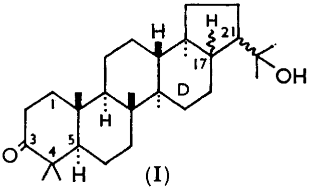
344. *The Chemistry of Triterpenes and Related Compounds. Part XXXVII.* The Stereochemistry of the* D/E *Ring Junction of Hydroxyhopanone.*

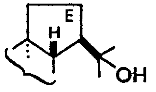
By G. V. Baddeley, T. G. Halsall, and E. R. H. Jones.

Rings D and E of hydroxyhopanone [1] (I) are *trans*-fused with the hydrogen atom at $C_{(17)}$ β-orientated (cf. III).

Hydroxyhopanone has structure (I),[1] only the configuration at $C_{(17)}$ and at $C_{(21)}$ being in doubt. If hydroxyhopanone is biosynthesised from squalene by a completely concerted cyclisation then the stereochemistry of rings D and E could be as in (II).[1,2]



(I)



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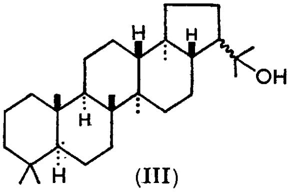

(III)

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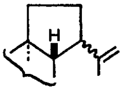

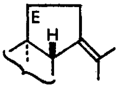

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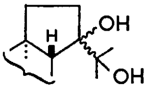

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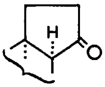

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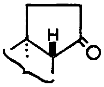

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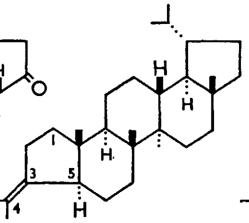

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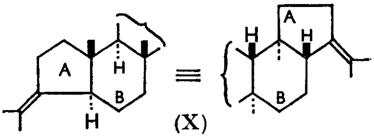
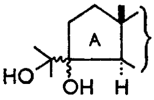
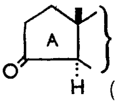


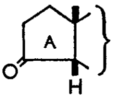
(X)

(XI)





(XII)



(XIII)

Conversion of the keto-alcohol (I) into hydroxyhopane (III) followed by dehydration gave a mixture (hopene) of hopene-a (IV) and hopene-b (V).[3] Treatment of the mixture with osmium tetroxide led to the isolation of hopene-a glycol (VI), fission of which with lead tetra-acetate in benzene–acetic acid gave [3] the trisnorketone (VII) ($[\alpha]_D$ +142°). This was also obtained [3] by ozonolysis of hopene and by oxidation of hydroxyhopane with chromic acid. Evidence based on molecular rotation and optical rotatory dispersion data showed [3] that the ketone had a *cis*-D/E ring junction. Since, however, this is the more stable configuration (see below) no conclusion could be drawn about the ring junction in hydroxyhopanone itself.

To investigate possible routes to the less stable trisnorketone (VIII), γ-lupene [4,5] (IX), obtained from lupanol by dehydration with phosphorus pentachloride, was used as a model, its rings A and B (X) corresponding to rings D and E of hopene-a (IV). Conversion of γ-lupene (X) into the glycol (XI) followed by treatment with lead tetra-acetate in acetic acid and purification of the product on alumina gives [5] a trisnorketone (XIII) ($[\alpha]_D$ +107°) in which the A/B rings are *cis*-fused [6] although in lupanol and γ-lupene the ring junction is *trans*. The experimental conditions used, however, permit the unstable ketone (XII), which must be formed initially, to isomerise. When γ-lupene glycol was cleaved with

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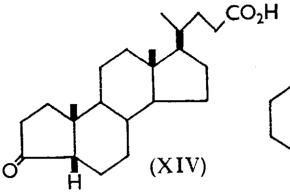
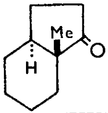
* Part XXXVI, *J.*, 1959, 2036.

[1] Fazackerley, Halsall, and Jones, *J.*, 1959, 1877.
[2] Schaffner, Caglioti, Arigoni, and Jeger, *Helv. Chim. Acta*, 1958, **41**, 152.
[3] Dunstan, Fazakerley, Halsall, and Jones, *Croat. Chim. Acta*, 1957, **29**, 173.
[4] Heilbron, Kennedy, and Spring, *J.*, 1938, 329.
[5] Ruzicka, Jeger, and Huber, *Helv. Chim. Acta*, 1945, **28**, 942.
[6] Klyne, *J.*, 1952, 2916.

