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,[6] 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 "Ruđer Bošković," Zagreb, Yugoslavia

Received August 7, 1963

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-

---

[1] H. E. Carter, W. C. Celmer, W. E. M. Lands, K. L. Mueller, and H. H. Tomizawa, *J. Biol. Chem.*, **206**, 613 (1954); H. E. Carter and H. S. Hendrickson, *Biochemistry*, **2**, 389 (1963).

[2] B. Palameta and N. Zambeli, *J. Org. Chem.*, **29**, 1026 (1964).

bon atom more in the straight chain. The decomposition of the diazo ketones was unsuccessfully attempted with glacial acetic acid and copper powder,[3] since it was not possible to use the resulting dark brown oil in the subsequent step. The trihydroxy ketones (V), probably in a mixture with partially acetylated products, were obtained by refluxing the diazo ketones (IV) with dilute sulfuric acid in dioxane.[4] Reduction with lithium aluminum hydride afforded 1,2,3,4-nonadecanetetrols (VI).

$$\underset{\text{I}}{R{-}CH(OH){-}CH(OH){-}COOH} \longrightarrow \underset{\text{II}}{R{-}CH(OAc){-}CH(OAc){-}COOH} \longrightarrow$$

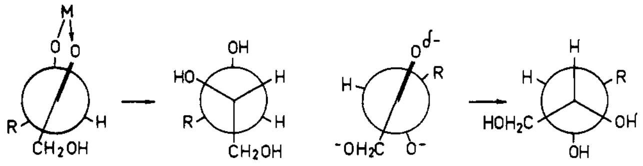
$$\underset{\text{III}}{R{-}CH(OAc){-}CH(OAc){-}COCl} \longrightarrow \underset{\text{IV}}{R{-}CH(OAc){-}CH(OAc){-}CO{-}CHN_2} \longrightarrow$$

$$\underset{\text{V}}{R{-}CH(OH){-}CH(OH){-}CO{-}CH_2OH} \longrightarrow \underset{\text{VI}}{R{-}[CH(OH)]_3{-}CH_2OH}$$

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

The configurational relationships between the hydroxyl substituents on carbon atoms C-3 and C-4 of the products remained unchanged with respect to the original 2,3-dihydroxy acids. However, it was necessary to establish whether the hydroxyl substituent on the newly formed asymmetric center had the *erythro* or *threo* configuration or if there was a mixture of both diastereoisomers in the reaction product. The whole reaction sequence was, therefore, repeated with 2-hydroxyoctadecanoic acid using both copper powder in glacial acetic acid and dilute sulfuric acid to obtain the hydroxy ketone, on which the stereospecificity of lithium aluminum hydride reduction had to be examined. In both cases only *threo*-1,2,3-nonadecanetriol was isolated as seen by comparing the product with 1,2,3-octadecanetriols of known configurations.[5]

This result may seem a little confusing, since a cyclic model (VII) of the transition state[6] is expected to control the stereochemical course of this reaction, because the hydroxyl substituent on the adjacent carbon atom forms a system which is capable of complexing with organometallic reagents.[7] The main product of this reaction should then be *erythro*-1,2,3-nonadecanetriol (VIII). However, if dipolar (IX) or open-chain models are used to depict the stereochemistry of lithium aluminum hydride reduction, *threo*-1,2,3-nonadecanetriol (X) is expected to predominate in the product.



