Chemical Synthesis of D-*xylo*-Hexos-5-ulose 6-Phosphate, a Putative Intermediate in the Biosynthesis of *myo*-Inositol

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Received March 19, 1968

The crystalline di(cyclohexylamine) salt of 1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranos-5-ulose dimethyl acetal 6-phosphate (**8**) has been synthesized from 3-*O*-benzyl-1,2-*O*-isopropylidene-6-*O*-triphenylmethyl-α-D-glucofuranose (**1**) by a series of steps involving structures **2** to **7**. The major product of the acidic hydrolysis of **8** has been reduced to a two-component mixture, and one of the components therein has been shown to be glucitol 6-phosphate (**10**). Dephosphorylation of the two-component mixture gave iditol and glucitol. It is, therefore, concluded that the major product of the hydrolysis of **8** is D-*xylo*-hexos-5-ulose 6-phosphate (**9**), a postulated intermediate in the biosynthesis of *myo*-isonitol from D-glucose 6-phosphate.

It has been shown that D-glucose[2-4] and D-glucose 6-phosphate[4,5] are incorporated without fragmentation in the synthesis of *myo*-inositol by several biological systems. In two such systems, D-*myo*-inositol 1-phosphate[6] has been found[7-9] to be an intermediate in the biosynthesis of *myo*-inositol from D-glucose 6-phosphate, and, in another system, the over-all conversion of D-glucose and of its 6-phosphate has been shown[10] to be nicotinamide–adenine dinucleotide dependent. The comparative stability of the D-glucopyranose ring structure and the absence in it of functions which might serve to activate the C-6 protons render an internal aldol condensation, involving C-1 and C-6, highly unlikely. For these reasons, and in view of the biochemical facts alluded to above, the suggestion that "5-ketoglucose 6-phosphate" (**9**, D-*xylo*-hexos-5-ulose 6-phosphate) may be an intermediate[3,11] is an attractive one. We have therefore undertaken the chemical synthesis of **9** and will report the details of it here; an independent study of the behavior of **9** in a biochemical system will be described elsewhere.

3-*O*-Benzyl-1,2-*O*-isopropylidene-6-*O*-triphenylmethyl-α-D-glucofuranose (**1**), a substance originally described by Gramera, *et al.*,[12] was oxidized at room temperature with a mixture of methyl sulfoxide and acetic anhydride[13] to give 3-*O*-benzyl-1,2-*O*-isopropylidene-6-*O*-triphenylmethyl-α-D-*xylo*-hexofuranos-5-ulose (**2**) which was isolated in crystalline form in 91% yield. From this derivative the trityl group was cleaved with warm aqueous acetic acid to give the crystalline hemihydrate of 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranos-5-ulose (**3**) in 57% yield. Tritylation of **3** was difficult, only 8% **2** being obtained from **3** even when a substantial excess of trityl chloride was used. However, the infrared absorption and nmr spectra of **3** were consonant with the structure assigned. See Scheme I.

The carbonyl group in **3** was masked as its dimethyl acetal (**4**, 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranos-5-ulose dimethyl acetal), and the hydroxyl group at C-6 was phosphorylated with diphenylphosphochloridate. The syrupy product, **5**, was freed of its benzyl group at C-3 by hydrogenolysis over palladium and of its two phenyl groups by hydrogenolysis in the presence of platinum. The product, 1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranos-5-ulose dimethyl acetal 6-phosphate (**7**), was isolated as its crystalline di(cyclohexylammonium) salt (**8**). Upon warming in aqueous solution in the presence of an acidic ion-exchange resin, **8** gave a major product (A), a minor product (B), and a trace of a third substance (C). These were readily separable by preparative paper chromatography; each contained organic phosphate, and each was isolated in amorphous form. In the solvent system used, A had the slowest rate of migration. A sample of A was reduced with sodium borohydride, dephosphorylated with alkaline phosphatase, and acetylated; glpc then revealed two components which were chromatographically indistinguishable from the hexaacetates of D-glucitol (**11**) and L-iditol (**13**). The minor product (B), which had an intermediate rate of migration, gave identical results, while the smallest component (C), which had the most rapid rate of migration gave **11**, **13**, and a third, unidentified product. The reduction of A with sodium borohydride, followed by trimethylsilylation of the product, gave a material which was examined by glpc and shown to contain two components, one of which had the chromatographic behavior of D-glucitol 6-phosphate[14] (**10**); L-iditol 6-phosphate (**12**) was not available for comparsion with the other component. A similar examination of B gave a product which failed to chromatograph under the conditions employed.