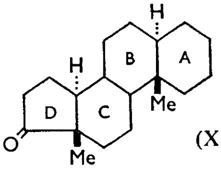
lead tetra-acetate in dry benzene the trisnorketone (XII) with a *trans*-A/B ring junction was obtained. It differed markedly in its rotation ($[\alpha]_D$ −88°) from the known ketone (XIII) into which it was converted on being heated with base. Mild ozonolysis of γ-lupene gave a mixture of the two ketones (XII) and (XIII), treatment of which with base gave the stable isomer (XIII).



(XIV)



(XV)



(XVI)

When hopene-a glycol (VI) was treated with lead tetra-acetate in benzene (as above) it afforded a trisnorketone (VIII) ($[\alpha]_D$ −42°), isomerised by base to the more stable oxo-trisnorhopane[3] (VII).

Optical rotatory dispersion data.

Compound	Position of min.	$10^{-2}[M]$	Position of max.	$10^{-2}[M]$	Solvent
(−)-*trans*-Perhydro-8-methylindan-1-one (XV)	3225 Å	−47°	2800 Å	+41°	Dioxan
trans-Oxotrisnorhopane (VIII)	3100	−90	2810	+118	MeOH–$CHCl_3$ (4 : 1)
trans-Oxotrisnorlupane (XII)	3100	−109	2800 *	+86	MeOH
Androstan-17-one (XVI)	2790	−65	3180	+74	Dioxan
cis-Oxotrisnorhopane (VII)	2750	−39	3130	+79	MeOH–$CHCl_3$ (4 : 1)
cis-Oxotrisnorlupane (XIII)	2780	−52	3140	+68	MeOH
3-Oxo-A-norcholanic acid (XIV)	2750	−37	3140	+70	MeOH

* Curve still rising at this wavelength.

Infrared data.

Compound	*cis*-Series	*trans*-Series	Solvent
Oxotrisnorlupane	1725 cm.$^{-1}$	1748 cm.$^{-1}$	" Nujol "
	1738	1744	CCl_4
	1729	1735	$CHCl_3$
Oxotrisnorhopane	1729	1752	" Nujol "
	1742	1751	CCl_4
	1729	1731	$CHCl_3$

The molecular-rotation differences between the two pairs of ketones are practically identical: $\Delta[M_D]$(XII) $\longrightarrow$ (XIII) $+ 752^\circ$: $\Delta[M_D]$(VIII) $\longrightarrow$ (VII) $+ 706^\circ$. The optical rotatory dispersion curves[7] (cf. Table) of the *cis*-fused ketones from γ-lupene and hopene-a were similar to one another and to that of 3-oxo-A-norcholanic acid[8] (XIV) with the same A/B ring structure. The curves for the *trans*-ketones were likewise similar to one another and to (—)-*trans*-perhydro-8-methylindan-3-one (XV)[8] and very different from those of the *cis*-ketones. The *trans*-ketone curves were a mirror image of that of androstan-17-one (XVI),[8] rings C and D of which are enantiomeric to rings A and B of the *trans*-ketones.

In each pair of *cis*- and *trans*-ketones the C=O stretching frequency of the less stable *trans*-ketone was higher than that of the more stable *cis*-ketone (cf. Table).

These results prove the structure (VIII) of the less stable ketone formed from hopene-a and hence the *trans*-fusion of rings D and E in hopene-a and hydroxyhopanone. The stereochemistry at $C_{(17)}$ is hence in accord with biogenetic predictions.[2,3]

[*Added, February* 12*th*, 1960: Evidence has now been obtained that the hydroxyisopropyl side chain of hydroxyhopanone at $C_{(21)}$ has the α-configuration, not the β-configuration as in (II). The carbon skeleton of this revised structure for hydroxyhopanone can be biosynthesised by cyclisation of the all-chair conformation of squalene.]

[7] Those for the ketones from hydroxyhopanone were kindly determined by Dr. W. Klyne and those for the ketones from γ-lupene by Professor C. Djerassi.

[8] Djerassi, Riniker, and Riniker, *J. Amer. Chem. Soc.*, 1956, **78**, 6362.

EXPERIMENTAL

M. p.s were determined on a Kofler block and are corrected. Rotations were determined for chloroform solutions at room temperature. The alumina used for chromatography was Peter Spence Grade " H " and, unless otherwise stated, was deactivated with 5% of 10% aqueous acetic acid. Light petroleum refers to the fraction with b. p. 60—80°.

