$$\underset{(554)}{3PrBr} + \underset{(6.2)}{AlCl_3} \rightleftharpoons \underset{(6.2)}{3PrCl} + \underset{(2.1)}{AlBr_3}$$

$$K_{eq} \approx \frac{(6.2)^3(2.1)}{(554)^3(6.2)} = 4.7 \times 10^{-7}$$

The symbols PrBr and PrCl represent sums of the propyl halides, (*n*-PrBr + *i*-PrBr) and (*n*-PrCl + *i*-PrCl), respectively. The number of mmoles of each species present at equilibrium, calculated from the data of Table I, is shown in parentheses under the reaction. In view of small equilibrium constant for the previous reaction, it is not surprising that the following analogous reactions were found to be essentially irreversible.[3]

$$MeCl + AlBr_3 \longrightarrow MeBr + AlCl_3$$

$$MeCl + AlI_3 \longrightarrow MeI + AlCl_3$$

Both AlY_3 + *n*-PrX and EtY + *n*-PrX exchange reactions proceed rapidly, and both interchanges yield initial products rich in the *n*-PrY isomer. These similarities suggest that the two exchange processes occur *via* the same mechanism and exchange of halogen between two alkyl halides may result from successive exchanges of alkyl halide with aluminum halide.

Unrearranged interchange products point to a non-carbonium ion mechanism for the exchange reaction, since carbonium ion intermediates would be expected to yield predominantly rearranged products.

Without implying ionization, a pathway involving bimolecular nucleophilic substitution could explain the observed results. A displacement mechanism for alkyl halide–aluminum halide interchange is consistent with the finding that the exchange of ethyl bromide (labeled with radioactive bromine) and aluminum bromide is a third-order reaction. The reaction rate is proportional to the concentration of ethyl bromide and to the square of the concentration of aluminum bromide.[2] Conductivity and transport measurements of solutions containing aluminum bromide in ethyl bromide are compatible with the absence of carbonium ions in the exchange mechanism. Formation of $AlBr_4^-$ and $RBrAlBr_2^+$ ions best explains the findings of these experiments.[8]

In many cases, Friedel–Crafts alkylations can yield unrearranged alkyl benzenes.[9] It is possible that these alkylations and the observed interchange reactions proceed by analogous displacement mechanisms of the type proposed by Brown based on kinetic data.[10,11]

Acknowledgment.—This work was supported in part by the National Science Foundation. We also wish to thank Dr. Gerard V. Smith of this laboratory for valuable advice during the course of the work and for the use of v.p.c. equipment.

(8) F. Fairbrother and N. Scott, *J. Chem. Soc.*, 452 (1955).
(9) See, for example, S. H. Sharman, *J. Am. Chem. Soc.*, **84**, 2945 (1962).
(10) H. C. Brown, *Ind. Eng. Chem.*, **45**, 1462 (1953).
(11) H. C. Brown and M. Grayson, *J. Am. Chem. Soc.*, **75**, 6285 (1953).

Synthesis of Eight New Halodeoxyinositols. Configurations of Chloro, Bromo, and Iodo Derivatives of Cyclohexanepentol[1,2]

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Received February 11, 1963

A 6-chloro, a 6-bromo, and a 6-iodo derivative of *cis*-quercitol, each of the *meso* configuration (12345/6), were prepared by reaction of 1,2-anhydro-*cis*-inositol (diketal) with the appropriate aqueous hydrohalic acid. Reaction of 1,2-anhydro-*allo*-inositol (diketal) with aqueous hydrochloric acid gave a mixture of two chloro quercitols, m.p. 215 and 236°, and with hydriodic acid, two iodoquercitols, m.p. 181 and 254°, the lower melting product predominating in each case. The predominant isomers were shown to have the configuration (125/346) corresponding to *gala*-quercitol, since the nonpredominant isomers on hydrogenolysis gave *talo*-quercitol and thus had the configuration (123/456). A bromoquercitol pentaacetate (m.p. 153°) prepared from *epi*-inositol in 1955 has for the first time been converted to the corresponding free bromoquercitol and by hydrogenolysis of the latter to *allo*-quercitol is now shown to have the configuration DL(1234/56), instead of the previously proposed (1235/46). New derivatives of *epi*-inositol and of pinitol are described.

The haloquercitols or halodeoxyinositols (6-halo-1,2,3,4,5-cyclohexanepentols, I) are of interest because of their possible inositol or anti-inositol activity in biological systems, as intermediates for synthesis of other cyclitols, and as model substances for the application to carbohydrates of such physical methods as nuclear magnetic resonance.[4]

Twenty diastereomers (eight *meso*, twelve active or racemic) are predicted for any such monosubstituted inositol, so that the stereochemistry of the haloquercitols is unusually complex and interesting. Previous work in our own and other laboratories has led to the synthesis of not less than ten of the twenty predicted bromoquercitols; not less than three of the chloroquercitols; but of only one of the iodoquercitols.[5]

We now wish to report the preparation and configurational characterization of three new chloroquercitols, two new bromoquercitols, and three new iodoquercitols. Crystalline pentaacetates have been obtained for all but two of these. The recently prepared haloquercitol diastereomers are summarized in Table I, which includes all known iodoquercitols. The previously known

(1) Paper XV on Cyclitol Stereochemistry by G. E. McCasland and coworkers: for preceding publication, see *J. Org. Chem.*, **28**, 894 (1963).
(2) Presented in part by V. B. to the 13th Annual Convention of the Student Affiliates of the American Chemical Society, Reno, Nev., May 4, 1962.
(3) Aided by the National Science Foundation Undergraduate Participation Program at the Department of Chemistry, University of San Francisco, 1962.
(4) See G. E. McCasland, S. Furuta, L. F. Johnson, and J. N. Shoolery, *J. Am. Chem. Soc.*, (a) **83**, 4243 (1961); (b) **83**, 2335 (1961).
(5) The number of known chloro and bromo isomers is somewhat uncertain because of similarities in melting points, and the fact that some haloquercitol pentaacetates have not yet been correlated with their parent haloquercitol.

