(assay 85%) in 65 ml. of water. The system was flushed with nitrogen and the mixture was heated under reflux for 2 hours. The resulting solution was cooled, treated with 13 ml. of acetic acid and concentrated by warming *in vacuo*. Recrystallization of the residual solid from methanol four times afforded 4.8 g. (50% yield) of needles which melted with gas evolution when immersed at 150°, resolidified and then melted at 209–211°. The sample was dried at 110°-(10 mm.) for 8 hr. whereupon it melted at 210–212° without prior change; $[\alpha]^{25}D$ +167.6° (1% in $CHCl_3$).

Anal. Calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67; neut. equiv., 302. Found: C, 75.5; H, 8.8; neut. equiv., 294.

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, COLLEGE OF AGRICULTURE, UNIVERSITY OF WISCONSIN, MADISON 6, WIS.]

Cyclitols and their Methyl Ethers. III. Catalytic Air Oxidation, the Hydrogenolysis of Inososes, and Some Pentol and Tetrol Methyl Ethers[1–3]

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L-Inositol, D-inositol and four inositol methyl ethers were oxidized by treatment, in solution, with air or oxygen and a platinum catalyst. In all cases, only axial hydroxyl groups were oxidized. Only monoketones (inososes) were obtained from the cyclitols with two axial hydroxyl groups (D- and L-inositol and their methyl ethers, pinitol and quebrachitol), and where the two axial hydroxyls were unlike (pinitol and quebrachitol), one of these was oxidized to the exclusion of the other. Catalytic oxidation is a useful method for the small-scale preparation of inososes, of which several new examples are described. The inososes related to D- and L-inositol, in which an axial hydroxyl is adjacent to the keto group, gave unexpectedly complex mixtures under the conditions normally used for the hydrogenolysis of keto groups in cyclitols. The mixtures consisted of the two inositols resulting from simple reduction, the deoxy compound (quercitol) resulting from loss of the oxo-oxygen, and the cyclohexanetetrol resulting from loss of both the axial hydroxyl and the oxo-oxygen. Two *O*-methylcyclohexane-1,2,3,4-tetrols and three *O*-methylquercitols, the first examples of monomethyl ethers in each of the respective series, were characterized in the course of the present work.

Investigations of the catalytic oxidation of cyclitols were undertaken in our laboratory, and in that of S. J. Angyal at the University of New South Wales,[5] following the report by Heyns and Paulsen[6] that *myo*-inositol[7] (II) could be smoothly converted to *myo*-inosose-2 (*scyllo*-inosose, XXVIII) by this technique. In our work, we used procedures patterned after those described by Heyns[8,9]—agitation of an aqueous solution of the substance to be oxidized with air or oxygen, in the presence of a platinum catalyst, at temperatures up to 90°— and applied these to the optically active inositols (D and L) and to the readily available inositol methyl ethers. The results, together with those of a study of the hydrogenolysis reaction of inososes, are presented here. The establishment of the absolute configurations of the optically active *myo*-inositol monomethyl ethers, which was made possible by the availability of the catalytic oxidation procedure, is described in the accompanying paper.

Catalytic Oxidation.—In the catalytic conversion of *myo*-inositol to *myo*-inosose-2, oxidation takes place at the single axial hydroxyl which is present in the preferred chair conformation of the molecule,[10] and is essentially restricted to this hydroxyl. This result suggested that the catalytic oxidation of cyclitols might, like the well known oxidation by *Acetobacter suboxydans*,[10] be specific for axial hydroxyls. Inasmuch as experiment confirmed this suggestion, these hydroxyls will be the focus of the discussion which follows.

Most of the work with the optically active inositols was done with L-inositol (I), the more readily available of the two isomers. Oxidized solutions of this inositol treated with phenylhydrazine gave, in yields of 55–65%, an inosose phenylhydrazone, from which the free inosose was obtained by reaction with benzaldehyde in the usual way. The melting point of the phenylhydrazone, and the melting point and optical rotation of the inosose tentatively identified it as the *enantiomorph* VI of the known L-*myo*-inosose-1 [(+)-*vibo*-inosose], and this identification was confirmed by reducing the inosose to a mixture of L-inositol (I) and *myo*-inositol (II). Thus VI is a product of the oxidation of one of the two axial hydroxyls (positions 2 and 3, formula I)[10] of L-inositol, and, since these two hydroxyls are sterically equivalent, VI is the only monoketone which can be formed by the oxidation of one of them. The oxidation of D-inositol gave L-*myo*-inosose-1 as expected.

In (+)-pinitol (V) and quebrachitol (XIX), which are, respectively, 5-*O*-methyl-D-inositol and 1-*O*-methyl-L-inositol,[10] the axial hydroxyls (at positions 2 and 3, as in the parent compounds) are no longer sterically equivalent, because of their different relationships to the methyl groups. Each of these inositol methyl ethers could thus give rise to two different monoketones by oxidation at an axial hydroxyl. However, only one inosose was ob-

(1) Published with the approval of the Director of the Wisconsin Agricultural Experiment Station. This investigation was supported by a research grant (E-385) from the National Institutes of Health, Public Health Service.

(2) Paper II of this series: L. Anderson, Emily S. DeLuca, A. Bieder and G. G. Post, *J. Am. Chem. Soc.*, **79**, 1171 (1957).

(3) Part of this work was presented orally: L. Anderson and G. G. Post, *Abstracts 134th Natl. Meeting Am. Chem. Soc.*, 12D (1958).

(4) To whom requests for reprints should be sent.

(5) We are grateful to Prof. Angyal for his willingness to participate in a free exchange of information while this investigation was underway.

