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TRITERPENE COMPOUNDS—IX

MERCURIC ACETATE OXIDATION OF A MELALEUCIC ACID DERIVATIVE

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Abstract—Methyl acetylmelaleucate (VIII) is shown to react with mercuric acetate to give the non-conjugated diene (IX).

IN A previous communication,[1,2] it was proposed, on NMR evidence, that the hindered carboxyl group in melaleucic acid was at C_{14} and this was confirmed by an X-ray study.[3] Before the results of this work came to hand structural work had involved the mercuric acetate oxidation of some betulic and melaleucic acid derivatives. This oxidation[4,5] has been claimed to insert unsaturation at C_{12} and the method has had application in the structural proof of ceanothenic acid.[6]

Before committing methyl acetylmelaleucate to the mercuric acetate oxidation the reaction was repeated on methyl acetylbetulinate. The product, formulated by Allison *et al.*[3] as I, showed no NMR absorption attributable to the vinylic proton at C_{12}, nor did the dihydro ester (II),[3] whereas the vinylic protons in methyl oleanolate, and methyl oleanolate acetate were readily detected in the NMR spectrum[7] as multiplets, centred at 5·25δ in both cases.

It was quite evident from the NMR spectrum that there was no trisubstituted double bond in the ester (II). This ester gave a yellow colour with tetranitromethane indicating the presence of a double bond. UV absorption at 210 mμ (ε = 5700) 215 mμ (ε = 4500) and 220 mμ (ε = 3700) also showed that this double bond was tetrasubstituted.[8] Thus, provided skeletal rearrangement did not occur, the most likely position for the tetrasubstituted double bond was at $C_{13(18)}$ in which case I and II should be represented as III and IV. If this were true, compounds formulated by Allison *et al.*[4,5] as 13,18-enes would be 19-epimers of the products obtained after mercuric acetate oxidation and hydrogenation of the lup 20,29-enes. The presence of the tetrasubstituted double bond was confirmed by hydroxylation with osmium

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tetroxide of IV to the diol V. Lead tetra-acetate cleaved the diol (V) to the di-keto ester (VI) which was hydrolysed and decarboxylated to the nordiketone (VII) by treatment with methanolic potassium hydroxide and then brief heating at 130–140°. The nordiketone (VII) had IR spectrum at 1740 (5-ring ketone) and 1708 cm^{-1} (6-ring ketone). Neither of the diketone VI or VII showed an aldehyde proton in NMR spectrum.

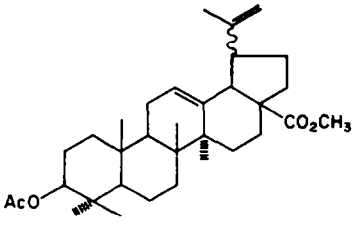
Oxidation of the ester (VIII) by mercuric acetate gave the non-conjugated diene (IX), λ_{max} 201 mμ ($\varepsilon = 7400$). The NMR spectrum showed two olefinic hydrogens as a multiplet centred at 4·75 δ, which could be attributed only to the vinylidene group. The non-conjugated diene was reduced over Pt, to give the dihydro ester (X), which showed no vinylic proton absorption in the NMR spectrum. This dihydro ester (X) gave a strong colour with tetranitromethane.

The ester (X) was successfully oxidized by chromic acid in acetic acid[9] to the conjugated ketone (XIa), with IR absorption at 1690 cm^{-1} (conjugated ketone) and UV absorption at 242 mμ ($\varepsilon = 13{,}500$). The NMR spectrum of the ketone (XIa) showed no absorption expected for a vinylic proton at C_{12},[10] eliminating the 12-en-11-one representation which had been formulated previously.[5,6]

The keto-ester (XIa) was partially hydrolysed by 5% methanolic potassium hydroxide during 4 hr[11] to give the dicarboxylic acid monoester. A methoxycarbonyl group at C_{17} in the triterpene series is not hydrolysed under these conditions,[6,12] and this view is supported by the recovery of conjugated ketone ester (XII) after the same treatment. The rate of hydrolysis of the C_{14}–CO_2CH_3 in melaleucic acid has been very greatly accelerated by the introduction of the conjugated carbonyl. It is known[13,14–15,16] that similar acceleration of axial function can be brought about by a γ-carbonyl group and we attribute the acceleration to the 12 ketone.

