THESIS

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by

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THE STRUCTURE AND STEREOCHEMISTRY OF FRIEDELIN AND CERIN

CONTENTS

INTRODUCTORY REVIEW TO TRITERPENOIDS

INTRODUCTORY REVIEW OF TRITERPENOIDS.

The name triterpene is applied to a class of naturally occurring hydrocarbons and oxygenated hydrocarbons containing 30 carbon atoms arranged in such a way that six isopentane residues can be recognised as component units in the molecular carbon skeleton. The more comprehensive term triterpenoid has been adopted as a result of the discovery, in recent years, of products with obvious triterpene characteristics which are in fact C_{31} compounds[1-4].

Apart from the aliphatic hydrocarbon squalene, all triterpenoids are alycyclic and the majority contain hydroxyl, carboxyl, or carbonyl functions. They fall into three main classes.

(a) The aliphatic compound, squalene, and the tricyclic compound, ambrein.

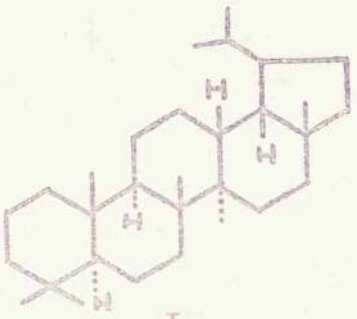
(b) The tetracyclic compounds such as lanosterol, agnosterol, the elemic acids, the polyporenic acids, eburicoic acid, euphol, tirucallol and butyrospermol, the molecules of which bear a close structural relationship to the steroids.

(c) The pentacyclic triterpenoids which form the largest class and include such compounds as α- and β-amyrin, lupeol, taraxasterol and taraxerol.

No mono- or di-cyclic triterpenoids are known. The recently characterised pentacyclic triterpenoids cycloartenol[5, 6], and

cyclolaudenol[3, 4], bear a close relationship to lanosterol and are best classified with the tetracyclic group. Similarly, the hexacyclic triterpenoid phyllanthol[5] which is closely related to α-amyrin, should be regarded as pentacyclic. Onocerin, a new triterpenoid type[7] is a symmetrical tetracyclic diol.

This thesis is concerned with the pentacyclic triterpenoids. The majority of these are polyfunctional compounds which can be related to simpler monohydric alcohols by standard methods[8-11] and which fall into four main classes based on α-amyrin, β-amyrin, lupeol and taraxasterol. The saturated hydrocarbons from which these alcohols could theoretically be derived are ursane (I), oleanane (II), lupane (III) and taraxastane (IV) respectively. All triterpenoids belonging to these classes can be named systematically as derivatives of the basic hydrocarbons, e.g. α-amyrin is urs-12-en-3β-ol (V), β-amyrin is olean-12-en-3β-ol (VI), lupeol is lup-20(29)-en-3β-ol (VII) and taraxerol is taraxast-20(30)-en-3β-ol (VIII). This rational nomenclature will be used wherever possible throughout this thesis.



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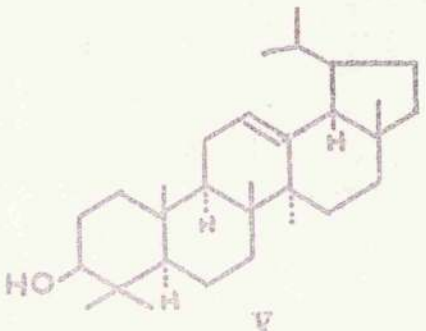

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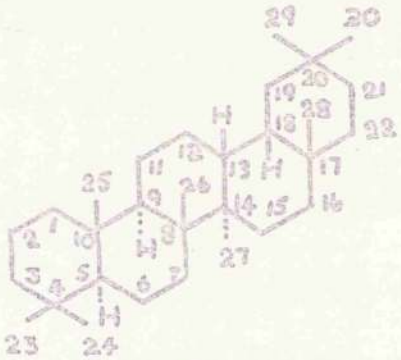

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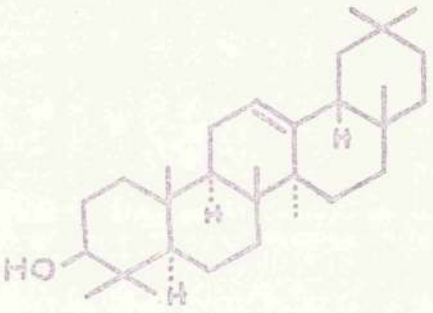

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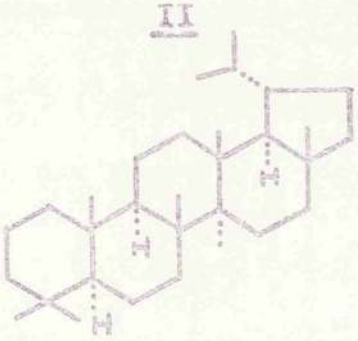

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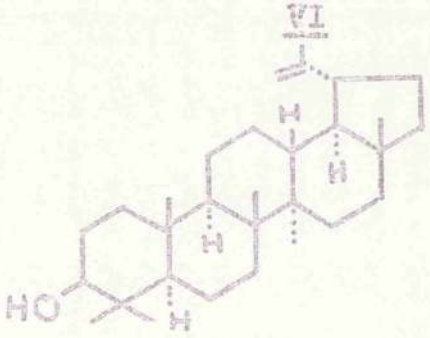
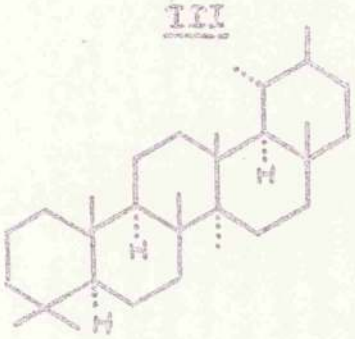


VII



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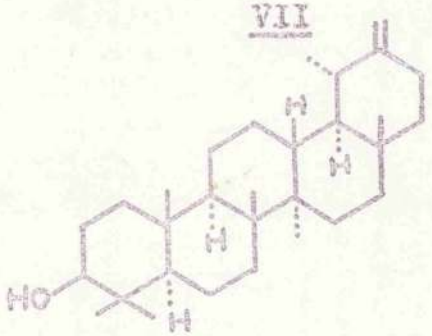


VIII

In addition to a large number of interconversions which have been achieved within each class, inter-relationships among the ursane, oleanane, lupane and taraxastane groups have also been reported.

For comprehensive discussions of the triterpenoids as a whole, and for descriptions of the general methods employed in structural elucidation, the reader's attention is directed to the reviews of Haworth[12], Spring[13], Noller[14], Jeger[15], Birch[16] and Barton[17] and to Elsevier's Encyclopaedia of Organic Chemistry[18].

SECTION A

The Structure and Stereochemistry of Friedelin and Cerin

This introduction gives a summary of the evidence available at the outset of the investigation, to be described in this thesis, aimed at establishing the structure and stereochemistry of two crystalline triterpenes, friedelin and cerin, isolated from cork.

I Introduction. - About one hundred and fifty years ago, the distinguished French chemist, Chevreul[19], obtained by alcohol extraction of cork a waxy compound which he designated "cérine". Later, Thoms[20] isolated and purified "cérine" (now contracted to cerin) and described the preparation of acetyl and benzoyl derivatives. It was Thoms contention that cerin was a phytosterol, since it gave typical sterol colour reactions. Friedel[22], suggested that cerin contained a carbonyl group and drew the attention of Istrati[21] to his own work and that of Chevreul. Istrati and Ostragovich[21] established that "cérine" was a mixture which could be separated into two components cerin and friedelin (so named in honour of Friedel[22]). From analyses and molecular weight determinations Istrati *et al.*[21] proposed the empirical formulae, $C_{27}H_{44}O_2$ for cerin and either $C_{21}H_{34}O$ or $C_{43}H_{70}O_2$ for friedelin.

In 1935 Drake and Jacobsen[23] extracted cork with ethyl acetate and by fractional crystallisation of the extract from

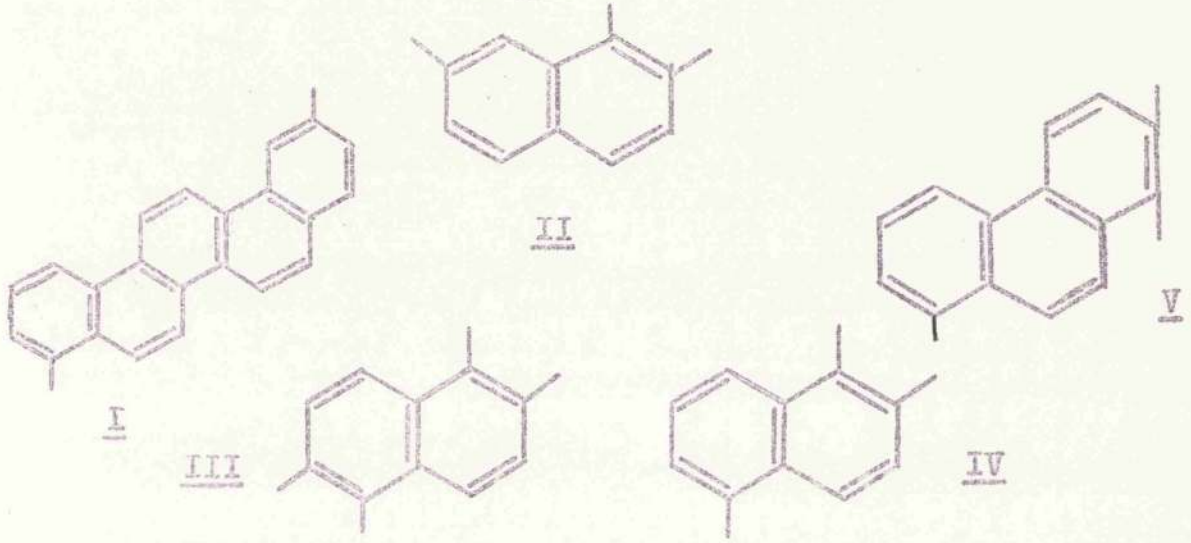
chloroform effected a satisfactory separation of cerin and friedelin. Analyses of these compounds, sublimed in high vacuum suggested the empirical formula, $C_{30}H_{50}O_2$ for cerin and $C_{30}H_{50}O$ for friedelin. In addition to cerin and friedelin a small quantity of impure material was obtained which gave characteristic sterol colour tests (Lieberman-Burchard, Salkowski and Lifshütz) - and to which Drake et al.[23] attributed the claim by Thoms[20] that cerin is a phytosterol.

Drake and Jacobsen[23] showed that friedelin did not form acetyl or benzoyl derivatives under normal conditions but that under drastic conditions an acetate and a benzoate were isolated from which pure friedelin could be regenerated. They suggested that the esters were formed through the enol form of a carbonyl group. In support of this view they showed that friedelin does not evolve any methane on treatment with methyl magnesium halide. Drake and Schrader[24] later confirmed the presence of a carbonyl group in friedelin by the preparation of ketonic derivatives e.g. an oxime and a 2:4 dinitrophenylhydrazone. Friedelin also showed a faint yellow colour with tetranitromethane but it was not easily brominated nor could it be hydrogenated under normal conditions. Cerin and friedelin gave the same hydrocarbon $C_{30}H_{52}$ on reduction with amalgamated zinc and hydrochloric acid; this hydrocarbon could not be hydrogenated or brominated. On the basis of this evidence Drake[23] suggested

that friedelin was a tetracyclic ketone which contained a centre of unsaturation not in conjugation with the carbonyl group.

In an examination of cerin Drake et al.[24] showed that it contained a hydroxyl group by the preparation of a monomethyl ether and a monoacetate. Reduction of cerin with sodium amyloxide in amyl alcohol[24] gave a diol which yielded a diacetate. Hence cerin contains both a hydroxyl group and a carbonyl group, which is in accord with the empirical formula proposed by Drake and Jacobsen[23]. Reduction of friedelin with sodium amyloxide in amyl alcohol yielded the related alcohol friedelanol.

Important evidence was forthcoming from the selenium dehydrogenation of friedelanol by Drake and Haskins[25]. Five products, 1:8-dimethylpicene (I), 1:2:7-trimethylnapthalene (II), 1:2:5:6-tetramethylnapthalene (III), 1:2:5-trimethylnapthalene (IV) and 1:2:8-trimethylphenanthrene (V) were isolated. Since 1:8-dimethylpicene is commonly obtained by dehydrogenation of pentacyclic triterpenes (e.g. α- or β-amyrin) this was strong evidence that friedelin is a pentacyclic triterpenoid.



II

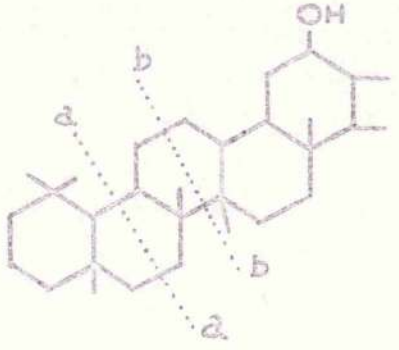
I

III

IV

V

At this juncture the claim that friedelin is unsaturated was withdrawn and a structure (VI) tentatively proposed for friedelanol[25].

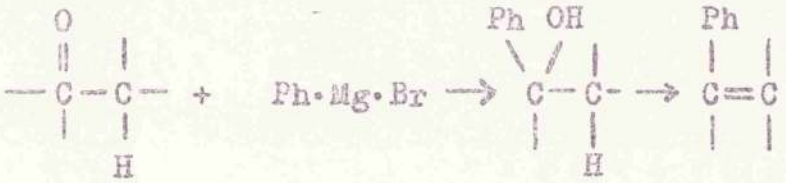


VI

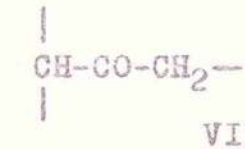
Cleavage by dehydrogenation across a····a could yield the phenanthrene product, and b····b rupture, the napthalene products.

Pyrolysis of the benzoyl derivative of friedelanol[26] at 300° gave an unsaturated hydrocarbon, $C_{30}H_{50}$, which was termed friedelene, together with benzoic acid. This reaction established the presence of at least one hydrogen atom ∝ with respect to the carbonyl group in friedelin. Further support for this decision was afforded by the reaction of friedelin

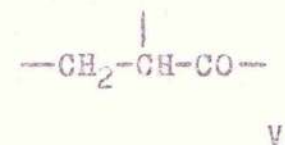
with phenyl magnesium bromide which yielded phenylfriedelene directly, viz:



Drake and Campbell[26] oxidised the unsaturated hydrocarbon, $C_{30}H_{50}$, friedelene with chromic anhydride and obtained a neutral product $C_{30}H_{48}O$ and an acidic fraction A (see below). The neutral compound, $C_{30}H_{48}O$ did not yield methane on Zerewitinoff determination of active hydrogen and was formulated as an $\alpha\beta$-unsaturated ketone. The formation of the $\alpha\beta$-unsaturated ketone, $C_{30}H_{48}O$, was attributed to the activation of the hydrogen atoms on the carbon atom adjacent to the double bond; hence the environment of the ketone could be depicted by the partial formula (VII) or (VIII)



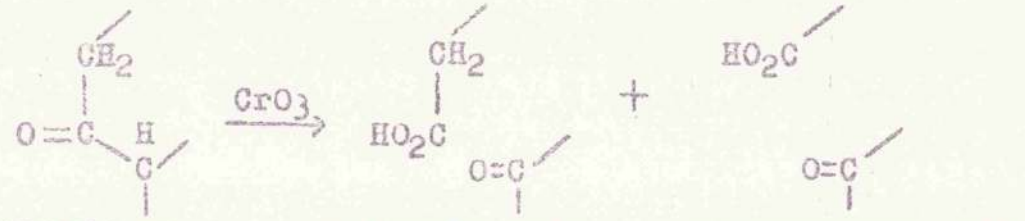
VII



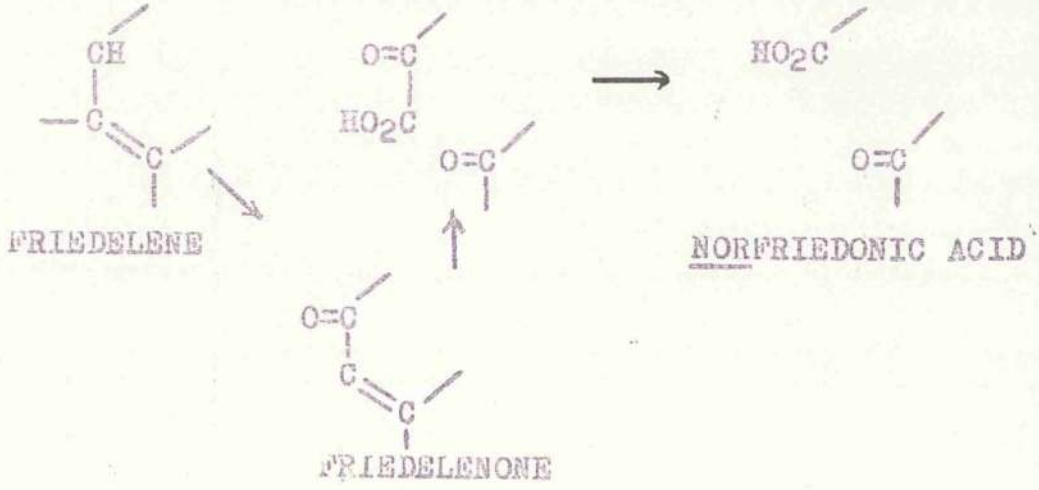
VIII

Oxidation of friedelin with chromic anhydride gave friedonic acid, $C_{30}H_{50}O_3$, shown to be a keto-acid by reduction with sodium amyloxide in amyl alcohol which yielded a neutral compound, $C_{30}H_{50}O_2$ and which was designated friedololactone. Purification of this lactone led to the isolation of a second product $C_{29}H_{48}O_2$, norfriedololactone which was also obtained by the sodium and alcohol reduction of the acid fraction A mentioned above. The isolation of this norlactone showed that

a norfriedonic acid is formed in both the oxidation of friedelene and friedelin. The authors represented the oxidation of friedelin as follows:-

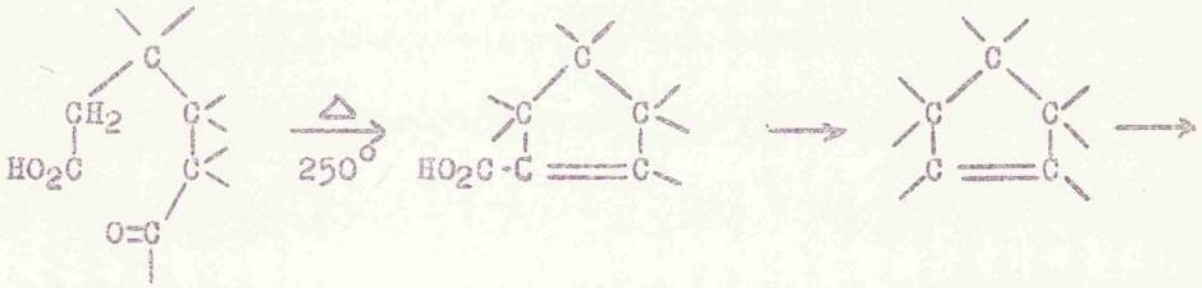


and the oxidation of friedelene as shown below.

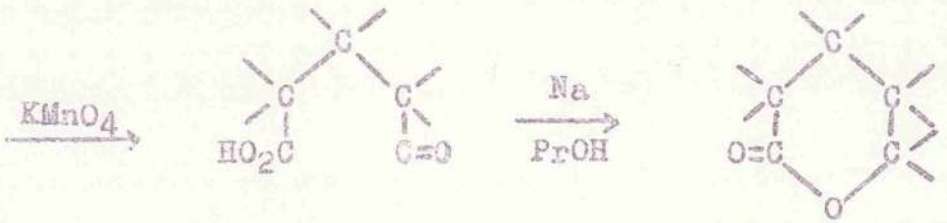


Drake and Wolfe[27] showed moreover that the carbonyl group in friedonic acid, $C_{30}H_{50}O_3$, is sterically hindered in that it will not form normal ketonic derivatives. Pyrolysis of friedonic acid[27] in an inert atmosphere at 250° gave an unsaturated hydrocarbon, $C_{29}H_{48}$, norfriedelene which was readily hydrogenated to the saturated hydrocarbon, $C_{29}H_{50}$, norfriedelane. Treatment of norfriedelane with potassium permanganate yielded the keto-acid, $C_{29}H_{48}O_3$,

norfriedonic acid (partially formulated above), in which the carbonyl group was no longer hindered and which on reduction with sodium propoxide in propyl alcohol gave norfriedololactone[26]. These reactions were formulated as follows:-



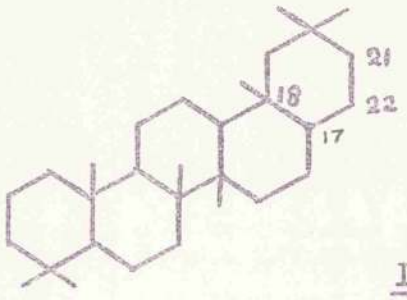
FRIEDONIC ACID NORFRIEDELENE



NORFRIEDONIC ACID NORFRIEDOLOLACTONE

A study of surface film measurements for cerin was carried out by Drake and Wolfe[28] from which they concluded that the functional groups were situated close to each other. They claimed, further that the hydroxyl groups were probably in a terminal ring. From the above facts concerning the dehydrogenation products of friedelin and the relationship of the dehydrogenation products of oleanane and lupane to the dehydrogenation products of friedelin, Drake and Wolfe[28] suggested a structure (IX) for friedelane, as a modified oleanane molecule in which the angular methyl group at carbon

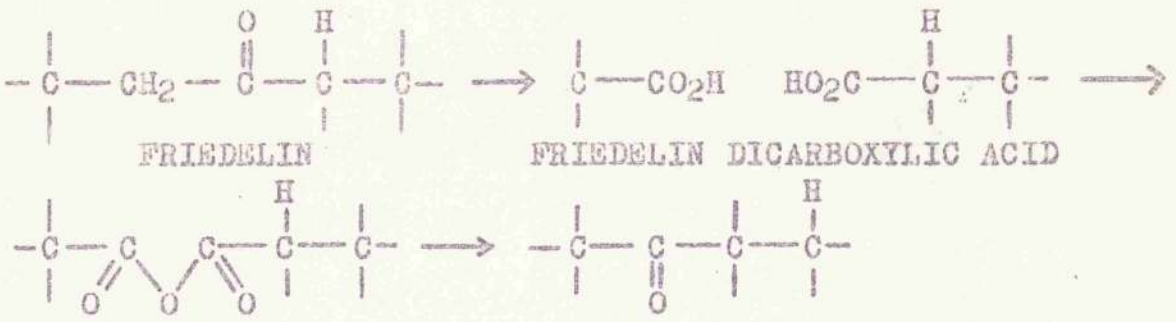
atom C_{17} is displaced to carbon atom C_{18}.



IX

They[28] also showed that the keto-acid, friedonic acid does not give a haloform test, i.e. that the carbonyl group is not a methyl ketone, which led them to suggest that the carbonyl group in friedelin is to be located on carbon atom C_{22}.

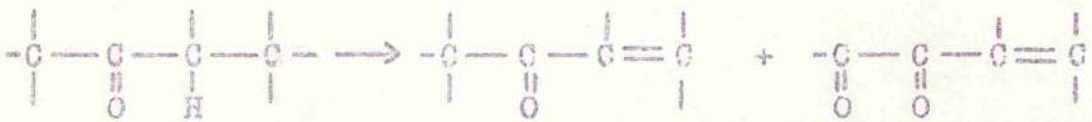
The problem was then taken up by Ruzicka, Jeger and Ringnes,[29] who reinvestigated the oxidative degradation of friedelin. By altering the conditions of the chromic acid oxidation of friedelin they were able to isolate two products (a) friedonic acid[26,29] and (b) a dicarboxylic acid, $C_{30}H_{50}O_4$, which they designated friedelin dicarboxylic acid and which was characterised as the dimethyl ester. Treatment of friedelin dicarboxylic acid with acetic anhydride gave a neutral compound, $C_{30}H_{48}O_3$, friedelin dicarboxylic acid anhydride. Pyrolysis of this anhydride in an inert atmosphere gave a saturated ketone by the loss of one mole of carbon dioxide per mole of anhydride. These reactions were partially formulated[29] viz:-



FRIEDELIN FRIEDELIN DICARBOXYLIC ACID

FRIEDELIN DICARBOXYLIC ACID ANHYDRIDE NORFRIEDELANONE

Mild oxidation of norfriedelanone with selenium dioxide gave a compound, $C_{29}H_{46}O$, the absorption spectrum of which showed an intense maximum at 2530 Å (ϵ,16,000) and which on Clemmensen reduction gave the parent norfriedelanone. Ruzicka et al.[29] formulated this compound as an $\alpha\beta$-unsaturated ketone, norfriedelenone. More drastic oxidation of norfriedelanone in dioxan at 200° yielded two products, norfriedelenone, described above, and a yellow orange coloured compound, $C_{29}H_{44}O_2$, which did not give a colour with tetranitromethane or a positive ferric chloride test. The ultraviolet absorption spectrum of this compound showed a maximum at 2800 Å(ϵ,11,000) and it gave a quinoxaline derivative with o-phenylenediamine. This compound was therefore formulated by Ruzicka[29] as an unsaturated α-diketone norfriedelenedione. This dione was also obtained by drastic oxidation of friedelin enol benzoate and norfriedelenone with selenium dioxide.



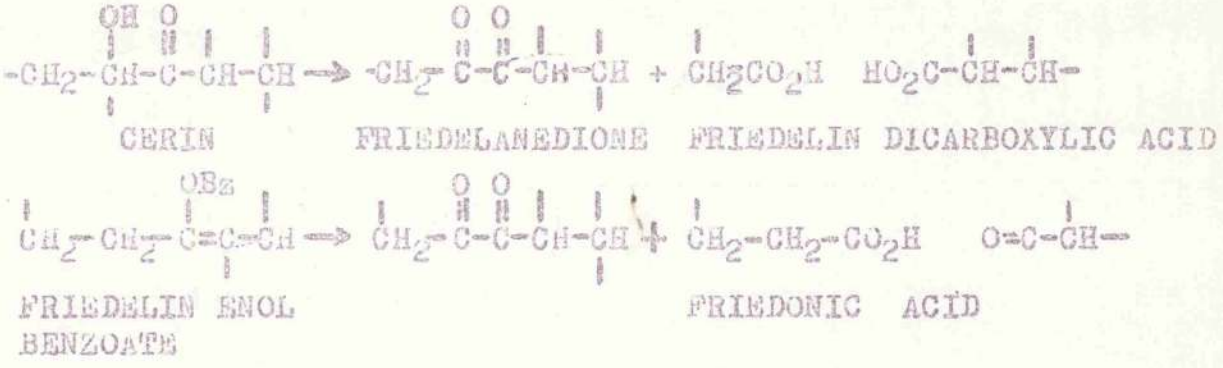
NORFRIEDELANONE NORFRIEDELENONE NORFRIEDELENEDIONE

On the basis of these reactions Ruzicka[29] suggested that the immediate environment of the ketone group in friedelin is represented by the partial structure

Bromination of norfriedelenone in acetic acid led to the isolation of a compound, $C_{29}H_{44}O\,Br_2$, nordibromofriedelenone, the ultra violet absorption spectrum of which showed a principal maximum at 2560 Å(E,8,900). Alkaline hydrolysis of the dibromo product gave a bromine-free compound, $C_{29}H_{44}O_2$, isomeric with norfriedelenedione and which gives a blue-green colouration with ferric chloride and shows an absorption maximum at 2650 Å, (E,14,500). The bromine-free product was easily acetylated to give a monoacetate which did not give a ferric chloride colour reaction. Ruzicka[29] designated the compound, $C_{29}H_{44}O_2$, enol-norfriedelenedione.

