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

3,4-Dihydro-1,3,2H-Benzoxazines. Reaction of Polyhydroxybenzenes with N-Methylolamines[1]

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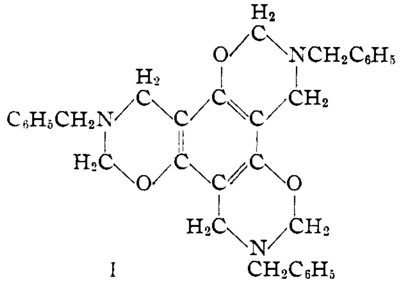
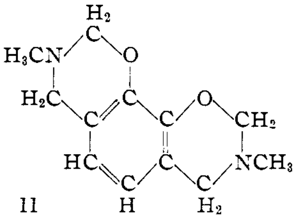
Several investigators[3,4,5,6] have studied the reaction of phenols with N-methylol derivatives obtained by condensing secondary amines with formaldehyde. For example, Bruson and MacMullen[5] obtained 2,4,6-tris-(dimethylaminomethyl)-phenol from phenol, formaldehyde and dimethylamine, and Caldwell and Thompson[6] reported related condensation products from hydroquinone and N-methyloldimethylamine. Less attention has been given to condensations involving phenols, formaldehyde and primary aliphatic amines. Such reactions offer a route to the related *o*- and *p*-alkylaminomethylphenols[7,8] and, as recently shown,[9] to the 3,4-dihydro-1,3,2H-benzoxazines.

The present investigation has been directed toward obtaining monomeric, heterocyclic products by the reaction of polyhydroxybenzenes with various N,N-dimethylolamines derived from representative primary aliphatic and alicyclic amines. From phloroglucinol, formaldehyde and benzylamine in dioxane solution 3,4,6,7,8,10,11,12-octahydro-3,7,11-tribenzyl-2H-benzo[1,2-*e*,3,4-*e*′,5,6-*e*″]tris-*m*-oxazine (I) was obtained in 48% yield. In view of the results obtained in a study[9] of the condensation of monohydric phenols with N,N-dimethylolamines and the fact that the reaction proceeds with the condensation of one mole of phloroglucinol to six of formaldehyde and three of the amine, a tris-*m*-oxazine structure has been assigned to this product.



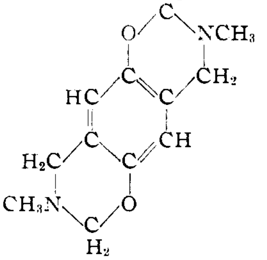
I

In an analogous fashion catechol, formaldehyde and methylamine reacted to give 2,3,4,7,8,9-hexahydro-3,8-dimethylbenzo[1,2-*e*,4,3-*e*′]-bis-*m*-oxazine (II). Related products were obtained by replacing methylamine with cyclohexylamine or benzylamine. The polybenzoxazine structures assigned the products from phloroglucinol and catechol are also consistent with infrared absorption spectra studies (Figs. 1 and 2). The several sharp absorption bands between 8 and 9 μ and that at 3.50 μ correspond to those produced by ether and aminomethylene groups, respectively. The absence of absorption maxima in the range of 2.66 to 2.98 μ indicates the absence of a phenolic hydroxyl. The curves obtained for the poly-*m*-benzoxazines resemble in considerable detail that given in Fig. 3 for 3,4-dihydro-3-benzyl-6-methyl-1,3,2H-benzoxazine.

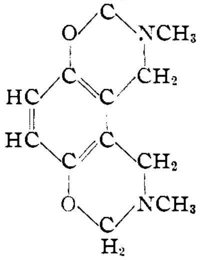


II

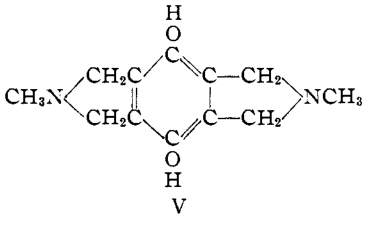
The condensation of N,N-dimethylolmethylamine with hydroquinone presents an interesting case since all of the four unsubstituted positions of the latter are ortho to phenolic hydroxyls, and hence potentially formaldehyde reactive. The compound obtained analyzed for $C_{12}H_{16}N_2O_2$, which is that required for structures III, IV and V. The product failed to give a test for active



III



IV



V

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(1) Presented in part before the Division of Organic Chemistry of the American Chemical Society at St. Louis, September 9, 1948.

