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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 alcuritic acid (I), a major component ($\sim 30\%$) 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-dicarbomethoxy-undec-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-(\omega-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 pf azelaic acid aldehyde² (III; $4.25 \,\mathrm{g}$) and dimethyl succinate ($4.4 \,\mathrm{g}$) in dry methanol ($10 \,\mathrm{ml}$) was added to a well-stirred solution of sodium methoxide ($0.64 \,\mathrm{g}$) in dry methanol ($12 \,\mathrm{ml}$). The reaction mixture was refluxed for 22 hr under dry N_2 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. Na_2CO_3 (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, CH_2 COOH), 5.23 (m, 1H, CH=C). (Found: C, 60.1; H, 8.0. $C_{15}H_{24}O_6$ requires C, 60.0; H, 8.0%).

Lactone ester (V)3

The half-ester (IV; 2 g) was refluxed with HBr-AcOH- $H_2O(3:2:1, v/v, 20 \text{ ml})$ 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 C_6H_6 ,60 ml × 2) gave unreacted V (0.3 g); Fr. (b) (EtOAc, $60 \text{ ml} \times 2$) gave a mixture (0.48 g); Fr. (c) $(20\% \text{ MeOH in EtOAc}, 250 \text{ ml} \times 1)$ 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 $\times CH_2OH$), 3.2 (br, 1H, CHOH), 1.2-1.4 (br, methylenes) (Found: C, 65.9; H, 11.9. Calc. for $C_{12}H_{26}O_3$: C, 66.0; H, 12.0%).

1,4,12-Trimethoxydodecane (VII)

VI (1.45 g) was methylated with CH_2N_2 - BF_3 . Et_2O 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 C_6H_6 (25 ml × 2) gave the pure VII as colourless liquid (0.2 g); b.p. 160-65° (bath)/0.8 mm [lite. 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, $2 \times CH_3OCH_2$

+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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