On the basis of the above evidence, the major product of the hydrolysis of **8** (A) is clearly D-*xylo*-hexos-5-ulose 6-phosphate (**9**). Its structure is portrayed in the acyclic form although doubtless it exists in one or more of the possible cyclic tautomers. The structure of B remains uncertain. On paper, the substance gives a noticeably weaker blue color with phosphomolybdate

(1) Staff Fellow, National Institutes of Health, 1966–1968.

(2) F. Eisenberg, Jr., A. H. Bolden, and F. A. Loewus, *Biochem. Biophys. Res. Commun.*, **14**, 419 (1964).

(3) H. Kindl and O. Hoffmann-Ostenhof, *Monatsh. Chem.*, **95**, 548 (1964).

(4) H. Kindl, J. Biedl-Neubacher, and O. Hoffmann-Ostenhof, *Biochem. Z.*, **341**, 157 (1965).

(5) I. W. Chen and F. C. Charalampous, *Biochem. Biophys. Res. Commun.*, **17**, 521 (1964).

(6) Under the rules of the IUB–IUPAC Commission on Biochemical Nomenclature (in press), this substance will be named "L-*myo*-inositol 1-phosphate."

(7) F. Eisenberg, Jr., and A. H. Bolden, *Biochem. Biophys. Res. Commun.*, **21**, 100 (1965).

(8) F. Eisenberg, Jr., *J. Biol. Chem.*, **242**, 1375 (1967).

(9) I. W. Chen and F. C. Charalampous, *ibid.*, **241**, 2194 (1966).

(10) I. W. Chen and F. C. Charalampous, *ibid.*, **239**, 1905 (1964).

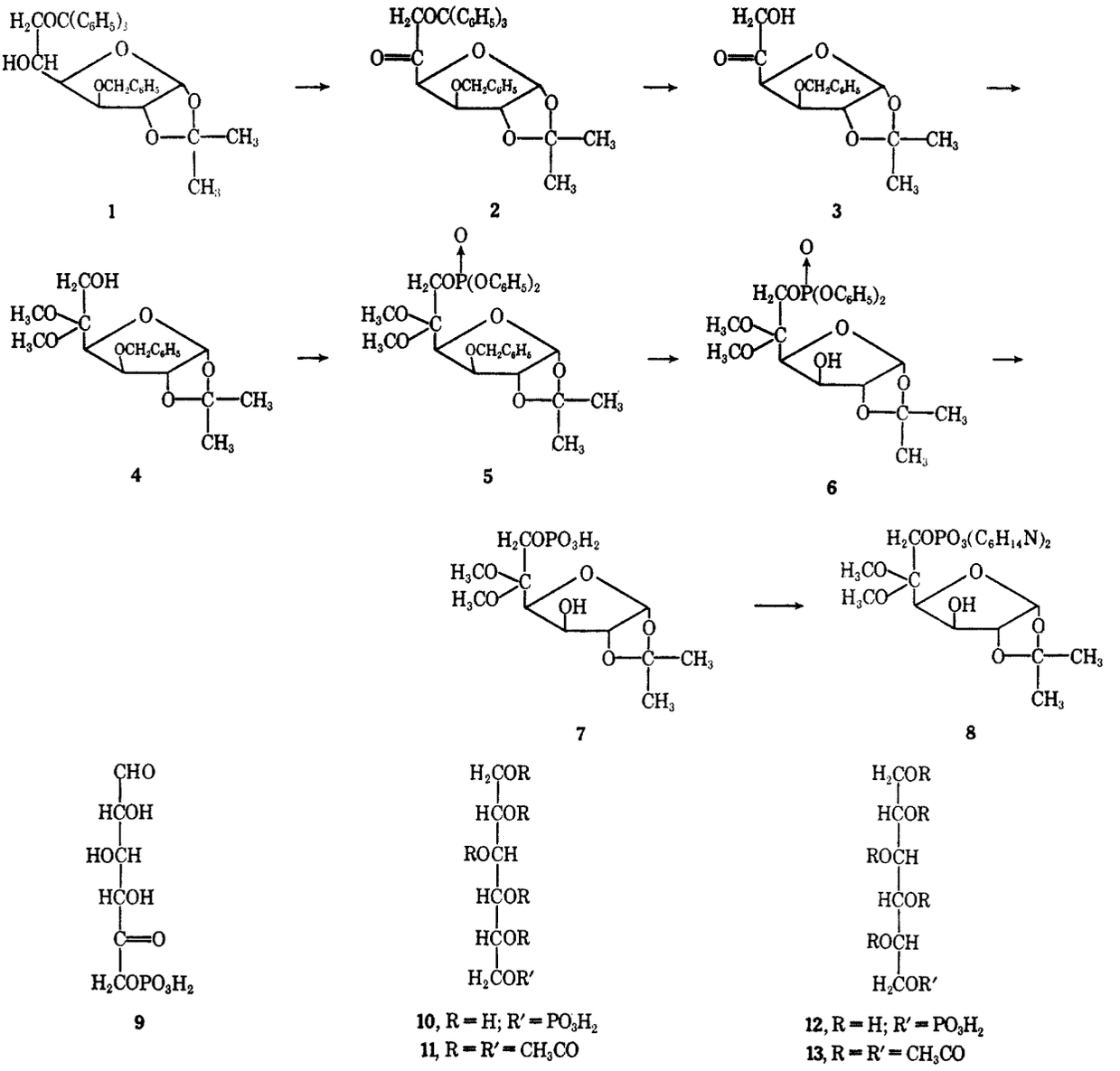
(11) F. A. Loewus and S. Kelly, *Biochem. Biophys. Res. Commun.*, **7**, 204 (1962).

