845. *Macrocyclic Musk Compounds. Part VIII.* New Syntheses of Cyclohexadecanone and Dihydroambrettolide from Hydnocarpic Acid*

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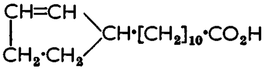
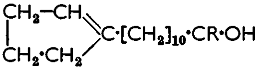
HYDNOCAPARIC ACID [1] on repeated hydrobromination and debromination [2] afforded the optically inactive isohydnocarpic acid [11-(cyclopent-1-enyl)undecanoic acid]. This isomerisation could also be effected by treatment with ethylenediaminelithium.[3] Isohydnocarpic acid (IIa) was oxidised with potassium permanganate in aqueous medium to yield 5-oxohexadecanedioic acid (IIIa). The latter, on Huang-Minlon [4] reduction, furnished hexadecanedioic acid (IVa) which was cyclised [5] to cyclohexadecanone (V). Isohydnocarpyl alcohol as the acetate, through a similar sequence of reactions, yielded 16-hydroxyhexadecanoic acid (IVb) which was cyclised [6] to dihydroambrettolide (VI).

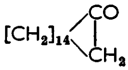

(I)

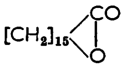

(II)

$\mathrm{HO_2C{\cdot}[CH_2]_3{\cdot}CO{\cdot}[CH_2]_{10}{\cdot}CR{\cdot}OH}$
(III)

$\mathrm{HO_2C{\cdot}[CH_2]_{14}{\cdot}CR{\cdot}OH}$
(IV)

a, R = O; b, R = $\mathrm{H_2}$.


(V)


(VI)

Experimental.—Infrared spectra were recorded on an Infracord model 137b with sodium chloride optics. The nuclear magnetic resonance spectrum was obtained on a Varian Associates A60 instrument at 60 Mc./sec. in carbon tetrachloride, using tetramethylsilane as the internal standard. Optical rotations were measured in chloroform solution at 25°. Light petroleum had b. p. 60—80°.

Isohydnocarpic acid (IIa). Chaulmoogra oil esters were distilled through a fractionating column and from the second fraction, b. p. 120—122°/0·2—0·3 mm., hydnocarpic acid † was isolated, m. p. 59—60° (from light petroleum), $[\alpha]_{\mathrm{D}}$ +70·3°, $\nu_{\max.}$ ($\mathrm{CHCl_3}$), 3049, 2653, 1695, 1600sh (CH=CH), 1444, 1401, 1280, 1160, 1092, 946, 908, 858, and 814w cm.$^{-1}$ ($\mathrm{CHCl_3}$). A solution of hydnocarpic acid (25 g.) in ether (200 ml.) was saturated with dry hydrogen bromide and kept for 24 hr. at room temperature. The hydrobromo-derivative was refluxed with ethanolic potassium hydroxide (8 g. in 60 ml.) for 1 hr. The isomeric acid was isolated, $[\alpha]_{\mathrm{D}}$ +30·67°, and subjected to repeated hydrobromination and debromination (thrice) to obtain *isohydnocarpic acid* (IIa) (21 g.), b. p. 147—150°/0·055 mm., m. p. 44—45° (from light petroleum), $[\alpha]_{\mathrm{D}}$ ±0°, $\nu_{\max.}$ ($\mathrm{CHCl_3}$), 3058, 2638, 1706, 1451, 1404, 1287, 1176, 950, 909, 866, and 818m cm.$^{-1}$ ($\mathrm{-CH{=}C{<}}$) (Found: C, 75·95; H, 11·1. $\mathrm{C_{16}H_{28}O_2}$ requires C, 76·1; H, 11·2%). Although chloroform absorbs in the region 815—650 cm.$^{-1}$, presence of the band at 818 cm.$^{-1}$ of enhanced intensity as compared with the spectrum of hydnocarpic acid, and absence of the shoulder at 1600 cm.$^{-1}$, indicated the presence of a trisubstituted double bond. This was confirmed by the n.m.r. spectrum (τ 7·22, 1 H).

5-*Oxohexadecanedioic acid* (IIIa). A solution of isohydnocarpic acid (20 g.) in aqueous potassium hydroxide (3·5 g. in 210 ml.) was added with stirring to a solution of potassium

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* Part VII, K. K. Chakravarti, U. G. Nayak, S. C. Bhattacharyya, V. K. Balakrishnan, and R. K. Razdan, *J.*, 1965, **3475**.

† Satisfactory elemental analyses were obtained from all the known compounds.

