pH was adjusted to 2.0, and the mixture was passed through a Dicalite-precoated filter. The aqueous layer was then extracted with 6.5 g. (0.0146 mole) of Aerosol OT in 80 ml. of methyl isobutyl ketone while the temperature was held at 0–5° and the pH held at 2.0. The organic layer was passed through a Dicalite-precoated filter and adjusted to a pH of 5.8 with triethylamine. Crystals of D-(−)-α-aminobenzylpenicillin sulfone separated. After stirring cold for 10 min. they were collected by filtration, washed with petroleum ether (b.p. 60–70°), and dried.

N,N'-Dibenzylethylenediamine Di-*dl*-α-phenoxyethylpenicillinate Sulfone.—This sulfone was prepared by the general procedure described before with these exceptions. The aqueous solution, after the manganese dioxide was removed, was mixed with 300 ml. of methyl isobutyl ketone, and the pH was adjusted to 2.0 with 10% phosphoric acid. The organic layer was dried over anhydrous sodium sulfate and, after the drying agent was removed, was treated with 4.2 g. (0.018 mole) of *sym*-dibenzylethylenediamine. The crystalline dibenzylethylenediamine salt of *dl*-α-phenoxyethylpenicillin sulfone precipitated almost immediately. After stirring cold for 1 hr., the mixture was filtered, washed with methyl isobutyl ketone and petroleum ether (b.p. 60–70°), and dried.

Synthesis of Trimethylhydroquinone

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It is known that tocopherols (vitamin E) are synthesized by condensation of trimethylhydroquinone with phytol[1] or its derivatives.[2–5]

Trimethylhydroquinone is an important starting material in synthesizing tocopherol. A number of investigations on the synthesis of trimethylhydroquinone have been carried out with 2,3,5-trimethylbenzene,[6] 2,3,5-trimethylphenol,[7] and 3,5-dimethylphenol[8] as the starting material.

Recently Burke[9] succeeded in a synthesis of trimethylhydroquinone from 4-benzyloxyphenol.

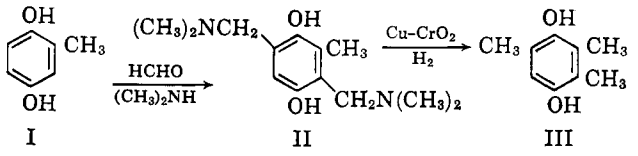
Caldwell and Thompson[8] prepared 3,5-dimethyl-2-dimethylaminomethylphenol by the condensation of 3,5-dimethylphenol with dimethylamine and formaldehyde, which was then converted into 2,3,5-trimethylphenol.

They also prepared 2,5-dimethylhydroquinone from 2,5-bis(dimethylaminomethyl)hydroquinone, obtained in the condensation of hydroquinone with dimethylamine and formaldehyde. However, efforts to obtain the required tris(dimethylaminomethyl)hydroquinone were not successful.

A new way of synthesizing trimethylhydroquinone presented in this paper comprises only two steps from 2-methylhydroquinone, which is the smallest in number ever attained in any procedures so far reported.

This investigation was carried out independently of the synthesis of trimethylhydroquinone from 4-benzyloxyphenol by Burke and co-workers.[9]

The conversion of 2-methylhydroquinone into trimethylhydroquinone involves the following steps.



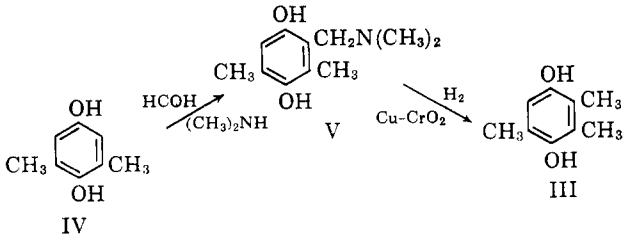
I II III

2-Methylhydroquinone (I) reacts smoothly with dimethylamine and formaldehyde to give 2-methyl-3,6-bis(dimethylaminomethyl)hydroquinone (II) in 72% yield.

The di-Mannich base (II), recrystallized from ether as colorless needles, is very unstable and upon heating or even exposure to air for a long time, polymerized to a dark brown sticky mass.

The base (II) was hydrogenolyzed in the presence of copper chromium oxide in dioxane at 180° under a pressure of about 140 atm. of hydrogen to trimethylhydroquinone (III) in 58% yield. From the fact that the base (II) shows a sharp melting point (97–99°) and no characteristic absorption band for the free phenolic group in the infrared spectrum, the position of the dimethylaminomethyl groups must be 3,6- or 5,6- and not a mixture, and from the point of the spacial effect it may be the 3,6-disubstituted compound as shown in II.

