solvate[1] was added. The suspension was stirred and refluxed for 64 hours under a drying tube without becoming a clear solution. The suspension was worked up in the same way as the reaction mixture from methyl reserpate, giving 0.39 g. of white crystals from methylene chloride, and 0.25 g. (21.8%) of white needles, m.p. 146–149°, after recrystallization from benzene–isopropyl alcohol. Its specific activity was 3.8×10^{-4} μc./μM.

Preparation of Neoreserpic Acid-C^{14} (IV) as its Hydrochloride Salt from III.—A cloudy solution of 1.80 g. of methyl neoreserpate-C^{14} (III) monoisopropanol solvate (specific activity, 4.2 μc./μM.) and 7.2 g. of potassium hydroxide in 108 ml. of methanol was stirred and refluxed for 4 hours. After being filtered, the solution was stripped to dryness at reduced pressure, and the residue was taken up in 36 ml. of water and washed four times with 18-ml. portions of chloroform. Water was removed at reduced pressure and the residue was taken up in 32 ml. of methanol, acidified by addition of 10 ml. of concentrated hydrochloric acid (36%) and filtered; the insoluble potassium chloride was washed with 14 ml. of chloroform–methanol (4:1). The combined filtrate and wash was stripped to dryness, taken up in 72 ml. of chloroform–methanol (4:3), and passed through a bed of Darco G-60. The filtrate was stripped to dryness, taken up in 50 ml. of chloroform–methanol (4:1), and passed again through a bed of Darco G-60; the Darco was washed with 25 ml. of fresh solvent mixture. Removal of solvent left 1.40 g. of yellow solid. Two precipitations from 15 ml. of methanol and 150 ml. of ether gave 0.69 g. (41.5%) of pale yellow solid, m.p. 244–249°, $[\alpha]^{22}D$ +57.3° (MeOH). The paper chromatogram showed that it was contaminated with about 5% reserpic acid. The specific activity was 0.37×10^{-4} μc./μM.

Anal. Calcd. for $C_{22}H_{28}N_2O_5 \cdot HCl \cdot 1/2H_2O$ (445.96): C, 59.38; H, 6.78; N, 6.29. Found: C, 59.50; H, 7.07; N, 6.28.

[CONTRIBUTION FROM VARIAN ASSOCIATES, PALO ALTO, AND THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF SAN FRANCISCO, SAN FRANCISCO 17, CALIF.]

Nuclear Magnetic Resonance Spectrum of a Diastereomer of Quercitol (Deoxyinositol). Synthesis of allo-Quercitol and its 6-Chloro, 6-Bromo and 6-Iodo Derivatives[1,2]

BY J. N. SHOOLERY,[3] L. F. JOHNSON,[3] STANLEY FURUTA AND G. E. MCCASLAND[4]

RECEIVED JUNE 6, 1961

A new racemic quercitol (cyclohexanepentol) has been prepared by hydrogenation of *meso*-5,6-anhydro-*allo*-inositol. The new quercitol has been assigned the DL(1234/5) or "allo" configuration on the basis of its nuclear magnetic resonance spectrum and other evidence. Reaction of the same anhydroinositol with concentrated aqueous hydrochloric, hydrobromic and hydriodic acids gave, respectively, a 6-chloro-, 6-bromo-, and 6-iodoquercitol. This is the first known iodoquercitol, and the first chloroquercitol of known configuration. Twenty diastereomeric configurations are predicted for the haloquercitols; the configuration (12346/5) has been assigned to each diastereomer here reported. Pentaacetate derivatives of the quercitol and the haloquercitols were prepared. Configurations are proposed for several other 6-bromoquercitol diastereomers of previously unknown or uncertain configuration. *allo*-Quercitol can also be prepared by hydrogenolysis of a bromoquercitol pentaacetate, m.p. 153°, which Reeves made from *epi*-inositol in 1955.

Nuclear magnetic resonance is one of the most powerful of all techniques for the assignment of diastereomeric configurations, but as yet has been relatively little used for this purpose. This is true in particular in the field of carbohydrates, and one purpose of our present studies is to extend the applicability of n.m.r. to carbohydrate diastereomers. As model compounds, the quercitols[5] (cyclohexanepentols) seemed especially suitable, for two reasons. First, the ten quercitols constitute possibly the largest family of diastereomers in the entire field of organic chemistry *all members of which are known*. Second, unlike ordinary carbohydrates, the quercitols are not subject to complications of structure and conformation resulting from the opening of hemiacetal rings. This initial simplification of the problem is desirable, since carbohydrate n.m.r. spectra[6] are in any event relatively difficult to interpret. The quercitols are also of intrinsic interest because of their natural occurrence and close relationship to that ubiquitous and essential substance, *myo*-inositol.[7]

In a recent publication,[2] the synthesis and n.m.r. characterization of two new quercitol diastereomers (*gala* and *talo*) were described, and a table summarizing all of the ten diastereomers was given. We now wish to report the synthesis of the racemic form of *allo*- or (1234/5)-quercitol (I) and the corresponding 6-chloro, 6-bromo and 6-iodo derivatives (IV-VI), (regarding nomenclature, see our previous article[2]).

