# 455. *Macrocyclic Musk Compounds. Part III.* A New Synthesis of Ambrettolide from Aleuritic Acid.*

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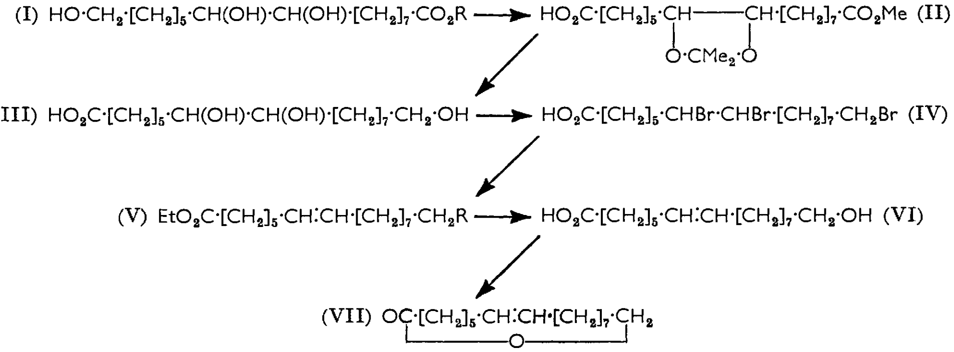
A practical synthesis of ambrettolide from aleuritic acid has been evolved. By interchanging the positions of the α-carboxyl and ω-hydroxyl groups in aleuritic acid, isoaleuritic acid was obtained which on hydrobromination and debromination yielded ambrettolic acid which on lactonisation afforded ambrettolide.

Ambrettolide (VII) is the main odorous principle of ambrette seed, *Hibiscus abelmochus* L. It was prepared by Kerschbaum,[1] and later by Stoll and Gardner,[2] by cyclising 16-hydroxyhexadec-7-enoic acid ambrettolic acid (VI), isolated from ambrette seed oil; and a somewhat complicated synthesis of ambrettolide in unspecified yield has been recorded by Baudart.[3]

In this paper we report a new and straightforward synthesis of ambrettolide from aleuritic acid[4] (I; R = H) (see Chart). Methyl aleuritate (I; R = Me) was converted into the isopropylidene derivative[5] and oxidised by permanganate in the presence of acetic acid to prevent hydrolysis of the ester group by alkali formed during the oxidation. Bouveault–Blanc reduction[6] of the resulting half-ester (II) and removal of the protecting group by deacetonylation yielded isoaleuritic acid (III) which was converted into *trans*-ambrettolic acid (VI) by way of compounds (IV), (V; R = Br), and (V; R =OAc). Cyclisation, essentially Spanagel and Carothers's method,[7] yielded ambrettolide (VII).



(I) $HO\cdot CH_2\cdot[CH_2]_5\cdot CH(OH)\cdot CH(OH)\cdot[CH_2]_7\cdot CO_2R \longrightarrow HO_2C\cdot[CH_2]_5\cdot \underset{O\cdot CMe_2\cdot O}{CH\text{——}CH}\cdot[CH_2]_7\cdot CO_2Me$ (II)

(III) $HO_2C\cdot[CH_2]_5\cdot CH(OH)\cdot CH(OH)\cdot[CH_2]_7\cdot CH_2\cdot OH \longrightarrow HO_2C\cdot[CH_2]_5\cdot CHBr\cdot CHBr\cdot[CH_2]_7\cdot CH_2Br$ (IV)

(V) $EtO_2C\cdot[CH_2]_5\cdot CH{:}CH\cdot[CH_2]_7\cdot CH_2R \longrightarrow HO_2C\cdot[CH_2]_5\cdot CH{:}CH\cdot[CH_2]_7\cdot CH_2\cdot OH$ (VI)

(VII) $\underbrace{OC\cdot[CH_2]_5\cdot CH{:}CH\cdot[CH_2]_7\cdot CH_2}_{O}$

Reduction[8] of the half-ester (II) by lithium borohydride was not fruitful. A mixture was obtained from which isoaleuritic acid could not be easily separated by crystallisation.