Drake and Jacobsen[23] had already demonstrated that cerin is a hydroxy ketone, Clemmensen reduction of which gives friedelane, thus proving a common carbon skeleton for friedelin and cerin. By the oxidation of friedelin enol benzoate with chromic anhydride, Ruzicka *et al.*[29] isolated two products, friedonic acid[26,29] and an enol-benzoate, $C_{37}H_{52}O_3$, which on hydrolysis gave friedelanedione. Oxidation of cerin also gave two products, friedelin dicarboxylic acid and a neutral compound,

$C_{30}H_{48}O_2$, identical with friedelanedione described above. This dione gave a brown colour with ferric chloride and showed an absorption maximum in the ultraviolet region at 2750 Å (ε,11,400). Treatment of friedelanedione with o-phenylene-diamine yielded a quinoxaline derivative and on acetylation a monoacetate which no longer gave a positive ferric chloride test and showed absorption in the ultraviolet region at 2470 Å (ε,11,000). The hypsochromic shift in wavelength of 28 mu between the dione and its acetate is comparable with the shift in wavelength between 11:12-dioxo-olean-3β-yl-acetate and its diacetate[30]. Friedelanedione was therefore formulated by Ruzicka[29] as an α-diketone and hence cerin is α-hydroxy friedelin, viz:-

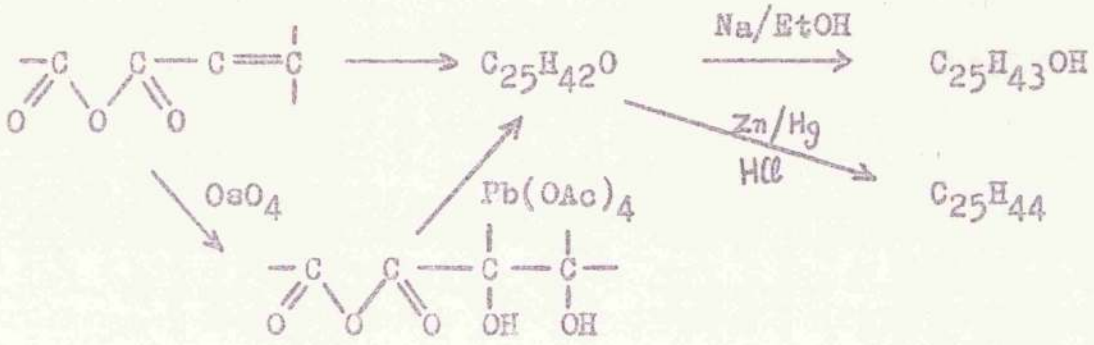


Ferold, Meyerhans, Jeger and Ruzicka[31], continued the study of the degradation products of friedelin and they were able to degrade friedelin *via* norfriedelenedione to a saturated tetracyclic ketone $C_{25}H_{42}O$. Treatment of norfriedelenedione with lead tetracetate or hydrogen peroxide gave a neutral product $C_{29}H_{44}O_3$ which absorbed at 2220 Å(ε,10,000) in the

ultraviolet region and which gave a dimethyl ester on treatment with alkaline dimethyl sulphate. Alkaline hydrolysis (2 equivalents) of the ester regenerated the neutral oxidation product $C_{29}H_{44}O_3$. This compound was therefore formulated[31] as an $\alpha\beta$-unsaturated anhydride, norfriedelendioic acid anhydride. Ozonolysis of the anhydride gave with the loss of four carbon atoms, a neutral

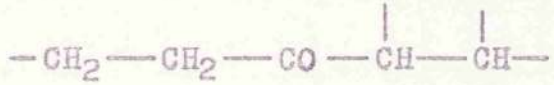
DIOIC ANHYDRIDE

product which showed the characteristic absorption spectrum of a carbonyl group at 2900 Å (ε,90). The compound $C_{25}H_{42}O$ would not react with perbenzoic acid or chromic acid at room temperature but was reduced to an alcohol, $C_{25}H_{44}O$, with sodium ethoxide in ethanol, the molecular weight of which was confirmed by the preparation of the corresponding tribromacetate. Treatment of norfriedelenedioic acid anhydride with osmium tetroxide yielded a neutral product, norfriedelandieldioic anhydride, $C_{29}H_{46}O_5$, which did not show an absorption maximum above 2200 Å. Treatment of norfriedelandieldioic anhydride with lead tetraacetate gave the tetracyclic ketone, $C_{25}H_{42}O$ described above. These reactions were partially formulated as follows:-

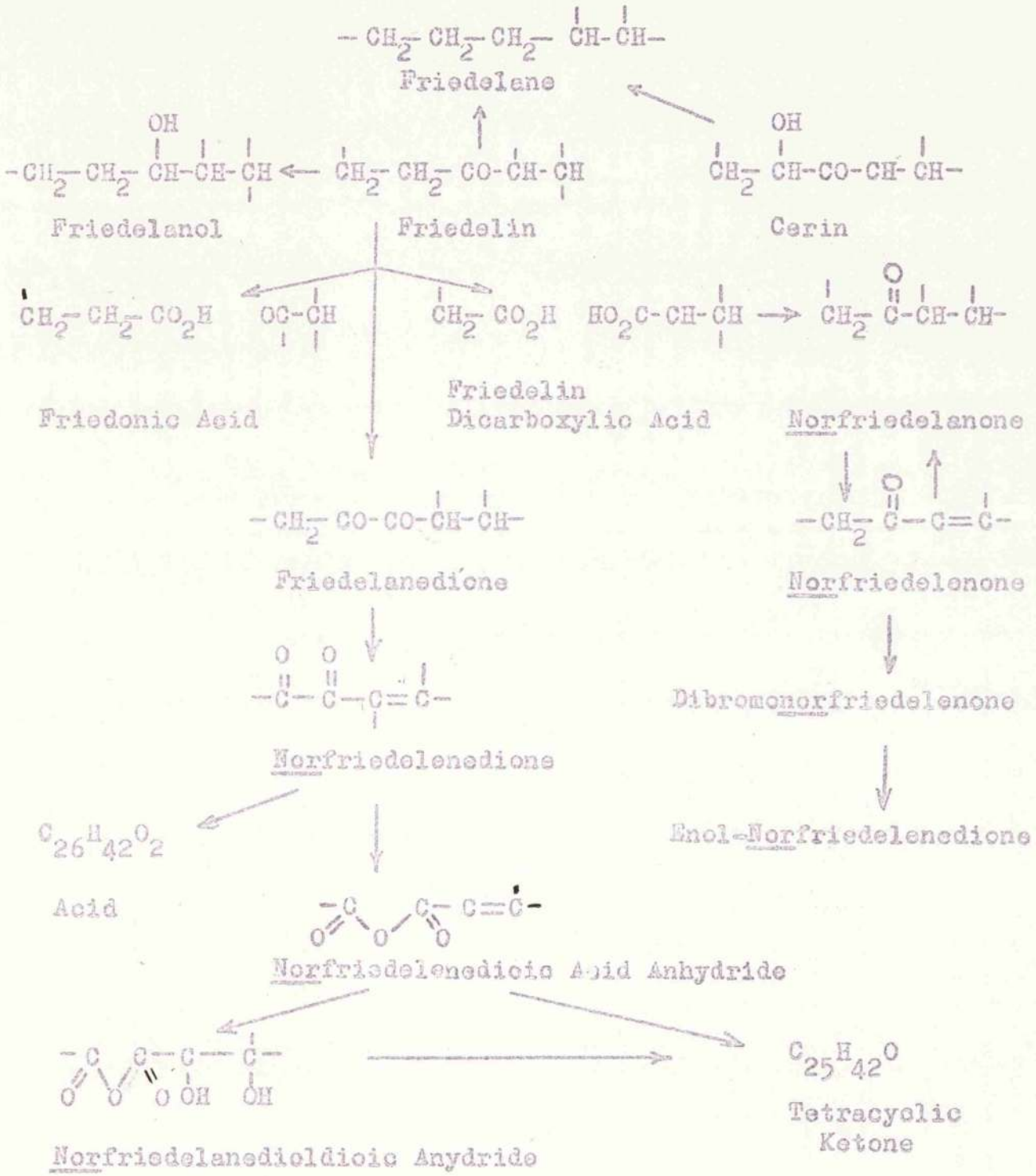


Norfriedelenedioic acid anhydride was shown[31] to be stable to alcoholic potassium hydroxide. However, similar treatment of norfriedelenedione caused a profound change which led to the isolation of an acid, $C_{26}H_{42}O_2$. It was established[31] that the carboxyl group in the acid, $C_{26}H_{42}O_2$, was unhindered and readily yielded esters which were quantitatively hydrolysed with mild alkali. The acid gave a colour with tetranitromethane indicating the presence of a double bond which is not α/β to the carboxyl group since the acid did not show absorption in the ultraviolet region near 2200 Å. Treatment of the methyl ester with osmic acid gives a saturated oxylactone which Ruzicka et al.[31] suggested, fixed the position of the double bond as $\beta\gamma$ or $\gamma\delta$, to the carboxyl group. They further showed[31] that heating the acid, $C_{26}H_{42}O_2$, above its melting point resulted in decarboxylation and the formation of a mixture of hydrocarbons which on treatment with alcoholic sulphuric acid gave a pure hydrocarbon $C_{25}H_{42}$, the molecular formula of which indicated the tetracyclic nature of the acid, $C_{26}H_{42}O_2$.

The major points arising out of the work of Drake[23-28], and Ruzicka[29,31] and their collaborators may be summarised. Friedelin and cerin are pentacyclic triterpenoids. Friedelin is a saturated ketone in which the carbonyl group is to be located in one of the terminal rings, i.e. Ring A or E. The environment of the ketone may be represented by the partial formula

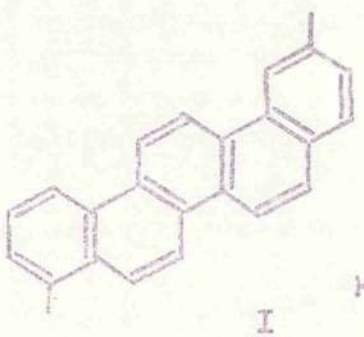


The reactions described in this Introduction are summarised below.

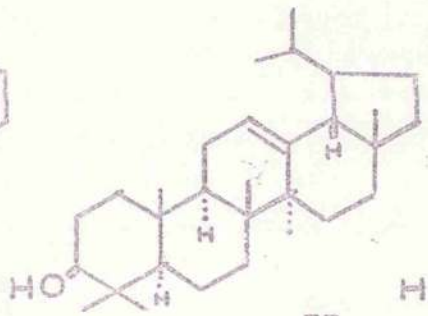

Friedelane
Friedelanol
Friedelin
Cerin
Friedonic Acid
Friedelin Dicarboxylic Acid
Norfriedelanone
Friedelanedione
Norfriedelenone
Dibromonorfriedelenone
Norfriedelenedione
Enol-Norfriedelenedione
Acid
Norfriedelenedioic Acid Anhydride
Norfriedelanedieldioic Anydride
Tetracyclic Ketone

II The Relationship of Friedelin with the Oleanane Series of Triterpenoids.

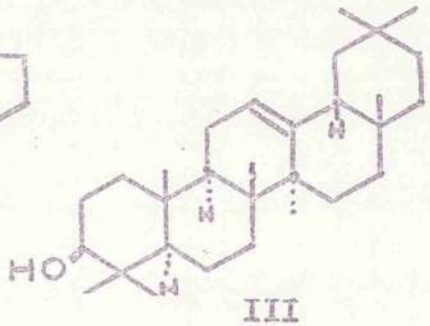
The formation of 1:8-dimethylpicene (I) by the dehydrogenation of friedelanol[25] indicates that friedelin may be related to the oleanane or ursane group of triterpenoids of which α-amyrin (II) and β-amyrin (III) are the parent alcohols, since this aromatic hydrocarbon is also obtained by similar dehydrogenation of members of each of these two groups.



I



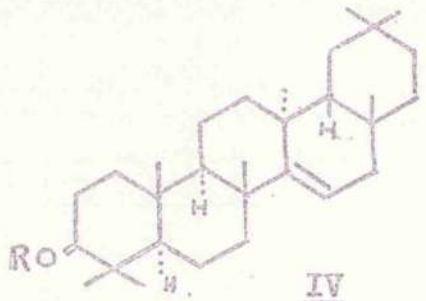
II



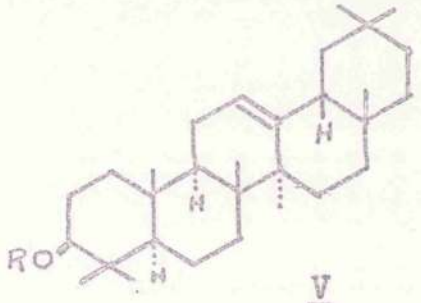
III

Clemmensen[23] or Wolff-Kishner[31] reduction of friedelin gives the saturated hydrocarbon, friedelane, which is isomeric, but not identical with either oleanane or ursane. These reactions were repeated and the results confirmed. A similar situation arose in the elucidation of the structure of taraxerol. It was found that Wolff-Kishner reduction of taraxerone[32] gave an unsaturated hydrocarbon, isomeric, but not identical with, olean-12-ene or urs-12-ene. In these laboratories it was

demonstrated by Beaton, Spring, Stevenson and Stewart[33] that treatment of taraxeryl acetate (IV; R=Ac) with mineral acid gives olean-12-en-3β-yl acetate (V; R=Ac)(β-amyrin acetate) which thus related taraxerol (IV; R=H) to the oleanane series of triterpenoids. From this, and other evidence it was concluded[33] that taraxerol has a modified oleanane skeleton in which the methyl group normally attached to carbon atom C_{14} is attached to carbon atom C_{13}.



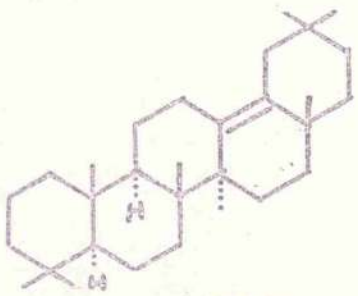
IV



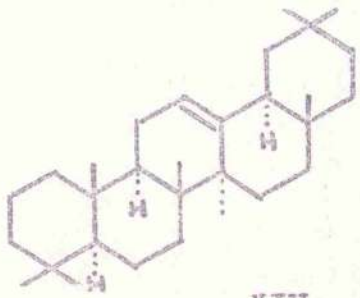
V

In view of the success of this method[33], it was hoped that treatment of the unsaturated hydrocarbon, friedelene, would give a product which might be identified as a member of one of the major triterpenoid series. Consequently the preparation of this hydrocarbon was undertaken. Treatment of friedelin with lithium aluminium hydride gives epifriedelanol previously isolated from a lichen[34,36] and from Ceratopetalum apetalum D. Don.[35,36]. epiFriedelanol has also been obtained by catalytic reduction of friedelin[35] and it was probably prepared by Drake[37]. Treatment of epifriedelanol with

phosphorous oxychloride in pyridine gives, in good yield, an unsaturated hyrdocarbon, $C_{30}H_{50}$, which was tested for homogeniety by the usual methods, and the constants of which were in agreement with those of the friedelene prepared by Drake *et al.*[26] by the pyrolysis of friedelanyl benzoate. A similar dehydration of epifriedelanol was described by Bruun[34] but the product was not characterised. Hydrogenation of friedelene gives friedelane, identical with the hydrocarbon obtained by Wolff-Kishner or Clemmensen reduction of friedelin from which it follows that friedelene is formed from friedelin without molecular rearrangement. Treatment of friedelene with concentrated hydrochloric acid in acetic acid at reflux over seventeen hours, gives a crystalline hydrocarbon which was identified[38] (see Section B) as an equilibrium mixture of olean-13(18)-ene (XIII) and 18α-olean-12-ene (XIV).



XIII

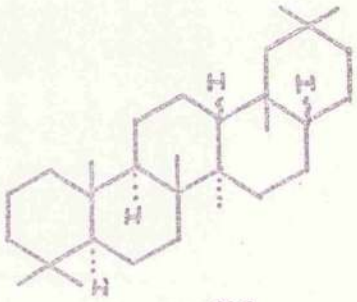


XIV

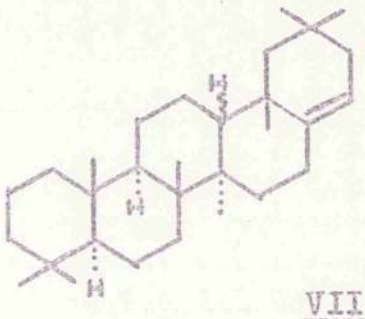
Thus for the first time, friedelin has been related to a derivative of one of the major triterpenoid series and hence friedelane must be represented as a modified oleanane molecule.

III The Structure of Friedelin

The acid isomerisation of friedelene to olean-13(18)-ene (XIII) is compatible with the structure (VI) proposed by Drake[28] for friedelane since olean-13(18)-ene could be formed by acid isomerisation of the hydrocarbon (VII). However, the isolation of 1:2:8-trimethylphenanthrene[25] from the

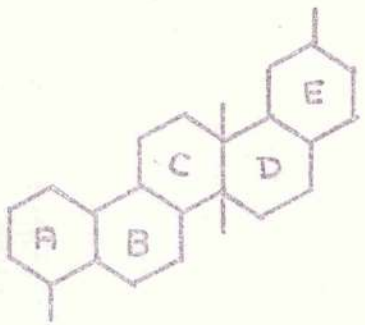


VI



VII

dehydrogenation of friedelanol suggests that in friedelane, methyl groups are attached to carbon atoms C_{13} and C_{14} thus leading to the development of partial formula A for friedelane, and in consequence the rejection of (VI).

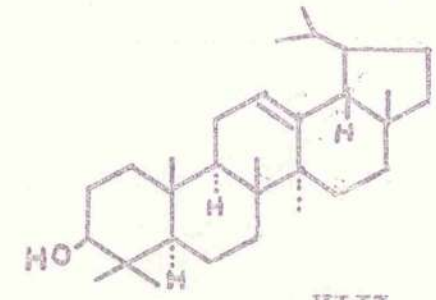


+ 4 Me

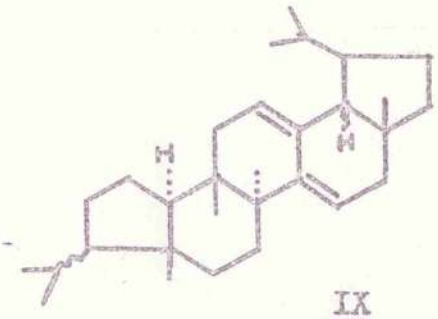
A

The demonstration by Drake and Wolfe[28] that the carbonyl group in friedelin is located in a terminal ring requires that this

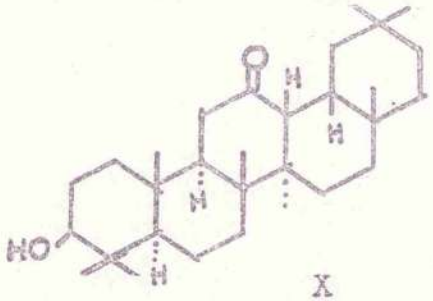
is ring A and not ring E since the latter alternative does not offer an acceptable mechanism for the friedelene ⟶ olean-13(18)-ene change. Furthermore, the location of the carbonyl group in ring A indicates that the friedelene ⟶ olean-13(18)-ene change involves the migration of a double bond from ring A to ring D. Such double bond movement is not without precedent. The most spectacular reactions of this type were described by Fayez, Grigor, Spring and Stevenson[39] and Allan, Fayez, Spring and Stevenson[40] in which acid induced dehydrations of α-amyrin (VIII) to "1-α-amyradiene" (IX), of β-amyranonol (X) to the $\alpha\beta$-unsaturated ketone (XI) and of α-amyranonol to the ursane analogue of (XI)[41] were shown to involve a series of 1:2 tertiary group shifts in which each migrating group or atom retains its axial configuration.



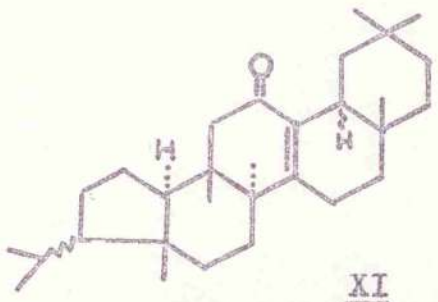
VIII



IX

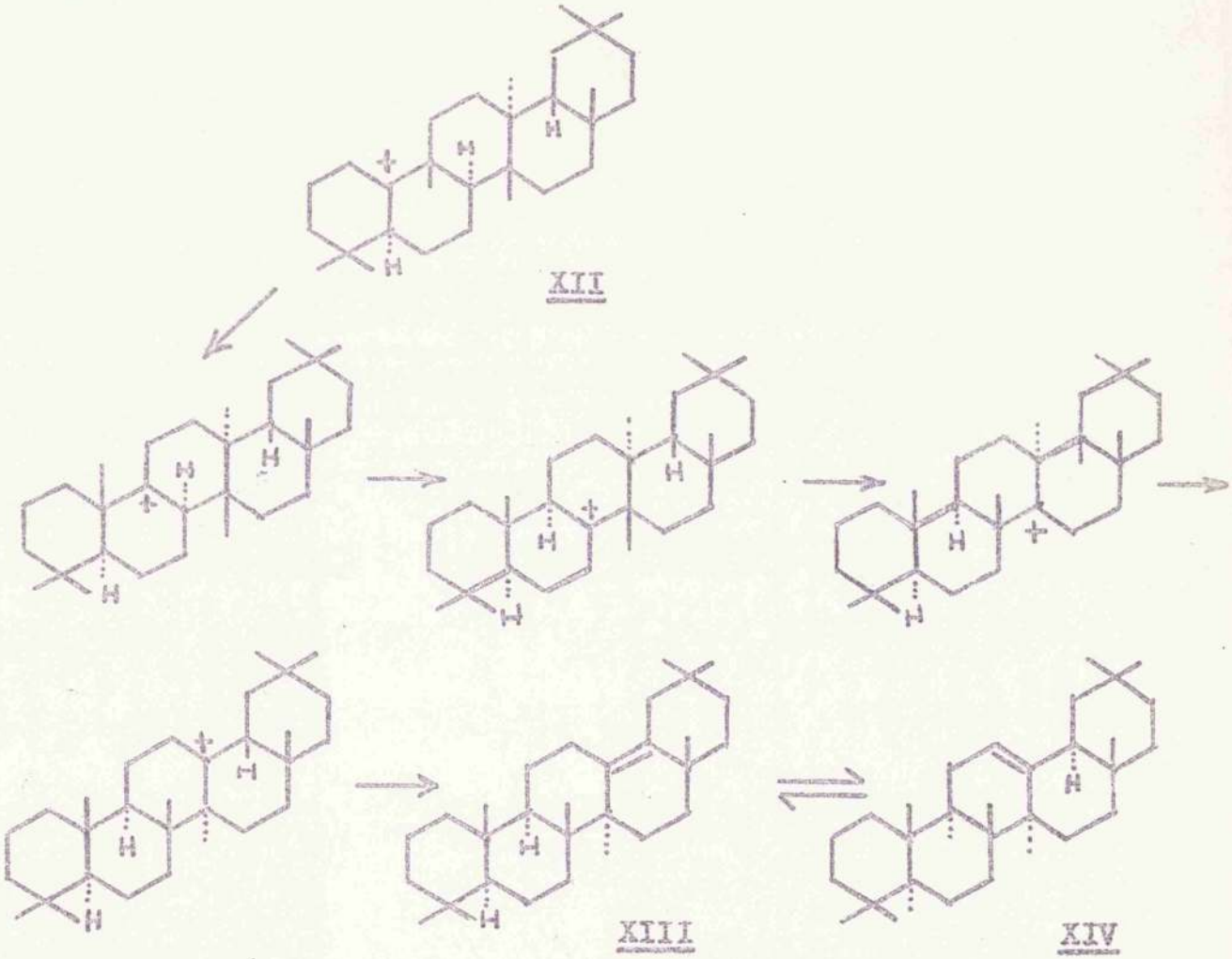


X



XI

Assuming partial formula A and, in analogy with the dehydration isomerisation reactions described above[39,40,41], the conversion of friedelene to olean-13(18)-ene must involve the cation (XII) or its equivalent. A mechanism for this conversion is shown below:-



XII

XIII

XIV

The friedelene ⟶ olean-13(18)-ene change establishes the stereochemistry of rings B, C, D and E in friedelin with the exception of the hydrogen atom attached to carbon atom C_{18}. This is considered to have the β -configuration since the

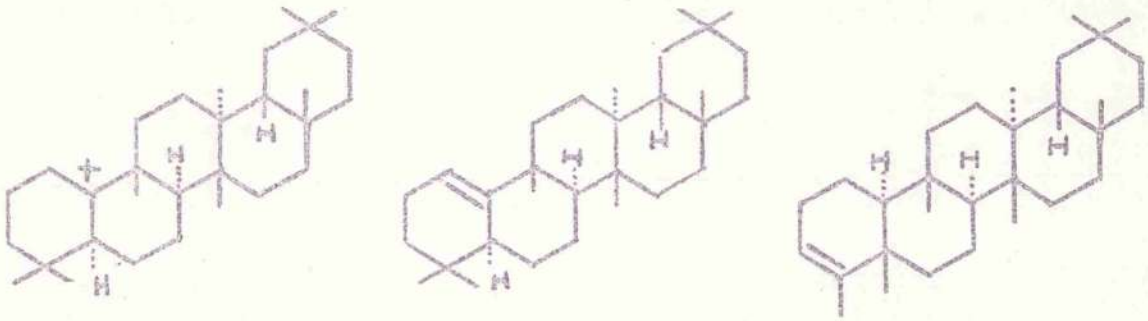
cis-locking of rings D and E is believed to be necessary for the dehydration isomerisation reactions[39,40,41], referred to above.

