576. *The Stereochemistry of Arjunolic Acid.*

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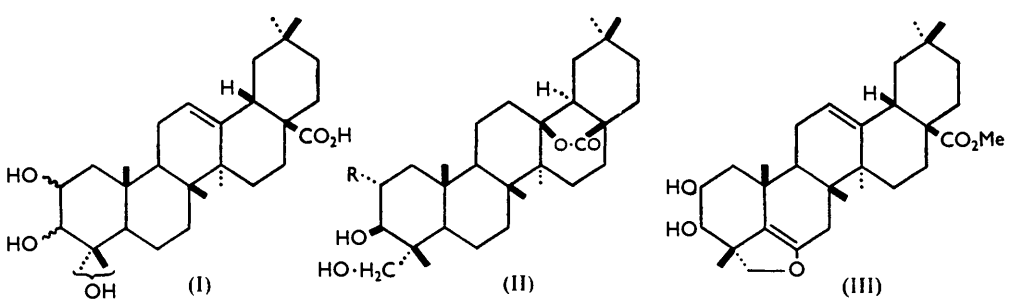
Arjunolic acid has been converted into 18α-hederagenin lactone, thereby demonstrating the conformation of the groups at positions 3 and 4. Stereospecific reduction, primarily of 2-oxo-18α-arjunolic lactone, indicate that the 2-hydroxyl substituent has the equatorial (α)-conformation; it follows that arjunolic acid is 2α : 3β : 23-trihydroxyolean-12-en-28-oic acid.

ARJUNOLIC ACID was discovered in *Terminalia arjuna* and its constitution shown [1] to be 2 : 3 : 23(or 24)-trihydroxyolean-12-en-28-oic acid (I). It has now been found in the wood, abura, of the West African tree, *Mitragyna ciliata*, from which it is conveniently isolated by ether-extraction.

When discussing the relative orientation of the secondary 2- and 3-hydroxyl groups of arjunolic acid it was suggested [1] that these substituents had the *trans*-equatorial (2α : 3β)-configuration, but no rigid support for this conclusion was then available, nor was there any evidence as to the conformation of the methyl and the hydroxymethyl groups at position 4. Experimental evidence has now been obtained which confirms our earlier opinions and establishes that the hydroxymethyl group has the equatorial (α-)conformation. The relevant observations are (i) the conversion of 18α-arjunolic lactone (II;

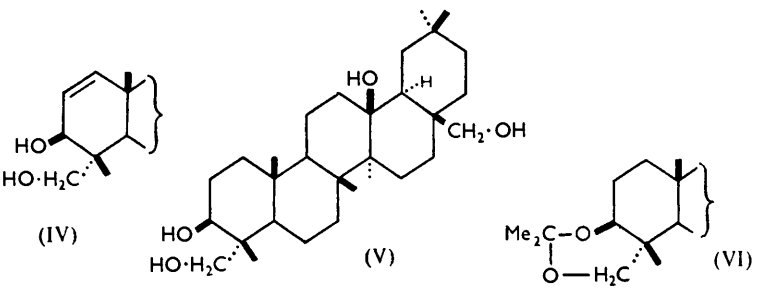


R = OH) into 18α-hederagenin lactone (II; R = H), the spatial arrangements at $C_{(3)}$ and $C_{(4)}$ then following from the well-known configuration of hederagenin,[2] and (ii) the results of stereospecific reduction of 2-oxoarjunolic lactone and the relative periodate oxidation rates of the two isomeric reduction products. Independent evidence bearing on

[1] King, King, and Ross, *J.*, 1954, 3995.
[2] Vogel, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1951, **34**, 2321.

the conformation of the hydroxymethyl group was obtained in our work on terminolic acid (6β-hydroxyarjunolic acid),[3] since the formation from methyl terminonate of the anhydroterminonate formulated as (III), appeared to necessitate for the hydroxymethyl substituent an equatorial configuration. In conformity, Djerassi *et al.*[4] have shown, by a study of its rate of oxidation by lead tetra-acetate, that arjunolic acid is properly represented as a 2α : 3β-diol and quote structure (III) suggested for methyl anhydroterminonate as proof of the position of the third hydroxy-group at $C_{(23)}$.

