T H E S I S

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DEGREE OF DOCTOR OF PHILOSOPHY

by

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

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I TRITERPENOIDS FROM ALDER BARK

II STUDIES ON α-AMYRIN.

C O N T E N T S.

INTRODUCTION.

The name triterpene is applied to a class of naturally occurring hydrocarbons and oxygenated hydrocarbons containing 30 carbon atoms. The molecular carbon skeleton is arranged in such a manner that six isopentane residues can be recognized as component units. Due to the fact that certain products have been isolated[1,2,3,4] which have obvious triterpene characteristics and which contain 31 carbon atoms, the more comprehensive term triterpenoid has been adopted.

With the exception of the aliphatic hydrocarbon squalene, all triterpenoids are alicyclic, and the greater majority contain hydroxyl, carboxyl or carbonyl oxygen functions. The triterpenoids can be divided into three main classes:

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

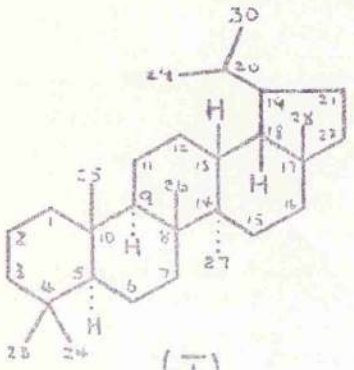
(ii) Tetracyclic compounds such as lanosterol, agnosterol, the elemic acids, the polyporenic acids, eburicoic acid, euphol, tirucallol and butyrospermol, the molecules of which bear a close structural relationship to the steroids.

(iii) Pentacyclic triterpenoids, which form the largest group, and include such compounds as α- and β-amyrin, lupeol, taraxasterol, etc.

The pentacyclic triterpenoids cycloartenol[5,6] and cycloläudenol[3,4] bear a close relationship to lanosterol, and are best classified as tetracyclic. The hexacyclic triterpenoid phyllanthol, which is closely related to α-amyrin, should be included in Group (iii). Onocerin, a new tetracyclic triterpenoid type[7], bears a resemblance to the tricyclic ambrein.

The majority of the pentacyclic triterpenoids are polyfunctional compounds which can be related to simpler monohydric alcohols by fairly 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. A member of any group can be named as a derivative of the corresponding basic hydrocarbon, e.g. α-amyrin is urs-12-en-3β-ol (V)

Comprehensive discussions of the triterpenoids, and descriptions of the general methods used in structural elucidations, can be found in the reviews of Haworth[12], Spring[13], Noller[14], Jeger[15], Birch[16], and Barton[17], and in Elsevier's Encyclopaedia of Organic Chemistry.[18]



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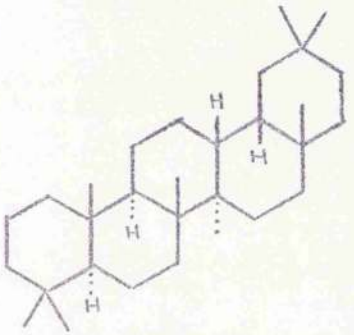

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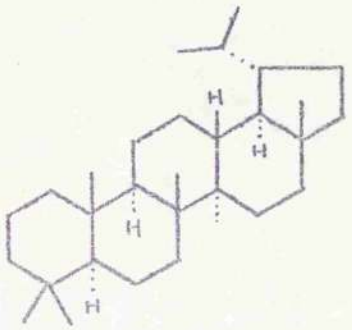

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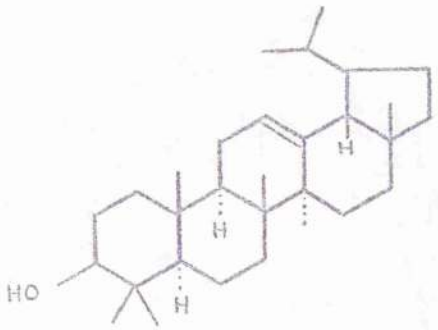

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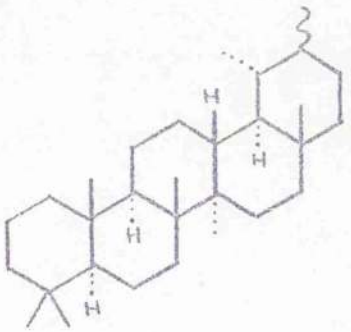

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THEORETICAL.

1. The Constitution of Taraxerol.

The constitution of the pentacyclic triterpenoid taraxerol has been shown to be (XXIII; R = H) by a partial synthesis of (XXIII) from β-amyrin (VI; R = H). The epoxide ring in taraxeryl acetate oxide has been shown to have the α-configuration, and the hydroxyl group in the diol monoacetate formed by acid treatment of the oxide to be equatorially (α) bound.

In 1923, Zellner and Roglsperger[19] isolated an alcohol, alnulin, from the bark of the grey alder (Alnus incana L.), [cf. Froschl and Zellner[20]], and it was later obtained from the bark of the black alder (Alnus glutinosa L.) by Zellner and Weiss[21]. Burrows and Simpson[22] isolated an alcohol, which they named taraxerol, from dandelion root (Taraxacum officinale). Taraxerol has also been isolated from the bark of Litsea dealbata (Lauraceae) by Dunstan, Hughes and Smithson[23]; from the bark of the red alder (Alnus rubra) by Kurth and Becker[24]; and from Euphorbia resinifera by Dupont, Julia and Wragg[25]. Jeger and his collaborators[26] established the identity of alnulin and taraxerol.

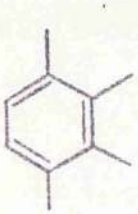
Meanwhile, Takeda[27,28,29,30] isolated an alcohol, skimmiol, from Skimmia (Rutaceae) species, and suggested that

it was identical with taraxerol. The identity was established conclusively by Brooks[31]. Beaton, Spring, Stevenson and Stewart[32] have suggested that the names alnulin and skimmiol be abandoned, and that these alcohols should in future be called taraxerol. It is probable that the alcohol tiliadin, isolated from Tilia cordata and Tilia platyphyllos[33], is also identical with taraxerol. The related unsaturated hydrocarbon, taraxerene, has been isolated from a lichen (Cladonia deformis Hoffm.) by Bruun[34].

When this study of taraxerol started, considerable contributions to the chemistry of the alcohol had been made by Takeda[27,28,29,30], Jeger and his collaborators[26], and Brooks[31]. By ether extraction of Skimmia japonica Thunb., followed by chromatography of the extract, Takeda[27] isolated taraxerol (skimmiol) and the related ketone taraxerone (skimmione). Takeda showed that taraxerol has the molecular formula $C_{30}H_{50}O$, and that it contains 1 hydroxyl group and 1 double bond. The hydroxyl group is acylable and taraxerol forms an acetate, a benzoate and a formate. The double bond in taraxerol slowly absorbs 1 mol. of hydrogen to give the saturated alcohol taraxeranol. Dry distillation of taraxerol with selenium at 340° for 36 hours gives[26] 1:2:3:4-tetramethylbenzene (I), 1:2:5:6-tetramethylnaphthalene (II), 1:2:7--trimethylnaphthalene (III), 2:7-dimethylnaphthalene (IV),

1:8-dimethylpicene (V) and a hydrocarbon, m.p. 68.5°.

Takeda concluded that taraxerol is a pentacyclic triterpenoid, probably having the same basic skeleton as β-amyrin (VI; R = H).



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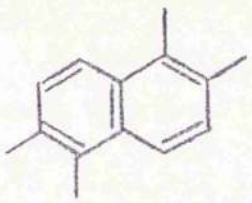

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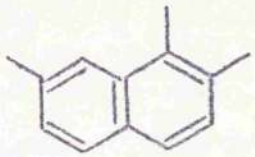

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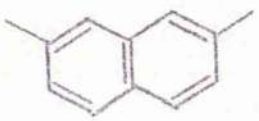

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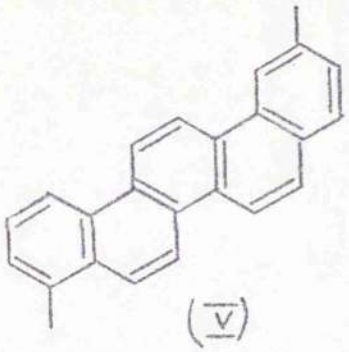

(V)

Takeda[30] noted the resemblance between the constants of a hydrocarbon, obtained by prolonged Clemmensen reduction of taraxerone, and olean-13(18)-ene (VII), obtained by Winterstein and Stein[35] from olean-12-en-3-one (VIII). Takeda showed that these two products are identical, thus establishing a direct relationship between taraxerol and the oleanane group of triterpenoids.[E] This was later confirmed

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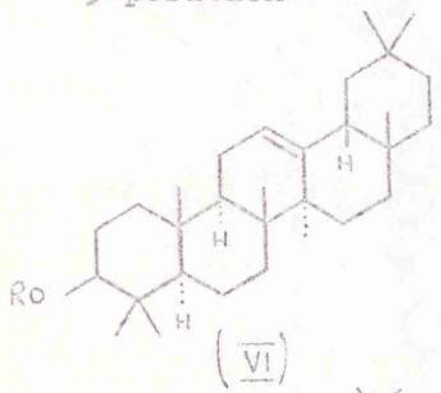
E It has been shown recently by Brownlie et al.[55] that the olean-13(18)-ene ("β-amyrene-III") obtained by Winterstein and Stein[35] is in fact a mixed crystal of olean-13(18)-ene and 18α-olean-12-ene. (For fuller details, see Alnusenone section). This does not affect the validity of Takeda's relationship of taraxerol and the oleanane group of triterpenoids. Throughout this section, therefore, when reference is made to olean-13(18)-ene obtained by other workers, the product is the mixture of olean-13(18)-ene and 18α-olean-12-ene.

by Koller et al.[26] Takeda concluded that taraxerol is olean-18-en-3β-ol (IX; R = H). This formulation had to be rejected when germanicol, which differs from taraxerol, was shown to have the structure (IX; R = H) by Barton and Brooks[11].

Koller et al.[26] confirmed the molecular formula $C_{30}H_{50}O$ for taraxerol. An examination of the infra-red spectrum of the alcohol showed that the double bond is of the type -C:CH-. It was also demonstrated by Koller et al.[26] that the hydroxyl group is present in a six-membered, or larger ring. They did not conclude that the formation of olean-13(18)-ene (VII) from taraxerone is proof that the latter is an oleanane derivative. They did report, however, that taraxerone is not reduced by the Wolff-Kishner method, and suggested that the oxygen function may not be in the 3-position.



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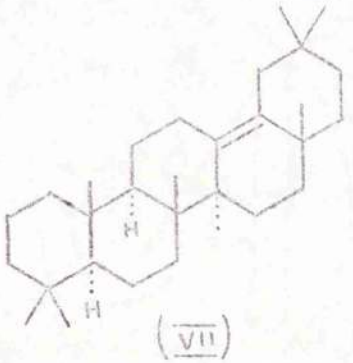

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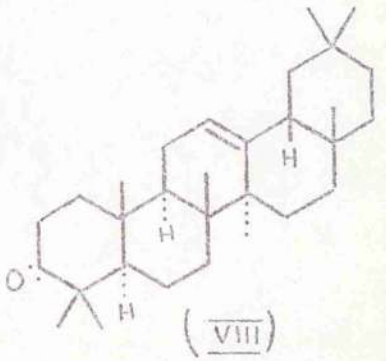

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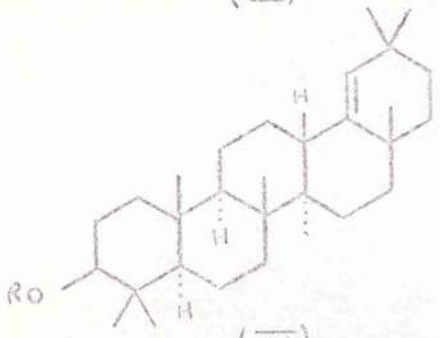

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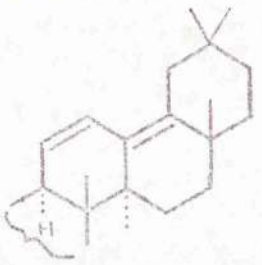

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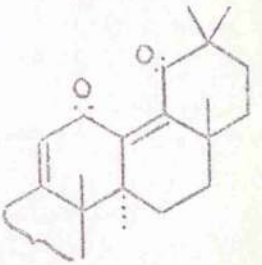

(XI)

Brooks[31] made an important contribution to the chemistry of taraxerol by showing that on treatment with selenium dioxide, taraxeryl acetate yields oleana-11:13(18)-dien-3β-yl acetate (X)[¤] and 12:19-dioxo-oleana-9(11):13(18)-dien-3β-yl acetate (XI). This proves that the hydroxyl group is attached to C_3 in taraxerol, and that it has the β-configuration. The contrary suggestion by Koller et al.[26] is disproved, since Brooks found that Wolff-Kishner reduction of taraxerone proceeds smoothly to give taraxerene in good yield. On this basis, Brooks suggested that taraxerol is 13α-germanicol (XII; R = H), with the proviso that no rearrangement of the carbon skeleton has taken place during the selenium dioxide oxidation.

Several disadvantages in structure (XII; R = H) for taraxerol become apparent in the light of some of the excellent work of Takeda. Takeda[29] prepared taraxeryl acetate oxide by perbenzoic acid oxidation of taraxeryl acetate. Treatment of the oxide with mineral acid yielded an unsaturated diol monoacetate, which on oxidation with chromium trioxide gave an unsaturated keto-acetate. The diol monoacetate gave a diacetate on treatment with acetic anhydride. If taraxeryl acetate is to be represented by (XII), the oxide is (XIII),

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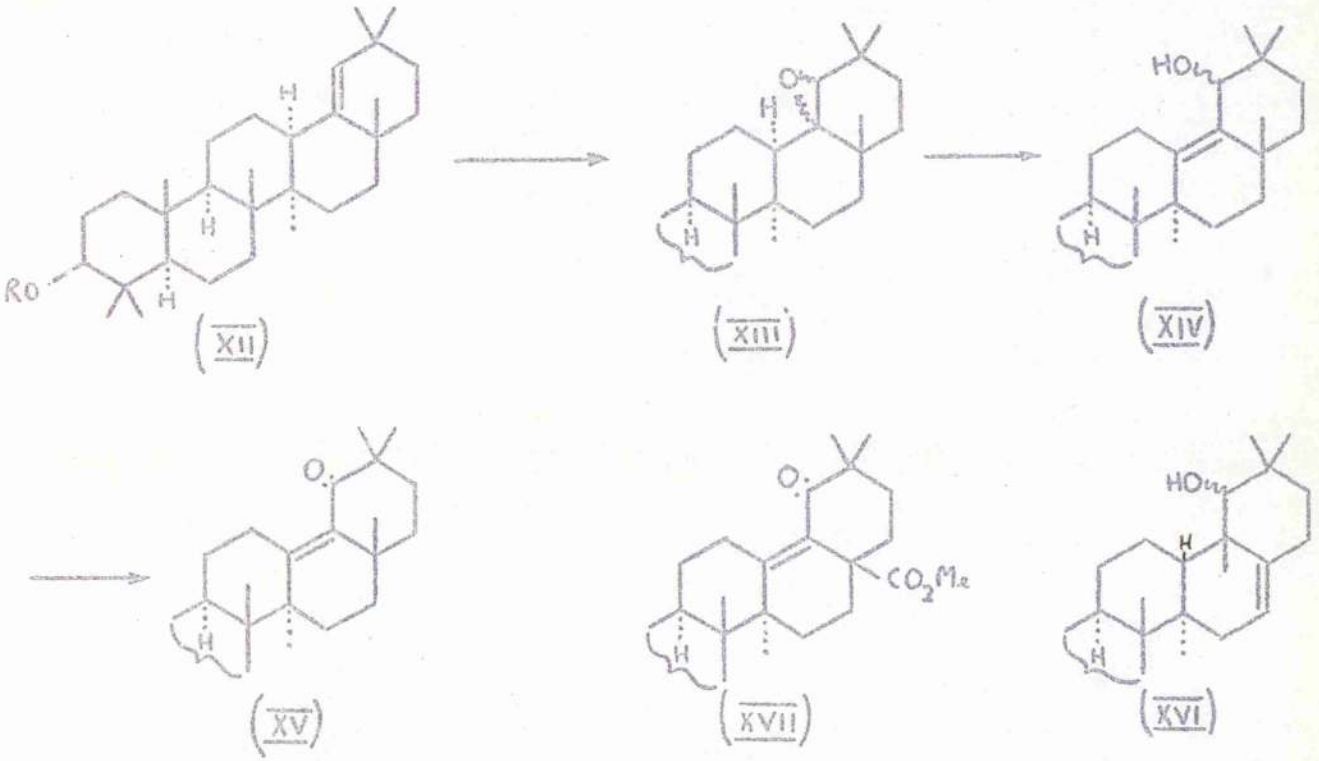
¤ In the formulae (X) - (XLVI), R = Ac unless otherwise stated.

the diol monoacetate is (XIV) and the keto-acetate is (XV) [19-oxo-olean-13(18)-en-3β-yl acetate]. It has been shown by Bilham, Kon and Ross[36] and by Ruzicka, Grob, Egli and Jeger[37] that methyl 3β-acetoxy-19-oxo-olean-13(18)-enoate (XVII) is strongly laevorotatory ($[\alpha]_D$ - 203°), as are its derivatives. By analogy, it is reasonable to assume that 19-oxo-olean-13(18)-en-3β-yl acetate (XV) will also be strongly laevorotatory. Takeda found that the unsaturated keto-acetate from taraxeryl acetate is dextrorotatory ($[\alpha]_D$ + 4°). In addition, the reaction sequence (XII) ⟶ (XIV) is not satisfactory for the conversion of taraxeryl acetate into the diol monoacetate, since (XIV) is formulated as an allylic alcohol, which would be unlikely to survive the acid condition used in its preparation from the oxide.

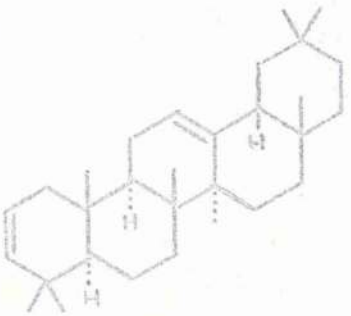


(XII) (XIII) (XIV)

(XV) (XVII) (XVI)

Alternative formulae [e.g.(XVI)] for the diol monoacetate can be devised which overcome the criticisms mentioned above Several other facts, however, are difficult to reconcile with the structure (XII; R = H) for taraxerol.

Takeda[30] reported that pyrolysis of taraxeryl benzoate gives a small yield of oleana-2:12-diene (XVIII). Also, Clemmensen reduction[26] of taraxerone for 24 hours gives olean-13(18)-ene (VII), whereas similar reduction for 8 hours gives a hydrocarbon, the constants of which (m.p. 164-165°, $[\alpha]_D$ + 25°) are in close agreement with those of a mixture of olean-12-ene (XIX) and olean-13(18)-ene (VII) described by Davy, Halsall and Jones[30].



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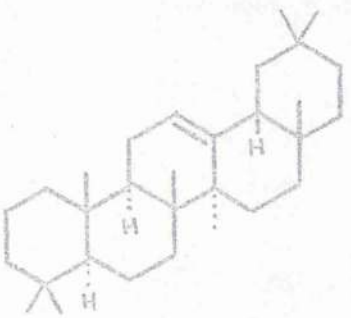

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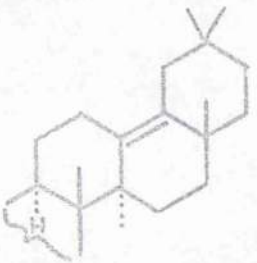
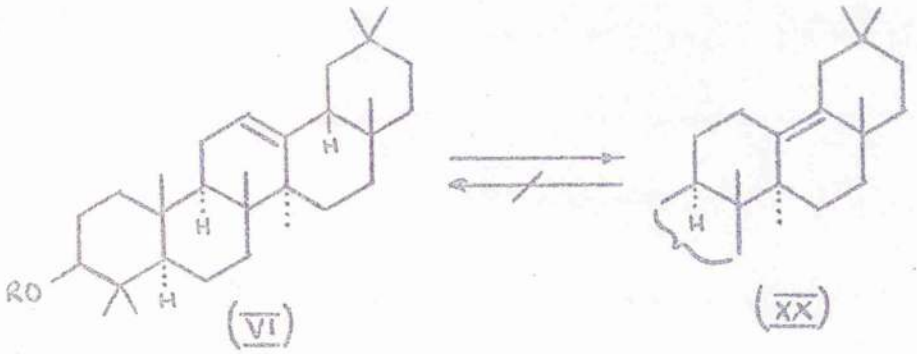


(VII)

If the hydrocarbon (m.p. 164-165°) isolated by Koller et al.[26] is a mixture of olean-12-ene (XIX) and olean-13(18)-ene (VII), its conversion into pure olean-13(18)-ene by continued acid treatment is in accordance

with the known facts.[3] Of greater importance, during the Clemmensen reduction, the double bond originally present in taraxerone is moving to the 13(18)-position via the 12:13--position.

This hypothesis was confirmed by the conversion[32] of taraxeryl acetate into β-amyrin acetate (VI) by mild treatment with mineral acid. Thus it has been shown conclusively that taraxerol cannot be (XII; R = H), since conversion of (XII) into β-amyrin acetate (VI) would require the conversion of the intermediate olean-13(18)-en-3β-yl acetate (XX) into the thermodynamically less stable β-amyrin acetate (VI).



(VI) (XX)

If it is assumed that the conversion of taraxeryl acetate into β-amyrin acetate consists of a simple double bond movement (without molecular rearrangement), then, by

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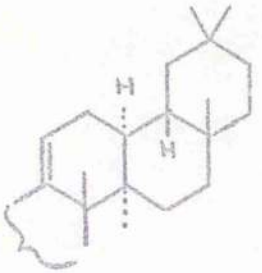
[3] The mixture must consist of olean-12-ene, olean-13(18)-ene and 18α-olean-12-ene, and the "pure" olean-13(18)-ene obtained by continued acid treatment is the mixed crystal of olean-13(18)-ene and 18α-olean-12-ene referred to previously.

elimination of the known double bond isomers of β-amyrin acetate, taraxeryl acetate must be 13α-olean-9(11)-en-3β-yl acetate (XXI), the conversion of which into β-amyrin acetate must be due to the abnormal configuration at C_{13}. It has been shown[39] that the 13β-isomer of (XXI), olean-9(11)-en--3β-yl acetate (XXII) is stable to mineral acid.