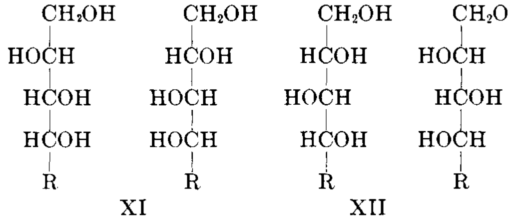
VII VIII IX X

$R = CH_3{-}(CH_2)_{15}{-}$

Here it is necessary to point out several differences between the systems usually employed as models for 1,2-asymmetric induction and ours. It is found that both open-chain and cyclic models predict the same stereochemical outcome only if the hydroxyl group on the adjacent carbon atom is the medium-sized group, phenyl being the largest group.[7] In our case, although methyl has been shown elsewhere to have larger effective bulk than hydroxyl,[8] it is by no means certain that the hydroxyl should flank one side of the carbonyl group. The reagents commonly used in stereochemical studies have been alkyl- and aryllithium compounds and magnesium halides, and in complexing with hydroxyl substituents they do not necessarily have the same steric requirements as lithium aluminum hydride. Even with the assumption that an alkyl group does occupy more space than a hydroxyl, the difference in size is not so great as that between phenyl and hydroxyl and could be overcome, for instance, by repulsions between the two electronegative charges, on carbonyl and secondary hydroxyl groups. By analogy with α-chloro ketones,[9] these repulsions lead finally to anti-*trans* conformation of dipoles in the transition state (IX) allowing a full polarization of the carbonyl group and thus enhancing its reactivity toward nucleophilic agents which approach from the least hindered side, that is, through the C-3 hydrogen atom.[10] *threo*-1,2,3-Nonadecanetriol (X) would, therefore, predominate in the product as predicted by the dipolar model. This may be the explanation of the unusual results on the basis of a cyclic transition state model, which are not surprising if we know that there are disagreements with this model in much less complicated examples.[11]

The same reasoning applies to the fraction in the product which has resisted acid hydrolysis and has retained its acetoxy group (as proved by the infrared spectrum), which, being reduced first by lithium aluminum hydride, becomes an oxygen–metal complex and behaves as described above.

From these considerations it is concluded that DL-*arabino*-[12] (XI) and DL-*xylo*- (XII) 1,2,3,4-nonadecanetetrols have been obtained from *erythro*- and *threo*-2,3-dihydroxyoctadecanoic acids, respectively. Their infrared spectra are shown in Fig. 1. Yields are unspecified in the Experimental section, since only the first crystallized fraction of the product has been isolated and further analyzed in order to avoid possible contamination with another diastereoisomeric pair.



XI XII

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

---

(3) F. Weygand and R. Schmiechen, *Chem. Ber.*, **92**, 535 (1959).

(4) L. Long, Jr., and A. Burger, *J. Org. Chem.*, **6**, 852 (1941); J. H. Burckhalter and J. Sam, *J. Am. Chem. Soc.*, **74**, 187 (1952).

(5) B. Palameta and M. Proštenik, *Tetrahedron*, in press.

(6) D. J. Cram and D. R. Wilson, *J. Am. Chem. Soc.*, **85**, 1245 (1963).

(7) D. J. Cram and K. R. Kopecky, *ibid.*, **81**, 2748 (1959).

(8) S. Winstein and N. J. Holness, *ibid.*, **77**, 5562 (1955).

(9) J. W. Cornforth, R. H. Cornforth, and K. K. Mathews, *J. Chem. Soc.*, 112 (1959).

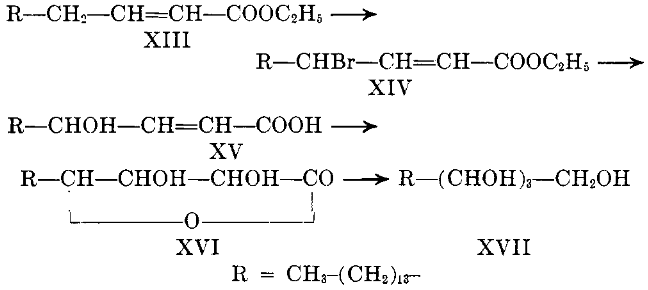
(10) D. J. Cram and F. A. A. Elhafez, *J. Am. Chem. Soc.*, **74**, 5828 (1952).

(11) J. H. Stocker, P. Sidisunthorn, B. M. Benjamin, and C. J. Collins, *ibid.*, **82**, 3913 (1960).

(12) For nomenclature see *J. Org. Chem.*, **28**, 281 (1963).

The other two tetrols, DL-*lyxo*- and DL-*ribo*-octadecanetetrols, were synthesized from 4-hydroxy-*trans*-2-octadecenoic acid (XV) which was obtained from ethyl *trans*-2-octadecenoate (XIII) by allylic bromination and subsequent hydrolysis of the bromo ester (XIV). Peracid hydroxylation of the unsaturated hydroxy acid (XV), in which lactonization was not possible owing to the *trans* double bond, afforded a mixture of two isomeric lactones (XVI), from which the tetrols (XVII) were obtained by lithium aluminum hydride reduction.

