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THE STEREOCHEMISTRY OF THE BOSWELLIC ACIDS

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Abstract—The configuration of the substituents at C(3), C(4), C(5), C(8), C(10), C(13) and C(17) in α- and β-boswellic acids have been shown to be identical by an ursane–oleanane interconversion. Synthetic and dehydration studies of the C(3) epimeric alcohols have confirmed the axial configuration of the hydroxyl group in the boswellic acids and indicated that coplanarity of participating groups need not be an essential requirement for ring contraction. Cyclization reactions of C(3) and C(24) dihydroxy derivatives of the boswellic acids have shown that ring A can readily change from a chair to a boat form to permit cyclic acetalization of *trans* diaxial hydroxy groups.

FRANKINCENSE, a fragrant and costly gum, is obtained from *Boswellia carteri* and other species of East Indian trees and was much used for sacrificial and religious purposes by the ancient Egyptians and Jews.[1]

Ursane and oleanane triterpenoids are among the main constituents of this material, and α- and β-boswellic acids were first isolated in admixture by Tschirch and Halbey[2] at the close of the nineteenth century. These acids, which occur as their acetates, were subsequently separated by Winterstein and Stein[3] and initially formulated[4–6] as 3α-hydroxyolean-12-en-24-oic acid (II*b*) and 3β-hydroxyurs-12-en-24-oic acid (I*a*) respectively, in which the hydroxyl groups have opposite and different configurations.

This paper details direct chemical evidence disclosing the stereoidentity of the hydroxyl and carboxyl functions and the configurations at C(5), C(8), C(10), C(13) and C(17) and firmly substantiating earlier suggested formulations[7] for α-boswellic and β-boswellic acids first derived from molecular rotation considerations.[8,9]

A key step in the establishment of the structure[10] and stereochemistry[11,12] of α-amyrin (I*c*) and the first example of the direct conversion of an ursane triterpenoid to an oleanane triterpenoid was the isomerization of ursa-9(11),12-dien-3β-yl acetate (III*a*) to oleana-11,13(18)-dien-3β-yl acetate (IV*a*).[13]

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[1] *Holy Bible*, New Testament, Matthew 2, 11.

[2] A. TSCHIRCH and O. HALBEY, *Arch. Pharm.* **236**, 487 (1898).

[3] A. WINTERSTEIN and G. STEIN, *Z. Physiol. Chem.* **208**, 9 (1932).

[4] L. RUZICKA and W. WIRZ, *Helv. Chim. Acta* **22**, 948 (1939); **23**, 132 (1940); **24**, 248 (1941).

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[7] G. G. ALLAN, *Chimia* **17**, 382 (1963).

[8] W. KLYNE and W. M. STOKES, *J. Chem. Soc.* 1979 (1954).

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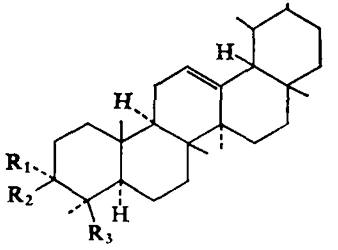
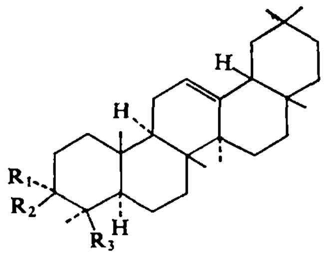
[12] G. G. ALLAN, M. B. E. FAYEZ, F. S. SPRING and R. STEVENSON, *J. Chem. Soc.* 456 (1956).

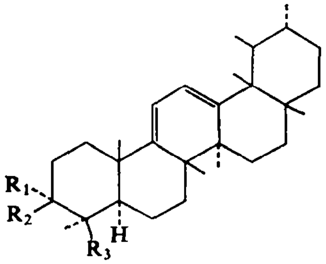
[13] G. G. ALLAN, J. M. BEATON, J. I. SHAW, F. S. SPRING, R. STEVENSON, J. L. STEWART and W. S. STRACHAN, *Chem. & Ind.* 281 (1955).



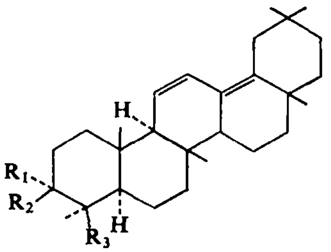
	R₁	R₂	R₃
I*a*	H	OH	COOH
b	OH	H	COOH
c	H	OH	H
d	H	H	COOMe
e	OBz	H	COOMe
f	OH	H	COOMe
g	H	OH	COOMe
h	H or	Cl	COOMe



	R₁	R₂	R₃
II*a*	H	OH	COOH
b	OH	H	COOH



	R₁	R₂	R₃
III*a*	H	OH	Me
b	OAc	H	COOMe



	R₁	R₂	R₃
IV*a*	H	OH	Me
b	OAc	H	COOMe
c	OH	H	COOMe

This noteworthy reaction has implicitly a much broader scope in stereochemical investigations in the triterpenoid field and its application could be considered in this case since β-boswellic acid (I*b*) can be readily converted to the homoannular diene (III*b*) by methylation, acetylation and oxidation with N-bromosuccimide.[14] Refluxing of this *ursane* derivative with hydrochloric acid in acetic acid for 24 hr gave the heteroannular diene acetate (IV*b*) in admixture with the related alcohol (IV*c*) in 85 per cent yield identical with the *oleanane* heteroannular conjugated diene acetate obtained from α-boswellic acid (II*b*) by methylation, acetylation and dehydrogenation with selenium dioxide. The configurations of the functional groups in ring A of both the boswellic acids are therefore clearly identical.

Since the configurations of the hydroxyl and carboxyl groups in α-boswellic acid have been established[4,15] as α and β respectively, the orientations of the same groups in β-boswellic acid are now clearly fixed in agreement with the suggestions initially prompted by molecular-rotation evidence.[8]

The configuration of the C(3) hydroxyl group finds further endorsement in dehydration experiments. Thus, the high yield of the ursane–oleanane interconversion of (III) to (IV) suggested that facile ring contraction was not a significant side reaction.