(2) Abstracted from a dissertation submitted by Carl Weatherbee to the Graduate School of the University of Utah in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(3) F. F. Blicke, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942. Chapter 10 is a general review of the Mannich reaction.

(4) Burckhalter, Tendick, Jones, Holcomb and Rawlins, THIS JOURNAL, **68**, 1894 (1946).

(5) Bruson and MacMullen, *ibid.*, **63**, 270 (1941).

(6) Caldwell and Thompson, *ibid.*, **61**, 765 (1939).

(7) Bruson, *ibid.*, **58**, 1741 (1936).

(8) Burckhalter, Tendick, Jones, Jones, Holcomb and Rawlins, *ibid.*, **70**, 1363 (1948).

(9) Burke, *ibid.*, **71**, 609 (1949).

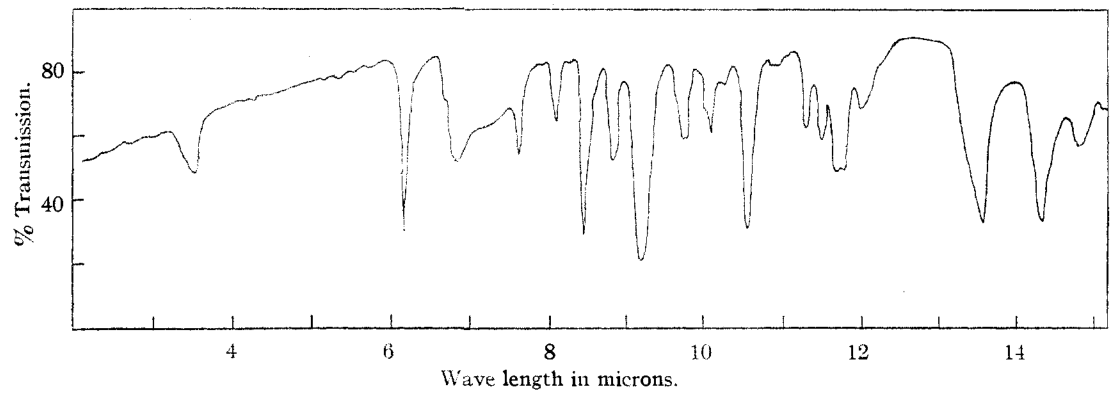


Fig. 1.—Infrared absorption spectra of 3,4,6,7,8,10,11,12-octahydro-3,7,11-tribenzyl-2H-benzo[1,2-*e*,3,4-*e*′,5,6-*e*″]tris-*m*-oxazine.

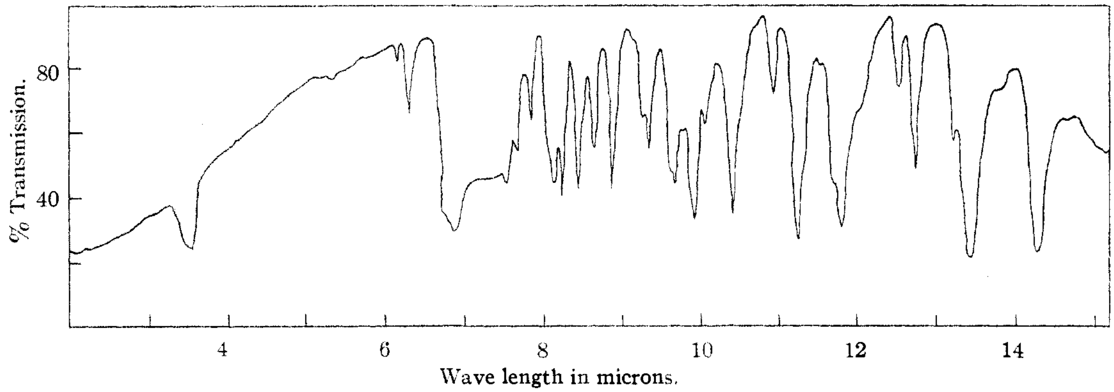


Fig. 2.—Infrared absorption spectra of 2,3,4,7,8,9-hexahydro-3,8-dibenzylbenzo[1,2-*e*,4,3-*e*′]bis-*m*-oxazine.

