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THE OXIDATION OF LUPENYL ACETATE BY MERCURIC ACETATE

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Abstract—The product of oxidation of lupenyl acetate (VIII) is 3β-acetoxylupa-18,20(29)-diene (V).

MERCURIC acetate effects oxidation[1,2] in the lup-20(29)-ene nucleus leading, in the presence of a carboxyl group at C-17, to the lactone (I)[3] and, in the presence of a hydroxymethyl group at C-17, to the allylic ether (II).[4] In the absence of a reactive substituent at C-17 the oxidation introduces a tetrasubstituted double bond, considered previously to be located at C-13(18) (III and IV) on the basis of spectroscopic and degradative evidence.[5]

UV spectral evidence (no max above 210 nm) has been invoked[2] to exclude the isomeric C-18(19) olefin (V) but π-orbital overlap would not be expected in the lupa-18,20(29)-diene series because of resultant severe steric interaction between the isopropenyl side-chain and 12β-H. The structure proposed[5] for the cleavage product (VI) derived from methyl acetylbetulate implies that the analogous product derived from lupenyl acetate would have the structure VII. The previously reported IR spectrum[2] of the latter product [ν_{max} 1739 (acetate), 1717 and 1706 cm^{-1}] gave no support for a cyclopentanone structure and a further investigation of the mercuric acetate oxidation of lupenyl acetate was therefore warranted.

The mercuric acetate oxidation product (III or V)* from lupenyl acetate (VIII) had physical constants identical with those recorded previously.[2] It reacted with hydrogen over platinum in acetic acid-ethyl acetate to give a product with properties identical with those recorded,[2] but which was shown by GLC and MS to be a mixture of dihydro and tetrahydro derivatives in the ratio 7:3. The tetrahydro derivative is not formed from the dihydro derivative since its proportion was not increased during extended reduction times. This preparatively inseparable mixture reacted with osmium tetroxide in pyridine-ether to give, after reduction by LAH, a mixture of three components separable by chromatography on alumina.

The least polar component, characterized as the acetate, gave no coloration with TNM and had a molecular ion at *m/e* 428. Gross skeletal rearrangement was unlikely since a significant M-43 peak (loss of isopropyl) appeared in the MS. The structure IX (but excluding lupanol) is proposed for this alcohol.

The major component was the expected triol (XI) which was cleaved by $Pb(OAc)_4$ to give the hydroxy-diketone (XIII). The IR absorption at 1714 and 1705 cm^{-1} (CCl_4) was not consistent with a cyclopentanone structure (cf. VII). The stereochemistry at

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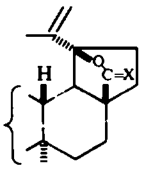
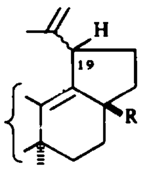
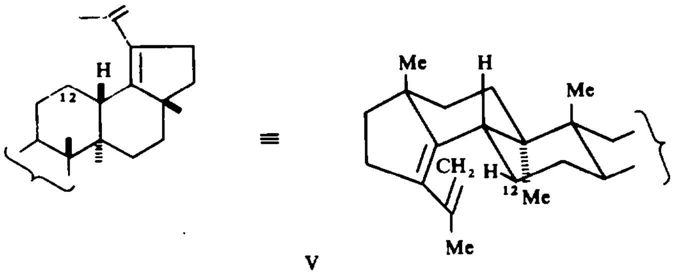
* For convenience, subsequent compounds will be formulated on the basis of structure (V)



