A 40-g. aliquot of the less polar gummy fractions (total wt. 240 g. from 35 lb. of plant) was dissolved in benzene–petroleum ether (1:2) and rechromatographed over 600 g. of alumina. Benzene–petroleum ether and benzene eluted oils. Benzene—chloroform (3:1, 2:1, 1:2) eluted semisolid material which was triturated with ether–petroleum ether, filtered, and recrystallized from ether–petroleum ether–acetone, yielding 4.0 g. of asperilin, m.p. 150–151°, undepressed on admixture with an authentic sample, infrared spectra superimposable. Chloroform eluted a noncrystallizable gum and chloroform–methanol (19:1) eluted an additional 1.3 g. of ivasperin. Altogether, 35 g. (0.22%) of asperilin and 29 g. (0.18%) of ivasperin were obtained from 35 lb. of plant material.

Acknowledgment.—We wish to thank Professor R. K. Godfrey and Dr. Norlan C. Henderson for plant collections and valuable advice. A grant from the Research Council for the Florida State University is gratefully acknowledged. The n.m.r. spectrometer was purchased with the aid of a grant from the National Science Foundation.

Configurational Studies with 2,3-Dihydroxyoctadecanoic Acids

B. PALAMETA AND N. ZAMBELI

Department of Biochemistry, Institute "Ruder Bošković," Zagreb, Yugoslavia

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The configurations of 2,3-dihydroxyoctadecanoic acids have been proved unambiguously by conversion to 2,3-octadecanediols. The properties of the intermediate cyclic ketals as well as of some other derivatives are compared and discussed. An attempt is made to explain the unusual melting points of long-chain 2,3-dihydroxyalkanoic acids in terms of unusual preferred conformations.

The interrelationship between 2,3-dihydroxyoctadecanoic acids was studied by Myers[1] and was based on Swern's previous work with 9,10-dihydroxyoctadecanoic acids.[2] Using stereospecific methods, Myers could transform the higher melting acid to the lower melting one, but their unusual melting points were probably the reason why he was unable to ascertain which of them had the *erythro* and which the *threo* configuration. In a recent review,[3] it was stated again that the unusual melting points are due to the proximity of the carboxyl group, but no explanation of this effect was given. The problem was, therefore, to determine unambiguously the configurations of 2,3-dihydroxyoctadecanoic acids, and, in addition, to explain some "anomalous" physical properties on the basis of preferred conformations.

The first question was settled by elimination of the bulky carboxyl group which could influence the configuration of the adjacent carbon atom.[4] This was done even though it is known[5] that the attack of a positively charged agent in hydroxylation reactions occurs preferentially on the adjacent carbon atom which is the most electronegative site of the double bond, and that it is preferentially the C-3 atom, the configuration of which might be influenced, and which is electron deficient. In spite of this evidence it seemed desirable to introduce at the end of the molecule a group which by itself would be unable to disturb the normal hydroxylation reaction. For preliminary studies, *trans*-2-octadecenol, prepared by the method of Grob and Jenny,[6] was subjected to the Woodward *cis* hydroxylation method. The product was 1,2,3-octadecanetriol (m.p. 91–94°) identical in all respects with the triol obtained by lithium aluminum hydride reduction of the 2,3-dihydroxyoctadecanoic acid, melting at 127°.[7] Thus it was confirmed that the *trans* double bond is hydroxylated in the same manner when vicinal to a primary hydroxyl or to a carboxyl group.

The most rigorous proof for the *threo* and *erythro* configurations of 2,3-dihydroxyoctadecanoic acids (I),[8] melting at 127 and 108°, respectively, was based on Swern's theoretical considerations for 9,10-dihydroxyoctadecanoic acids[9] and consisted in comparing steric relationships between hydroxyl groups of the two isomeric 2,3-octadecanediols (VII). The configurations of such vicinal diols are known with certainty as a result of lead tetraacetate cleavage experiments made by Criegee, *et al.*[10] Each acid (I) was esterified separately, and the free hydroxyl groups of these esters (II) were protected in the form of cyclic ketals. The ketal esters (III) were then reduced by lithium aluminum hydride to give ketal alcohols (IV), treated with *p*-toluenesulfonyl chloride, and the resulting tosyl esters (V) reduced with lithium aluminum hydride to VI from which the diols (VII) were obtained by acid hydrolysis. (See Scheme I.)

In the most favorable staggered conformation of *erythro*-2,3-octadecanediol (VIII) the hydroxyl substituents are on opposite sides of the axis between the C-2 and C-3 atoms and are, therefore, almost or wholly incapable of intramolecular hydrogen bonding, while *threo*-2,3-octadecanediol (IX), because of the proximity of hydroxyl substituents, allows a higher degree of intramolecular hydrogen bonding in the crystal lattice. Even in very dilute solutions *threo* diols show a greater tendency to form intramolecular hydrogen bonds than *erythro* diols,[11] and the anti-*trans* conformation is less abundant in the *threo* than in the *erythro* derivatives.[12] The diol having the lower melting point (70°) was de-

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[1] G. S. Myers, *J. Am. Chem. Soc.*, **73**, 2100 (1951); **74**, 1390 (1952).

[2] D. Swern, *ibid.*, **70**, 1235 (1948).

[3] H. J. Harwood, *Chem. Rev.*, **62**, 99 (1962).

[4] C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p. 382; W. Lwowski, *Angew. Chem.*, **70**, 490 (1958).

