

### 711. *Aliphatic Hydroxy-acids. Part II.*<sup>1</sup> *Some Terminally Substituted Iso-acids.*

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Anodic syntheses with *L*-(+)-5-acetoxy-4-methylpentanoic acid \* led to *L*-(+)-13-hydroxy-12-methyltridecanoic acid and *D*-(+)-2-methyltetradec-13-en-1-ol. Oxidation of the acetate of the latter gave *L*-(+)-13-acetoxy-12-methyltridecanoic acid. Anodic coupling of ( $\pm$ )-5-methoxy-4-methylpentanoic acid<sup>1</sup> with methylhydrogen decanedioate led to ( $\pm$ )-13-methoxy-12-methyltridecanoic acid. The preparation of 8-hydroxy-2(*D*),7(*L*)-dimethyloctanoic acid is also described.

It has been claimed<sup>2</sup> that two long-chain  $\omega$ -hydroxy-acids of the iso-series (I; R = H,  $n = 26$  and 28) are present in hydrolysed wool-wax, but the reported evidence only establishes the carbon skeleton of the two acids and excludes their formulation as  $\alpha$ -hydroxy-acids. Unbranched  $\omega$ -hydroxy-acids<sup>3</sup> and non-hydroxylated iso-acids<sup>4</sup> had previously been reported in hydrolysed wool-wax. The only recorded derivatives of  $\omega$ -hydroxy-acids of the iso-series containing more than ten carbon atoms are methyl

\* The symbols *D* and *L* are used in the sense defined by Linstead, Lunt, and Weedon, *J.*, 1950, 3333.

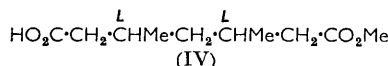
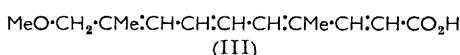
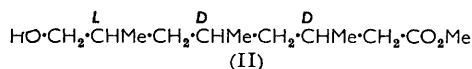
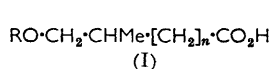
<sup>1</sup> Part I, *J.*, 1962, 4836.

<sup>2</sup> Downing, Kranz, and Murray, *Austral. J. Chem.*, 1960, **13**, 80.

<sup>3</sup> Horn and Pretorius, *Chem. and Ind.*, 1956, R 27.

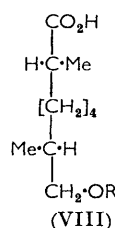
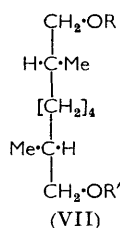
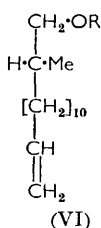
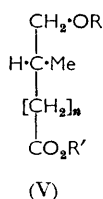
<sup>4</sup> Weitkamp, *J. Amer. Chem. Soc.*, 1945, **67**, 447.

8-hydroxy-3(*D*),5(*D*),7(*L*)-trimethyloctanoate (II)<sup>5</sup> and the methoxy-acid (III).<sup>6</sup> The hydroxy-ester (II) was prepared, in low yield, from methyl hydrogen 3(*L*),5(*L*)-dimethylheptanoate (IV), the requisite terminal group being constructed by a six-stage procedure.



We investigated an alternative route to both optically active and inactive  $\omega$ -hydroxy-acids of the iso-series, based on the chain extension of acids containing protected forms of the desired terminal group, *e.g.* (V; R = Ac, R' = H,  $n = 2$  and 10), (I, R = Me,  $n = 2$  and 10).