## Experimental †

16-*Methyl Hydrogen* 7,8-*Isopropylidenedioxyhexadecanedioate* (II).—Methyl aleuritate (I; R = Me) (50 g.), m. p. 72—73°, prepared from aleuritic acid by Davis and Gardner's method,[9]

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* Part II, *J.*, 1963, 114.

† Melting and boiling points are uncorrected. Infrared spectra were recorded for Nujol mulls, unless stated to the contrary, on a Grubb-Parsons double beam spectrometer with sodium chloride optics.

[1] Kerschbaum, *Ber.*, 1927, **60**, 902.

[2] Stoll and Gardner, *Helv. Chim. Acta*, 1934, **17**, 1609.

[3] Baudart, *Compt. rend.*, 1945, **221**, 205.

[4] Sabnis, Mathur, and Bhattacharyya, Indian P. 17,080/1961.

[5] Nagel and Mertens, *Ber.*, 1936, **69**, 2050; 1941, **74**, 976.

[6] Blatt, *Org. Synth.*, Coll. Vol. II, 1946, p. 372.

[7] Spanagel and Carothers, *J. Amer. Chem. Soc.*, 1936, **58**, 654.

[8] Nystrom, Chaikin, and Brown, *J. Amer. Chem. Soc.*, 1949, **71**, 3245: Paul and Joseph, *Bull. Soc. chim. France*, 1952, 550.

[9] Davis and Gardner, *J. Amer. Chem. Soc.*, 1942, **64**, 1902.

was stirred in pure dry acetone (1·2 l.) containing concentrated sulphuric acid (1 ml.) for 1 hr. and then left for 2 hr. It was neutralised with 30% aqueous potassium hydroxide (10 ml.). Finely powdered potassium permanganate (38·5 g.) and glacial acetic acid (60 ml.) were added in four instalments during 1 hr. with stirring which was continued for another 3 hr.; during the last hour the mixture was heated under reflux. The solution was filtered, acetone distilled off, and the residue extracted with ether. The ether solution was separated by treatment with 7% aqueous sodium carbonate (500 ml.), affording the unchanged neutral starting material (8·3 g.) and the *half-ester* (II) (45 g.), b. p. 200°/0·003 mm., $n_D^{23}$ 1·4620 (Found: C, 64·2; H, 9·5. $C_{20}H_{36}O_6$ requires C, 64·5; H, 9·7%).

*Isoaleuritic Acid* (III).—Sodium (16·1 g.) was pulverised in xylene (40 ml.) and the ester (II) (37·2 g.) in absolute ethanol (30 ml.) was added during 1·5 min., followed by ethanol (105 ml.) in 2 min. The exothermic reaction was controlled by the rate of addition. A jelly-like mass was obtained from which the solvents were distilled off under reduced pressure. The residue was dissolved in water (500 ml.), treated with concentrated sulphuric acid (25 ml.), and boiled for 30 min. On cooling, a pale solid separated which was washed free from mineral acid. The crude product (27 g.) was refluxed with 1 : 1 aqueous alcoholic potassium hydroxide (15 g. in 200 ml.) for 4 hr. to decompose any polyester. The solution was acidified and the liberated hydroxy-acid was washed and decolorised with carbon in alcohol, affording a white product, m. p. 86—90° (22 g.), which on crystallisation from ethanol furnished pure *isoaleuritic acid*, m. p. 92—93° [mixed m. p. with aleuritic acid (m. p. 100—101°) 88—90°], $\nu_{max.}$ 3200, 1714, 1660, 1139, 1069, and 1010 cm.$^{-1}$ (Found: C, 63·4; H, 10·7%; Equiv., 302. $C_{15}H_{31}O_3{\cdot}CO_2H$ requires C, 63·1; H, 10·6%; Equiv., 304).