The key intermediates used in our present syntheses were *meso*-5,6-anhydro-*allo*-inositol[8] (II) and its 1,2:3,4-diacetone ketal[8] III. The catalytic addition of hydrogen to II gave the quercitol. The addition of hydrogen chloride, bromide or iodide in aqueous solution to III gave, respectively, the chloro, bromo- and iodoquercitol, with simultaneous cleavage of both ketal groups. Because

(1) Presented in part at the Symposium on the Chemistry of Natural Products of the I.U.P.A.C. in August, 1960, at Sydney, Australia. Taken in part from the M.S. Thesis of Stanley Furuta, Graduate Division, University of San Francisco, 1961.

(2) Paper XII on Cyclitol Stereochemistry by G. E. McCasland and co-workers; for preceding paper see: G. E. McCasland, S. Furuta, L. F. Johnson and J. Shoolery, *J. Am. Chem. Soc.*, **83**, 2335 (1961).

(3) Varian Associates.

(4) To whom any requests for reprints should be sent: Address, Department of Chemistry, University of San Francisco, San Francisco 17, Calif.

(5) For an excellent review of previous work on the quercitols, see: (a) S. J. Angyal and L. Anderson in Vol. 14, "Advances in Carbohydrate Chemistry," Academic Press, Inc., New York, N. Y., 1959; also (b) R. L. Lohmer, Jr., in "The Carbohydrates" by W. Pigman (Editor), Academic Press, Inc., New York, N. Y., 1957, pp. 268–296.

(6) For previous work on n.m.r. spectra of carbohydrates and cyclohexane derivatives, see references to work of R. U. Lemieux and others given in Chapter 14 of Pople, Schneider and Bernstein (ref. 11); also see S. Brownstein and R. Miller, *J. Org. Chem.*, **24**, 1886 (1959).

(7) *myo*-Inositol occurs in nearly every plant or animal cell, and is essential for the growth of isolated human cells in tissue culture; see H. Eagle, *J. Biol. Chem.*, **226**, 191 (1957).

(8) S. Angyal and P. Gilham, *J. Chem. Soc.*, 3698 (1957).

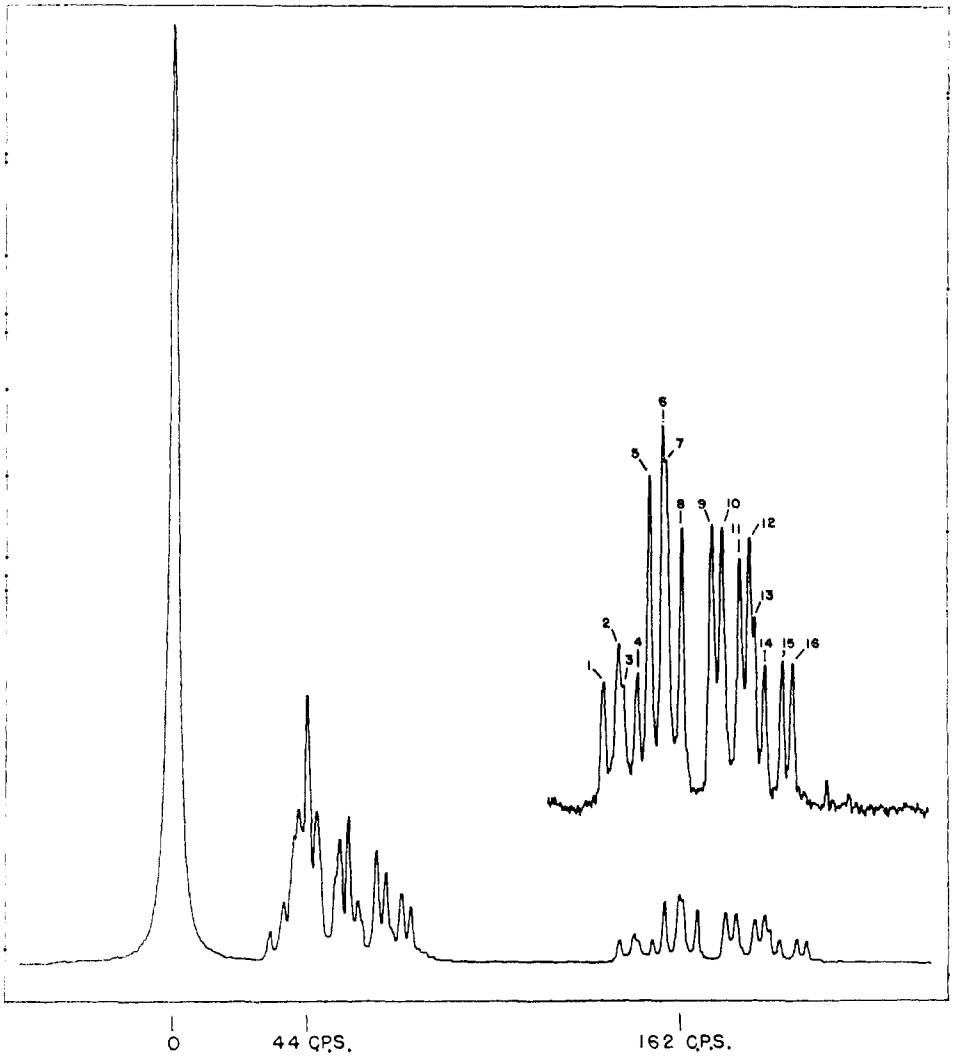


Fig. 1.—Sixty megacycle n.m.r. spectrum of racemic *allo*-quercitol in deuterium oxide (H increases left to right).

of the symmetry of the epoxide intermediates, only a single (racemic) product was obtained from each reaction.