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[3] B. S. Tyagi, B. B. Ghatge, and S. C. Bhattacharyya, *J. Org. Chem.*, 1962, **27**, 1430; *Tetrahedron*, 1963, **19**, 1189.

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permanganate (30·1 g. in 480 ml. water) during 1 hr. at 25°. The reaction was continued for another 3 hr. and then sulphur dioxide was bubbled in to decompose the manganese dioxide. Further acidification with cold dilute hydrochloric acid afforded 5-*oxohexadecanedioic acid* (17 g.), m. p. 119—120° (from benzene) (Found: C, 63·8; H, 9·2. $C_{16}H_{28}O_5$ requires C, 64·0; H, 9·4%).

Hexadecanedioic acid (IVa). A mixture of 5-oxohexadecanedioic acid (5·6 g.), diethylene glycol (10 ml.), hydrazine hydrate (7 ml.), and potassium hydroxide (3·6 g.) was heated at 140—210° according to the Huang-Minlon [4] procedure and then poured into cold dilute hydrochloric acid, filtered, washed free from mineral acid, and crystallised from acetic acid to obtain hexadecanedioic acid (3 g.), m. p. 124—125° (lit.,[7] 124—124·2°).

Cyclohexadecanone (V). Diethyl hexadecanedioate (20 g.) was cyclised to the acyloin [5] (10 g.), b. p. 133—135°/0·04 mm., which in dioxan solution was reduced with zinc and hydrogen chloride.[8] The product was distilled (8·5 g.), b. p. 125—135°/0·07 mm., and purified by way of the semicarbazone, m. p. 184—184·5° (lit.,[9] 184—185°), which on decomposition with oxalic acid furnished cyclohexadecanone, m. p. 63—63·5° (from methanol) (lit.,[9] 63—64·5°), $\nu_{max.}$ (Nujol) 1709 cm.$^{-1}$ (C=O).

Isohydnocarpyl alcohol (IIb). Isohydnocarpic acid (IIa) (5 g.) was reduced with lithium aluminium hydride (0·9 g.) in tetrahydrofuran. The solution was worked up and washed with sodium hydrogen sulphite to remove any aldehyde. The product was distilled to obtain *isohydnocarpyl alcohol* (4·1 g.), b. p. 135—138°/0·5 mm. (Found: C, 80·3; H, 12·7. $C_{16}H_{30}O$ requires C, 80·6; H, 12·7%).

The alcohol (IIb) was converted into *isohydnocarpyl acetate* by treatment with acetic anhydride and pyridine, and distilled (3·1 g.), b. p. 145—150° (bath)/0·055 mm. (Found: C, 77·1; H, 11·3. $C_{18}H_{32}O_2$ requires C, 77·1; H, 11·5%).

16-*Hydroxy*-5-*oxohexadecanoic acid* (IIIb). To a stirred solution of isohydnocarpic acetate (3 g.) in acetone (50 ml.), finely powdered potassium permanganate (5 g.) in glacial acetic acid (10 ml.) was added in four instalments during 1 hr. The stirring was continued for another 2 hr. and then with gentle reflux for 1 hr. Manganese dioxide sludge was filtered off and from the filtrate acetone was recovered. The residue was saponified and acidified to liberate the *oxo-hydroxy-acid* (IIIb) (1·8 g.), m. p. 96—97° (from benzene) (Found: C, 67·3; H, 10·25. $C_{16}H_{30}O_4$ requires C, 67·1; H, 10·6%).

16-*Hydroxyhexadecanoic acid* (IVb). A mixture of the oxo-hydroxy-acid (IIIb) (1 g.), diethylene glycol (5 ml.), hydrazine hydrate (1 ml.), and potassium hydroxide (0·7 g.) was heated and the product processed as described for the preparation of compound (IVa). The hydroxy-acid (IVb) was crystallised from ethanol and then from ethyl acetate, m. p. 94—95° (lit.,[10] 94°).

Dihydroambrettolide (IV).[11] The ω-hydroxy-acid (IVb) (5 g.) was cyclised by the thermal depolymerisation *in vacuo* of the polyester,[6] and the distillate (3·5 g.) in light petroleum (15 ml.) was chilled at 0°. A small amount of solid (polymeric lactone) which separated was filtered off, the filtrate concentrated, and again chilled, when no more solid was obtained. The solution was washed with 5% sodium carbonate solution and distilled to obtain dihydroambrettolide (2·8 g.), b. p. 118—120°/0·3 mm., m. p. 33°, $\nu_{max.}$ (thin film), 1730 cm.$^{-1}$.

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