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STEREOCHEMICAL STUDIES IN THE TRISNORLUPANE SERIES

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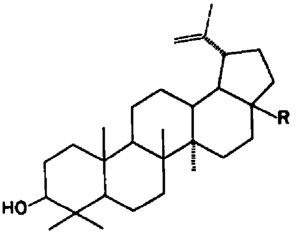
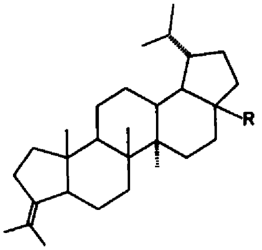
Abstract—γ-Lupene (VI) has been converted into four alcohols (IX–XII) epimeric at C_3 and C_5 whose configuration has been established.

THE two cyclopentanones (VII and VIII) were chosen as the basis for a study of the stereospecificity of the reduction of cyclopentanones by complex metal hydrides. The two ketones are readily available and are reduced to mixtures of epimeric alcohols which are readily separable by chromatography on alumina. We wish to describe the synthesis of the four alcohols (IX–XII) from γ-lupene (VI) and evidence which establishes their configuration at C_3 and C_5.



I R=COOH
II R=CH_3



III R=$COOCH_3$
IV R=CH_2OH
V R=CHO
VI R=CH_3

γ-Lupene (VI) was obtained by two routes, from betulic acid (I) and from Lupeol (II). Betulic acid is widely distributed in Western Australia and is a major component of the *Melaleuca* spp. or "paper barks". The acid was converted to the unsaturated ester (III)[1] which was reduced by LAH to the non-crystalline primary alcohol (IV) characterized as the acetate. The alcohol was oxidized by chromic acid–sulphuric acid with short contact time to minimize acid-catalyzed isomerization of the olefinic linkage[2] and formation of the carboxylic acid. The required aldehyde (V) was isolated in 76% yield and was reduced, by the Huang Minlon procedure, to γ-lupene. The overall yield of γ-lupene from betulic acid was 45%. Lupeol (II) is a principal component of Malayan Getah jelutong[3] and may be converted, by two steps,[2] into γ-lupene. The yield of γ-lupene from the horny jelutong was 11%.

The oxidative elimination of the isopropylidene group from γ-lupene can lead to

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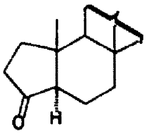
[1] A. B. Burns, A. R. H. Cole, B. J. Parkes and D. E. White, *Austr. J. Chem.* 9, 406 (1956).

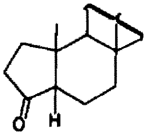
[2] R. Nowak, O. Jeger and L. Ruzicka, *Helv. Chim. Acta* 32, 323 (1949).

[3] R. E. Marker and E. L. Wittle, *J. Amer. Chem. Soc.* 61, 585 (1939).

two trisnorketones (VII, VIII) epimeric at C_5.[4] The free energy difference between the two ketones (2·7 k. cal mole^{-1}) makes the A/B *cis*-ketone (VIII) the major component (ca. 99%) in an equilibrium mixture.[5]



VII

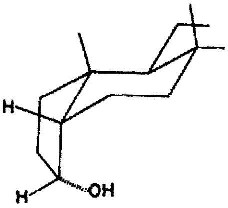


VIII

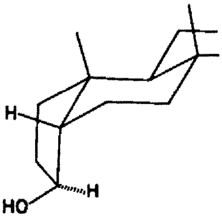
The reduction of the A/B *trans*-ketone (VII) by LAH gave a mixture of two alcohols, separable by chromatography on alumina. Neither of these alcohols resembled either of the alcohols obtained by the similar reduction of the A/B *cis*-ketone. Clearly, isomerization at C_5 had been avoided and the four alcohols represent the epimers at C_3 and C_5.

The configuration of the alcohols at C_5 was determined by that of the parent ketone and only that at C_3 remained to be established. The configurational assignments are deduced from the order of elution from alumina, the relative ease of acetylation and the molecular rotation differences associated with the introduction or modification of oxygenation at C_3.

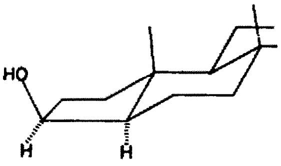
In both the A/B *cis*- and *trans*-series the principal component of the reduction product was eluted first from alumina and was considered to be the alcohol possessing the more hindered hydroxyl group (5β, 3α, 5α; 3β). Dreiding models revealed that, due to the puckering of ring A, these could be regarded as axial alcohols. In the 5β-series the 3α-hydroxyl group is axial (IX) and close to ring B. In the 5α-series the



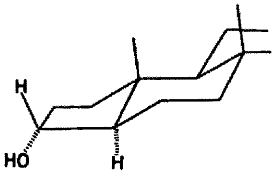
IX



X



XI



XII

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[4] G. V. Baddeley, T. G. Halsall and E. R. H. Jones, *J. Chem. Soc.* 1715 (1960).

