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STEREOSPECIFIC HYDROXYLATION OF *trans*-2-HEXADECEN-4-OL

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Abstract—Stereochemical isomers of 2,3,4-hexadecanetriol have been prepared by stereospecific hydroxylation of *trans*-2-hexadecen-4-ol. Their mechanism of formation has been based on polar effects, whereas the consideration of steric effects explains why only DL-arabino and DL-lyxo isomers were isolated although four racemates are possible. Their configurations were further confirmed by comparison of the I.R. spectra.

WITH the exception of carbohydrates, acyclic compounds with hydroxy substituents on three adjacent asymmetric carbon atoms have not been investigated in detail. Their preparation and identification is complicated by the fact that these structures permit the possibility of eight enantiomorphs or four racemates. Any attempts to synthesize long-chain compounds, resulted either in inseparable mixtures of isomers[1–4] or failure.[5]

In connection with configurational investigations in the sphingolipid field, our intention was to prepare stereochemically pure alkanetriols having hydroxy groups near one end of the carbon chain. The most obvious method to prepare long-chain polyols with sterically determined vicinal functional substituents would be the chain extension of shorter molecules carrying hydroxy substituents with known orientation. Unfortunately, such attempts beginning with short-chain acetylated polyhydroxy acid chlorides and alkylmagnesium bromides resulted in complete failure. The next approach was to prepare long-chain molecules in which functional groups could be introduced subsequently.

α,β-Unsaturated alcohols result from the reaction of α,β-unsaturated aldehydes with Grignard compounds. In this way, *trans*-2-hexadecen-4-ol (I) was prepared from dodecylmagnesium bromide and crotonaldehyde. In addition to analytical data and catalytic hydrogenation experiments, this structure was confirmed by the I.R. spectrum. Strong absorption bands appear at 3400 cm^{-1} (O—H stretching) and 970 cm^{-1} (out-of-plane C—H bending in symmetrically substituted alkenes[6]). Very weak bands appear at 1670 cm^{-1} (C=C stretching) and in the region 1100–1000 cm^{-1} (C—O stretching). Although it is impossible to isolate pure products from the reaction with bromine and phenyl isocyanate, the constitution of *trans*-2-hexadecen-4-ol was unambiguously confirmed by the following hydroxylation reactions.

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[1] R. Delaby and G. Morel, *C.R. Acad. Sci., Paris.* **180**, 1408 (1925); *Chem. Abstr.* **19**, 2326 (1925).
[2] S. Fujise and S. Sasaki, *J. Chem. Soc., Japan* **74**, 579 (1953); *Chem. Abstr.* **48**, 11294e (1954).
[3] E. Henry-Basch and P. Fréon, *C.R. Acad. Sci., Paris.* **248**, 1675 (1959).
[4] H. P. Kaufmann and H. Jansen, *Chem. Ber.* **92**, 2789 (1959).
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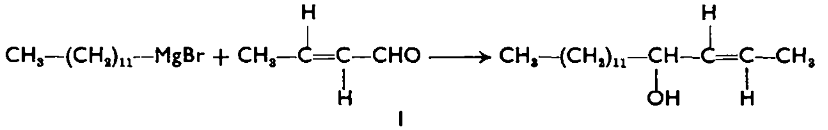
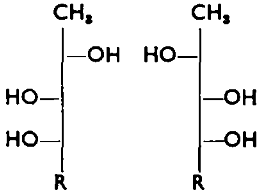


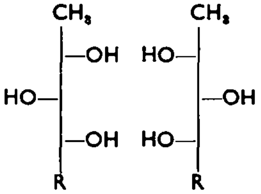
$$CH_3-(CH_2)_{11}-MgBr + CH_3-\underset{H}{\overset{H}{C}}=C-CHO \longrightarrow CH_3-(CH_2)_{11}-\underset{OH}{CH}-\overset{H}{C}=\underset{H}{C}-CH_3$$

I

The Woodward *cis* hydroxylation method,[7] adapted to long-chain olefinic compounds,[8] yields 26 per cent of 2,3,4-hexadecanetriols. The relationship of the newly introduced substituents to the hydroxy groups formerly present in the molecule suggested that two racemates could be expected in the product. If, according to the convention for configurational relationships among long-chain compounds,[9] the triols are oriented so that the carbon atom in the methyl group next to the hydroxy substituents is designated as C—1, then DL-arabino (II) and DL-xylo (III) triols may arise from the alkenol (I).