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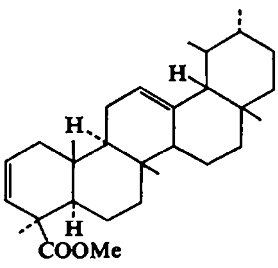
[14] L. Ruzicka, O. Jeger and W. Ingold, *Helv. Chim. Acta* 27, 1859 (1944).

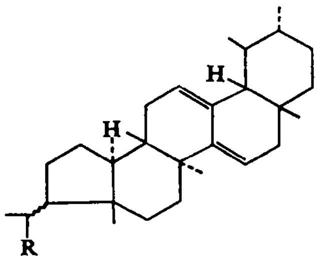
[15] G. G. Allan, *Chem. & Ind.* 1497 (1965).

This, of course, is entirely consistent with the presence of the 3α-axial configuration which normally leads to the formation of an ethenoid linkage without ring contraction. Dehydrative ring A contraction of a triterpenoid alcohol on the other hand is generally considered diagnostic of the presence of a 3β-equatorial hydroxyl group and satisfying stereochemical representations have been developed for both these cases.[16–18]

Thus, treatment of methyl 3α-hydroxyurs-12-en-24-oate (I*f*) with phosphorus pentachloride afforded the expected methyl ursa-2,12-dien-24-oate (V),[19,20] the constitution of which was confirmed by its hydrogenation to the known methyl urs-12-en-24-oate (I*d*)[21] and by its preparation by the pyrolysis of methyl 3α-benzoxyurs-12-en-24-oate (I*e*).



V

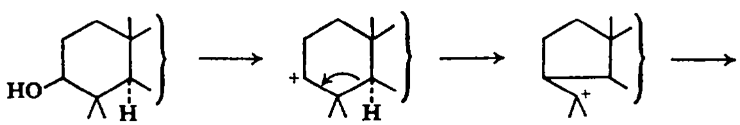


IX*a* R=H
b R=COOMe

These reactions can be recognized mechanistically as conventional *trans* diaxal ionic elimination and *cis* thermal elimination respectively[22] and are in accord with the stereochemistry represented in (I*f*).

In contrast, treatment of the 3β-epimer (I*g*)[9] did not afford the expected ring-contracted product. Instead, the product was methyl 3ξ-chlorours-12-en-24-oate (I*h*) identified by reductive conversion to (I*d*).

Thus neither 3α- nor 3β-ursane alcohols are subject to ring contraction with phosphorus pentachloride when a carbomethoxy group is located at C(24). The mechanism for ring-A contraction is usually depicted[24,25] in its initial stages as in (VI), (VII) and (VIII).



IV VII VIII

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[16] D. H. R. Barton, *Experientia* 6, 316 (1950).

[17] D. H. R. Barton and W. J. Rosenfelder, *J. Chem. Soc.* 1048 (1951).

[18] D. H. R. Barton, *J. Chem. Soc.* 1027 (1953).

[19] *Elsevier's Encyclopaedia of Organic Chemistry*, editor R. Radt, co-editor D. Stern, Vol. 14 and Supplement.

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[22] D. B. Cram, in *Steric Effects in Organic Chemistry* (edited by M. S. Newman), p. 304. John Wiley, New York (1956).

[23] A. Meyer, O. Jeger and L. Ruzicka, *Helv. Chim. Acta* 33, 672 (1950).

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[25] D. H. R. Barton and P. DeMayo, *J. Chem. Soc.* 3111 (1953).

The failure of the 3β-alcohol (I*g*) to follow this path is attributed to the inability of the carbonium ion (VII) or its chlorophosphorus precursor to compete successfully with the positive component of the dipole of the carbonyl moiety in the carbomethoxy group to capture the electrons of the 4:5 bond and consummate the ring contraction. Chloride ion approach or its equivalent then intervenes to permit stabilization by the formation of the 3-chloro compound.

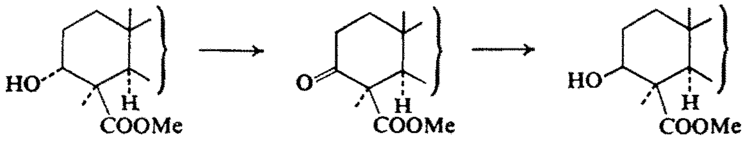
The intervention and retention of an anion as a means of stabilizing a carbonium ion is somewhat unusual in ring contractions in the triterpenoid field but is not without precedent; the formation of novic acid from quinovic acid providing an interesting intramolecular example of this phenomenon.[25]

Unexpected results were also observed when methyl 3α-hydroxyurs-12-en-24-oate was dehydrated with phosphoric oxide. The product obtained has three maxima in its u.v. absorption spectrum, λ_{max} 234 (ϵ = 14,700), 241 (ϵ = 1600) and 248 nm (ϵ = 10,500) and is laevorotatory, $[\alpha]_D - 108°$ and in these respects and its origins is an exact analogue of both *l*-α-amyradiene[24] (IX*a*) λ_{max} 236 (ϵ = 13,300), 241 (ϵ = 14,500) and 250 nm (ϵ = 8,500), $[\alpha]_D$-110°, and its β-amyrin relative *l*-β-amyradiene[12] λ_{max} 234 (ϵ = 15,000), 241 (ϵ = 16,000) and 249 nm (ϵ = 10,700), $[\alpha]_D - 83°$. It is therefore to be regarded as methyl 5,8α,9β-trimethyl-10α-novursa-12,14-dien-24-oate (IX*b*) and its formation is noteworthy as the first example where dehydration of a 3α-alcohol has led to ring contraction in spite of the *non-coplanarity* of the involved centers.

The failure of phosphoric oxide to dehydrate the 3α-alcohol towards the 2-position with its favorable coplanarity to afford the non-ring contracted diene (*trans* diaxial elimination) must reflect the powerful electron-withdrawing properties of the intermediate phosphorus oxyacid substituent which supersede these requirements and provoke the collapse of the 4:5 bond and the ensuing ring contraction. Phosphoric oxide dehydration of the epimeric 3β-alcohol also afforded the same heteroannular laevorotatory diene (IX*b*).

