Anal. Calcd. for $C_{14}H_{20}N_4O_4$: C, 54.53; H, 6.54; N, 18.17. Found: C, 54.80; H, 6.65; N, 18.30.

Benzoic Acid, N,N'-Dicarbobenzoxyhydrazide-phenylhydrazone (IIc).—Benzyl azodicarboxylate (2.0 g., 0.0067 mole) was dissolved in 15 ml. of refluxing ether. To this solution was added slowly through the condenser in approximately one-third portions 1.7 g. (0.0086 mole) of benzaldehyde phenylhydrazone. The condenser was washed with 5-ml. portions of ether after each addition. Reflux of the ether solution was continued until the solution turned a brilliant yellow. The ether was then removed on an aspirator and a yellow solid melting at 124–128° was obtained. The solid was recrystallized from methanol to furnish 2.45 g. (77%) of IIc, m.p. 130–131°.

Anal. Calcd. for $C_{29}H_{26}N_4O_4$: C, 70.41; H, 5.35; N, 11.33; active H, 0.40. Found: C, 70.18; H, 5.30; N, 11.20; active H, 0.48.

4-Carbethoxyamino-2,5-diphenyl-2,3-dihydro-3-oxo-1,2,4-triazole (IVa). Procedure A.—The treatment of IIa by the method of Büsch, *et al.*,[3] utilizing acid resulted in a white solid from methanol, m.p. 148–149° (lit., m.p. 149–150°[3]).

Procedure B.—One gram of IIa was placed in a solution of 40 ml. of methanol and 3 g. of potassium hydroxide and refluxed for 24 hr., whereupon the solution became clear. Upon cooling and acidification with sulfuric acid, a white solid precipitated which was filtered and dissolved in benzene. The benzene solution was then filtered to remove any potassium sulfate. Upon cooling the filtrant, 0.77 g. (88%) of IVa, m.p. 146–147°, was obtained. A mixed melting point determination with an authentic sample of IVa was undepressed and infrared spectra of the two samples were superimposable.

Procedure C.—The reflux of 0.5 g. of IIa in 30 ml. of benzene for 3.5 days resulted in a color change from bright yellow to a very light yellow. Concentration of the benzene solution and cooling resulted in crystallization of 0.39 g. (90%) of IVa, m.p. 147–148°. A mixed melting point with authentic material showed no depression.

4-Carbethoxyamino-5-methyl-2-phenyl-2,3-dihydro-3-oxo-1,2,4-triazole (IVb).—Treatment of IIb according to the method of Büsch, *et al.*,[3] resulted in the formation of IVb, m.p. 110–112° from benzene (lit., m.p. 112°[3]).

4-Carbobenzoxyamino-2,5-diphenyl-2,3-dihydro-3-oxo-1,2,4-triazole (IVc).—A 0.5-g. sample of IIc was dissolved in 25 ml. of refluxing methanol to which 3 ml. of 20% hydrochloric acid had been added. The solution was refluxed until clear. The methanol solution was concentrated and cooled in the refrigerator. A white solid IVc (0.33 g.; 88%) m.p. 127.5–129° crystallized. An analytical sample was recrystallized from a mixture of hexane and ether, m.p. 129–130°.

Anal. Calcd. for $C_{22}H_{18}N_4O_3$: C, 68.36; H, 4.70; N, 14.50. Found: C. 68.27; H, 4.76; N, 14.42.

4-Carbethoxyamino-2-methyl-5-phenyl-2,3-dihydro-3-oxo-1,2,4-triazole (IVd).—Ethyl azodicarboxylate (5.0 g.; 0.028 mole) was added dropwise to freshly distilled benzaldehyde methylhydrazone (3.8 g.; 0.028 mole) dissolved in 25 ml. of anhydrous ether. An exothermic reaction with decolorization of the solution resulted. The solution was allowed to stand for 4 days and a white solid melting at 132–134° crystallized. Recrystallization of this material from ether gave 4.0 g. (55%) of IVd, m.p. 135–136°.

Anal. Calcd. for $C_{12}H_{14}N_4O_3$: C, 54.93; H, 5.38; N, 21.37. Found: C, 55.00; H, 5.43; N, 21.42.

