Registry No.—**1**, 19647-34-8; **3**, 19647-35-9; **3** (Me = H), 551-72-4; **7**, 19647-36-0; **9**, 19647-37-1; **10**, 19647-38-2; **10** (pentaacetate), 19669-12-6; **11**, 527-42-4; **11** (pentabenzoate), 19647-40-6; **13** (X = Cl), 19647-41-7; **14** (X = Cl), 19647-42-8; **19**, 19647-43-9; **19** (diacetone ketal), 19647-44-0; **21**, 19669-13-7.

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Cyclization of D-*xylo*-Hexos-5-ulose, a Chemical Synthesis of *scyllo*- and *myo*-Inositols from D-Glucose[1,2]

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The recently described 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranos-5-ulose (**1**) serves as a convenient precursor for the preparation of D-*xylo*-hexos-5-ulose (**3**). While dicarbonyl sugar **3** was obtained only in amorphous form, its structure was confirmed through reduction to D-glucitol and L-iditol. On treatment with dilute alkali, **3** readily undergoes an intramolecular aldol condensation to give 2,4,6/3,5-pentahydroxycyclohexanone (**6**, *myo*-inosose-2). The identity of **6** was confirmed through its reduction to a mixture of *scyllo*- and *myo*-inositols (**7** and **8**). Chromatographic evidence indicates that dilute alkali converts **6** in part into DL-2,3,5/4,6-pentahydroxycyclohexanone (**9** and **10**). The conversion of **3** into **6** constitutes a step in the chemical synthesis of *myo*-inositol from D-glucose—the second such synthesis to be reported. The cyclization of **3** to **6** closely resembles a step in a postulated biosynthesis of **8**.

Over 80 years have passed since Maquenne[4] made the prescient suggestion that *myo*-inositol may arise in nature through the cyclization of D-glucose. While it is now well established that D-glucose[5-7] and D-glucose 6-phosphate[7,8] are indeed converted, without fragmentation, into *myo*-inositol by several biological systems, the mechanism whereby this takes place remains uncertain. In view of the comparative stability of the D-glucopyranose ring, it is hardly to be expected that an intramolecular aldol condensation, joining carbon atoms 1 and 6, would take place. Some form of active intermediate seems called for and the fact that at least one biogenetic route to *myo*-inositol is NAD^+–NADH dependent[9] has led to the suggestion[6,10] that D-*xylo*-hexos-5-ulose 6-phosphate ("5-keto-glucose 6-phosphate") may be such an intermediate. The cyclization of this substance could lead to the formation of 2,4,6/3,5-pentahydroxycyclohexanone phosphate and the suggestion is rendered more attractive by the recent discovery[11] of *myo*-inosose-2 in nature.

In view of these considerations, it seemed appropriate to synthesize D-*xylo*-hexos-5-ulose (**3**) and to investigate some of its properties.

A number of years ago, Helferich and Bigelow[12] described the synthesis of **3** through a lengthy sequence of reactions. In the course of a synthesis of D-*xylo*-hexos-5-ulose 6-phosphate which we have recently reported,[13] 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranos-5-ulose (**1**) served as an intermediate. We now report the conversion of **1** into D-*xylo*-hexos-5-ulose (**3**) and describe a study of the behavior of this dicarbonyl sugar with dilute alkali.

The benzyl group of **1** was readily removed by catalytic hydrogenolysis to give crystalline 1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose-5-ulose (**2**) in high yield (Scheme I). An aqueous suspension of an acidic ion-exchange resin served to remove the isopropylidene group from **2** and D-*xylo*-hexos-5-ulose (**3**) was obtained as a syrup which behaved as a single substance when chromatographed on microcrystalline cellulose. Although the substance decomposed on standing at room temperature, its aqueous solutions could be stored in the frozen state at −5° for several months without detectable change.[14] On reduction with sodium boro-

(1) For a preliminary account of some of the work described here, see D. E. Kiely and H. G. Fletcher, Jr., *J. Amer. Chem. Soc.*, **90**, 3289 (1968).

(2) For the nomenclature of the cyclitols, use is made in this paper of the system recommended by the IUPAC Commission on the Nomenclature of Organic Chemistry and the IUPAC-IUB Commission on Biochemical Nomenclature: *Eur. J. Biochem.*, **5**, 1 (1968). To assist the reader, synonyms from older systems are sometimes given in parentheses.