[5] B. M. Lynch and K. H. Pausacker, *J. Chem. Soc.*, 1525 (1955); F. D. Gunstone and L. J. Morris, *ibid.*, 487 (1957); R. B. Woodward and F. V. Brutcher, Jr., *J. Am. Chem. Soc.*, **80**, 209 (1958).

[6] C. A. Grob and E. F. Jenny, *Helv. Chim. Acta*, **36**, 1936 (1953).

[7] B. Palameta and M. Proštenik, *Tetrahedron*, in press.

[8] Each formula shown is considered to represent both enantiomers of the *erythro* (*cis*) series. The same reaction sequence applies to the *threo* (*trans*) series.

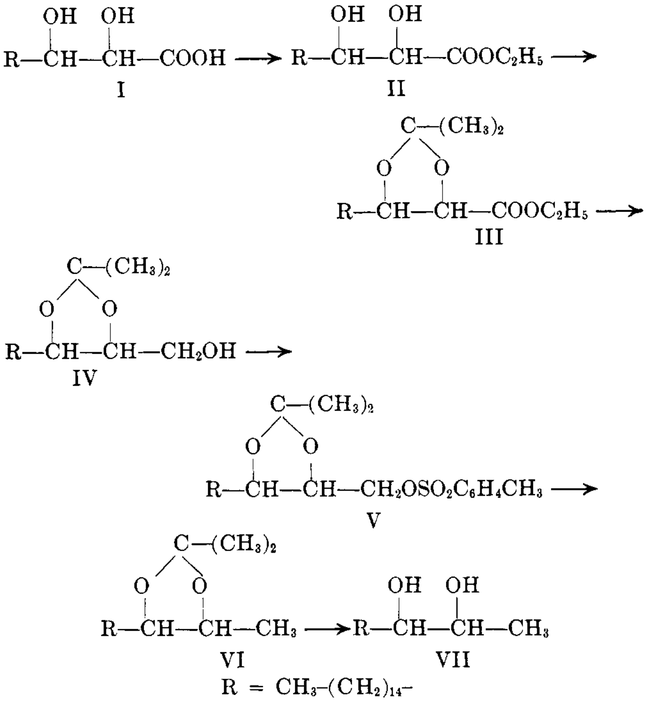
[9] D. Swern, L. P. Witnauer, and H. B. Knight, *J. Am. Chem. Soc.*, **74**, 1655 (1952).

[10] R. Criegee, E. Höger, G. Huber, P. Kruck, F. Marktscheffel, and H. Schellenberger, *Ann.*, **599**, 81 (1956).

[11] L. P. Kuhn, *J. Am. Chem. Soc.*, **80**, 5950 (1958).

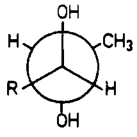
[12] G. Chiudoglu, R. de Groote, W. Masschelein, and M. H. van Risseghem, *Bull. soc. chim. Belges*, **70**, 342 (1961); *Chem. Abstr.*, **56**, 8185 (1962).

Scheme I

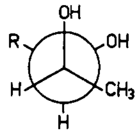


R = CH_3-$(CH_2)_{14}$-

rived from the higher melting *threo*-2,3-dihydroxyoctadecanoic acid. Therefore, all compounds in this series would have the *threo* configuration. By analogous considerations, the higher melting diol (m.p. 80–81°), derived from the lower melting 2,3-dihydroxyoctadecanoic acid, must belong to the *erythro* series, and its hydroxyls are not sterically hindered but are internally associated as in 1,2-octadecanediol (m.p. 79–80°). The infrared spectra of the 2,3-octadecanediols are shown in Fig. 1.



VIII



IX

R = CH_3-$(CH_2)_{14}$-

The second question was to explain some experimental facts in terms of the established configurations of 2,3-dihydroxyoctadecanoic acids and to suggest preferred conformations in the crystal state.

In our opinion, the "reversed" melting points of 2,3-dihydroxyoctadecanoic acids, as compared with 9,10-dihydroxy acids, might have their explanation in reversed conformations; namely, the influence of the adjacent carboxyl groups might be such as to drive the hydroxyl substituents into particular positions (X for the *erythro*, XI for the *threo* acid). This would have a profound effect on physical properties of the acids. This would be in accordance with the observation that the *threo* acid undergoes cyclization with acetone at a slower rate than the *erythro* acid owing to the unfavorable conformation in the initial state. The same would apply to the formation of a cyclic sulfite, although in this case the attack of thionyl chloride on carboxyl group probably precedes the attack on hydroxyl groups. The different conformations also might explain why the *threo* acid affords the diacetoxy derivative even under strenuous conditions, while with the *erythro* acid intermolecular condensation probably takes place.

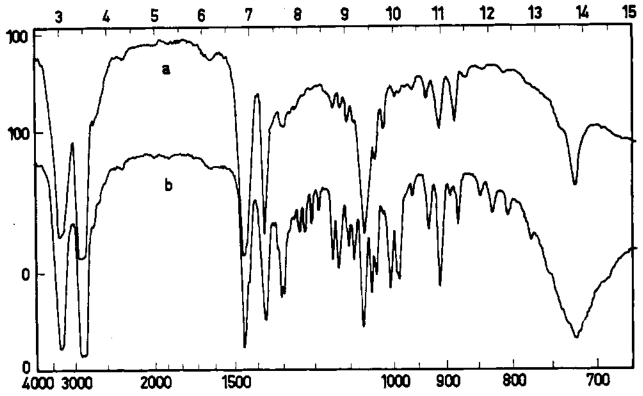
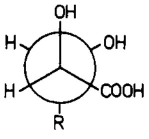
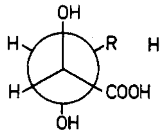


Fig. 1.—Infrared spectra in Nujol: (a) *erythro*-2,3-octadecanediol and (b) *threo*-2,3-octadecanediol.

