246. *Anodic Syntheses. Part IV. Synthesis of (+)- and (−)-Tuberculostearic Acids.*

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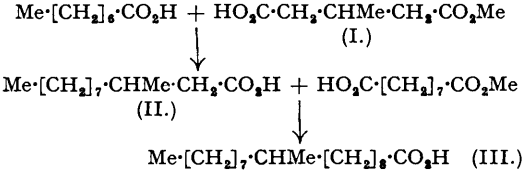
Optically active intermediates have been employed in the anodic synthesis of fatty acids previously described. In this manner the pure enantiomorphs of tuberculostearic acid have been prepared.

Electrolyses of mixtures of (+)- and (−)-(methyl hydrogen β-methylglutarate) (I) with octanoic acid led to (+)- and (−)-3-methylundecanoic acids (II). (+)- and (−)-Tuberculostearic acids were similarly obtained from mixtures of methyl hydrogen azelate with (−)- and (+)-3-methylundecanoic acid respectively.

Recently it has been demonstrated that the enantiomorphs of methyl hydrogen β-methylglutarate (I), unlike optically active α-alkyl acids, undergo the Kolbe electrolytic reaction without racemisation of the asymmetric centres (Part III, *J.*, 1950, 3333; Ställberg-Stenhagen, *Arkiv Kemi*, 1950, **2**, 95). It therefore seemed probable that the unsymmetrical coupling reactions, resulting from electrolyses of mixtures of a monocarboxylic acid and a half-ester of a dicarboxylic acid (cf. Parts I and II, *J.*, 1950, 3326, 3331), would furnish a valuable synthesis of pure optical isomers of branched-chain fatty acids, provided that neither component possessed an asymmetric centre in the position α to the carboxyl group. This has now been shown to be the case by substituting the enantiomorphs of (I) for the (±)-half ester in the synthesis of (±)-tuberculostearic acid (III) previously reported (Part II).

Electrolyses in methanol of mixtures of octanoic acid (2 mols.) with (+)- and (−)-(methyl hydrogen β-methylglutarate) (I) (1 mol.), and subsequent hydrolysis of the crude products, gave (+)- and (−)-3-methylundecanoic acids (II) in 48% yields (based on half-esters). Similar electrolyses of mixtures of the (+)- and the (−)-form of (II) (1 mol.) with methyl hydrogen



azelate (2 mols.) led to the isolation of slightly impure specimens of (−)- and (+)-10-methyloctadecanoic (tuberculostearic) acids (III) respectively in 30% yields (based on II). Purification was readily effected by regeneration of the (−)-acid from the amide and by low-temperature crystallisation of the (+)-acid. On admixture of equal amounts of the two enantiomorphs (±)-tuberculostearic acid was obtained.

The optical rotations of the branched-chain fatty acids described in this paper are in excellent agreement with those reported by previous authors (see Table).

Acid.	Optical rotation.* Cason *et al.*[1]	Ställberg-Stenhagen.[2]	Present authors.
(+)-3-Methylundecanoic acid	α_D^{25} +4·45°	α_D^{22} +4·50°	α_D^{23} +4·50°
(−)- ,, ,, ...	α_D^{25} −4·47°	α_D^{22} −4·53°	α_D^{18} −4·52°
(+)-10-Methyloctadecanoic acid	α_D^{26} +0·08°	α_D^{22} +0·09° ± 0·02°	α_D^{18} +0·07° ± 0·02°
(−)- ,, ,, ...	α_D^{26} −0·045°	α_D^{22} −0·11° ± 0·02°	α_D^{19} −0·08° ± 0·02°

* Homogeneous, 1-dm. cell. [1] Prout, Cason, and Ingersoll, *J. Amer. Chem. Soc.*, 1948, **70**, 298. [2] Ställberg-Stenhagen, *Arkiv Kemi, Min., Geol.*, 1948, **26**, *A*, No. 12.

While this work was in progress, Ställberg-Stenhagen (1950, *loc. cit.*) described the synthesis of optically active β-methyl-carboxylic acids by electrolysis of equimolar mixtures of fatty acids with enantiomorphs of (I). More recently the same author (1950, *loc. cit.*, p. 431) has prepared (−)-3(*L*) : 6(*D*)-dimethyltetracosanoic acid * by electrolysis of a mixture of stearic acid and (−)-[methyl hydrogen 3(*L*) : 6(*D*)-dimethylsuberate]. The yields (based on optically active intermediates) given by the Swedish worker for these unsymmetrical coupling reactions are somewhat lower than those which were obtained in the present investigation by using an excess of the optically inactive components.

Experimental.

Yields in unsymmetrical-coupling reactions are calculated on the optically active starting material. Commercial absolute methanol was used as a solvent in all electrolyses without purification. The optical rotations of the branched-chain fatty acids are given in the Table.