γ-Lupene (IX).—This was prepared as described by Heilbron, Kennedy, and Spring [4] but with a contact time of 10 min. γ-Lupene formed heavy prisms (from ethyl acetate–light petroleum), m. p. 198—201°, $[\alpha]_D$ −16° (*c* 1·43) (lit.: [4] m. p. 197—199°, $[\alpha]_D$ −19·7°).

Hydroxylation of γ-Lupene.—γ-Lupene (650 mg.) in dry ether (60 c.c.) was treated with pyridine (12 c.c.) and osmium tetroxide (485 mg.). The mixture was kept at 20° for 7 days. Insoluble inorganic material was filtered off and the filtrate was evaporated to dryness. The residue was heated under reflux for 6 hr. with mannitol (2·5 g.), potassium hydroxide (4·0 g.) in ethanol (20 c.c.), benzene (10 c.c.), and water (10 c.c.). Dilution with water and ethereal extraction afforded a pale yellow gum which was adsorbed from light petroleum–benzene (1 : 1) on alumina (25 g.). Elution with benzene afford gums which did not crystallise. Elution with benzene–ether (1 : 1) yielded *γ-lupene glycol* [5(4 → 3)*abeolupane*-3ξ,4-*diol* *] (XI) (470 mg.) as needles (from ethyl acetate), m. p. 187—191°, $[\alpha]_D$ −6° (*c* 3·57)[Ruzicka, Jeger, and Huber [5] give m. p. 164—165°, $[\alpha]_D$ −13·6° (*c* 0·74) for a hemihydrate] (Found: C, 80·7; H, 11·5. $C_{30}H_{52}O_2$ requires C, 81·0; H, 11·8%).

Fission of γ-Lupene Glycol (XI).—γ-Lupene glycol (129 mg.) was dissolved in dry benzene (50 c.c.) and lead tetra-acetate (140 mg.; 1·1 mol.) was added with stirring during 10 min. at 15°. The mixture was then stirred for 1 hr. After removal of insoluble yellow salts, the solvent was evaporated. Needles {121 mg.; m. p. 149—159°; $[\alpha]_D$ −89° (*c* 0·47)} remained. These were sublimed at 110—135°/0·01 mm. and recrystallised from ether–light petroleum, giving 4,23,24-*trisnor*-5(4 → 3)*abeolupan*-3-*one* (XII) as platelets, m. p. 164—168°, $[\alpha]_D$ −88° (*c* 1·16), $\nu_{max.}$ 1748 (in " Nujol "), 1744 (in CCl_4), 1735 cm.$^{-1}$ (in $CHCl_3$) (Found: C, 84·5; H, 11·3. $C_{27}H_{44}O$ requires C, 84·3; H, 11·5%).

Attempted purification of this ketone on alumina or silica gel caused some isomerisation, the products showing higher (positive) rotations ($[\alpha]_D$ −58°; $[\alpha]_D$ −73°).

Crude product (47 mg.) obtained directly from the fission of the glycol was purified by elution with light petroleum from cellulose (5 g.), platelets (from light petroleum), m. p. 161—165°, $[\alpha]_D$ −88° (*c* 0·48), being obtained.

Isomerisation of 4,23,25-*Trisnor*-5(4 → 3)*abeolupan*-3-*one* (XII).—The ketone (84 mg.) was heated under reflux for 2½ hr. in ethanol (20 c.c.) to which sodium (300 mg.) had been added. Dilution with water and extraction with ether afforded a crude product (83 mg.), $[\alpha]_D$ +60° (*c* 1·15), which was dissolved in benzene and filtered through alumina (4 g.). Evaporation of the filtrate gave platelets (66 mg.) which were crystallised from acetone–methanol, giving 4,23,24-trisnor-(5βH)-5(4 → 3)abeolupan-3-one as plates, m. p. 168—173°, $[\alpha]_D$ +103° (*c* 0·35) (lit.: m. p. 173·5—174°, $[\alpha]_D$ +107°), $\nu_{max.}$ 1738 (in CCl_4), 1729 (in $CHCl_3$), and 1725 cm.$^{-1}$ (in " Nujol ").

