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THE STEREOCHEMISTRY OF MANOYL OXIDE

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Abstract The stereochemistry of manoyl oxide at C_8 has been established by hydrogenolysis to 8α-hydroxylabd-13-ene. Electron-impact induced fission of the molecule shows that C_{13} has a β-configuration, and hence manoyl oxide is represented by I.

THE tetrahydropyran ring in dihydromanoyl oxide has been opened[1] to give a dichloride which has been obtained from sclareol; but no valid deductions can be made about the stereochemistry at C_8 and C_{13} in manoyl oxide.

Ohloff has shown[2] that a manoyl oxide can be prepared from sclareol. This synthetic material has m.p. 94–96°, $[\alpha]_D$ +37·5°, while natural manoyl oxide has m.p. 24·5–26°, $[\alpha]_D$ +23°. He suggested that either natural manoyl oxide was impure or that the synthetic material was an isomer at C_8 or C_9. Natural manoyl oxide behaves as a pure substance during gas–liquid chromatography with a retention time of 22·9 min at 195° on a column of 5 per cent Apiezon L on 120 mesh celite. A sample of the synthetic material, with m.p. 94–96°, showed two peaks with *rT*'s of 22·9 and 24·9 min. The first of these was inseparable from natural manoyl oxide by this technique and amounted to approx 2 per cent of the synthetic sample.

It is clear that the bulk of the synthetic oxide must be a stereoisomer of natural manoyl oxide, and will be designated as epi-manoyl oxide. It is probable that during the cyclization of sclareol the oxide ring in epi-manoyl oxide will be attached to C_8 from the α-face of the molecule. As is shown later, this is the configuration at C_8 in manoyl oxide, so it seemed likely that the material prepared by Ohloff was a C_{13} epimer. This was shown to be so, by hydrogenolysis of both epimers to give the same 8α-hydroxylabd-13-ene (II).

Dehydration of II with phosphorus oxychloride in pyridine produced an inseparable mixture of three products in the ratio of 75 : 16 : 9 (determined by gas-liquid chromatography). It would appear that all three possible dehydration products have been formed. That the major component was labda-8(20),13-diene was demonstrated by a quantitative comparison of the infra-red spectrum of the mixture with that of α-onocerin diacetate. The ΔM_D (olefin-alcohol) for the mixture had a value of +105 which is in reasonable agreement with that of +98° between sclareol and manool. Since this rotation difference corresponds to the removal of one asymmetric centre, it is probable that C_{20} in manoyl oxide has a β orientation.

Hydroxylation of manoyl oxide, followed by oxidation with lead tetracetate gave the aldehyde (IIIa). When this was oxidized with chromium trioxide, two products were formed; the lactone (IV) and the acid (IIIb). Since IV is known[3] to be less stable than the corresponding 8-epimer, its isolation from this reaction is further

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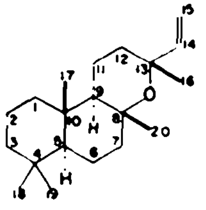
[1] J. R. Hosking and C. W. Brandt, *Ber. Dtsch. Chem. Ges.* **68**, 37 (1935).
[2] G. Ohloff, *Liebigs Ann.* **617**, 134 (1958).
[3] M. Hinder and M. Stoll, *Helv. Chim. Acta* **36**, 1995 (1953).

evidence of an 8α-oxido group in manoyl oxide. The sodium salt of the acid was treated with oxalyl chloride, followed by conversion to the diazoketone and heating with cupric oxide in toluene.[4] It was thought that, if the carboxyl group in IIIb was *cis* with respect to C_{20}, cyclization to V may take place. However, no pure ketonic material was isolated.