IIIa The Nature of the Double Bond in Friedelene

Treatment of friedelene with osmium tetroxide in cyclohexane yields a saturated glycol, $C_{30}H_{52}O_2$, which forms a monoacetate, $C_{32}H_{54}O_3$, only, and this is stable to a chromic-acetic acid mixture at room temperature and treatment with phosphorous oxychloride at 100°. The isolation of the diol monoacetate is proof, therefore, that the double bond in friedelene is trisubstituted, since isolation of a diacetate would indicate disubstitution, and a non-acylable glycol, a tetrasubstituted double bond. Drake[26] obtained an unsaturated hydrocarbon which he designated friedelene, by the pyrolysis of friedelanyl benzoate. This reaction was repeated several times using carefully purified friedelanyl benzoate, pyrolysis of which, in an inert atmosphere, gives a hydrocarbon, the physical properties (melting point, mixed melting point, specific rotation and infrared spectrum) of which are indistinguishable from those of the hydrocarbon obtained by dehydration of epifriedelanol. The hydrocarbon obtained by pyrolytic methods gives on treatment with osmium tetroxide and acetylation of the product, two compounds, the major portion being the diolmono-

acetate, $C_{32}H_{54}O_3$, described above and a small amount of a dioldiacetate $C_{34}H_{56}O_4$. Thus, the hydrocarbon obtained by Drake *et al.*[26] is a mixture which consists essentially of friedelene (as obtained by dehydration of *epi*friedelanol) contaminated with a small proportion of an isomer in which the double bond is disubstituted.

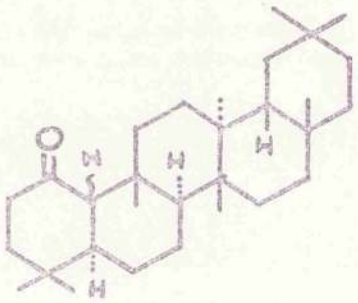
The cationic intermediate (XII), from which the equilibrium mixture of oleanene isomers is obtained, may now be expanded, since only two positions, as shown by (XV) and (XVI), are available in which a trisubstituted double bond, can be accommodated in ring A. If structure (XV) represents friedelene, formation of the cation (XII) is accomplished by



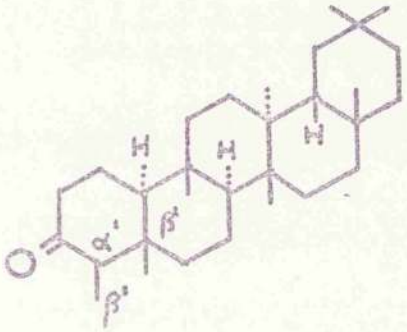
XII XV XVI

simple protonation of the double bond; if however, the unsaturated hydrocarbon is to be portrayed by (XVI) then the cation (XII) is developed by protonation of the double bond from the rear (α) side with movement of the axial

5-methyl group to carbon atom C_4 and the axial 10-hydrogen atom to carbon atom C_5. These structures (XV) and (XVI) correspond with structures (XVII) and (XVIII) for friedelin.



XVII

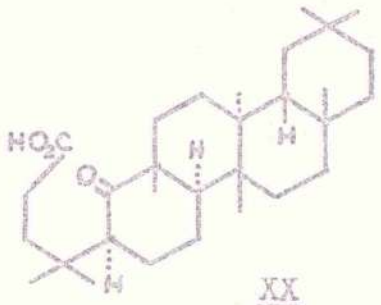


XVIII

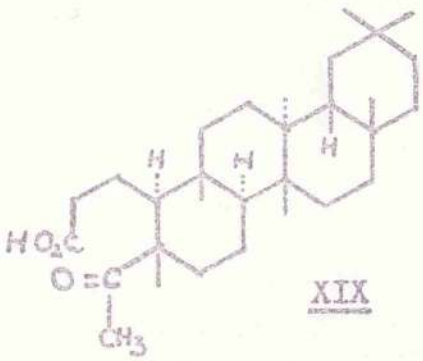
Consideration of the alternative formulae (XVII) and (XVIII) for friedelin shows that the former (XVII) satisfies the postulate that the environment of the ketone is given by the partial structure;

$$\underset{\beta}{-CH_2-}\ \underset{\alpha}{CH_2}-CO-\underset{\alpha'}{CH}-\underset{\beta'}{CH}-$$

the latter (XVIII) only does so if the β' carbon atom is a methyl group. Further, (XVIII) on oxidation would be expected to yield two products, a dicarboxylic acid and a keto-acid which would require to be formulated as a methyl ketone (XIX) which is



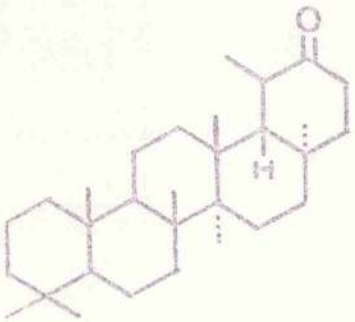
XX



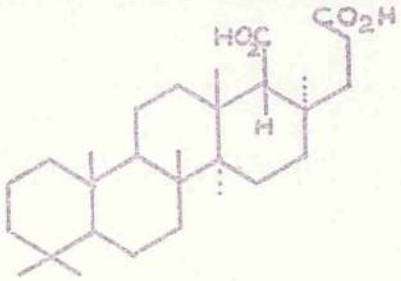
XIX

contrary to the evidence advanced by Drake[28], and Meyerhans[42], who showed that the keto-acid, friedonic acid, obtained by oxidation of friedelin, is not a methyl ketone. On this evidence, structure (XX) reasonably represents friedonic acid from which it follows that (XV) and (XVII) depict friedelene and friedelin respectively.

More evidence was forthcoming, from a contemporary investigation on the degradation products of friedelin by Ourisson and Takahashi[43]. From the evidence obtained during these studies they postulated a structure (XXI) for friedelin.



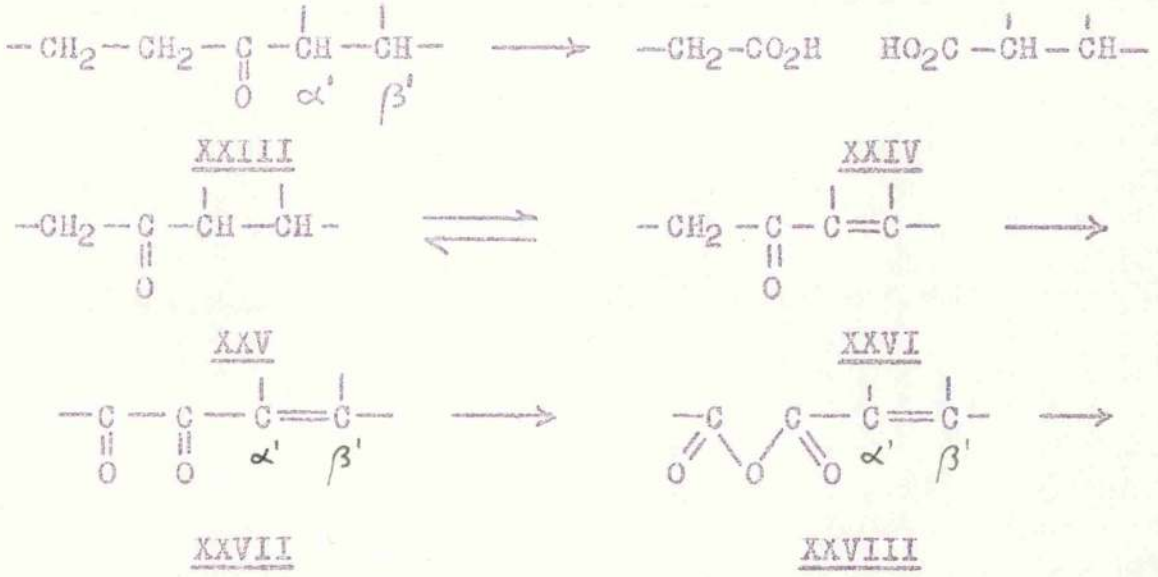
XXI



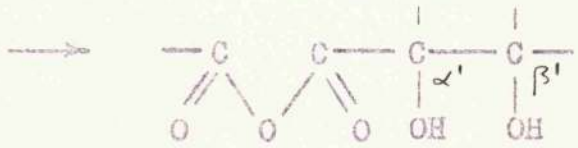
XXII

The location of a methyl group α to the ketone was justified by Ourisson[43] by the reaction of friedonic acid, $C_{30}H_{50}O_3$, with sodium hypobromite which gave a nordicarboxylic acid, $C_{29}H_{48}O_4$ which they formulated as (XXII). Hence, in spite of earlier reports to the contrary[28,42] friedonic acid is a methyl ketone which invalidates the formulation of friedonic acid as (XX) and which in consequence renders structure (XVII) for

friedelin incorrect. Equally, however, the conversion of friedelene to the equilibrium mixture of oleanene isomers necessitates the rejection of Ourissons's formula (XXI) for friedelin, since the unsaturated hydrocarbon derived from (XXI) could not yield an oleanane derivative on treatment with mineral acid. These results led to a reconsideration of the structure (XVIII) for friedelin and a consequent reconsideration of the evidence leading to the view that the environment of the ketone is represented by the partial structure $-CH_2-CH_2-CO-CH-CH-$. As stated earlier oxidation of friedelin (XXIII) gives friedelin dicarboxylic acid $C_{30}H_{50}O_4$ (XXIV), the anhydride of which on pyrolysis gives norfriedelanone, $C_{29}H_{48}O$, (XXV). Relatively mild oxidation of norfriedelanone with selenium dioxide gives an $\alpha\beta$-unsaturated ketone, norfriedelenone, $C_{29}H_{46}O$, (XXVI),



XXIII XXIV XXV XXVI XXVII XXVIII

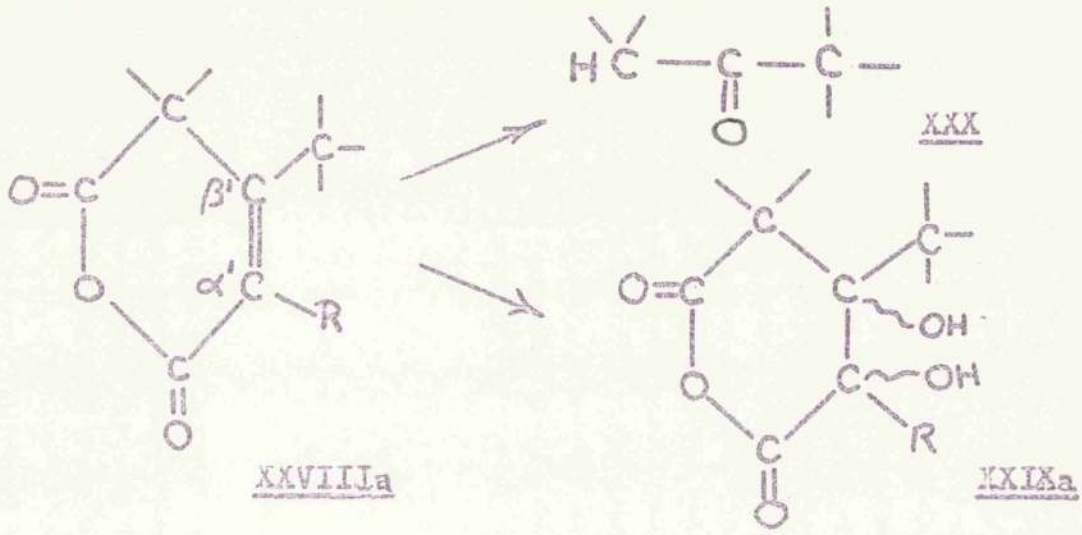


XXIX

reduction of which regenerates the saturated norketone (XXV). Oxidation of norfriedelenone with selenium dioxide at 170-180° yields an unsaturated α-diketone, norfriedelenedione, $C_{29}H_{44}O_2$ (XXVII), and this is also obtained by the same treatment of norfriedelanone (XXV). Hydrogen peroxide converts norfriedelenedione into an unsaturated dicarboxylic acid anhydride (XXVIII); a comparison of the ultraviolet absorption spectra of (XXVIII) and (XXVII) confirms the relationship implied by the partial formulae. Oxidation of the unsaturated anhydride (XXVIII) with osmic acid gives a saturated glycol (XXIX). Treatment of the glycol (XXIX) with lead tetra-acetate or ozonisation of the unsaturated anhydride (XXVIII) gives the tetracyclic ketone, $C_{25}H_{42}O$.

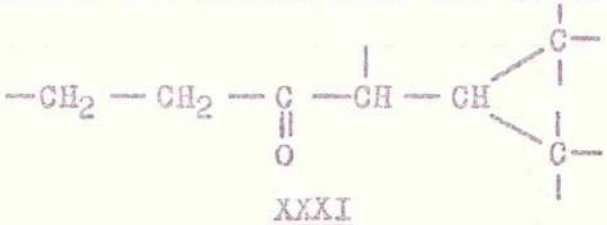
In the partial formulae (XXIII)-(XXIX) used by Ruzicka, Jeger and Ringnes[29], the β' carbon atom in (XXIX) is identified with the β' carbon in (XXVII) and it is therefore identified with the β' carbon atom in (XXIII). Hence the conversion of the unsaturated anhydride into the tetracyclic ketone[31] shows that the partial formula (XXVIII) for the former compound must be expanded to (XXVIIIa) and that the formation of the saturated ketone (XXX) from (XXVIIIa) and from the glycol

(XXIXa) is to be represented as follows. -



XXVIIIa XXX XXIXa

The carbonyl carbon atom in the tetracyclic ketone[31] (XXX) is derived from the β' carbon atom in friedelin (XXIII) and consequently this atom carries only one hydrogen atom. If the partial formulae for friedelin (XXIII) and for the enedione (XXVII) are correct relative to each other, the former must be expanded to (XXXI). Since this fragment is not present in (XVIII), either the latter does not correctly represent the

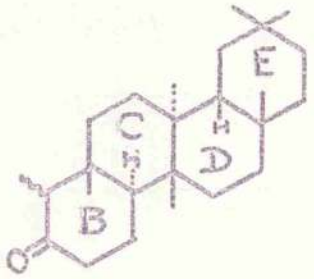


XXXI

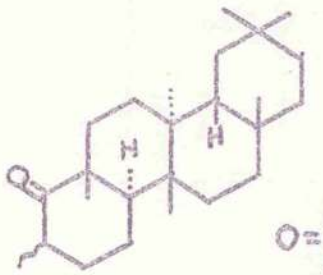
constitution of friedelin, or, the partial formulae (XXIII) and (XXVII) do not correctly represent the relationship between friedelin and the enedione. A decision in favour of the latter alternative was made as described below.

The methods by which the saturated tetracyclic ketone

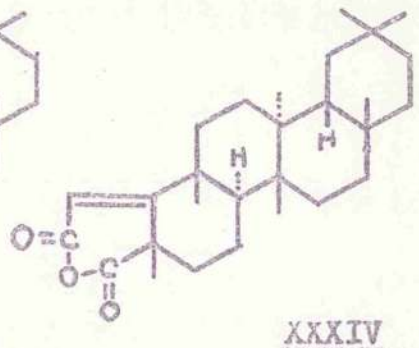
$C_{25}H_{42}O$, is obtained from friedelin establish that it is a substituted perhydrochrysene derived from rings B, C, D and E of friedelin and that its carbonyl group marks one of the A/B ring junctions. The exact molecular formula of the tetracyclic ketone, $C_{25}H_{42}O$, was established by Ruzicka, Jeger, and their collaborators[31] by analysis of the tribromoacetate of the derived alcohol. Now the structure and stereochemistry of rings B, C, D and E in friedelin (apart from the nature of the substituent at carbon atom C_5) follow from those of the cation (XII) and consequently only two formulae (XXXII) and (XXXIII) are to be considered for the tetracyclic ketone. Ourisson and Takahashi[43] have shown



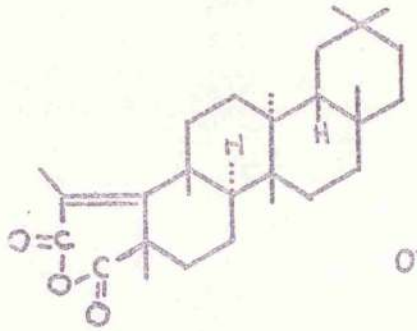
XXXII



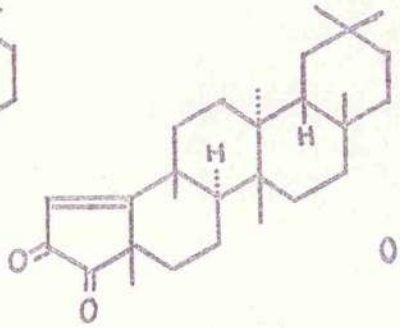
XXXIII



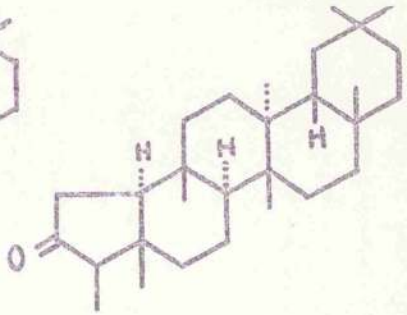
XXXIV



XXXV



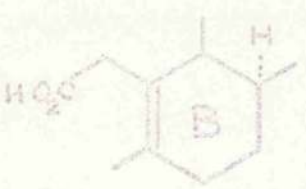
XXXVI



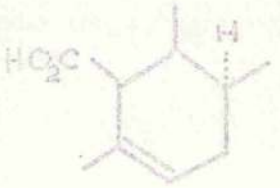
XXXVII

that bromination of the saturated tetracyclic ketone, $C_{25}H_{42}O$, gives an α-bromoketone, $C_{25}H_{41}OBr$, thus proving the presence of only one α-hydrogen atom. Together with the considerations discussed above, this important observation proves that the tetracyclic ketone is (XXXIII). The unsaturated dicarboxylic anhydride is consequently (XXXIV) $C_{28}H_{42}O_3$ or (XXXV) $C_{29}H_{44}O_3$. Although the majority of the analytical data given by Ruzicka, Jeger and their collaborators[31] for the anhydride and its derivatives is in excellent agreement with either of these formulae, the equivalent weight of the anhydride (Found: 214·1, $C_{29}H_{44}O_3$ requires 220·3; $C_{28}H_{42}O_3$ requires 213·3) and the elemental analysis of the derived glycol (XXIXa) favour the molecular formula $C_{28}H_{42}O_3$. At a conservative evaluation these data do not exclude the lower molecular formula (XXXIV) for the anhydride and which is a more acceptable formula than (XXXV). In order to test the accuracy of this formula (XXXIV) Mlle. Sternberg[44] kindly undertook a determination of its molecular weight by the crystallographic method (Found: 419±10, $C_{29}H_{44}O_3$ requires 440·6, $C_{28}H_{42}O_3$ requires 426·6)which has unequivocally confirmed the lower formula $C_{28}H_{42}O_3$. "Norfriedelenedione" is therefore identified as bisnor-friedelenedione (XXXVI) and its formation from norfriedelanone (XXXVII) involves the extrusion of the

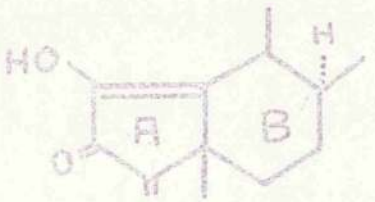
methyl group attached to carbon atom C_4. Oxidation of bisnorfriedelenedione with alkaline hydrogen peroxide yields a $\beta\gamma$-unsaturated acid which may be represented by either (XXXVIII) or (XXXIX). Bromination of norfriedelenone and treatment of the product with alkali yields a



XXXVIII

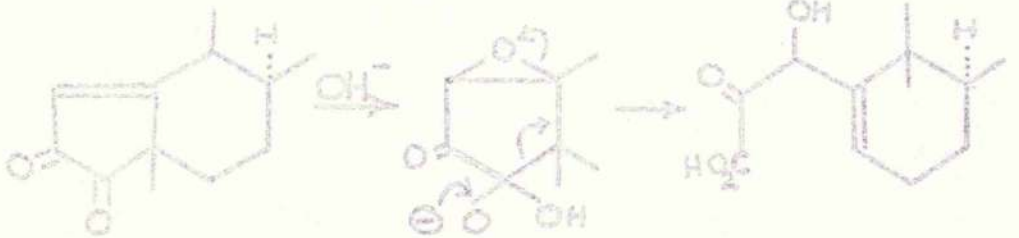


XXXIX



XL

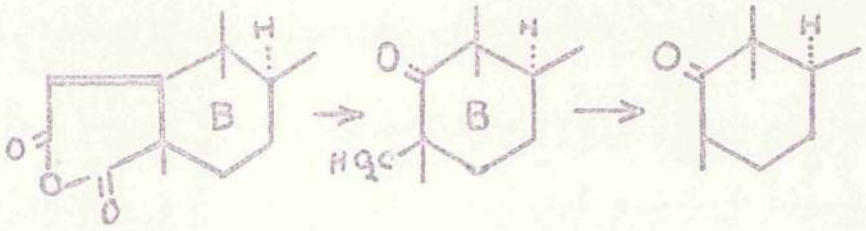
norfriedelenedione which gives a colour with ferric chloride and forms an enol-acetate. This can be formulated as (XL), enol-norfriedelenedione. A mechanism for the conversion of bisnorfriedelenedione (XXXVI) to the $\beta\gamma$-unsaturated acid $C_{26}H_{42}O_2$ with alkaline hydrogen peroxide by Ourisson et al.[43] is shown.-



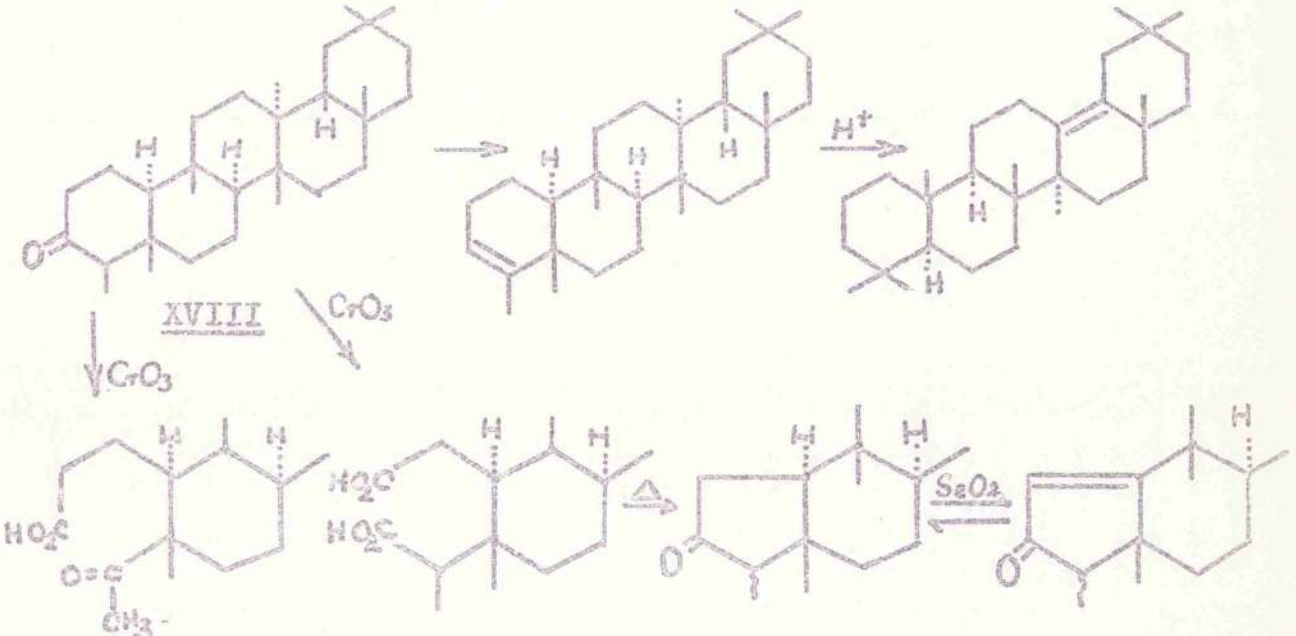
XXXVI

XXXIX

Similarly the conversion of the unsaturated dicarboxylic acid anhydride (XXXIV) to the saturated ketone (XXXIII), with ozone, may be envisaged as rupture of the double bond to yield a β-keto acid with the loss of two carbon atoms, which then decarboxylates to give the ketone, $C_{25}H_{42}O$, viz. -

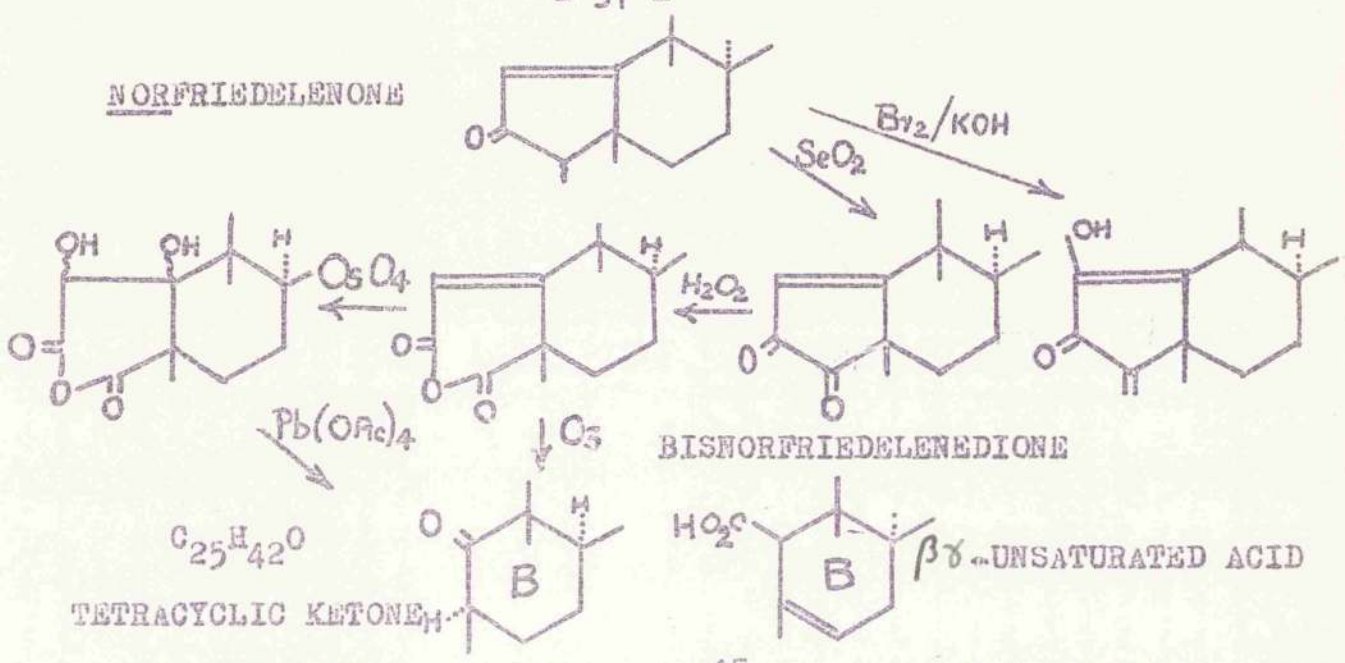


Hence the complex reactions of friedelin including its conversion to the equilibrium mixture of olean-13(18)-ene and 18α-olean-12-ene may be adequately accomodated by the steric formula (XVIII). A summary of these reactions is shown below:-

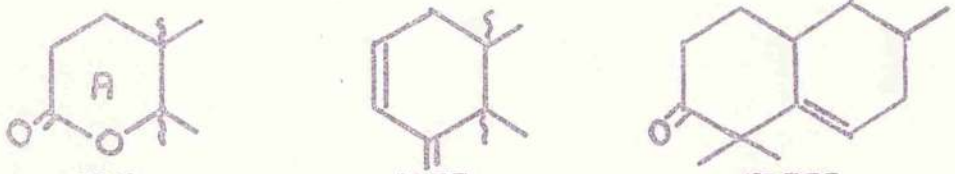


FRIEDONIC ACID

NORFRIEDELANONE



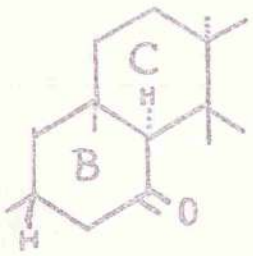
The work of Corey and Ursprung[45] has recently supplied evidence which strongly favours the formulation (XVIII) for friedelin. Briefly, the evidence they put forward is as follows. Firstly, a three stage oxidation of friedelin gives a C_{28}, 6 membered lactone formulated as (XLI). Secondly, bromination of friedel-2-ene followed by dehydrobromination gives an exomethylenic diene which they formulate as (XLII).

