

650. Anodic Syntheses. Part II. Synthesis of (\pm)-Tuberculostearic Acid.

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The anodic synthesis of fatty acids described in Part I has now been applied to the preparation of (\pm)-tuberculostearic acid (III).

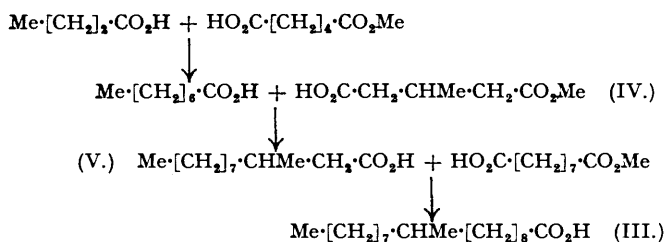
Electrolysis of a mixture of octanoic acid and methyl hydrogen β -methylglutarate (IV) led to 3-methylundecanoic acid* (V). A mixture of the latter with methyl hydrogen azelate on electrolysis furnished methyl (\pm)-tuberculostearate.

In Part I (preceding paper) the synthesis of a number of normal fatty acids by the electrolysis of a mixture of a monocarboxylic acid and a half-ester of a dicarboxylic acid was described. This modified Kolbe reaction can also be applied to the preparation of branched-chain fatty acids. These acids are of interest from their occurrence in Nature, *e.g.*, in chaulmoogra oil, in the tubercle bacillus (cf. Weitzel, *Angew. Chem.*, 1948, **60A**, 263), and in wool fat (Weitkamp, *J. Amer. Chem. Soc.*, 1945, **67**, 447), and because a number of them have been shown to possess marked physiological activity (cf. Brownlee, *Ann. Reports*, 1948, **45**, 292).

The selection of intermediates for the anodic synthesis of branched-chain compounds is influenced by the fact that acids possessing an alkyl substituent in the α -position have been shown to give small or negligible yields of coupled products in the Kolbe reaction (for references see Part I). However, alkyl substituents further removed from the carboxyl group than the



α -position do not in general appear to exert a similar adverse influence. Petersen (*Z. physikal. Chem.*, 1899, **33**, 295; *Z. Elektrochem.*, 1906, **12**, 141) demonstrated the marked difference in behaviour of α - and β -substituted acids by the electrolysis of the isomeric α -methylbutyric and isovaleric acids, whilst Farmer and Kracovski (*J.*, 1926, 2318) observed that, whereas electrolysis of β -carbethoxy- β -dimethylpropionic acid (I) gave ethyl $\alpha\alpha\alpha'$ -tetramethyladipate in 30–35% yield, the isomeric half-ester (II) gave ethyl $\beta\beta\beta'$ -tetramethyladipate in only 5–8% yield. Coupling of a β -substituted acid was also reported by Ruzicka and Stoll (*Helv. Chim. Acta*, 1934, **17**, 1308) as an undesired side reaction in the synthesis of muscone, while Karrer *et al.* (*ibid.*, 1932, **15**, 1218; 1933, **16**, 297) utilised the anodic coupling of γ -methyl acids in the synthesis of perhydrobixin and perhydrocroctin. More recently Hunsdiecker (*Ber.*, 1942, **75**, 1197), developing a new route to muscone, showed that electrolysis of a mixture of 11-methoxyundecanoic acid* and methyl hydrogen β -methylglutarate (IV) gives three products



formed by both symmetrical and unsymmetrical ("crossed") coupling of the two components.

The Kolbe reaction thus seemed eminently suitable for the synthesis of branched-chain fatty acids, provided that the components employed were not substituted in the α -position. To exemplify this synthetic route, the preparation of 10-methylstearic acid was undertaken. The levorotatory isomer of this acid, tuberculostearic acid, occurs in the tubercle bacillus (Anderson and Chargaff, *J. Biol. Chem.*, 1929, **85**, 77; cf. Prout, Cason, and Ingersoll, *J. Amer. Chem. Soc.*, 1948, **70**, 298), and syntheses of both the optically active and the inactive form have previously been recorded (Spielman, *J. Biol. Chem.*, 1934, **106**, 87; Prout, Cason, and Ingersoll, *loc. cit.*; Ställberg-Stenhagen, *Arkiv Kemi, Min., Geol.*, 1948, **26**, A, No. 12; Schmidt and Shirley, *J. Amer. Chem. Soc.*, 1949, **71**, 3804).