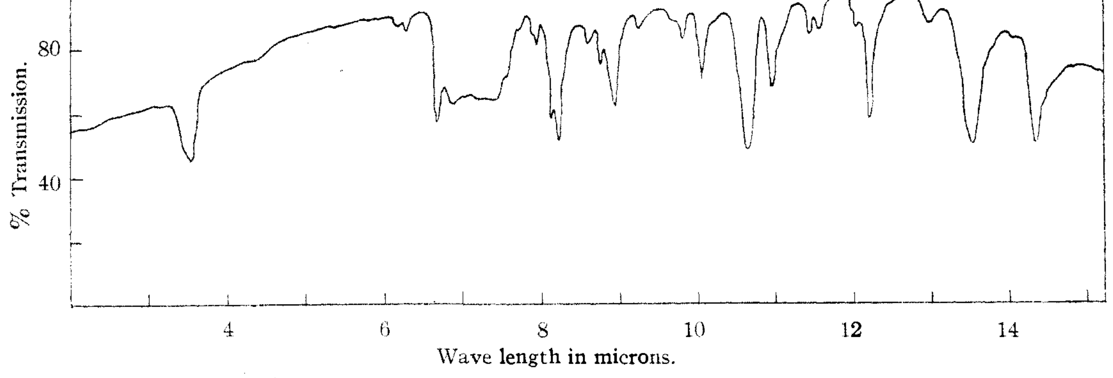
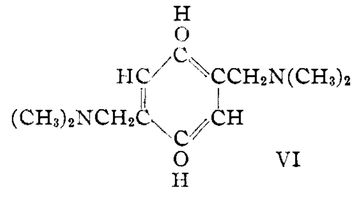


Fig. 3.—Infrared absorption spectra of 3,4-dihydro-3-benzyl-6-methyl-1,3,2H-benzoxazine.

hydrogen, and treatment with aqueous hydrochloric acid resulted in the liberation of formaldehyde and the formation of crystalline material analyzing for the dihydrochloride of bis-(methylaminomethyl)-hydroquinone. This behavior is consistent with structures III and IV but not V.

Treatment of the condensate from hydroquinone and N,N-dimethylolmethylamine with formic acid gave a crystalline product shown to be the same as that prepared directly from hydroquinone, formaldehyde and dimethylamine by Caldwell and Thompson[6] and characterized by them as 2,5-bis-(dimethylaminomethyl)-hydroquinone (VI). Compound III but not IV could



VI

be expected to react in this manner. The conversion of III to VI with formic acid is an in-

TABLE I

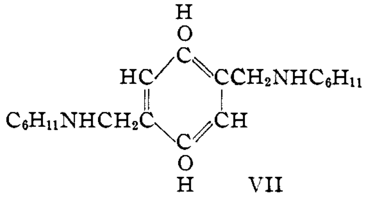
POLY-*m*-BENZOXAZINES FROM N,N-DIMETHYLOLAMINES AND POLYHYDROXYBENZENES

Primary amine	Phenol	M. p.,[a] °C.	Yield, %	Formula[b]	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Methyl	Catechol	174–175[c]	45	$C_{12}H_{16}N_2O_2$	...	...	..	..	12.72	12.77
Benzyl	Catechol	182–183[d]	48	$C_{24}H_{24}N_2O_2$	77.39	77.80	6.49	6.52	...	...
Cyclohexyl	Catechol	143–144[e]	29	$C_{22}H_{32}N_2O_2$	...	...	..	..	7.86	7.91
Methyl	Hydroquinone	182–183[e]	61	$C_{12}H_{16}N_2O_2$	65.43	65.20	7.32	7.05	12.72	12.72
Cyclohexyl	Hydroquinone	161–162[c]	31	$C_{22}H_{32}N_2O_2$	74.12	73.92	9.05	8.80	...	...
Benzyl	Toluhydroquinone[e]	105[f]	58	$C_{25}H_{26}N_2O_2$	77.69	77.65	6.78	6.52	...	...
Benzyl	Phloroglucinol	162–163[g]	48	$C_{33}H_{33}N_3O_3$	76.27	75.75	6.40	6.12	8.09	8.04