The quercitol diastereomer so obtained was a colorless, crystalline compound of m.p. 262°. Its pentaacetate was prepared in the usual manner, and melted at 92–94°. Nakajima,[9] by hydrogenolysis and acetylation of a bromoquercitol, has recently prepared the same quercitol pentaacetate (reported m.p. 88–91.5°) but not the free pentol. In a similar manner, Nakajima[9] prepared the pentaacetate (m.p. 168°) of the tenth and last (*muco*) diastereomer of quercitol IX, but not *muco*-quercitol itself. He also prepared the racemic pentaacetates (m.p. 92° and 172°) of *gala*- and *talo*-quercitols (X and XI) recently prepared by us[2] in active form, and free DL-*talo*-quercitol of m.p. 225° dec.[10]

In order to establish the configuration of our new quercitol, nuclear magnetic resonance spectra were employed.

The high resolution n.m.r. spectrum of the quercitol of m.p. 262° is shown in Fig. 1. This compound was studied in dilute deuterium oxide solution at 60 mc. (14,092 gauss). Exchange of the hydroxyl protons with the solvent resulted in the strong HDO line at the left side of the figure, which was employed as an internal reference for the measurement of other resonance maxima in cycles per second, using the audio side-band method.

The two methylene protons at C-6 (formula XV) produce the complex multiplet between 140 and 205 c.p.s., while the remaining five ring protons are responsible for the set of signals between 30 and 80 c.p.s. The individual peaks in the expanded spectrum (Fig. 1) of the methylene multiplet have been numbered from 1 to 16. Peaks 1–8 are assigned to the equatorial methylene proton, and 9–16 to the axial methylene proton in the favored conformation (XV). The four multiplets consisting of lines 1–4, 5–8, 9–12 and 13–16 comprise a small-large-large-small AB pattern characteristic of two protons on the same carbon atom. The multiplet

(9) M. Nakajima and N. Kurihara, *Chem. Ber.*, **94**, 515 (1961).

(10) In 1953, E. C. Horswill working with one of us at Toronto made extensive attempts to prepare quercitols by hydrogenation of benzenepentol or its derivatives. All such efforts failed, apparently because compounds with a 1,3-diol structure are destroyed by hydrogenolysis under conditions necessary to saturate the benzene ring.

character of each component of the pattern is a consequence of two neighboring carbon atoms each bearing a single proton.

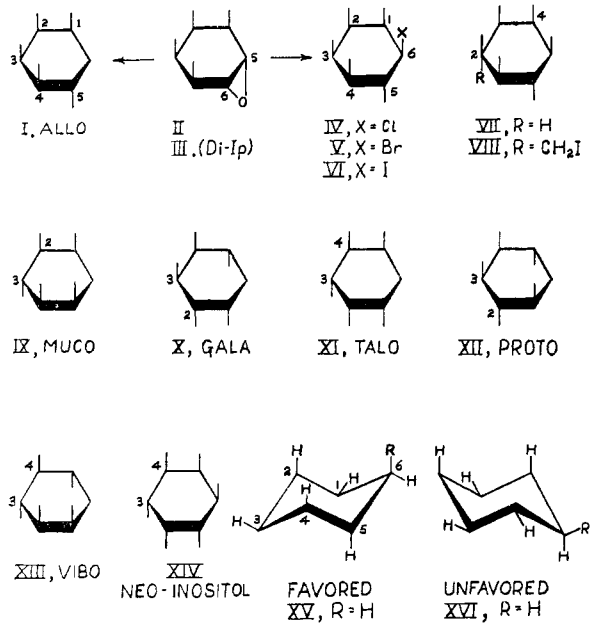
Peaks 9–12 and 13–16 reveal that the axial proton signal is split once by a spin coupling of about 9 c.p.s., and again by a coupling of 3 c.p.s. The larger spin coupling is characteristic of the 1,2-diaxial conformation of neighboring protons, while the smaller coupling is typical of the 1,2-axial-equatorial conformation.[11]

The signals 1–4 and 5–8 show that the equatorial methylene proton is coupled to two neighboring protons which might be either equatorial or axial, since the (e,e) and (e,a) coupling constants are approximately the same and less than the (a,a) constant.

The n.m.r. spectrum of the m.p. 262° quercitol thus demonstrates that its methylene group has one neighboring axial and one neighboring equatorial ring-proton. This conformation is equivalent to a 1,5-*trans* configuration for the hydroxyl groups.[12] Thus of the ten possible quercitol diastereomeric configurations, only the four configurations *proto*, *vibo*, *talo* and *allo* (see Chart I) needed to be considered.