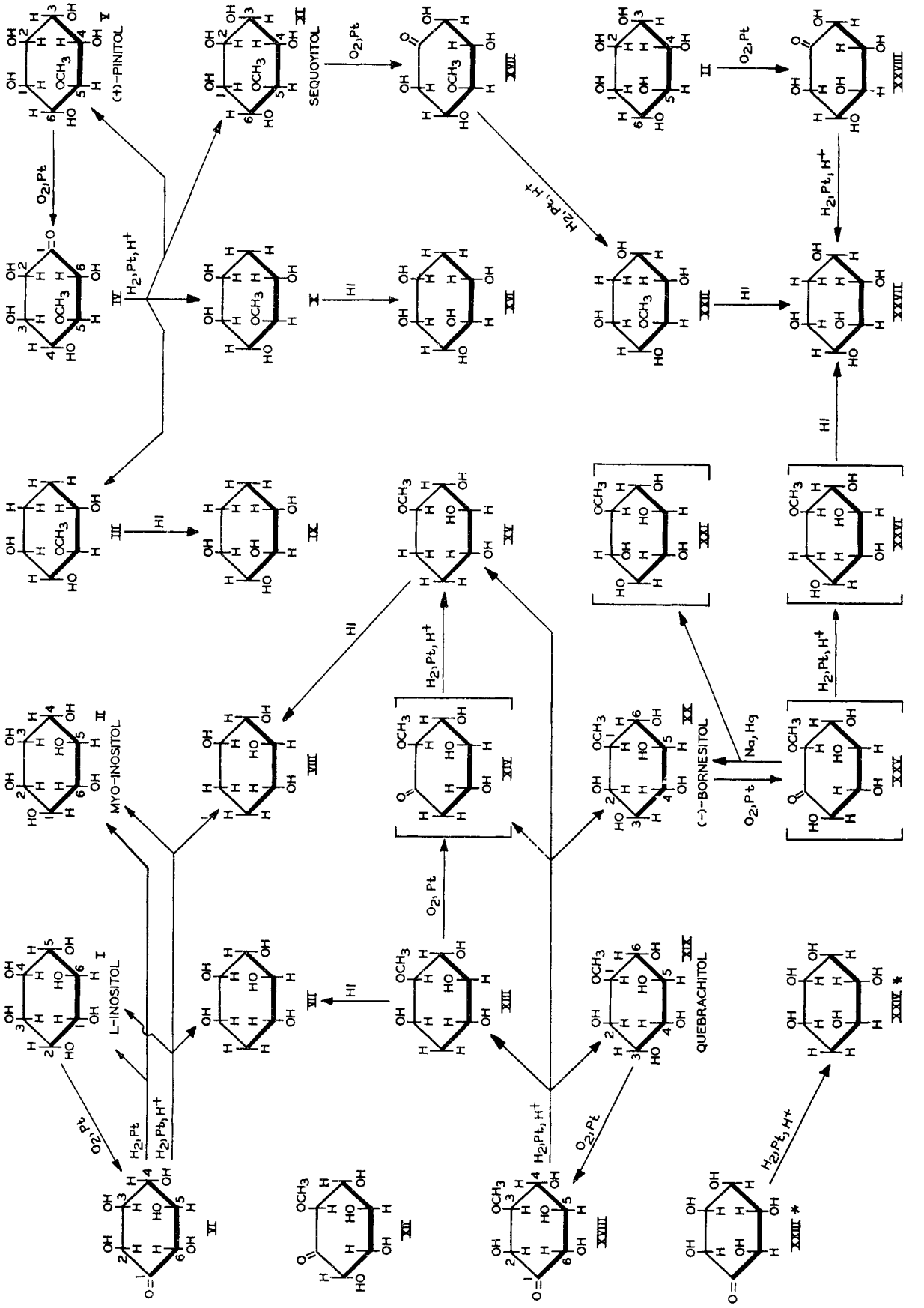
(6) K. Heyns and H. Paulsen, *Chem. Ber.*, **86**, 833 (1953).

(7) In this paper, cyclitols are named and numbered according to H. G. Fletcher, Jr., L. Anderson and H. A. Lardy, *J. Org. Chem.*, **16**, 1238 (1951). For inososes (pentahydroxycyclohexanones) and quercitols (pentahydroxycyclohexanes), the names suggested by S. J. Angyal, C. G. Macdonald and N. K. Matheson, *J. Chem. Soc.*, 686 (1952), are also given, in parentheses. The configurations of cyclohexane-1,2,3,4-tetrols are designated by the conventional "fractional" system. See also ref. 10.

(8) K. Heyns, *Ann.*, **558**, 177 (1947).

(9) K. Heyns and R. Heinemann, *ibid.*, **558**, 187 (1947).

(10) The literature relevant to this point is reviewed by S. J. Angyal and L. Anderson, *Adv. in Carbohydrate Chem.*, **14**, 135 (1959).



* Indicates racemic mixture; one enantiomorph, arbitrarily chosen, is shown.

tained from each. The oxidation of (+)-pinitol to a sirupy inosose, which was proved to have formula IV by reducing it to a mixture of starting material and sequoyitol (XI), has been described in an earlier p ublication.[2] Since that publication, IV has been crystallized, and its properties are given in the Experimental section.[11] The inosose from quebrachitol was shown to be either XII or XVIII by its reduction to a mixture of (−)-bornesitol and starting material. The arguments upon which we base the assignment of formula XVIII to this inosose are detailed in the succeeding paper.[12] The hydrogenolysis (see below) of XVIII gave the quercitol methyl ether XIII, which retains the "resistant" axial hydroxyl of the parent quebrachitol. The oxidation of XIII took place at this hydroxyl, yielding the deoxyinosose methyl ether XIV.

Sequoyitol (XI) and (−)-bornesitol (XX), the two *myo*-inositol methyl ethers which were tested, retain the axial hydroxyl (position 2) of the parent inositol. As expected, they were oxidized to the corresponding methyl ethers XVII and XXV of *myo*-inosose-2.

A search for oxidation products other than those just described was made by paper chromatographic analysis of the reaction mixtures. In all cases, this analysis indicated a single oxidation product, plus unchanged starting material. At most, only traces of other components were detectable. The course of the catalytic oxidation of the optically active inositols, their methyl ethers, and the *myo*-inositol methyl ethers under the conditions of Heyns may accordingly be summarized as: (1) Only axial hydroxyls are oxidized. Catalytic oxidation thus parallels bacterial oxidation (*Acetobacter suboxydans*), but is in a sense less specific, since it is applicable to the methyl ethers, most of which do not satisfy the subtle secondary specificity requirements of *Acetobacter*.[13] (2) The catalytic oxidation of these inositols stops at the monoketone stage, even if the original substrate contains a second axial hydroxyl. (3) In (+)-pinitol and quebrachitol, catalytic oxidation is selective for one of two unlike axial hydroxyls. In each case, the axial hydroxyl *meta* (and *trans*) to the methyl group is oxidized.

Catalytic oxidation is a useful method for the preparation of inososes on a small scale. Although the conversions achieved have not been high, they are usually over 50%. The inososes are easily separated from the reaction mixtures by precipitation as phenylhydrazones or by chromatography on cellulose powder, and unchanged starting material may be recycled. The restriction of the oxidation to a single step when two axial hydroxyls are present was unexpected, but because of this feature the method nicely complements bacterial oxidation. D- and L-inositol are oxidized to diketones by *Acetobacter*, and only in the case of the D-isomer has it been possible to isolate the monoketone, in poor yield, by interrupting the oxidation at an intermediate stage.[14] Four new inososes (IV, VI, XVII and XVIII) were made available for the first time by the work reported here, and the formation of two others (XIV and XXV) was established by chromatographic evidence.

Hydrogenolysis of Inososes.—The facile hydrogenolysis of the keto group of an inosose in mineral acid solution was first observed by Posternak[15] in 1941. Since that time, the reaction has been applied extensively, by Posternak and by others,[13,16] to ketones in the cyclitol series, from dihydroxycyclohexanones to pentahydroxycyclohexanones (inososes). And although the papers describing it contain considerable evidence to the contrary, it seems to have been assumed that the reaction always proceeds in a simple, straightforward way; the only products which were identified in previous work were the expected deoxy compounds and *traces* of cyclitols resulting from the simple reduction of the ketonic substrates. It was therefore of considerable interest to find, by paper chromatographic analysis, that the hydrogenolysis of XVIII gave a mixture of compounds. This finding led us to a reinvestigation of the hydrogenolysis reaction.