Electrolysis in methanol of a mixture of octanoic acid (prepared by the electrolytic method described in Part I) and methyl hydrogen β -methylglutarate (IV), in the molar proportions 1 : 2, led to the isolation of 3-methylundecanoic acid (V) in 46% yield (based on octanoic acid). A

* Geneva numbering is used for the longer fatty acids.

similar electrolysis of (V) and methyl hydrogen azelate, in the molar proportions 1 : 2, furnished methyl (\pm)-tuberculostearate, in 31—38% yield (based on V), which was hydrolysed to give (III). This acid after crystallisation from acetone had m. p. 21.0—21.4°, but on cooling the molten acid a second form, m. p. 24.1—24.5°, was obtained.

The investigation now described is being extended to the use of optically active intermediates in the Kolbe reaction to give branched-chain fatty acids of known stereochemical configuration.

EXPERIMENTAL.

Methyl Hydrogen β -Methylglutarate (IV).—Ethyl α -carbethoxy- β -methylglutarate, b. p. 108—110°/0.3 mm., n_D^{25} 1.4370, was prepared in 60% yield from ethyl crotonate and ethyl malonate by the method of Hunsdiecker (*Ber.*, 1942, **75**, B, 1197). The triester (297 g.) was refluxed with dilute (1 : 1) hydrochloric acid (350 c.c.) for 23 hours (cf. hydrolysis and decarboxylation of ethyl propane-1 : 1 : 2 : 3-tetracarboxylate, Clarke and Murray, *Org. Synth.*, Coll. Vol. I, p. 523) and the solution was then evaporated under reduced pressure. The residue of crude β -methylglutaric acid was heated under reflux with acetic anhydride (350 c.c.) for 7 hours. After removal of the excess of acetic anhydride and acetic acid under reduced pressure, the residue was distilled, giving β -methylglutaric anhydride (132 g., 95% based on triester), b. p. 118°/2 mm., m. p. 41.5—42.5° (Ställberg-Stenhagen, *Arkiv Kemi, Min., Geol.*, 1948, **25**, A, No. 10, gives b. p. 138—140°/9 mm.).

The anhydride (50.0 g., 0.39 mol.) and anhydrous methanol (12.5 g., 0.39 mol.) were heated under reflux on the steam-bath for 2—3 hours. Distillation of the product gave methyl hydrogen β -methylglutarate (54.2 g., 87%), b. p. 107—108°/0.5 mm., n_D^{25} 1.4388 (*idem, ibid.*, gives b. p. 114—116°/1 mm.) (Found: equiv., 159. Calc. for $C_7H_{12}O_4$: equiv., 160).

3-Methylundecanoic Acid (V).—A mixture of methyl hydrogen β -methylglutarate (22.4 g., 0.14 mol.) and octanoic acid (10.0 g., 0.07 mol.; cf. Part I) was added to a solution of sodium (0.1 g., 0.0043 mol.) in technical absolute methanol (65—70 c.c.). The resulting solution was cooled in an ice-bath and electrolysed using two platinum plates (4×2.5 cm. total surface area), placed *ca.* 1.5 mm. apart, as electrodes and a current of 2 amps. When the electrolyte became slightly alkaline the electrolysis was interrupted. Concentrated sulphuric acid (0.21 g.) was added to the cell contents, which were then filtered and evaporated under reduced pressure. The residue was extracted with ether, and the ethereal solution was washed with sodium hydrogen carbonate solution, and evaporated. The residue was heated under reflux for 2 hours with a solution of sodium hydroxide (25 g.) in methanol (100 c.c.) and water (30 c.c.). Isolation of the neutral and acidic fractions in the usual manner gave (i) *n*-tetradecane (3.2 g.), b. p. 150°/70 mm., n_D^{25} 1.4299, and (ii) an acidic fraction which on distillation yielded 3-methylundecanoic acid (12.7 g., 46%), b. p. 116°/0.4 mm., n_D^{25} 1.4406 (Prout, Cason, and Ingersoll, *J. Amer. Chem. Soc.*, 1948, **70**, 298, give b. p. 147.5—148.5°/2 mm., n_D^{25} 1.4389). The amide, crystallised from light petroleum (b. p. 40—60°), had m. p. 87.5—87.7° (*idem, ibid.*, give m. p. 88.3—89.3°, corr.).

