516. *Triterpenoids. Part LVIII.* The Synthesis of Isoursenol, the Ursane Analogue of Taraxerol.*

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The conversion of α-amyrin (VI; R = H) into isoursenol (X; R = H) is described; the behaviours of taraxerol and isoursenol on oxidation by peracid are compared.

MOST of the naturally occurring pentacyclic triterpenoids can be classified in the oleanane, ursane, and lupane groups although it is now appreciated that this division is biogenetically without significance, all three groups being unexceptionally derivable from the prelupeol cation (I).[1] Further, simple derivatives of ursane and lupane have been converted into oleanane derivatives. Although the naturally occurring ketones, taraxerone[2] (II), glutinone[3] (alnusenone) (III), and friedelin[4] (IV) do not have an oleanane

* Part LVII, *J.*, 1959, 216.

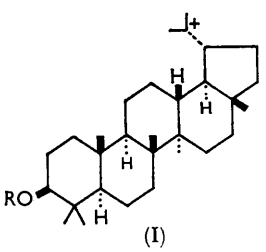
[1] Ruzicka, *Experientia*, 1953, **9**, 357; Eschenmoser, Ruzicka, Jeger, and Arigoni, *Helv. Chim. Acta*, 1955, **38**, 1890; Ruzicka, "Perspectives in Organic Chemistry," ed. Todd, Interscience Publ. Inc., New York, 1956.

[2] Beaton, Spring, Stevenson, and Stewart, *J.*, 1955, 2131.

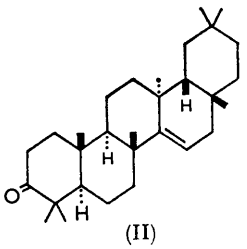
[3] Beaton, Spring, Stevenson, and Stewart, *Tetrahedron*, 1958, **2**, 246.

[4] Brownlie, Spring, Stevenson, and Strachan, *J.*, 1956, 2419; Corey and Ursprung, *J. Amer. Chem. Soc.*, 1956, **78**, 5041; Takahashi and Ourisson, *Bull. Soc. chim. France*, 1956, 353.

skeleton, they have been converted by acid-isomerisation of derived ethylenic hydrocarbons into a mixture of olean-13(18)-ene and 18α-olean-12-ene. They can consequently be regarded as members of a new sub-group, the " modified oleanane " group, which can be defined as consisting of pentacyclic triterpenes which by acid-isomerisation of suitable derivatives yield an oleanane derivative by migration of angular methyl groups or hydrogen atoms by a series of formal 1,2-shifts from and to axial conformations.



(I)



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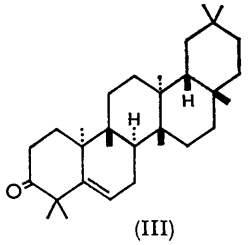

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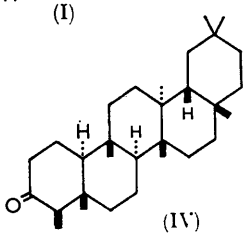

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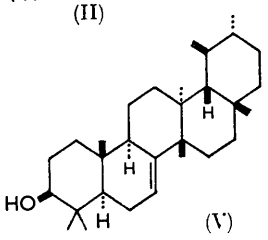


(V)

The existence of the modified oleanane group has been readily rationalized in current theories of biogenesis. On biogenetic grounds, the existence of a " modified ursane " group would also be considered extremely probable, although no ursane analogues of taraxerone, glutinone, or friedelin have been described. The report by Lahey and Leeding [5] of the isolation and structure of bauerenol (ilexol) (V) establishes it as the first naturally occurring member of the " modified ursane " class. The partial synthesis from α-amyrin (VI; R = H) of isoursenol (X; R = H), the ursane analogue of taraxerol and second member of the modified ursane group, is now reported.

