0.04 mole, m.p. 124–125°[11]) in dioxane (5.0 ml.) cooled in an ice bath was added 40% aqueous dimethylamine (9.1 g., 0.08 mole).

Then 38% aqueous formaldehyde (6.4 g., 0.08 mole) was added drop by drop to the previous mixture with stirring while keeping the temperature between 0–5°. The reaction mixture was allowed to stand in an ice–salt bath for 2 or 3 days, and the crude 2-methyl-3,6-bis(dimethylaminomethyl)hydroquinone was obtained in a yield of 6.0–6.9 g. (62–72%) as a light brown solid. It was readily soluble in cold water and organic solvents. By concentrating the ethereal solution of the crude product at room temperature, under reduced pressure, the di-Mannich base crystallized as colorless needles, m.p. 97–99°.

Infrared, 3300–2000 (cm.$^{-1}$) ν str. OH; 1042 (cm.$^{-1}$) ν asym. $N^{CH_3}_{CH_3}$; 990.1 (cm.$^{-1}$) ν sym. $N^{CH_3}_{CH_3}$; 902.5 (cm.$^{-1}$), 816.3 (cm.$^{-1}$), 752.4 (cm.$^{-1}$) ν C–N, ν C–C; 873.4 (cm.$^{-1}$), 863.6 (cm.$^{-1}$) ν arom. C–H; 1192 (cm.$^{-1}$), 1181 (cm.$^{-1}$), 1160 (cm.$^{-1}$), 1103 (cm.$^{-1}$), 1024 (cm.$^{-1}$) ν arom. C–H; 1195 (cm.$^{-1}$), 1182 (cm.$^{-1}$), 1161 (cm.$^{-1}$) ν C–O.

Anal. Calcd. for $C_{13}H_{22}O_2N_2$: C, 65.54: H, 9.24: N, 11.76. Found C, 65.36: H, 9.14: N, 11.60.

Trimethylhydroquinone (III).—2-Methyl-3,6-bis(dimethylaminomethyl)hydroquinone (II, 2.3 g., 0.01 mole) in dioxane (25 ml.) was hydrogenolized in the presence of copper chromium oxide[12] (3.0 g.) under an initial hydrogen pressure (146 atm.) at 160° for 4 hr. After opening the bomb, the catalyst was removed by filtration, and the solvent distilled. A solution of concentrated hydrochloric acid (3 ml.) in water (14 ml.) was added to the residue. The mixture was saturated with sodium sulfate and extracted with ether three times and the extract was dried with calcium chloride. After removing the ether, the solid residue (0.8 g., 58% yield) was recrystallized from water, m.p. 167–168° (lit.[13] m.p. 170°).

Anal. Calcd. for $C_9H_{12}O_2$: C, 71.05: H, 7.89. Found C, 70.85: H, 7.85.

3,5-Dimethyl-2-dimethylaminomethylhydroquinone (V).—Dimethylamine (40% aqueous, 3.5 g., 0.03 mole) was added to a solution of recrystallized 3,5-dimethylhydroquinone (IV, 4.2 g., 0.03 mole, m.p. 150–151°[7]) in ethanol (6.0 ml.) at room temperature (15–20°). Then 38% aqueous formaldehyde (2.5 g., 0.03 mole) was added drop by drop to preceding mixture with stirring while keeping the temperature between 15–20°. The oily layer, upon cooling in the ice–salt bath for a day, solidified to light brown crystals (4.0–4.5 g., 70–75% yield). They were insoluble in water or organic solvents and could not be purified by recrystallization. By washing with the ether several times, the mono-Mannich base was obtained as white needles, m.p. 102–103°.

Anal. Calcd. for $C_{11}H_{16}O_2N$: C, 67.66: H, 8.78: N, 7.19. Found C, 67.60: H, 8.57: N, 7.49.

Trimethylhydroquinone (III).—3,5-Dimethyl-2-dimethylaminomethylhydroquinone (V, 2.0 g., 0.01 mole) in dioxane (20 ml.) was hydrogenolized in the presence of copper chromium oxide[12] (3 g.) under an initial hydrogen pressure of 146 atm. at 160° for 4 hr. After opening the bomb, the catalyst was removed by filtration, and the solvent distilled. A solution of concentrated hydrochloric acid (3 ml.) in water (20 ml.) was added to the residue. The mixture was saturated with sodium sulfate and extracted with ether three times, and the extract was dried with calcium chloride. After removing the ether, the solid residue (0.9 g., 60% yield) was recrystallized from water, m.p. 168–169° (lit.[13] m.p. 170°).

Anal. Calcd. for $C_9H_{12}O_2$: C, 71.05: H, 7.89. Found C, 70.88: H, 7.91.

Acknowledgment.—The authors wish to express gratitude to Dr. Kuroiwa and the staff of the Tekkosha Company for measurements of infrared spectra. The authors are also grateful to Mr. G. Shioya and Mr. K. Kurihara of our laboratory for their great help in carrying out the study presented in this report.