Paper chromatograms of hydrogenolyzed XVIII showed four spots, and the four products responsible were easily separated by cellulose-powder chromatography. The two substances with the lowest mobility were readily identified as quebrachitol (XIX) and (−)-bornesitol (XX), both products resulting from the *reduction* of the keto group. The next product in order of increasing mobility was the expected monodeoxy compound (quercitol methyl ether). It was characterized as XIII by periodate oxidation and by demethylation (HI) to the known D-1-deoxy-*myo*-inositol [(−)-*vibo*-quercitol, *l*-viburnitol, VII]. The fourth product had a very high mobility, suggesting that it had lost more than one oxygen function, and it was subsequently identified as the 1-methyl ether XV of the known (−)-cyclohexane-1,3/2,4-tetrol (VIII). Clearly, XV is formed from XVIII by loss of the hydroxyl at position 2, as well as the oxo-oxygen.

Similar results were obtained on hydrogenolysis of two other inososes of the D- and L-inositol group—D-*myo*-inosose-1 (VI) and 5-*O*-methyl-L-*myo*-inosose-1 (IV). The products of the former were two epimeric inositols, a quercitol and a cyclohexanetetrol, and of the latter, a corresponding set of methyl ethers. The characterization of these products is described in the Experimental section.

To complete the study, we examined chromatographically the hydrogenolysis products of two inososes which have been subjected to the reaction in a number of other laboratories, *viz.*, *myo*-inosose-2 (XXVIII) and DL-*epi*-inosose-2 [(±)-*epi*-inosose, XXIII]. These inososes were nearly quantitatively converted to the monodeoxy compounds (quercitols) XXVII and XXIV, respectively. Traces of the reduction products (inositols) were formed, but no tetrols could be detected.

(11) The enantiomorph of IV has been obtained (ref. 13), in solution, by the *Acetobacter* oxidation of (−)-pinitol.

(12) See succeeding paper.

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

(14) B. Magasanik and E. Chargaff, *J. Biol. Chem.*, **175**, 929 (1948). The oxidation was done with resting cells, and was not studied in growing cultures.

(15) T. Posternak, *Helv. Chim. Acta*, **24**, 1045 (1941).

(16) B. Magasanik, R. E. Franzl and E. Chargaff, *J. Am. Chem. Soc.*, **74**, 2618 (1952).

In those inososes (IV, VI and XVIII) which gave a complex mixture of hydrogenolysis products, one of the hydroxyls flanking the keto group is axial (position 2 in each case), while in the others (XXIII and XXVIII), both the flanking hydroxyls are equatorial. More data will be required before generalizations about the hydrogenolysis reaction can be extended to all polyhydroxycyclohexanones, but it would appear from our results that the reaction proceeds cleanly only if there are no axial hydroxyls adjacent to the keto group. In the inososes related to D- and L-inositol, a neighboring axial hydroxyl has two effects on the course of hydrogenolysis under Posternak's conditions: (1) in part, hydrogenolysis is prevented, and the keto group is instead reduced in both possible steric directions; (2) in part, the axial hydroxyl is cleaved along with the oxo-oxygen to form a cyclohexanetetrol.

Presumably, the reaction of tetrol formation proceeds stepwise, the first step being the loss of the hydroxyl group to generate a deoxyinososе, which is then further hydrogenolyzed, apparently quantitatively,[17] to the tetrol. Consistent with this formulation is the fact that the deoxyinose XIV, formed (in solution, see Experimental) by the oxidation of the *O*-methyl-*vibo*-quercitol (XIII), gave the *O*-methyltetrol XV on hydrogenolysis. The alternate pathway, involving first the formation of a quercitol by hydrogenolysis of the keto group, then the cleavage of the axial hydroxyl, was ruled out. The quercitols in question are completely stable under the hydrogenolysis conditions. The evidence available does not, however, rule out a mechanism involving simultaneous cleavages of the two groups.

The foregoing observations on the hydrogenolysis reaction may help explain the considerable loss of hydroxyl groups which occurs in hydrogenations of hexahydroxybenzene and pyrogallol over palladium and Raney nickel catalysts.[18-20] It has been suggested that the loss results from the elimination of water from enediol intermediates,[18] but this explanation does not completely account for the observed products. The formation of inososes and lower hydroxyketones during these hydrogenations is well established,[18] and although neutral conditions have been used the direct hydrogenolysis of these intermediates would appear to merit further consideration as a mechanism for the loss of oxygen.

The *O*-methylquercitols and *O*-methylcyclohexane-1,2,3,4-tetrols reported here are apparently the first examples of monomethyl ethers in these two series of cyclitols.

Experimental

Unless otherwise specified all crystalline compounds were recrystallized to constant melting point. Melting points were determined in capillary tubes. The thermometer used has been calibrated against Anschütz thermometers calibrated by the National Bureau of Standards. Carbon-hydrogen analyses by the Micro-Tech Laboratories, Skokie, Ill., and by Drs. Weiler and Strauss, Oxford, England.

Paper chromatography was done on Whatman No. 1 paper, in the descending manner, with acetone–water 9:1 (v./v.) as the developing solvent. As a spray reagent, 5% ammoniacal silver nitrate was used.[21] With this reagent, inososes give brown to black spots at room temperature, while non-reducing cyclitols require heating.

Since the solvent drips from the paper during much of the 14–18-hr. development period, mobilities were determined relative to pinitol and expressed as R_p values. A large number of mobilities were measured during the course of the present work, making the data of some worth for future reference. They are accordingly presented in the accompanying table in the form of average R_p values. Considerable variation was observed from run to run; hence individual figures quoted later may differ somewhat from those in the table. The identification of unknowns was, in most cases, based on direct comparisons of their mobilities with those of authentic samples run on the same paper.

Column Chromatography.—Whatman cellulose powder was used, with acetone–water developers, as previously described.[2] Fractions of 25-ml. volume were collected. Columns were packed wet with slurries made by hand stirring, since excessive "leakage" of cellulose fibers was noted when the adsorbent was slurried with the Waring Blendor.

The isolation of cyclitols separated on the column was accomplished by combining appropriate fractions and concentrating them under vacuum. The concentrates were treated with charcoal (Darco G-60) if necessary, and in any case filtered through Celite to remove small amounts of suspended cellulose. After further concentration of the filtrates, ethanol was added, and if this did not effect satisfactory crystallization, the concentration was repeated. Acetone and ethyl acetate were occasionally used when a very soluble cyclitol (*e.g.*, cyclohexanetetrol) was being isolated.

Demethylation of Methyl Ethers.—The compound to be demethylated was refluxed for 0.5 hr. with 47% HI, and the bulk of the HI was removed *in vacuo*. The residual solution was subjected to repeated cycles of ethanol addition and vacuum concentration, until the product which precipitated from the concentrate was suitable for recrystallization. Or, in some cases, the residual solution was diluted with water and treated with silver carbonate, and the filtrate from the silver salts was worked up as described above for column eluates.

Catalytic Oxidations. Procedure A.—One part of cyclitol was dissolved in 100 parts of water and 1 part of catalyst was suspended in the solution. The catalyst used was 10% platinum-on-charcoal (Darco G-60); it was prepared by the procedure of Heyns.[8] The reaction was carried out in a three-necked flask fitted with a thermometer, condenser and a sintered-glass filter stick. The flask was heated in an oil-bath. A vigorous stream of air was forced through the solution *via* the filter stick by applying slight suction at the top of the condenser, or preferably, by connecting the filter stick to an air line. The latter method allows a better control of the temperature, which in the present work was maintained at 85–90°. When oxidation was terminated, the solution was cooled and the catalyst was filtered off and washed with water.