4-Amino-2,5-diphenyl-2,3-dihydro-3-oxo-1,2,4-triazole (V).—Five grams of IVa was mixed with 5 g. of potassium hydroxide in 50 ml. of ethylene glycol and the mixture was refluxed under nitrogen for 4.5 hr. The mixture was then poured into 300 ml. of water, and the total solution was extracted with two 200-ml. portions of ether. The combined ether extracts were concentrated on a steam bath, 100 ml. of methanol added, and the residual ether was driven off by heat. Upon cooling the alcoholic solution, 2.8 g. (77%) of white solid V, m.p. 154.5–156°, crystallized. An analytical sample prepared by recrystallization from ethanol melted 156–157°, and exhibited λ_{max} (EtOH) 271 mμ, log ϵ 4.2.

Anal. Calcd. for $C_{14}H_{12}N_4O$: C, 66.63; H, 4.79; N, 22.22. Found: C, 66.52; H, 4.94; N, 22.05.

4-Benzylideneamino-2,5-diphenyl 2,3-dihydro-3-oxo-1,2,4-triazole (VI).—In 10 ml. of boiling methanol was dissolved 0.1 g. of V. Benzaldehyde (1 ml.) was slowly added to the solution and a white precipitate formed. The solid was filtered and recrystallized from methanol to yield 0.11 g. (81%) of VI, which melted at 119–120° and exhibited λ_{max} (EtOH) 266 mμ, log ϵ 4.5.

Anal. Calcd. for $C_{21}H_{16}N_4O$: C, 74.08; H, 4.74; N, 16.47. Found: C, 73.89; H, 4.58; N, 16.59.

Direct Synthesis of Poly(morpholinomethyl)hydroquinones[1]

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High yields of tris- (III) and tetrakis(morpholinomethyl)hydroquinone (IV) were obtained directly from the condensation of hydroquinone with formaldehyde and morpholine. Factors influencing the condensation were studied and IV was hydrogenated to tetramethylhydroquinone (VI) and to 2,3,5,6-tetramethylcyclohexane-1,4-diol (VII).

It was recently shown that *p*-benzyloxyphenol is an attractive starting material for the synthesis of trimethylhydroquinone.[2] In further related studies it was found that reaction of 2,6-bis(morpholinomethyl)hydroquinone with morpholine and formaldehyde under certain conditions led to both tris- and tetrakis(morpholinomethyl)hydroquinone.

The formation of the latter was unexpected in view of the fact that Caldwell and Thompson[3] found that 2,5-bis(dimethylaminomethyl)hydroquinone was obtained when hydroquinone was condensed with the stoichiometric quantities required for the desired corresponding tris compound. They pointed out that hydrogenation of tris(dimethylaminomethyl)hydroquinone would provide a convenient route to trimethylhydroquinone,

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(1) This investigation was supported in part by a research grant CY-5211 from the National Cancer Institute of the Public Health Service.

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

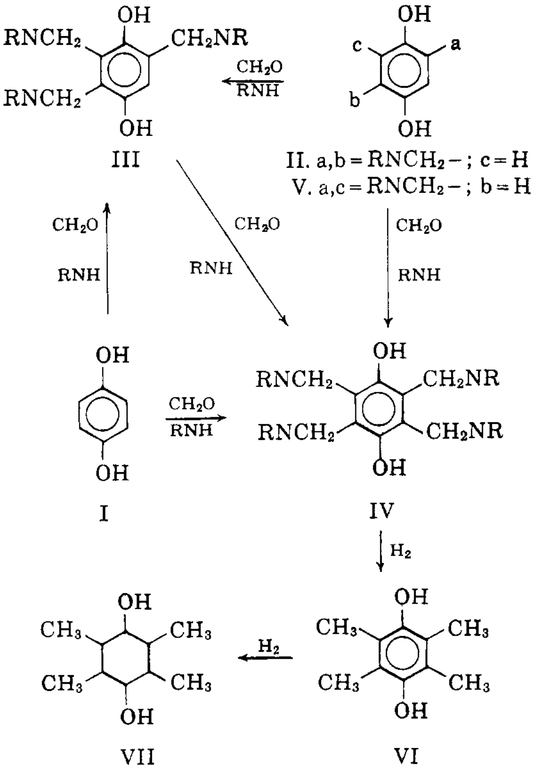
(3) W. T. Caldwell and T. R. Thompson, *J. Am. Chem. Soc.*, **61**, 765 (1939).

which is of interest in the synthesis of vitamin E. In an alternate approach, an unsuccessful attempt was made to introduce an aminomethyl group into 2,5-dimethylhydroquinone.[4]

The synthesis of tetrakis(morpholinomethyl)hydroquinone from 2,6-bis(morpholinomethyl)hydroquinone suggested the possibility of preparing both the tris (III) and tetrakis (IV) derivatives directly from hydroquinone. Since this would make possible an even more attractive route to trimethylhydroquinone than that reported earlier[2] and would open up a new route to tetramethylhydroquinone, the present work was undertaken.

