Anodic Syntheses. Part X. Synthesis of Nervonic (Selacholeic) Acid.*

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cis- and *trans*-Tetracos-15-enoic acid have been prepared by anodic chain extension of oleic and elaidic acid respectively. The *cis*-acid is identical with nervonic acid.

Both nervonic acid, from the brain cerebrosides of cattle and man (Klenk, *Z. physiol. Chem.*, 1925, **145**, 244; 1926, **157**, 283; 1927, **166**, 268, 287), and selacholeic acid, from shark- and ray-liver oils (Tsujimoto, *J. Soc. Chem. Ind., Japan*, 1927, **30**, 868; Hilditch, "The Chemical Constitution of Natural Fats," Chapman and Hall, London, 1947), were formulated as *cis*-tetracos-15-enoic acid on the basis of their reactions and degradation. These two, apparently identical, natural products have previously been synthesised by malonate chain extension of erucic (*cis*-docos-13-enoic) acid (Hale, Lycan, and Adams, *J. Amer. Chem. Soc.*, 1930, **52**, 4536; Veselý and Chudožilov, *Coll. Trav. chim. Tchécosl.*, 1930, **2**, 95; Müller and Binzer, *Ber.*, 1939, **72**, 615). This route normally gives mixtures of *cis*- and *trans*-tetracos-15-enoic acid which can, however, be separated by fractional crystallisation. Only in one instance has a product been obtained consisting essentially of the low-melting (*cis*-)isomer (Hale, Lycan, and Adams, *loc. cit.*).

Recently (Part IX) it has been shown that anodic chain extension of oleic and elaidic acid occurs without stereomutation about the double bond. This reaction has now been used to synthesise directly the pure geometrical isomers of tetracos-15-enoic acid.

$$\mathrm{CH_3{\cdot}[CH_2]_7{\cdot}CH{:}CH{\cdot}[CH_2]_7{\cdot}CO_2H + HO_2C{\cdot}[CH_2]_6{\cdot}CO_2Me}$$

$$\downarrow$$

$$\mathrm{CH_3{\cdot}[CH_2]_7{\cdot}CH{:}CH{\cdot}[CH_2]_{13}{\cdot}CO_2H} \quad \text{(I)}$$

Electrolysis of oleic and elaidic acid in the presence of an excess of methyl hydrogen suberate gave the expected mixtures of three products by both symmetrical and unsymmetrical coupling of the two components. By distillation, and hydrolysis of the unsym-

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* Part IX, *J.*, 1953, 2393.

metrical products, *cis*- and *trans*-tetracos-15-enoic acid (I) were obtained in 30—35% overall yields. The *cis*-acid was converted into the *trans*-form on treatment with nitrous acid. Each isomer on catalytic hydrogenation gave lignoceric (tetracosanoic) acid almost quantitatively. Oxidation of the *cis*-and the *trans*-acid with performic acid led to *threo*- and *erythro*-15 : 16-dihydroxylignoceric acid respectively, both of which yielded nonanal on treatment with periodic acid, thus confirming the position of the double bonds.

We have taken the opportunity to compare the melting points of *cis*- and *trans*-tetracos-15-enoic acid, prepared anodically, and of the derived saturated acid, with the values previously recorded for other samples of these substances. The variation in the melting point recorded for the unsaturated acids is surprisingly large (a range of 6° for the *cis*- and of 10° for the *trans*-isomer). A full direct comparison has not been possible as some of the earlier specimens are no longer available. However, we have been fortunate in obtaining a sample of methyl nervonate from Professor E. Klenk, and of synthetic *trans*-tetracos-15-enoic acid from Professor Roger Adams. Previously, Tsujimoto has compared selacholeic acid and its isomerisation product with Veselý and Chudožilov's synthetic materials. The melting points are summarised in the Table.

In interpreting these data, we are considerably influenced by the fact that the method of anodic synthesis gave no stereomutation in the erucic-brassidic series, and hence may be expected to give homogeneous products. Our main conclusions follow :

Melting points of tetracos-15-enoic and tetracosanoic acids.

