Anodic Syntheses. Part XIII. Chain Extension of Fatty Acids by Electrolysis with Benzyl Half Esters.*

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Chain extension of fatty acids by electrolysis with benzyl hydrogen succinate gives products of high purity. Evidence is presented for the *cis*-configuration of natural eicos-11-enoic acid.

Many fatty acids are conveniently synthesised by anodic crossed coupling of a monocarboxylic acid with a half ester of a dicarboxylic acid (cf. previous papers in this series) :

$$R{\cdot}CO_2H + \underset{(I)}{HO_2C{\cdot}[CH_2]_n{\cdot}CO_2R'} \longrightarrow R{\cdot}[CH_2]_n{\cdot}CO_2R' \longrightarrow R{\cdot}[CH_2]_n{\cdot}CO_2H$$

If the starting materials are suitably chosen, the product is free from substances of similar molecular weight, and is therefore readily purified.

Recently it has been observed that during the electrolysis of a fatty acid, some esterification with the methanol used as solvent may accompany the coupling processes. It has long been known that acids in which the carboxyl group is directly attached to an aromatic or alicylic ring do not couple to any appreciable extent. A number of such substances have been shown to undergo some esterification at the anode (Fichter and Meyer, *Helv. Chim. Acta*, 1934, **17**, 541 ; Fichter and Simon, *ibid.*, p. 1218 ; Fichter and Holbro, *ibid.*, 1938, **21**, 141 ; Fichter and Stenzl, *ibid.*, 1939, **22**, 971). These reactions are probably related to the formation of esters $R{\cdot}CO_2R$, by a process of the Hofer–Moest type, during the electrolysis of acids $R{\cdot}CO_2H$ in aqueous media (Kolbe, *Annalen*, 1849, **69**, 257 ; Petersen, *Z. physikal. Chem.*, 1900, **33**, 116 ; cf. Weedon, *Quart. Rev.*, 1952, **6**, 380). In small-scale preparations involving the anodic chain extension of a fatty acid by only a few carbon atoms, the side reaction with the solvent may result in contamination of the product with the starting material (cf. Part XII). Of the methods so far tried for avoiding this drawback, the use of the benzyl half ester (I ; $R' = CH_2Ph$) in place of the methyl or ethyl half ester has shown most promise. The benzyl ester then formed by crossed coupling with the monocarboxylic acid may be either separated by distillation from any methyl ester of the starting material and subsequently hydrolysed, or, alternatively, converted without isolation into the required acid by hydrogenolysis. Three examples of two-carbon homologation are given in this paper to illustrate these procedures. Three recent communications have described the use of benzyl esters in the anodic synthesis of dicarboxylic acids (Dolejš and Novotný, *Coll. Czech. Chem. Comm.*, 1954, **19**, 716 ; Šorm, Streibl, Jarolím, Novotný, Dolejš, and Herout, *Chem. Listy*, 1954, **48**, 575 ; cf. *Chem. and Ind.*, 1954, 252).

Electrolysis in methanol of myristic (n-C_{14}) acid with 3 mols. of benzyl hydrogen succinate, and alkaline hydrolysis of the benzyl esters formed, gave palmitic (n-C_{16}) acid in 30% yield. When stearic (n-C_{18}) and *threo*-9 : 10-dihydroxystearic acid were similarly electrolysed with benzyl hydrogen succinate (2·5—3 mols.), and the resulting esters hydrogenolysed, arachidic (n-C_{20}) and 11 : 12-dihydroxyarachidic acid were obtained in 25 and 13% yield respectively. No difficulty was encountered in the purification of these three products, only a single crystallisation of each of the " crude " materials being required. The expected products of symmetrical coupling were also formed : when benzyl hydrogen succinate was electrolysed alone in methanol, benzyl adipate was obtained in 50% yield.

Since *vic.*-dihydroxy-acids are readily derived from, and converted into, the corresponding ethylenic acids (cf. Bounds, Linstead, and Weedon, *J.*, 1953, 2393), the method used to synthesis 11 : 12-dihydroxyarachidic acid can obviously be extended to the preparation of unsaturated fatty acids.