(+)-L-*and* (−)-D-(*Methyl Hydrogen β-Methylglutarate*).—The resolution of (±)-(methyl hydrogen β-methylglutarate) was effected in batches of *ca.* 30 g. essentially as described previously (Linstead, Lunt, and Weedon, *J.*, 1950, 3333). By carrying out the successive crystallisations of each batch of product from the mother-liquors obtained in the corresponding crystallisation of the preceding batch, the overall yields of the (+)- and (−)-half-esters were raised to 48%.

(+)-D-3-*Methylundecanoic Acid* (cf. preparation of the inactive acid, *idem, ibid.*, p. 3331).—A mixture of (+)-*L*-(methyl hydrogen β-methylglutarate) (10·0 g., 0·0625 mol.) and octanoic acid (18·0 g., 0·125 mol.; prepared as described in Part I, *J.*, 1950, 3326) was added to sodium methoxide (from sodium, 0·09 g., 0·0039 mol.) in methanol (75—80 c.c.). The resulting solution was electrolysed in the usual manner, using two platinum plates (4 × 2·5 cm.), placed *ca.* 1·5 mm. apart, as electrodes and a current of 2 amps.

The preceding experiment was repeated, and the cell contents from the two electrolyses were combined, neutralised by the addition of a few drops of acetic acid, and evaporated under reduced pressure. The residue was hydrolysed with aqueous-methanolic potassium hydroxide, and the products were separated into neutral and acidic fractions. Distillation of the non-saponifiable fraction gave *n*-tetradecane (12·0 g., 49%), b. p. 128°/19 mm., n_D^{21} 1·4275. Distillation of the acidic fraction yielded (+)-*D*-3-methylundecanoic acid (11·9 g., 48%), b. p. 117°/0·5 mm., n_D^{26} 1·4350 (Ställberg-Stenhagen, *Arkiv Kemi, Min., Geol.*, 1948, **26**, *A*, No. 12, gives b. p. 99—101°/0·2 mm.). The amide crystallised from light petroleum (b. p. 40—60°) in needles, m. p. 86·5—86·7° [*idem, loc. cit.*, gives m. p. 87·2—87·7° (corr.)]. The residue (2·72 g.), m. p. 81·5—82·5°, from the distillation of the acidic fraction was crystallised from benzene–light petroleum (b. p. 60—80°) and finally from water containing a small amount of methanol, giving β(*D*) : β′(*D*)-dimethylsuberic acid (2·03 g.), m. p. 83—83·5° (Linstead, Lunt, and Weedon, *ibid.*, p. 3333, give m. p. 83·5°).

(−)-L-3-*Methylundecanoic Acid.*—Repetition of the preceding preparation after substituting (−)-*D*-(methyl hydrogen β-methylglutarate) (9·3 g.) for the (+)-half-ester in each of the electrolyses gave : (i) *n*-Tetradecane (12·2 g., 49%). (ii) (−)-*L*-3-Methylundecanoic acid (11·2 g., 48%), b. p. 114—117°/0·4 mm., $n_D^{18\cdot5}$ 1·4401. The amide crystallised from light petroleum (b. p. 40—60°) in needles, m. p. 86·3—86·7° [Ställberg-Stenhagen, 1948, *loc. cit.*, gives m. p. 87·2—87·7° (corr.)]. (iii) β(*L*) : β′(*L*)-Dimethylsuberic acid (1·57 g.), m. p. 83·2—83·5° (Linstead, Lunt, and Weedon, *loc. cit.*, give m. p. 83·5—83·7°).

(−)-D-10-*Methyloctadecanoic Acid* (*Tuberculostearic Acid*) (cf. preparation of the inactive acid, *idem, ibid.*, p. 3331). A mixture of (+)-*D*-3-methylundecanoic acid (5 g., 0·025 mol.) and methyl hydrogen azelate (9 g., 0·045 mol.) was added to a solution of sodium methoxide (from sodium, 0·03 g., 0·0014 mol.) in methanol (25—30 c.c.). The solution thus obtained was electrolysed in the usual manner using two platinum plates (2·5 × 2·5 cm.), placed 1·5 mm. apart, as electrodes and a current of 1·2 amps.

The preceding experiment was repeated, and the products from the two electrolyses were combined, and worked up in the manner described above for *D*-3-methylundecanoic acid.

Distillation of the non-saponifiable fraction gave (−)-9(L) : 12(D)-*dimethyleicosane* (1·25 g., 16%), b. p. 113—116°/0·5 mm., n_D^{26} 1·4421, α_D^{22} −0·94° (homogeneous, l = 1) (Found : C, 85·0; H, 14·9. $C_{22}H_{46}$ requires C, 85·05; H, 14·95%).