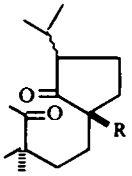
I: X=O
II: $X=H_2$



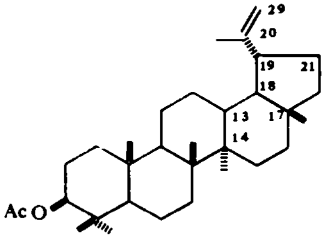
III: R=Me
IV: R=COOMe



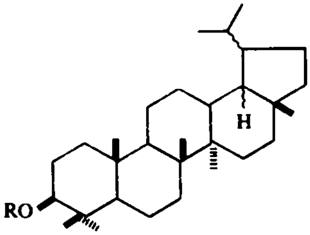
V



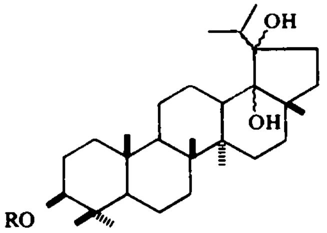
VI: R= COOMe
VII :R=Me



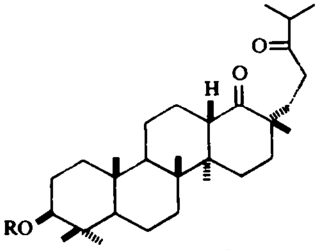
VIII



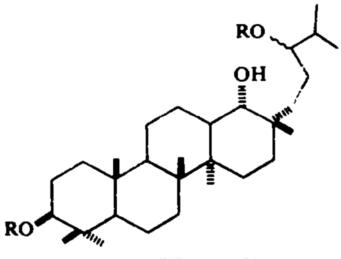
IX: R=H
X: R=Ac



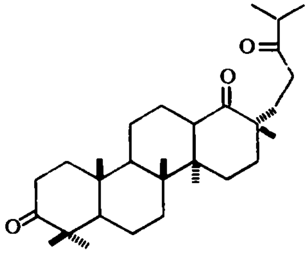
XI: R=H
XII: R=Ac



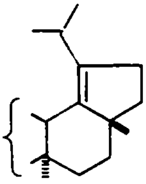
XIII: R=H
XIV: R=Ac



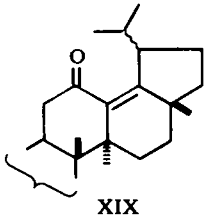
XV: R=H
XVI: R=Ac



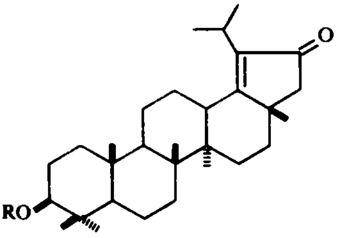
XVII



XVIII



XIX



XX: R=Ac
XXI: R=H

C-13 followed from the positive Cotton effect in the ORD spectrum (amplitude +12). The derived acetoxy-diketone (XIV) had the expected absorption at 1738 (acetate), 1713 and 1705 cm^{-1} (CCl_4) and had m.p. and $[\alpha]_D$ similar to that recorded previously.[2]

The most polar component from the hydroxylation reaction was the triol (XV) showing lowfield NMR due to three C$\underline{H}$OH protons. The oxidation of this triol by chromic acid gave the triketone (XVII) identical with that obtained from the similar oxidation of the hydroxy-diketone (XIII).

The MS of the acetoxy-diketone (XIV), the hydroxy-diketone (XIII) and the triketone (XVII) showed base peaks (100%) at M-98 due to loss of isopropyl vinyl ketone by rearrangement (metastable ions were observed in each case). Major peaks (20-50%) at M-43 were due to loss of isopropyl by α-cleavage in the side-chain. The other common features were ions of *m/e* 237 and 223 attributable to $C_{15}H_{25}O_2$ and $C_{14}H_{23}O_2$, respectively arising from cleavage of ring C.

The triol (XV) was acetylated to give the diacetate (XVI) with NMR due to two C$\underline{H}$OAc groups and one C$\underline{H}$OH group. The half-height width of the latter (3·5 Hz) favoured the formulation as the axial 18α-alcohol. This triol must arise through an anomalous osmate ester decomposition to the diketone[6] with subsequent LAH reduction. The product from the hydrogenation of the diene from lupenyl acetate is therefore the tetrasubstituted olefin (XVIII).

The parent diene must be formulated as III or V if the possibility of bond migration from C-13(18) to C-18(19) during hydrogenation cannot be excluded. We eliminate structure III on the basis of the NMR spectrum. A bis-allylic proton (19-H in III) is expected to show resonance at $\delta \geqslant 2{\cdot}45$.[7-19] No signal appears in the region $\delta 2{\cdot}45$–$4{\cdot}00$ and consequently the diene must have the structure V. The 13βH-stereochemistry is preferred in this oxidation product and its derivatives, since only this configuration permits the all-chair conformation of rings A-D. An analogous structure was previously proposed[20] as an intermediate in the mercuric acetate oxidation reaction.