Procedure B.—One part of platinum dioxide (Adams catalyst, American Platinum Works) was suspended in 100 parts water and reduced with hydrogen in a Parr hydrogenation apparatus (model 3911). The hydrogen was then removed by suction, and the apparatus was flushed with air three times. Two parts of the cyclitol was added to the suspension of platinum black in the reaction bottle along with 100 parts of water. The apparatus was then filled with oxygen (0.3–0.7 atm.) and the reaction mixture was shaken at room temperature. At the end of the oxidation the solution was filtered and the catalyst was washed with water.

During the course of the oxidation the yield of inosose increases to a maximum, then declines. The time of maximal yield may be established by copper reduction analysis[6] or by iodimetric titration.[24] The absolute yield is determined by these analyses for reducing power only if the

(17) *A priori*, the reduction of a portion of the deoxyinosose to a quercitol is possible, but if such reduction occurred, quercitol methyl ethers isomeric with X and XIII would have been formed from IV and XVIII. Such isomers would presumably have been detected by the paper chromatographic methods used, but no evidence for them was found.

(18) S. J. Angyal and D. J. McHugh, *J. Chem. Soc.*, 3682 (1957).

(19) R. C. Anderson and E. S. Wallis, *J. Am. Chem. Soc.*, **70**, 2931 (1948).

(20) W. R. Christian, C. J. Gogek and C. B. Purves, *Can. J. Chem.*, **29**, 911 (1951).

(21) We recommend the system of E. F. L. J. Anet and T. M. Reynolds, *Nature*, **174**, 930 (1954), as a superior one for locating the spots on paper chromatograms of cyclitols.

(24) R. Willstätter and G. Schudel, *Ber.*, **51**, 780 (1918).

MOBILITIES OF CYCLITOLS

WHATMAN NO. 1 PAPER, ACETONE–WATER 9:1

Cyclitol	Average R_p
Inositols	
myo-Inositol (II)	0.33
epi-Inositol[22]	.41
L-Inositol (I)	.49
Inosamines	
myo-Inosamine-1[23]	0.29
L-Inosamine-2[23]	.47
Inositol methyl ethers	
Bornesitol (XX)	0.55
Ononitol[12]	.62
O-Methyl-*scyllo*-inositol[13]	.65
Sequoyitol (XI)	.66
Quebrachitol (XIX)	.84
Pinitol (V)	1.00
Inososes	
myo-Inosose-1 (*vibo*-inosose, VI)	0.27
myo-Inosose-2 (*scyllo*-inosose, XXVIII)	.43
epi-Inosose-2 (*epi*-inosose, XXIII)	.56
***O*-Methylinososes**	
3-*O*-Methyl-*myo*-inosose-1 (3-*O*-methyl-*vibo*-inosose, XVIII)	0.59
5-*O*-Methyl-*myo*-inosose-1 (5-*O*-methyl-*vibo*-inosose, IV)	.73
1-*O*-Methyl-*myo*-inosose-2 (2-*O*-methyl-*scyllo*-inosose, XXV)	.92
5-*O*-Methyl-*myo*-inosose-2 (4-*O*-methyl-*scyllo*-inosose, XVII)	.92
3-Deoxy-1-*O*-methyl-*myo*-inosose-2 (XIV)	1.25
Deoxyinositols	
2-Deoxy-*myo*-inositol (*scyllo*-quercitol, XXVII)	0.61
2-Deoxy-*epi*-inositol (*epi*-quercitol, XXIV)[16]	.63
1-Deoxy-*myo*-inositol (*vibo*-quercitol, viburnitol, VII, XVI)	.65
Cyclohexane-1,3/2,4-tetrol (VIII, IX)	1.14
***O*-Methyldeoxyinositols**	
2-Deoxy-1-*O*-methyl-*myo*-inositol (1-*O*-methyl-*scyllo*-quercitol, XXVI)	1.04
3-Deoxy-1-*O*-methyl-*myo*-inositol (2-*O*-methyl-*vibo*-quercitol, XIII)	1.08
2-Deoxy-5-*O*-methyl-*myo*-inositol (2-*O*-methyl-*scyllo*-quercitol, XXII)	1.24
1-Deoxy-5-*O*-methyl-*myo*-inositol (4-*O*-methyl-*vibo*-quercitol, X)	1.37

method has been carefully standardized for the particular inosose concerned, because inososes vary considerably in the rate and extent of their reactions with copper reagents and hypoiodite. The times used for the oxidation of L-inositol, (+)-pinitol, quebrachitol and sequoyitol were optimal as established by analysis for reducing power; the oxidations of the other substrates were checked only by paper chromatography.

Recovery of Inososes from their Phenylhydrazones.—The phenylhydrazones were decomposed by treatment with benzaldehyde and acetic acid as described by Posternak.[25]

D-*myo*-Inosose-1 Phenylhydrazone [(−)-*vibo*-Inosose Phenylhydrazone] from L-Inositol.—A solution containing 2 g. of L-inositol[26] was oxidized according to procedure A for 2 hr. The clear filtrate, which strongly reduced Benedict solution, was concentrated *in vacuo* to a few ml. and the *p*H of the concentrate was raised to 5 by the addition of a little $NaHCO_3$. The slow addition, with swirling, of a solution of 1.1 ml. of phenylhydrazine in 2.2 ml. of 50% acetic acid gave a red precipitate. The mixture was kept in the cold for 0.5 hr., then the precipitate was filtered off and washed first with 95% ethanol and then with absolute ethanol; yield 1.70 g. (57% of the theoretical), m.p. 180–190° dec. A careful recrystallization from aqueous pyridine raised the melting point to 196–197°. The melting point reported[14] for the phenylhydrazone of L-*myo*-inosose-1 is 196–197°.

L-*myo*-Inosose-1 phenylhydrazone [(+)-*vibo*-Inosose phenylhydrazone] was similarly obtained from D-inositol. The phenylhydrazone was converted to free **L-*myo*-inosose-1 [(+)-*vibo*-inosose]** as described for the D-isomer in the next paragraph.

D-*myo*-Inosose-1 [(−)-*vibo*-Inosose, VI].—Three grams of the phenylhydrazone yielded 1.77 g. of the inosose (84%) melting at 130–132°. Recrystallization from aqueous ethanol raised the melting point to 138–139°, $[\alpha]^{23}D$ −17.0° (*c* 2.53, water). The values reported[14] for L-*myo*-inosose-1 hemihydrate are m.p. 138–139° and $[\alpha]D$ +19.6°.

One-half gram of the compound was dissolved in 25 ml. of water and 0.20 g. of platinum dioxide was added. The mixture was shaken for 4 hr. with hydrogen in a Parr hydrogenation apparatus, then filtered. Paper chromatograms of the filtrate, which did not reduce Benedict solution, showed spots with the R_p's of *myo*-inositol (II) and L-inositol (I). The crystalline mixture (0.31 g.) of inositols, obtained by concentrating the filtrate to a small volume and adding ethanol, was acetylated by refluxing with acetic anhydride and zinc chloride for 20 min. The addition of water to the reaction mixture precipitated an oily acetate, which crystallized from a few ml. of boiling ethanol. One recrystallization raised the melting point of the acetate to 215°, undepressed on admixture with authentic *myo*-inositol hexaacetate.

