by filtration, washed with acetone and dried. It decomposed slowly but did not melt below 360°. An analytical sample was prepared by recrystallization from a methanol-water (3:1) mixture and drying at 100°.

Anal. Calcd. for $C_{22}H_{48}N_6Br_4$: C, 36.88; H, 6.75; N, 11.73. Found: C, 36.60; H, 6.84; N, 12.09 (Dumas).

2,5-Bis-[bis-(piperidinomethyl)-methyl]-pyrazine (II).—Piperidine hydrochloride, prepared from 6.8 g. of piperidine, was mixed with 4.3 g. of dimethylpyrazine, 2.4 g. of paraformaldehyde and 40 ml. of isoamyl alcohol and the mixture heated to reflux. Solids started to separate after 15 minutes. After refluxing for 8 hours, the mixture was cooled and the solid removed by filtration, washed with alcohol and dried; m.p. 216–220°; yield 4.1 g. (30%). After two recrystallizations from 70% alcohol, the product melted at 232–233°.

Anal. Calcd. for $C_{30}H_{52}N_6 \cdot 4HCl \cdot 2H_2O$: C, 53.05; H, 8.92; N, 12.38. Found: C, 53.20; H, 8.74; N, 11.90.

2,5-Bis-[bis-(morpholinomethyl)-methyl]-pyrazine (III).—A mixture of 10.8 g. of dimethylpyrazine, 24.5 g. of morpholine hydrochloride and 2 ml. of water was heated to refluxing with stirring. A two-phase liquid–liquid mixture was formed. Then 16.2 g. of a 37% solution of formaldehyde was added dropwise over a period of two hours. The mixture was refluxed and stirred for an additional 15 minutes, then cooled. The crystals which formed were removed by filtration, washed with alcohol and dried at 100°.

On recrystallization from methanol-water (4:1), 3.5 g. of material melting at 220–221° with decomposition was obtained. Further recrystallization from this solvent gave a product melting at 224–226°.

Anal. Calcd. for $C_{26}H_{48}N_6O_4Cl_4 \cdot H_2O$: C, 46.71; H, 7.54; Cl, 21.21. Found: C, 46.74; H, 7.47; Cl, 21.52.

Further small amounts of bis compound but no mono compound were isolated from the mother liquors.

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

Monomeric Products from the Condensation of Phenol with Formaldehyde and Primary Amines

BY W. J. BURKE AND C. WAYNE STEPHENS[1]

3,4-Dihydro-3-substituted-1,3,2H-benzoxazines and N-substituted 2-aminomethylphenols were reprepared from phenol, formaldehyde and representative primary amines. Evidence was presented for the structures assigned.

Phenols having unsubstituted ortho or para positions have been shown to form Mannich bases by condensation with formaldehyde and either primary[2-4] or secondary[5-8] amines. Reaction of phenol with formaldehyde and dimethylamine has been reported to give 2-[7,8] 2,6-bis-[7] and 2,4,6-tris-(dimethylaminomethyl)-phenol.[6] 2,4,6-Tris-(morpholinomethyl)-phenol also has been prepared.[6] In the limited work with primary amines only resinous material was obtained from the condensation of equimolar quantities of 2-aminoethanol, formaldehyde and phenol, although several *o*- and *p*-substituted phenols gave crystalline products under similar conditions.[2] Use of two molar proportions of formaldehyde was reported to result in an even more rapid polymerization. More recently it has been shown that substituted phenols will react with formaldehyde and primary amines to form 3,4-dihydro-1,3,2H-benzoxazines[9] and N,N-bis-(hydroxybenzyl)-amines[10] directly in certain instances as well as the previously reported *o*- and *p*-alkylaminomethylphenols.[2,3]

The fact that phenol has three and primary amines two formaldehyde reactive positions makes possible a great complexity of products, including polymers, from such systems. For example, the reaction of phenol with formaldehyde and methylamine has been proposed as a source of basic resins.[11] In the present study, condensation of phenol with formaldehyde and cyclohexylamine in a molar ratio of 1:2:1, respectively, in refluxing dioxane led to a 60% yield of 3,4-dihydro-3-cyclohexyl-1,3-2H-benzoxazine (I). While analogous liquid benzoxazines from substituted phenols[9] can be obtained readily by simple distillation after removal of reaction solvents, such a procedure results in extensive polymer formation with such products from phenol. However extraction of an ether solution of the crude product with aqueous alkali made possible the subsequent smooth distillation of I with essentially no resin being formed. Similar results were obtained with benzylamine, methylamine and 2-aminoethanol.