Initial attempts to remove the 2-hydroxy-substituent in arjunolic lactone were unsuccessful: 2-oxoarjunolic lactone (II; R = O) was available through the previously unreported *iso*propylidenearjunolic lactone but was unstable to the conditions of the Huang-Minlon reduction and we were not able to convert it into a thioketal; pyrolysis of 2-benzoylarjunolic lactone (II; R = BzO) afforded a mixture which undoubtedly contained some of the olefin (IV) but catalytic reduction resulted mainly in hydrogenolysis, presumably of the 3-hydroxyl group in the allylic position. Success was achieved when 2-toluene-*p*-sulphonyl*iso*propylidenearjunolic lactone was reduced with lithium aluminium hydride. This reagent simultaneously reduced the lactone ring, and the product first isolated was a tetrol, presumably (V). Reconversion of this into the *iso*propylidene derivative for characterisation afforded a compound, the composition of which indicated partial loss of oxygen presumably by dehydration of the tertiary hydroxy-group. The structure of the tetrol and, in particular, the configuration of all four hydroxy-groups was established when hederagenin lactone diacetate gave an identical product on reduction with lithium aluminium hydride. Further proof of the configuration at positions 3 and 4 followed from the oxidation of the *iso*propylidene-diol (VI), obtained directly from the



*iso*propylidenetoluene-*p*-sulphonylarjunolic lactone, by permanganate to a lactone which was isolated as the diacetate and proved to be identical with hederagenin lactone diacetate.

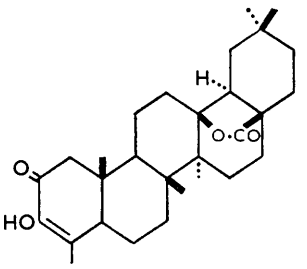
Before this direct proof of structure strong evidence for the 23-position of the primary hydroxy-group was gained from molecular-rotation considerations. The diosphenol (VII) obtained from arjunolic lactone [1] was reduced with sodium in alcohol to give, presumably, 2-hydroxyhedragenin lactone (VIII) whose molecular rotation was +128°. This corresponds to a change of +98° for the elimination of the CH_2·OH group from arjunolic lactone. This value agrees with the value of +103° for the rotation change in passing from methyl hederagenin to methyl hedragenin.

The β-equatorial orientation of the 3-hydroxy-group is further confirmed by the observation that diacetyl-3-oxoarjunolic lactone [1] is reduced by sodium borohydride to diacetylarjunolic lactone. It is well established that metal-hydride reduction of 3-oxo-groups in triterpenes gives predominantly the equatorial alcohol (the alkali-instability of the monoketone derived from arjunolic acid made it impossible to reduce by the more stereospecific sodium–alcohol). Further the absorption maximum shown by 2-oxo-arjunolic lactone (see above) at 270 mμ is at shorter wavelength than would be expected

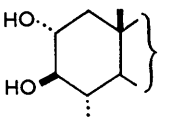
[3] King and King, *J.*, 1956, 4469.
[4] Djerassi, Thomas, Livingston, and Thompson, *J. Amer. Chem. Soc.*, 1957, **79**, 5292.

for a *cyclo*hexanone and it has been established [5] that the presence of a vicinal equatorial hydroxyl substituent shifts the absorption maximum of a carbonyl group by about 12 mμ to shorter wavelengths.

The stereochemistry at positions 3 and 4 having been established it remained only to fix the orientation at position 2. Here the evidence is not so direct but appears to be conclusive. Reduction of 2-oxoarjunolic lactone by sodium borohydride and by sodium in alcohol afforded different products which must be the pair of epimeric 2-alcohols. Sodium in alcohol produced arjunolic lactone: this method of reduction would be expected



(VII)



(VIII)

to give the thermodynamically more stable isomer and in the 2-position this should be the 2α-equatorial alcohol. Conversely metal-hydride reduction of sterically hindered ketones often gives the axial alcohol. 2-Oxoarjunolic lactone fails to give ketonic derivatives, so it is reasonable to assume that the borohydride reduction product (2-*epi*arjunolic lactone) consists of the 2β-axial isomer. In agreement, in semiquantitative experiments carried out in a spectrophotometer cell,[6] 2-*epi*arjunolic lactone was oxidised by periodate at least 10 times as fast as arjunolic lactone. The latter thus appears to be the *trans*- and the former the *cis*-isomer.

During other experiments 3 : 23 : 28-trihydroxyolean-12-ene was obtained by reduction of methyl *iso*propylidenehederagenin with lithium aluminium hydride.

