Alicyclic Carbohydrates. XXXVI. Participation by Neighboring Methoxyl in a Displacement of Hydroxyl by Halogen. Conversion of (−)-Inositol into *meso*-(1,3,5/2,4)-Cyclohexanepentol[1,2]

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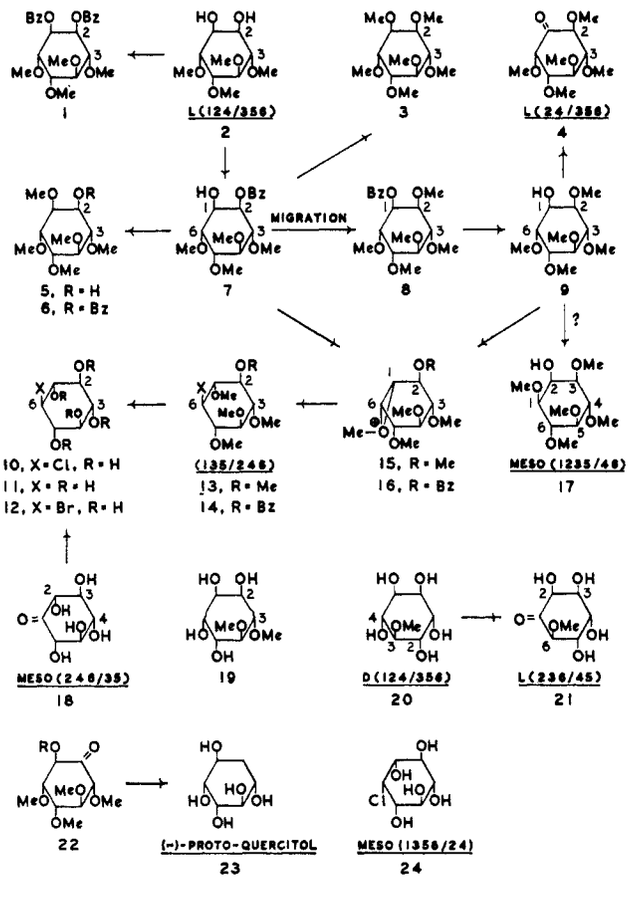
A neighboring methoxyl group appears to participate in the reaction of phosphorus pentachloride with the one free hydroxyl group in (−)-inositol 2,3,4,5,6-pentamethyl ether (**9**). The reaction product was the all-*trans* diastereomer (**13**, X = Cl) of chloropentamethoxycyclohexane identified by conversion into the previously known cyclohexanepentol (*"scyllo*-quercitol") (**11**), and to the chloropentol (**10**) pentaacetate. Tetramethyl ether **2** derived from (−)-inositol was selectively benzoylated at the (equatorial) position 2. The resulting tetramethyl ether monobenzoate (**7**) reacted with methyl iodide and silver oxide to give a mixture consisting mainly of 1-monobenzoate pentamethyl ether **8**, owing to acyl migration.[4,5] Similar reaction of tetramethyl ether monobenzoate **7** with phosphorus pentachloride gave chloropentol tetramethyl ether monobenzoate **14**, which was identified by conversion into the same chloropentol (**10**).

Recently we reported a synthesis of levorotatory form **23** of quercitol or *proto*-quercitol.[2] This synthesis was effected by oxidation of hexol pentamethyl ether **5**, a derivative of (−)-inositol (**3**, Me = H), to the ketopentol or inosose derivative, **22**.[6] Indirect conversion of the carbonyl group to methylene, followed by ether cleavage, gave the desired cyclohexanepentol stereoisomer, **23**.[7]

In the course of this research we also prepared diastereomeric hexol pentamethyl ether **9**. Efforts were made to replace the free hydroxyl group of this compound by halogen, which probably could easily be replaced by hydrogen to give a diastereomeric quercitol derivative (**9**, OH = H). However, the halogenation of **9** with phosphorus pentachloride gave quite unexpected and interesting results, which will now be described.[8]

Hexol pentamethyl ether **9** was prepared from the previously reported[2] tetramethyl ether **2** (Scheme I). This intermediate reacted selectively with benzoyl chloride under suitable conditions to give the equatorial monobenzoate **7**. When this derivative was methylated in the presence of silver oxide, the benzoyl group migrated from position 2 to axial position 1, so that the predominant product was the diastereomeric pentamethyl monobenzoate **8** instead of **6**. Intermediate **8** was readily hydrolyzed to hexol pentamethyl ether **9**. On reaction with excess benzoyl chloride, hexol tetramethyl ether **2** was converted into tetramethyl dibenzoate **1**, as expected.