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* Part XII, *J.*, 1954, 4219.

Another feature of the dihydroxyarachidic acid synthesis described above also deserves mention: it provides the first proof that natural eicos-11-enoic acid has the *cis*-configuration. This had previously been assumed by analogy with oleic acid (Hopkins, Chisholm, and Harris, *Canad. J. Res.*, 1949, **27**, 35). Eicos-11-enoic acid is the chief component acid of jojoba oil, the unique liquid seed wax of *Simmondsia californica* (Green, Hilditch, and Stainsby, *J.*, 1936, 1750; Eckey, "Vegetable Fats and Oils," Reinhold Publ. Corp., New York, 1954), and is a constituent of the glycerides in Atlantic cod liver oil, *Gadus callarias* (Hopkins *et al.*, *loc. cit.*) (for references to other minor sources, see *idem*, *loc. cit.*; Tsuchiya, *J. Chem. Soc. Japan*, 1951, **54**, 672; Hatt and Szumer, *J. Soc. Food Agric.*, 1953, **4**, 273). By stereospecific oxidations, the natural acid has been converted into both possible racemates of 11 : 12-dihydroxyarachidic acid (Green *et al.*, Hopkins *et al.*, Hatt and Szumer, *locc. cit.*; Baliga and Hilditch, *J.*, 1949, S 91); the properties reported for the low-melting form, obtained by oxidation with either peracetic or performic acid (*trans*-addition), are in good agreement with those of the anodic product. This, like the starting material which was prepared by performic acid oxidation of (*cis*-)oleic acid, must have the *threo*-structure, because the 9 : 10-dihydroxystearic acids are known to couple anodically with complete retention of configuration (Bounds, Linstead, and Weedon, *loc. cit.*). A stereochemical correlation between oleic and (natural) eicos-11-enoic acid has now, therefore, been established. No such connection was furnished by the partial syntheses of eicos-11-enoic acid from oleic acid (Vesely and Chudožilov, *Coll. Czech. Chem. Comm.*, 1930, **2**, 95; Fieser and Chamberlin, *J. Amer. Chem. Soc.*, 1948, **70**, 71), as the malonate method of chain extension used leads to extensive stereomutation (cf. Bounds, Linstead, and Weedon, *J.*, 1954, 448; Part XII).

EXPERIMENTAL

M. p.s were determined on samples in capillary tubes, and are uncorrected. In those experiments for which a recovery of starting material is given, allowance for this has been made in calculating the yields of the products. Conditions for the hydrolysis and hydrogenolysis of long-chain benzyl esters were established by pilot experiments on an authentic specimen of benzyl palmitate (Shonle and Row, *J. Amer. Chem. Soc.*, 1921, **43**, 361). The palladium catalysts used in the hydrogenolyses were prepared as described by Bowman (*J.*, 1950, 327).

Electrolyses.—These were carried out in cell "B" (Part IX, *J.*, 1953, 2393). The solvent used was commercial absolute methanol, to which sufficient sodium had been added to neutralise *ca.* 2% of the total acids. During the experiments the cell was cooled in an ice-bath (internal temp. of cell <50°), and the direction of the current was reversed from time to time. Electrolyses were continued until the electrolyte became slightly alkaline; this required *ca.* 3 times the number of Faradays calculated on the basis of the current and the amounts of acids used.

Benzyl Hydrogen Succinate (cf. Howard, *J. Amer. Chem. Soc.*, 1922, **44**, 1763).—A mixture of succinic anhydride (30 g.) and benzyl alcohol (33 g.) was heated under reflux for 4 hr. and then cooled. The product was extracted thoroughly with ether, and the ethereal solution was separated from the insoluble residue of succinic acid and washed repeatedly with saturated sodium carbonate solution. The alkaline extracts were acidified with 2N-hydrochloric acid, and the product (30 g., 48%), m. p. 58—59°, thus precipitated was isolated in the usual way with ether. Crystallisation from benzene–light petroleum (b. p. 80—100°) gave the half ester, m. p. 60° (Found: C, 63·7; H, 6·0. Calc. for $C_{11}H_{12}O_4$: C, 63·45; H, 5·8%) (*idem, loc. cit.*, gives m. p. 55—56°).