II

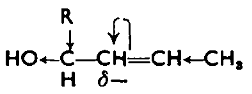


III

$R=CH_3-(CH_2)_{11}$

In order to isolate both racemates, light petroleum was added to the final reaction mixture. This procedure precipitated completely all triols present and separated them from other soluble components. The next step was to separate arabino triol (II) from the isomeric xylo compound (III). Since remarkable differences are shown in the I.R. spectra of isomeric alcohols having other physical properties almost identical,[10] the process of separation was followed by spectral analysis. As the I.R. spectrum of the analytically pure sample melting at 89–90° is identical in all characteristic details with the spectrum of the crude precipitate melting near 82°, only one diastereoisomeric pair results from the hydroxylation of the unsaturated alcohol and consideration of the reaction mechanism and steric factors alone can determine the structure of the isomers produced.

The unsaturated alcohol (I) has three groups (hydroxyl, methyl, and n-dodecyl) which could change the symmetrical electronic distribution in the double bond. It was proved elsewhere[11] that alkyl groups act by induction and not by hyperconjugation. There are, of course, differences between the methyl and n-dodecyl polar effects, but symmetrical attachment of the substituents to the double bond renders them negligible. The main influence resides therefore in the electron-attracting hydroxy group which forces the double-bond electrons predominantly to the carbon atom nearest to the OH group (IV).



$$HO\leftarrow\underset{H}{\overset{R}{\overset{\downarrow}{C}}}-\underset{\delta-}{CH}=CH\leftarrow CH_3$$

IV

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[7] R. B. Woodward and F. V. Brutcher Jr., *J. Amer. Chem. Soc.* **80**, 209 (1958).

[8] F. D. Gunstone and L. J. Morris, *J. Chem. Soc.* 487 (1957).

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[10] C. A. Stewart and C. A. VanderWerf, *J. Amer. Chem. Soc.* **76**, 1259 (1954).

[11] P. B. D. de la Mare and P. W. Robertson, *J. Chem. Soc.* 2838 (1950).

Disregarding the possibility of the cyclic transition state, the hydroxylation of the double bond proceeds through several steps:

$$CH_3{-}(CH_2)_{11}{-}CHOH{-}CH{=}CH{-}CH_3 \rightarrow$$

I

$$CH_3{-}(CH_2)_{11}{-}CH(OH){-}CHI{-}CH(OAc){-}CH_3 \rightarrow$$
$$CH_3{-}(CH_2)_{11}{-}CH(OH){-}CH(OH){-}CH(OAc){-}CH_3 \rightarrow$$
$$CH_3{-}(CH_2)_{11}{-}[CH(OH)]_3{-}CH_3$$

II and III

Since this reaction mechanism applies to the formation of both DL-arabino and DL-xylo triols, steric effects must determine the final product. As stated by the Cram's rule of asymmetric induction,[12] entering groups approach the double bond from the least hindered side assuming the opposite orientation from the bulkiest group of the adjacent asymmetric center. In this case, the solvated hydroxy group has the greatest steric requirements in the initial state thus forcing away the double bond as far as possible. In the following sequence of Newman projection formulae (Chart I) the steric interpretation of the foregoing reactions indicates the configurational relationship between substituents on carbon atoms C—2, C—3, and C—4.

