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Synthesis of 1,4,12-Trimethoxydodecane, a Juvenile Hormone Analogue

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1,4,12-Trimethoxydodecane (VII), a juvenile hormone analogue has been synthesised from aleuritic acid (I).

The synthesis of the title compound (VII), starting from traumatic acid was reported by Deodhar *et al.*¹ Presently we have obtained this compound starting from aleuritic acid (I), a major component (~30%) of shellac.

Oxidative cleavage of I with metaperiodate² affords azelaic acid aldehyde (II) as one of the products. The methyl ester of II on Stobbe condensation with dimethyl succinate affords 3,11-dicarbomethoxyundec-3-enoic acid (IV). Treatment of IV with HBr-AcOH-H₂O (3:2:1, v/v) for 13 hr at the reflux temperature furnishes 4-(ω -carbomethoxyheptyl)-1,4-butanolide (V), which on LAH reduction in ether affords 1,4,12-trihydroxydodecane (VI). Methylation of VI with CH₂N₂-BF₃.Et₂O reagent yields VII, identical (IR and PMR) with an authentic sample.

Half-ester (IV)

A mixture of methyl ester of azelaic acid aldehyde² (III; 4.25 g) and dimethyl succinate (4.4 g) in dry methanol (10 ml) was added to a well-stirred solution of sodium methoxide (0.64 g) in dry methanol (12 ml). The reaction mixture was refluxed for 22 hr under dry N₂ atmosphere, cooled and acidified with 1 N HCl. Methanol was distilled off under reduced pressure, the residue extracted with ether and the acidic fraction separated by washing repeatedly with ice-cold aq. Na₂CO₃ (10%). The combined alkaline extract on

acidification and usual work-up with ether gave IV as a viscous oil (1.5 g) which was purified by distillation, b.p. 180-85° (bath)/3-4 mm; m.p. 92-94° (methanol); IR (neat): 1730 (C=O of ester), 1700 (C=O of carboxyl), 1625 cm⁻¹ (C=C); PMR (CDCl₃, TMS internal ref.): δ 3.63 and 3.61 (s, 3H, each COOCH₃), 2.26 (t, 2H, CH₂COOH), 5.23 (m, 1H, CH=C). (Found: C, 60.1; H, 8.0. C₁₅H₂₄O₆ requires C, 60.0; H, 8.0%).

Lactone ester (V)³

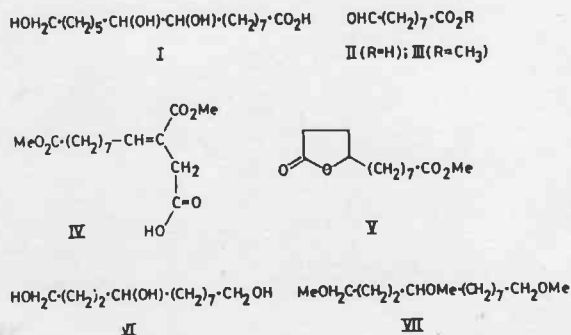
The half-ester (IV; 2 g) was refluxed with HBr-AcOH-H₂O (3:2:1, v/v, 20 ml) for 13 hr and extracted with ether. Evaporation of the solvent furnished V (1 g) as a liquid which was purified by column chromatography over silica gel using benzene as eluent; IR (neat): 1770 (C=O of lactone), 1732 cm⁻¹ (C=O of ester); PMR (CDCl₃): δ 3.65 (s, 3H, COOCH₃), 4.55 (bm, 1H, methine proton of lactone moiety). (Found: C, 64.4; H, 9.0. Calc. for C₁₃H₂₂O₄: C, 64.4; H, 9.2%).

1,4,12-Trihydroxydodecane (VI)

V (2.4 g) in dry ether (25 ml) was added to LiAlH₄ (0.5 g) in dry ether (50 ml) and stirred for 3 hr at the room temperature. This mixture was then treated, sequentially, with water (0.5 ml), 5% aq. NaOH (1 ml), and water (1.5 ml) with stirring. The precipitate obtained was filtered off and washed with ether. The ether washings were combined with the filtrate and dried (Na₂SO₄). The residue obtained by the removal of the solvent was purified by column chromatography over silica gel with TLC monitoring. Fr. (a) (10% EtOAc in C₆H₆, 60 ml \times 2) gave unreacted V (0.3 g); Fr. (b) (EtOAc, 60 ml \times 2) gave a mixture (0.48 g); Fr. (c) (20% MeOH in EtOAc, 250 ml \times 1) gave pure VI (1.4 g) as a liquid, b.p. 155-60° (bath)/3-4 mm; IR (neat): 3250 cm⁻¹ (OH); PMR (CDCl₃): δ 3.48 (t, 4H, 2 \times CH₂OH), 3.2 (br, 1H, CHOH), 1.2-1.4 (br, methylenes) (Found: C, 65.9; H, 11.9. Calc. for C₁₂H₂₆O₃: C, 66.0; H, 12.0%).

1,4,12-Trimethoxydodecane (VII)

VI (1.45 g) was methylated with CH₂N₂-BF₃.Et₂O according to the procedure reported in literature¹ to obtain crude VII (0.65 g), which was purified by column chromatography. Elution with 20% EtOAc in C₆H₆ (25 ml \times 2) gave the pure VII as colourless liquid (0.2 g); b.p. 160-65° (bath)/0.8 mm [lite.¹ b.p. 160° (bath)/0.8 mm]; IR (neat): 1140 and 1120 cm⁻¹ (-OCH₃); PMR (CCl₄): δ 3.23 (singlet superimposed on a broad multiplet, 14H, 2 \times CH₃OCH₂



+CH₃O.CH); MS: m/z 260 (Found: C, 69.2; H, 12.3. Calc. for C₁₅H₃₂O₃: C, 69.2; H, 12.4%).

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