The steric course of this reaction is not influenced by 1,2-asymmetric induction of the C-4 hydroxyl group, since the primary attack of the hydroxylating agent occurs on the C-2 carbon atom of the double bond, the inductive effect of the carboxyl group outweighing the attraction by C-4 hydroxyl substituent. The addition to the double bond is completed by a simultaneous attack on the C-3 carbon atom followed by inversion of configuration, but, since the system is not rigid with regard to the C-4 hydroxyl, the entering agent is allowed to approach from both sides, so that both diastereoisomeric pairs are to be expected in the product. They were actually separated by crystallization giving two fractions melting at 98–101 and 120°, respectively, and having essentially dissimilar infrared spectra. It follows, of course, from the preparative method that both isomers have the *erythro* configuration of hydroxyl groups on carbon atoms C-2 and C-3.



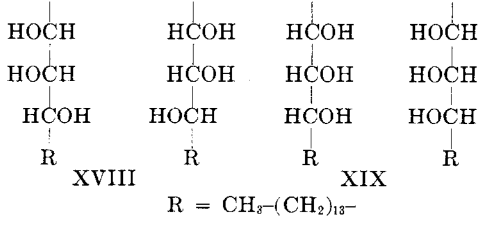
$$\underset{\text{XIII}}{R\text{—}CH_2\text{—}CH{=}CH\text{—}COOC_2H_5} \longrightarrow \underset{\text{XIV}}{R\text{—}CHBr\text{—}CH{=}CH\text{—}COOC_2H_5} \longrightarrow$$

$$\underset{\text{XV}}{R\text{—}CHOH\text{—}CH{=}CH\text{—}COOH} \longrightarrow$$

$$\underset{\text{XVI}}{R\text{—}\underbrace{CH\text{—}CHOH\text{—}CHOH\text{—}CO}_{O}} \longrightarrow \underset{\text{XVII}}{R\text{—}(CHOH)_3\text{—}CH_2OH}$$

$R = CH_3\text{–}(CH_2)_{13}\text{–}$

The configurations of these two tetrols have been assigned on the basis of their melting points and infrared spectra. It is expected that a certain degree of similarity should exist between the spectrum of the DL-*arabino* tetrol (with *threo–erythro* relationship between the hydroxyl groups) and the DL-*lyxo* isomer (with *erythro–threo* relationship).[13] The examination of infrared spectra (Fig. 1) reveals striking similarities between the bands of the DL-*arabino* isomer and the tetrol melting at 120°, to which, therefore, the DL-*lyxo* configuration can be ascribed (XVIII). The remaining tetrol is then DL-*ribo*-1,2,3,4-octadecanetetrol (XIX).



$$\underset{\text{XVIII}}{\begin{array}{cc} CH_2OH & CH_2OH \\ HOCH & HCOH \\ HOCH & HCOH \\ HCOH & HOCH \\ R & R \end{array}} \qquad \underset{\text{XIX}}{\begin{array}{cc} CH_2OH & CH_2OH \\ HCOH & HOCH \\ HCOH & HOCH \\ HCOH & HOCH \\ R & R \end{array}}$$

$R = CH_3\text{–}(CH_2)_{13}\text{–}$

By correlating the melting points of the four tetrols, it can be seen that the *xylo* isomer with hydroxyl groups in the *threo* configurations melts at 133°, the *arabino* and *lyxo* isomers with one *threo* and one *erythro* relationship melt at 120 and 110–114°, respectively, whereas the *ribo* isomer with both hydroxyls *erythro* related melts at 98–101°. This is, without doubt, the consequence of their packing in crystal lattices, which, in turn, depends on the nature of hydrogen bonds between their hydroxyl groups. There is one recent report concerned with hydrogen bonding in a series of monomethyl ethers of 1,2,4-butanetriol,[14] but in long-chain 1,2,3,4-alkanetetrols this should be even more complicated and awaits further studies.