CHART I

CONFIGURATIONAL AND CONFORMATIONAL FORMULAS MENTIONED IN TEXT (Ip = ISOPROPYLIDENE)



The *talo* configuration was at once excluded on the basis of its previously taken and decidedly different n.m.r., spectrum.[2] The spectra of the *proto*[5] and *vibo*[13a] isomers were obtained and were also found to differ markedly from that of the m.p. 262° quercitol. We have therefore assigned the one remaining, "*allo*" or (1234/5), configuration (I) to our new product. This configuration is consistent with the starting material used and the known mechanism of epoxide hydrogenations.

The First Iodoquercitol.—Twenty diastereomeric iodoquercitols (iododeoxyinositols) are predicted, but none had previously been prepared. Posternak[14a] did prepare a 2-C-iodomethyl derivative VIII of *epi*-inositol by reaction of aqueous hydriodic acid with the corresponding epicyclic epoxide. In earlier studies[14b] he prepared a similar iodomethyl derivative by replacement of a primary *p*-toluenesulfonoxy group. The iodine atom in each of these products is primary and not directly attached to the cyclohexane ring. Among the ordinary sugars, relatively few iododeoxy derivatives are known, and nearly all of these are primary iodides obtained by replacement of primary tosyloxy groups.[15]

Mild treatment of any cyclitol with hot hydriodic acid leaves the hydroxyl groups unchanged. More drastic treatment causes aromatization. The prototype compound, 2-iodocyclohexanol, has long been known; it was prepared[16] from cyclohexene by reaction with iodine and water in the presence of mercuric oxide.

It now appears that the most general and convenient method for preparing iodocyclitols will be the reaction of epoxides with aqueous hydriodic acid at room temperature. From the epoxide diacetone ketal III there was obtained a colorless crystalline iodoquercitol VI of m.p. 214° (pentaacetate 161°). This isomer has been assigned the DL (12346/5) configuration on the basis of the known starting material and presumed reaction mechanism.

Comparative reactivity tests of our iodoquercitol, using silver nitrate (see Experimental section), showed that it is decidedly more reactive than its bromo or chloro analog. Since cyclohexyl chlorides or bromides often show poor reactivity, we believe that iodocyclitols will be useful synthetic intermediates, leading in some instances to stereoisomers not directly available from the epoxide precursors.

The First Chloroquercitol of Known Configuration.—Twenty diastereomeric chloroquercitols are predicted. The known diastereomers are listed in Table I. In 1912, Müller,[17b] by reaction of hydrogen chloride–acetic acid with an inositol hexaacetate, obtained two free chloroquercitols, one chloroquercitol triacetate and three chloroquercitol pentaacetates. In 1915, Griffin and Nelson,[18] using acetyl chloride and free inositol, obtained a chloroquercitol pentaacetate, possibly identical with one of Müller's products. In 1926, Majima

(11) J. Pople, W. Schneider and H. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p. 392.

(12) It is important to note that the *axial* ring-protons mentioned in the n.m.r. discussion and shown in the conformational formulas are located on carbon atoms which bear *equatorial* functional groups and *vice versa*.

(13) (a) G. E. McCasland and E. C. Horswill, *J. Am. Chem. Soc.*, **76**, 4020 (1953); (b) **76**, 2373 (1954); (c) G. E. McCasland and J. Reeves, *ibid.*, **77**, 1812 (1955); (d) G. E. McCasland, *et al.*, *ibid.*, **79**, 160 (1957).

(14) (a) T. Posternak, *Helv. Chim. Acta*, **43**, 2142 (1960); (b) **27**, 457 (1944).

(15) See W. Pigman (Editor), "The Carbohydrates," Academic Press, Inc., New York, N. Y., 1957, p. 164, 397.

(16) L. Brunel, *Ann. chim. phys.*, [7] **6**, 219 (1905); W. Hickinbottom, "Reactions of Organic Compounds," 3rd Ed., Longmans, Green and Co., New York, N. Y., 1957, p. 37.

(17) H. Müller, (a) *J. Chem. Soc.*, **91**, 1790 (1907); (b) **101**, 2383 (1912).

(18) E. Griffin and J. Nelson, *J. Am. Chem. Soc.*, **37**, 1552 (1915).

and Simanuki,[19] using thionyl chloride, obtained one chloroquercitol, apparently a new diastereomer. The previous workers did not determine which acetates corresponded to which chloropentols, and they were unable to assign configurations to any of their products.[20]

TABLE I

THE KNOWN CHLOROQUERCITOLS OR CHLORODEOXYINOSITOLS, 1961[e]

Configuration (Cl at 6)	Parent quercitol	Related inositol[a]	—M.p., °C.— Chloroquercitol	Pentaacetate	References
(12346/5)	*Allo*	*Epi*-(1)	192	158	This paper
(123/456)?	*Talo*[b]	Neo-(1)	236 d.	177	25
(125/346)?	*Gala*[b]	DL-(4)	219 d.	...[c]	25
Unknown	Unknown	...	180–185	...[c]	17
Unknown	Unknown	...	200 d.	...[c]	17
Unknown	Unknown	...	248 d.	...[c]	19
Unknown	Unknown	...	Triacetate: 145[c,d]		17
Unknown	Unknown	...	...[d]	109–110	17
Unknown	Unknown	...	...[d]	118	17
Unknown	Unknown	...	...[d]	246–247	17
Unknown	Unknown	...	...[d]	250	18

[a] The number specifies the inositol hydroxyl which would need to be replaced, without inversion, to yield the chloroquercitol. [b] Optically active; all the other products listed are racemic or *meso*. Further work may reverse the *talo* and *gala* configurational assignments of these two products from the same reaction. [c] Pentaacetate unknown. [d] Free chloropentol unknown. [e] Eight *meso*, twelve active or racemic diastereomers predicted.

