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Absolute configurations of 13-hydroxydocosanoic and 17-hydroxyoctadecanoic acids[1]

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Methyl 13-D- and 13-L-hydroxydocosanoates have been synthesized from 9-D- and 9-L-hydroxyoctadecanoic acids. Comparison of these esters with the methyl ester of 13-hydroxydocosanoic acid, produced by *Candida bogoriensis*, shows that the natural product has the L-configuration. The known 2-D-octadecanol has been prepared from 17-hydroxyoctadecanoic acid, produced by *Torulopsis apicola*, showing that this acid also has the L-configuration. Most naturally occurring long-chain hydroxy acids, however, have the D-configuration.

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The hydroxy fatty acids, 17-hydroxyoctadecanoic acid and 13-hydroxydocosanoic acid, have been isolated from extracellular sophorosides produced by the yeasts *Torulopsis apicola* (1) and *Candida bogoriensis* (2) respectively. Because the methyl esters of both hydroxy acids were dextrorotatory, even though the specific rotation of the C_{22} ester was very small, both were provisionally assigned the L-configuration. However, other long-chain hydroxy acids from plants and microorganisms all have the D-configuration: 12-D-hydroxyoctadecanoic acid is obtained by hydrogenation of ricinoleic acid from castor oil (3), 9-D-hydroxyoctadecanoic acid by hydrogenation of the hydroxy acid of *Strophanthus* seed oil (4, 5), and a hydroxy acid from *Coriaria nepalensis* seed oil yields 13-D-hydroxyoctadecanoic acid on hydrogenation (6). These conclusions have been extended by optical rotatory dispersion studies (7). The 10-hydroxyoctadecanoic acid, produced microbiologically from oleic acid, also has the D-configuration (5).

In view of these results it seemed advisable to confirm the configuration of the hydroxy acids from the yeasts. This was done by synthesis, by chain extension of both methyl 13-L- and 13-D-hydroxydocosanoates from 9-D-hydroxyoctadecanoate, the configuration of which is firmly established (4, 5, 7), and by converting 17-hydroxyoctadecanoic acid to 2-D-octadecanol. Chain extension of hydroxy acids of known configuration has been used previously to establish the configuration of new hydroxy acids (3, 4, 8).

Methyl 9-D-hydroxyoctadecanoate was obtained from hydrogenated oil of *Dimorphotheca aurantiaca* (9, 10). The specific rotation in methanol solution is shown in Table I and is very similar to that reported previously (5). It was more convenient, however, to record the rotation in chloroform solution since it was nearly twice as large and also because methyl 13-hydroxydocosanoate was very poorly soluble in methanol.

The 9-acetoxy acid was required for the next step, but acetylation of the hydroxy acid always gave the anhydride (cf. 11) which could not be hydrolyzed to the desired compound in reasonable yield. However, partial hydrolysis of the acetoxy methyl ester with one molar equivalent of sodium hydroxide gave the acetoxy acid. Anodic coupling of 9-D-acetoxyoctadecanoic acid with methyl hydrogen adipate gave, after deacetylation, methyl 13-D-hydroxydocosanoate which had a specific rotation opposite to that of the ester from the glycoside of *C. bogoriensis* (Table I). Also, admixture of the two esters gave the racemic ester which had been previously synthesized (2).

Next 9-L-hydroxyoctadecanoic acid was prepared from the *p*-toluenesulfonate of methyl 9-D-hydroxyoctadecanoate by treatment with sodium acetate. This method was described previously by Schroepfer and Bloch (5), but the intermediate tosylate was not characterized. The specific rotation of the methyl 9-L-hydroxyoctadecanoate (Table I) indicated that very little racemization had occurred during inversion, whereas Schroepfer and Bloch estimated that their product had an optical purity of 89%. Coupling of 9-L-acetoxyoctadecanoic acid with methyl hydrogen adipate gave methyl 13-L-hydroxydocosanoate indistinguishable from the natural ester. The specific rotation is shown in Table I.