The synthetic route corresponded to that developed for the partial synthesis of taraxerol from β-amyrin.[2] The conversion of 12-oxours-9(11)-en-3β-yl acetate (VII) into 12-oxoisoursa-9(11),14-dien-3β-yl acetate (VIII) by selenium dioxide [6] was improved by curtailing the reaction time. The subsequent reduction by lithium in liquid ammonia and ether to give 12-oxoisours-14-en-3β-ol (IX) [7] was similarly improved. Application of the Barton modification of Huang-Minlon reduction to this alcohol, followed by acetylation, gave isoursenyl acetate (X; R = Ac) in over 50% yield; the alcohol (X; R = H) and benzoate (X; R = Bz) were prepared in the usual way. Under certain conditions of the forcing reduction, the intermediate 12-oxoisours-14-en-3β-yl acetate hydrazone was also isolated; it was characterized as the acetylhydrazone.

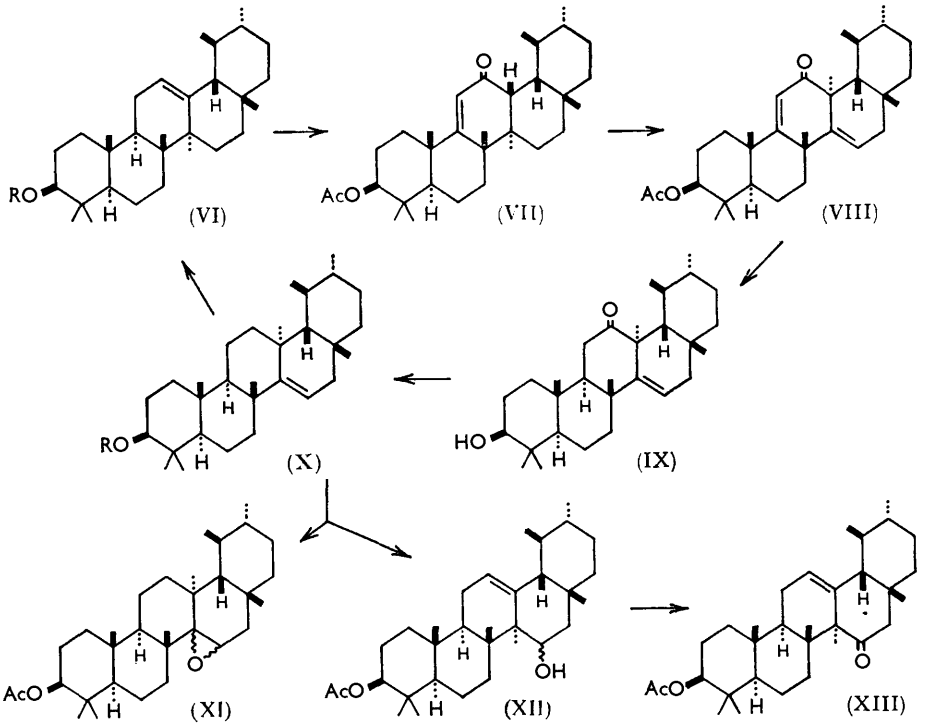
The physical constants of isoursenol and its derivatives are similar to those of calendenol, $C_{30}H_{50}O$, and its derivatives, isolated by Kasprzyk,[8] but direct comparison with a sample provided by Dr. Kaspryzk established the dissimilarity of these substances.

The behaviour of taraxeryl acetate towards mineral acid—molecular rearrangement to β-amyrin acetate—is paralleled by the clean conversion of isoursenyl acetate (X; R = Ac) into α-amyrin acetate (VI; R = Ac) under the same conditions.

Treatment of isoursenyl acetate with perbenzoic acid yielded two isomeric products,

[5] Lahey and Leeding, *Proc. Chem. Soc.*, 1958, 342.
[6] Ruzicka, Rüegg, Volli, and Jeger, *Helv. Chim. Acta*, 1947, **30**, 140; Easton and Spring, *J.*, 1955, 2120.
[7] Beaton, Easton, Macarthur, Spring, and Stevenson, *J.*, 1955, 3992.
[8] Kasprzyk, *Prace Glŏwnego Inst. Chem. Przemysl*, 1951, No. 2, 39; *Chem. Abs.*, 1953, **47**, 6918.