The mono-ester was decarboxylated by heating at 185–192° for 15 min under an atmosphere of N_2, to give the norketoester (XIb), thus establishing the β,γ-relationship of the double bond to the carbonyl group. The product still contained a conjugated ketone grouping, revealed by IR absorption at 1690 cm^{-1} and UV absorption at 240 mμ ($\varepsilon = 13{,}200$).

Melaleucic acid was thus shown to be 3β-hydroxylup-20(29)-en-27,28-dioic acid



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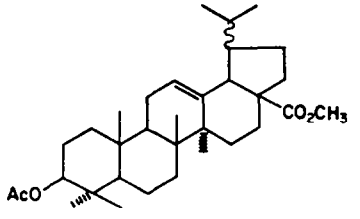

II

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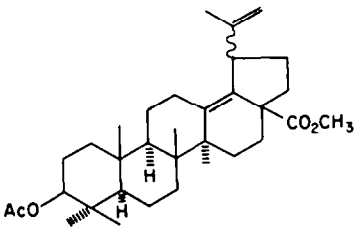

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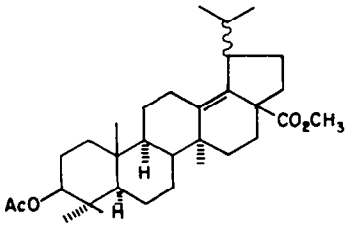

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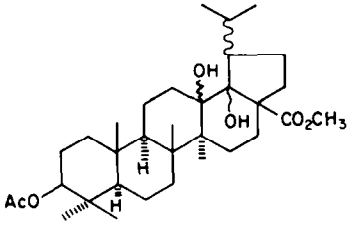

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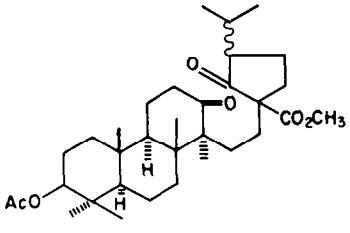

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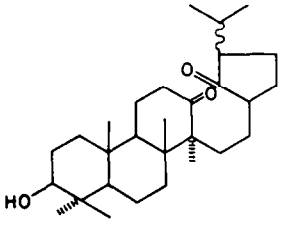

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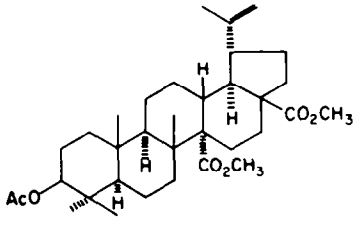

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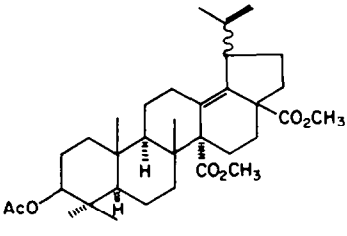

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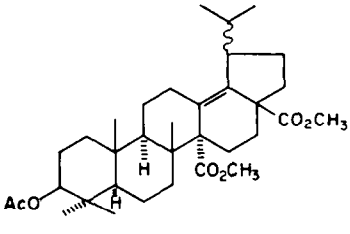

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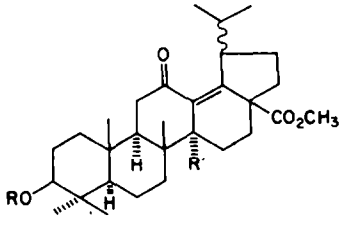
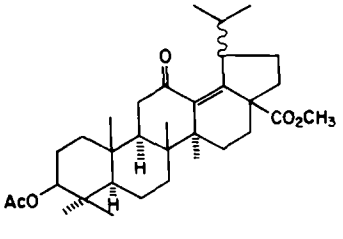