The benzoxazines from phenol are highly sensitive to mineral acids. Efforts to prepare a hydrochloride of I by procedures used successfully with analogous products from substituted phenols led to 2-cyclohexylaminomethylphenol (II) with the liberation of formaldehyde. II was also prepared directly from equimolar quantities of phenol, formaldehyde and cyclohexylamine, but in low yield (28%). None of the other possible Mannich bases was isolated. It has been shown, however, that in such condensations N-methylolamines can react selectively at either the ortho or para position of a phenol if both positions are free.[12,13] In contrast to the direct synthesis, the hydrolysis of I to II was essentially quantitative so that the over-all yield of II by this method was 60%. 2-Alkylaminomethylphenols were also prepared from the benzoxazines derived from methylamine, benzylamine and 2-aminoethanol. II was readily reconverted to I in 86% yield by reaction with

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[1] University of Utah Research Committee Fellow 1951.

[2] H. A. Bruson, THIS JOURNAL, **58**, 1741 (1936).

[3] J. H. Burckhalter, F. H. Tendick, E. M. Jones, W. F. Holcomb and A. L. Rawlins, *ibid.*, **70**, 1363 (1948).

[4] W. J. Burke and C. Weatherbee, *ibid.*, **72**, 4691 (1950).

[5] E. L. Eliel, *ibid.*, **73**, 43 (1951).

[6] H. A. Bruson and C. W. MacMullin, *ibid.*, **63**, 270 (1941).

[7] J. Decombe, *Compt. rend.*, **196**, 866 (1933).

[8] A. Madinaveitia, *Anales soc. españ. fis. quim.*, **19**, 259 (1921); *C. A.*, **16**, 1230 (1922).

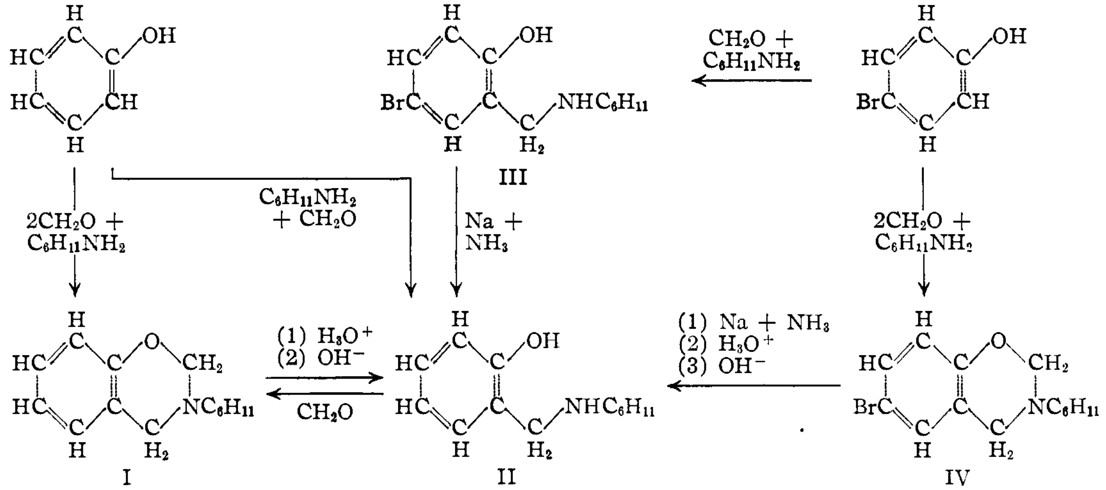
[9] W. J. Burke, THIS JOURNAL, **71**, 609 (1949).