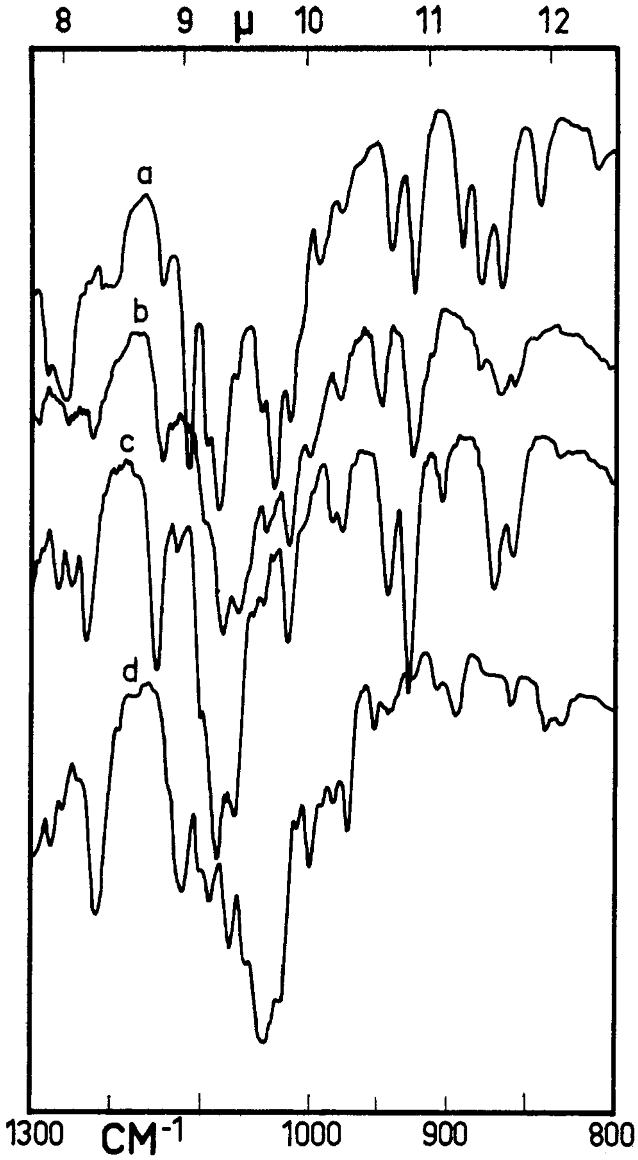


Fig. 1.—Infrared spectra in Nujol: (a) DL-*xylo*-1,2,3,4-nonadecanetetrol; (b) DL-*arabino*-1,2,3,4-nonadecanetetrol; (c) DL-*lyxo*-1,2,3,4-octadecanetetrol; and (d) DL-*ribo*-1,2,3,4-octadecanetetrol.

Experimental[15]

2-Acetoxyoctadecanoic Acid.—2-Hydroxyoctadecanoic acid was obtained as a by-product in the preparation of *trans*-2-octade-

---

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

[14] A. B. Foster, A. H. Haines, and M. Stacey, *ibid.*, **16**, 177 (1961).

[15] The melting points were determined on "Culatti" electrically heated 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.

cenoic acid from 2-bromooctadecanoic acid[16] and, after purification *via* copper chelate,[7] melted at 91°. A solution of 56.5 g. of 2-hydroxyoctadecanoic acid in 140 ml. of anhydrous pyridine and 75 ml. of acetic anhydride was kept at 80° for 3 hr. and was left overnight at 20°. The brown solution was poured into dilute hydrochloric acid, extracted with ether, washed, and dried. The solvent was evaporated, and the residue was crystallized from petroleum ether yielding 56 g. (87%) of colorless product, m.p. 70.5–71.5° (lit.[17] m.p. 70.1–70.3°). From the filtrate, there was obtained 5.8 g. of additional product, m.p. 67–68°.