Similarly, 3,5-dimethylhydroquinone is converted into trimethylhydroquinone.



IV III

The condensation of 3,5-dimethylhydroquinone (IV) with dimethylamine and formaldehyde in dioxane under mild conditions gives 3,5-dimethyl-2-dimethylaminomethylhydroquinone (V) in 75% yield.

The hydrogenolysis of the mono-Mannich base (V) in dioxane gives trimethylhydroquinone (III) in 60% yield.

This represents a new and more practical synthesis of trimethylhydroquinone.

Experimental[10]

2-Methyl-3,6-bis(dimethylaminomethyl)hydroquinone (II).—To a solution of recrystallized 2-methylhydroquinone (I, 5.0 g.,

(1) P. Karrer, H. Salmon, and H. Fritzshe, *Helv. Chim. Acta*, **21**, 309 (1938); Hoffmann-La Roche and Co., Swiss Patent 212,353 (1941); P. Karrer and O. Isler, U. S. Patent 2,411,968 (1946); O. Ehrman, German Patent 1,015,446 (1958).

(2) Hoffman-La Roche and Co., Swiss Patent 208,446 (1940); P. Karrer and O. Isler, U. S. Patent 2,411,969 (1946).

(3) P. Karrer, R. Esher, H. Fritzsche, K. Keller, B. Ringier, and H. Salmon, *Helv. Chim. Acta*, **21**, 939 (1938); P. Karrer and H. Keller, *ibid.*, **21**, 1161 (1938); J. D. Surmatis and J. Weber, U. S. Patent 2,723,278 (1955); J. D. Surmatis and J. Weber, Canadian Patent 530,254 (1956).

(4) L. I. Smith and H. E. Ungnale, U. S. Patent 2,421,811 (1947).

(5) J. Weicht, *Chem. Listy*, **52**, 722 (1958); L. Blaha, J. Hodosova, and J. Weicht, *Collection Czech. Chem. Commun.*, **24**, 2023 (1959); L. Blaha and J. Weicht, Czech. Patent 88,904 (1959).

(6) L. I. Smith, J. W. Opie, S. Wawzoneck, and W. Prichard, *J. Org. Chem.*, **4**, 318 (1939); A. Pongratz and K. L. Zirm, *Monatsh.*, **83**, 13 (1952); C. K. Hui, *J. Vitaminol.* (Japan), I, 8 (1957); F. L. Grinberg and A. A. Svishchuk, *Ukr. Khim. Zh.*, **23**, 79 (1957).

(7) H. J. Teuber and W. Reu, *Chem. Ber.*, **86**, 1036 (1953); R. J. Boscott, *Chem. Ind.* (London), 201 (1955).

(8) W. T. Caldwell and T. R. Thompson, *J. Am. Chem. Soc.*, **61**, 765 (1939).

(9) W. J. Burke, J. A. Warburton, J. L. Bishop, and J. L. Bilis, *J. Org. Chem.*, **26**, 4669 (1961).

(10) Melting points are uncorrected. Infrared spectra were recorded with a Shimadzu Model AR 275 spectrophotometer.

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.

(11) K. Schniter, *Ber.*, **20**, 2283 (1887).

(12) Prepared by slight modification of Adkins' method, Lazier and Arnold, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 144, note 11.

(13) R. Nietzki and Schneider, *Ber.*, **27**, 1430 (1894).

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

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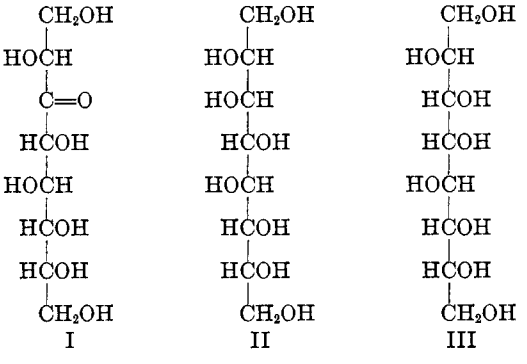
Our continuing studies of syntheses of higher, branched-chain aldoses[1] and higher ketoses[2] by aldol reactions have now led to discovery of the title compound (I), which is readily obtained from D-erythrose. Chromatography was used at first to obtain the crystalline product, but, in subsequent preparations, 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.