It was found that tris(morpholinomethyl)hydroquinone could be prepared in 89% yield by reaction of hydroquinone, formaldehyde, and morpholine in molar ratios of 1:3:4 in 1,4-dioxane under nitrogen in a sealed tube at 110° for seventeen hours. Slightly higher yields (up to 93%) were obtained when a longer reaction time was employed. Condensation of 1:4:4 molar ratios of the reactants in dioxane for three days at 75° gave only a 42% yield of the tris (III) compound along with a 54% yield of the 2,5-bis(morpholinomethyl)hydroquinone (II). Reaction of the latter compound (II) with formaldehyde and morpholine provided an alternate route to III.

Tetrakis(morpholinomethyl)hydroquinone (IV) was also obtained directly in high yield (87%) when hydroquinone, aqueous formaldehyde, and morpholine in molar ratios of 1:12.5:12.5 were heated in a sealed tube at 120° for forty-eight hours. Use of the calculated molar ratios of reactants (1:4:4) led to a major portion of the tris(III) and only about 40% of the tetrakis (IV) Mannich base, with ethanol or dioxane as solvent and reaction times from one to five days at 120°. Reaction of III with equimolar quantities of formaldehyde and morpholine in ethanol led to only 43% of the desired IV along with 37% of recovered III. The tetrakis derivative was also prepared in low yields from both 2,5- and 2,6-bis(morpholinomethyl)hydroquinone.



RNH = morpholine

In the study of the direct synthesis of the Mannich bases III and IV, it was found that dioxane was superior to methanol or ethanol as a reaction solvent and that it was advantageous to run the reaction under nitrogen. In the synthesis of IV with a large excess of morpholine and formaldehyde, best results were obtained without added solvent. Temperatures below 115–130° required undesirably long reaction times while at somewhat higher temperatures considerable discoloration occurred and only low yields of crystalline products were obtained. Mannich bases have been shown to undergo polymerization at elevated temperatures.[5] An excess of morpholine over formaldehyde was found to be advantageous in the synthesis of III.

Earlier routes to tetramethylhydroquinone have generally involved the preparation of tetramethyl-*p*-benzoquinone, which can be reduced in almost quantitative yield to the desired product. Tetramethyl-*p*-benzoquinone can be synthesized in various ways: by ring closure of 2,3-pentanedione[6] with alkali in 10% yield; by treatment of 3,3-dichloro-2-pentanone with potassium carbonate (10% yield)[7]; from pentamethylphenol by chromic acid oxidation[8]; from 2,3,5,6-tetramethylphenol in 60% yield[9] by coupling with diazotized sulfanilic acid, reducing, and then oxidizing; by direct oxidation of 2,3,5,6-tetramethylphenol with sodium dichromate (50% yield)[9] or with potassium nitrosodisulfonate (87% yield)[10]; or from 1,2,4,5-tetramethylbenzene[11,12] in 70–80% yield by nitration followed by reduction and then oxidation to the quinone. Tetramethylhydroquinone was also prepared directly[13] in 21% yield by reaction of 2-butyne with iron pentacarbonyl. In the same article it was shown that tetrakis(dimethylaminomethyl)hydroquinone (22% yield) resulted from the condensation of 1,4-bis(dimethylamino)-2-

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(4) W. T. Caldwell and T. R. Thompson, *J. Am. Chem. Soc.* **61**, 2354 (1939).

(5) W. J. Burke, B. A. Barton, P. D. Gardner, and J. D. Lewis, *ibid.*, **80**, 3438 (1958).

(6) H. von Pechmann, *Ber.*, **21**, 1420 (1888).

(7) A. Favorski, *J. prakt. Chem.*, **51**, 533 (1895).

(8) R. Monnberg, A. Ora, and U. Lehmuskoski, *Paperi ja Puu*, **35**, 8 (1953) [*Chem. Abstr.*, **48**, 362c (1954)].

(9) L. I. Smith, J. W. Opie, S. Wawzonek, and W. W. Prichard, *J. Org. Chem.*, **4**, 318 (1939).

(10) H. J. Teuber and W. Reu, *Chem. Ber.*, **86**, 1036 (1953).

(11) L. I. Smith and F. J. Dobrovolny, *J. Am. Chem. Soc.*, **48**, 1420 (1926).

(12) L. I. Smith, "Organic Syntheses," Coll. Vol. II, J. Wiley & Sons, Inc., New York, N. Y., 1943, p. 254.