The residue from the distillation of the acidic fraction consisted of $\beta\beta'$ -dimethylsuberic acid (4.2 g., 30%).

10-Methyloctadecanoic Acid [(\pm)-*Tuberculostearic Acid*] (III).—A solution of 3-methylundecanoic acid (5 g., 0.025 mol.), methyl hydrogen azelate (9 g., 0.045 mol.), and sodium (0.03 g., 0.0014 mol.) in methanol (25—30 c.c.) was electrolysed, two platinum plates (2.5×2.5 cm.) placed 1.5 mm. apart being used as electrodes, with a current of 1.1—0.8 amp. (it was found advantageous to reverse the direction of the current periodically to prevent the anode being coated with a film of insoluble material). When the electrolyte became slightly alkaline the electrolysis was interrupted.

The preceding experiment was repeated and the combined cell contents were warmed, to dissolve the dimethyl thapsate which crystallised on cooling, and filtered. The filtrate was neutralised by the addition of a few drops of glacial acetic acid and the solvent was then removed under reduced pressure. The solid residue was extracted with ether (80 c.c.) and the ethereal solution was washed with sodium hydrogen carbonate solution and evaporated.

The residue was heated under reflux for 30 minutes with a solution of potassium hydroxide (11.4 g.) in methanol (35 c.c.) and water (60 c.c.). After dilution of the mixture with water (150 c.c.), the non-hydrolysable material was extracted with light petroleum (b. p. 40—60°)-ether. Evaporation of the extract and distillation of the residue gave 9 : 12-dimethyleicosane (1.4 g., 18%), b. p. 131°/0.7 mm., n_D^{25} 1.4426 (Found: C, 84.75; H, 14.95. $C_{22}H_{44}$ requires C, 85.05; H, 14.95%).

The aqueous solution of potassium salts was acidified with dilute hydrochloric acid, and the liberated acid extracted with ether. The extract was washed with water, dried, and concentrated to small volume (65 c.c.); thapsic acid (2.1 g.), m. p. 120—122.5° (Carmichael, *J.*, 1922, **121**, 2545, gives m. p. 124°), crystallised on cooling and was removed by filtration. The filtrate was evaporated and the residual crude acids (11.2 g.) were dissolved in ethanol (85 c.c.). The solution was warmed and treated with an excess of a 6% alcoholic solution of lead acetate. The solution was kept for 1 hour at 0°, and the lead thapsate (3.5 g.) which had precipitated was filtered off. The filtrate was evaporated and the residual lead salts were acidified with 2*N*-nitric acid. The liberated organic acid was isolated by extraction with ether and then esterified by treatment with a slight excess of an ethereal solution of diazomethane. Evaporation of the ethereal solution and distillation of the residue gave methyl 10-methyloctadecanoate (5.7 g., 38%), b. p. 136—139°/0.14 mm., n_D^{25} 1.4440 (Spielman, *J. Biol. Chem.*, 1934, **106**, 87, gives b. p. 143—144.5°/1.5 mm., n_D^{25} 1.4438).

The preceding experiment was repeated and the crude product, after removal of the thapsic acid, *via* the lead salt, was distilled, giving 10-methyloctadecanoic acid (4.7 g., 31%), b. p. 148°/0.1 mm.,

m. p. 14.5—18.0°, n_D^{20} 1.4524, which was recrystallised from acetone, giving prisms, m. p. 21.0—21.4°. On cooling the molten acid, a second form crystallised out. This had m. p. 24.1—24.5° [Prout, Cason, and Ingersoll, *loc. cit.*, give m. p. 25.4—26.1° (corr.). Ställberg-Stenhagen, *Arkiv Kemi, Min., Geol.*, 1948, **26**, A, No. 10, describes two forms, m. p. 20.9—21.6° and 25.8—26.1°, respectively]. (Found: C, 76.5; H, 12.6. Calc. for $C_{19}H_{38}O_2$: C, 76.45; H, 12.85%). The amide crystallised from acetone in needles, m. p. 76.5—77.2° (*idem, ibid.*, give m. p. 77.5—78.1°, corr.).

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