It was then decided to alter the shape of the manoyl oxide molecule in such a way



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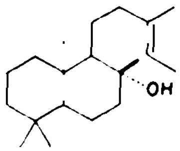

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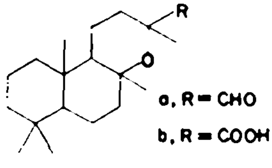

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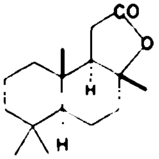

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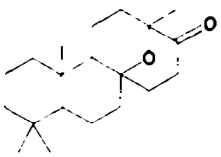

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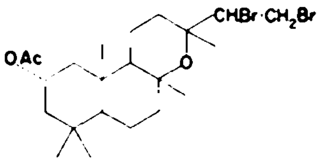

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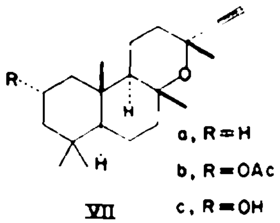

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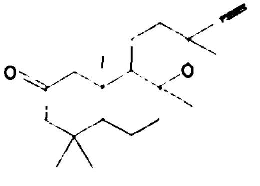
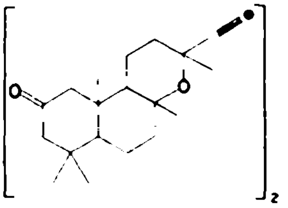
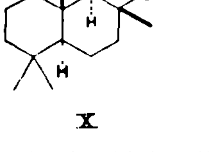


VIII



IX



X

that it should be distinguishable from its C_{13} epimer. 2-Oxomanoyl oxide was reduced with sodium borohydride, the alcohol acetylated and the product brominated giving 2α-acetoxy-14,15-dibromo-8α,13-oxido-labdane (VI). This was dehydrobrominated to the 2-acetoxyacetylene (VIIb) which was converted to the ketone (VIII).

This was oxidatively dimerized to 15,15′-di(8α,13-oxido-2-oxolabd-14-ynyl) (IX). Though the two C_{13} epimers of this structure have very different molecular dimensions no steric conclusions could be drawn from an X-ray determination of the size of the crystal unit cell of IX.

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[4] F. Greuter, J. Kalvoda and O. Jeger, *Proc. Chem. Soc.* 349 (1958).

The acid (IIIb) has infra-red absorption at 3360 cm^{-1} and 1780 cm^{-1} in dilute carbon tetrachloride solution, showing strong intramolecular hydrogen bonding. This bonding must be between the hydrogen of the carboxyl group and the ether oxygen, involving a five-membered ring, which may contribute towards the abnormally high frequency of the carbonyl absorption. In addition, this frequency would be increased by the presence of an α-oxygen substituent. The methyl ester IIIc showed two bands at 1731 and 1751 cm^{-1} comparable with those reported for many α-halogenoesters and for allyl phenoxyacetate.[5] It would appear, from models, that bonding of this type would be unlikely in a structure with a β-carboxyl group unless the tetrahydropyran ring was in a boat form. Hence it is probable that IIIb has an α-carboxyl group. Unfortunately, through lack of material, we were unable to confirm this by preparing the 13-epimer of IIIb. However, conclusive evidence on this point was obtained by electron-impact induced fission of manoyl oxide, which is discussed below.

Evidence has accumulated which suggests that the break-down of the molecular ions of epimeric compounds differs.[6] This gives rise to "cracking-patterns" which differ in the intensity of the fragment ions, rather than in the ion species formed. These differences in intensity have been interpreted in terms of the congestion of the molecular structure around the centres of cleavage.

Accordingly, an examination of the cracking-patterns of manoyl oxide and epimanoyl oxide was made. The relative ease of loss of a methyl group from both systems was compared. Clearly, because of the presence of five methyl groups in each molecule, the contribution to ions of mass 15, and of mass 275 representing the parent minus 15 (P-15), may be made up from fissions from any of these centres. The relative ease of loss of a methyl group from all positions except C_8 and C_{13} may be expected to be very nearly the same and consequently any inequality occuring in the intensities of the fragment ions mentioned may be attributed to the differing ease of loss of methyl groups at these centres. Experiment shows that there is proportionally greater loss from manoyl oxide than epimanoyl oxide suggesting that the substitutents on the oxide-ring are in a more congested environment in the former.