The readily available<sup>7</sup> (+)-5-acetoxy-4-methylpentanoic acid (V; R = Ac, R' = H,  $n = 2$ ), which is known<sup>7</sup> to belong configurationally to the *L*-series, is an ideal starting material for this type of synthesis. Anodic cross-coupling of this acid with methyl hydrogen



decanedioate gave (+)-methyl *L*-13-acetoxy-12-methyltridecanoate (V; R = Ac, R' = Me,  $n = 10$ ), which on hydrolysis gave *L*-(+)-13-hydroxy-12-methyltridecanoic acid (V; R = R' = H,  $n = 10$ ). It was hoped to obtain the long-chain acid (I;  $n = 26$ ) from an analogous anodic coupling of *L*-13-acetoxy-12-methyltridecanoic acid (V; R = Ac, R' = H,  $n = 10$ ) with the readily available<sup>8</sup> methyl hydrogen octadecanedioate, but the cross-coupled product could not be isolated from the electrolysis products. Since pure *L*-13-acetoxy-12-methyltridecanoic acid (V; R = Ac, R' = H,  $n = 10$ ) could not be obtained by acetylation of the hydroxy-acid (V; R = R' = H,  $n = 10$ ) or transesterification of the acetoxy-ester (V; R = Ac, R' = Me,  $n = 10$ ), it was prepared indirectly. Anodic coupling of *L*-(+)-5-acetoxy-4-methylpentanoic acid (V; R = Ac, R' = H,  $n = 2$ ) with undec-10-enoic acid, followed by hydrolysis of the crude product resulting from cross-coupling, gave *D*-(+)-2-methyltetradec-13-en-1-ol (VI; R = H). Oxidation of the derived acetate (VI; R = Ac) with potassium permanganate in acetic acid<sup>9</sup> then gave *L*-13-acetoxy-12-methyltridecanoic acid (V; R = Ac, R' = H,  $n = 10$ ).

The inaccessibility of ( $\pm$ )-5-acetoxy-4-methylpentanoic acid<sup>1</sup> (I; R = Ac,  $n = 2$ ) makes it unsuitable as the starting material for the synthesis of racemic  $\omega$ -hydroxy-acids of the iso-series, and so the use of ( $\pm$ )-5-methoxy-4-methylpentanoic acid<sup>1</sup> (I; R = Me,  $n = 2$ ) was investigated. Anodic cross-coupling of this acid with methyl hydrogen decanedioate gave, after hydrolysis, ( $\pm$ )-13-methoxy-12-methyltridecanoic acid (I; R = Me,  $n = 10$ ). The *L*-form of this acid was obtained for comparison by methylation of the *L*-hydroxy-acid (V; R = R' = H,  $n = 10$ ) with dimethyl sulphate in the presence of sodium *t*-butoxide.<sup>10</sup> Demethylation of the *L*-methoxy-acid (V; R = Me,

<sup>5</sup> Ahlquist, Asselineau, Asselineau, Stållberg-Stenhagen, and Stenhagen, *Bull. Soc. chim. France*, 1960, 1316.

<sup>6</sup> Ahmad and Weedon, *J.*, 1953, 2125.

<sup>7</sup> Bailey, Brice, Horne, and Polgar, *J.*, 1959, 661.

<sup>8</sup> (a) *Org. Synth.*, 1961, **41**, 33; (b) Hunsdiecker, *Ber.*, 1942, **75**, 291.

<sup>9</sup> Cf., Grün and Wirth, *Ber.*, 1922, **55**, 2206.

<sup>10</sup> Cf., Hallsworth, Henbest, and Wrigley, *J.*, 1957, 1969.

$R' = H$ ,  $n = 10$ ) with acetic anhydride-toluene-*p*-sulphonic acid<sup>1</sup> regenerated the *L*-hydroxy-acid in only 11% yield. The cross-coupled product could not be isolated from a mixed electrolysis employing ( $\pm$ )-13-methoxy-12-methyltridecanoic acid (I;  $R = Me$ ,  $n = 10$ ) and methyl hydrogen octadecanedioate.

The production of (+)-1,8-diacetoxy-2,7-dimethyloctane (VII;  $R = R' = Ac$ ) in cross-electrolyses using *L*-(+)-5-acetoxy-4-methylpentanoic acid (V;  $R = Ac$ ,  $R' = H$ ,  $n = 2$ ) provided an easy route to another  $\omega$ -hydroxy-acid of the iso-series, (–)-8-hydroxy-2(*D*),7(*L*)-dimethyloctanoic acid (VIII;  $R = H$ ). The diacetate (VII;  $R = R' = Ac$ ) was hydrolysed and partially esterified,<sup>11</sup> giving the monoacetate (VII;  $R = Ac$ ,  $R' = H$ ). Oxidation of this with chromium trioxide in aqueous acetic acid gave the acetoxy-acid (VIII;  $R = Ac$ ), which on saponification gave the desired hydroxy-acid (VIII;  $R = H$ ).