Experimental

Except where otherwise stated, acylations were in pyridine and were carried out for 12—15 hr. at room temperature or for 1 hr. at 100°, and hydrolyses with alkali were under reflux with 2N-methanolic potassium hydroxide for 1 hr.; optical rotations are recorded for $CHCl_3$ solutions and sodium light at room temperature; and analytical samples were normally dried to constant weight at 150° in a vacuum or at 10° below the m. p. whichever was the lower.

O-iso*Propylidene*-18α-*arjunolic Lactone*.—18α-Arjunolic lactone (3 g.) was shaken in acetone (40 c.c.) containing 3 drops of concentrated hydrochloric acid until it was completely dissolved. Excess of anhydrous potassium carbonate was then added and after a further 20 min. the filtered solution was evaporated until crystals appeared. The iso*propylidene derivative* (2·7 g.) recrystallised from acetone as felted needles, m. p. 282—283°, containing acetone of crystallisation (Found: C, 73·7; H, 9·7. $C_{33}H_{52}O_5,C_3H_6O$ requires C, 73·7; H, 10·0. Found, after drying at 180°: C, 75·4; H, 10·1. $C_{33}H_{52}O_5$ requires C, 75·0; H, 9·9%). The *benzoate* separated as plates (from acetone), m. p. 309—310°, [α] +8·6° (*c* 1·05) (Found: C, 75·7; H, 8·9. $C_{40}H_{56}O_6$ requires C, 75·9; H, 8·9%).

Pyrolysis of the benzoate at 520—540°/0·5 mm. afforded a sublimate which still contained 10—15% of benzoate, as shown by its ultraviolet absorption spectrum. The sublimate did not absorb hydrogen over palladium catalysts and with Adams catalyst in the presence of perchloric acid an amorphous solid was obtained, analysis of which showed the partial loss of an oxygen atom.

18α-*Oleanane*-3 : 13 : 23 : 28-*tetrol*.—(*a*) The *iso*propylidenearjunolic lactone above was esterified with excess of toluene-*p*-sulphonyl chloride in pyridine (1 hr. at 100°). Working up in the usual way gave an amorphous solid containing sulphur. The crude sulphonate (1·1 g.)

[5] Cookson and Dandegaonker, *J.*, 1955, 352.
[6] Cf. Aspinall and Ferrier, *Chem. and Ind.*, 1957, 1216.

with lithium aluminium hydride (0·1 g.) was heated under reflux during 1 hr. in tetrahydrofuran (20 c.c.). The excess of hydride was decomposed with ethyl acetate, and the mixture poured into dilute hydrochloric acid and extracted with ether. After it had been washed with sodium hydrogen carbonate solution and water and dried ($MgSO_4$) the ether was evaporated, leaving a residue of the *tetrol* which crystallised from methanol containing a little hydrochloric acid as plates (0·55 g.), m. p. 275—280° raised by further crystallisation from methanol to 290—291°, [α] +34° (*c* 0·19 in pyridine) (Found: C, 75·6; H, 10·7. $C_{30}H_{52}O_4$ requires C, 75·6; H, 11·0%). Material which was obtained from a solution of the tetrol in acetone containing a little hydrochloric acid had m. p. 223—224° (Found: C, 77·5; H, 11·2. Calc. for $C_{33}H_{56}O_4$: C, 76·7; H, 10·9%).

(*b*) Hederagenin lactone diacetate (1·0 g.) was reduced by lithium aluminium hydride at 40° for 2 hr. in tetrahydrofuran. Working up as above gave 0·72 g. of plates, m. p. 292° (mixed m. p. with material from arjunolic lactone 290°), [α] +37° (*c* 0·5 in pyridine) (Found: C, 75·2; H, 11·2%). The infrared absorption curves of the products (*a*) and (*b*) were indistinguishable.

Hederagenin Lactone Diacetate.—The crude toluene-*p*-sulphonate described in (*a*) above was reduced as before and worked up by treatment with aqueous alkali instead of acid. The crude *iso*propylidene derivative obtained was dissolved in acetone containing potassium permanganate (0·1 g.). The mixture was kept at 40° for 5 min., then poured into aqueous sodium hydrogen sulphite and acidified. The precipitated solid was collected and warmed with dilute hydrochloric acid in methanol; the lactone which separated when the solution was cooled was acetylated, to give 0·04 g. of hederagenin lactone diacetate as plates (from methanol), m. p. and mixed m. p. 240—241°.

