ERYTHRO AND THREO-1,2,3-OCTADECANETRIOLS

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Abstract—Erythro- and threo-1,2,3-octadecanetriols have been prepared by the lithium aluminum hydride reduction of the appropriate 2,3-dihydroxy carboxylic acids. A novel method is given for the quantitative separation of long-chain 2-hydroxyalkanoic acids from 2-alkenoic acids through copper chelate formation. The Woodward *cis* hydroxylation method with one equivalent of water was successfully applied to α,β -unsaturated acids. The configurations of dihydroxy acids and triols are discussed as well as the relations between their melting points.

THE stereochemistry of some long-chain compounds with vicinal functional groups is of particular interest to lipid chemists. This has resulted in extensive examination of configurational relationships e.g. between 9, 10- or 2,3-dihydroxyoctadecanoic acids.^{1,2} The constitution and configuration of sphingosine has been successfully determined in recent years.³ In addition to carbohydrates, there is an ever increasing number of straight-chain polyhydroxy compounds isolated from natural sources.^{4,5} Because of the similarity with compounds from brain hydrolysates, our first aim was to prepare sterically determined long-chain terminal alkanetriols.

In the chemical literature there are many examples of the preparation or attempted preparation of stereochemically pure compounds with more than two vicinal functional groups. The oldest is perhaps "dihydrosphingosol" (m.p. 54–55°) obtained by Levene and West⁶ from dihydrosphingosine sulfate and sodium nitrite in anhydrous acetic acid. As the formula of natural sphingosine was later corrected from C_{17} to $C_{18}H_{37}NO_2^7$, "dihydrosphingosol" is at least a complex mixture of optically active and inactive erythro- and threo-1,2,3-octadecanetriols. Mixtures of shorter 1,2,3-alkanetriols were synthesized by Delaby,⁸ by Wiemann and Gardan,⁹ and by Herault,¹⁰ and others. Ulagay¹¹ prepared 1,2,3-alkanetriols with 10 to 16 carbon atoms in a straight chain from the appropriate 2-alkenoic acids and potassium permanganate with subsequent reduction of the carboxylic group by lithium aluminum hydride in the overall yield of 1–2 per cent. The same author ascribes to these products the erythro configuration as the most probable. Since the Knoevenagel method of preparing

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- ² G. S. Myers, J. Amer. Chem. Soc. 74, 1390 (1952).
- ⁸ For reviews covering this field see: H. E. Carter et al., Canad. J. Biochem. Physiol. 34, 320 (1956); Federat. Proc. 16, 817 (1957).
- ⁴ E. Seoane, I. Ribas and G. Fandino, Chem. & Ind. 490 (1957).
- ^b E. R. H. Jones and J. S. Stephenson, J. Chem. Soc. 2197 (1959).
- ^e P. A. Levene and C. J. West, J. Biol. Chem. 24, 67 (1916).
- ⁷ E. Klenk, Z. Physiol. Chem. (Hoppe-Seyler's) 185, 169 (1929); Chem. Abstr. 24, 859 (1930).
- ⁸ R. Delaby, C.R. Acad. Sci. Paris 175, 1152 (1922); Chem. Abstr. 17, 537 (1923).
- ⁹ J. Wiemann and J. Gardan, Bull. Soc. Chim. Fr. 433 and 999 (1958).
- ¹⁰ V. Herault, C.R. Acad. Sci. Paris 252, 751 (1961).
- ¹¹ S. Ulagay, Rev. Fac. Sci. univ. Istanbul 22, 28 (1957); Chem. Abstr. 51, 15403a (1957).

2-alkenoic acids gives invariably the *trans* unsaturation, and since the permanganate hydroxylation is known to proceed exclusively by *cis* addition, this assumption would be hardly justified.

In our investigations, *trans*-2-octadecenoic acid (III) was prepared from octadecanoic acid (I) via 2-bromooctadecanoic acid (II). Since this type of dehydrohalogenation proceeds exclusively by a *trans* elimination mechanism (coplanar four-center transition state^{12,13}), the reaction product contains no *cis* unsaturated acid. We have vainly attempted to eliminate the hydrogen bromide by heating the bromo acid with quinoline, which was shown to be useful for 2-methyl substituted long-chain carboxylic acids.¹⁴ The unsaturated acid was obtained from the reaction with alkali but was always contaminated with 2-hydroxyoctadecanoic acid (IV), as the result of concurrent substitution at the C-2 atom. Myers¹⁵ separated the acids by fractional crystallization from ether due to the lower solubility of the hydroxy acid. This phase of purifying the unsaturated acid is essential because it would be very difficult to separate subsequently mono- from dihydroxy acids.