(13) W. Reppe and H. Vetter, *Ann.*, **582**, 133 (1953).

butyne with iron pentacarbonyl in 2-aminoethanol.

Hydrogenation of tetrakis(morpholinomethyl)-hydroquinone in the presence of copper–chromium oxide and dioxane followed by air oxidation to tetramethyl-*p*-benzoquinone and reduction of the latter with sodium hydrosulfite gave tetramethylhydroquinone (42%).[14] In another run for a longer period of time, the aromatic ring of IV was also hydrogenated with the formation of 2,3,5,6-tetramethylcyclohexane-1,4-diol (VII).

Experimental[15]

Tris(morpholinomethyl)hydroquinone (III). Direct Synthesis.—Morpholine (34.8 ml.; 0.40 mole) was added slowly with cooling to a Carius tube containing 22.5 ml. of 37% aqueous formaldehyde (0.30 mole). After addition of a solution of 11 g. of hydroquinone (0.10 mole) in 45 ml. of 1,4-dioxane, nitrogen was bubbled through the reaction mixture for 1 min. The sealed tube was heated at 115° for 56 hr. The solid product (4.1 g.) obtained upon cooling was removed by filtration and washed with dioxane to remove color; m.p. 154–160°. An additional 33.3 g. was obtained from the filtrate; m.p. 153–157°. The crude product was treated with warm methanol and the insoluble material (0.52 g.; m.p. 246°) was removed by filtration and identified as tetrakis(morpholinomethyl)hydroquinone (1% yield). The product (91% yield) recovered from evaporation of the methanol was recrystallized from ethanol; m.p. and mixed m.p. with a known specimen of III, 159–160° (lit.,[2] m.p. 159–160°).

An 89% yield of III was obtained from a mixture prepared as above when the sealed tube was heated at 110° for 17 hr. Condensation of 1:3:3 molar ratios of the reactants in dioxane for 8 days at 81° led to a 93% yield of III.

Synthesis of III from 2,5-Bis(morpholinomethyl)hydroquinone (II).—Morpholine (5.6 ml.; 0.064 mole) and 4.8 ml. of 37% aqueous formaldehyde (0.064 mole) were added with cooling to 10 g. of 2,5-bis(morpholinomethyl)hydroquinone (0.032 mole) in 40 ml. of dioxane. The solution was heated at 75° for 72 hr. in a closed system. Unchanged II (5.4 g.) was removed by filtration of the cooled reaction mixture. Concentration of the filtrate gave 5.5 g. of solid product; m.p. and mixed m.p. with III, after one recrystallization from ethanol, 156–159°; yield 42%.

2,5-Bis(morpholinomethyl)hydroquinone (II) Dihydrochloride.—A 90% yield of the free base (II) was obtained by treating a mixture of hydroquinone (0.5 mole), morpholine (1.5 moles), and 37% aqueous formaldehyde (1.5 moles) at 25° for 1.5 hr.; m.p. 203–204° after recrystallization from methanol.[16]

Anal. Calcd. for $C_{16}H_{24}N_2O_4$: C, 62.31; H, 7.85. Found: C, 62.28; H, 8.06.

The dihydrochloride melted at 317° dec.[17]

Anal. Calcd. for $C_{16}H_{26}Cl_2N_2O_4$: Cl, 18.6. Found: Cl, 18.8.

Tetrakis(morpholinomethyl)hydroquinone (IV).—Aqueous 37% formaldehyde (47 ml.; 0.625 mole) was added with cooling along with a stream of nitrogen to a Carius tube containing 5.51 g. of hydroquinone (0.050 mole) and 54.5 ml. of morpholine (0.625 mole). The sealed tube was heated at 115–120° for 48 hr. The white crystalline product (22.0 g.; 87% yield) was removed by filtration and washed with water; m.p. 250°. The melting point did not change after recrystallization from ethyl acetate.

Anal. Calcd. for $C_{26}H_{42}N_4O_6$: C, 61.63; H, 8.36; N, 11.06. Found: C, 61.55; H, 8.33; N, 11.20.

Under comparable reaction conditions except with dioxane (45 ml. per 1.76 g. of hydroquinone) as solvent a 73% yield was obtained. Use of 25 ml. of dioxane per 1.76 g. of hydroquinone for a 106-hr. reaction at 100° led to an 83% yield of IV.

The tetrahydrochloride melted at 243° dec.[17]

Anal. Calcd. for $C_{26}H_{46}Cl_4N_4O_6$: Cl, 21.7. Found: Cl, 21.3.