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TABLE I

Specific rotations of methyl 9-hydroxyoctadecanoates and 13-hydroxydocosanoates (±0.05°) at 25°

	Compound					
	9-D-Hydroxyoctadecanoate		9-L-Hydroxy-octadecanoate	13-D-Hydroxy-docosanoate	13-L-Hydroxy-docosanoate (Synthetic)	13-L-Hydroxy-docosanoate (Natural)
Wave-length (mμ)	Methanol (*c*, 11.1)	Chloroform (*c*, 10.4)	Chloroform (*c*, 11.3)	Chloroform (*c*, 10.1)	Chloroform (*c*, 8.3)	Chloroform (*c*, 9.3)
589	−0.22	−0.40	+0.37	−0.10	+0.11	+0.10
546	−0.24	−0.43	+0.50	−0.09	+0.14	+0.13
436	−0.38	−0.75	+0.80	−0.14	+0.20	+0.23
365	−0.58	−1.16	+1.22	−0.23	+0.27	+0.33

In assigning the configuration of 17-hydroxyoctadecanoic acid it was assumed that the ester group at the end of the chain would have little effect on the specific rotation and that it could be regarded as a 2-octadecanol (1) and would have the D-configuration since all dextrorotatory 2-alcohols have the D-configuration (12–14). The rules of nomenclature, however, require that the 17-hydroxy ester be named as an L-hydroxy compound.

Since the ester group might conceivably have had an effect on the rotation, the 17-hydroxy ester was converted to the 2-octadecanol. Also, 2-D-octadecanol has been previously isolated from the wax of tubercle bacteria (15). 17-Acetoxyoctadecanoic acid was prepared from the acetoxy ester and electrolyzed with acetic acid to give 2-D-octadecanol on hydrolysis. The specific rotations are shown in Table II; there is clearly very little difference between that of the 2-alcohol and that of the parent 17-hydroxy ester, so that the latter can be safely assigned the L-configuration. The considerably smaller, but still positive, rotation of the acetoxy ester is similar to the rotations of the acetates of homologous alcohols of shorter chain length (12).

The fact that hydroxy acids from yeast lipids have the opposite configuration to almost all of the others from natural sources may have some bearing on the biosynthesis of these compounds. 13-L-Hydroxyoctadecanoic acid has been prepared by reduction of the hydroperoxide obtained by the action of lipoxidase on linoleic acid (16). It seems unlikely, however, that dienoic acids would be involved in the biosynthesis of the yeast hydroxy acids. It is particularly unlikely in the case of 17-hydroxyoctadecanoic acid since unsaturated acids are always hydroxylated by *Torulopsis* at a position remote from the double bond (17).

Experimental

Specific rotations were measured at 25° in a 1-dm cell using a Perkin–Elmer model 141 Polarimeter. Nuclear magnetic resonance (n.m.r.) spectra were measured with carbon tetrachloride as solvent, using a Varian HA-100 spectrometer. Chemical shifts are in parts per million (p.p.m.) from tetramethylsilane (internal standard). Gas–liquid chromatography (g.l.c.) was carried out as described previously (18).

TABLE II

Specific rotations of methyl 17-L-hydroxyoctadecanoate and derived compounds in chloroform (±0.04 to ±0.06)

	Compound			
Wave-length (mμ)	Methyl 17-L-hydroxy-octadecanoate (*c*, 4.8)	Methyl 17-L-acetoxy-octadecanoate (*c*, 6.0)	17-L-Acetoxy-octadecanoic acid (*c*, 3.4)	2-D-Octadecanol (*c*, 4.2)
589	+3.6	+0.85	+1.02	+4.46
546	+4.3	+1.13	+0.91	+5.11
436	+6.9	+1.17	+0.85	+8.32
365	+10.6	+1.93	—	+12.56