It was shown earlier that hydroxy acids could form chelates with heavy metals,¹⁶ and the patent literature describes chelates of aldonic acids.¹⁷ There is one recent report¹⁸ on the copper complex of 2-hydroxyoctadecanoic acid. It was surprisingly almost colorless, differing from the copper derivatives of unsubstituted long-chain acids which are "deep blue precipitates" under the same conditions. These precipitates were obtained in neutral methanolic solution of cupric acetate in which copper salts of these acids were likely to be formed. We have found that from the same solution, but slightly acidified with acetic acid, only 2-hydroxyoctadecanoic acid was precipitated by cupric acetate leaving in solution saturated acids (octadecanoic and hexadecanoic), unsaturated acids (2-octadecenoic), and even hydroxy acids (erythroand threo-9,10-dihydroxyoctadecanoic) where the intramolecular complex formation is sterically unfavorable. As under these conditions the salt formation is almost certainly suppressed, the only product is a pale blue precipitate, for which the chelate structure V, by analogy with copper derivatives of amino acids, can be presumed. The practical significance of this chelate formation is the simple and quantitative separation of 2-octadecenoic acid (m.p. 59°) from 2-hydroxyoctadecanoic acid in one operation. The characteristic I.R. absorption bands of the thus purified unsaturated

- ¹⁶ N. S. Radin, J. R. Brown and F. B. Lavin, J. Biol. Chem. 219, 977 (1956).
- ¹⁷ A. G. Holstein, U.S. Pat., 2943100; Chem. Abstr. 54, 24431 h (1960).
- ¹⁸ M. M. Rapport, V. P. Skipski and C. C. Sweeley, J. Lipid. Research 2, 148 (1961).

¹⁸ D. H. R. Barton and E. Miller, J. Amer. Chem. Soc. 72, 1066 (1950).

¹⁹ M. L. Dhar, E. D. Hughes, C. K. Ingold, A. M. M. Mandour, G. A. Maw and L. I. Woolf, J. Chem. Soc. 2117 (1948).

¹⁴ J. Cason, N. L. Allinger and C. F. Allen, J. Org. Chem. 18, 857 (1953).

¹⁵ G. S. Myers, J. Amer. Chem. Soc. 73, 2100 (1951).

acid at about 1700 cm⁻¹ (C=O stretching), 1650 cm⁻¹ (C=C stretching), 1300 and 930 cm⁻¹ (COOH), and 980 cm⁻¹ (deformation of C—H on *trans* C=C) are in accordance with those reported previously for the *trans*-2-octadecenoic acid.¹⁹ The product shows absorption bands neither at 3500 cm⁻¹ (O—H stretching) nor at 1140, 1110 and 1090 cm⁻¹ which are typical for 2-hydroxyoctadecanoic acid.



The hydroxy acid can be recovered by shaking the chelate with aqueous hydrochloric acid giving the product m.p. 91°. Its identity with 2-hydroxy octadecanoic acid was further confirmed by lithium aluminum hydride reduction to 1,2-octadecanediol (m.p. 81°) followed by the preparation of the isopropylidene derivative, for which characteristic I.R. absorption bands are reported to occur at 1053 and 880 cm^{-1,20}

Organic peracids and halogens with silver acetate were found to be stereospecific hydroxylating agents, because their addition to the double bond proceeds exclusively in the *trans* and *cis* manner, respectively. Therefore, the erythro diol is expected to result from *trans* addition to the *trans* unsaturated compound, and the threo diol from *cis* addition to the same compound.

Threo-2,3-dihydroxyoctadecanoic acid (VI) m.p. 125° was prepared from *trans*-2-octadecenoic acid by the Woodward *cis* hydroxylation method in 29 per cent yield, using the equivalent quantity of water. The yield was somewhat higher (38 per cent if the amount of water, normally present in glacial acetic acid (about 3 per cent), was reduced by adding acetic anhydride to the reaction mixture. The product could be purified by crystallization or via copper chelate. Esterification and subsequent reduction with lithium aluminum hydride gave threo-1,2,3-octadecanetriol (VII) m.p. 94°. As far as we are aware, this is the first application of Woodward's procedure to an α,β -unsaturated long-chain acid and the first unambiguous synthesis of a sterically defined long-chain 1,2,3-alkanetriol.