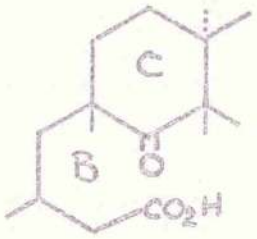


XLI XLII XLIII

Also, 4-bromofriedelin, obtained by bromination of friedelin enol benzoate is readily dehydrobrominated to give an unsaturated unconjugated ketone which cannot be isomerised to a conjugated structure. This product they formulate as

(XLIII), assuming that migration of the methyl group attached to carbon atom C_5 to C_4 has occurred during dehydrobromination. Corey and Ursprung[45] also present evidence for trans-fusion of rings A and B (more readily shown in this thesis by the acid isomerisation of friedel-3-one) and were able to show that the saturated tetracyclic ketone[31,43], $C_{25}H_{42}O$, (XXXIII) has only one α-hydrogen atom, thus confirming the conclusion reached by Ourisson[43], and which establishes the presence of a methyl group at carbon atoms C_9 and C_5. They[45] also demonstrated by further degradation of the $\beta\delta$-unsaturated acid (XXXIX) to a saturated tetracyclic ketone formulated as (XLIV) that there is a hydrogen atom at carbon atom C_8 (which would hold a methyl group in the oleanane series) by two methods. Firstly, by deuterium exchange of (XLIV) with

XLIV 

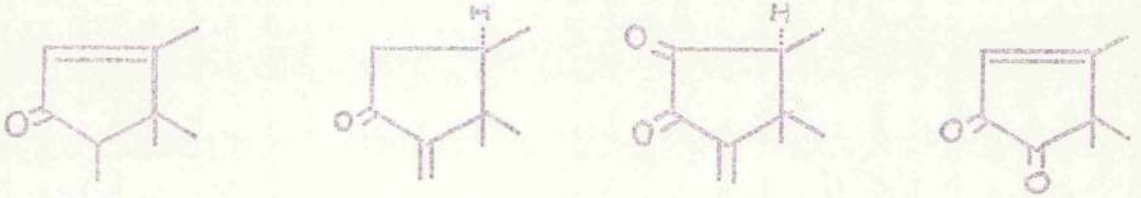


XLV

deuterium bromide (2·9 deuterium atoms/molecule) and secondly, by oxidation of the ketone (XLIV) to a keto-acid (XLV). Finally, they converted friedelan-3β-ol (epifriedelanol) to olean-13(18)-ene with hydrogen chloride in phenol. These reactions confirm the formula proposed in this thesis and by

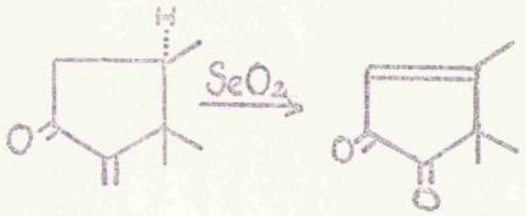
Corey for friedelin.

However, Corey[45](cf. 43) formulates norfriedelenone as an $\alpha\beta$-unsaturated ketone in which the double bond is exomethylenic (XLVII). The ultraviolet absorption spectrum of this compound as described by Ruzicka et al.[29] shows an absorption maximum at 2540 Å (ε,16,000).



XLVI XLVII XLVIII XXXVI

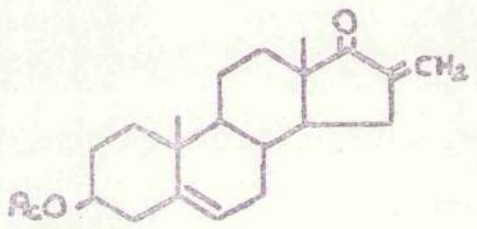
This is more in favour of a transoid $\alpha\beta$-unsaturated ketone (XLVI) than the cisoid type proposed by Corey[45]. Further, the enedione first isolated by Ruzicka et al.[29] by drastic oxidation of norfriedelanone (XXXVII) and designated by them norfriedelenedione is formulated by Corey[45] as (XLVIII). This formulation must be rejected since this compound has been shown to be bisnorfriedelenedione (XXXVI) (see page 34). However, on purely mechanistic grounds the conversion of norfriedelenone to bisnorfriedelenedione is better represented if the former has the cisoid structure (XLVII) viz. -

XLVII  XXXVI

The author has again examined the oxidation of norfriedelanone with selenium dioxide.

Oxidation of cerin or friedelin with chromic anhydride gives friedelin dicarboxylic acid. Pyrolysis of friedelin dicarboxylic acid anhydride gives norfriedelanone the physical constants of which are in good agreement with those quoted by Ruzicka et al.[29]. Selenium dioxide oxidation of norfriedelanone under mild conditions gives a compound, $C_{29}H_{46}O$, which agrees in melting point and specific rotation with the compound, $C_{29}H_{46}O$, designated norfriedelenone by Ruzicka[29]. However, the product obtained shows an absorption maximum at 2290 Å (ε,5,500) which is very different from the absorption maximum at 2540 Å (ε,16,000) reported by the Swiss workers[29]. This reaction was repeated several times under a variety of conditions and also exactly according to the experimental procedure adopted by Ruzicka[29], but in all cases the product had $\lambda_{max.}$ 2290 Å and not at 2540 Å, even after careful chromatography of the product. A search of the literature[46] revealed that the ultraviolet absorption spectrum of 17-oxo-androst-5:16(20)-dien-3β-yl acetate (XLIX) shows a maximum

at 2290 Å (ε,8,000). This is therefore convincing evidence that norfriedelenone is to be formulated as a cisoid $\alpha\beta$-unsaturated ketone (XLVII) in which the double bond is exomethylenic. Further proof of this was afforded by reduction of norfriedelenone with lithium aluminium hydride which gives a compound, $C_{29}H_{48}O$, which does not

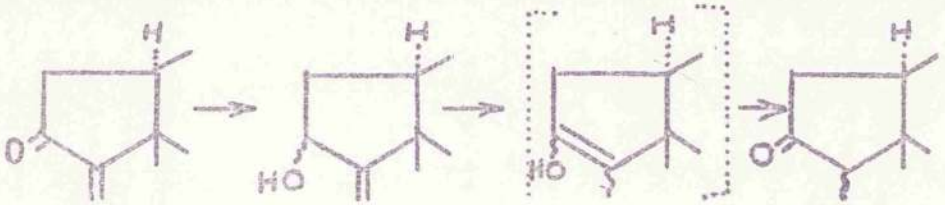


XLIX

show a colour with tetranitromethane. The ultraviolet absorption spectrum of this alcohol shows a maximum at 2040 Å the intensity of which (ε,1,100) is considerably lower than would be expected if norfriedelenone is to be formulated as a transoid $\alpha\beta$-unsaturated ketone (XLVI) in which the double bond is trisubstituted. Hence, the norfriedelenone $\lambda_{max.}$ 2290 Å is formulated as (XLVII).

The re-formulation of norfriedelenone may throw some light on one of the most peculiar reactions in the chemistry of friedelin in which it was claimed by Ruzicka[29] that Clemmensen reduction of norfriedelenone yields the parent saturated ketone norfriedelanone. However, if the first

step in the reaction is the reduction of the $\alpha\beta$ -unsaturated ketone (XLVII) to the allylic alcohol (L) the acid condition of the reaction medium could cause rearrangement of the double bond to form the enol (LI) which would then ketonise to give norfriedelanone (XXXVII).

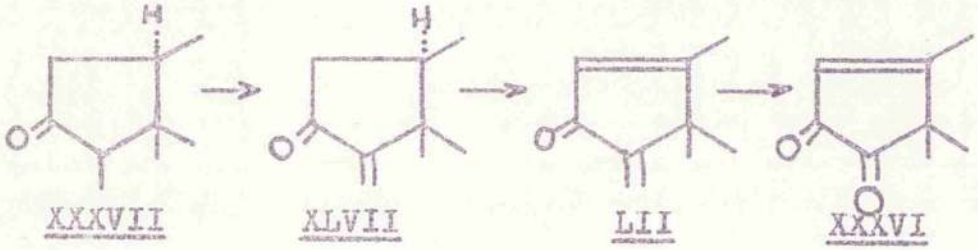


XLVII L LI XXXVII

The investigation of the degradation products of friedelin was continued by the drastic oxidation of norfriedelenone (XLVII) with selenium dioxide. This reaction resulted in the isolation of two products; a yellow orange coloured compound, $C_{28}H_{42}O_2$, bisnorfriedelenedione, and, in low yield, a colourless compound, $C_{29}H_{44}O$, which does not give a colour with ferric chloride or tetranitromethane and which shows a maximum at 2520 Å (ε,13,500) in the ultraviolet. On the basis of this evidence and its mode of formation, the compound, $C_{29}H_{44}O$, must be formulated as a conjugated dienone, for which, (if norfriedelenone (XLVII) and bisnorfriedelenedione (XXXVI) are correctly formulated), only one structure (LII) is possible. The compound, $C_{29}H_{44}O$, is therefore designated norfriedeladienone.

The isolation by Ruzicka *et al.*[29] from the oxidation of norfriedelanone (XXXVII) of a compound which shows the melting point and specific rotation of norfriedelenone (XLVII) and the ultraviolet absorption spectrum of norfriedeladienone (LII) cannot be explained.

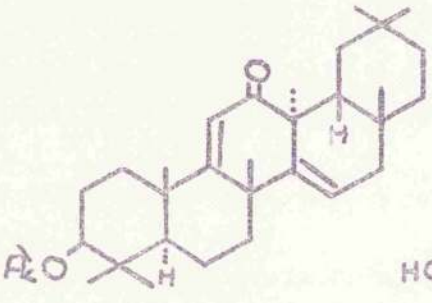
The oxidation of norfriedelanone with selenium dioxide is now considered to proceed as follows:-



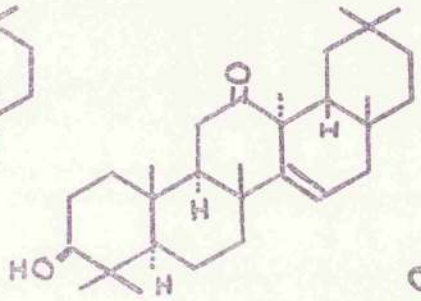
XXXVII XLVII LII XXXVI

The structure of friedelin having been established (apart from stereochemistry), attempts were made to effect a partial synthesis of friedelin from an oleanane derivative. Similarly, attempts were made to convert friedelin into a 3-oxygenated oleanane derivative. 12-Oxotaraxera -9(11): 14 -dienyl acetate (12-oxo-13-iso-oleana-9(11):14-dienyl acetate)(LIII) is recovered unchanged on treatment with mineral acid[48] i.e. it is not isomerised to the fully conjugated 12-oxo-oleana-9(11):13(18)-dienyl acetate. Reduction of 12-oxotaraxera-9(11):14-dienyl acetate with lithium in liquid ammonia[15] gives 12-oxotaraxer-14-en-3β-ol (LIV), which it was hoped would yield 3:12-dioxofriedelane

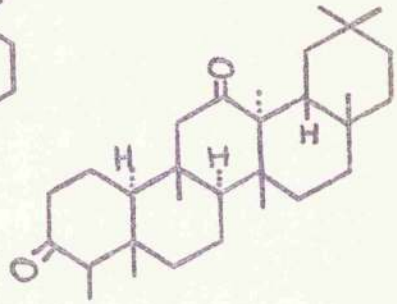
(LV) on treatment with mineral acid. However, treatment



LIII



LIV

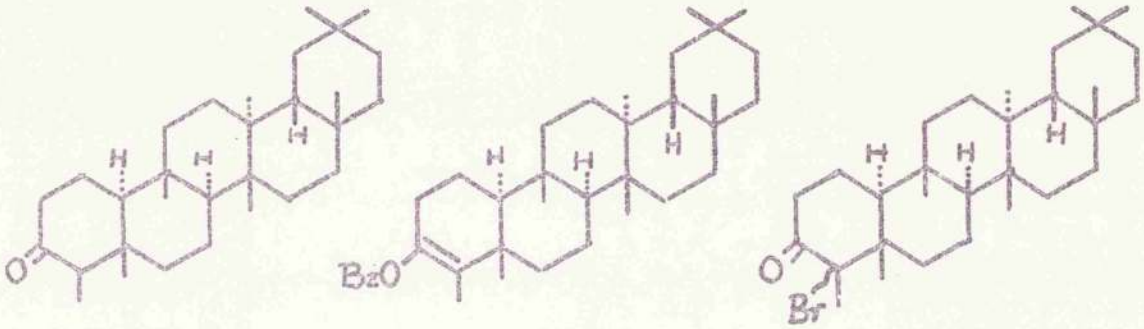


LV

of 12-oxotaraxer-14-en-3β-ol (LIV) with hydrochloric acid gives a gum which after acetylation and chromatography does not give a homogeneous crystalline solid, at which point the project was abandonned.

The conversion of friedelin (XVIII) to a β-amyrin derivative was attempted via 4-bromofriedelin (LVI) which was prepared by bromination of friedelin enol benzoate (LVII). 4-Bromofriedelin is unaffected by refluxing in a solution of pyridine or stabilised glacial acetic acid (over short periods). Treatment of 4-bromofriedelin with hydrochloric acid gives a mixture from which a homogeneous product could not be isolated. Wolff-Kishner reduction of this mixture did not give the isomeric mixture of olean-13(18)-one and 18α-olean-12-one.[47] Corey and Ursprung[45] claim that dehydrobromination of (LVI) gives an unconjugated unsaturated ketone (see page 37) which could

not be isomerised to a conjugated structure. An attempt



XVIII LVII LVI

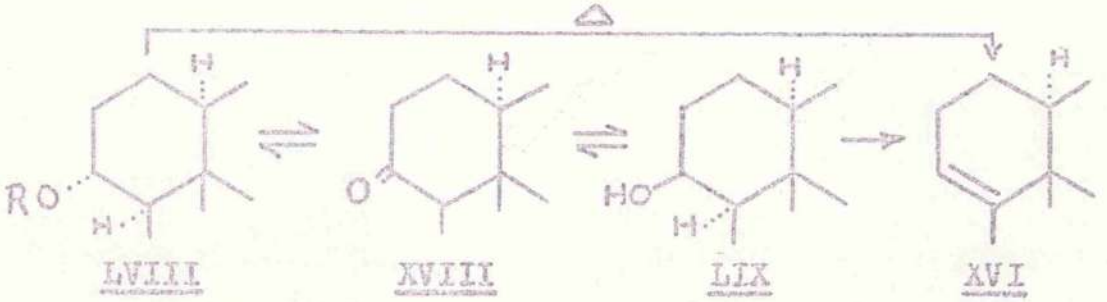
to dehydrobrominate (LVI) with silver acetate in pyridine gives a compound, the physical constants of which are in good agreement with those quoted for cerin acetate, and which does not depress the melting point of that compound.

Finally, 4-bromofriedelin (LVI) was successfully dehydrobrominated by refluxing with unstabilised acetic acid (under vacuum) to yield a compound $C_{30}H_{48}O$, which does not give a colour with tetranitromethane and which shows a maximum at 2270 Å (ε,4,500) in the ultraviolet. Reduction of this compound with lithium aluminium hydride gives a mixture of isomeric alcohols which does not give a homogeneous product on treatment with hydrochloric acid. Treatment of the compound, $C_{30}H_{48}O$, with hydrochloric acid gives a compound $C_{30}H_{48}O$ which shows a maximum at 2060 Å (ε, 6,600) in the ultraviolet region. It gives a yellow colour with tetranitromethane but is is not identical with any known

β-amyrenone isomers or with the unconjugated unsaturated ketone isolated by Corey et al.[27]

IV Stereochemistry of Friedelin

The only asymetric centre in friedelin which is not completely defined by the acid isomerisation of friedelene is that atcarbon atom C_4. Since friedelin is recovered unchanged after treatment with alkali or acid the orientation of the methyl group attached to carbon atom C_4 is the more stable of the two possible arrangements. Now friedelanol and epifriedelanol are C_3-epimers since each may be re-oxidised to friedelin (XVIII); friedelanol is the equatorial (α-)alcohol (LVIII; R=H) because it is formed from friedelin when equilibrating conditions are used and it is also formed when epifriedelanol is heated with sodium pentyloxide in air. The axial (β-) alcohol, epifriedelanol (LIX), is readily



LVIII XVIII LIX XVI

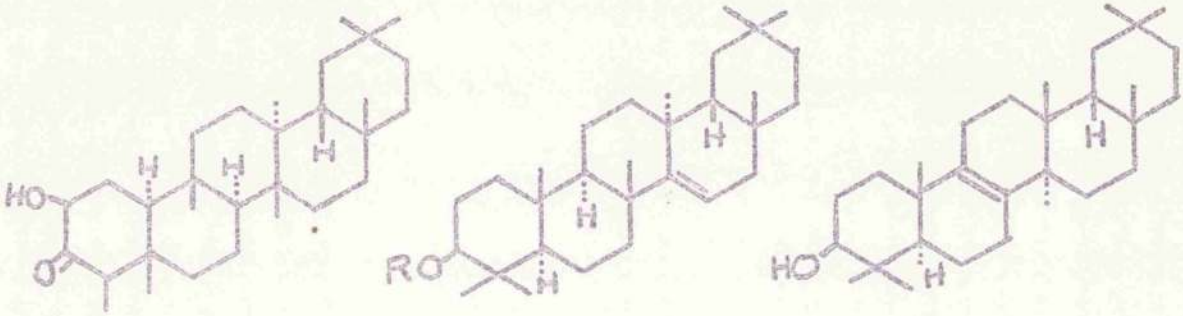
dehydrated under ionic conditions to give friedel-3-ene (XVI) in high yield, from which it must be concluded that this 3:4-ionic elimination is trans-diaxial, i.e. that the 4-methyl group is β-orientated. This decision is supported by the

formation of friedel-3-ene (cis-elimination) by pyrolysis of friedelanyl benzoate (LVIII, R=Bz).

Friedelin contains an unhindered ketone group in that it reacts with the usual carbonyl reagents and is reduced to friedelane by the Clemmensen and Wolff-Kishner methods under normal (non-forcing) conditions. It is somewhat surprising, therefore, to find that reduction of friedelin with lithium aluminium hydride gives the axial alcohol epifriedelanol in high yield. It is suggested that this is due to the directive effect of the 5β-axial methyl group which shields the carbonyl from frontal attack. The terminal position of the carbonyl group, however, renders it fully exposed to attack from the rear; for this reason the product obtained by oxidation of friedel-3-ene (XVI) with osmic acid is represented as the 3α:4α-diol. This behaviour of friedelin is comparable with that of cholest-4-one[49]. Another example of the directive effect exerted by the 5-axial methyl group is the hydrogenation of friedel-3-ene which gives friedelane in high yield.

The constitution of cerin, which occurs together with friedelin in cork wax, follows from that of friedelin (XVIII). Cerin is a saturated α-hydroxy ketone since on oxidation with chromic acid it gives a saturated α-diketone and friedelin-dicarboxylic acid $C_{30}H_{50}O_4$[29]. The infrared and ultraviolet

absorption spectrum of cerin show that the α-hydroxyl group is equatorial[43]. Cerin is therefore either 2β-hydroxy-friedelan-3-one (LX)(2β-hydroxyfriedelin) or 3α-hydroxyfriedelan-2-one.



LX IV LXI

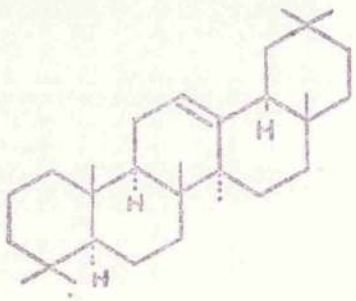
Treatment of cerin acetate with zinc dust in acetic acid[50] gives friedelin from which it is concluded that cerin is (LX).

The elucidation of the structure and stereochemistry of friedelin and its conversion into a mixture of olean-13(18)-ene and 18α-olean-12-ene support the initial postulate that β-amyrin and friedelin (XVIII) are genetically related and it is not unreasonable to assume that, since taraxerol (IV; R=H) is considered to be an intermediate in the biogenetic degeneration of β-amyrin, naturally occurring pentacyclic triterpenoids will be discovered, such as the euphol type (LXI) which will represent subsequent stages in the degeneration of taraxerol to friedelin.

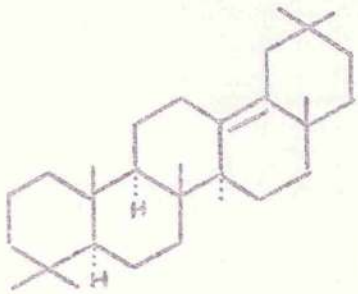
SECTION B

Olean-13(18)-ene

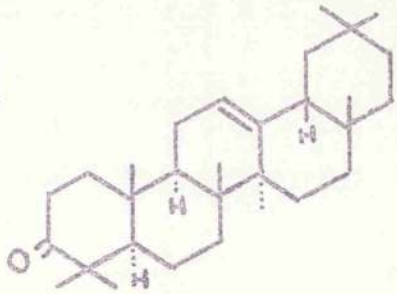
Treatment of friedelene m.p. 250-258°, $[\alpha]_D$ + 53°, with a hydrochloric-acetic acid mixture at reflux over seventeen hours gives a hydrocarbon which after repeated crystallisation has m.p. 186-187° and $[\alpha]_D$ - 20° ± 2° (see page 22). An examination of the literature revealed that this hydrocarbon may be olean-13(18)-ene, for which however, a diversity of constants was reported. It seemed desirable, therefore, to investigate these differences with a view to the identification of the acid isomerisation product from friedelene.



I



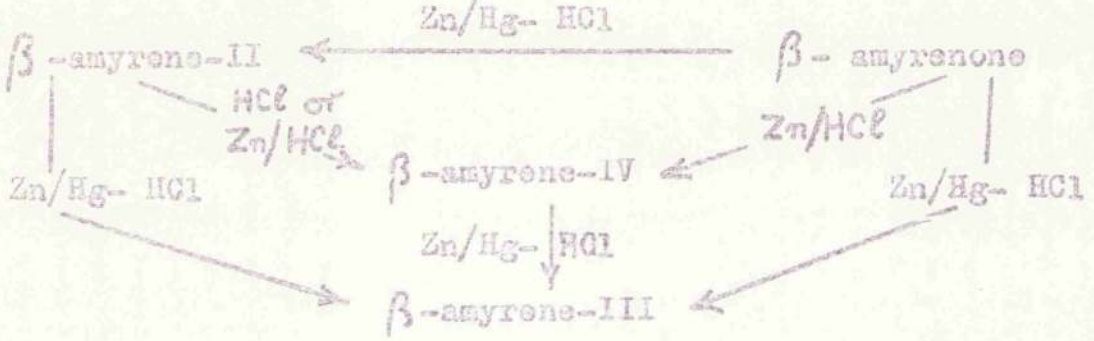
II



III

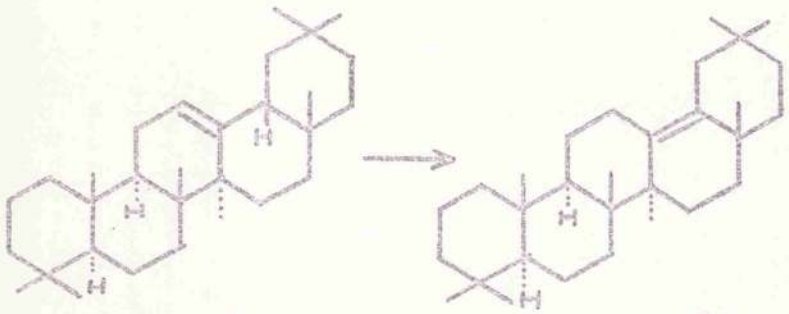
In 1933, Winterstein and Stein[52] reported that treatment of olean-12-ene (β-amyrene-II) (I) with hydrochloric acid and amalgamated zinc yields a hydrocarbon, β-amyrene-III, m.p. 187-189°, $[\alpha]_D$ -22°, and this hydrocarbon is also obtained by similar treatment of 3-oxo-olean-12-ene (III). These workers also described a hydrocarbon named β-amyrene-IV, m.p. 162-163°, $[\alpha]_D$ + 51° and formed by treatment of β-amyrene-II, with zinc

and hydrochloric acid. Treatment of β-amyrene-IV with amalgamated zinc in hydrochloric acid converts it into β-amyrene-III[52]. Ruzicka, Schellenberg and Goldberg[53] claimed that Wolff-Kishner reduction of 3-oxo-olean-12-ene (III) gives β-amyrene-IV.