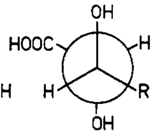
However, several facts cannot be reconciled with the proposed conformations. Why should these acids find their energy minimum in more crowded dispositions of functional groups (X and XI) and not in others (*e.g.*, XII and XIII) where the approach of substituents capable of hydrogen bonding simultaneously relieves the steric repulsions between the other two groups? Obviously, the tendency to form hydrogen bonds overcomes the steric hindrance in eclipsed conformations of these dihydroxy acids.



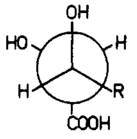
X



XI



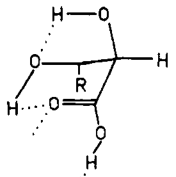
XII



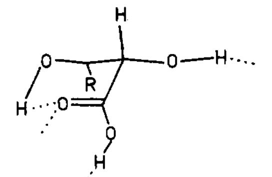
XIII

R = CH_3-$(CH_2)_{14}$-

Therefore, if we accept the above-mentioned conformations (X and XI) as most favorable and if we show the hydrogen-bonded oxygen functions of the Newman projection formulas in the form of a distorted six-membered ring, it can be seen that the *erythro* acid dimer (XIV) forms preferentially intramolecular hydrogen bonds, whereas the C-2 hydroxyl group of the *threo* acid dimer (XV), unsuitably located towards both carboxyl and C-3 hydroxyl functions, also forms intermolecular hydrogen bonds. This is reflected in the lower melting point, powdery appearance, and higher solubility in organic solvents of the *erythro* acid, as compared with the *threo* acid which has higher melting point, lower solubility, and scaly appearance.



XIV



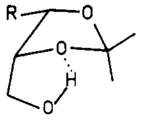
XV

R = CH_3-$(CH_2)_{14}$-

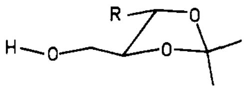
These assumptions are, of course, not without criticism. The identity of hydrogen bonds between the carboxyl and the C-3 hydroxyl groups in both proposed conformations does not explain the differences in the wave lengths of infrared carbonyl absorptions (the band of the *erythro* acid at 1695 cm.$^{-1}$, of the *threo* acid at 1745 cm.$^{-1}$). Jones and Sandorfy[13] ascribe these differences in 2- and 3-hydroxyoctadecanoic acids to exo- and endocyclic carbonyl functions in five- and six-membered hydrogen-bonded rings. In our case, this has not been attempted. The situation seems to be more complicated; in amides of 2,3-dihydroxyoctadecanoic acids it is just the *erythro* diastereoisomer for which the carbonyl band occurs at higher wave length, and in the esters both compounds have the carbonyl band at 1725 cm.$^{-1}$.

The *cis* and *trans* cyclic ketal esters (III) were prepared in boiling anhydrous acetone using anhydrous cupric sulfate as dehydrating agent, a shorter reflux time being necessary for the *erythro* dihydroxy ester than for the *threo* ester. In their experiments with 9,10,12-trihydroxyoctadecanoic acids, using anhydrous hydrogen chloride as condensing agent, Esafov and Torgashina[14] came to the opposite conclusion and were able to obtain quantitative cyclization of the *threo* acid, while the *erythro* acid remained completely unaffected under the same conditions.

The most striking and unexplainable feature of these compounds is the difference of 30° between the melting points of the *cis* and *trans* tosyl esters of ketals (V). In going from the diastereoisomeric dimeric cyclic ketal acids with similar melting points, to the cyclic ketal alcohols one observes the expected melting point decrease which is greater for the presumably intramolecularly hydrogen-bonded *cis* ketal alcohol (XVI) than for the presumably intermolecularly hydrogen-bonded *trans* ketal alcohol (XVII). The melting point of the *trans* cyclic tosyl ester remains practically constant, the loss of intermolecular hydrogen bonds being compensated by the enlargement of the molecule. However, the melting point of the *cis* compound is too high compared with the *trans* isomer, so that, in our opinion, other unknown factors may operate in this case. This is even more surprising in light of Haresnape's calculations[15] for the 1,2-dimethylcyclopentanes where the *cis* compound has higher internal energy content than the *trans* isomer.



XVI



XVII

R = CH_3-$(CH_2)_{14}$-

The infrared absorption bands in the 1300–800-cm.$^{-1}$ region of diastereoisomeric cyclic ketals are shown in Table I.[16] Their wave lengths are quite similar, and on the basis of these bands alone it is not possible to distinguish the *cis* from the *trans* cyclic compounds. Partial assignments of frequencies can be made by analogy with the results on substituted dioxolanes[17]: the bands at 1260–1240 and 1230–1190 cm.$^{-1}$ can be attributed to *gem*-methyl symmetrical and antisymmetrical rocking vibrations, bands at 1050–1030 and 1190–1170 cm.$^{-1}$ to symmetrical and antisymmetrical ring-stretching vibrations, and bands at 1115–1090 cm.$^{-1}$ to a skeletal stretch.

