313. *Anodic Syntheses. Part VIII.* New Syntheses of 3 : 13 : 19-Trimethyltricosanoic Acid.*

By R. P. Linstead, B. R. Shephard, B. C. L. Weedon, and (in part) J. C. Lunt.

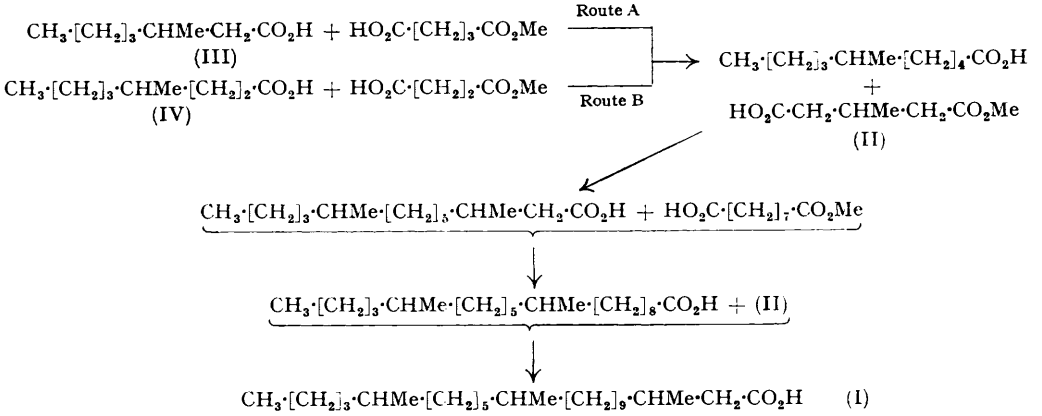
The anodic method for the synthesis of branched-chain fatty acids has been used for preparation of (±)-3 : 13 : 19-trimethyltricosanoic acid. The routes employed are capable of extension to the preparation of pure optical isomers.

When injected intraperitoneally in guinea-pigs, a number of synthetic branched-chain fatty acids cause granulomatous lesions (Ungar, Coulthard, and Dickenson, *Brit. J. Exp. Path.*, 1948, **29**, 322; Brownlee, *Ann. Reports*, 1948, **45**, 292) similar to those produced by Anderson's " phthioic acid " from the lipins of dried tubercle bacilli (Spielman and Anderson, *J. Biol. Chem.*, 1935—36, **112**, 759). " Phthioic acid," formerly believed to be an enantiomorph of 3 : 13 : 19-trimethyltricosanoic acid (I) (Polgar and Robinson, *J.*, 1945, 389), is now known to be a complex mixture, but the structure of the natural acid responsible for the cytological activity has not yet been fully determined (Polgar and Robinson, *Chem. and Ind.*, 1951, 685; Cason and Sumrell, *J. Biol. Chem.*, 1951, **192**, 405; Cason, Freeman, and Sumrell, *ibid.*, p. 415).

With one exception (2 : 13 : 17 : 21-tetramethyldocosanoic acid; Polgar, Robinson, and Seijo, *J.*, 1949, 1545) all synthetic acids tested biologically have been (±)-mixtures, in contrast to the natural acids which are optically active. It is therefore of interest to determine whether, with tubercle-forming acids such as 3 : 13-dimethyl- and 3 : 13 : 19-trimethyl-tricosanoic acid, activity is associated with all, or only one, of the various enantiomorphs. The syntheses so far described of these two acids (Polgar and Robinson, *loc. cit.*; David, Polgar, and Robinson, *J.*, 1949, 1541; Moroe, *J. Pharm. Soc. Japan*, 1950,

* Part VII, *J.*, 1952, 3624.

