Alicyclic Carbohydrates. XXXV. The Synthesis of *proto*-Quercitol. 220-MHz Proton Spectrum with the Superconducting Solenoid[1-3]

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The synthesis of (−)-*proto*-quercitol, a deoxyinositol (cyclohexanepentol) stereoisomer, discovered in the leaves of *Eucalyptus populnea* in 1961, is reported. Synthesis was effected by indirect removal of the position 2 hydroxyl group of (−)-inositol. Identical procedures applied to (+)-inositol would produce the well-known (+)-*proto*-quercitol, discovered in 1849 in acorns but never synthesized. Essentially identical procedures applied to DL-inositol would constitute a total synthesis of DL-*proto*-quercitol. The (−)-inositol 3,4,5,6-tetramethyl ether was converted into its 2-tosylate, which on methylation and detosylation gave the hexol pentamethyl ether. Oxidation of the latter produced (−)-*proto*-inosose pentamethyl ether, which on reaction with 1,2-ethanedithiol, and subsequent reduction, gave a pentol pentamethyl ether. This ether on cleavage gave the desired (−)-*proto*-quercitol, whose identity was confirmed by comparisons with authentic samples of the dextrorotatory form. Racemic *proto*-quercitol was prepared by mixing the two enantiomers. To verify the diastereomeric configuration (134/25) previously assigned by chemical correlations, the proton magnetic resonance spectrum of (+)-*proto*-quercitol was recorded at 220 MHz (51.7 kG), using a superconducting solenoid spectrometer. At this high resolution, configurational interpretation was greatly facilitated.

In 1849, Braconnot[6] isolated from the acorns of an oak tree (genus *Quercus*) a colorless, crystalline compound, $C_6H_{12}O_5$, which was named quercitol. Although the cyclohexanepentol structure, **24**, of this compound was established[7] in 1885, and its configuration, **20**, in 1932,[8] no synthesis has been reported.

Since some authors have used "quercitol" as a generic name[9,10] for the ten diastereomeric deoxyinositols (cyclohexanepentols), the more explicit name, *proto*-quercitol, has recently come into use for the diastereomer **20** (or **22**). The *proto*-quercitol first discovered was dextrorotatory; in 1961, the levorotatory form, **22**, was discovered by Plouvier[11] in leaves of the tree *Eucalyptus populnea* F. Muell.

The ten quercitols constitute possibly the largest all known family of diastereomers in organic chemistry, making them interesting candidates for systematic chemical and physical studies.[12-14] Although the *proto* diastereomer was the first discovered, it was the last synthesized. The long delay in synthesis may be attributed to the fact previously suggested,[12] "... nearly every synthetic scheme used for other cyclitols would lead stereospecifically to the 'wrong' product."

In 1965, Angyal, Gorin, and Pitman[9] did carry out an epimerization of natural (−)-*vibo*-quercitol (**25**) by heating it for a long time with 95% acetic acid (containing a little sulfuric acid). The resulting equilibrium mixture was shown by vapor phase chromatography to contain acetylated *proto*-quercitol, but none was actually isolated.[9]

The procedures here described[14] are for the synthesis of (−)-*proto*-quercitol from (−)-inositol. The identical procedures applied to (+)-inositol would produce the better known (+)-*proto*-quercitol (often called "*proto*-quercitol," or simply, "quercitol") derived from acorns. Essentially identical procedures[15] applied to DL-inositol would constitute a total synthesis of DL-*proto*-quercitol. Several total syntheses[16,17] of DL-inositol, *via* the intermediates quinonetetrol **26**,[9] *myo*-inositol,[16] or 3,5-cyclohexadiene-1,2-diol (**27**),[17] have previously been reported. Synthesis of (−)- or (+)-*proto*-quercitol by the route now described will not be "total" until the resolution[18] of DL-inositol (or DL-*proto*-quercitol) has been accomplished.

(1) For preliminary communication, see G. E. McCasland, M. O. Naumann, and L. J. Durham, *Carbohyd. Res.*, **4**, 516 (1967).

(2) For papers XXXIII and XXXIV in this series, see (a) G. E. McCasland, S. Furuta, and L. J. Durham, *J. Org. Chem.*, **33**, 2841 (1968); (b) G. E. McCasland, M. O. Naumann, and S. Furuta, in "Deoxy Sugars," S. Hanessian, Ed., Advances in Chemistry Series No. 74, American Chemical Society, Washington, D. C., 1968, pp 41–55.

(3) Presented in part by G. E. McCasland to the Division of Carbohydrate Chemistry at the 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 1966.

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(5) Stanford University.

(6) H. Braconnot, *Ann. Chim. Phys.*, (3) **27**, 392 (1849). Braconnot at first thought he had isolated lactose. Quercitol was recognized as a new compound by V. Dessaignes, *Compt. Rend.*, **33**, 308 (1851). For a recent discussion of the biosynthesis of quercitol in *Quercus* species, see H. Kindl, R. Scholda, and O. Hofmann-Ostenhof, *Phytochemistry*, **6**, 237 (1967).

(7) J. Kanonnikov, *J. Prakt. Chem.*, **140**, 497 (1885).

(8) T. Posternak, *Helv. Chim. Acta*, (a) **15**, 948 (1932); (b) **24**, 1045 (1941).

(9) (a) S. J. Angyal and D. J. McHugh, *J. Chem. Soc.*, 3682 (1957); (b) S. J. Angyal and C. G. MacDonald, *ibid.*, 686 (1952); (c) S. J. Angyal, P. A. J. Gorin, and M. Pitman, *ibid.*, 1807 (1965); (d) S. J. Angyal, personal communication, June 1966.

(10) In 1952, Angyal and MacDonald (ref 9) proposed that *quercitol* be adopted as a generic name for the ten diastereomeric deoxyinositols (cyclohexanepentols), and that the configurations be specified by the ten prefixes: *allo*, *cis*, *epi*, *gala*, *muco*, *neo*, *proto*, *scyllo*, *talo*, and *vibo*. We use some of these prefixes here to facilitate comparisons with previous literature, but prefer systematic fractional notation.

(11) V. Plouvier, *Compt. Rend.*, **253**, 3047 (1961). Plouvier called his new stereoisomer "L-quercitol;" although levorotatory, it actually has the D(134/25) configuration (see formulas in Chart I).

(12) For reviews on the chemistry of quercitols, see (a) T. Posternak, "Cyclitols," Holden-Day, Inc., San Francisco, Calif., 1965, Chapter IV; (b) T. Posternak, ref 12a, p 106; (c) G. E. McCasland, *Advan. Carbohyd. Chem.*, **20**, 11 (1965); (d) G. E. McCasland, *ibid.*, **20**, 21 (1965).

(13) For a review of the most recent work, see ref 2b.

(14) For previous work by us on quercitols, see (a) G. E. McCasland and E. C. Horswill, *J. Amer. Chem. Soc.*, **75**, 4020 (1953); (b) G. E. McCasland, S. Furuta, J. N. Shoolery, and L. F. Johnson, *ibid.*, **83**, 2335 (1961); (c) G. E. McCasland, S. Furuta, J. N. Shoolery, and L. F. Johnson, *ibid.*, **83**, 4243 (1961); (d) G. E. McCasland, S. Furuta, and V. Bartuska, *J. Org. Chem.*, **28**, 2096 (1963); (e) G. E. McCasland, S. Furuta, and A. Furst, *ibid.*, **29**, 724 (1964).

(15) It is possible that some of the racemic intermediates would have different solubilities than the corresponding active intermediates, and thus require different volumes of crystallizing solvents for best results.

(16) (a) H. Müller, *J. Chem. Soc.*, **101**, 2383 (1912); (b) H. G. Fletcher and G. R. Findlay, *J. Amer. Chem. Soc.*, **70**, 4050 (1948); (c) for the first synthesis of *myo*-inositol (used to make DL), see H. Wieland and R. S. Wishart, *Ber.*, **47**, 2082 (1914).