It now appears that the reaction of epoxides with concentrated aqueous hydrochloric acid at room temperature will provide the best method for preparing chloroquercitols. From the epoxide diacetone ketal III we obtained a chloroquercitol of m.p. 192° (pentaacetate m.p. 158°) which from the starting material and method of preparation is believed to possess the DL(12346/5) configuration IV.

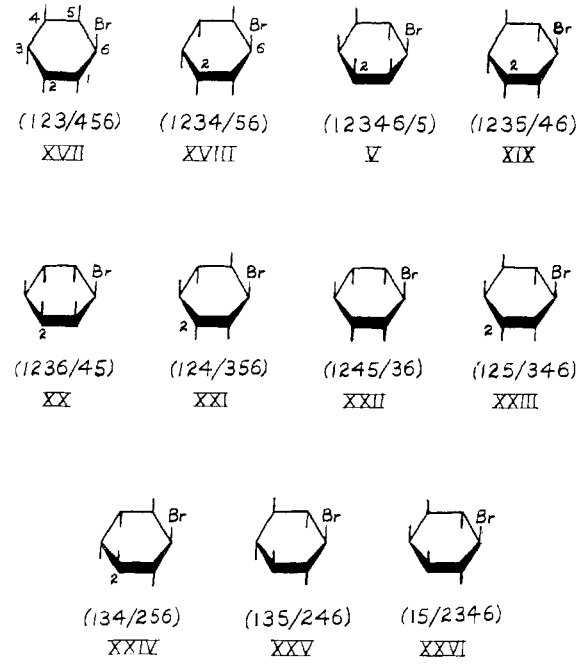
More recently we have treated 1,2-anhydro-*allo*-inositol diacetone ketal in a similar manner to obtain two new optically active chloroquercitol diastereomers (see Table I). These will be discussed in a subsequent publication.

The Bromoquercitols.—Not less than ten of the twenty predicted 6-bromoquercitol diastereomers have now been prepared, making this one of the largest, even though incomplete, known sets of diastereomers (see Table II and Chart II).

Although the bromoquercitols were briefly reviewed in our previous article,[2] Nakajima's subsequent preparation[9] of seven diastereomers by heating[21] anhydro-inositols with aqueous hydrogen bromide now makes a much more complete summary possible (see table). His method is not only more convenient than the sealed tube reactions of hexaacetates with hydrogen bromide formerly used, but more stereospecific, since on the assumption of *trans*-epoxide ring opening, only two products (in some cases, only one) are predicted for each reaction.

CHART II

CONFIGURATIONS OF THE KNOWN DIASTEREOMERS OF 6-BROMOQUERCITOL. ISOMER XIX IS UNKNOWN (SEE TEXT)



By re-examining the earlier literature in the light of these recent results we have been able to clarify the following previously unsettled questions of configuration.

(1) In 1908, Kubler[22] prepared two racemic bromoquercitols of m.p. 175° and 196° (latter not fully characterized) by reaction of hypobromous acid with natural conduritol (Table II). Assuming *trans* addition, the latter bromoquercitol probably corresponds to Nakajima's product[9] of m.p. 192° and (125/346) configuration XXIII, and the former (not prepared by Nakajima) must have the (134/256) configuration XXIV. The m.p. 192° compound is the racemic form of an optically active bromoquercitol prepared by McCasland and coworkers[2] in 1961 (m.p. 203°).

(2) In 1912, Müller[17] by reaction of *myo*-inositol hexaacetate with hydrogen bromide prepared a bromoquercitol of m.p. 170–175°, later assigned the racemic (124/356) or "*vibo*" configuration XXI by McCasland and Horswill[13a] (who first prepared the pentaacetate, m.p. 125°). Angyal's recent preparation[23] of the same pentaacetate by reaction of 1,2-anhydro-*myo*-inositol with hydrogen bromide in anhydrous acetic acid confirms the configuration assigned by McCasland and Hors-

(19) R. Majima and H. Simanuki, *Proc. Imp. Acad. Japan (Tokyo)*, **2**, 544 (1926).

(20) The inositol halohydrin table on page 282 in the first edition of Pigman and Goepp's "Carbohydrate Chemistry" (Academic Press, Inc., New York, N. Y., 1948) credits L. Maquenne with preparing a "chlorohydrin benzoate" (presumably a chloroquercitol pentabenzoate). So far as we can discover, Maquenne did not actually isolate any pure product which would meet this description; see *Compt. rend.*, **104**, 1720 (1887).