TABLE I

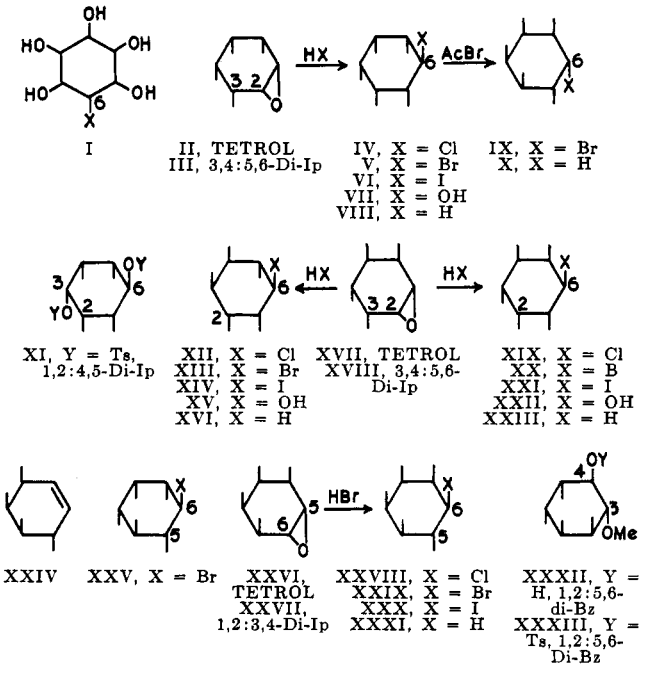
RECENTLY PREPARED DIASTEREOMERS OF 6-CHLORO-, 6-BROMO-, AND 6-IODOQUERCITOLS (HALODEOXYINOSITOLS)

Halogen	Configuration (X at 6)	Quercitol	Related inositol[a]	M.p.,[b] °C. (spec. rot.) Halopentol	Pentaacetate	Reference
Chlorine	*meso* (12345/6)	*cis*	*epi*-(6)	216	185	This article
Chlorine	D (125/346)	*gala*	L-(3)	215 (−53°)	Sirup	This article
Chlorine	D (123/456)	*talo*	*neo*-(1)	236 (−22°)	177 (+67°)	This article
Chlorine	DL (134/256)	*proto*	DL-(2)	206	144	12b
Chlorine	DL (124/356)?	*vibo*	DL-(1)	...	108	12b
Chlorine	DL (12346/5)	*allo*	*epi*-(1)	192	158	4a
Bromine	*meso* (12345/6)	*cis*	*epi*-(6)	202	191	This article
Bromine	D (125/346)	*gala*	L-(3)	203 (−44°) (DL 192)	... (DL 159)	4b, 12a
Bromine	D (123/456)	*talo*	*neo*-(1)	229 (−137°) (DL 214)	...	4b, 12a
Bromine	DL (1234/56)	*allo*	*allo*-(5) or *allo*-(6)	160	153	This article, 8, 12a
Bromine	DL (12346/5)	*allo*	*epi*-(1)	214	159	4a
Iodine	*meso* (12345/6)	*cis*	*epi*-(6)	202	183	This article
Iodine	D (125/346)	*gala*	L-(3)	181 (−31°)	Sirup	This article
Iodine	D (123/456)	*talo*	*neo*-(1)	254 (−45°)	190 (+65°)	This article
Iodine	DL (12346/5)	*allo*	*epi*-(1)	214 dec.	161	4a

[a] Number specifies inositol hydroxyl whose replacement without inversion would give the haloquercitol. [b] The halopentols typically melt with decomposition; the pentaacetates do not.

CHART I

(Ip = isopropylidene, Bz = benzylidene, Ts = *p*-toluenesulfonyl)



chloro and bromo diastereomers were tabulated in our recent publication.[4a]

The haloquercitols typically are colorless, crystalline, water-soluble compounds, which can be recrystallized from aqueous ethyl or isopropyl alcohol. On hydrogenolysis a haloquercitol is converted[6] to the corresponding quercitol (I, X = H).

Methods which have been used for the preparation of haloquercitols include: (1) reaction of a cyclohexenetetrol (conduritol) with hypobromous acid[7]; reaction of an inositol with (2) hot acetyl halide[6,8−10] or (3) thionyl chloride[11]; (4) reaction of an inositol hexaacetate with hot hydrogen halide[9] in acetic acid; reaction at room temperature of an anhydro-inositol or its diketal with hydrogen halide in (5) acetic acid,[4b] or (6) water.[4,12] Method 6 now appears to be by far the most convenient. Iodoquercitols have been prepared only by method 6.

Derivatives of *cis*-Quercitol

The reaction of an HX type reagent with 1,2-anhydro-*cis*-inositol (II) would be expected to yield only a single product, *e.g.*, I , which would be a *meso* diastereomer with the (12345/6) or *epi*-inositol configuration, VII.[13] Experimentally, the reaction of concentrated aqueous hydrochloric acid with the diketal,[14−16a] III, readily gave the expected chloroquercitol, IV, m.p. 216° dec. (pentaacetate 185°). Hydrobromic acid similarly gave the bromoquercitol, V, m.p. 202° dec. (pentaacetate 191°). Attempted preparation of the iodoquercitol with aqueous hydriodic acid gave at first only a discolored sirup (probably due to autoxidation of some of the hydrogen iodide). The procedure was then repeated under oxygen-free nitrogen and excess hy-

(6) G. E. McCasland and E. C. Horswill, *J. Am. Chem. Soc.*, **75**, 4020 (1953). The acetyl bromide was diluted with acetic anhydride to favor the monobromo product.