(17) M. Nakajima, I. Tomida, N. Kurihara, and S. Takei, *Chem. Ber.*, **92**, 173 (1959).

(18) See G. Tanret, *Bull. Soc. Chim.*, **17**, 921 (1897), for a possible microbiological resolution.

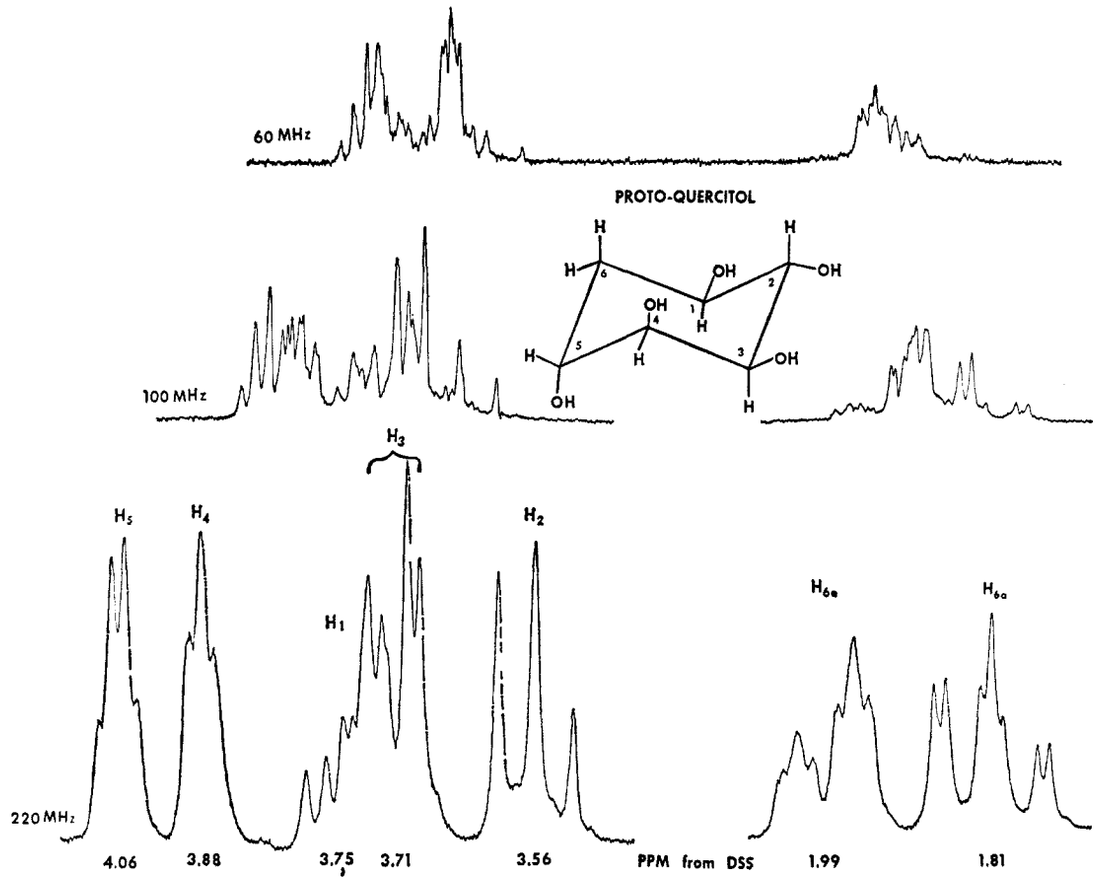


Figure 1.—Pmr spectra at 60, 100, and 220 MHz (14.1, 23.5, and 51.7 kG) of (+)-*proto*-quercitol in deuterium oxide.

Verification of Configuration by 220-MHz Pmr Spectroscopy.—Before starting our synthesis, it seemed desirable to verify the configuration **20,** of (+)-*proto*-quercitol, based on chemical correlations by Posternak.[8]

Early efforts to use proton magnetic resonance spectroscopy (pmr) to establish quercitol diastereomeric configurations were unsuccessful, with two exceptions,[14] because of complex spin–spin coupling and overlapping of the patterns at 60 MHz, and even at 100 MHz (see Figure 1).

However, when the pmr spectrum of (+)-*proto*-quercitol in deuterium oxide was observed at 220 MHz (51.7 kG), using the new superconducting solenoid spectrometer of Nelson and Weaver,[19] the patterns for individual ring protons were nearly all well separated, and configurational interpretation was greatly facilitated (see Figure 1).

The axial methylene proton H-6a (1.81 ppm) shows splittings (large, large, small) due to coupling with three protons (geminal, axial, and equatorial). (See formula in the figure). The equatorial proton H-6e similarly shows couplings (large, small, small) with the geminal and neighboring protons. The coupling constants of the axial proton H-2 triplet (3.56 ppm) indicate that the neighboring protons H-1 and H-3 also are axial. The narrowness of the patterns for H-4 and H-5 indicates that these two protons are equatorial.

The axial proton H-1 signal (3.75 ppm) is not so well separated but appears to consist of an eight-line pattern partially superposed on the axial H-3 signal (3.71 ppm), which is a pair of doublets.

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

The coupling constants observed for *proto*-quercitol were $J_{12} = 9.0$; $J_{23} = 9.0$; $J_{34} = 3.0$; $J_{45} = 3.1$; $J_{56e} = 3.1$; $J_{56a} = 2.9$; $J_{6a6e} = 13.8$; $J_{16e} = 5.0$; $J_{16a} = 11.5$ Hz.

These results are consistent only with the diastereomeric configuration (134/25) and the favored conformation (eeeaa) shown in the formula in Figure 1.[20] The 220-MHz pmr spectrum thus serves to confirm Posternak's configurational assignment, which was based on laborious chemical correlations.[8] These correlations involved oxidations of (+)-*proto*-quercitol to 4-deoxy-L-glucaric acid and *meso*-galactaric acid. Since the absolute configuration of L-glucaric acid is now known from X-ray studies on related compounds, Posternak's correlations serve also to establish the *absolute* L (134/25) configuration, **20,** for (+)-*proto*-quercitol.[21] This absolute assignment is confirmed by the optical rotation predictions of Whiffen.[22]

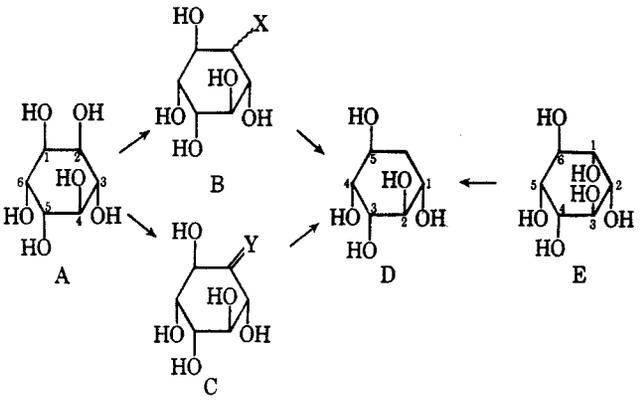
The Synthesis of (−)-*proto*-Quercitol.—Among the many possible synthetic approaches to a cyclohexanepentol considered by us were (1) introduction of a fifth hydroxyl group into a saturated or unsaturated

(20) We recommend that cyclitol diastereoisomers be designated by a modified Maquenne-type fractional notation, *e.g.*, (134/25). Accepted structural numbering and naming, *e.g.*, "1,2,3,4,5-cyclohexanepentol," is retained wherever feasible. Where accepted structural numbering is equivocal, *e.g.*, for cyclohexanehexol, the direction (*either* clockwise or counterclockwise), and if necessary, the starting point, for numbering are so chosen as to produce the set of numerator numbers with the lowest sum. For example, (−)-inositol is designated (124/356), *not* (235/416) or (356/124).

(21) To specify enantiomers, the *prenumbered* perspective formula, *e.g.*, **22**, is so oriented in three dimensions that numbering will proceed from right to left around the front. If the lowest numbered group is then oriented *down*, the prefix is D; if *up*, it is L. For further discussion, see G. E. McCasland, ref 12, pp 13–15, and further references cited therein.

