in this analysis are not "true" values, the relative values of the total nitrogen (Kjeldahl) and the amino nitrogen (Van Slyke) are a reliable index of the disposition of the nitrogens in the molecule.

Anal. Total nitrogen (Kjeldahl): 13.3; Van Slyke amino nitrogen: 12.2 (5 min.); 12.7 (30 min.).

This analysis thus indicates that all of the nitrogen in the molecule is in the form of primary amino nitrogen.

Owing to its extremely hygroscopic nature the compound could only be analyzed satisfactorily in the form of its derivatives. The picrate was obtained as yellow needles from water, m.p. 205–206° (uncor.), λ_{max} 356, $E^{1\%}_{1\,cm.}$ 475 (in *p*H 7.0 phosphate buffer).

Anal. Calcd. for $C_6H_{14}N_2O_2(C_6H_3N_3O_7)_2$: C, 35.76; H, 3.31; N, 18.54; mol. wt., 146. Found: C, 36.12; H, 3.55; N, 18.62; mol. wt., 144 (calcd. from ultraviolet absorption).

The hydrochloride was obtained as a white amorphous powder from methanol–ether, m.p. 153–155° (uncor.).

Anal. Calcd. for $C_6H_{14}N_2O_2 \cdot 2HCl$: C, 32.88; H, 7.36; N, 12.79; Cl, 32.36; carboxyl-nitrogen, 6.39. Found: C, 32.91; H, 7.40; N, 12.58; Cl, 32.50; carboxyl-nitrogen, 0.70.

The sulfate was obtained as white needles from methanol–water, m.p. 220–224° (dec.).

Anal. Calcd. for $C_6H_{14}N_2O_2 \cdot H_2SO_4$: C, 29.51; H, 6.55; N, 11.47. Found: C, 29.97; H, 6.60; N, 11.85.

It is evident from the analytical data given above that the compound is a diamino acid which is isomeric with lysine. Further proof was demonstrated by infrared analysis of its salts. Strong absorption in the region of the carboxyl group (5.76–5.90 μ) was found in each case. Furthermore, Dr. H. E. Carter and associates, at the 119th Meeting of the American Chemical Society, April, 1951, reported the demonstration, from paper chromatographic studies, of the presence of the same diamino acid in viomycin as that found in streptothricin.

Isolation of Guanidino Component.—The water eluates, from procedures (a) and (b) from the α,β-diaminopropionic acid isolation, were combined and concentrated to dryness *in vacuo*. The residue was dissolved in ethanol, and upon addition of ether, 0.200 g. of an amorphous white powder was obtained. The material gave a strong Sakaguchi test and a light pink ninhydrin color, R_F 0.25 in *t*-butanol, acetic acid, and water (50:25:25). Conversion to the *p*-hydroxyazobenzene *p*-sulfonic acid salt gave yellow needles from water, m.p. 212–215° (uncor.).

Anal. Found: C, 47.78; H, 5.06; N, 16.89; S, 7.52.

Acknowledgment.—We wish to express our appreciation to Mr. Albert Ryder for his technical assistance; to Dr. H. B. Devlin for the Van Slyke amino acid determinations; to Dr. O. D. Bird for the microbiological assays; to Mr. C. E. Childs and his associates for the microanalyses; to Dr. J. M. Vandenbelt for the ultraviolet and infrared absorption measurements and to Dr. A. J. Glazko for his helpful suggestions on paper chromatography.

DETROIT, MICHIGAN RECEIVED SEPTEMBER 4, 1951

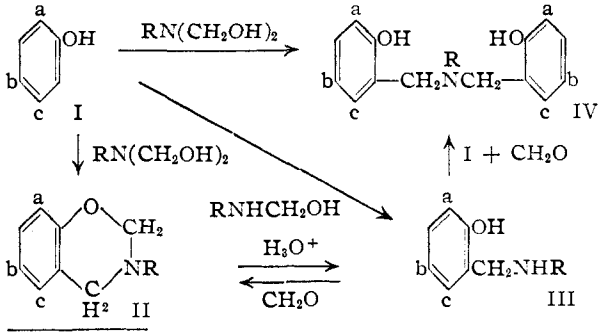
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF UTAH]