Scheme I



Hexol pentamethyl ether **9** was treated with phosphorus pentachloride in benzene for 6 hr at 80° under anhydrous conditions. The product, a colorless syrup, was shown by microanalysis and infrared spectroscopy to be a chlorocyclohexanepentol pentamethyl ether (**13** or stereoisomer, X = Cl). In order to characterize this product further, it was demethylated with hydrogen bromide, giving a colorless crystalline compound, mp 236–237°, whose microanalysis and ir spectrum

(1) Presented in part to the International Conference on Cyclitols and Phosphoinositides at the N. Y. Academy of Sciences, New York, N. Y., Sept 1968.

(2) For preceding paper, see G. E. McCasland, M. O. Naumann, and L. J. Durham, *J. Org. Chem.*, **33**, 4220 (1968); see also G. E. McCasland, M. O. Naumann, and L. J. Durham, *Carbohyd. Res.*, **4**, 516 (1967).

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(4) For recent studies indicating that acyl migration may be more common than often realized, see S. J. Angyal and G. J. H. Melrose, *J. Chem. Soc.*, 6494, 6501 (1965).

(5) For an example of acyl migration during methylation, see L. Anderson and A. M. Landel, *J. Amer. Chem. Soc.*, **76**, 6130 (1954).

(6) Hexol pentamethyl ether **9** on oxidation in a similar manner with sodium metaperiodate (catalyzed by ruthenium dioxide) gave a ketopentol (inosose) pentamethyl ether, presumably **4**, as a syrup. From this syrup was prepared a (not completely pure) 2,4-dinitrophenylhydrazone, yellow needles, mp 210° (*Anal.* Calcd for $C_{17}H_{24}N_4O_9$: C, 47.66; H, 5.64. Found: C, 41.37; H, 5.62). Material is not available at present for further characterization.

(7) For procedures used for oxidation of secondary alcohol groups, see (a) V. M. Parikh and J. K. N. Jones, *Can. J. Chem.*, **43**, 3452 (1965); (b) W. Sowa and G. H. S. Thomas, *ibid.*, **44**, 836 (1966); (c) J. Parrick and J. W. Rasburn, *ibid.*, **43**, 3453 (1965).

(8) At the time this work was started, we erroneously believed that hexol pentamethyl ether **9** had configuration **5**, so that the expected product of halogenation and dehalogenation would have been the pentamethyl ether of (−)-*proto*-quercitol **23**.

were consistent with its chlorocyclohexanepentol[9] structure (**10** or stereoisomer). The configuration of **10** was determined by dehalogenation in the usual manner[10b] to the previously known *meso*(135/24) or "*scyllo*" diastereomer of cyclohexanepentol (quercitol), **11**. The identity of **11** was confirmed by comparisons with authentic samples of "*scyllo*-quercitol" [10] and its pentaacetate[10] and pentabenzoate. Cyclohexanepentol **11** previously was prepared from ketopentol ("*scyllo*-inososе") **18** or bromopentol **12**.[10]

The ir spectra of the pentol and its pentaacetate and pentabenzoate contained characteristic absorption peaks at about 853 cm^{-1} (methylene C–H rock), and did not contain any peaks at about 873 cm^{-1} which could indicate the presence of equatorial HOC-H, or equatorial RCOOC–H. Thus no axial functional groups were present.[11]

Although epimeric chloropentol **24** presumably also would give cyclohexanepentol **11** on dehalogenation, configuration **24** is highly improbable for mechanistic reasons. Also the infrared spectra of our chloropentol and its pentaacetate and pentamethyl ether indicated it is the all-equatorial diastereomer **10**.

The spectra each contained peaks due to C–Cl stretching absorption at about 780 cm^{-1} (lit.[11] ranges, axial 646–730 and equatorial 736–856 cm^{-1}). Peaks corresponding to equatorial ClC–H rock, or equatorial HOC–H rock (lit.[11] about 873 cm^{-1}), were absent. The nmr spectrum of **10** has not been fully interpreted. However, by use of proton magnetic double resonance (see below) on its pentaacetate derivative, the all-equatorial or "scyllo" configuration was definitely established.

The over-all result in the reaction of hexol pentamethyl ether **9** with phosphorus pentachloride thus consisted of (1) inversions of configuration at positions 1 and 6, formula **9**; (2) migration of a methoxyl group from position 6 to 1; (3) replacement of position 6 functional group by chlorine. The most reasonable interpretation of these results, we believe, is participation by the neighboring methoxyl group at position 6 in the reaction with phosphorus pentachloride, giving the bicyclic methoxonium ion **15** (not isolated), which on nucleophilic attack by chloride ion with inversion, at position 6, would give chloropentol pentamethyl ether **13**.