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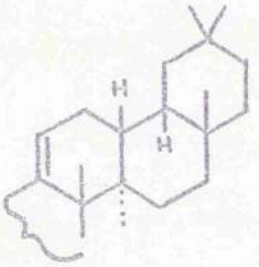


(XXII)

Takeda's oxide, unsaturated diol monoacetate and unsaturated keto-acetate have been re-examined in an attempt to obtain fresh evidence as to their constitutions. It has been found that the keto-acetate does not contain an αβ--unsaturated ketone chromophore, (it shows no high intensity absorption above 2100 Å. in the ultra-violet), and therefore the fission of taraxeryl acetate oxide must involve a molecular rearrangement. Dehydration of the diol monoacetate with phosphorus oxychloride in pyridine gives an unconjugated diene, catalytic hydrogenation of which yields β-amyrin acetate[32]. Hence, an oleanane derivative has been produced as a result of the molecular rearrangement, and taraxerol itself

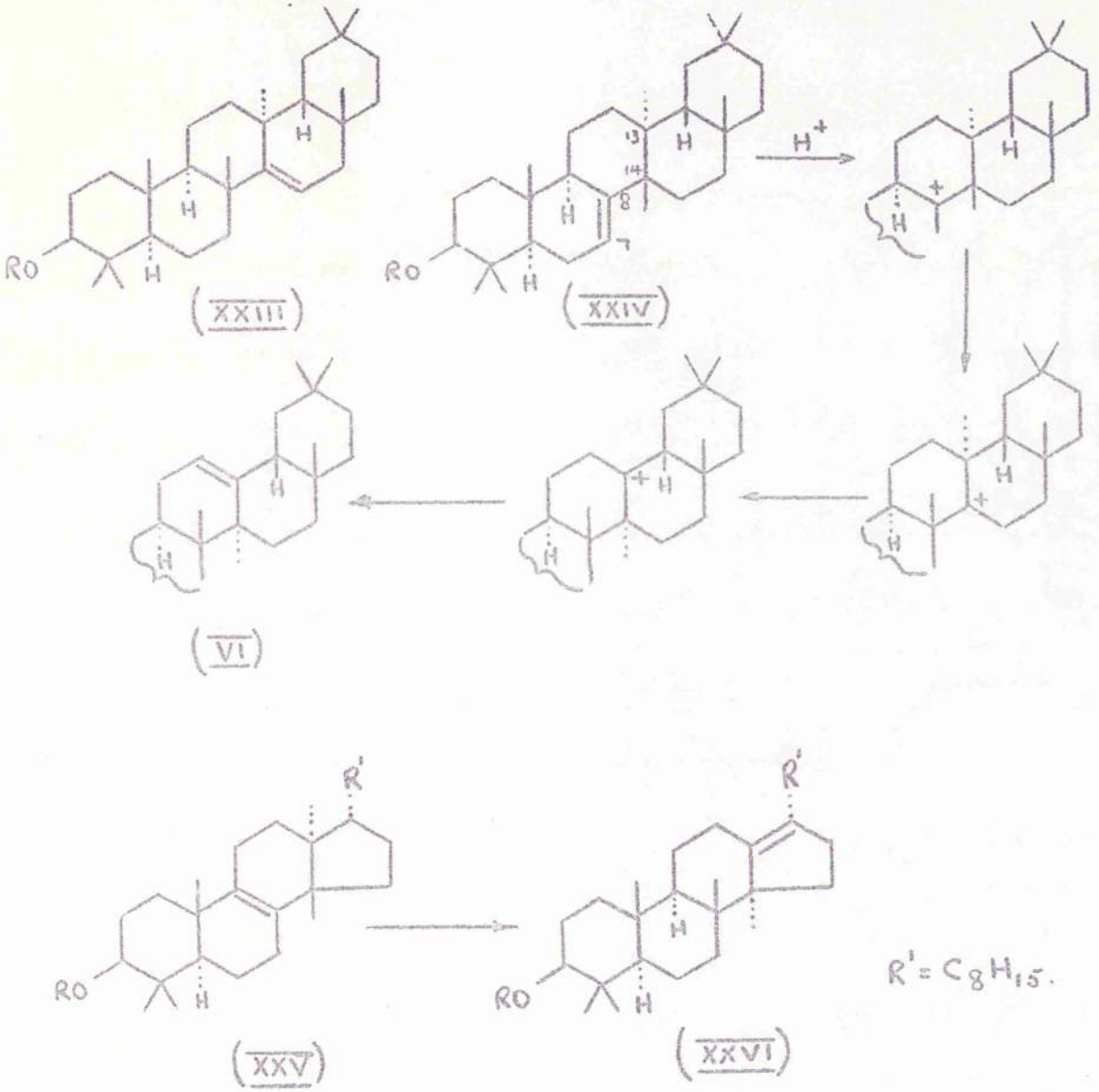
cannot be an oleanane derivative. It cannot, therefore, have the structure represented by (XXI; R = H). The diol monoacetate is a hydroxy-β-amyrin acetate, in which the position of the hydroxyl group marks the position of the double bond in taraxeryl acetate. Similarly, the keto-acetate is an oxygenated-β-amyrin acetate. Removal of the ketone group should give β-amyrin acetate. The keto-acetate was, however, recovered unchanged after being exposed to normal Wolff-Kishner reduction, followed by acetylation. This suggests that the carbonyl group is sterically hindered.

The molecular rearrangement evidence presented above leads to the consideration of (XXIII; R = H) and (XXIV; R = H) for taraxerol. The rearrangement of (XXIV) into β-amyrin acetate (VI) by treatment with mineral acid can be represented as initiated by the approach of a proton to the 7:8-double bond with synchronous movement of the methyl groups from $C_{14}(\beta)$ and $C_{13}(\alpha)$ to C_8 and C_{14} respectively, with final stabilisation by the elimination of a proton from C_{12}.

The mechanism described above is similar to that responsible for the conversion[40] of euphenyl acetate (XXV) to iseuphenyl acetate (XXVI).

The alternative structure (XXIII) for taraxeryl acetate is more satisfactory because of a close analogy between the

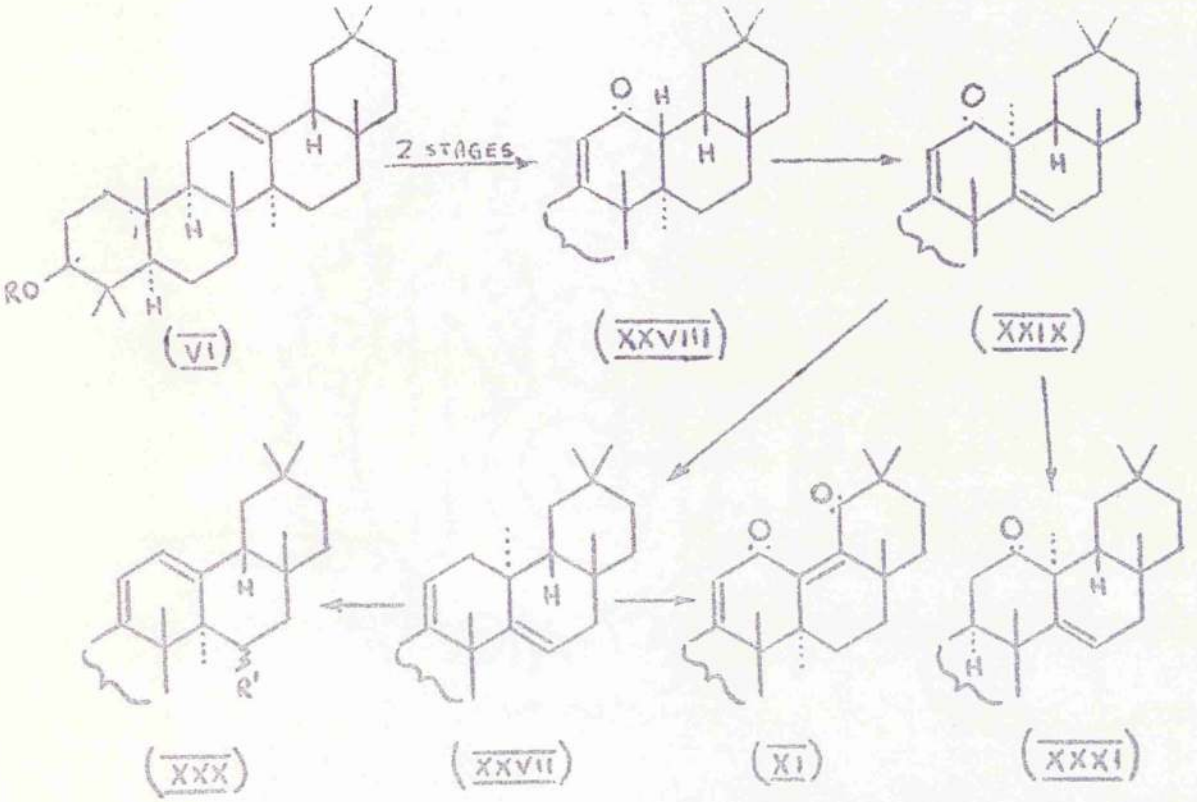
reactions of this acetate and those[41] of isooleana-9(11):14--dien-3β-yl acetate (XXVII). Oxidation of 12-oxo-olean--9(11)-en-3β-yl acetate (XXVIII) with selenium dioxide or



bromine gives 12-oxoisooleana-9(11):14-dien-3β-yl acetate (XXIX), which on Wolff-Kishner reduction gives (XXVII)[39,42].

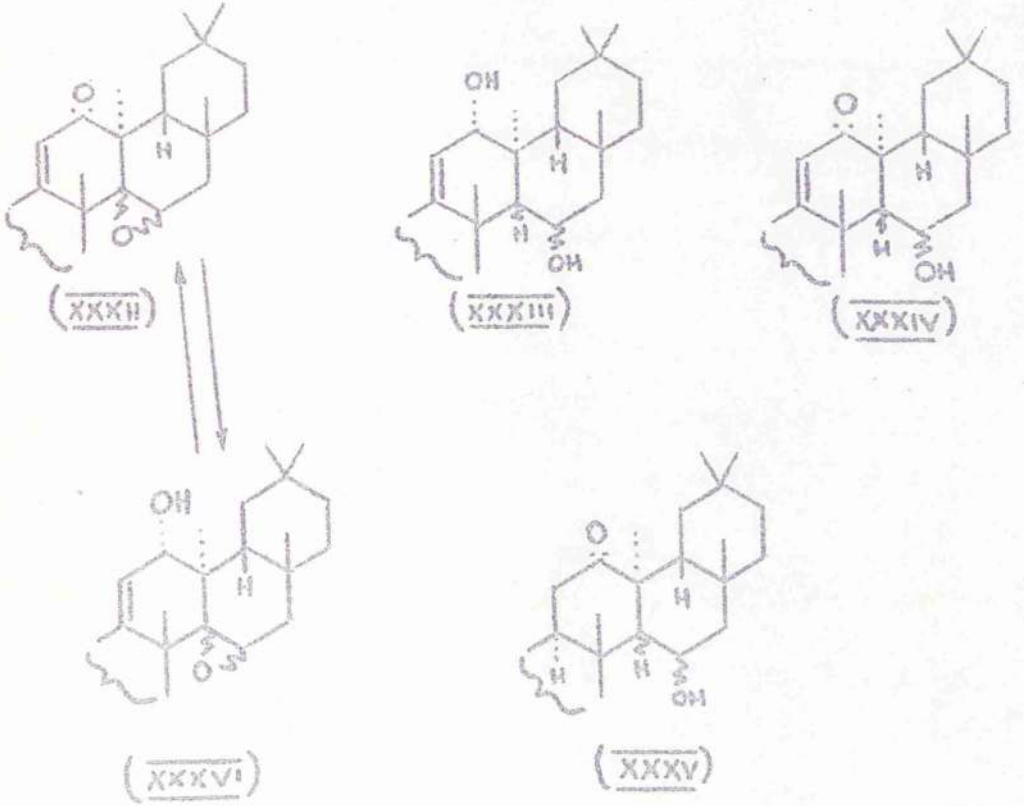
Treatment of the acetate (XXVII) with mineral acid gives oleana-9(11):12-dien-3β-yl acetate (XXX; R' = H),[41]. This reaction bears a striking resemblance to the conversion of taraxeryl acetate into β-amyrin acetate (VI). On treatment of the acetate (XXVII) with selenium dioxide, oxidation is accompanied by molecular rearrangement to give 12:19-dioxo--oleana-9(11):13(18)-dien-3β-yl acetate (XI), behaviour which again closely resembles that of taraxeryl acetate[81]. Oxidation of the acetate (XXVII) with perbenzoic acid yields 15-hydroxyoleana-9(11):12-dien-3β-yl acetate (XXX; R' = OH), presumably by rearrangement of an unstable oxide, a reaction comparable with the conversion of taraxeryl acetate via the oxide into the unsaturated diol monoacetate.

A partial synthesis of isoolean-14-en-3β-yl acetate (XXIII) from 12-oxoisooleana-9(11):14-dien-3β-yl acetate (XXIX) was at first unsuccessful. Reduction of the acetate (XXIX) with lithium in liquid ammonia yields 12-oxoisoolean--14-en-3β-yl acetate (XXXI), which will give isoolean-14-en--3β-yl acetate (XXIII) on removal of the carbonyl group. The ketone (XXXI) was, however, recovered unchanged after being exposed to normal Wolff-Kishner reduction, followed by acetylation.



An alternative synthesis was attempted which is based on the fact that the ketone group at C_{12} is less sterically hindered when there is no double bond in the 14:15-position. Lithium aluminium hydride reduction of 14:15-epoxy-12-oxoisoolean-9(11)-en-3β-yl acetate (XXXII), prepared by oxidation of 12-oxoisooleana-9(11):14-dien-3β-yl acetate (XXIX) with potassium permanganate[45], was expected to give isoolean-9(11)-ene-3β:12α:15-triol (XXXIII; R = H). Oxidation of (XXXIII; R = H) with manganese dioxide should give 12-oxoisoolean-9(11)-ene-3β:15-diol (XXXIV; R = H). Lithium in ammonia reduction to 12-oxoisooleana-3β:15-diol

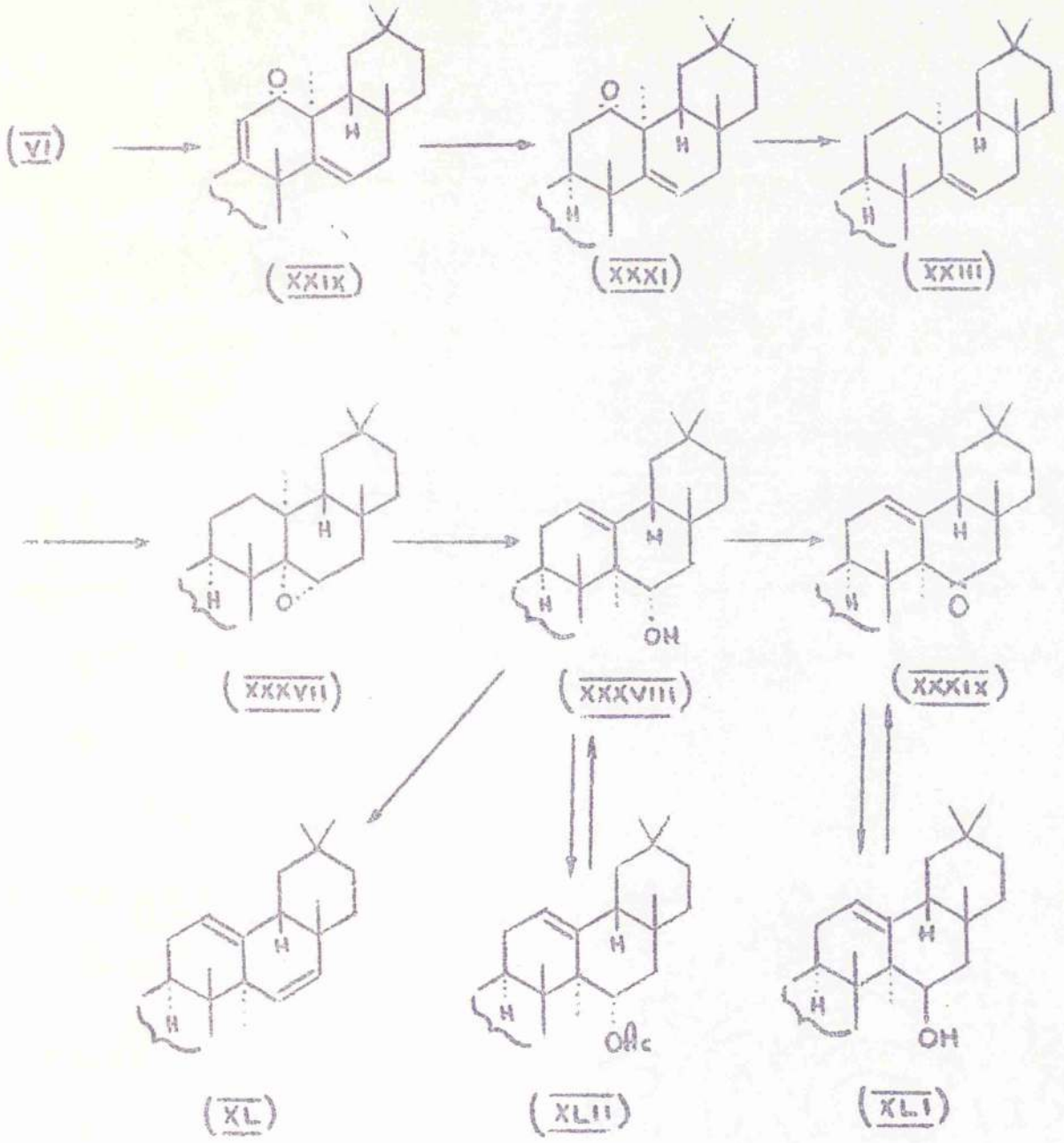
(XXXV; R = H) would have presented a possibility of attack on the 12-ketone by normal Wolff-Kishner methods. Reduction of (XXXII) with lithium aluminium hydride gives, as expected, a product showing no high intensity absorption in the ultra-violet above 2100 Å. Shaking a solution of the crude product in acetone with manganese dioxide gives, after acetylation, 14:15-epoxy-12-oxoisoolean-9(11)-en-3β-yl acetate (XXXII). Thus the 14:15-epoxide ring has not been affected on treatment of (XXXII) with lithium aluminium hydride, the product being 14:15-epoxyisoolean-9(11)-ene-3β:12α-diol (XXXVI; R = H).



By using a modified (forcing) variant of the Wolff-Kishner technique[46], the details of which were kindly supplied before publication by Professor D. H. R. Barton, F.R.S., a smooth reduction of 12-oxo*iso*olean-14-en-3β-yl acetate (XXXI) was effected to give, after acetylation, *iso*olean-14-en-3β-yl acetate (XXIII), which was found to be identical with taraxeryl acetate obtained from natural sources. Since the ketone (XXIX) is prepared from β-amyrin (VI; R = H), these reactions constitute a partial synthesis of taraxerol from β-amyrin. It has been suggested[32] that the name taraxerane be substituted for *iso*oleanane in the nomenclature of this series, (the orientation of the hydrogen attached to C_{14} being arbitrarily defined as α), since the use of the prefix *iso* is confusing and no longer necessary in a series which has been proved to be naturally-occurring. The derivatives described in the experimental section have been named accordingly. Thus taraxeryl acetate becomes taraxer-14-en-3β-yl acetate (XXIII). The saturated hydrocarbon obtained from dihydrotaraxerone by Clemmensen reduction[27] is almost certainly 14β-taraxerane.

Taraxeryl acetate oxide is (XXXVII), the diol mono-acetate is olean-12-ene-3β:15α-diol 3-acetate (XXXVIII) and the keto-acetate is 15-oxo-olean-12-en-3β-yl acetate (XXXIX). The non-conjugated dienyl acetate obtained by treatment of the

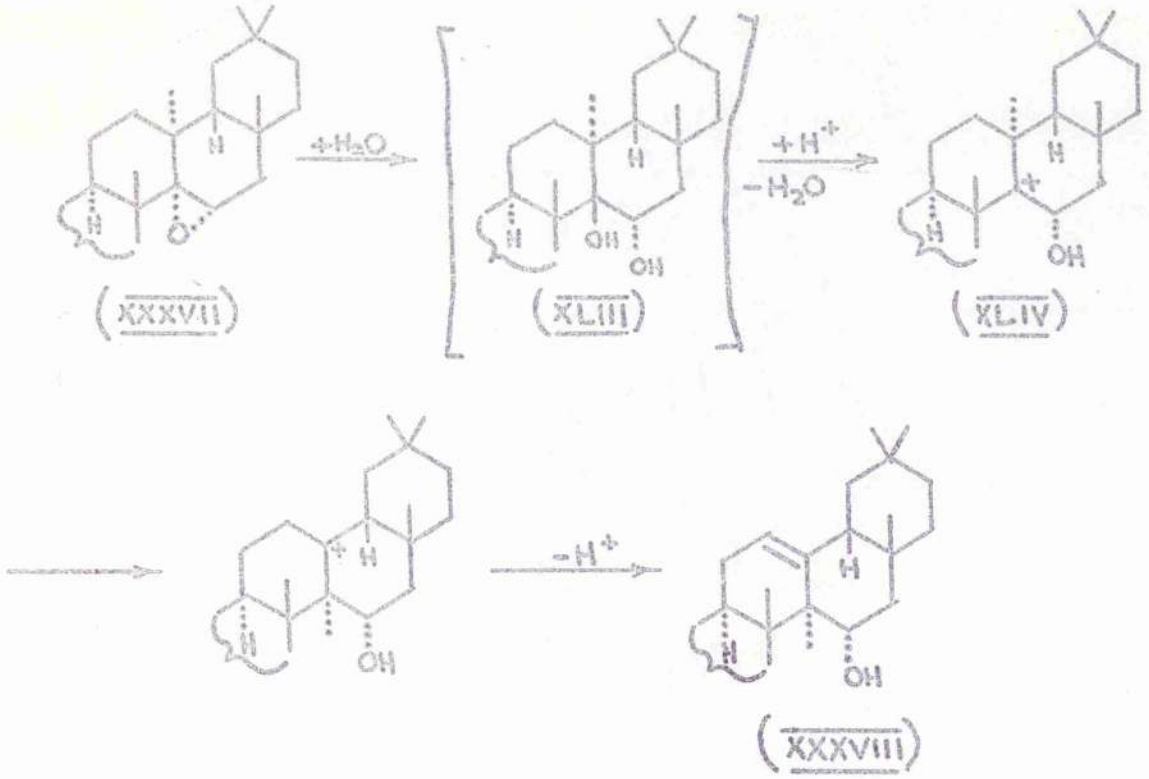
diol monoacetate with phosphorus oxychloride[32] is oleana-
-12:15-dien-3β-yl acetate (XL).



The configuration of the 15-hydroxyl group in (XXXVIII) has been shown to be equatorial (α) by a comparison of (XXXVIII) with olean-12-en-3β:15β-diol 3-acetate (XLI), obtained by lithium aluminium hydride reduction of 15-oxo-olean--12-en-3β-yl acetate (XXXIX) with acetylation of the product. The two diol monoacetates are different. The diol (XLI; R = H) gives a monoacetate (XLI) only, and in this respect it differs from its isomer (XXXVIII; R = H), which under the same conditions gives a diacetate (XLII). The relation of the diol monoacetates (XXXVIII) and (XLI) as epimers at C_{15} was confirmed by oxidation of (XLI) to 15-oxo-olean-12-en-3β-yl acetate (XXXIX). It follows that the hydroxyl group in the diol monoacetate obtained by acid fission of taraxeryl acetate oxide is equatorially (α) bound. This is supported by the fact that reduction of 15-oxo-olean-12-en-3β-yl acetate (XXXIX) with sodium in isoamyl alcohol gives[29] a diol (β-hydroxy-skimmiol) which is identical with that obtained by alkaline hydrolysis of (XLII). The isomeric diol monoacetate (XLI), prepared as described above, is the axial (15β) epimer. The formation of the axial alcohol (XLI; R = H) conforms to the rule that reduction of a heavily hindered ketone with lithium aluminium hydride gives an axial alcohol[44,48]. The

hindered nature of the carbonyl group has already been deduced from the fact that the ketone (XXXIX) is recovered unchanged after normal Wolff-Kishner reduction, followed by acetylation.

