituted. The fact that oxoapo-euphenyl acetate cannot be converted into an $\alpha\beta$-unsaturated ketone by treatment with either alkali or mineral acid also supports the decision that its structure cannot be represented by (LXXXIX) or (XC) and further indicates that the carbonyl oxygen, which is now established as being at $C_{(7)}$, is insulated from the unsaturated centre by a fully substituted carbon atom. That is, there is a methyl group attached to $C_{(8)}$ and, consequently, the formation of oxoapoeuphenyl acetate from dihydrobutyrospermyl acetate has included a molecular rearrangement.

Further evidence supporting this decision was obtained from a closer study of apoeuphenyl acetate. Brief treatment

of the latter in chloroform solution at 0° with dry hydrogen chloride gave a product identified as isoeuph-13(17)-enyl acetate (LXXVIII). Under the same conditions, euph-8-enyl acetate (LXXVI) is recovered unchanged while dihydrobutyrospermyl acetate is simply converted into euph-8-enyl acetate (LXXVI). apoEuphenyl acetate therefore represents a stabilised intermediate stage in the rearrangement of euph-8-enyl acetate to isoeuph-13(17)-enyl acetate and it may now be formulated as either euph-14-enyl acetate (XCII) or euph-12-enyl acetate (XCIII). Consequently, oxoapoeuphenyl acetate is either 7-oxoapoeuph-14-enyl acetate (XCIV) or 7-oxoapoeuph-12-enyl acetate (XCV) and its formation from dihydrobutyrospermyl acetate (XCVI) is represented as a fully synchronous reaction in which attack by the oxidising agent at the double bond, $C_{(7)}$, from the rear (α) side of the molecule is accompanied by the simultaneous movement of, in the first case, the 14β-methyl group

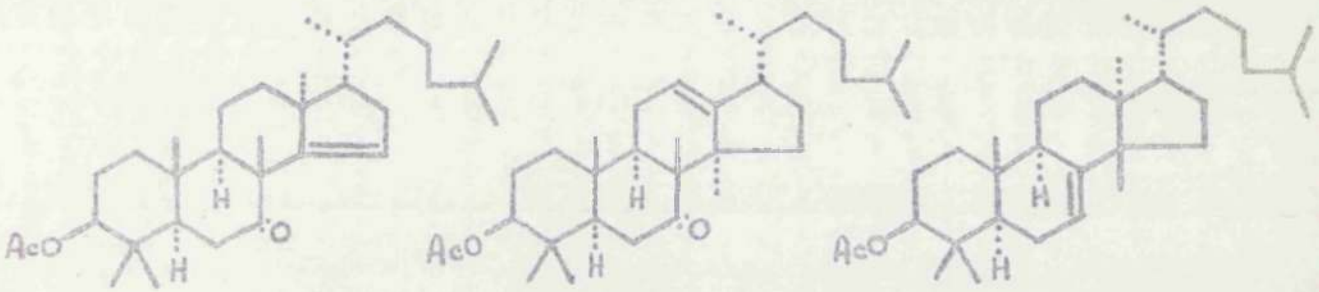


(XCII)



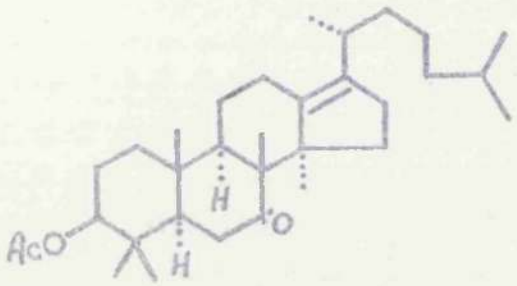
(XCIII)

to $C_{(8)}$ with the loss of a proton from $C_{(15)}$ to give (XCIV), or in the second case, the 14β-methyl group to $C_{(8)}$ and the 13α-methyl group to $C_{(14)}$, the 12β-hydrogen atom being lost as a proton to give (XCV). Thus, whichever path is followed, the

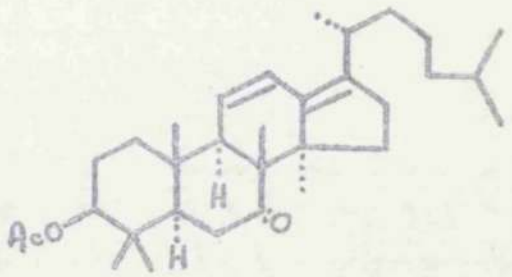


(XCIV) (XCV) (XCVI)

carbonyl group in oxoapoeuphenyl acetate is at $C_{(7)}$, and, according to the first mechanism 7-oxoapoeuphenyl acetate is (XCIV) and its acid induced isomerisation into 7-oxoisoeuph-13(17)-enyl acetate (XCVII) involves protonation of the 14:15-double bond with the simultaneous migration of the 13α-methyl group to $C_{(14)}$ and the loss of the 17β-hydrogen atom as a proton. If the second path is followed, 7-oxoapoeuphenyl acetate is (XCV) and its conversion into 7-oxoisoeuphenyl acetate (XCVII) is a simple carbonium-ion induced movement of the double bond from the 12- to the 13(17)-position. The oxoisodienyl acetate obtained by oxidation of 7-oxoisoeuph-13(17)-enyl acetate (XCVII) with selenium dioxide must then be 7-oxoisoeupha-11:13(17)-dienyl acetate (XCVIII).



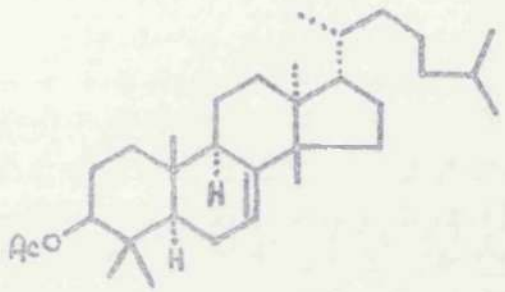
(XCVII)



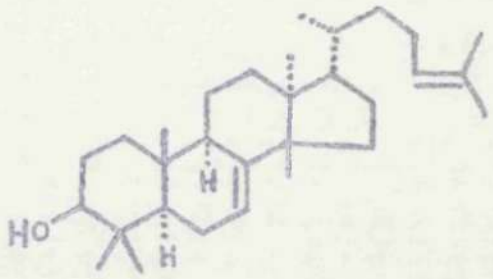
(XCVIII)

It will be noted that, in the formation of 7-oxo<u>apo</u>euph-enyl acetate by the above mechanisms, the $C_{(9)}$-hydrogen atom in dihydrobutyrospermyl acetate is not involved. It is concluded, therefore, that the orientation of the $C_{(9)}$-hydrogen atom in dihydrobutyrospermyl acetate is the same (α) as that in 7-oxo<u>iso</u>euph-13(17)-enyl acetate (XCVII). Consequently dihydrobutyrospermyl acetate is 9α-euph-7-enyl acetate (XCVI) and butyrospermol is 9α-eupha-7:24-dien-3β-ol (IC). The strained conformation of dihydrobutyrospermyl acetate (XCVI) which must include a boat (or half-boat) is considered to be the "driving force" responsible for its ready irreversible conversion into euph-8-enyl acetate (LXXVI) which is free to adopt an all-chair (or half-chair) conformation.

It has been shown above that 7-oxo<u>apo</u>euphenyl acetate is either (XCIV) or (XCV) and although a decision between these formulae is not pertinent to the argument concerning the structure and stereochemistry of butyrospermol, evidence in



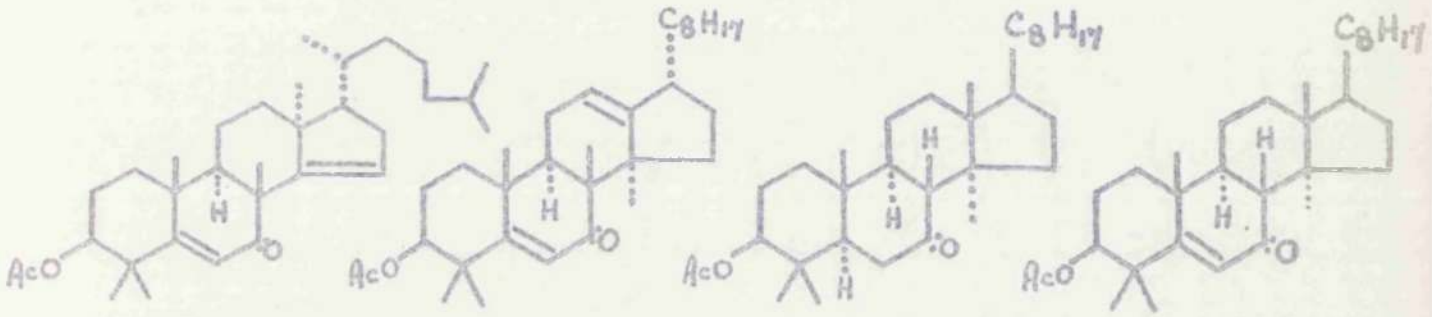
(XCVI)



(IC)

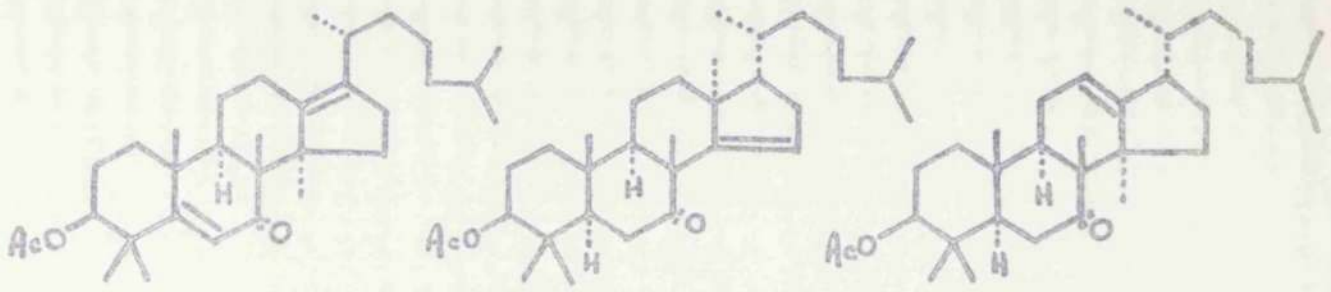
favour of the former has been obtained and is described below: Treatment of 7-oxoapoeuphenyl acetate with selenium dioxide in boiling acetic acid and purification of the product by chromatography gave, in almost quantitative yield a compound m.p. 104°, analysis of which indicated the formula $C_{32}H_{50}O_3$. The compound gave a bright yellow colour with tetranitromethane and showed the ultraviolet absorption characteristics of both an isolated double bond and of an αβ-unsaturated ketone with maxima at 2080 Å. and 2350 Å. (ε: 9,000 and 14,000 respectively). The presence of both systems was confirmed by an examination of the infrared absorption spectrum of the compound (in nujol). This showed a strong band at 1735 and one at 1240 $cm.^{-1}$ both due to the acetate group, at 1660 $cm.^{-1}$ due to the αβ-unsaturated ketone system and at 1634 $cm.^{-1}$ due to the isolated double bond. The oxidation of 7-oxoapoeuphenyl acetate with selenium dioxide has therefore resulted in the introduction of a double bond in the 5:6-position and the product must be either (C) or (CI), the reaction being analogous to the conversion of 7-oxolanostanyl

acetate (CII) into 7-oxolanost-5-enyl acetate (CIII) under similar conditions.[119]



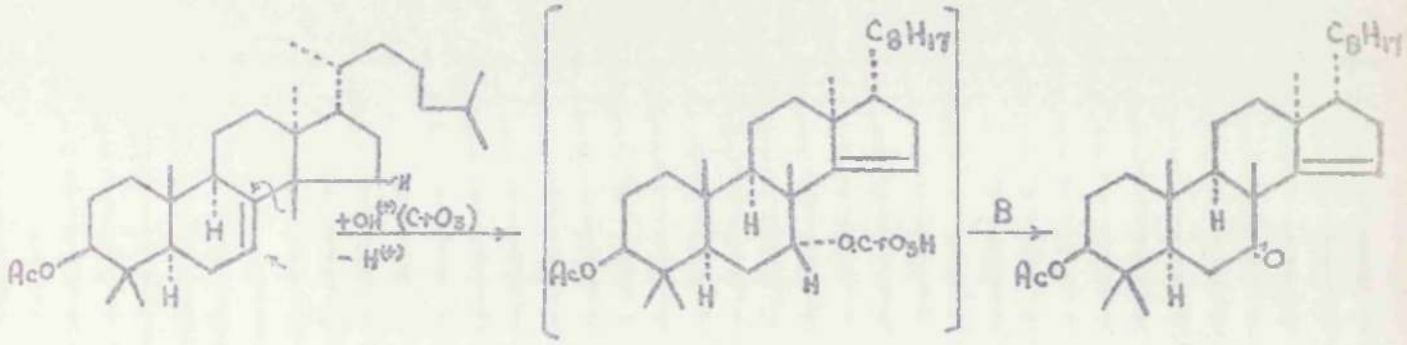
(C) (CI) (CII) (CIII)

Treatment of the above compound, $C_{32}H_{50}O_3$, with mineral acid converts it into an isomeric αβ-unsaturated ketone which also contains an isolated double bond since it shows light absorption maxima at 2080 and 2380 Å. (ε : 10,400 and 13,500 respectively). This isomer is formulated as 7-oxo<u>iso</u>-eupha-5:13(17)-dienyl acetate (CIV) being formed from the αβ-unsaturated ketone (C) or (CI) by a similar mechanism to that by which 7-oxo<u>iso</u>euphenyl acetate (XCVII) is formed from 7-oxo<u>apo</u>euphenyl acetate (XCIV) or (XCV).



(CIV) (XCIV) (XCV)

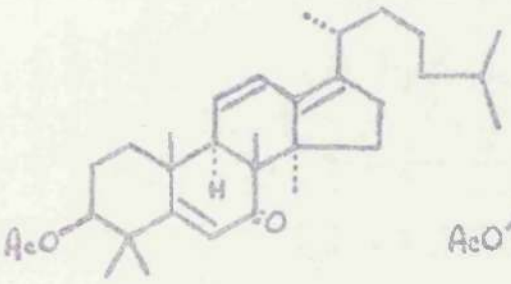
If 7-oxoapoeuphenyl acetate were (XCV), the product of selenium dioxide oxidation should contain a heteroannular diene system. Since, however, the double bond of 7-oxoapoeuphenyl acetate has not been attacked by selenium dioxide, it is concluded that the latter is (XCIV) and not (XCV). This decision is supported by the observation, already mentioned, that 7-oxoapoeuphenyl acetate is stable to treatment with chromic--acetic acid at 25°, which is to be expected if the double bond is in the 14:15-position (XCIV) but not if it is between $C_{(12)}$ and $C_{(13)}$, (XCV), since the analogously constituted α- and β-amyrin acetates are readily oxidised by this reagent. The formula (XCIV) is therefore preferred for 7-oxoapoeuphenyl acetate and its mechanism of formation from dihydrobutyrospermyl acetate (XCVI) may be represented as follows:



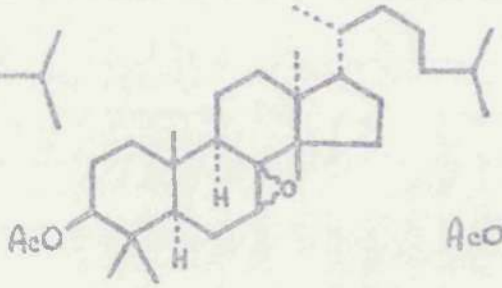
(XCVI) (XCIV)

To obtain further confirmation of the structure of 7-oxoisoeupha-5:13(17)-dienyl acetate (CIV), the latter was treated with selenium dioxide in acetic acid in an attempt to

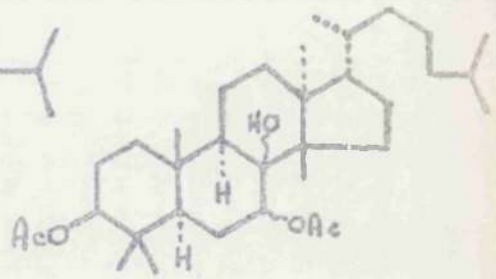
prepare 7-oxoisoeupha-5:11:13(17)-trienyl acetate (CV), a compound which would contain both the xβ-unsaturated ketone and the conjugated isoeuphadienyl systems. Only acidic non--crystalline products were, however, obtained probably because the molecule is unable to maintain the extremely strained conformation required by the introduction of another double bond in conjugation with the original isolated double bond.



(CV)



(CVI)



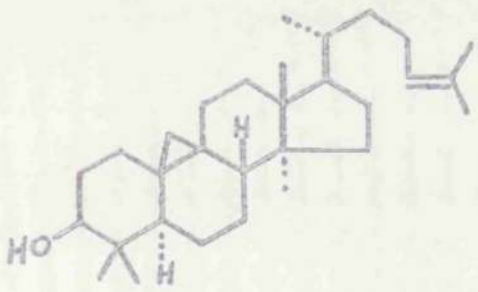
(CVII)

Attempts were also made to prepare 7-oxoapoeuph-14--enyl acetate (XCIV) by mild chromic acid oxidation of dihydrobutyrospermyl acetate oxide (CVI) and of the triol--diacetate (CVII), the preparations of which have already been described. In both experiments, a mixture was obtained, careful chromatography of which, failed to reveal any trace of (XCIV); the only identifiable product, in each case, was eupha-7:9(11)-dienyl acetate (LXXXIV).