(7) K. Kubler, *Arch. Pharm.*, **246**, 620 (1908).

(8) G. E. McCasland and John Reeves, *J. Am. Chem. Soc.*, **77**, 1812 (1955).

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

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

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

(12) (a) M. Nakajima and N. Kurihara, *Chem. Ber.*, **94**, 515 (1961); (b) M. Nakajima, personal communication, April, 1961.

(13) For explanation of configurational symbols such as "(12345/6)," see preceding articles in this series.

(14) The product III prepared by Angyal and Gilham's procedure contains considerable starting material, which must be removed by sublimation, even when the reaction time is increased from five to eight hours. The crude product also contains a by-product, m.p. 105–106°, which presumably is the monomethyl ether diketal [reported m.p. 104–105°; see *Advan. Carbohydrate Chem.*, **14**, 201 (1959)]. Yields of the pure product, which melted at 142–143° as reported, are often below the reported 54%. The over-all yield can be improved by recycling of the recovered starting material. The monomethyl ether diketal sublimes with the product.

(15) Each batch of the epoxide diketal (III or XVIII) should be tested for sulfur, to detect unchanged starting material sometimes present. An increase in reaction time may be helpful.

(16) (a) S. J. Angyal and P. Gilham, *J. Chem. Soc.*, 3691 (1957); (b) S. J. Angyal and D. McHugh, *ibid.*, 3686 (1957); (c) S. J. Angyal and N. Matheson, *J. Am. Chem. Soc.*, **77**, 4343 (1955); (d) S. J. Angyal and M. Tate, *J. Chem. Soc.*, 4116 (1961); (e) S. J. Angyal and C. Macdonald, *ibid.*, 686 (1952).

driodic acid was removed by use of an ion exchange resin prior to evaporation. A good yield of the colorless crystalline iodoquercitol, VI, was then obtained, m.p. 202° dec. (pentaacetate, m.p. 183°).

cis-Quercitol itself, VIII, also was prepared, by hydrogenolysis of 1,2-anhydro-*cis*-inositol[16a] (II, not the diketal) in aqueous solution with Raney nickel. This new method of preparation is more convenient than the hydrogenations of quinonetetrol or *cis*-inosose previously employed.[16b]

An inositol ditosylate of same (*epi*-inositol) configurational series as the preceding haloquercitols was prepared by reaction of 1,2:4,5-di-O-isopropylidene-*epi*-inositol[16c] (VII, diketal) with *p*-toluenesulfonyl chloride. The ditosyl diketal product (XI) was allowed to react with methanolic sodium methoxide in the hope of obtaining a 1,4-anhydroinositol, but after forty hours boiling only starting material was obtained.

Derivatives of *gala*- and *talo*-Quercitol

In a previous publication[4b] we described the reaction of the 1,2-anhydro-*allo*-inositol diketal[16c] (XVIII) with hydrogen bromide in acetic acid at room temperature to give a mixture of the two diastereomeric bromoquercitols, XIII and XX, whose configurations were established by nuclear magnetic resonance spectra. By hydrogenolysis, *gala*- and *talo*-quercitol themselves (XVI and XXIII) also were prepared.[4b]

In a similar manner, but using *aqueous* hydrohalic acids at room temperature, we have now converted the anhydro diketal, XVIII, to the two chloroquercitols, XII, m.p. 214° dec. (pentaacetate, a sirup), and XIX, m.p. 236° dec. (pentaacetate, m.p. 177°). Likewise, using hydriodic acid, there were obtained the two iodoquercitols, XIV, m.p. 180° dec. (pentaacetate, a sirup), and XXI, m.p. 254° dec. (pentaacetate, m.p. 190°).

The configuration XIX for the chloroquercitol, m.p. 236°, was established by hydrogenolysis to give the previously known[4b] *talo*-quercitol, XXIII. The other chloroquercitol, m.p. 214°, then necessarily has the remaining configuration XII and is a derivative of *gala*-quercitol.[4b] Hydrogenolysis of the two diastereomeric iodoquercitols similarly showed that the one of m.p. 254° has the configuration XXI (*talo*-quercitol derivative), so that the remaining configuration XIV can be assigned to the isomer, m.p. 180° (*gala*-quercitol derivative.

It is of interest that in the reaction of 1,2-anhydro-*allo*-inositol diketal, XVIII, with aqueous hydrochloric or hydroiodic acid the product of (125/346) configuration, *e.g.* XII, predominates over that of (123/456) configuration, *e.g.*, XIX, by a ratio of about three or four to one. A similar predominance of the (125/346) product previously was observed[4b] in the reaction with hydrogen bromide in glacial acetic acid. This predominance of (125/346) product corresponds to attack by bromide ion at position 2 of the protonated epoxide ring of XVII or XVIII in preference to position 1. From examination of Dreiding stereomodels it appears that the 2-position would be less hindered than 1 with respect to S_N2 attack. It should be noted that the cyclohexane ring in XVIII would be somewhat distorted by the two isopropylidene ketal rings and it is uncertain (especially when acetic acid is used as solvent) whether or not the ketal rings are cleaved before the epoxide ring is cleaved. The major product in each reaction has the configuration of *L*-inositol, XV; the minor product that of *neo*-inositol, XXII.

Derivatives of *allo*-Quercitol

In 1955, J. Reeves[8] working with one of us at Toronto treated *epi*-inositol (VII) with hot acetyl bromide and obtained the pentaacetate, m.p. 153°, of a bromoquercitol. All attempts at that time to obtain the pure bromoquercitol itself by hydrolysis of the pentaacetate were unsuccessful. However, on reaction with zinc in acetic acid the bromo pentaacetate did give the tetraacetate of conduritol-*C*, XXIV.[8] On the basis of limited evidence, the bromo pentaacetate, m.p. 153°, was tentatively assigned[8] the configuration (1235/46), XXV. We now find that the free bromoquercitol (unlike other isomers) is hygroscopic and can readily be prepared in a crystalline state by hydrolysis of the pentaacetate if the crystals are protected from atmospheric moisture. The crystals melt at 160° dec. We also find that this diastereomer actually has the configuration (1234/56), IX, since on hydrogenolysis it gives the known *allo*-quercitol, X. (The bromo pentaacetate, IX, also was prepared by Nakajima,[12] using a different method.) The epimer (12346/5) XXIX also yields *allo*-quercitol on hydrogenolysis,[4a] but is known to be nonidentical with Reeves' product.