5-*O*-Methyl-L-*myo*-inosose-1 Phenylhydrazone [Phenylhydrazone of 5-*O*-Methyl-(+)-*vibo*-inosose] from (+)-Pinitol.—Five grams of (+)-pinitol[2] (V) was oxidized by procedure A for 4 hr. After filtration, the solution was concentrated to approximately 20 ml. A mixture of 2.5 ml. of phenylhydrazine, 2.5 ml. of water and 0.25 ml. of acetic acid was added at 0° and the reaction mixture was allowed to stand in an ice-bath for 2 hr. The orange-red product was filtered off and washed with water; when dry it weighed 3.92 g. (51% of the theoretical).

The crude phenylhydrazone was dissolved in 50% ethanol and extracted 4 times with small portions of benzene. The aqueous alcohol phase was then allowed to stand in the cold, whereupon an orange precipitate was obtained. This was filtered off, washed with water, and dried. The product weighed 1.32 g. and melted at 139–140°. Other methods of purification gave the same melting point. When heated *in vacuo* at 80°, the phenylhydrazone lost 5.8% of its weight indicating that it was a monohydrate; $[\alpha]^{24}D$ (anhydrous basis) −71° (*c* 0.83, pyridine–ethanol 1:1).

Anal. Calcd. for $C_{13}H_{18}O_5N_2 \cdot H_2O$ (300.31): C, 51.99; H, 6.71; N, 9.33. Found: C, 51.53; H, 6.7; N, 8.16 (Dumas).

5-*O*-Methyl-L-*myo*-inosose-1 [5-*O*-Methyl-(+)-*vibo*-inosose, IV].—The inosose was obtained from the crude phenylhydrazone and successfully crystallized and recrystallized from aqueous acetone until its m.p. was 149–150°. When heated *in vacuo* at 100°, the inosose lost 4.7% of its weight, indicating that it had crystallized as the hemihydrate, and its melting point rose to 153–154°, $[\alpha]^{24}D$ (anhydrous basis) +25.2° (*c* 2.82, water). Apparently the analytical sample still contained some water of crystallization.

Anal. Calcd. for $C_7H_{12}O_6$ (192.17): C, 43.75; H, 6.30. Calcd. for $C_7H_{12}O_6 \cdot 1/2\ H_2O$ (201.18): C, 41.79; H, 6.51. Found: C, 42.61; H, 6.71.

3-*O*-Methyl-D-*myo*-inosose-1 [3-*O*-Methyl-(−)-*vibo*-inosose, XVIII] from Quebrachitol.—Crude quebrachitol (XIX) obtained from the Plantation Division, U. S. Rubber Co., Rockefeller Center, New York, was recrystallized from acetic acid and aqueous ethanol. Paper chroma-

(22) T. Posternak, *Helv. Chim. Acta*, **19**, 1333 (1936).

(23) G. G. Post (with L. Anderson), Ph.D. Thesis, University of Wisconsin, 1959.

(25) T. Posternak, *Biochem. Preparations*, **2**, 57 (1952).

(26) From quebrachitol. The demethylation was carried out as recommended for (+)-pinitol by A. B. Anderson, *Tappi*, **35**, 198 (1952).

tography showed that an inosose was formed when the compound was oxidized by either procedure. Two grams of quebrachitol was treated for 8 hr. by procedure B, which gave the best results, and the solution was concentrated to a small volume. Separation on the column (acetone–water 8:1) first gave unoxidized quebrachitol, then 1.26 g. (58%) of sirupy oxidation product. After crystallization from aqueous ethanol the inosose, which separated as the monohydrate, melted at 156–157° and had [α]D (anhydrous basis) −47.5° (*c* 1.79, water).

Anal. Calcd. for $C_7H_{12}O_6 \cdot H_2O$ (210.18): C, 40.00; H, 6.71. Found: C, 39.74; H, 7.09.

Hydrazones of 3-*O*-Methyl-D-*myo*-inosose-1.—The solution obtained by oxidizing 1 g. of quebrachitol by procedure A for 2 hr. was concentrated *in vacuo* to about 10 ml., and brought to *p*H 5 with a little sodium bicarbonate. Phenylhydrazine (0.55 ml.) in 1.1 ml. of 50% acetic acid was then added. The yellow **phenylhydrazone** (0.1 g., m.p. 175–176°) was eventually precipitated by concentrating the reaction mixture, after extracting it 3 times with ether.

Anal. Calcd. for $C_{13}H_{18}O_5N_2$ (282.29): C, 55.31; H, 6.43. Found: C, 55.51; H, 6.77.

A derivative presumed to be the **2,4-dinitrophenylhydrazone** was obtained from 1 g. of quebrachitol treated by procedure B for 8 hr. The filtrate from the oxidation was concentrated *in vacuo* to a small volume. A solution of 1.0 g. of 2,4-dinitrophenylhydrazine in 7.5 ml. of H_2SO_4 was diluted with 50 ml. of 50% ethanol and added to the concentrate. The orange precipitate which formed was filtered and washed with ethanol. It weighed 1.26 g. (64% of the theoretical from quebrachitol), melted at 232° dec., and on refluxing with benzaldehyde in ethanolic HCl gave 3-*O*-methyl-D-*myo*-inosose-1, identified by paper chromatography.

5-*O*-Methyl-*myo*-inosose-2 (4-*O*-Methyl-*scyllo*-inosose, XVII) from Sequoyitol.—One gram of sequoyitol (XI) was oxidized by procedure B for 8 hr. Since earlier attempts to isolate the oxidation product as the phenylhydrazone had met with failure, the reaction mixture was separated on the column (acetone–water 8:1). The inosose (126 mg., 12% of the theoretical) was crystallized by adding ethanol to concentrates of appropriate fractions. The m.p., 162–163°, was not changed by recrystallization from aqueous ethanol. When a sample of the crystals was heated *in vacuo* at 100°, it lost 4.7% of its weight, which corresponds closely to a 0.5 molar proportion of water (4.48%). The analytical sample was also dried at 100°, but it apparently retained some water.

Anal. Calcd. for $C_7H_{12}O_6$ (192.17): C, 43.75; H, 6.30. Calcd. for $C_7H_{12}O_6 \cdot 1/2\ H_2O$ (201.18): C, 41.79; H, 6.51. Found: C, 42.72, 42.31; H, 6.09, 6.63.

The hydrogenolysis (see below) of the inosose to a methyl ether (XXII) of 2-deoxy-*myo*-inositol (*scyllo*-quercitol, XXVII) shows that it is a derivative of *myo*-inosose-2 (XXVIII). Since the methyl group in sequoyitol is in the 5-position,[2] it is thereby established that the inosose is a *meso* compound with the structure and configuration XVII.