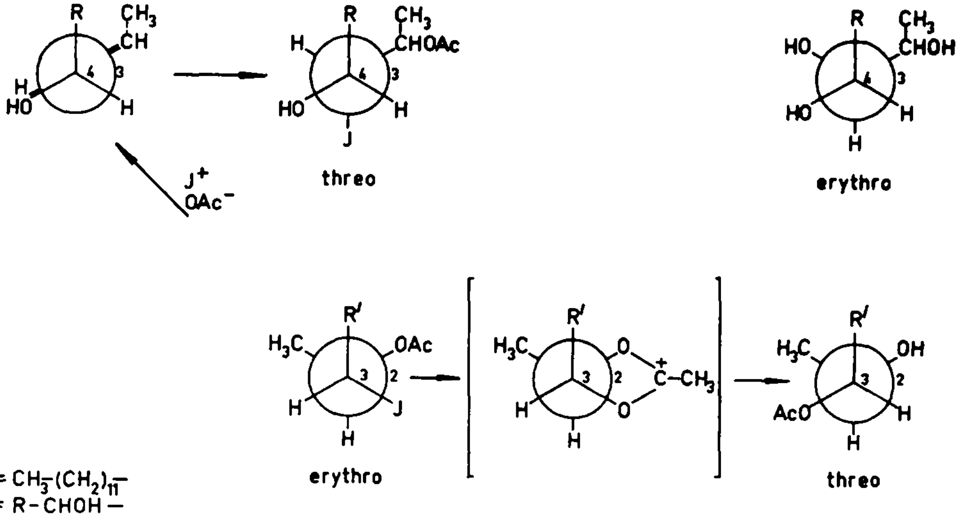

Chart I. Steric course of the Woodward *cis* hydroxylation method for *trans*-2-hexadecen-4-ol.

As the hydroxy substituents on carbon atoms C—3 and C—4 have the erythro configuration, and those on carbon atoms C—2 and C—3 the threo configuration, it may be concluded that only DL-arabino-2,3,4-hexadecanetriol (II) is produced from *trans*-2-hexadecen-4-ol by the Woodward *cis* hydroxylation method (I.R. spectrum, Fig. 1). This is in accord with the result obtained by Sasaki[13] who hydroxylated *trans*-3-penten-1,2-diol and only isolated 5-deoxy-DL-lyxo-pentitol free from any xylo isomer. (Differences between these prefixes and ours are due to opposite orientations of molecules.)

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[12] D. J. Cram and F. A. Abd Elhafez, *J. Amer. Chem. Soc.* **74**, 5828 (1952).

[13] S. Sasaki, *Nippon Kagaku Zasshi* **79**, 1173 (1958); *Chem. Abstr.* **54**, 4396 i (1960).

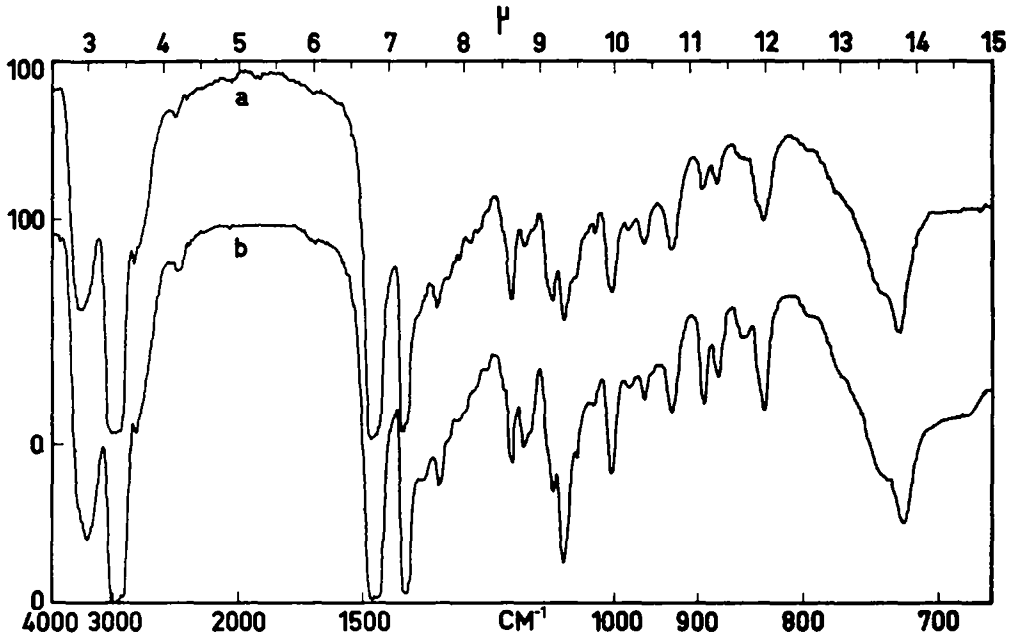
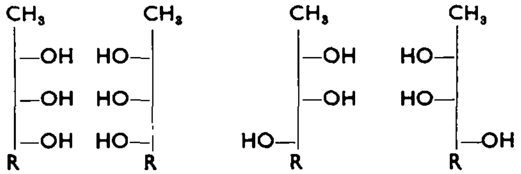


