131. *Intermediates for the Synthesis of Optically Active Methyl-substituted Long-chain Acids. Part IV.**

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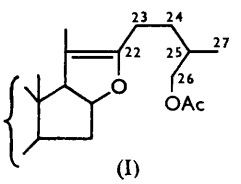
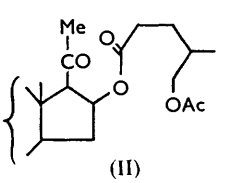
Synthetical studies starting from *L*-(+)-5-acetoxy-4-methylpentanoic acid † (IV), an industrial by-product, are reported.

Model experiments involving the synthesis of 2(*DL*) : 4(*L*)-dimethyldocosanoic acid (VII) with *L*-(−)-3-methylheneicosanoic acid (VI; R = H) as intermediate are also described.

Degradation of sapogenins in industrial syntheses of steroids (cf. ref. 1) yields, as by-products, optically active methyl-substituted acids which contain the asymmetric carbon atom $C_{(25)}$ of the parent sapogenin. We are grateful to Dr. A. G. Long, of Glaxo Laboratories Ltd., for drawing our attention to these degradation products and their possible use for syntheses of optically active methyl-substituted long-chain compounds. This paper reports preliminary experiments with an optically active acid, kindly provided by Glaxo Laboratories Ltd., which was obtained from hecogenin *via* ψ-hecogenin acetate (I) by oxidation with chromic acid, followed by hydrolysis of the resulting ester (II) as described by Cameron *et al.*[1] Hecogenin yields [2] on oxidation of the corresponding *pseudo*-compound an acidic fraction containing carbon atoms $C_{(22)}$ to $C_{(27)}$ inclusive as *D*-(−)-α-methylglutaric acid (III). The acid (found to be dextrorotatory) which resulted



(I)



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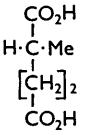

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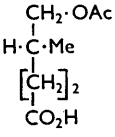


(IV)

on hydrolysis of the ester (II) may, therefore, be expected to have the structure of *L*-(+)-5-acetoxy-4-methylpentanoic acid (IV) (the change of prefix *D* to *L* is due to the conventional alteration of the reference group). This was confirmed by hydrolysis of the acidic material, followed by oxidation with potassium permanganate; the product was identified as (−)-α-methylglutaric acid (III).

For syntheses of long-chain compounds with the acetoxy-acid (IV) as starting material, anodic coupling (cf. ref. 3) with a long-chain acid appeared the most suitable approach. In earlier experiments we investigated the following scheme.

Electrolysis of a mixture of *D*-(−)-(methyl hydrogen β-methylglutarate) [4,5] (V) with stearic acid, followed by hydrolysis of the resulting ester (VI; R = Me), gave *L*-(−)-3-methylheneicosanoic acid (VI; R = H). The silver salt of this acid was degraded with bromine, and the resulting bromide condensed with ethyl methylmalonate, affording 2(*DL*) : 4(*L*)-dimethyldocosanoic acid (VII).

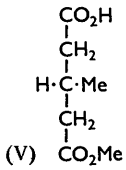
In further experiments we examined the anodic coupling of *L*-(+)-5-acetoxy-4-methylpentanoic acid (IV) with stearic acid. The product, 1-acetoxy-2-methylheneicosane (VIII; R = Ac), resulting from crossed coupling was hydrolysed to *D*-(+)-2-methylheneicosan-1-ol (VIII; R = H). Condensation of the corresponding iodide, obtained *via* the toluene-*p*-sulphonate, with ethyl sodiomethylmalonate afforded, by the usual successive

* Part III, *J.*, 1957, 2934.

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

[1] Cameron, Evans, Hamlet, Hunt, Jones, and Long, *J.*, 1955, 2807.
[2] James, *J.*, 1955, 637.
[3] Weedon, *Quart. Rev.*, 1952, **6**, 380.
[4] Ställberg-Stenhagen and Stenhagen, *Arkiv Kemi, Min., Geol.*, 1947, **25**, *A*, No. 10.
[5] Linstead, Lunt, and Weedon, *J.*, 1950, 3333.

stages (hydrolysis, decarboxylation), 2(*DL*) : 4(*D*)-dimethyltricosanoic acid (IX). In a similar case [6] the 2(*D*)- and the 2(*L*)-diastereoisomer were separable by chromatography of their methyl esters on alumina. Accordingly, on chromatography of the methyl ester of the acid (IX), the fraction more readily eluted yielded a methyl ester of $[\alpha]_D$ −5·1°



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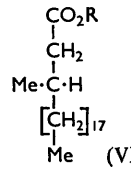

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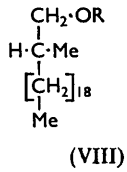

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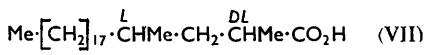
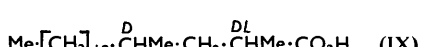


(VII)



(IX)