It is noteworthy that *L*-13-hydroxy-12-methyltridecanoic acid (V;  $R = R' = H$ ,  $n = 10$ ) is dextrorotatory,  $[M]_D +16.4^\circ$ , whereas 8-hydroxy-2(*D*),7(*L*)-dimethyloctanoic acid (VIII;  $R = H$ ) is levorotatory,  $[M]_D -4.9^\circ$ . The contribution to the molecular rotation of the second, remote, asymmetric centre in the latter case is in accord with the known high negative molecular rotations of 2(*D*)-methylsubstituted acids (cf.,<sup>12</sup> *D*-(–)-2-methylhexacosanoic acid,  $[M]_D -28^\circ$ ).

## EXPERIMENTAL

Solutions in organic solvents were dried over anhydrous sodium sulphate. Petrol refers to light petroleum of b. p. 60–80° and petroleum to the fraction of b. p. 40–60°. Rotations were measured in a 2 dm. tube. For chromatography, alumina (Spence type H, 30 g.) or silica (Silica Gel Co. Ltd., 30–120 mesh, 50 g.) were used per gram of substance. Electrolyses using a mercury cathode were performed in the cell described previously (cell A)<sup>13</sup> and were continued until the current, initially *ca.* 5 A, dropped to a low, steady value. Other electrolyses were performed in a water-cooled three-necked flask of 2 l. capacity using a nickel cathode and a rotating platinum anode (5 cm. in diameter) (cell B) and were continued until the solution became alkaline (pH 10). A D.C. power unit supplying 110–150 v was used.

(+)-Methyl *L*-13-Acetoxy-12-methyltridecanoate (V;  $R = Ac$ ,  $R' = Me$ ,  $n = 10$ ).—Methyl hydrogen decanedioate<sup>8b</sup> (7.2 g., 1 mol.) and *L*-(+)-5-acetoxy-4-methylpentanoic acid (17.4 g., 3 mol.) were added to sodium methoxide [from sodium (2.0 g., 3 mol.)] in methanol (400 ml.), the solution was electrolysed in cell A for 6 hr., and the methanol was distilled. The residues from four such electrolyses were dissolved in chloroform and the solution (100 ml.) was washed with aqueous sodium hydrogen carbonate and water, dried, added to urea [5.0 g., previously moistened with methanol (1 ml.)], and shaken periodically for 20 hr. The mixture was filtered and the filtrate treated with urea as before. The filtrate from the second treatment was washed with water, dried, and distilled, affording the *ester*, b. p. 150–160°/0.15 mm.,  $n_D^{25} 1.4400$ ,  $[\alpha]_D^{19} +0.87^\circ$  (*c* 20 in  $CHCl_3$ ) (Found: C, 67.8; H, 10.7.  $C_{17}H_{32}O_4$  requires C, 68.0; H, 10.7%).

*L*-(+)-13-Hydroxy-12-methyltridecanoic Acid (V;  $R = R' = H$ ,  $n = 10$ ).—Methyl hydrogen decane-1,10-dioate (108 g., 1 mol.) and *L*-(+)-5-acetoxy-4-methylpentanoic acid (261 g., 3 mol.) were added to sodium methoxide [from sodium (4.0 g., 0.3 mol.)] in methanol (1.5 l.) and the solution electrolysed in cell B for 72 hr. The methanol was distilled from the methanolic solutions resulting from two such electrolyses and the residue dissolved in ether. The ethereal solution was washed with 2*N*-hydrochloric acid, water, aqueous sodium hydrogen carbonate, and water, dried, and distilled. The fraction of b. p. 160–220°/16 mm. was heated under reflux for 16 hr. with ethanolic potassium hydroxide, most of the ethanol was distilled off, the mixture was diluted with water, and 1,8-dihydroxy-2(*D*),7(*L*)-dimethyloctane was removed by ether-extraction. Acidification of the mixture liberated the crude product, which was collected in ether and purified by chromatography on silica. Ether-petroleum (1:1) eluted the *hydroxy-acid*, m. p. 48–49° [from ether-petroleum (1:2) then petrol-benzene (1:8)]  $[\alpha]_D^{21} +6.72^\circ$