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D-*gluco*-L-*glycero*-3-Octulose, a Crystalline Ketose from D-Erythrose

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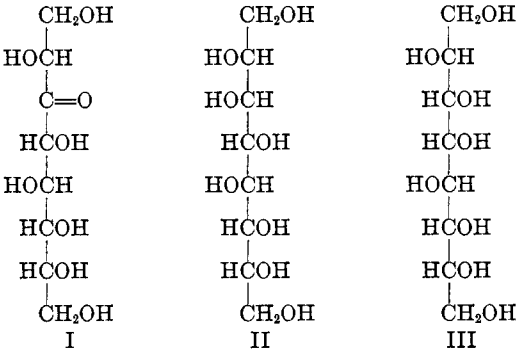
Received February 4, 1963

Our continuing studies of syntheses of higher, branched-chain aldoses[1] and higher ketoses[2] by aldol reactions have now led to discovery of the title compound (I), which is readily obtained from D-erythrose. Chromatography was used at first to obtain the crystalline product, but, in subsequent preparations, I was isolated directly from the reaction mixture in a yield of 16%. Compound I reduces Benedict solution, and, on chromatography, the new sugar travels slightly more slowly than D-glucose. It is readily visible with silver nitrate and sodium hydroxide sprays.

That compound I might be a branched-chain octose, *e.g.*, a 3-*C*-formylheptitol related to the aldols obtained with aldose reactants,[1] was ruled out by the stability it shows to hypoiodite oxidation. That it is, instead, a ketose follows from the isolation of two crystalline octitols after reduction. One of these octitols (II) is a new compound, but the other proved to be D-*erythro*-L-*galacto*-octitol (III), a known substance.[3] Acetylation of compound III gives an acetate identical with D-*erythro*-L-*galacto*-octitol octaacetate.[3c,d]



The normal-chain structure of III shows that a ketose having a carbonyl group at C-3 must have been produced by an aldol reaction in which carbon atom 1 of an enolized tetrose molecule had attacked the carbonyl carbon atom of a second molecule of tetrose; thus, carbon atoms 1 to 4 of a molecule of "D-erythrose-1,2-enediol" become carbon atoms 4 to 1 at the reducing end of the 8-carbon ketose, and carbon atoms 1 to 4 of a molecule of D-erythrose become the remainder, namely, carbons 5 to 8, respectively. The configurations of the asymmetric carbon atoms of such a ketose should be the same as they were in the reactants at C-2, C-6, and C-7, and, according to earlier studies of aldol syntheses of ketoses,[2] should be *threo* at C-4 and C-5.

(1) (a) R. Schaffer and H. S. Isbell, *J. Am. Chem. Soc.*, **80**, 756 (1958); (b) **81**, 2178 (1959); (c) R. Schaffer, *ibid.*, **81**, 2838 (1959); (d) **81**, 5452 (1959).

(2) R. Schaffer and H. S. Isbell, *J. Org. Chem.*, **27**, 3268 (1962).

(3) (a) E. Fischer, *Ann.*, **270**, 95, 101 (1892); (b) L. H. Philippe, *Ann. chim. phys.*, **26**, 356 (1912); (c) R. M. Hann, Alice T. Merrill, and C. S. Hudson, *J. Am. Chem. Soc.*, **66**, 1912 (1944); (d) the authors are indebted to N. K. Richtmyer for a sample of this compound.

In compound III, the configurations of its carbon atoms confirm those expectations, and, from this, the structure of the aldol product could be predicted to be that of I. However, in the alkaline medium in which it is formed, such a compound theoretically might isomerize to other octuloses[4] that would be reduced to compound III. All of these possibilities were eliminated by degrading compound I with an equimolecular proportion of periodic acid,[5] and finding D-arabinose and D-glucono-1,5-lactone among the products. No octulose structure other than that proposed for compound I can give both products; and, of the remaining 5 ketoses, the 2-octulose could give only D-arabinose. Furthermore, compound I cannot be this 2-octulose, D-*glycero*-D-*gulo*-octulose, for it is a known substance[6] whose properties are different from those of I. Thus, the new sugar has structure I; and compound II, the new octitol, is D-*erythro*-L-*gulo*-octitol.

The readiness with which D-erythrose undergoes aldol reaction to afford compound I makes it seem odd that the new sugar (or its phosphate) has not yet been observed in biological systems. Perhaps, this nondetection is due to its low sensitivity to the orcinol–trichloroacetic acid spray, which produces a faint gray spot on paper chromatograms; however, under ultraviolet light a resulting yellow-orange fluorescence can be detected more readily. D-*manno*-3-Heptulose, which has been synthesized[1c] and crystallized,[7] reacts analogously. This behavior may be characteristic of 3-ketoses.

Further work on this and related aldol syntheses is in progress. Additional details will be published later.