Takeda[54] showed that Clemmensen reduction of taraxerone (skimmione 3-oxo-13-iso-olean-14-ene) gives an unsaturated hydrocarbon $C_{30}H_{50}$, m.p. 189-190°, $[\alpha]_D$ - 20·5° which is identical with β-amyrene-III. According to Takeda[54], β-amyrene-III is olean-13(18)-ene (II), a view which was supported by Jones and his collaborators[55,56], who showed that the isomerisation of β-amyrene-II (olean-12-ene) (I) with a hydrochloric-acetic acid mixture in the presence or absence of zinc or mercury gives β-amyrene-III. The rotation quoted by Jones *et al.*[56] for β-amyrene-III ($[\alpha]_D$ - 33°), is appreciably more laevorotatory than the value obtained by Winterstein and Stein[52]. Jones *et al.*[56] attributed this difference in specific rotation to the higher purity of their

hydrocarbon. Further investigation by Jones and his collaborators[56] showed that if the isomerisation is not carried to completion, products of variable rotation are obtained which correspond with the values reported for β-amyrene-IV; they showed that this hydrocarbon is a mixture of β-amyrene-II and β-amyrene-III. According to Beaton, Spring, Stevenson, Strachan and Stewart[33], a hydrocarbon obtained by brief Clemmensen reduction of taraxerone, as described by Koller et al.[57] is a similar mixture. Finally, Jones et al.[56] demonstrated that the product obtained by Wolff-Kishner reduction of 3-oxo-olean-12-ene is β-amyrene-II (olean-12-ene) (I) and not β-amyrene-IV as reported by Ruzicka, Schellenberg and Goldberg[53]. Jones and his co-workers[56] concluded that treatment of olean-12-ene (I) with mineral acid results in double bond isomerisation and that when the reaction is carried to completion the product is olean-13(18)-ene, m.p. 190-191°, $[\alpha]_D$ - 33° viz. -



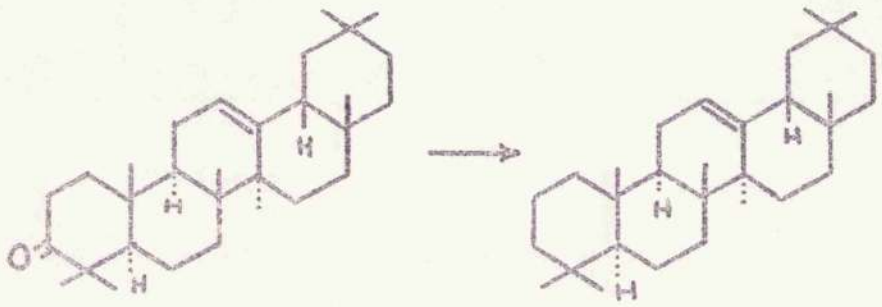
I II

The melting point and specific rotation given in the literature for preparations of olean-13(18)-ene(II) in which the reaction mixture had been exposed for a long time to mineral acid are given below.

Method	m.p.	$[\alpha]_D$ $CHCl_3$	Ref.
Clemmensen red$^{n.}$ of Olean-12-en-3-one	187-189.5°	-22°	52
Clemmensen red$^{n.}$ of Olean-12-en-3-one	191.5-192.5°	-32.5°	55
Clemmensen red$^{n.}$ of Taraxerone	189-190°	-20.5°	54
Clemmensen red$^{n.}$ of Taraxerone	184(183-184°)	-21°(-24°)	57
Olean-12-ene + HCl + acetic acid	190-191°	-33°	56
Olean-12-ene + HCl + acetic acid	186-187°	-20°	47
Acid catalysed isomer of olean-12-ene	186-187°	-13.9°	45
Friedelene + HCl	186-187°	-20°	47
Friedelanol + Phenol + HCl	186-187°	-12.5°	45
Friedelene + $ZnCl_2$ + Acetic Acid	183-184°	-13°	58

In order to establish whether the product obtained from the acid isomerisation of friedelene is identical with olean-13(18)-ene (β-amyrene-III) (II), the hydrocarbon, olean-12-ene (I)

was prepared by Wolff-Kishner reduction of 3-oxo-olean-12-ene (III).

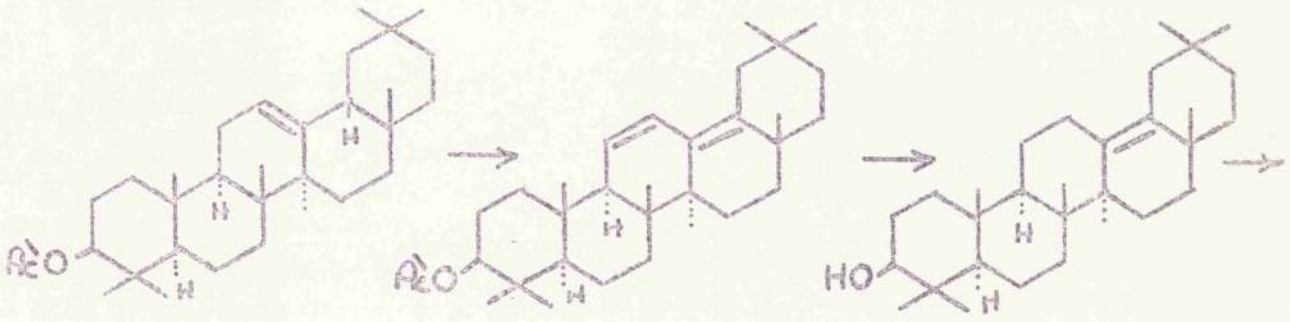


III I

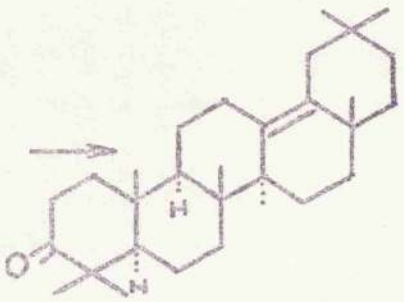
Treatment of olean-12-ene (I) with a hydrochloric-acetic acid mixture at reflux temperature for 17 hours gives a product $[\alpha]_D$ +10° ± 2°, repeated crystallisation of which yields a hydrocarbon $[\alpha]_D$- 20° ± 2°. The specific rotation and melting point of this hydrocarbon are not changed by repeated crystallisation or by careful chromatography and the product does not depress the melting point of the material obtained by acid isomerisation of friedelene. The rotation of this product is not in good agreement with that quoted by Jones *et al.*[55] who give $[\alpha]_D$- 33° for olean-13(18)-ene (II). The difficulty attending the isolation of the hydrocarbon $[\alpha]_D$- 20° suggested that the initial reaction product $[\alpha]_D$ *ca.* - 10°, is an equilibrium mixture of isomers. This view was confirmed by the observation that treatment of the hydrocarbon, $[\alpha]_D$- 20° ± 2°, with hydrochloric-acetic acid

mixture regenerates the mixture $[\alpha]_D$ - 10° ± 2°. Hence, if the product $[\alpha]_D$ - 20° ± 2° is pure olean-13(18)-ene then olean-13(18)-ene is unstable to mineral acid.

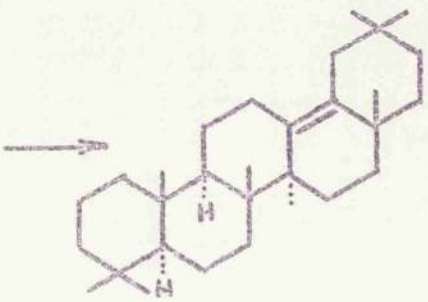
Olean-13(18)-ene was therefore prepared by methods which did not involve the use of mineral acid. Brief oxidation of olean-12-en-3β-yl acetate (β-amyrin acetate) (V) with selenium dioxide in acetic acid gives oleana-11:13(18)-dien-3β-yl acetate (VI). Hydrolysis of the heteroannular dienyl acetate gives oleana-11:13(18)-dien-3β-ol[60], which is converted to the unsaturated hydrocarbon olean-13(18)-en-3β-ol[55,61] (VII) by hydrogenation over a platinum catalyst prepared from platinum oxide from which traces of water-soluble platinum salts had been removed by careful washing with distilled water. The product is oxidised by the chromic acid-pyridine complex to 3-oxo-olean-13(18)-ene (VIII).



V VI VII



VIII

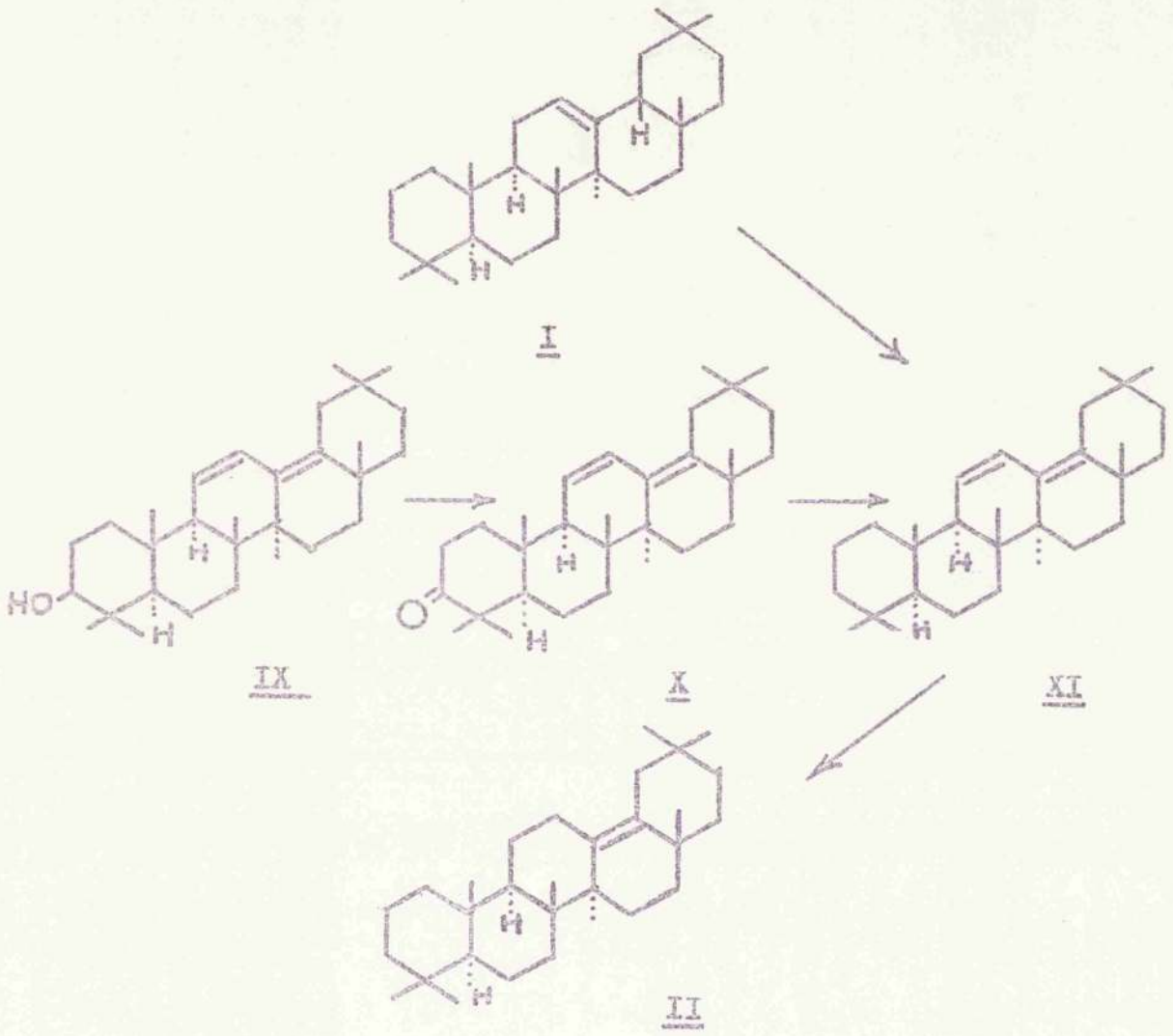


II

Wolff-Kishner reduction of 3-oxo-olean-13(18)-ene (VIII) gives a hydrocarbon m.p. 187-188° $[\alpha]_D$ - 48°. In contrast with the product obtained by methods in which mineral acid is employed, this hydrocarbon attains a constant specific rotation after one crystallisation. It is noteworthy that the compound m.p. 187-188°, $[\alpha]_D$ - 48°, does not depress the melting point of the product $[\alpha]_D$ - 20° ± 2° obtained by the action of mineral acid on friedelene or olean-12-ene.

Olean-13(18)-ene (II) was also prepared by oxidation of oleana-11:13(18)-dien-3β-ol (IX) with chromic acid to 3-oxo-oleana-11:13(18)-diene[62] (X), Wolff-Kishner reduction of which gives the conjugated heteroannular diene, oleana-11:13(18)-diene (XI); this hydrocarbon was also prepared by the oxidation of olean-12-ene with selenium dioxide[60]. Hydrogenation of oleana-11:13(18)-diene over a platinum catalyst (from purified platinum oxide) gives olean-13(18)-ene, m.p. 186-188°, $[\alpha]_D$ - 48°, identical with the specimen

obtained as described above.



I

IX

X

XI

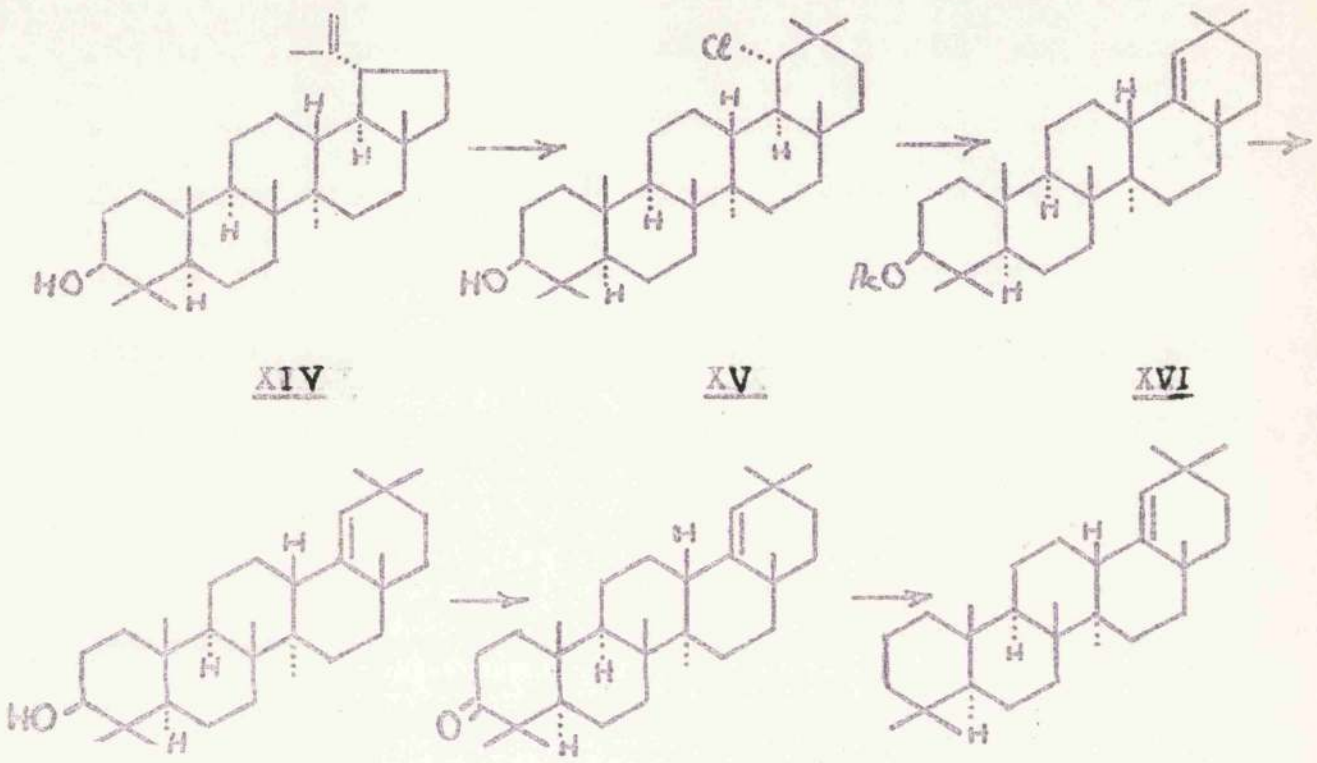
II

The hydrogenation of oleana-11:13(18)-diene at 70-80° over platinum described by Koller and his collaborators[57] gave a hydrocarbon $[\alpha]_D$ - 27°. The low rotation of their product may have been due to the presence of traces of mineral acid, derived from the catalyst, in the reaction solution.

Treatment of olean-13(18)-ene ($[\alpha]_D$ - 48°) with mineral

acid gives a product $[\alpha]_D$ ca. - 10°. Repeated crystallisation of this hydrocarbon was accompanied by a gradual change in specific rotation which finally had m.p. 186-187°, $[\alpha]_D$ - 20° ± 2° identical with the product obtained by treatment of olean-12-ene and friedelene with mineral acid described above.

With the object of identifying the hydrocarbon $[\alpha]_D$ - 20°, 18α-olean-12-ene (XII) and olean-18-ene (germanicene) (XIII) were prepared. The preparation of 18α-olean-12-ene was carried out in these laboratories by Dr. M.B.E. Fayez. Olean-18-ene (XIII) was prepared from lupeol by the method described by Halsall, Jones and Meakins[59]. Treatment of lupeol (XIV) with dry hydrochloric acid yields 19-chlor-olean-3β-ol (XV). Dehydrochlorination is accomplished by refluxing with acetic anhydride to yield olean-18-en-3β-yl acetate (XVI). Hydrolysis of this compound with alkali, followed by oxidation with the chromic acid-pyridine complex gives 3-oxo-olean-18-ene (XVII), Wolff-Kishner reduction of which gives olean-18-ene (germanicene) (XIII) m.p. 173-175°, $[\alpha]_D$ + 5° viz. -



XIV XV XVI

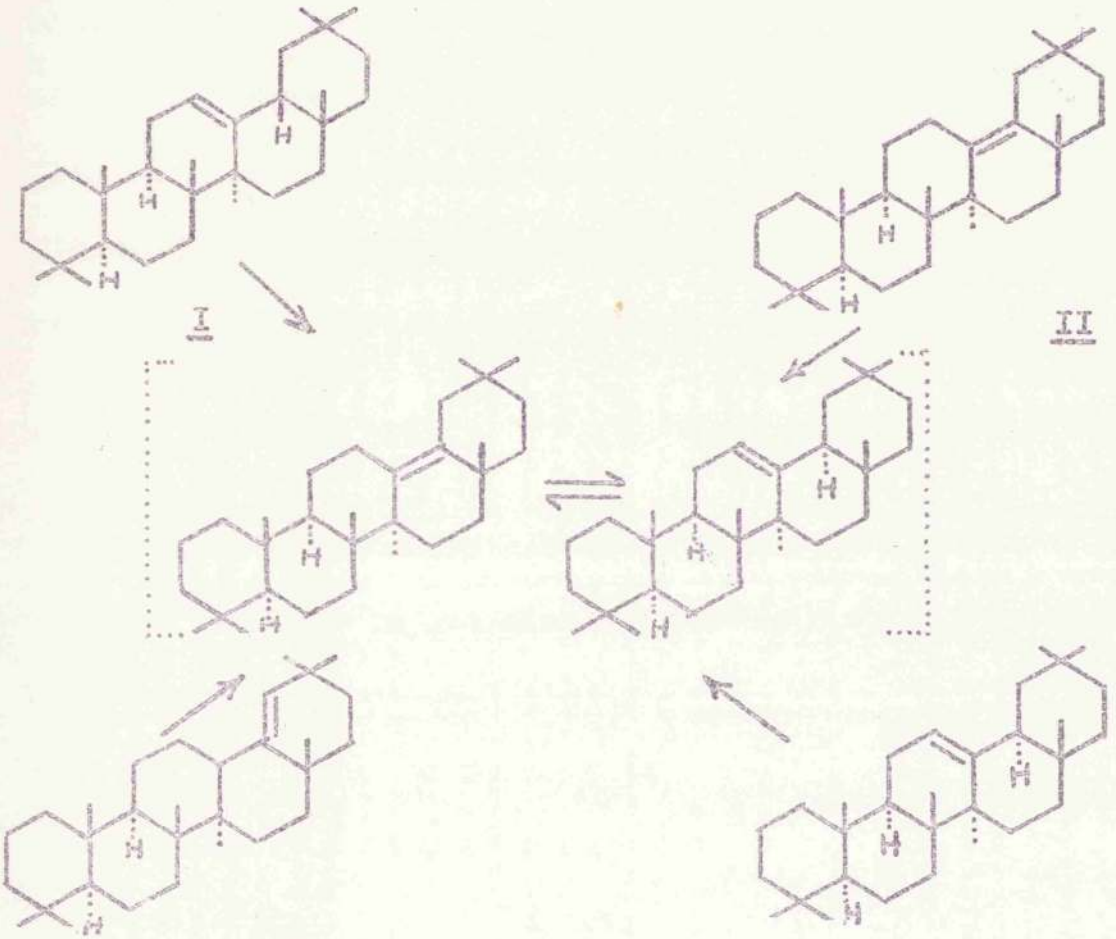
XVII XIII

Treatment of olean-18-ene (XIII) and 18α-olean-12-ene (XII) under the acid conditions employed in the acid isomerisation of olean-12-ene (I), olean-13(18)-ene (II) and friedelene, yields a product $[\alpha]_D$ ca. - 10° ± 2° which on repeated crystallisation gives the hydrocarbon $[\alpha]_D$ - 20° ± 2°. Thus, olean-12-ene (I), olean-13(18)-ene (II) 18α-olean-12-ene (XII) and olean-18-ene (XIII) are unstable to mineral acid and each gives the equilibrium mixture of isomers $[\alpha]_D$ ca. - 10° and after crystallisation the hydrocarbon $[\alpha]_D$ - 20° ± 2°.

18α-olean-12-ene, $[\alpha]_D$ + 37°, has m.p. 186-188° and olean-13(18)-ene, $[\alpha]_D$ - 48°, has m.p. 187-188° and random mixtures of the two hydrocarbons do not show greatly depressed melting points. This suggested that the hydrocarbon $[\alpha]_D$ - 20° ± 2°, is an inseparable (or difficultly separable) mixed crystal of olean-13(18)-ene (2 parts) and 18α-olean-12-ene (1 part). This view was confirmed by the preparation of a synthetic mixture of these two hydrocarbons in these proportions, a single crystallisation of which gave the hydrocarbon, m.p. 186-187°, $[\alpha]_D$ - 20° ± 2°, identical with the product isolated from the mixtures obtained by treatment of the hydrocarbons (I), (II), (XII), (XIII) with a hydrochloric-acetic acid mixture. Furthermore a synthetic mixture of olean-13(18)-ene and 18α-olean-12-ene in the ratio 4:3 gives, after one crystallisation, a product $[\alpha]_D$ - 10°, which is indistinguishable from the equilibrium mixture in its behaviour on crystallisation when the mixed crystal $[\alpha]_D$ - 20° ± 2° is obtained.

Mixtures of pairs of the four homogeneous hydrocarbons were prepared, which, when they contained either olean-12-ene or olean-18-ene, did not give a product which could be characterised. Furthermore a mixture of equal parts of germanicene, 18α-olean-12-ene and olean-13(18)-ene differs from

the equibilbrium mixture in that it forms crystals, the specific rotation of which ($[\alpha]_D \pm 0^\circ$) does not change after

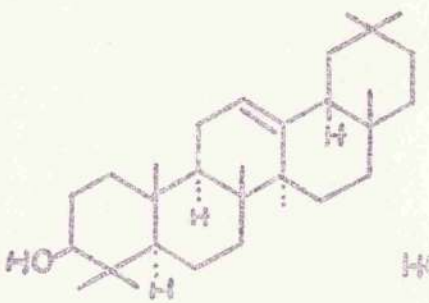


five crystallisations. Although the mixed crystal of olean-13(18)-ene and 18α-olean-12-ene $[\alpha]_D - 20^\circ \pm 2^\circ$ could not be isolated from the three component mixture by crystallisation, treatment of the mixture ($[\alpha]_D \pm 0^\circ$) with a hydrochloric-acetic acid mixture gives the equilibrium mixture $[\alpha]_D$ ca. $- 10^\circ$, from which the mixed crystal $[\alpha]_D - 20^\circ \pm 2^\circ$ was obtained by crystallisation. In view of these facts the behaviour of the unsaturated hydrocarbons (I), (II), (XII)

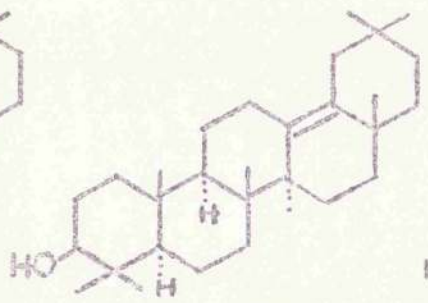
and (XIII) with mineral acid is represented as shown above.

The relatively low laevorotations of the hydrocarbons obtained by Corey and Ursprung[45] are not difficult to explain, since the isolation of a hydrocarbon of constant specific rotation from the mixture obtained by acid isomerisation of olean-12-ene requires many crystallisations during which the rotation increases slowly from ca. -10° to ca. -20°. The high laevorotations observed by Jones et al.[55,56] are however anomolous.

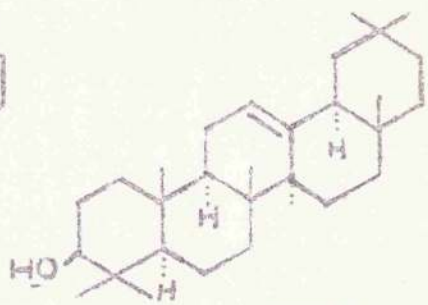
This investigation has shown that β-amyrene-III[52] (or skimmiene-III)[57] is not olean-13(18)-ene but is in fact a mixed crystal of olean-13(18)-ene and 18α-olean-12-ene and that neither zinc nor mercury is essential for the acid induced isomerisation of olean-12-ene (β-amyrene-II) to β-amyrene-III. A more important conclusion is that treatment of olean-12-en-3β-ol (β-amyrin) (XXII) with mineral acid will result in a mixture of δ-amyrin (olean-13(18)-en-3β-ol) (VII) and 18α-olean-12-en-3β-ol (XXIII).