N,N-Bis-(hydroxybenzyl)-amines: Synthesis from Phenols, Formaldehyde and Primary Amines[1]

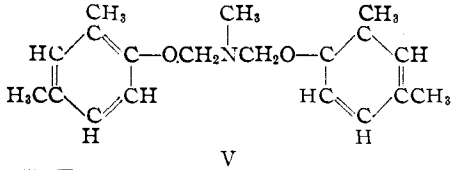
BY W. J. BURKE, RICHARD P. SMITH AND CARL WEATHERBEE

Condensation of phenols with formaldehyde and primary amines is shown to yield N,N-bis-(hydroxybenzyl)-amines directly in certain instances. Evidence is presented which indicates that the nature of the substituent ortho to the phenolic hydroxyl plays an important role in determining the course of the reaction.

Recent work[2] has shown that reaction of para-substituted phenols with formaldehyde and primary aliphatic amines offers a convenient route to either 3,4 - dihydro - (3,6 - disubstituted) - 1,3,2H - benzoxazines (II) or *o*-alkylaminomethylphenols (III), depending upon reaction conditions. Continuation of this study has demonstrated that a third type of product, N,N-bis-(2-hydroxybenzyl)-alkylamines (IV), can also be obtained directly in high yield from such systems in certain instances.



Auwers[3] has described the synthesis of substituted N,N-bis-(hydroxybenzyl)-alkylamines by a rather complicated procedure involving condensation of primary amines with bromohydroxybenzyl bromides, obtained by the bromination of various methylphenols. The method of preparation used in the present work is much less involved and in addition permits the synthesis of a greater variety of products. For example, simple refluxing of a methanol solution containing 2,4-dimethylphenol, formaldehyde and methylamine, in a molar ratio of 2:2.1, respectively, resulted in an 85% yield of N,N-bis-(2-hydroxy-3,5-dimethylbenzyl)-methylamine, IVa (a, b, R = CH_3; c = H). This structure was assigned rather than the isomeric N,N-bis-(2,4-dimethylphenoxymethyl)-methylamine (V), since a Zerewitinoff determination indicated the presence of two active hydrogens in



V

(1) Presented in part before the Organic Division of the American Chemical Society in San Francisco in March, 1949.

(2) W. J. Burke, THIS JOURNAL, **71**, 609 (1949).

(3) K. Auwers, *Ann.*, **344**, 93 (1906).