Ozonolysis of γ-Lupene.—γ-Lupene (1·2 g.) in hexane–chloroform (1 : 1) was cooled to −70° and ozonised oxygen (6%) (4 l.) was bubbled through the solution until, after ½ hr., a persistent blue colour was observed. Excess of ozone was removed by a stream of nitrogen, and the solution was then shaken with hydrogen in the presence of palladium catalyst; no uptake was observed during 2 hr. The catalyst was removed by filtration and the filtrate evaporated to give a solid (1·01 g.), $[\alpha]_D$ +32° (*c* 1·30), clearly a mixture of the *cis*- and the *trans*-isomer (XII and XIII). This was heated under reflux in ethanol with sodium ethoxide as described above. The product was dissolved in light petroleum–benzene (1 : 1) and filtered through alumina (50 g.) to give 4,23,24-trisnor-(5βH)-5(4 → 3)abeolupan-3-one (950 mg.) which crystallised from acetone–methanol as prisms, m. p. 173—175°, $[\alpha]_D$ +103° (*c* 1·21).

Hydroxyhopane [(21ξH)-17(22 → 21)abeogammaceran-22-ol] (III).—This, prepared as described,[3] crystallised as plates (from methanol–acetone), m. p. 254—256°, $[\alpha]_D$ +42° (*c* 0·86) (lit.,[3] m. p. 254—256°, $[\alpha]_D$ +45°).

Dehydration of Hydroxyhopane.—Hopene was prepared from hydroxyhopane as described.[3]

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* The prefix " abeo " and the accompanying numerals indicate a bond migration in the molecule named as parent. Thus, 5(4 → 3) abeolupane is lupane in which the 5,4-bond has been replaced by a 5,3-bond. This usage (following a suggestion by Professor D. H. R. Barton) and related nomenclature proposals are being considered by the Society. ED.

It is a mixture of hopene-a and hopene-b and crystallised from methanol–acetone as needles, m. p. 175—183°.

Hydroxylation of Hopene.—Hopene (273 mg.) in ether (30 c.c.) and pyridine (3 c.c.) was treated with osmium tetroxide (225 mg.; 1·3 mol.) at 20° for 18 hr. The solvents were then evaporated and the residual osmate ester was cleaved by potassium hydroxide–mannitol. The product (320 mg.) was acetylated in pyridine (8 c.c.) at 20° for 18 hr. with acetic anhydride (3 c.c.). The mixture was then warmed to 90° for 30 min., after which the solvents were evaporated. The pale yellow residue was adsorbed from benzene–ether (19 : 1) on alumina (40 g.). Elution with benzene–ether (5 : 1) gave a gum (81 mg.). Further elution with benzene–ether (1 : 1) afforded a crystalline solid (230 mg.) which was crystallised from methanol–acetone, giving hopene-a glycol [17(22 → 21)abeogammacerane-21ξ,22-diol] (VI) as plates, m. p. 272—281°, $[\alpha]_D$ +30° (*c* 0·87) (lit.,[3] m. p. 260—265°, $[\alpha]_D$ +31°).

Cleavage of Hopene-a Glycol (VI).—The glycol (92 mg.) was dissolved in dry benzene (40 c.c.), and lead tetra-acetate (125 mg.; 1·3 mol.) was added with stirring during 10 min. The temperature was kept at 10° and stirring was continued for 1¼ hr. After insoluble yellow salts had been filtered off, evaporation afforded a solid which was dissolved in light petroleum and filtered through cellulose (10 g.). Evaporation then afforded 22,29,30-*trisnor*-17(22 → 21)-*abeogammaceran*-21-*one* (VIII) (83 mg.) which crystallised from light petroleum–ether as plates, m. p. 175—180°, $[\alpha]_D$ −42° (*c* 0·53); $\nu_{max.}$ 1752 (in " Nujol "), 1751 cm.$^{-1}$ (in CCl_4), 1731 cm.$^{-1}$ (in $CHCl_3$) (Found: C, 84·45; H, 11·35. $C_{27}H_{44}O$ requires C, 84·3; H, 11·55%).

Isomerisation of 22,29,30-*Trisnor*-17-(22 → 21)*abeogammaceran*-21-*one* (VIII).—The ketone (1·05 g.) was heated under reflux for 1 hr. in ethanol (110 c.c.) to which sodium (600 mg.) had been added. Dilution with water and extraction with ether afforded a crude product which was adsorbed from light petroleum–benzene (6 : 1) on alumina (100 g.). Elution with light petroleum–benzene (1 : 1) afforded microcrystals (950 mg.) which were recrystallised twice from methanol–acetone, giving 22,29,30-trisnor-(17αH)-17(22 → 21)abeogammaceran-21-one (VII) as needles, m. p. 238—240°, $[\alpha]_D$ +140° (*c* 1·05) (lit.,[3] m. p. 240—241·5°, $[\alpha]_D$ +142°, $\nu_{max.}$ 1742 (in CCl_4), 1729 (in $CHCl_3$), and 1729 cm.^{81} (in " Nujol ").

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