perature for 20 hr. and at 40–50° for 3 hr. Attempts to crystallize this homolog were not successful; ϵ (265 mμ) 23,200 (in petroleum ether). The principal infrared bands are listed in Table I and compared with those of vitamin D_3.

Anal. Calcd. for $C_{16}H_{24}O$: C, 82.69; H, 10.41. Found: C, 82.61; H, 10.34.

The other fractions obtained in the chromatography were isolated and purified further, but qualitative ultraviolet spectroscopic analysis indicated the presence of a *trans* isomer, λ_{max} 270–275 mμ, and unreacted dienone, λ_{max} 290–310 mμ.

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CAMBRIDGE 39, MASSACHUSETTS

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE OHIO STATE UNIVERSITY]

Reaction of *keto*-Acetates with Diazomethane[1,2]

BY M. L. WOLFROM, J. B. MILLER,[3] D. I. WEISBLAT AND A. R. HANZE

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The reaction of diazomethane with *keto*-D-fructose pentaacetate and *keto*-L-sorbose pentaacetate yields 1,2-anhydroalditol acetates branched at C2. Treatment with mineral acids opens the ring with the formation of a 1-deoxy derivative and consequent retention of (the unknown) configuration at C2.

Reaction of diazomethane with an aldehyde or ketone yields an homologous epoxide or carbonyl compound with the ratio of epoxide to carbonyl product being larger for acyclic ketones than for the corresponding aldehydes and larger when electronegative substituents are present.[4] The reported formation of epoxides on treatment of *keto*-D-fructose pentaacetate[2] and *scyllo*-inosose pentaacetate[5] with diazomethane suggests that in general the grouping, –CHOAc–CO–CHOAc–, may be expected to yield epoxides on reaction with diazomethane. The work reported herein demonstrates this to be the case for *keto*-L-sorbose pentaacetate and presents proof of structure (but not configuration) for the epoxide from *keto*-D-fructose pentaacetate previously reported in a preliminary communication.[2] Only one epoxide has as yet been characterized in each of these diazomethane reactions although an epimeric product might also be expected.

The epoxide ring opens on treatment with hydrogen chloride,[6,7] hydrogen bromide[5] or magnesium bromide[8] and the resulting halohydrins may be reconverted to the epoxide on treatment with a variety of bases.[9] The products obtained using hydrogen chloride in acetic acid and hydrogen chloride in methanol represent the same direction of ring opening in agreement with the results of Wasserman and Aubrey[6] and contrary to the experience of Jörlander[7] who obtained different chlorohydrins on opening of an epoxide ring with hydrogen chloride depending on whether the solvent was acetic acid or ethanol. The position of ring opening was established herein by periodate oxidation of the deacetylated chlorohydrin III derived from D-fructose. Had the ring opened with cleavage of the C2 oxygen bond on treatment with acid then a tertiary halide would have resulted which would have reduced three moles of periodate and liberated one mole of formaldehyde per mole of chlorohydrin. Ring opening at the C1 oxygen bond, however, would give a chlorohydrin which would reduce five moles of periodate and liberate two moles of formaldehyde per mole of chlorohydrin. The latter was found to be the case (Table I). The rapid consumption of periodate by this compound and by N-acetyltetrahydrostreptobiosamine[10] (95% complete in fifteen minutes),[11] both of which contain a primary–tertiary glycol group, infers little difference in rate of oxidation between this group and a primary–secondary glycol group, although when the tertiary carbinol is in a five-membered ring there does exist a difference in rate sufficiently large to be of preparative value.[12]

TABLE I

PERIODATE OXIDATION OF COMPOUND III

Time, min.	Moles of oxidant consumed per mole of III at 0°[a]	Moles of HCHO produced per mole of III at 25°[b]
17	5.0	
27	5.2	
56	5.2	
60		2.0
91	5.2	
148	5.3	

[a] Arsenite method, E. L. Jackson, *Org. Reactions*, **2**, 361 (1944). [b] Chromotropic acid method, J. C. Speck, Jr., and A. A. Forist, *Anal. Chem.*, **26**, 1942 (1954). Analysis by Dr. D. S. Miyada.

(1) Paper No. 16 in the series entitled "The Action of Diazomethane upon Acyclic Sugar Derivatives"; previous communication: M. L. Wolfrom and H. B. Wood, Jr., THIS JOURNAL, **77**, 3096 (1955).

(2) A preliminary report of a portion of this work has appeared; M. L. Wolfrom, D. I. Weisblat and S. W. Waisbrot, *ibid.*, **63**, 632 (1941).

(3) Procter and Gamble Fellow (1955–1956); Visking Corporation Fellow (1956-1957).

(4) C. Gutsche, *Org. Reactions*, **8**, 369, 375 (1954).

(5) T. Posternak, *Helv. Chim. Acta*, **27**, 457 (1944).

(6) H. H. Wasserman and N. E. Aubrey, THIS JOURNAL, **78**, 1726 (1956).