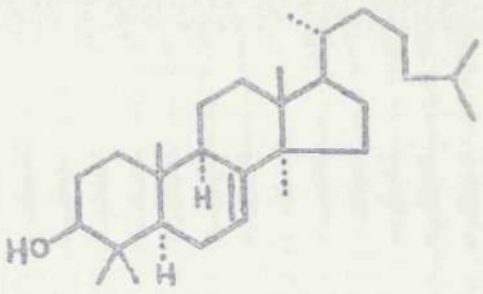
Molecular Rotation Considerations.

Confirmation, that the hydrogen atom attached to $C_{(9)}$ in butyrospermol has the α-configuration, was obtained from a study of molecular rotation data.

As early as 1951, Barton[35] observed that when cycloartenol and butyrospermol are oxidised to the corresponding 3-ketones, the change in molecular rotation (Δ_3) accompanying the conversion is, in each case, negative (Table III) whereas, for the majority of 3β-hydroxy-5α-steroids and 3β-hydroxytriterpenoids, this change is positive. He considered that this similarity was significant and suggested that the two alcohols may be related. Following the elucidation of the constitution and stereochemistry of cycloartenol as (LXXXVIII),[38,41,42] Jones and his collaborators,[114a,120] to explain these unusual Δ_3-values, suggested that butyrospermol, like cycloartenol, has a 9β--substituent and they tentatively formulated the former as 9β-cupha-7:24-dien-3β-ol. The observations recorded below, however, show that butyrospermol has the same configuration (α) at $C_{(9)}$ as lanost-7-en-3β-ol (CVIII).[101]



(LXXXVIII)

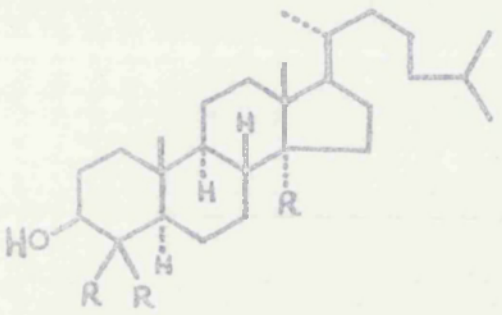


(CVIII)

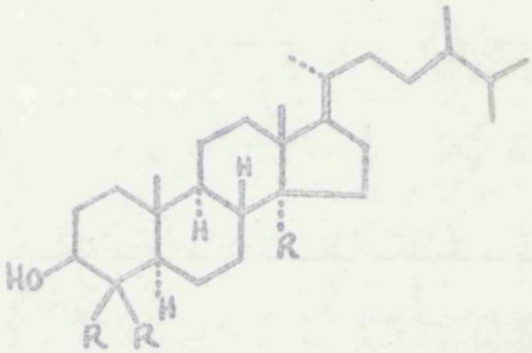
When applying the method of molecular rotation relations to the determination of structure and stereochemistry, particularly of steroid and triterpenoid molecules, it has been generally

accepted that terminal ring units of the same type make contributions towards 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.[96] In addition, it has been observed, that, for most types of compounds, the introduction of methyl groups to a terminal ring makes little difference to the molecular rotations of hydrocarbons and ketones provided that the substitution is not made at a ring junction.[96] Thus, the introduction of a carbonyl group at the 3-position in most 5α-steroid and 5α-triterpenoid hydrocarbons results in a positive change in molecular rotation while the molecular rotation change which accompanies the oxidation of most 3β--hydroxy-5α-steroids and 3β-hydroxytriterpenoids to the corresponding 3-ketones is also positive. It will be noted, however, that while the changes given by the steroids cholestanol (CIX, R = H) and ergostanol (CX, R = H) are in good agreement with the above generalisations, those given by their triterpanoid analogues lanostanol (CIX, R = Me) and laudanol (CX, R = Me) are exceptions to the rules. Thus, when lanostanol and laudanol are oxidised to the corresponding 3-ketones, the change in molecular rotation (Δ_S) is, in each case, negative as it also is when the hydrocarbons lanostane and laudane are converted into the corresponding 3-ketones. In Table I, the molecular rotation changes for lanostanol (CIX, R = Me) and laudanol (CX, R = Me)

are compared with the corresponding changes for cholestanol (CIX, R = H) and ergostanol (CX, R = H). The figures show



(CIX)



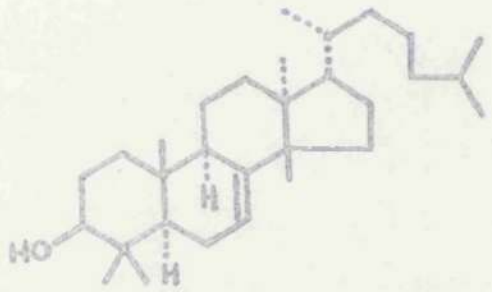
(CX)

TABLE I

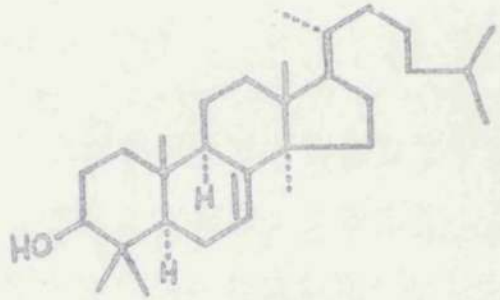
	$[M]_D$				
	3β-Alcohol	Hydrocarbon	3-Ketone	Δ_3	Δ_{30}
Lanostanol[31]					
(CIX, R = Me)	+ 150°	+ 149°	+ 116°	- 34°	- 33°
Laudanol[43]					
(CX, R = Me)	+ 93°	+ 107°	+ 62°	- 31°	- 45°
Cholestanol[181]					
(CIX, R = H)	+ 93°	+ 91°	+ 159°	+ 66°	+ 68°
Ergostanol[182]					
(CX, R = H)	+ 64°	+ 66°	+ 140°	+ 76°	+ 74°

that the introduction of methyl groups into the molecules of cholestanol and ergostanol at positions 4 and 14, has a profound effect upon the contribution of their terminal rings

towards the molecular rotation. The recognition of this effect led us now to compare the molecular rotation changes associated with the reactions of dihydrobutyrospermol (CXI), which also shows a negative Δ_3-value, with the corresponding changes for 9α-lanost-7-en-3β-ol (CVIII). The relevant data are shown in Table II.* It was found that the molecular



(CXI)



(CVIII)

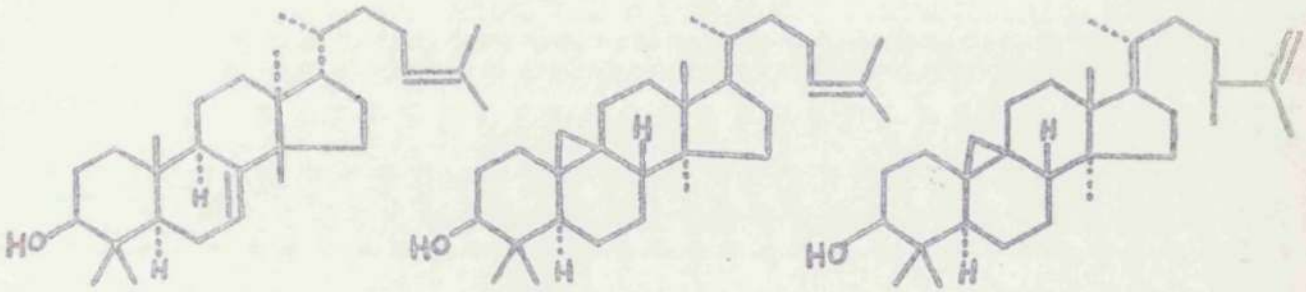
TABLE II

	$[M]_D$					
	Alcohol	Acetate	Benzoate	Ketone	Δ_1	Δ_2	Δ_3
9α-Lanost-7-en-3β-ol[65] (CVIII)	+ 45°	+156°	+266°	- 85°	+111°	+221°	-130
Dihydrobutyrospermol[118] (CXI)	- 60°	+ 56°	+164°	-182°	+116°	+224°	-122

*The 9α-lanost-7-en-3-one was prepared in this laboratory by Mr. William Hamilton who also confirmed the constants of the other lanost-7-enol derivatives and assisted in assembling the data recorded in Tables I, II, and III.

rotation change (Δ_3) occurring when lanost-7-en-3β-ol is converted into lanost-7-en-3-one is negative and almost identical with that associated with the oxidation of dihydrobutyrospermol and butyrospermol to the corresponding 3-ketones. In addition, it will be noted that the changes accompanying the acetylation (Δ_1) and benzoylation (Δ_2) of lanost-7-en-3β-ol are positive and nearly identical with the related values for dihydrobutyrospermol. This very close correspondence with lanost-7-en-3β-ol confirms the steric formula (IC) proposed above for butyrospermol.

The molecular rotation changes for cycloartenol (LXXXVIII) and its C_{31}-analogue cycloläudenol (XIV) are shown in Table III.



(IC) (LXXXVIII) (XIV)

TABLE III

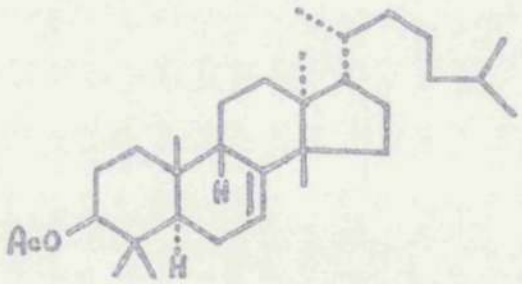
	$[M]_D$						
	Alcohol	Acetate	Benzoate	Ketone	Δ_1	Δ_2	Δ_3
cycloArtenol[58] (LXXXVIII)	+230°	+280°	+400°	+ 93°	+50°	+170°	-137°
cycloLaudenol[48] (XIV)	+206°	+265°	+343°	+ 83°	+59°	+137°	-123°
Butyrospermol[116] (IC)	- 51°	+ 48°	+159°	-170°	+99°	+210°	-119°

The reason why these alcohols also show negative Δ_3-values of the same order as butyrospermol probably finds an explanation in the fact that, in these compounds, the substituents at $C_{(8)}$, $C_{(9)}$ and $C_{(10)}$ all have the β-configuration. This will cause some distortion of the framework of the molecules and, in particular, will constrain ring B to adopt a half-chair conformation very similar to that found in lanost-7-enol in which this is brought about by the double bond between $C_{(7)}$ and $C_{(8)}$ and the hydrogen atom at $C_{(9)}$ in the α-configuration. In dihydrobutyrospermol, which has the same stereochemistry in rings A and B as lanost-7-enol, ring B is also constrained to adopt this half-chair conformation. Also, in the dihydrobutyrospermol molecule, the stereochemistry in rings C and D is the same as that in euphol and the opposite of that found in lanost-7-enol. Ring C in the latter must therefore be a boat (or half-boat) and this, although it does not appear to affect the molecular rotation changes, provides the driving force for its irreversible isomerisation into euph-8-enyl acetate which can adopt an all chair (or half-chair) conformation throughout the molecule.

9β-Euph-7-enyl Acetate.

With the identification of dihydrobutyrospermyl acetate as 9α-euph-7-enyl acetate (XCVI), the isomeric compound obtained by Wolff-Kishner reduction of 7-oxoeuph-8-enyl acetate followed

by acetylation of the product, may now be formulated as 9β-euph-
-7-enyl acetate (CXII). This is supported by the fact that its method of preparation requires it to adopt the more stable conformation. The configuration at $C_{(9)}$ must therefore be β since, as stated above, the stereochemistry of the 9α-isomer (dihydrobutyrospermyl acetate) constrains the molecule to adopt a conformation which includes a boat (in ring C), whereas 9β-euph-
-7-enyl acetate can assume an all-chair (or half-chair) conformation.



(CXII)

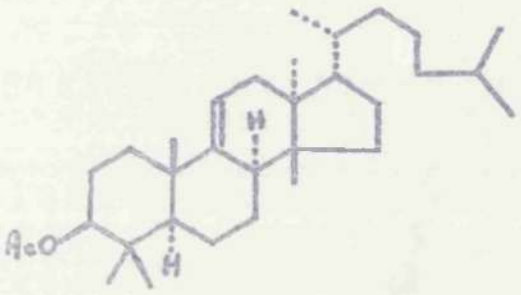
Chemical evidence supporting this structure has recently been obtained in this laboratory by Dr H. S. Watson who has again prepared 9β-euph-7-enyl acetate, using the original method, and examined in detail the relevant aspects of its chemistry. Watson found that, in its reactions, 9β-euph-7-enyl acetate resembles lanost-7-enyl acetate (CVIII, R = Ac) rather than dihydrobutyrospermyl acetate, and in particular that it is unchanged after treatment with hydrogen chloride under conditions which readily convert dihydrobutyrospermyl acetate

(XCVI) into euph-8-enyl acetate (LXXVI) so that 9β-euph-7-enyl acetate is the more stable isomer. Prolonged treatment with strong mineral acid, however, converts it partially into the Δ^{8}-isomer, a behaviour analogous to that of lanost-7-enyl acetate under similar conditions, and this Δ^{8}-isomer is, of course, itself partially converted into isoeuph-13(17)-enyl acetate (LXXVIII) so that the resulting product is a difficultly separable mixture of all three compounds.

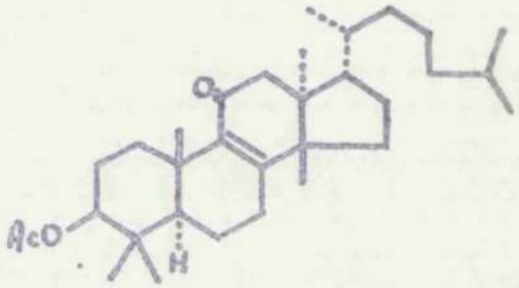
8α-Euph-9(11)-enyl Acetate.

During the course of the investigations into the structure of butyrospermol, when it became apparent that the latter was a member of the euphol series with its nuclear double bond either between $C_{(7)}$ and $C_{(8)}$ or between $C_{(9)}$ and $C_{(11)}$, the synthesis of the hitherto unknown euph-9(11)-enyl acetate (CXIII) was undertaken for direct comparison with dihydrobutyrospermyl acetate. The new isomer was obtained in relatively poor yield by Wolff-Kishner reduction of 11-oxoeuph-8-enyl acetate (CXIV), using anhydrous conditions,[110] and acetylation of the product. Extensive purification gave euph-9(11)-enyl acetate, m.p. 99-100°, $[\alpha]_D$ - 59°, which differed markedly both from dihydrobutyrospermyl acetate (m.p. 135-136°, $[\alpha]_D$ + 10°) and from the 9β-euph-7-enyl acetate (m.p. 78-79°, $[\alpha]_D$ - 98°) prepared by H. S. Watson. It is of interest to note, however, that its constants are in remarkable agreement with those quoted earlier

for euph-7-enyl acetate by Barton (m.p. 92-94°, $[\alpha]_D$ - 60°)[107b].



(CXIII)

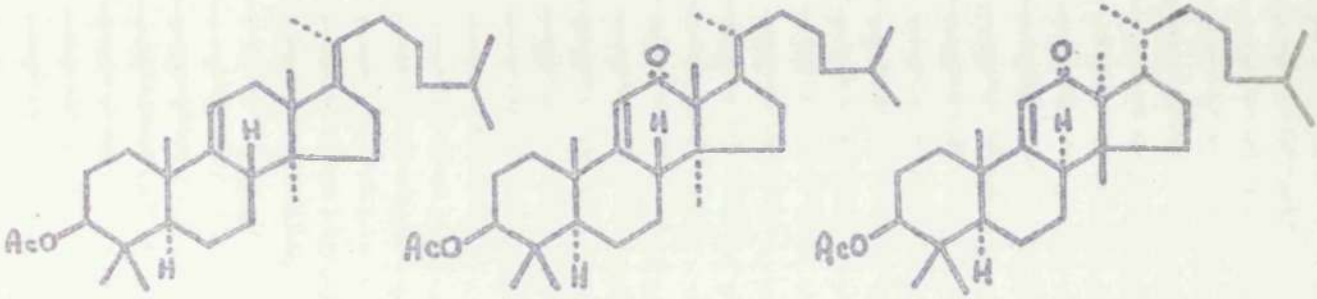


(CXIV)

The new isomer is considered to be 8α-euph-9(11)-enyl acetate (CXIII) since it has been formed from 11-oxoeuph-8-enyl acetate (CXIV) by a method which requires that the substituent at the new asymmetric centre should have the more stable configuration. The hydrogen atom attached to $C_{(8)}$ in euph-9(11)--enyl acetate must, therefore, have the α-configuration since, with this stereochemistry, the molecule can assume an all-chair (or half-chair) conformation. The reactions of euph-9(11)--enyl acetate which have, so far, been studied support this view. Like 9β-euph-7-enyl acetate, the more stable Δ^7-isomer, euph--9(11)-enyl acetate is recovered unchanged after treatment in chloroform at 0° with dry hydrogen chloride, conditions which, it is considered, would convert an 8β-isomer to euph-8-enyl acetate. More vigorous treatment with hydrochloric-acetic acid at 100°, however, converts euph-9(11)-enyl acetate directly into isoeuph-13(17)-enyl acetate, a rearrangement which was at first

surprising but which is only to be expected when it is considered that the same conditions cause the equally stable molecule of euph-8-enyl acetate (all-chair or half-chair) to undergo the same rearrangement, brought about by the conformational driving force due to the unfavourable configurations at $C_{(13)}$, $C_{(14)}$ and $C_{(17)}$.[107]

Oxidation of euph-9(11)-enyl acetate with selenium dioxide in acetic acid and filtration of the product in ether solution through alumina gave eupha-7:9(11)-dienyl acetate (LXXXIV) in good yield. Dihydrobutyrospermyl acetate and 9β-euph-7-enyl acetate are also oxidised to the diene (LXXXIV) under these conditions. The analogously constituted lanost-9(11)-enyl acetate (CXV) is, however, unchanged even after prolonged treatment with selenium dioxide, a fact which suggests that the hydrogen atom at $C_{(9)}$ in euph-9(11)-enyl acetate has the opposite configuration (α) to that in lanost-9(11)-enyl acetate (β).