3-Acetoxy-1-diazo-2-nonadecanone.—2-Acetoxyoctadecanoic acid (56 g.) was refluxed for 4 hr. with 48 ml. of freshly distilled thionyl chloride. After standing overnight at 20°, the solution was refluxed for an additional 4 hr. The excess thionyl chloride was evaporated under reduced pressure, and the remaining traces were removed by repeated evaporations with anhydrous benzene leaving 56.6 g. (96%) of brown oil which solidified and melted at 34–35°. The infrared spectrum showed bands at 1810 (C═O, acid chloride), at 1770 (C═O, acetate), and at 1230 cm.$^{-1}$ (acetate).

The solution of 51.8 g. of 2-acetoxyoctadecanoyl chloride in 120 ml. of anhydrous ether was added dropwise to a stirred and cooled (−20°) solution of diazomethane (prepared from 70 g. of N-nitrosomethylurea) in 700 ml. of ether. The whole reaction mixture was stirred for an additional 30 min. at −20°. The crystals which separated were collected yielding 44 g. (84%) of product, m.p. 73–75°. A portion was crystallized from ethyl acetate for analysis; pale yellow powder, m.p. 76°; infrared absorption bands at 3100, 2120 (N≡N), 1750 (C═O, acetate), 1640 (C═O, conj.), 1340, 1260, 1230 (acetate), 1050 and 1040 (C–O) cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{38}N_2O_3$ (366.53): C, 68.81; H, 10.45; N, 7.64. Found: C, 68.62; H, 10.11; N, 7.84.

Reactions of 3-Acetoxy-1-diazo-2-nonadecanone. (A) With Glacial Acetic Acid and Copper Powder.—The solution of 7 g. of 3-acetoxy-1-diazo-2-nonadecanone in 50 ml. of glacial acetic acid, containing 0.3 g. of copper powder, was cautiously heated on an oil bath. Vigorous evolution of nitrogen began at 90°. The reaction mixture was kept at 100° for an additional 1 hr. and was evaporated to dryness under reduced pressure. The solid residue was crystallized from 100 ml. of 80% ethanol giving 6.8 g. (89%) of pale yellow powder, m.p. 47–48°. After several recrystallizations and after chromatography over alumina (elution with benzene), the product melted at 48–49°, but it was not possible to obtain the correct elemental analysis. The infrared spectrum shows absorption bands at 1770–1750 (C═O, ketone and ester), 1230 (acetate), 1090, 1050, and 1030 cm.$^{-1}$ (C–O).

This 1,3-diacetoxy-2-nonadecanone (1 g.) was reduced with lithium aluminum hydride in the usual manner. Crystallization from ether gave 0.5 g. (63%) of pure *threo*-1,2,3-nonadecanetriol, m.p. 93°. Recrystallization from ethanol gave an analytical sample; infrared absorption bands at 3400, 1150, 1135, 1090, 1060, 1040, 1030, 1020, 910, and 895 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{40}O_3$ (316.51): C, 72.10; H, 12.74. Found: C, 72.49; H, 12.77.

The residual material was examined for *erythro*-1,2,3-nonadecanetriol, but the solid was completely soluble in cold petroleum ether and had a quite different infrared spectrum.

(B) **With Aqueous Sulfuric Acid in Dioxane.**—The diazo ketone (1.0 g.) was dissolved in 30 ml. of dioxane, and 10 ml. of 10% aqueous sulfuric acid was added. The slightly turbid solution was kept at 70–80° until the gas evolution ceased, and then at 90° for 30 min. The clear solution was poured into water and extracted with ether. The ethereal layer was washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness. The residue (m.p. 80–84°) was dissolved in anhydrous ether and reduced with lithium aluminum hydride. Only *threo*-1,2,3-nonadecanetriol could be isolated from the reaction mixture.

It was not possible to obtain *erythro*-1,2,3-nonadecanetriol using sodium and ethanol instead of lithium aluminum hydride.

DL-*xylo*-**1,2,3,4-Nonadecanetetrol (XII).**—*threo*-2,3-Diacetoxyoctadecanoic acid[2] (II, 6.9 g.) was refluxed for 2 hr. with 25 ml. of thionyl chloride. The excess thionyl chloride was evaporated under reduced pressure, and the last traces were removed azeotropically with anhydrous benzene.