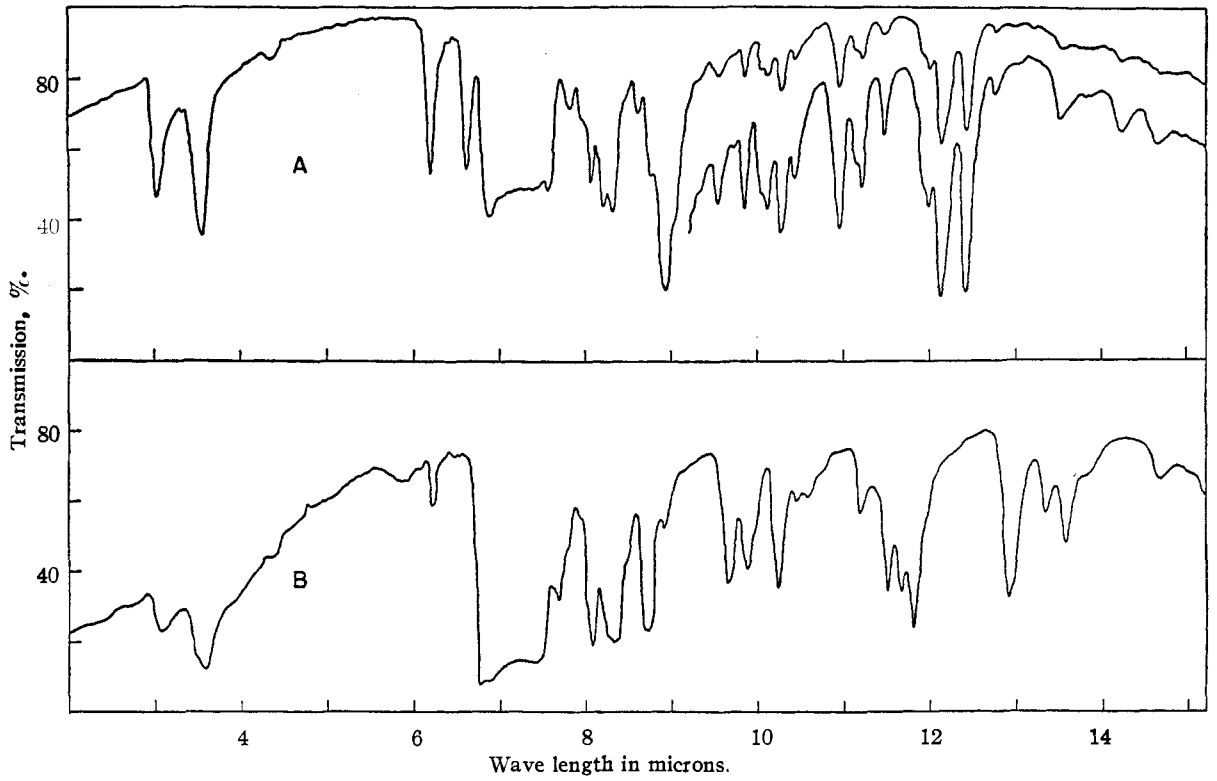


Fig. 1.—Infrared absorption spectra: A, N,N-bis-(3,5-dimethoxy-4-hydroxybenzyl)-methylamine; B, N,N-bis-(3,5-dimethyl-2-hydroxybenzyl)-methylamine.

the molecule. Moreover, the infrared absorption band near 3 microns shown by the product (Fig. 1) corresponds with that assignable to an hydroxyl group.

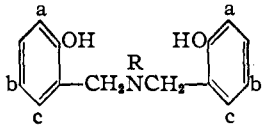
A series of related N,N-bis-(2-hydroxybenzyl)-amines was obtained through the condensation of a variety of *o,p*-substituted phenols with representative N,N-dimethylolamines in a molar ratio of 2:1, respectively. The properties of these products and their hydrochlorides are summarized in Table I.

phenol with N,N-dimethylolmethylamine, the only product isolated (59% yield, based on amine) was N,N-bis-(3,5-di-*t*-butyl-2-hydroxy-6-methylbenzyl)-methylamine, IVb (R, c = CH_3; a, b = $(CH_3)_3C$) even when the reaction ratio employed (1:1) was that calculated for benzoxazine formation.

In contrast, only 3,4-dihydro-3-cyclohexyl-6-*t*-butyl-1,3,2H-benzoxazine, IIa (R = C_6H_{11}; a, c = H; b = $(CH_3)_3C$) was isolated when *p*-*t*-butyl-

TABLE I

N,N-BIS-(2-HYDROXYBENZYL)-AMINES FROM PHENOLS, FORMALDEHYDE AND PRIMARY AMINES



Bis-(2-hydroxybenzyl)-amine R	a	b	c	Yield, %	M.p.,[a] °C.	Molecular formula	Nitrogen, % Calcd.	Found	Bis-(2-hydroxybenzyl)-amine·HCl M.p.,[a] °C.	Ionic Cl, % Calcd.	Found	Neut. equiv. Calcd.	Found
CH_3	CH_3	CH_3	H	85	124–125[b]	$C_{19}H_{25}NO_2$[c]	4.68	4.49	.....	..	..	...	...
C_6H_{11}	CH_3	CH_3	H	52	146–147[b]	$C_{24}H_{33}NO_2$	3.81	3.73	213–215[d]	8.78	8.90	404	399
$HOCH_2CH_2$	CH_3	CH_3	H	60	128–129[e]	$C_{20}H_{27}NO_3$	4.25	4.42	185–186[f]	9.69	9.79	366	364
CH_3	Cl	$C(CH_3)_3$	H	52[g]	.....	$C_{23}H_{31}Cl_2NO_2$	..	..	169–171[h]	7.70	7.83	461	457
C_6H_{11}	Cl	$C(CH_3)_3$	H	59	167–168[i]	$C_{28}H_{39}Cl_2NO_2$	2.84	2.63	149–150[b]	6.70	6.64	...	...
CH_3	$C(CH_3)_3$	$C(CH_3)_3$	CH_3	55	130–131[f]	$C_{32}H_{51}NO_2$	2.83	2.82[j]	.....	..	..	...	...