Authors *	*cis*-Acid	*trans*-Acid	Saturated acid [a]
Klenk	40—41° (nervonic)	61° [b]	85°
Tsujimoto	42·5—43 (selacholeic)	60·5 [b, c]	83·5
Hale, Lycan, and Adams	39—39·5 (synthetic)	61,[d] 62—63 [e]	83—84
Veselý and Chudožilov	44—45 ,,	66—67 [f]	—
Müller and Binzer †	41·1 ,,	70·6 [d]	84·0
Present authors †	40·5—41 ,,	65·5 [g]	83—84

Comparison of tetracos-15-enoic acid samples.

cis-Acid (from oleic)	Nervonic acid	Mixed m. p.	Veselý and Chudožilov's *cis*-acid	Selacholeic acid	Mixed m. p.
40·5—41°	39—39·5° [h]	39·5—40·5°	44—45°	43°	No depression[i]

trans-Acid (from elaidic)	*trans*-Acid of Adams *et al.*	Mixed m. p.	Veselý and Chudožilov's *trans*-acid	Tsujimoto's *trans*-acid	Mixed m. p.
65·5	61—63·5 [i]	61—63·5	66—67	68·5	64·5° [j]

* *Locc. cit.* † M. p.s corrected.

[a] Francis and Piper, *J. Amer. Chem. Soc.*, 1939, **61**, 577, give m. p. 84·15° for lignoceric acid. [b] Prepared by " elaidinisation " of the natural acid. [c] A revised value of 68·5° is quoted by Veselý and Chudožilov. [d] By-product in preparation of *cis*-acid from erucic acid. [e] Prepared by " elaidinisation " of the *cis*-acid. [f] Prepared both as in (*e*) and by malonate chain extension of brassidic acid. [g] Prepared both as in (*e*) and by anodic chain extension of elaidic acid. [h] Prepared by hydrolysis of Professor Klenk's methyl nervonate, and crystallisation of the resulting acid from methanol at 0°. [i] After crystallisation of Professor Adams's sample to constant m. p. from methanol. [j] Tsujimoto's report, quoted by Veselý and Chudožilov.

(1) The nervonic acid of Klenk and the selacholeic acid of Tsujimoto are essentially *cis*-tetracos-15-enoic acid, and identical with our synthetic acid and that of Adams *et al.* and of Müller and Binzer. The reason for the higher melting point recorded by Veselý and Chudožilov is not clear; there may be polymorphism, as with some other *cis*-acids.

(2) The *trans*-acid which we obtained by elaidinisation of the *cis*-isomer agreed exactly with that made by anodic synthesis, and the melting point is close to that reported by Veselý. We suspect that the lower-melting materials may contain a small amount of isomer.

(3) Veselý's synthetic *trans*-acid slightly depressed the m. p. of that obtained by the action of nitrous acid on selacholeic acid. It is possible that the elaidinisation was accompanied by a partial double bond migration. The high m. p. of the *trans*-acid reported by Müller may have a similar cause.

(4) There is a satisfactory general agreement on the m. p. of the saturated acid.

EXPERIMENTAL

Intermediates.—For the purification of oleic acid and the preparation of elaidic acid see Part IX. Methyl hydrogen suberate, b. p. 135—138°/0·12 mm., n_D^{17} 1·4461, was prepared from suberic acid and methyl suberate (cf. Swann, Oehler, and Buswell, *Org. Synth.*, Coll. Vol. II, p. 276), and methyl hydrogen glutarate as described in Part VIII (*J.*, 1953, 1538).

Electrolyses.—The two cells, " A " and " C," and the procedures used, were those described in Part IX. Cell " A " was fitted with two water-cooled glass U-tubes.