<sup>11</sup> Cf., Chuit and Hausser, *Helv. Chim. Acta*, 1929, **12**, 463.

<sup>12</sup> Stållberg-Stenhagen, *Arkiv Kemi*, 1949, **1**, 153.

<sup>13</sup> Brettle, Polgar, and Smith, *J.*, 1960, 2802.

(*c* 9·5 in  $\text{CHCl}_3$ ) (Found: C, 68·7; H, 11·5%; Equiv., 240.  $\text{C}_{14}\text{H}_{28}\text{O}_3$  requires C, 68·8; H, 11·5%; Equiv., 244).

*D*-(+)-2-Methyltetradec-13-en-1-ol (VI; R = H).—*L*-(+)-5-Acetoxy-4-methylpentanoic acid (522 g., 3 mol.) and undec-10-enoic acid (184 g., 1 mol.) were added to sodium methoxide [from sodium (3 g., 0·13 mol.)] in methanol (1·2 l.) and the solution electrolysed in cell B for 130 hr. The surfaces of the anode were kept clean by causing them to rotate against glass-wool pads. The solution was concentrated to half its original volume, treated with 10*N*-aqueous sodium hydroxide (700 ml.), and heated under reflux for 12 hr. The methanol was distilled, the aqueous residue diluted with water, and the solution extracted successively with ether (2 × 800 ml.) and petrol (2 × 800 ml.). The combined extracts were washed with water, dried, and distilled, and the fraction of b. p. 150—190°/10 mm. (277 g.) was chromatographed on alumina in three portions. Eicosa-1,19-diene (32 g.), b. p. 180—185°/10 mm.,  $n_D^{25}$  1·4530 (lit.,<sup>14</sup> b. p. 125—130°/0·2 mm.,  $n_D^{24}$  1·4511) was eluted first, by petroleum. Elution with ether then gave the *tetradecenol* (124 g., 54%), b. p. 164—168°/13 mm.,  $n_D^{21}$  1·4550,  $\nu_{\text{max}}$  910, 990  $\text{cm}^{-1}$  ( $-\text{CH}=\text{CH}_2$ ),  $[\alpha]_D^{25} + 7·31^\circ$  (homog.) (Found: C, 79·3; H, 13·5.  $\text{C}_{15}\text{H}_{30}\text{O}$  requires C, 79·6; H, 13·4%). The *phenylcarbamate* had m. p. 46° (from petroleum) (Found: C, 76·55; H, 10·2; N, 4·3.  $\text{C}_{22}\text{H}_{35}\text{NO}_2$  requires C, 76·5; H, 10·2; N, 4·1%) and the *acetate* had b. p. 174—177°/13 mm.,  $[\alpha]_D^{22} + 0·53^\circ$  (homog.),  $\nu_{\text{max}}$  910, 990  $\text{cm}^{-1}$  ( $-\text{CH}=\text{CH}_2$ ) (Found: C, 76·0; H, 11·8.  $\text{C}_{17}\text{H}_{32}\text{O}_2$  requires C, 76·1; H, 12·0%). Elution with methanol gave 1,8-dihydroxy-2(*D*),7(*L*)-dimethyloctane (62 g.), b. p. 164—170°/14 mm.,  $n_D^{20}$  1·4595 (supercooled liquid), m. p. 31—32° (lit.,<sup>13</sup> 33—34°).