$C_{32}H_{52}O_3$, readily separated by chromatography on alumina. The more readily eluted product shows no high-intensity ultraviolet absorption, does not give a colour with tetranitromethane, and is considered to be isoursenyl acetate oxide (XI). The second product, however, possesses a double bond (yellow colour with tetranitromethane, ultraviolet absorption) and a hydroxyl group. In analogy with the behaviour of taraxeryl acetate for which the structures of the peracid oxidation products were rigorously established, the second product is tentatively considered to be 3β-acetoxyurs-12-en-15ξ-ol (XII). This



diol monoacetate is also readily obtained by the action of mineral acid on the oxide (XI) in chloroform–methanol or acetic acid, and with the chromium trioxide–pyridine reagent gave a non-conjugated ketone formulated here as 15-oxours-12-en-3β-yl acetate (XIII).

Although in this behaviour towards perbenzoic acid isoursenyl acetate resembles taraxeryl acetate, structures of the products cannot be assigned with certainty, for the following reasons. The diol monoacetate, formulated as (XII), resists acetylation under conditions whereby 3β-acetoxyolean-12-en-15α-ol is acetylated. Further, the rotatory disperion curve of the derived ketone, formulated as (XIII), shows a positive Cotton effect in contrast to the negative Cotton effect shown by the oleanan-15-one derivative, 15-oxoerythrodiol diacetate.[9] Although these differences between the two series are possibly explicable by conformational distortion in the C/D/E region of the ursane series, as compared with the oleanane series, the possibility that the molecular rearrangement undergone by the isoursenyl acetate oxide on treatment with mineral acid is not of isoursenol ⟶ α-amyrin type has not been excluded.

Experimental

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

[9] Djerassi, Osiecki, and Closson, *J. Amer. Chem. Soc.*, 1959, **81**, 4587.

12-Oxoisoursa-9(11),14-dien-3β-yl Acetate (VIII).—A solution of 12-oxours-9(11)-en-3β-yl acetate (36 g.) in glacial acetic acid (580 c.c.) was refluxed for 2 hr. with selenium dioxide (54 g.). The product, isolated in the usual way, crystallized from methanol to give needles (23 g.), m. p. 220—221°, $[\alpha]_D$ +14·5° (*c* 6·1), a solution of which in benzene–light petroleum (1 : 4; 1 l.) was chromatographed on alumina (1 kg.). Elution with light petroleum–benzene (3 : 2, 4 l.; 1 : 1, 2·5 l.; 2 : 3, 3·5 l.) yielded 12-oxoisoursa-9(11),14-dien-3β-yl acetate (17·5 g.) as needles (from methanol), m. p. 218—220°, $[\alpha]_D$ +8·5° (*c* 3·3), $\lambda_{max.}$ 2370 Å (ε 10·000) (lit.,[6] m. p. 221—222°, $[\alpha]_D$ +8°).

12-Oxoisours-14-en-3β-ol (IX).—A solution of 12-oxoisoursa-9(11),14-dien-3β-yl acetate (2·0 g.) in dry ether (100 c.c.) was added in 2 min. with stirring to a solution obtained by adding lithium (600 mg.) to liquid ammonia (400 c.c.), and the mixture was stirred for a further 3 min. After the addition of acetone, the product was isolated in the usual manner and crystallized from methanol, to give 12-oxoisours-14-en-3β-ol (0·8 g.) as needles, m. p. 230—231°, $[\alpha]_D$ −39° (*c* 1·4) (lit.,[7] m. p. 233—234°, $[\alpha]_D$ −39°), ε 5500 at 2050 Å, giving a yellow colour with tetranitromethane.