The departing group, perhaps $-OPCl_4$, presumably is displaced by the neighboring *trans*-methoxyl to give methoxonium ion **15**. The *trans*-diaxial conformation of the groups at positions 1 and 6 (formula **9**) should be favorable to such an internal displacement.

Other possible mechanisms, *e.g.*, the direct epimerization of the position 6 methoxyl group to give diastereomer **17**, followed by displacement of a hydroxyl (or possibly, phosphate ester) group at position 2 (formula **17**) seem much less probable.

Thus the reaction here described is one of a growing number of instances in which a supposedly "inert" methoxyl or alkoxyl group serves as a participating neighboring group in a displacement reaction.

For example, previous studies[12] have shown that a neighboring methoxyl group may participate in certain solvolyses of alkyl arylsulfonates, and in certain substitution reactions of alkyl halides with silver acetate. This participation leads to kinetic effects (anchimeric assistance) and in some cases to otherwise unexpected configurational inversions or retentions, racemization, methoxyl migration, or demethylation. There have been few, if any, examples reported of such participation by neighboring methoxyl in the displacement of *hydroxyl by halogen*.

Hexol tetramethyl ether monobenzoate **7** was treated with phosphorus pentachloride in a similar manner. The product, a colorless syrup, was shown by microanalysis and infrared spectroscopy to have the constitution of a chlorocyclohexanepentol tetramethyl ether monobenzoate (**14** or stereoisomer, X = Cl). The nmr spectrum has not been fully interpreted, but apparently is that of a mixture containing other stereoisomers or by-products as well as **14**. However, when this syrup was cleaved with hydrogen bromide, the only product isolated was a chlorocyclohexanepentol, mp 234–236°, shown to be identical with diastereomer **10** above. The over-all yield, based on **7** (not **14**), was 27%.

Although the tetramethyl ether monobenzoate may react in more than one manner with phosphorus pentachloride, these preliminary results suggest that the (*trans*) neighboring methoxyl at position 6 (formula **7**) has a greater tendency to "participate" than the (*cis*) neighboring benzoyloxy group at position 2.

In the course of our synthetic work, we also prepared hexol tetramethyl ether dibenzoate **1**. Also, we converted the diacetone ketal of (+)-pinitol (**20**) into the corresponding ketopentol (inosose) monomethyl ether **21**. Also, we prepared samples of the previously reported[13] 3,4-dimethyl ether **19** of (−)-inositol and its 1,2:5,6-diacetone ketal.[14] These various compounds were used for proton magnetic resonance studies (see below).

Proton Magnetic Resonance Studies.—Proton magnetic resonance spectroscopy at 60 and 100 MHz was used to establish or confirm the constitution and configuration of most of the products and intermediates here reported (for details, see the Experimental Section).

The special reagent, trichloroacetyl isocyanate,[15] was added directly to the sample tube in the case of the hexol pentamethyl ether **9**, causing cancellation of the –OH and HOCH signals and the appearance of new signals, for the RNHCOOCH and -NH– protons. The

(9) During the period 1907–1915, Müller, and Griffin and Nelson, by reaction of *myo*-inositol with hot acetyl chloride (or its hexaacetate with hydrogen chloride) prepared 6-chlorocyclohexanepentol pentaacetate samples of mp 247 and 250°, respectively, which probably were identical with each other, and with our isomer of mp 248° (**10**, pentaacetate). No samples of their products are available for comparison. See (a) *J. Chem. Soc.*, **91**, 1790 (1907); **101**, 2383 (1912); (b) *J. Amer. Chem. Soc.*, **37**, 1552 (1915).

(10) (a) T. Posternak, *Helv. Chim. Acta*, **24**, 1045 (1941); (b) G. E. McCasland and E. C. Horswill, *J. Amer. Chem. Soc.*, **75**, 4020 (1953).

(11) For discussions of axial–equatorial effects in the ir spectra of substituted cyclohexanes, see (a) S. A. Barker, E. J. Bourne, R. Stephens, and D. H. Whiffen, *J. Chem. Soc.*, 4211 (1954); (b) A. R. H. Cole, P. R. Jeffries, and G. T. A. Muller, *ibid.*, 1222 (1959); (c) M. Larnaudie, *J. Phys. Radium*, **15**, 650 (1954); (d) D. H. R. Barton, J. E. Page, and C. W. Shoppee, *J. Chem. Soc.*, 331 (1956).

