Synthesis of Methyl 3-Methyltridecanoate and 3,6-Dimethyltridecanoate

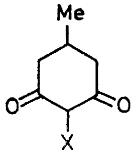
By **P. D. Grimwood, D. E. Minnikin, N. Polgar,* and J. E. Walker,** Dyson Perrins Laboratory, South Parks Road, Oxford OX1 3QY

Methyl 3-methyltridecanoate and 3,6-dimethyltridecanoate have been prepared as synthetic intermediates by routes involving methyl-substituted cyclohexane-1,3-diones as chain extenders.

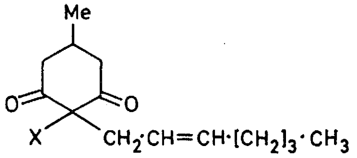
In connection with investigations[1] involving syntheses of 3,12,15-trimethyldocosanoic and related acids for biological studies methyl 3-methyltridecanoate (IV; R = Me) and 3,6-dimethyltridecanoate (VI; R = Me) were needed as intermediates. The present paper describes their syntheses by a route involving methyl-substituted cyclohexane-1,3-diones (dihydroresorcinols) as chain-extenders.[2]

The starting point was 5-methylcyclohexane-1,3-dione (I; X = H), obtained by a slight modification of the procedure of Crossley *et al.*[3] It has been shown[4] that *C*-alkylation of 1,3-diones is favoured when allyl halides in an aqueous medium are used as alkylating agents. Accordingly, for the synthesis of methyl 3-methyltridecanoate (IV) the dione (I; X = H) was alkylated by the action of 1-bromohept-2-ene[4] in the presence of aqueous di-isopropylethylamine.[5] The resulting alkylation product, 2-hept-2′-enyl-5-methylcyclohexane-1,3-dione (II; X = H) was subjected to reductive cleavage[6] by the action of sodium hydroxide and hydrazine to give the acid (III; R = H) which, after esterification and catalytic hydrogenation afforded the methyl ester (IV; R = Me).

(I)



(II)



(III) $CH_3\cdot[CH_2]_3\cdot CH{=}CH\cdot[CH_2]_4\cdot CHMe\cdot CH_2\cdot CO_2R$

(IV) $CH_3\cdot[CH_2]_9\cdot CHMe\cdot CH_2\cdot CO_2R$

(V) $CH_3\cdot[CH_2]_3\cdot CH{=}CH\cdot CH_2\cdot CHMe[CH_2]_2\cdot CHMe\cdot CH_2\cdot CO_2R$

(VI) $CH_3\cdot[CH_2]_6\cdot CHMe\cdot[CH_2]_2\cdot CHMe\cdot CH_2\cdot CO_2R$

3,6-Dimethyltridecanoic acid (VI; R = H) was previously[1] obtained *via* 3-methyldecanoic acid by a multi-stage route. In the present work, for the synthesis of the methyl ester (VI; R = Me), the dione (I; X = H) was methylated according to the procedure described by Stetter and Meisel[7] to give 2,5-dimethylcyclohexane-1,3-dione (I; X = Me) which on alkylation with 1-bromohept-2-ene, followed by reductive cleavage, as described for the acid (III; R = H) gave 3,6-dimethyltridec-8-enoic acid (V; R = H); the latter, after esterification and catalytic hydrogenation gave methyl 3,6-dimethyltridecanoate (VI; R = Me).

EXPERIMENTAL

The light petroleum used had b.p. 40—60°. Solutions in organic solvents were dried with $MgSO_4$. The alumina used for chromatography (Camag, neutral) was treated with water and the activity determined by the method of Heřmánek *et al.*[8] T.l.c. and unidimensional multiple chromatography[9] (u.m.c.) were carried out on plates of Kieselgel G, and the spots were detected with iodine vapour, unless otherwise stated.

5-*Methylcyclohexane*-1,3-*dione* (I; X = H).—This was prepared by Michael addition of ethyl sodioacetoacetate to ethyl crotonate as described by Crossley *et al.*,[3] except that on hydrolysis of the intermediate diketo-ester the mixture was heated under reflux for 1 hr. (the hydrolysis, followed by examining small portions of the mixture by t.l.c., was incomplete after boiling the mixture for 15 min. as directed by the earlier[3] paper). The product obtained on decarboxylation of the liberated acid crystallised from ethyl acetate to give the dione, m.p. 127° (Found: C, 66·4; H, 7·7. Calc. for $C_7H_{10}O_2$: C, 66·7; H, 7·9%) (lit.,[3] m.p. 128°).

2,5-*Dimethylcyclohexane*-1,3-*dione* (I; X = Me).—The preceding dione was methylated according to the directions given by Stetter *et al.*[7] The methylated product had, after crystallisation from ethyl acetate, m.p. 175—176° (Found: C, 68·3; H, 8·8. Calc. for $C_8H_{12}O_2$: C, 68·6; C, 8·6%) (lit.,[7] m.p. 175·5°).