Experimental

D-*gluco*-L-*glycero*-**3-Octulose** (I).—A solution of 2.4 g. of D-erythrose (prepared from 2,4-*O*-ethylidene-D-erythrose[1c]) in 200 ml. of a filtered, saturated solution of calcium hydroxide (prepared at 5°) was kept at room temperature until a maximum dextrorotation was reached (about 2 hr.), and then treated with excess carbon dioxide, filtered, and concentrated under reduced pressure. After removal of an additional precipitate, the concentrate was taken up in methanol, from which compound I crystallized; yield 16%, m.p. 164–165°, $[\alpha]^{26}D$ +59.3° (*c* 10, water), no mutarotation observed.

Anal. Calcd. for $C_8H_{16}O_8$: C, 40.0; H, 6.7. Found: C, 39.8; H, 6.7.

On being paper chromatographed, I traveled only a little more slowly than D-glucose in 1-butanol–ethanol–water (40:11:19) and in 1-butanol–pyridine–water (6:4:3). It reacts readily with silver nitrate and sodium hydroxide sprays, but poorly with orcinol and trichloroacetic acid (faint gray that is yellow-orange under ultraviolet light), and gives no reaction with aniline hydrogen phthalate.

Degradation with Periodic Acid.—At 0°, a solution of 5 mg. of compound I in 1 ml. of water was treated with 5 mg. of periodic acid. The mixture was allowed to warm to room temperature after 1 hr., and, an hour later, a sample was paper chromatographed using 1-butanol–ethanol–water (40:11:19) containing 1% of ammonium hydroxide. Aniline hydrogen phthalate spray gave a reddish pink color at a position corresponding to that for D-arabinose. The remainder of the oxidation mixture was neutralized with barium carbonate, treated with Amberlite IR-120 H^+, and concentrated under reduced pressure. The concentrate was dissolved in 2-methoxyethanol and reconcentrated, and this process was repeated several times. A sample of the concentrate was chromatographed in a solution of 1-butanol saturated with water and containing 2% of formic acid. Silver nitrate and sodium hydroxide sprays showed a spot corresponding to D-glucono-1,5-lactone. The 3-octulose and D-arabinose spots were near the spot for D-glucono-1,4-lactone, and this circumstance made difficult the positive identification of this D-gluconic acid derivative, too.

Reduction with Sodium Borohydride.—At 0°, a stirred solution of 1 g. of I in 50 ml. of water was treated with 1 g. of sodium borohydride, and allowed to warm to room temperature overnight. Excess borohydride was decomposed with Amberlite IR-120 H^+. Boric acid was removed by repeated evaporation with methanol; during this process, a new, crystalline material appeared. From the first crops, there was obtained D-*erythro*-L-*gulo*-octitol (II), m.p. 164.5–165°, $[\alpha]^{23}D$ 171° (in 5% ammonium molybdate[8]).

Anal. Calcd. for $C_8H_{18}O_8$: C, 39.7; H, 7.5. Found: C, 40.0; H, 7.7.

Acetylation with acetic anhydride in pyridine gave the octaacetate, m.p. 110–111°, $[\alpha]^{20}D$ 47° (*c* 0.4, chloroform).

Anal. Calcd. for $C_{24}H_{34}O_{16}$: C, 49.8; H, 5.9. Found C, 49.8; H, 5.8.

The mother liquor contained some of II, together with D-*erythro*-L-*galacto*-octitol (III). The latter was obtained crystalline from methanol–water. Its m.p. of 153–154°, undepressed mixture melting point, and the correspondence of its infrared spectrum with that of the authentic material[3c,d] established its identity. Its octaacetate, obtained from its interaction with acetic anhydride in pyridine, had m.p. 88–89°, an undepressed mixture melting point, and an identity of infrared spectrum with that of authentic D-*erythro*-L-*galacto*-octitol octaacetate.[3c,d]

Acknowledgment.—The authors express their appreciation to R. A. Paulson of this bureau for microanalyses.

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3,4,6-Tri-*O*-acetyl-2-*O*-nitro-α-D-glucopyranosyl Chloride and the Anomeric Tetraacetates of 2-*O*-Nitro-D-glucopyranose

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Received December 7, 1962

The synthesis of α-D-glucosides in a Koenigs–Knorr reaction[3] has been of great difficulty either because of the unavailability of stable poly-*O*-acyl-β-D-glucosyl halides or because of the tendency of these materials to react with hydroxylic compounds by a mechanism involving participation of the *trans* 2-*O*-acyl group in the displacement at C-1 leading to products of the β-D-configuration. Schlubach[4] prepared an unstable tetra-*O*-acetyl-β-D-glucopyranosyl chloride from the treatment of tetra-*O*-acetyl-α-D-glucopyranosyl bromide with "active" silver chloride. Lemieux and Brice[5] reported an improved synthesis of this material by the action of titanium tetrachloride on β-D-glucopyranose pentaacetate. The β-D-glucosyl chloride readily isomerized to the α-D-anomer and was thus unsuited for the synthesis of α-D-glucosides. Brigl[6] has shown that

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(2) Research Associate (A. T.) and Fellow of the Corn Industries Research Foundation.

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