(12) See for examples (a) B. Capon, *Quart. Rev.* (London), **18**, 48 (1964); (b) S. Winstein, *et al.*, *J. Amer. Chem. Soc.*, **65**, 2196 (1943); **74**, 1160 (1952); **75**, 145, 155 (1953); **79**, 3278 (1957); *Tetrahedron*, **3**, 1 (1958); (c) D. S. Noyce, *et al.*, *J. Amer. Chem. Soc.*, **82**, 884, 1246 (1960).

(13) L. Anderson, R. Takeda, S. J. Angyal, and D. J. McHugh, *Arch. Biochem. Biophys.*, **78**, 518 (1958).

(14) (a) S. J. Angyal, C. G. Macdonald, and N. K. Matheson, *J. Chem. Soc.*, 3321 (1953); (b) S. J. Angyal and C. G. Mcdonald, *ibid.*, 686 (1952); (c) M. Pitman, M.S. Thesis (with Professor S. J. Angyal), University of N. S. W., Sydney, Australia, 1957.

(15) V. W. Goodlett, *Anal. Chem.*, **37**, 431 (1965).

use of trichloroacetyl isocyanate also permitted all five of the methoxyl groups to be observed as well-resolved individual three-proton singlets.

The spectrum of free chloropentol **10** was found difficult to interpret, even when recorded at 220 MHz with the superconducting solenoid pmr spectrometer.[16] However, the 100-MHz spectrum of the corresponding pentaacetate was successfully interpreted by means of spin decoupling (double resonance). The Cl–CH signal was thus demonstrated to be a triplet centered at 4.00 ppm, with the sum of its coupling constants (J) equal to at least 20 Hz. The Cl–CH proton must then be axial and have two axial neighboring protons, so that the all-equatorial conformation and configuration **10** is correct.

The spectrum of *meso*-(1,3,5/2,4)- or *scyllo*-quercitol[10] was recorded (apparently for the first time), using deuterium oxide at 60 MHz. The equatorial methylene proton produced a pair of triplets, due to coupling with the geminal proton (J = 12 Hz), and the two neighboring axial protons (J = 4 Hz). The axial methylene proton produced a quartet further upfield, due to approximately equal coupling (J = 12 Hz) with the geminal and two neighboring axial protons. The remaining five, very similar (all axial) ring protons produced a complicated narrow multiplet in the region 3.1–3.8 ppm.

In the course of this work, the spectra of the previously known (−)-inositol dimethyl ether **19** and its diacetone ketal, and of the new inosose monomethyl ether **21** were observed.

Experimental Section[17]

All melting points have been corrected, and were measured on a Nalge–Axelrod micro hot stage. Microanalyses were performed by the Micro-Tech Laboratories, Skokie, Ill. Optical rotations were measured with a Rudolph Model 62 laboratory polarimeter. Infrared spectra were recorded on Perkin-Elmer Model 137 and 437 spectrometers. Darco G-60 brand[18] of decolorizing charcoal was used. Petroleum ether of boiling point 60–80° was used.

Proton magnetic resonance spectra at 60 MHz were recorded and integrated with Varian A-60 and A-60D spectrometers, and at 100 MHz were recorded with Varian HR-100 and HA-100 spectrometers. The HA-100 was operated in the frequency-sweep mode. Unless otherwise noted, each spectrum was run both at 60 and 100 MHz. For spectra in chloroform-*d*, tetramethylsilane (TMS) was used as internal reference. For spectra in deuterium oxide, sodium 2,2-dimethyl-2-silapentanesulfonate (DSS) was used as internal reference. Chemical shifts are reported in parts per million (δ) from the TMS or DSS reference taken as zero. Field-swept double-resonance experiments on the HR-100 spectrometer were conducted according to the method of Johnson.[19] Modulation was provided by the fixed oxcillator of the Varian V-3521-A nmr integrator (operated on its lower side band), and a Hewlett–Packard hp-200-J audiooscillator (monitored by a Hewlett–Packard 521-C frequency counter), for fixed and variable modulation, respectively. Triple-resonance experiments were conducted with additional modulation from a Hewlett–Packard 200-CD oscillator.

