suspension was kept at room temperature to evaporate the ammonia and finally was refluxed for 1 hr. to remove a trace of ammonia. To this lithium amide suspension in ether 12.1 g. (0.05 mole) of trimethyltin bromide in 30 ml. of anhydrous ether was added. Refluxing for 3 hr. followed by vacuum distillation gave 7.0 g. (83%) of white crystals, b.p. 130° (14 mm.), m.p. 22–24°.

Tris(triethyltin)amine and Tris(tri-*n*-propyltin)amine were prepared also in about 70% yields by an analogous method.

Tris(triethyltin)amine was obtained from triethyltin chloride,[14] b.p. 86–88° (9 mm.), as white crystalline needles, b.p. 192–194° (4 mm.), redistillation, m.p. 21–22°.

Anal. Calcd. for $C_{18}H_{45}NSn_3$: N, 2.22; Sn, 56.38. Found: N, 2.23; Sn, 56.48.

As soon as 2.52 g. (0.0400 mole) of the substance was exposed to air, ammonia was evolved and 2.81 g. (0.0596 mole) of white crystals were obtained. These crystals were identified as triethyltin carbonate by the infrared spectra (1540, 1370, 1070, and 833 cm.$^{-1}$ [11]) and analyses. During air decomposition, a strong band at 775 cm.$^{-1}$ (Sn–O–Sn) appeared, but this disappeared in several minutes.

Tris(tri-*n*-propyltin)amine, prepared from tri-*n*-propyltin chloride,[14] b.p. 122–123° (10 mm.), was a colorless liquid, b.p. 143–145° (0.6 mm.), on redistillation.

Anal. Calcd. for $C_{27}H_{63}NSn_3$: N, 1.85; Sn, 46.98. Found: N, 1.94; Sn, 46.79.

On similar air exposure, from 1.06 g. (0.0140 mole) of the substance, 1.15 g. (0.0207 mole) of pasty viscous oil was obtained. This was identified as tri-*n*-propyltin carbonate by an analogous method.

Trimethyl(diethylamino)tin.[15]—An ether solution of diethylaminolithium prepared from 0.76 g. (0.11 g.-atom) of lithium metal and 6.9 g. (0.05 mole) of *n*-butyl bromide and 4.0 g. (0.055 mole) of diethylamine in 30 ml. of anhydrous ether was added dropwise to a solution of 7.3 g. (0.03 mole) of trimethyltin bromide[12] in 30 ml. of ether. After refluxing for 3 hr., the solvent was distilled and the reaction product was fractionated under atmospheric pressure. A fraction boiling at 156–162°, lit.[15] b.p. 162°, was collected, yielding 4.3 g. (61%). The infrared spectrum of this compound had the characteristic absorptions of the diethylaminotin grouping at 1455, 1372, 1290, 1185, 1170, 1150, 1116, 1075, 1048, 1007, and 872 cm.$^{-1}$. All these bands immediately disappeared on exposure to air and a characteristic band of trimethyltin hydroxide at 917 cm.$^{-1}$ appeared.

Decomposition of Bis(triethyltin) Oxide by Exposure to Air.—On exposing 2.97 g. (0.00694 mole) of bis(triethyltin) oxide[16] (b.p. 142–143° at 13 mm., n^{20}D 1.5005) to air for 12 hr., 3.26 g. of white crystals were obtained. The weight increase of 0.29 g. corresponds to the 0.0066 mole of carbon dioxide. These crystals were identified also as triethyltin carbonate by infrared spectrum, analysis, and decomposition point.

Bis(triethyltin) Oxide from Triethyltin Carbonate.—Upon heating 3.2 g. of triethyltin carbonate at 140–150° *in vacuo*, the white crystals melted with evolution of carbon dioxide. After an additional heating for 5 hr., the product was distilled at 155–156° (20 mm.) to obtain 2.7 g. (93%) of bis(triethyltin) oxide, n^{20}D 1.4990. The infrared spectrum had a strong band at 775 cm.$^{-1}$, but no bands at 1540, 1370, 1070, and 833 cm.$^{-1}$.