The chromic acid oxidation of the dihydro-dienes in this and related series led to conjugated ketones.[2, 5, 21] The mixture containing the olefin (XVIII) was oxidized with chromic acid to give a separable mixture containing the saturated acetate, X (identical with the product of acetylation of the alcohol, IX) and the conjugated ketone, XX.[2] The lack of vinylic proton resonance in the NMR spectrum of this ketone was consistent with both structures XIX and XX. The IR spectrum, however, showed absorption at 1736 (acetate), 1698, 1606 and 1413 cm^{-1} (CCl_4). The relative intensities of the 1698 and 1606 cm^{-1} bands (6:1) are not in accord with the cisoid arrangement[22] in XIX and the cyclopentenone structure (XX) is confirmed by the methylene absorption at 1413 cm^{-1}.

The UV spectrum of the acetate (XX) (λ_{max} 244 nm, ε 13700) and that of the derived alcohol (XXI) (λ_{max} 244 nm, ε 14000) are charateristic of transoid cyclopentenones[23] but not of $\Delta^{8(14)}$-7-ketosteroids[24] in which the chromophore is similar to that in XIX. The analogous αβ-unsaturated ketones derived from melaleucic acid,[5] betulic acid,[5] and ceanothenic acid[21] all show UV absorption at λ_{max} ca. 240 nm, ε ca. 13000 which is not consistent with the $\Delta^{13(18)}$-12-one formulation[5] (cf. XIX). Attempts to reduce the alcohol (XXI) to the saturated ketone using Li/NH_3 failed to give a tractable product.

EXPERIMENTAL

M.ps were determined on a Kofler hot stage. Specific rotations were for ca. 1% solns in $CHCl_3$. UV spectra were determined on a Beckman DB-G spectrophotometer. IR spectra were carried out using a Hilger and Watts Infrascan Spectrophotometer with CCl_4 as solvent unless otherwise stated. NMR spectra were for $CDCl_3$ solutions with TMS as internal reference on a Varian A-60 spectrometer. Mass spectra were determined on an AEI MS-9 spectrometer. GLC was carried out on a Pye Series 104 Model 24 instrument equipped with a FI detector. Column used was 1% QF1 on Gas Chrom Q (5′ × 1/4″).Alumina for chromatography was Peter Spence grade H. Light petroleum refers to the fraction b.p. 68–72°.

Oxidation of lupenyl acetate (VIII) *by mercuric acetate*

Lupenyl acetate (15·0 g) in $CHCl_3$ (300 ml) and AcOH (3 l) was refluxed for 5 hr with mercuric acetate (180·0 g). The reaction mixture was worked up according to the described method.[2] Chromatography on alumina (150 g) and elution with light petroleum-benzene (1:1) gave V which recrystallized from MeOH as needles (2·1 g), m.p. 230–231°, $[\alpha]_D$ +44° (lit.[2] m.p. 229–231°, $[\alpha]_D$ +47°), λ 210 nm (ε 7000), 215 nm (ε 4830) and 220 nm (ε 3820), ν_{max} (nujol) 1733, 1624, 1245 and 887 cm^{-1}; NMR 0·84-1·07 (6 Me groups), 1·81 (vinylic Me), 2·04 (acetoxy-H), 4·49 (m, 3α-H), δ 4·72 (m, $C{=}CH_2$). (Found: M, mass spectrum, 466; C, 82·3; H, 11·0. $C_{32}H_{50}O_2$ requires M 466; C, 82·3; H, 10.8%).

*Hydrogenation of 3β-acetoxylupa-*18,20(29)*-diene* (V)

The diene, V (1·5 g) in EtOAc-AcOH (1:1; 600 ml) was catalytically reduced over Pt (0·5 g) to give a product which was shown by GLC and MS to be a mixture of dihydro and tetrahydro compounds. This mixture, which was preparatively inseparable, crystallized from MeOH as plates, m.p. 247–251°, $[\alpha]_D$+9° (lit.[2] m.p. 249–251°, $[\alpha]_D$ + 9°). Analysis (GLC and MS) indicated a mixture consisting of 70% XVIII and 30% X.