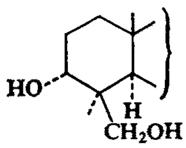
These ring contraction experiments therefore suggest, firstly, that the configuration of the 3-alcohol may be irrelevant to ring contraction with phosphoric oxide and second, that the carbonium ion precursor produced at C(3) by phosphoric oxide is significantly more electrophilic than that attained at the same position with phosphorus pentachloride since the former can overcome the competitive positivity of the carbonyl dipole of the carbomethoxy group to achieve ring contraction and the latter cannot.

These formulations of the boswellic acids (I) and (II) can be still further substantiated by reduction of methyl 3-oxours-12-en-24-oate (X) with sodium borohydride. With this reductant an equatorial (β) hydroxyl group is invariably generated from a ketone group in a six-membered carbocyclic ring, and in this case the hydroxyester (I*g*) obtained is not identical with the hydroxyester (I*f*) prepared by methylation of β-boswellic acid.[9]

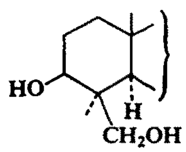


I*f* X I*g*

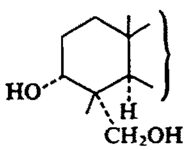
Chemical evidence has also been presented to confirm the β-configuration of the 4-carboxyl group in β-boswellic acid. Thus reduction of β-boswellic acid and its 3-epimer with lithium aluminum hydride affords two distinct diols formulated as (XI) and (XII). The oleanane analogs of XI and XII were also similarly prepared and characterized.



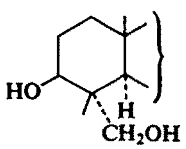
XI



XII



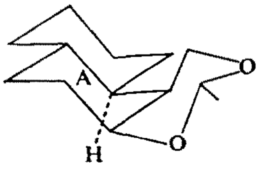
XIII



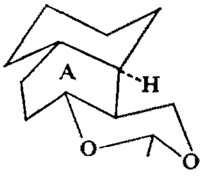
IV

Treatment of each of the two ursane diols with acetone containing 1 per cent of sulfuric acid afforded a cyclic isopropylidene derivative[9] only in the case of (XI). This behavior was rationalized by the suggestion that of the four diols of this type, (XI), (XII), (XIII) and (XIV), all would be expected to form condensation products except (XI), where the two transaxial groups (hydroxy and hydroxymethyl) are not suitably disposed.[9]

Implicit in this generalization [26–28] that *trans* substituents in a carbocyclic ring are too stereochemically remote for interaction is the seldom stated corollary that the chair conformation must be retained. If the chair form is even only somewhat distorted then isopropylidene groupings bridging *trans* substituents can be introduced.[29] In our experience, diols (XI) and (XII) *each* afforded cyclic acetals on treatment with acetaldehyde.



XV



XVI

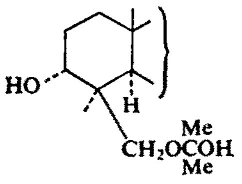
Examination of Dreiding stereomodels of rings A and B shows that in the case of the 3β 4β (equatorial, axial) diol a cyclic acetal in a chair form can be readily fused to ring A also in the chair form (XV). Although this fusion cannot be achieved in the case of the diaxial 3α 4β arrangement in (XI) with retention of the chair form it can be accomplished if ring A is in the boat form with the prow at 3 (and the stern at 6). The 3 and 4 substituents then become effectively equatorial and the dioxolane ring can readily be attached. This heterocyclic ring will of course have the chair conformation (XVI) and the orientation of the methyl group attached to the carbon between the oxygen atoms can probably be regarded as equatorial since in this configuration 1,3-interactions are minimized.

This transformation of the more stable chair form to the less stable boat, while rare, is not unique and other cases have been noted where either the terminal ring A or E of pentacyclic triterpenoids have undergone well-authenticated similar conformational changes resulting from bromination[31] or lactonization[32–34] reactions.

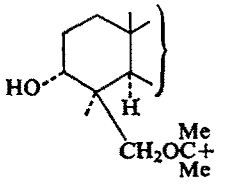
[26] J. Boeseken and H. G. Derx, *Rec. Trav. Chim.* **40**, 529 (1921).
[27] H. G. Derx, *Rec. Trav. Chim.* **41**, 318 (1922).
[28] N. L. Wendler and H. L. Slates, *Chem. & Ind.* 167 (1955).
[29] S. J. Angyal and C. G. McDonald, *J. Chem. Soc.* 686 (1952).
[30] S. J. Angyal and R. M. Hoskinson, *J. Chem. Soc.* 2985 (1962).
[31] D. H. R. Barton, D. A. Lewis and J. F. McGhie, *J. Chem. Soc.* 2907 (1957).
[32] H. R. Arthur, A. R. H. Cole, K. J. L. Thieberg and D. E. White, *Chem. & Ind.* 926 (1956).
[33] C. Djerassi and J. S. Mills, *J. Am. Chem. Soc.* **80**, 1236 (1958).
[34] B. Tursch, E. Tursch, I. T. Harrison, G. B. C. T. de D. B. da Silva, H. J. Monteiro, B. Gilbert, W. B. Mors and C. Djerassi, *J. Org. Chem.* **29**, 2393 (1964).

The formation of boat derivatives[35] under such relatively mild conditions need not be regarded as excessively surprising since the energy difference between the two cyclohexane conformations has been estimated[36] as being about twice the internal rotation potential barrier in ethane (2·8 kcal/mole) and the skew boat form has an enthalpy 1·6 kcal/mole less than that of the true boat.[37]

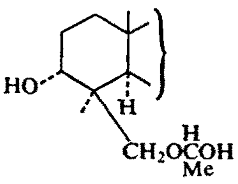
The failure of acetone to participate in an analogous boat-form genesis may be ascribed to electronic and steric factors. Thus, electronically the lower positivity of the carbonyl carbon atom in ketones compared to that in aldehydes does not facilitate initial attack by the alcohol. Any limited hemiacetal formation which does occur can be assumed to involve the primary aliphatic alcohol group at C(24) rather than the secondary alicyclic hydroxyl at C(3) because ethanol can be acetalized more readily than cyclohexanol.[42]



XVII

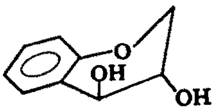


XVIII

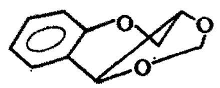


XIX

Models of this first intermediate (XVII) and the subsequent derived carbonium ion (XVIII) show that severe steric interactions could occur between the pair of methyl groups, originating from the acetone, and C(3) of ring A during its change from the chair to the boat geometry. The absence of the second methyl group and higher electrophilicity of the aldehydic carbonyl carbon in acetaldehyde apparently results in an intermediate (XIX) sufficiently stable to endure and sterically structured to permit the conformational rearrangement of ring A before finally cyclizing.