(12) R. E. Gramera, R. M. Bruce, S. Hirase, and R. L. Whistler, *J. Org. Chem.*, **28**, 1401 (1963).

(13) J. D. Albright and L. Goldman, *J. Amer. Chem. Soc.*, **87**, 4214 (1965); *ibid.*, **89**, 2416 (1967).

(14) J. B. Wolff and N. O. Kaplan, *J. Biol. Chem.*, **218**, 849 (1956).

SCHEME I



spray than do either A or C. This observation suggests that it may be the 3,6 cyclic phosphate, for, as Khorana and his coworkers[15] have observed, cyclic phosphates with seven-membered rings are notably stable. However, removal of the phosphate residue (after reduction with sodium borohydride) with alkaline phosphatase clearly eliminates a cyclic phosphate structure since it has been shown[16] that such phosphates are stable to the action of alkaline phosphatase. There remains the possibility that B is a 3-phosphate. If this were true, reduction would have given a mixture of hexitol 3-phosphates, and one would expect the TMS derivatives of these to chromatograph under the conditions used for the TMS derivatives of the hexitol 6-phosphates.

The very minor component, C, also remains unidentified; comparison of its infrared spectrum with those of compounds **1**–**6** and **8** suggests that an isopropylidene group may be present.

Some aspects of the chemistry of D-*xylo*-hexos-5-ulose are currently under investigation in this laboratory and will be the topic of a future communication.

(15) H. G. Khorana, G. M. Tener, R. S. Wright, and J. G. Moffatt, *J. Amer. Chem. Soc.*, **79**, 430 (1957).

(16) L. A. Heppel, D. R. Harkness, and R. J. Hilmoe, *J. Biol. Chem.*, **237**, 841 (1962).

Experimental Section[17]

3-*O*-Benzyl-1,2-*O*-isopropylidene-6-*O*-triphenylmethyl-α-D-*xylo*-hexofuranos-5-ulose (2).—3-*O*-Benzyl-1,2-*O*-isopropylidene-6-*O*-triphenylmethyl-α-D-glucofuranose (1) was prepared by the method of Gramera, *et al.*:[12] mp 116°; $[\alpha]^{25}D$ −36.0° (*c* 2.97, chloroform). The compound (1, 37.0 g) was dissolved in methyl sulfoxide (Fisher Certified Reagent Grade, 160 ml), and a mixture of methyl sulfoxide (200 ml) and acetic anhydride (69 ml) was added. After storage at room temperature for 24 hr, the reaction mixture was examined by tlc on 5 × 20 cm plates using ether–benzene (1:9) and ammonium phosphomolybdate spray.[18] A major product (2) and a faster moving minor one were visible, but no trace of 1 was detected. The migration rates of **1** and **2** are very similar in the solvent system employed. It was found

(17) Melting points correspond to the corrected values. Thin layer chromatography was conducted on silica gel G (E. Merck AG, Darmstadt) using the solvent systems specified; the components were detected (unless otherwise specified) by spraying with 10% sulfuric acid and heating at 100°. Column chromatography was carried out on no. 7734 silica gel (0.05–0.20 mm, E. Merck AG). When not otherwise noted, nmr spectra were obtained in $CDCl_3$ solution using a Varian A-60 spectrometer and tetramethylsilane as an internal standard.

(18) W. Meyer zu Reckendorf, *Tetrahedron*, **19**, 2033 (1963).

that warming the plate prior to and then subsequent to spraying caused **1** to give a yellow spot which turned to green, while **2** gave a yellow spot which turned to blue; **1** and **2** are thus readily distinguished.