(21) M. Nakajima treated his anhydro-inositols with *hot* aqueous hydrobromic acid. We now find that this reaction (and also similar reactions with hydrochloric or hydriodic acid) proceed easily at room temperature. The low temperature reactions appear to give haloquercitols of higher purity. Before learning of Nakajima's work, we had treated anhydro-inositols with hydrogen bromide in acetic acid, but now prefer aqueous hydrobromic acid.

(22) K. Kubler, *Arch. pharm.*, **246**, 620 (1908).

(23) S. J. Angyal, personal communication, April, 1960. In these particular experiments, Professor Angyal used an acetic acid solution of hydrogen bromide, approximately as described by McCasland, *et al.* (ref. 2).

TABLE II

THE KNOWN BROMOQUERCITOLS OR BROMODEOXYINOSITOLS, 1961[f]

Configuration (Br at 6)	Parent quercitol	Related inositol[a]	M.p., °C., and (spec. rot.) Bromoquercitol	Pentaacetate	References (bromopentol; pentaacetate)
Meso diastereomers					
(1245/36)	Muco	Muco-(3)	...[b]	179	9
(15/2346)	Neo	Myo-(5)	216 (?)	210	25; 9
(135/246)	Scyllo	Scyllo-(1)	223	240	24, 13a; 17, 18, 13a, 23
Active or racemic diastereomers					
(12346/5)	Allo	Epi-(1)	DL 204	DL 159	This article
(1234/56)[e]	Allo	Allo-(5)	DL 160	DL 153	25; 9, 13c, 25
(125/346)	Gala	DL-(3)	203 (−44°)	...[c]	2(DL: 22; 9)
			DL 192	DL 159	
(134/256)	Proto	DL-(2)	DL 175	...[c,d]	22
(123/456)	Talo	Neo-(1)	229 (+17°); DL 214 *dec.*	...[c]	2(DL, 9)
(1236/45)	Talo	Allo-(1)	Syrup	DL 140	9
(124/356)	Vibo	DL-(1)	DL 171	DL 125	17, 13a, 9; 13a, 9, 23

[a] Number specifies inositol hydroxyl whose replacement without inversion would give the bromoquercitol. [b] Free bromopentol unknown. [c] Pentaacetate unknown. [d] DL-Pentaphenylurethan, m.p. 154. [e] See discussion in text. [f] Eight meso, 12 active or racemic diastereomers predicted.

will. Nakajima[9] reportedly has obtained this same diastereomer with his aqueous hydrogen bromide method, although melting points were lower.

(3) In 1907, Müller had obtained a bromoquercitol pentaacetate,[17b,24] m.p. 240° as another product from the same reaction mentioned above. This product was assigned the *meso* (135/246) or "*scyllo*" configuration XXV by McCasland and Horswill.[13a] This configuration is now confirmed by Angyal's isolation[23] of this diastereomer from the same 1,2-anhydro-*myo*-inositol reaction mentioned above. With the same anhydro-inositol and aqueous hydrogen bromide, Nakajima[9] obtained only the (124/356) diastereomer.

(4) In 1955, McCasland and Reeves[13c] discussed four possible configurations (XVIII, XIX, XX, XXVI) for a bromoquercitol pentaacetate, m.p. 153°, which they had prepared from *epi*-inositol. On the basis of the limited evidence then available, the configuration XIX was favored. Recent studies[25] of this product in our laboratory at San Francisco reveal that it actually has the (1234/56) configuration XVIII, since on hydrolysis and hydrogenolysis it gave *allo*-quercitol, identical with that obtained from anhydro-inositol (see above). (The epimer V would also give *allo*-quercitol, but is known to be non-identical with Reeves' product.) Nakajima,[9] using a different synthesis, also has prepared a bromoquercitol pentaacetate (m.p. 148–149°) of configuration XVIII; a sample was found[25] to be identical with Reeves' product.

(5) In 1960, Furuta[25] prepared a bromoquercitol of m.p. 216° by reaction of *neo*-inositol (XIV) with acetyl bromide, and hydrolysis. For mechanistic reasons this diastereomer has tentatively been assigned the racemic configuration (15/2346), XXVI, and thus should correspond to the bromoquercitol pentaacetate of this configuration (Table II) which Nakajima[9] prepared by a different route.

(6) In 1961, Furuta[2] prepared an optically active bromoquercitol, m.p. 229°, by reaction of 1,2-anhydro-*allo*-inositol with hydrogen bromide–acetic acid. This product of (123/456) configuration XVII must correspond to Nakajima's racemic product[9] of m.p. 214°. Nakajima also prepared the pentaacetate (m.p. 140°) of the epimeric (1236/45) compound (XX).

In our present research (see Experimental section) we have treated 5,6-anhydro-*allo*-inositol with aqueous hydrogen bromide at room temperature.[21] This reaction gave as its only isolated product a new bromoquercitol of m.p. 204° (pentaacetate m.p. 159°) which has been assigned the racemic (12346/5) configuration V. This diastereomer was not prepared by Nakajima (since he did not have this particular epoxide).

An attempt to complete the haloquercitol series IV-VI by reaction of 5,6-anhydro-*allo*-inositol with concentrated aqueous *hydrofluoric* acid was unsuccessful, since the epoxide was merely hydrolyzed to *epi*-inositol (IV, X = OH). Further work on the preparation of fluoroquercitols is in progress.