Oxidation of (−)-Bornesitol.—Two batches (25 and 30 mg.) of (−)-bornesitol[12] (XX) were treated by procedure B for 8 hr. Paper chromatography showed the presence of a new inosose with R_p 0.92. The inosose in one of the solutions was reduced with 3% sodium amalgam, the *p*H being held at 6 by the addition of acetic acid. After removal of the sodium ions with Dowex-50 (H^+), paper chromatography revealed two compounds with the mobilities of bornesitol and *O*-methyl-*scyllo*-inositol[13] (XXI), respectively. The formation from oxidized bornesitol of XXI and 2-deoxy-*myo*-inositol (*scyllo*-quercitol, XXVII) (see Hydrogenolysis, below) demonstrates that the oxidation product was a derivative of *myo*-inosose-2 (XXVIII). The formulation of this derivative as **L-1-*O*-methyl-*myo*-inosose-2 [(?)-2-*O*-methyl-*scyllo*-inosose,[27] XXV]** follows from the known formula, XX, of (−)-bornesitol.[12] The enantiomorph of XXV has been obtained, in solution, by the *Acetobacter* oxidation of (+)-bornesitol.[13]

Oxidation of L-3-Deoxy-1-*O*-methyl-*myo*-inositol (XIII).—The deoxy compound (24 mg.) was oxidized by procedure B. Paper chromatography of the reaction mixture showed the presence of a new inosose (R_p 1.25), which was not isolated. The formula of the starting material, and the fact that the inosose was converted to the *O*-methylcyclohexanetetrol XV (see Hydrogenolysis, below), permit one to formulate it as **L-3-deoxy-1-*O*-methyl-*myo*-inosose-2 (XIV)**

Hydrogenolyses. General Procedure.—Unless otherwise specified, one part of inosose was dissolved in 55 parts of 5% (v./v.) sulfuric acid, or concd. sulfuric acid was added to oxidized solutions of cyclitols to arrive at similar concentrations.[28] Adams platinum catalyst, 0.25–1.0 part, was then suspended in the solutions and they were shaken under 0.3–0.7 atm. of hydrogen on the Parr apparatus for 3–6 hr. at room temperature. Complete hydrogenolysis and/or reduction was indicated by a negative Benedict test. Catalyst was filtered off, and the sulfuric acid was removed by passage over Dowex-1 (OH^-), or by precipitation with barium hydroxide. The sulfate-free solution was then concentrated under vacuum for further workup.

Hydrogenolysis of 3-*O*-Methyl-D-*myo*-inosose-1 (XVIII).—The inosose (2.7 g.) was subjected to reaction. The four products revealed by paper chromatography were separated on the cellulose column (acetone–water 9:1), isolated, and characterized. The amounts of recrystallized products obtained reflect the proportions present in the hydrogenolysis mixture, but a quantitative accounting of the material eluted from the column was not made.

Band 3 (in order to emergence) yielded 80 mg. of crystalline substance melting at 191.5–192° and showing R_p 0.79, and was therefore quebrachitol. Similarly, band 4 (70 mg.) was identified as a bornesitol by its R_p (0.49) and by the following melting point data: substance of band 4, 198–201°; authentic (−)-bornesitol, 205°; mixture 201–202°.

L-3-Deoxy-1-*O*-methyl-*myo*-inositol [2-*O*-Methyl-(−)-*vibo*-quercitol, XIII] from XVIII.—Band 2 from the above chromatogram gave, on crystallization from water–ethanol, 0.16 g. of material with m.p. 148–149°, [α]D −71.4° (*c* 0.96, water).

Anal. Calcd. for $C_6H_{11}O_4(OCH_3)$ (178.18): C, 47.18; H, 7.92; OCH_3, 17.41. Found: C, 47.17; H, 7.93; OCH_3, 17.8.

A periodate analysis was carried out by adding 5.00 ml. of 0.05 *M* sodium metaperiodate to 4.32 mg. of the compound and allowing the solution to stand at room temperature. The periodate consumption in moles per mole was as follows: at 1 hr., 1.82; at 2 hr., 2.00; at 4 hr., 1.98; at 18 hr., 1.96.

Demethylation of a small portion (19 mg.) gave a white substance which, after recrystallization from aqueous ethanol, had m.p. 176–177°. A mixture with D-1-deoxy-*myo*-inositol (VII, see D-*myo*-Inosose-1, below) of m.p. 174–175° melted at 175–177°.

The foregoing data established the formula XIII for the substance of band 2.

L-2,4,5,6-Tetra-*O*-acetyl-3-deoxy-1-*O*-methyl-*myo*-inositol.—Twenty-five mg. of XIII and 24 mg. of anhydrous sodium acetate were refluxed for 0.5 hr. with 2 ml. of acetic anhydride. The acetate was obtained by concentrating the reaction mixture in vacuum, then adding water. After recrystallization from aqueous alcohol, it melted at 188–189°.

Anal. Calcd. for $C_{15}H_{22}O_9$ (346.33): C, 52.02; H, 6.40. Found: C, 52.30; H, 6.54.

1-*O*-Methyl-(−)-cyclohexane-1,3/2,4-tetrol (XV) from XVIII.—The first band obtained from the chromatographic separation of the hydrogenolysis products of XVIII yielded 0.31 g. of a substance melting at 127.5–128°, [α]D −56.3° (*c* 0.98, water).

Anal. Calcd. for $C_6H_{11}O_3(OCH_3)$ (162.18): C, 51.84; H, 8.70; OCH_3, 19.13. Found: C, 52.38; H, 8.91; OCH_3, 19.1.

A periodate analysis was carried out by adding 5.00 ml. of 0.05 *M* sodium metaperiodate to 4.19 mg. of the compound and allowing the solution to stand at room temperature. The consumption of periodate in moles per mole was: at 0.5 hr., 1.82; at 2 hr., 1.98; at 19 hr., 2.02.

The carbon, hydrogen and methoxyl analyses and the periodate consumption data show that the substance of band 1 is a methyl ether of a cyclohexane-1,2,3,4-tetrol, with the methyl group in the 1-position. The only such methyl

(27) The symbol (?) indicates an optically active compound, direction of rotation not established.

(28) Several of the inososes were also hydrogenolyzed in hydrochloric acid of various concentrations. The results were the same as with 5% sulfuric acid.

ether which can be derived from the inosose XVIII by hydrogenolysis is XV, which has the 1,3/2,4 configuration. Further confirmation of the formula assignment was obtained by demethylating a small portion of the ether. The product, which should be (−)-cyclohexane-1,3/2,4-tetrol (VIII), had the same mobility on paper as an authentic sample of VIII (see D-*myo*-inosose-1, below).

Hydrogenolysis of D-*myo*-Inosose-1 (VI).—The mixture from the hydrogenolysis of 1 g. of VI gave 4 bands when it was chromatographed on the cellulose column with acetone–water 4:1.

As with the products from XVIII, no effort was made to effect a quantitative recovery in purifying the products by recrystallization (from ethanol–water). Band 4 (in order of emergence) was *myo*-inositol (II), identified by its R_p (0.23; authentic II on the same paper, 0.25) and melting point (219–220°), which was undepressed on admixture with an authentic sample. The yield of II was 40 mg.