[10] W. J. Burke, R. P. Smith and C. Weatherbee, *ibid.*, **74**, 602 (1952).

[11] J. Harmon and F. M. Meigs, U. S. Patent 2,098,869 (1937).

[12] W. T. Caldwell and T. R. Thompson, THIS JOURNAL, **61**, 2354 (1939).

[13] R. B. Carlin and H. P. Landerl, *ibid.*, **72**, 2762 (1950).



formaldehyde. In a similar fashion, 2-benzylaminomethylphenol condensed with formaldehyde to give the corresponding benzoxazine (80% yield).

There is considerable evidence to indicate that phenolic compounds undergo the Mannich reaction only at unsubstituted *o*- and *p*-positions.[5,6,12] In order to get more definite information as to the structure of the products under investigation, a study of their relationship to the similar compounds from *p*-bromophenol was undertaken. The synthesis of 4-bromo-2-cyclohexylaminomethylphenol (III) from equimolar quantities of *p*-bromophenol, formaldehyde and cyclohexylamine took place smoothly. The essentially quantitative conversion of III to II by treatment with sodium in liquid ammonia indicates that the cyclohexylaminomethyl group of II is in the ortho position. It was also possible to convert IV to II by removal of bromine and subsequent hydrolysis. The ready interconversion of I and II supports the benzoxazine structure proposed for I.

The preparation of 2- and 4-methylaminomethylphenol hydrochlorides through the reduction of the Schiff bases from methylamine and 2- and 4-hydroxybenzaldehyde, respectively, has been described.[14] The melting point recorded for the 2-isomer is in agreement with that found in the present study for the hydrochloride obtained by the hydrolysis of the product for which a 3,4-dihydro-3-methyl-1,3,2H-benzoxazine structure is proposed. This is additional evidence that the ortho rather than the para position of phenol was involved in the synthesis of the compounds presently reported.

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Experimental

3,4-Dihydro-3-substituted-1,3,2H-benzoxazines.—A general procedure for preparing these compounds is given in (A). In the isolation of (B) and (C) it was found desirable to use a saturated salt solution of potassium hydroxide in the extraction step.

A. **3,4-Dihydro-3-cyclohexyl-1,3,2H-benzoxazine.**—Cyclohexylamine (9.9 g., 0.1 mole) was added portionwise with cooling to 70 ml. of dioxane containing 15 ml. of 37% aqueous formaldehyde (0.2 mole). After addition of 10.6 ml. of a methanol solution of 9.4 g. of phenol (0.1 mole) the reaction mixture was heated under reflux for two hours. Upon removal of the volatile solvents under reduced pressure at room temperature, the resulting sirup was treated with 60 ml. of 10% aqueous potassium hydroxide and extracted twice with ether. The combined ether extracts were washed twice with water and dried over anhydrous calcium chloride. Removal of ether and distillation of the residue gave 13.1 g. (60% yield) of an almost colorless oil; b.p. 133–135° (0.75 mm.); n^{25}_D 1.5500.

Anal. Calcd. for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.08; H, 8.78; N, 6.52.

B. **3,4-Dihydro-3-methyl-1,3,2H-benzoxazine.**—The colorless mobile liquid boiled at 70–71° (0.1 mm.); n^{25}_D 1.5472; yield 34%.

Anal. Calcd. for $C_9H_{11}NO$: N, 9.39. Found: N, 9.27.

C. **3,4-Dihydro-3-(β-hydroxyethyl)-1,3,2H-benzoxazine.**—The product was obtained in 30% yield and melted at 52–53°, after recrystallization from carbon tetrachloride.

Anal. Calcd. for $C_{10}H_{13}NO_2$: N, 7.82. Found: N, 7.66.

D. **3,4-Dihydro-3-benzyl-1,3,2H-benzoxazine.**—The product melted at 66° after recrystallization from ethanol; yield 74%.