XXII



VII

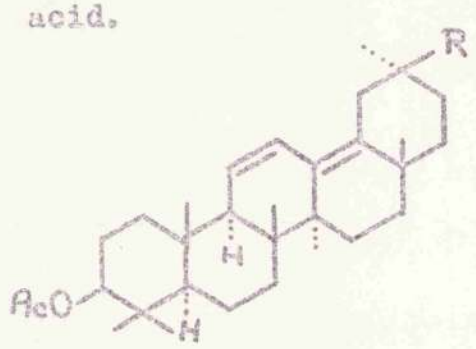


XXIII

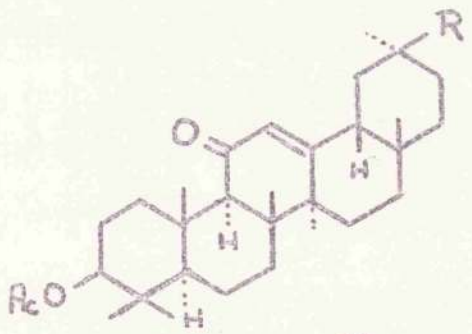
SECTION C

The Structure of the Acetate $C_{33}H_{46}O_7$ Derived from Glycyrrhetic Acid.

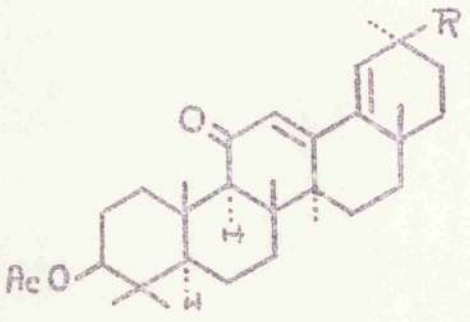
It has been known for a number of years that oxidation of oleana-11:13(18)-dienyl acetate (I; R=Me) with chromic acid[66] gives, in high yield, an acetate, $C_{32}H_{46}O_5$, (O_5 acetate). The O_5 acetate is also obtained as a major product of the oxidation of 11-oxo-olean-12-en-3β-yl acetate (II; R=Me)[67] or of 11-oxo-oleana-12:18-dienyl acetate (III; R = Me), with selenium dioxide[67] and of olean-13(18)-en-3β-yl acetate (IV; R =Me) with chromic acid[68]. Compounds directly related to the O_5 acetate are obtained by the same methods from corresponding derivatives of oleanolic acid and glycyrrhetic acid.



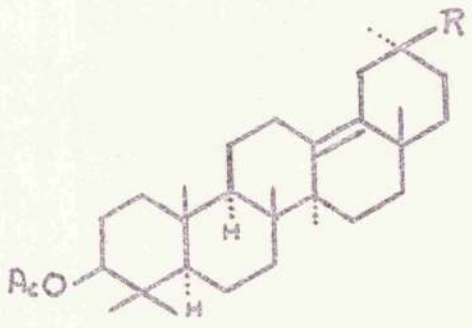
I



II

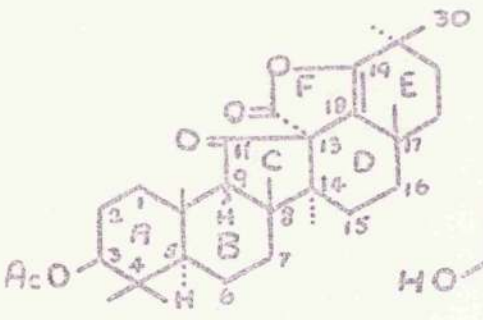


III

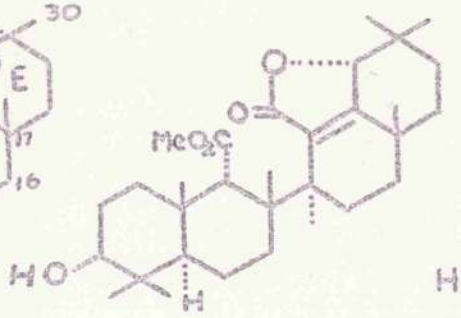


IV

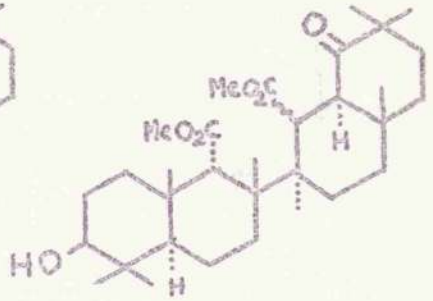
McKean and Spring[69] suggested that the constitution of the O_5 acetate is represented by (V). This proposal is supported by the behaviour of the O_5 acetate with methanolic potassium hydroxide when an $\alpha\beta$-unsaturated lactone ester, $C_{31}H_{48}O_5$, formulated as (VI) is obtained, vigorous alkaline hydrolysis of which gives an amorphous acid characterised as the crystalline saturated dimethyl-oxo-ester, $C_{32}H_{52}O_6$, represented by (VII). The expression (V) affords a satisfactory



V

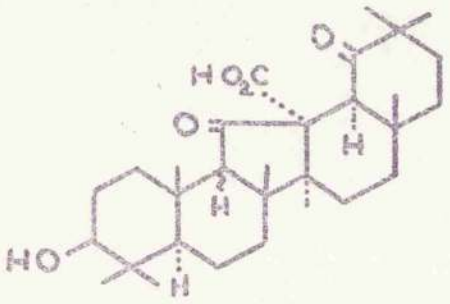


VI

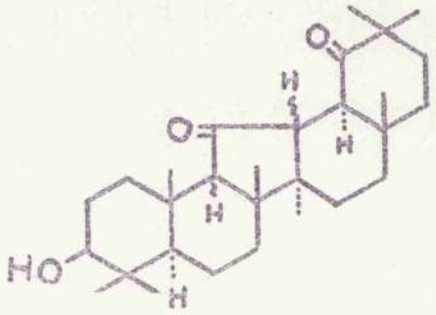


VII

interpretation of the conversion of the O_5 acetate into a hydroxy ketone, $C_{29}H_{46}O_3$, (VIII), the formation of which is attributed to hydrolysis of the 3-acetate and the $\beta\gamma$-unsaturated lactone groups with spontaneous decarboxylation of the resulting β-oxo-acid (VIIIa). The evidence now presented supports the formula (V) proposed by McKean and Spring[69], by a study of the analogous ester, $C_{33}H_{46}O_7$ (IX) obtained from glycyrrhetic acid.



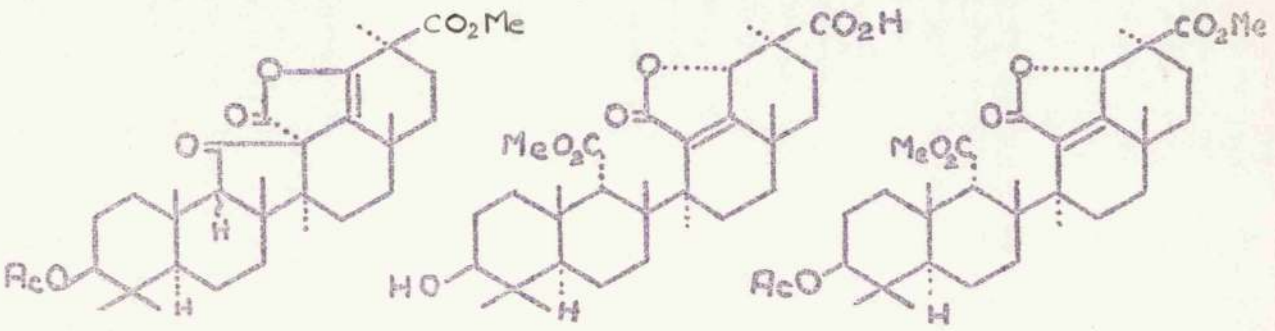
VIIIa



VIII

Oxidation of methyl glycyrrhetate acetate (II; R = CO_2Me) with selenium dioxide gives an ester, $C_{33}H_{46}O_7$, previously prepared by Jeger, Norymberski and Ruzicka[68] by oxidation with chromic acid of methyl 3β-acetoxyoleana-11:13(18)-dien-30-oate (I; R = CO_2Me) and methyl 3β-acetoxyolean-13(18)-en-30-oate (IV; R = CO_2Me) and by oxidation of methyl-3β-acetoxy-11-oxo-oleana-12:18-dien-30-oate (III; R = CO_2Me) with selenium dioxide. The ester, $C_{33}H_{46}O_7$, resembles the O_5 acetate in giving a faint yellow colour with tetranitromethane and in its ultraviolet absorption spectrum which shows a broad band near 2300 Å (ε, 4,400). These properties, its molecular formula, and the methods by which it is prepared support the view that it has a structure analogous to that of the O_5 acetate and this view is confirmed by the reactions below. If the O_5 acetate is correctly represented by (V), the ester $C_{33}H_{46}O_7$ from

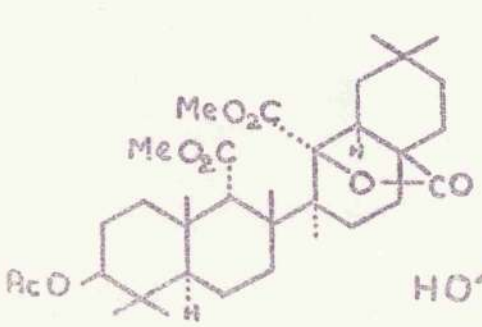
glycyrrhetic acid is (IX). Treatment of the ester (IX)



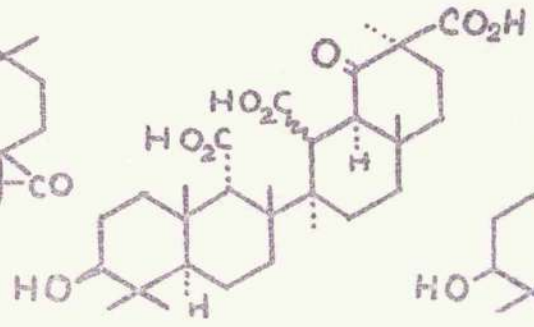
IX X Xa

with methanolic potassium hydroxide or with methanolic sodium methoxide, gives, in good yield, a crystalline acid, $C_{31}H_{46}O_7$. In addition to a carboxyl group, this compound contains a methoxycarbonyl and a hydroxyl group and it was characterised by the preparation of an acetate dimethyl ester, $C_{34}H_{50}O_8$. Furthermore, the acid, $C_{31}H_{46}O_7$, contains an $\alpha\beta$-unsaturated lactone group as shown by the absorption spectrum ($\lambda_{max.}$ 2240 Å; ε 11,000) and by a positive Legal test. These properties and its method of formation show that it is an analogue of the $\alpha\beta$-unsaturated lactone ester (VI) and that its formula is to be derived from that of (VI) by the replacement of the 30-methyl by a carboxyl group. The formula (X) is to be preferred to that of the isomer in which carbon atom C_{30} is a methoxycarbonyl group, and carbon atom C_{11}, a carboxyl group because the methyl ester (VI) is the major product obtained by treatment of

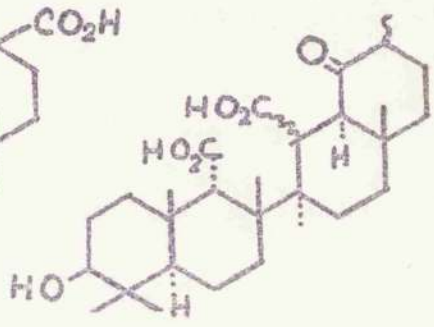
the O_5 acetate with methanolic potassium hydroxide. On the assumption that ring E in the derived acetate dimethyl



XI



XII

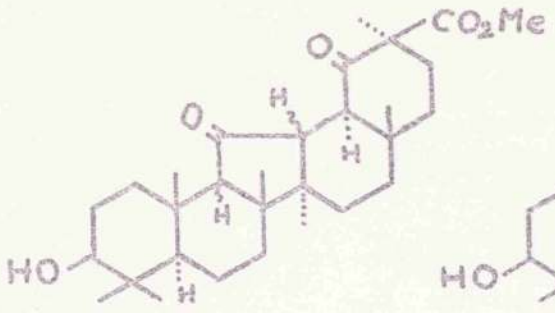


XIII

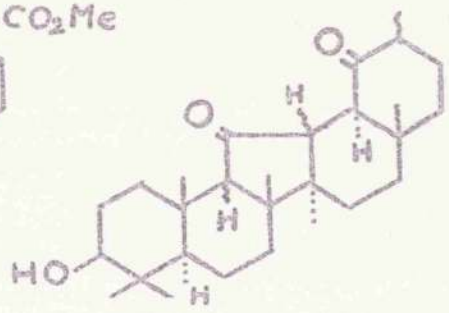
ester (Xa) has the chair conformation, the 30-methoxycarbonyl group is equatorial and, in analogy with the behaviour of methyl 18α-glycyrrhetate[70], relatively easy hydrolysis of this group is expected; treatment of the acetate dimethyl ester (Xa) with 4% alcoholic potassium hydroxide regenerates the monomethyl ester. The stability to alkali of the methoxycarbonyl group in both (VI) and (X) shows that it is axially bound and that this is the more stable of the two possible arrangements at carbon atom C_9. The C_9 axial ester (XI) derived from oleanolic acid is known to be more stable than its C_9 epimer[71,72].

An attempt was made to confirm the formula (X) for the acid, $C_{31}H_{46}O_7$, by alkaline hydrolysis using forcing conditions in the hope that the saturated oxo-dicarboxylic acid (XIII) would be formed via the unstable

oxo-tricarboxylic acid (XII). The attempt was not conclusive because the acid product is not crystalline and does not give crystalline derivatives. Proof of the proximity of the enol lactone and the methoxycarbonyl in the O_7 ester was obtained by hydrolysis of this compound with aqueous alcoholic alkali, a crystalline hydroxy-diketone, $C_{28}H_{44}O_3$ being isolated in good yield. The infrared absorption of the hydroxy diketone (XV) which was



XIV



XV

characterised as its acetate, $C_{30}H_{46}O_4$, contains bands at 1720 (5-ring ketone) and at 1720 cm^{-1} (6-ring ketone), values in good agreement with those observed for the higher homologue[69] (VIII). In each case the 5-ring carbonyl band is at a lower frequency than usual.

The lactone-carbonyl group in the O_5 acetate is α-orientated because only this arrangement will allow the junction of the two fragments A/B and D/E/F through a methylene group bridging C_9 and C_{13} with either α- or β-configuration at carbon atom C_9. The configuration at

carbon atom C_9 in the O_5 acetate is the more stable arrangement because the compound is recovered unchanged after prolonged treatment with mineral acid[67]. Although the reasons given above indicate that the 9-methoxycarbonyl groups in (VI) and (X) are α-orientated it does not follow that the 9-hydrogen atoms in the parents (V) and (IX)[69] are β-orientated, since inversion at carbon C_9 may accompany, precede, or follow, methanolysis of the 11:13 bond. As stated above, if ring E in the lactone (X) has the chair conformation, the carboxyl group (β) is equatorial, a conclusion supported by the ease of hydrolysis of the corresponding ester; it follows that the 19-hydrogen atom in the lactones (VI) and (X) are β-orientated since the equatorial C_{19}-bond must be part of the unsaturated lactone ring. The 18-hydrogen atom in (XV) and (VIII) is provisionally represented as α-orientated because of the relative ease with which the 30-methoxycarbonyl group in (IX) is hydrolysed by aqueous alkali, a property which suggests that in the intermediate (XIV) the methoxycarbonyl group is equatorial. This can only be a provisional allocation because hydrolysis of the methoxycarbonyl group may be facilitated by the neighbouring carbonyl group.

Thus, the structure for the O_5 acetate (V) postulated by McKean and Spring[69] is confirmed and the stereochemistry of the O_5 ester and its glycyrrhetic analogue deduced by a comparison of their behaviour under similar conditions.

EXPERIMENTAL

Rotations were measured in $CHCl_3$ and ultraviolet absorption spectra in EtOH. Grade II alumina and light petroleum b.p. 60-80°, were used for chromatography.

Friedelin (Friedelan-3-one) (Friedelanone). - Cork (2 lb., 16-32 mesh) was extracted with ethyl acetate (12ℓ) or with boiling benzene (12ℓ.) for 7 hr. The extracted matter was boiled with chloroform (800 c.c.), the mixture concentrated to 300 c.c., and, after cooling, the solid (4·3 g.) was collected. The filtrate was evaporated to dryness and a solution of the residue in benzene was chromatographed on alumina (12 x 1½"). Elution with benzene (2ℓ.) followed by crystallisation of the eluate (3·5 g.) from chloroform-acetone gave friedelanone as needles, m.p. 255-262°, m.p. 264-266° (vac.), $[\alpha]_D$ -22°, -21° (c, 2·3, 1·1). Drake and Jacobsen[23] give m.p. 255-261°, $[\alpha]_D$ - 29°, Ruzicka, Jeger and Ringnes[29] give m.p. 264-265° (vac), $[\alpha]_D$ - 28° and Bruun[34] gives m.p. 262-263° (vac.), $[\alpha]_D$ - 21°.

Hydrogenation of Friedelanone. - A solution of friedelanone (500 mg.) in stabilised acetic acid (200 c.c.) was treated with a solution of hydrobromic acid (48%; 0·1 c.c.) in acetic acid (10 c.c.). The reaction solution was shaken for 1 hr. at 90° with freshly reduced platinum catalyst (250 mg. PtO_2) in an

atmosphere of hydrogen. The catalyst was removed and the solution reduced to dryness under reduced pressure. A solution of the solid in benzene was chromatographed on alumina. Elution with benzene gave a fraction, crystallisation of which from chloroform-methanol yielded needles, m.p. 255-260°, 263-265° (vac.) $[\alpha]_D$ - 23° (c, 1·5), which was undepressed in admixture with an authentic specimen of friedelanone.

Stability of Friedelanone to Mineral Acid. - A solution of friedelanone (180 mg.) in stabilised acetic acid (40 c.c.) was treated with concentrated hydrochloric acid (6 c.c.) and the reaction mixture heated on the steam bath for 24 hr. The solution was reduced to dryness under reduced pressure to give a solid which was dissolved in benzene and chromatographed on a column of alumina. Crystallisation of the benzene eluate from chloroform-methanol gave unchanged friedelanone as needles, m.p. and mixed m.p. 255-260°, $[\alpha]_D$ - 21° (c, 1·1).

Friedelan-3β-ol (epiFriedelanol).- Lithium aluminium hydride (500 mg.) was added to a solution of friedelanone (500 mg.) in dry ether (250 c.c.) and the mixture kept at + 4° for 16 hr. Excess lithium aluminium hydride was destroyed by the addition of iced water. The ether layer was decanted and the product worked up in the usual way and crystallised

from chloroform or chloroform-methanol to give friedelan-3β-ol as blades, m.p. 279-283°, m.p. 287-288°(vac.), $[\alpha]_D$+ 22° (c, 0·3). (Found: C, 83·9; H, 12·2. Calc. for $C_{30}H_{52}O$: C, 84·0; H 12·2%) Bruun and Jefferies[36] give m.p. 272-275°, 280-281° (vac.), $[\alpha]_D$+ 20°.

Friedelan-3β-ol (170 mg.) was dissolved in pyridine (25 c.c.) and acetic anhydride (5 c.c.) and the mixture heated on the steam bath for 1 hr. Crystallisation of the reaction product from chloroform-methanol gave friedelan-3β-yl-acetate as plates, m.p. 288-290°, $[\alpha]_D$ +34° (c, 0·75). Bruun and Jefferies[36] give m.p. 282-285°, $[\alpha]_D$+ 35°.

A solution of friedelan-3β-yl acetate (120 mg.) in ether (100 c.c.) was allowed to stand overnight at room temperature with lithium aluminium hydride (120 mg.). After the addition of iced water the product was isolated in the usual way and crystallised from chloroform-methanol to give friedelan-3β-ol as blades, m.p. and mixed m.p. 288-290°, $[\alpha]_D$ + 22° (c, 0·3).

A solution of friedelan-3β-ol (200 mg.) in hot pyridine (30 c.c.) and was treated with benzoyl chloride (10 c.c.) and the mixture heated on the steam bath for 5 hr. Ethanol (30 c.c.) was added to the cold solution and the product isolated in the usual way. The benzoate was purified by chromatography on alumina and by crystallisation from

chloroform-methanol from which it separates as plates, m.p. 253-256°, $[\alpha]_D$ + 33° + 34° (c, 1·0, 1·1). Bruun and Jefferies[36] give m.p. 246-248°, $[\alpha]_D$ + 34°.

Lithium aluminium hydride (100 mg.) was added to a solution of friedelan-3β-yl benzoate (100 m.g.) in dry ether (50 c.c.) and the mixture refluxed for 1 hr. The product was worked up in the usual way to give friedelan-3β-ol (blades, from chloroform-methanol) m.p. 279-283°, $[\alpha]_D$ + 22° (c, 0·3).

A solution of friedelan-3β-ol (100 mg.) in pyridine (15 c.c.) was added to a mixture of the complex prepared from chromium trioxide (1 g.) and pyridine (10 c.c.) and the mixture kept for 16 hr. with occasional shaking. The product was isolated in the usual way and crystallised from chloroform-methanol to give friedelanone as needles, m.p. and mixed m.p. 255-260°, $[\alpha]_D$ - 20° (c, 1·2).

Friedelan-3α-ol (Friedelanol). -

Sodium (3 g.) was added to a boiling solution of friedelanone (1·19 g.) in n-amyl alcohol (120 c.c.) and the mixture refluxed for 17 hr. The product was isolated in the usual way and its solution in benzene chromatographed on alumina. Elution with benzene (650 c.c.) yielded gummy solids (450 mg.). Elution with benzene-ether (1:1, 450 c.c.) gave fractions (610 mg.) which crystallised from chloroform-

methanol to give friedelan-3α-ol as small plates, m.p. 299-302°, $[\alpha]_D$ + 18° (c, 0·3). In another experiment in which the reflux time was 45 minutes chromatography of the reaction mixture yielded successively friedelanone, m.p. 255-258°, $[\alpha]_D$ + 24° (c, 1·5) eluted by benzene, friedelan-3β-ol, m.p. 277-280° (no depression), $[\alpha]_D$ + 23° (c, 0·6) eluted by benzene-ether (1:1), and friedelan-3α-ol, m.p. 300-305° (no depression), $[\alpha]_D$ + 17° (c, 0·3) eluted by ether. Drake and Campbell[26] give m.p. 250-251° for friedelanol.

A solution of friedelan-3α-ol (220 mg.) in pyridine (50 c.c.) was treated with acetic anhydride (10 c.c.) and the reaction heated for 1 hr. at 100°. The reaction product was worked up in the usual way and crystallised from chloroform-methanol to give friedelan-3α-yl acetate as plates, m.p. 316-318°, $[\alpha]_D$ - 12° (c, 1·0). Drake and Campbell[26] give m.p. 315-316°. In admixture with a specimen of friedelan-3β-yl acetate m.p. 288-290° the mixture had m.p. 271-290°. Hydrolysis of friedelan-3α-yl acetate (90 mg.) was effected by lithium aluminium hydride (90 mg.) in ether (100 c.c.). The product was worked up in the usual way and crystallised from chloroform-methanol to give friedelan-3α-ol as plates, m.p. and mixed m.p. 303-305°, $[\alpha]_D$ + 18° (c, 0·3).

A solution of friedelan-3α-ol (1 g.) in pyridine (40 c.c.)

was treated with benzoyl chloride (11 c.c.) and the reaction mixture heated on the steam bath for 2 hr. Ethanol (100 c.c.) was added to the cooled solution and the product isolated in the usual way. Crystallisation from chloroform-methanol gave friedelan-3α-yl benzoate as plates, m.p. 249-250°; $[\alpha]_D$ - 16°, - 17°, (c, 0·9, 1·0). Drake and Campbell[26] give m.p. 250-251°. A mixed m.p. with friedelan-3β-yl benzoate m.p. 253-256° had m.p. 215-230°.

Hydrolysis of friedelan-3α-yl benzoate (100 mg.) was effected by refluxing for 1 hr. with lithium aluminium hydride (100 mg.) in ether (50 c.c.). The product was worked up in the usual way and crystallised from chloroform-methanol to give friedelan-3α-ol, m.p. and mixed m.p. 299-304°, $[\alpha]_D$ + 17° (c, 0·4).

Conversion of Friedelan-3β-ol to Friedelan-3α-ol. - A solution of friedelan-3β-ol (200 mg.) in n-amyl alcohol (30 c.c.) containing sodium n-amyloxide (1 g. Na; 20 c.c. AmOH) was refluxed for 17 hr. The reaction product was worked up in the usual way to give friedelan-3α-ol as plates, (110 mg.) m.p. 298-300°; $[\alpha]_D$ + 17° (c, 0·3) which did not depress the m.p. of an authentic specimen of the alcohol.

Friedelene (Friedel-3-ene). - Phosphorous oxychloride (15 c.c.) was added dropwise to a solution of friedelan-3β-ol (250 mg.) in pyridine (120 c.c.) and the mixture kept for 16 hr. at room temperature then heated on the steam bath for 30 min. The cold solution was poured slowly on to crushed ice. The product was isolated by extraction with light petroleum and the dried extract filtered through alumina. Evaporation of the petroleum eluate and crystallisation of the product from chloroform-methanol gave friedel-3-ene as blades, m.p. 250-258°, m.p. 261-264° (vac.), $[\alpha]_D$ + 53° (c, 0·3), λ max. 2040 Å, (ε, 4,600). (Found: C, 87·9; C, 12·5. $C_{30}H_{50}$ requires C, 87·7; H, 12·3%.) The compound gives a pale yellow colour with tetranitromethane.

Pyrolysis of Friedelan-3α-yl Benzoate. - Friedelan-3α-yl benzoate (250 mg.) was heated at 310° for 3 hr. in an atmosphere of nitrogen. A solution of the product in light petroleum was chromatographed on alumina. Light petroleum (30 c.c.) eluted a fraction (180 mg.), which crystallised from chloroform-methanol to give the hydrocarbon as elongated blades, m.p. 256-258° (vac.), $[\alpha]_D$ + 53° (c, 0.5). A mixture with friedel-3-ene (described above) from the dehydration of epifriedelanol m.p. 261-264° (vac.) had m.p. 258-263° (vac.).

Drake and Campbell[26] give m.p. 257-258° for a hydrocarbon prepared by this method. Further elution with benzene-light petroleum (1:1) gave a fraction (30 mg.) which crystallised from chloroform-methanol yielding friedelan-3α-yl benzoate as plates, m.p. and mixed m.p. 249-250°.

Pyrolysis of Friedelan-3β-yl Benzoate. - Friedelan-3β-yl benzoate (200 mg.) was pyrolysed in an atmosphere of nitrogen over 3 hr. The pyrolysate and sublimate were worked up in the way described above. A solution of the product in light petroleum was chromatographed on a column of alumina. Elution with light petroleum (30 c.c.) gave a fraction (120 mg.) which after crystallisation from chloroform-methanol had m.p. 247-250°, $[\alpha]_D$ + 53° (c, 0·3), A mixture with the hydrocarbon obtained by the pyrolysis of the 3α-yl benzoate was undepressed in m.p. Further elution with light petroleum-benzene (1:1) gave a fraction (30 mg.) which after crystallisation from chloroform-methanol gave friedelan-3β-yl benzoate m.p. and mixed m.p. 253-256°, $[\alpha]_D$ + 33° (c, 0·8).