FIG. 1. Infrared spectra in nujol: (a) DL-arabino-2,3,4-hexadecanetriol; (b) DL-lyxo-2,3,4-hexadecanetriol.

Peracetic acid also hydroxylates the unsaturated alcohol (I) to 2,3,4-hexadecanetriols. In accordance with the stereospecific preparative method (*trans* hydroxylation) and the relation of the C—3 to C—4 hydroxy substituents, DL-ribo (V) and DL-lyxo (VI) triols are to be expected in the product. As peracetic acid dissociates mainly into $RCOO^-$ and OH^+, the reaction consists in the electrophilic attack of OH^+ on the most negative part of the double bond.



V VI

$R{=}CH_3-(CH_2)_{11}-$

$CH_3-(CH_2)_{11}-CH(OH)-CH{=}CH-CH_3 \rightarrow$

I

$CH_3-(CH_2)_{11}-CH(OH)-CH(OH)-CH(OAc)-CH_3 \rightarrow$

$CH_3-(CH_2)_{11}-[CH(OH)]_3-CH_3$

V and VI

The final reaction mixture was treated with light petroleum to precipitate all the trihydroxy compounds. The crude product was then fractionately crystallized from acetonitrile in order to separate both racemates. Three fractions were separated accounting for 96 per cent of triols present. It was anticipated that the I.R. spectrum of the lyxo isomer (VI) having an erythro-threo relationship between the hydroxy groups would be different from the spectrum of ribo isomer (V) having an erythro-erythro configuration. Since the three fractions had identical I.R. spectra, it was concluded that again only one racemate was produced. The erythro relationship between the C—2 and C—3 hydroxy groups follows from the hydroxylation stereospecificity, whereas steric factors together with the reaction mechanism suggest a threo relationship between the C—3 and C—4 hydroxy groups (Chart II). The steric course of the reaction is shown by the Newman projection formulae (peracetic acid is shown instead of performic acid to enable correlation with the Woodward method): the peracid reagent does not approach the double bond from the n-dodecyl side which hinders the reactive center, but exclusively through the hydrogen atom. The only product from peracid hydroxylation of *trans*-2-hexadecen-4-ol is therefore DL-lyxo-2,3,4-hexadecanetriol (VI) with I.R. spectrum as shown in Fig. 1.

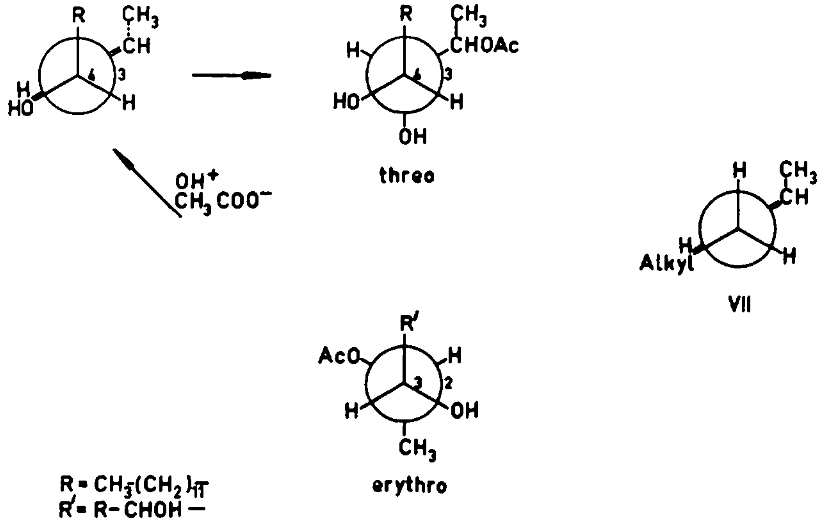


Chart II. Steric course of the peracid hydroxylation method for *trans*-2-hexadecen-4-ol.