Anal. Calcd. for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: C, 80.09; H, 6.98; N, 6.22.

Hydrolysis of 2,3-Dihydro-3-substituted-1,3,2H-benzoxazines.—A general procedure for the preparation of N-substituted-2-aminomethylphenols from the corresponding benzoxazines is given in (A).

A. **2-Cyclohexylaminomethylphenol (II).**—To a solution of 10.85 g. of I (0.05 mole) in boiling ethanol was added portionwise 5 ml. of concentrated hydrochloric acid (0.06 mole) in 15 ml. of ethanol. The reaction mixture was boiled until formaldehyde was no longer evolved. Upon cooling 10.2 g. of a crystalline **hydrochloride** separated; m.p. 209–210° (dec.) after recrystallization from ethanol. An additional 1.8 g. of product was obtained from the mother liquor; yield 99%.

Anal. Calcd. for $C_{13}H_{20}ClNO$: Cl, 14.67. Found: Cl, 14.74.

The **free base** was obtained by addition of excess solid potassium carbonate to 6.5 g. of hydrochloride (0.027 mole) in 200 ml. of distilled water. The product (4.6 g., 83% yield) was removed by filtration and washed with water; m.p. 58–59°, after recrystallization from petroleum ether (b.p. 60–90°).

Anal. Calcd. for $C_{13}H_{19}NO$: C, 76.05; H, 9.33; N, 6.82. Found: C, 76.48; H, 9.27; N, 6.72.

B. **2-Methylaminomethylphenol.**—The **hydrochloride**[15] melted at 144–145° after recrystallization from ethanol; yield 67%.

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[14] N. H. Cromwell and H. Hoeksema, THIS JOURNAL, 67, 1658 (1945).

[15] Cromwell and Hoeksema (ref. 14) reported melting points of 146 and 183° for 2- and 4-methylaminomethylphenol hydrochloride, respectively. They prepared these compounds by the reduction of the corresponding Schiff bases. They did not characterize the free base from 2-methylaminomethylphenol hydrochloride.

Anal. Calcd. for $C_8H_{12}ClNO$: Cl, 20.42. Found: Cl, 20.35.

The free base melted at 45–47°; yield 76%.

Anal. Calcd. for $C_8H_{11}NO$: N, 10.21. Found: N, 10.19.

C. **2-β-Hydroxethylaminomethylphenol.**—The hydrochloride melted at 151–152° (dec.) after recrystallization from ethanol; yield 96%.

Anal. Calcd. for $C_9H_{14}ClNO_2$: Cl, 17.41. Found: Cl, 17.50.

The free base melted at 64–65°, after recrystallization from chloroform–carbon tetrachloride (1:5, by vol.) to which petroleum ether (b.p. 30–60°) was added to the point of incipient opalescence: yield 74%.

Anal. Calcd. for $C_9H_{13}NO_2$: N, 8.38. Found: N, 8.23.

D. **2-Benzylaminomethylphenol.**—The free base was an oil which was characterized as the hydrochloride; m.p. 190–191° (dec.) after recrystallization from ethanol; yield 90%.

Anal. Calcd. for $C_{14}H_{16}ClNO$: N, 5.61. Found: 5.56.

Synthesis of 2-Cyclohexylaminomethylphenol from Phenol.—Cyclohexylamine (44.8 ml., 0.4 mole) was added portionwise with cooling to 30 ml. of 37% aqueous formaldehyde (0.4 mole) in 200 ml. of dioxane. After addition of 42.4 ml. of a methanol solution containing 37.6 g. of phenol (0.4 mole) the reaction mixture was heated under reflux for two hours. The dioxane was removed under reduced pressure and the residue treated with 250 ml. of 10% aqueous potassium hydroxide and extracted with ether. The ether extract was washed with water and dried over calcium chloride. The residue obtained by removal of the ether was dissolved in 100 ml. of ethanol. The resulting solution was heated to boiling and 40 ml. of concentrated hydrochloric acid (0.51 mole) was added portionwise. The boiling was continued for ten minutes, but at no time was the odor of formaldehyde evident. Upon cooling and filtration, 20 g. of a white crystalline hydrochloride was obtained. An additional 7.0 g. was obtained from the mother liquor; m.p. 209–210° (dec.) after recrystallization from ethanol; yield 28%. A portion of the hydrochloride was dissolved in water and treated with excess potassium carbonate. The solid which separated melted at 58–60° after recrystallization from petroleum ether and did not depress the m.p. of 2-cyclohexylaminomethylphenol prepared from I by hydrolysis.