[5] N. L. Allinger, R. B. Hermann and C. Djerassi, *J. Org. Chem.* **25**, 922 (1960).

3β-hydroxyl group is axial (XI) and close to the C_{10} methyl group. In both the 5α- and 5β-series the axial alcohols (IX, XI) were only partially acetylated under conditions which completely acetylated the equatorial alcohols (X, XII).

In order to determine the molecular rotation differences associated with the introduction of oxygenation at C_3 in the 5β-series, a route to the A/B *cis*-fused hydrocarbon was required. The reduction of the *cis*-ketone (VIII) by the Huang Minlon procedure gave a hydrocarbon thought to retain the *cis*-A/B ring junction. This was likely since, at the temperature of reduction (ca. 500°K), the equilibrium concentration of the 5α-series can be only ca. 6% and it is unlikely that the rate of reduction in the 5α-series is greater than that in the 5β-series by a factor exceeding fifteen.

An unambiguous synthesis of the 5β-hydrocarbon was achieved via the toluene-*p*-sulphonate derived from the alcohol (X). A similar route was employed for the removal of 19-oxygenation in ring E of the lupane nucleus without affecting the stereochemistry of the D/E ring junction.[6] The toluene-*p*-sulphonate solvolyzed in acetone to give a mixture of olefins but was cleaved by lithium aluminium hydride to the same hydrocarbon as was obtained by the Huang Minlon method.

The molecular rotations and $\Delta[M_D]$ values for the 5β-series are summarized in Table 1 and are in accord with those expected[7] for the assigned configurations.

TABLE 1

5β	$[M]_D$		$[M]_D$			$\Delta[M]_D$	
Configuration	CH_2	CHOH	CHOAc	$CHOB_z$	Δ_{OH}	Δ_{OAc}	Δ_{OBz}
3α (IX)	+10	−97	−39	−69	−107	−49	−79
3β (X)	+10	+62	+142	+295	+ 52	+132	+285

In the 5α-series the hydrocarbon was not synthesized but the values for $\Delta[M_D]$ (3β–3α) are consistent (Table 2) with the configurational assignment.

TABLE 2

5α	$[M]_D$		$\Delta[M]_D$	(3β−3α)
Configuration	CHOH	CHOAc	CHOH	CHOAc
3α (XII)	−151	−112	+132	+65
3β (XI)	− 19	− 47		

Further evidence in favour of the assigned stereochemistry at C_3 in the 5β-series was supplied by the equilibration of the 3α-alcohol (IX) catalyzed by sodium ethoxide. This led to a mixture whose composition (24% IX, 76% X) was very similar to that of the mixture obtained by the reduction of the A/B *cis*-ketone by sodium in butanol (22% IX, 78% X).

The assignment of the stereochemistry at C_3 coupled with the facile separation of the epimeric alcohols made these series particularly suitable for a study of the stereospecificity of reduction of cyclopentanones by complex metal hydrides. The results of this investigation will be reported elsewhere.

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[6] G. V. Baddeley, T. G. Halsall and Sir Ewart R. H. Jones, *J. Chem. Soc.* 1173 (1964).

[7] W. Klyne and W. M. Stokes, *J. Chem. Soc.* 1979 (1954).

EXPERIMENTAL

M.ps were determined on a Kofler hot-stage and are uncorrected. Specific rotations were determined for ca. 1% solutions in $CHCl_3$. IR spectra were for CS_2 solutions on Perkin–Elmer Spectrophotometer Models 137 and 137G. Analyses were by the Australian Microanalytical Service, Melbourne. Alumina for chromatography was prepared by acidifying Peter Spence Grade H with dil. HNO_3, washing with water until neutral and heating to Activity II on the Brockmann scale of activity.[8] Light petroleum refers to the fraction b.p. 56–60°.

Reduction of methyl 5(4–3)*abeolup*-3(4)-*en*-28-*oate*[1] (III). The ester (1·01 g) in ether (80 ml) was reduced by LAH (0·5 g) in ether (40 ml) under reflux during 3 hr to give a gum which was filtered through alumina (25 g) in benzene to give IV as an amorphous solid (850 mg), ν_{max} 3605, 1020 cm^{-1}.

The *acetate* was prepared by the acetic anhydride–pyridine method and formed plates from $CHCl_3$–MeOH, m.p. 154–155°; $(\alpha)_D$ −17°; ν_{max} 1740, 1235, 1030 cm^{-1}. (Found: C, 82·0; H, 11·2. $C_{32}H_{52}O_2$ requires: C, 82·0; H, 11·2%.)

The alkaline hydrolysis of this acetate regenerated the amorphous alcohol.