70, 416; 1951, **71**, 123) are unsuitable for the preparation of all the various stereoisomers required to elucidate the relationship between biological and optical activity. However,



anodic routes, such as those illustrated in the above reaction scheme, would be capable of giving all the isomers with known configurations. Each stage involves crossed coupling of a fatty acid with a half-ester, and since none of these intermediates is α-substituted, coupling would occur with complete retention of asymmetric centres in the starting materials (for references see Weedon, *Quart. Reviews*, 1952, **6**, 380). Both (+)- and (−)-form of methyl hydrogen β-methylglutarate (II) are readily available (Part IV, *J.*, 1951, 1130) and their stereochemical relation to D-glyceraldehyde has been established (Ställberg-Stenhagen, *Arkiv Kemi, Min., Geol.*, 1948, **25**, *A*, No. 10). The (−)-isomers of 3-methylheptanoic (III) (Levene and Marker, *J. Biol. Chem.*, 1932, **95**, 1; Ställberg-Stenhagen, *Arkiv Kemi*, 1950, **2**, 95) and 4-methyloctanoic acid (IV) (Levene and Marker, *loc. cit.*, p. 153) have been described, and no doubt their diastereoisomers could be obtained by standard methods.

The present paper describes syntheses of (±)-3 : 13 : 19-trimethyltricosanoic acid which were undertaken to confirm the feasibility of the routes proposed above. The molar proportions of half-ester to monocarboxylic acid used in each of the electrolyses, and the yields of the resulting branched-chain acid formed by cross-coupling, are given in the Table. The expected products formed by symmetrical coupling of the components were also isolated.

Syntheses of branched-chain acids.

Acid product	Molar proportion of half-ester to acid	Yield (%)
6-Methyldecanoic (route A)	3 : 1	36
,, (route B)	4 : 1	32
3 : 9-Dimethyltridecanoic	4 : 1	50
10 : 16-Dimethyleicosanoic	4 : 1	55
3 : 13 : 19-Trimethyltricosanoic	5 : 1	20

Experimental

Percentage yields, except those of diacids or diesters, are based on the total amount of monocarboxylic acid introduced.

Electrolyses.—The mixture of half-ester and monocarboxylic acid was electrolysed in technical absolute methanol to which sufficient sodium had been added to neutralise 2% of the total acids used. Two cells, A and B, were employed. These consisted of cylindrical glass vessels containing two platinum plates, placed 1—2 mm. apart, as electrodes. In cell A the electrodes measured 4 × 2·5 cm., and in cell B 8 × 5 cm. A current (*ca.* 0·1—0·2 amp./sq. cm. anode current density) was passed until the electrolyte became slightly alkaline. The cell contents were neutralised by the addition of glacial acetic acid, and the solvent was evaporated. The residue was then either distilled or hydrolysed, and the products were separated into neutral and acidic fractions.

Half-esters.—Methyl hydrogen glutarate, b. p. 107°/0·3 mm., n_D^{23} 1·4372, was prepared in 83% yield by heating equimolar quantities of glutaric anhydride (Caunt, Crow, Haworth, and Vodoz, *J.*, 1950, 1631) and methanol on a steam-bath for *ca.* 2 hr. Methyl hydrogen succinate was prepared similarly from succinic anhydride (Shriner and Struck, *Org. Synth.*, Coll. Vol. II, p. 560), methyl hydrogen β-methylglutarate as described in Part II (*J.*, 1950, 3331), and methyl hydrogen azelate as described by Schmidt and Shirley (*J. Amer. Chem. Soc.*, 1949, **71**, 3804).

3-*Methylheptanoic Acid.*—Hexan-2-ol (Barrow and Atkinson, *J.*, 1939, 638) was converted into 2-bromohexane in 73% yield, by the method described for 2-bromodecane (Prout, Cason, and Ingersoll, *J. Amer. Chem. Soc.*, 1948, **70**, 298; Hsueh and Marvel, *ibid.*, 1928, **50**, 855); the bromide had b. p. 78—80°/90 mm., n_D^{22} 1·4421 (Ellis and Reid, *ibid.*, 1932, **54**, 1674, give b. p. 77·8—78·1°/90 mm., n_D^{25} 1·4432).

2-Bromohexane (139 g.) was added dropwise to a stirred, boiling solution of ethyl sodiomalonate (from 19·4 g. of sodium and 139 g. of ethyl malonate) in anhydrous alcohol (420 c.c.), and the mixture was heated under reflux for 15 hours. Isolation of the product in the usual way gave ethyl 2-methylhexane-1 : 1-dicarboxylate (157 g., 77%), b. p. 86—87°/0·5 mm., n_D^{17} 1·4307.