Band 3 consisted of 0.21 g. of L-inositol (I), R_p 0.45, m.p. 238–240°, undepressed on admixture with an authentic sample.

Band 2 yielded 0.14 g. of crystalline substance melting, after recrystallization, at 174–175°, $[\alpha]_D$ −49.7° (*c* 0.97, water). These values, and its method of preparation, identify the substance as D-1-deoxy-*myo*-inositol [(−)-*vibo*-quercitol, *l*-viburnitol, VII], lit.[29] m.p. 180°, $[\alpha]_D$ −49.5°.

Band 1 consisted of 0.11 g. of crystalline compound, m.p. 149–150°, $[\alpha]_D$ −33.4° (*c* 1.11, water). These values, and the known formula VI for the precursor, establish that the compound is (−)-cyclohexane-1,3/2,4-tetrol (VIII), lit.[30] m.p. 146–148°, $[\alpha]_D$ −28.8°.

Hydrogenolysis of 5-*O*-Methyl-L-*myo*-inosose-1 (IV).—The filtrate from the oxidation of 1 g. of (+)-pinitol (V) was concentrated and sufficient hydrochloric acid was added to give 10 ml. of 0.1 *N* solution. Platinum dioxide (250 mg.) was added and the solution was shaken with hydrogen (0.7 atm.) for 6 hr. The acid was removed with Dowex-1 (OH^-) and the effluent was concentrated to a small volume. A paper chromatogram of the concentrate had spots for the four expected products, and an additional spot, R_p 1.14, in the *O*-methylquercitol region.

Four bands were obtained by separating the mixture on the cellulose column with acetone–water 9:1. The third and fourth bands, on concentration and the addition of ethanol, yielded, respectively, 214 mg. of (+)-pinitol (m.p. 183–184°) and 40 mg. of sequoyitol (XI), R_p 0.68, m.p. 237–239°.

Because of the evidence that a second, slow moving *O*-methylquercitol was present in the hydrogenolysis mixture the trailing fractions of the second band were worked up separately from the main portion. Neither portion of the band yielded crystalline material. The main portion, 0.12 g. of sirup, on demethylation with HI gave 77 mg. of a crystalline product melting at 170–175°. This substance was purified through its acetate. The derivative was formed with hot acetic anhydride–sodium acetate, and hydrolyzed with aqueous ethanolic hydrochloric acid. The melting points of the purified, demethylated substance (180–181°) and its acetate (125–126°) identify it as a 1-deoxy-*myo*-inositol (*vibo*-quercitol, viburnitol); lit.[29] for "*d*-viburnitol," 180°; pentaacetate, 126°. The sirupy parent compound, the main component of the second band of the chromatogram, is therefore an *O*-methylviburnitol. As it is presumably the product of a simple hydrogenolysis of the inosose IV, it is formulated as L-1-deoxy-5-*O*-methyl-*myo*-inositol [4-*O*-methyl-(+)-*vibo*-quercitol, X]. The demethylated product is L-1-deoxy-*myo*-inositol [(+)-*vibo*-quercitol, *d*-viburnitol, XVI].

The trailing fractions of the second band were combined and concentrated to a sirup. This sirup on demethylation yielded 3.5 mg. of a substance which was identified as 2-deoxy-*myo*-inositol (*scyllo*-quercitol, XXVII) by its R_p (0.62) and the melting point (188–189°, lit.[15] 190°) of its pentaacetate. It is therefore likely that the minor component of the second band was 2-deoxy-5-*O*-methyl-*myo*-inositol (XXII), derived from the sequoyitol (XI) present as a contaminant[2] in the pinitol used as the starting material for the oxidation and hydrogenolysis.

2-*O*-Methyl-(+)-cyclohexane-1,3/2,4-tetrol (III) from IV.—The first band obtained by the chromatographic separation of the hydrogenolysis products of IV yielded a substance which could be recrystallized from ethyl acetate. The product weighed 0.15 g. and melted at 153–154°, $[\alpha]^{24}_D$ +40.4° (*c* 2.97, water).

Anal. Calcd. for $C_7H_{14}O_4$ (162.18): C, 51.84; H, 8.70. Found: C, 52.33; H, 8.32.

A periodate oxidation was carried out by adding 5.00 ml. of 0.05 *M* sodium metaperiodate to 8.89 mg. of the compound and allowing the solution to stand at room temperature. The consumption of periodate in moles per mole was: at 0.5 hr., 0.945; at 2 hr., 0.973; at 21 hr., 1.01.

The demethylation of the compound gave a product which could be precipitated by the addition of ethyl acetate. On recrystallization from absolute ethanol, it had m.p. 148–149°, which corresponds well with the melting point of 146–148° reported[30] for (−)-cyclohexane-1,3/2,4-tetrol.

These data, and arguments analogous to those used in support of the structure XV, establish the formula III. The demethylated product must be the hitherto unknown (+)-cyclohexane-1,3/2,4-tetrol, IX.

Hydrogenolysis of *myo*-Inosose-2 (XXVIII) and DL-*epi*-Inosose-2 (XXIII).—An amount of 20 mg. of each inosose[25] was used. After removal of the catalyst and the H_2SO_4, aliquots of the solutions were chromatographed on paper. Hydrogenolyzed *myo*-inosose-2 showed a main spot with R_p 0.61 (2-deoxy-*myo*-inositol, *scyllo*-quercitol, XXVII) and a minor spot which probably was *myo*-inositol (II). Similarly, hydrogenolyzed DL-*epi*-inosose-2 showed a major spot with R_p 0.63 (2-deoxy-*epi*-inositol, *epi*-quercitol, XXIV) and a minor spot which probably was *epi*-inositol. Each mixture gave a barely perceptible spot of fast-running substance, possibly tetrol.

Hydrogenolysis of 5-*O*-Methyl-*myo*-inosose-2 (XVII).—The filtrate from the oxidation of 1 g. of sequoyitol (XI) was treated according to the general procedure set forth above. Separation on the column (acetone–water 8:1) gave four bands. The first and third of these, containing 60 and 80 mg. of material, respectively, gave on demethylation complex mixtures that were not further characterized. The fourth band (280 mg.) consisted of sequoyitol, presumably representing unchanged starting material in view of the low yield of inosose obtained by oxidation of this cyclitol. A portion of the sequoyitol may have derived from the *reduction* of the inosose XVII.

2-Deoxy-5-*O*-methyl-*myo*-inositol (3-*O*-Methyl-*scyllo*-quercitol, XXII).—The second band from the above chromatogram consisted of 0.23 g. of crystalline substance. After recrystallization the substance melted at 215°.

Anal. Calcd. for $C_7H_{14}O_5$ (178.18): C, 47.18; H, 7.92. Found: C, 46.82; H, 7.84.

Demethylation of a small portion (19 mg.) of the compound gave a product which melted at 234–235° after recrystallization from ethanol. A mixture with authentic 2-deoxy-*myo*-inositol[15] (XXVII) had the same m.p. and the two samples showed identical behavior on paper chromatography.

The demethylation to 2-deoxy-*myo*-inositol, and the formula XVII for the inosose derived from sequoyitol, required the assignment of formula XXII to the hydrogenolysis product.