Evidently, the reason for the high stereospecifity of these two methods lies in the solvated hydroxy substituent the polar effects of which are responsible for the non-equivalency of the two double-bonded carbon atoms and the large steric requirements of which orientate it as far as possible from the double bond, forcing the n-dodecyl group into the position which renders one side of the reactive center inaccessible to the approach of the active agent. Without the hydroxy group, the alkene would attain its energy minimum in another conformation (VII).

The whole peracid hydroxylation process was repeated under conditions which permitted the isolation of an epoxide intermediate. From *trans*-2-hexadecen-4-ol (I), using perbenzoic acid in benzene, *trans*-2,3-epoxy-4-hexadecanol was obtained in 15 per cent yield. Acetylation of the unsaturated alcohol did not raise the yield. The *trans* configuration of substituents on the oxirane ring follows from the preparative method (*cis* addition) and from the I.R. absorption band at 870 cm^{-1}. Since only erythro diols result from acid hydrolysis of *trans* epoxides, the product was expected to consist of DL-ribo (V) and DL-lyxo (VI) triols. The above mentioned facts explain why only DL-lyxo-2,3,4-hexadecanetriol (VI) was actually found.

Apart from the O—H stretching absorption bands in the 3400 cm^{-1} region, no other band in the I.R. spectra of the hexadecanetriols could be assigned with certainty, and therefore, only clear-cut absorptions in the 800–1200 cm^{-1} region are given: DL-arabino isomer 830, 875, 890, 925, 960, 1000, 1070, 1090, 1130 and 1150 cm^{-1}; DL-lyxo isomer 830, 875, 890, 925, 960, 1000, 1070, 1080, 1130 and 1160 cm^{-1}. The comparison between the wavelengths of these absorption bands reveals striking similarities. This becomes evident if configurations on asymmetric centers of both triols are correlated: the relation between the hydroxy groups on carbon atoms C—2, C—3, C—4 is threo-erythro for the DL-arabino compound and erythro-threo for the DL-lyxo isomer. As it is not likely that such a slight distinction in the constitution of these long-chain polyols could be reflected in the I.R. spectra, this is further proof that each hydroxylation method yields only one diastereoisomeric pair of triols.

EXPERIMENTAL

M.ps. are uncorrected. I.R. spectra were measured with Perkin-Elmer Infracord spectrophotometer. Light petroleum refers to the fraction b.p. 45–60°.

Trans-2-*Hexadecen-4-ol* (I). The solution of dodecylmagnesium bromide was prepared in the usual manner from 1-bromododecane (25 g; 0·1 mole), magnesium turnings (2·4 g; 0·1 g atom), anhydrous ether (50 ml) and a small crystal of iodine. After stirring at reflux temp. for 2 hr, heating was discontinued, and crotonaldehyde (6·3 g; 0·09 mole) was added from the dropping funnel. Refluxing was continued for an additional 2 hr. The reaction mixture was cautiously hydrolysed with saturated aqueous ammonium chloride, filtered, the organic layer washed with water and dried (Na_2SO_4). The ether was evaporated and the residue distilled under red. press. The fraction b.p. 0·05 114–140° was collected, and after crystallization from acetonitrile melted at 27–30°. This product was further purified chromatographically through an alumina column (50 ml of solvent for each fraction). Elution was begun with light petroleum (fractions 1–3) and gave an oil which was discarded. The main product was obtained by elution with light petroleum–benzene (1 : 1, fractions 4–10) and benzene (fractions 11–17) and melted near 33°. Several crystallizations from acetonitrile raised the m.p. to 36°. (Found: C, 80·21; H, 13·31. $C_{16}H_{32}O$ requires: C, 79·93; H, 13·42%).

The presence of the double bond was further confirmed by catalytic hydrogenation with Adams catalyst and by addition of bromine in tetrachloromethane.