In 1961 the nuclear magnetic resonance spectrum of a bromoquercitol of m.p. 229°, XX, related to *talo*-quercitol was interpreted successfully.[4b] More recently we have examined the n.m.r. spectra of 6-chloro, 6-bromo, and 6-iodo derivatives of *allo*-quercitol (XXVIII–XXX) in an attempt to confirm their previously assigned[4a] configurations. This attempt has so far been unsuccessful due to the complex spin–spin coupling resulting in these isomers from the six neighboring ring protons in each molecule. Spectra are described in Experimental.

Benzylidenepinitol. — Although numerous isopropylidene derivatives of cyclitols are known, and cyclohexylidene derivatives[16d] have recently been employed, very few benzylidene[17] derivatives have been reported. In connection with experiments on diisopropylidene derivatives of (−)-inositol, the synthesis and characterization of the dibenzylidene derivative XXXII of (+)-inositol 3-methyl ether (*pinitol*) was carried out.[18,19] The corresponding monotosylate XXXIII also was prepared (see Experimental).

Mercaptoquercitol.—By reaction of 1,2-anhydro-*cis*-inositol diketal (III) with benzylmercaptan, reduction, and hydrolysis we have prepared recently a mercaptoquercitol (VIII, X = SH). Details will be given in a subsequent publication.

Experimental

All melting points were corrected and were measured with a Nalge-Axelrod micro hot stage, if not otherwise noted. Micro-

(17) See E. Shneour and C. E. Ballou, *J. Am. Chem. Soc.*, **80**, 3960 (1958).

(18) Preparation conducted by Robert Horvat, formerly of this laboratory.

(19) Dibenzylidenepinitol should be able to exist in four different configurations due to the two additional asymmetric carbon atoms in the benzylidene groups. The product isolated by us appears to consist of a single pure stereoisomer, whose configuration at the benzylidene asymmetric carbon atoms has not been determined.

analyses were by the Micro-Tech Laboratories, Skokie, Ill. Nuclear magnetic resonance spectra were recorded with a Varian Model HR-60 high resolution n.m.r. spectrometer. Infrared spectra using potassium bromide pellets were recorded with a Perkin-Elmer Model 137 Infracord spectrometer. Optical rotations were measured with a Kern Full-Circle polarimeter.

The infrared spectrum was recorded for each new compound prepared; the spectra for haloquercitols and their pentaacetates showed absorption at the usual frequencies. It appears that haloquercitols of the same configuration have fingerprint regions of nearly identical shape; the exact locations of the fingerprint region absorption maxima shift in a regular manner for each Cl:Br:I series. Further work will be necessary to find out if these relationships are general.

Acetylation products were isolated by evaporation of the excess acetic anhydride and distribution of the residue between chloroform and water. The separated, washed, and dried chloroform phase was evaporated to give the crude product.

A qualitative sodium fusion test for halogen was made on each new halogen compound.

All nonaqueous solutions to be evaporated were dried with an appropriate desiccant. All evaporations were performed under reduced pressure. Crystals were washed with an appropriate solvent, and dried *in vacuo* to constant weight. Darco G-60 brand[20] of decolorizing charcoal was used.

1,2-Anhydro-*cis*-inositol, II.—A 300-mg. portion of the diketal[14-16a] (m.p. 143°) was treated by the procedure of Angyal and Gilham,[16a] giving 110 mg. (55%) of colorless crystals, m.p. 161–163°. This material was recrystallized twice more from absolute ethanol, giving 50 mg. of product, m.p. 164–165°.

Since the desired product previously had been reported[16a] to melt at 59–60° (yield not reported), we confirmed the identity of our own preparation by microanalysis.

Anal. Calcd. for $C_6H_{10}O_5$: C, 44.44; H, 6.22. Found: C, 44.01; H, 6.36.

The structure was further confirmed by an infrared spectrum which showed no hydroxyl absorption, excluding the monoketal structure, and a reaction with hydrobromic acid, which gave the expected 6-bromoquercitol, V, m.p. 202° dec.

In a second run, on 390 mg. of diketal, a product of the same m.p. 164–165° was again obtained.

New Method for Preparation of *meso*(12345) or All-*cis* Diastereomer of Quercitol (Deoxyinositol, Cyclohexanepentol), VIII.—A 220-mg. portion of 1,2-anhydro-*cis*-inositol was dissolved in 50 ml. of water, and 3.0 g. (moist weight) of commercial Raney nickel catalyst was added (probably the amount of catalyst can be reduced). The mixture was hydrogenated at 3 atm. at room temperature for 12 hr. The filtered mixture was evaporated and oily residue taken up in 80% ethanol (treated with charcoal). The crystals, which had separated from the filtrate after 12 hr., were collected, giving 100 mg. of colorless product, m.p. 238–240° (reported[16b] 235–240°). Including a 20-mg. second crop (m.p. 236–240°), the yield was 55%.

epi-Inositol Configurational Series

***meso*(12345/6) Diastereomer of 6-Chloroquercitol, M.p. 216°. 6-Chloro-6-deoxy-*epi*-inositol, IV.**—A mixture of 200 mg. of the anhydro-inositol diketal[16a] (m.p. 143°) with 5.0 ml. of 12 *M* aqueous hydrochloric acid was stirred for 1 hr. at room temperature, and the resulting solution evaporated. To the residue was added 5.0 ml. of 2-propanol and the evaporation repeated; the addition and evaporation were then again repeated. The residue was taken up in 7.0 ml. of water, the solution treated with charcoal, and the filtrate evaporated. The crystalline residue was recrystallized from 75% aqueous ethanol, giving 150 mg. (91%) of colorless crystals, m.p. 214–215° dec. This product was again recrystallized, for analysis, giving 130 mg. of pure product, m.p. 215–216° dec. (preheat stage for each m.p. to 190°).