(22) D. H. Whiffen, *Chem. Ind.* (London), 964 (1956).

tetrol, or suitable derivative and (2) removal of one hydroxyl group from a hexol (inositol), or suitable derivative. The latter approach seemed more promising, and the starting material thus might be either (−)-inositol A or *muco*-inositol E. The former inositol



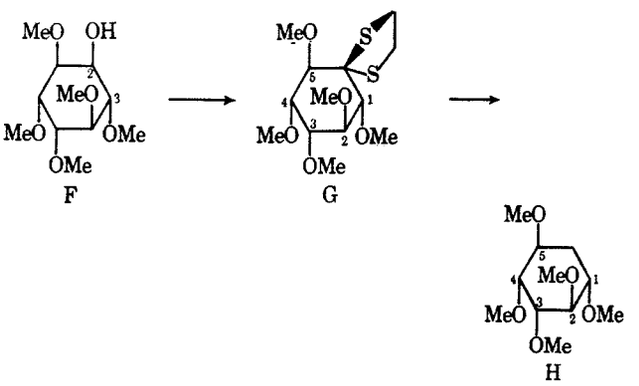
had the advantage of being optically active and readily available.

Since direct replacement of hydroxyl by hydrogen is not usually feasible, it was necessary to replace the position 2 hydroxyl group[23] in (−)-inositol A by some group easily removed by reduction. Suitable univalent groups would be chloro, bromo, iodo, or mercapto.[24] Suitable bivalent groups would be 2-keto, 2,2-di(alkylthio), 1,2-epoxy, or 2,3-epoxy.

Because the position 2 hydroxyl group in (−)-inositol is equatorial, there was little hope that it could be selectively displaced or oxidized so long as other, free hydroxyl groups were present in the molecule. Difficulties were also encountered in the preparation of a 1,2- or 2,3-epoxy derivative.

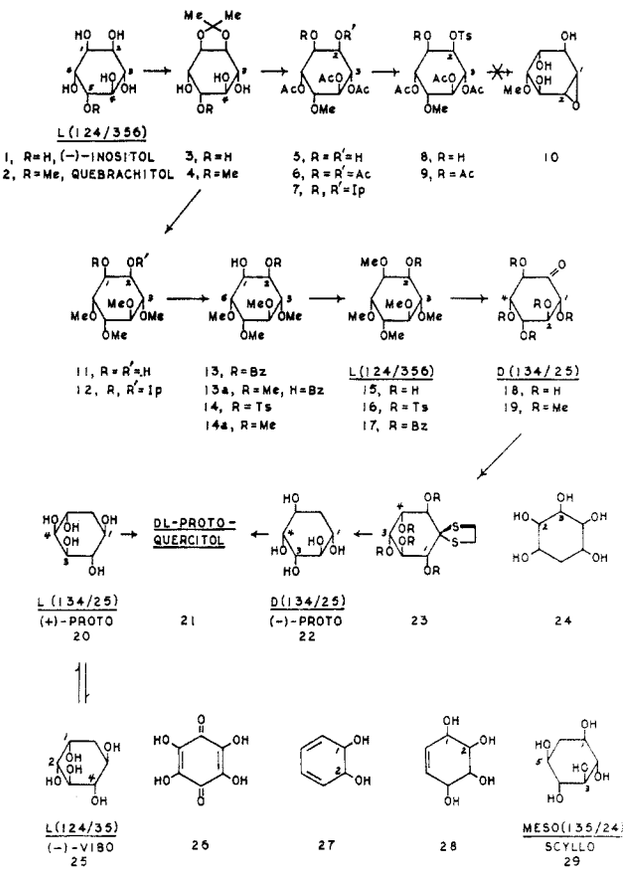
It was thus necessary to place protective groups on the remaining five hydroxyl groups before attempting to alter the group at position 2. Methyl ether groups were found best for this purpose. Although methyl protective groups are rarely used in syntheses of true sugars because of difficulty in removal, cyclitol methyl ethers are readily cleaved in high yield to the corresponding free cyclitols.

Attempted substitution by halogen of the free hydroxyl group in the pentamethyl ether F led to unexpected complications (see below); however, oxidation to carbonyl was readily accomplished. Attempts to reduce the ketone were unsuccessful, but its mercaptal derivative G on reduction did give the pentamethyl ether H of the desired cyclohexanepentol final product.



The synthetic steps may now be considered in greater detail. Direct conversion of (−)-inositol, **1** (see Chart I), into its pentamethyl ether, **15**, would scarcely be

Chart I



feasible. However, the previously reported[9] 1,2-O-isopropylidene derivative, **3**, was successfully converted into its tetramethyl ether, **12**, by reaction with methyl iodide in the presence of silver oxide. The ketal tetramethyl ether, obtained only as a syrup, was converted by mild acid hydrolysis into the hexol 3,4,5,-6-tetramethyl ether **11**, mp 92°. This tetramethyl ether was somewhat more conveniently obtained by methylation and subsequent deacetonation of the ketal monomethyl ether, **4**, a derivative of the well-known (−)-quebrachitol (**2**), derived from rubber latex.[25]

To methylate the axial (position 1) hydroxyl group in the tetramethyl ether **11**, we first had to protect the equatorial (position 2) hydroxyl group, which probably

(23) It should be noted that although (−)-inositol (formula 1) is dissymmetric, the molecule in its favored chair conformation does have a proper rotation axis of order 2 (symmetry C_2). For this reason, the 1-, 2-, and 4-monomethyl ethers are *identical* with the 6-, 5-, and 3-monomethyl ethers, respectively. Similar relationships apply to many other derivatives of (−)- or (+)-inositol. In this article, to avoid confusion, we have uniformly assigned the number 2 (not 5) to the ring position in (−)-inositol derivatives which was transformed into methylene in the final steps of our synthesis of *proto*-quercitol.

(24) For examples of preparations of various quercitols from the corresponding 6-chloro, 6-bromo, 6-iodo, or 6-mercapto derivatives, or from 1,2-anhydroinositols, see ref 12.

(25) The quebrachitol used was isolated from rubber latex and provided by the Plantation Division, U. S. Rubber Co. The preparation of highly pure (−)-quebrachitol and (−)-inositol (standard reference materials) is discussed by A. J. Fatiadi in National Bureau of Standards Technical Note 427, U. S. Government Printing Office, Washington, D. C., Oct 1967.

would be more reactive.[26,27] The needed equatorial monobenzoate, **13**, was readily obtained, but on attempted methylation, a (2 → 1) acyl migration occurred, so that the principal product was the 2,3,4,5,6-pentamethyl 1-benzoate (**13a**), and only a low yield of the desired 1,3,4,5,6-pentamethyl 2-benzoate, **17**, was obtained. The preparation and reactions of the "migrated" and nonmigrated benzoates provided some interesting and surprising results, which will be described in a subsequent article.[28]

Since sulfonate esters are not ordinarily subject to acyl migration, we next prepared the equatorial 2-*p*-toluenesulfonate tetramethyl ether **14**, mp 116°.[29] This derivative was successfully methylated to the corresponding pentamethyl ether, **16**, obtained only as a syrup; detosylation with sodium methoxide in ethanol gave the desired hexol 1,3,4,5,6-pentamethyl ether **15**. This ether has also been obtained only as a syrup; however, it was characterized by conversion into the crystalline pentamethyl monobenzoate **17**, mp 90°.

Reduction to methylene of the tosyloxy function (-CHOTs-) in the pentamethyl tosylate **16**, either directly or *via* a halogen substitution product, would have provided a short-cut to *proto*-quercitol pentamethyl ether, but unfortunately could not be accomplished. The substitution or reduction to methylene of alicyclic secondary tosyloxy groups is often difficult.