(7) H. Jörlander, *Ber.*, **49**, 2782 (1916).

(8) (a) R. E. Buckles and J. E. Maurer, *J. Org. Chem.*, **18**, 1585 (1953); (b) C. L. Stevens and S. J. Dykstra, THIS JOURNAL, **76**, 4402 (1954); (c) G. N. Richards, L. F. Wiggins and W. S. Wise, *J. Chem. Soc.*, 496 (1956); (d) E. T. McBee, C. E. Hathaway and C. W. Roberts, THIS JOURNAL, **78**, 3851 (1956).

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(10) M. L. Wolfrom and C. W. De Walt, Jr., *ibid.*, **70**, 3148 (1948).

(11) C. W. De Walt, Jr., Ph. D. Dissertation, The Ohio State University, 1948.

(12) D. A. Prins and T. Reichstein, *Helv. Chim. Acta*, **24**, 396 (1941); R. J. Woods and A. C. Neish, *Can. J. Chem.*, **32**, 404 (1954).

The crude chlorohydrin III showed three spots on a paper chromatogram. The fastest moving spot was shown to be the chlorohydrin, RCl. The slowest moving spot had an R_{gluc} value identical with that of a sirup, thought to be the heptitol, ROH, formed by the addition of the elements of water to IV. Analysis of the crude chlorohydrin indicated the presence of methoxyl groups presumably due to the product, ROMe, obtained by the addition of methanol to the epoxide ring. The rate of migration of the spots, RCl > ROMe > ROH, is that predictable for their partition chromatography and the relative intensities of the spots, RCl > ROMe > ROH, is in agreement with the mole fraction composition, $N_{RCl} = 0.9068$, $N_{ROMe} = 0.0905$, $N_{ROH} = 0.0027$, as calculated from the carbon, hydrogen, chlorine and methoxyl analyses.

Assuming kinetic control, a bimolecular course of reaction is suggested since the product distribution indicates that the nucleophilicity of the species present is of more importance than their concentration. If a unimolecular course of reaction were being taken, then one would expect the primary carbonium ion formed to be less selective in its reactivity with the consequent formation of a large proportion of the methoxy derivative in view of the high methanol concentration. When II was refluxed in aqueous hydrochloric acid, a chlorine-free sirup was obtained whose R_{gluc} value is identical with that of the slowest moving component, ROH, of the crude chlorohydrin III. The failure to form a chlorohydrin under these conditions may be due to the incursion of a unimolecular reaction path.[13] It should be noted that, regardless of the course of the reaction, the chlorohydrins obtained must necessarily have the same configuration as the epoxide II since no bonds to the asymmetric carbon atom were cleaved.

Although these chlorohydrins are produced, they are not formed as readily as with the unsubstituted epoxides, since II and its analog from *keto*-L-sorbose pentaacetate were inert toward the conditions of epoxide analysis, with 0.2 *N* hydrogen chloride in acetic acid, described by Durbetaki.[14] This is in accord with the known inhibitory action of hydroxyl functions on the cleavage of oxygen rings by acids.[15]

Reaction of II with hydrogen bromide in acetic acid for a short time yielded a bromohydrin VI whose structure is assumed to be analogous to that of the chlorohydrin VII. This assumption is strengthened by the fact that: (a) reconversion to the epoxide II is possible and (b) the nearly identical X-ray powder diffraction patterns for the bromohydrin VI and the chlorohydrin VII implies isomorphism which might be expected for structures VI and VII.

Reaction of II with hydrogen bromide in acetic acid for longer periods of time yielded the dibromide V whose structure is based on: (a) the known ease of conversion of a tertiary carbinol to a halide; (b) the methanolytic instability of the dibromide compared to the stability of the bromohydrin, the difference presumably arising from the partial tertiary nature of the dibromide and the presence of neighboring groups to assist methanolysis; and (c) the reaction of the dibromide with a solution of sodium iodide in 1,2-dimethoxyethane to give sodium bromide and an iodine colored solution whose color is discharged by sodium bisulfite. The configurational relationship between the bromohydrin and the dibromide is unknown.

The epoxide derived from *keto*-L-sorbose pentaacetate did not yield crystalline derivatives and the sirupy chlorohydrin acetate was selected for analysis because of the possibility of purification by silicate column chromatography. This analysis, together with the infrared data presented below, suffice to show the epoxide nature of the compound.