The reported data concerning long-chain 2,3-alkanediols are very scarce and lacking adequate configurational interpretation. One 2,3-dodecanediol (m.p. 68–69°) has been prepared by Lüttringhaus, *et al.*,[18] in the perbenzoic acid hydroxylation of the mixture of 1- and 2-dodecenes. From a similar starting material 2,3-alkanediols have been prepared by Asahara and Ito[19] and were readily distinguishable from the 1,2-diols by their higher melting points. We could not prove this statement, but, in comparison with the *erythro* and *threo*-9,10-octadecanediols,[20] it is significant that moving of the two vicinal hydroxyl substituents to the middle of the hydrocarbon chain raises considerably the melting point of the *erythro* compound (2,3-diol 80–81°, 9,10-diol 130°) and has only minor effect on the *threo* diols (2,3-diol 70°, 9,10-diol 77–78°).

Of the other derivatives, cyclic sulfites have been prepared from the dihydroxy acids (I) and thionyl chloride. Their infrared spectra reveal the presence of S=O stretching frequencies near 1220 cm.$^{-1}$,[21] although the derivative of the *threo* acid could not be purified to give the correct elemental analysis. Both dihydroxy acids can be recovered from these cyclic sulfites with unchanged original configurations by acid hydrolysis. The formation of cyclic sulfites also can probably explain the apparent unreactivity of hydroxyl groups of 9,10-dihydroxyoctadecanoic acids during the reaction with thionyl chloride.[22] The dihydroxy acids (I) also have been treated with acetic anhydride in pyridine. From the *threo* acid only the normal diacetyl derivative could be isolated, and with the *erythro* acid at 80° intermolecular dehydration probably took place giving predominantly a product melting at 95–96°. The normal diacetylated acid remains impure in the residual oil which is the sole product if the acetylation is carried out at 20°.

Experimental[23]

2,3-Dihydroxyoctadecanoic Acids (I).—*erythro* and *threo*-2,3-dihydroxyoctadecanoic acids were prepared from *trans*-2-octadecenoic acid by peracid *trans* hydroxylation and Woodward *cis* hydroxylation methods in 33 and 38% yields, respectively, and, after purification *via* copper chelate, melted at 108 and 127°, respectively.[7]

Ethyl 2,3-Dihydroxyoctadecanoates (II). *erythro* **Isomer.**—*erythro*-2,3-Dihydroxyoctadecanoic acid (10.8 g.) was esterified by refluxing for 5 hr. with 65 ml. of anhydrous ethanol and 1.5 ml. of concentrated sulfuric acid. The bulk of the solvent was evaporated; the residue was extracted with ether, washed with water, with sodium hydrogen carbonate solution, and again with

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[13] R. N. Jones and C. Sandorfy, "Chemical Applications of Spectroscopy," A. Weissberger, Ed., Interscience, New York, N. Y., 1956, p. 491.

[14] V. I. Esafov and Z. I. Torgashina, *J. Gen. Chem. USSR*, **8**, 1594 (1938); *Chem. Abstr.*, **33**, 4583 (1939); *cf.* also P. A. Artamonov, *Zh. Obshch. Khim.*, **27**, 2726 (1957).

[15] J. N. Haresnape, *Chem. Ind.* (London), 1091 (1953).

[16] The infrared data were obtained with a Perkin-Elmer Infracord 137 double beam spectrophotometer with sodium chloride prism. Measurements were carried out in Nujol mull or in liquid films.

[17] S. A. Barker, E. J. Bourne, R. M. Pinkard, and D. H. Whiffen, *J. Chem. Soc.*, 807 (1959).

[18] A. Lüttringhaus, G. Wagner-Sääf, E. Sucker, and G. Borth, *Ann.*, **577**, 51 (1947).

[19] T. Asahara and T. Ito, *J. Soc. Org. Syn. Chem.* (Japan), **9**, No. 7, 19 (1951); *Chem. Abstr.*, **47**, 6855 (1953).

[20] A. N. Wrigley, F. D. Smith, and A. J. Stirton, *J. Org. Chem.*, **24**, 1793 (1959).

[21] H. H. Szmant and W. Emerson, *J. Am. Chem. Soc.*, **78**, 454 (1956); P. B. D. de la Mare, D. J. Millen, J. G. Pritchard, and D. Watson, *J. Chem. Soc.*, 1813 (1956); D. Ben-Ishay, *J. Org. Chem.*, **23**, 2013 (1958).

[22] J. A. Lamberton, *Australian J. Chem.*, **9**, 528 (1956).

[23] All melting points were determined on "Culatti" apparatus and are uncorrected. Chromatographic separations were carried out on Fluka alumina, Type 507c, neutral, activity stage 1, according to Brockmann. The petroleum ether refers to the fraction boiling at 45–60°. Microanalyses were carried out by Mrs. J. Zake and Mrs. E. Galogaža.

