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SOME KETOMANOYL OXIDES

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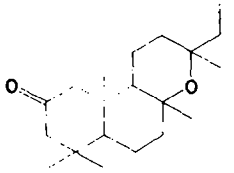
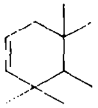
Abstract—1-Keto and 3-ketodihydromanoyl oxides have been prepared and their rotatory dispersion curves compared with that of 2-ketodihydromanoyl oxide.

In view of the strong positive Cotton effect exhibited by 2-ketomanoyl oxide,[1] it was thought desirable to prepare the corresponding 1- and 3-ketones.

Accordingly, 8α,13-oxidolabdan-2-one[2] (2-ketodihydromanoyl oxide) (I) was reduced with sodium borohydride to an alcohol identical with that obtained by Grant[3] and considered to be the β-epimer. This reacted with phosphorus pentachloride giving a mixture of the olefin II and the chloro-compound III which could be dehydrochlorinated to II. When phosphorus oxychloride in pyridine was used for the dehydration, II was the sole product. Epoxidation of II, followed by reduction of the product with lithium aluminium hydride yielded an alcohol which was not characterized, but oxidized to the ketone IV.



I



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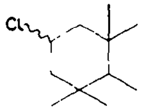

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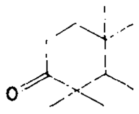

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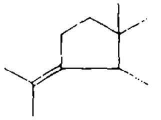
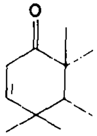


V



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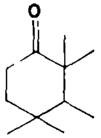

VII

That this was, in fact, 8α,13-oxidolabdan-3-one was demonstrated, first by hydrogenation of II to 8α,13-oxidolabdane to show that no skeletal changes had taken place; and second by the usual retropinacol ring contraction on the 3β-alcohol, by which V was obtained as an oil. Ozonolysis of this gave acetone, isolated as its 2,4-dinitrophenylhydrazone in high yield, together with a substance having I.R. absorption at 1746 cm^{-1} characteristic of a cyclopentanone.

The preparation of the 1-ketone was accomplished by oxidation of II with selenium dioxide in acetic acid. The resulting crude allylic acetate was hydrolysed, then

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[1] P. K. Grant and R. Hodges, *Chem. & Ind.* 1300 (1960).

[2] Prepared by hydrogenation of 2-ketomanoyl oxide extracted from the wood oil of Dacrydium Colensoi, and generously supplied by Dr. P. K. Grant.

[3] P. K. Grant, *J. Chem. Soc.* 860 (1959).

oxidized to the en-one VI. This had U.V. absorption (in methanol) at 225 mμ, ε 8400, consistent with its structure. On hydrogenation it yielded 8α,13-oxidolabdan-1-one (VII). In order to confirm its structure this was reduced by the Wolff-Kishner procedure to 8α,13-oxidolabdane. These experiments support the placing of the carbonyl group in natural ketomanoyl oxide at C_2 making it the only diterpene known to be oxygenated at this position.

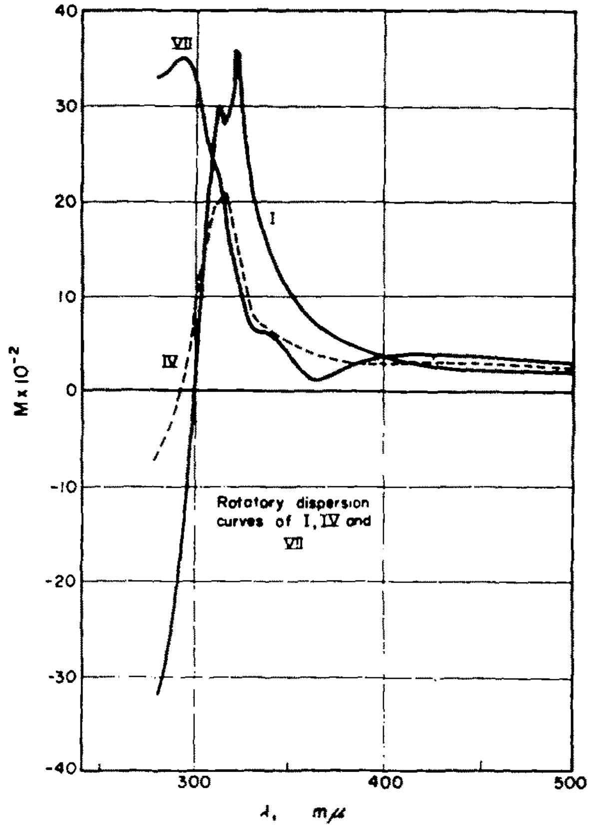

FIG. 1.

The frequency of the carbonyl I.R. absorption bands of the 1-, 2- and 3-ketones are in the expected order at 1706·5, 1711·5 and 1708 cm^{-1} (in CCl_4) though that of the 2-ketone is appreciably lower than is normal for a cyclohexanone with no α-substituents. This might conceivably be caused by the strain which must be introduced into ring A by the four axial substituents at C_4, C_8, C_{10} and C_{13}.

The rotatory dispersion curves of I, IV and VII are similar to those of their steroid analogues, though it might be expected that the methyl substituents at C_4 would cause a considerable difference in I and IV. The curve of IV is also similar to those of 8β-methyl triterpenes, e.g. dipterocarpol and onocerone dione-I, which are thought[4] to exist largely in the true A-boat form in solution. Hence IV, which is even more congested on the β-face than dipterocarpol, probably has ring A in a boat form.

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[4] R. Hanna, J. Levisalles and G. Ourisson, *Bull. Soc. Chim.* 1936 (1960).