The other diastereoisomeric pair was prepared from the unsaturated acid using peracetic acid as hydroxylating agent. The success of this reaction depends on the

 ¹⁹ R. G. Sinclair, A. F. McKay, G. S. Myers and R. N. Jones, J. Amer. Chem. Soc. 74, 2578 (1952).
²⁰ D. Ginsburg, J. Amer. Chem. Soc. 75, 5746 (1953).

concentration of peracid formed *in situ*. In a too dilute solution even 90 per cent hydrogen peroxide gives no dihydroxy acid, but with less acetic acid yields up to 33 per cent were usual. Erythro-2,3-dihydroxyoctadecanoic acid (VIII) m.p. 106° thus obtained was first esterified and then reduced by lithium aluminum hydride to erythro-1,2,3-octadecanetriol (IX), m.p. 102° . Erythro-2,3-dihydroxy octadecanoic acid was not the sole product from *trans*-2-octadecenoic acid using the Woodward hydroxy-lation method under anhydrous conditions.²¹ Although the solid reagents were carefully dried and the acetic acid was strictly anhydrous, the product of this reaction, with no water subsequently added, was approximately an equal mixture of erythro-and threo-2,3-dihydroxyoctadecanoic acids, as seen from their m.p.s and I.R. spectra.



The I.R. spectra of 2,3-dihydroxy acids and 1,2,3-triols are shown in Figs. 1 and 2. The most striking feature of these spectra is their nonidentity, which offers a good means for differentiating such structurally related compounds. The difference in the wavelength of C=O stretching absorption of 2,3-dihydroxy acids (1752 cm⁻¹ for the threo and 1692 cm⁻¹ for the erythro acid) was pointed out earlier.²² The spectra of copper chelates of 2-hydroxy- and 2,3-dihydroxyoctadecanoic acids are themselves different as well as different from the parent acids. The carbonyl stretching absorption bands are shifted to lower wavelengths (1600 cm⁻¹ for the copper chelate of the threo acid, 1630 cm⁻¹ for the erythro compound). Absent is the broad carboxylic absorption near 930 cm⁻¹.

Chemists still hesitate using prefixes "erythro" and "threo" for 2,3-disubstituted carboxylic acids. One reason lies perhaps in the fact that *cis* hydroxylation of the *trans* unsaturated acid gives the product melting at 126° (presumably with the threo configuration), whereas the dihydroxy acid from *trans* hydroxylation (presumably with the erythro configuration) melts at 106° . Otherwise, there are many examples where it is just the erythro diastereoisomer which has a higher m.p. This cannot be explained as yet, but the reduction of 2,3-dihydroxyoctadecanoic acids to 1,2,3-octadecanetriols "reestablishes the rule" (the erythro compound melting at 102° , the threo at 94°) thus showing that this anomaly of 2,3-dihydroxy carboxylic acids may be due to the specific intramolecular hydrogen bonding between the carboxylic and hydroxy groups in these molecules. Interaction of this kind is, of course, absent in those cases where the hydroxy substituents are far enough from the carboxylic group e.g. in 6,7- or 9,10-dihydroxyalkanoic acids, being thus unsuitable for cyclization to favorable five or six-membered hydrogen bonded rings.

³¹ S. Winstein and R. E. Buckles, J. Amer. Chem. Soc. 64, 2780 (1942).

²² B. Palameta and M. Proštenik, Croat. Chem. Acta 32, 177 (1960).







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EXPERIMENTAL

All m.ps. were determined on "Culatti" apparatus and are uncorrected. I.R. spectra were recorded on the Perkin-Elmer "Infracord", M 137, except that of 2,3-dihydroxyoctadecanoic acids for which spectrophotometer M 221 was used.

trans-2-Octadecenoic acid (III)

This acid was prepared by a modification of Myers' procedure¹⁶ from octadecanoic acid.

To the fused octadecanoic acid (446 g; 1.58 mole) and red phosphorus (18 g) on the water bath (80°) dry bromine (200 ml) was added dropwise with stirring in the course of 7 hr. Heating was continued for an additional 22 hr. The excess of bromine was expelled under red. press., and the residue poured into cold water. After standing overnight, the solid was filtered off by suction, taken up with ether, washed with sodium sulfite solution, then with water, and finally dried (Na₂SO₄). The solvent was evaporated giving the crude 2-bromooctadecanoic acid, which was used in the subsequent reaction without purification. The bromo acid was treated with finely powdered potassium iodide (420 g) in 95% ethanol (3 1.). After 6 hr refluxing, potassium hydroxide (300 g) was added and the mixture refluxed for another 4 hr. The bulk of ethanol was removed by distillation and the remainder treated with conc hydrochloric acid (650 ml) in water (61.). The product was filtered, extracted with ether, and the organic layer washed with water. After evaporation of the solvents, the residue was dissolved in 95% ethanol (500 ml), acidified with acetic acid (30 ml) and heated under reflux on a water bath. Solid cupric acetate was added in small portions until no more dissolution occurred. The bulk of solvent was removed under red. press., the residue treated with ether and washed with dil. acetic acid to remove the excess of cupric acetate. The copper chelate remained suspended in the organic layer. This was filtered by suction, washed thoroughly with ether and dried to give 61.5 g (6%) of the chelate. trans-2-Octadecenoic acid (160 g m.p. 58°) was isolated by evaporating the ethereal solution and crystallizing from 800 ml of a 1 : 1 mixture ethanol-light petroleum (b.p. 45-60°). The second crop (45 g m.p. 54-55°) was obtained by concentrating the filtrate. Overall yield of trans-2-octadecenoic acid was 46% (based on octadecanoic acid).