It seems reasonable to assume that, since the hydroxyl group in (XXXVIII) has the α-configuration, the epoxide ring in taraxeryl acetate oxide also has the α-configuration. The conversion of the epoxide (XXXVII) into the diol monoacetate (XXXVIII) can be represented as follows:



(XXXVII) (XLIII) (XLIV) (XXXVIII)

Fission of the epoxide ring appears to follow the rule of axial opening[45]. This can be seen more readily if it is assumed that an intermediate (trans-) glycol (XLIII) is formed, in which both hydroxyl groups are axially bound

with respect to ring D. The degeneration of the cation (XLIV) consists in the movement of the methyl group from C_{13} to C_{14}, and the elimination of a proton from C_{12} with formation of the 12:13-double bond; these operations are probably synchronous. The change from a taraxeran-15α-ol derivative (XLIII), in which the 15-hydroxyl group is axial, to an olean-15α-ol derivative (XXXVIII), in which the 15-hydroxyl group is equatorial, is accompanied by a change in the conformation of ring D.

The acid-catalysed isomerisation of taraxeryl acetate (XXIII) to β-amyrin acetate (VI) can be represented in a similar manner to that outlined above for the fission of the epoxide; approach of a proton to C_{14} is accompanied by synchronous transference of the methyl group from C_{13} to C_{14}, and elimination of a proton from C_{12}. It is surprising that in both cases the proton elimination takes place from C_{12}, and not from C_{18}, to give the thermodynamically less stable Δ^{12}-compound rather than the more stable $\Delta^{13(18)}$-isomer. The reason for this can possibly be found in the geometry of the molecule.

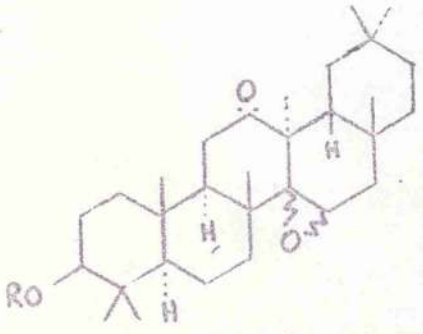
The ease of isomerisation of taraxerol derivatives is remarkable. The oxidation of taraxeryl acetate with selenium dioxide in boiling acetic acid yields the derivatives to be expected by similar treatment of β-amyrin acetate, showing

that these reagents are sufficiently acidic to bring about rearrangement. In the preparation of the epoxide (XXXVII) by oxidation of taraxeryl acetate with perbenzoic acid, great care must be taken in the preparation of the reagent. If the per-acid solution is not freshly-prepared, isomerisation takes place to give directly the diol monoacetate (XXXVIII). The constants given by Koller et al.[36] for "taraxeryl acetate oxide" show that their product is in fact the diol monoacetate (XXXVIII), (see Experimental section).

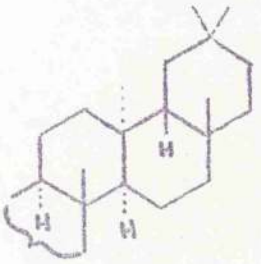
Oxidation of 12-oxotaraxer-14-en-3β-yl acetate (XXXI) with potassium permanganate gives 14ξ:15ξ-epoxy-12-oxotaraxeran-3β-yl acetate (XLV), which was treated with mineral acid in an attempt to carry out an oxide fission analogous to that found in the preparation of the diol monoacetate (XXXVIII) from the epoxide (XXXVII). In this case, no crystalline material was isolated.

A comparison of the saturated alcohol, taraxeran-3β-ol (XLVI; R = H) with alnusanol, the saturated alcohol obtained from alnusenol, (see Alnusenone section), has shown that these two alcohols are different:

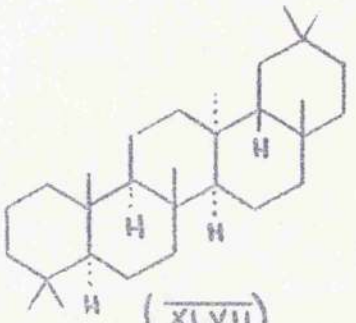
	Taraxeran-			Alnusan-	
	m.p.	$[\alpha]_D$	mixed m.p.	m.p.	$[\alpha]_D$
-ol	259-261°	+22°	220-225°	255-256°	+28°
-yl acetate	248-250°	+34°		264-265°	+11°



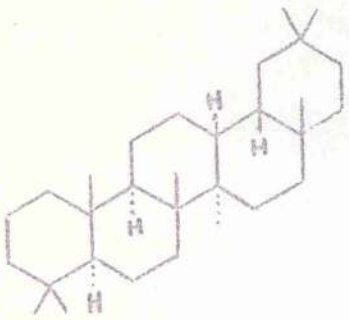
(XLV)



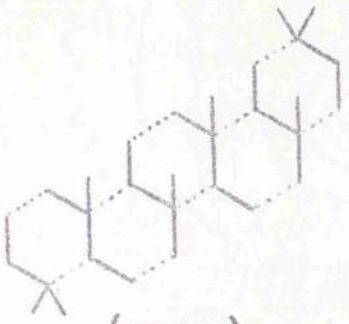
(XLVI)



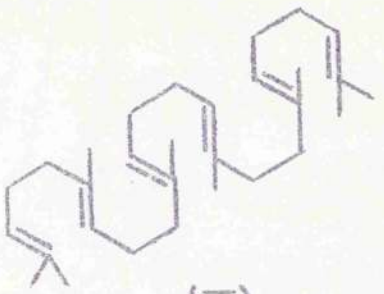
(XLVII)



(XLIX)

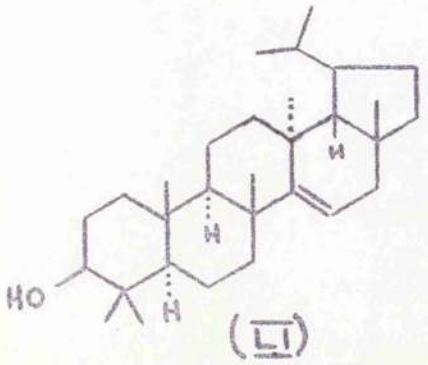


(XLVIII)



(L)

Taraxerol is the first naturally-occurring isooleanane derivative to be identified. The carbon skeleton of taraxerane (XLVII) can be regarded as made up of six isopentane residues symetrically linked head to tail as shown in (XLVIII). When this fact was first observed, it was suggested[32] that taraxerol may be the precursor of the oleanane (XLIX) group of triterpenoids. In a recent paper, Eschenmoser, Ruzicka, Jeger and Arigoni[47] have suggested possible mechanisms for the derivation of the constitutional formulae of the known triterpenoids from the formula of squalene (L). Eschenmoser et al.[47] suggest that the taraxerane and oleanane groups of triterpenoids are formed independently from squalene by slightly different biogenetic routes.



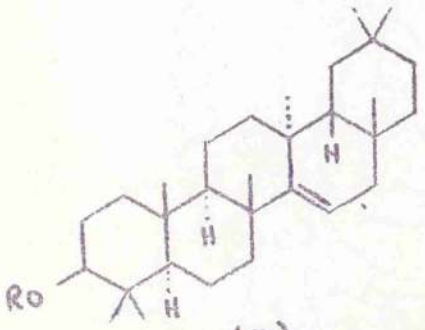
(LI)

The isoursane analogue of taraxerol, isours-14-en-3β-ol (Ll)has been prepared by Laird[48].

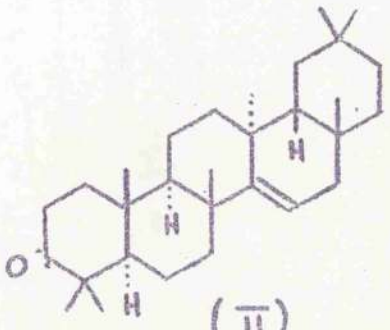
2. The Constitution of Alnusenone (Glutinone).

An examination of alnusenone, a pentacyclic triterpenoid ketone isolated[49,51] from the bark of the black alder (Alnus glutinosa L.), has shown that its constitution is represented by (XIV). An isomeric ketone, obtained from alnusenone by treatment with mineral acid, has been shown to have the constitution (XXIII). A partial synthesis of alnusenone (XIV) from friedelin (XXXIX) has been accomplished.

In Part 1 of this thesis, experiments are described which lead to the elucidation of the constitution (I; R = H) for taraxerol, a pentacyclic triterpenoid alcohol, which is readily isolated[21], together with the related ketone, taraxerone (II), from the bark of the black alder (Alnus glutinosa L.). During an examination of two samples of the bark, Chapon and David[49] found that one sample, collected in November, yielded taraxerol and taraxerone in agreement with the experience of Koller et al.[26] From the corresponding fraction of a second sample, collected in February, Chapon and David[49a] isolated a ketone $C_{30}H_{48}O$, which is not identical with taraxerone, and which they later[49b] named glutinone.



(I)



(II)

The isolation was repeated by Beaton, Spring and Stevenson[81], who, unaware that the compound had been named by Chapon and David[49b], called the ketone alnusenone, and confirmed the molecular formula $C_{30}H_{48}O$. Beaton et al.[81] demonstrated the homogeneity of alnusenone by conversion to the corresponding alcohol, alnusenol, which forms an acetate, a benzoate, a tribromoacetate, etc. Oxidation of alnusenol with chromic acid regenerates alnusenone. The molecular formula of alnusenone, and its close association with taraxerone, led these authors to the view that alnusenone is a pentacyclic triterpenoid ketone. Alnusenone has been shown to contain a reactive carbonyl group and a reactive double bond by means of the following experiments, which were carried out independently by Beaton et al.[81] and by Chapon and David[50]. Wolff-Kishner reduction of alnusenone gives the unsaturated hydrocarbon alnusene, which is catalytically reduced to the parent, saturated hydrocarbon alnusane.

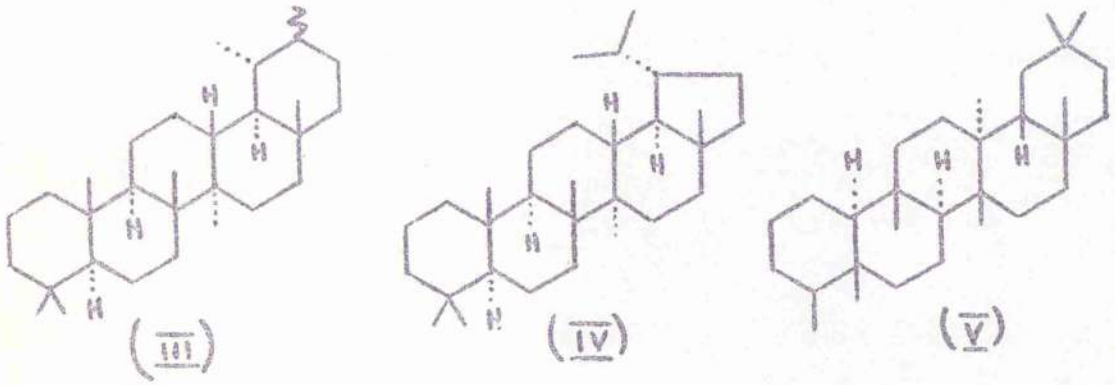
Catalytic hydrogenation of alnusenol gives the saturated alcohol alnusanol, oxidised by chromic acid to alnusanone. Wolff-Kishner reduction of alnusanone gives alnusane.

Beaton[52] noted a difference in the breadth of the ethylenic absorption bands of alnusenone and alnusenyl acetate, and suggested that this can be explained if the carbonyl group and the double bond in alnusenone are in close proximetry. Beaton also deduced that the carbonyl group must occupy a relatively non-hindered position in the molecule, firstly because alnusenone readily forms an oxime, and secondly because it yields the same alcohol, alnusenol, on reduction[51] with either sodium and ethanol or with lithium aluminium hydride. Hindered and non-hindered ketones are both reduced by sodium and alcohol to give an equilibrium mixture in which the more stable, equatorial alcohol largely predominates. On reduction with lithium aluminium hydride, non-hindred ketones give the same equilibrium mixture, but strongly hindered ketones give the axial alcohol[44]. It follows that the hydroxyl group in alnusenol has the equatorial configuration[52].

The ultra-violet absorption spectrum of alnusenyl acetate indicates that the double bond is probably trisubstituted. The infra-red absorption spectra[51] of alnusenone

and alnusanone both include a band at 1702 cm.$^{-1}$, typical of a ketone in a six-membered carbocyclic ring. Alnusenone gives a negative reaction in the Zimmermann test[51], and in this respect it differs from taraxerone (II), and from other known 3-oxo-derivatives of the pentacyclic triterpenoids[53]. Also, the molecular rotation differences between alnusenol derivatives show some marked deviations from those between corresponding derivatives of 3-hydroxy-triterpenoids. These facts led Beaton[52] to suggest that the oxygen function in alnusenone may not be situated at C_3.

A comparison[54] of alnusane with taraxastane (III), lupane-I (IV) and friedelane (V) has shown that alnusane is not identical with any of these saturated hydrocarbons. It was also shown in Part 1. of this thesis that alnusanol is not identical with taraxeranol.

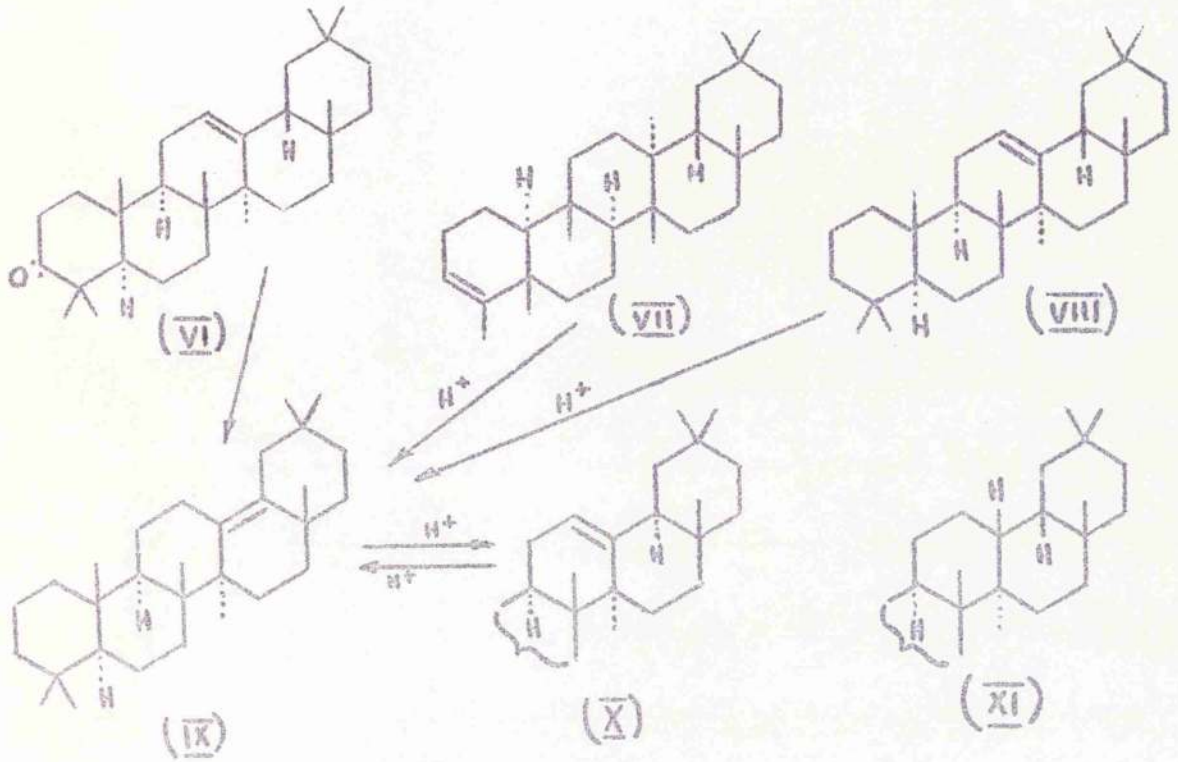


(III) (IV) (V)

An attempt by the author to relate alnusenone and its derivatives to a known group of triterpenoids has been

successful. Treatment of the unsaturated hydrocarbon alnusene with hydrochloric-acetic acid mixture gives a compound (m.p. 185-186°, $[\alpha]_D$ - 19°) identical with that obtained by Winterstein and Stein[38] by Clemmensen reduction of olean-12-en-3-one (VI), and by Takeda[30] by similar reduction of taraxer-14-en-3-one (II). This compound (m.p. 185-186°, $[\alpha]_D$ - 20°) was also obtained by Brownlie, Spring, Stevenson and Strachan[54] by treatment of friedelene (VII) with hydrochloric-acetic acid mixture, and by similar treatment of olean-12-ene (VIII). It has been shown by Brownlie, Fayez, Spring, Stevenson and Strachan[55] that this material is a mixed crystal containing olean-13(18)-ene (IX) and 18α-olean-12-ene (X) in the ratio 2:1. The same mixture has been obtained[55] from a variety of double bond isomers of olean-12-ene by treatment with hydrochloric-acetic acid mixture.

The formation of (IX) and (X) from alnusene establishes a specific relationship between alnusenone and the oleanane group of triterpenoids. The author has interpreted this to mean that the constitutions of alnusane and oleanane (XI) differ only in the position of one or more tertiary methyl groups.



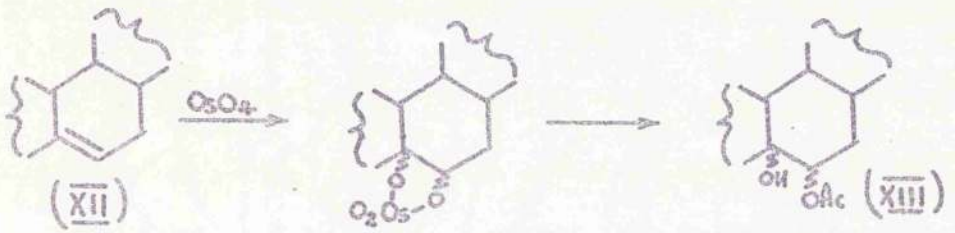
Beaton reported[83] that treatment of alnusenone with hydrochloric-acetic acid mixture, under milder conditions than those used in the isomerisation described above, gives an isomeric unsaturated ketone (alnusenone-II) (m.p. 250-252°, $[\alpha]_D$ - 90°), in which the double bond is tetrasubstituted, and not in conjugation with the ketone group. Since alnusenone is recovered unchanged after treatment with alkali[83], it is probable that alnusenone-II differs from alnusenone only in the position of the double bond, and not in the orientation at an unstable centre. Alnusenone-II was also obtained by Chapon[80a], who examined the infra-red spectrum of the corresponding hydrocarbon, alnusene-II, and concluded[80b] that the double bond is tetrasubstituted.

During the acid-catalysed isomerisation of alnusene to the mixed crystal of olean-13(18)-ene (IX) and 18α-olean--12-ene(X), the double bond may have a transient existence in the position occupied by the double bond in alnusene-II. This can be deduced from the following evidence. Firstly, alnusenone-II is formed by milder acid treatment of alnusenone, and secondly, treatment of alnusene-II under the more stringent acid conditions gives the same mixture of (IX) and (X) as obtained from alnusene. Alnusenone-II was also prepared by Chapon[80a] by an attempted Clemmensen reduction of alnusenone.

Attempts to obtain oxygenated-oleanane derivatives by treatment of alnusenone and alnusenol with mineral acid have been unsuccessful; the product in each case could not be obtained pure.

The double bond in alnusenyl acetate has been shown to be of the type -C(OH):CH- as follows: oxidation of alnusenyl acetate with osmium tetroxide, followed by treatment with lithium aluminium hydride and room temperature acetylation of the product, gives, in 51% yield, a triol diacetate $C_{34}H_{56}O_6$, [infra-red absorption in Nujol: bands at 1730, 1230 (acetate), and 3570 $cm.^{-1}$ (hydroxyl)]. In this compound the hydroxyl group and one of the acetate groups mark the position of the double bond in alnusenyl acetate. The

non-acylable hydroxyl group is stable to chromic acid at room temperature, and is therefore tertiary. The formation of the triol diacetate from alnusenyl acetate can be represented by the reaction sequence (XII) ⟶ (XIII).



(XII) (XIII)

Unchanged alnusenyl acetate (17%) was also recovered from this reaction.

Treatment of alnusenyl acetate with osmium tetroxide to give taraxeryl acetate (I)[R] in 7% yield was described by Chapon[49b,56]. Also, similar treatment[49b,56] of alnusenone is claimed to give taraxerone (II) in yields varying from 22 to 91%. The author has not been able to confirm these results.

Oxidation of alnusenyl acetate with monperphthalic acid gives an epoxide, which is stable to (a) lithium aluminium hydride and (b) hydrogen and platinum at room temperature.

Consideration will now be given to some possible structures for alnusenone, based on the evidence so far presented. An initial assumption that the ketone group in alnusenone is at C_3 in the triterpenoid nucleus is reasonable, since all known naturally-occurring triterpenoid alcohols and ketones contain an oxygen function in this position. The

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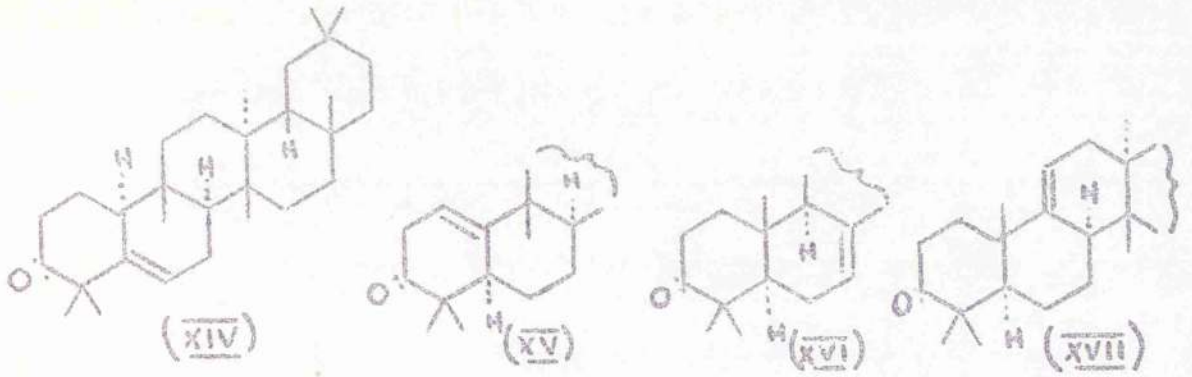
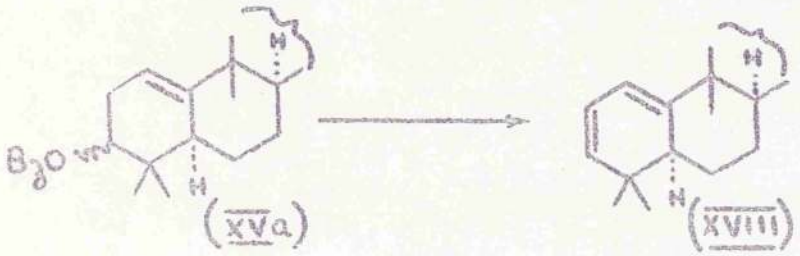
[R] In the formulae (I)-(XLI), R = Ac unless otherwise stated.

structures which will be examined are (XIV), (XV) and (XVI). Structure (XVII) for alnusenone is not satisfactory, because the double bond and the ketone group are not in close proximetry, and there is therefore no apparent explanation for the difference in behaviour of alnusene and alnusenone to mineral acid. Since it has been shown that the double bond in alnusenyl acetate is trisubstituted, it cannot occupy positions 5:10, 6:7 or 8:9 in the molecule. The reasons for choosing the configurations shown at C_8, C_9, C_{10}, C_{13} and C_{14} will be discussed later.



