

799. The Structure of Hyptolide.

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The bitter principle hyptolide, $C_{18}H_{24}O_8$, is an unsaturated lactone (II).

HYPTOLIDE, from the leaves of *Hyptis pectinata* Poit., was found by Gorter¹ to be an optically active lactone containing three acetoxy groups, and was formulated as $C_{18}H_{26}O_8$. A fourth molecule of acetic acid obtained after silver oxide oxidation, apparently arose from $CHMe \cdot OH$. Some acetone was produced by the action of alkali. Hydrogenation followed by oxidation gave two dibasic acids, $C_7H_{12}O_4$ and $C_9H_{16}O_4$, which were thought to be, respectively, 2,2-dimethylglutaric acid and a trimethyladipic acid; an acid from nitric acid oxidation was shown to be succinic acid. From these results Gorter deduced¹ a formula (I) which is now shown to be incorrect, but which attracted our attention to the substance as of possible interest for biogenetic studies, particularly in view of the high yields reported.

An ethanolic extract of *Hyptis pectinata*, obtained from Java through the courtesy of Dr. L. Mattsson (U.N.E.S.C.O., Djakarta), gave several grams of hyptolide, the nuclear magnetic resonance (n.m.r.) spectrum of which was so seriously at variance with the suggested structure that the problem was re-examined. The m. p. 88.5° and rotation, $[\alpha]_D +7.4^\circ$ (ethanol), seem to have no doubt that the substance is hyptolide for which Gorter¹ gives m. p. 88.5° , $[\alpha]_D +6.75^\circ$ (ethanol).

The ultraviolet (λ_{max} , 212 $m\mu$, ϵ 8700) and infrared (ν_{max} , 1739 cm^{-1}) spectra are in accord with the presence of a six-membered $\alpha\beta$ -unsaturated lactone² as in formula (II). The n.m.r. spectrum is in accord with the presence of three acetoxy-groups (τ 7.9—8.0) and $CHMe$ (a doublet at τ 8.78). Since there are eight protons in the region τ 3.0—5.2 and only four of these can be situated on carbon bearing oxygen (one lactone, three acetoxy) there must be more unsaturation than was suspected by Gorter. Two of the four protons attached to double-bonded carbon with resonances in the region of τ 3.09 and 3.96 correspond³ to the β - and α -protons, respectively, of the lactone double bond in (II).³ These appear as sextets, the protons being coupled to themselves ($J = 10$ c.p.s.) and to the two allylic protons ($J = 4$ c.p.s. for the β -proton and $J = 2$ c.p.s. for the α -proton) centred at τ 7.57. The general conclusions are supported by analyses for 1 C-Me and 3 OAc, and lead to a revised empirical formula $C_{18}H_{24}O_8$.

To examine the unsaturation, hyptolide was hydrogenated. It absorbs 3.2 molecules in two stages, the first, involving 2.2 molecules, being much more rapid than the second. The product is an acid, unlike the neutral "diol" described by Gorter who, however, dried his product with potassium carbonate and may have isolated some other minor products. The saturated product after esterification, was separated by chromatography on florex into the ester of a dihydroxy-acid, converted by hydrolysis into the acid, m. p. $68-71^\circ$, and the ester of a trihydroxy-acid, hydrolysed to the acid, m. p. $67-67.5^\circ$. The structures of these were determined by periodate oxidation; the dihydroxy-acid is cleaved to acetaldehyde and sebacaldehydic acid, m. p. $56-57^\circ$, characterised by the semicarbazone, m. p. $168-170^\circ$, and by oxidation to sebacic acid, m. p. 134° . The trihydroxy-acid on similar treatment gives acetaldehyde and a β -hydroxyaldehyde acid, dehydrated by acid treatment to an $\alpha\beta$ -unsaturated aldehyde which was characterised by hydrogenation to sebacaldehydic acid. The structures of the acids must be, respectively, 10,11-dihydroxy-dodecanoic acid and 8,10,11-trihydroxydodecanoic acid. The formula (II) is the only one which fits the facts, including the n.m.r. spectrum; the double bond in the side-chain must be in the position shown in order to permit hydrogenolysis of the lactone and of the 8-acetoxy-group. The steric configuration of the double bond is not completely certain

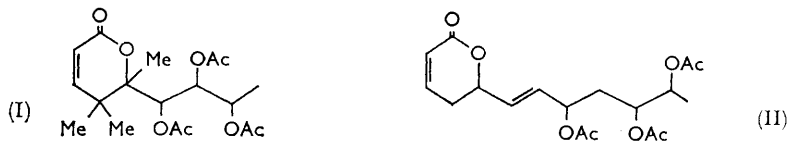
¹ Gorter, cf. *Chem. Soc. Abstracts*, 1920, **118**, 494.