Epoxides are reported to exhibit absorption in the 7.9 and 11.1 μ regions with the former being the more reliable.[16] Absorption in the 10.52–11.58 and 11.57–12.72 μ regions also has been reported.[17] In agreement with these assigned regions, the carbohydrate epoxides studied here exhibit absorption at 7.9, 11.1 and 11.6 μ (Table II). Unfortunately,

TABLE II

INFRARED SPECTRA

Substance	Infrared absorption, microns[a]			Dispersing medium
II	7.9	11.1	11.6	U.S.P. $CHCl_3$[b]
2-Acetoxymethyl-3,4,-5,6-tetra-*O*-acetyl-1,2-anhydro-L-iditol (gulitol?)	7.9	11.1	11.6	U.S.P. $CHCl_3$[b]
IV	7.9	11.1	11.6	Nujol mull
III	..	11.3	..	Nujol mull
VII	7.9	..	11.5	U.S.P. $CHCl_3$[b]

[a] Infrared recording spectrophotometer, model B, Baird Associates, Inc., Cambridge, Mass. [b] Compensated; United States Pharmacopoeia chloroform, containing ethanol.

these absorption regions are ambiguous since alcohols may exhibit absorption in the 7.4–7.9 μ region,[18] acetates exhibit a characteristic absorption in the 8 μ region,[19] and pyranoses in general will show absorption in the 11–12 μ region.[20] These results illustrate the difficulties inherent in the interpretation of the infrared spectra of polyfunctional compounds.

Experimental

2-Acetoxymethyl-3,4,5,6-tetra-*O*-acetyl-1,2-anhydro-D-glucitol (mannitol?) (II). (a) **From *keto*-D-Fructose Pentaacetate.**[21]—The diazomethane generated by the decomposition of 10 ml. of ethyl *N*-methyl-*N*-nitrosocarbamate[22] (2 molar ratio) was distilled in an ether stream through a spiral, reflux condenser directly into an absolute chloroform solution (containing 1–2 ml. of methanol) of 17 g. of *keto*-D-fructose pentaacetate[23] cooled to 0–5°. There was a steady and

(13) F. A. Long and J. G. Pritchard, THIS JOURNAL, **78**, 2663 (1956); J. G. Pritchard and F. A. Long, *ibid.*, **78**, 2667 (1956).

(14) A. J. Durbetaki, *J. Am. Oil Chemists' Soc.*, **33**, 221 (1956).

(15) F. Shafizadeh and A. Thompson, *J. Org. Chem.*, **21**, 1059 (1956).

(16) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954, pp. 99–104.

(17) W. A. Patterson, *Anal. Chem.*, **26**, 823 (1954).

(18) Reference 16, p. 84.

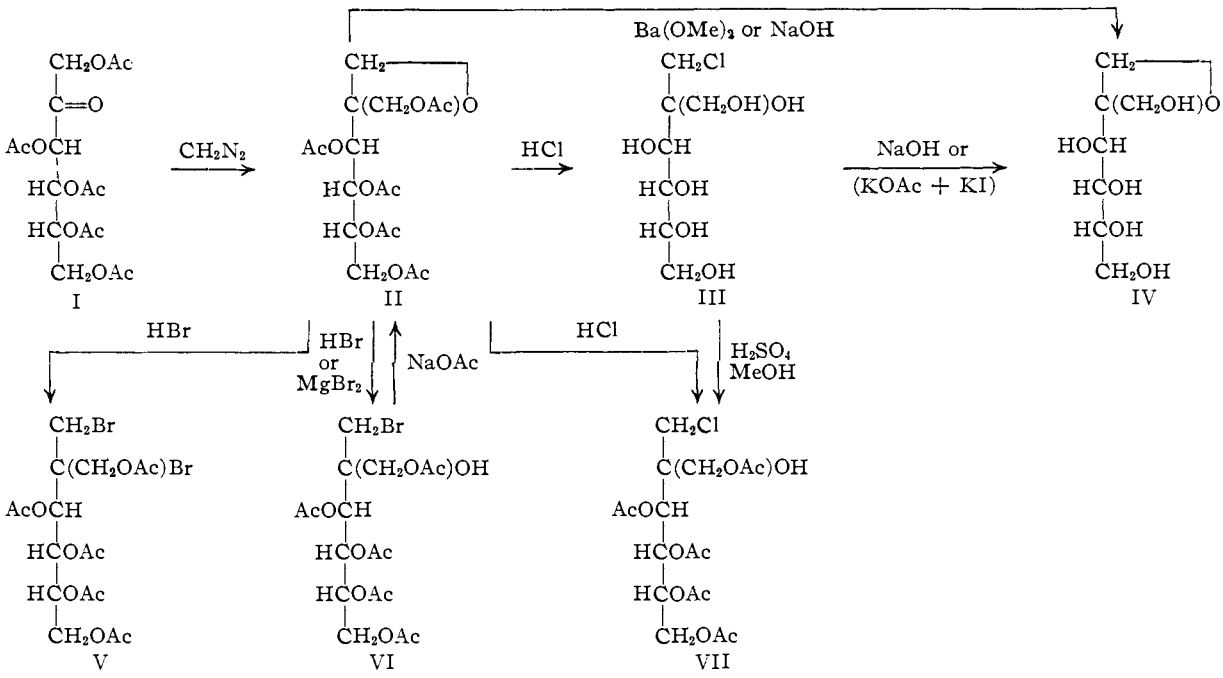
(19) H. W. Thompson and P. Torkington, *J. Chem. Soc.*, 640 (1945).