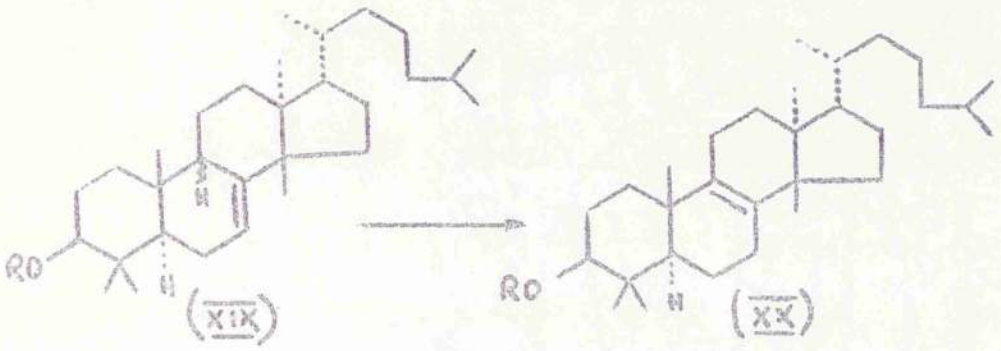
(XIV) (XV) (XVI) (XVII)

Structure (XV) for alnusenone has been eliminated by means of two simple experiments. Pyrolysis of alnusenyl benzoate yields an unconjugated diene [$\lambda_{max.}$ 2110 Å. (ε = 6,500)], and since removal of the elements of benzoic acid from a C_3-benzoylated triterpenoid containing a gem-dimethyl group at C_4 can only lead to the introduction of a double bond in the 2:3-position, alnusenone cannot be (XV), because pyrolysis of the benzoate (XVa) would give the conjugated diene (XVIII).



In addition, the enol acetate of alnusenone does not contain a conjugated diene system [$\lambda_{max.}$ 2060 Å. (ε = 5,850)], and therefore structure (XV) can be eliminated for reasons similar to those outlined above. The formation of these non-conjugated dienes from alnusenyl benzoate and alnusenone is in agreement with (XIV) and (XVI) for alnusenone.

A choice between formulae (XIV) and (XVI) for alnusenone has been made in favour of the former for the following reasons. Firstly, alnusenyl acetate is readily reduced[51] with hydrogen and platinum to give alnusanyl acetate. The ease with which this reduction takes place is not in agreement with the known properties of a double bond in the 7:8-position, e.g. on similar treatment[57,58] of dihydrobutyrospermyl acetate, the constitution of which has been shown[57,58,59] with almost complete certainty to be (XIX), isomerisation without reduction takes place to give euph-8-enyl acetate (XX), and lanost-7-enyl acetate is not reduced by hydrogen and platinum.

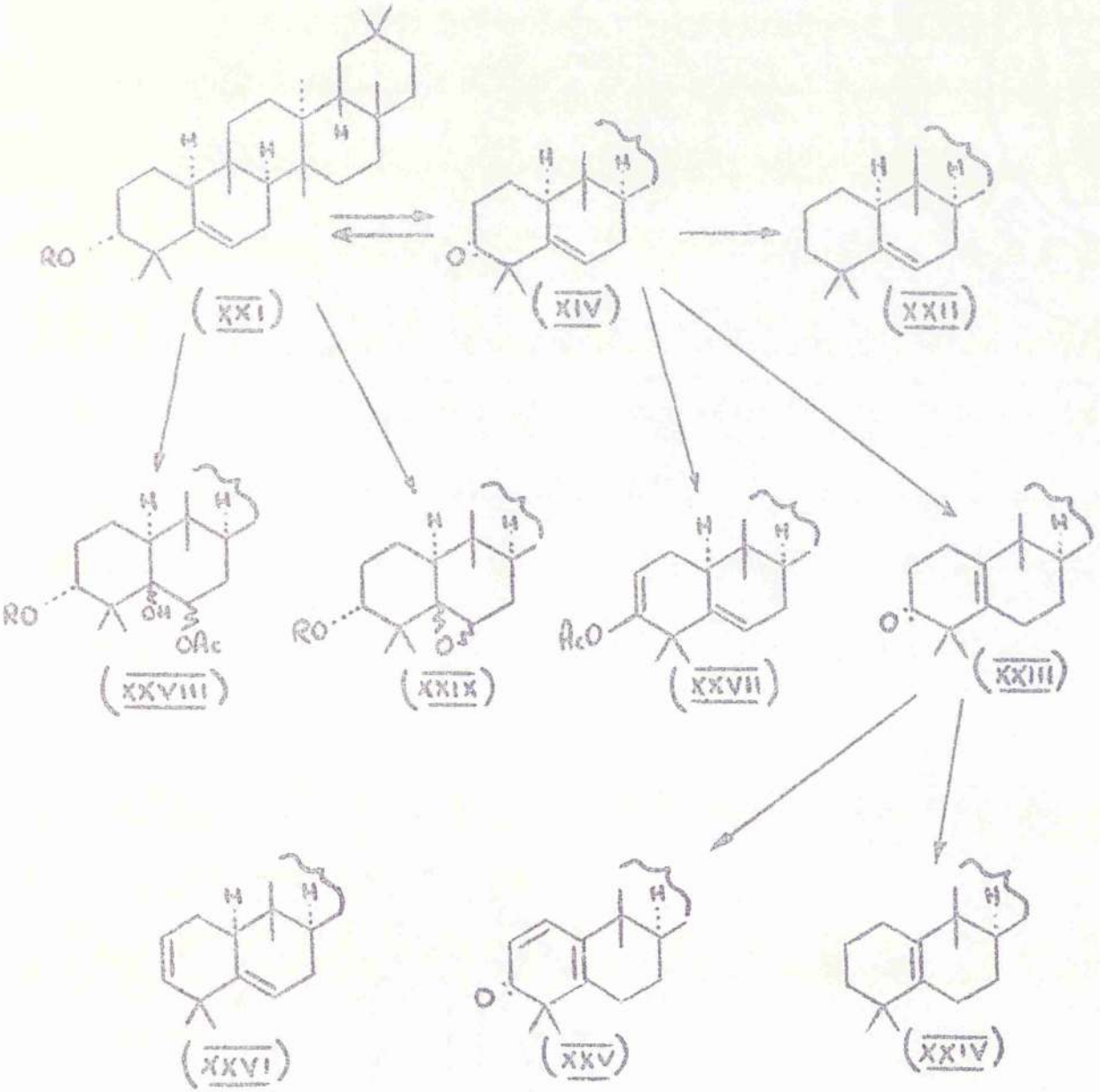


It follows that the ease of hydrogenation of alnusenyl acetate is in agreement with (XIV) rather than (XVI) for alnusenone.

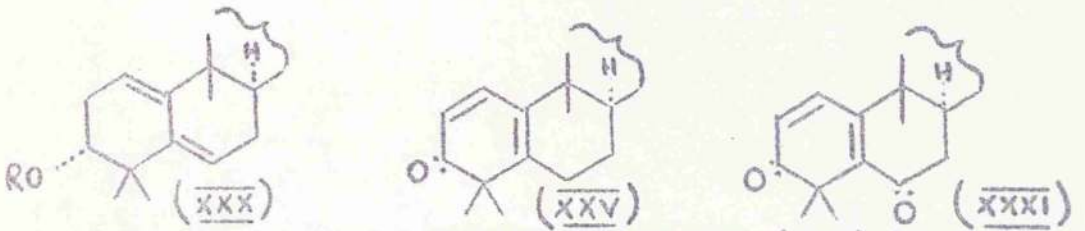
Secondly, Beaton has shown[60] that treatment of alnusenone-II with bromine, followed by dehydrobromination of the product, gives a fully conjugated dienone, $C_{30}H_{44}O$. It is impossible to formulate such a dienone on the basis of (XVI) unless, during the conversion of alnusenone to alnusenone-II, the double bond has migrated from the 7:8-position towards the 5:10-position.

The constitution and stereochemistry of alnusenone are, therefore, represented by (XIV), and the reactions already described can be adequately explained on this formulation. Alnusenyl acetate is (XXI), alnusene is (XXII), alnusenone-II is (XXIII), and alnusene-II is (XXIV). The conjugated dienone obtained from alnusenone-II by Beaton[60] is (XXV). The

unconjugated diene obtained by pyrolysis of alnusenyl benzoate is (XXVI). Alnusenone enol acetate is (XXVII). The triol diacetate prepared from alnusenyl acetate by treatment with osmium tetroxide is (XXVIII). Alnusenyl acetate oxide is (XXIX).

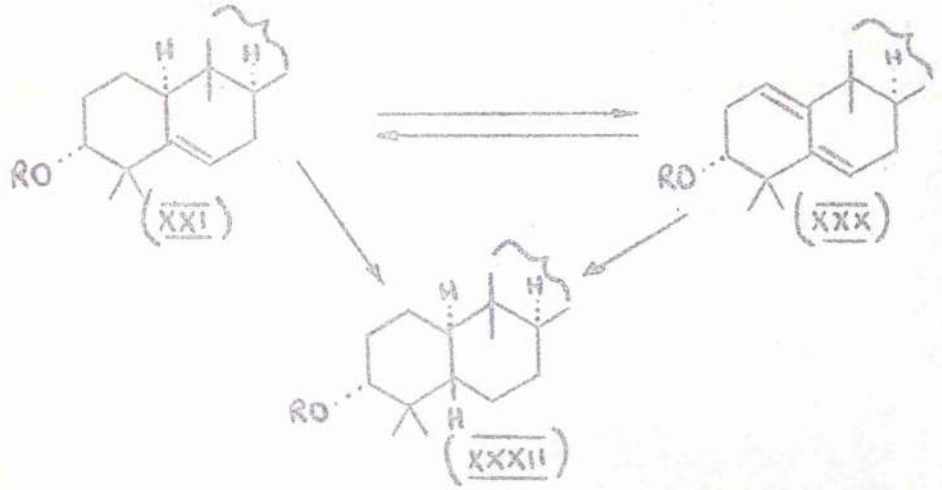


Oxidation of alnusenyl acetate with selenium dioxide gives[50a,52] a conjugated dienyl acetate $C_{32}H_{50}O_2$. The ultra-violet absorption spectrum of this compound [$\lambda_{max.}$ 2300 and 2380 Å. (ε = 16,000 and 18,000); point of inflection at 2480 Å. (ε = 11,000)] indicates that the diene system is of the fully transoid type. Alnusadienyl acetate has been assigned the structure (XXX). Oxidation of alnusadienol (XXX; R = H) with chromium trioxide-pyridine complex gives a product, [$\lambda_{max.}$ 2180 and 3190 Å. (ε = 11,000 and 8,300)] which was initially formulated as the dienone $C_{30}H_{46}O$ (XXV). An analysis of this product has shown, however, that it has the molecular formula $C_{30}H_{44}O_2$, i.e. that it is a dienedione, [Found: C,82.5; H,10.09. $C_{30}H_{44}O_2$ requires C,82.5; H,10.16%. An oxygen analysis of another sample supports this view. Found: O,7.1. $C_{30}H_{44}O_2$ requires O,7.3%]. The compound does not contain a cis-diketone group, since it is recovered unchanged after treatment with o-phenylenediamine, and has been tentatively formulated as (XXXI). The introduction of the second ketone group during the oxidation is dependent on the presence of the original ketone group in alnusenone, because alnusadienyl acetate is recovered unchanged after treatment with chromium trioxide-pyridine complex.



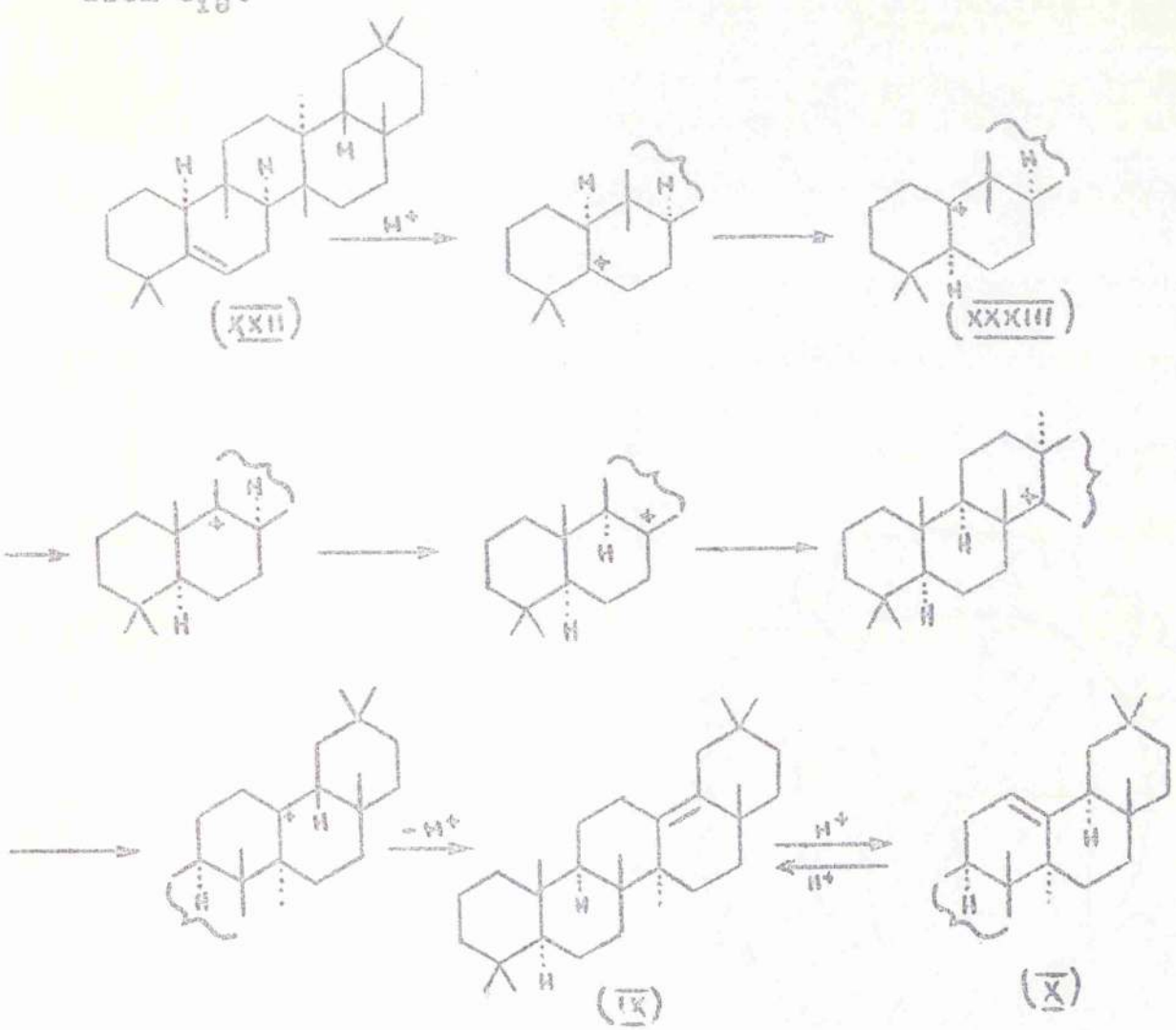
(XXX) (XXV) (XXXI)

Reduction of alnusadienyl acetate (XXX) by shaking its solution in cyclohexane-acetic acid mixture with hydrogen in the presence of platinum at room temperature gives alnusenyl acetate (XXI). This is surprising in view of the ease with which alnusenyl acetate is itself reduced to alnusanyl acetate (XXXII) under similar conditions[51] using acetic acid as solvent. Reduction of alnusadienyl acetate in acetic acid gives alnusanyl acetate (XXXII). The isolation of alnusenyl acetate by partial reduction of alnusadienyl acetate is proof that no rearrangement of the carbon skeleton has taken place during the selenium dioxide oxidation of the former to give the latter. Chapon[56] reported that reduction of alnusadienyl acetate gives a saturated acetate, not identical with alnusanyl acetate. This is not in agreement with the experience of the author.



(XXI) (XXX) (XXXII)

The acid-induced isomerisation of alnusene (XXII) to a mixture of olean-13(18)-ene (IX) and 18α-olean-12-ene (X) is represented as a "backbone" reaction, in which the double bond attains the 13:18-position as a result of a series of tertiary group migrations through the molecular spine [cf. the conversion[54] of friedelene (VII) to this mixture]. The reaction is induced by the approach of a proton to C_5, and final stabilisation takes place by the elimination of a proton from C_{19}.

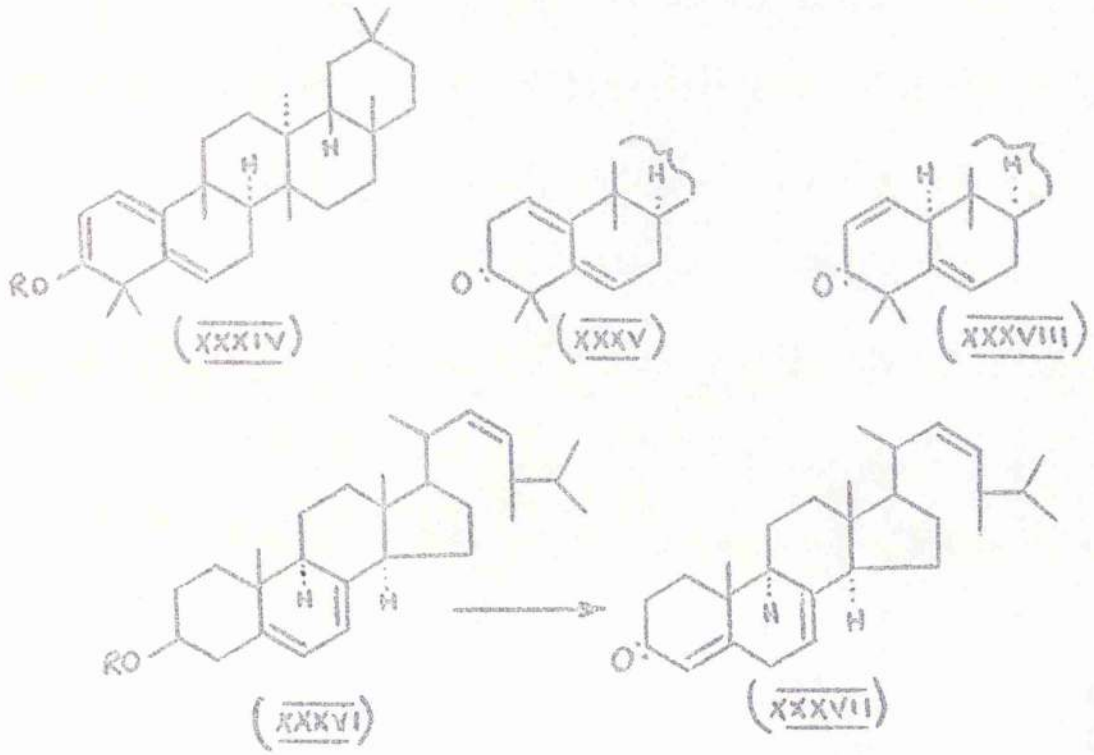


It will be noted that the configurations at C_8, C_9, C_{10}, C_{13} and C_{14} in (XXII) have been chosen so that the more stable anti-trans-anti arrangement has been preserved throughout. The hydroxyl group in alnusenol (XXI; R = H) has been shown[52] to be equatorial. This has been confirmed by treatment of alnusenyl acetate with sodium and amyl alcohol, under equilibrating conditions[54], which gives, on acetylation of the product, unchanged alnusenyl acetate. The hydroxyl group in alnusenol has, therefore, the α-configuration. The formation of alnusenone-II (XXIII) by mild acid treatment of alnusenone (XIV) can be explained by the elimination of a proton from C_{10} in the cation (XXXIII), with formation of a 5:10-double bond.

An attempt has been made to provide conclusive proof that the constitution of alnusenone is correctly represented by (XIV). The preparation from alnusenone of the conjugated triene (XXXIV) would unequivocally eliminate (XVI) for alnusenone. As a first step, the preparation of the dienone (XXXV) has been attempted. The susceptibility of alnusadienol to oxidation with introduction of a second oxygen atom has already been described, and an oxidation procedure has therefore been sought which will specifically convert the hydroxyl group to a ketone group. Oxidation under the conditions of

Oppenauer[61] was chosen. In order to determine the best conditions for the reaction, three trial oxidations have been carried out on α-amyrin using, as hydrogen acceptors (1) p-benzoquinone; (2) acetone; and (3) cyclohexanone. By using p-benzoquinone and aluminium t-butoxide in benzene solution, oxidation of α-amyrin proceeds smoothly to give urs-12-en-3-one.

Oppenauer oxidation[62] of ergosta-5:7:20-trien-3β-ol (XXXVI; R = H) is accompanied by movement of the 5:6-double bond to give ergosta-4:7:20-trien-3-one (XXXVII). The possibility that similar oxidation of alnusadienol might be accompanied by double bond movement to give (XXXVIII) was therefore considered.



Oppenauer oxidation of alnusadienol gives a product $C_{30}H_{46}O$, the infra-red spectrum of which does not contain a band attributable to an αβ-unsaturated ketone group. The product is therefore a dienone of the type (XXXV) and not (XXXVIII). Although a satisfactory analysis has been obtained for this compound, several facts suggest that it is not a homogeneous material. The ultra-violet absorption spectrum includes a maximum at 2340 Å. of lower intensity ($\varepsilon = 8,300$) than that of alnusadienyl acetate ($\varepsilon_{2380} = 18,000$). Also, the secondary maximum and the point of inflection to be expected in a diene system of this type are less well defined than in alnusadienyl acetate. Furthermore, although the melting point (211-213°) remains constant on repeated crystallisation from a number of solvents, the specific rotation ($[\alpha]_D$) varies between 122° and 137°. Chromatography on alumina of a solution of this material in light petroleum fails to effect a separation.