² Eisner, Eldridge, and Linstead, *J.*, 1953, 1372.

³ Varian n.m.r. Spectra Catalogue.

but appears from the infrared spectrum (ν_{\max} 965 cm^{-1}) to be *trans*. The stereochemistry of the portion containing the acetoxy-groups could probably be determined by oxidation at the double bond to a derivative of a 3,6-dideoxyhexose. Two biogenetically similar unsaturated lactones are known: parasorbic acid and massoialactone, neither of which has oxygen in the side-chain. The positions of the oxygens and double bonds in hyptolide suggest that it is probably more closely related to a polyketide than to a fatty acid.

It is not possible to explain Gorter's oxidation results.



EXPERIMENTAL

Isolation.—The aqueous-ethanolic extract of dried leaves (1.25 kg.), treated according to Gorter, was evaporated in a rotary evaporator to 1.5 l. and decanted from black tar. After leaving at 0° for several weeks, crude hyptolide (3.1 g.) crystallised (ether) to give the pure substance (2.34 g.), m. p. 88.5°, $[\alpha]_D^{23} + 7.43$ (ethanol); λ_{\max} 212 $\text{m}\mu$, ϵ 8700 (ethanol); ν_{\max} 1739 cm^{-1} (CCl_4) (Found: C, 58.5; H, 6.5; C-Me, 15.0. Calc. for $\text{C}_{18}\text{H}_{24}\text{O}_8$: C, 58.7; H, 6.6; 4 CMe, 16.3%).

Hydrogenation.—Hyptolide (0.542 g.) in ethanol (60 c.c.) was hydrogenated (Pd/C 10%, 49 mg.) until uptake ceased (134 c.c.). After filtration, the product was hydrolysed with 2N-potassium hydroxide solution (30 c.c.) and evaporated to 20 c.c. After acidification the product was isolated by ether-extraction as a semi-crystalline mass (273 mg.), which was taken into ether (200 c.c.) and reacted with ethereal diazomethane. The resulting ester was chromatographed on florex (100 g.) to yield two fractions: (i) 53 mg. eluted with ether and (ii) 190 mg. eluted with methanol. Each fraction was hydrolysed with 2N-potassium hydroxide and the acids isolated in the usual way. (+)-10,11-Dihydroxydodecanoic acid (37 mg.) from (i) had m. p. 68–71° (ether), $[\alpha]_D^{23} + 13.8$ (ethanol) (Found: C, 62.4; H, 10.45. $\text{C}_{12}\text{H}_{24}\text{O}_4$ requires C, 62.0; H, 10.4%) and 8,10,11-trihydroxydodecanoic acid (111 mg.) had m. p. 67–67.5° after crystallisation from ether (Found: C, 58.3; H, 10.0. $\text{C}_{12}\text{H}_{24}\text{O}_5$ requires C, 58.0; H, 9.7%).

Periodate Fissions.—The above dihydroxydodecanoic acid (37 mg.) was left overnight in a solution of sodium periodate (45 mg.) in water (3 c.c.). Arsenious oxide (100 mg.) was added and the mixture steam-distilled into a 0.5% solution of 2,4-dinitrophenylhydrazine in 2N-hydrochloric acid. The acetaldehyde derivative, m. p. 144–146° (22 mg., 62%) was shown to be identical with authentic material by paper chromatography in a tetralin–dimethylformamide system. The aqueous phase was acidified and extracted with chloroform to give sebacaldehydic acid (24.3 mg., 82%) m. p. 45–49°, which after crystallisation from acetone–light petroleum was raised to m. p. 54–56° (lit.,⁴ m. p. 56–57°). The semicarbazone had m. p. 168–170° from aqueous methanol (lit.,⁴ m. p. 170°). Oxidation with silver oxide gave sebacic acid, m. p. 134°, undepressed by an authentic specimen.

Fission of the 8,10,11-trihydroxydodecanoic acid was carried out as above to yield acetaldehyde 2,4-dinitrophenylhydrazone, and a gummy product which could not be obtained crystalline even after chromatography on florisil; ν_{\max} (CCl_4), 3450 (OH), 1720 (CHO), and 1704 cm^{-1} (CO_2H). The gum (47 mg.) was warmed with 5N-hydrochloric acid for 10 min. and the product (28 mg.) also failed to crystallise; ν_{\max} (CCl_4), 1704 (CO_2H), and 1690 cm^{-1} ($\alpha\beta$ -unsaturated CHO). Catalytic hydrogenation gave sebacaldehydic acid (18 mg.) m. p. 54–56, characterised as above.

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⁴ Harvreaves and Owen, *J.*, 1947, 753.