Hydroxylation of the hydrogenation product

Osmium tetroxide (1·0 g) in dry ether (15 ml) was added to the hydrogenated product (1·0 g) in pyridine (10 ml) and dry ether (15 ml). After standing for 14 days the osmate ester was decomposed with

LAH (4·0 g) in dry ether (150 ml) at reflux for 1 hr. Decomposition of excess LAH with EtOAc followed by extraction with EtOAc-Et_2O (1:1) gave an oil (0·93 g). This was shown by TLC to be composed of three main components. Chromatography on alumina (30 g) and elution with light petroleum gave the *tetrahydro compound* (IX) which formed needles from MeOH (260 mg), m.p. 197–199°, $[\alpha]_D$ + 7°; ν_{max} (nujol) 3398 cm^{-1} (Found: M, mass spectrum, 428; C, 84·0; H, 12·0. $C_{30}H_{52}O$ requires; M 428; C, 84·0; H, 12·2%).

The acetate (X) on recrystallization from CH_2Cl_2—MeOH gave plates m.p. 270–272°, $[\alpha]_D$+21° (lit.[2] m.p. 272–274°, $[\alpha]_D$ +24°), ν_{max} (nujol) 1733 and 1252 cm^{-1} (Found: M, mass spectrum, 470; C, 81·3; H, 11·4. $C_{32}H_{54}O_2$ requires: M 470; C, 81·6; H, 11·6%).

Elution with benzene gave the *glycol* XI (415 mg) as prisms from CH_2Cl_2—MeOH, m.p. 240–270°, $[\alpha]_D$ (pyridine) +4°; ν_{max} (nujol) 3323 cm^{-1} (Found: M, mass spectrum, 460; C, 78·3; H, 11·4. $C_{30}H_{52}O_3$ requires: M 460; C, 78·2; H, 11·4%).

The mono-acetate XII crystallized from CH_2Cl_2–MeOH as prisms, m.p. 215–246°, $[\alpha]_D$ (pyridine) +11° (lit.[2] m.p. 215–245°, $[\alpha]_D$ +9°), ν_{max} (nujol) 3505, 3450, 1708 and 1268 cm^{-1} (Found: M, mass spectrum, 502; C, 76·4; H, 10·8. $C_{32}H_{54}O_4$ requires: M 502; C, 76·4; H, 10·8%).

Elution with Et_2O–$CHCl_3$ (4:1) gave the *triol* XV which was recrystallized from CH_2Cl_2–MeOH as needles (195 mg), m.p. 210–235°, $[\alpha]_D$ (pyridine) +31°; ν_{max} (nujol) 3300 cm^{-1}; NMR δ 3·27 (m, 3 C$\underline{H}$OH) (Found: M, mass spectrum, 462; C, 77·7; H, 11·6. $C_{30}H_{54}O_3$ requires: M 462; C, 77·9; H, 11·8%).

The *di-acetate* XVI, prepared by the Ac_2O-pyridine method at 25° for 17 hr crystallized from MeOH as needles, m.p. 160–175°, $[\alpha]_D$ (pyridine) +47°; ν_{max} (nujol) 3560, 1735 and 1243 cm^{-1}; NMR 0·82–1·10 (8 Me groups), 2·02 (acetoxy-H), 3·18 (m, 18β-H, $W_{\frac{1}{2}}$ 3·5 Hz), δ 4·58 (m, 2C$\underline{H}$OAc). (Found: M, mass spectrum, 546; C; 74·6; H, 10·4. $C_{34}H_{58}O_5$ requires: M 546; C, 74·7; H, 10·7%).

3β-*Hydroxy*-18,19-*secolupane*-18,19-*dione* (XIII)

The glycol XI (195 mg) was dissolved in benzene (30 ml) and $CHCl_3$ (30 ml). Lead tetra-acetate (208 mg) was added and the mixture was stirred for 16 hr at 25°. Addition of water followed by extraction with benzene gave the *hydroxy-diketone* (XIII) as needles from MeOH (153 mg), m.p. 170–172°, $[\alpha]_D$ +35°; ν_{max} 3595 and 1704 cm^{-1} (Found: M, mass spectrum, 458; C, 78·4; H, 10·8. $C_{30}H_{50}O_3$ requires: M 458; C, 78·5; H, 11·0%).