Isours-14-en-3β-yl Acetate (X; R = Ac).—12-Oxoisours-14-en-3β-ol (1·0 g.) was added to a solution obtained by the addition of sodium (2·5 g.) to freshly distilled diethylene glycol (125 c.c.) and the mixture heated to 180°. Anhydrous hydrazine 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 ether, was treated on the steam-bath with acetic anhydride and pyridine. The product was dissolved in light petroleum, filtered through alumina (40 g.), and crystallized from methanol to give *isours-14-en-3β-yl acetate* (250 mg.) as plates, m. p. 214—216°, $[\alpha]_D$ +36° (*c* 1·3) (Found: C, 81·9; H, 11·4. $C_{32}H_{52}O_2$ requires C, 82·0; H, 11·2%). It gives a yellow colour with tetranitromethane.

Elution with light petroleum–benzene (9 : 1; 200 c.c.) gave 12-oxoisours-14-en-3β-yl acetate (300 mg.), m. p. and mixed m. p. 227—228°, $[\alpha]_D$ −27° (*c* 0·8).

The residue obtained on elution with methanol–benzene crystallized from methanol, to give *12-oxoisours-14-en-3β-yl acetate hydrazone* as needles (350 mg.), m. p. 245—247°, $[\alpha]_D$ +19° (*c* 1·2), $\lambda_{max.}$ 2120 and 2370 Å (ε 12,400 and 10,000), ν (in CS_2) 3175, 1736, and 1675 cm.$^{-1}$ (Found: C, 76·9, 77·3; H, 10·4, 10·1; N, 5·2. $C_{32}H_{52}N_2O_2$ requires C, 77·4; H, 10·55; N, 5·6%). It gives a yellow colour with tetranitromethane. Refluxing the hydrazone with acetic anhydride for 2 hr. gave the *acetylhydrazone* as prisms, m. p. 201—202°, $[\alpha]_D$ +35° (*c* 1·4), $\lambda_{max.}$ 2040 and 2390 Å (ε 8400 and 5000), ν (in CS_2) 1736, 1718, and 1667 cm.$^{-1}$ (Found: C, 75·6; H, 10·1; N, 5·0. $C_{34}H_{54}N_2O_3$ requires C, 75·8; H, 10·1; N, 5·2%).

Isoursenyl acetate was isolated in 55% yield without contamination by hydrazone if the entire reduction process was repeated with fresh hydrazine.

Isours-14-en-3β-ol (X; R = H).—A solution of isoursenyl acetate (250 mg.) in ether (150 c.c.) was refluxed with lithium aluminium hydride (250 mg.), and the product, isolated in the usual way, crystallized from methanol to give *isours-14-en-3β-ol* as needles, m. p. 195—197°, $[\alpha]_D$ +30° (*c* 1·6) (Found: C, 84·1; H, 11·6. $C_{30}H_{50}O$ requires C, 84·4; H, 11·8%). Reacetylation gave isoursenyl acetate, m. p. and mixed m. p. 214—216°, $[\alpha]_D$ +35° (*c* 1·1). Benzoylation yielded *isours-14-en-3β-yl benzoate*, as blades (from chloroform–methanol), m. p. 237—239°, $[\alpha]_D$ +55° (*c* 2·0) (Found: C, 83·3; H, 10·3. $C_{37}H_{54}O_2$ requires C, 83·7; H, 10·25%).

Conversion of Isoursenyl Acetate into α-Amyrin Acetate.—To a suspension of isoursenyl acetate (25 mg.) in acetic acid (15 c.c.) at 100° was added concentrated hydrochloric acid (2 c.c.). After the mixture had been heated for 25 min., the solvent was removed under reduced pressure. The residue crystallized from methanol to give α-amyrin acetate (urs-12-en-3β-yl acetate), plates, m. p. and mixed m. p. 221—223°, $[\alpha]_D$ +77° (*c* 0·7).