(CXV) (CXVI) (CXVII)

Treatment of euph-9(11)-enyl acetate with chromic-acetic acid at 100° and purification of the product by chromatography gave, in addition to starting material a crystalline fraction m.p. 166-167° in 30% yield. This compound gave no colour with tetranitromethane and showed the ultraviolet absorption characteristics with a maximum at 2400 Å. (ε:11,000) of a ββ-disubstituted, αβ-unsaturated ketone. In this one reaction, therefore, euph-9(11)-enyl acetate resembles lanost-9(11)-enyl acetate (CXV) which is oxidised by chromic acid to give 12-oxo-lanost-9(11)-enyl acetate (CXVI), showing light absorption maximum at 2420 Å., (ε:10,000).[86] By analogy the above product is formulated as 12-oxoeuph-9(11)-enyl acetate (CXVII).

S E C T I O N II.

The Constitution of Parkeol.

Parkeol, a minor constituent of the non-saponifiable fraction from shea-nut fat, has been identified as lanosta-9(11):24-dien-3β-ol.

As stated in the preceding section, the non-saponifiable fraction of shea-nut fat contains the triterpenoid alcohols α-amyrin, β-amyrin, lupeol[110] and butyrospermol[125]. Another component was discovered by Bauer and Moll[47] in 1939. The new compound, which was also an alcohol (m.p. 164°) having the approximate molecular formula $C_{30}H_{50}O$, was named parkeol, (from Butyrospermum parkii) and was characterised by the formation of an acetate (m.p. 154°) and a benzoate (m.p. 197°). Several years later, Dawson, Halsall, Jones, and Robins[48] isolated a small amount of an acetate which they considered to be parkeyl acetate, from the acetylated non-saponifiable fraction of shea-nut fat. After purification, this acetate had melting point 154-157°, $[\alpha]_D$ + 95° and on alkaline hydrolysis yielded parkeol, m.p. 162-165°, $[\alpha]_D$ + 65°. No attempt to elucidate the structure of parkeol was described and no subsequent investigations on the subject have been reported in the literature.

Parkeol has again been isolated by the author and it has now been identified as lanosta-9(11):24-dien-3β-ol[123].

The non-saponifiable fraction of shea-nut fat was acetylated by boiling with acetic anhydride. The resulting pale yellow solution was allowed to cool to 20° and kept at this temperature for 18 hours. During this time a white semicrystalline solid,

consisting mainly of the acetates of the higher melting pentacyclic triterpenoids was deposited and was removed. During the filtration, a fine granular solid (fraction A, m.p. 130-145°) slowly separated from the filtrate and after a short period was collected. The clear filtrate was kept at room temperature for 2 days when a third crop (fraction B, m.p. 112-150°) of small white crystals was obtained. Fractions A and B were combined and their solution in light petroleum was chromatographed on alumina. After the removal of a number of fractions which consisted mainly of crude butyrospermyl acetate ("basseol acetate"), a fraction was obtained which, after several crystallisations from chloroform-methanol, had the constants, m.p. 157-158°, $[\alpha]_D$ + 87°. This acetate, which amounted to only 0.25% of the non-saponifiable matter and to 0.008% of the shea-nut fat itself, corresponded closely in melting point to the parkeyl acetate obtained by Bauer and Moll[47] (m.p. 154°) and by Jones and his colleagues[48] (m.p. 154-157°) although the specific rotation is somewhat lower than that recorded by the latter authors, (+ 95°).

Hydrolysis of the acetate m.p. 157-158°, $[\alpha]_D$ + 87°, using either potassium hydroxide in methanol or lithium aluminium hydride in ether, and crystallisation of the product gave the parent alcohol, the melting point of which (161-163°) was in

agreement with that reported for parkeol by Bauer (164°) and by Jones (162-165°). The specific rotation of the alcohol (+75°) was, however, higher than that found by Jones (+65°). Reacetylation of the alcohol gave an acetate having the same constants as the original specimen. Benzoylation of the alcohol followed by chromatography and repeated fractional crystallisation of the product gave parkeyl benzoate, m.p. 202°, $[\alpha]_D$ + 95°. Treatment of the benzoate with lithium aluminium hydride in ether gave an alcohol the melting point (162-163°) and specific rotation (+76.5°) of which were in agreement with the values obtained above for parkeol. Repeated recrystallisation of this material, however, resulted in a gradual lowering of the melting point until this finally remained constant at 159.5-160°. The specific rotation at this stage was + 76.8°. The constants thus obtained are considered to be those of pure parkeol. Pure parkeyl acetate, m.p. 160-161°, $[\alpha]_D$ + 86°, was obtained by acetylation of this material.

The physical properties of parkeol and its derivatives were compared with those of all the known tetracyclic and pentacyclic triterpenoids. No similarity with any was, however, apparent.

Analyses of parkeol and its derivatives were in agreement with the molecular formula $C_{30}H_{50}O$, first assigned by Bauer, for the parent alcohol although the formula $C_{31}H_{52}O$ could not be excluded at this stage.

The hydroxyl group in parkeol was shown to be secondary when oxidation using the pyridine-chromium trioxide complex gave a ketone, parkeone, m.p. 126°, $[\alpha]_D$ + 66°. The infrared spectrum of the latter (in nujol) contained a strong band at 1708 $cm.^{-1}$ characteristic of a ketone group at postion-3 in a normal triterpene ring A. Reduction of parkeone with lithium aluminium hydride in ether regenerated the parent alcohol and, if it can be assumed that parkeol has a normal triterpene ring A, this indicated that the hydroxyl group attached to $C_{(3)}$ has the more stable equatorial conformation. This conclusion was supported by a study of the molecular rotation changes which accompany the acylation of parkeol. Halsall, Heakins and Swayne[124] have observed that in triterpenoids containing a 3β-hydroxyl group, the changes in molecular rotation on acetylation and on benzoylation, although variable in size, are positive whereas compounds having a $C_{(3)}$-hydroxyl group in the α-configuration show a large negative change. The change in molecular rotation Δ_1, following the acetylation of parkeol is + 74° and the change Δ_2, on benzoylation is + 175°.

These figures are therefore in agreement with those expected from a 3β-(equatorial)-hydroxyl group in a triterpenoid (or steroid) nucleus having a normal trans-fused A:B ring system. The infrared spectrum of parkeol measured in nujol and in chloroform included a band at 1041 cm.$^{-1}$ which is considered to be a characteristic of an equatorial hydroxyl group.

In the Liebermann-Burchard reaction, parkeol gave an initial reddish-yellow colour which slowly darkened to a deep blood-red colour having a blue-green fluorescence. This behaviour, which is distinct from that of either the pentacyclic triterpenoids or the steroids, and the fact that parkeol and its derivatives all have relatively low melting points, gave the first indication that parkeol might be a member of the tetracyclic group of triterpenoids. This was confirmed when parkeol was shown to contain two double bonds.

The alcohol and its derivatives gave a strong yellow colouration with tetranitromethane in chloroform-solution and readily absorbed bromine from acetic acid solution. The ultraviolet spectra showed relatively strong absorption at 2040 Å. (ε, 9000 - 10,000) suggesting that two ethylenic linkages are present. These are not conjugated, however, since parkeol does not show selective absorption above 2200 Å. On hydrogenation at 20° over a platinum catalyst in either ethyl acetate or acetic acid, parkeyl acetate readily absorbed one

molecular proportion of hydrogen. The product, a dihydro-acetate, $C_{32}H_{54}O_2$, m.p. 172-173°, $[\alpha]_D$ + 87°, still contains one double bond evidenced by a persistent yellow colour with tetranitromethane and by its ultraviolet absorption ($\varepsilon_{max.}^{2050A.}$ = 4,900).

The nature of the readily reducible double bond in parkeol was disclosed when treatment of parkeyl acetate with osmic acid gave a diol, oxidation of which with lead tetra-acetate gave a 50% yield of acetone isolated as its 2:4-dinitrophenylhydrazone.

From the experiments so far described it was concluded that parkeol is a tetracyclic, secondary alcohol containing two double bonds one of which is not reduced at room temperature by hydrogen and platinum, and which presumably is in the nucleus. The nature of the ultraviolet absorption curve indicated that it may be trisubstituted. The reactive double bond must be present in an isopropylidene group which possibly terminates a side-chain as in lanosterol or euphol.

The chemical properties of dihydroparkeyl acetate were now investigated in an attempt to examine the environment of the double bond. Dihydroparkeyl acetate was treated with mineral acid, first under the relatively mild conditions, using dry hydrogen chloride in chloroform at 0°, which bring about the isomerisation of dihydrobutyrospermyl acetate to euph-8-enyl acetate[46] and which partially convert lanost-8-enyl acetate into

lanost-7-enyl acetate.[78] No reaction was observed, however, and dihydroparkeyl acetate was recovered quantitatively unchanged as was the case when the more vigorous conditions (concentrated hydrochloric acid in acetic acid at 100°) which are required for the euph-8-enyl acetate to isoeuphenyl acetate rearrangement,[108] were employed.

In an attempt to convert dihydroparkeyl acetate into the corresponding heteroannular diene to determine from its ultraviolet spectrum whether it belonged to the euphol or the lanosterol series, the acetate was treated with selenium dioxide in acetic acid. Even after 30 hours under reflux, however, dihydroparkeyl acetate was recovered in good yield although the ultraviolet spectrum of the crude product, which showed a very weak band at 2440 Å. (ϵ, 900) in addition to one at 2040 Å. (ϵ, 4,800) due to the double bond, did indicate that a very small amount of diene had been formed. The position of the former band (2440 Å.) suggested that the diene belonged to the lanosterol series rather than to the euphol series.

The effect of chromic acid on dihydroparkeyl acetate was next examined. The majority of naturally occurring tetracyclic triterpenoids contain a nuclear double bond, oxidation of which with chromic acid in acetic acid results in the formation of characteristic 1:4-dione-enes. Treatment of dihydroparkeyl

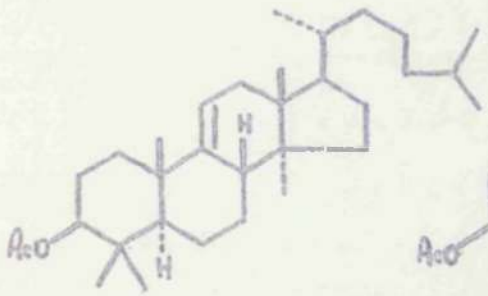
acetate with this reagent at 100° and then under reflux gave a product, careful chromatography of which failed to reveal any trace of yellow dione-ene. Instead a colourless compound containing one additional oxygen atom and with probable molecular formula $C_{32}H_{52}O_3$ was obtained in 30% yield together with some unchanged starting material. This compound, which was named oxodihydroparkeyl acetate, showed the characteristic ultraviolet absorption spectrum, with a maximum at 2420 Å. (ε, 12,000), of a ββ-disubstituted - αβ-unsaturated ketone. In the tetracyclic group, this type of αβ-unsaturated ketone has been previously obtained only by oxidation of compounds which have a double bond between $C_{(9)}$ and $C_{(11)}$, the product being the corresponding 12-oxo-$\Delta^{9(11)}$-derivative with light absorption maximum at 2420 Å.(ε, 10,000). The physical properties of dihydroparkeyl

TABLE A.

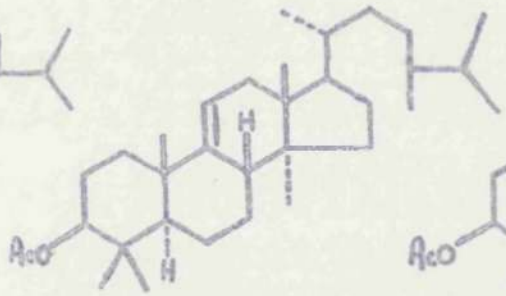
	m.p.	$[\alpha]_D$	λmax.	ε
Dihydroparkeyl Acetate	172-173°	+ 87°	2060 Å.	4,900
Oxodihyroparkeyl Acetate	181-183°	+ 90°	2420 Å.	12,000
Lanost-9(11)-enyl Acetate (CXV)[38]	173-174°	+ 84°	2060 Å.	4,300
12-oxolanost-9(11)--enyl Acetate (CXVI)[38]	184-185°	+ 91°	2420 Å.	9,800
Laud-9(11)-enyl Acetate (CXVIII)[43]	173-174°	+ 81°	2060 Å.	3,100
12-oxolaud-9(11)-enyl Acetate (CXIX)[43]	194°	+ 87°	2410 Å.	10,300
euph-9(11)-enyl Acetate (CXIII)	99-100°	- 59°	2030 Å.	4,000.
12-oxoeuph-9(11)-enyl Acetate (CXVII)	166-167°	- 66°	2400 Å.	11,600.

acetate and of its oxidation product were therefore compared with those of the only known compounds of this type. Three examples were found as indicated in Table A.

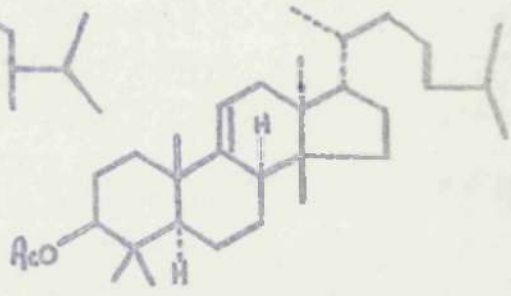
From this comparison, it appeared that dihydroparkeyl acetate could be identical with either lanost-9(11)-enyl acetate (CXV) or with laud-9(11)-enyl acetate (CXVIII). The constants of the oxo-derivatives, however, favoured the identity with the former.



(CXV)



(CXVIII)



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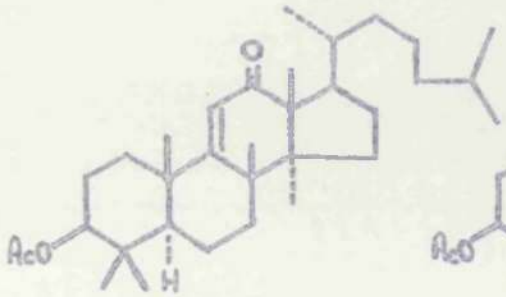
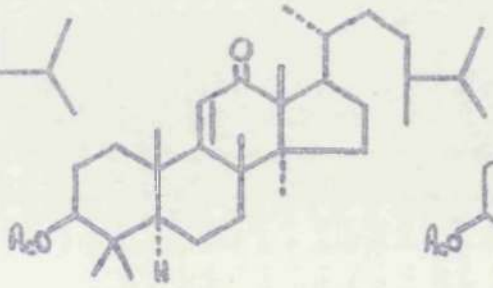
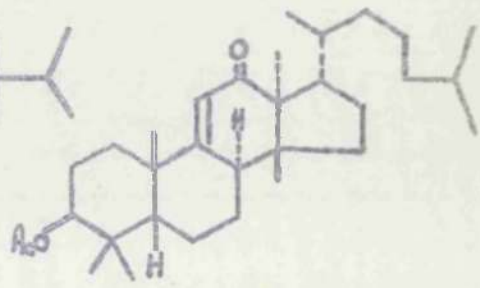


(CXVI)



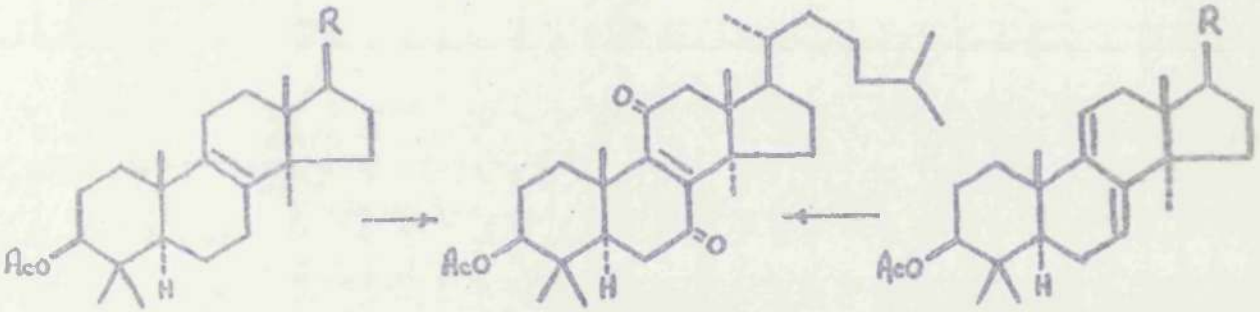
(CXIX)



(CXVII)

As no lanost-9(11)-enyl acetate was available and in order to establish identity with dihydroparkeyl acetate by direct comparison, a sample was prepared from "isocholesteryl acetate" which is obtained by acetylation of the neutral fraction from sheep wool fat after the removal of cholesterol. isoCholesteryl