Decomposition of Bis(tri-*n*-propyltin) Oxide by Exposure to Air.—On exposing 1.45 g. (0.00283 mole) of bis(tri-*n*-propyltin) oxide[17] (b.p. 161–166° at 5 mm., n^{20}D 1.4917) to air for 12 hr., 1.56 g. of viscous pasty oil was obtained. The weight increase of 0.11 g. corresponds to 0.0025 mole of carbon dioxide. This was identified as tri-*n*-propyltin carbonate by infrared spectrum.

Bis(tri-*n*-propyltin) Oxide from Tri-*n*-propyltin Carbonate.—A 2.9-g. sample of tri-*n*-propyltin carbonate was heated for 5 hr. at about 150° under diminished pressure and the content was distilled at 161–165° (5 mm.) when bis(tri-*n*-propyltin) oxide, n^{20}D 1.4911, was obtained, yielding 2.4 g. (90%). The infrared spectrum had a strong band at 775 cm.$^{-1}$, but no bands at 1540, 1370, and 833 cm.$^{-1}$.

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(15) E. W. Abel, D. Brady, and B. R. Lerwill, *Chem. Ind.* (London), 1333 (1962). In this report no detailed preparation has been described.

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(17) T. Harada, *Sci. Papers Inst. Phys. Chem. Res.* (Tokyo), **42**, 57 (1947); *Chem. Abstr.*, **43**, 7900 (1949).

Condensation of Halophenols with Formaldehyde and Primary Amines[1]

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The reaction of *o*- and *p*-halogen-substituted phenols with formaldehyde and representative primary aliphatic amines was studied. The number of halogen substituents on the phenol and the specific amine used were found to be important factors in determining both the course of the condensation and the stability of the benzoxazines, which were obtained with substituted N,N-bis(hydroxybenzyl)amines and substituted 2-aminomethylphenols.

The Mannich reaction involving phenols, formaldehyde, and primary amines has been used as a convenient source of a variety of compounds. The course of this generally facile condensation is, however, greatly influenced by a number of reaction variables.[4,5] In particular, the size of the *ortho* substituent on the phenol has been shown to play an important role. For example, by merely utilizing the calculated quantities of reactants in the condensation of 2,4-dimethylphenol with formaldehyde and cyclohexylamine, high yields (70–90%) of either 2-cyclohexylaminomethyl-4,6-dimethylphenol (Ia), or 3-cyclohexyl-3,4-dihydro-6,8-dimethyl-2*H*-1,3-benzoxazine (IIa), or bis(3,5-dimethyl-2-hydroxybenzyl)cyclohexylamine (IIIa) can be obtained.[4] Use of 4-*t*-butylphenol in place of 2,4-dimethylphenol, however, resulted in a high yield of a benzoxazine (II) even when the molar ratio of reactants was that calculated for the formation of a bis(hydroxybenzyl)amine (III). In contrast, efforts to prepare benzoxazines (II) from a phenol having an *o*-*t*-butyl substituent were unsuccessful, and only the bis(hydroxybenzyl)amine (III) was obtained.[4]

In view of the striking manner in which the course of the condensation can be shifted by steric factors, it was of interest to determine the effect of varying the electrophilic character of substituents on the phenol. A comparison of *o*-chloro- and *o*-methylphenols in such studies appeared to have attractive possibilities for substantially eliminating steric factors since the chloro and methyl groups are approximately equivalent in size.

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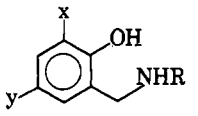
(3) This paper was abstracted in part from a dissertation presented to the faculty of the University of Utah by E. L. Mortenson in partial fulfillment of the requirements for the Ph.D. degree.

(4) W. J. Burke, R. P. Smith, and C. Weatherbee, *J. Am. Chem. Soc.*, **74**, 602 (1952).

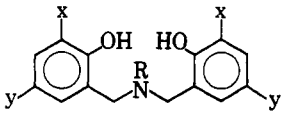
(5) W. J. Burke, M. J. Kolbezen, and C. W. Stephens, *ibid.*, **74**, 3601 (1952).