Anal. Calcd. for $C_6H_{11}ClO_5$: C, 36.28; H, 5.58; Cl, 17.85. Found: C, 36.33; H, 5.65; Cl, 17.61.

***meso*(12345/6) Diasteromer of 6-Chloroquercitol Pentaacetate, M.p. 185°, IV.**—A mixture of 50 mg. of the chloropentol (m.p. 216°) with 50 mg. of fused sodium acetate and 3.0 ml. of redistilled acetic anhydride was boiled under reflux for 4 hr. (anhydrous conditions). The product was isolated in the usual manner and recrystallized twice from 2-propanol, giving 50 mg. (49%) of the pure product, m.p. 184.5–185°.

Anal. Calcd. for $C_{16}H_{21}ClO_{10}$: C, 47.01; H, 5.18; Cl, 8.67. Found: C, 46.89; H, 5.10; Cl, 8.43.

To test for possible displacement of chlorine by the sodium acetate catalyst used, a sample of the acetylation mixture was evaporated and the residue distributed between chloroform and water. The separated aqueous phase gave a negative silver nitrate test for halogen.

***meso*(12345/6) Diastereomer of 6-Bromoquercitol, M.p. 202°. 6-Bromo-6-deoxy-*epi*-inositol, V.**—The anhydro diketal (m.p. 143°, 200 mg.) was treated with 8.8 *M* hydrobromic acid in exactly the manner described above for the chlorine analog. There was obtained 170 mg. (84%) of the once recrystallized product, m.p. 200–201° dec., and 140 mg. of the twice recrystallized product, m.p. 201–202° dec. (preheat to 190°).

Anal. Calcd. for $C_6H_{11}BrO_5$: C, 29.65; H, 4.56; Br, 32.86. Found: C, 29.77; H, 4.68; Br, 33.16.

***meso*(12345/6) Diastereomer of 6-Bromoquercitol Pentaacetate, M.p. 191°, V.**—A 50-mg. sample of the bromopentol (m.p. 202°) was acetylated in the same manner described before for the chlorine analog, giving 60 mg. (64%) of the twice recrystallized product, m.p. 190–191°.

Anal. Calcd. for $C_{16}H_{21}BrO_{10}$: C, 42.40; H, 4.67; Br, 17.63. Found: C, 42.29; H, 4.54; Br, 17.63.

A silver nitrate test on the acetylation mixture for free bromide ion (see chlorine analog) gave only a trace of silver bromide precipitate.

***meso*(12345/6) Diastereomer of 6-Iodoquercitol, M.p. 202°. 6-Iodo-6-deoxy-*epi*-inositol, VI.**—Oxygen-free nitrogen gas was passed slowly through a solution of 150 mg. of the anhydro diketal (m.p. 143°) in 0.5 ml. of colorless 5.5 *M* hydriodic acid at room temperature. After 1 hr. the colorless solution was diluted with 5.0 ml. of water, and deionized by treatment with 2.5 ml. (moist volume) of Amberlite IR-45 exchange resin.[21] The solution (pH 5 or higher) was evaporated and the colorless crystalline residue recrystallized from 75% ethanol (treated with charcoal). The cooled filtrate gave 120 mg. (67%) of colorless product, m.p. 197–198° dec. (preheat to 190°). This material was again recrystallized, giving 90 mg. of product, m.p. 202° dec., which was analytically pure.

Anal. Calcd. for $C_6H_{11}IO_5$: C, 24.84; H, 3.82; I, 43.75. Found: C, 24.93; H, 4.18; I, 43.63.

An earlier attempt to prepare the iodoquercitol without use of nitrogen, and without deionization before evaporation, gave only a dark oil.

***meso*(12345/6) Diastereomer of 6-Iodoquercitol Pentaacetate, M.p. 183°, VI.**—A 50-mg. portion of the iodopentol (m.p. 202°) was acetylated in the same manner described for the chlorine analog, giving 70 mg. (81%) of once recrystallized (from absolute ethanol) product, m.p. 176–177.5°. After a second recrystallization there was obtained 55 mg. of colorless crystals, m.p. 182.5–183°, which were analytically pure.

Anal. Calcd. for $C_{16}H_{21}IO_{10}$: C, 38.41; H, 4.23; I, 25.37. Found: C, 38.32; H, 4.46; I, 25.15.

***meso*-1,2:4,5-Di-O-Isopropylidene-*epi*-inositol 3,6-Di-*p*-toluenesulfonate, XI.**—The diketal[16c] (0.5 g., m.p. 181°) and 1.5 g. of recrystallized *p*-toluenesulfonyl chloride were dissolved in 5.0 ml. of anhydrous pyridine. The solution was kept for 7 days at 25°. Crystals of pyridine hydrochloride were visible by the second day. The mixture was poured into 75 ml. of water at 0° with stirring. A colorless sirup separated and soon solidified. The crude product was collected, washed with 10 ml. of water, and without drying was dissolved in 35 ml. of chloroform. The chloroform solution was washed with sodium bicarbonate solution, dried, and evaporated to dryness. The amorphous residue was taken up in 30 ml. of hot chloroform, and the solution evaporated to 15 ml. This solution on standing deposited crystals which were collected, washed, and dried, giving 0.7 g. of product, m.p. 223–226° dec. This material was recrystallized from chloroform, giving 0.5 g. (63%) of pure product, m.p. 228–229° dec.