The crude acid chloride (III) was dissolved in 50 ml. of anhydrous ether and was added with stirring during 30 min. to the ethereal solution of diazomethane (from 15 g. of N-nitrosomethylurea) maintained at −15°. The reaction mixture was stirred for additional 30 min. and was kept overnight at 0°, well-protected from moisture. Since no precipitation occurred, the solution was evaporated to dryness leaving 7.0 g. (96%) of crude diazo ketone. Crystallized once from acetonitrile it melted at 62–67°. The infrared spectrum shows bands at 3180, 2120 (N≡N), 1750 (C═O, acetate), 1640 (C═O, conj.), 1340, 1230 (acetate), 1150, 1080, and 1040 cm.$^{-1}$.

The diazo ketone (IV, 3.0 g.) was dissolved in 40 ml. of dioxane, and 10 ml. of 10% aqueous sulfuric acid was added. The mixture was warmed at 90° (oil bath) until the evolution of nitrogen ceased. The dark yellow solution was poured into water, taken up with ether, washed with water, aqueous sodium hydrogen carbonate solution, and again with water, and dried. The solid residue (about 2 g.) was reduced with 1 g. of lithium aluminum hydride in the usual manner. The excess reagent was carefully decomposed with water, and excess 10% aqueous sulfuric acid was added. The aqueous layer was discarded, and, since the product was insoluble in ether, the remaining ethereal suspension was evaporated to dryness and crystallized from ethanol. The tetrol (0.6 g.) melted at 120–125°. Several recrystallizations from ethanol raised the melting point to 133°.

Anal. Calcd. for $C_{19}H_{40}O_4$ (332.51): C, 68.63; H, 12.13. Found: C, 68.22; H, 11.76.

DL-*arabino*-**1,2,3,4-Nonadecanetetrol (XI).**—This isomer was obtained essentially like DL-*xylo*-1,2,3,4-nonadecanetetrol, from 5.3 g. of crude oily *erythro*-2,3-diacetoxyoctadecanoic acid.[2] The crude tetrol was crystallized many times from acetonitrile. It had constant m.p. 95° but incorrect elemental analysis. Several recrystallizations from ethanol–water raised the melting point to 110–114° (with sintering at 105°).

Anal. Calcd. for $C_{19}H_{40}O_4$ (332.51): C, 68.63; H, 12.13. Found: C, 68.43; H, 11.60.

Ethyl *trans*-**2-Octadecenoate (XIII).**—*trans*-2-Octadecenoic acid[15] (25.5 g.) was esterified with 100 ml. of anhydrous ethanol containing 2 ml. of concentrated sulfuric acid. After refluxing for 5 hr., the bulk of the ethanol was evaporated under reduced pressure, and the residue was poured into water. The organic layer was washed with aqueous sodium hydrogen carbonate solution and with water. Evaporation of ether left a dark brown oil which was distilled yielding 27.3 g. (97%) of colorless oil, b.p. 224° (10 mm.); infrared absorption bands at 1740 (C═O), 1670 (C═C), 1320, 1270, 1190, 1140, 1110, 1050, 990 (*trans* C═C), and 865 cm.$^{-1}$.

4-Hydroxy-*trans*-2-octadecenoic Acid (XV).—Ethyl *trans*-2-octadecenoate (31 g.) in 200 ml. of carbon tetrachloride (dried over P_2O_5) was refluxed for 3 hr. with 21.4 g. of N-bromosuccinimide. The cooled reaction mixture was poured into water and taken up with ether. The ethereal layer was washed with water and dried. The solvents were evaporated leaving 39 g. of crude ethyl 4-bromo-*trans*-2-octadecenoate, which was chromatographed over alumina. Elution with petroleum ether yielded 29 g. of colorless oil which showed infrared absorption bands at 1740 (C═O), 1670 (C═C), 1310, 1270, 1210, 1180, 1110, 1050, 985 (*trans* C═C), and 870 cm.$^{-1}$.