The reaction mixture was poured into 2 l. of ice–water and stirred until the gummy precipitate had settled. After 2–3 hr, the aqueous phase was decanted, and the crude product was washed with several portions of water. It was then dissolved in dichloromethane (400 ml), and the solution was washed with two 50-ml portions of saturated aqueous sodium bicarbonate solution. Moisture was removed with magnesium sulfate, and the solution was concentrated *in vacuo* to a residue which was crystallized from benzene–hexane: yield, 33.6 g (91%); mp 169–171°; $[\alpha]^{20}D$ −17.8° (*c* 1.46, chloroform); infrared absorption (KBr) at 1720 (vs) (CO), 1480 (s) (phenyl), 1382 (s), and 1375 cm^{-1} $[(CH_3)_2C]$; nmr (100 MHz) signals at δ 1.28 and 1.45 [singlets, $(CH_3)_2C$], 4.10 (singlet, benzyl CH_2), 4.36 and 4.52 (doublets of 3.0 Hz, H-4 and H-3), 4.85 and 5.92 (doublets of 4.0 Hz, H-2 and H-1), and 4.36 and 4.5 (doublets, $J_{6,6}$ = 11 Hz).

Anal. Calcd for $C_{35}H_{34}O_6$ (550.66): C, 76.34; H, 6.22. Found: C, 76.35; H, 6.14.

3-*O*-Benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose-5-ulose (3).—A solution of **2** (5.00 g) in glacial acetic acid (100 ml) was warmed to 60° and stirred while water (25 ml) was added. Some **2** precipitated, but, as the mixture was stirred at 60°, it redissolved and, after *ca.* 4 hr, the clear, colorless solution was found (tlc, ether–benzene, 1:9) to contain triphenylmethanol and another, slower moving substance, but no **2**. Concentration of the reaction mixture *in vacuo* at 40° (bath) gave a white, crystalline mass which was dissolved in chloroform. The solution was washed with two 75-ml portions of saturated aqueous sodium bicarbonate solution, dried over magnesium sulfate, and concentrated *in vacuo* to give a crystalline residue which was dissolved in benzene. The crude product was then chromatographed on a column of *ca.* 180 g of silica gel which had previously been washed with acetic acid–benzene (1 1, 4:96).[19] Elution was carried out with acetic acid–ether–benzene (1:10:90), 23-ml portions of eluate being collected. In a typical experiment, fractions 14 to 28 contained only triphenylmethanol, while fractions 47 to 95 contained only **3**. These latter fractions were pooled and concentrated *in vacuo*, and **3** was crystallized from either cyclohexane or benzene–hexane as its **hemihydrate**: yield, 1.70 g (57%); mp 115–116°, $[\alpha]^{20}D$ −110.5° (*c* 1.13, chloroform); infrared absorption (KBr) at 3600 (s), (OH), 1720 (vs) (CO), and 1375 (s) with a shoulder at 1380 cm^{-1} $[(CH_3)_2C]$; nmr signals ($CDCl_3$ + D_2O) at δ 1.32 and 1.47 [singlets, $(CH_3)_2C$], and 6.04 (doublet, $J_{1,2}$ = 3.8 Hz, H-1).

Anal. Calcd for $C_{16}H_{20}O_6 \cdot {}^1/_2H_2O$ (317.35); C, 60.56; H, 6.67. Found: C, 60.73; H, 6.64; mol wt, 315.[20]

A sample (144 mg) of the hemihydrate of **3** was dissolved in dry pyridine, and the solvent was removed *in vacuo*. This process was repeated and the resulting syrup, dissolved in more pyridine (5 ml), was treated with chlorotriphenylmethane (163 mg, 1.29 mol equiv). The course of the tritylation was followed by tlc (ether–benzene, 1:9) and, after 48 hr, very little of the **3** was found to have been converted into **2**. More chlorotriphenylmethane (128 mg, to make a total of 2.3 mol equiv) was added, and, after a further 48 hr, more **2** was detected. The reaction mixture was concentrated *in vacuo* to a syrup which was dissolved in benzene, and the solution was applied to three thin layer plates (1 × 200 × 200 mm) which were developed with ether–benzene (1:7). The **2** thus separated was crystallized from benzene–hexane: yield, 20 mg (8%); mp and mmp 169–171°.