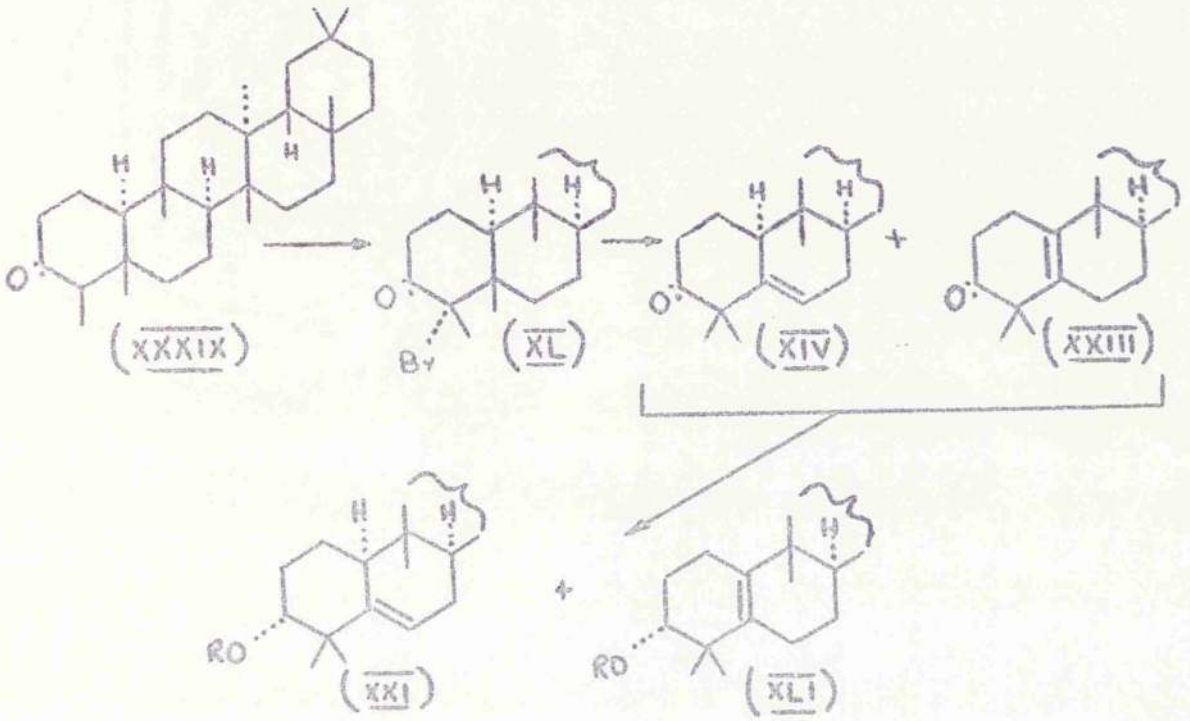
Oxidation of alnusenone with selenium dioxide gives a material (m.p. 208-210°, $[\alpha]_D$ + 140°), the m.p. of which is not depressed on mixing with a sample of the Oppenauer oxidation product (m.p. 211-213°) described above.

Treatment of the Oppenauer oxidation product with isopropenyl acetate gives a material, the ultra-violet

absorption spectrum of which contains a maximum at 3160 Å. (ξ = 6,600). The intensity of this maximum is lower than might be expected of a triene system such as (XXXIV), and suggests that the enol acetate is not homogeneous, presumably containing an impurity derived from that present in the Oppenauer oxidation product. Chromatography fails to effect a separation. The formation of the conjugated triene (XXXIV) cannot be explained on the basis of (XVI) for alnusenone, and although the latter experiments are not completely satisfactory, it is the opinion of the author that sufficient indications of the presence of a conjugated triene system in the enol acetate have been obtained to eliminate (XVI).

Final proof that alnusenone is correctly represented by (XIV) has been obtained by the conversion of friedelin to alnusenyl acetate. The constitution of friedelin has been shown[54, 63, 64, 65] with almost complete certainty to be (XXXIX). During a study of the degradation products of friedelin, Corey and Ursprung[64] prepared 4-bromofriedelin (XL), treatment of which with silver acetate gave a product $C_{30}H_{48}O$ (m.p. 247-248°, $[\alpha]_D$ - 48.6°), which they formulated as (XIV). A re-examination of this product by the author has shown that it is not homogeneous; it is a mixed crystal of alnusenone (XIV), (m.p. 245-246°, $[\alpha]_D$ + 31°), and alnusenone-II (XXIII)

(m.p. 250-252°, $[\alpha]_D$ - 90°) in the ratio 1:2.



Treatment of 4-bromofriedelin (XL) with silver acetate in acetic acid gives a compound (m.p. 247-249°, $[\alpha]_D$ - 50°) which is identical (m.p. and mixed m.p., $[\alpha]_D$ and infra-red) with a synthetic mixture (m.p. 247-249°, $[\alpha]_D$ - 51°) of alnusenone and alnusenone-II in the ratio 1:2. Chromatography on alumina of a light petroleum solution of the mixed crystal obtained from friedelin yields fractions (m.p. 247-249°), the specific rotations ($[\alpha]_D$) of which lie between - 65° and -32°. Reduction of the mixture with lithium aluminium hydride, and acetylation of the product, gives a material from which alnusenyl acetate (XXI) (m.p. and mixed m.p. 233-236°, $[\alpha]_D$ + 44°) and alnusenyl-II acetate (XLI) (m.p. and mixed m.p. 290-292°, $[\alpha]_D$ - 25°) are readily obtained by fractional crystallisation from

chloroform-methanol.

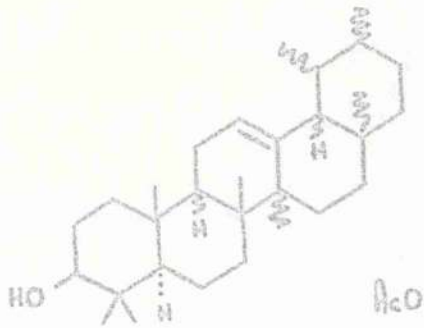
The reactions described above constitute a partial synthesis of alnusenone from friedelin (XXXIX), since alnusenyl acetate has been converted into alnusenone, and they confirm that the constitution of the latter is represented by (XIV).

3. α-Amyrin.

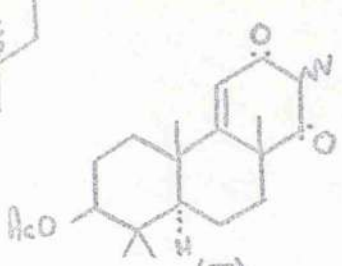
The constitution and stereochemistry of α-amyrin (urs-12-en-3β-ol) is discussed in the light of some recent observations. The constitution of the acetate $C_{32}H_{48}O_4$, obtained as one product by chromic acid oxidation of ursa-9(11):12-dien-3β-yl acetate, has been established as (XXXII). The saturated alcohol of the ursane series, ursan-3β-ol, has been prepared and characterised as its acetate, and as the corresponding ketone ursan-3-one. The parent hydrocarbon of the series, ursane, has also been prepared.

The constitution (I) for α-amyrin (urs-12-en-3β-ol) was proposed in 1949 by Meisels, Jeger and Ruzicka[66], and until recently was generally accepted. The configurations at C_3, C_5, C_8 and C_{10} were established by the conversion of α-amyrin into two enol ethers, derived from the diketone (II), which were also obtained from β-amyrin (III) by a parallel series of reactions. It follows that the configurations at C_3, C_5, C_8 and C_{10} in both α- and β-amyrin are identical, and since the constitution and stereochemistry of β-amyrin (III) have been established[15,45,66] with almost complete certainty, these configurations are as shown in (I). Also, there was

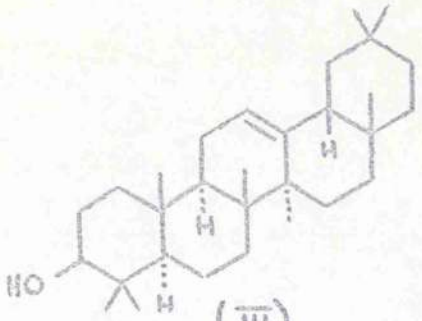
some evidence[66,67b] that the configurations at C_9 and C_{14} are the same in both series, although an absolute proof was lacking At this time, the configurations at C_{17}, C_{18}, C_{19} and C_{20} had not been determined. The stereochemistry of the interlocking of rings D and E has since been extensively studied, and each of the four theoretically possible arrangements has been suggested as the true structure.



(I)

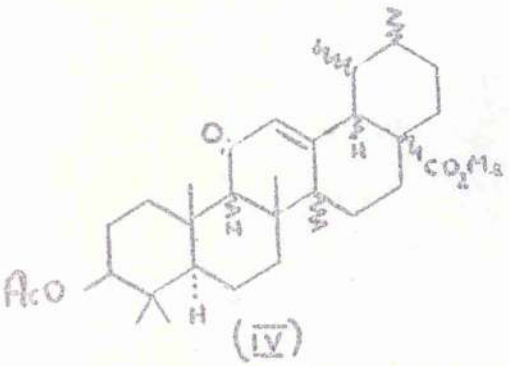


(II)

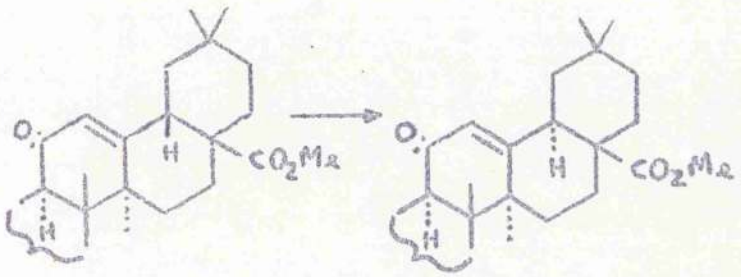


(III)

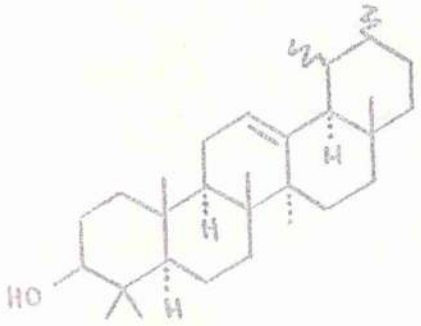
Barton and Holness[68] found that treatment of methyl 3β-acetoxy-11-oxours-12-enoate (IV) with either acid or alkali does not cause isomerisation at C_{18} (or at C_9). In this respect, (IV) differs from the corresponding oleanane derivative (V), which does isomerise to give methyl 3β-acetoxy--11-oxo-18α-olean-12-enoate (VI). On the basis of this evidence, Ruzicka[69] proposed that α-amyrin is to be represented by (VII), in which the hydrogen attached to C_{18} has been assigned the α-configuration.



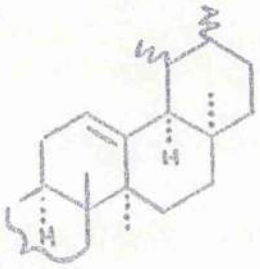
(IV)



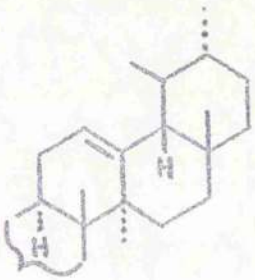
(V) (VI)



(VII)



(VIII)

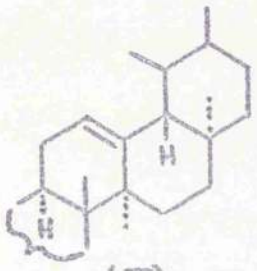


(IX)

Jeger[70] carried out a series of degradations of α- and β-amyrin to give two tricarboxylic esters, which contain the original C_{17} of the amyrins as the only asymetric centre. Jeger stated that these two compounds are enantiomorphs, and since the configuration at C_{17} in β-amyrin has been established as β, he concluded that in α-amyrin the configuration at C_{17} must be α. Zurcher, Jeger and Ruzicka[71] subsequently stated that rings D and E in α-amyrin may be cis-α-fused as shown in (VIII), but their evidence for this assumption was not disclosed.

The third possible arrangement for the interlocking of rings D and E (IX) was suggested by Corey and Ursprung[72]. These authors concluded that since the configurations at C_5, C_6, C_8 and C_{10} are as shown in (VII), and since the hydrogen attached to C_9 is not epimerisable when adjacent to an 11-carbonyl function[68], then this hydrogen must have the more stable (α) configuration as in β-amyrin. Assuming this to be correct, there are now eight possible formulae for α-amyrin which differ in the orientations of the three remaining asymetric centres involved in ring fusion (viz. C_{14}, C_{17} and C_{18}). Corey and Ursprung rejected six of these formulae as being unlikely for reasons of stereochemistry, leaving the two structures (VII) and (IX). The structure (VII) is analogous to 18α-β-amyrin, and (IX) to β-amyrin. By a study of the stabilities of lactones derived from ursolic acid, oleanolic acid and 18α-oleanolic acid, and by molecular rotation considerations, Corey and Ursprung proposed (IX) for α-amyrin. By assigning the equatorial configurations to the methyl groups attached to C_{19} (β) and C_{20} (α), they suggested an explanation for the stability of the cis-fusion of rings D and E. Under these conditions, epimerisation at C_{18} would be difficult since the methyl groups would be forced into the axial conformations.

The final arrangement (X) of the interlocking of rings D and E was proposed by Beton and Halsall[73]. This suggestion was based on assumptions which have since proved to be erroneous, and for this reason the arguments which led to the adoption of (X) for α-amyrin by Beton and Halsall will not be discussed.



(X)

Consideration will now be given to evidence upon which a new stereo-formula for α-amyrin is based. As stated earlier, the conversion of α- and β-amyrin into common degradation products indicates that the asymetric centres at C_3, C_5, C_8 and C_{10} have the same configurations in both compounds. Also it seems likely that the configuration at C_9 is the more stable arrangement. This was shown to be correct by an examination[74a,75] of the enol acetate of 11-oxours-12-en-3β-yl acetate (XI)[x]. The latter compound is prepared by oxidation of α-amyrin with chromic acid[76]. It is reduced to α-amyrin acetate on catalytic hydrogenolysis[77]. The enol acetate obtained from (XI) is strongly dextro-rotatory ($[\alpha]_D$ + 275°), and shows a single absorption

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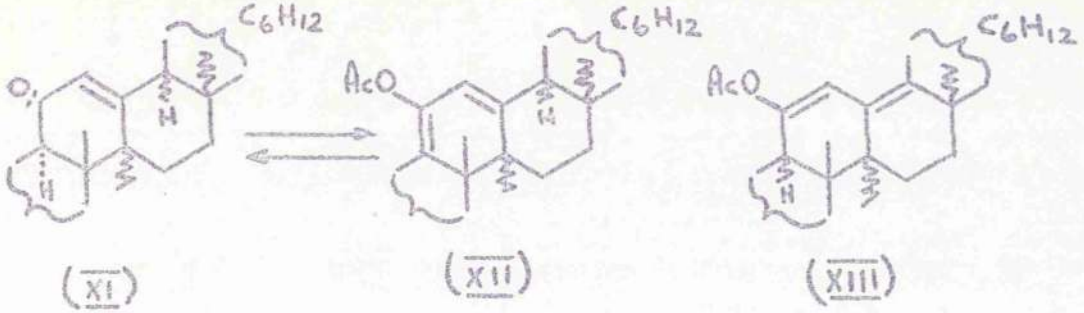
x In the formulae (XI)-(XXXVIII), R = Ac unless otherwise stated.

maximum at 2760 Å.(ε = 8,000). This is similar to known 9(11):12-dienes derived from oleanane and ursane, and in contrast to the isomeric 11:13(18)-dienes, which are laevo-rotatory, and show an intense triplet absorption maximum, the major peak of which is at approximately 2500 Å. (ε = 30,000). These facts show that the enol acetate is 3β:11-diacetoxyursa-9(11):12-diene (XII), and not the 11:13(18)-isomer (XIII).



(XI) (XII) (XIII)

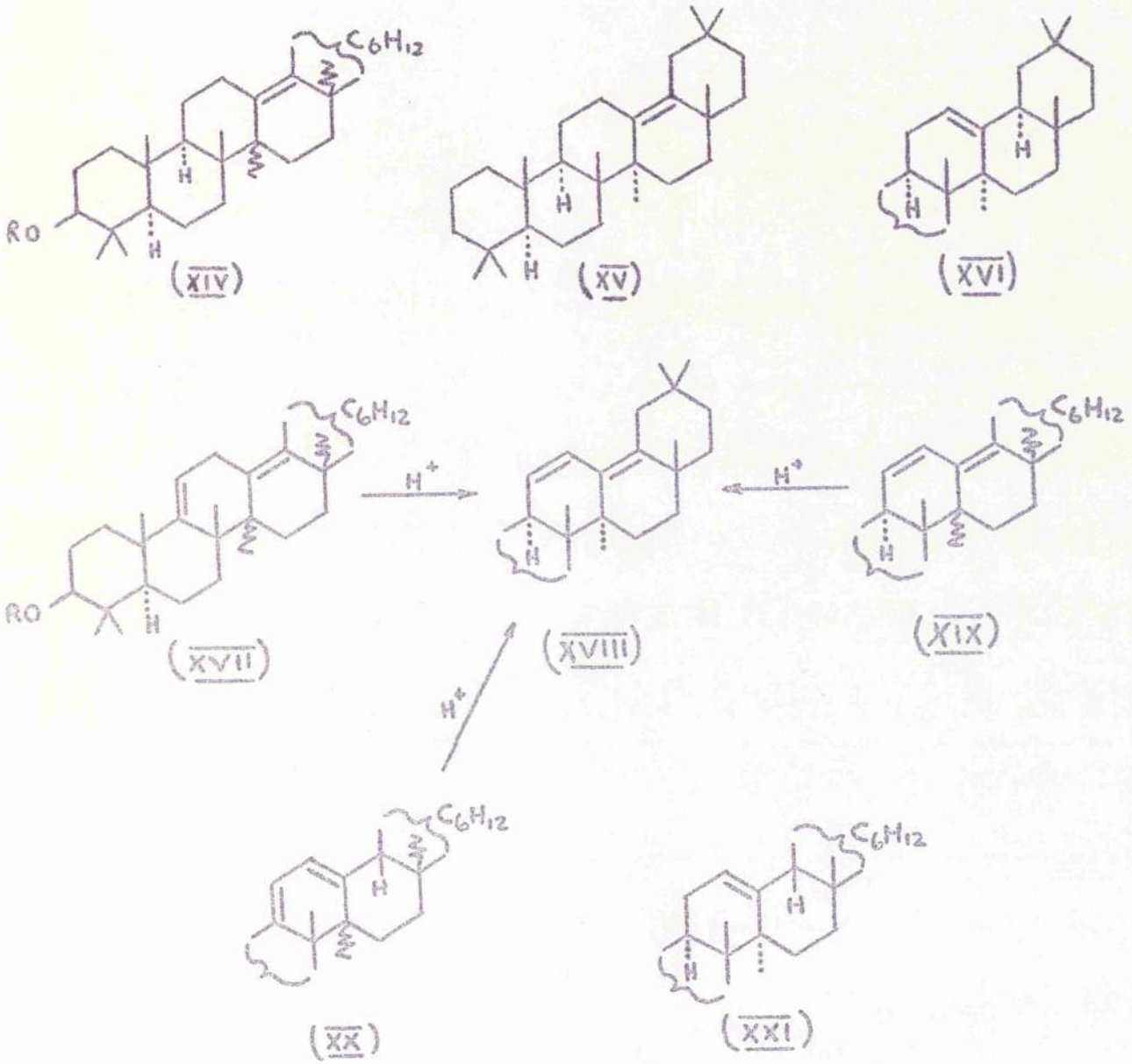
Hydrolysis of the enol acetate (XII) with either acid or alkali[74a,75], followed by acetylation of the product, regenerates 11-oxours-12-en-3β-yl acetate (XI), thus proving that the hydrogen attached to C_9 in α-amyrin has the more stable (α) configuration.

The hydrogen attached to C_{18} in α-amyrin was shown to have the more stable (β) configuration by the conversion[75] of urs-13(18)-en-3β-yl acetate (XIV) into α-amyrin acetate by treatment with sulphuric-acetic acid mixture. The

observation that the Δ^{12}-compound in the α-amyrin series is more stable than the $\Delta^{13(18)}$-isomer is in direct contrast to the situation in the β-amyrin series[78]. Thus, treatment of olean-12-ene with mineral acid gives[55] the mixture of olean-13(18)-ene (XV) and 18α-olean-12-ene (XVI) described in Part 2.

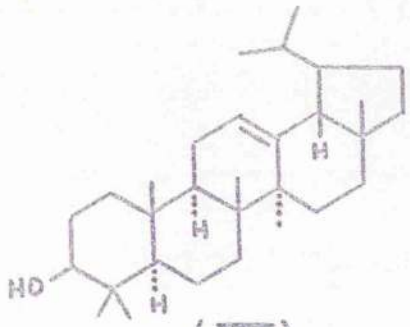
The configurations at the two remaining asymetric centres involved in ring fusion (C_{14} and C_{17}) were deduced by Beaton, Spring, Stevenson and Strachan[75] as follows. Treatment of ursa-9(11):13(18)-dien-3β-yl acetate (XVII) with hydrochloric-acetic acid mixture gives oleana-11:13(18)--dien-3β-yl acetate (XVIII). On similar treatment, ursa--11:13(18)-dien-3β-yl acetate(XIX) and ursa-9(11):12-dien--3β-yl acetate (XX) also give (XVIII). This indicates that the configurations at C_3, C_5, C_8, C_9, C_{10}, C_{14} and C_{17} in α-amyrin are the same as those in β-amyrin (III), and α-amyrin is represented by partial formula (XXI; R = H).

The stability of the cis-fusion of rings D and E in α-amyrin must be due to some conformational factor in ring E. This factor must also account for the greater stability of urs-12-en-3β-yl acetate compared with the 13(18)-isomer, and for the profound hindering effect on the double bond in α-amyrin, and on the ketone group in 12-oxoursan-3β-yl acetate.



Also, ring E of the ursane group, although different from ring E of the oleanane group, must be so constituted that it can rearrange to the latter under suitable conditions. These requirements can be satisfied if ring E is considered

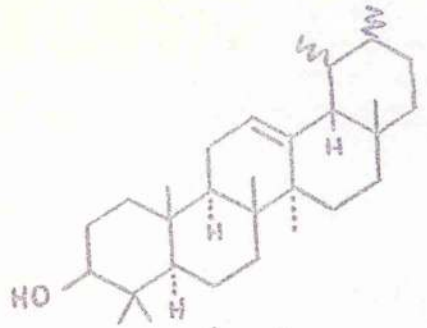
to be 5-membered, with an isopropyl group attached to C_{19}. The β-configuration of the isopropyl group is more likely than the α-configuration, since the latter would cause severe interaction between the side-chain and the C_{14}(α)--methyl group. In addition, a β-orientated side-chain protects the double bond in α-amyrin and the carbonyl group in 12-oxoursan-3β-yl acetate, thus offering an explanation of the inertness of these two functional groups. α-Amyrin can thus be represented by (XXII), and this formulation will be used throughout the remainder of this section.



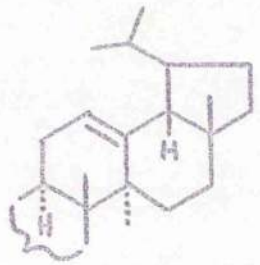
(XXII)

Meakins[79] has produced additional evidence in favour of (XXII) for α-amyrin by a study of the infra-red absorption spectra of α-amyrin and its derivatives. Since the Me_2C-grouping produces a characteristic maximum at ca. 1367 $cm.^{-1}$, the number of these groups in a compound can be estimated. Meakins prepared the trisnor-hydrocarbons (XXIII) from α-amyrin (Ia) or (XXII), β-amyrin (III) and lupanol (XXIV).