L(1,2,4/3,5,6) Stereoisomer of 3,4,5,6-Tetramethoxy-1,2-cyclohexanediol 2-Monobenzoate [Tetra-O-methyl-(−)-inositol Monobenzoate], 7.—To a 2.36-g portion of tetramethyl ether **2**,[2] mp 90–92°, in 15 ml of pyridine was added 1.5 ml of benzoyl chloride dropwise at room temperature. The mixture after standing for 24 hr was slowly poured with stirring into 100 ml of ice–water. The resulting mixture was extracted with two 50-ml portions of ethyl acetate and the extract processed in the usual manner. After three recrystallizations from light petroleum, the product was obtained as colorless needles: 2.1 g (62%); mp 120–121°; $[\alpha]^{25}D$ −94.1° (c 3, CCl_4); ir (Nujol) 720, 1100, 1275, 1615, 1725, and 3750 cm^{-1}; nmr (60 MHz, $CDCl_3$); δ 8.08 (m, 2, aromatic *ortho*), 7.3–7.6 (m, 3, *meta* plus *para*), 5.27 (m, 1, poorly resolved, sum of J = 18 Hz, H-2), 4.38 (m, 1, sum of J = 10 Hz, H-1, collapses to three-line pattern on adding D_2O), 3.2–3.9 (m, partially obscured by methoxy singlets, 4, H-3, H-4, H-5, H-6), 3.63 (s, 3, –OMe), 3.54 (s, 6, –OMe), 3.52 (s, 3, –OMe), 2.42 (d, 1, J = 3.5 Hz, –OH, disappears upon addition of D_2O). On the addition of D_2O, a large singlet appeared at 4.63 ppm (HDO).

Anal. Calcd for $C_{17}H_{24}O_7$: C, 59.99; H, 7.11. Found: C, 59.90; H, 7.35.

L(1,2,4/3,5,6) Stereoisomer of 3,4,5,6-Tetramethoxy-1,2-cyclohexanediol Dibenzoate [Tetra-O-methyl-(−)-inositol Dibenzoate], 1. A. From the Tetramethyl Ether.—To a solution of 0.24 g of tetramethyl ether **2** (mp 90–92°) in 3.0 ml of pyridine was added 0.35 ml of benzoyl chloride. After 50 hr the mixture was slowly poured into 25 ml of ice-cold 2% sodium bicarbonate solution, with stirring. After 12 hr of stirring, the mixture was extracted with two 25-ml portions of ethyl acetate. The ethyl acetate extract was processed in the usual manner, giving 0.36 g (80%) of the once-recrystallized (from petroleum ether) product, colorless prisms: mp 106–108°; $[\alpha]^{25}D$ −111.1° (c 7, CCl_4); ir (Nujol) 715, 1110, 1265, 1610 and 1730 cm^{-1}; nmr (60 MHz, $CDCl_3$) δ 7.85–8.15 (m, 4, aromatic *ortho*), 7.3–7.8 (m, 6, *meta* plus *para*), 5.89 (t, 1, J = 3.5 Hz, H-1). 5.51 (m, 1, sum of J = 13 Hz, H-2), 3.5–4.0 (m, partially obscured by methoxy singlets, 4, H-3, H-4, H-5, H-6), 3.71, 3.63, 3.58, and 3.54 (singlets, total 12 H, –OMe), spectrum unchanged by addition of a little D_2O.

Anal. Calcd for $C_{24}H_{28}O_8$: C, 64.85; H, 6.35. Found: C, 65.15; H, 6.33.

B. From the Tetramethyl Ether Monobenzoate.—When monobenzoate **7** (mp 121°) was treated in a similar manner (using less benzoyl chloride), the dibenzoate, mp 106–108°, was obtained in 85% yield, and shown by ir spectrum and mixture melting point to be identical with the product above.

L(1,2,4/3,5,6) Stereoisomer of 2,3,4,5,6-Pentamethoxycyclohexanol [Penta-O-methyl-(−)-inositol], 9.—A 2.0-g portion of tetramethyl ether monobenzoate **7** (mp 121°) was methylated in the manner previously described,[2] giving 0.51 g (24%) of the crystallized (from *n*-heptane) product, 2-O-benzoyl-1,3,4,5,6-penta-O-methyl-(−)-inositol, **6**, resulting from methylation *without* acyl migration, mp 88–90°.

The *n*-heptane mother liquor on evaporation yielded a larger amount of the 1-O-benzoyl-2,3,4,5,6-penta-O-methyl-(−)-inositol, **8**, in the form of a colorless syrup: ir (liquid film) 715, 925, 1110, 1150, 1275, 1610, 1730, and 2900 cm^{-1}. This product is the result of acyl migration during methylation.

This syrup was hydrolyzed with hot aqueous ethanolic sodium hydroxide in the usual manner, giving 0.48 g (52%) of crystallized (from *n*-heptane) hexol pentamethyl ether, **9**: mp 65–66°; colorless prisms; $[\alpha]^{25}D$ −37.2° (c 4, CCl_4); ir (Nujol) 1020, 1100, 1150, 1190, and 3640 cm^{-1}; nmr (chloroform-*d*, 60 and 100 MHz) δ 4.15 (m, 1, poorly resolved, H-1), 3.2–3.8 (partially obscured by methoxyl singlets, 5, H-2, H-3, H-4, H-5 and H-6), 3.59, 3.60 (s, 6, –OMe, three each, OMe, not resolved at 60 MHz), 3.51 (s, 6, –OMe), 3.48 (s, 3, –OMe), 2.92 (d, poorly resolved, 1, –OH) [at 100 MHz after addition of a little **trichloroacetyl isocyanate**,[15] δ 8.77 (s, 1, –NH–), 5.45 (t, 1, J =

(16) F. A. Nelson and H. E. Weaver, *Science*, **146**, 223 (1964).