Synthesis of I from II.—To 1.5 g. of paraformaldehyde (0.05 mole) dissolved in 50 ml. of methanol containing 0.05 g. of potassium hydroxide was added 10.25 g. of 2-cyclohexylaminomethylphenol (0.05 mole) and 50 ml. of methanol. After the reaction mixture was heated under gentle reflux for one and a half hours the methanol was removed under reduced pressure. The residue was treated with 30 ml. of 10% aqueous potassium hydroxide and extracted with ether. The ether extract was dried over sodium sulfate. The product obtained by removal of ether distilled at 133–135° (0.7 mm.) to give 9.4 g. (86% yield) of an almost colorless oil; $n^{25}D$ 1.5503.

Condensation of 2-Benzylaminomethylphenol with Formaldehyde.—2-Benzylaminomethylphenol, obtained by the action of aqueous potassium carbonate on the hydrochloride, reacted with an equimolar quantity of formaldehyde, under conditions similar to those described above for the conversion of II to I, to give a solid melting at 64–65°. This product did not depress the m.p. of 3,4-dihydro-3-benzyl-1,3,2H-benzoxazine prepared directly from phenol; yield 80%.

2-Cyclohexylaminomethyl-4-bromophenol (III).—Cyclohexylamine (11.2 ml., 0.1 mole) was added portionwise with cooling to 50 ml. of dioxane containing 7.5 ml. of 37% aqueous formaldehyde (0.1 mole). *p*-Bromophenol (17.3 g., 0.1 mole) was added and the solution heated under reflux for two hours. The dioxane was removed by vacuum distillation and the residue crystallized from ethanol; yield 15 g. (53%); m.p. 87–88°, after recrystallization from ethanol.

Anal. Calcd. for $C_{13}H_{18}BrNO$: C, 55.00; H, 6.38; Found: C, 55.38; H, 6.34.

Reaction of 2-Cyclohexylaminomethyl-4-bromophenol. (III) **with Metallic Sodium in Liquid Ammonia.**—To 2.0 g of sodium dissolved in 200 ml. of liquid ammonia in a 500 ml. three-necked flask equipped with a mechanical stirrer and a reflux condenser was added with stirring a solution containing 2.5 g. of 2-cyclohexylaminomethyl-4-bromophenol in 60 ml. of absolute ether which had been cooled in a Dry Ice–acetone-bath. After four minutes, sufficient ammonium chloride was added with stirring to destroy the blue color. The ammonia was evaporated and the residue treated with 50 ml. of water and acidified with concentrated hydrochloric acid. The mixture was then made basic with 2-aminoethanol, diluted with 150 ml. of water and extracted twice with ether. The combined ether extracts were dried over sodium sulfate. The solid residue (1.8 g., 100% yield) obtained by removal of ether was recrystallized from petroleum ether (b.p. 60–90°); m.p. 58–60°. The product did not depress the melting point of II prepared from I.

Synthesis of II from IV.—Three grams of IV[9] in 80 ml. of absolute ether was treated with 2 g. of sodium in 200 ml. of liquid ammonia and the product isolated essentially as described with III above. The resulting oil was dissolved in 25 ml. of boiling ethanol and 1.5 ml. of concentrated hydrochloric acid was added. The ethanol was removed by distillation and the residue dissolved in 100 ml. of water and treated with an excess of potassium carbonate. The solid (2.0 g.) which separated was washed thoroughly with water; m.p. 57–59°; yield 96%. The m.p. of this product was not depressed by admixture with a sample of II prepared from I.

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