TABLE I

INFRARED ABSORPTION BANDS OF CYCLIC KETALS

a	b	c	d	e	f	g	h	i		k	l
1260 (s)[m]	1260 (s)		1270 (vs)		1270 (m)						
1250 (s)		1240 (vs)		1240 (vs)	1255 (s)	1250 (s)	1250 (vs)	1250 (s)	1250 (m)	1250 (s)	1240 (vs)
		1230 (vs)			1235 (vs)			1230 (s)			1230 (s)
1220 (s)			1220 (vs)		1220 (vs)	1220 (vs)	1220 (vs)		1220 (m)	1220 (vs)	
	1210 (vs)			1215 (vs)	1210 (vs)						
1190 (vs)	1190 (vs)							1190 (vs)	1195 (vs)		
		1175 (m)	1175 (s)	1170 (s)	1175 (m)	1175 (m)	1170 (s)	1180 (vs)	1185 (vs)		
			1140 (m)	1130 (w)	1140 (w)			1130 (m)			
		1110 (s)		1115 (vs)				1115 (s)			
1100 (vs)	1100 (vs)	1090 (vs)	1090 (vs)	1090 (vs)	1105 (vs)	1100 (m)	1100 (vs)	1105 (s)	1105 (s)	1090 (vs)	1100 (vs)
		1055 (m)	1045 (w)	1045 (m)		1050 (vs)	1050 (vs)	1045 (vs)			
1040 (m)	1035 (m)	1030 (m)	1020 (w)	1030 (s)				1020 (m)	1020 (w)		
		1010 (w)	1005 (m)	1010 (m)	1000 (w)		1000 (m)				1010 (m)
990 (w)			995 (w)	980 (w)	990 (w)			990 (vs)	990 (vs)		
			955 (w)	955 (w)	950 (w)			950 (w)		945 (w)	
			930 (w)		930 (w)	925 (w)	925 (m)	925 (w)	930 (w)		935 (m)
				915 (s)	920 (w)		905 (m)	905 (w)			
		885 (m)	895 (m)	885 (s)	890 (m)	880 (m)	880 (m)	890 (m)			
875 (m)		870 (w)	875 (m)		870 (s)						
	860 (m)		850 (w)			850 (m)	860 (s)	865 (s)	860 (w)	865 (m)	865 (m)
				840 (w)	845 (m)		845 (m)	845 (vs)	835 (s)		
	810 (m)	810 (m)	820 (m)	815 (w)	815 (m)		815 (w)	820 (vs)	820 (s)		

[a] Ethyl *cis*-2,2-dimethyl-5-*n*-pentadecyl-1,3-dioxolane-4-carboxylate. [b] Ethyl *trans*-2,2-dimethyl-5-*n*-pentadecyl-1,3-dioxolane-4-carboxylate. [c] Amide of *cis*-2,2-dimethyl-5-*n*-pentadecyl-1,3-dioxolane-4-carboxylic acid. [d] Amide of *trans*-2,2-dimethyl-5-*n*-pentadecyl-1,3-dioxolane-4-carboxylic acid. [e] *cis*-2,2-Dimethyl-5-*n*-pentadecyl-1,3-dioxolane-4-carboxylic acid. [f] *trans*-2,2-Dimethyl-5-*n*-pentadecyl-1,3-dioxolane-4-carboxylic acid. [g] *cis*-2,2-Dimethyl-4-hydroxymethyl-5-*n*-pentadecyl-1,3-dioxolane. [h] *trans*-2,2-Dimethyl-4-hydroxymethyl-5-*n*-pentadecyl-1,3-dioxolane. [i] *cis*-2,2-Dimethyl-4-hydroxymethyl-5-*n*-pentadecyl-1,3-dioxolane *p*-toluenesulfonate. [j] *trans*-2,2-Dimethyl-4-hydroxymethyl-5-*n*-pentadecyl-1,3-dioxolane *p*-toluenesulfonate. [k] *cis*-5-*n*-Pentadecyl-2,2,4-trimethyl-1,3-dioxolane. [l] *trans*-5-*n*-Pentadecyl-2,2,4-trimethyl-1,3-dioxolane. [m] vs = very strong, s = strong, m = medium, w = weak.

water, and dried over anhydrous sodium sulfate. The solvent was evaporated, and the residue was crystallized from petroleum ether to give 10.4 g. (89%) of colorless product melting at 68–69°. Recrystallization from petroleum ether raised the melting point to 69°; main infrared absorption bands at 3430, 3270, 1725, 1240, 1220, 1205, 1130, 1080, 1050, 1035, 1020, and 960 cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{40}O_4$ (344.52): C, 69.72; H, 11.70. Found: C, 69.47; H, 11.39.

threo **Isomer.**—The *threo* ester was prepared by the same procedure from 10.5 g. of *threo*-2,3-dihydroxyoctadecanoic acid. The yield was 10.1 g. (88%) of the crude product which, after two crystallizations from acetonitrile, melted at 71–72°. Infrared spectrum shows absorptions at 3360, 1725, 1310, 1290, 1275, 1255, 1235, 1215, 1135, 1115, 1090, 1080, 1030, and 870 cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{40}O_4$ (344.52): C, 69.72; H, 11.70. Found: C, 70.03; H, 11.45.

Ethyl 2,2-Dimethyl-5-*n*-pentadecyl-1,3-dioxolane-4-carboxylates (III). *cis* **Isomer.**—The crude ethyl *erythro*-2,3-dihydroxyoctadecanoate (2.4 g.) was dissolved in 25 ml. of anhydrous acetone (dried over calcium sulfate), and 4 g. of anhydrous cupric sulfate was added. After refluxing for 6 hr., the acetone solution was filtered off, and acetone was evaporated under reduced pressure. The slightly colored oily residue was dissolved in petroleum ether and chromatographed over alumina. Elution with benzene gave 1.5 g. (56%) of colorless oil.

trans **Isomer.**—Under exactly the same conditions as above, 2.4 g. of ethyl *threo*-2,3-dihydroxyoctadecanoate afforded, after chromatography over alumina, 0.8 g. (30%) of the pure product.

Better yields (*cis* ester 91%, *trans* ester 80%) were obtained by prolonging the refluxing time to 10 hr. for the *erythro*, and to 20 hr. for the *threo* ester.