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

(4) L. Maquenne, *Ann. Chim.* (Paris), **12**, 129 (1887); see also L. Maquenne, "Les sucres et leurs principaux dérivés," G. Carré and C. Naud, Paris, 1900, p 189.

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

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

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

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

(9) I.-W. Chen and F. C. Charalampous, *J. Biol. Chem.*, **239**, 1905 (1964).

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

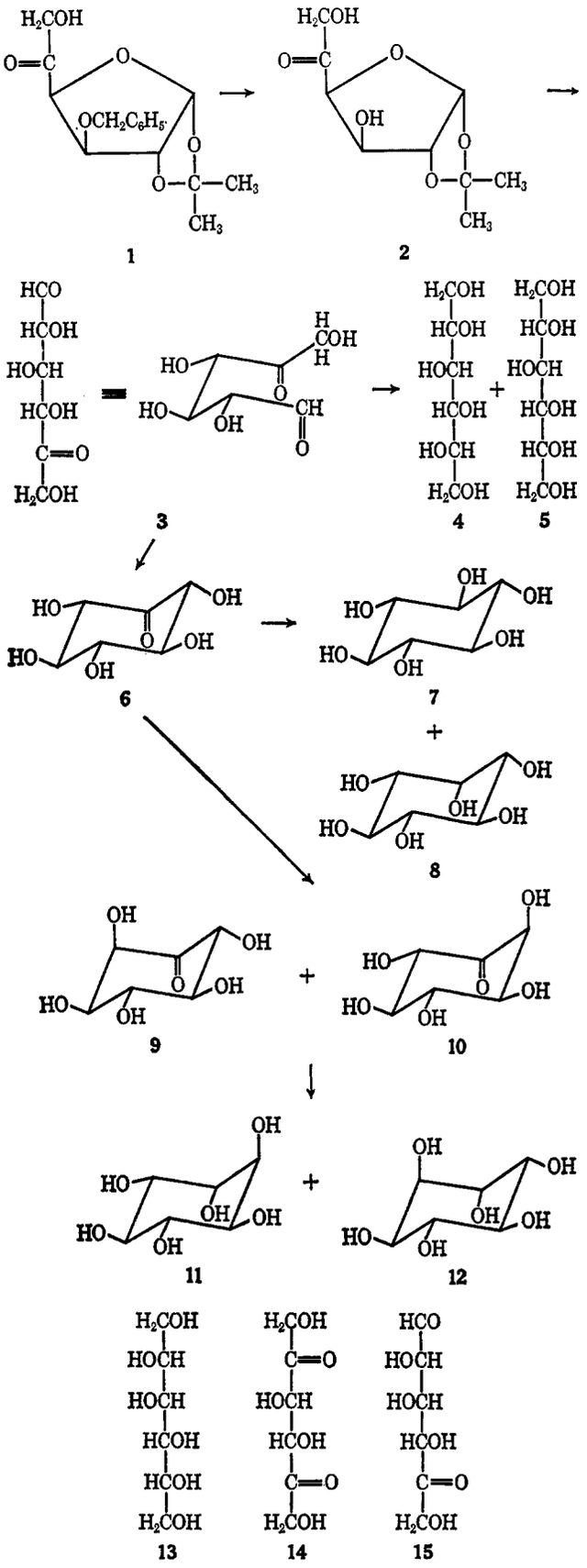
(11) W. R. Sherman, M. A. Stewart, P. C. Simpson, and S. L. Goodwin *Biochemistry*, **7**, 819 (1968).

(12) B. Helferich and N. M. Bigelow, *Z. Physiol. Chem.*, **200**, 263 (1931).

(13) D. E. Kiely and H. G. Fletcher, Jr., *J. Org. Chem.*, **33**, 3723 (1968).

(14) Whether the product obtained by Helferich and Bigelow[12] was identical with that made during the course of the present research is uncertain. However, the last step in the synthesis used by the earlier researchers involved exposure of **3** to alkali; in view of the alkali lability of **3** reported in the present paper, a synthesis which releases **3** under mildly acidic conditions appears preferable to one which uses alkaline conditions.

SCHEME I



hydride and subsequent acetylation with acetic anhydride–pyridine, **3** gave only two products and these were indistinguishable from the hexaacetates of D-glucitol (**5**) and L-iditol (**4**) when examined by glpc. The formation of D-glucitol and L-iditol on reduction confirms the structure of the dicarbonyl sugar as D-*xylo*-hexos-5-ulose (**3**) but which of the various possible tautometric forms may be present in solution is not known as yet. After trimethylsilylation of **3**, glpc shows the presence of four components; whether these represent the anomeric forms of two cyclic tautomers remains a matter for speculation.