2-*Hept*-2′-*enyl*-2,5-*dimethylcyclohexane*-1,3-*dione* (II; X = Me).—1-Bromohept-2-ene[4] (43 g., 0·23 mole) was added with vigorous stirring to 2,5-dimethylcyclohexane-1,3-dione (29·4 g., 0·21 mole) and di-isopropylethylamine[5] (27·1 g., 0·21 mole) in water (15 ml.); the stirring was continued for 36 hr. The resulting mixture, found by t.l.c. to contain three main components, was diluted with water, and extracted with ether. The extract was washed with 2N-hydrochloric acid, in order to hydrolyse any enol ether formed, water, and then with 10% aqueous sodium hydrogen carbonate (to remove regenerated 2,5-dimethylcyclohexane-1,3-dione); it was then distilled to give 2-*hept*-2′-*enyl*-2,5-*dimethylcyclohexane*-1,3-*dione* (42 g.), b.p. 126—127°/0·5 mm., $n_D^{18.5}$ 1·4780 (Found: C, 75·9; H, 9·9. $C_{15}H_{24}O_2$ requires C, 76·3; H, 10·2%).

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[7] H. Stetter and H. Meisel, *Chem. Ber.*, 1957, **90**, 2928.

[8] S. Heřmánek, V. Schwarz, and Z. Čekan, *Coll. Czech. Chem. Comm.*, 1961, **26**, 3170.

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3,6-*Dimethyltridec*-8-*enoic Acid* (V; R = H).—Hydrazine hydrate (1·06 g.) and 2-hept-2′-enyl-2,5-dimethylcyclohexane-1,3-dione (2·18 g.) were added to a solution of sodium hydroxide (1·85 g.) in diethylene glycol (15 ml.), and the mixture was heated under reflux for 3 hr., the temperature of the boiling solution being maintained at 115° by the addition of methanol. Water, methanol, and excess of hydrazine were then boiled off until the temperature of the mixture reached 195°; it was maintained at this temperature for 12 hr. The cooled solution was acidified with dilute hydrochloric acid and extracted with ether. Evaporation of the dried extract gave 3,6-*dimethyltridec*-8-*enoic acid* (1·9 g.) which had b.p. 139—141°/0·4 mm., n_D^{19} 1·4560 (Found: C, 74·7; H, 11·4. $C_{15}H_{28}O_2$ requires C, 75·0; H, 11·7%); t.l.c. of the acid (light petroleum–ether–acetic acid, 40 : 10 : 1) gave R_F 0·45.

Methyl 3,6-*Dimethyltridecanoate* (VI; R = Me).—The foregoing acid (25 g.) was esterified with 2·5% methanolic sulphuric acid (500 ml.) to give the ester (V; R = Me), b.p. 147—151°/8 mm. This ester (18·5 g.) was hydrogenated in ethanol (15 ml.) at 5 atm./room temperature in the presence of platinic oxide (5 hr.). The solution was evaporated and the residue chromatographed on alumina (activity IV; 100 g.); Light petroleum eluted *methyl* 3,6-*dimethyltridecanoate* (18·3 g.), b.p. 160°/12 mm., n_D^{20} 1·4393 (Found: C, 74·9; H, 12·4. $C_{16}H_{32}O_2$ requires C, 74·9; H, 12·6%).

Methyl 3-*methyltridec*-8-*enoate* (III; R = Me).—5-Methylcyclohexane-1,3-dione (26·4 g., 0·21 mole) and di-isopropylethylamine (27·1 g., 0·121 mole) were dissolved in water (14 ml.), 1-bromohept-2-ene (24·8 g., 0·14 mole) was added and the mixture was stirred vigorously for 56 hr. The solution was diluted with sodium hydroxide solution (1N; 400 ml.) and washed twice with light petroleum. The alkaline solution was aerated for 10 min. to remove traces of light petroleum and acidified with dilute hydrochloric acid to pH 5. The white crystals which separated were collected and dried *in vacuo* (20·0 g.). T.l.c. (light petroleum–ether–acetic acid, 25 : 75 : 1) showed that this material was essentially homogeneous (R_F 0·50, 5-methylcyclohexane-1,3-dione R_F 0·23). Attempts to recrystallize small amounts of this product resulted in decomposition to a brown oil.

The above crude product (18·9 g.), hydrazine hydrate (10 ml.), and methanol (15 ml.) were added to a solution of sodium hydroxide (17·1 g.) in diethylene glycol (127 ml.) and the mixture was subjected to the same procedure as described in the preparation of 3,6-dimethyltridec-8-enoic acid. The resulting crude acid was esterified with hot 5% methanolic sulphuric acid and the brown oil so obtained was chromatographed in light petroleum on a column of alumina (50 g.; activity II/III). Light petroleum eluted a colourless oil which on distillation gave *methyl* 3-*methyltridec*-8-*enoate* (12·4 g.), b.p. 151—153°/13 mm., n_D^{25} 1·4421 (Found: C, 75·1; H, 11·6. $C_{15}H_{28}O_2$ requires C, 75·0; H, 11·7%).

Methyl 3-*methyltridecanoate* (IV; R = Me).—Methyl 3-methyltridec-8-enoate (12·0 g.) was hydrogenated as described for methyl 3,6-dimethyltridecanoate; distillation of the product gave methyl 3-methyltridecanoate (11·2 g.), b.p. 147—149/10 mm. (Found: C, 75·1; H, 11·6. Calc. for $C_{15}H_{30}O_2$: C, 74·9; H, 11·7%).

[0/1308 *Received, July* 29*th*, 1970]