XX



XXI

It is noteworthy that cyclic isopropylidene bridges can be constructed between *trans* diaxial hydroxyls in the dihydropyran ring of a flavanol (XX).[38,39] In this situation an examination of molecular models shows that the steric inhibition of the change to the required quasi-boat form (XXI) is completely relieved by the coplanarity distortion occasioned by the fused aromatic ring.

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[35] E. L. ELIEL, N. L. ALLINGER, S. J. ANGYAL and G. A. MORRISON, *Conformation Analysis*, p. 469. Interscience, New York (1966).

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[37] J. B. HENDRICKSON, *J. Am. Chem. Soc.* **83**, 4537 (1961).

[38] B. R. BROWN, *Nature* **191**, 234 (1961).

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[42] J. D. ROBERTS and M. C. CASERIO, *Basic Principles of Organic Chemistry*, p. 447. W. A. Benjamin, New York (1965).

EXPERIMENTAL

M.p.s were determined using a standardized N.P.L. thermometer. Rotations were measured in $CHCl_3$ solution in 1 dm tube at approximately 15°. U.v. absorption spectra were determined in ethanol solution with a Unicam SP.500 spectrophotometer. For chromatography, alumina (Brockman Grade II) was used, in the ratio 30:1of substance chromatographed, and light petroleum refers to that fraction of b.p. 40–60°.

The phrase "in the usual way" implies, in general, dilution with water, extraction with ether, washing consecutively with aqueous NaOH, water, aqueous HCl and aqueous $NaHCO_3$, followed by drying of the ethereal extract over Na_2SO_4, filtration and evaporation to dryness under reduced pressure. Hydrogenations were carried out, at room temperature, in glacial acetic acid which had been refluxed over and distilled from CrO_3. Acetylations were carried out using acetic anhydride in pyridine solution at 100° for 30 min unless otherwise specified.

Methyl 3α-Acetoxyursa-9(11),12-dien-24-oate (III*b*)

A solution of methyl 3α-acetoxyurs-12-en-24-oate (5 g) in CCl_4 (100 ml) was refluxed with N-bromosuccinimide (3 g) for 3 hr. The product, isolated in the usual way, crystallized from methanol to yield the homoannular diene acetate as prisms (3 g), m.p. 173–175°, $[\alpha]_D$ +335° (*c*, 1·8). λ_{max} 282 nm (ϵ=9750). Ruzicka, Jeger and Ingold[14] give m.p. 175° cor., $[\alpha]_D$ +338° λ_{max}, in dioxan, 281 nm (ϵ=11,220).

Methyl 3α-Acetoxyoleana-11,13(18)-dien-24-oate (IV*b*)

To a refluxing solution of methyl 3α-acetoxyolean-12-en-24-oate (500 mg) in acetic acid (40 ml) was added dropwise, a solution of SeO_2 (500 mg) in water (1 ml) and acetic acid (10 ml), during 20 min. After refluxing for a further 1·5 hr the reaction mixture was filtered and evaporated to dryness. The residue obtained was dissolved in benzene (50 ml) and filtered through a short column of alumina. The column was washed with benzene (500 ml) and the combined eluates were evaporated to dryness. The residue was dissolved in hot methanol (25 ml) and filtered through diatomaceous earth. Concentration of the filtrate caused crystallization yielding the *heteroannular diene acetate* (IV*b*) as fine needles (300 mg), m.p. 180–182° $[\alpha]_D$ −70° (*c*, 1·5). (Found: C, 77·4; H, 9·7. $C_{33}H_{50}O_4$ required: C, 77·6; H, 9·9 per cent). λ_{max} at 242 nm (ϵ=28,700), 250 (32,600) and 260 nm (21,200).

Methyl 3α-Hydroxyoleana-11,13(18)-dien-24-oate (IV*c*)

A solution of methyl 3α-acetoxyoleana-11,13(18)-dien-24-oate (700 mg) in methanolic KOH (5 per cent, 350 ml) was refluxed for 1 hr. Isolation of the product in the usual way yielded, after three crystallizations from $CHCl_3$–methanol, *methyl 3α-hydroxyoleana-11,13(18)-dien-24-oate* as prisms (800 mg), m.p. 248–250°, $[\alpha]_D$ −27° (*c*, 2·6). (Found: C, 79·43; H, 10·3. $C_{31}H_{48}O_3$ required: C, 79·43; H, 10·32 per cent.) λ_{max} at 242 (ϵ=22,400), 249 (25,200) and 258 nm (16,000). Acetylation of this 3α-alcohol using pyridine–acetic anhydride yielded (IV*b*) from methanol as needles, m.p. and mixed m.p. 180–182°, $[\alpha]_D$ −70° (*c*, 1·1).