2-Hydroxyoctadecanoic acid was easily recovered from the copper chelate by shaking it with aqueous hydrochloric acid (1 : 1) and ether extraction. The crude product (m.p. 88–90°) yielded after one crystallization from ether colorless leaflets m.p. 91°.

From the purified 2-hydroxy acid (1 g) copper chelate was made as above in quantitative yield, m.p. (dec) 215°. (Found: C, 65·47; H, 10·72; Cu, 9·96; C₃₆H₇₀CuO₆ requires: C, 65·27; H, 10·65; Cu, 9·59%). I.R. absorption bands at: 3200, 1640, 1160, 1070, 915, 890, 805 and 790 cm⁻¹.

1,2-Octadecanediol

Pure 2-hydroxyoctadecanoic acid was esterified by refluxing for 5 hr in anhydrous ethanol with catalytic amounts of conc sulfuric acid. The solution was extracted with ether, and ethyl 2-hydroxyoctadecanoate obtained as a colorless powder m.p. 62° .

A dry ethereal solution of the crude ester was added dropwise to a stirred suspension of lithium aluminum hydride in anhydrous ether at 20°. Stirring was continued for 30 min and the excess of reagent decomposed. The ether extraction yielded 1,2-octadecanediol as a colorless powder, which, after one crystallization from ethanol melted at 81° (Lit. m.p. $79\cdot0-79\cdot5^\circ$).³⁸ I.R. absorption bands at: 3420, 3300, 1150, 1110, 1080, 995, 970, 940, 880, and 855 cm⁻¹.

The isopropylidene derivative was made according to Niemann and Wagner.³³ The product m.p. 31° showed strong I.R. absorption bands at 1250, 1220, 1160, 1065 and 860 cm⁻¹.

Threo-2,3-dihydroxyoctadecanoic acid (VI)²⁴

A. The mixture of *trans*-2-octadecenoic acid (5.6 g; 0.02 mole), dry silver acetate (7.4 g; 0.044 mole), iodine (5.0 g; 0.02 mole) and glacial acetic acid (d. 1.055-1.058; 130 ml) was mechanically shaken for 30 min. Then water (0.4 ml; 0.022 mole) in glacial acetic acid (20 ml) was added to the yellow suspension, and the mixture refluxed for 1 hr on an oil bath (130-140°). The cooled reaction mixture was filtered, the bulk of the acetic acid evaporated under red. press. the residue extracted

²⁸ C. Niemann and C. D. Wagner, J. Org. Chem. 7, 227 (1942).

24 F. D. Gunstone and L. J. Morris, J. Chem. Soc. 487 (1957).

with ether and the organic layer washed with dil. hydrochloric acid to remove the silver salts. After filtration, the organic layer was washed with water, dried (Na_2SO_4) and evaporated. Potassium hydroxide (8·4 g) in 1 : 1 water-ethanol mixture (50 ml) was added to the viscous oil and refluxed on a boiling water bath for 1 hr. The alkaline solution was acidified and extracted with ether. After cooling the dried ethereal solution to 0°, threo-2,3-dihydroxyoctadecanoic acid separated as colorless crystals (1·4 g), m.p. 125°. Cooling the filtrate to -20° the unreacted *trans*-2-octadecenoic acid (1·2 g; m.p. 58°) was recovered. The yield of dihydroxy acid was 29%, based on the consumed unsaturated acid.

Heating threo-2,3-dihydroxyoctadecanoic acid (1·1 g) with ethanolic solution of cupric acetate slightly acidified with acetic acid and treating as before yielded copper chelate (0·9 g) as a pale blue powder m.p. 205° (dec). (Found: C, 62·01; H, 10·05; Cu, 8·91. $C_{39}H_{70}CuO_8$ requires: C, 62·26; H, 10·16; Cu, 9·15%) I.R. absorption bands at : 3350, 1600, 1140, 1120, 1090, 1075, 870, 845 and 830 cm⁻¹.