XI a; R=Ac, R'=CO_2CH_3
XI b; R=H, R'=H



XII

EXPERIMENTAL

M.ps were recorded on a Kofler stage. Optical rotations, UV and IR spectra were recorded for $CHCl_3$, EtOH and CS_2 solutions respectively. NMR spectra were recorded, on a Varian A60 high-resolution spectrometer, for $CDCl_3$ solutions with tetramethylsilane as internal reference. All peak positions are recorded on δ-scale. Alumina for chromatography was Peter Spence grade H standardized[17] at activity II. Light petroleum refers to the fraction b.p. 56–60°. Micro-analyses were carried out by the C.S.I.R.O. Microanalytical service in the University of Melbourne.

Mercuric acetate oxidation of methyl 3β-acetoxy-lup-20(29)-en-28-oate. Methyl acetylbetulinate (2·4 g) in $CHCl_3$ (100 ml) was heated under reflux with mercuric acetate (35 g) in acetic acid (500 ml) for 5 hr. The reaction mixture was worked up in the manner described[4] to give the crude product which was dissolved in light petroleum–benzene (10:1; 200 ml) and chromatographed on alumina (40 g). Elution with light petroleum–benzene (1:4) gave *methyl 3β-acetoxylupa-13(18),20(29)-dien-28-oate* (111; 600 mg) as prisms from MeOH, m.p. 216–218°, $[\alpha]_D$ +58° (*c*, 0·64) (cf. Lit.[4] m.p. 217–219°, $[\alpha]_D$ +60°). (Found: C, 77·7; H, 10·0. $C_{33}H_{50}O_4$ requreis: C, 77·6; H, 9·9%.)

The NMR spectrum showed a singlet at 3·67 (3H) attributed to the protons of methoxy-carbonyl group; a multiplet centred at 4·75 (2H) (protons of the vinylidene group); a broad multiplet centered at 4·42 (1H) (3α proton); a singlet at 1·96 (3H) (protons of acetoxy group) and showed no absorption attributable to the vinylic proton at C_{12}. The UV spectrum showed an absorption at 205 mμ (ε = 7300).

Methyl 3β-acetoxylup-13(18)-en-28-oate (IV). Methyl 3β-acetoxylupa-13(18),20(29)-dien-28-oate (200 mg) in ethyl acetate–acetic acid (1:5; 50 ml) was catalytically reduced over Pt (50 mg) to give IV(180 mg) as plates from $CHCl_3$–MeOH, m.p. 214–216°, $[\alpha]_D$ +20° (*c*, 0·68). (cf. Lit.[4] m.p. 215–217°, $[\alpha]_D$ +19°.). (Found: C, 77·5; H, 10·1. $C_{33}H_{52}O_4$ requires: C, 77·3; H, 10·2%.)

The NMR spectrum showed a singlet at 3·65 (3H) attributed to the protons of methoxycarbonyl group; a broad multiplet centered at 4·42 (1H)(3α proton); a singlet at 1·98 (3H) (protons of acetoxy group) and showed no absorption attributable to the vinylic proton at C_{12}.

Methyl 3β-acetoxy-13,18-dihydroxy-lupan-28-oate-(V). Methyl 3β-acetoxylup-13(18)-en-28-oate (210 mg) in pyridine (3 ml) was treated with OsO_4 (250 mg) for 7 days at room temp. After dilution with pyridine (10 ml) the mixture was saturated with H_2S.[8] The black precipitate was filtered off and the pyridine solution evaporated to dryness under red. press. The residue was dissolved in benzene–chloroform (3:1) and chromatographed on alumina (10 g). Elution with chloroform gave the *dihydroxy ester* (V; 60 mg) as prisms from MeOH, m.p. 172–174°, $[\alpha]_D$ +16° (*c*, 0·82). (Found: C, 72·8; H, 10·1. $C_{33}H_{54}O_6$ requires: C, 72·5; H, 10·0%.) ν_{max} 3540 cm^{-1} (OH), δ2·05 and 3·70 (one acetate Me and one ester Me).