The bromo ester (XIV) was hydrolyzed by refluxing for 4 hr. with 20 g. of potassium hydroxide in 300 ml. of 1:1 ethanol–water mixture. The bulk of ethanol was evaporated, and the cooled residue was poured into dilute hydrochloric acid, extracted with ether, washed, and dried. The ether was evaporated, and petroleum ether was added. After standing at 0° overnight, 12.3 g. (41%) of yellowish powder was filtered off, m.p. *ca.* 65°. Several recrystallizations from petroleum ether yielded the pure colorless product, m.p. 74.5–76°. The infrared spectrum shows bands at 3550, 1750, 1690, 1640, 1300, 1240, 1210, 1140, 1105, 1080, 1060, 1050, 980, 970, 930, 890 cm.$^{-1}$.

Anal. Calcd. for $C_{18}H_{34}O_3$ (298.45): C, 72.43; H, 11.48. Found: C, 72.32; H, 11.47.

2,3,4-Trihydroxyoctadecanoic Acid and γ-Lactone (XVI).—To the solution of 10 g. of 4-hydroxy-*trans*-2-octadecenoic acid in 25 ml. of glacial acetic acid and 0.3 ml. of concentrated sulfuric acid, there was added 10 ml. of 90% hydrogen peroxide in 0.5-ml. portions during 5 hr. with stirring and at an oil-bath temperature of 90°. The reaction mixture was stirred and heated for an additional 3 hr. and was left overnight at 20°. The mixture was diluted with water, taken up with ether, washed, and evaporated

---

(16) G. S. Myers, *J. Am. Chem. Soc.*, **73**, 2100 (1951).

(17) A. C. Chibnall, S. H. Piper, and E. F. Williams, *Biochem. J.*, **30**, 100 (1936).

under reduced pressure. The residue was refluxed for 2 hr. with 25 g. of potassium hydroxide in 150 ml. of 1:1 ethanol–water mixture. The bulk of the ethanol was evaporated; the remaining solution was poured into dilute hydrochloric acid and extracted with ether. By filtering off the ethereal suspension, a colorless powder (1.2 g.), m.p. 129°, was isolated showing only infrared absorption bands of a trihydroxy acid: O–H stretching vibrations at 3650, 3450, and 3350 cm.$^{-1}$, COOH vibrations at 1710 and 920 cm.$^{-1}$, other distinctive bands at 1280, 1140, 1090, 1055, and 950 cm.$^{-1}$. The free acid, m.p. 129°, could not be recrystallized unchanged from ethanol but yielded a product, m.p. 113°, which was a mixture of trihydroxy acid and its γ-lactone, as evidenced by a new strong infrared spectral band at 1780 cm.$^{-1}$.

The preparation of copper chelate with cupric acetate in methanol acidified with glacial acetic acid[5] was attempted. The greenish blue powder remained suspended in the ethereal layer.

Anal. Calcd. for $C_{36}H_{70}CuO_{10}$ (726.49): C, 59.52; H, 9.71; Cu, 8.75. Found: C, 58.99; H, 9.24; Cu, 8.65.

DL-*lyxo*- and DL-*ribo*-1,2,3,4-Octadecanetetrols (XVIII and XIX).—A mixture of 2,3,4-trihydroxyoctadecanoic acid and its γ-lactone (1.0 g.) was reduced with lithium aluminum hydride in anhydrous ether in the usual manner. The first crop of crystals (0.2 g.) has been obtained from the ethereal suspension at 20°. One crystallization from ethanol yielded the pure colorless powder, m.p. 120°, to which the DL-*lyxo* configuration was assigned on the basis of its infrared spectrum.

Anal. Calcd. for $C_{18}H_{38}O_4$ (318.48): C, 67.88; H, 12.03. Found: C, 68.01; H, 11.90.

The second isomer (0.3 g.) was isolated from the ethereal filtrate cooled to 0°. Several crystallizations from ethanol gave the colorless DL-*ribo* tetrol, m.p. 98–101° (with sintering at 91°).

Anal. Calcd. for $C_{18}H_{38}O_4$ (318.48): C, 67.88; H, 12.03. Found: C, 67.83; H, 11.80.

Acknowledgment.—With regard to this and the preceding paper, the authors are indebted to Professor M. Proštenik for his interest.