(17) (a) In Scheme I, each perspective formula of a (−)-inositol derivative is numbered to correspond with the Maquenne configurational prefix "L(124/356)," and so oriented that position 2 will be in the upper right hand corner, with numbering running from right to left around the front. For consistency in the present article, ring carbon 2 in each of these formula is so chosen that it corresponds to ring carbon 2 in the *starting material*, compound **2**. (b) For each such (−)-inositol derivative, an alternative numbering is possible, in which positions 1, 2, 3, 4, 5, and 6 become, respectively, 6, 5, 4, 3, 2, and 1, without invalidating the prefix "L(124/356);" *e.g.*, consider compound **3**. (c) Since *Chemical Abstracts* index names typically are based on constitution *without regard to configuration*, the *Chemical Abstracts* numbering may differ from that used here (see Experimental Section). For example, *Chemical Abstracts* presumably would designate compound **9** (or **5**) "2,3,4,5,6-pentamethoxycyclohexanol" (*Chemical Abstracts* assigns alkoxyl groups higher numbers than hydroxyl groups when a choice must be made; thus the name 1,2,3,4,5-pentamethoxy-6-cyclohexanol presumably would not be used).

(18) The reagents mentioned are products of the following companies: (a) Darco Division, Atlas Powder Co., Wilmington, Del.; (b) Resinous Products Division, Rohm and Haas Co., Philadelphia, Pa.

(19) L. F. Johnson, "Varian Associates Technical Information Bulletin," Vol. 3, No. 3, Varian Associates, Palo Alto, Calif., 1963, pp. 5–7, 11–13.

2.5, RNHCOOCH, H-1), 3.61, 3.59, 3.54, 3.51, and 3.48 (singlets, total 15 H, -OMe)].

The ratio of migrated to nonmigrated product in the methylation is about 2:1.

Anal. Calcd for $C_{11}H_{22}O_6$: C, 52.78; H, 8.86. Found: C, 53.03; H, 8.80.

L(1,2,4/3,5,6) Stereoisomer of Hexamethoxycyclohexane [Hexamethyl Ether of (−)-Inositol], 3.—A mixture of 5.0 g of tetramethoxycyclohexanediol monobenzoate **7** (mp 121°), 5.0 ml of methyl iodide, 5.0 g of KOH, and 30 ml of dry benzene was boiled under reflux for 2 hr with vigorous stirring. The cooled mixture was filtered, and the filtrate washed with sodium bicarbonate solution and with water. The dried solution was evaporated, giving the hexamethyl ether, 3.00 g (77%), as an almost colorless syrup: nmr (chloroform-*d*, 60 and 100 MHz, HA-100 frequency sweep) δ 3.80 (m, broad low, 2, equatorial, H-1 and H-6), 3.30–3.75 (singlets, total 4 H, partially obscured, chemical shifts nearly identical, axial H-2, H-3, H-4, and H-5), 3.60 (s, 6, -OMe), 3.50 (s, 12, -OMe). For analysis, the syrup was distilled, bp 110–112° (2 mm).

Anal. Calcd for $C_{12}H_{24}O_6$: C, 54.53; H, 9.15. Found: C, 54.21; H, 9.12.

***meso*-(1,3,5/2,4,6) Diastereomer of 6-Chloro-1,2,3,4,5-cyclohexanepentol (Chlorodeoxyinositol), 10. A. From Inositol Pentamethyl Ether.**—A solution of 0.25 g of hexol pentamethyl ether **9** (mp 66°) in 2.0 ml of dry benzene was heated with 0.30 g of phosphorus pentachloride for 6 hr at 80° under anhydrous conditions. After cooling, the mixture was stirred with 20 ml of ice-cold water, extracted with two 20-ml portions of chloroform, and the chloroform–benzene extract was washed with two 15-ml portions of saturated sodium bicarbonate and water (15 ml). The separated and dried organic phase on evaporation gave a syrup.

Microanalysis indicated that this syrup was the nearly pure chloropentol pentamethyl ether (containing a little phosphorus impurity).