A solution of **3** in 0.1 *N* sodium hydroxide at room temperature and under nitrogen became pale brown over the course of 30–60 min. Deionization removed the color completely and, after concentration, the solution yielded a syrup which strongly reduced Fehling solution and amounted to approximately one-half the weight of the **3** which was used. Trimethylsilylation of this syrup, followed by glpc, revealed several components, one of which was chromatographically indistinguishable from the TMS derivative of 2,4,6/3,5-pentahydroxycyclohexanone (**6**, *myo*-inosose-2). The deionized product from the alkaline treatment of **3** was reduced with sodium borohydride, and a white precipitate which formed was collected and dried. The infrared spectrum (KBr disk) of this product very closely matched that of an authentic sample of disodium *scyllo*-inositol diborate.[15,16] Acetylation with acetic anhydride–sulfuric acid[15,17] gave *scyllo*-inositol hexaacetate from which the free *scyllo*-inositol (**7**) was obtained. The material remaining in the mother liquor from which the disodium *scyllo*-inositol diborate had been removed was decationized, free of boric acid, and acetylated to give the crystalline hexaacetate of *myo*-inositol (**8**), identified by its melting point and infrared spectrum and by comparison with authentic material.

The above facts clearly establish the cyclization of **3** to **6**; the fact that the reaction proceeds under such mild conditions tends to support the postulated biosynthesis of *myo*-inositol. The reaction is, however, a complex one and components which are as yet unidentified have been detected. In this regard, we have investigated the behavior of 2,4,6/3,5-pentahydroxycyclohexanone (**6**) under the conditions of the cyclization. Treatment of **6** with alkali, followed by deionization and sodium borohydride reduction, gave a product which was examined as its TMS derivative by glpc. No component with the chromatographic characteristics of the TMS derivatives of glucitol or iditol was detected. This fact may be interpreted as indicating that the conversion of **3** into **6** is not a significantly reversible reaction or that, if it is reversible, **3** is quite rapidly converted under these conditions into ionic products. No component with the chromatographic characteristics of the TMS derivatives of *neo*-, *cis*-, and *epi*-inositols[18] was detected but a peak with the retention time of the TMS derivative of DL-*chiro*-inositol (**11** and **12**) was noted. It is apparent, then, that **6** is, in part, isomerized by alkali into DL-2,3,5/4,6-pentahydroxycyclohexanone (**9** and **10**) and that this ketose must be present when **3** cyclizes to **6**. It may be noted that DL-2,3,5/4,6-pentahydroxycyclohexanone (**10**), but not its enantiomorph **9**, might have arisen

(15) A. Weissbach, *J. Org. Chem.*, **23**, 329 (1958).
(16) Th. Posternak, E. A. C. Lucken, and A. Szente, *Helv. Chim. Acta*, **50**, 326 (1967).
(17) D. Reymond, *ibid.*, **40**, 492 (1957).
(18) We wish to thank Dr. Laurens Anderson of the University of Wisconsin for authentic specimens of these three inositols.

directly in the cyclization of **6**; however, such an event would have involved the formation of a *cis* pair of vicinal hydroxyl groups and we know of no precedent for this, although it may be pointed out that the cyclization of 6-deoxy-6-nitro-D-glucose and -L-idose gives, *inter alia*, a deoxynitroinositol in which the newly formed hydroxyl group is *cis* to the nitro group.[19]

Under alkaline conditions **3** might be expected to undergo a Lobry de Bruyn rearrangement to form D-*threo*-2,5-hexodiulose (**14**, "5-ketofructose")[20] or D-*lyxo*-hexos-5-ulose (**15**, "5-ketomannose"). However, both of these substances should have yielded D-mannitol (**13**) on reduction and none of this hexitol was detected after reduction of the mixture from the cyclization of **3**.