[a] Uncorrected. [b] Recrystallized from propanol-2. [c] Calcd.: C, 76.22; H, 8.42; active hydrogen, 2.00. Found: C, 76.44; H, 8.55; active hydrogen (Zerewitinoff), 2.06. [d] Recrystallized from propanol-1. [e] Recrystallized from xylene. [f] Recrystallized from methanol. [g] Compound isolated and characterized as hydrochloride; yield based on hydrochloride. [h] Recrystallized from ethyl acetate. [i] Recrystallized from acetone. [j] Calcd.: C, 79.94; H, 10.78. Found: C, 80.00; H, 10.46.

Results obtained in the course of this investigation indicate that the substituent ortho to the phenolic hydroxyl group plays an important role in determining the course of the reaction. For example, in the reaction of 2,4-di-*t*-butyl-5-methyl-

phenol reacted with N,N-dimethylolcyclohexylamine. This occurred even when the molar ratio of phenol to amine was 2:1, that stoichiometrically required for the formation of N,N-bis-(5-*t*-butyl-2-hydroxybenzyl)-cyclohexylamine. In this case the

yield of benzoxazine was 90% based on the amine, and 86% of the *p-t*-butylphenol unaccounted for as IIa was recovered. This indicates that little, if any, of the corresponding N,N-bis-(hydroxybenzyl)-amine was formed. Analogous results were obtained when *p-t*-butylphenol was replaced with *p*-bromophenol.

With 2,4-dimethylphenol good yields of either N,N-bis-(2-hydroxy-3,5-dimethylbenzyl)-cyclohexylamine (IVc) (52% yield, R = C_6H_{11}; a, b = CH_3; c = H) or 3,4-dihydro-3-cyclohexyl-6,8-dimethyl-1,3,2H-benzoxazine (IIb)[2] (81% yield, R = C_6H_{11}; a, b = CH_3; c = H) can be obtained as desired through use of molar ratios of phenol to N,N-dimethylolcyclohexylamine of 2:1 and 1:1, respectively. In an alternate indirect synthesis IVc was obtained by reaction of 2-cyclohexylaminomethyl-4,6-dimethylphenol (IIIa) (R = C_6H_{11}; a, b = CH_3; c = H) with equivalent quantities of formaldehyde and 2,4-dimethylphenol. No difficulty was encountered in the preparation of a benzoxazine, IIb (R, c = CH_3; a = $(CH_3)_2CH$; b = Cl) from N,N-dimethylolmethylamine and *p*-chlorothymol, which has an isopropyl radical ortho to the phenolic hydroxyl group. The results obtained with phenols having alkyl substituents in the ortho position are consistent with those of Stillson, Sawyer and Hunt,[4] who found that a tertiary butyl group in the ortho position was much more effective than isopropyl or methyl in reducing the reactivity of the phenolic hydroxyl group.

The possibility of benzoxazine formation is, of course, avoided when 2,6-disubstituted phenols are reacted with formaldehyde and primary amines. In condensations of this type good yields of N,N-bis-(3,5-dimethoxy-4-hydroxybenzyl)-amines were obtained from 2,6-dimethoxyphenol, and the N,N-dimethylol derivatives of methyl- and cyclohexylamines. Both of these products gave a positive test for active hydrogen with methylmagnesium iodide. The infrared absorption spectra for N,N-bis-(3,5-dimethoxy-4-hydroxybenzyl)-methylamine is shown in Fig. 1. The strong absorption bands near 3 and 9 microns are characteristic of hydroxyl and ether groups, respectively.