Methyl 3β-acetoxy-13,18-dioxo-13,18-secolupan-28-oate (VI). Methyl 3β-acetoxy-13,18-dihydroxy-lupan-28-oate (100 mg) in $CHCl_3$ (10 ml) and dry benzene (20 ml) containing lead tetra-acetate (300 mg) was kept at room temp for 20 hr. After filtration the mixture was diluted with H_2O and extracted with ether. The residue was dissolved in benzene–chloroform (4:1) and chromatographed on alumina (5 g). Elution with $CHCl_3$ gave the *diketo ester* (VI; 40 mg) as needles from MeOH, m.p. 169–171° (dec), $[\alpha]_D$ +65° (*c*, 0·64). The IR spectrum showed no hydroxyl absorption. The NMR spectrum showed no aldehyde proton. (Found: C, 73·1; H, 9·7. $C_{33}H_{52}O_6$ requires: C, 72·8; H, 9·6%.)

3β-Hydroxy-13,18-dioxo-13,18-seco-28-nor-lupane (VII). A solution of methyl 3β-acetoxy-13,18-dioxo-13,18-seco-lupan-28-oate (100 mg) and KOH (2 g) in MeOH (40 ml) was refluxed for 4 hr in the atmosphere of N_2. The mixture was acidified (HCl), diluted with water, and extracted with ether. The crude product was decarboxylated during 10 min at 130–140° under an atmosphere of N_2. The product was dissolved in ether, washed free of acids by 3% NaOH, and the residue was filtered through alumina (5 g) in $CHCl_3$ to give the *nor diketone* (VII; 35 mg), m.p. 136–137°, $[\alpha]_D$ +58° *c*, 0·78). ν_{max} 3628 (OH), 1740 (5-ring ketone) and 1708 cm^{-1} (6-ring ketone). The NMR showed no ester protons. (Found: C, 78·1; H, 11·0. $C_{30}H_{46}O_2$ requires: C, 78·3; H, 10·9%.)

Methyl 3β-acetoxylupa-13(18),20(29)-dien-27,28-dioate (IX). Methyl 3β-acetoxylup-20(29)-en-27,28-dioate (6·5 g) and mercuric acetate (95 g) were heated in refluxing $CHCl_3$ (208 ml) and acetic acid (1·3 l) for 5 hr. The reaction mixture was worked up in the manner described[4] to give the crude product which was dissolved in light petroleum–benzene (4:1; 150 ml) and chromatographed on

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alumina (150 g). Elution with light petroleum–benzene (1:1) gave the *non-conjugated diene* (IX; 1·5 g) as prisms from MeOH, m.p. 206–207°, $[\alpha]_D$ +114° (*c*, 0·87). (Found: C, 73·6; H, 8·9. $C_{34}H_{50}O_6$ requires: C, 73·6; H, 9·1%.) The NMR spectrum showed singlets at 3·63 (3H) and 3·62 (3H) attributed to the protons of methoxycarbonyl groups; a multiplet centred at 4·75 (2H) (protons of the vinylidene group); a broad multiplet centred at 4·42 (1H) (3α proton); and a singlet at 1·93 (3H) (protons of acetoxy group).

Methyl 3β-acetoxylup-13(18)-en-27,28-dioate (X). Methyl 3β-acetoxylupa-13(18),20(29)-dien-27,28-dioate (600 mg) in ethyl acetate–acetic acid (1:5; 200 ml) absorbed H_2 (1 mole) in the presence of Pt (140 mg) to give the *dihydro ester* (X; 560 mg) as needles from MeOH–water, m.p. 151–152°, $[\alpha]_D$ +72° (*c*, 0·79). (Found: C, 73·4; H, 9·4. $C_{34}H_{52}O_6$ requires: C, 73·3; H, 9·4%.) The NMR spectrum showed singlets at 3·62 (3H) and 3·60 (3H) attributed to the protons of methoxycarbonyl groups; a broad multiplet centered at 4·42 (1H) (3α proton); and a singlet at 1·97 (3H) (protons of acetoxy group). The UV spectrum showed absorption at 210 mμ (ε = 6050), 215 mμ (ε = 4900), 220 mμ (ε = 3800).