The hexol pentamethyl ether **15** on treatment with the new oxidant[30] ruthenium dioxide–sodium metaperiodate gave the desired *proto*-inosose pentamethyl ether **19** in the form of a syrup, which was characterized by conversion into the crystalline 2,4-dinitrophenylhydrazone, mp 203°. In some preparations, another convenient new oxidant,[31] dimethyl sulfoxide–acetic anhydride, was used (see Experimental Section), but the yield and purity of the product were not quite so good.

We now wished to convert the *proto*-inosose pentamethyl ether, **19**, into the (as yet unknown) free *proto*-inosose **18**. The latter, in all probability, would give a good yield of *proto*-quercitol when hydrogenated with a platinum catalyst in the presence of strong acid.[9] Unfortunately, all attempts to cleave the inosose pentamethyl ether with hydrohalic acids, or with boron trichloride,[29] were unsuccessful.[32] The unavailability of the *proto* isomer of inosose is one reason that the synthesis of *proto*-quercitol has never previously been accomplished.

Since the direct reduction of carbonyl to methylene[8] could not be accomplished, we next tried the conversion of the inosose pentamethyl ether, **19**, into a mercaptal derivative, which might more easily be reduced, using various alkanethiols, such as α-toluenethiol and 1,2-ethanedithiol. In no case could a crystalline mercaptal be obtained. However, when the crude syrupy mercaptal, **23**, from the ethanedithiol reaction was reduced with Raney nickel catalyst in boiling ethanol (without use of hydrogen gas), the desired pentol pentamethyl ether was successfully produced. This product, also, was a syrup, but on cleavage with hydrogen bromide in glacial acetic acid, it gave us the long sought crystalline final product, (−)-*proto*-quercitol.

The optical rotation of synthetic (−)-*proto*-quercitol was equal and opposite to that of natural (+)-*proto*-quercitol, and it had the same melting point, solubilities, ir spectrum, and pmr spectrum as an authentic sample of the dextro form. The properties of synthetic (−)-*proto*-quercitol were also in good agreement with those reported by Plouvier[11] for his natural levo form.

Since the dextro pentaacetate reportedly was amorphous, we prepared the pentabenzoate derivative of synthetic (−)-*proto*-quercitol. Its melting point, solubilities, and ir spectrum were identical with those of the dextro form,[33] and its optical rotation was equal and opposite. (Plouvier apparently did not prepare the levo pentabenzoate from his natural pentol.)

By recrystallization of a mixture of equal weights of natural (+)-*proto*-quercitols and synthetic (−)-*proto*-quercitols, we obtained racemic *proto*-quercitol. The only previous preparation of the racemic form was that of Plouvier,[11] who mixed the natural (+) and natural (−) enantiomers. Our racemic product had the expected zero optical rotation, within experimental error. Its melting point and (solid-state) ir spectrum were identical with those of (+)- or (−)-*proto*-quercitol, perhaps indicating that DL-*proto*-quercitol exists as a solid solution (not a racemate or conglomerate). The properties of our racemic form were in agreement with those reported by Plouvier.[11]

The racemic pentabenzoate was also prepared (apparently for the first time) by recrystallizing a mixture of equal weights of the (+)- and (−)-pentabenzoates. The product had the expected zero optical rotation. Its melting point (138–140°) was lower than that of the active form (155°), perhaps indicating that the racemic pentabenzoate exists as a conglomerate or racemate (not a solid solution; compare the properties of the racemic pentol). Although the solid-state ir spectra of the racemic and active pentabanzoates showed no significant differences, it is possible that differences would be apparent at very high resolution.

In an earlier attempt to synthesize (−)-*proto*-quercitol, we treated the hexol 2,3,4,5,6-pentamethyl ether (**14a**, R = Me) with phosphorus pentachloride.[28] The product on demethylation gave a chloropentol, which on dehalogenation surprisingly gave *meso*-scylloquercitol (**29**). Details will be given in a subsequent publication.[28]

(26) After experiments on the preparation of (−)-inositol benzyl ethers, Angyal and Steward [*Aust. J. Chem.*, **19**, 1683 (1966)] suggested that "... the reactivity of the axial hydroxyl groups in (−)-inositol is simliar to that of the equatorial hydroxyl groups." However, in our own synthesis now reported it appears that certain (−)-inositol equatorial hydroxyl groups *do* react preferentially at least in the formation of benzoate or *p*-toluenesulfonate esters.

(27) The etherification reaction transition state presumably contains five groups arranged around the halogen-bearing carbon in trigonal-bipyramid orientation (SN2 mechanism). The acylation (at least by benzoyl chloride) transition state presumably contains four groups arranged around the carbonyl carbon in tetrahedral orientation (nucleophilic substitution at an unsaturated carbon atom). *Both* the axial and equatorial forms of the etherification transition state seem to involve moderately strong steric repulsions by the cyclitol axial groups. In acylation, the axial form of the transition state is less hindered, and the equatorial form much less hindered, than in the etherification transition state.

(28) G. E. McCasland, M. O. Naumann, and L. J. Durham, manuscript in preparation.

(29) For an interesting preparation of 1-O-*p*-toluenesulfonyl-(−)-inositol by demethylation of the 1-O-tosyl-5-O-methyl derivative with boron trichloride, see S. D. Gero, *Tetrahedron Lett.*, 591 (1966).

(30) V. M. Parikh and J. K. N. Jones, *Can. J. Chem.*, **43**, 3452 (1965).

(31) J. D. Albright and L. Goldman, *J. Amer. Chem. Soc.*, **87**, 4214 (1965).

(32) However, V. Prey and F. Stadler have reported a successful cleavage of an inosose tetramethyl ether, using hydrogen bromide in acetic acid; see *Ann.*, **660**, 155 (1962).

(33) K. H. Bauer and H. Moll, *Arch. Pharm.*, **280**, 37 (1942).

In still earlier experiments we sought to prepare *proto*-quercitol (dextro, levo, or DL) by a synthetic route involving hydrogenation of the active monomethyl ether, **10**, of 1,2-anhydro-*muco*-inositol. The quebrachitol tosylate tetraacetate **9** was prepared for use in this synthesis (see Experimental Section), but since efforts to convert it into the epoxide **10** were unsuccessful, this approach was abandoned.

Pmr Studies on the Synthetic Intermediates.—Proton magnetic resonance spectra at 60 and 100 MHz were recorded for most of the intermediates prepared, as described in detail in the Experimental Section. The intermediates so studied included (−)-quebrachitol, its 1,2-O-isopropylidene derivative, its 3,4,6-triacetate, its pentaacetate, its 3,4,6-triacetate 2-*p*-toluenesulfonate, and its 1,3,4,6-tetraacetate 2-*p*-toluenesulfonate. Even at 100 MHz, configurational interpretation of the pmr spectra of such cyclitols still is often difficult.

Double resonance and exchange with deuterium oxide were found helpful in the case of the (−)-quebrachitol 3,4,6-triacetate and the 3,4,6-triacetate 2-*p*-toluenesulfonate (see Experimental Section).

The spectra were also recorded for (−)-inositol 3,4,5,6-tetramethyl ether and its 2-*p*-toluenesulfonate, and for (−)-inositol 1,3,4,5,6-pentamethyl ether 2-monobenzoate.

The spectrum of (+)-*proto*-quercitol and its pentabenzoate were recorded at 60 and 100 MHz, and the former also at 220 MHz (see above). The spectrum of (−)-*proto*-quercitol was recorded at 100 MHz.

Experimental Section

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. Infrared spectra were recorded on Perkin-Elmer Models 421 and 137 spectrometers. Solutions were concentrated at 30–40° under reduced pressure with a rotary evaporator. The petroleum ether used had a 60–80° boiling range.

Proton magnetic resonance spectra at 220 MHz (51.7 kG) were recorded with a Varian Model HRSC-IX or -220 spectrometer, using a superconducting niobium–zirconium solenoid in liquid helium (sample at room temperature in deuterium oxide).