The transformation of **3** into **8** reported here may be regarded as a sequence in the second chemical synthesis of *myo*-inositol from D-glucose. The first such synthesis was carried out *via* 6-deoxy-6-nitro-D-glucose.[21-24]

Experimental Section[25]

1,2-*O*-Isopropylidene-α-D-*xylo*-hexofuranos-5-ulose (2).—A suspension of 10% palladium on carbon (1.60 g) in absolute ethanol (40 ml) was stirred with hydrogen until saturated, and a solution of the hemihydrate of **1**[18] (2.00 g) in absolute ethanol (100 ml) was added. The resulting mixture was stirred vigorously with hydrogen for 7 hr and the catalyst was then removed. A suspension of fresh catalyst (1.30 g) in absolute ethanol (presaturated with hydrogen) was added and the hydrogenolysis was continued for a further 5 hr. Tlc (ether and ether–benzene, 1:1) then showed the presence of but a trace of the faster moving **1**, the slower running **2** being the major component. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo* at 40° (bath) to give syrupy **2** which crystallized spontaneously on storage overnight. After recrystallization from benzene, **2** (1.21 g, 88%) had mp 114.5–116°; $[\alpha]^{21}D$ −63.2° (*c* 2.0, water); infrared absorption (KBr disk) at 3400 (vs) (OH), 1725 (vs) (C=O), 1375 (s), and 1385 (s) cm^{-1} (Me_2C); nmr signals at δ 1.38 and 1.55 (singlets, Me_2C) and 6.08 (doublet, H-1, $J_{1,2}$ = 4.0 Hz).

Anal. Calcd for $C_9H_{14}O_6$ (218.21): C, 49.54; H, 6.47. Found: C, 49.55; H, 6.76.

D-*xylo*-Hexos-5-ulose (3).—Dowex 50W-X8 (H^+) (2.1 g), which had been washed with water and with acetone and dried, was added to a solution of **2** (381 mg) in water (6 ml). The mixture was stored, without stirring, at 38–40° for 48 hr; tlc (ether–methanol, 9:1) then showed the hydrolysis to be complete, only **3** being detectable. The resin was removed by filtration and the filtrate was lyophilized to give **3** in quantitative yield as a colorless glass: $[\alpha]^{20}D$ −14.6° (*c* 3.12, water). On storage at room temperature, amorphous **3** decomposed; frozen aqueous solutions of the compound stored at −5° appeared to be stable indefinitely.

Converted at room temperature into its trimethylsilyl derivative and subjected to glpc at 150° on column A, **3** characteristically gave four peaks as shown in chromatogram *i* of Figure 1. Even in the presence of an excess of the silylating reagent, the TMS derivative of **3** appeared to be unstable at room temperature, discoloration of the solution and changes in the pattern of glpc peaks being noted after 24 hr.

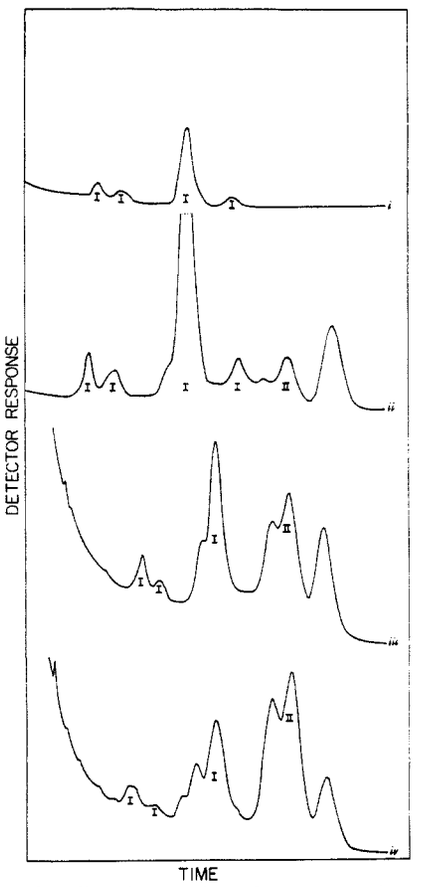


Figure 1.—Gas–liquid partition chromatography on column A of the trimethylsilyl derivatives of (*i*) D-*xylo*-hexos-5-ulose (**3**), (*ii*) **3** after 10 min in 0.1 *N* sodium hydroxide, (*iii*) after 25 min, and (*iv*) after 45 min.

Using the procedure of Frush and Isbell,[26] **3** was reduced with sodium borohydride. A sample (7 mg) of the dicarbonyl sugar was dissolved in borate buffer (3 ml, pH 4.9) and the solution was cooled. Over the course of 15 min, a solution of sodium borohydride (40 mg) in water (4 ml) was added. The reaction mixture was stored at room temperature overnight and the slightly alkaline solution (pH 9.1) was passed through a column of Amberlite IR-120 (H^+) (40 ml). The effluent (60 ml) was concentrated *in vacuo* and boric acid was removed from the residue as trimethyl borate. The syrup was finally held at room temperature and a pressure of <1 mm for 0.5 hr and then acetylated with acetic anhydride–pyridine at 110°. The acetylation mixture was concentrated under a stream of nitrogen to a volume of *ca.* 0.25 ml and samples of the resulting solution were chromatographed on column C[27] at 200°, using a flow rate of 60 ml/min. Two components, chromatographically indistinguishable from the hexaacetates of L-iditol (**4**) and D-glucitol (**5**), were detected. The ratio of the two (in the order named) was 1.3:1.