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

Experimental

N,N-Bis-(3,5-dimethyl-2-hydroxybenzyl)-methylamine.—Methylamine (24.8 g. of a 25% aqueous solution; 0.2 mole) was added with cooling to a solution prepared by dissolving 12 g. of paraformaldehyde (0.4 mole) in 60 ml. of methanol containing 0.1 g. of potassium hydroxide. To this solution was added 48.8 g. of 2,4-dimethylphenol (0.4 mole) in 60 ml. of methanol. After the reaction mixture was gently refluxed for two hours, the solvent was removed by evaporation at room temperature. The resulting solid product was crystallized from propanol-1; yield 51 g. (85%), m.p. after recrystallization from propanol-1, 124–125°.

Anal. Calcd. for $C_{19}H_{25}NO_2$: C, 76.22; H, 8.42; N, 4.68; active hydrogen, 2.00. Found: C, 76.44; H, 8.55; N, 4.49; active hydrogen (Zerewitinoff), 2.06.

N,N-Bis-(3,5-di-*t*-butyl-2-hydroxy-6-methylbenzyl)-methylamine.—Methylamine (6.2 g. 25% solution, 0.05 mole) dissolved in 30 ml. of dioxane was added portionwise with agitation to a cooled solution of 7.5 ml. of 37% aqueous formaldehyde (0.1 mole) in 20 ml. of dioxane. After addition of 22 g. (0.1 mole) of 2,4-di-*t*-butyl-5-methylphenol[5] in 25 ml. of dioxane, the mixture was kept at room temperature for three hours. Removal of solvent in the hood yielded a solid (10.3 g.) which was removed by filtration and washed with cold methanol. An additional 3.5 g. of product was obtained from the filtrate: yield 56%, m.p. 128–130°; after recrystallization from methanol, m.p. 130–131°.

Anal. Calcd. for $C_{33}H_{53}NO_2$: C, 79.94; H, 10.78; N, 2.83. Found: C, 80.00; H, 10.46; N, 2.82.

Reaction of 12.4 g. of 25% aqueous methylamine (0.1 mole) with 15 ml. of 37% aqueous formaldehyde (0.2 mole) and 22 g. of 2,4-di-*t*-butyl-5-methylphenol (0.1 mole) under reaction conditions similar to the above resulted in 14.7 g. of crude product (yield 59%, based on the phenol) which melted at 130–131° after recrystallization from methanol. The m.p. of this material was not depressed when mixed with N,N-bis-(3,5-di-*t*-butyl-2-hydroxy-6-methylbenzyl)-methylamine, prepared as described above.

Synthesis of N,N-Bis-(3,5-dimethyl-2-hydroxybenzyl)-cyclohexylamine from 2-Cyclohexylaminomethyl-4,6-dimethylphenol.—A mixture of 22.8 g. of 2-cyclohexylaminomethyl-4,6-dimethylphenol (0.094 mole), 11.5 g. of 2,4-dimethylphenol (0.094 mole) and 20 ml. of dioxane was warmed until a solution resulted. After cooling to 20°, 7.1 ml. of 37% formaldehyde (0.094 mole) was added. This mixture was shaken vigorously for five minutes, heated under reflux for one hour on a steam-bath, and finally allowed to cool and stand at room temperature for 16 hours. Most of the solvent was removed under reduced pressure, and warm ethanol (19 ml.) was added to the sirupy residue. A white solid (11.1 g.) was obtained upon cooling and filtration: m.p. 144–146°. An additional 3.7 g. was isolated from the filtrate, yield 43%. The product melted at 146–147° after recrystallization from propanol-2. A mixture of the product and N,N-bis-(3,5-dimethyl-2-hydroxybenzyl)-cyclohexylamine (m.p. 146–147°) prepared directly from 2,4-dimethylphenol, formaldehyde and cyclohexylamine, melted at 146–147°.