*Ethyl* trans-*16-Bromohexadec-7-enoate* (V; R = Br).—Isoaleuritic acid (23·5 g.) was heated on a water-bath with a 15% w/v solution (500 ml.) of hydrogen bromide in acetic acid for 8 hr. and the acetic acid distilled off under reduced pressure. The crude tribromo-acid (IV) (32 g.), obtained as a residue, was esterified azeotropically (ethanol 50 ml., benzene 200 ml., and sulphuric acid 1 ml.), and the ester (31·7 g.), $n_D^{27}$ 1·500, was refluxed for 30 min. with zinc dust (21 g.) in absolute ethanol (230 ml.) containing the 15% hydrogen bromide solution (0·3 ml.). Zinc dust was filtered off and from the filtrate alcohol was recovered, leaving the *bromo-ester* (20·3 g.), b. p. 139—140°/0·03 mm., $n_D^{27}$ 1·4690 (Found: C, 60·1; H, 9·1; Br, 21·9. $C_{18}H_{33}BrO_2$ requires C, 59·8; H, 9·2; Br, 22·1%). The infrared spectrum showed absence of hydroxyl absorption and a band at 971 cm.$^{-1}$ for *trans* –CH=CH–.

*Ethyl* trans-*16-Acetoxyhexadec-7-enoate* (V; R = OAc).—The ω-bromo-ester (20 g.) was refluxed with glacial acetic acid (40 ml.) and fused sodium acetate (20 g.) for 12 hr. with stirring, poured into cold water, and extracted with hexane. The hexane solution was washed until neutral, dried, and evaporated, affording the *acetoxy-ester* (18·5 g.), b. p. 143—144°/0·025 mm., $n_D^{27}$ 1·4535 (Found: C, 70·7; H, 10·7. $C_{20}H_{36}O_4$ requires C, 70·5; H, 10·7%).

trans-*Ambrettolic Acid* (VI).—The acetoxy-ester (6 g.) was saponified with 10% alcoholic potassium hydroxide (100 ml.) and acidified, to liberate *trans*-ambrettolic acid which, crystallised from benzene (4·2 g.), had m. p. 53—54° (lit.; natural, 20—21°; [2] synthetic acid, 53—55° [3]), $\nu_{max.}$ 3200, 1698, 1061, and 963 cm.$^{-1}$ (Found: C, 71·3; H, 11·4. Calc. for $C_{16}H_{30}O_3$: C, 71·1; H, 11·2%).

*Ambrettolide* (VII).—*trans*-Ambrettolic acid (3·5 g.) in toluene solution (100 ml.) containing toluene-*p*-sulphonic acid (0·5 g.) was refluxed for 8 hr. under an azeotropic head to remove the water. Toluene was then distilled off and the residue was washed in benzene with water until neutral, dried, and recovered. The polyester, obtained as the residue, was depolymerised by distilling it during 1·5 hr. with magnesium oxide (0·3 g.) at a bath-temperature of 270—280°/0·1 mm. The distillate (1·5 g.) was dissolved in ether and washed with sodium carbonate solution. The ether solution was washed, dried, and evaporated. The product (1·4 g.) was passed through a column (20 × 1 cm.) of neutral alumina, grade III (15 g.), and eluted with benzene. Ambrettolide, obtained after removal of the benzene, was redistilled (1·2 g.); it had b. p. 94—95°/0·005 mm., $n_D^{26}$ 1·4875 [lit.: natural, 154—156°/1·0 mm., $n_D^{20}$ 1·4815; [2] synthetic, 170°/2 mm.[3]], $\nu_{max.}$ (liquid film) 1729 (C=O in a macrocyclic lactone),[10] 1447, 1348, 1239, 1180, 1118, 1060, and 968 cm.$^{-1}$ (Found: C, 76·2; H, 11·0. Calc. for $C_{16}H_{28}O_2$: C, 76·1; H, 11·2%).

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[*Received, September 24th,* 1962.]

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[10] Jones, Angell, Ito, and Smith, *Canad. J. Chem.*, 1959, **37**, 2007.