(20) S. A. Barker, E. J. Bourne, R. Stephens and D. H. Whiffen, *ibid.*, 3468, 4211 (1954).

(21) Experimental work by D. I. Weisblat.

(22) H. von Pechmann, *Ber.*, **27**, 1888 (1894).

(23) C. S. Hudson and D. H. Brauns, THIS JOURNAL, **37**, 2736 (1915); F. B. Cramer and E. Pacsu, *ibid.*, **59**, 1148 (1937).



vigorous evolution of nitrogen as the reaction progressed. The permanent yellow color of diazomethane was attained when about 60% of the total quantity had been added. Upon standing overnight at room temperature the solution became colorless. The solvent was removed by concentration under reduced pressure and the resultant sirup was dissolved in ether and the solution again concentrated whereupon crystallization occurred. The semi-crystalline mass was dissolved in 15 ml. of absolute ethanol and crystallized by the addition of 15 ml. of dry ether by cooling at 15°; yield 15.48 g. (88%), m.p. 80–84°, $[\alpha]^{23}D$ +40.4° (*c* 3, abs. $CHCl_3$). The crude product was reducing toward Fehling solution. Pure material was obtained after four crystallizations from 5 parts of an ethanol–ether mixture (1/1.5); yield 75%, m.p. 86–87°, $[\alpha]^{24}D$ +32° (*c* 3, abs. $CHCl_3$).

The substance showed no reduction toward Fehling solution, showed no coloration on heating with a methanolic solution of potassium hydroxide but reduced Tollens reagent in pyridine solution. It showed no acid consumption under the conditions of the epoxide assay of Durbetaki.[14] It exhibited the characteristic solubilities of a sugar acetate and was soluble in ethanol, methanol, acetone, pyridine and chloroform. It was only moderately soluble in ether and was insoluble in petroleum ether and water.

Anal. Calcd. for $C_7H_9O_6(CH_3CO)_5$: C, 50.49; H, 5.98; CH_3CO, 53.2. Found: C, 50.40; H, 6.06; CH_3CO, 53.2.

(b) From **2-Acetoxymethyl-3,4,5,6-tetra-*O*-acetyl-1-bromo-1-deoxy-D-glucitol (mannitol?) (VI).**—To a solution of 100 mg. of the bromohydrin VI in 60 ml. of ethanol was added 30 mg. of freshly fused sodium acetate. After refluxing for 1 hr. the solvent was removed under reduced pressure. The residue was extracted with chloroform and the chloroform removed under reduced pressure to yield a sirup. The sirup was dissolved in benzene and the solvent again removed under reduced pressure to yield a sirup which slowly crystallized. Recrystallization from benzene–petroleum ether (b.p. 30–60°) gave 50 mg. (60%) of crystals, m.p. 84–86° undepressed on admixture with authentic epoxide II.

2-Acetoxymethyl-3,4,5,6-tetra-*O*-acetyl-1,2-anhydro-L-iditol (gulitol?).[24]—An amount of 17 g. of *keto*-L-sorbose pentaacetate[25] was treated with ethereal diazomethane as described above for *keto*-D-fructose pentaacetate and the resultant crude sirup, isolated in the same manner, was dissolved in 150 ml. of ether and maintained at 15°. A small amount of material crystallized (0.35 g.), which was identified as starting substance. The solution was filtered, concentrated, and dissolved in a minimum of hot abs. ethanol. Crystallization ensued on standing at 15°; yield 14.95 g. (85%), m.p. 61–65°, $[\alpha]^{25}D$ −28.6° (*c* 3, abs. $CHCl_3$).

The crude product was reducing toward Fehling solution. Pure material was obtained after five recrystallizations from dry ether; yield 12.5 g. (71%), m.p. 64–66°, $[\alpha]^{25}D$ −27.5° (*c* 3, abs. $CHCl_3$).

The pure substance showed no reduction toward Fehling solution and no coloration on heating with methanolic potassium hydroxide, but reduced Tollens reagent (pyridine solution). It was inert toward the epoxide assay of Durbetaki.[14] The substance was soluble in ethanol, methanol, acetone, pyridine and chloroform. It was moderately soluble in ether and was insoluble in petroleum ether and water.

Anal. Calcd. for $C_7H_9O_6(CH_3CO)_5$: C, 50.49; H, 5.98; CH_3CO, 53.2. Found: C, 50.47; H, 6.00; CH_3CO, 53.0.

The reactions which led to crystalline derivatives with the corresponding substance obtained from *keto*-D-fructose pentaacetate, gave only sirupy products when applied to this substance.