TABLE I

SUBSTITUTED 2-AMINOMETHYLPHENOLS AND N,N-BIS(2-HYDROXYBENZYL)AMINES



I



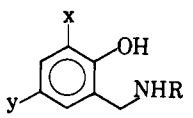
III

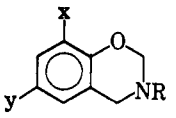
Structure	R	x	y	Yield,[a] %	Recrystn. solvent	M.p., °C.	Molecular formula	—Carbon, %— Calcd.	Found	—Hydrogen, %— Calcd.	Found	—Nitrogen, %— Calcd.	Found
I	CH_3	Cl	Cl	61	CH_3OH	191–192	$C_8H_9Cl_2NO$[b]	46.62	46.86	4.40	4.17		
I	C_6H_{11}	Cl	Cl	67	CH_3OH	157–158	$C_{13}H_{17}Cl_2NO$	56.96	57.45	6.25	6.50	5.11	4.70
I	CH_3	Br	Br	73[c]	C_6H_6	194–195	$C_8H_9Br_2NO$	32.57	33.01	3.08	3.39	4.75	4.66
I	C_6H_{11}	Br	Br	90	C_2H_5OH	168–169	$C_{13}H_{17}Br_2NO$	43.00	43.01	4.72	4.75	3.86	3.57
I	$C_6H_5CH_2$	Cl	Cl	72	C_2H_5OH	112–113	$C_{14}H_{13}Cl_2NO$[d]	59.59	59.74	4.64	4.49		
III	CH_3	Cl	Cl	18	CH_3OH	118–119	$C_{15}H_{13}Cl_4NO_2$[e]	47.27	47.45	3.44	3.48		
III	CH_3	Br	Br	88[f]	C_6H_6	129–130	$C_{15}H_{13}Br_4NO_2$	32.23	32.33	2.34	2.68	2.56	2.51
III	CH_3	CH_3	Cl	66	CH_3OH	104–105	$C_{17}H_{19}Cl_2NO_2$	60.02	60.34	5.63	5.97	4.12	4.36
III	C_6H_{11}	CH_3	Cl	53	ligroin	140–141	$C_{22}H_{27}Cl_2NO_2$	64.70	64.55	6.67	6.76		
III	C_6H_{11}	Cl	CH_3	48	ligroin	124–125	$C_{22}H_{27}Cl_2NO_2$	64.70	64.54	6.67	7.09		
III	CH_3	Br	$C(CH_3)_3$	50	C_2H_5OH	122–123	$C_{23}H_{31}Br_2NO_2$	53.82	53.83	6.09	6.12		
III	C_6H_{11}	Br	$C(CH_3)_3$	43	ligroin	167–168	$C_{28}H_{39}Br_2NO_2$[g]	57.84	58.49	6.76	6.70		

[a] In all instances the reactant ratio of phenol–formaldehyde–amine was 2:2:1, that calculated for structure III. The yields given for compounds of structure I were based on this amine. [b] The **hydrochloride** melted at 193–194° after recrystallization from methanol. *Anal.* Calcd. for $C_8H_{10}Cl_3NO$: Cl^-, 14.62. Found: Cl^-, 14.56. [c] A 93% yield was obtained by the condensation of equimolar condensation of reactants. [d] **Hydrochloride,** m.p. 207–208°, from methanol. *Anal.* Calcd. for $C_{14}H_{14}Cl_3NO$: Cl^-, 11.13. Found: Cl^-, 11.04. [e] **Hydrochloride,** m.p. 164–166°, from methanol. *Anal.* Calcd. for $C_{15}H_{14}Cl_5NO_2$: Cl^-, 8.49. Found: Cl^-, 8.43. [f] Yield in 2 weeks; yield was 13% after 3 days. [g] **Hydrochloride,** m.p. 170–173°, from methanol. *Anal.* Calcd. for $C_{28}H_{40}Br_2ClNO_2$: Cl^-, 5.72. Found: Cl^-, 5.62.

A further variation in electronegative effects was visualized through use of di- as well as monohalophenols (see Table I).