2,2-Dimethyl-5-*n*-pentadecyl-1,3-dioxolane-4-carboxylic Acids. *cis* **Isomer.**—Ethyl *cis*-2,2-dimethyl-5-*n*-pentadecyl-1,3-dioxolane-4-carboxylate (3.7 g.) was refluxed for 3 hr. with a solution of 5.6 g. of potassium hydroxide in 100 ml. of ethanol. The bulk of solvent was removed under reduced pressure; the residue was poured into dilute hydrochloric acid and extracted with ether. The organic layer was washed with water and dried over anhydrous sodium sulfate; ether was evaporated. The residue was dissolved in petroleum ether, cooled, filtered from traces of 2,3-dihydroxyoctadecanoic acid, and evaporated to dryness leaving 3.2 g. (94%) of the product melting at 54.5–56°. Recrystallization from acetonitrile yielded a colorless product melting at 56–58°.

Anal. Calcd. for $C_{21}H_{40}O_4$ (356.53): C, 70.74; H, 11.31. Found: C, 70.40; H, 11.25.

trans **Isomer.**—The same procedure was repeated with 7.2 g. of ethyl *trans*-2,2-dimethyl-5-*n*-pentadecyl-1,3-dioxolane-4-carboxylate giving 90% of the crude product, m.p. 48–50°. Two recrystallizations from acetonitrile yielded the product melting at 53–54°.

Anal. Calcd. for $C_{21}H_{40}O_4$ (356.53): C, 70.74; H, 11.31. Found: C, 70.98; H, 11.11.

From both *cis* and *trans* acids the original 2,3-dihydroxyoctadecanoic acids have been obtained by acid hydrolysis, as seen by comparing their melting points and infrared spectra with authentic samples.

2,2-Dimethyl-4-hydroxymethyl-5-*n*-pentadecyl-1,3-dioxolanes (IV). *cis* **Isomer.**—A solution of 9.3 g. of ethyl *cis*-2,2-dimethyl-5-*n*-pentadecyl-1,3-dioxolane-4-carboxylate in 50 ml. of anhydrous ether was added dropwise to a suspension of 1.5 g. of lithium aluminum hydride in 50 ml. of anhydrous ether, and the whole refluxed for 30 min. Water was added cautiously and was followed by 10% aqueous potassium hydroxide until two layers were formed. The ethereal layer was filtered off and evaporated under reduced pressure leaving 7.2 g. (87%) of an oily residue. Further purification was effected by dissolving the oil in acetonitrile and keeping in a refrigerator overnight. The colorless crystals melted at 30°.

Anal. Calcd. for $C_{21}H_{42}O_3$ (342.55): C, 73.63; H, 12.36. Found: C, 74.08; H, 12.14.

trans **Isomer.**—The reduction of ethyl *trans*-2,2-dimethyl-5-*n*-pentadecyl-1,3-dioxolane-4-carboxylate (4.0 g.) was carried out in the same manner as described for the *cis* cyclic ester yielding 2.85 g. (80%) of the crude product, m.p. 37–40°. Several recrystallizations from acetonitrile raised the melting point to 44–45°.

Anal. Calcd. for $C_{21}H_{42}O_3$ (342.55): C, 73.63; H, 12.36. Found: C, 74.01; H, 12.57.

2,2-Dimethyl-4-hydroxymethyl-5-*n*-pentadecyl-1,3-dioxolane *p*-Toluenesulfonates (V).[24] *cis* **Isomer.**—To a solution of 7.2 g. of *cis*-2,2-dimethyl-4-hydroxymethyl-5-*n*-pentadecyl-1,3-dioxolane in 20 ml. of anhydrous pyridine was added 8 g. of *p*-toluenesulfonyl chloride in several portions with stirring and keeping the temperature below 10°. Stirring was continued for additional 3 hr., while the temperature was not allowed to raise above 20°. The thick paste was poured into ice-cooled dilute hydrochloric acid. The precipitate was collected, thoroughly washed with water, dissolved in ether, and again washed with water. Evaporation under reduced pressure left 8.6 g. of the crude product which was crystallized from petroleum ether giving 7.25 g. (69%) of colorless powder melting at 63–65.5°. A sample was recrystallized from petroleum ether and melted at 66°.

Anal. Calcd. for $C_{28}H_{48}O_5S$ (496.76): C, 67.70; H, 9.74. Found: C, 67.31; H, 9.47.

trans **Isomer.**—The preparation of *trans* cyclic *p*-toluenesulfonate was performed in the same manner as for the corresponding *cis* derivative. The crude product from 2.8 g. of *trans*-2,2-dimethyl-4-hydroxymethyl-5-*n*-pentadecyl-1,3-dioxolane was crystallized from ethanol to yield 2.7 g. (66%) of colorless powder melting near 35°. Recrystallizations from acetonitrile and then from ethanol raised the melting point to 36–37°.

Anal. Calcd. for $C_{28}H_{48}O_5S$ (496.76): C, 67.70; H, 9.74. Found: C, 68.09; H, 9.43.

5-*n*-Pentadecyl-2,2,4-trimethyl-1,3-dioxolanes (VI). *cis* **Isomer.**—A solution of 2.0 g. of *cis*-2,2-dimethyl-4-hydroxymethyl-5-*n*-pentadecyl-1,3-dioxolane *p*-toluenesulfonate in 30 ml. of anhydrous ether was added dropwise with stirring and cooling to the suspension of 1.0 g. of lithium aluminum hydride in 30 ml. of anhydrous ether. Well protected from moisture, the suspension was refluxed with stirring for 10 hr. Water was added cautiously to the reaction mixture and was followed by 10% aqueous potassium hydroxide. The organic layer was washed with water, dried over anhydrous sodium sulfate, and evaporated under reduced pressure. There was obtained 1.2 g. (92%) of colorless oil without *p*-toluenesulfonyl absorption bands in the infrared spectrum.

trans **Isomer.**—The above reduction was repeated with 2.3 g. of *trans*-2,2-dimethyl-4-hydroxymethyl-5-*n*-pentadecyl-1,3-dioxolane *p*-toluenesulfonate, but the reaction mixture was refluxed for 12 hr. The crude oil had no *p*-toluenesulfonyl absorption bands in the infrared spectrum.