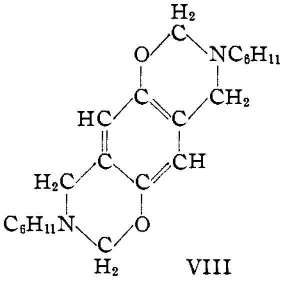
[a] Uncorrected. [b] The product from phloroglucinol is a tris-*m*-benzoxazine. All of the other products are bis-*m*-benzoxazines. [c] Recrystallized from 95% ethanol. [d] Recrystallized from benzene. [e] An experimental sample was received through the courtesy of the Tennessee Eastman Corp. [f] Recrystallized from methanol. [g] Recrystallized from benzene–ethanol solution (90:10).

teresting variation of the procedure[10] by which primary and secondary amines are methylated through reaction with formaldehyde in combination with formic acid.

Yields of poly-*m*-benzoxazines ranging from 31 to 61% were obtained when various N,N-dimethylolalkylamines and polyhydroxybenzenes were heated in dioxane solution. One mole of amine was employed for each hydroxyl group in the phenol. A summary of the products prepared in this manner is given in Table I. An alternate method of synthesis involved the preparation of an intermediate bis-(cyclohexylaminomethyl)-hydroquinone (VII) by condensation of cyclohexylamine, formaldehyde and hydroquinone in a molar ratio of 2:2:1, respectively. Condensation of VII with formaldehyde gave a product (VIII) identical with that obtained directly from the reaction of cyclohexylamine, formaldehyde and hydroquinone in a molar ratio 2:4:1, respectively. In view of the results obtained with methylamine, formaldehyde and hydroquinone, the indicated symmetrical structures were assigned to the products.



VII



VIII

Upon heating under reflux in the presence of acetic anhydride, III was converted to 2,5-bis-(N-acetyl-N-methylaminomethyl)-hydroquinone. Analogous results were obtained with VIII. This indicates that the 2,5-bis-(methylaminomethyl)-hydroquinone, assumed to be an intermediate in the reaction, behaved quite differently than the related dialkylaminomethylphenols, which under similar conditions are converted to the corresponding acetoxymethylphenyl acetates.[5]

Acknowledgment.—The assistance given by the Research Corporation in the form of a Frederick Gardner Cottrell Research Grant is gratefully acknowledged.

Experimental

3,4,6,7,8,10,11,12-Octahydro-3,7,11-tribenzyl-2H-benzo[1,2-*e*,3,4-*e*',5,6-*e*"]tris-*m*-oxazine (I).—To 16.5 ml. of aqueous 37% formaldehyde (0.22 mole) in 50 ml. of dioxane at 15–18° was added dropwise with shaking 10.7 g. (0.1 mole) of benzylamine. The resulting solution was agitated and 4.9 g. (0.03 mole) of phloroglucinol dihydrate added. The original yellow solution turned yellowish-orange upon refluxing for 1.5 hours. The solvent was removed by evaporation under the hood. Upon recrystallization of the resulting white solid from benzene–ethanol (90:10), 7.5 g. of crystalline material was obtained; m. p. 162–163°, yield 48%. The product was insoluble in methanol and 40% aqueous potassium hydroxide and partially soluble in hot ethanol. It was soluble in aqueous hydrochloric acid, benzene and hot carbon tetrachloride and ethyl acetate.