1,3,4,6-Tetra-*O*-acetyl-2-deoxy-5-*O*-methyl-*myo*-inositol.—Twenty mg. of XXII was acetylated by refluxing with 2 ml. of acetic anhydride and 20 mg. of anhydrous sodium acetate for 50 minutes. After cooling, water was added and the solution was concentrated until the tetraacetate crystallized. It was filtered off and washed with water; yield 26.7 mg., m.p. 184–185°. The melting point was not changed by recrystallization from water.

Anal. Calcd. for $C_{15}H_{22}O_9$ (346.33): C, 52.02; H, 6.40. Found: C, 52.20; H, 6.56.

Hydrogenolysis of L-1-*O*-Methyl-*myo*-inosose-2 (XXV).—One ml. of the solution of oxidized bornesitol described above was treated by the general hydrogenolysis procedure. Paper chromatography of the solution, after removal of the catalyst and the sulfuric acid, showed the presence of bornesitol and a component with R_p 1.04. The solution was taken to dryness and the residue was demethylated. Paper chromatography then showed the presence of two

(29) T. Posternak, *Helv. Chim. Acta*, **33**, 1594 (1950).

(30) T. Posternak and D. Reymond, *ibid.*, **38**, 195 (1955).

compounds with mobilities identical to those of *myo*-inositol (II) and 2-deoxy-*myo*-inositol (XXVII). The evidence for the formation of XXVII by demethylation, together with the evidence, already presented, that the oxidized bornesitol solution contains the inosose XXV, indicate that the hydrogenolysis product of R_p 1.04 is **L-2-deoxy-1-*O*-methyl-*myo*-inositol [(?)-1-*O*-methyl-*scyllo*-quercitol, XXVI]**.[27]

Hydrogenolysis of L-3-Deoxy-1-*O*-methyl-*myo*-inososе-2 (XIV).—The solution of oxidized L-3-deoxy-1-*O*-methyl-*myo*-inositol (XIII) described above was treated by the general hydrogenolysis procedure. Paper chromatography of aliquots of the solution, after removal of the catalyst and the sulfuric acid, showed the presence of XIII and a small amount of material with the mobility of (−)-1-*O*-methylcyclohexane-1,3/2,4-tetrol (XV).

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, COLLEGE OF AGRICULTURE, UNIVERSITY OF WISCONSIN, MADISON 6, WIS.]

Cyclitols and Their Methyl Ethers. IV. The Absolute Configurations of the *myo*-Inositol Monomethyl Ethers[1,2]

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(−)-Bornesitol and (+)-ononitol were synthesized by the reduction of inososes derived from quebrachitol (1-*O*-methyl-L-inositol). These syntheses confirm the conclusions of other workers as to the positions of the methyl groups in the bornesitols and ononitols, and establish the absolute configurations of these *myo*-inositol monomethyl ethers. (+)-Bornesitol is D- and (−)-bornesitol is L-1-*O*-methyl-*myo*-inositol; (−)-ononitol is D- and (+)-ononitol is L-4-*O*-methyl-*myo*-inositol.

The task of determining the locations of the methyl groups in the *myo*-inositol monomethyl ethers, *i.e.*, of deciding which of the six possible formulas corresponds to each of the known isomers, was partly accomplished in this Laboratory several years ago.[4] At that time, it was shown that sequoyitol and the synthetic ether of m.p. 212° are the *meso* compounds XI and X, respectively. The remaining four formulas VI–IX, comprising two DL-pairs, are asymmetric, and completion of the task required that these formulas be correctly allocated among the optically active isomers,[5] *viz.*, (+)-bornesitol, (−)-bornesitol, (+)-ononitol and (−)-ononitol. Evidence is now presented which establishes the absolute configurations of these compounds, and thus completes the formula assignments.

When the present work was undertaken, only one effort had been made to determine the positions of the methyl groups in the optically active *O*-methyl-*myo*-inositols. On the basis of a comparison of the electrophoretic mobilities of various cyclitols in borate buffer, Foster and Stacey[6] had concluded that (+)-bornesitol is either VI or VII, *i.e.*, that the bornesitols are the 1-*O*-methyl-*myo*-inositols.[4,7] If this conclusion could be accepted, it followed that the ononitols (not known at the time) would be the 4-*O*-methyl-*myo*-inositols (VIII and IX). However, it seemed important to have a more direct proof,[8] and in any case the experiments in question did not distinguish between enantiomorphs.

Our success in synthesizing sequoyitol by an unequivocal method from a naturally occurring cyclitol of known constitution led us to consider a similar approach to the optically active mono-*O*-methyl-*myo*-inositols. Our attention focused on quebrachitol, a naturally occurring monomethyl ether of L-inositol, for which the formula I had been established.[5] It can be seen (formula I) that there are two, and only two, positions (2 and 3) in quebrachitol at which oxidation followed by reduction in the opposite steric sense will effect a conversion to *myo*-inositol derivatives. It can also be seen that in one case the product will be L-4-*O*-methyl-*myo*-inositol (VIII), and in the other L-1-*O*-methyl-*myo*-inositol (VI); *i.e.*, one of the products must be a bornesitol and the other an ononitol. A further important point is that positions 2 and 3 in quebrachitol are precisely those which were expected to be subject to catalytic oxidation.

As described in the preceding paper[2] quebrachitol was readily oxidized, and an inosose was isolated in good yield from the reaction. The problem of establishing the formula of this inosose was solved in part, and the first of the projected syntheses was accomplished, by reducing the inosose with sodium borohydride. The reduction products were identified as quebrachitol and (−)-bornesitol, showing that the oxidation of quebrachitol had taken place in the predicted way, either at position 3 to give II, or at position 2 to give III. A tentative choice between the two possibilities was made by determining the periodate consumption of the phenylhydrazone of the inosose. Two molar equivalents of the reagent were required, indicating that the oxidation was at position 3 and that the inosose was therefore II [3-*O*-methyl-D-*myo*-inosose-1, 3-*O*-methyl-(−)-*vibo*-inosose]. Corroborating evidence was the fact that one of the products of the hydrogenolysis of the inosose was an *O*-methylquercitol which likewise consumed two molar equivalents of periodate.[2]

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(2) Paper III of this series *J. Am. Chem. Soc.*, **84**, 471 (1962).

(3) To whom requests for reprints should be sent.

(4) Paper II of this series: L. Anderson, Emily S. DeLuca, A. Bieder and G. G. Post, *J. Am. Chem. Soc.*, **79**, 1171 (1957). The reason for considering the isomerism of the inositol methyl ethers in terms of positions on the ring, and the numbering applicable to the *myo*-derivatives, is discussed in footnotes 4 and 9 of this paper.

(5) S. J. Angyal and L. Anderson, *Adv. Carbohydrate Chem.*, **14**, 135 (1959).

(6) A. B. Foster and M. Stacey, *Chemistry & Industry*, 279 (1953).

(7) For further clarification of the nomenclature see footnote 7 of the preceding paper.

(8) Although the conclusions of Foster and Stacey have been substantiated, the interactions of cyclitols with borate are more complex than these authors supposed; see S. J. Angyal and D. J. McHugh, *J. Chem. Soc.*, 1423 (1957).