Methyl 9-D-Hydroxyoctadecanoate

Oil of *Dimorphotheca auriantica* was kindly supplied by Dr. Glenn Fuller of the United States Department of Agriculture, Albany, California. The oil (60 g) was hydrogenated in glacial acetic acid using 10% palladium on charcoal as catalyst (10). Methyl esters (56 g) were obtained by refluxing the hydrogenated oil with 4% methanolic hydrogen chloride. Two crystallizations of the esters from hexane gave methyl 9-D-hydroxyoctadecanoate (16.7 g), m.p. 52.0–52.5° (lit. (7) gives 51.5–52.8°). Examination of the mother liquors by g.l.c. before and after acetylation (18) indicated that the oxygenated esters remaining in the oil consisted mainly of an oxo ester, probably methyl 9-oxooctadecanoate. The formation of oxo esters during hydrogenation of this and related compounds has been reported previously (10).

9-D-Acetoxyoctadecanoic Acid

The 9-hydroxy ester (4.8 g) was acetylated with acetic anhydride and the resulting acetoxy ester was distilled; yield (4.6 g); b.p. 145–155°/0.2 mm. The acetoxy ester (4.6 g) was allowed to stand for 24 h at room temperature in a mixture of aqueous sodium hydroxide (0.1 *N*, 129 ml) and acetone (300 ml) and then refluxed for 4 h. Most of the acetone was taken off, the solution acidified, and the product extracted with chloroform. Crystallization from hexane gave 9-D-acetoxyoctadecanoic acid (3.4 g), m.p. 34.5–35.5°. Nuclear magnetic resonance: CH_3, 0.88; CH_2, 1.28 (shoulder 1.32, cf. (19)); acetoxyl 1.96; α-CH_2, 2.29; H-9, 4.75 (multiplet).

Anal. Calcd. for $C_{20}H_{38}O_4$: C, 70.13; H, 11.18. Found: C, 70.31; H, 11.24.

Methyl 13-D-Hydroxydocosanoate

The 9-acetoxy acid (4.0 g) and methyl hydrogen adipate (4.3 g) were electrolyzed in a mixture of 0.022 *N* methanolic sodium methoxide (16 ml) and methanol (8 ml) until the solution was alkaline. The apparatus and conditions were those used by Greaves *et al.* (20) in their method B1. The solution was acidified with acetic acid, the methanol taken off, and the crude product refluxed with 4% methanolic hydrogen chloride. The reaction mixture was poured into water and the deacetylated product (5.8 g) was extracted with ether. Crystallization from methanol (50 ml) at 25° gave a white solid (1.4 g), m.p. 102–103° (probably 10,25-dihydroxytetratriacontane). After concentrating the filtrate to 25 ml and cooling to 0°, crude 13-hydroxydocosanoate (2.4 g) was obtained. This product was recrystallized from methanol and gave the ester (1.1 g), m.p. 65–66°. The ester was saponified and the acid obtained crystallized from acetone giving 13-hydroxydocosanoic acid (0.65 g), m.p. 85–86°. This acid was converted to the methyl ester with diazomethane and the ester crystallized from methanol to give pure methyl 13-D-hydroxydocosanoate (0.35 g), m.p. 69.5–70°.

Anal. Calcd. for $C_{23}H_{46}O_3$: C, 74.54; H, 12.51. Found: C, 74.60; H, 12.35.

A mixture of equal weights of the above D-ester and the ester isolated from *C. bogoriensis* (m.p. 70–70.5°) had m.p. 62.5–63°. After one crystallization from methanol this material had m.p. 62.5–63.5°. Racemic methyl 13-hydroxydocosanoate was previously found to have m.p. 63–63.5° (2). The infrared spectra (KBr disk) of the D-ester and the naturally occurring ester were indistinguishable. The spectra of the racemate obtained by mixing the two isomers and that obtained by synthesis (2) were also indistinguishable from each other, but differed from the spectra of the optically active isomers in the regions 1150–1225 and 1325–1375 cm^{-1}.