*L*-13-Acetoxy-12-methyltridecanoic Acid (V; R = Ac, R' = H, n = 10).—*D*-(+)-2-Methyltetradec-13-en-1-yl acetate (26·8 g., 1 mol.) in acetic acid (250 ml.) was treated with powdered potassium permanganate (63·2 g., 4 mol.) in twelve portions during 3 hr. and the mixture was heated at 100° for 2 hr., cooled, diluted with water (1 l.) and ice (500 g.), and treated with sulphur dioxide until a colourless solution resulted. The solution was extracted with petrol (3 × 800 ml.) and the extracts washed with water, dried, and distilled, giving the *acid* (22 g., 77%), b. p. 164—166°/0·07 mm.,  $[\alpha]_D^{23}$  0°  $\pm$  0·1° (homog.) (Found: C, 67·05; H, 10·3%; Equiv., 291.  $\text{C}_{16}\text{H}_{30}\text{O}_4$  requires C, 67·1; H, 10·55%; Equiv., 286).

*L*-(+)-13-Methoxy-12-methyltridecanoic Acid (V; R = Me, R' = H, n = 10).—*L*-(+)-13-Hydroxy-12-methyltridecanoic acid (37 g., 1 mol.) in *t*-butyl alcohol (100 ml.) was added to sodium *t*-butoxide [from sodium (18 g., 2·6 mol.)] in *t*-butyl alcohol (350 ml.) and the solution was heated under reflux for 24 hr. Dimethyl sulphate (50 g., 2·6 mol.) in *t*-butyl alcohol (70 ml.) was added during 0·5 hr. and the solution was heated under reflux for 12 hr. The solvent was distilled, and the residue heated under reflux with 10*N*-aqueous sodium hydroxide (100 ml.) and methanol (200 ml.) for 4 hr. The methanol was distilled, the alkaline solution acidified, and the product collected in ether. Distillation gave the *acid* (18 g., 50%), b. p. 165—170°/0·1 mm.,  $n_D^{22}$  1·4503,  $[\alpha]_D^{25} + 2·0^\circ$  (homog.) (Found: C, 69·8; H, 11·6%; Equiv., 254.  $\text{C}_{15}\text{H}_{30}\text{O}_3$  requires C, 69·7; H, 11·7%; Equiv., 258).

( $\pm$ )-13-Methoxy-12-methyltridecanoic Acid (I; R = Me, n = 10).—( $\pm$ )-5-Methoxy-4-methylpentanoic acid<sup>1</sup> (5·0 g., 1 mol.) and methyl hydrogen decanedioate (21·6 g., 3 mol.) were added to sodium methoxide [from sodium (2·0 g., 2·5 mol.)] in methanol (400 ml.) and the solution electrolysed in cell A for 6 hr. The methanolic solutions from six such electrolyses were combined and the solvent distilled. The residue was dissolved in ether, and this solution washed with aqueous sodium hydrogen carbonate and water and dried. Distillation gave two fractions, (i) b. p. 108—109°/117 mm.,  $n_D^{22}$  1·4322 and (ii) b. p. 122—134°/0·06 mm.,  $n_D^{22}$  1·4458. Fraction (i) was heated under reflux with potassium hydroxide (50 g.) in water (400 ml.) and methanol (300 ml.) for 12 hr. The methanol was distilled and the aqueous residue extracted with ether. The extracts were washed with water, dried ( $\text{Na}_2\text{SO}_4$ , then Na wire for 2 weeks) and distilled to give ( $\pm$ )-1,8-dimethoxy-2,7-dimethyloctane, b. p. 112—113°/10 mm.,  $n_D^{18}$  1·4280 (Found: C, 71·8; H, 12·6.  $\text{C}_{12}\text{H}_{26}\text{O}_2$  requires C, 71·3; H, 12·9%). Fraction (ii) was heated under reflux with potassium hydroxide (50 g.) in water-methanol (1 : 1; 800 ml.) for 12 hr. The methanol was distilled and the aqueous solution acidified and extracted with ether. The extracts were washed with water and dried, and the ether distilled. The residue was chromatographed on silica. Ether-petroleum (1 : 4) eluted the *methoxy-acid*, b. p. 155—160°/0·02 mm.,  $n_D^{22}$  1·4500 (Found: C, 70·0; H, 11·35%; equiv., 256.  $\text{C}_{15}\text{H}_{30}\text{O}_3$  requires

<sup>14</sup> Bounds, Linstead, and Weedon, *J.*, 1953, 2393.