2-Acetoxymethyl-3,4,5,6-tetra-*O*-acetyl-1-chloro-1-deoxy-D-glucitol (mannitol?) (VII).—To a solution of 500 mg. of the epoxide II in 1.8 ml. of acetic acid was added 6 ml. of acetic acid nearly saturated with hydrogen chloride. The mixture was allowed to stand at 15° for 23 hr. and then at room temperature for 1.5 hr. The solution was poured into 30 ml. of a saturated aqueous sodium bicarbonate solution followed by the addition of small portions of solid sodium bicarbonate until the solution was neutral to litmus. The solution was extracted with four 10-ml. portions of chloroform, the combined extracts were dried with sodium sulfate, filtered and the solvent removed under reduced pressure. The resultant sirup crystallized on scratching. Recrystallization was effected from benzene–petroleum ether (b.p. 30–60°); yield 260 mg., m.p. 82–85.5°. Pure material was obtained after two recrystallizations from ether–petroleum ether (b.p. 30–60°); m.p. 85–87°, $[\alpha]^{24.5}D$ +37.0° (*c* 2.1, $CHCl_3$); X-ray powder diffraction data: $9.46^{26}s^{27}$, 7.78w, 6.73s, 5.72w, 5.08vw, 4.68s, 4.48vw, 3.95s, 3.72s, 3.55vw.

Anal. Calcd. for $C_{17}H_{25}O_{11}Cl$: C, 46.32; H, 5.73; Cl, 8.04. Found: C, 46.34; H, 5.72; Cl, 7.92.

The nearly identical melting points of II and VII, and of III and IV, suggested the possibility of epoxide formation on heating the halohydrins. This was shown not to be the case by bringing a sample of VII to a full melt which then slowly

(24) Experimental work by A. R. Hanze.

(25) H. H. Schlubach and J. Vorwerk, *Ber.*, **66**, 1251 (1933); F. B. Cramer and E. Pacsu, THIS JOURNAL, **59**, 1467 (1937).

(26) Interplanar spacing, Å., $CuK\alpha$ radiation.

(27) Relative intensity, estimated visually; vs, very strong; s, strong; m, medium; w, weak; vw, very weak.

crystallized at room temperature. This melted material had: (a) the same melting point as before melting; (b) an undepressed mixed melting point with fresh VII; and (c) a large depression (m.p. 65–85°) on admixture with II.

1-Chloro-1-deoxy-2-hydroxymethyl-D-glucitol(mannitol?) (III). (a) **From 2-Acetoxymethyl-3,4,5,6-tetra-*O*-acetyl-1,-2-anhydro-D-glucitol(mannitol?) (II).**—An amount of 1.52 g. g. of the acetylated epoxide II was covered with 50 ml. of a 1% methanolic hydrogen chloride solution. After standing for 3 days at 5° all but a trace of material was in solution. The solvent was removed under reduced pressure at 60°. The resultant sirup was dissolved in ethanol and the solvent was removed as before. This treatment was repeated, followed by a similar one using benzene. The sirup was dissolved in water and the solution was brought to neutrality with silver carbonate. After filtration, treatment with hydrogen sulfide, and refiltering, a neutral solution was obtained which gave a sirup upon solvent removal under reduced pressure. Crystallization was induced by the addition of a little ethanol and cooling at 5°. After thorough washing with ethanol, the crystals had m.p. 126° dec. A second crop was obtained from the combined washings and mother liquor; m.p. 107–122° dec. The first crop of crystals was recrystallized from ethanol; yield 210 mg., m.p. 127.5–130° dec.

Paper chromatography of this crude material, using butanol:ethanol:water (40:11:19 by vol.) as developer and sodium periodate–potassium permanganate-benzidine[28] as the indicator, revealed two spots: R_{glue} 1.4 (very faint) and 1.9 (intense with tailing). For the purpose of interpreting the analytical results, a ternary mixture was assumed whose components represented opening of the epoxide ring by hydrogen chloride, methanol and water, the products being RCl, ROMe and ROH (deacetylated in each case).

Anal. Calcd. for N_{RCl} = 0.9068, N_{ROMe} = 0.0905 and N_{ROH} = 0.0027: C, 37.00; H, 6.69; Cl, 13.97; OMe, 1.22. Found: C, 36.93; H, 6.94; Cl, 13.97; OMe, 1.22.