Since it is known that allylic bonds are very susceptible to fission,[7] experiments were carried out in which the electron beam energy was in the region of the appearance potential of the ion obtained by the loss of a methyl group from the parent molecular ion. Comparison of the ratio of the intensities P-15/P were made, giving ratios which varied slightly with the accelerating voltage, but were of the order of ·46 and ·35 for manoyl oxide and epimanoyl oxide respectively. Notwithstanding the variations with ionizing potential, the ratio for manoyl oxide was always the greater under the same bombardment conditions. This confirms the observation that the groups are in the more congested position in manoyl oxide.

Some ambiguity remains; as the configuration around C_{13}, which bears both the methyl and vinyl group, will depend upon which group exerts the greatest steric congestion in the β-configuration. Hence, similar experiments were conducted upon the corresponding compounds in which the vinyl group was replaced by an acetylene residue. In this series the interaction of an 8β-methyl group with a 13β-ethynyl group

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[5] M. L. Josien and C. Castinel, *Bull. Soc. Chim. Fr.* 801 (1958).

[6] K. Bjemann and J. Seibl, *J. Amer. Chem. Soc.* **81**, 3149 (1959).

[7] R. A. Brown and E. Gillams, A.S.T.M. Committee E-14 on Mass Spectrometry, 2nd Annual Meeting, New Orleans (1954).

must certainly be less than that with a 13β-methyl. The intensity of the parent molecular ion was rather low, but a comparison was made between the fragment ions of mass 273 and 263 corresponding to the loss of a methyl and an ethynyl group respectively. For 8α,13-oxidolabd-14-yne (VIIa) the ratio of intensity of the ions is 3·10 which is greater than 1·97 for 8α,13-epioxidolabd-14-yne (X). This indicates a preferential loss of a methyl group in the acetylenic derivative having the same conformation as manoyl oxide. A check upon this deduction was made by examining the relative intensities of the two ions, methyl and ethynyl, which gave the same result. Finally a low energy analysis of P-15/P for both these compounds supported this conclusion. Consequently one may deduce that in manoyl oxide, C_{16} is in the axial β-position which is the more congested one. Though, of necessity, the 8α,13-epioxidolabd-14-yne was not available in sufficient quantity for elemental analysis, there can be no doubt as to the validity of this conclusion.

It has been assumed that the tetrahydropyran ring in manoyl oxide and its derivatives is in a chair form. Should this not be so, the interpretation of the "cracking-patterns" becomes difficult, but it would seem likely that manoyl oxide has C_{16} in an α-configuration.

EXPERIMENTAL

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

8α-Hydroxylabd-13-ene (II). 8α,13-Oxidolabd-14-ene (I, manoyl oxide, 500 mg) in ether (15 ml) was added to a solution of lithium (1 g) in liquid ammonia (75 ml). After 30 min the excess lithium was destroyed with ammonium chloride and the product adsorbed on alumina (50 g) from light petroleum. Elution with benzene ether (9:1) gave II as needles (445 mg) from aqueous methanol, m.p. 99 100·5°, $[\alpha]_D$ 1° (*c*, 1·0). (Found: C, 82·1; H, 12·4. $C_{20}H_{36}O$ requires: C, 82·1; H, 12·4%). Infra-red absorption in Nujol at 826 cm^{-1} (CH C). Hydrogenolysis of epi-manoyl oxide under the same conditions gave the same product. Reaction of II, in acetic acid, with ozonized oxygen gave acetaldehyde, isolated as its 2,4-dinitrophenylhydrazone in 63% yield.