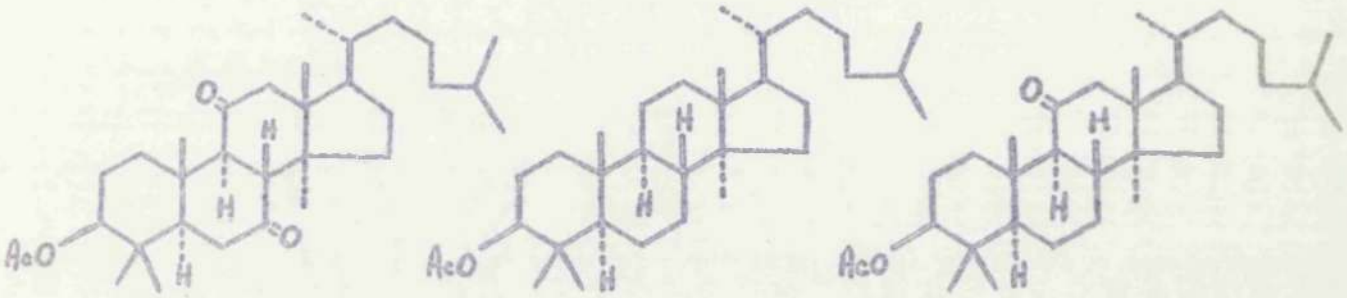
acetate is a crude mixture composed of the acetates of lanosterol (CXX, R = C_8H_{16}), dihydrolanosterol (CXX, R = C_8H_{17}), agnosterol (CXXI, R = C_8H_{16}) and dihydroagnosterol (CXXI, R = C_8H_{17})[14]. By hydrogenation in acetic acid over platinum catalyst, the number of components was reduced to two and a mixture consisting of dihydrolanosteryl acetate and dihydroagnosteryl acetate was obtained. Since oxidation of both these



(CXX) (CXXII) (CXXI)

compounds with chromic acid is known to yield 7:11-dioxolanost-8--enyl acetate (CXXII)[77a], the mixture was treated with a solution of chromium trioxide in acetic acid at 100° according to the method of Cavalla and McGhie[77b] for the oxidation of lanost-8--enyl acetate. From the neutral product, which was purified by filtration, in benzene solution, through a short column of activated alumina, 7:11-dioxolanost-8-enyl acetate (CXXII) was obtained in good yield. Treatment of the latter with zinc in boiling acetic acid gave the saturated diketone (CXXIII)[128] which was reduced using the Huang-Minlon modification of the Wolff-Kishner reaction[63] to a mixture from which, after acetylation, both lanostanyl acetate (CXXIV) and 11-oxolanostanyl acetate

(CXXV) were separated by chromatography. In view of the



(CXXIII) (CXXIV) (CXXV)

differences, referred to below, between certain compounds derived from this 11-oxolanostanyl acetate and the corresponding compounds previously described by Voser, Montavon, Günthard, Jeger and Ruzicka,[81] and by McGhie, Pradhan and Cavalla[83], it is of significance to point out at this stage that the 11-oxolanostanyl acetate obtained in this work was identical both in melting point characteristics and in specific rotation with that described by Voser. The 11-oxolanostanyl acetate prepared as outlined above had a melting point of 144-146° after drying under vacuum at 100°. After sublimation at 130-140° in high vacuum, however, the melting point was 156-157°. The specific rotation, both before and after sublimation, was + 63° and when the sublimed material was crystallised from chloroform-methanol 11-oxolanostanyl acetate of melting point 143-145° was again obtained. For "acetoxylanostanone", Voser[81] gives m.p. 142-144° rising after sublimation to 156-158° and reverting to 139-141° on recrystallisation of the sublimed material; $[\alpha]_D$ + 60 to + 63°.

Reduction of the 11-oxolanostanyl acetate m.p. 144-146°, $[\alpha]_D$ + 63° with lithium aluminium hydride in ether exactly according to the method given by Voser and his colleagues[81] gave a diol $C_{30}H_{54}O_2$, the specific rotation of which was found to be considerably greater than that recorded by these authors for lanostanediol, although the melting point was in fairly good agreement. The diol obtained in the present work had the constants m.p. 193-194°, $[\alpha]_D$ + 54°, unchanged either by repeated recrystallisation or by acetylation followed by hydrolysis, whereas the lanostanediol described by Voser[81] had m.p. 190-191°, $[\alpha]_D$ + 29°. McGhie, Pradhan and Cavalla[83] have also reported the preparation of a lanostanediol by the method of Voser and give m.p. 190-191°, $[\alpha]_D$ + 28.4° for this compound. The preparation of this 3:11-dihydroxylanostane has been repeated in this laboratory, twice by the author and once, independently, by Mr. W. Hamilton, B.Sc., starting from a fresh sample of "isocholesterol". In all three experiments the diol obtained had the constants: m.p. 193-194°, $[\alpha]_D$ + 54° ± 1°.

Treatment of the diol ($[\alpha]_D$ + 54°) with acetic anhydride in pyridine either at 18° for 20 hours or at 100° for 3 hours gave a diol-monoacetate, $C_{32}H_{56}O_3$, which differed slightly in melting point and very markedly in specific rotation from the lanostanediol-monoacetate (acetoxylanostanol) described first

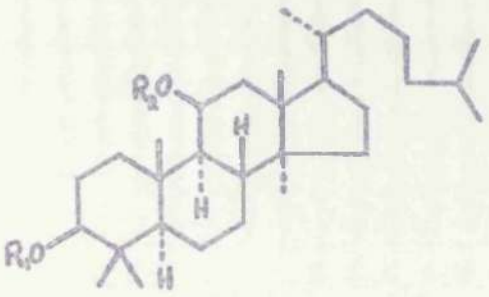
by Voser[81] and shortly afterwards by McGhie[83]. The constants of this acetate and of the parent diol are compared with those of the corresponding compounds of Voser and of McGhie in Table B.

TABLE B.

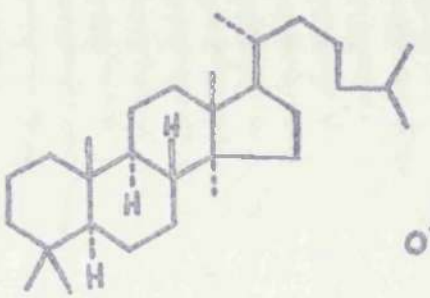
	Lanostanediol. (11β-hydroxylanostanol)		Lanostanediol-Monoacetate. (11β-Hydroxylanostanyl Acetate)	
	m.p.	$[\alpha]_D$	m.p.	$[\alpha]_D$
Voser et al.[81]	190-191°	+ 29°	219-220°	+ 23°.
McGhie et al.[83]	190-191°	+ 28.4°	215-216°	+ 22.8°
This Work.	193-194°	+ 54°	210.5-211°	+ 62.5°

The fact that the constants of the diol and of the monoacetate obtained in the present investigation differed from those of the corresponding compounds described by Voser and by McGhie is surprising since the same starting material and the same preparative methods have been used in all three cases. It was at first considered possible that the differences might be due to an inversion in the configuration of either the $C_{(11)}$-hydroxyl group or of the hydrogen atom attached to $C_{(9)}$. The chemical properties of the diol ($[\alpha]_D$ + 54°) were therefore examined in more detail, a comparison being made with the properties described by Voser and his colleagues[81,91b] for the

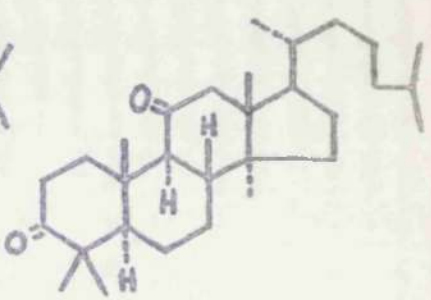
diol having $[\alpha]_D$ + 29°. From the inability of the latter to undergo complete acetylation when treated with acetic anhydride in pyridine at room temperature, the Swiss workers[91b] have deduced that the hydroxyl group attached to $C_{(11)}$ is sterically hindered and, by analogy with the corresponding 11β-hydroxy--steroids, have assigned to this compound the structure (CXXVI, $R_1 = R_2 = H$) in which the 11-hydroxyl group has the β-(axial)--configuration. Similarly, since the diol ($[\alpha]_D$ + 54°) obtained in this work gives only a monoacetate on acetylation at 100°, it must be concluded that the $C_{(11)}$-hydroxyl group in this compound is sterically hindered. Thus, provided the molecule has maintained its original all-chair conformation, the $C_{(9)}$-hydrogen atom being α (axial) as in the precursor 11-oxolanostanyl acetate (CXXV), this hindered 11-hydroxyl group must also have the β-(axial)-configuration. That the molecule still has in fact the same basic stereochemistry as lanostane (CXXVII) is shown by the experiments described below.



(CXXVI)



(CXXVII)



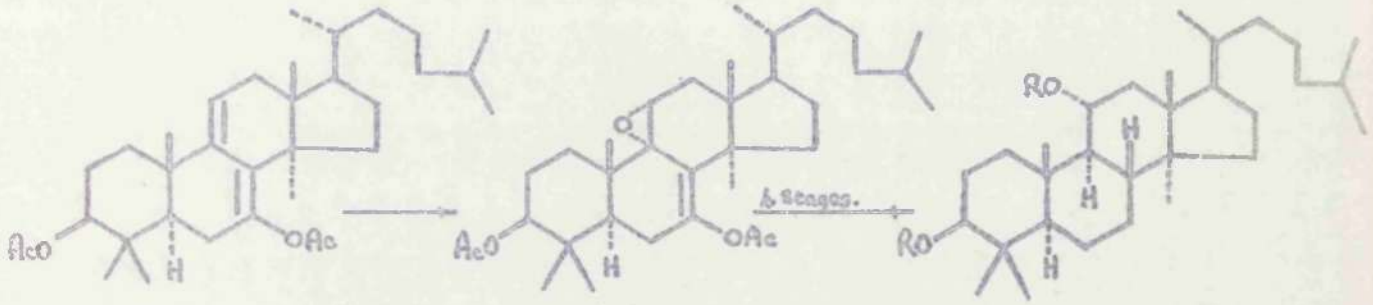
(CXXVIII)

Treatment of the diol-monoacetate ($[\alpha]_D$ + 62.5°) with chromic acid at room temperature gave, in almost quantitative yield, 11-oxolanostanyl acetate (CXXV) identical in melting point characteristics and in specific rotation with the original starting material. The diol-monoacetate and the diol itself, therefore have the same stereochemistry at $C_{(9)}$ and throughout the molecule as 11-oxolanostanyl acetate.

Similar oxidation of the diol ($[\alpha]_D$ + 54°) readily gave 3:11-dioxolanostane (CXXVIII), the constants of which (m.p. 120-121°, $[\alpha]_D$ + 66.5°) were in good agreement with those quoted by Voser et al.[91a,91b] for the lanostanedione which they obtained by chromic acid oxidation of 11-oxolanostanol[91a], of the 3β:11β-diol (CXXVI, $R_1 = R_2 = H$; $[\alpha]_D$ + 29°)[91b] and of the 3β:11α-diol (CXXIX, R = H)[91b]. It follows that the $C_{(9)}$-hydrogen atom of the diol ($[\alpha]_D$ + 29°) prepared by Voser has the same configuration (α) as that of the diol obtained in this work. The compounds are therefore identical chemically and stereochemically and it would appear that there has been an error either in measuring or in reporting the earlier values of the specific rotation of this diol (CXXVI, $R_1 = R_2 = H$) and of its monoacetate (CXXVI, R_1 = Ac, $R_2 = H$).

As a matter of interest an attempt was made, during the course of the above investigation, to prepare the diacetate of

the diol (CXXVI, $R_1 = R_2 = H$) since it is well known that a hindered 11β-hydroxyl group can be acetylated under certain conditions. In this experiment the diol-monoacetate (CXXVI, $R_1 = Ac$, $R_2 = H$) in chloroform solution was boiled under reflux with a mixture of acetyl chloride and dimethylaniline for 20 hr.[126] The product was a saturated compound $C_{34}H_{52}O_4$, m.p. 182°, $[\alpha]_D$ + 71°, which did not contain a hydroxyl group and which must be the required 3β:11β-diacetate (CXXVI, $R_1 = R_2 = Ac$). It is quite distinct from the starting material and from the corresponding 3β:11α-diacetate (CXXIX, R = Ac) first prepared by Mijovic, Voser, Heusser and Jeger[91b] from the enol diacetate (CXXX) of



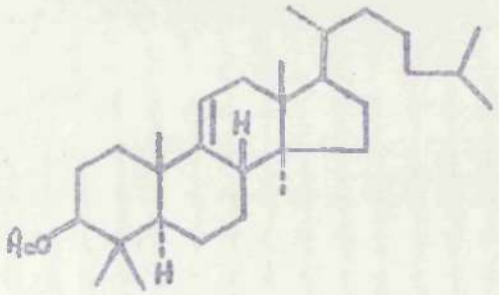
(CXXX) (CXXXI) (CXXXIX)

7-oxolanost-8-enyl acetate *via* the 9α:11α-epoxide (CXXXI), although its infrared spectrum (in nujol) which showed strong bands at 1739 $cm.^{-1}$ and between 1238 and 1253 $cm.^{-1}$ due to the acetate groups, closely resembled that of the latter. For the present work the 3β:11α-diacetate (CXXIX, R = Ac) was readily obtained from 11-oxolanostanyl acetate (CXXV) by reduction with sodium in *n*-propyl alcohol followed by acetylation of the product

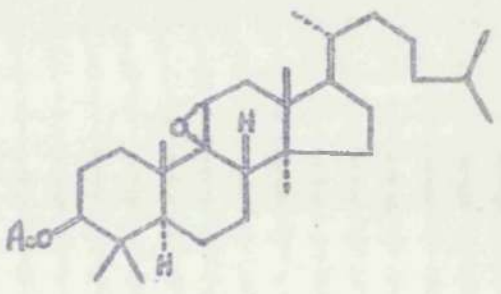
at room temperature.

Support for the decision that the diol and the monoacetate prepared in this work are identical with those described by Voser was obtained when treatment of the monoacetate (CXXVI, R_1 = Ac, R_2 = H) with phosphorus oxychloride in pyridine at 100° for 3 hr. gave lanost-9(11)-enyl acetate (CXV) m.p. 173-174°, $[\alpha]_D$ + 89° in high yield. The identity of this material with dihydroparkeyl acetate m.p. 172-173°, $[\alpha]_D$ + 87° was quickly established by mixed melting point determination (172-174°) and by the coincidence of their infrared spectra. Confirmation of this was obtained in a number of ways.

Oxidation of lanost-9(11)-enyl acetate (CXV) with chromic acid as described by Bentley, Henry, Irvine and Spring[33] gave 12-oxolanost-9(11)-enyl acetate (CXVI) which proved to be identical with the αβ-unsaturated ketone obtained by the similar oxidation of dihydroparkeyl acetate.



(CXV)



(CXXXII)

Oxidation of dihydroparkeyl acetate with hydrogen peroxide in acetic acid gave a saturated epoxide identified as lanost-

-9(11)-enyl acetate oxide (CXXXII)[80] by direct comparison with an authentic specimen and by its ready conversion into lanosta--7:9(11)-dienyl acetate (CXXI, R = C_8H_{17})[75] on mild treatment with sulphuric acid.

It had previously been found that prolonged hydrogenation of dihydroparkeyl acetate in acetic acid at 80° over a platinum catalyst gave tetrahydroparkeyl acetate, $C_{32}H_{56}O_2$, m.p. 160-161.5°, $[\alpha]_D$ + 40.5°. It showed no colouration when treated with tetranitromethane in chloroform and no selective light absorption in the ultraviolet. The melting point of this compound, which is unchanged either by repeated recrystallisation or by careful chromatography, is somewhat higher than that recorded in the literature (see Table C) for lanostanyl acetate (CXXIV) although the specific rotation is in good agreement. For direct comparison, therefore, a sample of lanost-9(11)-enyl acetate (CXV) was hydrogenated at 80° for 20 hr.[80] The lanostanyl acetate obtained had m.p. 156-157° in agreement with the highest value quoted by previous workers[83,118] for this compound; its specific rotation was + 40.4°. Extensive attempts to purify further both tetrahydroparkeyl acetate and this lanostanyl acetate and thereby reduce the 4° - difference between their melting points were without success. However, a mixture of the two specimens showed no depression on melting (m.p. 157-160°) and their infrared absorption spectra were

identical.

In Table C, the constants of dihydroparkeyl acetate and of its oxidation and reduction products are compared with those of synthetic lanost-9(11)-enyl acetate and its corresponding derivatives.

TABLE C.