Cyclization of D-*xylo*-Hexos-5-ulose (3) in Sodium Hydroxide Solution.—A solution of **3** (102 mg) in water (3.2 ml) was deoxygenated by passing a stream of nitrogen through it for 10 min. The solution was cooled in an ice bath and a similarly deoxygenated solution of sodium hydroxide (0.8 ml, 0.52 *N*) was added dropwise, making the reaction mixture *ca.* 0.1 *N* in sodium hydroxide. Nitrogen was bubbled through the reaction mixture at room temperature for 30 min and the brownish solution was deionized (and decolorized) by passage through a column containing a mixture of Duolite A-4 (CO_3^{2-}) (30 ml) and Amber-

(19) F. W. Lichtenthaler, *Chem. Ber.*, **94**, 3071 (1961).

(20) G. Avigad and S. Englard, *J. Biol. Chem.*, **240**, 2290 (1965).

(21) M. Grosheintz and H. O. L. Fischer, *J. Amer. Chem. Soc.*, **70**, 1476 (1948).

(22) M. Grosheintz and H. O. L. Fischer, *ibid.*, **70**, 1479 (1948).

(23) B. Iselin and H. O. L. Fischer, *ibid.*, **70**, 3946 (1948).

(24) Th. Posternak, *Helv. Chim. Acta*, **33**, 1597 (1950).

(25) Melting points correspond to corrected values. Thin layer chromatography was conducted on silica gel 254 (E. Merck AG, Darmstadt) using the solvent systems specified and detecting the components by spraying with sulfuric acid and heating at 100°. Nmr spectra were obtained in $CDCl_3$ solution using a Varian A-60 spectrometer and tetramethylsilane as an internal standard. Glpc was carried out with F & M Models 500 and 5750, equipped with flame ionization detectors. Three columns were employed: (A) 3% SE-52 on Gas-Chrom A, 0.25 in. o.d. × 6 ft with nitrogen as a carrier gas; (B) 15% Apiezon N on Chromosorb P, 0.25 in. o.d. × 6.5 ft with helium as the carrier gas; (C) 3% ECNSS-M on Gas-Chrom Q, 0.25 in. o.d. × 10 ft with nitrogen as a carrier gas. These media were the products of the Applied Science Laboratories, Inc., State College, Pa. Trimethylsilyl derivatives were prepared according to the method of C. C. Sweeley, R. Bentley, M. Makita, and W. W. Wells, *J. Amer. Chem. Soc.*, **85**, 2497 (1963).

(26) H. L. Frush and H. S. Isbell, *ibid.*, **78**, 2844 (1956).

(27) The utility of this system for the separation of alditol acetates was originally noted by J. S. Sawardeker, J. H. Sloneker, and A. Jeanes, *Anal. Chem.*, **37**, 1602 (1965).

lite IR-120 (H^+) (20 ml). The effluent (*ca.* 110 ml) was concentrated *in vacuo* (40° bath) to a syrup (51 mg) which strongly reduced Fehling solution at room temperature.

Investigation of the Products. A. Reduction.—The syrupy product, prepared as described above, was dissolved in water (3.5 ml) and the solution was cooled in an ice bath. While this solution was stirred, sodium borohydride (47 mg)[28] was added. On standing overnight at room temperature, the reaction mixture deposited long, colorless needles which were removed by filtration, washed with a little cold water, and dried *in vacuo*. The ir spectrum of this material (KBr disk) closely resembled that of a pure authentic specimen of disodium *scyllo*-inositol diborate.[15,16] A small sample (*ca.* 1 mg) of the salt was dissolved in water and the solution was decationized with IR-120 (H^+) (3 ml) and concentrated *in vacuo* at 44° (bath). The syrupy residue was trimethylsilylated and then subjected to glpc at 170° on column A. A major peak (90%) was obtained which was identical with one shown by authentic disodium *scyllo*-inositol diborate when treated in a similar manner. The retention time of this component was identical with that of the TMS derivative of *scyllo*-inositol (7) and thus it appears that *scyllo*-inositol diborate is broken down to the normal TMS derivative of *scyllo*-inositol on trimethylsilylation.