Action of Perbenzoic Acid on Isoursenyl Acetate.—A solution of isoursenyl acetate (750 mg.) in chloroform (10 c.c.) was treated with a fresh solution of perbenzoic acid (2·0 mol.) in chloroform and set aside at 0° for 18 hr., then washed with sodium hydrogen carbonate solution and water, dried (Na_2SO_4), and evaporated below 15°. The residue was chromatographed in light petroleum–benzene (9 : 1; 100 c.c.). Elution with light petroleum–benzene (4 : 1; 300 c.c.) gave a solid which recrystallized from chloroform–methanol to give *14ξ,15ξ-epoxyisoursan-3β-yl acetate* (XI) (320 mg.), plates, m. p. 249—251°, $[\alpha]_D$ +57° (*c* 1·0) (Found: C, 79·5; H, 10·8. $C_{32}H_{52}O_3$ requires C, 79·3; H, 10·8%). It gives no colour with tetranitromethane and shows no high-intensity ultraviolet absorption above 2000 Å. Elution with benzene (300 c.c.) yielded a

solid which crystallized from aqueous methanol to give 3β-*acetoxyurs*-12-*en*-15ξ-*ol* (XII), needles, m. p. 223—225°, $[\alpha]_D$ +75° (*c* 1·5) (Found: C, 79·0; H, 11·1. $C_{32}H_{52}O_3$ requires C, 79·3; H, 10·8%). It gives a yellow colour with tetranitromethane. It was recovered unchanged on attempted acetylation at room or steam-bath temperature.

Acid Rearrangement of 14ξ,15ξ-*Epoxyisoursan*-3β-*yl Acetate*.—(*a*) 2N-Sulphuric acid (5 c.c.) was added to a solution of the epoxide (100 mg.) in acetic acid (100 c.c.), and the mixture heated on the steam-bath for 30 min. The product, isolated in the usual way, was chromatographed in light petroleum (10 c.c.) on alumina, and the fraction eluted by benzene–ether (9 : 1; 300 c.c.) crystallized from aqueous methanol to give 3β-acetoxyurs-12-en-15ξ-ol (45 mg.), m. p. and mixed m. p. 222—225°, $[\alpha]_D$ +73° (*c* 0·8). (*b*) Concentrated hydrochloric acid (4 c.c.) and water (4 c.c.) were added to a solution of the epoxide (200 mg.) in methanol (100 c.c.) and chloroform (30 c.c.). The mixture was set aside at room temperature for 18 hr., and the product isolated in the usual manner and crystallized from aqueous methanol to give the diol monoacetate (125 mg.), m. p. and mixed m. p. 222—225°, $[\alpha]_D$ +75° (*c* 1·1).

15-*Oxours*-12-*en*-3β-*yl Acetate* (XIII).—A solution of 3β-acetoxyurs-12-en-15ξ-ol (275 mg.) in pyridine (10 c.c.) was added to a solution of chromium trioxide (1·0 g.) in pyridine (10 c.c.) and set aside for 16 hr. The product was isolated by means of ether and crystallized from aqueous methanol to give 15-*oxours*-12-*en*-3β-*yl acetate* (195 mg.), needles, m. p. 220—222° $[\alpha]_D$ +128°, +129° (*c* 0·8, 0·85) (Found: C, 79·4; H, 10·4. $C_{32}H_{50}O_3$ requires C, 79·6; H, 10·4%). It gives a yellow colour with tetranitromethane. Rotatory dispersion in dioxan (*c* 0·050) (kindly determined by Professor C. Djerassi): $[\alpha]_{700}$ +43°; $[\alpha]_{589}$ +62°; $[\alpha]_{321}$ +450°; $[\alpha]_{275}$ −700°.

We thank the Department of Scientific and Industrial Research for a Maintenance Award (to W. L.). One of us (R. S., present address, Department of Chemistry, Brandeis University, Waltham, Mass., U.S.A.) acknowledges support from the Research Corporation and the National Institute of Arthritis and Metabolic Diseases, Public Health Service, U.S.A.

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[*Received, November 1st,* 1960.]