(0.0908 g.) was purified chromatographically[8] to yield a mixture of methyl hydroxystearates (IV), m.p. 39–41°.

Anal. Calcd. for $C_{19}H_{38}O_3$: C, 72.5; H, 12.2. Found: C, 70.3; H, 11.5%.

Infrared analysis of OH gave $\epsilon_{2.8\,\mu}$ 19.5 compared to 22.0 for methyl 12-hydroxystearate. Gas-liquid chromatography of this material (200° 50 ml./min. Argon flow) showed one double peak (peak retention volume, relative to methyl palmitate 6.41 and 6.52), the first component of which coincided with methyl 12-hydroxystearate and methyl (9,10)-monohydroxystearate.

Dehydration of methyl hydroxystearates IV. IV from hydrogenated I was dehydrated by heating with boric acid[32] to determine the position of the hydroxyl group in the fatty acid chain. Methyl 12-hydroxystearate was used as control material to determine whether positional shifts of unsaturation occur through dehydration. In the dehydration procedure 10 g. of crude methyl 12-hydroxystearate (contained 12% methyl stearate as determined chromatographically) and an equal molar weight of boric acid (2.0 g.,) in a 100-ml. round-bottom flask were gradually heated on a rotating evaporator under vacuum (2 cm. mercury pressure). When the vigorous boiling occurring between 100° and 150° subsided, the temperature was raised to 200–210° and allowed to remain there for 1 hr. The cooled reaction mixture was transferred into a separatory funnel with water, extracted with ether, and dried over sodium sulfate. The product (9.3 g.) was saponified, and the acids were purified by partition chromatography[8] to yield 65% monomeric nonhydroxy acids. Infrared analyses showed the absence of hydroxyl and the presence of isolated *trans* double bond ($\epsilon_{10.4\,\mu}$ 46.1; methyl elaidate, $\epsilon_{10.4\,\mu}$ 141). The dehydration procedure was applied to 0.790 g. of IV from hydrogenated methyl linolenate hydroperoxides to yield 0.568 g. of monoenoic esters V which on partition chromatography of the acids obtained after saponification, gave 71% monomeric-nonhydroxy acids (infrared analysis: no hydroxyl; isolated *trans*, $\epsilon_{10.4\,\mu}$ 54.4).

Portions of V were remethylated with diazomethane and the methyl esters subjected to gas-liquid chromatography (temperature 173°, 33 ml./min. Argon flow rate). The esters of dehydrated methyl 12-hydroxystearate showed the presence of methyl stearate and a monoenoic ester corresponding to methyl oleate (peak retention volume relative to methyl palmitate, 2.26). The dehydrated hydroxystearates from I showed the presence of four peaks. The first and principal peak corresponded to methyl oleate (peak retention time relative to methyl palmitate, 2.22, 2.35, 2.61, 2.82, respectively; methyl oleate, 2.23). The remaining portions of V were subjected to oxidative cleavage with permanganate-periodate[33] to locate position of the unsaturation.

The short-chain monobasic acids (C_9 and lower) obtained by oxidative cleavage were removed by steam distillation. The dibasic acids VI were analyzed by liquid-partition chromatography (Table II). This method could not separate and identify dibasic acids higher than C_{13}. Therefore, a sample of the dibasic acids was methylated with methanol, hydrochloric acid, and 2,2-dimethoxypropane.[34] The methyl esters of the dibasic acids were analyzed by gas-liquid chromatography (188°, 33 ml./min. Argon flow), and identification was made by comparison with known standards. Peaks were obtained for C_8, C_9, C_{11}, C_{12}, C_{13}, C_{15}, C_{16} with retention times relative to methyl stearate of 0.34, 0.48, 0.92, 1.27, 1.77, 3.37, 4.66, respectively.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF UTAH]

New Synthesis of Trimethylhydroquinone[1]

W. J. BURKE, JOE A. WARBURTON, JAY L. BISHOP, AND JAMES L. BILLS

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Condensation of 4-benzyloxyphenol with formaldehyde and morpholine, followed by treatment with concentrated hydrochloric acid and neutralization gave a high yield of 2,6-bis(morpholinomethyl)hydroquinone. Reaction of this product with equimolar quantities of morpholine and formaldehyde yielded the tris-Mannich base, which upon catalytic hydrogenation led to trimethylhydroquinone.

