566. *Synthesis of* (—)-2(D),4(D)-*Dimethylheptacosanoic Acid.**

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(—)-2(*D*),4(*D*)-Dimethylheptacosanoic acid (III) has been synthesised, with *D*-(+)-2-methylpentacosan-1-ol * (II; R = H) as intermediate; the latter was obtained from *L*-(+)-5-acetoxy-4-methylpentanoic acid [1] (I) by anodic coupling with docosanoic acid. The preparation of (+)-2(*D*),4(*D*)-dimethylheptacosan-1-ol (IV) by reduction of the acid (III) is also described.

In continuation of previous [1] experiments we have now synthesised (—)-2(*D*),4(*D*)-dimethylheptacosanoic acid (III). The synthesis was undertaken in connection with studies of the lipids of tubercle bacilli; from earlier work [2,3] the acid (III) was believed to arise on stepwise degradation of mycoceranic acid, but this now appears to be doubtful in view of the recently published [4] indication that mycoceranic acid is a mixture of several closely related acids. *L*-(+)-5-Acetoxy-4-methylpentanoic acid [1] (I) was used as starting

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

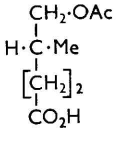
[1] Bailey, Brice, Horne, and Polgar, *J.*, 1959, 661.

[2] Polgar, *J.*, 1954, 1011.

[3] Asselineau, Ryhage, and Stenhagen, *Acta Chem. Scand.*, 1957, **11**, 196.

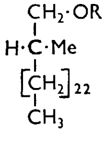
[4] C. Asselineau, J. Asselineau, Ryhage, Ställberg-Stenhagen, and Stenhagen, *Acta Chem. Scand.*, 1959, **13**, 822.

material. Anodic coupling of this acid with docosanoic acid, followed by hydrolysis of the acetoxy-derivative (II; R = Ac) resulting from crossed coupling, gave *D*-(+)-2-methylpentacosan-1-ol (II; R = H). This alcohol was converted, *via* the toluene-*p*-sulphonate, into the corresponding iodide which by condensation with ethyl sodiomethylmalonate, followed by hydrolysis and decarboxylation, afforded a mixture of the acid (III) with its 2(*L*)-diastereoisomer. Chromatography of the corresponding methyl esters on alumina resulted in the isolation of the 2(*D*)-ester. The latter on reduction with lithium aluminium hydride gave (+)-2(*D*),4(*D*)-dimethylheptacosan-1-ol (IV); hydrolysis of the 2(*D*)-ester under the conditions described in the Experimental section resulted in the acid (III) with $[\alpha]_D$ −4·2°.



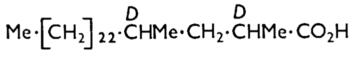
$$\begin{array}{c} CH_2\cdot OAc \\ | \\ H\cdot C\cdot Me \\ | \\ [CH_2]_2 \\ | \\ CO_2H \end{array}$$

(I)



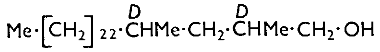
$$\begin{array}{c} CH_2\cdot OR \\ | \\ H\cdot C\cdot Me \\ | \\ [CH_2]_{22} \\ | \\ CH_3 \end{array}$$

(II)



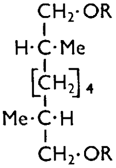
$$Me\cdot[CH_2]_{22}\cdot\overset{D}{C}HMe\cdot CH_2\cdot\overset{D}{C}HMe\cdot CO_2H$$

(III)



$$Me\cdot[CH_2]_{22}\cdot\overset{D}{C}HMe\cdot CH_2\cdot\overset{D}{C}HMe\cdot CH_2\cdot OH$$

(IV)



$$\begin{array}{c} CH_2\cdot OR \\ | \\ H\cdot C\cdot Me \\ | \\ [CH_2]_4 \\ | \\ Me\cdot C\cdot H \\ | \\ CH_2\cdot OR \end{array}$$

(V)

In the course of this work electrolysis of the (+)-acetoxy-acid (I) gave (+)-1,8-diacetoxy-2,7-dimethyloctane (V; R = Ac) which on prolonged alkaline hydrolysis afforded the (+)-diol (V; R = H).

EXPERIMENTAL

Optical rotations were measured in a 1-dm. tube. Petrol refers to light petroleum, b. p. 40—60°. The alumina used for chromatography (Spence, type H) was washed with acid, and had activity II on Brockmann and Schodder's scale.[5]