The remainder of the disodium *scyllo*-inositol diborate derived from **3** was dissolved in acetic anhydride (2 ml) containing 1 drop of concentrated sulfuric acid.[15,17] The solution was heated at 85° (bath) for 10 min, cooled, and poured into ice water. The mixture was stirred for 1 hr and the light brown, amorphous precipitate was removed by filtration and then dissolved in dichloromethane. The dichloromethane solution was transferred to a conical 13-ml centrifuge tube and concentrated under a stream of nitrogen to an amorphous mass which was dissolved in boiling absolute ethanol (0.5 ml). Upon cooling to room temperature, the solution deposited fine, short, colorless needles which were successively recrystallized from absolute ethanol and from acetic anhydride; thus purified, the product had mp 289–290° (sealed capillary) and showed an ir spectrum (KBr disk) identical with that of *scyllo*-inositol hexaacetate; mp 290° has been reported[29] for this substance. The *scyllo*-inositol hexaacetate, prepared as described above, was deacetylated with methanolic sodium methoxide and the cyclitol then converted into its TMS derivative which was subjected to glpc at 170° on column A. A single peak, indistinguishable from that of the TMS derivative of authentic **7**, was obtained.

The original aqueous mother liquor from which the disodium *scyllo*-inositol diborate had been removed was passed through a column of IR-120 (H^+) (20 ml) and the eluent (50 ml) was concentrated *in vacuo* at 44° (bath) to a flocculent mass. The residue was freed of boric acid as the trimethyl ester and the syrupy material was then acetylated with acetic anhydride–pyridine (2 ml, 1:1) at 78° for 1.25 hr. Worked up in conventional fashion, the product (83 mg) was treated with hot absolute ethanol and the insoluble portion removed by filtration. On cooling, the filtrate deposited colorless platelets which were recrystallized from absolute ethanol; they had mp 217–218° either alone or in admixture with authentic *myo*-inositol hexaacetate. The ir spectrum of the product (KBr disk) was indistinguishable from that of an authentic sample. A portion of the hexaacetate was deacetylated and converted into the TMS derivative which was chromatographed at 170° on column A. A single peak, indistinguishable from that afforded by the TMS derivative of **8**, was obtained.

B. Glpc Study of Cyclization Mixture.—D-*xylo*-Hexos-5-ulose (**3**, 31 mg) was treated with 0.1 *N* sodium hydroxide solution as described earlier, aliquots being removed from the reaction mixture at 5-min intervals. Each aliquot was deionized and decolorized by passage through a mixture of Duolite A-4 (CO_3^{2-}) and Amberlite IR-120 (H^+) and the solution were concentrated *in vacuo* at 40° (bath), to give syrups which were converted into their TMS derivatives and then subjected to glpc on column A at 150°. Chromatograms *ii*, *iii*, and *iv* in Figure 1 correspond, respectively, to aliquots taken after 10, 25, and 45 min. Peak II was indistinguishable from that of the TMS derivative of authentic 2,4,6/3,5-pentahydroxycyclohexanone (**6**, *myo*-inosose-2). Inspection of chromatograms *ii* to *iv* in Figure 1 clearly shows how the peaks due to D-*xylo*-hexos-5-ulose (marked "I") diminish with time while that due to **6** increases. The unmarked peaks are as yet unidentified.

C. Glpc Study of Cyclization Mixture after Reduction with Sodium Borohydride.—Reduction of the mixture from the alkaline cyclization of **3**, followed by glpc of the TMS derivative on column A, afforded a highly reproducible pattern of peaks such as that shown in Figure 2. Peak V corresponds to the TMS

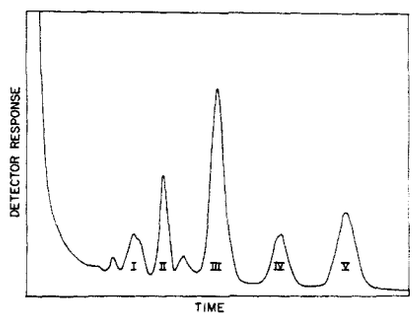


Figure 2.—Gas–liquid partition chromatography on column A of the trimethylsilyl derivatives of the sodium borohydride reduced products from the cyclization of **3**.

derivative of *myo*-inositol while peak IV denotes a retention time equal to that of the TMS derivative of *scyllo*-inositol. Peak III represents the TMS derivatives of glucitol and iditol, arising from the reduction of unreacted **3**. The TMS derivative of DL-*chiro*-inositol also falls in this peak as will be discussed later. *epi*-Inositol cochromatographs with *scyllo*-inositol in this system but its presence is rendered unlikely since DL-2,3,4,6/5-pentahydroxycyclohexanone (*epi*-inosose-2) was not detected in the direct glpc of the TMS derivative of the unreduced cyclization mixture. Peaks I and II are as yet unidentified.