The wide diversity of important biological effects shown by vitamin E has stimulated considerable current interest in the tocopherols and related compounds.[2] Since vitamin E can be readily prepared from phytyl bromide and trimethylhydroquinone, much attention has been given to the synthesis of the latter.

Proposed routes to trimethylhydroquinone have involved rather complex, multistep syntheses

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starting with pseudocumene[3] or have utilized less readily available derivatives such as pseudocumidine,[4] pseudocumenol-6[5] or pseudocumenol-3.[6]

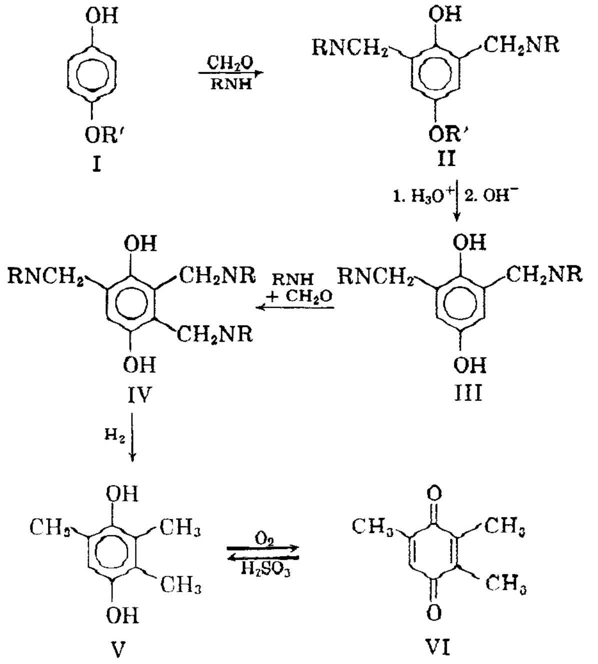
Caldwell and Thompson[7] employed the reaction of 3,5-dimethylphenol with formaldehyde and dimethylamine as a source of 3,5-dimethyl-2-dimethylaminomethylphenol, which was then hydrogenated to pseudocumenol-6. They also studied the related condensation of hydroquinone with formaldehyde and dimethylamine. The 2,5-bis(dimethylaminomethyl)hydroquinone obtained in this way was converted to 2,5-dimethylhydroquinone by hydrogenation. They pointed out that a similar reduction of tris(dimethylaminomethyl)hydroquinone would provide an elegant route to the desired trimethylhydroquinone. However, efforts to obtain the required Mannich base were not successful.

Smith and co-workers[8] indicated the possibility of utilizing monoethers of hydroquinone in the Mannich reaction as a route to polymethylhydroquinones, and Reeve and Saddle[9] later used this type of condensation to obtain 2,6-bis(dimethylaminomethyl)-4-methoxyphenol. Reduction followed by cleavage of the ether gave 2,6-dimethylhydroquinone.

In another investigation in this laboratory it was observed that the benzyl group was readily removed from 4-benzyloxy-2-cyclohexylaminomethylphenol by treatment with concentrated hydrochloric acid under mild conditions. This result and the availability of an inexpensive commercial source of 4-benzyloxyphenol prompted this study directed toward the utilization of phenolic Mannich bases in the synthesis of trimethylhydroquinone.