Friedelane. - A solution of friedel-3-ene (150 mg.) in cyclohexane (50 c.c.) and acetic acid (100 c.c.) was shaken with platinum (from 100 mg. PtO_2) for 6 hr. at 60° in an atmosphere of hydrogen. The catalyst was removed and the

product worked up in the usual way and crystallised from chloroform-methanol to give friedelane as plates, m.p. 248-250°, $[\alpha]_D$ + 22° (c, 0·9) which was undepressed in m.p. when mixed with a specimen, m.p. 248-250°, $[\alpha]_D$ + 22° prepared by Wolff-Kishner reduction of friedelanone. Ruzicka, Jeger and Ringnes[29] give m.p. 243-244°, $[\alpha]_D$ + 42°, Huang-Minlon[51] gives m.p. 244-245°, $[\alpha]_D$ + 42·5° and Bruun[34] gives m.p. 245-246°, $[\alpha]_D$ + 21°.

Friedelane-3α:4α-diol. - A solution of oxmium tetroxide (370 mg.) in cyclohexane (20 c.c.) was added to a solution of friedel-3-ene (prepared by the dehydration of epifriedelanol) (500 mg.) in cyclohexane (200 c.c.) and the mixture set aside at room temperature for 14 days. Lithium aluminium hydride (500 mg.) in ether (100 c.c.) was added to the mixture and the solution allowed to stand at room temperature overnight. Excess lithium aluminium hydride was destroyed by the addition of iced water and the reaction worked up in the usual way. Crystallisation of the product from methanol gave friedelane-3α:4α-diol as plates, m.p. 243-245°, $[\alpha]_D$ + 7° (c, 0·8). (Found: C, 80·9; H, 11·7. $C_{30}H_{52}O_2$ requires C, 81·0; H, 11·8%). It does not give a colour with tetranitromethane in chloroform.

3α-Acetoxyfriedelan-4α-ol. - Acetic anhydride (5 c.c.) was added to a solution of friedelane-3α:4α-diol (250 mg.) in pyridine (10 c.c.) and the mixture heated at 100° for 2½ hr. or alternatively allowed to stand at room temperature overnight. The product, isolated in the usual way, was crystallised from chloroform-methanol to give 3α-acetoxyfriedelan-4α-ol, as needles, m.p. 252-254°, $[\alpha]_D$ + 2°, + 2°, (c, 2·0, 3·0.) (Found: C, 78.9; H, 11·3. $C_{32}H_{54}O_3$ requires C, 79·0; H, 11·2%.) It does not give a colour with tetranitromethane in chloroform. Infrared spectrum (Nujol); bands at 1735, 1246, 1026 and 952 cm.$^{-1}$ (acetate) and 3600 cm.$^{-1}$ (hydroxyl).

A solution of chromium trioxide (16·5 mg.) in stabilised acetic acid (21 c.c.) was added to a solution of 3α-acetoxy-friedelan-4α-ol (120 mg.) in acetic acid (50 c.c.). The mixture was kept at room temperature overnight. Excess oxidant was destroyed by the addition of methanol and the product worked up in the usual way to give unchanged 3α-acetoxyfriedelan-4α-ol as needles, (114 mg.) from methanol, m.p. and mixed m.p. 252-254°, $[\alpha]_D$ + 2° (c, 2·0). Hydrolysis of the diol monoacetate with 3% methanolic potassium hydroxide gave friedelane-3α:4α-diol as plates, from methanol m.p. and mixed m.p. 243-245°, $[\alpha]_D$ + 7° (c, 1·0).

Treatment of 3α-Acetoxyfriedelan-4α-ol with Phosphorous Oxychloride. - A solution of the diol monoacetate (50 mg.) in pyridine (5 c.c.) was treated with phosphorous oxychloride

(5 c.c.) and heated on the steam bath for ½ hr. The product was isolated by pouring the reaction mixture cautiously into iced water and extraction of the precipitated solid with ether-chloroform. A solution of the product in benzene was filtered through alumina to give 3α-acetoxyfriedelan-4α-ol, m.p. and mixed m.p. 252-253°, $[\alpha]_D$ + 2° (c, 1·2).

Friedelane-2ξ:3ξ-diol Diacetate (2ξ:3ξ-Diacetoxyfriedelane) The unsaturated hydrocarbon (560 mg.) obtained by the pyrolysis of friedelan-3α-yl benzoate was dissolved in cyclohexane (50 c.c.) and added to a solution of osmium tetroxide (415 mg.) in cyclohexane (5 c.c.). The reaction mixture was kept for 14 days and after the addition of lithium aluminium hydride (600 mg.) in ether (100 c.c.) the product was worked up in the usual way. The crude product which was not purified was acetylated with acetic anhydride (10 c.c.) in pyridine (10 c.c.) and worked up in the usual way. A solution of the acetylated product in light petroleum was chromatographed on alumina. Elution with light petroleum-benzene (4:1) gave a fraction (250 mg.) which crystallised from methanol as needles, m.p. 252-254° undepressed in admixture with an authentic specimen of 3α-acetoxyfriedelan-4α-ol m.p. 252-254°. Further elution with light petroleum-benzene (1:1) yielded a fraction (80 mg.) which on crystallisation from chloroform-methanol gave needles, m.p. 262-264°, $[\alpha]_D$ - 40° (c, 1·3).

A mixture with 3α-acetoxyfriedelan-4α-ol m.p. 252-254° had m.p. 225-240°. (Found: C, 77·0; H, 10·7. $C_{34}H_{56}O_4$ requires C, 77·2; H, 10·7%). The compound does not give a colour with tetranitromethane in chloroform.

Conversion of Friedel-3-ene to a Mixture of Olean-13(18)-ene and 18α-Olean-12-ene. - A refluxing solution of friedel-3-ene (350 mg.) in acetic acid (450 c.c.) was treated with concentrated hydrochloric acid (100 c.c.) over 15 min. and refluxing continued for 18 hr. The reaction mixture was reduced to dryness under reduced pressure and a solution of the product in light petroleum was filtered through alumina; the eluate (290 mg.) crystallised from chloroform-methanol as blades m.p. 184-185°, $[\alpha]_D$ - 9·4° (c, 0·8) which after four recrystallisations from the same solvent gave the mixed crystal[38] of olean-13(18)-ene and 18α-olean-12-ene as blades, m.p. 186-187°, $[\alpha]_D$ - 20°, (c, 1·0). Further recrystallisation did not alter the melting point or specific rotation of the product which was undepressed in m.p. when mixed with specimens obtained from the acid induced isomerisation of olean-12-ene, olean-13(18)-ene, 18α-olean-12-ene and germanicene.

Bromination of the Hydrocarbon from the pyrolysis of epiFriedelanyl Benzoate. - A solution of the hydrocarbon (100 mg.) in warm chloroform (40 c.c.) was allowed to cool to

room temperature. Bromine (39 mg.) in acetic acid (18·6 c.c.) was added with shaking over ¾ hr. and the reaction mixture allowed to stand overnight. The product was isolated in the usual way. Crystallisation from chloroform-methanol gave needles, (10 mg.) m.p. 215-217°, $[\alpha]_D$ - 2·3°, -3·0° (c, 0·3, 0·3). (Found: C, 60·4; H, 9·09, $C_{30}H_{48}Br$. requires C, 73·8; H 9·8. $C_{30}H_{50}Br_2$ requires C, 63·2; H, 8·76%) Hydrolysis of the reconstituted mother liquors (80 mg.) in 3% methanolic potassium hydroxide gave after chromatography a mixture of low melting solids m.p. 140-145° unchanged by further crystallisation.

Friedelin Dicarboxylic Acid. - A solution of friedelanone (2 g.) in acetic acid (300 c.c.) at 110° was treated with a solution of chromium trioxide (2 g.) in stabilised acetic acid (100 c.c.) and added to the solution over 10 min. with mechanical stirring. The mixture was stirred for 2 hr. at 100-110°. Water was added to the cold solution and the acidic reaction product isolated by extraction with aqueous sodium hydroxide to give a clear gum (1·95 g.) which could not be crystallised. A solution of the acid product (1·95 g.) in ether (200 c.c.) was treated with an excess of ethereal diazomethane and the mixture allowed to stand overnight. The product was worked up in the usual way and its solution

in light petroleum-benzene (10:1) chromatographed on a column of alumina. Elution with light petroleum-benzene (1:2) gave a fraction (167 mg.) which on crystallisation from chloroform-methanol gave plates, m.p. 175-177°, $[\alpha]_D$ + 2·5° (c, 1·4). Ruzicka, Jeger and Ringnes[29] give m.p. 174-176°, $[\alpha]_D$ + 9·8° for friedelin dicarboxylic acid dimethyl ester. Elution of the column with increasingly polar solvents gave gums which could not be crystallised. Hydrolysis of friedelin dicarboxylic acid dimethyl ester (50 mg.) was effected by refluxing with 5% methanolic potash for 3 hr. The acid product was worked up in the usual way and crystallised from methanol (insoluble in chloroform) as prisms m.p. 287-288° (decomp.). Ruzicka *et al.*[29] give m.p. 288°, $[\alpha]_D$ + 21·4° for friedelin dicarboxylic acid.

Friedonic Acid Methyl Ester (Methyl Friedonate). - A suspension of friedelanone (2 g.) in stabilised acetic acid (450 c.c.) was titrated with a solution of chromium trioxide (2 g.) in acetic acid (50 c.c.) over 10 min. and the reaction mixture heated on the steam bath for 1½ hr. The reaction product was separated into acid and neutral fractions in the usual way. The acid product (1·9 g.) was crystallised from methanol to give a small quantity of an amorphous material m.p. 244-250°. A solution of the acid fraction in ether

was esterified with ethereal diazomethane and the neutral product worked up in the usual way. A solution of the methylated material in light petroleum-benzene (10:1) was chromatographed on a column of alumina. Elution with light petroleum-benzene (2:1) gave friedelin dicarboxylic acid dimethyl ester (140 mg.) m.p. 174-176°, $[\alpha]_D$ + 3° (c, 1·2) after crystallisation from chloroform-methanol. Elution with benzene and crystallisation of the eluate from methanol gave friedonic acid methyl ester as needles (120 mg.) m.p. 152-154°, $[\alpha]_D$ + 13° (c, 1·2). Ruzicka[29] gives m.p. 153-154°, $[\alpha]_D$ + 11·8°.

Oxidation of Cerin. - Crude cerin (m.p. 248-253°, $[\alpha]_D$ - 50°, 1 g.) was suspended in a mixture of carbon tetrachloride (38 c.c.) and stabilised acetic acid (85 c.c.). Chromium trioxide (212 mg.) dissolved in a trace of water and acetic acid (5 c.c.) was added to the cerin suspension and the reaction shaken for 3 hr. at room temperature. More chromium trioxide (170 mg.) in acetic acid was added and the solution shaken for 18 hr. The reaction product in ether was shaken with aqueous sodium hydroxide to give an acid fraction (500 mg.). Crystallisation of the acid fraction from methanol gave friedelin dicarboxylic acid (480 mg.) as prisms m.p. 287-288° (decomp.) undepressed when mixed with

a specimen obtained from the oxidation of friedelanone described above.

Friedelin Dicarboxylic Acid Anhydride. - A solution of friedelin dicarboxylic acid (200 mg.) in boiling acetic anhydride (10 c.c.) was refluxed for 30 min. The reaction mixture was cooled, when the product separated as needles. Recrystallisation from acetic anhydride gave friedelin dicarboxylic acid anhydride, m.p. 264-266°, $[\alpha]_D$ + 75·5° (c, 0·9). Ruzicka, Jeger and Ringnes[29] give m.p. 264-265°, $[\alpha]_D$ + 74°.

Norfriedelanone. - Friedelin dicarboxylic acid anhydride (1 g.) was heated to 280° (bath temperature) at atmospheric pressure for 1 min. The mixture was then sublimed at 14 m.m. (water pump). The sublimate and the residue in the still were dissolved in light petroleum and chromatographed on alumina. Elution with benzene and crystallisation of the eluate from chloroform-methanol gave norfriedelanone (600 mg.) as glistening plates m.p. 232-235°, $[\alpha]_D$ + 84° (c, 1·2) (Found: C, 84·1; H, 11·85, Calc. for $C_{29}H_{48}O$, C 84·4; H, 11·73%). Ruzicka et al.[29] give m.p. 231-232°, $[\alpha]_D$ - 83·7°. The compound does not give a colour with tetranitromethane in chloroform and it does not show selective absorption above

2200 Å. Infrared absorption (Nujol); band at 1730 cm.$^{-1}$ (ketone, 5-membered ring).

Norfriedelenone. - A solution of norfriedelanone (100 mg.) in acetic acid (10 c.c.) was refluxed with selenium dioxide (220 mg.) for 30 min. The solution was filtered and the yellow filtrate worked up in the usual way. Crystallisation of the product (70 mg.) from chloroform-methanol gave blades, m.p. 259-261°, $[\alpha]_D$ - 95°, - 97° (c, 1·1, 1·2), $\lambda_{max.}$ 2290 Å (ε, 5,300). Infrared absorption (Nujol); bands at 1736 cm.$^{-1}$, 1724 cm.$^{-1}$ (conjugated ketone, 5-membered ring); 1639 cm.$^{-1}$ (vinylidene); 1608 cm.$^{-1}$ (conjugated double bond). (Found: C, 84·85; H, 11·61, $C_{29}H_{46}O$ requires C, 84·81; H, 11·29%) Ruzicka et al.[29] give m.p. 260-261°, $[\alpha]_D$ - 108°, $\lambda_{max.}$ 2530 Å (ε, 14,300). To remove a slight yellow colouration, the product was dissolved in light petroleum and chromatographed on alumina. Elution with light petroleum-benzene (3:1) gave norfriedelenone which after crystallisation from chloroform-methanol had m.p. 261-263°, $[\alpha]_D$ - 104°, - 104°, (c, 1·1, 1·1), $\lambda_{max.}$ 2290 Å (ε, 5,500). Elution with benzene gave a small fraction (10 mg.) which could not be crystallised and which showed selective absorption at 2440 Å. Repetition of this reaction under a variety of conditions and also exactly

according to the method of Ruzicka *et al.*[29] failed to yield a compound having the ultraviolet absorption spectrum observed by these authors. The compound described above does not give a colour with tetranitromethane in chloroform.

Reduction of Norfriedelenone. - A solution of norfriedelenone (50 mg.) in ether (20 c.c.) was treated with lithium aluminium hydride (50 mg.) and allowed to stand overnight. The product was worked up in the usual way but avoiding the use of mineral acid. Crystallisation of the product from chloroform-methanol gave small plates, m.p. 250-253°, $[\alpha]_D$ + 41° (*c*, 0·5) (Found: C, 84·0; H, 11·4; $C_{29}H_{48}O$ requires, C, 84·4; H, 11·73%). Light absorption, $\lambda_{max.}$ 2040 Å (ε, 1,150). The alcohol does not show a colour with tetranitromethane in chloroform.

The allylic alcohol (17 mg.) was kept overnight with acetic anhydride (1 c.c.) and pyridine (1 c.c.). Crystallisation of the product from chloroform-methanol gave plates, m.p. 254-256°, $[\alpha]_D$ + 43° (*c*, 0·4). The product was reconstituted and acetylated on the steam bath for ½ hr. Crystallisation of the acetylated material from chloroform-methanol gave plates, m.p. 253-255° undepressed with the product of the cold acetylation. In admixture with the parent

allylic alcohol (m.p. 250-253°) the mixture had m.p. 220-235°, $\lambda_{max.}$ 2040 Å (ε, 1,200). The compound gives no colour with tetranitromethane in chloroform.

Oxidation of Norfriedelenone. - A solution of norfriedelenone (280 mg.) in dioxan (12 c.c.) was heated with a solution of SeO_2 (1 gm) in dioxan (3 c.c.) in a sealed tube at 190° overnight. The reaction mixture was cooled, filtered and worked up in the usual way. The product, a red gum, was dissolved in light petroleum-benzene (2:1) and chromatographed on alumina. Elution with benzene gave a solid (50 mg.) which crystallised from chloroform-methanol as blades, m.p. 253-255°, $[\alpha]_D$ + 190°, + 191°, (c, 0·75, 0·8) (Found: C, 85·5; H, 11·2; $C_{29}H_{44}O$ requires C, 85·2; H, 10·9%) Ultraviolet absorption spectrum $\lambda_{max.}$ 2520 Å (ε, 13,500). Infrared absorption (Nujol); bands at 1695 cm.$^{-1}$ (conjugated ketone in 5-membered ring); 1646 cm.$^{-1}$ (vinylidene); 1587 cm.$^{-1}$ (conjugated double bond); 944 cm.$^{-1}$ (vinylidene); 875 cm.$^{-1}$ (conjugated double bond). Elution with benzene-ether (1:1) gave a product (30 mg.) which crystallised from methanol as orange needles, m.p. 266-268°, $[\alpha]_D$ + 235°, (c, 2·0) $\lambda_{max.}$ 2800 Å (ε, 7,500). Infrared absorption (chloroform); bands at 1764 cm.$^{-1}$

(α-diketone in 5-membered ring); 1705 cm.$^{-1}$, (conjugated ketone in 5-membered ring); 1647 cm.$^{-1}$ (vinylidene); 1575 cm.$^{-1}$ (conjugated double bond). Ruzicka et al.[29] give m.p. 269-270° (vac.), $[\alpha]_D$ + 241°, $\lambda_{max.}$ 2800 Å (ε, 10,000) and Ourisson et al.[43] give m.p. 269-270°, $[\alpha]_D$ + 231°, for bisnorfriedelenedione. Infrared absorption (Nujol);[43] bands at 1765 cm.$^{-1}$ (ketone in 5-membered ring); 1708 cm.$^{-1}$ (conjugated ketone in 5-membered ring); 1575 cm.$^{-1}$ (conjugated double bond).

Friedelin enol Benzoate. - A mixture of friedelin (5 g.) and benzoyl chloride (25 c.c.) was heated for 1 hr. at 190-195° (reaction mixture temperature). The brown solution, after cooling, was poured into water and excess benzoyl chloride destroyed by the addition of sodium carbonate to the heated mixture. The brown solid thus obtained was extracted with a chloroform-ether mixture and the product worked up in the usual way. Crystallisation from chloroform-methanol gave friedelin enol benzoate (4·8 g.) as plates, m.p. 257-261° m.p. 265-267° (vac.), $[\alpha]_D$ + 62°, + 63° (c, 0·6, 1·6). Drake et al.[23] give m.p. 255-262°. Ruzicka et al.[29] give m.p. 265-266° (vac.), $[\alpha]_D$ + 64°.

4-Bromofriedelin. - A solution of friedelin enol benzoate (5 g.) in chloroform (275 c.c.) was treated with a solution of bromine (1·65 g. = 1·1 mole.) in chloroform over 10 min. at -20°. The reaction mixture was kept at -20° for a further 5 min. then quickly washed with a saturated solution of sodium bicarbonate, and the chloroform extract reduced to dryness at room temperature. Treatment of the residue with aqueous sodium carbonate at 100°, followed by extraction with chloroform gave a product which crystallised from light petroleum as needles, m.p. 198-199° (decomp.) $[\alpha]_D$ + 88° (c, 1·8). Corey and Ursprung [45] give m.p. 196-197°, $[\alpha]_D$ + 90° for 4-bromofriedelin.

4-Bromofriedelin was recovered unchanged after treatment with boiling pyridine for 3 hr. and stabilised acetic acid for ½ hr.

Action of Silver Acetate on 4-Bromofriedelin. - A solution of 4-bromofriedelin (100 mg.) in pyridine (20 c.c.) was refluxed with freshly crystallised silver acetate (200 mg.) for 30 min. The reaction mixture was allowed to cool, water added, and extracted with ether. The ether extract was washed exhaustively with water and worked up in the usual way, but avoiding the use of mineral acid. A solution of the

product in benzene-ether (1:1) was filtered through alumina. Crystallisation of the eluate from acetone gave needles, (20 mg.) m.p. 248-250°, $[\alpha]_D$ - 34° (c, 0.75). The compound does not give a colour with tetranitromethane. Repetition of this reaction for 1½ hr. gave a higher yield of the product described above m.p. 250-252°, $[\alpha]_D$ - 36°, - 37·5° (c, 1·0, 0·8) $\lambda_{max.}$ 2050 Å (ϵ, 2,700) (Found: C, 79·7; H, 10·8. $C_{32}H_{52}O_3$ requires C, 79·3; H, 10·8%). A mixture with a specimen of cerin acetate, (m.p. 262-263°, $[\alpha]_D$ - 36°), had m.p. 252-256°.

Action of Hydrochloric Acid on 4-Bromofriedelin. - A solution of 4-bromofriedelin (200 mg.) in glacial acetic acid (50 c.c.) was refluxed for 18 hr. with concentrated hydrochloric acid (14 c.c.). The product was worked up in the usual way and a solution in light petroleum chromatographed on a column of alumina (8 g.). Elution with light petroleum and light petroleum-benzene gave mixtures which could not be characterised. The reaction mixture was reconstituted (170 mg.) and reduced by the method of Wolff-Kishner. Chromatography of the resultant product and crystallisation of the eluates gave mixtures which had m.p. 130-155°, and finally 162-180°.

Treatment of 4-Bromofriedelin with Acetic Acid. - 4-Bromofriedelin (1 g.) was suspended in stabilised glacial acetic acid (500 c.c.), heated under vacuum until distillation of acetic acid took place, and the process continued for a further 30 min. The solution was reduced to dryness and the product crystallised from chloroform-methanol to give plates, m.p. 285-295°, m.p. 308-310° (vac.), $[\alpha]_D$ - 11°, (c, 1·2), $\lambda_{max.}$ 2270 Å (ε, 4,500) (Found: C, 84·7; H, 11·5. $C_{30}H_{48}O$ requires C, 84·8; H, 11·4%). The compound does not give a colour with tetranitromethane.

Reduction of the compound $C_{30}H_{48}O$ (100 mg.) was effected by lithium aluminium hydride (100 mg.) in ether (30 c.c.). The product was worked up in the usual way and crystallised from chloroform-methanol (cloudy solution) as plates, m.p. 253-255°, finally 264-266°, $[\alpha]_D$ + 12°, (c, 0·3) $\lambda_{max.}$ 2040 Å (ε, 1,450). The product does not give a colour with tetranitromethane. The reaction product was reconstituted and treated with a solution of hydrochloric acid (1 c.c.) in acetic acid (50 c.c.) for 3 hr. at 100°. The product was worked up in the usual way and chromatographed on alumina but a homogeneous compound was not isolated from the chromatogram.

12-Oxotaraxer-14-en-3β-yl Acetate. - A solution of 12-oxotaraxera-9(11):14-dien-3β-yl acetate (2 g.) (12-oxo-13iso-oleana-9(11):14-dien-3β-yl acetate) in ether (100 c.c.) was added over 2 min. to a solution of lithium (900 mg.) in liquid ammonia (600 c.c.) with stirring. The reaction was allowed to continue for a further 3 min. then halted by the addition of acetone (10 c.c.). The ammonia solution was allowed to evaporate at room temperature overnight. The red residue was worked up in the usual way, and a solution of the product in light petroleum-benzene (5:1) was chromatographed on a column of alumina. Elution with light petroleum-benzene (2:1) gave a fraction (1·2 g.) and a further fraction (600 mg.) was obtained by elution with light petroleum-benzene (1:1). Crystallisation of the eluates from chloroform-methanol gave needles, m.p. 295-297° $[\alpha]_D$ - 32°, (c, 1·3), $\lambda_{max.}$ 2060 Å (ε, 4,300); in chloroform λ 2850 Å (ε, 50). The compound gave a pale yellow colour with tetranitromethane in chloroform. Beaton, Spring, Stevenson and Stewart[33] give 298-300°, $[\alpha]_D$ - 30° for 12-oxotaraxer-14-en-3β-yl acetate prepared by this method. A solution of the acetate in 5% methanolic potassium hydroxide was refluxed for 3 hr. The product was worked up in the usual way to give 12-oxotaraxer-14-en-3β-ol, m.p. 276-277°,

$[\alpha]_D$ - 44° (c, 1·3). Beaton et al.[33] give m.p. 276-278°, $[\alpha]_D$ - 45°, - 43°.

Treatment of 12-Oxotaraxer-14-en-3β-ol with Hydrochloric Acid.- A solution of 12-oxotaraxer-14-en-3β-ol (200 mg.) in hot acetic acid (50 c.c.) was treated with concentrated hydrochloric acid (10 c.c.) over 5 min. and heated on the steam bath for a further 2½hr. The red solution was reduced to dryness and worked up in the usual way and the product acetylated with acetic anhydride (5 c.c.) in pyridine (5 c.c.). Chromatography of the acetylated product gave on elution with light petroleum and light petroleum-benzene fractions which could not be crystallised. Elution with benzene gave a fraction (15 mg.) which separated as needles from chloroform-methanol, m.p. 295-297° $\lambda_{max.}^{2060}$ (ε, 6,000) undepressed in m.p. when mixed with an authentic specimen of 12-oxotaraxer-14-en-3β-yl acetate (m.p. 295-297°).

3-Oxo-Olean-12-ene. - A solution of olean-12-en-3β-ol (10 g.) in stabilised acetic acid (1ℓ.) was treated with a solution of chromium trioxide (1·73 g. ≡ 1·1 mole) in acetic acid (50 c.c.) added dropwise over 20 min. and the solution allowed to stand at room temperature overnight. Excess chromic acid was destroyed by the addition of methanol and

the reaction solution worked up in the usual way. A solution of the product in benzene was filtered through alumina. Crystallisation of the eluate from chloroform-methanol gave 3-oxo-olean-12-ene as needles, m.p. 197-199°, $[\alpha]_D$+ 110° (c, 1·3).

Olean-12-ene. - A mixture of 3-oxo-olean-12-ene (700 mg.), alcoholic sodium ethoxide (15 c.c. EtOH, 700 mg. Na) and hydrazine hydrate (5 c.c. 100%) was heated in a tube autoclave at 180° for 12 hr. The product was isolated in the usual way and crystallised from chloroform-methanol to give olean-12-ene as blades, m.p. 160-162°, $[\alpha]_D$+ 94°, (c, 1·0).