Acid Isomerization of Methyl 3α-Acetoxyursa-9(11),12-dien-24-oate (III*b*)

A solution of methyl 3α-acetoxyursa-9(11),12-dien-24-oate (2 g) in acetic acid (250 ml) was treated with conc. HCl (25 ml) and heated on the steam-bath for 2 hr when conc. HCl (25 ml) was again added. The mixture was heated on the steam-bath for 22 hr and evaporated to dryness under reduced pressure. The residue was dissolved in ether, washed with NaOH solution and water, and the ethereal solution dried. Acidification of the NaOH washings gave no precipitate. Evaporation of the ethereal solution gave a residue (1·8 g) which was dissolved in petrol–benzene (1:1, 100 ml) and chromatographed on alumina (50 g). Elution with petrol (300 ml) gave a gum (10 mg) which was not further examined. Elution with petrol–benzene (19:1, 100 ml, 9:1, 200 ml, 7:3, 100 ml, 3:2, 100 ml, 1:1, 100 ml) gave only traces of material. Further elution with petrol–benzene (2:3, 100 ml) gave a gum (30 mg) which could not be crystallized. Continued elution with petrol–benzene (2:3, 200 ml, 7:13, 100 ml, 3:7, 300 ml, 1:4, 200 ml, 1:9, 100 ml) and benzene (1000 ml) gave a gum (1·35 g) which crystallized from methanol to yield methyl 3α-acetoxyoleana-11,13(18)-dien-24-oate (IV*b*) as fine needles, m.p. and mixed m.p. 180–182°, $[\alpha]_D$ −70° (*c*, 2·1). λ_{max} at 242 (ϵ=28,000) 250 (31,400) and 260 nm (20,600). Stripping of the column with acetone–methanol (1:1, 500 ml) gave a fraction (300 mg) which after three recrystallizations from methanol–$CHCl_3$ yielded methyl 3α-hydroxyoleana-11,13(18)-dien-24-oate (IV*c*) as prisms (90 mg), m.p. and mixed m.p. 248–250°, $[\alpha]_D$ −27° (*c*, 0·9). λ_{max} at 242 (ϵ=25,800), 250 (29,400) and 260 nm (19,200).

Methyl Ursa-2,12-dien-24-oate (V)

(*a*) A solution of methyl 3α-hydroxyurs-12-en-24-oate (500 mg) in petrol (30 ml) was treated with PCl_5 (500 mg), shaken for 1 hr and refluxed for 2 min. The product (525 mg) was isolated in the usual way using benzene, dissolved in petrol (100 ml) and chromatographed on alumina (30 g). Elution with petrol (1600 ml) gave a fraction which crystallized from methanol to yield *methyl ursa-2:12-dien-24-oate* as plates (250 mg), m.p. 156–157°, $[\alpha]_D$ +171° (*c*, 2·0). (Found: C, 82·2; H, 10·9. $C_{31}H_{48}O_2$ required C, 82·2; H, 10·7 per cent) λ_{max} at 205 nm (ϵ=3500) (ϵ_{210} 2220; ϵ_{215} 930; ϵ_{220} 248). Elution with more polar solvents gave no crystallizable fractions. Attempted hydrolysis using 5 per cent methanolic KOH for 1 hr gave a quantitative recovery of starting material, m.p. and mixed m.p. 155–157°, $[\alpha]_D$ +171° (*c*, 2·1).

(*b*) Methyl 3α-benzoxyurs-12-en-24-oate (400 mg) was heated at 300°, in an atmosphere of N_2, for 3 hr. The product was isolated through ether in the usual way and the gum obtained was dissolved in petrol (100 ml) and filtered through a column of alumina (10 g). The column was washed with petrol (750 ml) and evaporation of this eluate gave a gum (100 mg) which crystallized from methanol to yield V as plates (80 mg), m.p. and mixed m.p. with above, 155–156°, $[\alpha]_D$ +170° (*c*, 0·5). Further elution using petrol–benzene (1:1, 750 ml) gave a gum (250 mg) which crystallized from $CHCl_3$–methanol to yield methyl 3α-benzoxyurs-12-en-24-oate as prismatic rods (220 mg), m.p. and mixed m.p. 155–156°, $[\alpha]_D$ +48° (*c*, 1·8).

Methyl Urs-12-en-24-oate (I*d*)

(*a*) A solution of methyl ursa-2,12-dien-24-oate (170 mg, m.p. 156–157°, $[\alpha]_D$ +171°) in acetic acid (100 ml) was added to a suspension of freshly reduced Pt (from 100 mg PtO_2) in acetic acid (50 ml) and the mixture shaken with H_2 at room temperature for 8 hr when absorption was complete. The catalyst was removed by filtration and the filtrate evaporated to dryness under reduced pressure to yield a residue which crystallized from $CHCl_3$–methanol to yield methyl urs-12-en-24-oate as needles (150 mg), m.p. 176–177°, $[\alpha]_D$ +132° (*c*, 1·3). (Found: C, 81·8; H, 11·0. $C_{31}H_{50}O_2$ required: C, 81·9; H, 11·1 per cent.) λ_{max} at 204 nm (ϵ=4620) (ϵ_{210} 2650; ϵ_{215} 975).

(*b*) A mixture of methyl 3-oxours-12-en-24-oate (200 mg, m.p. 159–160°, $[\alpha]_D$ +111°), acetic acid (50 ml), amalgamated Zn (6 g) and conc. HCl (2 ml) was refluxed for 3 hr with the addition of conc. HCl (2 ml) after 1 and 2 hr. The product, isolated through ether in the usual way, was dissolved in petrol (100 ml) and filtered through a column of a alumina (10 g). The column was washed with petrol (500 ml) and petrol–benzene (1:1, 500 ml). Evaporation of the eluates gave a gum which crystallized from $CHCl_3$–methanol to yield needles (110 mg), m.p. 166–168°. After four recrystallizations, I*d* was obtained as long fine needles, m.p. 175–177°, $[\alpha]_D$ +130° (*c*, 1·6). Methyl urs-12-en-24-oate, m.p. 166–167°, $[\alpha]_D$ +131°, had previously been prepared[21] by the same method using a 30-min reduction period. A specimen on admixture with the material described above showed no m.p. depression.

Methyl 3ξ-Chlorurs-12-en-24-oate (I*h*)

A suspension of methyl 3β-hydroxyurs-12-en-24-oate (652 mg) in petrol (20 ml) was treated with PCl_5 (400 mg), shaken for 1 hr and refluxed for 5 min. The product, isolated in the usual way, crystallized from $CHCl_3$–methanol to yield *methyl 3ξ-chlorours-12-en-24-oate* as prisms (460 mg), m.p. 225–227°, $[\alpha]_D$ +110° (*c*, 2·3) which gave a positive Beilstein test. (Found: C, 75·7; H, 9·9; Cl, 8·2. $C_{31}H_{49}O_2Cl$ required: C, 75·7; H, 10·1; Cl, 7·8 per cent.) λ_{max} at 203 nm (ϵ=4950).