Condensation of 4-benzyloxyphenol with morpholine and formaldehyde in refluxing dioxane gave 4-benzyloxy-2,6-bis(morpholinomethyl)phenol (II). The benzyl group was removed with hot concentrated hydrochloric acid and upon neutralization 2,6-bis(morpholinomethyl)hydroquinone (III) was obtained. While the yields in each of these reactions were in excess of 80%, a better over-all yield (80%) was obtained by a modification involving isolation of the Mannich base (II) as the hydrochloride and removal of the benzyl group from the salt with concentrated hydrochloric acid at room temperature. Reaction of III with equimolar proportions of morpholine and formaldehyde gave tris(morpholinomethyl)hydroquinone (IV).

High pressure hydrogenation of tris(morpholinomethyl)hydroquinone at 220° for three hours in ethanol with copper–chromium oxide as catalyst gave a 50% yield of trimethylhydroquinone. A slightly higher yield (55%) was obtained by oxidation of the crude product to trimethyl-1,4-benzoquinone (VI), which was removed by steam distillation and reduced to the desired product (V) with sulfur dioxide. The trimethylhydroquinone (V) was characterized as the diacetate and dibenzoate and the trimethyl-1,4-benzoquinone was converted to the monoxime.



RN = morpholino; R' = benzyl

The 2,6-bis(morpholinomethyl)hydroquinone was hydrogenated to the known 2,6-dimethylhydroquinone, which was characterized by oxidation to 2,6-dimethyl-1,4-benzoquinone and by acetylation to 2,6-dimethylhydroquinone diacetate.

EXPERIMENTAL[10]

4-Benzyloxy-2,6-bis(morpholinomethyl)phenol (II). Morpholine (11.7 ml.; 0.135 mole) and 9.0 ml. of 37% aqueous formaldehyde (0.12 mole) were added to a solution of 12.0 g. of recrystallized 4-benzyloxyphenol[11] (0.06 mole) in 25 ml. of dioxane. The solution was refluxed gently for 2 hr., and the solvent removed under reduced pressure. The residue was dissolved in a minimum of hot methanol. The product (19.5 g.; 81.5% yield) crystallized upon cooling; m.p. 100–101°, after recrystallization from methanol.

Anal. Calcd. for $C_{23}H_{30}N_2O_4$: C, 69.32; H, 7.59; N, 7.03. Found: C, 69.28; H, 7.55; N, 7.05.

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

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(9) W. Reeve and A. Sadle, *J. Am. Chem. Soc.*, **72**, 3252 (1950).

(10) All melting points are uncorrected.

(11) Obtained from B. F. Goodrich Co. The compound melted at 121–122°, after recrystallization from benzene.

A slightly higher yield (82.5%) was obtained when the product was isolated as the *hydrochloride;* m.p. 246–247°, after recrystallization from methanol–propanol-2 (1:3 by vol.).

Anal. Calcd. for $C_{23}H_{32}Cl_2N_2O_4$: Cl, 15.04. Found: Cl, 15.00.

The *benzoate* melted at 120–121°.

Anal. Calcd. for $C_{30}H_{34}N_2O_5$: C, 71.69; H, 6.82. Found: C, 71.16; H, 6.85.

2,6-Bis(morpholinomethyl)hydroquinone (III). 4-Benzyloxy-2,6-bis(morpholinomethyl)phenol dihydrochloride (50 g.; 0.106 mole) was dissolved in 200 ml. (2.4 mole) of concd. hydrochloric acid. The solution was heated to reflux and distilled under reduced pressure to one half the original volume. The residue was dissolved in 100 ml. of methanol and cooled in ice water. The *hydrochloride* (39.4 g.; 98% yield) was removed by filtration; m.p. 242°, after recrystallization from propanol-1.[12]

Anal. Calcd. for $C_{16}H_{26}Cl_2N_2O_4$: C, 50.40; H, 6.87; Cl, 18.60. Found: C, 50.21; H, 6.86; Cl, 18.48.

The *hydrochloride* was converted to the free base in essentially quantitative yield by treatment with aqueous 2-aminoethanol; m.p. 182–183°, after recrystallization from methanol.

Anal. Calcd. for $C_{16}H_{24}N_2O_4$: C, 62.32; H, 7.85; N, 9.09. Found: C, 62.50; H, 7.85; N, 8.85.