Anal. Calcd. for $C_{26}H_{23}O_{10}S_2$: C, 54.91; H, 5.67; S, 11.28. Found: C, 54.63; H, 5.46; S, 11.09.

Attempted Conversion of the 3,6-Ditosylate to a 3,6-Anhydro Derivative.—A 285-mg. portion of the previous ditosylate diketal (m.p. 229°) was mixed with an absolute methanolic solution of

(20) A product of the Darco Division, Atlas Powder Co., Wilmington, Del.

(21) A product of the Resinous Products Division, Rohm and Haas Co., Philadelphia, Pa.

sodium methoxide. The suspension was boiled for 40 hr. under reflux. The starting material did not appear to dissolve or react. From the precipitate and solution there was recovered a total of 263 mg. of material. This was shown to be identical with the starting material by means of mixture melting point and infrared spectra.

neo and DL-Inositol Configurational Series

D(123/456) Stereoisomer of 6-Chloroquercitol, M.p. 236°. 1-Chloro-1-deoxy-*neo*-inositol, XIX.—A mixture of 980 mg. of 1,2-anhydro-*allo*-inositol diketal[16c] (m.p. 108°) with 5.0 ml. of 12 *M* hydrochloric acid was stirred at room temperature for 2 hr., and the resulting solution evaporated to dryness. To the residue three 5.0-ml. portions of absolute 2-propanol were successively added and evaporated. The crystalline residue was recrystallized from 60% 2-propanol (treated with charcoal). After 12 hr. the crystals which had separated were collected, giving 130 mg. of colorless matted needles, m.p. 234–235° dec. A second crop of 40 mg., m.p. 232–234° dec., was obtained.

The second crop filtrate was reserved for preparation of the m.p. 215° isomer (see following text).

Recrystallization of the combined crops (170 mg., m.p. 232–235°) from 65% 2-propanol gave 140 mg. of nearly pure product, melting at 234–235° dec., $[\alpha]^{23}D$ −22° (*c* 0.5, water), MR −44° A sample recrystallized again, for analysis, melted at 235–236° dec.

Anal. Calcd. for $C_6H_{11}ClO_5$: C, 36.28; H, 5.58; Cl, 17.85. Found: C, 36.28; H, 5.67; Cl, 18.05.

A sample of this isomer on hydrogenation was converted to *talo*-quercitol (see following text).

D(125/346) Stereoisomer of 6-Chloroquercitol, M.p. 215°. 3-Chloro-3-deoxy-*L*-inositol, XII.—Second crop filtrate from the m.p. 236° isomer (see preceding) was evaporated. Colorless crystalline residue was recrystallized from 65% 2-propanol (treated with charcoal). After 6 hr. the crystals which had separated were collected, giving 220 mg. of material, m.p. 214–215° dec. A second crop of 250 mg., m.p. 212–214° dec., was obtained. (Attempted isolation of a third crop gave 10 mg. of the other isomer, m.p. 230–234° dec.)

Recrystallization of the combined lower melting isomer crops (470 mg.) from 65% 2-propanol gave 350 mg. of colorless crystals, m.p. 214–215°, $[\alpha]^{23}D$ −53° (*c* 0.3, water), MR −105°. A sample recrystallized for analysis showed no change in melting point.

Anal. Calcd. for $C_6H_{11}ClO_5$: C, 36.28; H, 5.58; Cl, 17.85. Found: C, 36.13; H, 5.55; Cl, 17.83.

Attempted acetylation of a 200-mg. sample of this chloroquercitol in the usual manner gave an oil, which we have not yet been able to crystallize.

D(123/456) Stereoisomer of 6-Chloroquercitol Pentaacetate, M.p. 177°, XIX.—A 50-mg. portion of the chloroquercitol (m.p. 236°) was acetylated in the same manner as that described for the (12345/6) diastereomer, giving 50 mg. of colorless once recrystallized (from absolute ethanol) product, m.p. 175–176°. Including a 30-mg. second crop, the yield was 78%. By recrystallization of the first crop there was obtained 40 mg. of colorless crystals, m.p. 176–177°, $[\alpha]^{25}D$ +67° (*c* 0.3, chloroform), MR +274°. A sample recrystallized again, for analysis, showed no change in melting point.

Anal. Calcd. for $C_{16}H_{21}ClO_{10}$: C, 47.01; H, 5.18; Cl, 8.67. Found: C, 47.22; H, 5.02; Cl, 8.84.

D(123/456) Stereoisomer of 6-Iodoquercitol, M.p. 254°. 1-Iodo-1-deoxy-*neo*-inositol, XXI.—A mixture of 980 mg. of the 1,2-anhydro diketal (m.p. 108°) with 5.0 ml. of colorless 5.5 *M* hydriodic acid was stirred at room temperature for 2 hr. The resulting solution was evaporated. To the residue two 5.0-ml. portions of 2-methyl-1-propanol were successively added and evaporated. The residue was stirred for 10 min. with 25 ml. of acetone, and the mixture filtered. The residue was washed with 5 ml. more of acetone. (Evaporation of the combined, brown filtrates gave a discolored sirup, which has not been further characterized.)

The crude product was recrystallized from 65% 2-propanol, giving 100 mg. of colorless crystals, m.p. 246–248° dec. (closed capillary, preheat to 240°), $[\alpha]^{23}D$ −45° (*c* 0.2, water), MR −176°.

The mother liquor was reserved for preparation of the lower-melting isomer (see following text).

The crystals were recrystallized from 70% 2-propanol, giving 70 mg. of product, m.p. 248–249° dec. A sample recrystallized again, for analysis, melted at 253–254° dec.

Anal. Calcd. for $C_6H_{11}IO_5$: C, 24.84; H, 3.82; I, 43.75. Found: C, 24.73; H, 3.43; I, 43.10.