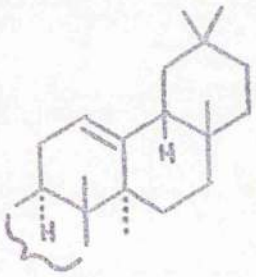
This procedure removes the gem-dimethyl group from ring A, leaving one such group in the case of the hydrocarbons derived from (XXII), (III) and (XXIV). The hydrocarbon derived from (Ia) will contain no gem-dimethyl group. Meakin's results indicated that the hydrocarbon (XXIII) prepared from α-amyrin does contain a gem-dimethyl group, and thus α-amyrin itself must contain two such groups. This is in agreement with formula (XXII) for α-amyrin, and not with formula (Ia). Meakins did not, however, exclude alternative formulae, such as (XXV), for α-amyrin.



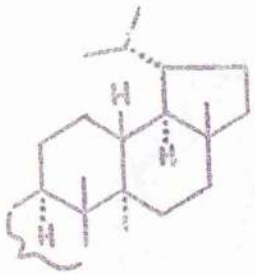
(Ia)



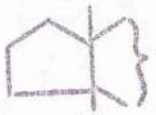
(XXII)



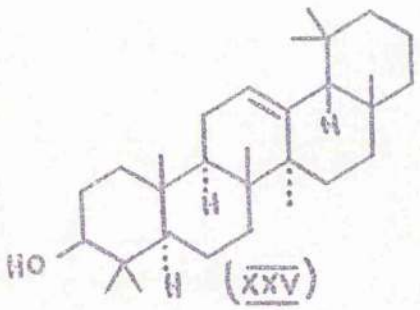
(III)



(XXIV)



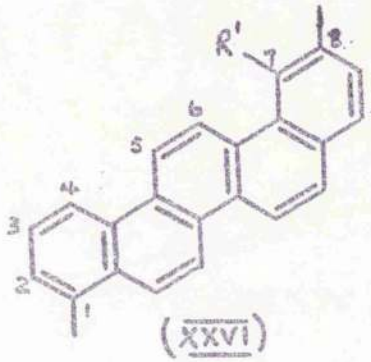
(XXIII)



(XXV)

Further evidence in support of the constitution (XXII) for α-amyrin was reported by Phillips and Tuites[80]. These authors drew attention to a discrepancy in structure (Ia), previously noted by Jeger[15]; viz. that the dehydrogenation

products from α-amyrin are the same as those from β-amyrin, and seem to include 1:8-dimethylpicene (XXVI; R' = H), instead of the expected 1:7:8-trimethylpicene (XXVI; R' = Me)



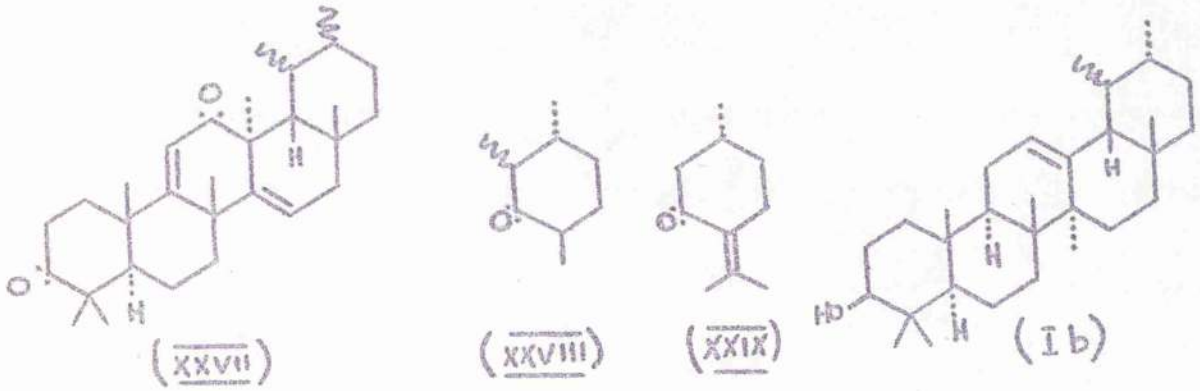
(XXVI)

Phillips and Tuites[80] eliminate a suggestion by Jeger[15] that the hydrocarbon (m.p. 306°) of unknown constitution, obtained by Spring and Vickerstaff[76] and by Ruzicka and Morgeli[81], is the trimethyl derivative (XXVI; R' = Me). Phillips and Tuites synthesised 1:7:8-trimethylpicene, and although no direct comparison with the hydrocarbon (m.p. 306°) has been made, the melting point (252-254°) of their product makes the identity of these two compounds unlikely.

The constitution (Ia) for α-amyrin, in which ring E is shown as six-membered, is still preferred by Corey and Ursprung[72b], Meisels, Ruegg, Jeger and Ruzicka[82], and Melera, Arigoni, Eschenmoser, Jeger and Ruzicka[83].

Melera *et al.*[83] treated 3:12-dioxoisoursa-9(11):14-diene

(XXVII) at 320-340° for a half-hour, and isolated from the products a volatile fraction, containing two compounds. Treatment of this mixture with perbenzoic acid gave a mixture of two epoxides which on treatment with boron trifluoride-ether complex gave a homogeneous ketone. Melera et al.[83] identified the ketone as (-)-2:3:6--trimethylcyclohexanone-1 (XXVIII) by a synthesis of this compound from D-(+)-pulegone (XXIX), and concluded that α-amyrin is represented by formula (Ib), in which the methyl group attached to C_{20} has the equatorial (α) configuration.



(XXVII) (XXVIII) (XXIX) (Ib)

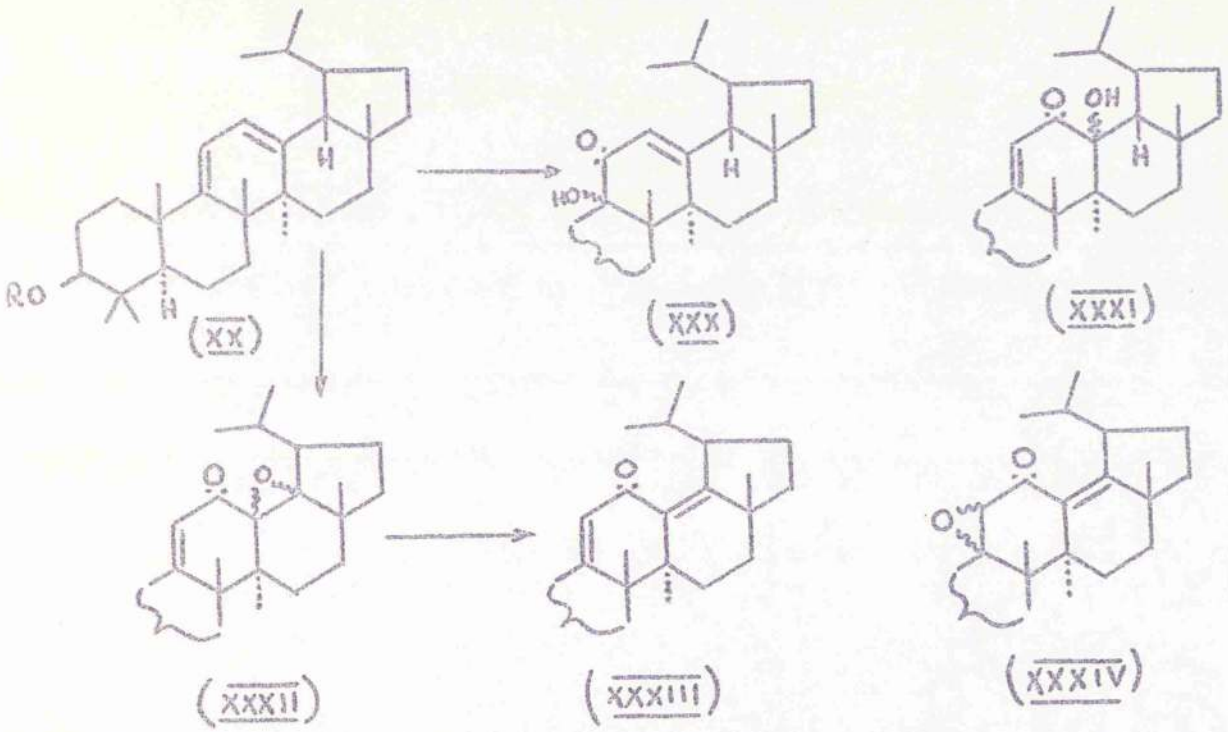
The deduction from the evidence outlined above that ring E in α-amyrin is six-membered is based on the assumption that no molecular rearrangement has taken place under the conditions of the reaction. It will be necessary to carry out more significant and specific reactions (degradative or otherwise) on α-amyrin and its derivatives before a definite

choice can be made between formulae (Ib) and (XXII) as representing the true constitution of this series.

An examination by the author of the chromic acid oxidation products of ursa-9(11):12-dien-3β-yl acetate (XX) will now be described. The dienyl acetate (XX) is obtained from α-amyrin acetate by oxidation with N-bromosuccinimide[84]. Oxidation of (XX) with chromic acid gives an acetate $C_{32}H_{50}O_4$, in which the presence of an αβ-unsaturated ketone group and a tertiary hydroxyl group has been established, and which was formulated by Beynon, Sharples and Spring[85] as (XXX) or (XXXI). Ruzicka, Jeger, Redel and Volli[86] repeated this reaction and isolated, in addition to the acetate $C_{32}H_{50}O_4$, a second acetate $C_{32}H_{48}O_4$, which they suggested contains the group -CO.C:C.CO-. In terms of either formula (Ib) or (XXII) for α-amyrin, it is impossible to formulate such an enedione unless molecular rearrangement is assumed to have taken place during the oxidation.

A re-examination of the oxidation products has confirmed the formation of the two acetates, which differ appreciably in their solubilities in ether and in chloroform-methanol. The less soluble product, $C_{32}H_{50}O_4$, which shows an absorption maximum at 2500 Å. (ε = 13,500),

indicative of an αβ-unsaturated ketone group, has been identified as (XXX). Reduction of (XXX) with zinc dust and acetic acid[74] gives 11-oxours-12-en-3β-yl acetate (IV). The more soluble product, $C_{32}H_{48}O_4$, which shows an absorption maximum at 2570 Å.(ε = 13,000), has been identified as 13β:18β-epoxy-12-oxours-9(11)-en-3β-yl acetate (XXXII). When reduced with zinc dust and ethanol, (XXXII) gives 12-oxoursa-9(11):13(18)-dien-3β-yl acetate (XXXIII).



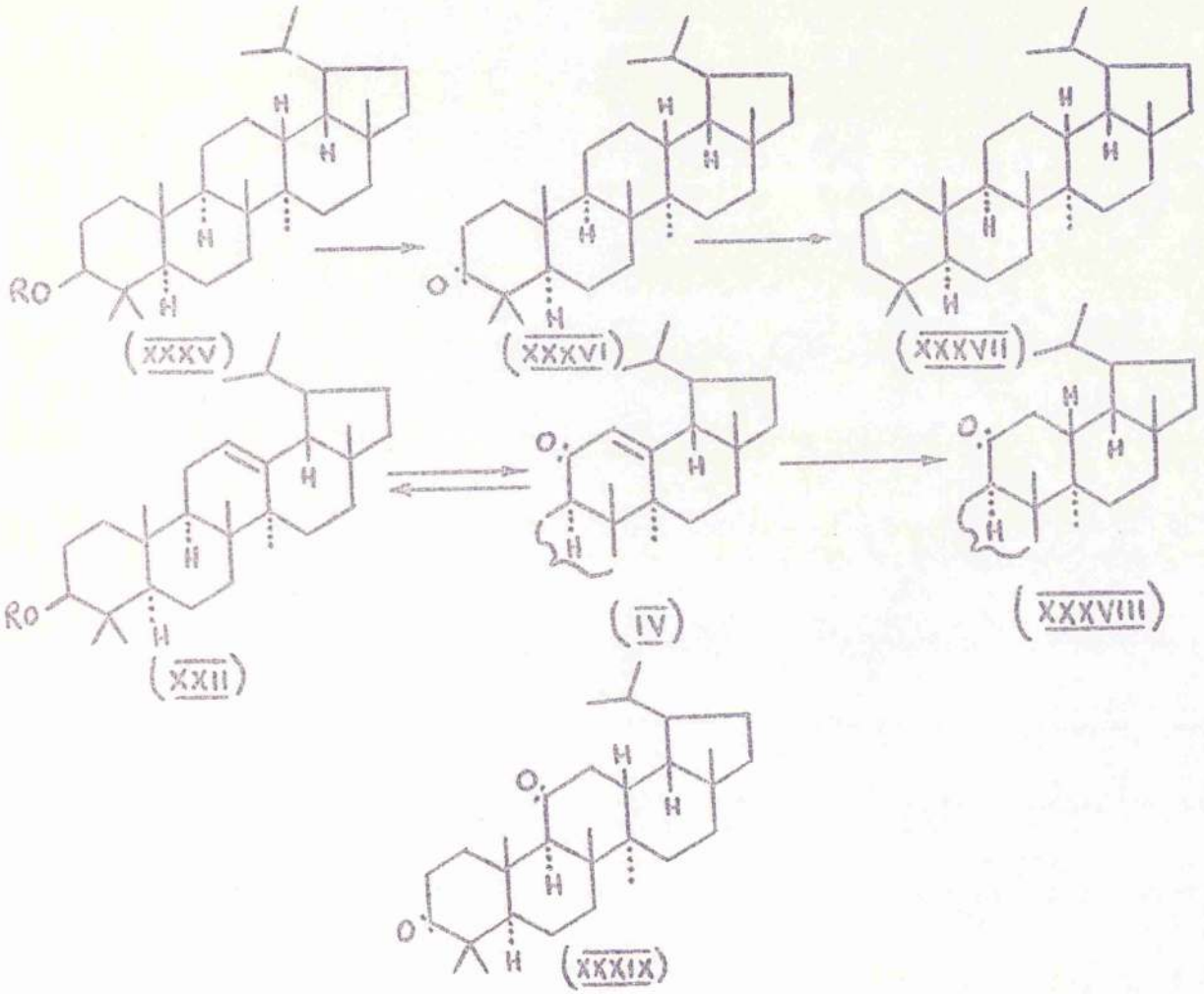
The oxygen atom removed from the acetate $C_{32}H_{48}O_4$ by treatment with zinc dust and ethanol has been shown to be an oxidic function, since the infra-red absorption spectrum of the acetate includes bands attributable to the acetoxyl group and the αβ-unsaturated ketone group, but does not

include bands due to either a hydroxyl or an isolated ketone group. These facts do not exclude formula (XXXIV) for the acetate $C_{32}H_{48}O_4$, but the alternative formula (XXXII) is preferred for the following reasons. The acetate is recovered unchanged after treatment with hydrochloric-acetic acid mixture, and the secondary-tertiary oxide group in (XXXIV) would not be expected to survive this treatment. Also, the intensity (ε = 13,000) of the ultra-violet absorption band of this acetate is not in agreement with the presence of a cisoid $\alpha\beta$-unsaturated ketone as in (XXXIV).

The reduction of (XXXII) to (XXXIII) by zinc dust and ethanol is, surprisingly, paralleled by treatment of (XXXII) with lithium and ammonia. Also isolated from this reaction in small yield (ca. 5%), is a product (m.p. 170-172°, $[\alpha]_D$ + 156°; no selective absorption above 2,000 Å.) of unknown constitution. Treatment of the dienone (XXXIII) with lithium in ammonia gives principally unchanged material, together with a small amount of the compound (m.p. 170-172°) mentioned above. The dienone (XXXIII) is recovered unchanged after treatment with (a) sodium borohydride in methanol and (b) hydrochloric-acetic acid mixture.

The saturated alcohol of the α-amyrin series, ursan-3β-ol (XXXV; R = H) has been prepared, and characterised by conversion to the acetate (XXXV) and to the corresponding

ketone, ursan-3-one (XXXVI). Wolff-Kishner reduction of (XXXVI) gives the parent hydrocarbon of the series, ursane (XXXVII).



Treatment of α-amyrin acetate (XXII) with chromic acid gives 11-oxours-12-en-3β-yl acetate (IV). This reaction has previously been carried out[76] under reflux, when the yield of (IV) obtained was of the order of 30-35%. By carrying out the reaction at room temperature, however, the yield has been increased to ca. 90%. Reduction of (IV) with

lithium in ammonia, followed by acetylation, gives a poor yield of 11-oxoursan-3β-yl acetate (XXXVIII), which on Wolff-Kishner reduction, using the forcing conditions devised by Barton, Ives and Thomas[46], followed by acetylation, gives ursan-3β-yl acetate (XXXV). Oxidation of the alcohol (XXXV; R = H) with chromic acid yields ursan-3-one (XXXVI). The parent hydrocarbon of the series, ursane (XXXVII) is obtained from ursan-3-one (XXXVI) by normal Wolff-Kishner reduction. Wolff-Kishner reduction of 11-oxours-12-en-3β-yl acetate (IV) under the forcing conditions[46] gives α-amyrin acetate (XXII).

The preparation of 11-oxoursan-3β-yl acetate (XXXVIII), ursan-3β-yl acetate (XXV) and ursane (XXXVII) was carried out independently by Lyssy and Jeger[88], by a slightly modified route. Oxidation of (XXXVIII; R = H) with chromic acid gave 3:11-dioxoursane (XXXIX), which on Wolff-Kishner reduction gave ursane (XXXVII). The constants reported by these authors differ in some respects from those found in this work; these are tabulated below:

	Lyssy and Jeger		This work	
	m.p.	$[\alpha]_D$	m.p.	$[\alpha]_D$
11-oxoursan-3β--yl acetate	337-338°	-5°,-4°	326-329°	-8.9°, -8.5°
ursan-3β-yl acetate	247-249°	+42°	249-251°	+26°, +25°
ursane	139-140°	+18°	124-128°	+50°, +53°

EXPERIMENTAL.

M.p's. are uncorrected. Specific rotations were measured in chloroform solution at room temperature, with a 1 dm. tube. Ultra-violet absorption spectra were measured in ethanol solution (unless otherwise stated), with a Unicam SP.500 and a Hilger H700.307 spectrophotometer. Grade II alumina and a light petroleum fraction, b.p.60-80°, were used for chromatography.

1. Taraxerol Derivatives:

Isolation of Taraxerone-Alnusenone Mixture from the Bark of Alnus glutinosa L. - Chopped bark (3.85 kg.) was extracted with light petroleum (b.p. 60-80°; 3 x 12.5 l.), each extraction being for 6 hr. at boiling point, then overnight at room temperature. Evaporation of the solvent gave a dark resin (125 g.). A solution of the combined resin (480 g.) from four batches of bark (15.9 kg.) in benzene (1 l.) and methanolic potassium hydroxide (5%; 5 l.) was refluxed for 5 hr. The solution was reduced in volume and extracted with ether (4 x 1 l.) after the addition of water. Filtration of the ether layer gave an insoluble fraction (50 g.), which was dissolved in benzene (1.5 l.) and the solution passed down a column of alumina (1.5 kg.). Elution with the same

solvent (12 l.) gave a white crystalline solid (32 g.), m.p. 222-234°, $[\alpha]_D$ + 27° (c,1.75).

This material consists essentially of a mixture of taraxerone and alnusenone in the approximate ratio of 1 to 3 respectively.

Reduction of the Ketone Mixture with Lithium Aluminium Hydride: Separation of Taraxeryl and Alnusenyl Acetates. - A solution of the ketone mixture (10.5 g.) in benzene (350 c.c.) and ether (350 c.c.) was refluxed with lithium aluminium hydride (10 g.) for 1½ hr., then allowed to stand at room temperature overnight. The combined product (31 g.) from three such reactions was treated with pyridine and acetic anhydride on the steam bath for 2 hr. Crystallisation of the product from chloroform-methanol gave a mixture of needles and plates which was washed on the filter with chloroform--methanol (1:1) until only plates remained, and the washings concentrated to give again a mixture of plates and needles. This procedure was repeated until concentration of the washings gave alnusenyl acetate as needles (10 g.), m.p. and mixed m.p. 233-235°, $[\alpha]_D$ + 46° (c,1.0). Concentration of the mother liquors gave a second crop of needles (10 g.), which crystallised from chloroform-methanol to give alnusenyl acetate (6 g.), m.p. and mixed m.p. 233-235°, $[\alpha]_D$ + 45° (c,1.2).

Recrystallisation of the plates (from the washing procedure above) from chloroform-methanol gave taraxeryl acetate as plates (6 g.), m.p. 302-304°, $[\alpha]_D$ + 10.5° (c,0.8). Koller et al.[26] give m.p. 304-305°, $[\alpha]_D$ + 9°, and Takeda[27] gives m.p. 298-299°, $[\alpha]_D$ + 13.8° for this material.

Taraxerol. - A solution of taraxeryl acetate (300 mg.) in benzene (20 c.c.) and methanolic potassium hydroxide (3%; 100 c.c.) was refluxed for 1½ hr. The product crystallised from chloroform-methanol to give taraxerol as small plates (210 mg.), m.p. 283-285°, $[\alpha]_D \pm 0°$ (c,0.42). Koller et al.[26] give m.p. 282-283°, $[\alpha]_D \pm 0°$, and Takeda[27] give m.p. 279-281°, $[\alpha]_D$ + 3°.

In the later stages of this work, taraxerol isolated from Skimmia by Dr. K. Takeda was used; the author is indebted to Dr. C. J. W. Brooks for a generous gift of this material.

14α:15α-Epoxytaraxeran-3β-yl Acetate. - A solution of taraxeryl acetate (150 mg.) in chloroform (50 c.c.) was treated at 0° with a freshly prepared solution of perbenzoic acid (1.2 mol.) in chloroform, and the solution kept at 0° for 18 hr. The solution was washed with sodium hydrogen carbonate solution, dried (Na_2SO_4), and the solvent removed below 15°. Crystallisation of the residue from chloroform-methanol gave

14α:15α-epoxytaraxeran-3β-yl acetate as plates (110 mg.), m.p. 257-260°, $[\alpha]_D$ + 43° (c,1.0); no selective light absorption above 2,000 Å. The oxide does not give a colour with tetranitromethane. Found: C,78.9; H,11.0. Calc. for $C_{32}H_{52}O_3$. C,79.3; H,10.8%. Takeda[29] gives m.p. 257-260°, $[\alpha]_D$ + 47°.

It is essential that the per-acid solution should be freshly prepared. Thus, part of a freshly made solution of perbenzoic acid in chloroform was successfully used for the preparation of the epoxide as described above. Use of the remaining part of the same solution after storage at 0° in the dark for 2 days gave olean-12-ene-3β:15α-diol 3-acetate and not the epoxide. The constants (m.p 287°, $[\alpha]_D$ + 73°) given by Koller *et al.*[26] show that their product is the diol monoacetate.