3-*O*-Benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranos-5-ulose Dimethyl Acetal (4).—The procedure used was patterned after that which Ballou and Fischer[21] employed for the conversion of mono-*O*-acetyldihydroxyacetone into its dimethyl acetal. Granular ammonium chloride (820 mg) was dissolved in methanol (80 ml), and to this solution was added redistilled trimethyl orthoformate (32 ml) and **3** hemihydrate (4.0 g). The reaction mixture was heated at 37–39° (bath) for 5 days, tlc (benzene–ether, 1:1) then showing the presence of only a trace of **3** which migrated very close to but faster than **4** in this solvent system. The light yellow solution was diluted with methanol (75 ml), stirred with methanol-washed Dowex 1-X8 (OH^-) (40 ml) for 2 min, and filtered; the resin was washed with methanol. Concentration of the combined filtrate and washings *in vacuo* at 40° (bath) gave a light yellow syrup from which trimethyl orthoformate was evaporated and which was finally held at 40° (<1 mm) for 3 hr. The syrupy **4** thus obtained showed a very weak carbonyl absorption in the infrared (neat) at 1718 cm^{-1} and was suitable for direct conversion into **5**. In order to obtain a pure sample of **4**, a portion (310 mg) of it was dissolved in the minimum quantity of ether–benzene (1:10), and the solution was applied to a column of silica gel (10 g) packed in the same solvent mixture which was also used for elution; 10-ml portions of eluate were collected. Fractions 12 to 16 contained chromatographically pure but slightly colored **4** (153 mg) which was dissolved in methanol (20 ml), and the solution was treated with Norit B at room temperature for 10 min. The solution was filtered, and the filtrate was concentrated *in vacuo* to yield a syrup which was held at room temperature and a pressure of <1 mm for 3.5 hr: $[\alpha]^{20}D$ −62.5° (*c* 0.80, chloroform); infrared absorption (neat) at 3500 (s) (OH), 1380 (s) and 1366 (s) $[(CH_3)_2C]$, but none at 1720 cm^{-1}; nmr signals at δ 1.32 and 1.47 [singlets, $(CH_3)_2C$], 3.33 and 3.35 [singlets, $(CH_3O)_2C$], 3.83 (broad doublet, J = 5 Hz, H-6,6′ coupling with OH), 4.05 and 4.37 (doublets, J = 3.3 Hz, H-4 and H-3), 4.58 and 5.95 (doublets, J = 4.0 Hz, H-2 and H-1), and 4.67 (singlet, CH_2 of benzyl).

Anal. Calcd for $C_{18}H_{26}O_7$ (354.41): C, 61.00; H, 7.39. Found: C, 60.95; H, 7.40.

Di(cyclohexylammonium) 1,2-*O*-Isopropylidene-α-D-*xylo*-hexofuranos-5-ulose Dimethyl Acetal 6-Phosphate (8).—A solution of **4** (2.28 g) in dry pyridine (15 ml) was cooled in an ice bath and stirred while diphenylphosphochloridate (Aldrich Chemical Co.) was added dropwise over the course of 20 min; moisture was excluded from the reaction mixture. The solution was held at 5° for 16 hr, cooled in an ice bath, and stirred, while water (5 ml) was added dropwise. The solvent was then removed *in vacuo* at 30°, and the resulting syrup was dissolved in benzene (225 ml). The solution was washed successively with cold water (25 ml), 1 *N* hydrochloric acid (2 ml), and 1 *M* potassium bicarbonate solution. Moisture was removed with magnesium sulfate, and the solution was concentrated *in vacuo* at 30° (bath) to give **3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranos-5-ulose dimethyl acetal 6-(diphenyl)phosphate (5**, 3.44 g, 91%) as a reddish brown syrup which was chromatographically homogeneous (tlc, benzene–ether, 1:1) and appeared as a rust-colored spot on tlc after spraying with 10% sulfuric acid. The infrared spectrum of **5** (neat) showed absorption at 1580 (s) (phenyl), 1373 (s) and 1380 $[(CH_3)_2C]$, and 1300 (s) (PO), but none at 3650–3590 cm^{-1} (OH); the nmr spectrum included signals at δ 1.20 and 1.35 [singlets, $(CH_3)_2C$], 3.10 [broad singlet, $(CH_3O)_2C$], 5.54 (doublet, $J_{1,2}$ = 3.5 Hz, H-1), 6.80, and 6.85 (multiplets, aromatic protons).

The syrup was dissolved in methanol (75 ml); 10% palladium on charcoal[22] (1.00 g, freshly saturated with hydrogen) was added to the solution; and the suspension was stirred with hydrogen for 5–6 hr. Examination by tlc (ether–benzene, 1:1) then showed that the benzyl group had not been removed. Filtration gave a clear, colorless solution.[23] Palladium black, freshly made by the reduction of palladium chloride (1.03 g) with hydrogen in methanol solution and well washed with methanol, was added, and the suspension was stirred with hydrogen; the catalyst was replaced twice over the course of 18 hr with approximately double the original quantity of palladium black. At the end of this period tlc (ether–benzene, 1:1) failed to detect **5**. It was found desirable to conduct the hydrogenolysis as rapidly as possible, since prolonged exposure to these conditions caused the formation of some product other than the desired one and led to the liberation of phenol, detected on tlc by the bright blue spot which it gave with Gibbs reagent.[24] The catalyst was removed by filtration, and the filtrate, containing **1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranos-5-ulose dimethyl acetal 6-(diphenyl)phosphate (6)**, was found to be stable indefinitely at −5°. Concentration of a sample of the filtrate gave syrupy **6** with infrared absorption (neat) at 3330 (s) (OH), 1580 (s) (phenyl), 1373 (s), 1380 (s) $[(CH_3)_2C]$, and 1300 cm^{-1} (s) (PO); the nmr spectrum included signals at δ 1.32 and 1.47 [singlets, $(CH_3)_2C$], 3.44 [singlet, $(CH_3$-

(19) Omission of this conditioning of the silica gel led to decomposition of **3** on the column.