Methyl 3β-acetoxy-12-oxolup-13(18)-en-27,28-dioate (XIa). A solution of methyl 3β-acetoxylup-13(18)-en-27,28-dioate (410 mg) in glacial acetic acid (150 ml) was oxidized with CrO_3 (210 mg) in water (7 ml) and acetic acid (63 ml) for 20 hr. The solution was diluted with MeOH (5 ml) and water (500 ml) and worked up in the usual way with ether to give the *conjugated ketone* (XIa; 240 mg) as prisms from MeOH–water, m.p. 237–238°, $[\alpha]_D$ +78° (*c*, 0·60). (Found: C, 71·8; H, 8·9. $C_{34}H_{50}O_7$ requires: C, 71·6; H, 8·8%.)

Methyl 3β-hydroxy-12-oxo-27-norlup-13(18)-en-28-oate (XIb). A solution of methyl 3β-acetoxy-12-oxolup-13(18)-en-27,28-dioate (330 mg) and KOH (6·5 g) in MeOH (130 ml) was refluxed for 4 hr in the atmosphere of N_2. The mixture was acidified (HCl), diluted with water, and extracted with ether. The organic layer was extracted several times with 3% NaOH and evaporated to give a neutral product (28 mg) as a gum which was not investigated further. The NaOH washings were re-acidified (HCl) and extracted with ether to give, on evaporation, an acid (280 mg).

This acid was decarboxylated during 15 min at 185–192° under an atmosphere of N_2. The product was dissolved in ether, washed free of acids by 3% NaOH, and the yellow residue (190 mg) was dissolved in light petroleum–benzene (1:4; 25 ml) and chromatographed on neutral alumina (5 g). Elution with benzene gave the *norketo-ester* (XIb; 125 mg) as needles from MeOH, m.p. 182–183°, $[\alpha]_D$ +75° (*c*, 0·98). (Found: C, 76·3; H, 9·9. $C_{30}H_{46}O_4$ requires: C, 76·5; H, 9·8%.) The NMR spectrum showed a singlet at 3·60 (3H) attributed to the protons of the remaining methoxycarbonyl group.

Methyl 3β-acetoxy-12-oxolup-13(18)-en-28-oate (XII). A solution of methyl 3β-acetoxylup-13(18)-en-28-oate (205 mg) in glacial acetic acid (75 ml) was oxidized with CrO_3 (100 mg) in water (4 ml) and acetic acid (30 ml) for 20 hr to give the *conjugated ketone* (XII; 100 mg) as plates from MeOH, m.p. 208–209°, $[\alpha]_D$ +26° (*c*, 0·98). (Found: C, 75·2; H, 9·9. $C_{32}H_{50}O_5$ requires: C, 75·2; H, 9·6%.) The UV spectrum showed absorption maximum at 240 mμ (ε = 12,500). The NMR spectrum showed no absorption due to the vinylic proton at C_{12}.

Attempted hydrolysis of methyl 3β-acetoxy-12-oxolup-13(18)-en-28-oate (XII). A solution of XII(110 mg) and KOH (2·1 g) in MeOH (40 ml) was refluxed for 4 hr in the atmosphere of N_2. The mixture was acidified (HCl), diluted with water, and extracted with ether. The organic layer was extracted several times with 3% NaOH and evaporated to give the neutral product (100 mg) which was acetylated by the acetic anhydride–pyridine method to give the starting material m.p. and mixed m.p.

The NaOH washings were re-acidified and extracted with ether to give no residue.

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