On hydrogenation this isomer of 6-iodoquercitol gave *talo*-quercitol (see following text).

D(123/456) Stereoisomer of 6-Iodoquercitol Pentaacetate, M.p. 190°, XXI.—A 50-mg. portion of the iodoquercitol (m.p. 254°) was acetylated in the usual manner. The crude product, a sirup, was crystallized from 2-propanol (treated with charcoal). After 12 hr., the crystals were collected, giving 70 mg. (82%) of nearly pure product, m.p. 189–190°. A sample was recrystallized again for analysis, melting point unchanged, $[\alpha]^{25}D$ + 65° (*c* 0.2, chloroform), MR + 325°.

Anal. Calcd. for $C_{16}H_{21}IO_{10}$: C, 38.41; H, 4.23; I, 25.37. Found: C, 38.55; H, 4.26; I, 25.06.

D(125/346) Stereoisomer of 6-Iodoquercitol, M.p. 181°. 3-Iodo-3-deoxy-L-inositol, XIV.—The mother liquor from the previous m.p. 254° isomer was concentrated, giving 300 mg. of material, m.p. 179–184°. Two additional concentrations of the mother liquor yielded 160 mg. of material, m.p. 180–183°, and 5 mg., m.p. 180–181° (all melting points with decomposition).

Recrystallization of these combined crops (465 mg.) from 70% 2-propanol gave 350 mg. of colorless crystals, m.p. 180–181° dec. A sample recrystallized again, for analysis, showed no change in melting point, $[\alpha]^{27}D$ −31° (*c* 1, water), MR − 90°.

Anal. Calcd. for $C_6H_{11}IO_5$: C, 24.84; H, 3.82; I, 43.75. Found: C, 25.44; H, 4.34; I, 43.91.

Attempted acetylation of the iodoquercitol, m.p. 181°, in the usual manner gave an oil, which we have not been able to crystallize.

Conversion of the Chloro- and Iodoquercitols, M.p. 236° and 254°, to (123/45) or *talo*-Quercitol, XXIII. (A) From Chloroquercitol.—To a 150-mg. sample of the chloroquercitol (m.p. 236°) in 50 ml. of water was added 3.0 g. (moist weight) of commercial Raney nickel catalyst and 2.0 g. (moist weight) of Amberlite IR-45 ion exchange resin.[21] The mixture was hydrogenated at 3 atm. and room temperature for 12 hr. The solids were removed by filtration and the filtrate evaporated to a sirup. Volatile impurities were removed by repeated additions and evaporations of 2-propanol, giving finally a crystalline residue. This residue was recrystallized from 90% ethanol, giving 100 mg. (80%) of colorless crystals, m.p. 245–248° dec. This product was recrystallized (treated with charcoal), giving 60 mg. of colorless product, m.p. 246–248° dec. The melting point was unchanged on further recrystallization. The infrared spectrum was identical with that of D-*talo*-quercitol.[4b] A portion was acetylated, giving a product, m.p. 181–183°, identical by mixture melting point and infrared spectrum with D-*talo*-quercitol pentaacetate.

(B) From Iodoquercitol.—A 160-mg. sample of the iodoquercitol (m.p. 254°) was hydrogenated in the same manner, giving 55 mg. of twice recrystallized product, m.p. 246–248° dec., identical by infrared spectrum with D-*talo*-quercitol.[4b] A portion was acetylated, giving a product identical by mixture melting point and infrared spectrum with D-*talo*-quercitol pentaacetate.

1,2:5,6-Di-O-benzylidene-D-inositol 3-Methyl Ether[18] (Dibenzylidenepinitol), XXXII.—A mixture of 25 g. of finely ground, fused zinc chloride with 18.7 ml. of freshly distilled benzaldehyde was stirred at room temperature for 40 min. A 5.0-g. portion of finely powdered dry pinitol (see Acknowledgment) was then added, and the mixture stirred for 50 hr. and allowed to stand an additional 24 hr. The mixture was poured into a mixture containing 200 ml. of petroleum ether (b.p. 60–90°), 25 g. of anhydrous potassium carbonate, and 400 ml. of water. The precipitate which separated was collected, giving 3.8 g. of product, m.p. 118–120°. A sample recrystallized from aqueous ethanol, for analysis, melted at 119–120°.

Anal. Calcd. for $C_{21}H_{22}O_6$: C, 68.09; H, 5.99. Found: C, 67.74; H, 6.26.

D(124/356) Stereoisomer of 1,2:5,6-Di-O-benzylidene-3-O-methyl-4-O-*p*-toluenesulfonylinositol[18] (Dibenzylidenepinitol Tosylate, XXXIII).—A solution of 1.0 g. of dibenzylidenepinitol (m.p. 120°) and 0.86 g. of *p*-toluenesulfonyl chloride in 10.0 ml. of dry pyridine was allowed to stand for 4 days at room temperature. Three-fourths of the pyridine was evaporated and the remaining sirup poured into 50 ml. of ice-cold water containing

1.0 g. of sodium bicarbonate. The oil which separated was collected with chloroform, and the separated chloroform extract washed successively with 0.1 *N* hydrochloric acid, sodium bicarbonate solution, and water, and dried. Evaporation gave an oil, which was taken up in 15 ml. of absolute ethanol. Two milliliters of petroleum ether (b.p. 30–80°) was added. After 4 days at 0–5°, the crystals which had separated were collected, giving 224 mg. (16%) of colorless product, m.p. 125–127°. A sample recrystallized again, for analysis, melted at 133–134°.

Anal. Calcd. for $C_{28}H_{28}O_8S$: C, 64.10; H, 5.34. Found: C, 64.22; H, 5.36.