[essentially the 2(*D*)-isomer, the (−)-form of 2-methyl-substituted carboxylic acids having *D*-configuration [7]]; the more strongly absorbed fractions were dextrorotatory. Thus, by using in place of stearic acid a higher homologue with the appropriate chain-length a convenient route is provided for the synthesis of mycoceranic acid.[8]

Experimental

Optical rotations were measured in a 1-dm. tube. Petrol refers to light petroleum, b. p. 40—60°. The alumina used for chromatography was acid-washed, and had activity II on Brockmann and Schodder's scale.[9]

L-(+)-5-*Acetoxy*-4-*methylpentanoic Acid* (IV).—The crude acid, supplied by Glaxo Laboratories Ltd., gave on distillation material, b. p. 167·5°/15 mm., $[\alpha]_D^{20}$ +4·02° (*c*, 14·92 in ether). A 5-g. sample of the latter was hydrolysed with aqueous sodium hydroxide, and the resulting solution oxidised with aqueous 5% potassium permanganate, the mixture being kept below 4°. After filtration, the solution was concentrated, acidified, and extracted with ether. Evaporation of the dried (Na_2SO_4) ethereal extract gave (−)-α-methylglutaric acid, m. p. 81° (from 1 : 1-ether–petrol), $[\alpha]_D^{17·5}$ −21·25° (*c*, 8·37 in water); its p-*bromophenacyl ester* had m. p. 108° (from ethanol) (Found: C, 48·9; H, 3·6; Br, 29·4. $C_{22}H_{20}O_6Br_2$ requires C, 48·9; H, 3·7; Br, 29·6%). Berner and Leonardsen [10] record m. p. 81°, $[\alpha]_D^{20}$ +20·04° (*c*, 7·28 in water), for the (+)-acid.

An authentic specimen of (±)-α-methylglutaric acid, obtained by condensation of ethyl β-iodopropionate with ethyl sodiomethylmalonate, followed by hydrolysis and decarboxylation of the product, had m. p. 76° (from 1 : 1 ether–petrol) (Berner and Leonardsen [10] give m. p. 77°); its *p*-bromophenacyl ester had m. p. 95·5°, after crystallisation from ethanol (Found: C, 49·1; H, 3·9%). For comparison, a 0·7-g. sample of the above (−)-acid was esterified with ethereal diazomethane, and the methyl ester racemised [11] with boiling ethanolic sodium ethoxide (from 1 g. of sodium in 20 c.c. of ethanol) for 4 hr. Aqueous sodium hydroxide (20%; 10 c.c.) was then added, and the mixture refluxed for 2 hr., then concentrated to about half its volume and acidified with hydrochloric acid. Ether-extraction afforded (±)-α-methylglutaric acid, m. p. 76° (from 1 : 1 ether–petrol), which formed a *p*-bromophenacyl ester of m. p. 95·5° (from ethanol); the m. p.s were undepressed on admixture with the authentic specimens.

D-(+)-2-*Methylheneicosan*-1-*ol* (VIII; R = H).—*L*-(+)-5-Acetoxy-4-methylpentanoic acid (19·2 g., 1·5 mol.) and stearic acid (20·6 g., 1 mol.) were added to a solution of methoxide (from 0·9 g. of sodium and 800 c.c. of methanol), and the mixture electrolysed in a cell fitted with a reflux condenser, a cooling coil (through which water was passed), and two parallel platinum plate cathodes (2 × 3 cm.) placed about 2 mm. on either side of a similar anode. The cell was cooled by immersion in an ice-bath, and a current of about 2·5 amp. was passed until the solution became alkaline (3·5 hr.). It was then neutralised with glacial acid and evaporated. The product was refluxed with ether, the ethereal solution filtered, and the filtrate washed with 5% aqueous potassium hydroxide, then with water, and dried ($MgSO_4$). Distillation gave a

[6] Millin and Polgar, *J.*, 1958, 1902.
[7] Ställberg-Stenhagen and Stenhagen, *Arkiv Kemi, Min., Geol.*, 1947, **24**, *B*, No. 9.
[8] Marks and Polgar, *J.*, 1955, 3851.
[9] Brockmann and Schodder, *Ber.*, 1941, **74**, 73.
[10] Berner and Leonardsen, *Annalen*, 1939, **538**, 1.
[11] Kenyon and Young, *J.*, 1940, 216.

fraction, b. p. 158°/10 mm. (5·2 g.), followed by material of b. p. 165°/0·1 mm. (3·6 g.), $[\alpha]_D^{13}$ +1·17° (*c*, 11·12 in ether). The latter was hydrolysed by refluxing it with 10% aqueous-ethanolic (1 : 2) potassium hydroxide for 4 hr. Dilution with water, followed by acidification and ether-extraction, afforded D-(+)-2-*methylheneicosan*-1-*ol*, m. p. 54·5° (from methanol), $[\alpha]_D^{20}$ + 5·49° (*c*, 10·24 in chloroform) (Found: C, 80·5; H, 14·1. $C_{22}H_{46}O$ requires C, 80·9; H, 14·2%).