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C, 69.7; H, 11.7%; equiv., 258). The infrared spectrum was identical with that of the (+)-*L*-acid.

8-Acetoxy-2(*D*),7(*L*)-dimethyloctan-1-ol (VII; R = Ac, R = H).—(+)-1,8-Dihydroxy-2(*D*),7(*L*)-dimethyloctane (26.5 g., 1 mol.), acetic anhydride (19.5 g., 1.25 mol.), and anhydrous sodium acetate (1.5 g., 0.1 mol.) were heated under reflux for 6 hr. Water was added, the mixture was extracted with petrol, and the extract dried. Calcined, powdered, calcium chloride (70 g.) was added and the suspension shaken for 4 hr. The resultant solid was filtered off, washed with petrol, and the washings discarded. The solid was decomposed with water, the organic material collected in petrol, and the petrol solution washed, dried, and distilled, affording the *octanol* (5.5 g., 16%), b. p. 162–164°/12 mm.,  $n_D^{22}$  1.4448 (Found: C, 66.4; H, 11.9.  $C_{12}H_{24}O_3$  requires C, 66.6; H, 12.2%). In a large-scale preparation, in which the calcium chloride treatment was omitted, the product had b. p. 168–170°/14 mm.,  $n_D^{20}$  1.4438.

(–)-8-Acetoxy-2(*D*),7(*L*)-dimethyloctanoic Acid (VIII; R = Ac).—Chromic oxide (95 g., 1.1 mol.) in 50% aqueous acetic acid (200 ml.) was added during 2 hr. to 8-acetoxy-2(*D*),7(*L*)-dimethyloctan-1-ol (70 g., 1 mol.) in acetic acid (500 ml.) heated on a steam-bath. The mixture was stirred for 4 hr., ethanol (50 ml.) was added, and the mixture stirred for a further 0.5 hr. The solution was diluted with water (1 l.) and extracted with petrol (3 × 1 l.). The extracts were washed with water and extracted with saturated aqueous sodium hydrogen carbonate (3 × 1 l.). The aqueous extract was acidified, extracted with ether (3 × 800 ml.), and the ethereal extracts washed with water, dried, and distilled, giving the *acid*, b. p. 188–192°/16 mm.,  $n_D^{21}$  1.4448,  $[\alpha]_D^{24}$  –7.9° (homog.) (Found: C, 62.0; H, 9.2%; Equiv., 226.  $C_{12}H_{22}O_4$  requires C, 62.6; H, 9.6%; Equiv., 230).

(–)-8-Hydroxy-2(*D*),7(*L*)-dimethyloctanoic Acid (VIII; R = H).—(–)-8-Acetoxy-2(*D*),7(*L*)-dimethyloctanoic acid was hydrolysed by heating it under reflux for 18 hr. with an excess of methanolic potassium hydroxide. Some of the methanol was distilled and the solution was acidified with hydrochloric acid and extracted with ether. The ethereal extracts were washed with water, dried, and distilled, affording the *hydroxy-acid*, b. p. 164–165°/0.2 mm.,  $n_D^{22}$  1.4567,  $[\alpha]_D^{22}$  –2.6° (homog.) (Found: C, 63.4; H, 10.9%; Equiv., 189.  $C_{10}H_{20}O_3$  requires C, 63.8; H, 10.7%; Equiv., 188). The acid solidified at –15° and had m. p. ca. 10°.

We thank Messrs. Glaxo Laboratories Ltd. for a supply of (+)-5-acetoxy-4-methylpentanoic acid and the D.S.I.R. for a maintenance award (to F. S. H.).

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[Received, December 20th, 1963.]

\* In order to designate the configurations of the asymmetric centres in this compound a minor extension of the convention of Linstead, Lunt, and Weedon, *J.*, 1950, 3333, is necessary; the group –OH is given priority over the group –OAc.