IV from 2,5-Bis(morpholinomethyl)hydroquinone (II).—A solution of 27.8 ml. of morpholine (0.32 mole), 24 ml. of 37% aqueous formaldehyde (0.32 mole), and 10.0 g. of 2,5-bis(morpholinomethyl)hydroquinone (II; 0.032 mole) in 40 ml. of dioxane was heated under gentle reflux and the system was closed. After 113 hr., the solid (4.4 g.; 27% yield) which separated from the hot reaction mixture was removed by filtration, m.p. 242–250°; after recrystallization from ethyl acetate m.p. and mixed m.p. with IV, 248–250°. Unchanged II was recovered in 23% yield.

IV from 2,6-Bis(morpholinomethyl)hydroquinone (V).—A solution of 12 ml. of aqueous 37% formaldehyde (0.16 mole), 13.9 ml. of morpholine (0.16 mole), and 5.0 g. of 2,6-bis(morpholinomethyl)hydroquinone (V; 0.016 mole) in 40 ml. of dioxane was heated under gentle reflux for 3 days. The product (2.4 g.; 30% yield) obtained upon removal of solvent and recrystallization from ethyl acetate melted at 247–249°.

IV from Tris(morpholinomethyl)hydroquinone (III).—A mixture of 1.5 ml. of 37% formaldehyde (0.02 mole), 1.8 ml. of morpholine (0.02 mole), 8.15 g. of III (0.02 mole), and 10 ml. of ethanol was heated under nitrogen in a sealed tube for 122 hr. at 120°. The product (4.36 g.; 43% yield), which was separated from the solution at 25° and washed with methanol, melted at 248°. Unchanged III (m.p. 157°) was recovered from the filtrate in 37% yield.

Tetramethylhydroquinone (VI).—A mixture of 13 g. of IV, 2.0 g. of copper–chromium oxide, and 50 ml. of dioxane was heated for 2 hr. at 225° under 3000 p.s.i. of hydrogen. The catalyst was removed by filtration and washed with methanol. The solid (1.8 g.) obtained by pouring the filtrate on crushed ice was recrystallized from butanol-1; m.p. 110–111°, lit. m.p. for tetramethyl-*p*-benzoquinone, 111–112°,[9] 111°.[11] Treatment of the solid with hot aqueous sodium hydrosulfite for 10 min. gave an essentially quantitative yield of tetramethylhydroquinone, m.p. 225–228°; lit., m.p. 210°,[18] 210–224°,[19] 220°,[6] 226–227°,[20] 233°,[11] 242–243°.[21]

2,3,5,6-Tetramethylcyclohexane-1,4-diol.—A mixture of 15 g. of IV (0.03 mole) and 2 g. of copper–chromium oxide in dioxane was heated at 225° under 3000 p.s.i. of hydrogen for 8 hr. The white crystalline product (1.1 g.; 21% yield) melted at 205–207° after recrystallization from ethanol.

Anal. Calcd. for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 69.35; H, 11.44.

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[14] After this work was completed our attention was drawn to the report of E. P. Previc, E. B. Hotelling, and M. B. Neuworth, *Ind. Eng. Chem.*, **53**, 469 (1961). They showed that phenolic Mannich bases could be hydrogenated to the corresponding methylphenols in almost quantitative yields by the proper choice of catalyst composition. Accordingly the rather low yields of the corresponding methylhydroquinones we obtained by hydrogenation of II (55%), III (55%),[2] IV (42%), and V (38%)[2] might be expected to be improved considerably by the proper choice of reaction conditions.

[15] All melting points are uncorrected.

[16] H. A. Bruson, U.S. Patent 2,040,040, gave a m.p. of 205° for II but did not report elemental analyses.

[17] These hygroscopic salts were obtained in quantitative yields as follows: Benzene solutions of the free bases were swirled a few minutes in a hydrogen chloride atmosphere, the solvent was evaporated, and the residues were dried under vacuum for 24 hr. at temperatures of 100 and 130°, respectively, for the bis and tetrakis derivatives.

[18] J. U. Nef, *Ber.*, **18**, 2806 (1885); *Ann.*, **237**, 5 (1887).

[19] L. Rugheimer and M. Hankel, *Ber.*, **29**, 2172 (1896).

[20] J. B. Conant and L. F. Fieser, *J. Am. Chem. Soc.*, **45**, 2200 (1923).

[21] A. A. Bothner-By, *ibid.*, **75**, 728 (1953).