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SYNTHESIS OF ANALOGUES OF THE IRIDOLACTONES[1]

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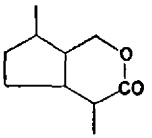
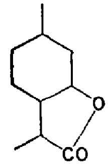
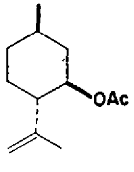
Abstract—Two stereoisomeric lactones of 2(2′-hydroxy-4′-methylcyclohex-1′-yl)propionic acid, analogues of the iridolactones, have been synthesized from D-citronellal.

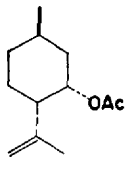
Following recent studies[2,3] on the synthesis of the iridolactones (I) from citronellal, the same starting material has been used to prepare two analogues, stereoisomers of structure (II).[4]

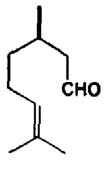

I

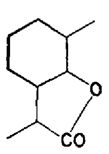

II

Isopulegyl acetate, obtained as a mixture of stereoisomers IIIa and IIIb[5] by the action[6] of acetic anhydride on D-citronellal (IV),[7] was oxidized with selenium dioxide in ethanol (cf. ref. 2), and the aldehydic product was treated with silver oxide in aqueous alkali to afford two stereoisomeric unsaturated hydroxy-acids, which were separated by crystallization.


IIIa


IIIb


IV


V

The infra-red spectra of these compounds clearly showed that they were αβ-unsaturated acids, but structure VI was ruled out by the absence of the band near 11·2 μ which is characteristic of the CH_2:CRR′ grouping.[8] The acids must therefore be represented by VIIa and VIIb.

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[1] The term iridolactones has been used[2] to cover both iridomyrmecin and isoiridomyrmecin.

[2] K. J. Clark, G. I. Fray, R. H. Jaeger, and Sir Robert Robinson, *Tetrahedron* **6**, 217 (1959).

[3] R. H. Jaeger and Sir Robert Robinson, *Tetrahedron Letters* No. 15, 14 (1959).

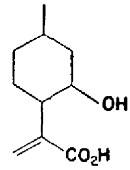
[4] Since this work was completed, F. Korte, J. Falbe, and A. Zschocke, *Tetrahedron* **6**, 201 (1959), have published syntheses of a number of iridolactone analogues, including (V).

[5] *Chemistry of Carbon Compounds* (Edited by E. H. Rodd) Vol. IIB, p. 521. Elsevier, Amsterdam (1953).

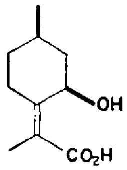
[6] F. Tiemann and R. Schmidt, *Ber. Dtsch. Chem. Ges.* **30**, 27 (1897).

[7] W. Klyne, *Progress in Stereochemistry* Vol. I, p. 189. Butterworths, London (1954).

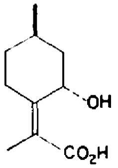
[8] L. J. Bellamy, *The Infra-Red Spectra of Complex Molecules* p. 58. Methuen, London (1958).



VI

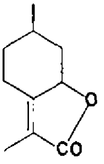


VIIa

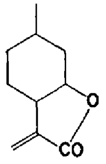


VIIb

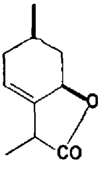
Treatment of the hydroxy-acids with hydrochloric acid yielded unsaturated lactones, of which the infra-red spectra each exhibited a carbonyl band (at 5·64 μ) in the region characteristic of saturated γ-lactones,[9] indicating that the double bond was neither in the lactone ring as in VIII, nor in the exocyclic position as in IX. The structures of these stereoisomeric lactones were therefore considered to be Xa and Xb (the configurations of the α-carbon atoms being uncertain).



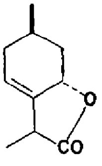
VIII



IX

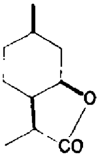


Xa

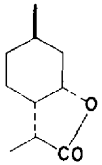


Xb

Hydrogenation of the unsaturated lactones finally afforded the corresponding saturated compounds, in which the lactone ring would be expected to be fused to the cyclohexane ring in the *cis* manner. The probable configurations of the saturated lactones were therefore XIa and XIb.



XIa



XIb

EXPERIMENTAL

Unless otherwise stated, light petroleum refers to the fraction of b.p.40–60°. Infra-red spectra were determined for Nujol mulls.

Stereoisomers of 2(2′-*hydroxy*-4′-*methylcyclohexylidene*)*propionic acid* VIIa *and* VIIb

A solution of selenium dioxide (22 g) in ethanol (150 cc) was added during 1½ hr to a stirred mixture of isopulegyl acetate[6] $[\alpha]_D^{27}$ −1·30° (homog, 39 g) and ethanol (75 cc) at 50° (bath). The temperature was then raised to 95–100° for 24 hr, with continuous stirring. The reaction mixture was filtered, the filtrate evaporated, and the residue taken up in ether; the ethereal solution was washed with water and sodium hydrogen carbonate solution, and was dried and evaporated. Fractional distillation of the residue gave a pale yellow oil (8·9 g), b.p. 90–100°/0·2 mm. (Found: C, 68·2; H, 8·5. $C_{12}H_{18}O_3$ requires: C, 68·5; H, 8·6%). Gas chromatographic analysis showed that the fraction was a mixture. Attempts to isolate a pure aldehydic product by extraction with sodium hydrogen sulphite solution failed; the mixture was almost completely soluble, but could not be

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[9] L. J. Bellamy, *The Infra-Red Spectra of Complex Molecules* p. 186. Methuen, London (1958).

recovered by the addition of alkali or acid. The mixture was therefore used directly for the next stage.