Anal. Calcd for $C_{11}H_{21}ClO_5$: C, 49.16; H, 7.82; Cl, 13.26; P, 0.00. Found: C, 49.51; H, 7.69; Cl, 13.42; P, 0.32.

The ir spectrum of the syrup was recorded (Nujol) at 720, 780, 1030, 1070–1200 (broad, C–O str), 1400, 1480 (C–H bend), 3050 cm^{-1} (C–H str).

To the syrup was added 5.0 ml of a 32% solution of hydrogen bromide in anhydrous acetic acid, and the mixture boiled under reflux for 1 hr, then evaporated. The residue was taken up in 10 ml of water, and the resulting solution treated with charcoal, and evaporated, giving a syrupy residue. The residue was crystallized from 95% ethanol, giving 60 mg (30%) of chloropentol **10**: colorless needles; mp 234–237° dec; ir (Nujol) 778, 985, 1090, and 3450 cm^{-1}.

Anal. Calcd for $C_6H_{11}ClO_5$: C, 36.28; H, 5.58; Cl, 17.85. Found: C, 35.99; H, 5.59; Cl, 17.69.

B. From Tetramethoxycyclohexanediol Monobenzoate.—A 2.0-g portion of tetraether monobenzoate **7** (mp 121°) in 4.0 ml of benzene was treated with 2.4 g of phosphorus pentachloride, and the crude product isolated in the form of a syrup. Microanalysis indicated that this syrup was the nearly pure chloropentol tetramethyl ether monobenzoate (**14**) (containing a little phosphorus impurity).

Anal. Calcd for $C_{17}H_{23}ClO_6$: C, 56.90; H, 6.41; Cl, 9.62; P, 0.00. Found: C, 56.59; H, 6.40; Cl, 9.75; P, 0.49.

The ir spectrum of the syrup was recorded (Nujol) at 710, 760, 1100 (broad), 1260, 1450, 1730 (C=O str), 3050 cm^{-1} (CH str). The nmr spectrum indicated more than one compound was present. The syrup was cleaved with hydrogen bromide, in a manner similar to that described above. The crude chloropentol was taken up in 25 ml of ice-cold water, and the mixture extracted with three 20-ml portions of ethyl acetate. The aqueous phase was treated with charcoal and evaporated. The residue was crystallized and recrystallized from 95% ethanol, giving 0.32 g (27%) of the chloropentol as colorless needles, mp 234–236°. The product was shown by its spectrum and mixture melting point to be identical with the above.

***meso*-(1,3,5/2,4,6) Diastereomer of 6-Chloro-1,2,3,4,5-cyclohexanepentol Pentaacetate (Chlorodeoxyinositol Pentaacetate).**—A mixture of 20 mg of chloropentol **10** (mp 234–237° dec) with 5 ml of acetic anhydride and 100 mg of fused sodium acetate was boiled under reflux for 2 hr. The product, isolated in the usual manner, was recrystallized from 95% ethanol, giving 26 mg (64%) of the pentaacetate: colorless needles; mp 247–248° (sealed capillary tube); ir (Nujol) 795, 1220, 1260, and 1750 cm^{-1}; nmr (chloroform-*d*, 60 and 100 MHz) δ 5.15–5.40 (overlapping multiplets, total 5 H, poorly resolved, AcOCH protons H-1, H-2, H-3, H-4, and H-5), 4.00 (t, 1, sum of *J* about 20 Hz, H-6, collapses to singlet on simultaneous irradiation of H-1 and H-5), 2.08 (s, 6, acetate methyl), 2.00 (singlet, 9, acetate methyl).

Anal. Calcd for $C_{16}H_{21}ClO_{10}$: C, 47.01; H, 5.18; Cl, 8.67. Found: C, 47.28; H, 5.17; Cl, 8.92.

***meso*-(1,3,5/2,4) Diastereomer of 1,2,3,4,5-Cyclohexanepentol (*scyllo*-Quercitol, Deoxyinositol), 11.**—To a solution of 80 mg of chloropentol **10** (mp 234–237° dec) in 10 ml of water was added 1.0 g of moist Raney nickel catalyst and 1.0 g of moist Amberlite IR-45, anion-exchange resin.[18] The mixture was hydrogenated (3 atm, 25°, 24 hr). The filtrate was evaporated and the residue crystallized from 95% ethanol, giving 55 mg (83%) of pentol **11**: colorless needles; mp 242–243° (lit.[10] mp 235°); ir (Nujol) 945, 999, 1040, 1110, and 3750 cm^{-1}; nmr (D_2O, 60 MHz) δ 4.58, 3.1–3.8 (m, 5, H-1, H-2, H-3, H-4, and H-5), 2.28 and 2.08 (pair of triplets, total area 1 H, J_{gem} = 12 Hz; $J_{1,6e} = J_{5,6e} = 4$ Hz, equatorial methylene H_{6e}), 1.40 (q, 1, $J_{gem} = J_{1,6e} = J_{1,6a} =$ 12 Hz, axial methylene H_{6a}).