Olean-12-ene-3β:15α-diol 3-Acetate. - (a) 2N-Sulphuric acid (5 c.c.) was added to a solution of 14α:15α-epoxytaraxeran-3β-yl acetate (80 mg.) in acetic acid (100 c.c.), and the mixture heated on the steam bath for 1 hr. A solution of the product in benzene-light petroleum (2:1; 25 c.c.) was chromatographed on alumina. Elution of the column with benzene gave a solid (35 mg.) which, after crystallisation from chloroform-methanol, gave olean-12-ene-3β:15α-diol 3-acetate

as needles, m.p. 284-288°, $[\alpha]_D$ +73°, + 72° (c, 0.9 and 1.5). $\lambda_{max.}$ 2060 Å. (ε = 4,500). It gives a pale yellow colour with tetranitromethane. Found: C, 79.1; H, 10.6. Calc. for $C_{32}H_{52}O_3$: C, 79.3; H, 10.8%. Takeda[29] gives m.p. 283-286°, $[\alpha]_D$ + 78.7.

(b) Concentrated hydrochloric acid (4 c.c.) and water (4 c.c.) was added to a solution of 14α:15α-epoxytaraxeran-3β-yl acetate (135 mg.) in methanol (100 c.c.) and chloroform (25 c.c.). The mixture was kept at room temperature for 18 hr. Crystallisation of the product from chloroform-methanol gave olean-12-ene-3β:15α-diol 3-acetate as needles (80 mg.), m.p. and mixed m.p. 284-288°, $[\alpha]_D$ + 74° (c, 1.3).

15-Oxo-olean-12-en-3β-yl Acetate. - A solution of olean-12-ene-3β:15α-diol 3-acetate (100 mg.) in benzene (10 c.c.) and acetic acid (100 c.c.) was treated at room temperature with an acetic acid solution of chromium trioxide (1.1 mol.), added with stirring during 15 min. The mixture was allowed to stand at room temperature overnight, then worked up in the usual way. Crystallisation of the product from chloroform-methanol gave 15-oxo-olean-12-en-3β-yl acetate as needles (70 mg.), m.p. 278-280°, $[\alpha]_D$ + 27° (c, 1.2 and 1.0). $\lambda_{max.}$ 2040 Å. (ε = 4,800), with no high

intensity selective absorption above 2200 Å. It gives a pale yellow colour with tetranitromethane. Found: C,79.7; H,10.4. Calc. for $C_{32}H_{50}O_3$. C,79.6; H,10.4%. Takeda[29] gives m.p. 278-279°, $[\alpha]_D$ + 4.1°.

Attempted Wolff-Kishner Reduction of 15-Oxo-olean-12-en-3β-yl Acetate. - 15-Oxo-olean-12-en-3β-yl acetate (50 mg.) was added to a solution of sodium methoxide (from 500 mg. sodium and 25 c.c. dry methanol) and hydrazine hydrate (100%; 1c.c.), and the mixture heated in an autoclave at 200° for 18 hr. The product was treated with pyridine and acetic anhydride on the steam bath for 20 min. Crystallisation from chloroform-methanol gave the unchanged ketone as needles (35 mg.), m.p. and mixed m.p. 278-280°, $[\alpha]_D$ + 26° (c,1.1).

12-Oxotaraxer-14-en-3β-yl Acetate. - A solution of 12-oxotaraxera-9(11):14-dien-3β-yl acetate (2 g.) in ether (75 c.c.) was added during 2 min. with stirring to a solution of lithium (600 mg.) in liquid ammonia (400 c.c.). After 3 min. stirring, acetone was added, and the ammonia allowed to evaporate. The product was heated for 1 hr. with acetic anhydride and pyridine, and the acetylated material purified by chromatography of its solution in light petroleum-benzene (5:1) on alumina (60 g.). Elution of the column with light petroleum-benzene (1:1) yielded a solid which crystallised

from chloroform-methanol to give 12-oxotaraxer-14-en-3β-yl acetate as needles (700 mg.), m.p. 298-300°, $[\alpha]_D$ - 30°, - 29° (c,1.2 and 1.1). $\lambda_{max.}$ 2060 Å. (ε = 4,300); $\lambda^{CHCl_3}_{max.}$ 2850 Å. (ε = 50). It gives a pale yellow colour with tetranitromethane. Found: C,79.9; H,10.45. $C_{32}H_{50}O_3$ requires C,79.6; H,10.4%.

Hydrolysis of the acetate for 1 hr. by refluxing 5% methanolic potassium hydroxide solution and working up in the usual way gave 12-oxotaraxer-14-en-3β-ol as needles (from methanol), m.p. 276-278°, $[\alpha]_D$ - 45°, - 43° (c,1.1. and 0.9). Found: C,80.95; H,10.9. $C_{30}H_{48}O_2$, $\frac{1}{4}CH_3OH$ requires C,81.0; H,10.9%.

Reduction of 12-Oxotaraxer-14-en-3β-yl Acetate to Taraxeryl Acetate[x]. - 12-Oxotaraxer-14-en-3β-yl acetate (200 mg.) was added to a solution obtained by the addition of sodium (500 mg.) to freshly distilled diethylene glycol (25 c.c.), and the mixture heated to 180°. Anhydrous hydrazine (prepared by refluxing 100% hydrazine hydrate with sodium hydroxide for 3 hr.) was distilled into the mixture until the solution refluxed gently at 180°. After refluxing at this temperature for 18 hr., the mixture was distilled until the temperature rose to 210°, whereafter refluxing was continued for 24 hr. The product, isolated by means of benzene, was

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x The ketone was recovered unchanged after being exposed to normal Wolff-Kishner reduction, followed by acetylation.

heated on the steam bath with pyridine and acetic anhydride. Crystallisation from chloroform-methanol gave taraxer-14-en-3β-yl acetate as plates (110 m.g.), m.p. 302-304°, $[\alpha]_D$ + 10.5° (c,1.8), undepressed in m.p. on mixing with an authentic specimen of taraxeryl acetate, m.p. 302-305°, isolated from alder bark.

14ξ:15ξ-Epoxy-12-oxotaraxer-9(11)-en-3β-yl Acetate. - A solution of 12-oxotaraxera-9(11):14-dien-3β-yl acetate (3 g.) in acetic acid (450 c.c.) was treated with a solution of potassium permanganate (2.25 g.) in water (225 c.c.), added with stirring at room temperature during 30 min. After stirring for 1 hr., the solution was treated with aqueous sodium metabisulphite (10%), and water (1 l.), and filtered. The dried solid crystallised from chloroform-methanol to give 14ξ:15ξ-epoxy-12-oxotaraxer-9(11)-en-3β-yl acetate as plates (2.8 g.), m.p. 280-282°, $[\alpha]_D$ - 12.5° (c,1.7).

Reduction of 14ξ:15ξ- Epoxy-12-oxotaraxer-9(11)-en-3β-yl Acetate with Lithium Aluminium Hydride. - A solution of 14ξ:15ξ -epoxy-12-oxotaraxer-9(11)-en-3β-yl acetate (1 g.) in ether (300 c.c.) was refluxed for 4 hr. with lithium aluminium hydride (1 g.), and the mixture allowed to stand overnight at room temperature. Light absorption of crude product; $\lambda_{max.}$

2080 and 2420 Å. (ε = 4,500 and 300). It gives no colour with tetranitromethane. This material was not purified further.

Manganese Dioxide Oxidation of the Crude Product. - A solution of the above product (940 mg.) in acetone (70 c.c.) was shaken with freshly prepared manganese dioxide[≡] (20 g.) for 36 hr. at room temperature. The product was treated with pyridine and acetic anhydride at room temperature for 24 hr. Crystallisation from chloroform-methanol gave 14ξ:15ξ-epoxy-12-oxotaraxer-9(11)-en-3β-yl acetate as plates (600 mg.), m.p. and mixed m.p. 279-281°, $[\alpha]_D$ - 13° (c,1.2).

Olean-12-ene-3β:15β-diol. - A solution of 15-oxo-olean--12-en-3β-yl acetate (207 mg.) in ether (130 c.c.) was refluxed for 1 hr. with lithium aluminium hydride (210 mg.), and the mixture allowed to stand overnight at room temperature. The product, isolated in the usual way, crystallised from aqueous acetone to give olean-12-ene-3β:15β-diol as needles (150 mg.), m.p. 194-196°, $[\alpha]_D$ + 68° (c,1.1 and 0.9). It gives a pale yellow colour with tetranitromethane. Found: C,81.35; H,11.3. $C_{30}H_{50}O_2$ requires C,81.4; H,11.4%.

≡ See Attenburrow et al., J., 1952, 1104

Olean-12-ene-3β:15β-diol 3-Acetate. - (a) A solution of olean-12-ene-3β:15β-diol (100 mg.) in pyridine and acetic anhydride was kept at room temperature overnight. The product, obtained in the usual way, crystallised from chloroform--methanol to give olean-12-ene-3β:15β-diol 3-acetate as plates (70 mg.), m.p. 273-276°, $[\alpha]_D$ + 65°, + 64° (c,0.9 and 1.1). It gives a pale yellow colour with tetranitromethane. Found: C,79.25; H,11.0. $C_{32}H_{52}O_3$ requires C,79.3; H,10.8%.

(b) The diol (45 mg.) was treated with pyridine and acetic anhydride at 100° for 1 hr. Crystallisation of the product from chloroform-methanol gave the diol monoacetate as plates (20 mg.), m.p. and mixed m.p.273-276°, $[\alpha]_D$ + 64° (c,0.45). A mixture of the 3β:15β-diol 3-acetate with the 3β:15α-diol 3-acetate (m.p. 284-288°) had m.p. 277-282°.

Chromic Acid Oxidation of Olean-12-ene-3β:15β-diol 3-Acetate. - A solution of olean-12-ene-3β:15β-diol 3-acetate (75 mg.) in acetic acid (60 c.c.) was treated with an acetic acid solution of chromium trioxide (1.2 mol.), added with stirring during 15 min., and the mixture allowed to stand at room temperature overnight. The product, isolated in the usual way, crystallised from chloroform-methanol to give 15-oxo-olean-12-en-3β-yl acetate as needles (30 mg.), m.p. and mixed m.p. 277-279°, $[\alpha]_D$ + 25° (c,1.0).

3β:15α-Diacetoxyolean-12-ene. - Olean-12-ene-3β:15α--diol 3-acetate (70 mg) was treated at 100° with pyridine and acetic anhydride for 1 hr. Crystallisation of the product from chloroform-methanol gave 3β:15α-diacetoxyolean-12-ene as needles (40 mg.), m.p. 203-205°, $[\alpha]_D$ + 51°, +50° (c, 0.8 and 1.3). $\lambda_{max.}$ 2060 Å. (ϵ = 5,000). It gives a pale yellow colour with tetranitromethane. Found: C, 77.3; H, 9.85. Calc. for $C_{34}H_{54}O_4$. C, 77.5; H, 10.3%. Takeda[29] gives m.p. 207-208.5°.

Treatment of olean-12-ene-3β:15α-diol 3-acetate (70 mg.) with pyridine and acetic anhydride at room temperature for 18 hr. gave, on chromatography of the product, a small yield (ca. 10%) of the diacetate. The remainder of the diol monoacetate was recovered unchanged.

Olean-12-ene-3β:15α-diol. - A solution of 3β:15α--diacetoxyolean-12-ene (80 mg.) in methanolic potassium hydroxide (5%; 25 c.c.) was refluxed for 1½ hr. The product crystallised from aqueous acetone to give olean-12-ene-3β:15α--diol as needles (55 mg.), m.p. 244-246°, $[\alpha]_D$ + 82°, + 83° (c, 0.95 and 1.0). It gives a pale yellow colour with tetranitromethane. Found: C, 81.1; H, 11.4. Calc. for $C_{30}H_{50}O_2$. C, 81.4; H, 11.4%. Takeda[29] gives m.p. 246-247°, $[\alpha]_D$ + 85°.

14ξ:15ξ-Epoxy-12-oxotaraxeran-3β-yl Acetate. - A solution of 12-oxotaraxer-14-en-3β-yl acetate (100 mg.) in acetic acid (50 c.c.) was treated at room temperature with a solution of potassium permanganate (75 mg.) in water (8 c.c.), added with stirring during 15 min. After 1 hr. stirring, aqueous sodium metabisulphite (10%) and water were added, and the solution filtered. Crystallisation of the dried solid from chloroform-methanol gave 14ξ:15ξ-epoxy-12-oxotaraxeran-3β-yl acetate as plates (75 mg.), m.p. 281-283°, $[\alpha]_D$ + 15° (c,1.3 and 1.5). It shows no high intensity specific absorption in the range 2,000-2,800 Å., and gives no colour with tetranitromethane. Found: C,77.16; H,10.07. $C_{32}H_{50}O_4$ requires C,77.06; H,10.11%.

Treatment of 14ξ:15ξ-Epoxy-12-oxotaraxeran-3β-yl Acetate with Mineral Acid. - Concentrated hydrochloric acid (1 c.c.) was added to a solution of 14ξ:15ξ-epoxy-12-oxotaraxeran-3β-yl acetate (100 mg.) in acetic acid (30 c.c.), and the mixture heated on the steam bath for 3 hr. A solution of the product in light petroleum (20 c.c.) was chromatographed on alumina. No crystalline material was obtained.

Taraxeran-3β-ol. - A solution of taraxerol (taraxer-14-en-3β-ol) (250 mg.) in cyclohexane (100 c.c.) and acetic acid (100 c.c.) was shaken with hydrogen in the presence of platinum

(from 150 mg. PtO_2), until absorption was complete. The product crystallised from chloroform-methanol to give taraxeran-3β-ol as needles (190 mg.), m.p. 259-261°, $[\alpha]_D$ + 22° (c, 1.3 and 1.2). It shows no specific absorption in the range 2,000-2,800 Å., and gives no colour with tetranitromethane. Takeda[27] gives m.p. 261-262°, $[\alpha]_D$ + 24.3°.

Taraxeran-3β-yl acetate crystallised from chloroform--methanol as needles, m.p. 248-250°, $[\alpha]_D$ + 34° (c, 1.1). Takeda[27] gives m.p. 248-250°, $[\alpha]_D$ + 35.9°.

2. Alnusenone Derivatives.

For isolation of alnusenone and purification via alnusenyl acetate, see part 1.

Alnusenol crystallised from methanol as needles, m.p. 203-205°, $[\alpha]_D$ + 62° (c,1.1).

Alnusenone crystallised from chloroform-methanol as plates, m.p. 245-246°, $[\alpha]_D$ + 30° (c,1.5)

Alnusene. - Alnusenone (1 g.) was added to a solution of sodium methoxide (from 700 mg. sodium and 40 c.c. dry methanol) and hydrazine hydrate (100%; 5 c.c.), and the mixture heated in an autoclave at 200° for 18 hr. A solution of the product in benzene (70 c.c.) was chromatographed on alumina (30 g.). Benzene (300 c.c.) eluted fractions which crystallised from chloroform-methanol as blades (675 mg.), m.p. 180-182°, $[\alpha]_D$ + 56° (c,1.0).

Conversion of Alnusene into Olean-13(18)-ene and 18α--Olean-12-ene. - A solution of alnusene (205 mg.) in acetic acid (250 c.c.) and concentrated hydrochloric acid (60 c.c.) was refluxed for 20 hr. Several recrystallisations of the product from chloroform-methanol gave the mixed crystal of olean-13(18)-ene and 18α-olean-12-ene as blades (100 mg.), m.p. 185-186°, [α] - 19°, - 18.5° (c,1.0 and 1.3), undepressed

in m.p. when mixed with olean-13(18)-ene, m.p. 185-186°, $[\alpha]_D$ - 48°.

Alnusenone-II. - Concentrated hydrochloric acid (3 c.c.) was added to a solution of alnusenone (300 mg.) in acetic acid (150 c.c.), and the mixture heated on the steam bath for 19 hr. The product crystallised from chloroform-methanol to give alnusenone-II as plates (220 mg.), m.p. 249-251°, $[\alpha]_D$ - 89° (c,1.1). Beaton[82] gives m.p. 249-251°, $[\alpha]_D$ - 90°, and Chapon[80a] gives m.p. 248°, $[\alpha]_D$ - 84° for this material.

Alnusene-II. - Alnusenone-II (180 mg.) was added to a solution of sodium methoxide (from 300 mg. sodium and 25 c.c. dry methanol) and hydrazine hydrate (100%; 2 c.c.), and the mixture heated in an autoclave at 180° for 18 hr. The product crystallised from chloroform-methanol to give alnusene-II as blades (110 mg.), m.p.224-226°, $[\alpha]_D$ - 40° (c,1.3 and 1.1). Chapon[80a] gives m.p. 225°, $[\alpha]_D$ - 38° for this material.

Conversion of Alnusene-II into Olean-13(18)-ene and 18α-Olean-12-ene. - A solution of alnusene-II (110 mg.) in acetic acid (125 c.c.) and concentrated hydrochloric acid (30 c.c.) was refluxed for 18 hr. Several recrystallisations of the product from chloroform-methanol gave the mixed crystal

of olean-13(18)-ene and 18α-olean-12-ene as blades (50 mg.), m.p. and mixed m.p. 185-186°, $[\alpha]_D$ - 19.5° (c,1.2).

No homogeneous material could be obtained after similar treatment of (a) alnusenone (203 mg.) and (b) alnusenol (200 mg.).

Treatment of Alnusenyl Acetate with Osmium Tetroxide. - Osmium tetroxide (350 mg.) in ether (5 c.c.) was added to alnusenyl acetate (507 mg.) in pyridine (50 c.c.), and the mixture kept in the dark for 21 days at room temperature. After dilution with ether (100 c.c.), the mixture was refluxed for 1 hr. with lithium aluminium hydride (750 mg.). The product was isolated in the usual manner and treated with acetic anhydride and pyridine for 18 hr. at room temperature. A solution of the dry acetylated material in light petroleum-benzene (9:1; 70 c.c.) was chromatographed on alumina (15 g.). Light petroleum-benzene (9:1; 300 c.c.) eluted fractions which crystallised from chloroform-methanol to give alnusenyl acetate as needles (85 mg.), m.p. and mixed m.p. 232-235°, $[\alpha]_D$ + 43° (c,1.25). Light petroleum-benzene (1:1; 400 c.c.) and benzene (400 c.c.) eluted fractions which crystallised from chloroform-methanol to give the triol diacetate as needles (300 mg.), m.p. 266-268°, $[\alpha]_D$ ± 0° (c,2.3 and 1.95). No specific absorption in the range 2,000-2,800 Å. Infra-red absorption (in Nujol): bands at 1730, 1230 (acetate), 3570, 1033 and

970 cm.$^{-1}$ (hydroxyl). It gives no colour with tetranitromethane. Found: C,75.1; H,10.5. $C_{34}H_{56}O_5$ requires C,74.95; H,10.36%.

Treatment of the Triol Diacetate $C_{34}H_{56}O_5$ with Chromic Acid. - A solution of the triol diacetate (85 mg.) in acetic acid (50 c.c.) was treated at room temperature with an acetic acid solution of chromium trioxide (1.2 mol.), added with stirring during 10 min., and the mixture allowed to stand at room temperature for 18 hr. Isolation in the usual way, and crystallisation from chloroform-methanol gave the triol diacetate $C_{34}H_{56}O_5$ as needles (60 mg.), m.p. and mixed m.p. 265-268°, $[\alpha]_D$ + 1° (c,1.5).

Treatment of Alnusenyl Acetate with Monoperphthalic Acid. - A solution of alnusenyl acetate (250 mg.) in chloroform (25 c.c.) was treated at 0° with an ether solution of monoperphthalic acid (1.2 mol.), and the mixture kept at 0° for 18 hr. The product, obtained in the usual way, crystallised from chloroform-methanol to give the epoxide acetate as needles (190 mg.), m.p. 225-227°. $[\alpha]_D$ ± 0°, + 1.8° (c,1.3 and 1.7). No specific absorption in the range 2,000-2,800 Å. Infra-red absorption (in Nujol): bands at 1735, 1238 (acetate), 1026 and 974 cm.$^{-1}$ (acetate and oxide); no ketone band. It gives no colour with tetranitromethane. Found: C,79.41; H,10.95. $C_{32}H_{52}O_3$ requires C,79.28; H,10.81%.

Treatment of the Epoxide Acetate with Lithium Aluminium Hydride. - A solution of the epoxide acetate (125 mg.) in ether (25 c.c.) was refluxed with lithium aluminium hydride (150 mg.) for 2 hr., and the mixture allowed to stand at room temperature for 2 hr. The product was treated with acetic anhydride and pyridine at room temperature for 18 hr., and crystallised from chloroform-methanol to give the unchanged acetate epoxide as needles (100 mg.), m.p. and mixed m.p. 224-227°, $[\alpha]_D$ + 2° (c,1.0).

Treatment of the Epoxide Acetate with Hydrogen and Platinum. - A solution of the epoxide acetate (165 mg.) in acetic acid (150 c.c.) was shaken with hydrogen in the presence of platinum (from 200 mg. PtO_2) at room temperature for 5 hr. Crystallisation from chloroform-methanol gave the unchanged acetate epoxide as needles (130 mg.), m.p. and mixed m.p. 224-227°, $[\alpha]_D$ ± 0° (c,1.5).

Pyrolysis of Alnusenyl Benzoate. - Alnusenyl benzoate (500 mg.) was heated at 290-300° for 3 hr. in an atmosphere of nitrogen. A solution of the product in light petroleum (30 c.c.) was chromatographed on alumina (15 g.). Light petroleum (400 c.c.) eluted fractions which crystallised from chloroform-methanol to give alnusadiene as blades (110 mg.),

m.p. 182-184°, $[\alpha]_D$ + 53°, + 52° (c,1.0 and 1.5). $\lambda_{max.}$ 2110 Å. (ϵ = 6,500). It gives a yellow colour with tetranitromethane. Found: C,88.12; H,12.2. $C_{30}H_{48}$ requires C,88.16; H,11.84%.

Alnusenone Enol Acetate. - Concentrated sulphuric acid (1 drop) was added to a solution of alnusenone (160 mg.) in isopropenyl acetate (25 c.c.), and the mixture refluxed for 7 hr. in an atmosphere of nitrogen, with periodic removal of the condenser. After the addition of sodium acetate, the solvent was removed under vacuum. A solution of the product, isolated by means of ether, in benzene-light petroleum (1:1; 30 c.c.) was chromatographed on alumina (5 g.). Benzene-light petroleum (1:1; 200 c.c.) eluted fractions which crystallised from chloroform-methanol to give the enol acetate as plates (110 mg.), m.p. 254-257°, $[\alpha]_D$ + 41° (c,1.3 and 2.0). $\lambda_{max.}$ 2060 Å. (ϵ = 5,850). It gives a yellow colour with tetranitromethane. Found: C,82.17; H,10.84. $C_{32}H_{50}O_2$ requires C,82.34; H,10.8%.

A solution of alnusenone enol acetate (115 mg.) in benzene (5 c.c.) and methanolic potassium hydroxide (5%; 25 c.c.) was refluxed for 1½ hr. The product crystallised from chloroform-methanol to give alnusenone as plates (85 mg.) m.p. and mixed m.p. 243-245°, $[\alpha]_D$ + 33° (c,1.1).

