Synthesis of the Racemic and Optically Active Forms of 10-Methylnonadecanoic Acid

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The synthesis of the racemic and optically active forms of 10-methylnonadecanoic acid is described and several physical constants for the acids, methyl esters and amides are given.

The synthesis of the racemic and the optically active forms of 11-methylnonadecanoic acid was described in a previous communication¹. It was pointed out that none of the acids synthesized could be identical with phytomonic acid from *Agrobacterium tumefaciens* and that data already at hand also showed the non-identity of the racemic or one of the optically active forms of 10-methylnonadecanoic acid with phytomonic acid. The suggestion was made that phytomonic acid was a cyclopropane derivative similar to the lactobacillic acid isolated by Hofmann and Lucas² from *Lactobacillus arabinosus*. A large-scale growth of *Agrobacterium tumefaciens* was then undertaken at the Istituto Superiore di Sanità in Rome, with the object of preparing phytomonic acid and investigating its structure. For reasons outside our control the analytical work had to be postponed, and in the meantime Hofmann and collaborators³ showed that phytomonic acid is indeed a cyclopropane derivative as suggested by Stållberg-Stenhagen and the writer¹. According to Hofmann *et al.* the acid is identical with lactobacillic acid with the proposed structure of *cis*-11,12-methyleneoctadecanoic acid^{4,5}.

The details of the preparation of the 10-methylsubstituted acids are now given. The synthetic routes used were the same as those for the 11-methylsubstituted isomers. 10DL-Methylnonadecanoic acid of m.p. 26.8–27.2° was prepared by Clemmensen reduction of 8-oxo-10DL-methylnonadecanoic acid. The oxo-acid of m.p. 47.0–47.2° was prepared by the β -oxo-ester synthesis⁶ from methyl 3-oxo-5DL-methyltetradecanoate and methyl 6-iodohexanoate. 10DL-Methylnonadecanoic acid prepared from the enantiomorphs melted at 26.8–27.1°.

The optically active forms were synthesized by the Kolbe reaction (*cf.* Ref. 1) from the enantiomorphs of 3-methyldodecanoic acid and methyl hydro-

gen azelate. The active 3-methyldodecanoic acids were also prepared by the Kolbe reaction using the enantiomorphs of methyl hydrogen β -methylglutarate⁷ and *n*-nonanoic acid as initial material.

After solidification from the melt optically active 10-methyl-nonadecanoic acids remelt at 12.5°. After crystallization from solvents slightly higher melting points have been recorded. Similar behaviour was encountered by Hallgren⁸ in the case of (+)-9D-methyloctadecanoic acid, when it was possible to obtain a higher-melting form by slow crystallization from methanol at a low temperature. It seems likely that the behaviour of the 10-methylnonadecanoic acids also indicates the existence of a higher-melting modification although the conditions for obtaining the acids in this form alone have not been established.

The D-acid, the derived amide, and the methyl ester are all dextrorotatory, although the specific rotations are very small. 9D-Methyloctadecanoic acid and 11D-methylnonadecanoic acid¹ are both dextrorotatory⁸, whereas 10D-methyloctadecanoic acid (tuberculostearic acid) is laevorotatory^{9,10}.

EXPERIMENTAL¹

3DL-Methyl-5-oxododecanoic acid. Methyl 3DL-methyl-5-ketopimelate (40 g) was alkylated with *n*-hexyl iodide (45 g of b.p. 46°, 4 mm) using dry potassium carbonate (60 g) and methyl-*n*-propyl ketone (300 ml). For details of alkylations of this type see Ref.⁴. After refluxing for 24 h, hydrolysis and ketonic cleavage were performed in the standard manner, using potassium hydroxide (85 g) in water (80 ml) and methanol (1000 ml). The reaction mixture was kept overnight at a temperature of 50°. The product was isolated from the reaction mixture in the usual way. Distillation gave 3DL-methyl-5-oxododecanoic acid as a colourless oil of b.p. 140°, 1 mm. Yield 26 g or 49 % of the theoretical. (Found: C 68.68; H 10.42. Calc. for C₁₃H₂₄O₃ (228.3): C 68.50; H 10.51.)

Ethyl 3DL-methyldodecanoate was obtained by Clemmensen reduction of the oxo-acid (15 g) with 250 g of amalgamated zinc in 250 ml of absolute ethanol. A moderate stream of dry hydrogen chloride was led into the reaction mixture for 15 min. every 7th hour. After 70 h the reduced ester was isolated and distilled through a 1 m Podbielniak column. Yield 8 g of b.p. 104°, 0.3 mm (50 % of the theoretical). (Found: C 74.04; H 12.46. Calc. for C₁₆H₃₀O₂ (242.4): C 74.32; H 12.48).