(20) Determined in chloroform solution with a Model 301A vapor pressure osmometer of Mechrolab, Inc., Mountain View, Calif.

(21) C. E. Ballou and H. O. L. Fischer, *J. Amer. Chem. Soc.*, **78**, 1659 (1956).

(22) Engelhard Industries, Inc., Newark, N. J.

(23) How the colored impurity was removed here is not known. A solution of crude **5** in methanol was not decolorized by Norit B.

(24) H. D. Gibbs, *J. Biol. Chem.*, **72**, 649 (1926).

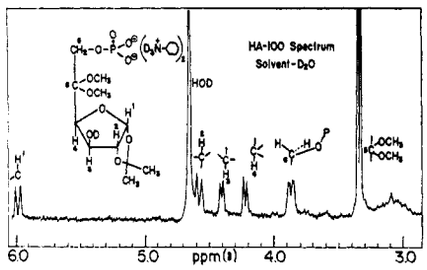


Figure 1.—Nmr spectrum (100 MHz) of **8**.

$O)_2C]$, 6.03 (doublet, $J_{1,2}$ = 3.5 Hz, H-1), and 7.38 (sharp singlet, aromatic protons).

Platinum oxide (1.04 g) was added to the solution, and the phenyl groups were removed by hydrogenolysis. Again, it proved advisable to maintain a relatively rapid rate of hydrogenolysis through replacement of the catalyst with fresh catalyst at 5–6-hr intervals. In the early stages of the reaction, progress was monitored by tlc using benzene–ether (1:1) and observing the disappearance of **6**. The product (**7**), being very polar, did not migrate in this system; in the latter stages of the reaction, progress was monitored by nmr. For this purpose, samples of the solution were freed of methanol *in vacuo* at 30° (bath) and dissolved in deuteriochloroform. When the reaction was complete, the broad signal at δ 7.38 (aromatic protons) had disappeared, and the **1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranos-5-ulose dimethyl acetal 6-phosphate** (**7**) gave signals at δ 1.32 and 1.47 [singlets, $(CH_3)_2C$], 3.48 [broad singlet, $(CH_3O)_2C$], and 5.98 (doublet, $J_{1,2}$ = 3.5 Hz, H-1).

The catalyst was removed from the solution by filtration, and redistilled cyclohexylamine was carefuly added to the filtrate to a pH of *ca.* 11 (moist pH paper). The solution was concentrated *in vacuo* at 35° (bath) to give a light brown, amorphous product which was dissolved in the minimum quantity of water. The solution was filtered; absoute ethanol was added to the filtrate; and the product (**8**) was crystallized at 5°. Three crops of short, colorless needles were obtained: yield 1.26 g (36% from **4**). After recrystallization from absolute ethanol, **8** had mp 158–160° and $[\alpha]^{20}D$ +1.0° (*c* 3.0, water); infrared absorptions (KBr) were at 3400 (s) (OH), 1385 (s), and 1375 cm^{-1} (s) $[(CH_3)_2C]$; its nmr (100 MHz) spectrum in D_2O, using sodium 3-(trimethylsilyl)propane sulfonate as a standard, included signals at 1.33 and 1.50 [singlets, $(CH_3)_2C$], 3.32 and 3.35 [singlets, $(CH_3O)_2C$], 4.20 and 4.37 (doublets of 3.0 Hz, H-4 and H-3), 4.56 and 5.98 (doublets of 4.0 Hz, H-2 and H-1). Part of the 100-MHz nmr spectrum is shown in Figure 1. A two-proton signal, centered at δ 3.9, is attributed to the nonequivalent geminal protons at C-6 ($J_{6,6'}$ = 11 Hz). This signal, two unsymmetrical quartets, constitutes the AB part of an ABX system. A and B are H-6 and H-6′, respectively, and X is phosphorus ($J_{6,P}$ and $J_{6',P}$ = 1.5 Hz). The small peaks are of such low intensity that they are difficult to detect.[25]

The material was subjected to tlc on microcrystalline cellulose,[26,27] development being with molybdate spray.[28] With both acetone–water (8:2) and isopropyl alcohol–ammonia–water (7:1:2), the material was homogeneous; in the former solvent system an R_f of 0.38 was observed, while in the latter **8** had R_f 0.50.

Anal. Calcd for $C_{23}H_{47}N_2O_{10}P$ (542.62): C, 50.91; H, 8.73; N, 5.16; P, 5.71. Found: C, 51.04; H, 8.74; N, 5.10; P, 5.59.