2(DL) : 4(D)-*Dimethyltricosanoic Acid* (IX).—Toluene-*p*-sulphonyl chloride (4 g.) was added in four portions during 20 min. to a solution of the above alcohol (4·7 g.) in dry pyridine (28 c.c.) at 0°, the mixture being shaken. After a further 6 hr. at 0° with shaking, the mixture was set aside in a refrigerator. Next day it was poured into water, and the precipitate filtered off, then taken up in hot methanol. Cooling gave the *toluene*-p-*sulphonate*, m. p. 43° (Found: C, 72·3; H, 10·8. $C_{29}H_{52}O_3S$ requires C, 72·4; H, 10·9%). This ester was refluxed with a solution of anhydrous sodium iodide (3·6 g.) in dry acetone (35 c.c.) for 24 hr. After dilution with water, the product was extracted with ether, and the extract washed with aqueous sodium thiosulphate and then with water, dried (Na_2SO_4), and evaporated. The resulting crude iodide was refluxed with ethyl sodiomethylmalonate (from 3·2 g. of ethyl methylmalonate, 0·3 g. of sodium, and 10 c.c. of ethanol) for 6·5 hr. After acidification (acetic acid) and dilution with water, the product was isolated by means of ether, then refluxed with a solution of potassium hydroxide (8 g.) in aqueous ethanol (1 : 2; 20 c.c.) for 8·5 hr. The resulting solution was diluted with water and acidified with sulphuric acid, and the product, isolated by ether-extraction, was decarboxylated at 170° (bath) for 1·5 hr., then distilled. The resulting acid (1·7 g.), b. p. 180° (bath)/0·05 mm., was esterified with ethereal diazomethane, and the methyl ester chromatographed in petrol on alumina (100 g.; 30 × 2 cm.) prepared in petrol. The following fractions were taken ($[\alpha]_D$ refers to *c* 5—14 in chloroform at 19°): (1) petrol (100 c.c.) (0·21 g.); (2) petrol (150 c.c.) (0·02 g.); and, all in petrol–benzene (9 : 1): (3) (100 c.c.) (0·15 g., $[\alpha]_D$ −1·05°); (4) (50 c.c.) (0·31 g., $[\alpha]_D$ −5·10°) (Found: C, 78·9; H, 13·4. Calc. for $C_{26}H_{52}O_2$: C, 78·8; H, 13·1%); (5) (50 c.c.) (0·2 g., $[\alpha]_D$ +0·94°); (6) (50 c.c.) (0·12 g., $[\alpha]_D$ +2·28°); (7) (50 c.c.) (0·07 g., $[\alpha]_D$ +2·69°); (8) (100 c.c.) (0·1 g., $[\alpha]_D$ +4·37°).

L-(−)-3-*Methylheneicosanoic Acid* (VI; R = H).—Stearic acid (30 g.; m. p. 69·1—69·5°) was electrolysed with *D*-(−)-(methyl hydrogen β-methylglutarate) [4,5] (8 g.; added in several portions during 2 hr.) in methanol (150 c.c.) and light petroleum (b. p. 60—80°; 150 c.c.) in the presence of potassium methoxide (from 0·7 g. of potassium) at about 2 amp. for 3 hr. The mixture was then cooled (0°) and filtered, and the filtrate diluted with water. The organic layer was separated, and the aqueous layer extracted with ether. The combined extracts were washed with 5% aqueous potassium carbonate and water, dried ($MgSO_4$), and distilled, to give, after a forerun, an ester fraction of b. p. 150—154°/0·04 mm. (4·6 g.). Hydrolysis of the latter with ethanolic potassium hydroxide gave L-(−)-3-*methylheneicosanoic acid* which crystallised from acetic acid as plates, m. p. 56·9°, $[\alpha]_D^{10}$ −3·8° (*c*, 3·0 in chloroform) (Found: C, 77·5; H, 12·9. $C_{22}H_{44}O_2$ requires C, 77·6; H, 12·9%). Its *amide* crystallised from ethanol as needles, m. p. 92° (Found: N, 3·9. $C_{22}H_{45}ON$ requires N, 4·1%).

2(DL) : 4(L)-*Dimethyldocosanoic Acid* (VII).—Reaction of silver *L*-(−)-3-methylheneicosanoate (obtained from the acid *via* the potassium salt, and dried over phosphoric oxide at 100°) with bromine in ethyl bromide by Rottenberg's procedure,[12] followed by condensation of the resulting bromide with ethyl sodiomethylmalonate as described previously for the synthesis of (±)-2 : 4-dimethyldocosanoic acid [13] gave the 2(*DL*) : 4(*L*)-form of the latter. This acid crystallised from petrol as plates, m. p. 54·7°; its *p*-bromophenacyl ester crystallised from ethanol as needles, m. p. 74° (Found: C, 67·6; H, 9·25. Calc. for $C_{32}H_{53}O_3Br$: C, 68·0; H, 9·4%).

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Dyson Perrins Laboratory, Oxford University. [*Received, September 29th,* 1958.]

[12] Rottenberg, *Helv. Chim. Acta*, 1952, **35**, 1286.
[13] Bailey, Polgar, and Robinson, *J.*, 1953, 3031.