Tris(morpholinomethyl)hydroquinone (IV). Morpholine (19.5 ml.; 0.224 mole) and 16.8 ml. of 37% aqueous formaldehyde (0.224 mole) were added to a solution of 30 g. of 2,6-bis(morpholinomethyl)hydroquinone (0.097 mole) in 75 ml. of dioxane. The reaction mixture was heated under gentle reflux for 2 hr. and cooled. The reaction mixture in 300 ml. of ether was washed with water. The ether layer was dried and a crystalline product (35.6 g.; 90% yield) was obtained upon removal of the ether; m.p. 159–160°, after recrystallization from methanol.

Anal. Calcd. for $C_{21}H_{33}N_3O_5$: C, 61.89; H, 8.16; N, 10.3. Found: C, 61.68; H, 8.24; N, 10.4.

The *trihydrochloride*[12] melted at 189°.

Anal. Calcd. for $C_{21}H_{36}Cl_3N_3O_5$: Cl, 20.58. Found: Cl, 20.65.

Trimethylhydroquinone. A high pressure bomb containing 14.5 g. (0.036 mole) of tris(morpholinomethyl)-hydroquinone in 125 ml. of ethanol and 2.2 g. of copper-chromium oxide catalyst was heated at 220° for 3 hr. under an initial hydrogen pressure of 2180 p.s.i. The catalyst was removed by filtration and washed with methanol. Normal sulfuric acid (110 ml.) was added to the filtrate, which was saturated with sodium sulfate and then extracted four times with 50-ml. portions of ether. The ether was removed under reduced pressure and the solid residue (2.6 g.; 50% yield) was recrystallized from water, m.p. 170–172°; lit.[13] m.p. 170°.

A 55% yield was obtained from a similar procedure in which potassium dichromate and dilute sulfuric acid were added to the crude reaction mixture after hydrogenation. The quinone was removed by steam distillation and reduced to the hydroquinone with aqueous sulfur dioxide.

Several derivatives of trimethylhydroquinone were prepared: the *diacetate* melted at 109.5–111°; lit.[4] m.p. 108.5–110°: the *dibenzoate* melted at 179–180°; lit.[4] m.p. 179.5–180.5°: the *trimethyl-1,4-benzoquinone* melted at 27°; lit. m.p. 11°,[14] 25°,[4] 29–30°;[4] 32°.[13] The *monoxime* of the quinone melted at 183–184°; lit.[13] m.p. 184°.

2,6-Dimethylhydroquinone. A solution of 7.8 g. of 2,6-bis(morpholinomethyl)hydroquinone (0.025 mole) in 100 ml. of ethanol to which 2.0 g. of copper-chromium oxide catalyst had been added, was hydrogenated for 3 hr. at 220° under 2400 p.s.i. of hydrogen. The product was recrystallized from carbon tetrachloride, yield 1.3 g. or 38%, m.p. 146–149°; lit.[14] m.p. 149–151°.

The *diacetate* melted at 91–93°; lit.[15] m.p. 91–92°. The *2,6-dimethyl-1,4-benzoquinone* was made by oxidation with manganese dioxide in dilute sulfuric acid; m.p. 71–72°; lit.[14] m.p. 72–73°.

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[12] It was necessary to dry the compound for several hours under reduced pressure (0.2 mm.) at 60° in order to get a consistent melting point. NOTE ADDED IN PROOF: After this paper was submitted, our attention was drawn to an article in which F. F. Blicke and F. J. McCarty [*J. Org. Chem.*, **24**, 1061 (1959)] described an alternate synthesis of 2,6-bis(morpholinomethyl)hydroquinone dihydrochloride involving the hydrolysis of 4-benzoyloxy-2,6-bis(morpholinomethyl)phenol dihydrochloride. These authors reported a melting point of 193–194° for 2,6-bis(morpholinomethyl)hydroquinone dihydrochloride and did not describe the free base.

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