2-α-*Hydroxy*-18α-*hederagenin Lactone.*—To the diosphenol [1] (VII) (70 mg.) in ethanol (50 c.c.) was added, in small quantities, a total of 1 g. of sodium. The mixture was poured into water; the precipitated *lactone* crystallised from methanol as plates, m. p. 330° (decomp.), [α] +28° (*c* 0·11) (Found: C, 75·7; H, 9·9. $C_{29}H_{46}O_4$ requires C, 75·9; H, 10·1%).

Reduction of Diacetyl-3-*oxo*-18α-*arjunolic Lactone.*—The ketone diacetate [1] (60 mg.) in dry methanol containing sodium hydrogen carbonate (100 mg.) was reduced overnight at room temperature with sodium borohydride (6 mg.). When the product was isolated in the usual way and acetylated, triacetyl-18α-arjunolic lactone, m. p. and mixed m. p. 263°, was obtained.

2-*Oxo*-18α-*arjunolic Lactone.*—*iso*Propylidenearjunolic lactone (1 g.) and potassium permanganate (75 mg.) were warmed in acetone at 40° for 30 min., then worked up in the usual way. Crystallisation of the product from methanol containing a trace of hydrochloric acid gave the *ketone* (0·9 g.) as needles, m. p. 340—344° (decomp.), [α] +22° (*c* 0·34 in EtOH) (Found: C, 73·9; H, 9·2. $C_{30}H_{46}O_5$ requires C, 74·0; H, 9·5%), $\lambda_{max.}$ 270 mμ (ε 40 in EtOH). The *diacetate*, purified by chromatography on acid-washed alumina, separated from methanol in needles, m. p. 292—293°, [α] +9° (*c* 0·1) (Found: C, 71·8; H, 9·2. $C_{34}H_{50}O_7$ requires C, 71·6; H, 8·8%).

The ketone failed to give an oxime, semicarbazone, or dinitrophenylhydrazone and did not react with ethane-thiol or -dithiol. After attempted Huang-Minlon reduction, only acidic material was recovered. The lactone ring in these compounds is stable to these conditions and the acidic products must have been formed by degradation of ring A.

Reduction of 2-*Oxo*-18α-*arjunolic Lactone.*—(*a*) Sodium (0·1 g.) was added to a solution of the ketone (0·1 g.) in dry ethanol. When the sodium had dissolved the mixture was poured into water, and the precipitated solid was crystallised from aqueous methanol, to give 18α-arjunolic lactone, m. p. 350—355° (decomp.) (triacetate, m. p. and mixed m. p. 263°).

(*b*) The ketone (75 mg.) was kept overnight at room temperature in dry methanol (25 c.c.) containing sodium borohydride (10 mg.), then the excess of borohydride was destroyed by dilute acid. The precipitated solid crystallised from methanol, giving 2-epi-18α-*arjunolic lactone* (55 mg.) as needles, m. p. 350—355° (Found: C, 73·7; H, 9·9. $C_{30}H_{48}O_5$ requires C, 73·7; H, 9·9%). The *triacetate* crystallised from methanol in needles, m. p. 268°, mixed m. p. with triacetylarjunolic lactone 235—242°, [α] ~0° (*c* 1·0) (Found: C, 70·3; H, 9·1. $C_{36}H_{54}O_8$ requires C, 70·3; H, 8·9%).

5 mg. of each of the above epimers were dissolved in 200 ml. of spectroscopic ethanol and mixed with 4 mg. of sodium periodate in 50 ml. of aqueous alcohol (1 : 1). The absorption of the resulting solutions at 223 mμ was observed. The solution containing arjunolic lactone showed a steady absorption value after 25 min. while that containing the epimer reached a steady state after only 2 min.

Olean-12-*ene*-3 : 23 : 28-*triol*.—Methyl *iso*propylidenehederagenin (0·2 g.) was reduced at room temperature in ether with lithium aluminium hydride (50 mg.). The mixture was worked up in the usual manner and the product was crystallised from methanol containing a little hydrochloric acid, to give the *triol* as needles, m. p. 250°, [α] +77° (*c* 0·42) (Found: C, 78·3; H, 11·0. $C_{30}H_{50}O_3$ requires C, 78·6; H, 11·0%).

Dibenzoyl-18α-*hederagenin Lactone*.—18α-Hederagenin lactone was benzoylated in the usual way, to give the *dibenzoate* as plates (from benzene), m. p. 314—315°, [α] +76° (*c* 0·48) (Found: C, 77·7; H, 8·6. $C_{44}H_{56}O_6$ requires C, 77·6; H, 8·3%).

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