3DL-Methyldodecanoic acid was obtained in 75 % yield after hydrolysis of the ester and distillation of the acid. B.p. 137°, 0.5 mm. (Found: C 73.20; H 12.20. Calc. for C₁₃H₂₆O₂ (214.3): C 72.84; H 12.23).

Methyl 3-oxo-5DL-methyltetradecanoate was prepared by the general procedure of Stållberg-Stenhagen¹¹. 3-DL-Methyldodecanoyl chloride (prepared from 8 g of the acid by means of 5 ml of oxalyl chloride in 25 ml of dry benzene) was condensed with ethyl sodioacetoacetate (from 15 ml of the ethyl acetoacetate and 1.5 g of sodium). Hydrolysis and ketonic cleavage was performed with 1.5 g of sodium in 45 ml of methanol. The oxo-ester distilled at 134°, 0.5 mm. Yield, 6 g (59 % of the theoretical). (Found: C 71.00; H 11.04. Calc. for C₁₆H₃₀O₃ (270.4): C 71.06; H 11.18).

8-Oxo-10DL-methylnonadecanoic acid was synthesized from the above oxo-ester (6 g) and methyl 6-iodohexanoate (5.7 g prepared from the silver salt of methyl hydrogen pimelate by bromine degradation according to Hunsdiecker and Hunsdiecker¹²). After hydrolysis and ketonic cleavage in the usual way (cf. Ref. ¹) using 15 g of potassium hydroxide in 15 ml of water and 200 ml of methanol, the oxo-acid was crystallized from light petroleum (b.p. below 40°) at a temperature of -18°. Two recrystallizations from the same solvent gave the oxo-acid in the form of fine needles melting at 47.0-47.2°. The X-ray diffraction pattern of the oxo-acid did not show any characteristic series of 00l reflexions. (Found: C 73.68; H 11.75. Calc. for C₂₀H₃₈O₃ (326.5): C 73.57; H 11.73).

Amide of 10DL-methylnonadecanoic acid. 0.6 g of the oxo-acid was reduced by Clemmensen's method in the manner described for the C₁₃ oxo-acid. After saponification, the crude acid was converted into the amide *via* the acid chloride prepared by means of

oxalyl chloride in benzene solution. The amide was crystallized from methanol-water (85:15 by volume). Yield 0.32 g (56 % of the theoretical), m.p. 78.8–79.2°. Long X-ray spacing 41.0 Å. No polymorphism has been observed. (Found: N 4.61. Calc. for $C_{20}H_{41}ON$ (311.5): N 4.50).

10DL-Methylnonadecanoic acid was obtained by saponification of the amide. Crystallization from light petroleum (b.p. below 40°) gave acid in the form of white crystals melting at 26.8–27.2°. The X-ray diffraction pattern was similar to that of 9DL-methyloctadecanoic acid in that it showed no distinct series of 00l reflexions. (Found: C 77.15; H 12.92. Calc. for $C_{20}H_{40}O_2$ (312.5): C 76.86; H 12.90).

10DL-Methylnonadecanoic acid from the enantiomorphs. Equal amounts of the enantiomorphs described below were mixed, a little ether being added for mixing, and the solvent evaporated at room temperature. After removing the last traces of solvent *in vacuo* the liquid solidified to a mass of fine, hard crystals. The DL-acid prepared in this manner melted without recrystallization at 26.8–27.1°.

(+)-3D-Methyldodecanoic acid was prepared in a similar way to that described for the next lower homologue in Part I. The initial materials were (+)-methyl hydrogen β -methylglutarate (20.8 g, 0.13 mole) and *n*-nonanoic acid (27 g, 0.171 mole, 25 % excess; the acid had been purified *via* the methyl ester). The anodic synthesis was performed as described in the previous paper¹. Saponification of the methyl ester and distillation gave 10.2 g of (+)-3D-methyldodecanoic acid, b.p. 121°, 0.2 mm. The optical rotation was $[\alpha]_D^{25} + 4.16^\circ$ (homogeneous, *l*, 1). n_D^{25} 1.4408. Found: C 72.71, H 12.20. Calc. for $C_{13}H_{26}O_2$ (214.3): C 72.84; H 12.23. Hallgren⁸ gives $[\alpha]_D^{25.5} + 4.23^\circ$ (homogeneous), $d_4^{25.5}$ 0.8848 and n_D^{25} 1.4405.

