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 communication. It was pointed out that none of the acids synthesized could be identical with phytomononic 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 phytomononic acid. The suggestion was made that phytomononic acid was a cyclopropane derivative similar to the lactobacillic acid isolated by Hofmann and Lucas 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 phytomononic acid and investigating its structure. For reasons outside our control the analytical work had to be postponed, and in the meantime Hofmann and collaborators showed that phytomononic acid is indeed a cyclopropane derivative as suggested by Ställberg-Stenhagen and the writer. According to Hofmann et al. the acid is identical with lactobacillic acid with the proposed structure of cis-11,12-methyleneoctadecanoic acid.

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 synthesis 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-methyldecanoic acid and methyl hydro-
gen azelate. The active 3-methyldecanoic acids were also prepared by the Kolbe reaction using the enantiomorphs of methyl hydrogen β-methylglutarate\(^7\) and \(n\)-nonanoic acid as initial material.

After solidification from the melt optically active 10-methyl-nonadecanoic acids remelt at 12.5\(^\circ\). After crystallization from solvents slightly higher melting points have been recorded. Similar behaviour was encountered by Hallgren\(^8\) in the case of (+)-9\(d\)-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. 9\(d\)-Methyloctadecanoic acid and 11\(d\)-methylnonadecanoic acid\(^1\) are both dextrorotatory\(^8\), whereas 10\(d\)-methyloctadecanoic acid (tuberculostearic acid) is laevorotatory\(^9,10\).

EXPERIMENTAL\(^1\)

3-\(d\)-Methyl-\(5\)-oxodecanoic acid. Methyl 3-\(d\)-methyl-5-ketopimelate (40 g) was alkylated with \(n\)-hexyl iodide (45 g of b.p. 46\(^\circ\), 4 mm) using dry potassium carbonate (80 g) and methyl-\(n\)-propyl ketone (300 ml). For details of alkylations of this type see Ref.\(^1\). 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\(^\circ\). The product was isolated from the reaction mixture in the usual way. Distillation gave 3-\(d\)-methyl-5-oxodecanoic acid as a colourless oil of b.p. 140\(^\circ\), 1 mm. Yield 26 g or 49 % of the theoretical. (Found: C 68.68; H 10.42. Calc. for \(C_{13}H_{22}O_4\) (228.3): C 68.50; H 10.51.)

Ethyl 3-\(d\)-methyldecanoate was obtained by Clemmensen reduction of the o xo-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 Podbielski column. Yield 8 g of b.p. 104\(^\circ\), 0.3 mm (50 % of the theoretical). (Found: C 74.04; H 12.46. Calc. for \(C_{14}H_{26}O_2\) (242.4): C 74.32; H 12.48.)

3-\(d\)-Methyldecanoic acid was obtained in 75 % yield after hydrolysis of the ester and distillation of the acid. B.p. 137\(^\circ\), 0.5 mm. (Found: C 73.20; H 12.20. Calc. for \(C_{13}H_{22}O_4\) (214.3): C 73.84; H 12.23.)

Methyl 3-oxo-5-\(d\)-methyltetradecanoate was prepared by the general procedure of Ställberg-Stenhagen\(^11\). 3-\(d\)-Methyldecanoyl 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 dichloroacetate (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\(^\circ\), 0.5 mm. Yield, 6 g (59 % of the theoretical). (Found: C 71.00; H 11.04. Calc. for \(C_{14}H_{24}O_4\) (270.4): C 71.06; H 11.18.)

3-Oxo-10\(d\)-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 Hunsdiecker\(^12\)). 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\(^\circ\)) at a temperature of -18\(^\circ\). Two recrystallizations from the same solvent gave the oxo-acid in the form of fine needles melting at 47.0—47.2\(^\circ\). The X-ray diffraction pattern of the oxo-acid did not show any characteristic series of 00l reflections. (Found: C 73.68; H 11.75. Calc. for \(C_{15}H_{26}O_4\) (326.5): C 73.57; H 11.73.)

Amide of 10\(d\)-methylnonadecanoic acid. 0.6 g of the oxo-acid was reduced by Clemmensen's method in the manner described for the \(C_9\) oxo-acid. After saponification, the crude acid was converted into the amide via the acid chloride prepared by means of

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oxysyl chloride in benzene solution. The amide was crystallized from methanol-water (85:15 by volume). Yield 0.32 g (66 % 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 C₃₇H₇₄ON (311.5): N 4.50).

10DL-Methylmononadecanoic 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 C₃₇H₇₄O₂ (312.5): C 76.86; H 12.90).

10DL-Methylmononadecanoic 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 without recrystallization melted at 26.8—27.1°.

(±)-3DL-Methylidydecanoic 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 paper 1. Saponification of the methyl ester and distillation gave 10.2 g of (+)-3DL-methyldecanoic acid, b.p. 121°; 0.2 mm. The optical rotation was [α]D²⁵ +4.18° (homogeneous, l, l). nD²⁵ 1.4408. (Found: C 72.71, H 12.20. Calc. for C₁₃H₂₄O₂ (214.3): C 72.84; H 12.23). Hallgren 8 gives [α]D³⁴ +4.23° (homogeneous), d₄³⁴ 0.8848 and nD³⁴ 1.4405.

(---)-3DL-Methylidydecanoic 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. nD³⁴ 1.4408. Optical rotation [α]D³⁴ —2.06° (homogeneous; l, 0.5). (Found: C 72.84; H 12.16. Calc. for C₁₃H₂₄O₂ (214.3): C 72.84; H 12.23).

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

(---)-16DL-Methylmononadecanoic acid. 10.2 g (0.05 mole) of methyl hydrogen azelate was electrolyzed together with 8.6 g (0.04 mole) of (+)-3DL-methyldecanoic 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 (---)-16DL-methylmononadecanoic acid as a thick colourless oil, b.p. 173—174°, 0.1 mm. The properties of the optically active hydrocarbon ((---)-16DL,13DL-dimethyl-docosane) found in the unsaponifiable material have been described by Hallgren 8.

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. nD³⁴ 1.4521. d₄³⁴ 0.880. (Found: C 76.8; H 13.1. Calc. for C₃₇H₇₄O₂ (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 αD +0.05° (chloroform; l, l; c, 21.5). (Found: N 4.6. Calc. for C₃₇H₇₄ON (311.5): N 4.56).

Methyl 16DL-methylmononadecanoate 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 αD +0.03° (homogeneous, l, 0.5). d₄³⁴ 0.861 (Found C 77.0; H 12.6. Calc. for C₃₇H₇₄O₂ (326.5): C 77.72; H 12.42).

(---)-16DL-Methylmononadecanoic acid was prepared in an analogous manner starting from (---)-3DL-methyldecanoic 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. nD³⁴ 1.4524; d₄³⁴ 0.879. Optical rotation αD +0.03° ± 0.01° (homogeneous, l, l). αmax —0.07° (homogeneous, l, l). Hydrolysis of 0.5 g of the amide described below was carried out with a solution of 5 g of potassium hydroxide in

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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°C. Solidification took place at 9.5—9.6°C. (Found: C 76.7; H 12.8. Calc. for C₉H₁₄O₄ (312.5): C 76.86; H 12.90).

(--)-10α-Methylmononadecanamide was prepared in the same way as the α,α-amine, and crystallized from acetone. M.p. 75.0—75.5°C. The melting point was the same after the amide had been chromatographed on aluminium oxide. Long X-ray spacing 40.0 Å. Optical rotation α₂₀ ≈ 0.08° (chloroform; l,1; c,21.25). (Found: N 4.6. Calc. for C₉H₁₄ON (311.5): N 4.50).

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