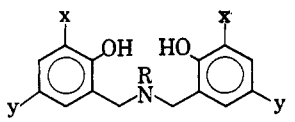
Condensation of 2,4-dichlorophenol with formaldehyde and cyclohexylamine in the proportions required for the formation of a bis(hydroxybenzyl)amine (IIIb) resulted in the isolation of only the corresponding Mannich base (Ib, 67% yield). However, replacement of cyclohexylamine with methylamine in this reaction led to the isolation of both the Mannich base (Ic, 61% yield) and the bis(hydroxybenzyl)amine (IIIc, 18% yield). Use of benzylamine in this reaction led to the isolation of a high yield of Mannich base (Id) along with some benzoxazine (IIc) but no bis(hydroxybenzyl)amine.





Ia, R = C_6H_{11}; x = y = CH_3
b, R = C_6H_{11}; x = y = Cl
c, R = CH_3; x = y = Cl
d, R = $C_6H_5CH_2$; x = y = Cl
e, R = CH_3; x = y = Br
f, R = C_6H_{11}; x = y = Br

IIa, R = C_6H_{11}; x = y = CH_3
b, R = C_6H_{11}; x = y = Cl
c, R = $C_6H_5CH_2$; x = y = Cl
d, R = CH_3; x = y = Br



IIIa, R = C_6H_{11}; x = y = CH_3
b, R = C_6H_{11}; x = y = Cl
c, R = CH_3; x = y = Cl
d, R = CH_3; x = y = Br

Efforts to convert the Mannich base from cyclohexylamine (Ib) to the corresponding bis(hydroxybenzyl)amine (IIIb) by reaction with equimolar quantities of formaldehyde and 2,4-dichlorophenol at room temperature gave a 60% yield of the corresponding benzoxazine (IIb). In contrast, reaction of 2-cyclohexylaminomethyl-4,6-dimethylphenol (Ia) with formaldehyde and 2,4-dimethylphenol was shown earlier to form bis(3,5-dimethyl-2-hydroxybenzyl)methylamine (IIIa) readily.[4] The benzoxazine (IIb) also was obtained directly from the reaction of 2,4-dichlorophenol with formaldehyde and cyclohexylamine in the calculated proportions at 85°. The analogous benzoxazines (II) were obtained when cyclohexylamine was replaced with methyl- or benzylamine. The new benzoxazines prepared in this work are listed in Table II.

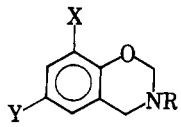
Reaction of 2,4-dibromophenol with formaldehyde and methylamine in a 2:2:1 molar ratio at room temperature for 3 days gave a 73% yield of Mannich base (Ie) along with a 13% yield of the bis(2-hydroxybenzyl)-amine (IIId). However, when the reaction time was 2 weeks, a much higher yield (88%) of the bis compound (IIId) was obtained. These results suggest that the Mannich base may be an intermediate in the formation of IIId. This is of particular interest in view of earlier indications that the Mannich base is not an intermediate in the synthesis of naphthoxazines from 2-naphthol, formaldehyde, and primary aromatic amines.[6] When 2,4-dibromophenol reacted with formaldehyde and cyclohexylamine in a molar ratio of 2:2:1, only the Mannich base (If) was isolated. High yields of the benzoxazine (IId) were obtained directly from 2,4-dibromophenol, formaldehyde, and methylamine in a 1:2:1 molar ratio, and also from 2,4-dibromo-6-methylaminomethylphenol and formaldehyde in equimolar proportions.

Replacement of the 4-methyl group in 2,4-dimethylphenol with chlorine did not lead to significantly dif-

(6) W. J. Burke, K. C. Murdock, and G. Ek, *J. Am. Chem. Soc.*, **76**, 1677 (1954).