Acknowledgment.—This research was made possible by generous grants to the University of San Francisco from the National Science Foundation, the Research Corporation, and the Roscoe and Margaret Oakes Foundation. We wish to thank Professor Minoru Nakajima of the University of Kyoto, Japan, for helpful discussions at Melbourne, Australia, in August, 1960. We are grateful to Professor Arthur Furst of the University of San Francisco for assistance and advice.

Experimental

All melting points have been corrected and were measured on a Nalge–Axelrod micro hot-stage. Microanalyses by the Micro-Tech Laboratories, Skokie, Ill. Nuclear magnetic resonance spectra were measured with a Varian model HR-60 high resolution n.m.r. spectrometer. Infrared spectra were measured on a Perkin–Elmer model 137 Infracord recording infrared spectrometer.

DL(1234/5) or *allo* Diastereomer of Quercitol (Deoxyinositol, 1,2,3,4,5-Cyclohexanepentol), I.—To a solution of 0.40 g. of 5,6-anhydro-*allo*-inositol[8] (m.p. 120–122°) in 50 ml. of water was added about 1 g. of commercial Raney nickel catalyst. The mixture was hydrogenated at three atmospheres for 12 hours. After filtration the filtrate was vacuum distilled. The sirupy residue was dissolved in 4.0 ml. of hot 75% ethanol. The solution was cooled and allowed to stand at 0° to 25° for 12–18 hours. The crystals which separated were collected, washed (75% ethanol,

(24) E. H. Flynn, Ph.D. Thesis, University of Illinois, 1949.

(25) S. Furuta and G. E. McCasland, unpublished work.

1 ml.), and vacuum dried at 70°, giving 0.39 g. (87%) of product melting at 254–259° dec.

After two recrystallizations from the same solvent, there was obtained 0.24 g. of pure DL-*allo*-quercitol, m.p. 261–262° dec.

Anal. Calcd. for $C_6H_{12}O_5$: C, 43.90; H, 7.37. Found: C, 43.40; H, 7.31.

The infrared spectrum was determined with a Perkin-Elmer model 21 recording infrared spectrometer, using a potassium bromide pellet, and showed a strong O–H stretching absorption at 3300 cm.$^{-1}$, and C–O stretching at 1030 and 1080 cm.$^{-1}$.

The nuclear magnetic resonance spectrum was in accord with the assigned structure and configuration (see Introduction).

DL(1234/5) Diastereomer of Quercitol Pentaacetate (I).—The above quercitol (150 mg., m.p. 261–262° dec.) was mixed with 2 ml. of redistilled acetic anhydride and 150 mg. of fused sodium acetate. The mixture was boiled under reflux for 3 hours. The hot solution was vacuum distilled to dryness, and the residue distributed between chloroform and water (5 ml. of each). The separated aqueous phase was washed with chloroform (5 ml.), and the combined chloroform phases washed with *M* sodium bicarbonate solution, then dried over anhydrous sodium sulfate.

The residue from the filtered, evaporated chloroform extract was purified by chromatography. A solution in 3.0 ml. of anhydrous reagent grade benzene was passed over a 40 mm. × 15 mm. column of Woelm Grade 1 (acid) aluminum oxide. The chromatogram was developed with 50 ml. of the same solvent. The first and fourth 15-ml. fractions of eluent were empty, while the second and third fractions gave sirupy residues. The combined residues were taken up in 6.0 ml. of 2-propanol, and the solution concentrated to 1.0 ml.

The crystals which separated after 24 hours standing were collected, washed (2-propanol, 0.5 ml.), and vacuum-dried at 60°, giving 280 mg. (83%) of product melting at 90–94°. After two more crystallizations from the same solvent, there was obtained 175 mg. of the pure pentaacetate, m.p. 92–94° (reported[9] 88–91.5°).

Anal. Calcd. for $C_{16}H_{22}O_{10}$: C, 51.33; H, 5.93. Found: C, 51.35; H, 5.89.

The pentaacetate infrared spectrum showed strong C=O stretching at 1750 cm.$^{-1}$ and did not show any O—H absorption.

DL(12346/5) Diastereomer of 6-Chloroquercitol; 1-Chloro-1-deoxy-*epi*-inositol (IV).—A mixture of 470 mg. of 5,6-anhydro-*allo*-inositol 1,2:3,4-diacetone ketal (m.p. 96–98°) with 5.0 ml. of 12 *M* hydrochloric acid was stirred at 25° for 3 hours. The resulting solution was vacuum distilled to dryness. Absolute ethanol (5.0 ml.) was added and the evaporation repeated; the addition and evaporation were then repeated once more. The colorless crystalline residue was recrystallized from 90% (v./v.) ethanol, giving 325 mg. (86%) of washed and vacuum-dried product, m.p. 191–192° dec. A sample when tested by the sodium fusion method gave a positive chlorine test.

Anal. Calcd. for $C_6H_{11}ClO_5$: C, 36.28; H, 5.58; Cl, 17.85. Found: C, 36.26; H, 5.36; Cl, 17.81.