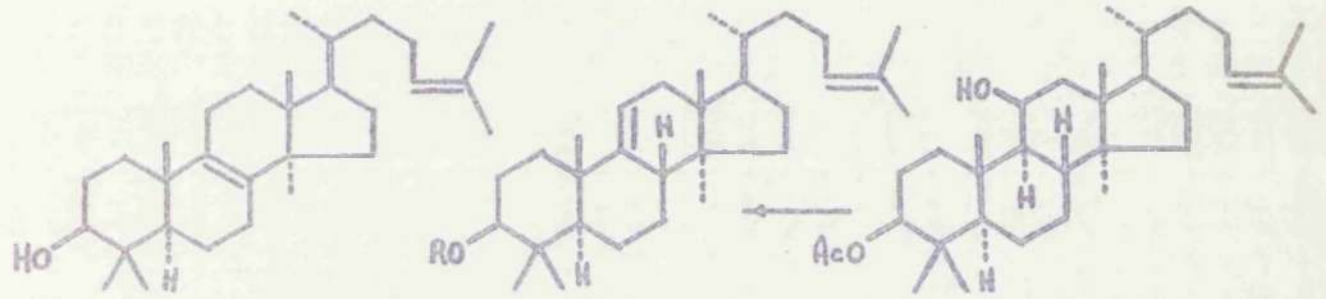
	m.p.	$[\alpha]_D$	λmax.	ε
Dihydroparkeyl acetate	172-173°	+67°	2060 Å.	4,900
Lanost-9(11)-enyl acetate (CXV)				
This Work	173-174	+89	2060	4,300
Voser et al.[91]	170-171	+81		
McGhie et al[93]	177-178	+83		
Bentley et al.[38]	173	+84	2060	4,300
Oxodihydroparkeyl acetate	181-183	+90	2420	12,000
12-Oxolanost-9(11)-enyl acetate (CXVI)				
This Work	183-184	+94	2420	10,100
Bentley et al.[38]	184-185	+91	2420	9,800
Dihydroparkeyl acetate oxide	181-183	+27	-	-
Lanost-9(11)-enyl acetate oxide[38]. (CXXXII)	181-182	+29	-	-
Dehydroparkenyl acetate	164-165	+89	2450	22,700
Lanosta-7:9(11)-dienyl acetate (CXXI, R = C_8H_{17})	165-166	+89	2430	17,400
Tetrahydroparkeyl acetate Lanostanyl acetate(CXXIV)	160-161.5	+40.5	-	-
This Work	156-157	+40.4	-	-
Voser et al.[91]	150-151	+41	-	-
McGhie et al.[93]	156-157	+45	-	-
Bentley et al.[38]	155-156	+41	-	-
Barton et al.[110]	156-157	+40	-	-

The foregoing experiments have established that dihydroparkeyl acetate is identical with lanost-9(11)-enyl acetate (CXV). Parkeol, which contains an isopropylidine group must therefore be lanosta-9(11):24-dien-3β-ol (CXXXIII, R = H). Final confirmation of the structure (CXXXIII, R = H) for parkeol was obtained when the latter was synthesised from lanosterol by H. S. Watson in these laboratories.

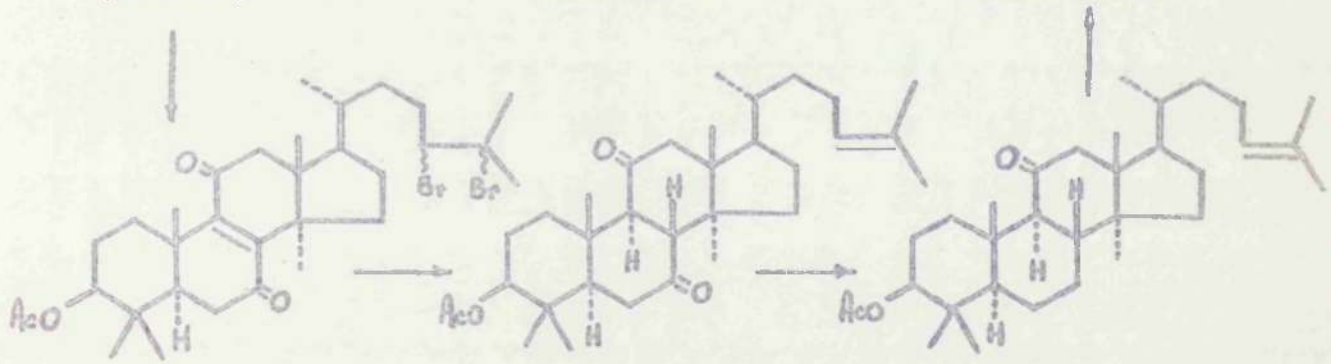
Lanosterol (CXXXIV) was converted via the dibromo-derivative (CXXXV) into 7:11-dioxolanost-24-enyl acetate (CXXXVI) by the method described by Voser, Jeger and Ruzicka[68b]. Reduction of this diketone (CXXXVI) using the Huang-Minlon modification of the Wolff-Kishner method followed by acetylation gave 11-oxolanost--24-enyl acetate (CXXXVII), treatment of which with lithium aluminium hydride in ether followed by acetylation of the crude product at room temperature gave 11β-hydroxylanost-24-enyl acetate (CXXXVIII). Dehydration of the latter was then effected by vigorous treatment with phosphorus oxychloride in pyridine. The product, lanosta-9(11):24-dienyl acetate (CXXXIII, R = Ac) had the same melting point and specific rotation as parkeyl acetate and a mixture of the two specimens showed no depression on melting. Identity was confirmed by comparison of their infrared spectra.

Hydrolysis of the synthetic parkeyl acetate (CXXXIII, R = Ac) gave lanosta-9(11):24-dien-3β-ol (CXXXIII, R = H) identical with

parkeol. Benzoylation then yielded lanosta-9(11):24-dienyl benzoate (CXXXIII, R = Ph.CO) identical with parkeyl benzoate.



(CXXXIV) (CXXXIII) (CXXXVIII)



(CXXXV) (CXXXVI) (CXXXVII)

A comparison of the physical constants of natural and synthetic parkeol and of their corresponding derivatives is given in Table D below.

TABLE D.

	m.p.	$[\alpha]_D$
Parkeol	159.5-160°	+76.8
Lanosta-9(11):24-dien-3β-ol (CXXXIII, R = H)	157-158	+76
Parkeyl Acetate	160-161	+86
Lanosta-9(11):24-dienyl acetate(CXXXIII, R = Ac)	161-162	+86
Parkeyl benzoate	201.5-202	+95.4
Lanosta-9(11):24-dienyl benzoate (CXXXIII,R=Ph.CO)	199 -200	+94

This work further confirms the structure (CXXXIII, R = H) for Parkeol.

EXPERIMENTAL

The melting points are uncorrected. Specific rotations were measured at room temperature in a 1 dm. tube using chloroform as solvent unless otherwise specified. Ultraviolet absorption spectra were measured in absolute ethanol 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 analysts were Dr. A. C. Syme and Mr. Wm. McCorkindale of the Royal College of Science and Technology, Glasgow. C.1.

I. Butyrospermol.

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. To avoid the formation of emulsions during the isolation of the non-saponifiable matter, the following procedure was adopted. 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 then reduced in bulk to about 4 litres by distillation under reduced pressure, washed once with aqueous alcohol (30%) and finally

six times with water to remove soaps. The resulting golden yellow ethereal solution was dried over anhydrous sodium sulphate and evaporated to give the non-saponifiable fraction as a pale brown gum (180 g.). An attempt to isolate butyrospermol by chromatography of this material failed to yield any crystalline fractions.

Butyrospermyl Acetate. - The non-saponifiable fraction (180 g.) was boiled under reflux with acetic anhydride (850 c.c.) 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 c.c.) for 1 hour and left overnight at room temperature. The solid which separated was removed by filtration and rejected. During the filtration a crop of fine granular solid deposited 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). The two fractions were combined and recrystallised a total of nine times from ethanol-ethyl acetate to give

pure butyrospermyl acetate as fine needles (2.1 g.), m.p. 143-145°, $[\alpha]_D$ + 11.5° (c,2.9), unchanged by further crystallisation.

[Found: C,81.7; H,11.4. Calc. for $C_{32}H_{52}O_2$: C,82.0; H,11.2%].

Dihydrobutyrospermyl Acetate. - (a) Butyrospermyl acetate (1.5 g.) in ethyl acetate (200 c.c.) was shaken with hydrogen over acid-free platinum catalyst (from 500 mg. platinum oxide) for 6 hours at room temperature. The filtered solution was evaporated and the residue crystallised twice from chloroform-methanol to give dihydrobutyrospermyl acetate as prismatic needles (1.2 g.), m.p. 135-136°, $[\alpha]_D$ + 11° (c,2.0).

(b) Crude butyrospermyl acetate (m.p. 134-136°, $[\alpha]_D$ + 23°, 5 g.) in ethyl acetate (250 c.c.) was shaken with hydrogen over a platinum catalyst (500 mg.) 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 (220 g.). Elution with the same solvent (2.5 l.) gave a fraction (3.0 g.) which crystallised from chloroform-methanol as prismatic needles (2.74 g.), m.p. and mixed m.p. 134-136°, $[\alpha]_D$ + 10.8° (c,2.6).

Treatment of Dihydrobutyrospermyl Acetate with Chromic Acid. - Dihydrobutyrospermyl acetate (100 mg.) in benzene (5 c.c.) and acetic acid (30 c.c.) was treated dropwise with stirring at room temperature with a solution of chromium

trioxide in acetic acid (7.1 mg./c.c.; ≡ 5 atoms oxygen), added during 30 minutes. After standing overnight, methanol was added and the green solution poured into water and extracted with ether. The neutral product was obtained as a pale yellow gum (95 mg.) which failed to crystallise. Its ultraviolet absorption spectrum showed maxima of equal intensity at 2080 and 2480 Å. The gum was re-treated with chromic acid as described above and the product was chrometographed. No crystalline fractions were obtained.

Dihydroisobutyrospermyl Acetate. - Dihydrobutyrospermyl Acetate (150 mg.) in dry chloroform (25 c.c.) was cooled to 0° in an ice-bath and treated with a stream of dry hydrogen chloride for 2 hours. The solution was diluted with chloroform (50 c.c.), washed with water till neutral, dried over anhydrous sodium sulphate and evaporated. Crystallisation of the residue (145 mg.) from chloroform-methanol gave dihydroisobutyrospermyl acetate as needles (107 mg.), m.p. 124.5-125.5°, $[\alpha]_D$ + 33.6°, (c,1.6). The melting point was undepressed on mixing with an authentic specimen of euph-8-enyl acetate.

Oxidation of Dihydroisobutyrospermyl Acetate with Chromic Acid. - Dihydroisobutyrospermyl acetate (137 mg.) in stabilised acetic acid (80 c.c.) was heated on the steam bath. A solution of chromium trioxide in acetic acid (8 mg./c.c., 10 c.c. ≡ 4.2 atoms oxygen) was added dropwise with stirring during 30 minutes

and heating was continued for a further 90 minutes. The neutral product (140 mg.) isolated by means of ether, was dissolved in light petroleum (15 c.c.) and filtered through a column of alumina (5 g.). Elution with light petroleum-benzene (4:1, 300 c.c.) gave a pale yellow fraction (40 mg.) which after three crystallisations from methanol gave 7:11-dioxo-euph-8-enyl acetate as yellow needles (19 mg.), m.p. 110-111°, $[\alpha]_D$ + 19.7° (c,1.0). The melting point was undepressed on mixing with an authentic specimen prepared by similar oxidation of euph-8-enyl acetate.[106] $\lambda_{max.}$: 2710 Å., (ε: 8,100).

Stability of Euph-8-enyl Acetate to Treatment with Hydrogen Chloride at 0°. - Euph-8-enyl acetate (200 mg.) in dry chloroform (30 c.c.) was cooled to 0° and treated with a vigorous stream of dry hydrogen chloride for 2 hours. The product, isolated as described above for dihydroisobutyrospermyl acetate, crystallised from chloroform-methanol as needles (182 mg.), $[\alpha]_D$ + 33° (c,1.2), m.p. 124-125° alone or mixed with starting material.

Conversion of Dihydroisobutyrospermyl Acetate into iso-Euphenyl Acetate. - A solution of dihydroisobutyrospermyl acetate (82 mg.) in a mixture of acetic acid and concentrated hydrochloric acid (20:1, 3 c.c.) was kept at 100° for 3 hours. The product was isolated by means of ether and crystallised from chloroform-methanol to give isoeuphenyl acetate as plates (58 mg.),

$[\alpha]_D$ - 10° (c,1.6), m.p. 111° alone or mixed with an authentic specimen prepared from euph-8-enyl acetate in a similar manner.[108]

Treatment of Dihydroisobutyrospermyl acetate with Perbenzoic Acid. - Dihydroisobutyrospermyl acetate (100 mg.) was dissolved in a chloroform solution of perbenzoic acid (118 mg./c.c., 4 c.c.) and the solution kept at 0° for 2 days then at room temperature for a further 2 days. The solution was diluted with chloroform (100 c.c.), washed with potassium carbonate solution (10%), water and dried over anhydrous sodium sulphate. Removal of the solvent gave a gum (95 mg.) which crystallised from chloroform-methanol as colourless needles, m.p. 159-169°. Three further crystallisations from methanol gave 8ξ:9ξ-epoxyeuphanyl acetate as needles (64 mg.), m.p. and mixed m.p. 175-177°, $[\alpha]_D$ + 62° (c,0.9). The product gave no colour with tetranitromethane in chloroform and was transparent to ultraviolet light.

Conversion of Butyrospermyl Acetate into Euphyl Acetate (Eupha-8:24-dienyl Acetate). - Butyrospermyl acetate (200 mg.) in chloroform (25 c.c.) was treated at 0° with a 1% solution of bromine in chloroform (5.82 c.c. ≡ 1 mol.). Dry hydrogen chloride was passed through the colourless solution for 1½ hours at 0°. The mixture was diluted with chloroform (100 c.c.), washed with sodium hydrogen carbonate solution, water, and dried over anhydrous sodium sulphate. Evaporation of the chloroform

under reduced pressure gave a colourless gum which failed to crystallise when sprinkled with methanol. A solution of this gum in acetic acid (27 c.c.) was boiled under reflux with zinc dust (2 g.) for 2 hours. The filtered solution was diluted with water and the product isolated as a pale yellow gum by means of ether. After four crystallisations from chloroform-methanol, euphyl acetate was obtained as needles (40 mg.), m.p. and mixed m.p. 106.5-107.5°, $[\alpha]_D$ + 40° (c,0.8).

Hydrogenation of Butyrospermyl Acetate in Acetic Acid. - Butyrospermyl acetate (20 mg.) in glacial acetic acid (100 c.c.) was shaken with hydrogen over a platinum catalyst (from 200 mg. platinum oxide) for 30 hours, the temperature being maintained at 60° throughout. The filtered solution was evaporated under reduced pressure and the residue (20 mg.) crystallised from chloroform-methanol as needles, m.p. 115-116°. Two further crystallisations gave euph-8-enyl acetate as needles, m.p. and mixed m.p. 120-122°, $[\alpha]_D$ + 25° (c,0.6).

Treatment of Dihydrobutyrospermyl Acetate with Osmium Tetroxide. - Dihydrobutyrospermyl acetate (1.0 g.) in dry pyridine (10 c.c.) was treated with a solution of osmium tetroxide in dry ether (1.0 g.: 12.4 c.c.; 10 c.c. ≡ 1.5 mol.), and the mixture kept in complete darkness at room temperature for 14 days. The resulting greenish-brown suspension was diluted with dry ether (50 c.c.) and heated under gentle reflux

while a solution of lithium aluminium hydride (2.25 g.) in ether was added dropwise during 30 minutes. Heating was continued for a further hour before excess lithium aluminium hydride was destroyed by the cautious addition of ethyl acetate and water. The mixture was finally poured into water and the resulting dark brown suspension was extracted with ether. The extract was washed with water, dried and evaporated under reduced pressure to yield a dark brown gum which was acetylated using pyridine (15 c.c.) and acetic anhydride (15 c.c.) at 100° for 2 hours. A solution of the dry acetylated product (950 mg.) in light petroleum (100 c.c.) was chromatographed on alumina (27 g.). The fraction (300 mg.) eluted with light petroleum (400 c.c.) gave dihydrobutyrospermyl acetate as prismatic needles m.p. and mixed m.p. 134-135°, $[\alpha]_D$ + 10° (c,1.5). Elution with light petroleum-benzene (4:1, 300 c.c.; 1:1, 250 c.c.) and finally with pure benzene (150 c.c.) gave a fraction (462 mg.) crystallisation of which from chloroform-methanol gave the triol diacetate as prismatic needles, m.p. 181-182°, $[\alpha]_D$ - 82° (c,1.2). The product gave no colour with tetranitromethane in chloroform and was transparent to ultraviolet light.

[Found: C,74.9; H,10.9. $C_{34}H_{58}O_6$ requires C,74.7; H,10.7%]

Hydrolysis of the triol diacetate with either methanolic

potassium hydroxide solution (10%) or with lithium aluminium hydride in ether gave the triol as a colourless gum, acetylation of which (either at 20° or at 100°) regenerated the triol diacetate.

Eupha-7:9(11)-dienyl Acetate from the Triol Diacetate. - (a) A mixture of the triol diacetate (200 mg.), acetic anhydride (25 c.c.), and freshly fused potassium acetate (300 mg.) was boiled under reflux for 4 hours, and left overnight at room temperature. The product, isolated by means of ether, was dissolved in light petroleum (50 c.c.) and chromatographed on alumina (6 g.). Elution with light petroleum (75 c.c.) gave a fraction (97 mg.) which crystallised from methanol to give eupha-7:9(11)-dienyl acetate as needles (60 mg.), m.p. and mixed m.p. 111-112°, $[\alpha]_D$ - 78° (c, 1.0). [The authentic specimen used for the comparison was prepared by treating 8β:9β-epoxyeuphanyl acetate with mineral acid as described by Barbour, Bennett, and Warren[55]]. The compound gave a reddish brown colour with tetranitromethane in chloroform and showed light absorption maxima at 2320, 2400, and 2470 Å., (ε: 15,000 17,000, and 10,500).

(b) The triol diacetate (125 mg.) was kept at 100° under vacuum for 41 hours. The solid, although unchanged in appearance, had m.p. 120-155° and showed light absorption maxima at 2320, 2400, and 2470 Å., (ε: 5,900, 6,500, and 4,200). The material

in light petroleum (25 c.c.) was chromatographed on alumina (4 g.). The fraction (40 mg.), eluted with light petroleum, crystallised from methanol to give eupha-7:9(11)-dienyl acetate as needles m.p. and mixed m.p. 111-112°. Light petroleum-benzene mixtures eluted fractions, crystallisation of which from chloroform-methanol gave the triol diacetate (60 mg.) as needles m.p. and mixed m.p. 177-178°.