The Behavior of 2,4,6/3,5-Pentahydroxycyclohexanone (6) with Alkali.—The cyclose (**6**, 29 mg) was treated with 0.1 *N* sodium hydroxide in the manner described earlier for the cyclization of **3**. Aliquots were withdrawn at 15, 30, and 45 min and, after deionization and concentration, these samples were converted into the TMS derivatives and subjected to glpc at 150° on column A. All three samples gave the pattern of peaks shown in Figure 3. The peak with the longest retention time

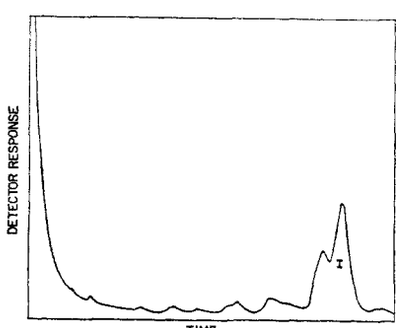


Figure 3.—Gas–liquid partition chromatography on column A of the trimethylsilyl derivative of the products obtained by treatment of **6** with 0.1 *N* sodium hydroxide.

(I) corresponds to **6**; while the adjacent peak with slightly shorter retention time has not been identified, the appearance of this partially resolved pair of peaks closely resembles that shown in chromatogram *iv* of Figure 1. The peaks of shorter retention time are very small; they will be referred to later in this paper.

In a separate experiment, 2,4,6/3,5-pentahydroxycyclohexanone (**6**, 29 mg) was treated with 0.1 *N* sodium hydroxide for 20 min and the solution was then deionized as described earlier. One-half (6 ml) of the solution was treated with sodium borohydride (45 mg) while the other half was treated with platinum oxide (70 mg) and shaken with hydrogen; after removal of solvent, the products from both reductions were trimethylsilylated. In each case, glpc on column A gave a similar pattern of peaks; that obtained with the portion which had been reduced with sodium borohydride is shown in Figure 4. Material from each reduction procedure was also chromatographed (at 210°) on column B with the results shown in Figure 5. Peak IV arises from *scyllo*-inositol while peak V represents *myo*-inositol.

(28) A parallel experiment in which a boric acid buffer was used gave identical results.

(29) J. Müller, *Ber.*, **40**, 1821 (1907).

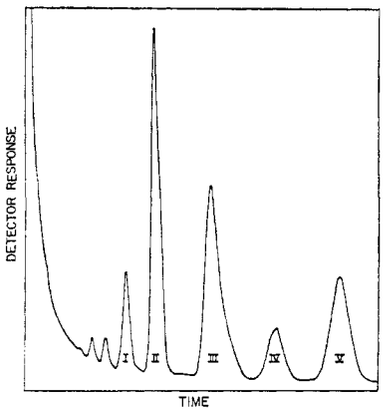


Figure 4.—Gas–liquid partition chromatography on column A of the trimethylsilyl derivative of the sodium borohydride reduced products from the alkaline treatment of 6.

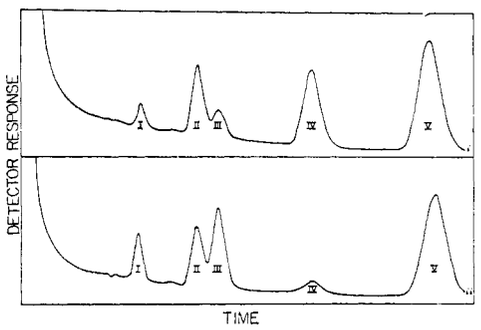


Figure 5.—Gas–liquid partition chromatography on column B of the trimethylsilyl derivative of alkali-treated 6 which had been (*i*) reduced with sodium borohydride and (*ii*) reduced with hydrogen in the presence of platinum oxide.