Reaction of *p-t*-Butylphenol, Cyclohexylamine and Formaldehyde in Bis-(hydroxybenzyl)-amine Proportions.—Paraformaldehyde (6 g., 0.2 mole) was dissolved in 10 ml. of warm methanol containing 0.05 g. of potassium hydroxide. The solution was cooled during the portionwise addition of 9.9 g. of cyclohexylamine (0.1 mole). This resulting solution was added quickly to a cooled solution of 30 g. of *p-t*-butylphenol (0.2 mole) in 10 ml. of methanol. The mixture was shaken well and then set aside in a stoppered flask at room temperature for one day. Most of the white solid which separated dissolved upon the addition of 50 ml. of benzene. After adding 8 g. of sodium hydroxide (0.2 mole) and 450 ml. of water, the benzene layer was separated. The aqueous layer was further extracted with three 50-ml. portions of benzene. The combined benzene extracts upon removal of the solvent by vacuum distillation gave 24.6 g. of product, m.p. 93–94°, which did not depress the melting point of 3,4-dihydro-3-cyclohexyl-6-*t*-butyl-1,3,2H-benzoxazine (m.p. 93–94°): yield 90% based on the cyclohexylamine.

The aqueous alkaline extract was acidified with 30 ml. of concentrated hydrochloric acid to yield a white solid, which readily dissolved upon the addition of 100 ml. of ether. The ether was separated, and the aqueous portion further extracted with three 50-ml. portions of ether. Removal of the ether gave 14.3 g. of crystalline solid, m.p. 98–99°, after recrystallization from carbon tetrachloride and then water. The product did not depress the melting point of *p-t*-butylphenol (m.p. 98–99°). This represents an 86% recovery of *p-t*-butylphenol not converted to benzoxazine. The acidic aqueous extracts were neutralized with sodium bicarbonate and extracted with 150 ml. of ether and 50 ml. of chloroform. Removal of solvent from the combined extracts gave only a trace of solid material.

Condensation of *p*-Bromophenol with Formaldehyde and Cyclohexylamine in Bis-(hydroxybenzyl)-amine Proportions.—Cyclohexylamine (4.95 g., 0.05 mole) was added with cooling to 3 g. of paraformaldehyde (0.1 mole) in 8 ml. of methanol containing 0.05 g. of potassium hydroxide. This

(4) G. H. Stillson, D. W. Sawyer and C. K. Hunt, THIS JOURNAL, **67**, 303 (1945).

(5) We are indebted to the Koppers Co., Pittsburgh, Penna., for a supply of this material.

solution was added to 17.3 g. of *p*-bromophenol (0.1 mole) in 15 ml. of methanol. After 18 hours at room temperature most of the solvent was removed under reduced pressure. Upon cooling, a crystalline product (3.1 g.) separated and was removed by filtration: m.p. 91–92°, after recrystallization from 95% ethanol. The mother liquor was taken up in 60 ml. of *i*-propyl ether, washed with 60 ml. of 10% aqueous potassium hydroxide and then with water, and dried over sodium sulfate. Upon removal of *i*-propyl ether a solid (2.0 g.) was obtained which melted at 90–92°, after recrystallization from 95% ethanol. The m.p. of neither of the above products was depressed when they were mixed with 3,4-dihydro-3-cyclohexyl-6-bromo-1,3,2H-benzoxazine (m.p. 91–92°); yield 35% based on cyclohexylamine.

The aqueous alkaline fractions were acidified with concentrated aqueous hydrochloric acid and extracted with *i*-propyl ether; removal of the ether resulted in 10.2 g. of a light tan solid; m.p. 63–64°, after recrystallization from carbon tetrachloride. Admixture with *p*-bromophenol (m.p. 64°) did not lower the melting point of the product: recovery of *p*-bromophenol not accounted for as benzoxazine, 71%.

3,4-Dihydro-6-chloro-3,5-dimethyl-8-*i*-propyl-1,3,2H-benzoxazine.—Paraformaldehyde (2.4 g., 0.08 mole) was dissolved in 5 ml. of warm methanol containing 0.1 g. of potassium hydroxide. The solution was cooled in ice and water and 4.96 g. of 25% aqueous methylamine (0.04 mole) was added. After addition of 7.4 g. of *p*-chlorothymol (0.04 mole) in 8 ml. of methanol, the reaction mixture was heated under gentle reflux for three hours. The resulting mixture, which had separated into two layers, was taken up in 40 ml. of benzene, washed three times with 5% aqueous potassium hydroxide and then with water. The benzene extract was dried over sodium sulfate and the benzene removed under reduced pressure. Distillation of the resulting light brown sirup (9 g.) gave 6.8 g. of a light yellow oil; b.p. 120–122° at 0.3 mm.; yield 71%.