(c) Sublimation of the triol diacetate (100 mg.) under high vacuum (0.001-0.005 mm.) at 135-165° gave a product, [m.p. 70-90°, λ max. 2060, 2320, 2400, and 2470 Å. (ε:2,100, 4,600, 5,000, and 3,200)] which was dissolved in light petroleum (25 c.c.) and chromatographed on alumina (3 g.). The fraction (47 mg.) eluted with light petroleum (150 c.c.) gave eupha-7:9(11)-dienyl acetate as needles from methanol, m.p. and mixed m.p. 109-110°. Elution with light petroleum-benzene (4:1, 150 c.c.) gave a fraction which failed to crystallise and which showed low intensity light absorption at 2060 Å. Elution with benzene (150 c.c.) gave a fraction (30 mg.) which crystallised from chloroform-methanol to give the triol-diacetate m.p. and mixed m.p. 177-178°.

(d) A solution of the triol diacetate (100 mg.) in acetic acid (10 c.c.) was kept at 100° with zinc dust (600 mg.) for 2 hours. The filtered solution was poured into water and the product, isolated by means of ether, crystallised from methanol

to give the 7:9(11)-dienyl acetate (80 mg.) as needles, m.p. and mixed m.p. 109-111°, $[\alpha]_D$ - 77° (c,1.2).

(e) The triol diacetate (50 mg.) in stabilised acetic acid (20 c.c.) was treated dropwise with a solution of chromium trioxide in acetic acid (5 mg./c.c., 1.2 c.c. ≡ 1 atom oxygen) and the mixture kept at room temperature for 18 hours. The product, isolated in the usual way, was dissolved in light petroleum (25 c.c.) and chromatographed on alumina (3 g.). The fraction (11.5 mg.) eluted with light petroleum (100 c.c.) crystallised from methanol to give the 7:9(11)-dienyl acetate as needles, m.p. and mixed m.p. 110-111°. No other crystalline fraction was obtained.

(f) The triol diacetate (50 mg.) in acetic acid (15c.c.) was treated with a mixture of concentrated hydrochloric acid and acetic acid (1:5, 6 c.c.) and the solution allowed to stand at room temperature for 3 hours. The product, isolated by means of ether, was dissolved in light petroleum (25 c.c.) and filtered through a column of alumina (4 g.). Light petroleum (100 c.c.) eluted a fraction (24 mg.) which crystallised from methanol to give supha-7:9(11)-dienyl acetate as needles m.p. 111-112° (no depression). (The triol-diacetate was recovered quantitatively after treatment with glacial acetic acid at 20° for 18 hours.).

Treatment of the Triol Diacetate with Phosphorus Oxychloride. - The triol diacetate (100 mg.) in pyridine (5 c.c.) was treated with a mixture of phosphorus oxychloride (1 c.c.) and pyridine (5 c.c.) and the solution was allowed to stand at room temperature overnight. The product (100 mg.), isolated by means of ether, crystallised from methanol to give the triol diacetate (80 mg.) as needles, m.p. and mixed m.p. 177-178°, $[\alpha]_D$ - 80°. The experiment was repeated under reflux for 2 hours. Again a quantitative yield of starting material was obtained.

Dihydrobutyrospermyl Acetate Oxide. - Dihydrobutyrospermyl acetate (250 mg.) in ethyl acetate (60 c.c.) was treated at -30° with a moderate stream of ozonised oxygen for 1 hour. The solution was diluted with ethyl acetate (100 c.c.), washed with water and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure gave a white solid which crystallised from methanol to give dihydrobutyrospermyl acetate oxide as plates (160 mg.), m.p. 154-155°, $[\alpha]_D$ - 21.5° (c,1.0 in benzene). The oxide did not show selective absorption between 2000 and 3000 Å. It gave no colour with tetranitromethane in ethyl acetate, but its solution in chloroform containing this reagent gradually developed a deep yellow colouration.

[Found: C,78.8; H,11.2. $C_{32}H_{54}O_3$ requires C,79.0; H,11.2%]

Eupha-7:9(11)-dienyl Acetate from Dihydrobutyrospermyl Acetate Oxide. - The oxide (35 mg.) in chloroform (5 c.c.) was treated at 0° with dry hydrogen chloride for 5 minutes, then kept at room temperature for 2 hours. The resulting yellow solution was diluted with chloroform (50 c.c.), washed with 10% sodium carbonate solution, water, and dried (Na_2SO_4). Evaporation of the solvent gave the product as a yellow gum which was dissolved in light petroleum (25 c.c.) and chromatographed on alumina (3 g.). Elution with light petroleum (50 c.c.) gave a fraction (23 mg.) which crystallised from methanol to give eupha-7:9(11)-dienyl acetate as needles m.p. 110-111°, (no depression), λmax. 2320, 2400, and 2470 Å., (ε: 16,000, 18,000, and 11,000).

Treatment of Dihydrobutyrospermyl Acetate with Selenium Dioxide. - Dihydrobutyrospermyl acetate (100 mg.) in acetic acid (15 c.c.) was boiled under reflux with selenium dioxide (60 mg.) for 3 hours. The dark yellow solution was filtered, poured into water and extracted with ether. The extract was washed with 10% sodium carbonate solution, water, and dried (Na_2SO_4). Evaporation under reduced pressure gave a pale yellow gum which crystallised from methanol to give eupha-7:9(11)--dienyl acetate as needles identified by m.p., mixed m.p., specific rotation, and ultraviolet absorption.

7-Oxoapoeuph-14-enyl Acetate. - Dihydrobutyrospermyl acetate (2 g.) in methylene chloride (20 c.c.) and acetic acid (250 c.c.) was treated dropwise during 30 minutes at room temperature with a solution of chromium trioxide in acetic acid (12 mg./c.c., 70.3 c.c. ≡ 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 c.c.) and chromatographed on alumina (60 g.). Elution with light petroleum (1200 c.c.) gave fractions (total 442 mg.) which yielded dihydrobutyrospermyl acetate as prismatic needles m.p. and mixed m.p. 134-135°, on crystallisation from chloroform-methanol. Elution with light petroleum-benzene (9:1, 1350 c.c.; then 4:1, 750 c.c.) gave fractions (450 mg.) each of which showed selective absorption between 2500 and 2700 Å. Fractional crystallisation of these fractions 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, 1500 c.c.) 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 carbon

tetrachloride): bands at 1640 cm.$^{-1}$ (isolated double bond), 1710 cm.$^{-1}$ (six-membered ring-ketone), and 1735 cm.$^{-1}$ (acetate). The compound gave a bright yellow colour with tetranitromethane [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.

Treatment of 7-Oxoapoeuph-14-enyl Acetate with Chromic Acid. - 7-Oxoapoeuph-14-enyl acetate (100 mg.) in methylene chloride (1 c.c.) and acetic acid (30 c.c.) was treated dropwise during 15 minutes with chromium trioxide in acetic acid (5 mg./c.c., 3 c.c. ≡ 1.1 atoms oxygen), and the orange coloured mixture kept at 20-25° for 24 hours. The chromium trioxide was not reduced and 7-oxoapoeuph-14-enyl acetate m.p. and mixed m.p. 118-120° was recovered quantitatively from the solution.

Attempts to Bring the Double Bond in 7-Oxoapoeuph-14-enyl Acetate into Conjugation with the Carbonyl Group. -

(a) 7-Oxoapoeuph-14-enyl acetate (30 mg.) was dissolved in a mixture of acetic acid and concentrated sulphuric acid (75 c.c.: 6 drops; 1.7 c.c.) and the solution kept at 20° for 24 hours. The product (30 mg.), isolated in the usual way, crystallised from methanol as needles, m.p. 119-120° alone or mixed with starting material. The same result was obtained using dry hydrogen chloride -chloroform at 0° for 2 hours.

(b) A solution of 7-oxoapoeuph-14-enyl acetate (30 mg.) in 3%

methanolic potassium hydroxide (10 c.c.) was boiled under reflux for 2 hours. The hydrolysis product was isolated in the usual way and acetylated with acetic anhydride and pyridine for 1 hour at 100°. The acetate was crystallised from methanol, yield-ing 7-oxoapoeuph-14-enyl acetate (28 mg.) as needles, m.p. and mixed 119-120°.

(c) 7-Oxoapoeuph-14-enyl acetate (20 mg.) in a mixture of concentrated hydrochloric acid and acetic acid (1:20; 2 c.c.) was kept at 100° for 3 hours. The solution was poured into water and the product (20 mg.), isolated by means of ether, was crystallised from methanol to yield 7-oxoiseuph-13(17)-enyl acetate as plates, m.p. 112-113°, $[\alpha]_D$ - 50° (c, 1.3). A mixture with 7-oxoapoeuph-14-enyl acetate (m.p. 118-120°) had m.p. 93-105°. 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%].

Wolff-Kishner Reduction of 7-Oxoiseuph-13(17)-enyl Acetate. - 7-Oxoiseuph-13(17)-enyl acetate (90 mg.) in diethylene glycol (10 c.c.) was mixed with a solution obtained by reaction of sodium (250 mg.) with diethylene glycol (15 c.c.) and the mixture heated to 200°. Anhydrous hydrazine, prepared by refluxing hydrazine hydrate (100%) over an equal weight of sodium hydroxide in an atmosphere of nitrogen for 3 hours, was

distilled into the reaction mixture until it refluxed gently at 180°. After boiling for 18 hours at 180°, the mixture was distilled until the temperature reached 210°, and refluxing was then continued for 24 hours. The solution was cooled, poured into water and extracted with ether. The ether extract was washed with dilute hydrochloric acid (3N), with water till neutral, and dried over anhydrous sodium sulphate. Evaporation of the extract under reduced pressure gave the product as a pale brown gum (87 mg.) which was acetylated with acetic anhydride and pyridine at 100°. A solution of the dry acetylated product in light petroleum (25 c.c.) was chromatographed on alumina (5 g.). Elution with light petroleum (175 c.c.) gave a crystalline fraction (37 mg.) recrystallisation of which from methanol gave iso-euph-13(17)-enyl acetate as hexagonal plates, m.p. and mixed m.p. 110°, $[\alpha]_D$ - 9° (c,2.0).
[Found: C,81.7; H,11.7. Calc. for $C_{32}H_{54}O_2$: C,81.6; H,11.6%].

iso-Eupha-11:13(17)-dienyl Acetate.[1075] - iso-Euph-13(17)-enyl acetate (70 mg.) in acetic acid (6.5 c.c.) was mixed with a solution of selenium dioxide (35 mg.) in the minimum of water and the solution boiled under reflux for 3 hours. The product, isolated in the usual way, was dissolved in light petroleum (50 c.c.) and chromatographed on alumina (4 g.). The fraction (30 mg.) eluted with light petroleum, crystallised from methanol to give iso-eupha-11:13(17)-dienyl acetate (20 mg.) as

needles m.p. 93-94°, $[\alpha]_D$ + 16° (c,0.8), $\lambda_{max.}$ 2470, 2550, and 2640 Å. (ε:18,000, 19,500, and 14,000).

7-Oxoisoeupha-11:13(17)-dienyl Acetate. - To a solution of 7-oxoisoeuph-13(17)-enyl acetate (140 mg.) in acetic acid (14 c.c.) was added selenium dioxide (80 mg.) dissolved in the minimum of water, and the mixture was refluxed for 3 hours. The product was isolated by means of ether and its solution in light petroleum (300 c.c.) was chromatographed on alumina (6 g.). Elution with light petroleum-benzene (4:1; 350 c.c.) gave a fraction (32 mg.) which was crystallised twice from methanol to give 7-oxoisoeupha-11:13(17)-dienyl acetate as plates, m.p. 107-109°, $[\alpha]_D$ - 44.5° ± 5° (c,0.2), $\lambda_{max.}$ 2470, 2550, and 2640 Å. (ε:19,000, 21,000, and 14,500). The compound gave a deep reddish-brown colour with tetranitromethane in chloroform. [Found: C,79.4; H,10.45. $C_{32}H_{50}O_3$ requires C,79.6; H,10.4%].

Wolff-Kishner Reduction of 7-Oxoapoeuph-14-enyl Acetate. - 7-Oxoapoeuph-14-enyl acetate (125 mg.) was reduced as described above for 7-oxoisoeuph-13(17)-enyl acetate. The product was isolated by means of ether and acetylated to give a pale yellow gum (130 mg.) which was dissolved in light petroleum (50 c.c.) and chromatographed on alumina (4 g.). Elution with light petroleum (150 c.c.) gave a fraction (74 mg.) which, when crystallised twice from methanol, gave apoeuph-14-enyl acetate

as needles, m.p. 114-115°, $[\alpha]_D$ - 12° (c,1.1). A mixture with isoeuph-13(17)-enyl acetate had m.p. 85-90°. 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%]

Conversion of apoEuph-14-enyl Acetate into isoEuph-13(17)-enyl Acetate. - apoEuph-14-enyl acetate (14 mg.) in dry chloroform (3 c.c.) 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 c.c.) filtered through alumina (3 g.). Light petroleum (200 c.c.) eluted a fraction (11.6 mg.) which crystallised from methanol to yield isoeuph-13(17)-enyl acetate as plates, m.p. and mixed m.p. 109-110°, $[\alpha]_D$ - 10° (c,0.4). A mixture with apoeuph-14-enyl acetate (m.p. 114-115°) had m.p.88-102°.

Oxidation of 7-Oxoapoeuph-14-enyl Acetate with Selenium Dioxide. - A boiling solution of 7-oxoapoeuph-14-enyl acetate (118 mg.) in acetic acid (4.8 c.c.) was treated dropwise with a solution of selenium dioxide (60 mg.) in the minimum of water and acetic acid (2 c.c.). The mixture was refluxed for 2 hours, filtered, diluted with water and extracted with ether. The extract was washed with saturated sodium hydrogen carbonate solution, water and dried (Na_2SO_4). Evaporation of the ether

under reduced pressure gave the product as a pale yellow gum which was dissolved in light petroleum (25 c.c.) and chromatographed on alumina (4 g.). The fractions (102 mg.) eluted with light petroleum (450 c.c.) and light petroleum-benzene (4:1; 200 c.c.) crystallised from methanol to give 7-oxoapoeupha--5:14-dienyl acetate as prisms, m.p. 103-104°, $[\alpha]_D$ - 126° (c,1.2). The compound gave a yellow colour with tetranitromethane in chloroform and showed light absorption maxima at 2080 and 2350 Å., (ε: 9,000 and 14,100).

[Found: C,79.4; H,10.4. $C_{32}H_{50}O_3$ requires C,79.6; H,10.4%].

Conversion of 7-Oxoapoeupha-5:14-dienyl Acetate into 7-Oxoisoeupha-5:13(17)-dienyl Acetate. - 7-Oxoapoeupha-5:14--dienyl acetate (217 mg.) in a mixture of concentrated hydrochloric acid and acetic acid (1:20; 10 c.c.) was kept at 100° for 2 hours. The product (212 mg.), isolated by means of ether, was dissolved in light petroleum (25 c.c.) and chromatographed on alumina (4 g.). Elution with light petroleum and mixtures of light petroleum with up to 50% of benzene gave fractions (158 mg.) which crystallised from methanol to give 7-oxoisoeupha-5:13(17)-dienyl acetate (105 mg.) as prisms, m.p. 119-120°, $[\alpha]_D$ - 52° (c,2.1). The compound gave a bright yellow colour with tetranitromethane in chloroform and showed light absorption maxima at 2080 and 2380 Å., (ε: 10,400 and 13,500).

[Found: C,79.3;- H,10.3. $C_{32}H_{50}O_3$ requires C,79.6; H,10.4%].

Treatment of 7-Oxoisoeupha-5:13(17)-dienyl Acetate with Selenium Dioxide. - 7-Oxoisoeupha-5:13(17)-dienyl acetate (90 mg.) in acetic acid (4 c.c.) was heated to the boiling point and treated dropwise with a solution of selenium dioxide (90 mg.) in the minimum of water and acetic acid (1.5 c.c.). The mixture was boiled under reflux for 2 hours and the product (95 mg.) isolated in the usual way as a dark brown gum. This was dissolved in light petroleum-benzene (4:1; 300 c.c.) and chromatographed on alumina (8 g.). Development of the column in the usual manner failed to yield any crystalline fractions. The fraction (39 mg.) eluted with methanol (600 c.c.) was a brown gum with acidic characteristics.

Lanost-7-enyl Acetate (with W. Hamilton, B.Sc.). - This was prepared using the original method of Marker, Wittle, and Mixon.[84] It was obtained as plates, from methanol-ethyl acetate, m.p. 144-145°, $[\alpha]_D$ + 33.2° (c,2.6). Barton, Fawcett, and Thomas[78] give m.p. 145°, $[\alpha]_D$ + 32°. Treatment of the acetate with lithium aluminium hydride in ether gave lanost-7-en-3β-ol which crystallised from methanol-ethyl acetate as needles, m.p. 157-158°, $[\alpha]_D$ + 10.4° (c,1.5). Woodward, Patchett, Barton, Ives, and Kelly[201] give m.p. 162-163°, $[\alpha]_D$ + 10° for this compound. Treatment of the alcohol with benzoyl chloride and

pyridine gave lanost-7-enyl benzoate as needles (from methanol), m.p. 207-209°, $[\alpha]_D$ + 50° (c,1.9). Woodward[101] gives m.p. 207-208°, $[\alpha]_D$ + 51°.

Lanost-7-en-3-one, (with W. Hamilton, B.Sc.). - A solution of lanost-7-en-3β-ol (2 g.) in pyridine (40 c.c.) was kept for 24 hours at 16° with the complex prepared from chromium trioxide (2 g.) and pyridine (20 c.c.). 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[84] gives m.p. 149° and recently Barton[64] has quoted m.p. 144-146°, $[\alpha]_D$ - 15° (c,2.04), for this compound. [Found: C,84.7; H,12.0. Calc. for $C_{30}H_{50}O$. C,84.4; H,11.8%].