In a succeeding preparation using 5 g. of starting material and omitting the silver carbonate treatment, 2.16 g. of product (m.p. 122–130° dec.) was obtained from the strongly acidic sirup by adding a little ethanol, seeding, and refrigerating overnight. This material gave three spots on paper chromatography (as described above): R_{glue} 0.95 (very faint), 1.5 (faint) and 1.9 (large and intense). This material was chromatographed[29,30] on a 3 × 59 cm. powdered cellulose (Whatman, standard grade) column. The column had been prewashed continuously for 2 weeks with the butanol: ethanol: water (40:11:19 by vol.) developer and its performance was checked by the separation of dyes.[29] Methyl violet was placed on the column with the sample to serve as a marker for the solvent front. Fractions were collected every 23 min. (about 5 ml.) after the methyl violet had been eluted from the column. This forerun, containing methyl violet, gave a negative Beilstein halogen test. Fractions 1 through 19 gave positive Beilstein tests. Fractions 20 and beyond gave negative Beilstein tests and the presence of material was detected by spotting a sample on paper and spraying with sodium periodate–potassium permanganate–benzidine indicator.[28] With this indicator fractions 20 through 27 were negative, fractions 28 through 36 weakly positive, and fractions 37 through 76 negative. Fractions 28 through 76 were combined and the solvent was removed under reduced pressure to yield a sirup, R_{glue} = 0.92, which has resisted crystallization but is believed, from other methods of synthesis, to be the product obtained by opening of the epoxide ring with water.

Fractions 1–19 were combined and the solvent was removed under reduced pressure to yield a crystalline product, m.p. 120–125° dec. Recrystallization was effected from hot methanol; yield 870 mg., m.p. 127–130° dec., R_{glue} 1.9 and 1.6 (very weak). Recrystallization from hot 1-butanol:ethanol:water (40:11:19 by vol.) followed by recrystallization from hot ethanol gave pure material, m.p. 132.5–133°, $[\alpha]^{25}D$ −8.5°(*c* 4.1, $CHCl_3$), chromatographically homogeneous on paper (using developer previously cited), R_{glue} 1.89. The periodate assay of the substance is given in Table I. The compound crystallized as white needles with a very sweet, then bitter, taste; it was soluble in water, methanol and hot ethanol and was insoluble in acetone and ether.

Anal. Calcd. for $C_7H_{15}O_6Cl$: C, 36.44; H, 6.57; Cl, 15.37. Found: C, 36.41; H, 6.53; Cl, 15.42.

(b) **From 2-Acetoxymethyl-3,4,5,6-tetra-*O*-acetyl-1-chloro-1-deoxy-D-glucitol (mannitol?) (VII).**—To a solution of 200 mg. of the chlorohydrin acetate VII in 30 ml. of methanol, was added 1 drop of dilute sulfuric acid (1:1 by vol.). The mixture was allowed to stand at 15° for 9 days and was then neutralized with IR-4B ion exchange resin[31] and the solvent was removed under reduced pressure to yield a sirup which, when covered with methanol and refrigerated, slowly deposited crystals, m.p. 123° dec. Recrystallization was effected from 1-butanol:ethanol:water (40:11:19 by vol.) and then from ethanol; yield 10 mg., m.p. 128.5° dec., m.p. 130° on admixture with authentic III of m.p. 132.5–133°, R_{glue} value identical with that of III on paper chromatography.

1,2-Anhydro-2-hydroxymethyl-D-glucitol(mannitol?) (IV). (*a*) **From 2-Acetoxymethyl-3,4,5,6-tetra-*O*-acetyl-1,-2-anhydro-D-glucitol(mannitol?) (II) with Barium Methoxide.**[21]—An amount of 500 mg. of the acetylated epoxide II was dissolved in 6 ml. of methanol and the solution was cooled to room temperature. A volume of 0.5 ml. of 0.42 *N* barium methoxide (0.05 ml. calcd.) was added and the whole allowed to stand overnight at 15°. The solution was then saturated with carbon dioxide and after the addition of 2 ml. of water, again saturated with carbon dioxide. The reaction mixture was then heated to boiling and held at this temperature for several minutes. The barium carbonate precipitated and was removed by filtration. The solvent was removed by concentration and the sirupy residue was dissolved in the minimum of abs. ethanol and again filtered. The product crystallized in beautiful, transparent, rectangular prisms on cooling; yield 60 mg., m.p. 134–136°. Pure material was obtained on recrystallization from the minimum of water by the addition of 2 volumes of ethanol; m.p. 136°, $[\alpha]^{25}D$ −13° (*c* 3.1, H_2O).

This substance had a very sweet, then bitter, taste, showed no reduction toward Fehling solution, developed no color with a warm methanolic solution of potassium hydroxide, but reduced Tollens reagent. The substance was soluble in water and pyridine but was insoluble in ethanol, chloroform and ether.

Anal. Calcd. for $C_7H_{14}O_6$: C, 43.29; H, 7.22. Found: C, 43.37; H, 7.40.

(*b*) **From 2-Acetoxymethyl-3,4,5,6-tetra-*O*-acetyl-1,2-anhydro-*D*-glucitol(mannitol?) (II) with Sodium Hydroxide.**—To 20 ml. of water containing 2 g. of sodium hydroxide was added 2 g. of the epoxide acetate II. The mixture was heated to boiling until solution resulted and then was maintained for 18 hr. at room temperature. Neutralization of the solution with MB-1 resin,[31] followed by removal of the solvent under reduced pressure, yielded a sirup which crystallized on scratching. This material was recrystallized from boiling methanol; yield 220 mg., m.p. 133–135.5°, mixed m.p. with authentic IV undepressed, identical R_{glue} value with that for authentic IV.