TABLE II

SUBSTITUTED 3,4-DIHYDRO-2*H*-1,3-BENZOXAZINES



R	x	y	Yield,[a] %	Recrystn. solvent	M.p., °C.	Molecular formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
CH_3	Cl	Cl	69	ligroin	56–57	$C_9H_9Cl_2NO$	49.56	49.58	4.16	4.25
C_6H_{11}	Cl	Cl	36[b]	ligroin	56–57	$C_{14}H_{17}Cl_2NO$	58.75	58.48	5.99	5.87
$C_6H_5CH_2$	Cl	Cl	39[c]	CH_3OH	62–63	$C_{15}H_{13}Cl_2NO$	61.24	61.47	4.45	4.56
CH_3	Br	Br	68	ligroin	78–79	$C_9H_9Br_2NO$	35.21	35.44	2.95	2.95
$C_6H_5CH_2$	Br	Br	78	CH_3OH	77–78	$C_{15}H_{13}Br_2NO$	47.02	47.36	3.42	3.61
CH_3	CH_3	Cl	69	C_2H_5OH	55–56	$C_{10}H_{12}ClNO$	60.76	60.42	6.12	6.11
C_6H_{11}	CH_3	Cl	44	CH_3OH	48–49	$C_{15}H_{20}ClNO$	67.78	68.18	7.59	7.81
$C_6H_5CH_2$	CH_3	Cl	73	CH_3OH	77–78	$C_{16}H_{16}ClNO$	70.19	69.99	5.89	5.95

[a] Based on the reaction of the phenol with formaldehyde and the amine in a 1:2:1 molar ratio. [b] Obtained in 60% yield from Mannich base. [c] Obtained in 83% yield from Mannich base.

ferent results in most of the condensations studied. Reaction of 4-chloro-2-methylphenol and formaldehyde with methylamine, cyclohexylamine, or benzylamine in a 1:2:1 molar ratio at 85° gave the expected benzoxazines. Similarly, N,N-bis(5-chloro-2-hydroxy-3-methylbenzyl)amines (III) were obtained by condensation of the calculated quantities of 4-chloro-2-methylphenol and formaldehyde with methyl- or cyclohexylamine. However, reaction with benzylamine under these conditions led to the isolation of only the corresponding benzoxazine. It was shown earlier[4] that 4-*t*-butyl-2-chlorophenol and formaldehyde reacted with methylamine and with cyclohexylamine in a 2:2:1 molar ratio to give the corresponding bis(hydroxybenzyl)amines.

If an N-methylol Mannich base is considered as an intermediate, the competitive reactions then involve either ring closure with the phenolic hydroxyl (benzoxazine formation), or an electrophilic attack on the *ortho* position of another molecule of the phenol to yield a bis(hydroxybenzyl)amine. Any lowering of the electron density at the free *ortho* position would, accordingly, be expected to be unfavorable to the latter reaction. This is consistent with the results of the present study which show that replacement of both methyl groups in 2,4-dimethylphenol with chloro or bromo substituents results in a marked reduction in the tendency to form bis(hydroxybenzyl)amines. The replacement of the 4-methyl group in 2,4-dimethylphenol with chlorine apparently did not bring about a sufficient reduction in the electron density at the free *ortho* position to produce any significant changes in the condensations investigated except with benzylamine.

The stability of the benzoxazines in alcohols was shown to be dependent upon the particular phenol and primary amine used in the synthesis. For example in a comparison of benzoxazines derived from cyclohexylamine, those from 2,4-dimethylphenol and 4-chloro-2-methylphenol were stable in hot ethanol. However, the analogous benzoxazine from 2,4-dichlorophenol was readily converted to the corresponding Mannich base (Ib) in 89% yield by treatment of the benzoxazine in refluxing 95% ethanol for 10 min. Benzoxazines from methylamine and either 2,4-dichloro- or 2,4-dibromophenols were sufficiently unstable in methanol that the transformation to the Mannich base occurred even at room temperature. It was possible, however, to convert the Mannich base, 2,4-dibromo-6-methylaminomethylphenol, to the benzoxazine (IId) by heating with excess formaldehyde in methanol. In condensations employing the molar proportions calculated for bis(hydroxybenzyl)amine formation, the products were commonly recrystallized from alcohols. Under such conditions any benzoxazines formed from 2,4-dihalophenols and methyl- or cyclohexylamine would be expected to convert to the corresponding Mannich bases.

In contrast to the results with methyl- or cyclohexylamine, the benzoxazines from benzylamine and either 2,4-dichloro- or 2,4-dibromophenol were stable in hot methanol and could be recrystallized readily from this solvent. However, the benzoxazines from 4-chloro-2-methylphenol and both methyl- and benzylamine were stable in hot methanol.

Compounds representative of those prepared in this study are being screened for antitumor activity by the Cancer Chemotherapy Center of the National Institutes of Health.