The acetate (XIV) was recrystallized from MeOH as needles, m.p. 188–189°, $[\alpha]_D$ +39°; ν_{max} 1737, 1713, 1704 and 1245 cm^{-1} (lit.[2] m.p. 186–188°, $[\alpha]_D$ +39·5°; ν_{max} 1739, 1717, 1706 and 1240 cm^{-1}). ORD $[\phi]_{314}$ +699°, $[\phi]_{291}$ 0°, $[\phi]_{270}$ −479°. (Found: M, mass spectrum, 500; C, 76·8; H, 10·5. $C_{32}H_{52}O_4$ requires: M 500; C, 76·8; H, 10·5%).

18,19-*Secolupane*-3,18,19-*trione* (XVII)

(i) The hydroxy-diketone XIII (220 mg), dissolved in acetone (150 ml) was oxidized with Jones reagent at 15°. Addition of water precipitated the *triketone* which formed needles from MeOH (203 mg), m.p. 141–143°, $[\alpha]_D$ +64°; ν_{max} 1708 cm^{-1} (Found: M, mass spectrum, 456; C, 79·0; H, 10·5. $C_{30}H_{48}O_3$ requires: M 456; C, 78·9; H, 10·6%).

(ii) The triol XV (115 mg) was oxidized as above using Jones reagent. The product on recrystallization from MeOH was XVII obtained as needles (78 mg), m.p. 141–143°, $[\alpha]_D$ + 65°. This was shown by IR, NMR, m.m.p., TLC and MS to be identical with XVII obtained above.

3β-*Acetoxylup*-18-*en*-21-*one* (XX)

3β-Acetoxylup-18-ene XVIII (700 mg) in AcOH (150 ml) was treated with CrO_3 (0·5 g) in 90% aqueous AcOH (50 ml) for 17 hr at 25°. Addition of water gave a crystalline solid, isolated by filtration (λ_{max} 244 nm, ε 7900). Elution with light petroleum-benzene (10:1) from alumina (40 g) gave initially X, m.p. 270–272°, $[\alpha]_D$ + 19°; m.m.p., IR and NMR spectra confirmed its identity with the acetate obtained *via* the osmylation reaction (see above). Continued elution with light petroleum-benzene (10:1) gave mixtures and subsequently XX was obtained by elution with light petroleum-benzene (7:1). Recrystallization from MeOH gave needles(165 mg), m.p. 293–295°, $[\alpha]_D$ −59°, λ_{max} 244 nm (ε 13700), ν_{max} 1736, 1698, 1606 and 1413 cm^{-1}. (lit.[2] m.p. 290–292°, $[\alpha]_D$ −61°, λ_{max} 244 nm (ε 13500), ν_{max} 1730, 1689 and 1235 cm^{-1}); ORD $[\phi]_{355}$ −2251°, $[\phi]_{348}$ −1900°, $[\phi]_{343}$ −2020°, $[\phi]_{332}$ 0°, $[\phi]_{300}$ +5000°, $[\phi]_{262}$ 0°, $[\phi]_{251}$ −1260°, $[\phi]_{246}$ 0°, $[\phi]_{216}$ +33600°. (Found: C, 79·7; H, 10·5. $C_{32}H_{50}O_3$ requires: C, 79·6; H, 10·4%).

3β-*Hydroxylup*-18-*en*-21-*one* (XXI)

Hydrolysis of XX using aqueous methanolic K_2CO_3 for 2 hr at reflux temp gave the *hydroxy-ketone* (XXI) which crystallized from MeOH as needles, m.p. 272–275°, $[\alpha]_D -75°$, λ_{max} 244 nm (ε 14000), ν_{max} 1697, 1605 and 1412 cm^{-1} (Found: C, 81·2; H, 10·9. $C_{30}H_{48}O_2$ requires: C, 81·7; H, 11·0%).

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