(*c*) **From 1-Chloro-1-deoxy-2-hydroxymethyl-D-glucitol-(mannitol?) (III) with Sodium Hydroxide.**—To 0.44 ml. of water containing 40 mg. of sodium hydroxide was added 110 mg. of the chlorohydrin III. The solution was allowed to stand for 1 day at room temperature at the end of which time the solution gave a positive halide test. Deionization of the solution with MB-1 resin[31] gave a clear, colorless solution which gave a faintly positive Beilstein halogen test. Removal of the solvent under reduced pressure at 100° gave a sirup which crystallized on vigorous scratching. Recrystallization was effected from hot methanol; yield 25 mg., m.p. 133.5–136°, mixed m.p. with authentic IV undepressed, negative Beilstein halogen test.

(*d*) **From 1-Chloro-1-deoxy-2-hydroxymethyl-D-glucitol-(mannitol?) (III) with Potassium Acetate and Potassium Iodide.**—To 10 ml. of abs. methanol containing 50 mg. of freshly fused potassium acetate and one very small crystal of potassium iodide, was added 110 mg. of the chlorohydrin III. The solution was refluxed for 1.25 hr. and then maintained overnight at room temperature. Deionization of the solution with MB-1 resin,[31] followed by removal of the solvent under reduced pressure, yielded a sirup which gave a negative Beilstein halogen test. The sirup was dissolved in

(28) M. L. Wolfrom and J. B. Miller, *Anal. Chem.*, **28**, 1037 (1956).

(29) L. Hough, J. K. N. Jones and W. H. Wadman, *J. Chem. Soc.*, 2511 (1949).

(30) J. Augestad and E. Berner, *Acta Chem. Scand.*, **8**, 251 (1954).

(31) A product of the Rohm and Haas Company, The Resinous Products Division, Washington Square, Philadelphia, Pa.

ethanol and benzene was added to incipient crystallization; yield 20 mg., m.p. 128–133°, 109–125° dec. on admixture with starting material, m.p. 130–136° on admixture with authentic IV, R_{glue} identical with that of authentic IV.

2-Acetoxymethyl-3,4,5,6-tetra-*O*-acetyl-1-bromo-1-deoxy-D-glucitol(mannitol?) (VI). (*a*) **With Hydrogen Bromide in Acetic Acid.**—To a solution of 2 g. of the epoxide acetate II in 3 ml. of acetic acid was added 3 ml. of acetic acid nearly saturated with hydrogen bromide. After 2 min. at room temperature, the solution was poured slowly into 40 ml. of a saturated aqueous sodium bicarbonate solution. Solid sodium bicarbonate was added in small portions until the solution was slightly basic to litmus. This mixture was extracted with three 10-ml. portions of chloroform, the combined extracts dried with sodium sulfate and the solvent removed under reduced pressure to yield a thin sirup. Solution in benzene followed by removal of the solvent under reduced pressure gave a sirup which crystallized spontaneously. Recrystallization was effected from ether–petroleum ether (b.p. 30–60°); yield 1.06 g., m.p. 91–98°. Two additional recrystallizations from ether–petroleum ether (b.p. 30–60°) gave pure material, m.p. 99–101° unchanged on recrystallization from methanol, $[\alpha]^{24}D$ +30.9° (*c* 3.9, $CHCl_3$); X-ray powder diffraction data: 11.22[26] vw[27], 9.46w, 7.78w, 6.76s, 5.69vw, 4.68w, 4.47vw, 3.97m, 3.73s, 3.10m.

Anal. Calcd. for $C_{17}H_{25}O_{11}Br$: C, 42.07; H, 5.19; Br, 16.46. Found: C, 41.97; H, 5.15; Br, 17.01.

(*b*) **With Magnesium Bromide.**—To prepare active magnesium bromide,[8b] an excess of ethylene bromide was added to 10 mg. of magnesium in 50 ml. of benzene–ether (1–1 by vol.). After all the magnesium had dissolved, 200 mg. of the epoxide acetate II was added and the solution was stirred overnight at room temperature. An equal volume of water was added, the ether layer separated, and the aqueous layer was extracted with 20 ml. of chloroform. The combined ether and chloroform extracts were dried with sodium sulfate and the solvent was removed under reduced pressure to yield a sirup. Solution in benzene followed by solvent removal as before gave a sirup which crystallized spontaneously; yield 0.105 g., m.p. 96.5–98°, mixed melting point with authentic bromohydrin acetate VI undepressed, strong positive Beilstein halogen test.