Condensation of Acetals with Cyanoacetic Acid

J. Klein and A. Y. Meyer[1]

Department of Organic Chemistry, The Hebrew University, Jerusalem, Israel

Received May 20, 1963

Acetals of benzaldehydes containing +M substituents in the ring condense with cyanoacetic acid more slowly than the free aldehydes, whereas *p*-anisaldehyde acetal condenses at a higher rate than the aldehyde. Cyanoacetic acid condenses more rapidly with acetals than ethyl cyanoacetate, but, in the presence of bases, the ester is more reactive. Addition of strong acid lowers the rate of condensation.

Acetals of aromatic aldehydes condense with malonic acid and ethyl hydrogen malonate in the Knoevenagel–Doebner reaction to give the unsaturated acids or esters, respectively. *p*-Tolualdehyde diethyl acetal and cinnamaldehyde diethyl acetal can also be condensed in benzene with ethyl hydrogen malonate in the presence or absence of added catalyst to give the monoethyl esters of the corresponding unsaturated dicarboxylic acids; the aldehyde is not an intermediate in these reactions, since it does not condense under the same conditions.[2]

Further experiments have now shown that in benzene solution benzaldehyde diethyl acetal does not condense with ethyl hydrogen malonate. In the hope that this lack of reactivity of the acetal could be compensated by a greater reactivity of the active methylene compound employed, the reaction of a series of aromatic acetals with cyanoacetic acid has been studied.

The condensations were carried out in tetrahydrofuran or in benzene–dioxane (cyanoacetic acid being only slightly soluble in benzene alone) and in the presence or absence of acidic and basic catalysts.

The influence of substituents in the phenyl ring on the course of the reaction was also studied, the condensations being performed under similar conditions so that the yield could be considered to reflect the reactivity of the acetals (the acetal which did not condense was recovered after the reaction either unchanged or in the form of the corresponding aldehyde). Yields were determined by the isolation of the products. Quantitative estimation of the course of the reaction by physical methods was difficult since competitive reactions were taking place, *e.g.*, esterification of the acids with formation of the aldehydes from the acetals. The results obtained in the absence of catalyst are summarized in Table I.

TABLE I

CONDENSATION OF ACETALS WITH CYANOACETIC ACID

Diethyl acetal of	Yield[a] of acid, % T[b]	 B[b]	M.p. of acid, °C.
Benzaldehyde	18	15	185[c]
p-Tolualdehyde	26	20	211[d]
p-Anisaldehyde	35	65	237[d]
m-Nitrobenzaldehyde	10		165
p-Nitrobenzaldehyde	2		209[d]
Cinnamaldehyde	60	40	212[e]
3,4-Dimethoxybenzaldehyde	47	93	204[f]
p-Chlorobenzaldehyde		60	203[g]

[a] After 6-hr. reflux. [b] Solvent used: T, tetrahydrofuran; B, benzene + 10% dioxane. [c] E. Fiquet, *Ann. chim.*, [6]**29,** 472 (1893). [d] E. J. Corey and C. Fraenkel, *J. Am. Chem. Soc.*, **75,** 1168 (1953). [e] G. Wittig, R. Kethur, A. Klein, and R. Wietbrock, *Ber.*, **B69,** 2078 (1936). [f] See footnote *d* and A. Lapworth and J. A. McRae, *J. Chem. Soc.*, **121,** 1699 (1922). [g] R. von Walther and W. Raetze, *J. prakt. Chem.*, [2]**65,** 258 (1902).

It appears that electron-donating groups raise the yield of the α-cyanocinnamic acids formed, whereas electron-attracting groups, like the nitro group, but not the chlorine atom, lower the yield. The results support the view that a dissociation process (1) with formation of a positive charge on the carbon α to the phenyl ring

$$\mathrm{RCH(OEt)_2 + CH_2(CN)COOH \longrightarrow R\overset{+}{C}HOEt + CH_2(CN)COO^- + EtOH} \qquad (1)$$

determines the rate of the reaction. The formed ion pair condenses, or gives the free aldehyde which may also undergo the condensation.

---

(1) Taken in part from the M.S. thesis of A. Y. M., The Hebrew University, 1960. A preliminary communication was published: *Bull. Res. Council Israel, Sect. A*, **9,** 62 (1960).

(2) J. Klein and E. D. Bergmann, *J. Am. Chem. Soc.*, **79,** 3452 (1957).