Benzyl Adipate.—A solution of benzyl hydrogen succinate (5 g.) in methanol (12·5 c.c.) was electrolysed (0·5 amp.). The cell contents were filtered, acidified with glacial acetic acid, and evaporated under reduced pressure. The residue was extracted with benzene (500 c.c.), and the solution was washed with saturated sodium carbonate, dried, and evaporated. Distillation of the residue gave a liquid (0·5 g.), b. p. 65—70°/0·2 mm., and benzyl adipate (2·0 g.), b. p. 170—175°/0·25 mm., which crystallised from light petroleum (b. p. 40—60°) and had m. p. 38·5—39·5°, undepressed on admixture with a specimen prepared from sodium adipate and benzyl chloride (Found: C, 73·8; H, 6·9. Calc. for $C_{20}H_{22}O_4$: C, 73·6; H, 6·8%) (Millat, *Ann. pharm. franç.*, 1949, **7**, 105, gives m. p. 39°). Alkaline hydrolysis gave adipic acid, m. p. and mixed m. p. 149—150°.

Palmitic Acid.—(a) *Hydrolysis of benzyl palmitate.* Benzyl palmitate (0·5 g.) was added to sodium hydroxide (0·5 g.) in methanol (2 c.c.) and water (0·5 c.c.), and the mixture was heated under reflux for 3 hr. Water was added, the methanol was distilled off, and the aqueous solution was boiled with excess of 30% hydrochloric acid. After the mixture had been cooled, the product was isolated with ether and crystallised from methanol, giving palmitic acid (0·35 g., 95%), m. p. and mixed m. p. 60—62°.

(b) *Hydrogenolysis of benzyl palmitate.* A solution of benzyl palmitate (0·7 g.) in ethyl acetate (50 c.c.) was shaken in an atmosphere of hydrogen, first with 10% palladised charcoal (0·2 g.) overnight, and then with 10% palladised strontium carbonate (0·3 g.) for 4 hr. Removal of catalyst and solvent, and crystallisation of the residue from methanol, gave palmitic acid (0·45 g., 87%), m. p. and mixed m. p. 60—62°.

(c) *Anodic synthesis from myristic acid.* A solution of myristic acid (5·5 g.; m. p. 54°) and benzyl hydrogen succinate (15 g., 3 mols.) in methanol (70 c.c.) was electrolysed (1·0 amp.). The cell contents were filtered, acidified with glacial acetic acid, and evaporated. The residue was extracted with benzene (500 c.c.), and the solution was washed thoroughly with 2N-potassium hydroxide. On acidification of the alkaline extract myristic acid (0·6 g.), m. p. and mixed m. p. 54—55°, was recovered. The benzene layer was washed with water, dried ($CaCl_2$), and evaporated. Distillation of the residue gave three fractions: (i) A liquid (1·8 g.), b. p. 70—90°/0·3 mm. (ii) A fraction (1·0 g.), b. p. 150—175°/0·6 mm., which partly solidified. (iii) A fraction (8·1 g.), b. p. 175—210°/0·6 mm., which partly solidified. Fraction (iii) and sodium hydroxide (8·1 g.) in water (8·1 c.c.) and methanol (32·4 c.c.) were boiled under reflux for 4 hr. The excess of alkali was then neutralised by 2N-hydrochloric acid, and the resulting mixture was evaporated to dryness. The residue was extracted (Soxhlet) with benzene for 24 hr. Evaporation of the benzene solution, and crystallisation of the product from light petroleum (b. p. 40—60°), gave hexacosane (0·9 g., 23%), m. p. and mixed m. p. 55—56°. Treatment of the benzene-insoluble material with hot hydrochloric acid yielded a solid, m. p. 60—61°. One crystallisation from methanol gave palmitic acid (1·7 g., 30%), m. p. and mixed m. p. 62—63° (Found: C, 74·85; H, 12·7%; equiv., 261. Calc. for $C_{16}H_{32}O_2$: C, 74·95; H, 12·6%; equiv., 256). On concentration of the mother-liquors from the acidification, adipic acid (1·0 g., 19%), m. p. and mixed m. p. 149—150°, was obtained.