Heating the ester (50·0 g.) and potassium hydroxide (30 g.) in alcohol (150 c.c.) and water (30 c.c.) under reflux for 1 hour gave 2-methylhexane-1 : 1-dicarboxylic acid (32·6 g., 85%), needles, m. p. 91·5—93·5° (Found : equiv., 94·8. Calc. for $C_9H_{16}O_4$: equiv., 94·1).

The dicarboxylic acid (50·0 g.) was heated at 165—185° until evolution of carbon dioxide ceased (*ca.* 40 min.). Distillation of the residue gave 3-methylheptanoic acid (36·4 g., 95%), b. p. 121°/15 mm., n_D^{16} 1·4276 (Found : equiv., 144·4. Calc. for $C_8H_{16}O_2$: equiv., 144·2).

4-*Methyloctanoic Acid.*—4-Hydroxy-4-methyloctanoic lactone, prepared (57% yield) from ethyl lævulate, was converted into ethyl 4-methyloct-3- and -4-enoate (63% yield) (cf. Wilson, *J. Amer. Chem. Soc.*, 1945, **67**, 2161). After sulphur-containing impurities had been removed (Raney nickel), the unsaturated esters were hydrogenated over Adams' catalyst at atmospheric temperature and pressure (cf. Cason, Adams, Bennett, and Register, *ibid.*, 1944, **66**, 1764). Hydrolysis of the product gave 4-methyloctanoic acid in 75% yield, b. p. 140°/17 mm. [Levene and Marker, *J. Biol. Chem.*, 1932, **95**, 153, give b. p. 149°/22 mm. for the (−)-isomer]. The *tribromoanilide* crystallised from alcohol in needles, m. p. 116° (Found : Br, 50·8. $C_{15}H_{20}ONBr_3$ requires Br, 51·0%).

6-*Methyldecanoic Acid.*—(*a*) A solution of 3-methylheptanoic acid (36 g.) and methyl hydrogen glutarate (110 g.) in methanol (270 c.c.) was electrolysed (cell B). Isolation and hydrolysis of the crude product gave 6-methyldecanoic acid (16·3 g.), b. p. 127°/1·5 mm., n_D^{23} 1·4381 (Wilson, *loc. cit.*, gives b. p. 160—164°/17 mm., n_D^{21} 1·4393) [*p*-bromophenacyl ester, plates (from methanol), m. p. 50° (*idem*, *loc. cit.*, gives m. p. 51°)], and 5 : 8-*dimethyldodecane* (7·8 g., 31%), b. p. 130°/40 mm., n_D^{25} 1·4270 (Found : C, 84·1; H, 15·1. $C_{14}H_{30}$ requires C, 84·8; H, 15·2%).

(*b*) A solution of 4-methyloctanoic acid (53 g., 0·33 mole) and methyl hydrogen succinate (176 g., 1·33 mole) in methanol (400 c.c.) was electrolysed (cell B). Isolation and hydrolysis of the crude product gave : (i) 5 : 10-*Dimethyltetradecane* (10·0 g., 27%), b. p. 140°/15 mm., n_D^{20} 1·4342 (Found : C, 84·9; H, 15·2. $C_{16}H_{34}$ requires C, 84·9; H, 15·1%). (ii) An acidic fraction which was extracted thoroughly with light petroleum (b. p. 40—60°). Separation of the insoluble portion and crystallisation from water gave adipic acid (23·5 g., 24%), m. p. 153°. The petroleum extract was dried and evaporated; distillation of the residue gave 6-methyldecanoic acid (20 g.), b. p. 135°/0·6 mm., n_D^{24} 1·4370 (Found : equiv., 184. Calc. for $C_{11}H_{22}O_2$: equiv., 186). The *p*-bromophenacyl ester had m. p. 50·5°, undepressed on admixture with a specimen from (*a*).