2,3-Octadecanediols (VII). *erythro* **Isomer.**—The crude *cis*-5-*n*-pentadecyl-2,2,4-trimethyl-1,3-dioxolane (1.0 g.) was refluxed for 8 hr. with 40 ml. of 10% aqueous sulfuric acid in 60 ml. of dioxane. The cooled reaction mixture was poured into water and taken up with ether. The ethereal layer was thoroughly washed with water, dried over anhydrous sodium sulfate, and evaporated under reduced pressure to dryness. The yield of once crystallized product (from acetonitrile) was 0.5 g. (56%), m.p. 79–79.5°. The recrystallized product melted at 80–81°.

Anal. Calcd. for $C_{18}H_{38}O_2$ (286.48): C, 75.46; H, 13.37. Found: C, 75.73; H, 13.27.

threo **Isomer.**—The same procedure was applied to 1.0 g. of *trans*-5-*n*-pentadecyl-2,2,4-trimethyl-1,3-dioxolane. The crude product was crystallized from petroleum ether to give 0.65 g. (74%) of colorless leaflets melting at 69°. Recrystallization from the same solvent yielded the pure product, m.p. 70°.

Anal. Calcd. for $C_{18}H_{38}O_2$ (286.48): C, 75.46; H, 13.37. Found: C, 75.59; H, 13.11.

2,3-Diacetoxyoctadecanoic Acids. *threo* **Isomer.**—The solution of 10 g. of *threo*-2,3-dihydroxyoctadecanoic acid in 10 ml. of acetic anhydride and 25 ml. of anhydrous pyridine was maintained at 80° for 5 hr. The cooled mixture was poured into cold dilute hydrochloric acid and extracted with ether. The ethereal layer was washed with water, dried over anhydrous sodium sulfate, and evaporated under reduced pressure. The oily residue was treated with petroleum ether and left in the refrigerator overnight. There was obtained 6.9 g. (54%) of colorless powder melting at 65–68°. Several recrystallizations from petroleum ether raised the melting point to 71–72°; main infrared absorption bands at 1770–1740 (C=O ester and acid), 1260, 1210 (acetate), 1165, 1120, 1090, 1075, 1045, 1030, 1010, 980, 935, 910, 865, and 705 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{40}O_6$ (400.54); C, 65.97; H, 10.07. Found: C, 66.44; H, 9.97.

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(24) C. S. Marvel and V. C. Sekera, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 366.

erythro **Isomer.**—Under exactly the same conditions, 25.3 g. of *erythro*-2,3-dihydroxyoctadecanoic acid yielded 15.3 g. of crude product. Repeated crystallizations from petroleum ether and acetonitrile gave a sample melting at 95–96°; main infrared absorption bands at 1780, 1720, 1670, 1290, 1210, 1165, 1090, 1010, 940–915, 885, and 760 cm.$^{-1}$.

Anal. Found: C, 70.73; H, 10.31.

One gram of this compound, refluxed for 2 hr. with 1 g. of potassium hydroxide in 10 ml. of water and 10 ml. of ethanol, gave, after the usual treatment, a solid product melting at 75–76°. After several recrystallizations from acetonitrile the melting point remained constant at 76°; infrared absorption bands at 1720, 1290, 1270, 1080, 1050, 1020, and 900 cm.$^{-1}$.

Anal. Found: C, 73.15; H, 11.40.

A solution of 3 g. of *erythro*-2,3-dihydroxyoctadecanoic acid in 3 ml. of acetic anhydride and 7.5 ml. of anhydrous pyridine was kept overnight at 20°. After the treatment as above, a slightly colored oil was obtained which was completely soluble in ice-cold petroleum ether and had infrared absorption bands at 1760 (C=O), 1220 (acetate), 1120, 1075, 1030 (C–O), and 960 (COOH) cm.$^{-1}$, but no satisfactory analysis could be obtained. It has not been possible to induce crystallization of this oil. Alkaline hydrolysis gave high yield of the original *erythro*-2,3-dihydroxyoctadecanoic acid, proved by its melting point and infrared spectrum.

Cyclic Sulfites of 2,3-Dihydroxyoctadecanoic Acids. *cis* **Isomer.**—*erythro*-2,3-Dihydroxyoctadecanoic acid (1 g.) was refluxed for 3 hr. with 10 ml. of thionyl chloride. The excess of thionyl chloride was carefully removed under reduced pressure. The residual dark brown oil was hydrolyzed by shaking with a great excess of cold water. The precipitate was extracted with ether, washed, and dried. The residue, after evaporation of ether, was crystallized from petroleum ether yielding 0.45 g. (39%) of colorless product melting at 96–97°. Recrystallization from petroleum ether containing several drops of ether did not change the melting point. The infrared spectrum showed bands at 1720, 1250, 1220, 1010, 940, 835, 815, and 790 cm.$^{-1}$ and had no absorption bands in the 3600–3400-cm.$^{-1}$ region.