Methyl 9-L-Hydroxyoctadecanoate

A solution of methyl 9-D-hydroxyoctadecanoate (9.0 g) in dry pyridine (500 ml) was cooled to −15° and a solution of recrystallized *p*-toluenesulfonyl chloride (25 g) in pyridine (200 ml), also at −15°, was added. The mixture was kept at −15° for one week and at 0° for a further week. Water (250 ml) was cooled to +2° and added to the reaction mixture; after 4 h more water (1500 ml) was added and the product extracted with ether; the extract was washed 10 times with water and dried over sodium sulfate. The product obtained after removal of the ether was crystallized from hexane to give the *p*-toluenesulfonate of methyl 9-D-hydroxyoctadecanoate (9.1 g). The m.p. was 32° and $[\alpha]_D$ +1.35°, $[\alpha]_{546}$ +1.66°, $[\alpha]_{436}$ +2.93°, $[\alpha]_{365}$ +4.98° (*c*, 11.4 in chloroform).

Nuclear magnetic resonance: terminal CH_3, 0.88; CH_2, 1.25; α-CH_2, 2.20; CH_3 on aromatic ring, 2.44; OCH_3, 3.60; H-9, 4.46; aromatic protons, 7.26, 7.72 (doublets $J = 8$ c.p.s.).

Anal. Calcd. for $C_{26}H_{44}O_5S$: C, 66.68; H, 9.47. Found: C, 66.39; H, 9.32.

A solution of the *p*-toluenesulfonate (8.0 g) in acetic acid (120 ml) containing anhydrous sodium acetate (8.0 g) was heated at 60° for 18 h and then refluxed for 4 h. Acetic acid was taken off and the residue deacetylated with 4% methanolic hydrogen chloride. The crude product was chromatographed on silicic acid (Bio-Sil A, 100 g) when unsaturated by-products were eluted with hexane–ether (92:8). Elution with hexane–acetone (95:5) gave methyl 9-L-hydroxyoctadecanoate (3 g), m.p. 52–53°.

Anal. Calcd. for $C_{19}H_{38}O_3$: C, 72.56; H, 12.18. Found: C, 72.27; H, 11.97.

Methyl 13-L-Hydroxydocosanoate

Methyl 9-L-hydroxyoctadecanoate (3.0 g) was converted to the acetoxy acid (2.8 g) and electrolyzed with methyl hydrogen adipate (5.0 g) and the reaction mixture worked up as described in the preparation of methyl 13-D-hydroxydocosanoate. After purification methyl 13-L-hydroxydocosanoate (0.30 g) was obtained. The m.p. was 69–70° and was not depressed by admixture with an equal weight of the ester from the glycoside of *C. bogoriensis*. The infrared spectra of the synthetic and natural isomers were very similar.

Methyl 17-L-Hydroxyoctadecanoate

Crude esters (400 g) were prepared from the sophoroside as previously described (1) and crystallized three times from acetone (10% solution, charcoal); yield 95 g; m.p. 54.5–55.5°.

Methyl 17-L-Acetoxyoctadecanoate

The above hydroxy ester (10.5 g) was acetylated with acetic anhydride and pyridine at 100° for 2 h. After removal of the reagents the product was distilled, b.p./0.25 mm 168–172°, to give the acetate (11.1 g). A portion (2.1 g) was crystallized from hexane giving acetoxy ester (1.4 g) as large leaflets with m.p. 35–36°.

Anal. Calcd. for $C_{21}H_{40}O_4$: C, 70.74; H, 11.31. Found: C, 70.54; H, 11.09.

17-L-Acetoxyoctadecanoic Acid

Acetoxy ester (9.0 g) was hydrolyzed with 0.1 *N* aqueous sodium hydroxide (252 ml) in acetone (500 ml) and the product worked up as described in the preparation of 9-D-acetoxyoctadecanoic acid. Crystallization of the crude product from hexane first gave material (1.3 g) which appeared to be hydroxy acid and then the desired acetoxy acid (6.1 g), m.p. 53–54°.