Cochromatography with authentic samples of *neo*-inositol, *cis*-inositol, and *epi*-inositol clearly showed that none of these three inositols was present in either mixture. The material giving rise to peaks I–III in Figure 5, chromatogram *ii*, was separated on a preparative scale using column B, equipped with a stream splitter. The homogeneity of each of the three fractions was confirmed by rechromatography on columns A and B. The material from peak III had the same retention time as the TMS derivative of DL-*chiro*-inositol; after hydrolysis and acetylation, it was chromatographed on column C at 180° and found to migrate as a single compound with the retention time of authentic DL-*chiro*-inositol hexaacetate. In column B the component from peak II had a retention time which was indistinguishable from that of the TMS derivatives of iditol, mannitol, and glucitol; in column A, however, the component from peak II shows a retention time which sharply differentiates it from these three hexitols. It is unlikely, therefore, that the minor peaks of short retention time in Figure 3 represent D-*xylo*-hexos-5-ulose. The identity of the material represented by peaks I and II remains unknown.

The identification of peaks III–V in Figure 5 is supported by further considerations. The catalytic reduction of inososes in neutral solution and in the presence of platinum oxide leads largely to the formation of axial hydroxyl groups while reduction with sodium borohydride gives a mixture of the epimeric axial and equatorial products.[30] This generalization is reflected in features of Figure 5, the ratio of *scyllo*-inositol to *myo*-inositol being much lower in the catalytic reduction (chromatogram *ii*) than when sodium borohydride was used (chromatogram *i*). Similarly, the ratio of DL-*chiro*-inositol to *myo*-inositol is larger when the mixture is reduced catalytically (chromatogram *ii*) than when sodium borohydride is used (chromatogram *i*); these are the results to be expected in the reduction of 9 and 10.

Registry No.—**2**, 19684-32-3; **3**, 19684-22-1; **7**, 488-59-5; **8**, 87-89-8.

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(30) Th. Posternak, "The Cyclitols," Hermann, Paris, 1965, p 157.

Nucleosides. LVIII. Transformations of Pyrimidine Nucleosides in Alkaline Media. III.[1] The Conversion of 5-Halogenouridines into Imidazoline and Barbituric Acid Nucleosides[2,3]

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Reaction of 2′,3′-*O*-isopropylidene-5-bromouridine (**3b**) with alkoxide affords 5′,6-anhydro-2′,3′-*O*-isopropylidene-6-hydroxyuridine (**15**) which is converted by acid hydrolysis into 1-β-D-ribofuranosylbarbituric acid ("6-hydroxyuridine") (**18**) in high over-all yield. Treatment of **15** with NaOBz–DMF gives the 5′-*O*-benzoate of isopropylidene-6-hydroxyuridine (**19**). In aqueous alkali, 2′,3′-*O*-isopropylidene-5-fluorouridine (**3a**) is converted into 1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-2-oxo-4-imidazoline-4-carboxylic acid (**20**) which, after acid hydrolysis, gives the unblocked imidazoline ribo nucleoside (**2**) in good over-all yield. A total synthesis of **2** *via* condensation of methyl 2-oxo-4-imidazoline-4-carboxylate with tri-*O*-benzoyl-D-ribofuranosyl chloride is given. Unlike the 5-fluoro derivative (**3a**), the 5-bromo (**3b**) and the 5-iodo (**3c**) analogs in aqueous alkali give poor yields of **20** along with other 2′,3′-*O*-isopropylidenated products, namely, 5′,6-anhydro nucleoside (**15**), uridine (**12**), 5-hydroxyuridine (**17**), and barbituric acid ribo nucleoside (**13**). It is shown that the conversion of nucleosides **3** into **12**, **17**, and **20** involves anchimeric assistance by the 5-hydroxyl group of the sugar moiety and, further, that the presence of a 2′,3′-*O*-isopropylidene group promotes this participation. Evidence obtained from a study of the 5′-deoxy analog (**9b**) of **3b** suggests that the formation of **13** from **3b** or **3c** occurs mainly by direct attack by hydroxide ion on C-6 and to a lesser extent by solvolysis of **15**.

Recent investigations in this laboratory have shown that 5-halogenated 1-β-D-arabinofuranosyluracils are converted in alkaline media into 2′,6-anhydro-6-hydroxyuracil- and 2-oxo-4-imidazoline-4-carboxylic acid

(1) For the previous paper in this series, see R. J. Cushley, S. R. Lipsky, and J. J. Fox, *Tetrahedron Lett.*, 5393 (1968).

(2) This investigation was supported in part by funds from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service (Grant No. CA 08478).

(3) A preliminary account of part of this work has been published: B. A. Otter, E. A. Falco, and J. J. Fox, *ibid.*, 2967 (1968).