Proton magnetic resonance spectra at 60 and 100 MHz were recorded on a Varian A-60 and a Varian HR-100 spectrometer. Spectra of free pentols were obtained from deuterium oxide solutions containing sodium 2,2-dimethyl-2-silapentanesulfonate (DSS) as internal standard. Unless otherwise noted, all other spectral were taken on chloroform-*d* solutions containing tetramethylsilane (TMS) as the internal reference. All chemical shifts are reported in parts per million relative to TMS (or DSS) taken as zero.

The (−)-quebrachitol **2** used was isolated from the latex of *Hevea Brasiliensis* by the Plantation Division, U. S. Rubber Co.; it was converted into (−)-inositol **1** by reaction with hydriodic acid in the usual manner.[25] The 1,2-O-isopropylidene derivative of (−)-inositol (**3**) and of (−)-quebrachitol (**4**) and the 3,4,6-tri-O-acetyl-1,2-O-isopropylidene (**7**), and 3.4,6-tri-O-acetyl (**5**) derivatives of (−)-quebrachitol were prepared by the procedures of Angyal and coworkers.[9]

Pmr Spectrum of L(124/356) Stereoisomer of 5-Methoxy-1,2,3,4,6-cyclohexanepentol [(−)-Quebrachitol] (2).—The spectrum at 100 MHz using deuterium oxide contained a sharp methoxyl proton singlet at 3.42 ppm. The two equatorial ring protons (H-1, H-6) at 4.03 and 4.23 ppm (not known which is which) each appeared as a pair of doublets, with splittings of about 3.8 and 2.5 Hz. The four axial ring protons produced signals in the region 3.3–3.8 ppm, which could not be interpreted because of overlapping, although some sharp lines were visible. When the frequency was changed to 60 MHz, extra lines appeared in the pair of doublets at 4.03 ppm, presumably due to increased virtual coupling.

Pmr Spectrum of 1,2-O-Isopropylidene-(−)-quebrachitol (4).—The spectrum at 100 MHz using deuterium oxide contained a methoxyl singlet at 3.44 ppm and ketal methyl singlets at 1.39 and 1.52 ppm. Ring proton signals were observed at 3.1–3.8 ppm (3–4 **H**, several sharp lines), 4.15 ppm (1 **H**, poorly resolved multiplet), and 4.32 ppm (2 H). The ring proton patterns could not be interpreted because of overlapping.

Pmr Spectrum of (−)-Quebrachitol 3,4,6-Triacetate (5).—The spectrum at 100 MHz using chloroform-*d* contained sharp three-proton singlets for the axial acetate methyl (2.12 ppm), the two equatorial acetate methyls (2.08 and 2.06 ppm), and the equatorial methoxyl methyl (3.38 ppm).

The equatorial AcO–C**H** ring proton H-6 produced a triplet at 5.48 ppm (spacing 3.5 Hz). The signals due to the axial AcO–C**H** ring protons H-3 and H-4 at 5.0–5.3 ppm resembled part of an A_2X_2 pattern (unchanged at 60 MHz). The remaining ring protons and the two hydroxyl protons appeared in the region 3.5–4.2 ppm.

The midfield spectrum was simplified by addition of a little deuterium oxide. The equatorial HO–C**H** proton (H-1) then appeared as a triplet at 4.05 ppm (spacing 3.5 Hz). Signals for the axial HO–C**H** proton (H-2) and and the axial MeO–C**H** proton (H-5) still overlapped, however.

Assignments for the protons H-2 (3.85 ppm) and H-5 (3.70 ppm) were confirmed by double resonance. The H-6 triplet was collapsed to a doublet by irradiation of H-5 (176 Hz upfield) and also by irradiation of H-1 (143 Hz upfield). The signal of H-2 was considerably simplified by irradiation of H-3 (130 Hz downfield), probably due in part to reduction of virtual coupling between H-2 and H-4. The signal for H-5 was considerably simplified by irradiation of H-6 (160 Hz downfield) or H-4 (143 Hz downfield); it was also affected by irradiation of H-3.

Pmr Spectrum of (−)-Quebrachitol Pentaacetate (6).—The spectrum at 100 MHz using chloroform-*d* contained sharp singlets for the three equatorial acetate methyls at 1.92, 2.01, and 2.05 ppm, and a six-proton singlet for the two axial acetate methyls at 2.15 ppm. The methoxyl methyl singlet was observed at 3.36 ppm. The equatorial MeO–C**H** proton (H-5) produced a complex multiplet at about 3.6 ppm. The remaining five ring protons produced complex overlapping multiplets in the region 5.0–5.2 ppm which could not be resolved at 100 MHz.

3,4,6-Tri-O-acetyl-5-O-methyl-2-O-*p*-toluenesulfonyl-(−)-inositol (Quebrachitol Tosylate Triacetate) (8).—To a solution of 0.5 g of the methyl ether triacetate (mp 130°) in 2.0 ml of pyridine was added at room temperature during 3 hr a solution of 0.40 g of *p*-toluenesulfonyl chloride in 3.0 ml of pyridine. The mixture was kept at room temperature for 6 days and then poured with stirring into 100 ml of water at 0°. After 1 hr the product was collected and recrystallized three times from 95% ethanol to give 0.40 g (54%) of the desired product, colorless needles, mp 135–136°.

Anal. Calcd for $C_{20}H_{26}O_{11}S$: C, 50.65; H, 5.49; S, 6.75. Found: C, 51.08; H, 5.71; S, 6.54.

The ir spectrum was recorded: ν_{max}^{Nujol} 3700, 1750, 1600, 1230, 840, 820, and 740 cm^{-1}.

Pmr Spectrum of (−)-Quebrachitol 2-*p*-Toluenesulfonate 3,4,6-Triacetate (8).—The spectrum at 100 MHz using chloroform-*d* contained sharp singlets for equatorial methoxyl methyl (3.55 ppm), for equatorial tosyl methyl (2.45 ppm) and for the three acetate methyls (2.13, 2.02, and 1.73 ppm). (The axial–equatorial assignments for the acetate methyl signals remain uncertain.) The hydroxyl proton produced a doublet at 3.28 ppm. The four tosyl aromatic protons produced an A_2B_2 pattern with components centered at 7.37 and 7.77 ppm.

Signals for the six ring protons (3.5–5.7 ppm) were sufficiently well separated to permit individual assignments, which were confirmed by double resonance. The quartetlike pattern of axial H-1 (4.23 ppm) was collapsed to a triplet (spacing 3.5 Hz, probably not *J*) by addition of a little deuterium oxide. The triplet was further collapsed to a doublet by irradiation of H-2 or H-6.

The axial proton H-2 (4.70 ppm) was observed as a pair of doublets (spacings 10 and 3 Hz), which was collapsed to a single small doublet by irradiation of H-3 or H-1. The axial proton H-3 produced a tripletlike signal (5.45 ppm, spacing 9.5–10 Hz). The axial proton H-4 appeared as a triplet (5.18 ppm, spacing 9.5–10 Hz). The axial proton H-5 produced a pair of doublets (3.70 ppm, spacings 9.5 and 3.5 Hz), which was collapsed to a

small doublet by irradiation of H-4 and to a large doublet by irradiation of H-6. The equatorial proton H-6 produced a small triplet at 5.53 ppm, with spacing about 4 Hz (probably not J). This sequence of double resonance experiments served to confirm that H-1 and H-6 are equatorial, while H-2, H-3, H-4, and H-5 are axial.

On reaction with acetic anhydride in pyridine, the product was converted into the previously reported[9] tetraacetate (**9**), mp 141–143° (lit.[9] mp 142–143°).

Pmr Spectrum of (−)-Quebrachitol 2-*p*-Toluenesulfonate 1,3,4,6-Tetraacetate (**9**).—The tosyl methyl and methoxy methyl groups produced sharp singlets at 2.42 and 3.33 ppm, respectively. The two axial and two equatorial acetate methyl groups produced sharp singlets at 1.88, 2.04, 2.08, and 2.15 ppm; the axial–equatorial assignments remain uncertain. The tosyl aromatic protons produced an A_2B_2 pattern with components centered at 7.37 and 7.73 ppm.