2,5-Bis-(methylaminomethyl)-hydroquinone Hydrochloride from 2,3,4,7,8,9-Hexahydro-3,8-dimethylbenzo[1,2-*e*,4,5-*e*']bis-*m*-oxazine (III).—Four-tenths of a gram (0.0018 mole) of the oxazine was dissolved in 20 ml. of warm 95% ethanol. After cooling in an ice-bath, 4 ml. of concentrated hydrochloric acid was added. The mixture was then slowly distilled. The distillate was collected in a flask containing an alcoholic solution of 2,4-dinitrophenylhydrazine. As the alcohol distilled off, 20 ml. of water was added gradually to the distilling flask. Distillation was continued until a white solid began to separate. The contents of the distilling flask were then decanted to an evaporating dish and placed under a hood. After evaporation of the solvents, 0.35 g. of grayish-white solid remained; yield 72%. Upon three recrystallizations from 15 ml. of water, the product melted at 269–270° (dec.).

Anal. Calcd. for $C_{10}H_{18}Cl_2N_2O_2$: C, 44.62; H, 6.74. Found: C, 44.67; H, 6.67.

A yellow solid had formed in the distillate. Upon recrystallization from 15 ml. of 95% ethanol, it melted at 165–166°. A mixed melting point with the 2,4-dinitrophenylhydrazone of formaldehyde showed no depression.

Reaction of 2,3,4,7,8,9-Hexahydro-3,8-dimethylbenzo-[1,2-*e*,4,5-*e*']bis-*m*-oxazine with Formic Acid.—Two and a half grams (0.011 mole) of the oxazine was placed in a

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(10) Icke and Wisegarver, *Org. Syntheses*, **25**, 89 (1945).

round-bottom flask equipped with a dropping funnel and reflux condenser. After cooling the flask in an ice-bath, 10.8 g. (0.2 mole) of 85% formic acid was added dropwise with agitation. A portion of the oxazine dissolved; the balance formed a sirup. After addition of 3.8 ml. of 37% aqueous formaldehyde, the flask was immersed in an oil-bath at 90°, and then allowed to cool to 70° over a period of 30 minutes. Some evolution of gas was noted. The bath was then warmed at 90° for 2 hours and finally overnight (12 hours) at 85°.

After cooling, 5 ml. concentrated hydrochloric acid was added. Removal of the solvent under reduced pressure gave a light brown solid which was readily soluble in 15 ml. of warm water. This was made basic with sodium bicarbonate and the solution extracted with four 20-ml. portions of ethyl acetate. The solvent was removed by vacuum distillation yielding 1.8 g. (71% yield) of crude product. Recrystallization from ethanol gave m. p. 190–191°; mixed m. p. with 2,5-bis-(dimethylaminomethyl)-hydroquinone (VI), prepared directly from hydroquinone, formaldehyde and dimethylamine[6] (m. p. 190–191°) was 190–191°. Caldwell and Thompson[6] reported a m. p. of 190° for VI.

2,5-Bis-(cyclohexylaminomethyl)-hydroquinone (VII).—To a cooled solution of 16.5 ml. (0.22 mole) of 37% aqueous formaldehyde in 75 ml. of dioxane was added with vigorous shaking 25.3 ml. (0.22 mole) of cyclohexylamine over a period of two minutes. Then 11 g. (0.1 mole) of hydroquinone was added and the mixture warmed at 55° for 2.5 hours under a reflux condenser. Upon removal of the solvents by vacuum distillation a viscous liquid remained. This was washed into a beaker with methanol. Upon concentrating the solution by air jet evaporation, followed by filtration, 11.6 g. of crude crystalline product was obtained. Upon recrystallization from ethyl acetate white fluffy crystals resulted; m. p. 173–174°, yield 35%. The product was soluble in dilute hydrochloric acid, potassium hydroxide, hot 95% ethanol, methanol, acetone and ethyl acetate; slightly soluble in hot chloroform and insoluble in cold or hot water, benzene and carbon tetrachloride.

Anal. Calcd. for $C_{20}H_{32}N_2O_2$: C, 72.25; H, 9.70. Found: C, 72.10; H, 9.75.

The hydrochloride of (VII) melted at 284–285°.

Anal. Calcd. for $C_{20}H_{34}Cl_2N_2O_2$: neut. equiv., 203. Found: neut. equiv., 207.