Experimental[7]

2-Cyclohexylaminomethyl-4,6-dichlorophenol.—The molar reactant ratio is that calculated for the formation of N,N-bis(3,5-dichloro-2-hydroxybenzyl)cyclohexylamine. Cyclohexylamine (4.95 g., 0.05 mole) in 15 ml. of dioxane was added dropwise to a solution of 7.5 ml. of 37% aqueous formaldehyde (0.1 mole) in 10 ml. of dioxane. 2,4-Dichlorophenol (16.4 g., 0.1 mole) in 25 ml. of dioxane was added, and the resulting solution was shaken thoroughly, stoppered, and kept at room temperature for 5 days. The solvents were removed under reduced pressure and the yellow liquid residue dissolved in 20 ml. of warm methanol. Upon cooling, a solid (9 g., 67% yield) precipitated and was removed by filtration, m.p. 157–158° after recrystallization from methanol.

In another run under comparable conditions the product was isolated as the **hydrochloride,** 11.5 g., 74% yield, m.p. 237–238°, after recrystallization from ethanol–water (1:1).

Anal. Calcd. for $C_{13}H_{18}Cl_3NO$: Cl^-, 11.41. Found: Cl^-, 11.35.

Only the Mannich base (28% yield) was isolated when the above reaction was repeated at room temperature.

Reaction of 2,4-Dichlorophenol with Methylamine and Formaldehyde.—Aqueous 25% methylamine (12.2 g., 0.1 mole) followed by 60 ml. of dioxane was added dropwise to an ice-cooled, stirred solution of formaldehyde (15 ml., 37%, 0.2 mole) in 40 ml. of dioxane. After addition of 2,4-dichlorophenol (32.8 g., 0.2 mole) in 100 ml. of dioxane, the solution was stirred vigorously on an ice bath for 5 min. The stoppered flask was kept at room temperature for 16 days. The solvents were removed

(7) All melting points are uncorrected.

under reduced pressure at room temperature over a period of 18 hr. Upon addition of 200 ml. of ether to the resulting viscous oil, 4.1 g. of 2,4-dichloro-6-methylaminomethylphenol, m.p. 180–182°, precipitated. The melting point after one recrystallization from methanol was 191–192°.

The filtrate was concentrated to half the original volume but no further solid separated. After addition of 10 g. of sodium hydroxide, the ether layer was separated. The aqueous layer was further extracted with 50 ml. of ether. Upon removal of the ether less than 0.1 g. of oil remained. Any benzoxazine would be expected in this fraction.

The aqueous extracts were neutralized to pH 1 with hydrochloric acid and extracted with one 100-ml. and two 50-ml. portions of ether. The combined ether extracts were dried over anhydrous sodium sulfate. Removal of the ether gave 15.5 g. of 2,4-dichlorophenol (47% recovery).

The aqueous extracts containing an insoluble layer were neutralized with potassium bicarbonate. An additional 0.8 g. of 2,4-dichloro-6-methylaminomethylphenol, m.p. 185–187°, was removed by filtration. The filtrate was extracted with one 150-ml. and one 100-ml. portions of ether. After drying the solution over sodium sulfate for 1 hr., the ether was removed by evaporation under the hood. The resulting oil was dissolved in acetone and 8 ml. of 37% hydrochloric acid was added. No precipitation resulted. The acetone was removed by evaporation under the hood. Upon addition of 150 ml. of water, 6.8 g. of N,N-bis-(3,5-dichloro-2-hydroxybenzyl)methylamine hydrochloride (18% based on the amine), m.p. 150–162°, was removed by filtration; the melting point was 164–166° after recrystallization from methanol solution to which water was added. Neutralization of the filtrate gave 7.65 g. of 2,4-dichloro-6-methylaminomethylphenol, m.p. 180–190°; after recrystallization from methanol, the melting point was 190–191°. The total yield of the Mannich base was 12.55 g. (61%).

When the condensation was repeated except that the reaction time was 5 days, only Mannich base (70% yield) was isolated from the reaction mixture.