The axial ring protons H-2 and H-5 each produced a pair of doublets, centered at 4.88 and 3.53 ppm, respectively. In each case the spacings indicated the presence of one axial and one equatorial neighboring proton.

The four remaining ring protons appeared as complex overlapping multiplets in the region 5.2–5.5 ppm. By means of double resonance, the axial proton H-4 was estimated to be at 5.20 ppm, and the equatorial proton H-6 at approximately 5.40 ppm. The signals for protons H-1 and H-3 were not located.

Efforts to replace the tosyloxy group by hydrogen, either by direct reduction or by preliminary displacement of the *p*-toluenesulfonate group by an iodo or bromo group, were unsuccessful. Efforts to replace the 2-tosyloxy group and the neighboring *trans*-3-acetoxy group by a 2,3-epoxy group also gave no good result. Attempts to facilitate the SN2 reactions by use of a special solvent (such as dimethyl sulfoxide) were not helpful.

L(124/356) Stereoisomer of 3,4,5,6-Tetramethoxy-1,2-cyclohexanediol [Tetra-O-methyl-(−)-inositol] (11). A. From Isopropylidenequebrachitol (Silver Oxide Method).—To a 2.34-g portion of the finely powdered 1,2-O-isopropylidene derivative (mp 135°) of (−)-quebrachitol was added 12.0 g of silver oxide and 25 ml of methyl iodide, and the mixture was boiled under reflux with stirring for 30 hr. The mixture was filtered, and the residue was extracted with hot chloroform (four 20-ml portions). The combined filtrate was evaporated, giving a syrupy residue. The residue was remethylated with 5.0 g of silver oxide and 10 ml of methyl iodide in the same manner, giving **1,2-O-isopropylidene-3,4,5,6-tetra-O-methyl-(−)-inositol** (**12**), in the form of a syrup, bp 128° (3.5 mm). The infrared spectrum was recorded ($\nu_{max}^{liq\ film}$ 2900, 1460, 1370, 1100, and 865 cm^{-1}.

To this syrup was added 20 ml of aqueous acetic acid (1:1), and the mixture was boiled for 2 hr under reflux. The residue, obtained on evaporation of the solvent, was crystallized from a mixture of benzene and petroleum ether (bp 60–80°), giving 1.1 g (47% based on isopropylidenequebrachitol) of the desired **tetramethyl ether 11** as colorless needles: mp 90–92°; $[\alpha]^{25}D$ −71.2° (*c* 3.3, water).

Anal. Calcd for $C_{10}H_{20}O_6$: C, 50.83; H, 8.53. Found: C 51.15; H, 8.66.

The ir spectrum was recorded (ν_{max}^{Nujol} 3640, 1150, 1100, and 1060 cm^{-1}).

The pmr spectrum was recorded at 60 MHz only, using chloroform-*d*. The four methoxyl groups produced sharp singlets at 3.48, 3.52, 3.61, and 3.64 ppm. A small triplet at 4.17 ppm was produced by one of the two equatorial ring protons. A broad unresolved multiplet centered at about 3.2 ppm was produced by two more of the ring protons. Signals for the three remaining ring protons were in the same region as the methoxyl signals.

B. From Isopropylidenequebrachitol (Potassium Hydroxide Method).—To a 10.0-g portion of the finely powdered 1,2-O-isopropylidene derivative (mp 135°) of (−)-quebrachitol was added 200 ml of benzene, 45 ml of methyl iodide, and 25.0 g of finely powdered potassium hydroxide, and the mixture was boiled under reflux with vigorous stirring for only 4 hr. After cooling, the supernatant solution was decanted, and the residue was washed by decantation with hot benzene. The combined decantate was evaporated giving **1,2-O-isopropylidene-3,4,5,6-tetra-O-methyl-(−)-inositol** (**12**) as a syrup. The ir spectrum was recorded and was identical with that of the product prepared by procedure A.

To this syrup was added 100 ml of aqueous acetic acid (1:1), and the mixture was boiled for 2 hr under reflux. The residue obtained on evaporation of the solvent was crystallized and recrystallized from ethyl acetate–petroleum ether, giving 7.0 g (70%) of the **tetramethyl ether 11** as colorless needles, mp 90–92°. A mixture melting point with the product from procedure A was not depressed, and the ir spectra were identical.

C. From Isopropylidene-(−)-inositol.—A 1.1-g portion of 1,2-O-isopropylidene-(−)-inositol (mp 157°), methylated and then hydrolyzed in the same manner as procedure A above, gave 0.40 g (35%) of the **tetramethyl ether 11** as colorless needles, mp 90–92°. A mixture melting point with the product from procedure A was not depressed, and the ir spectra were identical.

3,4,5,6-Tetra-O-methyl-2-O-*p*-toluenesulfonyl-(−)-inositol (**14**).—To a 10.0-g portion of the tetramethyl ether (mp 90–92°) in 30 ml of pyridine was added 10.0 g of *p*-toluenesulfonyl chloride, and the mixture was kept at room temperature for 48 hr. After addition of 5 ml of water, the mixture was evaporated to dryness. The syrupy residue was taken up in ethyl acetate, and the extract was washed with 1 *N* sulfuric acid, saturated sodium bicarbonate, and water. After drying, the ethyl acetate solution was evaporated, and the residue, a syrup, was crystallized from petroleum ether. After two recrystallizations from the same solvent the desired product (9.5 g, 58% yield) was obtained in the form of colorless needles: mp 116–117°; $[\alpha]^{25}D$ −89.3 (*c* 2.8, carbon tetrachloride).

Anal. Calcd for $C_{17}H_{26}O_8S$: C, 52.31; H, 6.67; S, 8.21. Found: C, 52.74; H, 6.58; S, 8.31.

The ir spectrum was recorded (ν_{max}^{Nujol} 3570, 1610, 1170, 1100, 850, and 820 cm^{-1}).

The pmr spectrum and integral were recorded at 60 and 100 MHz using chloroform-*d*. The four methoxyl groups produced signals at 3.21, 3.44, 3.48, and 3.54 ppm. The tosyl methyl group appeared at 2.46 ppm. The tosyl aromatic protons produced an A_2B_2 pattern with components centered at 7.35 and 7.82 ppm. A broad signal at 2.55 ppm presumably was produced by the hydroxyl proton. Three of the ring protons produced signals at 3.70 (H-6?, a pair of doublets, J = 3 and 5 Hz), at 4.30 (H-1?, triplet, spacing 4 Hz), and 4.50 ppm (H-2?, pattern resembling a pair of doublets with additional fine structure), respectively. Signals of the remaining three ring protons were partly obscured by the methoxyl signals.

2-O-Benzoyl-1,3,4,5,6-penta-O-methyl-(−)-inositol (Pentamethoxycyclohexyl Benzoate) (17). A. From the Tetramethyl Monobenzoate.—To a solution of 2.0 g of 2-O-benzoyl-3,4,5,6-tetramethyl-(−)-inositol[28] (mp 121°) in 15.0 ml of methyl iodide was added 12.0 g of freshly prepared silver oxide. The mixture was boiled for 48 hr under reflux with stirring, cooled, and filtered. The residue was extracted with chloroform (four 15-ml portions), and the combined filtrates were evaporated. The residual syrup was crystallized from *n*-heptane, giving 0.51 g (24%) of the product as colorless prisms: mp 88–90°; $[\alpha]^{25}D$ −95.4° (*c* 1.3, carbon tetrachloride). The low yield was due primarily to benzoyl migration.[28]

Anal. Calcd for $C_{18}H_{26}O_7$: C, 61.00; H, 7.40. Found: C, 60.67; H, 7.41.

The ir spectrum was recorded (ν_{max}^{Nujol} 1730, 1610, 1275, 1110, 980, and 715 cm^{-1}). The heptane mother liquors were reserved for preparation of the migrated pentamethyl ether monobenzoate.