However, a very high degree of compression would be needed for the A-boat form to be preferred in I, for in this case the additional unfavourable interaction between the 3β-hydrogen and the methyl group at C_{10} would be introduced.

The octant rule[6] would predict that if ring A assumes a chair form, I should exhibit a positive Cotton effect of low amplitude, since the nearest atoms to the carbonyl group to make any contribution should be C_8 and C_{11}. The nature of the Cotton effect of the A-boat conformation of I is hard to predict in view of the asymmetry introduced into ring A itself in this form. Until other 2-keto di- and triterpenes with varying amounts of 1,3-diaxial substitution are available for comparison, no reliable deductions regarding the shape of ring A in these compounds can be made.

EXPERIMENTAL

Rotations were measured in chloroform at room temperature unless otherwise stated. M.p.'s were taken on a Kofler block and are corrected. The alumina used for chromatography had activity II. Light petroleum refers to the fraction with b.p. 60–80°.

8α,13-*Oxido-labd*-2-*ene* (II). 8α,13-Oxidolabdan-2-one (260 mg, $[\alpha]_D$ +34° c, 1·1) was allowed to react with sodium borohydride (100 mg) in aqueous methanol (15 ml, 80%) for 2 hr. After crystallization from aqueous methanol the product (193 mg) had m.p. 81·5–83°, $[\alpha]_D$ +40° (*c*, 0·9). Dehydration of this alcohol using the conditions described by Grant gave 8α,13-oxidolabd-2-ene, m.p. 84–85°, $[\alpha]_D$ +37° (*c*, 1·0). When the dehydration was carried out by shaking the alcohol (305 mg) with phosphorus pentachloride (300 mg) in light petroleum (20 ml), the product was an oil consisting of a mixture of the choro-compound (III) and II, which could be isolated by repeated crystallization from methanol.

8α,13-*Oxidolabdan*-3-*one* (IV). II (125 mg) was allowed to react with a solution of monoperphthalic acid in ether (7 ml, 0·5 molar) for four days at 20°. The resulting oil was heated under reflux with lithium aluminium hydride (60 mg) in tetrahydrofuran (10 ml) for 10 hr. The product was adsorbed from benzene on alumina, eluted with ether, then oxidized in acetone with 8 N chromic acid/sulphuric acid. After dilution with water, ether extraction and chromatography on alumina, 8α,13-*oxidolabdan*-3-*one* formed needles (81 mg) from aqueous methanol, m.p. 70–71·5°, $[\alpha]_D$ +33° (*c*, 0·9). (Found: C, 78·45; H, 10·85. $C_{20}H_{34}O_2$ requires: C, 78·4; H, 11·2%).

Retropinacol rearrangement. IV (205 mg) was allowed to react with sodium borohydride (100 mg) in aqueous methanol (20 ml, 80%) for 1 hr. The product in light petroleum (15 ml) was shaken with phosphorus pentachloride (300 mg) for 10 min, then filtered through alumina. Evaporation gave an oil (V) which could not be crystallized and whose I.R. spectrum did not show absorption bands characteristic of an —OH group, a disubstituted double bond or a chloro-compound. Ozonolysis of V (184 mg) in acetic acid (18 ml) yielded acetone, isolated as its 2,4-dinitrophenylhydrazone (112 mg), together with a gum with I.R. absorption at 1746 cm^{-1} (in CCl_4).

8α,13-*Oxidolabd*-2-*en*-1-*one* (VI). II (85 mg) was heated under reflux with selenium dioxide (150 mg) in acetic acid (5 ml) for 15 min. The crude product which had I.R. absorption at 1726 cm^{-1}, was hydrolyzed by heating for 1 hr with sodium hydroxide (1 g) in aqueous methanol (10 ml, 80%). Chromatography on alumina afforded an alcohol which was not characterised but oxidised in acetone with 8 N chromic acid/sulphuric acid to VI. This crystallized as needles (51 mg) from methanol, m.p. 135–136°, $[\alpha]_D$ +86° (*c*, 0·8). (Found: C, 78·9; H, 10·6. $C_{20}H_{32}O_2$ requires C 78·6; H, 10·5%).

A similar selenium dioxide oxidation was carried out on the crude product (140 mg) from the reaction of phosphorus pentachloride with the 2-alcohol. After hydrolysis, two products were separated by chromatography; an alcohol (76 mg) as before, and 2-*chloro*-8α,13-*oxidolabdane* (III) which formed needles (29 mg) from methanol, m.p. 111–112°, $[\alpha]_D$ 0° (*c*, 0·6). (Found: C, 73·95; H, 10·85; Cl, 10·85. $C_{20}H_{35}OCl$ requires: C, 73·5; H, 10·8; Cl, 10·85%).

8α,13-*Oxidolabdan*-1-*one* (VII). Hydrogenation of VI (40 mg) in ethyl acetate using 10% palladium on charcoal catalyst gave VII (35 mg) as needles from aqueous methanol, m.p. 80–81°, $[\alpha]_D$ +75° (*c*, 1·1). (Found: C, 78·8; H, 11·2. $C_{20}H_{34}O_2$ requires: C, 78·4; H, 11·2%).

Dehydrochlorination of III. III (20 mg) was heated under reflux with sodium hydroxide (1 g) in

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[6] C. Djerassi, *Optical Rotatory Dispersion* p. 178. McGraw-Hill, New York (1960).

diethylene glycol (5 ml) for 15 hr. Isolation in the usual manner afforded II (15 mg), m.p. 84–85° undepressed with an authentic specimen. Catalytic hydrogenation of II gave 8α,13-oxidolabdane, m.p. 19–21° $[\alpha]_D$ +12° (*c*, 0·8), identical with a specimen prepared by the usual Wolff-Kishner reduction of either VII or I.

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