Acidic Hydrolysis of 8.—Dowex 50W-X8 (H^+) (1.2 g), which had been washed with water and dried in the air, was added to a solution of **8** (82 mg) in water (1.5 ml). The suspension was agitated gently for 2 min, and the resin was then removed by filtration. The combined filtrate and washings (4.5 ml) were then treated with fresh resin (1.3 g), and the mixture was heated at 40° for 42 hr without stirring. After removal of the resin, the filtrate was lyophilized to give a white, amorphous product (40 mg). An aqueous solution of this product was applied to two sheets of Whatman No. 3MC paper (46 × 56 cm) and chromatographed in a descending manner with butyl alcohol–propionic acid–water (10:5:7) for 48 hr. The chromatograms were dried in the air for 3 hr—more prolonged drying was found to lead to extensive decomposition of the compounds on the paper. The bands were located by spraying with molybdate reagent[28] strips cut from the edges and center of the papers. The major component (A) was found at 6.5 in., while a much smaller component (B) was at 9.5 in., and a very small component (C) at 16 in. The slowest product (A) gave the most intensive color, while B gave the least intense. Each of the three bands was eluted separately with water, and the eluates were lyophilized to give amorphous products which were stored at −5°.

Examination of Component A.—The reduction procedure of Frush and Isbell[29] was used. A sample (3 mg) of A was dissolved in water (1 ml), and to the solution boric acid (*ca.* 0.2 *M*, 3 ml, pH 4.9) was added. The solution was cooled in an ice bath and treated with 1 ml of aqueous sodium borohydride solution (14 mg/ml). After 20 min, another 1-ml portion of sodium borohydride solution was added, and the reaction mixture was left at room temperature overnight. It then had a pH of 9.0 and was passed through a column of IR-120 (H^+) (20 ml). The combined effluent and washings (25 ml) were lyophilized; the residue was freed of boric acid by successive solution in four 50-ml batches of methanol; and the solution was concentrated *in vacuo* at 40°. The resulting mixture was dissolved in water (1 ml), and tris(hydroxymethyl)aminomethane/Mg^{2+} buffer[30] (2 ml) was added. The solution was treated with bacterial alkaline phosphatase[31] (100 λ), and the mixture was incubated at 40° for 2.5 hr. It was then deionized with Amberlite MB-3 (15 ml), and the combined solution and washings (30 ml) were lyophilized to give a clear, colorless syrup which was acetylated with acetic anhydride–pyridine. The acetylation mixture was concentrated to a volume of *ca.* 0.25 ml, and samples of it were subjected to glpc isothermally at 190–200° on a column (0.25 in. o.d. × 10 ft) of 3% ECNSS-M on Gas-Chrom Q,[32,33] using nitrogen as a carrier gas at a flow rate of 60 ml/min and an F & M Model 5750 instrument equipped with a flame ionization detector. Two components, chromatographically indistinguishable from authentic samples of D-glucitol hexaacetate (**11**) and L-iditol hexaacetate (**13**), were detected; the ratio of the two (in the order named) was 3:1.

In another experiment, the mixture of alditol phosphates, prepared as described above, was trimethylsilylated with "Tri-Sil" reagent,[34] and the product was examined by glpc at 200° on a stainless steel column (0.25 in. O.D. × 6 ft) containing 1% SE-30 on Gas-Chrom Q;[33] helium was used as a carrier gas at a flow rate of 50 ml/min. Two peaks with a ratio of 2.4:1 were observed; the larger peak (13 min) corresponded to that shown by an authentic sample of the trimethylsilyl derivative of D-gluctiol 6-phosphate (**10**). An authentic sample of the corresponding L-iditol derivative (**12**) was not available for comparison with the smaller peak (14 min).

Examination of Components B and C.—The material of intermediate mobility (B) was converted into a mixture of alditol acetates as described above for A; glucitol hexaaceate and iditol hexaacetate, in a ratio of 1.6:1 were detected; no other product was found.

Similar treatment of C gave glucitol hexaacetate, iditol hexaacetate, and a third, unidentified product in the ratio of 2:1:2. The infrared spectrum (KBr) of C showed a peak at 1380 cm^{-1} (s) which was absent from the spectrum of A; it may be noted that compounds **1–6** and **8** showed absorption between 1385 and 1365 cm^{-1} which we attribute to the isopropylidene group.

(25) In a letter dated April 8, 1968, Professor L. D. Hall of the University of British Columbia has kindly pointed out that the magnitude of the ^1H-^{31}P coupling (1.5 Hz) suggests that the bulky phosphate group is *gauche* to H-6 and H-6′.