Preparation of 2,3,5,7,8,9-Hexahydro-3,8-dicyclohexylbenzo[1,2-*e*,4,5-*e*′]bis-*m*-oxazine (VIII) from 2,5-Bis-(cyclohexylaminomethyl)-hydroquinone (VII).—To 0.5 g. (0.0015 mole) of 2,5-bis-(cyclohexylaminomethyl)-hydroquinone in 50 ml. of cooled dioxane was added 0.4 ml. (0.0053 mole) of 37% aqueous formaldehyde with vigorous shaking. The solution was warmed for two hours at 55° under a reflux condenser and allowed to cool to room temperature and stand for one hour. Removal of the solvent by vacuum distillation gave 0.46 g. of white crystalline product; m. p. 158–160°; upon recrystallization from ethyl acetate, m. p. 161–162°; yield 86%. A mixed m. p. determination with the product (VIII) obtained by reaction of 0.1 mole cyclohexylamine, 0.2 mole formaldehyde and 0.05 mole hydroquinone (m. p. 161–162°) showed no depression.

Acetylation of 2,3,4,7,8,9-Hexahydro-3,8-dicyclohexylbenzo[1,2-*e*,4,5-*e*′]bis-*m*-oxazine (VIII).—To 6 g. (0.017 mole) of (VIII) in a 200-ml. round-bottom flask was added 15 ml. (0.16 mole) of acetic anhydride. The solid did not dissolve upon warming for four hours at 50–60° but it dissolved upon further heating at 90–95° for two hours. It was warmed at 80° for two hours and then allowed to stand at room temperature for three hours. A brown viscous liquid separated and carbon dioxide was evolved upon addition of sodium bicarbonate until the solution became basic. The liquid solidified to a brown solid upon standing and was removed by filtration. The filtrate was extracted with four 25-ml. portions of chloroform and this was combined with an alcoholic solution (90 ml.) of the above brown solid. Upon removing the solvents, and recrystallization of the resulting product from 95% ethanol (40 ml.) approximately 3 g. of white product was obtained; m. p. 290° (dec.). The analytical results obtained for the product correspond to those calculated for 2,5-bis-(N-acetyl-N-cyclohexylaminomethyl)-hydroquinone.

Anal. Calcd. for $C_{24}H_{36}N_2O_4$: C, 69.20; H, 8.71. Found: C, 69.34; H, 8.43.

2,5-Bis-(N-acetyl-N-methylaminomethyl)-hydroquinone.—2,3,4,7,8,9-Hexahydro-3,8-dimethylbenzo[1,2-*e*,4,-5-*e*′]bis-*m*-oxazine (III) was subjected to acetylation under conditions comparable to those employed with VIII, as described above. The resulting product melted at 273–275° (dec.).

Anal. Calcd. for $C_{14}H_{20}N_2O_4$: C, 59.99; H, 7.19. Found: C, 60.47; H, 7.01.

Tests for Active Hydrogen.—No evolution of methane was observed when dry benzene solutions of compounds assigned the structures III, VIII and 2,3,4,7,8,9-hexahydro-3,8-dibenzylbenzo[1,2-*e*,4,3-*e*′]bis-*m*-oxazine were treated with a solution of methylmagnesium iodide in butyl ether. When sodium was added to dry benzene solutions of III and VIII no evolution of hydrogen was detected. In contrast, addition of methylmagnesium iodide in butyl ether to either VI or VII in dry benzene resulted in the definite evolution of a gas.

Infrared Absorption Spectra.—The infrared absorption spectra reported were determined with a Baird double beam recording spectrophotometer through the courtesy of Samuel P. Sadtler and Son, Inc. In all cases the sample was mulled in mineral oil.

Summary

1. A series of novel poly-*m*-benzoxazines has been prepared by condensation of polyhydroxybenzenes with formaldehyde and primary aliphatic and alicyclic amines.

2. Reaction of the bis-*m*-benzoxazine from hydroquinone, formaldehyde and methylamine with formic acid yielded 2,5-bis-(dimethylaminomethyl)-hydroquinone.

3. The action of aqueous hydrochloric acid and acetic anhydride on representative poly-*m*-benzoxazines was studied.

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