A solution of the acidic fraction in ether (*ca.* 65 c.c.) was cooled to 0° and the solid (2·55 g.), m. p. 119—121°, which separated was removed by filtration and recrystallised from methanol yielding thapsic

* See note on nomenclature in Part III, *J.*, 1950, 3333.

acid (tetradecane-1 : 14-dicarboxylic acid) (2·14 g.) as plates, m. p. 123—124° (Carmichael, *J.*, 1922, **121**, 2545, gives m. p. 124°). The ethereal mother-liquors were evaporated, the residual thapsic acid was removed as the lead salt (2·13 g.), and the monocarboxylic acids distilled giving (i) an unsaturated liquid (1·75 g.), b. p. 75—130°/0·2 mm. and (ii) crude (−)-*D*-10-methyloctadecanoic acid (4·64 g., 31%), b. p. 160—162°/0·2 mm., n_D^{28} 1·4501, m. p. 8—11°. The crude tuberculostearic acid (4·28 g.) was converted into the amide (by Ställberg-Stenhagen's method, 1948, *loc. cit.*). After two crystallisations from ether and one from acetone, this was obtained as plates (2·52 g., 54%), m. p. 75·7—76·2° [*idem*, *loc. cit.*, gives m. p 76·4—76·6° (corr.)]. Hydrolysis of the amide gave the pure acid (1·82 g., 82% based on amide), b. p. 180° (bath-temp.)/0·1 mm., m. p. 12·5—12·9° [*idem*, *loc. cit.*, gives b. p. 175—178°/0·7 mm., m. p. 12·4—12·8° (corr.)] (Found: C, 76·6; H, 12·55. Calc. for $C_{19}H_{38}O_2$: C, 76·45; H, 12·85%).

(+)-L-10-*Methyloctadecanoic Acid.*—Repetition of the preceding experiment with the use of (−)-*L*-3-methylundecanoic acid instead of the (+)-acid gave: (i) (+)-9(D) : 12(L)-*dimethyleicosane* (1·27 g., 16%), b. p. 122°/0·6 mm., $n_D^{19\cdot5}$ 1·4445, α_D^{16} +0·92° (homogeneous, l = 1) (Found: C, 84·95; H, 14·8. $C_{22}H_{46}$ requires C, 85·05; H, 14·95%); (ii) thapsic acid (2·52 g.), m. p. 123—124°; (iii) lead thapsate (1·9 g.); (iv) an unsaturated acidic liquid (2·0 g.), b. p. 72—145°/0·1 mm.; and (v) crude (+)-*L*-10-methyloctadecanoic acid (4·42 g., 30%), b. p. 160—162°/0·1 mm., n_D^{26} 1·4508, m. p. 10·5—12·0°, which after one recrystallisation from acetone at *ca.* −20° yielded the pure acid as prisms (2·2 g.), m. p. 12·3—12·8° [*idem*, *loc. cit.*, gives m. p. 12·5—12·8° (corr.)] (Found: C, 76·7; H, 12·65. Calc. for $C_{19}H_{38}O_2$: C, 76·45; H, 12·85%).

Investigation of the Unsaturated Acidic Fractions from the Preparation of (−)- *and* (+)-*Tuberculostearic Acids.*—The unsaturated materials were redistilled and the fractions with b. p. 125—127°/16 mm. (1·0 g.) and 72—75°/0·2 mm. (1·0 g.) were combined. Redistillation gave a mixture of octanoic and octenoic acids (1·1 g.), b. p. 123—124°/13 mm., n_D^{22} 1·4350 (Found: hydrogen number, 251. Calc. for octenoic acid, $C_8H_{14}O_2$: hydrogen number, 142).

A solution of the mixed acids (1·0 g.) in ethyl acetate (15 c.c.) was shaken in hydrogen in the presence of palladium–calcium carbonate catalyst (0·6 g.; 3% of Pd) until absorption was complete. After removal of catalyst and solvent, the residue was distilled giving slightly impure octanoic acid (0·8 g.), b. p. 140° (bath-temp.)/15 mm., m. p. 11—15·5°, n_D^{21} 1·4274 (Greaves *et al.*, *J.*, 1950, 3326, give f. p. 15·5—15·3°, n_D^{27} 1·4251). The *p*-bromophenacyl ester had m. p. 65·5—66° undepressed on admixture with a specimen, m. p. 65·5—66°, prepared from authentic octanoic acid.

(±)-10-*Methyloctadecanoic Acid.*—On admixture of equal amounts of the two enantiomorphs described above and crystallisation of the mixture from acetone at −15°, the racemic acid was obtained as prisms, m. p. 20·9—21·2°. The solid obtained on rapid cooling of the molten acid had m. p. 24·1—24·4°. On slow cooling of the molten acid, another form, m. p. 25·8—26·4°, was obtained (Ställberg-Stenhagen, 1948, *loc. cit.*, gives m. p. 20·9—21·6° and 25·8—26·1°; Linstead, Lunt, and Weedon, *J.*, 1950, 3331, give m. p. 21·0—21·4° and 24·1—24·5°).

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