(–)-3L-Methyldodecanoic acid was obtained in the same way, starting from (–)-methyl hydrogen β -methylglutarate (27 g) and *n*-nonanoic acid (34 g). Yield, 13.5 g of acid distilling at 107°, 0.1 mm. n_D^{25} 1.4408. Optical rotation $[\alpha]_D^{24} - 2.06^\circ$ (homogeneous; *l*, 0.5). (Found: C 72.84; H 12.16. Calc. for $C_{13}H_{26}O_2$ (214.3): C 72.84; H 12.23).

Methyl hydrogen azelate was prepared by partial esterification of azelaic acid. The mono-ester used distilled at 137°, 0.5 mm.

(+)-10D-Methylnonadecanoic acid. 10.2 g (0.05 mole) of methyl hydrogen azelate was electrolyzed together with 8.6 g (0.04 mole) of (+)-3D-methyldodecanoic acid in 250 ml of methanol containing 0.28 g of sodium. The reaction was started with half the above amounts of reagents, the second half being added when the pH of the electrolysis mixture had risen to 7. A current of 5 A were passed through the cell for a total time of 1 h. Near the end of the reaction more methyl hydrogen azelate (2 g) was added in order to use up as much of the optically active acid as possible. The reaction mixture was extracted and saponified in the usual way (*cf.* Ref.¹). Distillation gave 3.0 g (24 % of the theoretical) of (+)-10D-methylnonadecanoic acid as a thick colourless oil, b.p. 173–174°, 0.1 mm. The properties of the optically active hydrocarbon ((–)-10L,13D-dimethyl-docosane) found in the unsaponifiable material have been described by Hallgren⁸.

The amount of D-acid of m.p. 12.5° purified *via* the amide was too small to allow the determination of the optical rotation in the 0.5 dm polarimeter tube available. n_D^{25} 1.4521. d_4^{24} 0.880. (Found: C 76.8; H 13.1. Calc. for $C_{20}H_{40}O_2$ (312.5): C 76.86; H 12.90). The D-amide melted after crystallization from acetone at 75.0–75.5°. Long X-ray spacing at room temperature 40.0 Å. Optical rotation $\alpha_D^{25} + 0.05^\circ$ (chloroform; *l*, 1; *c*, 21.5). (Found: N 4.6. Calc. for $C_{20}H_{41}ON$ (311.5): N 4.50).

Methyl 10D-methylnonadecanoate was prepared by means of diazomethane from a specimen of acid that had been chromatographed on de-activated aluminium oxide. The ester distilled at 142°, 0.2 mm, and had an optical rotation $\alpha_D^{25} + 0.03^\circ$ (homogeneous, *l*, 0.5). d_4^{24} 0.861 (Found C 77.0; H 12.6. Calc. for $C_{21}H_{42}O_2$ (326.5): C 77.72; H 12.42).

(–)-10L-Methylnonadecanoic acid was prepared in an analogous manner starting from (–)-3L-methyldodecanoic acid. The acid distilled at 176–177°, 0.15 mm. The distilled material (5 g) had m.p. 12.5°. After two crystallizations from acetone at –25° the m.p. was 13.0–13.3°. Yield 4.17 g. n_D^{25} 1.4524; d_4^{24} 0.879. Optical rotation $\alpha_D^{25} - 0.03^\circ \pm 0.01^\circ$ (homogeneous, *l*, 1); $\alpha_{4358}^{25} - 0.07^\circ$ (homogeneous, *l*, 1). Hydrolysis of 0.5 g of the amide described below was carried out with a solution of 5 g of potassium hydroxide in

water (5 ml) and ethanol (30 ml). The solution was refluxed for two days. After acidification the acid was extracted in the usual way and distilled, giving 0.12 g of distilled material of m.p. 12.0–12.6°. Solidification took place at 9.5–9.0°. (Found: C 76.7; H 12.8. Calc. for $C_{30}H_{40}O_2$ (312.5): C 76.86; H 12.90).

(–)-10 α -Methylnonadecanamide was prepared in the same way as the DL-amide, and crystallized from acetone. M.p. 75.0–75.5°. The melting point was the same after the amide had been chromatographed on aluminium oxide. Long X-ray spacing 40.0 Å. Optical rotation α_D^{25} –0.08° (chloroform; l , 1; c , 21.25). (Found: N 4.6. Calc. for $C_{20}H_{31}ON$ (311.5): N 4.50).

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