On hydrolysis with 50% acetic acid, this product gave 4-O-*p*-toluenesulfonylpinitol, m.p. 191° dec. (reported m.p.[16c] 193° dec.).

allo-Inositol Configurational Series

DL(1234/56) Diastereomer of 6-Bromoquercitol, M.p. 160°. 6-Bromo-6-deoxy-*allo*-inositol, IX.—A mixture of 3.2 g. of the pentaacetate[3] (m.p. 153°), derived from *epi*-inositol by reaction with acetyl bromide, with 64 ml. of *M* hydrochloric acid in 50% ethanol was boiled under reflux for 5 hr. On evaporation a light brown sirup was obtained. Volatile impurities were removed by repeated addition and evaporation of absolute ethanol. The resulting sirup was taken up in 15 ml. of 2-methyl-2-propanol (treated with charcoal). After the solution had stood 24 hr. at room temperature, the *hygroscopic* crystals which had separated were collected on a sintered glass funnel *from which moist air was excluded*, and dried over phosphorus pentoxide *in vacuo*. The colorless crystals obtained weighed 0.95 g., m.p. 159–160° dec. Including a second crop, m.p. 158–160°, and a third crop, m.p. 158–160° dec., the yield was 1.40 g. (82%). A sample recrystallized again, for analysis, showed no change in melting point.

Anal. Calcd. for $C_6H_{11}BrO_5$: C, 29.65; H, 4.56; Br, 32.86. Found: C, 29.80; H, 4.73; Br, 32.27.

On hydrogenolysis, this product gave DL-*allo*-quercitol[4a] (see following text).

Conversion of the Bromoquercitol, M.p. 160°, to DL-*allo*-Quercitol, XXXI.—A 950-mg. sample of the bromoquercitol (m.p. 160°) was hydrogenated with Raney nickel and Amberlite IR-45 resin[12] in the same manner described for the m.p. 236° chloroquercitol isomer. The crude hydrogenation product was taken up in 15 ml. of absolute ethanol, and the solution kept at room temperature for 24 hr. The crystals which had separated were collected, giving 300 mg. of colorless product, m.p. 260–261° dec. The product was shown by mixture melting point and infrared spectrum to be identical with DL-*allo*-quercitol.[4a]

A sample of the quercitol was acetylated, giving DL-*allo*-quercitol pentaacetate, m.p. 92–94°, identical by mixture melting point and infrared spectrum with an authentic sample.[4a]

Nuclear Magnetic Resonance Spectra of the DL-(12346/5) Diastereomers of 6-Chloro-, 6-Bromo-, and 6-Iodoquercitol (XXVIII-XXX).—The spectra were taken in deuterium oxide, using tetramethylsilane external reference. A strong HDO peak appeared in each spectrum at about δ 5.2 p.p.m. The chloroquercitol[4a] (m.p. 192°) showed a 1-proton multiplet (about 8 peaks) centered at δ 4.1; another 1-proton multiplet (about 5 peaks) centered at 4.3; and a 4-proton multiplet (about 7 peaks) centered at δ 4.6. The 4-proton multiplet was almost split at its center into two 2-proton multiplets (δ 4.5, 4.7).

The spectra of the bromoquercitol[4a] (m.p. 203°) and iodoquercitol[4a] (m.p. 214°) were similar to that of the chloro analog, but showed no tendency for separation of the 4-proton multiplet at δ 4.6 into two smaller multiplets.

Acknowledgment.—This research was made possible by generous grants to the University of San Francisco from the National Science Foundation (G-15893-R) and the Roscoe and Margaret Oakes Foundation. Supplies of quebrachitol were kindly provided by the Plantation Division, U. S. Rubber Company, and of pinitol by Dr. A. B. Anderson of Forest Products Laboratory (Richmond) and Professor Robert Elderfield (University of Michigan). Nuclear magnetic resonance spectra were recorded at Varian Associates, Palo Alto, California, by Dr. J. N. Shoolery and Leroy F. Johnson. We wish to thank Dr. Robert Horvat for assistance in the preparation of dibenzylidenepinitol and its *p*-toluenesulfonate.

Synthesis of Δ⁵-Pregnene-3α,16α,20α-triol[1]

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Received February 11, 1963

The partial syntheses of Δ⁵-pregnene-3α,16α,20α-triol and its 20β-epimer are described.

Recently[3] we reported the isolation and characterization of Δ⁵-pregnene-3α,16α,20α-triol (Ha) from the urine of a patient with adrenocortical carcinoma, which was the first description of the natural occurrence of a 3α-hydroxy-Δ⁵ steroid. The partial synthesis of this unsaturated triol by an unambiguous route is described in the present report. In addition, all four Δ⁵-pregnene-3,16α,20-triols isomeric at positions 3 and 20 have been prepared by another route.

The starting material in both instances was 3β-acetoxy-Δ⁵,¹⁶-pregnadien-20-one (A). The 16α-hydroxyl group was introduced by the method of Julian and coworkers.[4] Selective oxidation of the Δ¹⁶ bond of A with alkaline hydrogen peroxide followed by reacetylation gave 3β-acetoxy-16α,17-oxido-Δ⁵-pregnen-20-one (B).[4] Reduction of the oxide B with chromous acetate[5] yielded 3β-acetoxy-16α-hydroxy-Δ⁵-pregnen-20-one (C). Impure C was generally carried directly to the next stage. Lithium aluminum hydride reduction of C gave a mixture of Δ⁵-pregnene-3β,16α,20α- and 20β-triols (D and Ea) which were separated readily by partition chromatography on silica gel. These epimers had been prepared and the configuration at C-20 assigned by Hirschmann and co-workers.[6] The triol Ea has been isolated from natural sources.[3,7,8]

The inversion of the 3β-hydroxy group of the 20α-triol E, while preserving the configurations at 16 and 20, was accomplished by a procedure based on studies of

(1) This investigation was supported in part by a grant from the American Cancer Society and a research grant (CA 03207) from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service.

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