The pmr spectrum was recorded at 60 MHz only, using chloroform-*d*. The five methoxyl groups produced sharp singlets at 3.42, 3.50 (six protons), 3.55, and 3.62 ppm. Aromatic proton signals were observed in the region 7.3–7.7 and 8.0–8.2 ppm. Two (or three) of the six ring protons produced poorly resolved multiplets centered at about 3.94 and 5.28 ppm; the remaining ring proton signals were partly obscured by the methoxyl signals.

By hydrolysis of the "nonmigrated" monobenzoate (1.0 g) with sodium hydroxide, there was obtained 0.55 g of **1,3,4,5,6-penta-O-methyl-(−)-inositol** (**15**) as a colorless syrup, whose ir spectrum was identical with that for the product prepared from the 5-tosyl pentamethyl ether (see below).

B. From the Tetramethyl Monotosylate.—To a solution of 10.0 g of the 3,4,5,6-tetramethyl ether 2-tosylate (mp 116–117°) in 75 ml of benzene was added 20 ml of methyl iodide and 10.0 g of finely powdered potassium hydroxide, and the mixture was boiled under reflux with vigorous stirring. After cooling, the supernatant solution was decanted, and the residue was washed by decantation with warm benzene. The combined decantate, after drying, was evaporated to give 9.5 g of **1,3,4,5,6-penta-O-methyl-2-O-*p*-toluenesulfonyl-(−)-inositol** (**16**) as a colorless syrup. The ir spectrum was recorded (ν_{max} 2900, 1600, 1460, 1370, 1100, 840, 815, and 740 cm^{-1}).

A mixture of 9.0 g of this syrup with 15 g of sodium methoxide and 80 ml of anhydrous ethanol was boiled under reflux for 14 hr. The solvent was evaporated, and to the residue was added 100 ml of water. The mixture was neutralized with 3 *M* hydrochloric acid. The aqueous mixture was extracted with chloroform, and the combined chloroform extract was washed successively with 3% sodium carbonate, 1 *M* hydrochloric acid, saturated sodium bicarbonate, and water. After drying, the chloroform solution was evaporated, giving 40 g of the **hexol 1,3,4,5,6-pentamethyl ether (15)** as a yellow syrup. The infrared spectrum was recorded ($\nu_{max}^{liq\ film}$ 3640, 2900, 1460, 1370, 1190, 1140, 1100, 1000, and 960 cm^{-1}).

A 0.70-g portion of this syrup was dissolved in 5 ml of pyridine, and 0.33 ml of benzoyl chloride was added. The mixture was heated at 100° for 20 min, then cooled. Chloroform (25 ml) was added, and the resulting mixture was washed with 1 *M* hydrochloric acid, saturated sodium bicarbonate, and water. After drying, the chloroform solution was evaporated, and the syrup residue was crystallized from *n*-heptane, giving 0.70 g (76%) of the **1,3,4,5,6-pentamethyl ether 2-monobenzoate (17)**, colorless prisms, mp 88–90°. A mixture melting point with the product from procedure A was not depressed and the ir spectra were identical.

D(**134/25**) **Stereoisomer of 1,2,3,4,5-Pentamethoxy-6-cyclohexanone** (*proto*-**Inosose Pentamethyl Ether**) (**19**). **A. Ruthenium Dioxide Method.**—To a solution of 4.0 g of the syrupy hexol 1,3,4,5,6-pentamethyl ether (derived from the monobenzoate, mp 88–90°) in 80 ml of carbon tetrachloride containing a catalytic amount (100 mg) of ruthenium dioxide was added, at intervals with vigorous stirring, small quantities of 5% aqueous sodium metaperiodate solution. The pH of the mixture was maintained between 6 and 7 by the occasional addition of small amounts of dilute sodium bicarbonate solution, using a pH meter. The reaction was continued until a change in color occurred from black (ruthenium dioxide) to blackish yellow (ruthenium tetroxide). The aqueous layer was extracted with carbon tetrachloride (two 25-ml portions), and to the combined carbon tetrachloride extract was added a little 1-propanol to destroy any excess ruthenium tetroxide. The solution was filtered and washed with 1% aqueous sodium thiosulfate and with water. Evaporation of the solvent, after drying, gave 2.8 g of the product as a colorless syrup. The infrared spectrum was recorded ($\nu_{max}^{liq\ film}$ 2900, 1730, 1460, 1370, 1115, 1020, and 790 cm^{-1}).

Treatment of 50 mg of the above syrup with 2,4-dinitrophenylhydrazine in aqueous methanol containing sulfuric acid gave 63 mg (74%) of the **2,4-dinitrophenylhydrazone** as yellow needles, mp 198–201°. Recrystallization of the product from ethanol raised the melting point to 202–203°.

Anal. Calcd for $C_{17}H_{24}N_4O_9$: C, 47.66; H, 5.64. Found: C, 47.34; H, 5.72.

The infrared spectrum was recorded (ν_{max}^{Nujol} 1640, 1610, 1530, 1110, and 1020 cm^{-1}).

B. Dimethyl Sulfoxide Method.—To a solution of 2.5 g of the syrupy hexol 1,3,4,5,6-pentamethyl ether (derived from the monobenzoate, mp 88–90°) in 30 ml of dimethyl sulfoxide was added 20 ml of acetic anhydride, and the mixture was kept at room temperature for 48 hr. Evaporation of the solvent under reduced pressure (0.5 mm) gave the product as a yellow syrup, whose ir spectrum was identical with that of the product from procedure A.

The syrup was dissolved in 6 ml of dimethyl sulfoxide, and a solution of 2.5 g of 2,4-dinitrophenylhydrazine in 20 ml of dimethyl sulfoxide and 4 drops of concentrated hydrochloric acid were added. After 5 hr at 0° the precipitated product was collected. A second crop was collected after an additional 12 hr at 0°. Recrystallization of the combined precipitates from 95% ethanol gave 2.2 g (51% based on hexol pentamethyl ether) of the **2,4-dinitrophenylhydrazone**, as yellow needles, mp 202–203°. A mixture melting point with the product from procedure A was not depressed, and the ir spectra were identical.

D(**134/25**) **Stereoisomer of Cyclohexanepentol** [(−)-*proto*-**Quercitol**] (**22**).—A mixture of 1.0 g of the syrupy *proto*-inosose pentamethyl ether (derivative of the 2,4-dinitrophenylhydrazone, mp 203°) and 1.5 ml of ethanedithiol was stirred with 1.0 ml of 12 *M* hydrochloric acid at room temperature for 24 hr. The mixture was poured into water (10 ml) and extracted with benzene (two 10-ml portions). The benzene extract was washed with ice-cold saturated sodium bicarbonate and with water. Evaporation of the benzene solution, after drying, gave 1.4 g of the dithioacetal **23** as a colorless syrup. The ir spectrum was recorded ($\nu_{max}^{liq\ film}$ 2950, 1460, 1370, 1115, and 1090 cm^{-1}).

A solution of 1.35 g of the syrupy dithioacetal in 30 ml of ethanol was boiled under reflux for 2 hr with 12 g (wet weight) of Raney nickel. After cooling, the supernatant solution was decanted, and the residue was washed by decantation with warm ethanol. The combined decantate was filtered. Evaporation of the solvent gave 0.55 g of *proto*-**quercitol pentamethyl ether (pentamethoxycyclohexane)** as a colorless syrup. The ir spectrum was recorded ($\nu_{max}^{liq\ film}$ 2950, 1460, 1370, 1100, and 1030 cm^{-1}).

A solution of 0.55 g of the above syrup dissolved in 5.0 ml of a commercial acetic acid solution containing 32% of hydrogen bromide (and probably a small amount of water) was boiled under reflux for 1 hr. Evaporation of the solvent gave a syrup, to which small amounts of ethanol were repeatedly added and evaporated. The residual syrup was dissolved in water (10 ml) and treated with decolorizing charcoal. After filtration and evaporation of the solvent, the syrupy residue was crystallized and recrystallized from 95% ethanol to give 120 mg of the desired (−)-*proto*-**quercitol (22)** as colorless needles: mp 238–239°; $[\alpha]^{25}D$ −25.1° (*c* 1, water).