Anal. Calcd. for $C_{18}H_{34}O_5S$ (362.52): C, 59.64; H, 9.46; S, 8.84. Found: C, 59.81; H, 9.44; S, 8.6.

trans **Isomer.**—*threo*-2,3-Dihydroxyoctadecanoic acid was treated with thionyl chloride as above, but after evaporation of ether there remained a semisolid mass from which only dark brown powder, melting at 62–67°, could be separated by acetonitrile. The infrared spectrum showed strong bands at 1770, 1230, and 1040 cm.$^{-1}$, and medium bands at 950, 870, 835, 820, and 790 cm.$^{-1}$.

Alkaline hydrolysis of *cis* and *trans* cyclic sulfites afforded *erythro*- and *threo*-2,3-dihydroxyoctadecanoic acids, respectively, identical in all respects with the original acids.

Amides of 2,3-Dihydroxyoctadecanoic Acids.—Ethyl *erythro*- and *threo*-2,3-dihydroxyoctadecanoates (about 2 g.) were separately dissolved in 10 ml. of anhydrous methanol and mixed with 30 ml. of saturated solution of ammonia in anhydrous methanol. The solutions were maintained at room temperature until the precipitation was complete (1 or 2 days). The precipitates were filtered, washed with ice-cold methanol, and dried. The yield was almost quantitative. The crude *erythro* amide melted at 133–135°, and after crystallization from methanol had m.p. 135–136°.

Anal. Calcd. for $C_{18}H_{37}NO_3$ (315.48): C, 68.52; H, 11.82; N, 4.44. Found: C, 68.78; H, 11.60; N, 4.45.

The crude *threo* amide, m.p. 150–154°, was crystallized from methanol. The analytical sample had m.p. 154°.

Anal. Calcd. for $C_{18}H_{37}NO_3$ (315.48): C, 68.52; H, 11.82; N, 4.44. Found: C, 68.96; H, 11.57; N, 4.35.

Amides of 2,2-Dimethyl-5-*n*-pentadecyl-1,3-dioxolane-4-carboxylic Acids.—These amides have been prepared essentially like amides of 2,3-dihydroxyoctadecanoic acids.

After standing for 4 days in saturated methanolic ammonia, ethyl *trans*-2,2-dimethyl-5-*n*-pentadecyl-1,3-dioxolane-4-carboxylate gave an almost quantitative yield of the *trans* amide, which was recrystallized from ether and melted at 70°.

Anal. Calcd. for $C_{21}H_{41}NO_3$ (355.55): C, 70.94; H, 11.62; N, 3.94. Found: C, 70.94; H, 11.30; N, 4.26.

From ethyl *cis*-2,2-dimethyl-5-*n*-pentadecyl-1,3-dioxolane-4-carboxylate (2 g.) only 1.2 g. (65%) of the product, m.p. 76–77°, was isolated after standing for 5 days at 20°, owing to its higher solubility in methanolic ammonia. A sample for analysis was twice recrystallized from petroleum ether yielding a colorless powder, m.p. 81–82°. Another crop of crystals (0.4 g.) was obtained by saturating the filtrate with ammonia.

Anal. Calcd. for $C_{21}H_{41}NO_3$ (355.55): C, 70.94; H, 11.62. N, 3.94. Found: C, 71.06; H, 11.23; N, 4.01.

Hydroxylation of *trans*-2-Octadecenol.—A mixture of 2.6 g. of crude *trans*-2-octadecenol,[8] 3.7 g. of dry silver acetate, and 2.5 g. of iodine in 65 ml. of glacial acetic acid was mechanically shaken for 1 hr. at 20°. Water (0.2 ml.) and 10 ml. of glacial acetic acid were added, and all were refluxed on an oil bath (130–140°) for 3 hr. The cooled suspension was filtered; the filtrate was evaporated under reduced pressure to remove acetic acid, poured into dilute hydrochloric acid, and extracted with ether. The filtered ethereal solution was evaporated, and the residue was hydrolyzed with 4.2 g. of potassium hydroxide in 25 ml. of 1:1 ethanol–water mixture. The cooled solution was neutralized with dilute hydrochloric acid and extracted with ether. By cooling the organic layer to 0°, 0.6 g. (21%) of a colorless powder was obtained, m.p. 91–94°, identical with an authentic sample of *threo*-1,2,3-octadecanetriol, m.p. 94°.

Stereospecific Syntheses of Long-Chain 1,2,3,4-Alkanetetrols

B. PALAMETA AND N. ZAMBELI

Department of Biochemistry, Institute "Ruder Bošković," Zagreb, Yugoslavia

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The four possible stereochemically pure isomers of long-chain DL-1,2,3,4-alkanetetrols have been synthesized in reactions involving stereospecific additions to the double bond, chain lengthening by one carbon atom, and stereospecific lithium aluminum hydride reductions. Cyclic and dipolar transition state models for lithium aluminum hydride reduction of α-hydroxy ketones are discussed. The postulated configurations of tetrols are correlated and explained with the aid of infrared spectra.

Phytosphingosine is 2-amino-1,3,4-octadecanetriol of D-*ribo* configuration.[1] In an approach to the synthesis of this molecule we have prepared the four possible long-chain DL-1,2,3,4-alkanetetrols. Two of them have been synthesized from *erythro*- and *threo*-2,3-dihydroxyoctadecanoic acids in a reaction of chain lengthening by one carbon atom, while the remaining two have been obtained from 4-hydroxy-*trans*-2-octadecenoic acid.

erythro- and *threo*-2,3-dihydroxyoctadecanoic acids (I) were separately acetylated in order to protect the hydroxyl groups. The difficulties with the *erythro* acid have been avoided by keeping the temperature at 20°.[2] Diacetoxy acids (II) were treated with thionyl chloride, and the resulting acid chlorides (III) with diazomethane gave diazo ketones (IV) having one car-

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