Nuclear magnetic resonance: CH_3 (doublet), 1.15; CH_2, 1.25; acetoxyl, 1.93; α-CH_2, 2.28; H-17 (multiplet), 4.77.

Anal. Calcd. for $C_{20}H_{38}O_4$: C, 70.13; H, 11.18. Found: C, 70.31; H, 11.11.

2-D-Octadecanol

17-Acetoxyoctadecanoic acid (5.0 g) and acetic acid (5.1 g) were electrolyzed in a mixture of 0.022 *N* methanolic sodium methoxide solution (40 ml) and methanol (10 ml) for 5 h when the solution was alkaline. After working up as before the crude product was treated with warm methanol (25 ml) and the solution filtered from insoluble material (probably long chain diol). The product (1.2 g) crystallized at 10°. Recrystallization from ethyl acetate gave the pure alcohol (0.9 g); m.p. 54–55° (lit. (15) gives m.p. 56° and $[\alpha]_D^{25}$ +5.7°).

Nuclear magnetic resonance: terminal CH_3's, 0.88 (triplet) and 1.10 (doublet); CH_2, 1.26; H-2, 3.64 (multiplet).

Anal. Calcd. for: $C_{18}H_{38}O$: C, 79.87; H, 13.98. Found: C, 79.92; H, 14.16.

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1. P. A. J. Gorin, J. F. T. Spencer, and A. P. Tulloch. Can. J. Chem. **39**, 846 (1961).
2. A. P. Tulloch, J. F. T. Spencer, and M. H. Deinema. Can. J. Chem. **46**, 345 (1968).
3. K. Serck-Hanssen. Chem. Ind. London, 1554 (1958).
4. C. D. Baker and F. D. Gunstone. J. Chem. Soc. 759 (1963).
5. G. J. Schroepfer and K. Bloch. J. Biol. Chem. **240**, 54 (1965).
6. W. H. Tallent, J. Harris, I. A. Wolff, and R. E. Lundin. Tetrahedron Letters, 4329 (1966).
7. T. H. Applewhite, R. G. Binder, and W. Gaffield. J. Org. Chem. **32**, 1173 (1967).
8. T. H. Applewhite. Tetrahedron Letters, 3391 (1965).
9. C. R. Smith, T. L. Wilson, E. H. Melvin, and I. A. Wolff. J. Am. Chem. Soc. **82**, 1417 (1960).
10. R. G. Powell, C. R. Smith, C. A. Glass, and I. A. Wolff. J. Org. Chem. **30**, 610 (1965).
11. A. P. Tulloch, A. Hill, and J. F. T. Spencer. Can. J. Chem. **46**, 3337 (1968).
12. R. H. Pickard and J. Kenyon. J. Chem. Soc. **105**, 830 (1914).
13. K. Serck-Hanssen, S. Ställberg-Stenhagen, and E. S. Stenhagen. Arkiv Kemi, **5**, 203 (1953).
14. J. A. Mills and W. Klyne. *In* Progress in stereochemistry. Vol. 1. *Edited by* W. Klyne. Butterworth and Co., London. 1954. p. 205.
15. M. C. Pangborn and R. J. Anderson. J. Am. Chem. Soc. **58**, 10 (1936).
16. M. Hamberg and B. Samuelsson. J. Biol. Chem. **242**, 5329 (1967).
17. A. P. Tulloch, J. F. T. Spencer, and P. A. J. Gorin. Can. J. Chem. **40**, 1326 (1962).
18. A. P. Tulloch. J. Am. Oil Chemists Soc. **41**, 833 (1964).
19. A. P. Tulloch. J. Am. Oil Chemists Soc. **43**, 670 (1966).
20. W. S. Greaves, R. P. Linstead, B. R. Shephard, S. L. S. Thomas, and B. C. L. Weedon. J. Chem. Soc. 3326 (1950).