D-(+)-2-*Methylpentacosan*-1-*ol* (II; R = H).—Crude *L*-(+)-acetoxy-4-methylpentanoic acid,[1] kindly supplied by Glaxo Laboratories Ltd., was purified by fractional distillation; the product had b. p. 160°/10 mm., n_D^{18} 1·4400, d_4^{18} 1·0805, $[\alpha]_D^{18}$ 4·76° (homogeneous). A hot solution of docosanoic acid (9 g.; obtained from octadecan-1-ol, purified by distillation of its acetate through an 18-inch electrically heated column packed with wire-gauze rings, by standard chain-lengthening procedures) in light petroleum (b. p. 60—80°; 300 c.c.) was added to a solution of the above acetoxy-acid (30 g.) and methoxide (from 3 g. of sodium) in hot methanol (250 c.c.), and the mixture electrolysed in a cell essentially as described by Nguyen Dinh-Nguyen,[6] except that it was fitted with a cooling coil; more methoxide [from sodium (0·3 g.)] in methanol (50 c.c.) was added after 0·5 hr. Mercury (25—30 c.c.) was used as the cathode, and a rotating platinum disc as the anode (the rotation inhibiting the coating of this electrode with sparingly soluble electrolysis products). Throughout the electrolysis the temperature of the mixture was maintained at 47° by adjustment of the rate of flow of water through the cooling coil and the outer jacket of the cell. The initial current was 2·6 A; after 4 hr. it fell to a steady value of 0·65 A. The mixture was then separated from the sodium amalgam formed during the electrolysis, and evaporated. The residue was refluxed with ether, and the ethereal solution filtered, washed with aqueous sodium hydroxide and then with water, dried ($MgSO_4$), and distilled. Three runs on the above scale were worked up together, and the fraction, b. p. >107°/0·1 mm., hydrolysed by refluxing it with a solution of potassium hydroxide (20 g.) in water (35 c.c.) and ethanol (160 c.c.) for 16 hr. Isolation of the product by extraction with ether afforded a wax (15·3 g.) which, after crystallisation from petrol followed by crystallisation from acetone, gave D-(+)-2-*methylpentacosan*-1-*ol*, m. p. 67—67·5°, $[\alpha]_D^{25}$ +5·5° (*c*, 8·15 in chloroform) (Found: C, 81·6; H, 14·2. $C_{26}H_{54}O$ requires C, 81·6; H, 14·2%): the infrared spectrum showed bands at 3300 and 1050 cm.$^{-1}$ (OH).

D-1-*Iodo*-2-*methylpentacosane*.—Toluene-*p*-sulphonyl chloride (6·49 g.) was added in small portions to an ice-cold solution of *D*-2-methylpentacosan-1-ol (7·5 g.) in dry pyridine (250 c.c.) during ½ hr., the mixture being shaken continually. The temperature of the solution was then allowed to rise to 20°, and shaking continued for a further 2 hr. After a further 48 hr. at 20° the mixture was acidified with dilute hydrochloric acid (at 0°), extracted with ether, and the

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[5] Brockmann and Schodder, *Ber.*, 1941, **74**, 73.

[6] Nguyen Dinh-Nguyen, *Acta Chem. Scand.*, 1958, **12**, 585.

ethereal solution washed with dilute hydrochloric acid and water. Evaporation of the dried ($MgSO_4$) extract afforded the toluene-*p*-sulphonate (9·98 g.) (Found: C, 73·4; H, 11·3; S, 5·9. $C_{33}H_{60}O_3S$ requires C, 73·8; H, 11·3; S, 5·9%), m. p. 54—55° (from petrol). This ester (9·8 g.) was refluxed with a solution of anhydrous sodium iodide (5·7 g.) in dry acetone (150 c.c.) for 42 hr.; the mixture was then poured into water and extracted with ether. The extract was washed successively with aqueous sodium hydrogen sulphite and water, dried ($MgSO_4$), and evaporated. The residue was taken up in petrol, and the solution filtered through a small amount of alumina and then evaporated, affording D-1-*iodo*-2-*methylpentacosane* (8·3 g.), m. p. 43—44° (Found: C, 63·3; H, 10·7; I, 26·1. $C_{26}H_{53}I$ requires C, 63·4; H, 10·9; I, 25·8%).