Dehydration of 8α-hydroxylabd-13-ene. 8α-Hydroxylabd-13-ene (93 mg), phosphorus oxychloride (200 ml) and pyridine (2 ml) were maintained at 20° for 15 hr. The product, in pentane was filtered through alumina (activity I) and distilled at 100°/0·05 mm, $[\alpha]_D$ + 37·3° (*c*, 1·3). (Found: C, 87·9; H, 12·2. $C_{20}H_{34}$ requires: C, 87·5; H, 12·5%).

Oxidation of manoyl oxide. Manoyl oxide (1·31 g), osmium tetroxide (1·25 g) and pyridine (5 ml) were allowed to react in ether at 0° for 48 hr. The resulting osmate ester was decomposed with hydrogen sulphide. The product was adsorbed on alumina (100 g) from benzene and eluted with ether–methanol (19:1) as a black oil (1·35 g). This was heated under reflux for 30 min with lead tetracetate (3·5 g) in benzene (60 ml), adsorbed from benzene on alumina and the aldehyde (IIIa) eluted with benzene ether (9:1) as a colourless oil (390 mg). This was characterized as its semicarbazide which crystallized as fine needles from aqueous ethanol, m.p. 225 227·5°. (Found: C, 68·45; H, 10·15; N, 11·85. $C_{20}H_{35}O_2N_3$ requires: C, 68·75; H, 10·1; N, 12·0%). (Lit.[8], m.p. of the 13-epimer: 210–212°).

Oxidation of the aldehyde (IIIa). IIIa (169 mg) and chromium trioxide (39 mg) were allowed to react in acetic acid (5 ml) for 12 hr at 20°. The acidic product was adsorbed on silica gel (20 g) from benzene and eluted with chloroform as needles (72 mg from aqueous methanol) of the acid (IIIb), m.p. 45 47°, m.p. 97 98° after drying for 48 hr at 40°/0·05 mm, $[\alpha]_D$ · 42° (*c*, 0·7). (Found: C, 74·4; H, 10·3. $C_{19}H_{32}O_3$ requires: C, 74·0; H, 10·45%).

Methylation of IIIb with ethereal diazomethane gave the ester (IIIc) as needles from aqueous methanol, m.p. 83–85°, $[\alpha]_D$ · 14° (*c*, 0·5). (Found: C, 74·65; H, 10·7. $C_{20}H_{34}O_3$ requires: C, 74·5; H, 10·65%). Infra-red absorption in CCl_4 at 1731 and 1751 cm^{-1}).

The neutral product from the chromium trioxide oxidation was adsorbed on alumina (20 g) from light petroleum and eluted with benzene ether (9:1) as flat needles (21 mg from light petroleum) of the lactone (IV), m.p. 125–126·5°, $[\alpha]_D$ +41° (*c*, 0·8 in benzene). (Lit.[8] values: m.p. 125°, $[\alpha]_D$ +41°). (Found: C, 77·0; H, 10·05. $C_{16}H_{26}O_2$ requires: C, 76·75; H, 10·45%). The infra-red spectrum in nujol was identical with that published in the literature.

2α-*Acetoxy*-8α,13-*oxidolabd*-14-*ene*. 8α,13-Oxido-2-oxolabd-14-ene (2-oxomanoyl oxide, 250 mg) was treated with sodium borohydride (250 mg) in aqueous methanol (15 ml) for 2 hr. The crude product was heated under reflux for 1 hr with acetic anhydride (4 ml) and sodium acetate (500 mg), then adsorbed on alimina (25 g) from light petroleum and eluted with light petroleum benzene (9:1) as prisms of 2α-*acetoxy*-8α,13-*oxidolabd*-14-*ene* (200 mg) from light petroleum, m.p. 107·5–109°, $[\alpha]_D$ +37° (*c*, 1·5). (Found: C, 75·8; H, 10·45. $C_{22}H_{36}O_3$ requires: C, 75·8; H, 10·4%).