Euphol Derivatives. - All the authentic euphol derivatives described in this section were prepared from euphol isolated from the commercial latex known as Gum Euphorbia, by the method of Newbold and Spring.[49] Euphol, (eupha-8:24-dien-3β-ol) crystallised from acetone as needles, m.p. 114-116°, $[\alpha]_D$ + 33° (c,1.7). Newbold and Spring[49] give m.p. 116°, $[\alpha]_D$ + 32°. Treatment of euphol with acetic anhydride and pyridine at 100° and crystallisation of the product from chloroform-methanol gave euphyl acetate as needles, m.p. 106-108°, $[\alpha]_D$ + 40° (c,1.2). Newbold and Spring[49] give m.p. 109°, $[\alpha]_D$ + 41°. Hydrogenation of euphyl acetate either in ethyl acetate-acetic acid (1:1) or in

ethyl acetate alone, over a platinum catalyst gave euph-8-enyl acetate which crystallised from chloroform-methanol as needles m.p. 124-126°, $[\alpha]_D$ + 34° (c,1.1). Newbold and Spring[49] give m.p. 124°, $[\alpha]_D$ + 34.5°.

7:11-Dioxoeuph-8-enyl Acetate.[106]- Euph-8-enyl acetate (11 g.) in methylene chloride (56 c.c.) and acetic acid (225 c.c.) was treated dropwise at room temperature during 30 minutes with a solution of chromium trioxide (11 g.) in acetic acid (90%; 170 c.c.). The mixture was kept at 50° for 4 hours and the neutral product (11.1 g.) isolated in the usual way by means of ether. A solution of this material in light petroleum (150 c.c.) was chromatographed on alumina (300 g.). Elution with light petroleum-benzene (4:1; 1600 c.c. and 1:1, 600 c.c.) gave fractions (total 7.2 g.) which crystallised from methanol to give 7:11-dioxoeuph-8-enyl acetate as yellow needles, m.p. 111-112°, $[\alpha]_D$ + 21° (c,1.0). Light absorption: $\lambda_{max.}$ at 2720 Å., (ε:8,750). Christen et al.,[106] give m.p. 113-114°, $[\alpha]_D$ + 20°.

11-Oxoeuph-8-enyl Acetate.[107b] - 7:11-dioxoeuph-8-enyl acetate (1.5 g.) in redistilled diethylene glycol (75 c.c.) and hydrazine hydrate (100%; 1.5 c.c.) was heated at 185-190° for 1 hour, cooled to 70°, and a solution of sodium (1.5 g.) in diethylene glycol (25 c.c.) added. The mixture was then boiled

under reflux at 220° for a further 6 hours. The product, isolated by means of ether, was treated with acetic anhydride and pyridine at 100° and a solution of the dry acetylated material (1.5 g.) in light petroleum-benzene (9:1; 100 c.c.) was chromatographed on alumina (45 g.). Elution with light petroleum-benzene (9:1, 900 c.c.; 4:1, 700 c.c.; 3:2, 200 c.c.) gave fractions (1.2 g.) which crystallised from methanol to give 11-oxoeuph-8-enyl acetate as stout blades (939 mg.), m.p. 127-129°, $[\alpha]_D$ + 26° (c,2.0). Light absorption: max. at 2570 Å., (ε : 8,500). Barton[107b] gives m.p. 130-131°, $[\alpha]_D$ + 28°.

Euph-9(11)-enyl Acetate. - 11-oxoeuph-8-enyl acetate (2.5 g.) in diethylene glycol (100 c.c.) was mixed with a solution obtained by reaction of sodium (7.2 g.) with diethylene glycol (300 c.c.) and the mixture heated to 200°. Anhydrous hydrazine was distilled in until the mixture refluxed gently at 180°. After boiling for 18 hours at this temperature, the mixture was distilled until the temperature reached 216°, and refluxing was then continued for 24 hours. The product, a brown gum isolated by means of ether, was acetylated in the usual way and a solution of the dry acetylated material (2.4 g.) in light petroleum (100 c.c.) was chromatographed on alumina (75 g.). Elution with light petroleum (400 c.c.) gave a fraction (350 mg.) which was crystallised four times from acetone-methanol to yield euph-9(11)-enyl acetate as needles, m.p. 99-100°, $[\alpha]_D$ - 59° (c,1.7).

Light absorption: max. at 2030 Å., (ε:4,000). The compound gave a yellow colour with tetranitromethane in chloroform. [Found: C,81.5; H,11.6. $C_{32}H_{54}O_2$ requires, C,81.6; H,11.6%]. Continued elution of the column with light petroleum (600 c.c.) and light petroleum-benzene (9:1; 1600 c.c.) gave fractions (769 mg.) which crystallised from methanol to give unchanged 11-oxoeuph-8-enyl acetate as blades, m.p. and mixed m.p. 126-127°.

Treatment of Euph-9(11)-enyl Acetate with Mineral Acid. - (a) Euph-9(11)-enyl acetate (50 mg.) in dry chloroform (10 c.c.) was treated at 0° with a stream of dry hydrogen chloride for 2 hours. The solution was diluted with ether (100 c.c.), washed with saturated sodium hydrogen carbonate solution, water, and dried (Na_2SO_4). Evaporation of the ether gave a pale yellow gum (50 mg.) which was dissolved in light petroleum (20 c.c.) and chromatographed on alumina (4 g.). Elution with light petroleum (100 c.c.) gave fractions (44 mg.) which, after two crystallisations from acetone-methanol, gave unchanged euph-9(11)--enyl acetate as needles, m.p. and mixed m.p. 98-100°.

(b) Euph-9(11)-enyl acetate (55 mg.) in a mixture of acetic acid and concentrated hydrochloric acid (20:1; 10 c.c.) was kept at 100° for 3 hours. The solution gradually developed a greenish yellow colour which faded to pale yellow after two hours. The product, isolated in the usual way, was dissolved in light

petroleum (20 c.c.) and filtered through a column of alumina (4 g.). Elution with the same solvent (120 c.c.) gave a fraction (36 mg.) which crystallised from acetone-methanol to give isoeuph-13(17)-enyl acetate as plates, m.p. 111-112°, $[\alpha]_D$ - 9.2° (c,1.03). A mixture with authentic isoeuph-13(17)--enyl acetate showed no depression in melting point but a mixture with euph-9(11)-enyl acetate (m.p. 99-100°) had m.p. 82-95°.

Treatment of Euph-9(11)-enyl Acetate with Selenium Dioxide. - Euph-9(11)-enyl acetate (55 mg.) in boiling acetic acid (10 c.c.) was treated with a solution of selenium dioxide (50 mg.) in the minimum of water, and acetic acid (2 c.c.) and the mixture refluxed for 10 hours. The product, a pale yellow gum, was dissolved in ether (25 c.c.) and filtered through a short column of alumina (4 g.). Elution with the same solvent gave a fraction (52 mg.) which was crystallised three times from methanol to yield eupha-7:9(11)-dienyl acetate as needles, m.p. 108.5-109°, (no depression). Light absorption: max. at 2320, 2390, and 2460 Å., (ε: 14,600, 16,100, and 10,500).

Oxidation of Euph-9(11)-enyl Acetate with Chromic Acid. Euph-9(11)-enyl acetate (89 mg.) in stabilised acetic acid (9 c.c.) was treated dropwise at 100° during 10 minutes with a solution of chromium trioxide in acetic acid (4.4 mg./c.c.; 12 c.c. ≡ 4 atoms oxygen). The mixture was then boiled under

reflux for 1 hour and allowed to stand overnight at room temperature. A little methanol was added; the mixture was evaporated to dryness under reduced pressure and the product, a pale yellow gum, was isolated by means of ether. A solution of the gum in light petroleum (20 c.c.) was chromatographed on alumina (5 g.). Elution with light petroleum (200 c.c.) and light petroleum-benzene (9:1; 100 c.c.) gave fractions (10 mg.) which on crystallisation from acetone-methanol yielded unchanged euph-9(11)-enyl acetate as fine needles m.p. and mixed m.p. 96-98°. Elution with light petroleum-benzene (4:1; 230 c.c.; 1:1, 180 c.c.) gave fractions (30 mg.) which crystallised from methanol as needles, m.p. 162-163°. Two recrystallisations of the material from methanol gave 12-oxoeuph-9(11)-enyl acetate as needles, m.p. 166-167°, $[\alpha]_D$ - 66.4° (c, 0.9). The compound gave no colour with tetranitromethane. Light absorption: max. at 2400 Å., (ε: 10,700)

[Found: C, 79.0; H, 10.9. $C_{32}H_{52}O_3$ requires C, 79.3; H, 10.8%].

II PARKEOL.

The Isolation of Parkeyl Acetate from Shea-nut Fat. - The non-saponifiable fraction of shea-nut fat (182 g.), obtained as described above (p. 94), was boiled under reflux for 1½ hr. with redistilled acetic anhydride (875 c.c.) and the resulting solution kept at 20-25° for 18 hr. The semi-crystalline solid

which separated was removed by filtration. During this filtration, a second crop of solid separated from the filtrate and, after one hour, was collected, washed with cold methanol (25 c.c.) and dried to give a fine, granular solid (fraction A, 4.96 g.), m.p. 130-145°. The filtrate was then kept at 16° for 48 hr. when a further crop of solid, (fraction B, 5.3 g.), m.p. 112-150°, was obtained. Fractions A and B were combined, dried by co-distillation with benzene, and dissolved in light petroleum (150 c.c.). This solution was percolated through a column (3.25 x 67 cm.) of alumina (500 g.) and the chromatogram developed as indicated in the summary below.

Fraction	Eluant	Vol. c.c.	Wt. g.	Description	m.p.
1-5	Light petroleum	2250	0.140	Gum	-
6-17	Light petroleum -benzene (9:1)	5400	4.495	Crystalline mixtures	130-145°
18-25	Light petroleum -benzene (3:1)	3600	2.005	Crystalline mixtures	130-150°
26-27	Light petroleum -benzene (3:2)	400	0.458	Crystalline mixtures	130-155°
28-35	Light petroleum -benzene (3:2)	1600	0.763	Plates from ether-methanol	145-153°
36-40	Light petroleum -benzene (2:3)	1000	0.152	Plates from ether-methanol	147-152°
41-46	Light petroleum -benzene (1:4)	1000	0.150	Plates from ether-methanol	146-152°
47-52	Benzene	1400	0.114	White solid	above 160°
53-67	Benzene-ether mixtures	3000	0.234	Gum	-
68	Methanol	400	1.642	Crystals from methanol	150-154°

Parkeyl Acetate. - Fractions (28-46) were combined and crystallised several times from ether-methanol to give almost pure parkeyl acetate (450 mg.) as lustrous plates, m.p. 157-158°, $[\alpha]_D$ + 87° (c,2.8). Pure material was obtained by hydrolysis of the derived benzoate and acetylation as described below.

Parkeol. - (i) Fraction (68) after many recrystallisations from methanol gave parkeol as felted needles, m.p. 159-161°, $[\alpha]_D$ + 77°, (c,1.7).

(ii) Parkeyl acetate (m.p. 157-158°; 100 mg.) in benzene (1 c.c.) was boiled under reflux with a methanolic solution of potassium hydroxide (3%; 20 c.c.) for 3 hr. The product, isolated in the usual way, crystallised from methanol to give parkeol as felted needles (60 mg.) m.p. 161-163°, $[\alpha]_D$ + 74.8° (c,1.5).

(iii) Parkeyl acetate (m.p. 157-158°, 430 mg.) in dry ether (20 c.c.) was added to a suspension of lithium aluminium hydride (500 mg.) in dry ether (40 c.c.) and the mixture refluxed gently for 45 minutes. Ether (100 c.c.) was added and the excess reagent decomposed by the cautious addition of ice-water. The ethereal solution was washed with dilute sulphuric acid (5N), water, and dried (Na_2SO_4). Evaporation of the ether under reduced pressure gave parkeol which crystallised from methanol as needles, (360 mg.), m.p. 161-163°, $[\alpha]_D$ + 75° (c,1.6). The parkeol thus obtained was further purified by hydrolysis of the derived benzoate as described below.

Parkeyl Benzoate. - Parkeol (m.p. 161-163°, 400 mg.) was treated at 100° for 2 hours with a mixture of benzoyl chloride (1 c.c.) and pyridine (7 c.c.). The crude benzoate was isolated by means of ether as a pale yellow solid (502 mg.) which was dissolved in light petroleum (25 c.c.) and chromatographed on alumina (15 g.). Elution with light petroleum (700 c.c.) gave a fraction (400 mg.) which crystallised from chloroform-methanol as needles, m.p. 198-199°, $[\alpha]_D$ + 94° (c,1.3). Five recrystallisations of this material from chloroform-methanol gave pure parkeyl benzoate as needles, m.p. 201.5-202°, $[\alpha]_D$ + 95.4° (c,2.0).

[Found: C,83.7; H,10.3. Calc. for $C_{37}H_{54}O_2$. C,83.7; H,10.25%]

Bauer and Moll[47] give m.p. 197° for parkeyl benzoate.

Hydrolysis of Parkeyl Benzoate. - Treatment of the benzoate m.p. 201.5-202°, $[\alpha]_D$ + 95.4°; 270 mg.) with lithium aluminium hydride (400 mg.) in dry ether (40 c.c.) as described for the acetate above gave a product which crystallised from chloroform-methanol as needles (186 mg.), m.p. 162-163°, $[\alpha]_D$ + 76.5° (c,1.3). Four recrystallisations of this material from chloroform-methanol gave pure parkeol as needles, m.p. 159.5-160°, $[\alpha]_D$ + 76.8° (c,1.7). Light absorption: max. at 2040 Å., (ε : 8300).

[Found: C,84.2; H,11.6. Calc. for $C_{30}H_{50}O$. C,84.4; H,11.8%]

It gave a yellow colour with tetranitromethane in chloroform

and with the Liebermann-Burchard reagent it showed an initial reddish-yellow colour which slowly became deep red with a blue-green fluorescence.

Acetylation of parkeol (m.p. 159.5-160°, $[\alpha]_D$ + 76.8°) gave a product which crystallised as plates from chloroform-methanol, m.p. 156-158°, $[\alpha]_D$ + 87° (c,2.1). Six recrystallisations gave pure parkeyl acetate, m.p. 160-161°, $[\alpha]_D$ + 86° (c,2.2). Light absorption: max. at 2040 Å. (ε: 10,000).
[Found: C,82.1; H,11.15. Calc. for $C_{32}H_{52}O_2$. C,82.0; H,11.2%].

Parkeone. - Parkeol (95 mg.) in pyridine (5 c.c.) was mixed with the complex obtained by reacting chromium trioxide (95 mg.) with redistilled pyridine (5 c.c.). The dark brown suspension which resulted was shaken at intervals for 3 hours and left overnight at room temperature. The mixture was diluted with water, extracted with ether and the ethereal solution washed with dilute hydrochloric acid (3N), sodium hydroxide solution (2%), water, and dried (Na_2SO_4). Evaporation of the ether gave the product as a clear gum which was dissolved in light petroleum (50 c.c.) and chromatographed on alumina (4 g.). Elution with light petroleum (320 c.c.) gave a fraction (75 mg.) which crystallised from methanol as needles, m.p. 111-114°. Five recrystallisations of this material from methanol gave parkeone as needles, m.p. 125-126°, $[\alpha]_D$ + 66.5°

(c,2.2). Infrared absorption: Strong band at 1708 cm.$^{-1}$ (carbonyl group in six-membered ring).

[Found: C,84.6; H,11.8. $C_{30}H_{48}O$ requires C,84.8; H,11.4%]

Reduction of parkeone (30 mg.) in ether (25 c.c.) with lithium aluminium hydride (100 mg.) and crystallisation of the product from chloroform-methanol gave parkeol as needles, m.p. 158-159° (no depression).

Dihydroparkeyl Acetate. - Parkeyl acetate (120 mg.) in ethyl acetate (100 c.c.) was shaken with hydrogen over a platinum catalyst (from 60 mg. platinum oxide), at room temperature for 18 hours. Evaporation of the filtered solution and five crystallisations of the product from ether-methanol gave dihydroparkeyl acetate as plates (50 mg.), m.p. 172-173°, $[\alpha]_D$ + 87° (c,2.0). Light absorption: Max. at 2060 Å., (ε: 4,900). The compound gave a bright yellow colour with tetranitromethane in chloroform but did not absorb bromine. In another experiment, acetic acid was used as solvent and the product was purified by chromatography to give dihydroparkeyl acetate m.p. 172°, $[\alpha]_D$ + 86° (c,2.7).

[Found: C,81.8; H,11.5. $C_{32}H_{52}O_2$ requires C,81.6; H,11.6%].

At a later stage dihydroparkeyl acetate was shown to be identical with lanost-9(11)-enyl acetate (see below).

Treatment of Parkeyl Acetate with Osmium Tetroxide. - Parkeyl acetate (270 mg.) in dry pyridine (5.4 c.c.) was mixed

with a solution of osmium tetroxide in dry ether (20 mg./c.c.; 18 c.c. ≡ 2.2 mols.) and the mixture kept in the dark for 7 days. The dark brown suspension was diluted with ether (100 c.c.) and treated under reflux with lithium aluminium hydride (1.2 g.) added during 20 minutes. Refluxing was continued for a further hour; excess reagent was decomposed by the addition of crushed ice and the mixture diluted with water and ether. The ethereal solution was washed with dilute hydrochloric acid solution (3N), water and dried (Na_2SO_4). Evaporation of the ether gave a pale yellow resinous solid (250 mg.) which was treated with lead tetra-acetate as described below.