DL-*Arabino-*2,3,4-*hexadecanetriol* (II). The mixture of crude *trans*-2-hexadecen-4-ol (2·4 g; 0·01 mole; m.p. 27–30°), dried silver acetate (3·7 g; 0·022 mole), iodine (2·5 g; 0·01 mole) and glacial acetic acid (65 ml) was mechanically shaken for 30 min at 20°. Water (0·2 ml; 0·011 mole) in glacial acetic acid (10 ml) was added, and the mixture refluxed on an oil bath (130–140°) for 1 hr. The cooled suspension was filtered by suction and the filtrate evaporated under red. press. to remove acetic acid. The residue was extracted with ether and washed with dil. hydrochloric acid to precipitate the remaining silver salts. The solvent was evaporated leaving a pale yellow oil (2·9 g) which was refluxed for 1 hr on a boiling water bath with potassium hydroxide (4·2 g) in water–ethanol 1 : 1 mixture (25 ml). The cooled solution was treated with dil. hydrochloric acid and extracted with ether. Evaporation of the solvent left an oil (1·2 g) from which a colorless powder (0·7 g; 28%) was precipitated with light petroleum. One crystallization from acetonitrile raised the m.p. to 87–88°. Further crystallization from methanol at −10° gave an analytical sample m.p. 89–90°. (Found: C, 69·78; H, 12·42. $C_{16}H_{34}O_3$ requires: C, 70·02; H, 12·49%).

DL-*Lyxo*-2,3,4-*hexadecanetriol* (VI). To the solution of *trans*-2-hexadecen-4-ol (6 g) in formic acid (21 ml; 98–100%) hydrogen peroxide (3 ml; 30%) was added dropwise with stirring during 5 min. The temp. was then raised to 40°, and stirring was continued for 2 hr. The mixture was diluted with water and extracted with ether. After evaporation of ether, the residue was hydrolysed with an excess of 3N aqueous sodium hydroxide on a water bath, poured into 3N hydrochloric acid and extracted with ether. The organic layer was washed with water, dried (Na_2SO_4) and evaporated. A colorless powder (1·0 g) m.p. 88–90° was precipitated from the residue by light petroleum. Crystallization from acetonitrile gave a sample m.p. 93–94°. (Found: C, 70·18; H, 12·60. $C_{16}H_{34}O_3$ requires: C, 70·02; H, 12·49%).

The crude product from 3 preparations was fractionally crystallized from acetonitrile in order to isolate the DL-ribo isomer. The following fractions were obtained having identical I.R. spectra: (1) 0·8 g; m.p. 93–94°, (2) 1·1g; m.p. 91·5°, and (3) 0·4g; m.p. 81°.

Trans-2,3-*Epoxy-4-hexadecanol. trans*-2-Hexadecen-4-ol (3·2 g; 0·0133 mole) in benzene (20 ml) was mixed with a solution of perbenzoic acid in benzene (25 ml; 0·0152 mole) and left 2 days at 5° and then 6 days at 20°. The whole was diluted with ether, washed with 2N sodium carbonate, then with water, and dried (Na_2SO_4). The drying agent was filtered off, and solvent was removed leaving an oily residue (3·0 g) which was placed on a chromatographic column prepared from 80 g of alumina (Fluka, activity 1). Elution was carried out in the following order (50 ml of solvent for each fraction): 1–8 light petroleum, 9–14 light petroleum–benzene (1 : 1), 15–21 benzene, 22–29 benzene–ether (1 : 1), 30–32 ether. After fraction 17, the residue was solid. Fractions 18–26 were collected and crystallized from light petroleum at 0° to give glistening colorless leaflets (0·5 g; 15%) m.p. 50°. (Found: C, 74·66; H, 12·48. $C_{16}H_{32}O_2$ requires: C, 74·94; H, 12·58%).

The epoxide was hydrolysed on a water bath with a solution of conc. sulfuric acid (0·5 ml) in water (3 ml) and ethanol (7 ml). The resulting product was purified as in the preceding preparation and after recrystallization from acetonitrile melted at 91·5–92·0°.

Acknowledgements—We are indebted to Mrs. N. Zambeli and Mrs. J. Zake for microanalyses.