DL(12346/5) Diastereomer of 6-Chloroquercitol Pentaacetate (IV).—The chloroquercitol (130 mg., m.p. 192°) was acetylated in essentially the manner described for the bromoquercitol (see below). Since the sirupy residue from the chloroform extract did not crystallize on standing with ethanol, it was taken up instead in 2-propanol. On standing, crystals did then separate, giving 260 mg. of washed and vacuum-dried product, m.p. 154–158°. This material was recrystallized from 2-propanol, giving 200 mg. (75%) of pure product, m.p. 156–158°.

Anal. Calcd. for $C_{16}H_{21}ClO_{10}$: C, 47.01; H, 5.18; Cl, 8.67. Found: C, 47.34; H, 5.25; Cl, 8.51.

DL(12346/5) Diastereomer of 6-Bromoquercitol; 1-Bromo-1-deoxy-*epi*-inositol (V).—A mixture of 0.40 g. of finely ground 5,6-anhydro-*allo*-inositol 1,2:3,4-diacetone ketal[8] (m.p. 96–98°) with 8.0 ml. of 8.8 *M* aqueous[21] hydrobromic acid was stirred at 25° for 12 hours. The resulting solution was vacuum-distilled to dryness. To the residue was added 10 ml. of absolute ethanol, and the evaporation repeated. The colorless crystalline residue was recrystallized from 70% v./v. ethanol, giving 220 mg. (55%) of vacuum-dried (70°) product, m.p. 203°–204° dec. A sample was recrystallized again for analysis (melting range unchanged).

Anal. Calcd. for $C_6H_{11}BrO_5$: C, 29.65; H, 4.56; Br, 32.86. Found: C, 29.85; H, 4.77; Br, 32.89.

Partial evaporation of the mother liquor yielded a second crop of 45 mg., m.p. 197–200°.

DL(12346/5) Diastereomer of 6-Bromoquercitol Pentaacetate (V).—A mixture of the above bromoquercitol (100 mg., m.p. 203–204°) with 150 mg. of fused sodium acetate and 5.0 ml. of acetic anhydride was boiled under reflux for 3 hours (anhydrous conditions). The resulting solution was vacuum distilled to dryness, and the residue taken up in 10 ml. of chloroform. The chloroform solution was washed with water and sodium bicarbonate solution, and dried. The dry solution on vacuum distillation gave a sirupy residue, which was taken up in 3.0 ml. of hot ethanol absolute. The crystals which separated on standing were collected, washed and dried, giving 150 mg. (80%) of product melting at 156–159°. This material was recrystallized again, for analysis, from absolute ethanol, giving 120 mg. of pure product, m.p. 158–159°.

Anal. Calcd. for $C_{16}H_{21}BrO_{10}$: C, 42.40; H, 4.67; Br, 17.63. Found: C, 42.35; H, 4.54; Br, 17.70.

DL(12346/5) Diastereomer of 6-Iodoquercitol; 1-Iodo-1-deoxy-*epi*-inositol (VI).—A mixture of the above anhydro diketal (275 mg., m.p. 96–98°) with 5.0 ml. of 5.5 *M* hydriodic acid was stirred at 25° for 3 hours. The resulting solution was vacuum distilled to dryness. Absolute ethanol (5 ml.) was added and the evaporation repeated; the addition and evaporation were then repeated once more. The residue was taken up in 3.0 ml. of hot absolute ethanol. The crystals which separated on standing were collected, washed and vacuum dried, giving 305 mg. of product, m.p. 212–214° dec.

This material was recrystallized from 95% ethanol, giving 200 mg. (61%) of pure product, m.p. 213–214° dec. A sample gave a positive sodium fusion test for iodine.

Anal. Calcd. for $C_6H_{11}IO_5$: C, 24.84; H, 3.82; I, 43.75. Found: C, 25.04; H, 3.96; I, 43.71.

DL(12346/5) Diastereomer of 6-Iodoquercitol Pentaacetate (VI).—The iodoquercitol (58 mg., m.p. 214°) was acetylated, and the pentaacetate crystallized, in essentially the same manner used for the bromoquercitol (see above). There were obtained 90 mg. of crude product, m.p. 159–161°. This material was recrystallized from 2-propanol, giving 80 mg. (80%) of pure product, m.p. 160–161°.

Anal. Calcd. for $C_{16}H_{21}IO_{10}$: C, 38.41; H, 4.23; I, 25.37. Found: C, 38.51; H, 4.12; I, 25.31.

Relative Reaction Rates of Haloquercitols with Silver Nitrate.—The relative rates of reaction of the 6-chloro-, 6-bromo- and 6-iodoquercitols, each of the DL(12346/5) configuration, were compared in the following manner. Each haloquercitol (20 mg.) was dissolved in 1.0 ml. of water, and 0.2 ml. of 0.1 *M* silver nitrate solution was added. Each mixture was maintained at 25° and examined for precipitated silver halide after 30, 60 and 90 minutes. Then each mixture was heated to 100°, and examined after 30 minutes.

The iodoquercitol gave a substantial yellow precipitate at 25° after 30 minutes; the bromo- and chloroquercitols at this temperature had not reacted after 90 minutes. At 100° the bromoquercitol gave a precipitate within 30 minutes, but the chloroquercitol did not. Each silver halide precipitate was insoluble in dilute nitric acid.