Methyl Suberate and Suberic Acid.—A solution of methyl hydrogen glutarate (200 g.) in methanol (300 c.c.) was electrolysed in cell " C " (4 amps.; faradays passed, *ca.* 1·25 times theoretical). Isolation of the neutral product and distillation gave methyl suberate (92·5 g.), b. p. 128—132°/9 mm., n_D^{17} 1·4350. Hydrolysis with 10% aqueous-alcoholic sodium hydroxide gave suberic acid (62% overall yield), m. p. 136—139°, raised by crystallisation (charcoal) from water to 140° (Found : equiv., 87·2. Calc. for $C_8H_{14}O_4$: equiv., 87·1).

cis-*Tetracos*-15-*enoic Acid.*—A mixture of oleic acid (10·0 g., 0·036 mole) and methyl hydrogen suberate (19·0 g.) in methanol (40 c.c.) was electrolysed (1·4 amp.; faradays passed, *ca.* 1·2 times theoretical). A considerable amount of a colourless solid began to separate from the electrolyte at an early stage in the electrolysis. Towards the end of the reaction the current tended to drop, but was restored to its former value by the addition of further half ester (altogether 24·5 g., 0·13 mole, of the latter were used). After the electrolysis the alkaline cell contents were acidified and then evaporated. The residue was separated in the usual way into acidic and neutral fractions. Distillation of the latter from a Kon flask gave : (i) An unsaturated oil (1·6 g.), b. p. 70—120°/10^{-5} mm., n_D^{19} 1·4409. (ii) Methyl tetradecanedioate (10·5 g., 57%), b. p. 127—130°/10^{-5} mm., m. p. 39—41°, which was not purified further (Chuit, *Helv. Chim. Acta*, 1926, **9**, 264, gives m. p. 43°). (iii) A product (5·9 g.), b. p. 186—202°/10^{-5} mm., m. p. 12—13·5°. Two crystallisations (charcoal) of a small portion from acetone at −25° gave methyl nervonate, m. p. 14—15°, n_D^{23} 1·4563 (Found : C, 79·35; H, 12·85. Calc. for $C_{25}H_{48}O_2$: C, 78·9; H, 12·7%). Hydrolysis (in nitrogen) of the bulk with excess of hot 2N-aqueous-methanolic sodium hydroxide furnished a solid which was extracted with light petroleum (b. p. 60—80°; 20 c.c.). Evaporation of the extract yielded nervonic acid (4·4 g., 37%), m. p. 37—39° (Found : equiv., 389. Calc. for $C_{24}H_{46}O_2$: equiv., 367).

Further purification of the nervonic acid was effected in the following manner. The acid was converted into its lithium salt which was extracted with boiling light petroleum (b. p. 60—80°), and then crystallised once from aqueous alcohol, giving plates, m. p. 218—221° (uncorr., sealed capillary). Regeneration from the salt gave a product (3·0 g.), m. p. 39·5—40·5°, n_D^{46} 1·4535. Two crystallisations from alcohol at 0° yielded nervonic acid as plates, m. p. 40·5—41° (Found : C, 78·7; H, 12·8%; equiv., 366. Calc. for $C_{24}H_{46}O_2$: C, 78·6; H, 12·65%; equiv., 367). The amide, from alcohol, had m. p. 86·5—87·5° (Veselý and Chudožilov, *loc. cit.*, give m. p. 87—88°).

The residue from the preceding distillation gave crude tetratriaconta-*cis*-9 : *cis*-25-diene (0·9 g., 11%), b. p. 150—160° (bath-temp.; short-path still)/10^{-4} mm., m. p. 15·5—16·5°, n_D^{22} 1·4638.