The product (250 mg.) in chloroform (3 c.c.) and acetic acid (23 c.c.) was treated with lead tetra-acetate (500 mg.) and the mixture was shaken until all the solid had dissolved. The resulting pale yellow solution was kept in the dark at room temperature for 20 hr.; water (10 c.c.) was added and the mixture was slowly distilled. Three fractions of 3 c.c. were collected. To each fraction a solution (2 c.c.), prepared by dissolving 2:4-dinitrophenylhydrazine (540 mg.) in ethanol (7 c.c.) and concentrated sulphuric acid (1.8 c.c.), was added and the mixtures allowed to stand for 1 hour. During this time orange needles (34 mg.), m.p. 120-123° separated from the second fraction. Two recrystallisations

of this material from ethanol gave acetone 2:4-dinitrophenylhydrazone as long orange-yellow blades, m.p. 124-126°, alone or mixed with an authentic specimen. Fraction- 1, from which no crystals separated, was diluted with ether (50 c.c.), washed quickly with dilute hydrochloric acid, water, and dried over anhydrous sodium sulphate. Evaporation of the ether under reduced pressure gave an orange residue which crystallised from ethanol to give acetone 2:4-dinitrophenylhydrazone as needles (24.6 mg.), m.p. 120-123°. Recrystallisation from ethanol gave small needles, m.p. 124-126°, (no depression).

Treatment of Dihydroparkeyl Acetate with Mineral Acid. - (a) Dihydroparkeyl acetate (54 mg.) in chloroform (10 c.c.) was treated at 0° with a stream of dry hydrogen chloride for 2 hours. The product, isolated in the usual way, crystallised from chloroform-methanol as plates (38 mg.), m.p. 166-167°, alone and mixed with starting material.

(b) Dihydroparkeyl acetate (50 mg.) in a mixture of concentrated hydrochloric acid and acetic acid (1:20; 7 c.c.) was kept at 100° for 3 hr. The product, isolated by means of ether, crystallised from chloroform-methanol as plates (32 mg.), m.p. 166.5-167° alone and mixed with starting material, $[\alpha]_D$ + 87° (c, 1.2).

Treatment of Dihydroparkeyl Acetate with Selenium Dioxide. - Dihydroparkeyl acetate (50 mg.) in boiling acetic acid (5 c.c.)

was treated dropwise with a solution of selenium dioxide (50 mg.) in the minimum of water and acetic acid (5 c.c.). Refluxing was continued for 3 hours and the product isolated by means of ether as a white solid, crystallisation of which from chloroform-methanol gave plates, m.p. 169-171°, $[\alpha]_D$ + 86° (c,1.1). The material gave a pale yellow colour with tetranitromethane in chloroform and showed no depression in melting point when mixed with starting material. Light absorption: Max. at 2050 and 2440 Å., (ε: 3,530 and 380). The reaction was repeated for a further 27 hr.; again starting material, m.p. and mixed m.p. 167-169°, was recovered. Light absorption: Max. at 2050 and 2400 Å., (ε: 4,800 and 910).

Oxidation of Dihydroparkeyl Acetate with Chromic Acid. - Dihydroparkeyl acetate (60 mg.) in stabilised acetic acid (10 c.c.) at 100° was treated dropwise during 10 minutes with a solution of chromium trioxide in acetic acid (4.4 mg./c.c.; 6 c.c.). The green mixture was refluxed for 1 hr. and allowed to stand overnight at room temperature. The product isolated by means of ether, was dissolved in light petroleum (15 c.c.) and chromatographed on alumina (3 g.). Elution with light petroleum (350 c.c.) and light petroleum-benzene (1:1; 250 c.c.) gave fractions (21 mg.) which on crystallisation from chloroform-methanol yielded dihydroparkeyl acetate as plates, m.p. and mixed m.p. 168-170°. Elution with benzene

(200 c.c.) gave a fraction (20 mg.) which crystallised from methanol to give oxodihydroparkeyl acetate as needles, m.p. 181-183°, $[\alpha]_D$ + 90° (c,0.4). The compound gave no colour with tetranitromethane. Light absorption: Max. at 2420 Å., (ε:12,000).

[Found: C,79.5; H,10.6. $C_{32}H_{52}O_3$ requires C,79.3; H,10.8%].

Oxodihydroparkeyl acetate was shown to be identical with 12-oxolanost-9(11)-enyl acetate, (see below).

Hydrogenation of Dihydroparkeyl Acetate at 80°. - A solution of dihydroparkeyl acetate (60 mg.) in glacial acetic acid (60 c.c.) was shaken with hydrogen over a platinum catalyst (from 100 mg. platinum oxide), for 27 hr. at 80°. The filtered solution was evaporated to dryness under reduced pressure and the product crystallised twice from chloroform-methanol to give tetrahydroparkeyl acetate (35 mg.) as needles, m.p. 160-161.5°, $[\alpha]_D$ + 40.5° (c,1.2), unchanged by further crystallisation or chromatography. It gave no colour with tetranitromethane and showed no selective light absorption in the ultraviolet region.

[Found: C,81.6; H,11.7. $C_{32}H_{56}O_2$ requires C,81.3; H,11.9%].

Tetrahydroparkeyl acetate was shown to be identical with lanostanyl acetate (see below).

Authentic Lanosterol Derivatives.

7:11-Dioxolanost-8-enyl Acetate.[77b] 'isoCholesteryl acetate' (30 g.) in glacial acetic acid (400 c.c.) was shaken

with hydrogen over a platinum catalyst (from 2 g. platinum oxide) for 6 hours at 70°. The product, obtained by evaporation of the filtered solution, was dissolved in stabilised acetic acid (1500 c.c.) and stirred at 100° while a solution of chromium trioxide (20 g.) in water (45 c.c.) was added during 30 minutes. The green solution was stirred for a further 1½ hr. at 100°; a little methanol (10 c.c.) was added and the cooled solution poured into ice-water (5 l.). The resulting suspension was coagulated by the addition of sodium chloride, filtered and washed with water. The solid was dissolved in ether (1 l.), washed twice with aqueous sodium hydroxide solution, water and dried (Na_2SO_4). Evaporation of the ether under reduced pressure gave a pale yellow solid (24 g.) which was dissolved in benzene (300 c.c.) and chromatographed on alumina (500 g.). Elution with benzene (1.5 l.) gave a fraction (15.6 g.) which was crystallised from methanol to give 7:11-dioxolanost-8-enyl acetate as yellow blades (13.5 g.), m.p. 156-158°, $[\alpha]_D$ + 91° (c,2.0). Light absorption: Max. at 2700 Å., (ε: 7,500).

7:11-Dioxolanostanyl Acetate.[124] - 7:11-Dioxolanost-8-enyl acetate (13 g.) in boiling acetic acid (700 c.c.) was treated with zinc dust (93 g.) added portionwise during 30 minutes. The mixture was refluxed for a further hour, filtered, reduced in bulk to 350 c.c. by distillation and poured into water. The

solid which was deposited was washed with water and dissolved in ether. The ethereal solution was washed with saturated sodium hydrogen carbonate solution, water, and dried (Na_2SO_4). Evaporation of the ether gave a white solid, two crystallisations of which from chloroform-methanol gave 7:11-dioxolanostanyl acetate as plates m.p. 220-222°, $[\alpha]_D$ + 59° (c,1.6).

11-Oxolanostanyl Acetate.[88] - A solution of 7:11-dioxolanostanyl acetate (5 g.) in redistilled diethylene glycol (167 c.c.) was heated with hydrazine hydrate (100%; 2.6 c.c.) at 200° for 1 hr. The mixture was cooled to 70° and a solution of sodium (5 g.) in diethylene glycol (50 c.c.) was added before heating was continued at 220-230° for a further 6 hr. The mixture was cooled, poured into water, acidified with hydrochloric acid and extracted with ether. The ether solution was washed with water, dried over anhydrous sodium sulphate and evaporated to give a pale brown solid. This was treated with acetic anhydride in pyridine at 100° and a solution of the dry acetylated product (5 g.) in light petroleum (100 c.c.) was chromatographed on alumina (150 g.). Elution with the same solvent (100 c.c.) gave a fraction which after three crystallisations from chloroform-methanol gave lanostanyl acetate as needles, m.p. 152-154°, $[\alpha]_D$ + 41° (c,1.75). Continued elution with light petroleum (500 c.c.) gave fractions (1.05 g.) which were combined and crystallised twice from chloroform-methanol to give 11-oxo-

-lanostanyl acetate as needles m.p. 144-146°. If the melted specimen was cooled until it just solidified and then reheated, the melting point was 156-157°, $[\alpha]_D$ + 62.8° (c,2.85). Sublimation of the acetate, m.p. 144-146°, $[\alpha]_D$ + 62.8° under high vacuum (0.0001 m.m.) 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. 143-145° cf.[81] Infrared absorption (in nujol): bands at 1242 and 1743 cm.$^{-1}$ (acetate) and 1702 cm.$^{-1}$ (carbonyl group).

3β:11β-Dihydroxylanostane. - A solution of 11-oxolanostanyl acetate (900 mg.) in dry ether (50 c.c.) was added dropwise to a suspension of lithium aluminium hydride (1.2 g.) in dry ether (40 c.c.) and the mixture was boiled gently under reflux for 2½ hr. and then kept overnight at room temperature. Ether (75 c.c.) was added and the excess hydride was decomposed by the cautious addition of crushed ice. The suspension was washed with dilute sulphuric acid (5N), water, and dried (Na_2SO_4). The residue remaining after evaporation of the ether was crystallised from chloroform-methanol to give 3β:11β--dihydroxylanostane as fine needles (590 mg.) m.p. 193-194°, $[\alpha]_D$ + 54° (c,2.4), unchanged by further crystallisation. The compound gave no colour with tetranitromethane in chloroform and was transparent to ultraviolet light. The infrared spectrum showed absorption due to the hydroxyl groups 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%]. Vosser[81] has quoted m.p. 190-191°, $[\alpha]_D$ + 29° for this compound while McGhie[83] gives the constants m.p.190-191°, $[\alpha]_D$ + 28.4°.

11β-Hydroxylanostan-3β-yl Acetate. - A solution of the diol (390 mg.) in pyridine (10 c.c.) and acetic anhydride (10 c.c.) was kept at room temperature for 17 hr. by which time long needles had separated from the mixture. The product was isolated by means of ether and crystallised from chloroform--methanol to give 11β-hydroxylanostan-3β-yl acetate (350 mg.) as needles m.p. 210.5-211°, $[\alpha]_D$ + 62.5° (c,2.3) unchanged by further crystallisation. The compound gave no colour with tetranitromethane in chloroform and 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 hr., the monoacetate m.p. 209-210°, $[\alpha]_D$ + 62° (c,2.02) 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%]. Vosser[81] gives m.p. 219-220°, $[\alpha]_D$ + 23° and McGhie[83] m.p. 215-216°, $[\alpha]_D$ + 22.8° for this compound.

3β:11β-Diacetoxylanostane. - A solution of 11β-hydroxylanostan-3β-yl acetate (200 mg.) in dry chloroform (5 c.c.) and redistilled dimethylaniline (6 c.c.) was treated with acetyl

chloride (4 c.c.) and the mixture boiled gently under reflux for 20 hr. The product was isolated in the usual way by means of ether and crystallised four times from chloroform-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. $C_{34}H_{52}O_4$ 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 c.c.) and benzene (2 c.c.) was treated at room temperature during 3 minutes with Kiliani solution (0.176 g. sodium dichromate/c.c.; 0.3 c.c.). The mixture was allowed to stand for 10 minutes before methanol (5 c.c.) was added and the product was isolated by means of ether. Evaporation of the ethereal solution gave a white solid which after two crystallisations 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,2.04).

3:11-Dioxolanostane from 3β:11β-Dihydroxylanostane. - A solution of the diol (170 mg.) in stabilised acetic acid (5 c.c.)

was treated dropwise at room temperature with a solution of chromium trioxide (155 mg.) in stabilised acetic acid (30 c.c.) and the mixture kept in the cold for 18 hr. The product isolated in the usual way was dissolved in light petroleum (20 c.c.) and filtered through a column of alumina (4 g.). Elution with light petroleum-benzene (4:1; 100 c.c.) 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[91,91b] 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-propyl alcohol (10 c.c.) was boiled gently under reflux. Sodium metal (500 mg.) was added in small portions to the refluxing solution over 2 hr. Excess sodium was destroyed by the addition of ethanol and the product, isolated in the usual way, was treated with acetic anhydride (10 c.c.) and pyridine (10 c.c.) at room temperature for 18 hr. Three crystallisations of the acetylated material from methanol gave 3β:11α-diacetoxylanostane (320 mg.) as needles, m.p. 122-124°, $[\alpha]_D$ + 24° (c,3.1). Its infrared absorption (measured in carbon tetrachloride) showed bands at 1737 and 1240-1250 $cm.^{-1}$. Mijovic et al.[91b] give m.p. 127-128°, $[\alpha]_D$ + 13°, + 11° for this compound.

Lanost-9(11)-enyl Acetate. - 11β-Hydroxylanostanyl acetate (700 mg.) in dry pyridine (40 c.c.) was treated with phosphorus oxychloride (5 c.c.) and the mixture kept for 3 hr. at 100°. The mixture was cooled, poured on to crushed ice and extracted with ether. The extract was washed with dilute hydrochloric acid (3N), saturated sodium hydrogen carbonate solution, water and dried (Na_2SO_4). Evaporation of the ether gave a pale yellow solid (692 mg.) which was dissolved in light petroleum (60 c.c.) and chromatographed on alumina (20 gm.). Elution with light petroleum (900 c.c.) gave fractions (580 mg.) which after four crystallisations from chloroform-methanol yielded pure lanost-9(11)-enyl acetate as plates m.p. 173-174°, $[\alpha]_D$ + 89° (c,2.90). The compound showed a bright 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%].

The identity of dihydroparkeyl acetate, m.p. 172-173°, $[\alpha]_D$ + 87°, with lanost-9(11)-enyl acetate was established by mixed melting point determination (m.p. 172-174°) and by the coincidence of their infrared absorption spectra.

Lanostanyl Acetate[38]. - A solution of lanost-9(11)-enyl acetate (200 mg.) in stabilised acetic acid (40 c.c.) was shaken with hydrogen over platinum (from 190 mg. platinum oxide not previously reduced) at 87° for 20 hr. Two crystallisations

of the product from chloroform-methanol gave lanostanyl acetate as needles m.p. 156-157°, $[\alpha]_D$ + 40.4° (c,1.83). These constants remained unaltered after three further recrystallisations and also after careful chromatography. The identity of tetrahydroparkeyl acetate m.p. 160-161.5°, $[\alpha]_D$ + 40.5° with lanostanyl acetate was established by mixed melting point determination (m.p. 157-160°) and by comparison of their infrared spectra.

12-Oxolanost-9(11)-enyl Acetate. - Lanost-9(11)-enyl acetate (60 mg.) in stabilised acetic acid (20 c.c.) was oxidised with chromic acid according to the method of Bentley et al.[38] The crude product was dissolved in light petroleum (20 c.c.) and chromatographed on alumina (3 g.). Elution with the same solvent (200 c.c.) gave unchanged lanost-9(11)--enyl acetate (10 mg.) as plates from chloroform-methanol, m.p. and mixed m.p. 172-173°. The fraction (29 mg.) eluted with light petroleum-benzene (1:1; 100 c.c.) crystallised from methanol to give 12-oxolanost-9(11)-enyl acetate as needles, m.p. 183-184°, $[\alpha]_D$ + 94° (c,0.75). Light absorption: Max. at 2420 Å., (ε : 10,100). A mixture with oxodihydroparkeyl acetate had m.p. 181-183° (no depression).

Lanosta-7:9(11)-dienyl Acetate from Dihydroparkeyl Acetate. - A solution of dihydroparkeyl acetate (90 mg.) in acetic acid (15 c.c.) containing hydrogen peroxide (30%; 0.5 c.c.) was

heated at 100° for 2 hr., cooled, poured into water and extracted with ether. The ether solution was washed with ferrous sulphate solution, sodium carbonate solution (10%), water, and dried (Na_2SO_4). The product obtained by evaporation of the ether crystallised from acetone-methanol as plates (65 mg.), m.p. 181-183°, $[\alpha]_D$ + 27° (c, 1.6). A mixture of this material with authentic lanost-9(11)-enyl acetate oxide[38] (m.p. 181-182°, $[\alpha]_D$ + 29°) had m.p. 181-183° (no depression).

The above product (60 mg.) was dissolved in a mixture of acetic acid and concentrated sulphuric acid (75 c.c.: 12 drops; 10 c.c.) and kept for 48 hours at room temperature. The product, isolated by means of ether, was dissolved in light petroleum (20 c.c.) and filtered through a column of alumina (4 g.). Elution with light petroleum (50 c.c.) gave a fraction (22 mg.) which was crystallised twice from chloroform-methanol to give lanosta-7:9(11)-dienyl acetate as plates, m.p. 164-165°, $[\alpha]_D$ + 89° (c, 0.81). A mixture with an authentic specimen of lanosta-7:9(11)-dienyl acetate (m.p. 165-166°, $[\alpha]_D$ + 89°) prepared from lanost-8-enyl acetate by oxidation with selenium dioxide in acetic acid[88], had m.p. 164-165°. Light absorption: Max. at 2360, 2450, and 2520 Å., (ε: 14,500, 22,700, and 11,400).

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