Dechlorination of Methyl 3ξ-Chlorours-12-en-24-oate (I*h*)

A solution of the chloro-compound (100 mg) in ethanol (10 ml) was refluxed with Raney Ni (500 mg) for 3 hr. The Ni was removed by filtration and the filtrate evaporated to dryness to give a residue which crystallized from $CHCl_3$–methanol to yield methyl urs-12-en-24-oate (I*d*) as plates (60 mg), m.p. and mixed m.p. 170–172°, $[\alpha]_D$ +134° (*c*, 1·4).

Methyl 5:8α:9β-Trimethyl-10α-novursa-12,14-dien-24-oate (IX*b*)

(*a*) A solution of methyl 3α-hydroxyurs-12-en-24-oate (500 mg) in benzene (10 ml) was treated with P_2O_5 (1 g) and shaken for 24 hr. The reaction mixture was diluted with warm water and extracted with benzene. Isolation of the product, in the usual way, gave a gum which crystallized from methanol to yield *methyl 5:8α:9β-trimethyl-10α-novursa-12,14-dien-24-oate* (IX*b*) as needles (100 mg), m.p. 191–192°, $[\alpha]_D$ −110° (*c*, 2·5). (Found: C, 82·1; H, 10·6. $C_{31}H_{48}O_2$ required: C, 82·2; H, 10·7 per cent.) λ_{max} at 234 (ϵ=14,700), 241 (16,000) and 248 nm (10,500).

(*b*) A solution of methyl 3β-hydroxyurs-12-en-24-oate (400 mg) in benzene (10 ml) was treated with P_2O_5 (1 g) and shaken for 20 hr. The reaction mixture was diluted with warm water and extracted with benzene to give a residue which was dissolved in petrol–benzene (7:3, 50 ml) and filtered through a column of alumina (10 g). The column was washed with the same solvent mixture (300 ml) and the combined eluates evaporated to dryness. Crystallization of the residue from methanol gave the l-diene (IX*b*) as needles (40 mg), m.p. and mixed m.p. with above, 190–191°, $[\alpha]_D$ −118° (*c*, 0·7). λ_{max} at 234 (ϵ=14,400), 241 (15,500) and 248 nm (10,100).

Lithium Aluminum Hydride Reduction of Methyl 3α-Hydroxyurs-12-en-24-oate (I*f*)

A solution of methyl 3α-hydroxyurs-12-en-24-oate (1·7 g) in ether (300 ml) was refluxed with $LiAlH_4$ (2 g) for 8 hr. The product was isolated in the usual way and crystallized from methanol to yield 3α,24-dihydroxyurs-12-ene (XI) as blades (1·4 g), m.p. 184–185°, $[\alpha]_D$ +69° (*c*, 5·7). (Found: C, 81·1; H, 11·4.

$C_{30}H_{50}O_2$ required: C, 81·4; H, 11·4 per cent.) Beton, Halsall and Jones[9] report m.p. 183–185° and $[\alpha]_D$ +73° though unable to obtain satisfactory analytical figures for this diol which was characterized by conversion to its diacetate, m.p. 161–163°, $[\alpha]_D$ +34°. Acetylation of the diol (XI) using pyridine–acetic anhydride on the steam-bath for 30 min gave 3α,24-diacetoxyurs-12-ene which crystallized from methanol as plates, m.p. 165–167°, $[\alpha]_D$ +40° (*c*, 2·3). (Found: C, 77·9; H, 10·0. $C_{34}H_{54}O_4$ required: C, 77·5; H, 10·3 per cent.) Attempted reduction of the diol (XI) to *epi-α*-amyrin using *p*-toluene sulfonyl chloride in pyridine followed by $LiAlH_4$[41] yielded no crystallizable products.

Lithium Aluminum Hydride Reduction of 3*α-Hydroxyurs*-12-*en*-24-*oic Acid* (I*b*)

A solution of 3α-hydroxyurs-12-en-24-oic acid (1 g) in ether (250 ml) was refluxed with $LiAlH_4$ (1 g) for 3 hr. The product, isolated in the usual way, was dissolved in pyridine and heated with acetic anhydride on the steam-bath for 30 min. Isolation of the acetylated product yielded 3α,24-diacetoxyurs-12-ene which crystallized from methanol as plates (350 mg), m.p. and mixed m.p. with the diol diacetate above, 165–167°, $[\alpha]_D$ +40° (*c*, 3·2).

Methyl 3-*Oxours*-12-*en*-24-*oate* (X)

A solution of methyl 3α-hydroxyurs-12-en-24-oate (2 g) in pyridine (20 ml) was treated with chromic trioxide (2 g) in pyridine (20 ml) and allowed to stand at room temperature for 40 hr. The product was isolated by extraction with benzene–ether (1:1) in the usual way and crystallized from methanol to yield the keto-methyl ester (X) as prismatic needles (1·7 g), m.p. 159–160°, $[\alpha]_D$ +111° (*c*, 2·7). (Found: C, 79·4; H, 10·0. $C_{31}H_{48}O_3$ required: C, 79·4; H, 10·3 per cent.) λ_{max} at 206 nm (ϵ=3180) (ϵ_{210} 1830, ϵ_{215} 183). Simpson and Williams[20] give m.p. 159–160° and Trost[40] gives m.p. 155–157°; neither paper quotes optical rotation values.