3 : 9-*Dimethyltridecanoic Acid.*—Electrolysis of 6-methyldecanoic acid (30·0 g., 0·16 mole) and methyl hydrogen β-methylglutarate (105·3 g., 0·67 mole) in methanol (180 c.c.) in 2 batches (cell A), and isolation and hydrolysis of the products as described in the preceding experiment gave 5 : 14-*dimethyloctadecane* (4·7 g., 18%), b. p. 115°/0·2 mm., n_D^{24} 1·4436 (Found : C, 84·7; H, 15·0. $C_{20}H_{42}$ requires C, 85·0; H, 15·0%), crude ββ′-dimethylsuberic acid, m. p. 70—80° (35 g., 60%), and 3 : 9-*dimethyltridecanoic acid* (20·0 g.), b. p. 154°/0·2 mm., n_D^{20} 1·4480. Titration (equiv., 220, 221) showed that the last acid was contaminated with some of the dicarboxylic acid. A sample was purified for analysis by precipitation of the dicarboxylic acid as the lead salt from alcohol. The recovered dimethyltridecanoic acid had n_D^{23} 1·4471 (Found : C, 73·8; H, 12·3%; equiv., 240, 241. $C_{15}H_{30}O_2$ requires C, 74·3; H, 12·5%; equiv., 242). The *tribromoanilide* after many crystallisations from methanol had m. p. 115°, not raised by further recrystallisation (Found : N, 2·6. $C_{21}H_{32}ONBr_3$ requires N, 2·5%).

10 : 16-*Dimethyleicosanoic Acid.*—Electrolysis (cell A) of 3 : 9-dimethyltridecanoic acid

(17·0 g., 0·07 mole) and methyl hydrogen azelate (56·5 g., 0·28 mole) in methanol (100 c.c.), and isolation and hydrolysis of the products, gave 5 : 11 : 14 : 20-*tetramethyltetracosane* (3·0 g., 21%), b. p. 150°/5 × 10^{-4} mm., n_D^{24} 1·4508 (Found : C, 85·2; H, 14·8. $C_{28}H_{58}$ requires C, 85·0; H, 15·0%), thapsic acid (20·0 g., 37%), m. p. 122°, and 10 : 16-*dimethyleicosanoic acid* (13·0 g.), b. p. 150°/10^{-4} mm., n_D^{20} 1·4568 (Found : C, 77·7; H, 12·8. $C_{22}H_{44}O_2$ requires C, 77·6; H, 13·0%). The equiv. (Found : 328. Calc. : 340) showed that the last acid was slightly contaminated with thapsic acid. No attempt was made to purify it further before the next stage as dicarboxylic acids do not give products of the Kolbe type at the anode (cf. Weedon, *loc. cit.*).

3 : 13 : 19-*Trimethyltricosanoic Acid.*—Electrolysis (cell A) of 10 : 16-dimethyleicosanoic acid (10·2 g., 0·03 mole) and methyl hydrogen β-methylglutarate (24·0 g., 0·15 mole) in methanol (50 c.c.), isolation, and distillation of the product gave methyl ββ′-dimethylsuberate (11·9 g., 68%), b. p. 100°/0·3 mm., n_D^{17} 1·4388 (Linstead, Lunt, and Weedon, *J.*, 1950, 3333, give $n_D^{18\cdot5}$ 1·4376), and a fraction (6·0 g.), b. p. 180—200°/10^{-3} mm., n_D^{23} 1·4520—1·4588. The latter was heated under reflux for 12 hours with alcoholic potassium hydroxide (20% w/v). Separation of the neutral and the acidic products in the usual way gave 5 : 11 : 28 : 34-*tetramethyloctatriacontane* (2·2 g., 25%), b. p. 200°/10^{-3} mm., n_D^{25} 1·4570 (Found : C, 85·35; H, 14·8. $C_{42}H_{86}$ requires C, 85·3; H, 14·7%), and 3 : 13 : 19-trimethyltricosanoic acid (2·2 g.), b. p. 190°/10^{-3} mm., n_D^{18} 1·4594 (Found : C, 78·3; H, 13·1%; equiv., 392. Calc. for $C_{26}H_{52}O_2$: C, 78·7; H, 13·2%; equiv., 396) (Polgar and Robinson, *J.*, 1945, 389, give n_D^{17} 1·4620; Moroe, *loc. cit.*, gives n_D^{18} 1·4600).

The authors thank Mr. D. G. Coe for assistance during the early stages of this work, the Chemical Society for a grant from the Research Fund (to B. C. L. W.), and the London County Council for a grant (to B.R.S.). Analyses were carried out in the microanalytical (Mr. F. H. Oliver) laboratory of this Department.

Department of Organic Chemistry,
Imperial College of Science and Technology,
S. Kensington, London, S.W.7.

[*Received, February 5th,* 1952.]