5(4→3)*Abeolup*-3(4)-*en*-28-*al* (V). The alcohol (IV; 192 mg) in acetone (20 ml) was treated for 10 min with H_2CrO_4–H_2SO_4 (from 20·7 g CrO_3 and 9·5 ml H_2SO_4 in 100 ml water; 5 ml). The excess of oxidant was destroyed by MeOH and the product was isolated through ether. The aldehyde (146 mg) was eluted by light petroleum–benzene (1:1) from alumina and afforded needles from $CHCl_3$–MeOH, m.p. 169–170°; $(\alpha)_D$ −25°; ν_{max} 2690, 1720 cm^{-1}. (Found: C, 84·5; H, 11·4. $C_{30}H_{48}O$ requires: C, 84·8; H, 11·4%.)

γ-Lupene (VI). The aldehyde (V; 78 mg) in diethylene glycol (30 ml) was heated under reflux with hydrazine hydrate (100%; 3 ml) for 1 hr. The solution was distilled until the internal temp reached 210° when KOH (400 mg) was added and the solution was heated at reflux for 6 hr. The product was isolated through ether and crystallized from light petroleum–ethyl acetate as prisms, m.p. 192–195°; $(\alpha)_D$ −16°; lit.[9] m.p. 197–199°; $(\alpha)_D$ −19·7°.

γ-Lupene prepared, via lupanol,[2] from lupeol had m.p. 196–198°.

Reduction of 4,23,24-*trisnor*-5(4→3)*abeolupan*-3-*one*[4] (VII) *by lithium aluminium hydride*. The ketone (348 mg) in hexane–ether (1:2; 60 ml) was stirred under reflux with LAH (300 mg) for 2 hr. The product was adsorbed from light petroleum–benzene (4:1) on alumina (20 g). Elution with light petroleum–benzene (1:1) gave 4,23,24-*trisnor*-5(4→3)*abeolupan*-3β-*ol* (XI, 239 mg) which formed prisms, from acetone–MeOH, m.p. 159–161°; $(\alpha)_D$ −5°. (Found: C, 84·0; H, 12·1. $C_{27}H_{46}O$ requires: C, 83·8; H, 12·0%).

The *acetate* (acetic anhydride–pyridine method) formed plates, from acetone, m.p. 205–206°; $(\alpha)_D$ −11°. (Found: C, 81·2; H, 11·3. $C_{29}H_{48}O_2$ requires: C, 81·2; H, 11·3%.)

Elution with ether gave 4,23,24-*trisnor*-5(4→3)*abeolupan*-3α-*ol* (XII; 81 mg) as needles, from acetone–MeOH, m.p. 224–225°; $(\alpha)_D$ −39°. (Found: C, 83·4; H, 12·0. $C_{27}H_{46}O$ requires: C, 83·8; H, 12·0%.)

The *acetate* (acetic anhydride–pyridine method) formed plates, from acetone–MeOH, m.p. 222–223°; $(\alpha)_D$ −26°. (Found: C, 80·9; H, 11·2. $C_{29}H_{48}O_2$ requires: C, 81·2; H, 11·3%.)

Mild acetylation of alcohols XI *and* XII. The alcohol XI (20 mg) was treated with acetic anhydride (1 ml) in pyridine (1 ml) at room temp for 10 hr. The product was adsorbed from light petroleum–benzene (4:1) on alumina (3 g). Elution with light petroleum–benzene (1:1) gave the acetate (11 mg). Elution with benzene–ether (1:1) gave the unchanged alcohol (7 mg).

The alcohol XII (20 mg) was treated under the same conditions and the acetate alone (18 mg) was obtained after chromatography on alumina.

Reduction of 4,23,24-*trisnor*-(5βH)-5(4→3)*abeolupan*-3-*one*[10] *by lithium aluminium hydride*. The ketone (198 mg) was reduced by LAH (420 mg) in ether (80 ml) under reflux during 1 hr. The product was adsorbed on alumina (20 g). Elution with light petroleum–benzene (1:1) gave 4,23,24-*trisnor*-(5βH)-5(4→3)*abeolupan*-3α-*ol* (IX, 120 mg) which formed fine needles, from MeOH, m.p. 121–122°; $(\alpha)_D$ −25°. (Found: C, 83·6; H, 12·0. $C_{27}H_{46}O$ requires: C, 83·8; H, 12·0%.)

The *acetate* (acetic anhydride–pyridine method) was a gum, $(\alpha)_D$ −9°; ν_{max} 1730, 1240, 1035 cm^{-1} (no hydroxyl absorption). (Found: C, 81·2; H, 11·4. $C_{29}H_{48}O_2$ requires: C, 81·2; H, 11·3%.)

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[9] I. M. Heilbron, T. Kennedy and F. S. Spring, *J. Chem. Soc.* 329 (1938).