3-Cyclohexyl-6,8-dichloro-3,4-dihydro-2*H*-1,3-benzoxazine (IIb).—Cyclohexylamine (9.9 g., 0.1 mole) in 30 ml. of 1,4-dioxane was added dropwise to a solution of 7.0 g. of paraformaldehyde (0.23 mole) in 10 ml. of ethanol containing 1 sodium hydroxide pellet and 10 ml. of 1,4-dioxane. 2,4-Dichlorophenol (16.4 g., 0.1 mole) in 30 ml. of 1,4 dioxane was added then and the solution was warmed at 65° for 1 hr. The temperature was increased to 85° and kept there for 4 hr. The solution was cooled and the solvents were evaporated at room temperature under reduced pressure. The liquid residue was added to 30 ml. of ethanol. Crystals (10.2 g., 36% yield) were removed by filtration; the melting point was 56–57° after recrystallization from petroleum ether (b.p. 60–110°).

Attempted Synthesis of N,N-Bis(3,5-dichloro-2-hydroxybenzyl)-cyclohexylamine (IIIb) from 2-Cyclohexylaminomethyl-4,6-dichlorophenol (Ib).—A solution of 1 ml. of 37% aqueous formaldehyde (0.012 mole) in 5 ml. of dioxane was added to 3.0 g. of Ib (0.011 mole) dissolved in 25 ml. of dioxane. A solution of 2.0 g. of 2,4-dichlorophenol (0.012 mole) in 5 ml. of dioxane was added, and the reaction solution was kept at room temperature for 13 days. The solvents were removed at room temperature under reduced pressure. The yellow oily residue was dissolved in 15 ml. of methanol and cooled. The solid (1.88 g., 60% yield) was removed by filtration; the melting point was 54–55° after recrystallization from petroleum ether. A mixture melting point with the product (IIb) from the above procedure was not depressed.

Conversion of 3-Cyclohexyl-6,8-dichloro-3,4-dihydro-2*H*-1,3-benzoxazine (IIb) to 2-Cyclohexylaminomethyl-4,6-dichlorophenol (Ib) in Hot Ethanol.—3-Cyclohexyl-6,8-dichloro-3,4-dihydro-2*H*-1,3-benzoxazine (1.3 g., 0.045 mole) was dissolved in 30 ml. of hot ethanol and the solution was refluxed for 10 min. and then cooled. The solid (1.1 g., 89% yield), m.p. 155–156°, which separated was removed by filtration. A mixture melting point with an authentic sample of 2-cyclohexylaminomethyl-4,6-dichlorophenol (Ib) was not depressed.

Reaction of 2,4-Dibromophenol with Formaldehyde and Methylamine.—To 6.2 g. of 25% methylamine (0.05 mole) in 20 ml. of dioxane was added dropwise with cooling 7.5 ml. of 37% formaldehyde (0.10 mole) in 10 ml. of dioxane. To the resulting solution was added 25.19 g. of 2,4-dibromophenol (0.1 mole) in 20 ml. of dioxane. The mixture was agitated throughout the addition of the reagents and was cooled in an ice bath. After the reagents had been added, the solution was stirred for 5 min. and then kept in the dark for 3 days at room temperature. Upon removal of the solvents under reduced pressure at room temperature a solid began to form. After addition of 75 ml. of ether, the mixture was cooled and 90 ml. of water containing 65 ml. of 37% hydrochloric acid was added. The mixture was shaken well and the aqueous layer was separated. The aqueous layer was further extracted with three 50-ml. portions of ether. The combined ether extracts were placed in a beaker and the ether was allowed to evaporate; 16 g. of 2,4-dibromophenol, m.p. 59–63°, was recovered.

2-Aminoethanol was added to the aqueous extracts until no further precipitate formed. The resulting white solid (7.5 g.), m.p. 187–189°, was removed by filtration and washed with 25 ml. of cold methanol; after three recrystallizations from toluene, the melting point was 195–196°. The analysis of the product was consistent with that for 2,4-dibromo-6-methylaminomethylphenol. An additional 0.3 g. of this product was obtained from the methanol washings. The total yield of Mannich base was 73%. Concentration of the methanol filtrate yielded 1.3 g. of solid, m.p. 115–126°, which melted at 125–128° after recrystallization from toluene. This corresponded to a 13% yield of N,N-bis(3,5-dibromo-2-hydroxybenzyl)methylamine.

When the reaction time in the above experiment was extended from 3 days to 2 weeks an 88% yield of the latter product was obtained.