Methyl 3*β-Hydroxyurs*-12-*en*-24-*oate* (I*a*)

(*a*) A solution of methyl 3-oxours-12-en-24-oate (1 g, m.p. 159–160°, $[\alpha]_D$ +111°) in acetic acid (100 ml) was added to a freshly reduced suspension of Pt (from 400 mg PtO_2) in acetic acid (20 ml) and the mixture shaken with H_2 for 4 hr. The reaction was diluted with $CHCl_3$ and filtered. Evaporation of the filtrate gave a residue which crystallized from methanol to yield I*a* as large plates (300 mg), m.p. 175–177°, $[\alpha]_D$ +130° (*c*, 2·8). (Found: C, 78·9; H, 10·8. $C_{31}H_{50}O_3$ required: C, 79·0; H, 10·6 per cent). Acetylation using pyridine–acetic anhydride on the steam-bath gave methyl 3β-acetoxyurs-12-en-24-oate which crystallized from $CHCl_3$–methanol as prismatic needles, m.p. 201–203°, $[\alpha]_D$ +90° (*c*, 1·8). (Found: C, 77·2; H, 10·1. $C_{33}H_{52}O_4$ required: C, 77·3; H, 10·2 per cent.) Hydrolysis using 5 per cent methanolic KOH for 1 hr gave methyl 3β-hydroxyurs-12-en-24-oate, m.p. and mixed m.p. 174–176°, $[\alpha]_D$ +130° (*c*, 1·9). Mixtures of methyl 3α-hydroxyurs-12-en-24-oate, m.p. 199–201°, and methyl 3β-hydroxyurs-12-en-24-oate, m.p. 175–177°, and methyl 3α-acetoxyurs-12-en-24-oate, m.p. 198–199°, and methyl 3β-acetoxyurs-12-en-24-oate, m.p. 201–203°, showed m.p. depressions, melting over the range 165–170° in both cases.

(*b*) A solution of methyl 3-oxours-12-en-24-oate (500 mg, m.p. 159–160°, $[\alpha]_D$ +111°) in ethanol (50 ml) was treated with $NaBH_4$ (70 mg), allowed to stand for 1 hr and diluted with water. Isolation of the product using ether in the usual way gave a product which was dissolved in benzene (100 ml) and filtered through a column of alumina (10 g). The column was washed with benzene (500 ml) and the combined eluates on evaporation gave only a trace of oily material. The column was stripped using ether–acetone–methanol (1:1:1, 300 ml) and evaporation of the eluate gave a crystalline residue (370 mg). Recrystallization from methanol yielded I*a* as plates, m.p. and mixed m.p. 175–177°, $[\alpha]_D$ +128° (*c*, 1·9). Beton, Halsall and Jones[9] crystallized this compound from aqueous methanol and obtained m.p. 155–157°, $[\alpha]_D$ +123°. This m.p. discrepancy could be due to hydrate formation or a typographical error. Acetylation using pyridine–acetic anhydride gave methyl 3β-acetoxyurs-12-en-24-oate, m.p. and mixed m.p. 200–201°, $[\alpha]_D$ +90° (*c*, 1·1). Beton, Halsall and Jones[9] observed m.p. 182–185° $[\alpha]_D$ +104°.

Lithium Aluminum Hydride Reduction of Methyl 3*β-Hydroxyurs*-12-*en*-24-*oate*

(*a*) A solution of methyl 3β-hydroxyurs-12-en-24-oate (300 mg) in ether (200 ml) was treated with $LiAlH_4$ (500 mg), allowed to stand at room temperature for 24 hr, refluxed for 3 hr and finally allowed to stand at room temperature for a further 24 hr. The product, isolated in the usual way, crystallized from methanol to yield 3β,24-dihydroxyurs-12-ene (XII) as prisms (200 mg), m.p. 230–232°, $[\alpha]_D$ +102° (*c*, 2·3). (Found: C, 81·2; H, 11·3. $C_{30}H_{50}O_2$ required: C, 81·4; H, 11·4 per cent.) Beton, Halsall and Jones[9] recorded m.p. 223–225° $[\alpha]_D$ +84° for this diol.

(*b*) A solution of methyl 3-oxours-12-en-24-oate (190 mg) in ether (100 ml) was treated with $LiAlH_4$ (500 mg) and allowed to stand overnight. The product was isolated in the usual way and crystallized from methanol to yield 3β,24-dihydroxyurs-12-ene as prisms (90 mg), m.p. and mixed m.p. 228–230°, $[\alpha]_D$ +103° (*c*, 1·3). Acetylation of the diol using pyridine–acetic anhydride on the steam-bath for 30 min gave a product which crystallized from methanol to yield 3β,24-diacetoxyurs-12-ene as needles, m.p. 187–188°, $[\alpha]_D$ +80° (*c*, 1·0). (Found: C, 77·3; H, 10·3. $C_{34}H_{54}O_4$ required: C, 77·5; H, 10·3 per cent.) Hydrolysis of the diol diacetate using 10 per cent metahnolic KOH for 30 min gave 3β, 24-dihydroxyurs-12-ene as prisms from methanol, m.p. and mixed m.p. 230–232°, $[\alpha]_D$ +102° (*c*, 2·6).

3α,24-*Ethylidenedioxyurs*-12-*ene* (XVI)

A solution of 3α,24-dihydroxyurs-12-ene (500 mg, m.p. 184–185°, $[\alpha]_D$ +69°) in ether (30 ml) was treated with acetaldehyde (5 ml) and conc. H_2SO_4 (0·2 ml) added. The solution was allowed to stand at room temperature for 20 hr, treated with Na_2CO_3, diluted with water, and the product isolated using ether. The product obtained crystallized from methanol to yield 3α,24-*ethylidenedioxyurs*-12-*ene* as long needles (200 mg), m.p. 194–195°, $[\alpha]_D$ +114° (*c*, 3·4). (Found: C, 82·0; H, 11·2. $C_{32}H_{52}O_2$ required: C, 82·0; H, 11·2 per cent.) Hydrolysis of this acetal (100 mg) could be effected by refluxing with conc. HCl (0·2 ml) in ethanol (10 ml) for 1 hr. The product, isolated in the usual way, crystallized from methanol to yield XI as plates (50 mg), m.p. and mixed m.p. 184–185°, $[\alpha]_D$ +68° (*c*, 0·8).

3β,24-*Ethylidenedioxyurs*-12-*ene* (XV)

A solution of 3β,24-dihydroxyurs-12-ene (150 mg, m.p. 230–232°, $[\alpha]_D$ +102°) in ether (10 ml) was treated with acetaldehyde (2 ml) and conc. H_2SO_4 (0·1 ml) added. The solution was allowed to stand at room temperature for 20 hr, treated with Na_2CO_3, diluted with water and extracted with ether. Evaporation of the ethereal extract gave a residue which was dissolved in benzene (20 ml) and filtered through a column of alumina (10 g). The column was washed with benzene (500 ml) and the eluate evaporated to dryness. Crystallization of the residue from methanol yielded 3β,24-*ethylidenedioxyurs*-12-*ene* as prisms (90 mg), m.p. 166–167°, $[\alpha]_D$ + 67° (*d*, 2·0). (Found: C, 82·2; H, 11·3. $C_{32}H_{52}O_2$ required: C, 82·0; H, 11·2 per cent.)