(–)-2(D),4(D)-*Dimethylheptacosanoic Acid* (III).—The above iodide (3·1 g.) was refluxed with ethyl methylsodiomalonate (from 0·25 g. of sodium, 2·6 c.c. of ethyl methylmalonate, and 30 c.c. of ethanol) for 6 hr. After acidification with dilute hydrochloric acid, the product was isolated by means of ether, then refluxed with potassium hydroxide (15 g.) in water (20 c.c.) and ethanol (80 c.c.) for 15 hr. Most of the ethanol was then distilled off, and the residue poured into dilute hydrochloric acid. The product, isolated by extraction with ether, was decarboxylated by heating it at 180° for 2 hr.; it was then refluxed with aqueous-ethanolic potassium hydroxide (as above) for 20 hr., and the liberated acid again subjected to the decarboxylation procedure, affording a mixture of the acid (III) and its 2(*L*)-diastereoisomer (2·3 g.); in another experiment 13·1 g. of iodide by the above procedure gave 10·65 g. (91%) of the diastereoisomeric acids. This mixture was esterified with methanolic sulphuric acid, and a 5 g. portion of the methyl ester chromatographed in petrol on alumina (200 g.; 3·5 × 25 cm.). On elution with petrol, the earlier fractions contained material of low rotatory power; the later fractions yielded material of $[\alpha]_D$ –2·25° (1·97 g.). Rechromatography of the latter afforded *methyl* (–)-2(D),4(D)-*dimethylheptacosanoate*, $[\alpha]_D^{17}$ –4·9° (*c* 9·35 in chloroform), m. p. 46·5—47·5° after crystallisation from petrol at –40° (Found: C, 79·1; H, 13·1. $C_{30}H_{60}O_2$ requires C, 79·4; H, 13·2%); the rotatory power remained unchanged on further chromatography on alumina. This ester (0·39 g.) was refluxed with a solution of potassium hydroxide (1 g.) in water (3 c.c.) and ethanol (7 c.c.) for 1 hr. Acidification with dilute hydrochloric acid, followed by extraction with ether, afforded the 2(D),4(D)-*acid*, m. p. 54—55° after crystallisation from petrol at –6°, $[\alpha]_D^{23}$ –4·2° (*c* 6·05 in chloroform) (Found: C, 79·3; H, 13·1. $C_{29}H_{58}O_2$ requires C, 79·4; H, 13·3%); there was no change in rotatory power on recrystallisation of the acid from petrol.

When the 2(*D*),4(*D*)-ester was refluxed with aqueous-ethanolic potassium hydroxide for 3 hr., acid, $[\alpha]_D$ –2·75°, resulted; on refluxing the ester with 10% aqueous-ethanolic potassium hydroxide for 25 hr. the resulting acid had, after purification by chromatography over silica, $[\alpha]_D$ –0·65°.

(+)-2(D),4(D)-*Dimethylheptacosan*-1-*ol* (IV).—The 2(*D*),4(*D*)-ester (0·42 g.) in ether was added to an ethereal suspension of lithium aluminium hydride, and the mixture refluxed for 30 min. The excess of lithium aluminium hydride was decomposed by ethyl acetate; water was then added, followed by dilute sulphuric acid. The aqueous phase was extracted with ether, and the combined ethereal solutions were washed with water, dried ($MgSO_4$), and evaporated. The residue was chromatographed in petrol on alumina (15 g.). The fractions eluted by petrol, followed by petrol–benzene (9 : 1) were rejected; benzene eluted 2(D),4(D)-*dimethylheptacosan*-1-*ol* which, after crystallisation from petrol, had m. p. 63—64°, $[\alpha]_D^{22}$ +3·17° (*c* 4·42 in chloroform) (Found: C, 81·6; H, 14·0. $C_{29}H_{60}O$ requires C, 82·0; H, 14·2%).

(+)-1,8-*Dihydroxy*-2(D),7(L)-*dimethyloctane* (V; R = H).—A solution of *L*-(+)-5-acetoxy-4-methylpentanoic acid (8·5 g.; 0·049 mole) and methoxide [from sodium (0·75 g.; 0·0326 mole)] in methanol (300 c.c.) was electrolysed in the cell described above for 1·5 hr., the temperature being maintained at 20—40°; the initial current was 4·5 A, dropping to a steady value of 0·6 A. After removal of the sodium amalgam formed, the solution was evaporated, the residue taken up in ether, and the ethereal extract washed with aqueous sodium hydroxide and water, then dried ($MgSO_4$), and evaporated. The product (4·04 g.) gave on distillation the *diacetoxy-derivative* (V; R = Ac), b. p. 158·5—159°/9·5 mm., n_D^{18} 1·4370, $[\alpha]_D^{18.5}$ +2·08° (homog.) (Found: C, 65·5; H, 9·9. $C_{14}H_{26}O_4$ requires C, 65·1; H, 10·1%). More diacetoxy-derivative was obtained, as by-product, in the mixed electrolyses described above. Hydrolysis of the diacetoxy-derivative (43·3 g.) by a refluxing solution of potassium hydroxide (56 g.) in water (90 c.c.) and ethanol (200 c.c.) for 20 hr. gave a mixture of acetoxy- and hydroxy-derivatives. Further refluxing with a solution of potassium hydroxide (125 g.) in water (100 c.c.) and ethanol

(300 c.c.) for 70 hr., followed by acidification and extraction with ether, gave (+)-1,8-*dihydroxy*-2(D),7(L)-*dimethyloctane* as an oil which slowly crystallised (2 days), and had m. p. 33—34°, $[\alpha]_D^{18}$ +22·5° (*c* 17·16 in chloroform) (Found: C, 69·2; H, 12·4. $C_{10}H_{22}O_2$ requires C, 69·0; H, 12·6%).

When, in a comparative experiment, the electrolysis of (+)-5-acetoxy-4-methylpentanoic acid (8·5 g.) was performed in the presence of methoxide from 1 g. (0·0435 mole) of sodium at a slightly higher temperature (20—50°), a mixture of the 1,8-dihydroxy- and the 1,8-diacetoxy-compound resulted.

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