The product was shown by ir spectrum and mixture melting point to be identical with an authentic sample of deoxyscyllo-inositol.[10]

Anal. Calcd for $C_6H_{12}O_5$: C, 43.90; H, 7.37. Found: C, 43.83; H, 7.47.

Acetylation in the usual manner gave the **pentaacetate**: colorless needles; mp 187–189° (lit.[10] mp 190°); ir (Nujol) 1235, 1265, and 1750 cm^{-1}. The pentaacetate was shown by ir spectrum and mixture melting point to be identical with an authentic sample.[10]

The **pentabenzoate** was prepared from a 16.4-mg sample of pentol **11** (mp 242–243°) by reaction with excess benzoyl chloride in pyridine (heat 20 min at 100°). The recrystallized (from 95% ethanol) product, 51.5 mg (75%), was obtained as colorless needles: mp 295–296°; ir (Nujol) 704, 1100, 1610, 1620, and 1725 cm^{-1}.

Anal. Calcd for $C_{41}H_{32}O_{10}$: C, 71.71; H, 4.99. Found: C, 70.98; H, 4.67.

The pentabenzoate was shown by ir spectrum and mixture melting point to be identical with a sample prepared from authentic *scyllo*-quercitol.

L(2,3,6/4,5) Stereoisomer of 6-Methoxy-2,3,4,5-Tetrahydroxycyclohexanone (Inosose Monomethyl Ether), 21.—A solution of 1,2;5,6-di-O-isopropylidene-(+)-pinitol (2.5 g, **20**) in 30 ml of dimethyl sulfoxide and 20 ml of acetic anhydride was kept at 25° for 48 hr. The solvent was removed by evaporation, giving a red-brown syrup, consisting presumably of the di-O-isopropylideneketopentol monomethyl ether: ir 1070, 1100, 1200, 1370, 1450, 1730 (ketone C=O), 2850 cm^{-1} (C–H stretch).

A solution of the syrup in 100 ml of 50% acetic acid was boiled under reflux for 2 hr, and evaporated. The residual dark-brown syrup was dissolved in 50% aqueous ethanol (treat with charcoal), and the solution evaporated. The residue was crystallized twice from 95% ethanol, giving the ketopentol monomethyl ether as colorless needles: 1.2 g (68%); mp 178–180°; ir 1080, 1110, 1140, 1280, 1450, 1730 (ketone C=O, 2900 (C–H), 3400 cm^{-1} (O–H stretch); nmr (D_2O, 60 and 100 MHz) δ 4.77 (q, 1, *J* = 1.5, 4.0), 3.5–4.4 (overlapping multiplets, total 3 H, HOCH, 3.9 (q, 1, *J* = 10.5, 2.5), 3.50 (s, 3, -OMe). At 100 MHz, using trifluoroacetic acid as solvent, no additional information was obtained.

Anal. Calcd for $C_7H_{12}O_6$: C, 43.67; H, 6.29. Found: C, 43.67; H, 6.59.

Proton Magnetic Resonance Spectrum of L(1,2,4/3,5,6) Stereoisomer of 3,4-Dimethoxy-1,2,5,6-cyclohexanetetrol [Di-O-methyl-(−)-inositol], 19.—This compound[17] was prepared as previously described: mp 189–191° (lit.[13] mp 191–192°); nmr (D_2O, 60 and 100 MHz, HA-100 frequency sweep) δ 3.3–4.1 (overlapping multiplets for two MeOCH and four HOCH protons), 3.65 (s, 6, -OMe).

Proton Magnetic Resonance Spectrum of the L(1,2,4/3,5,6) Stereoisomer of 3,4-Dimethoxy-1,2;5,6-di-(isopropylidenedioxy)-cyclohexane [Di-O-methyl-(−)-inositol Diacetone Ketal], 19.—This compound was prepared as previously described; mp 86–88° (lit.[14] mp 88–89°); nmr ($CDCl_3$, 60 and 100 MHz, HA-100 frequency-sweep) δ 4.25 [singlet, almost split, 4, $Me_2C(OCH)_2$], 3.3 (multiplets, 2, not resolved, MeOCH, H-3 and H-4), 3.60 (s, 6, -OMe), 1.54 (singlet, 6, acetal methyl, *endo?*), 1.35 (s, 6, acetal methyl, *exo?*).

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.

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(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.