Partial Hydrolysis of 3α,24-*Diacetoxyurs*-12-*ene*

A solution of 3α,24-diacetoxyurs-12-ene (3·4 g, m.p. 165–167°, $[\alpha]_D$ +40°) in ethanol (200 ml) and dioxan (75 ml) was treated with a solution of KOH (400 mg) in water (6 ml) and refluxed for 1 hr. The mixture was allowed to stand at room temperature overnight, diluted with water and extracted with $CHCl_3$. Evaporation of the $CHCl_3$ solution (dried over sodium sulfate) gave a gum (3 g) which was dissolved in petrol–benzene (1:1, 100 ml) and chromatographed on alumina (150 g). Elution with petrol (750 ml), petrol–benzene (9:1, 200 ml; 7:3, 200 ml; 1:1, 200 ml; 1:4, 200 ml), benzene (1500 ml) and benzene–ether (9:1, 250 ml; 1:1, 250 ml) gave only traces of uncrystallizable material. Elution with ether (2000 ml) gave a fraction which crystallized from methanol to yield 3α-*acetoxy*-24-*hydroxyurs*-12-*ene* (?) as prismatic needles (700 mg), m.p. 190–192°, $[\alpha]_D$ +82° (*c*, 1·2). (Found: C, 79·03; H, 10·6. $C_{32}H_{52}O_3$ required: C, 79·28; 10·8 per cent.) Stripping of the column with acetone–methanol (1:1, 2000 ml) gave a gummy solid (2·2 g) which on acetylation with pyridine–acetic anhydride on the steam-bath gave the diol diacetate starting material which crystallized from methanol as plates (2·37 g), m.p. and mixed m.p. 164–165°, $[\alpha]_D$ +38° (*c*, 2·5).

Lithium Aluminum Hydride Reduction of Methyl 3α-*Hydroxyolean*-12-*en*-24-*oate*

A solution of methyl 3α-hydroxyolean-12-en-24-oate (500 mg) in ether (200 ml) was treated with $LiAlH_4$ (1 g), allowed to stand overnight, and refluxed for 2 hr. The product was isolated in the usual way and crystallized from methanol to yield 3α,24-*dihydroxyolean*-12-*ene* as prismatic needles (350 mg), m.p. 248–250°, $[\alpha]_D$ +88° (*c*, 1·5). (Found: C, 81·5; H, 11·2. $C_{30}H_{50}O_2$ required: C, 81·4; H, 11·4 per cent.) A solution of the diol in pyridine was acetylated in the usual way to yield 3α,24-*diacetoxyolean*-12-*ene* which crystallized from methanol as plates, m.p. 225–226°, $[\alpha]_D$ +38° (*c* 1·7). (Found: C, 77·3; H, 10·3. $C_{34}H_{54}O_4$ required: C, 77·5; H, 10·3 per cent.) Hydrolysis of the diacetate using $LiAlH_4$ in ether reafforded 3α,24-dihydroxyolean-12-ene, m.p. and mixed m.p. 248–250°, $[\alpha]_D$ +88° (*c*, 2·3).

Lithium Aluminum Hydride Reduction of Methyl 3β-*Hydroxyolean*-12-*en*-24-*oate*

A solution of methyl 3β-hydroxyolean-12-en-24-oate (500 mg) in ether (500 ml) was refluxed with $LiAlH_4$ (1 g) for 2 hr and allowed to stand overnight at room temperature. The product, isolated in the usual way, crystallized from $CHCl_3$–methanol as needles (400 mg), m.p. 246–248°, $[\alpha]_D$ +90° (*c*, 1·1). Meyer, Jeger and Ruzicka[23] quote m.p. 248–250°, $[\alpha]_D$ +87°. A specimen on admixture with the diol, m.p. 248–250°, $[\alpha]_D$ +88°, obtained by the $LiAlH_4$ reduction of methyl 3α-hydroxyolean-12-en-24-oate showed no m.p. depression. Acetylation of the product in the usual way yielded 3β,24-diacetoxyolean-12-ene which crystallized from $CHCl_3$–methanol as needles, m.p. 187–189°, $[\alpha]_D$ +76° (*c*, 1·6). Chromatography and recrystallization failed to bring the physical constants into closer conformity with those of Meyer, Jeger and Ruzicka,[23] who reported m.p. 194–195°, $[\alpha]_D$ +74°.

Methyl 3β-*Acetoxyolean*-12-*en*-24-*oate*

Acetylation of methyl 3β-hydroxyolean-12-en-24-oate using pyridine–acetic anhydride on the steam-bath gave the acetate as needles from $CHCl_3$–methanol, m.p. 215–217°, $[\alpha]_D$ +102° (*c*, 1·0). (Found: C, 77·4; H, 9·8. $C_{33}H_{52}O_4$ required: C, 77·3; H, 10·2 per cent.) Hydrolysis using 5 per cent methanolic KOH for 1 hr afforded the parent alcohol, m.p. and mixed m.p. 191–193°, $[\alpha]_D$+ 124° (*c*, 1·6).

Methyl 3α-*Benzoxyurs*-12-*en*-24-*oate* (I*e*)

A solution of 3α-hydroxyurs-12-en-24-oate (600 mg) in pyridine (10 ml) was heated with benzoyl chloride (5 ml) on the steam-bath for 2 hr, diluted with water and allowed to stand overnight. Isolation of the product in the usual way afforded I*e* as prismatic rods (515 mg), m.p. 155–156°, $[\alpha]_D$ +48° (*c*, 1·1) after crystallization from $CHCl_3$–methanol. (Found: C, 79·5; H, 9·4. $C_{38}H_{54}O_4$ required: C, 79·4; H, 9·5 per cent.)