Alnusadienyl Acetate. - A solution of selenium dioxide (1 g.) in water (1 c.c.) and acetic acid (25 c.c.) was added to a solution of alnusenyl acetate (1 g.) in acetic acid (250 c.c.), and the mixture kept at 60-70° for 1 hr. A solution of the product isolated in the usual way, in light petroleum (60 c.c.) was chromatographed on alumina (30 g.). Light petroleum (600 c.c.) eluted fractions which crystallised from chloroform--methanol to give alnusadienyl acetate as needles (650 mg.), m.p. 164-166°, $[\alpha]_D$ + 35° (c,1.5 and 1.2). $\lambda_{max.}$ 2300 and 2380 Å. (ε = 16,000 and 18,000); point of inflection at 2480 Å. (ε = 11,000). It gives a brown colour with tetranitromethane. Found: C,82.17; H,10.99. Calc for $C_{32}H_{50}O_2$: C,82.34; H,10.8%. Beaton[52] gives m.p. 164-166°, $[\alpha]_D$ + 22°, and Chapon[50a] gives m.p. 163°, $[\alpha]_D$ + 33° for this material.

Alnusadienol. - A solution of alnusadienyl acetate (250 mg.) in ether (50 c.c.) was refluxed with lithium aluminium hydride (300 mg.) for 20 min. Alnusadienol crystallised from chloroform-methanol as needles (210 mg.), m.p. 195-197°, $[\alpha]_D$ + 83° (c,1.9 and 1.1). $\lambda_{max.}$ 2320 and 2390 Å. (ε = 14,500 and 17,000); point of inflection at 2480 Å. (ε = 11,000). It gives a brown colour with tetranitromethane. Found: C,85.18; H,11.74. $C_{30}H_{48}O$ requires C,84.84; H,11.39%.

Oxidation of Alnusadienol with Chromium Trioxide - Pyridine Complex. - A solution of alnusadienol (180 mg.) in

pyridine (10 c.c.) was added to a slurry of the chromium trioxide-pyridine complex (prepared from 1 g. CrO_3 and 10 c.c. pyridine), and the mixture allowed to stand at room temperature for 17 hr. A solution of the product, isolated by means of ether, in light petroleum (30 c.c.) was chromatographed on alumina (10 g.). Benzene-light petroleum (1:2; 100 c.c.) eluted a fraction which crystallised from methanol to give the dienedione as pale yellow blades (50 mg.), m.p. 253-255°, $[\alpha]_D$ + 62°, + 63° (c, 1.2 and 0.95). $\lambda_{max.}$ 2180 and 3190 Å. (ε = 11,000 and 8,300). Found: C, 82.5; H, 10.09; O, 7.1. $C_{30}H_{44}O_2$ requires C, 82.51; H, 10.16; O, 7.3%.

Treatment of the Compound $C_{30}H_{44}O_2$ with o-Phenylenediamine. - o-Phenylenediamine (200 mg.) and sodium acetate (300 mg.) were added to a solution of the compound $C_{30}H_{44}O_2$ (100 mg.) in acetic acid (25 c.c.), and the mixture refluxed for 2 hr. Isolation by addition of water and ether extraction, followed by crystallisation from methanol gave the unchanged compound $C_{30}H_{44}O_2$ as pale yellow blades (80 mg.), m.p. and mixed m.p. 252-255°, $[\alpha]_D$ + 62° (c, 1.0).

Treatment of Alnusadienyl Acetate with Chromium Trioxide-Pyridine Complex. - A solution of alnusadienyl acetate (120 mg.) in pyridine (10 c.c.) was added to a slurry of the chromium trioxide-pyridine complex (prepared from 1 g.

CrO_3 and 10 c.c. pyridine), and the mixture allowed to stand at room temperature for 17 hr. Isolation in the usual way, and crystallisation from chloroform-methanol gave unchanged alnusadienyl acetate as needles (100 mg.), m.p. and mixed m.p. 164-166°, $[\alpha]_D$ + 34° (c, 1.1.).

Catalytic Reduction of Alnusadienyl Acetate. - (a) A solution of alnusadienyl acetate (205 mg.) in cyclohexane (45 c.c.) and acetic acid (20 c.c.) was shaken with hydrogen and platinum (from 200 mg. PtO_2) for 6 hr. The product crystallised from chloroform-methanol to give alnusenyl acetate as needles (120 mg.), m.p. and mixed m.p. 232-235°, $[\alpha]_D$ + 46° (c, 1.4). It gives a yellow colour with tetranitromethane. (b) A solution of alnusadienyl acetate (208 mg.) in acetic acid (150 c.c.) was shaken with hydrogen and platinum (from 200 mg. PtO_2) for 2½ hr. The product crystallised from chloroform-methanol to give alnusanyl acetate as small plates (135 mg.), m.p. and mixed m.p. 261-263°, $[\alpha]_D$ + 10°, + 11° (c, 1.4 and 1.0). It gives no colour with tetranitromethane.

Treatment of Alnusenyl Acetate with Sodium and Amyl Alcohol. - Sodium (1.5 g.) was added to a solution of alnusenyl acetate (500 mg.) in amyl alcohol (60 c.c.), and the mixture refluxed for 17 hr. The product, isolated in the usual way, was heated with acetic anhydride and pyridine at

100° for 30 min. Crystallisation from chloroform-methanol gave unchanged alnusenyl acetate as needles (420 mg.) m.p. and mixed m.p. 233-235°, $[\alpha]_D$ + 45° (c,0.91).

Oppenauer Oxidation of Alnusadienol. - To a solution of alnusadienol (1 g.) in benzene (30 c.c.) was added a solution of p-benzoquinone (4 g.) in benzene (20 c.c.) and a solution of aluminium t-butoxide (1 g.) in benzene (50 c.c.), and the mixture refluxed for 18 hr., and then steam-distilled for 3 hr. Filtration of the aqueous residue gave a black solid which was extracted with ether. A solution of the product in benzene was chromatographed on alumina. Benzene (400 c.c.) eluted a material which crystallised from chloroform-methanol as pale yellow blades (90 mg.), m.p. 209-212°, $[\alpha]_D$ + 121° (c,0.97). It gives a yellow colour with tetranitromethane. A solution of this material (55 mg.) in light petroleum (20 c.c.) was chromatographed on alumina (1.5 g.). Light petroleum (200 c.c.) eluted a material (43 mg.) which crystallised from chloroform--methanol as blades (35 mg.), m.p. 211-213°, $[\alpha]_D$ + 122° (c,0.97). $\lambda_{max.}$ 2340 Å. (ε = 8,300). It gives a yellow colour with tetranitromethane. Found: C,85.06; H,11.35. $C_{30}H_{46}O$ requires C,85.24; H,10.97%. The material was subsequently recrystallised as follows to give: blades from light petroleum, m.p. 211-213°, $[\alpha]_D$ + 134° (c,1.5); blades

from acetone, m.p. 211-213°, $[\alpha]_D$ + 137° (c,0.77); blades from ethyl acetate, m.p. 211-213°, $[\alpha]_D$ + 134° (c,0.8).

Treatment of the Oppenauer Oxidation Product with isoPropenyl Acetate. - Concentrated sulphuric acid (1 drop) was added to a solution of compound $C_{30}H_{46}O$ (220 mg.) in isopropenyl acetate (25 c.c.), and the mixture refluxed for 6 hr. in an atmosphere of nitrogen, with periodic removal of the condenser. A solution of the product in benzene-light petroleum (1:1; 25 c.c.) was chromatographed on alumina (10 g.). Benzene-light petroleum (1:1; 300 c.c.) eluted fractions which crystallised from chloroform-methanol as blades (40 mg.), m.p. 209-215°, $[\alpha]_D$ + 155°, + 157° (c,1.5 and 1.0). $\lambda_{max.}$ 2060 and 3160 Å. (ε = 7,500 and 6,600). No satisfactory analysis could be obtained for this material.

Selenium Dioxide Oxidation of Alnusenone. - Selenium dioxide (200 mg.) in water (1 c.c.) and acetic acid (10 c.c.) was added to a solution of alnusenone (200 mg.) in acetic acid (90 c.c.), and the mixture kept at 60-70° for 1 hr. A solution of the product, isolated in the usual way, in light petroleum (30 c.c.) was chromatographed on alumina. Light petroleum (200 c.c.) eluted a clear gum (36 mg.) which crystallised from chloroform-methanol to give blades (20 mg.), m.p. 208-210°, $[\alpha]_D$ + 140° (c,0.9). $\lambda_{max.}$ 2340 Å. (ε = 10,000).

It gives a yellow colour with tetranitromethane. A mixture of this material with the Oppenauer oxidation product (m.p. 211-213°) had m.p. 208-211°.

Conversion of 4-Bromofriedelin into Alnusenone and Alnusenone-II. - A solution of 4-bromofriedelin (m.p. 198-199°, $[\alpha]_D$ + 88°; 375 mg.) in ether (150 c.c.) was added to a solution of silver acetate (375 mg.) in water (4 c.c.) and acetic acid (190 c.c.), and the mixture boiled until the vapour temperature was 110°, and then refluxed for 20 min. The product crystallised from chloroform-methanol to give the mixed crystal of alnusenone and alnusenone-II as plates (220 mg.), m.p. 247-249°, $[\alpha]_D$ - 52° (c,1.6). A solution of this material in light petroleum (80 c.c.) was chromatographed on alumina (10 g.). Light petroleum (800 c.c.) eluted fractions (m.p. 247-249°), the specific rotations ($[\alpha]_D$) of which lay between -65° and -32°. The fractions were combined and crystallised from chloroform-methanol to give plates (220 mg.), m.p.247-249°, $[\alpha]_D$ - 50° (c,1.2). A synthetic mixture of alnusenone (m.p. 245-246°, $[\alpha]_D$ + 31°) and alnusenone-II (m.p. 250-252°, $[\alpha]_D$ - 90°) in the ratio 1:2 crystallised from chloroform-methanol to give the mixed crystal as plates, m.p. and mixed m.p. 247-249°, $[\alpha]_D$ - 51°. Corey and Ursprung[64] give m.p. 247-248°, $[\alpha]_D$ - 48.6° for this material.

Reduction of the Ketone Mixture with Lithium Aluminium Hydride: Separation of Alnusenyl and Alnusenyl-II Acetates. - A solution of the mixed crystal (220 mg.) in ether (30 c.c.) and benzene (25 c.c.) was refluxed with lithium aluminium hydride (220 mg.) for 20 min. The product was treated with acetic anhydride and pyridine on the steam bath for 1 hr. Crystallisation of the acetylated material from chloroform-methanol gave alnusenyl-II acetate as plates (80 mg.), m.p. and mixed m.p. 290-292°, $[\alpha]_D$ - 25° (c,1.5). Concentration of the mother liquors gave a mixture of plates and needles, which was washed on the filter with 1:1 chloroform-methanol until only plates remained. Concentration of the washings gave needles (50 mg.), which crystallised from chloroform-methanol to give alnusenyl acetate as needles, (30 mg.), m.p. and mixed m.p. 233-236°, $[\alpha]_D$ + 44° (c,0.85). The infra-red absorption spectrum of this material was identical with that of alnusenyl acetate obtained from natural sources.

3. α-Amyrin Derivatives.

Oxidation of Ursa-9(11):12-dien-3β-yl Acetate with Chromic Acid. - A solution of chromium trioxide (8 g.) in water (8 c.c.) and acetic acid (80 c.c.) was added during 20 min. with vigorous stirring to a solution of ursa-9(11):12--dien-3β-yl acetate (8 g.) in acetic acid (300 c.c.). The mixture was refluxed for 2 hr., treated with methanol, concentrated under reduced pressure, and diluted with water. During the ether extraction of the mixture, a solid remained suspended in the ether layer. This was collected and crystallised from chloroform-methanol to give 3β-acetoxy--9ξ-hydroxyurs-12-en-11-one as blades (1.3 g.), m.p. 315-317°, $[\alpha]_D$ + 55° (c,2.2). $\lambda_{max.}$ 2,500 Å. (ε = 13,500). It does not give a colour with tetranitromethane. Found: C,77.3; H,10.3. Calc. for $C_{32}H_{50}O_4$. C,77.1; H,10.1%. Beynon, Sharples and Spring[86] give m.p. 312°, $[\alpha]_D$ + 61°; Ruzicka, Jeger, Redel and Volli[86] give m.p. 316° (high vac.)., $[\alpha]_D$ + 62° for this compound.

The ether extract was evaporated and the residue crystallised from chloroform-methanol to give the diol monoacetate (200 mg.), m.p. and mixed m.p. 315-317°. Concentration of the chloroform-methanol mother liquors yielded 13ξ:18ξ--epoxy-12-oxours-9(11)-en-3β-yl acetate which, after recrystallisation from the same solvent mixture, separated as plates

(500 mg.), m.p. 269-271°, $[\alpha]_D$ + 71° (c,1.1). $\lambda_{max.}$ 2570 Å. (ε = 13,000). Infra-red absorption (in Nujol): bands at 1250, 1722 (acetate), 1603 and 1652 $cm.^{-1}$ (αβ-unsaturated ketone): no hydroxyl band. It does not give a colour with tetranitromethane. Found: C,77.7; H,9.6. $C_{32}H_{48}O_4$ requires C,77.4; H,9.7%. Ruzicka et al.[86] give m.p. 258°, $[\alpha]_D$ + 70°; $\lambda_{max.}$ 2590 Å. ($\log\varepsilon$ = 4.1) for a compound $C_{32}H_{48}O_4$ obtained by the same method.

Treatment of 13ξ:18ξ-Epoxy-12-oxours-9(11)-en-3β-yl Acetate with Mineral Acid. - Concentrated hydrochloric acid (0.5 c.c.) was added to a solution of 13ξ:18ξ-epoxy-12-oxours-9(11)-en-3β-yl acetate (120 mg.) in acetic acid (15 c.c.), and the mixture heated on the steam bath for 1 hr. Crystallisation from chloroform-methanol gave the unchanged acetate epoxide as plates (70 mg.), m.p. and mixed m.p. 269-271°, $[\alpha]_D$ + 70° (c,1.0). A repetition of this reaction by Shaw[87] using stronger conditions also gave unchanged material.

12-Oxoursa-9(11):13(18)-dien-3β-yl Acetate. - (a) Zinc dust (10 g.; activated by warm 10% ammonium chloride solution) was added to a solution of 13ξ:18ξ-epoxy-12-oxours-9(11)-en-3β-yl acetate (500 mg.) in ethanol (250 c.c.), and the mixture refluxed for 5 hr. Evaporation of the filtered solution gave

a yellow solid, which crystallised from methanol as pale yellow plates, m.p. 202-204°, $[\alpha]_D$ - 42° (c,1.8). Recrystallisation from the same solvent yielded 12-oxoursa-9(11):13(18)--dien-3β-yl acetate as pale yellow plates (430 mg.), m.p. 203-205°, $[\alpha]_D$ - 43° (c,2.0). $\lambda_{max.}$ 2080, 2620 and 2940 Å. (ε = 7,900, 9,300 and 7,700). Found: C,79.8; H,10.0. $C_{32}H_{48}O_3$ requires C,79.95; H,10.1%. A mixture with 12-oxo-oleana-9(11):13(18)-dien-3β-yl acetate (m.p. 205-207°) had m.p. 172-179°.

(b) A solution of 13ξ:18ξ-epoxy-12-oxours-9(11)-en-3β-yl acetate (500 mg.) in ether (15 c.c.) and dioxan (10 c.c.) was added with vigorous stirring during 2 min. to a solution of lithium (150 mg.) in liquid ammonia (100 c.c.). After 3 min. stirring, acetone was added, and the ammonia allowed to evaporate. The residue was treated with pyridine and acetic anhydride at room temperature for 15 hr., and the acetylated product chromatographed on alumina. Benzene-light petroleum (1:9; 100 c.c.) eluted a fraction which crystallised from chloroform-methanol as needles (20 mg.), m.p. 170-172°, $[\alpha]_D$ + 156° (c,0.7). It shows no selective light absorption above 2,000 Å. and does not give a colour with tetranitromethane. Found: C,74.1; H,10.2%. The fractions eluted by benzene-light petroleum (1:1; 400 c.c.) crystallised from aqueous methanol to

give 12-oxoursa-9(11):13(18)-dien-3β-yl acetate as pale yellow plates (210 mg.), m.p. and mixed m.p. 203-205°, $[\alpha]_D$ - 44° (c,0.8). $\lambda_{max.}$ 2080, 2620 and 2940 Å.(ϵ = 9,600, 10,000 and 8,100).

Treatment of 12-Oxoursa-9(11):13(18)-dien-3β-yl Acetate with Lithium in Ammonia. - A solution of the dienone (400 mg.) in ether (25 c.c.) was added with stirring during 2 min. to a solution of lithium (150 mg.) in liquid ammonia (100 c.c.). After 3 min. stirring, acetone was added, and the ammonia allowed to evaporate. The product was heated for 1 hr. on the steam bath with pyridine and acetic anhydride. The acetylated material crystallised from chloroform-methanol to give needles (70 mg.), m.p. 170-172, $[\alpha]_D$ + 157° (c,0.89), undepressed in m.p. on mixing with the compound (m.p. 170-172°) described above. The mother liquors were evaporated and a solution of the residue (300 mg.) in light petroleum (50 c.c.) was chromatographed on alumina (10 g.). Benzene-light petroleum (1:3; 300 c.c.) eluted fractions which crystallised from aqueous methanol to give the unchanged dienone as pale yellow plates (110 mg.), m.p. and mixed m.p. 203-205°, $[\alpha]_D$ -42° (c,0.9).

Treatment of 12-Oxoursa-9(11):13(18)-dien-3β-yl Acetate with Sodium Borohydride. - A solution of the dienone (400 mg.) in methanol (200 c.c.) was added to a solution of sodium

borohydride (1 g.) in water (8 c.c.), and the mixture allowed to stand at room temperature for 72 hr. The product was treated with acetic anhydride and pyridine at room temperature for 15 hr., and crystallised from aqueous methanol to give the unchanged dienone as pale yellow plates (290 mg.), m.p. and mixed m.p. 203-205°, $[\alpha]_D$ - 41° (c,0.96).

Treatment of 12-Oxoursa-9(11):13(18)-dien-3β-yl Acetate with Hydrochloric-Acetic Acid. - Concentrated hydrochloric acid (3 c.c.) was added to a solution of the dienone (190 mg.) in acetic acid (25 c.c.), and the mixture heated on the steam bath for 18 hr. The residue on evaporation of the solvent was heated on the steam bath for 30 min. with acetic anhydride and pyridine. The acetylated material crystallised from aqueous methanol to give the unchanged dienone as pale yellow plates (110 mg.), m.p. and mixed m.p. 202-204°, $[\alpha]_D$ - 42° (c,0.8).

11-Oxours-12-en-3β-yl Acetate. - A solution of chromium trioxide (7.5 g.) in water (7 c.c.) and acetic acid (75 c.c.) was added during 20 min. with stirring to a solution of α-amyrin acetate (10 g.) in acetic acid (500 c.c.), and the mixture allowed to stand at room temperature for 18 hr.

Crystallisation of the product, isolated in the usual way, from chloroform-methanol gave 11-oxours-12-en-3β-yl acetate as plates (8.2 g.), m.p. 284-286°, $[\alpha]_D$ + 100° (c, 2.8). $\lambda_{max.}$ 2040 and 2500 Å. (ε = 5,800 and 11,800). It gives no colour with tetranitromethane. Concentration of the mother liquors yielded a second crop (1.1 g.) which, after two recrystallisations from chloroform-methanol, gave 11-oxours-12-en-3β-yl acetate as plates (700 mg.), m.p. and mixed m.p. 284-286°.

11-Oxoursan-3β-yl Acetate. - A solution of 11-oxours-12-en-3β-yl acetate (2 g.) in ether (70 c.c.) and dioxan (30 c.c.) was added during 3 min. with stirring to a solution of lithium (600 mg.) in liquid ammonia (400 c.c.). After 4 min. stirring, acetone was added, and the ammonia allowed to evaporate. The product was heated on the steam bath for 1 hr. with acetic anhydride and pyridine, and the acetylated material purified by chromatography of its solution in light petroleum on alumina. Elution of the column with benzene-light petroleum (1:3; 300 c.c.) yielded a solid which crystallised from chloroform-methanol to give 11-oxoursan-3β-yl acetate as plates (150 mg.), m.p. 326-329°, $[\alpha]_D$ - 8.9°, - 8.5° (c, 1.7 and 1.75). It shows no high intensity absorption above 2,000 Å., and gives no colour with tetranitromethane. Found: C, 78.92; H, 11.2. $C_{32}H_{52}O_3$ requires C, 79.28;

H,10.8%. Lyssy and Jeger[88] give m.p. 337-338°, $[\alpha]_D$ -5°, -4° for this compound.

Ursan-3β-yl Acetate. - Hydrazine (prepared by refluxing 100% hydrazine hydrate with sodium hydroxide) was distilled into a solution, obtained by the addition of sodium (700 mg.) to diethylene glycol (35 c.c.), until the mixture refluxed gently at 180°. 11-Oxoursan-3β-yl acetate (500 mg.) was added to the cooled solution, and refluxing continued for 18 hr. The mixture was then distilled until the temperature rose to 210°, and refluxing continued for 7 hr. The product, isolated by means of ether, was heated on the steam bath for 1 hr. with acetic anhydride and pyridine. Crystallisation from chloroform-methanol gave ursan-3β-yl acetate as needles (170 mg.) m.p. 249-251°, $[\alpha]_D$ + 26, + 25° (c, 0.95 and 1.65). It shows no specific absorption above 2,000 Å., and gives no colour with tetranitromethane. Found: C,81.9; H,11.6. $C_{32}H_{54}O_2$ requires C,81.6; H,11.5%. Lyssy and Jeger[88] give m.p. 247-249°, $[\alpha]_D$ + 42°.

Ursan-3β-ol crystallised from aqueous acetone as needles m.p. 183-185°, $[\alpha]_D$ + 32°, + 31° (c, 1.3). Found: C,84.3; H,12.2. $C_{30}H_{52}O$ requires C,84.0; H,12.2%.

Ursan-3-one. - A solution of ursan-3β-ol (85 mg.) in acetic acid (40 c.c.) was treated at room temperature with an acetic acid solution of chromium trioxide (1.2 mol.),

added with stirring during 10 min., and the mixture allowed to stand at room temperature overnight. Crystallisation of the product from aqueous acetone gave ursan-3-one as needles (50 mg.), m.p. 109-111°, $[\alpha]_D$ + 55°, + 56° (c,1.6 and 1.2). Found: C,84.8; H,12.0. $C_{30}H_{50}O$ requires C,84.4; H,11.8%.

Ursane. - Ursan-3-one (35 mg.) was added to a solution of sodium methoxide (from 500 mg. sodium and 25 c.c. dry methanol) and hydrazine hydrate (100%; 1 c.c.), and the mixture heated at 200° in an autoclave for 16 hr. The product crystallised from aqueous acetone to give ursane as plates (10 mg.), m.p. 124-128°, $[\alpha]_D$ + 50°, + 53° (c,0.76 and 0.31). It shows no specific absorption above 2,000Å., and gives no colour with tetranitromethane. Lyssy and Jeger[88] give m.p. 139-140°, $[\alpha]_D$ + 18°.

Modified Wolff-Kishner Reduction of 11-Oxours-12-en-3β-yl Acetate. - 11-Oxours-12-en-3β-yl acetate (500 mg.) was added to a solution of sodium (700 mg.) in diethylene glycol (35 c.c.) containing hydrazine (see previous method). The mixture was refluxed at (a) 180° for 18 hr., and (b) 210° for 24 hr. The product, after acetylation, crystallised from chloroform-methanol to give α-amyrin acetate as blades (350 mg.), m.p. and mixed m.p. 224-226°, $[\alpha]_D$ + 70° (c,2.2)

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