[10] L. Ruzicka, W. Huber and O. Jeger, *Helv. Chim. Acta* **28**, 195 (1945).

The *benzoate* (benzoyl chloride–pyridine method) formed needles, from acetone–MeOH, m.p. 139–140°; $(\alpha)_D$ −14°. (Found: C, 83·0; H, 10·3. $C_{34}H_{50}O_2$ requires: C, 83·2; H, 10·3%.)

Elution with benzene–ether (4:1) gave 4,23,24-*trisnor*-(5βH)-5(4→3)*abeolupan*-3β-*ol* (X, 60 mg) which formed needles, from acetone–MeOH, m.p. 174–175°; $(\alpha)_D$ +16°. (Found: C, 83·6; H, 11·8. $C_{27}H_{46}O$ requires: C, 83·8; H, 12·0%.)

The *acetate* formed plates, from acetone–MeOH, m.p. 136–137°; $(\alpha)_D$ +33°. (Found: C, 81·1; H, 11·4. $C_{29}H_{48}O_2$ requires: C, 81·2; H, 11.3%.)

The *benzoate* formed prisms, from acetone–MeOH, m.p. 112–113°; $(\alpha)_D$ +60°. (Found: C, 82·9; H, 10·3. $C_{34}H_{50}O_2$ requires: C, 83·2; H, 10·3%.)

Mild acetylation of alcohols IX *and* X. The alcohol IX (20 mg) was treated with acetic anhydride (0·4 ml) in pyridine (0·4 ml) at room temp for 1 hr. The product was adsorbed on alumina. Elution with light petroleum–benzene (4:1) gave the acetate (9 mg). Elution with light petroleum–benzene (1:1) gave unchanged alcohol (10 mg).

The alcohol X (20 mg) was completely acetylated under the same conditions, affording only the corresponding acetate (19 mg) after chromatography of the product on alumina.

4,23,24-*Trisnor*-(5βH)-5(4→3)*abeolupane*. The ketone VIII (150 mg) was heated under reflux for 1 hr with hydrazine hydrate (100%; 6 ml) in diethylene glycol (60 ml). The internal temp was raised to 210° by distillation when KOH (800 mg) was added and the solution was heated at reflux for 4·5 hr. The product (141 mg) was isolated through ether and filtered in light petroleum through alumina (10 g) to give the hydrocarbon as cubes, from acetone, m.p. 164–165°; $(\alpha)_D$ +2·7°. (Found: C, 87·3; H, 12·3. $C_{27}H_{46}$ requires: C, 87·5; H, 12·5%.)

The alcohol X (150 mg) in pyridine (3 ml) was treated with toluene-*p*-sulfonyl chloride (150 mg) at 4° for 60 hr. The crude toluene-*p*-sulphonate (128 mg) was isolated through ether and was cleaved by LAH (200 mg) in ether (30 ml) under reflux during 4 hr to give a hydrocarbon identical to that obtained above.

Solvolysis of the toluene-p-sulphonate from the alcohol X. The crude toluene-*p*-sulphonate was heated under reflux in acetone to give a mixture of olefins from which 4,23,24-*trisnor*-5(4→3)*abeolup*-3-*ene* was obtained as cubes, from acetone, m.p. 187–188°; $(\alpha)_D$ +6·2°. (Found: C, 87·6; H, 12·1. $C_{27}H_{44}$ requires: C, 87·9; H, 12·1%.)

The NMR spectrum[*] showed a broad band at 310 c/s (0·8H) attributable to the vinylic proton of a trisubstituted olefin. Additional absorption at 335 c/s (0·2H) was attributed to contamination by the disubstituted olefinic isomer. The hydrocarbon gave a strong coloration with tetranitromethane.

Equilibration of the alcohol IX *by sodium ethoxide*. The alcohol (100 mg) was heated in anhydrous xylene (2 ml) with EtONa (from 0·5 g Na) at 140–150° for 7 hr. Solvent was removed *in vacuo* and the residue was treated with water and the product (94 mg) was isolated through ether and adsorbed on alumina (10 g). Elution with light petroleum–benzene (1:1) gave unchanged IX (22 mg). Elution with ether gave the epimeric alcohol X (68 mg).

Reduction of ketone VIII *by sodium in butanol*. The ketone (100 mg) was heated under reflux in *n*-butanol (40 ml) during the addition of Na (2·5 g) over a period of 1·5 hr. The solution was heated under reflux for a further 0·5 hr, cooled, acidified by 1 N HCl and extracted with ether. The product was adsorbed on alumina (10 g). Elution with light petroleum (4:1) gave unchanged ketone (8 mg). Elution with light petroleum–benzene (1:1) gave the alcohol IX (20 mg) and with ether, the alcohol X (71 mg).

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[*] Recorded for deuteriochloroform solution with a Varian A-60 spectrometer and tetramethylsilane as internal reference.