A solution of sodium hydroxide (8 g) in water (250 cc) was added during 1 hr to a stirred mixture of the above aldehydic product (7·6 g), ethanol (100 cc), silver nitrate (14 g), and water (50 cc), and stirring was continued for 5 hr. The mixture was filtered, and the filtrate acidified with dil. sulphuric acid and extracted with ether. Extraction of the ethereal solution with sodium carbonate solution, followed by acidification, yielded a yellow viscous oil (4·2 g), which crystallized on trituration with light petroleum. Recrystallization from ether–light petroleum afforded an unsaturated *hydroxy-acid* as hard colourless prisms, m.p. 98·5–99°, $[\alpha]_D^{22}$ −37° (*c*, 1·17 in $CHCl_3$) (Found: C, 65·3; H, 9·1. $C_{10}H_{16}O_3$ requires: C, 65·2; H, 8·8%). The infra-red spectrum showed bands at 2·92 (free O—H), 5·93 (conjugated C═O), and 6·13 μ (conjugated C═C).

The mother-liquors from the above crystallizations, on standing, deposited crystals (0·33 g) of m.p. 101–102° (depressed on admixture with the above hydroxy-acid of m.p. 98·5–99°). Recrystallization from benzene–light petroleum then yielded a second unsaturated *hydroxy-acid* as microscopic prisms, m.p. 102–103°, $[\alpha]_D^{26}$ −10° (*c*, 0·93 in $CHCl_3$) (Found: C, 65·2; H, 8·6%). The infra-red spectrum exhibited bands at 2·98, 5·89, and 6·15μ.

Stereoisomeric lactones of 2(2′-*hydroxy*-4′-*methylcyclohex*-6′-*en*-1-*yl*)*propionic acid* Xa *and* Xb

(a) A solution of the hydroxy-acid of m.p. 98·5–99° (0·57 g) in hydrochloric acid (ca. 15%) was kept overnight, and then extracted with light petroleum. Evaporation of the solvent and recrystallization of the residue (0·23 g) from light petroleum (b.p. below 40°) at −10° gave the unsaturated *lactone* as flexible elongated prisms, m.p. 42–43°, $[\alpha]_D^{24}$ +63° (*c*, 0·99 in CCl_4) (Found: C, 71·9; H, 8·5. $C_{10}H_{14}O_2$ requires: C, 72·3; H, 8·5%). The carbonyl band in the infra-red spectrum appeared at 5·64 μ.

On extraction of the remaining acidic solution with chloroform, hydroxy-acid (0·27 g) was recovered. Treatment as above then gave a further quantity (0·11 g) of the lactone.

Dissolution of the lactone (100 mg) in sodium hydroxide solution, followed by acidification with hydrochloric acid and extraction with chloroform, yielded the hydroxy-acid (105 mg), m.p. 98·5–99° (after crystallization), undepressed on admixture with a specimen of the original hydroxy-acid.

(b) Similar treatment of the hydroxy-acid of m.p. 102–103° (140 mg) afforded the unsaturated *lactone* (40 mg). Recrystallization from light petroleum (b.p. below 40°) at −10° gave elongated prisms, m.p. 31–31·5°, $[\alpha]_D^{24}$ +14° (*c*, 1·43 in CCl_4) (Found: C, 71·6; H, 8·5%).[10] The infra-red spectrum showed a carbonyl band at 5·64 μ.

Stereoisomeric lactones of 2(2′-*hydroxy*-4′-*methylcyclohex*-1′-*yl*)*propionic acid* XIa *and* XIb

(a) The unsaturated lactone of m.p. 42–43° (105 mg) in ethanol was hydrogenated at atm press in the presence of 2% palladized strontium carbonate to afford the saturated *lactone* as colourless leaflets (100 mg), m.p. 49–49·5°, $[\alpha]_D^{27}$ +17° (*c*, 0·96 in CCl_4), after crystallization from light petroleum (b.p. below 40°) at −20° (Found: C, 71·2; H, 9·3. $C_{10}H_{16}O_2$ requires: C, 71·4; H, 9·6%). The infra-red spectrum showed a band at 5·64 μ corresponding to the carbonyl group.

(b) Similar hydrogenation of the unsaturated lactone of m.p. 31–31·5° (55 mg) yielded the saturated *lactone* (50 mg). Recrystallization from light petroleum (b.p. below 40°) at −20° gave microscopic prisms, m.p. 33·5–34·5°, $[\alpha]_D^{22}$ −5° (*c*, 0·98 in CCl_4) (Found: C, 71·1; H, 9·5%). The infra-red spectrum exhibited a carbonyl band at 5·64 μ.

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[10] Consistently low C values were obtained on repeated analyses.