2-Acetoxymethyl-3,4,5,6-tetra-*O*-acetyl-1,2-dibromo-1,2-dideoxy-D-glucitol(mannitol?) (V).—The preparation of this compound follows that of the bromohydrin acetate VI part (a), except that 6 ml. of acetic acid saturated with hydrogen bromide was used with a reaction time of 21 hr. at about 10°. After slowly pouring the reaction mixture into 40 ml. of saturated aqueous sodium bicarbonate solution, solid sodium bicarbonate was added in small portions until the solution was no longer acidic to congo red paper but was still acidic to litmus paper. The frothy white gum, initially formed, became crystalline on thorough trituration. Filtration was followed by washing with water until the filtrate was no longer acidic to litmus paper; yield 2.39 g., m.p. 79–82°. Two recrystallizations were effected from ether–petroleum ether (b.p. 30–60°) (a small amount of the bromohydrin acetate VI may be obtained from the mother liquors); m.p. 81–84°, $[\alpha]^{24}D$ +35.0° (*c* 3.3, $CHCl_3$), whose melting point range was unchanged on recrystallization from hot 1,2-dimethoxyethane.

Anal. Calcd. for $C_{17}H_{24}O_{10}Br_2$: C, 37.24; H, 4.41; Br, 29.16. Found: C, 37.94; H, 4.94; Br, 28.65.

On attempted recrystallization of this compound from hot methanol, sirups were obtained except on one occasion when a small amount of a solid was obtained, m.p. 126° dec., strongly positive Beilstein halogen test. This material was not further characterized.

2-Acetoxymethyl-3,4,5,6-tetra-*O*-acetyl-1-chloro-1-deoxy-D-iditol(gulitol?).—An amount of 1 g. of the epoxide acetate, obtained, as described above, from *keto*-L-sorbose pentaacetate, was treated with an acetic acid solution of hydrogen chloride as described above for the corresponding derivative II from *keto*-D-fructose pentaacetate except that the reaction mixture was maintained at room temperature for 4 min. The resultant crude, sirupy product was isolated in the same manner. This sirup was divided in half and each half was chromatographed on a Magnesol[32]–Celite[33] (5–1 by wt.) column (17.5 × 3.5 cm., diam.) using 350 ml. of benzene–*tert*-butyl alcohol (100–1 by vol.) as developer. Extrusion of the columns and streaking with alkaline permanganate indicator revealed a single large zone located 1–8 cm. from the column top. The zones from the two columns were dissected, combined, and eluted with acetone. On evaporation of the solvent a yellow sirup was obtained. This sirup was divided into thirds and each third was chromatographed as before except that 700 ml. of developer was used for each column. Alkaline permanganate indicator (1% potassium permanganate in 2.5 *N* sodium hydroxide) revealed a single zone on each column located 7–11 cm. from the column top. The bottom half of each of these zones was dissected, combined, and eluted with acetone. Removal of the solvent under reduced pressure gave a yellow sirup. The sirup was decolorized by two treatments with Darco G60[34] in ethanol and then dried at 78° in vacuum over phosphorus pentoxide; yield 110 mg., $[\alpha]^{24}D$ +14.2° (*c* 4.3, $CHCl_3$).

Anal. Calcd. for $C_{17}H_{25}O_{11}Cl$: C, 46.32; H, 5.73; Cl, 8.04. Found: C, 46.57; H, 5.52; Cl, 8.54.

(32) A product of the Westvaco Chemical Division of Food Machinery and Chemical Corp., South Charleston, W. Va.

(33) A siliceous filter-aid produced by the Johns-Manville Co., New York, N. Y.

(34) An activated carbon produced by the Darco Corporation, 60 East 42nd Street, New York, N. Y.

COLUMBUS 10, OHIO

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF G. D. SEARLE AND CO.]

7-Keto Steroids. I. Steroidal 3-Hydroxy-3,5-dien-7-ones

BY C. W. MARSHALL, RICHARD E. RAY, IVAR LAOS AND BYRON RIEGEL

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A series of steroidal 3-hydroxy-3,5-dien-7-ones was prepared for evaluation as anti-cortisone agents. Of the compounds studied, 7-keto-desoxycorticosterone 21-acetate appears to have the greatest biological interest. Two synthetic routes were employed. 3β-Hydroxyandrost-5-ene-7,17-dione and 3β-hydroxypregn-5-ene-7,20-dione were subjected to Oppenauer oxidation for 30 minutes; whereas the other members of the series were made by *t*-butyl chromate oxidation of the corresponding Δ^5-3-ethylene ketal with subsequent ketal cleavage.

Early in 1953 our Division of Biological Research reported that 7-ketocholesterol possessed marked anti-cortisone properties but caused toxic effects in animals. Accordingly we embarked on a concerted effort to explore this area of steroid chemistry which had long lain fallow. There were at that time few 3-hydroxy Δ^5-7-keto steroids reported in the literature, and we have since added a number of new members to this series which are concurrently reported in Paper II.[1] However, when this program was initiated in our laboratories, the chemical literature revealed only one example

(1) C. W. Marshall, Richard E. Ray, Ivar Laos and Byron Riegel, THIS JOURNAL, **79**, 6308 (1957).