Arachidic Acid.—A solution of stearic acid (5·9 g.; m. p. 68·5°) and benzyl hydrogen succinate (13 g.; 2·5 mols.) in methanol (80 c.c.) was electrolysed (1·3 amp.). Isolation of the products as in the preceding experiment yielded stearic acid (1·5 g.), m. p. and mixed m. p. 68—68·5°, and a neutral fraction. Distillation of the latter gave a liquid (2 g.), b. p. 80—120°/0·2 mm., and a liquid (7·8 g.), b. p. 180—265°/0·25 mm., which partly solidified. A solution of the high-boiling fraction in ethyl acetate (500 c.c.) was cooled to 0°, and the solid which separated was collected. Crystallisation from ether giving tetratriacontane (1·0 g., 27%), m. p. 73—74° (Found: C, 85·3; H, 14·85. Calc. for $C_{34}H_{70}$: C, 85·25; H, 14·7%) (Petersen, *Z. Electrochem.*, 1906, **12**, 144, gives m. p. 72·9°).

The ethyl acetate solution was shaken in hydrogen, first with 10% palladised charcoal (2 g.) overnight, and then with 10% palladised strontium carbonate (2 g.) for 7 hr. The catalyst and solvent were removed, and the residue was extracted with benzene. Separation of the insoluble material gave adipic acid (1·3 g., 29%), m. p. and mixed m. p. 149—150°. The benzene solution was washed thoroughly with 2N-potassium hydroxide, and the extract was boiled with excess of 30% hydrochloric acid. Isolation of the product with ether gave a solid, m. p. 73°. One crystallisation from alcohol furnished arachidic acid (1·2 g., 25%), m. p. 74·5—75·5° (remelt 75—75·5°) unchanged by further crystallisation (Found: C, 76·9; H, 13·05%; equiv., 308·5. Calc. for $C_{20}H_{40}O_2$: C, 76·85; H, 12·9%; equiv., 312). Francis and Piper (*J. Amer. Chem. Soc.*, 1939, **61**, 577) give m. p. 75·35°.

threo-11 : 12-*Dihydroxyarachidic Acid.*—A solution of *threo*-9 : 10-dihydroxystearic acid (4·6 g.; m. p. 93°) and benzyl hydrogen succinate (9·2 g.; 3 mols.) in methanol (60 c.c.) was electrolysed (1·2 amp.). The solid which separated during the electrolysis was filtered off, giving tetratriaconta-*threo*-9 : 10-*threo*-25 : 26-tetraol (1·2 g.; 30%), m. p. and mixed m. p. 123° (Bounds, Linstead, and Weedon, *J.*, 1953, 2393, give m. p. 124—124·5°). The filtrate was neutralised with glacial acetic acid and evaporated. The residue was extracted with benzene (500 c.c.), and the solution was washed with N-potassium hydroxide and water. Acidification of the alkaline extract gave *threo*-9 : 10-dihydroxystearic acid (0·1 g.), m. p. and mixed m. p. 92—93°. Evaporation of the benzene solution gave a liquid (7·4 g.) which was hydrogenolysed in ethyl acetate (500 c.c.) in the usual way. Isolation of the products as in the preceding experiment gave adipic acid (0·7 g., 22%), m. p. and mixed m. p. 149—150°, and a solid, m. p.

94°. One crystallisation of the latter from benzene gave *threo*-11 : 12-dihydroxyarachidic acid (0·6 g., 13%), m. p. 95—96° (Found: C, 69·9; H, 11·8%; equiv., 345. Calc. for $C_{20}H_{40}O_4$: C, 69·7; H, 11·7%; equiv., 344·5). Hopkins, Chisholm, and Harris (*Canad. J. Res.*, 1949, **27**, 35) give m. p. 95—96° for the dihydroxy-acid prepared by peracetic acid oxidation of natural eicos-11-enoic acid.

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