Anal. Calcd for $C_6H_{12}O_5$: C, 43.90; H, 7.37. Found: C, 43.92; H, 7.34.

A mixture melting point with natural (+)-*proto*-quercitol [mp 238–239°; $[\alpha]^{25}D$ +25.3° (*c* 2, water)] was not depressed (see below), and the ir spectra were identical.

DL(**134/25**) **Diastereomer of Cyclohexanepentol (Racemic** *proto*-**Quercitol) (21)**.—A mixture of 15.0 mg of natural (+)-*proto*-quercitol (mp 239°) and 15.0 mg of synthetic (−)-*proto*-quercitol (mp 239°) was recrystallized from 95% ethanol to give DL-*proto*-**quercitol** as colorless needles: mp 238–239° (lit.[11] mp 237°); optical rotation zero within experimental error.

(−)-*proto*-**Quercitol Pentabenzoate (22, H = Bz)**.—A mixture of 20 mg of (−)-*proto*-quercitol (mp 239°), 1.0 ml of pyridine, and 150 mg of benzoyl chloride was heated at 100° for 10 min. After cooling, water (0.5 ml) was added, and after 10 min, the mixture was poured into ethyl acetate (15 ml). The ethyl acetate solution was washed with 2 *M* hydrochloric acid, saturated sodium bicarbonate solution, and water. Evaporation of the ethyl acetate, after drying, gave a syrup which was crystallized from 95% ethanol to give 55.0 mg of the pentabenzoate, as colorless needles: mp 154–155°; $[\alpha]^{25}D$ −62.8° (*c* 1, ethyl acetate).

Anal. Calcd for $C_{41}H_{32}O_{10}$: C, 71.71; H, 4.99. Found: C, 71.33; H, 4.69.

A mixture melting point with (+)-*proto*-**quercitol pentabenzoate** (mp 155°)[33] was depressed (see below). The pmr spectrum of (+)-*proto*-quercitol pentabenzoate was recorded. The methylene proton signals appeared at 2.5 (axial) and 2.75 ppm (equatorial), with appropriate splitting patterns. The ring proton H-2 appeared as a triplet at 6.2. The remaining ring proton signals (5.6–6.2) overlapped. Aromatic proton signals were observed in the regions 7.2–7.7 (*meta*, *para*), and 7.8–8.2 (*ortho*).

Racemic *proto*-**Quercitol Pentabenzoate**.—A mixture of 15 mg of (+)-*proto*-quercitol pentabenzoate (mp 155°) and 15 mg of (−)-*proto*-quercitol pentabenzoate (mp 155°) was recrystallized from 95% ethanol to give the racemic pentabenzoate as colorless needles: mp 138–140°; optical rotation zero within experimental error. No difference between the solid-state ir spectra of the racemic and active forms of the pentabenzoate could be observed with the Perkin-Elmer Model 421 spectrometer under the conditions used.

Registry No.—**2**, 3409-28-7; **4** 17230-37-4; **5**, 17230-38-5; **6**, 17230-39-6; **8**, 17230-40-9; **9**, 17230-41-0; **11**, 17230-42-1; **12**, 17278-10-3; **14**, 17230-43-2; **16**, 17230-44-3; **17**, 17278-11-4; **19**, 17230-45-4; 2,4-dinitrophenylhydrazone of **19**, 17230-46-5; **22**, 17278-12-5; **22** (H = Bz), 17230-47-6; **23**, 17230-48-7.

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Anomeric 2-Amino-2-deoxy-D-glucofuranosyl Nucleosides of Adenine and 2-Amino-2-deoxy-β-D-glucopyranosyl Nucleosides of Thymine and 5-Methylcytosine

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Fusion of 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl chloride (1) with bis(trimethylsilyl)-thymine gave a relatively low yield of 1-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)thymine (2) which on controlled acidic hydrolysis gave either 1-(2-acetamido-2-deoxy-β-D-glucopyranosyl)thymine or the previously reported 1-(2-amino-2-deoxy-D-glucopyranosyl)thymine hydrochloride, herein established as the β-D anomer. Treatment of 2 with phosphorus pentasulfide and subsequent heating with methanolic ammonia at 100° gave 1-(2-amino-2-deoxy-β-D-glucopyranosyl)-5-methylcytosine dihydrochloride (6). In selected cases, therefore, the *N*-acetyl group can serve as an amino-protective group in these reactions. The previously reported ethyl tri-*O*-acetyl-2-acetamido-2-deoxy-1-thio-α-D-glucofuranoside (7) was completely deacetylated by successive treatment with phosphorus pentasulfide and methanolic ammonia. After introduction of the *N*-(2,4-dinitrophenyl) group and acetylation, ethylthio replacement by chlorine yielded a glycosyl chloride derivative 12 which was brought into reaction with *N*-acetylchloromercuriadenine to yield, after removal of the acetyl and 2,4-dinitrophenyl groups, a crystalline anomeric mixture of 9-(2-amino-2-deoxy-D-glucofuranosyl)adenine nucleosides which, by separation on a column of ion-exchange resin, yielded the pure, crystalline components in a ratio of three parts of the β-D to two parts of the α-D form. Anomeric assignments were made on the basis of nmr and polarimetric data.

In continuation of our program in establishing methods for the synthesis of nucleosides of 2-amino-2-deoxyglycoses, we report herein work done in a pyranose structure with the *N*-acetyl group as the amino-protective agent and the glycosyl chloride as the reagent. The condensation yield, by the trimethylsilylpyrimidine fusion method, was low. With an aldose in which the 2-acetamido group is in a trans position to a hydroxyl group, the acetamido group has been removed by base only with great difficulty. However, the de-*N*-acetylation procedure of Fox, *et al.*,[1] obviates this difficulty.

Fusion of 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-α-D-glucopyranosyl chloride[2] (1) and bis(trimethylsilyl)-thymine[3,4] gave a blocked nucleoside (2) in 14% yield (Figure 1). The nuclear magnetic resonance spectrum of 2, measured in deuteriochloroform, revealed a long doublet at δ 5.97 ppm with a first-order coupling constant, $J_{1',2'}$ = 9 cps, characteristic of an axial–axial relationship of the 1′ and 2′ protons. Since the *C1* D conformation for 2 is highly probable, these data establish the β-D configuration of 2. Hydrolysis of 2 with hydrochloric acid[5] yielded the nucleoside 1-(2-amino-2-deoxy-β-D-glucopyranosyl)thymine hydrochloride (5) whose synthesis had been reported by Wolfrom and Bhat[6] by another method and in much higher yield. Pyrimidine, but not purine, nucleosides are stable to such acid treatment. The β-D configuration is, therefore, established for the compound which Wolfrom and Bhat isolated. Treatment of 2 with methanolic hydrogen chloride[4] yielded 1-(2-acetamido-2-deoxy-β-D-glucopyranosyl)thymine, hitherto unreported.

Following the general de-*N*-acetylation procedure of Fox and associates,[1] 2 was brought into reaction with phosphorus pentasulfide in pyridine to give the syrupy intermediate 3. Compound 3 was purified by preparative thin layer chromatography and, without further characterization, was treated with methanolic ammonia[1] at 100° to give 1-(2-amino-2-deoxy-β-D-glucopyranosyl)-5-methylcytosine, isolated as the dihydrochloride (6).

Thus, although the *N*-acetyl is not the amino-protective group of choice in these reactions, this group can nevertheless be utilized, in certain cases, under properly selected conditions. Other workers[5,7,8] have utilized the *N*-acetyl blocking group with amino sugars containing the pyranose ring, although the *N*-acetyl was not always removed from the reaction product. When applied to the more reactive furanose structure, we have encountered oxazoline formation.[9]

The anomeric forms of 9-(2-amino-2-deoxy-D-glucopyranosyl)adenine have been synthesized[10] through the use of the *N*-(2,4-dinitrophenyl) group in the chloromercuri procedure of Davoll and Lowy.[11] We have described[9] the synthesis, in low yield, of a nucleoside derivative of 2-amino-2-deoxy-D-glucofuranose through

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