trans-*Tetracos*-15-*enoic Acid.*—(a) *From elaidic acid.* A mixture of elaidic acid (5·0 g., 0·018 mole; m. p. 44—44·3°) and methyl hydrogen suberate (total 13·3 g., 0·071 mole) in methanol (30 c.c.) was electrolysed as described above (1·2 amp.; faradays passed, *ca.* 1·5 times theroetical). After the electrolysis the cell contents were boiled and then cooled slightly. The solid, consisting of crude tetratriaconta-*trans*-9 : *trans*-25-diene (0·7 g., 17%), m. p. 53—54°, was collected and the filtrate was acidified and evaporated. The residue was separated into an acidic and a neutral fraction. Distillation of the latter from a Kon flask gave: (i) An unsaturated oil (1·05 g.), b. p. 70—80°/10^{-5} mm., n_D^{19} 1·4406. (ii) Methyl tetradecanedioate (4·9 g., 48%), b. p. 115—140°/10^{-5} mm., m. p. 40·5—42°, n_D^{48} 1·4355. Hydrolysis yielded the diacid which crystallised (charcoal) from alcohol–benzene as needles, m. p. 126·5° (Chuit, *loc. cit.*, gives m. p. 125·8°). (iii) Methyl *trans*-tetracos-15-enoate (2·45 g.), b. p. 180—190°/10^{-5} mm., m. p. 36·5—37·5°. Two crystallisations of a small portion from acetone at 0° gave needles, m. p. 37·0—37·2°, n_D^{45} 1·4471. Hydrolysis of the bulk gave a solid (1·94 g., 32%), m. p. 64—67°, which after two crystallisations (charcoal) from 90% aqueous alcohol yielded *trans*-tetracos-15-enoic acid as needles, m. p. 65·5°, unchanged on further crystallisation (Found : C, 78·6; H, 12·7%; equiv., 368. Calc. for $C_{24}H_{46}O_2$: C, 78·6; H, 12·65%; equiv., 367). The amide, from alcohol, had m. p. 97—98° (Veselý and Chudožilov, *loc. cit.*, give m. p. 98—99°).

(b) *From* cis-*tetracos*-15-*enoic acid* (cf. Dorée and Pepper, *J.*, 1942, 481). Sodium nitrite (60 mg.) was added gradually to a well-shaken mixture of *cis*-tetracos-15-enoic acid (0·3 g.), nitric acid (2·3 c.c.; *d* 1·42), and water (5·25 c.c.) at 55°. The mixture was heated at 75° for 15 min. and then cooled. The solid was collected and crystallised four times from alcohol, giving *trans*-tetracos-15-enoic acid as needles, m. p. 65·5°, undepressed on admixture with the specimen described above.

Tetracosanoic Acid.—Hydrogenation of *cis*-tetracos-15-enoic acid (90 mg.) in ethyl acetate (8 c.c.) in the presence of Adams's catalyst (7 mg.) gave a solid (90 mg.), m. p. 81—83°. Crystallisation from alcohol yielded tetracosanoic acid as plates, m. p. 83—84°.

Similarly the *trans*-isomer gave tetracosanoic acid in 90% yield, m. p. and mixed m. p. 83·5—84°.

15 : 16-*Dihydroxytetracosanoic Acid.*—(i) Oxidation of *cis*-tetracos-15-enoic acid (1·5 g.) with performic acid at 40°, and hydrolysis of the initial product (cf. Swern, Billen, Findlay, and Scanlan, *J. Amer. Chem. Soc.*, 1945, **67**, 1786) gave a product (1·52 g., 93%), m. p. 100—102°, which was extracted with light petroleum (b. p. 60—80°). Crystallisation of the residue from 80% aqueous alcohol gave threo-15 : 16-*dihydroxytetracosanoic acid* (52%) as rectangular plates, m. p. 104—105° (Found : C, 72·15; H, 12·35%; equiv., 402. $C_{24}H_{48}O_4$ requires C, 71·95; H, 12·1%; equiv., 401).

(ii) Similarly *trans*-tetracos-15-enoic acid (0·55 g.) gave a solid (0·51 g., 85%), m. p. 127—128·5°. Crystallisation from methanol yielded erythro-15 : 16-*dihydroxytetracosanoic acid* (67%) as hexagonal plates, m. p. 130·5—131° (Found : C, 72·0; H, 12·2. $C_{24}H_{48}O_4$ requires C, 71·95; H, 12·1%).

Periodic acid oxidation (cf. Huber, *ibid.*, 1951, **73**, 2730) of the *erythro*- and the *threo*-acid gave nonanal, which was isolated as its 2 : 4-dinitrophenylhydrazone, in 32 and 45% overall yield respectively. The derivatives crystallised from alcohol in needles, m. p. 102—103°, undepressed on admixture with an authentic specimen of m. p. 103—104° (*idem, loc. cit.*, gives m. p. 105—106°).

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