B. The mixture of *trans*-2-octadecenoic acid (5.6 g; 0.02 mole), silver acetate (7.4 g; 0.044 mole), iodine (5.0 g; 0.02 mole), acetic anhydride (10 ml) and glacial acetic acid (d. 1055–1.058; 130 ml) was mechanically shaken for 30 min, after which the yellow suspension was refluxed for 1 hr on an oil bath (130–140°), followed by treatment as described for threo-2,3-dihydroxyoctadecanoic acid. From the final cooled ethereal solution colorless crystals (1.4 g; m.p. 125°) separated. The ether was then evaporated, the residue treated with light petroleum (b.p. 45–60°) giving further amounts of the product (0.2 g; m.p. 115°). Both m.ps. and I.R. spectra confirmed the threo configuration of these products. From the concentrated final filtrate at 0° *trans*-2-octadecenoic acid (1.9 g; m.p. 59°) was recovered thus increasing the yield of 2,3-dihydroxy acid to 38%).

C. This procedure was similar to B except that the solvent was made anhydrous by refluxing glacial acetic acid ($d \cdot 055 - 1 \cdot 058$) with half its volume of acetic anhydride and finally distilling at 118°. Acetic anhydride (10 ml) was added as above, and the whole system was carefully protected against moisture. On cooling, the final ethereal solution yielded a white precipitate (0.2 g; m.p. 123 $\cdot 5$ -124°) the I.R. spectrum of which confirmed the threo configuration. After evaporating the solvent, the residue was treated with light petroleum (b.p. 45-60°) giving a further crop of white precipitate (0.3 g; m.p. near 107°) with I.R. spectrum typical for the erythro dihydroxy acid contaminated with very small amounts of the threo compound.

Threo-1,2,3-octadecanetriol (VII)

Threo-2,3-dihydroxyoctadecanoic acid (1.0 g) was esterified with anhydrous ethanol and a few drops of conc sulfuric acid. The solution of the ester in anhydrous ether was added dropwise to the ethereal suspension of lithium aluminum hydride. After the usual treatment, the dried solution in ether was cooled to 0°. The crude product was recrystallized from methanol several times to give analytically pure threo-1,2,3-octadecanetriol (0.2 g) as a colorless powder m.p. 94°. (Found; C, 71.49; H, 12.87: C₁₈H₃₈O₃ requires: C, 71.47; H, 12.66%).

Erythro-2,3-dihydroxyoctadecanoic acid (VIII)

To *trans*-2-octadecenoic acid (2.8 g; 0.01 mole) in glacial acetic acid (10 ml) with conc sulfuric acid (0.5 ml) on an oil bath (90–100°) 90% hydrogen peroxide (5 ml) was added in 10 portions during 5 hr with continuous stirring. The clear solution was treated with water and extracted with ether. The organic solvents were evaporated, the oily residue hydrolysed with potassium hydroxide (4.2 g) in a 1 : 1 mixture water-ethanol (25 ml) on a boiling water bath for 2 hr. The cooled solution was poured into dil. hydrochloric acid, ether was added, the organic layer separated and washed thoroughly with water. By chilling the dried ether solution to 0° erythro-2,3-dihydroxyoctadecanoic acid (0.7 g) precipitated as a colorless powder m.p. 106°. The filtrate after standing at -10° overnight yielded the unreacted *trans*-2-octadecenoic acid (0.9 g; m.p. 55°). The yield of dihydroxy acid was 33%, based on the consumed unsaturated acid.

By heating the dihydroxy acid in ethanolic solution of cupric acetate with a few drops of acetic acid, the copper chelate was obtained as a pale blue precipitate m.p. 195° (dec). I.R. absorption bands at: 3600, 1630, 1110, 1080, 1030, 890, 875 and 840 cm⁻¹.

Erythro-1,2,3-octadecanetriol (XI)

Erythro-2,3-dihydroxyoctadecanoic acid (0.5 g) was suspended in anhydrous ether (30 ml) and added dropwise with stirring in the course of 15 min to an excess of lithium aluminum hydride in

anhydrous ether at 20°. Stirring was continued with refluxing for 30 min. After the usual treatment, erythro-1,2,3-octadecanetriol separated from the ice-cold ether solution as colorless crystals m.p. 95–98°. It was recrystallized several times from methanol at -10° to give a sample for analysis (0.05 g) m.p. 102°. (Found: C, 71.16; H, 12.46; C₁₈H₃₈O₃ requires: C, 71.47; H, 12.66%).

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