2α-*Acetoxy*-14,15-*dibromo*-8α,13-*oxidolabdane* (VI). 2α-Acetoxy-8α,13-oxidolabd-14-ene (54 mg) in carbon tetrachloride (3 ml) was treated with bromine (0·85 ml, 2·9% soln. in CCl_4) at 0°. When the reaction was complete the solution was washed with sodium bicarbonate. Removal of the solvent gave the dibromide (VI) as prisms (48 mg) from light petroleum, m.p. 125 134°. (Found: C, 52·95; H, 7·0. $C_{22}H_{36}O_3Br_2$ requires: C, 52·0; H, 7·15%).

2α-*Hydroxy*-8α,13-*oxidolabd*-14-yne (VIIc). The dibromide (VI, 950 mg) in ether (20 ml) was stirred for 3 hr with a suspension of sodamide (from 2 g Na) in liquid ammonia (100 ml) at 33°. After reacetylation, the product was adsorbed on alumina (100 g, grade V) from light petroleum and eluted with light petroleum benzene (9:1) as prisms (370 mg from light petroleum) of 2α-*acetoxy*-8α,13-*oxidolabd*-14-*yne* (VIIb), m.p. 115–116·5°, $[\alpha]_D$ +12° (*c*, 1·2). (Found: C, 76·4; H, 10·0. $C_{22}H_{34}O_3$ requires: C, 76·25; H, 9·9%). Hydrolysis of VIIb gave the corresponding alcohol (VIIc) as prisms from light petroleum, m.p. 104 105°, $[\alpha]_D$ +38° (*c*, 0·8). (Found: C, 78·7; H, 11·1. $C_{20}H_{32}O_2$ requires: C, 78·9; H, 10·6%).

8α,13-*Oxido*-2-*oxolabd*-14-*yne* (VIII). Oxidation of VIIc (125 mg) in acetone (10 ml) with 8N chromic acid/sulphuric acid gave VIII (112 mg) as prisms from light petroleum, m.p. 98–100°, $[\alpha]_D$ +29° (*c*, 0·9). (Found: C, 79·7; H, 10·0. $C_{20}H_{30}O_2$ requires: C, 79·4; H, 10·0%).

15,15′-*Di*(8α,13-*oxido*-2-*oxolabd*-14-*ynyl*) (IX). 8α,13-Oxido-2-oxolabd-14-yne (92 mg), cupric acetate (200 mg) and pyridine (2 ml) were heated together under reflux for 20 min. The product crystallized as needles of IX (78 mg) from methylene chloride methanol, m.p. 258–260°, $[\alpha]_D$ 40° (*c*, 0·65). (Found: C, 79·5; H, 9·95. $C_{40}H_{58}O_4$ requires: C, 79·7; H, 9·7%). $\lambda_{max}(CH_2Cl_2)$ 232, 243, 254, 284 mμ; ε 405, 410, 310, 136.

8α,13-*Oxidolabd*-14-*yne* (VIIa). Manoyl oxide (25 mg) was converted to the corresponding acetylene (VIIa) by the method described for the preparation of VIIb. Distillation at 130°/0·1 mm gave VIIa (10 mg) as a colourless oil, $[\alpha]_D$ +7° (*c*, 1·2). (Found: C, 83·05; H, 11·45. $C_{20}H_{32}O$ requires: C, 83·25; H, 11·2%).

8α,13-*Epioxidolabd*-14-*yne* (X). Epimanoyl oxide (2·5 mg) gave X (0·5 mg), subliming as prisms, m.p. 99 102°.

The electron impact studies were carried out on a Metropolitan Vickers Ltd. M.S.2. Mass-spectrometer. The "cracking-patterns" were obtained in the conventional way using an ion accelerating voltage of 2 kV with an electron beam energy of 50 eV. The appearance potentials were obtained by known methods.[9]

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[9] R. J. Reed, *Trans. Faraday Soc.* **52**, 1195 (1956).