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Registry No.—*myo*-Inositol, 87-89-8; **2**, 17278-21-6; **3**, 17231-20-8; **4**, 17231-21-9; **5**, 17231-22-0; **6**, 17231-23-1; **7**, 17231-24-2; **8**, 17278-22-7; **9**, 13445-86-8.

Acknowledgment.—It is a pleasure to acknowledge our indebtedness to Professor Th. Posternak of the University of Geneva for calling the attention of one of us (H. G. F.) to the need for a synthesis of **9**. We also wish to thank Dr. Frank Eisenberg, Jr., and Dr. Livio Paolillo of this institute for stimulating discussions and the staff of the Section on Microanalytical Services and Instrumentation of this institute for elemental analyses and spectra.

Intramolecular Displacement by Neighboring Thiolbenzoate. Formation of Sugar Episulfides[1]

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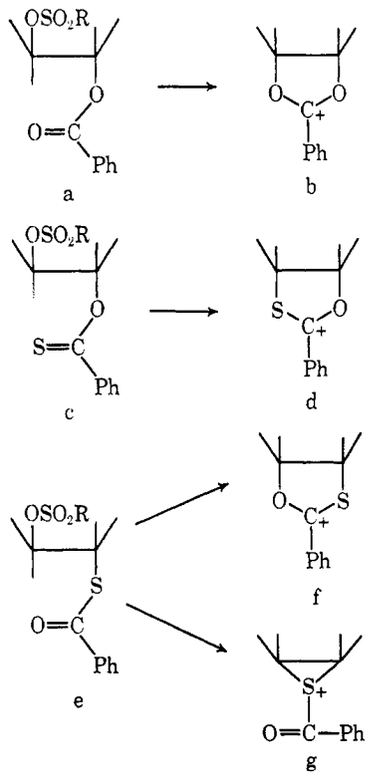
Received April 15, 1968

The epoxide ring of methyl 2,3-anhydro-5-*O*-trityl-β-D-lyxofuranoside was attacked nearly equally at C-2 and C-3 on fusion with pyridine–thiolbenzoic acid. The resultant 2-benzoylthio-*xylo* and 3-benzoylthio-*arabino* isomers were separated by chromatography. The tosylates of these were treated with sodium benzoate–*N*,*N*-dimethylformamide at 110°, and methyl 2,3-thioanhydro-5-*O*-trityl-β-D-ribofuranoside was formed as the only product. Sulfur participation through a three-membered cyclic intermediate thus occurred to the exclusion of oxygen participation through a five-membered cyclic intermediate.

The displacement of sulfonates with configurational inversion is a useful process for the synthesis of new sugars, but, when the sulfonate is attached to a furanose ring, direct SN2 displacement is often difficult. Internal displacement is then required, with the participation of a *trans* substituent adjacent to the sulfonate.[2] When the displacement is assisted by an *O*-benzoyl group (as in a), the result is the conversion of a *trans* into a *cis* glycol system, *via* the acylonium ion b. Syntheses of furanose derivatives of 5-deoxy-D-ribose,[3] homoribose (5-deoxy-D-allose),[4] and L-ribose[5] have been achieved, using sodium benzoate–*N*,*N*-dimethylformamide as the reaction medium. When the displacement is assisted by an *O*-thionobenzoyl group (as in c), the *trans* glycol system is converted into a *cis*-mercapto alcohol, by attack of sulfur to form the cyclic ion d, as in the recent synthesis of 3′-thioadenosine.[6] It was of interest to compare the participation of a neighboring *S*-benzoyl group (as in e) and its synthetic utility. Two possibilities seemed likely, either oxygen participation or sulfur participation, through the intermediate five-membered or three-membered cyclic ions (f and g), respectively. Occurrence of benzoylepisulfonium ions (g) has been postulated in a few cases in the literature,[2] but has not been demonstrated conclusively. If displacement were found to occur *via* the thioacylonium ion (f) on the other hand, it would constitute another synthesis of the relatively inaccessible *cis*-mercapto alcohol system. In the present study, inversion by sulfur participation is established by isolation of episulfide derived from g.



The *trans*-mercapto alcohol system required for this study is readily obtained from the opening of sugar epoxides with sulfur nucleophiles. Since we were interested in a compound which might lead, *via* the pathway e → f, to 2-thioribofuranose derivatives, we sought to obtain a 2-benzoylthioxylofuranose (precursor to e) from methyl 2,3-anhydro-β-D-lyxofuranoside[7] (**1**). The recently described fusion of epoxides with pyridinium thiolbenzoate[8] appeared to be a promising procedure, and we were encouraged to expect extensive attack at C-2 of **1**, since reaction of this epoxide with sodium benzyl mercaptide[9] gave 2-

(1) This work was carried out under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Public Health Service, Contract No. PH-43-64-500. The opinions expressed in this paper are those of the authors and not necessarily those of the Cancer Chemotherapy National Service Center.

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