Acid Rearrangement of Olean-12-ene. - A solution of olean-12-ene (β-amyrene-II) (450 mg.) in acetic acid (200 c.c.) was treated over 30 min. with concentrated hydrochloric acid (40 c.c.). A further addition of hydrochloric acid (40 c.c.) caused precipitation of solid and the mixture was refluxed for 18 hr. The mixture was reduced to dryness under reduced pressure and a solution of the product in light petroleum was filtered through alumina. Crystallisation of the eluate from chloroform-methanol gave a mixture, m.p. 168-175°, $[\alpha]_D$ - 2·5° (c, 1·2) continued crystallisation of which from the same solvent

mixture gave blades, m.p. 186-187°, $[\alpha]_D$ - 19° (c, 0·9). The specific rotation was not changed by repeated crystallisation. In another experiment olean-12-ene (300 mg.) was dissolved in acetic acid (150 c.c.) at reflux temperature. Concentrated hydrochloric acid (37 c.c.) was added over 15 min. and the solution refluxed for 18 hr. The solution was reduced to dryness and the product dried. Crystallisation from chloroform-methanol gave blades $[\alpha]_D$ - 11° (c, 1·0) which after continued crystallisation from the same solvent mixture had m.p. 186-187°, $[\alpha]_D$ - 20° (c, 1·1). The product gave a deep yellow colour with tetranitromethane.

Acid Rearrangement of the Hydrocarbon $[\alpha]_D$ - 20°. - Treatment of the hydrocarbon $[\alpha]_D$ - 20° (100 mg.) with hydrochloric acid (13 c.c.) in acetic acid (54 c.c.) at reflux temperature over 18 hr. gave after crystallisation from chloroform-methanol blades, m.p. 184-185°, $[\alpha]_D$ - 10·4° (c, 1·0).

Oleana-11:13(18)-dien-3β-yl Acetate. - A solution of olean-12-en-3β-yl acetate (10 g.) in acetic acid (800 c.c.) was treated with a solution of selenium dioxide (10 g.) in water (4 c.c.) and the mixture refluxed for 30 min. The

hot solution was filtered and the filtrate poured into water. The product was worked up in the usual way and purified by chromatography and crystallised from chloroform-methanol to give oleana-11:13(18)-dien-3β-yl acetate as hexagonal plates, m.p. 226-227°, $[\alpha]_D$ - 61° (c, 2·0). It gives a red brown colour with tetranitromethane.

3-Oxo-Oleana-11:13(18)-diene. A solution of oleana-11:13(18)-dien-3β-ol (800 mg.) in acetic acid (120 c.c.) was treated with chromium trioxide (140 mg.≡ 1·1 mole) in acetic acid (10 c.c.) added dropwise at 30° and the mixture allowed to stand at room temperature overnight. Excess oxidant was destroyed by the addition of methanol and the solution reduced to dryness. The product was worked up in the usual way and crystallised from chloroform-methanol to give 3-oxo-oleana-11:13(18)-diene as needles, m.p. 231-235°, $[\alpha]_D$ - 49·5°, (c, 1·2).

Oleana-11:13(18)-diene. - A mixture of 3-oxo-oleana-11:13(18)-diene (400 mg.) alcoholic sodium methoxide (40 c.c. MeOH, 1 g. Na), and hydrazine hydrate (5 c.c. 100%), was heated overnight in a tube autoclave at 180°. The product was isolated in the usual way and its solution in light petroleum chromatographed on alumina. Crystallisation of

the eluate from chloroform-methanol gave oleana-11:13(18)-diene as blades, m.p. 217-218°, $[\alpha]_D$ - 66·2° (c, 1·1). Ruzicka et al.[60] give m.p. 218-219°, $[\alpha]_D$ - 73°; Takeda[54] gives m.p. 222-224°, $[\alpha]_D$ - 67°. Ultraviolet absorption $\lambda_{max.}$ 2420, 2500, 2600 Å (ε, 27,000, 30,000 and 20,000).

Olean-13(18)ene. - A solution of oleana-11:13(18)-diene (170 mg.) in cyclohexane (50 c.c.) and acetic acid (50 c.c.) was shaken for 18 hr. at 60° in an atmosphere of hydrogen over freshly reduced platinum catalyst (PtO_2, 200 mg.). The reaction was worked up in the usual way to give a product which gives a strong yellow colour with tetranitromethane; crystallisation from chloroform-methanol gave olean-13(18)-ene as blades, m.p. 186-187°, $[\alpha]_D$ - 48°, (c, 1·1). Ultraviolet absorption $\lambda_{max.}$ 2100 Å (ε, 7,000). (Found: C, 88·0; H, 12·3. $C_{30}H_{50}$ requires C, 87·7; H, 12·3%). Olean-13(18)-ene showed no depression in m.p. in admixture with the product m.p. 186-187°, $[\alpha]_D$ - 20° obtained from the acid rearrangement of friedelene and olean-12-ene. The reaction was repeated at room temperature with the same result.

Olean-13(18)-en-3β-ol. - A solution of oleana-11:13(18)-dien-3β-ol in cyclohexane (50 c.c.) and acetic acid (150 c.c.) was shaken vigorously in an atmosphere of hydrogen over freshly reduced platinum catalyst (250 mg. PtO_2) for 16 hr. The solution was filtered to remove the catalyst and reduced to dryness. Crystallisation of the residue from methanol and aqueous methanol gave olean-13(18)-en-3β-ol as needles, m.p. 212-213°, $[\alpha]_D$ - 52° (c, 1·2). The compound gives a strong yellow colour with tetranitromethane in chloroform. Jones et al.[55] give m.p. 212-212·5°, $[\alpha]_D$ - 50·5°; Ruzicka[61] gives m.p. 213-213·5°, $[\alpha]_D$ - 52°.

3-Oxo-olean-13(18)-ene. - Chromium trioxide (800 mg.) was dissolved in portions in pyridine (30 c.c.) with shaking at room temperature to give a bright yellow precipitate of a chromic acid-pyridine complex. A solution of olean-13(18)-en-3β-ol (800 mg.) in pyridine (20 c.c.) was added to the oxidant and the mixture shaken at intervals over 1½ hr. then allowed to stand at room temperature overnight. Ether was added to the reaction mixture and the ether extract worked up in the usual way but avoiding the use of mineral acid. The reaction product was purified

by chromatography on alumina and crystallised from chloroform-methanol to give 3-oxo-olean-13(18)-ene as blades, m.p. 199-200°, $[\alpha]_D$ - 11·5° (c, 1·2). It gives a strong yellow colour with tetranitromethane.

Olean-13(18)-ene. - A mixture of 3-oxo-olean-13(18)-ene (500 mg.) alcoholic sodium ethoxide (15 c.c. EtOH, 500 mg. Na) and hydrazine hydrate (3 c.c. 100%) was heated in a tube autoclave at 190° for 12 hr. The contents of the autoclave were poured into water and worked up in the usual way. The product was purified by chromatography on alumina and crystallised from chloroform-methanol to give olean-13(18)-ene as blades, m.p. 186-187°, $[\alpha]_D$ - 48° (c, 1·3), identical with the product $[\alpha]_D$ - 48° obtained by hydrogenation of olean-11:13(18)-diene.

Acid Rearrangement of Olean-13(18)-ene. - A solution of olean-13(18)-ene (150 mg.) in acetic acid (150 c.c.) at reflux temperature was treated with concentrated hydrochloric acid (37 c.c.) over 15 min. and refluxed overnight. The solution was taken to dryness under reduced pressure and dried. The product ($[\alpha]_D$ - 12° (c, 2·3)) was repeatedly crystallised from chloroform-methanol to give blades, m.p. 187-188°, $[\alpha]_D$ - 19·5° (c, 2·3), unchanged by further

crystallisation or careful chromatography. A mixed m.p. with the product, m.p. 186-187°, $[\alpha]_D$ - 20° obtained by acid isomerisation of olean-12-ene had m.p. 186-187°(undepressed).

Oleana-11:13(18)-diene. - A solution of olean-12-ene (400 mg.) in acetic acid (150 c.c.) was treated with a solution of selenium dioxide (400 mg.) in water (4.c.c.) and acetic acid (50 c.c.) and refluxed for 30 min. The hot solution was filtered and the filtrate worked up in the usual way. The product was purified by chromatography and crystallised from chloroform-methanol to give oleana-11:13(18)-diene as blades, m.p. 217-218°, $[\alpha]_D$ - 66° (c, 1·2). Ruzicka gives m.p. 218-219°, $[\alpha]_D$ - 73°.

Lupeol Hydrochloride (cf. Halsall, Jones and Meakins[59]). - Dry hydrogen chloride was passed for 6 hr. into "Grignard dry" ethanol (800 c.c.) cooled in an ice water bath. A solution of lupeol (10 g.) in dry ethanol (500 c.c.) was added to the saturated ethanol solution and the mixture set aside at room temperature for 6 days. The reaction mixture was poured into water and worked up in the usual way. The product was crystallised from ethanol to give lupeol hydrochloride as needles, m.p. 203-205° (dec.), $[\alpha]_D$ - 29° (c, 1·3). Halsall et al.[59] give m.p. 211-213°, $[\alpha]_D$ - 31°.

Olean-18-en-3β-yl Acetate.- A solution of lupeol hydrochloride (4·2 g.) in acetic anhydride (100 c.c.) was refluxed overnight. The solution was allowed to cool to room temperature and the crystalline material which separated was filtered off, washed with methanol and recrystallised from chloroform-methanol to give olean-18-en-3β-yl acetate as plates, m.p. 276-278°, $[\alpha]_D$ + 18° (c, 1·4). Halsall et al.[59] give m.p. 276-277°, $[\alpha]_D$ + 18·5°.

Olean-18-en-3β-ol, (Germanicol). - A solution of olean-18-en-3β-yl acetate (1·4g.) in ether (250 c.c.) was treated with lithium aluminium hydride (1 g.) and set aside at room temperature overnight. Excess lithium aluminium hydride was destroyed by the cautious addition of iced water and the product worked up in the usual way to give, after crystallisation from methanol, olean-18-en-3β-ol (germanicol) as needles, m.p. 177-178°, $[\alpha]_D$ + 6° (c, 2·3). Halsall et al.[59] give m.p. 180-181°, $[\alpha]_D$ + 7°.

3-Oxo-olean-18-ene (Germanicone). - Chromium trioxide (1 g.) was dissolved in portions in pyridine (10 c.c.) with shaking at room temperature to give a bright yellow precipitate of a chromic acid-pyridine complex. A solution of olean-18-en-3β-ol (800 mg.) in pyridine was added to the

oxidant and the mixture shaken at intervals over 2 hr. then allowed to stand overnight at room temperature. Ether was added to the reaction mixture and the ether extract worked up in the usual way but avoiding the use of mineral acid. The reaction product was purified by chromatography on alumina and crystallised from chloroform-methanol to give 3-oxo-olean-18-ene as plates, m.p. 187-188°, $[\alpha]_D$ + 38°, (c, 1·3). Halsall et al.[59] give 188-189°, $[\alpha]_D$ + 37°.

Olean-18-ene (Germanicene) (cf. Simpson[63], David[64]). - A mixture of 3-oxo-olean-18-ene (400 mg.) hydrazine hydrate (3 c.c. 100%) and alcoholic sodium methoxide (MeOH, 20 c.c. Na 400 mg.) was heated in a tube autoclave at 200° for 18 hr. The contents of the autoclave were poured into water and worked up in the usual way but avoiding the use of mineral acid. Crystallisation of the reaction product from chloroform-methanol gave olean-18-ene as plates, m.p. 173-175°, $[\alpha]_D$ + 6° (c, 4·5). Simpson[63] gives m.p. 171-172°, $[\alpha]_D$ + 3°. Barton[65] gives m.p. 171-172°, $[\alpha]_D$ + 3°.

Acid Rearrangement of Olean-18-ene. - A solution of olean-18-ene (150 mg.) in stabilised acetic acid (100 c.c.) at reflux temperature was treated with hydrochloric acid

(25 c.c.) over 10 min. and the solution refluxed for 18 hr. The reaction mixture was reduced to dryness and dried. The product $[\alpha]_D$ - 10°, (c, 3·0) was crystallised from chloroform-methanol to give blades, m.p. 186-187°, $[\alpha]_D$ - 18°, (c, 1·3) identical with the product obtained from the acid isomerisation of friedel-3-ene, olean-12-ene, and olean-13(18)-ene.

A solution of 18α-olean-12-ene (prepared by Dr. M.B.E. Fayez) (150 mg.) in stabilised acetic acid (120 c.c.) was refluxed for 18 hr. with concentrated hydrochloric acid (20 c.c.). The product was isolated in the usual way to give blades, m.p. 186-187°, $[\alpha]_D$ - 18°, (c, 2·3) unchanged by further recrystallisation and identical with the product described above.

Synthetic Mixture of Olean-13(18)-ene and 18α-Olean-12-ene. - A mixture of olean-13(18)-ene (m.p. 186-187°, $[\alpha]_D$ - 48°, 50·4 mg.) and 18α-olean-12-ene (m.p. 186-188°, $[\alpha]_D$ + 37°, 37·8 mg.) was dissolved in, and crystallised from chloroform-methanol to give blades, m.p. 185-186°, $[\alpha]_D$ - 13°, (c, 1·5) which on further recrystallisation from the same solvent mixture gave the mixed crystal (45 mg.) as blades, m.p. 186-187°, $[\alpha]_D$ - 18°, unchanged by further crystallisation.

Synthetic Mixture of Olean-13(18)-ene, 18α-Olean-12-ene and Germanicene. - Germanicene (m.p. 173-175°, $[\alpha]_D$ + 6°, 100 mg.), olean-13(18)-ene (100 mg.) and 18α-olean-12-ene (100 mg.) were mixed and the mixture crystallised from chloroform-methanol to give needles, m.p. 175-177°, $[\alpha]_D$ 0°, (c, 3·3) which for three recrystallisations had m.p. 176-178°, $[\alpha]_D$ 0°, 0°, (c, 2·7, 2·0).

The mixture (260 mg.) was reconstituted and dissolved in acetic acid (150 c.c.) at reflux temperature. Concentrated hydrochloric acid (37 c.c.) was added and the solution refluxed overnight. The solution was reduced to dryness and dried. The product $[\alpha]_D$ - 10°, (c, 2·6) was crystallised from chloroform-methanol to give blades, m.p. 186-187°, $[\alpha]_D$ - 18°, (c, 2·1) unchanged by further crystallisation.

Acetyl Glycyrrhetic Acid. - "Extractum Glycyrrhizae" (3 kg.) was dissolved in hot water (6 ℓ.) and cooled. Concentrated sulphuric acid (600 c.c.) was cautiously added to the aqueous solution with stirring and the black viscous sludge which separated was isolated by decantation and kneaded with water (1 ℓ.). Treatment of the crude product with aqueous sulphuric acid (3%. 6 ℓ.) at 100° for

5 hr. gave a black brittle solid which was removed by decantation of the liquor, and the product dried, mixed with asbestos fibre and extracted with chloroform (Soxhlet). Removal of the solvent under vacuum gave a residue (230 g.) which was dissolved in pyridine (150 c.c.) and acetic anhydride (150 c.c.) and heated on the steam bath for 2 hr. The acetylated product was worked up in the usual way to give acetyl glycyrrhetic acid (55 g.) as plates from chloroform-methanol, m.p. 309-313°, $[\alpha]_D$ + 144°, (c, 1·1). A second crop (5 g.) was obtained from the mother liquors, m.p. 304-309°, $[\alpha]_D$ + 133°, (c, 1·1).

Glycyrrhetic Acid. - Treatment of acetyl glycyrrhetic acid (250 mg.) with methanolic potassium hydroxide (25 c.c. 3%) for 1 hr. at reflux gave, after work up of the reaction product in the usual way, glycyrrhetic acid, m.p. 300-302°, $[\alpha]_D$+ 157°, (c, 1·2), $\lambda_{max.}$ 2480 Å (ε, 11,200).

Acetyl Glycyrrhetic Acid Methyl Ester. - A solution of glycyrrhetate acetate (220 mg.) in ether (100 c.c.) was treated with an ethereal solution of diazomethane and allowed to stand overnight. Excess diazomethane was destroyed by the cautious addition of acetic acid. The product was worked up in the usual way to yield, methyl glycyrrhetate acetate, as

plates, from chloroform-methanol, m.p. 300-302°, $[\alpha]_D$ + 147°, (c, 1·2).

Ester, $C_{33}H_{46}O_7$(IX). - A solution of methyl glycyrrhetate acetate (15 g.) in glacial acetic acid (400 c.c.) was refluxed with selenium dioxide (15 g.) for 24 hr. After filtration, the solution was again treated with selenium dioxide (15 g.) and refluxed for 24 hr. The product was isolated in the usual way and crystallised from chloroform-methanol to give the ester (7·0 g.) as needles, m.p. 288-290°, $[\alpha]_D$ + 2.4°, (c, 3·5), $\lambda_{max.}$ 2260 Å (ε, 4,400). (Found: C, 71·7; H, 8·4. Calc. for $C_{33}H_{46}O_7$ C, 71·4; H 8·4%.) Jeger et al.[68] give m.p. 285-286°, $[\alpha]_D$ + 4°, + 2·6° for this compound.

Acid, $C_{31}H_{46}O_7$ (X). - (a) A solution of the ester, $C_{33}H_{46}O_7$ (2·5 g.) in 5% methanolic potassium hydroxide was refluxed for 3 hr. The product was separated into neutral and acid fractions in the usual way. Crystallisation of the acid fraction from acetone-light petroleum gave the acid, $C_{31}H_{46}O_7$, m.p. 206-208°, $[\alpha]_D$ - 2°, - 1·7°, (c, 2·0, 5·0), $\lambda_{max.}$ 2240 Å (ε, 11,000). (Found: C, 70·1; H, 9·0; OMe, 6·1. $C_{30}H_{43}O_6OCH_3$ requires C, 70·2; H, 8·7; OMe, 5·85%.) The acid does not give a colour with

tetranitromethane in chloroform. The neutral fraction is described below.

(b) A solution of the ester, $C_{33}H_{46}O_7$ (1 g.), in methanolic sodium methoxide (50 c.c. MeOH; 2g. Na.) was refluxed for 5½ hr. The product was separated into acid and neutral fractions in the usual way; the latter is described below. Crystallisation of the acid fraction from acetone-light petroleum gave the acid $C_{31}H_{46}O_7$ (730 mg.) as needles, m.p. and mixed m.p. 206-208°, $[\alpha]_D$ - 2·2°, (c, 4·0).

Acetate Dimethyl Ester, $C_{34}H_{50}O_8$ (Xa). - The acid, (250 mg.) in pyridine (5 c.c.) and acetic anhydride (5 c.c.) was kept at 100° for 2 hr. The acetylated product was worked up in the usual way and a solution of the product in ether was treated with an excess of ethereal diazomethane at 16° overnight. Excess diazomethane was destroyed by the addition of acetic acid and the product isolated in the usual way. Crystallisation of the neutral product from acetone-light petroleum gave the acetate dimethyl ester as needles, m.p. 204-205°, $[\alpha]_D$ - 1·4°, (c, 4·0), $\lambda_{max.}$ 2230 Å, (ε, 12,700). (Found: C, 69·4; H, 8·7; OMe, 10·8. $C_{32}H_{44}O_6(OCH_3)_2$ requires C, 69·8; H, 8·6; OMe, 10·8%.) A mixed m.p. with the acid $C_{31}H_{46}O_7$ had m.p. 183-195°. A solution of the acetate dimethyl ester (800 mg.) and potassium hydroxide (1 g.

in 80% aqueous methanol (25 c.c.) was heated under reflux for 13 hr. The solution was diluted with water then extracted with ether and the extract evaporated. A negligible amount of neutral fraction was obtained. The acid fraction was isolated in the usual way and crystallised from acetone-light petroleum to give the acid, $C_{31}H_{46}O_7$ (X) (750 mg.) as needles, m.p. and mixed m.p. 206-208°, $[\alpha]_D$ - 2°, (c, 2·0).

Conversion of the O_7 Ester (IX) into the Hydroxy-diketone (XV)

(a) Aqueous potassium hydroxide (30 c.c., 33%) was added to a solution of the O_7 ester (2 g.) in methanol (170 c.c.) and the solution refluxed for 8 hr. After dilution with water, the neutral fraction was isolated by ether-extraction and crystallised from methanol, to give the hydroxy-diketone (800 mg.) as needles, $[\alpha]_D$ + 124°, (c, 1·5). (Found: C, 78·4, 78·3; H, 10·4, 10·4. $C_{28}H_{44}O_3$ requires C, 78·45; H, 10·35%.) It does not give a colour with tetranitromethane in chloroform. The hydroxy-diketone separates in a solvated form, m.p. 125-130° from methanol. On drying in a high vacuum, or sublimation, the unsolvated form has m.p. 173-175°.

The hydroxy-diketone (200 mg.) was heated with acetic anhydride (5 c.c.) in pyridine (5 c.c.) at 100° for 1½ hr.

The product was worked up in the usual way and crystallised from methanol as needles, m.p. 171-173° (after sublimation in a vacuum), $[\alpha]_D$ + 119°, (c, 1·0). (Found: C, 76·8; H, 9·85. $C_{30}H_{46}O_4$ requires C, 76·55; H, 9·85%.)

(b) The neutral fractions obtained during the preparation of the acid, $C_{31}H_{46}O_7$ (methods (a) and (b) above) were worked up in the usual way and crystallised from aqueous methanol to give the hydroxy-diketone as needles, (a) (350 mg.) m.p. 125-130° (170-173° after drying in a vacuum), $[\alpha]_D$ + 126°, (c, 0·9), (b) m.p. 125-130° (171-173° after drying in a vacuum), $[\alpha]_D$ + 125°, (c, 1·2).

Hydrolysis of Acetate Dimethyl Ester, $C_{34}H_{50}O_8$ (Xa). - A solution of the ester (Xa) (500 mg.) in ethanol (40 c.c.) water (10 c.c.) and potassium hydroxide (10 g.) was heated at 200° in a tube autoclave for 11 hr. The contents of the autoclave were cooled, poured into water and worked up for neutral and acidic fractions in the usual way. No neutral fraction was isolated. Work up of the acid fraction gave a white resinous solid (256 mg.), m.p. 250-252°, $\lambda_{max.}$ 2080 Å (ε, 950). The product did not give a colour with tetranitromethane nor would it crystallise from the normal solvents.

The acid product (300 mg.) was dissolved in pyridine

(5 c.c.) and acetic anhydride (5 c.c.) and heated on the steam bath for 1 hr. The acetylated product was worked up in the usual way to give material (280 mg.) which could not be crystallised. An attempt to prepare a benzoyl derivative was also unsuccessful. Treatment of a solution of the acetylated acid product (200 mg.) in ether (50 c.c.) with an excess of ethereal diazomethane failed to yield a crystalline product after work up in the usual way. Methylation of the benzoyl derivative was also unsuccessful.

12:19-Dioxo-Oleana-9(11):13(18)-dien-3β-yl Acetate. - A solution of β-amyrin acetate (10 g.) in hot benzoyl acetate (200 c.c.) was refluxed with selenium dioxide (12 g.) for 18 hr. The cold solution was filtered from selenium and the filtrate reduced to dryness under reduced pressure (oil bath). A solution of the product in benzene was filtered through a column of alumina; crystallisation of the benzene eluate from light petroleum-ether gave blades, m.p. 236-240° which on recrystallisation from aqueous methanol gave the diendionyl, m.p. 241-243°, $[\alpha]_D$ - 90°, (c, 0·9) $\lambda_{max.}$ 2100 Å, 2760 Å (ε, 6,840, 11,800). The product does not give a colour with tetranitromethane in chloroform.

The following experiments were carried out in an attempt to obtain information concerning the mechanism of the formation of the O_5 acetate from oleanane derivatives. The attempt was unsuccessful.

12:19-Dioxo-olean-9(11)-en-3β-yl Acetate. - A solution of 12:19-dioxo-oleana-9(11):13(18)-dien-3β-yl acetate (10g.) in hot ethanol (100 c.c.) was treated with activated zinc (60 g.) in ethanol (900 c.c.). A few crystals of zinc bromide were added to catalyse the reaction and the solution was refluxed for 5 hr. The hot solution was filtered and reduced in volume to give a product, which on recrystallisation from chloroform-methanol gave 12:19-dioxo-olean-9(11)-en-3β-yl acetate (8 g.) as blades, m.p. 288-291°, $[\alpha]_D$ + 132°, (c, 1·3), $\lambda_{max.}$ 2460 Å (ε, 13,000).

12:19-Epoxy-oleana-9(11):12:18-trien-3β-yl Acetate. - 12:19-Dioxo-olean-9(11)-en-3β-yl acetate (8 g.) was refluxed in a solution of isopropenyl acetate (90 c.c.) and concentrated sulphuric acid (1 c.c.) for 3 hr. on the steam bath. The reaction mixture was poured into water and worked up through ether in the usual way. Removal of the solvent under vacuum gave a product which was crystallised from methanol to give 12:19-epoxy-oleana-9(11):12:18-trien-3β-yl acetate as plates, m.p. 180-182°, $[\alpha]_D$ + 168°, (c, 1·3). Ultraviolet light

Absorption showed maxima at $\lambda_{max.}$ 2190, 3220 Å, (ε, 5,500, 13,400). McKean[73] gives m.p. 180-181°, $[\alpha]_D$ + 170° for this compound.

Oxidation of 12:19-Epoxy-Oleana-9(11):12:18-trien-3β-yl Acetate.

(a) A solution of 12:19-epoxy-oleana-9(11):12:18-trien-3β-yl acetate (300 mg.) in stabilised acetic acid (50 c.c.) was refluxed overnight with selenium dioxide (300 mg.). The hot solution was filtered and reduced to dryness. A solution of the product was filtered through alumina and the eluate crystallised from aqueous methanol as plates, m.p. 238-240°, $[\alpha]_D$ - 88°, (c, 1·1). A mixed melting point determination with 12:19-dioxo-oleana-9(11):13(18)-dien-3β-yl acetate (m.p. 241-243°) showed no depression.

(b) 12:19-Epoxy-oleana-9(11):12:18-trien-3β-yl acetate (800 mg.) was dissolved in stabilised glacial acetic acid (75 c.c.) to which was added, a solution of chromic anhydride (800 mg.) in water (2 c.c.) and acetic acid (10 c.c.) over 15 min. The reaction mixture was refluxed for 2 hr. and allowed to stand overnight. Excess oxidant was destroyed by the addition of methanol and the solution reduced to dryness and worked up in the usual way. Crystallisation of the residue from aqueous methanol gave plates,

m.p. 285-287°, $[\alpha]_D$ + 69°, (c, 2·0). (Found: C, 71·7; H, 8·4. Calc. for $C_{32}H_{46}O_5$, C, 71·4; H, 8·4%.) $\lambda_{max.}$ 2560 Å (ε, 9,700). Ruzicka *et al.*[74] give m.p. 290-291° (cor.), $[\alpha]_D$ + 72°, $\lambda_{max.}$ 2585Å(ε, 11,750) for 12:19-dioxo-13(18)-epoxy-olean-9(11)-en-3β-yl acetate obtained by chromic oxidation of 12:19-dioxo-oleana-9(11):13(18)-dien-3β-yl acetate.

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