Anal. Calcd. for $C_{13}H_{18}ClNO$: C, 65.13; H, 7.57; N, 5.84. Found: C, 65.53; H, 7.55; N, 5.71.

N-Methyl-(5-chloro-2-hydroxy-6-methyl-3-*i*-propylbenzyl)-amine Hydrochloride.—A solution containing 2.2 g. of 3,4-dihydro-6-chloro-3,5-dimethyl-8-*i*-propyl-1,3,2H-benzoxazine, 5 ml. of 20% aqueous hydrochloric acid and 25 ml. of 95% ethanol was distilled. During the course of the distillation formaldehyde was evolved and 30 ml. of 50% aqueous ethanol and 10 ml. of water were added. The distillation was continued until about 20 ml. of liquid remained in the flask. Water (20 ml.) was then added until the residue just became cloudy. Upon cooling a crystalline product (1.1 g.) separated; m.p. 172–174°.

Anal. Calcd. for $C_{12}H_{19}Cl_2NO$: C, 54.55; H, 7.25. Found: C, 54.89; H, 7.23.

N,N-Bis-(4-hydroxy-3,5-dimethoxybenzyl)-cyclohexylamine.—Cyclohexylamine (9.9 g., 0.1 mole) was added with cooling to 50 ml. of dioxane containing 15 ml. of 37% aqueous formaldehyde (0.2 mole). After addition of 30.8 g. of 2,6-dimethoxyphenol (0.2 mole) the reaction mixture was refluxed gently for one and two-thirds hours. Upon concentration of the solution and cooling a crystalline product (28 g., 65% yield) was obtained; m.p. 141°, after recrystallization from propanol-2.

Anal. Calcd. for $C_{24}H_{33}NO_6$: C, 66.80; H, 7.71; active hydrogen, 2.00. Found: C, 66.70; H, 8.04; active hydrogen (Zerewitinoff), 2.06.

N,N-Bis-(4-hydroxy-3,5-dimethoxybenzyl)-methylamine.—This compound was prepared in essentially the same manner as N,N-bis-(4-hydroxy-3,5-dimethoxybenzyl)-cyclohexylamine except that 12.4 g. of 25% aqueous methylamine (0.1 mole) was used in place of the cyclohexylamine. The product (25 g., 69% yield) melted at 137° after recrystallization from propanol-1 and gave a positive test for active hydrogen with methylmagnesium iodide.

Anal. Calcd. for $C_{19}H_{25}NO_6$: N, 3.85. Found: N, 3.70.

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 both cases the sample was mulled in mineral oil.

SALT LAKE CITY 1, UTAH RECEIVED JULY 30, 1951

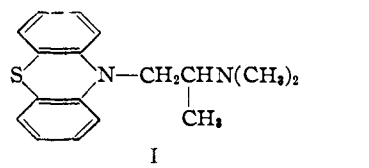
[CONTRIBUTION FROM ABBOTT LABORATORIES]

Histamine Antagonists. IV. C-Methyl Derivatives of 1,4-Disubstituted Piperazines[1]

BY KARL M. BECK, K. E. HAMLIN AND ARTHUR W. WESTON

Several analogs of 1-(*p*-chlorobenzhydryl)-4-methylpiperazine (II) containing C-alkyl substituents on the piperazine nucleus have been prepared as antihistaminic drugs. The branching produced by these C-alkyl groups did not improve the antihistaminic activity. The structure of the N-methyl derivative of 2-methylpiperazine, prepared as an intermediate in the synthesis of one of these analogs, has been established as 1,2-dimethylpiperazine by an unequivocal synthesis.

The activity of certain antihistaminic drugs has been enhanced by replacement of the usual ethylenediamine side-chain by a propylenediamine grouping, as illustrated by Phenergan (I). This type of branching also appears in other physiologically active substances, such as Methadone (6-dimethylamino-4,4-diphenyl-3-heptanone) and Amphetamine (α-methylphenethylamine). Previous investigation[2] of 1,4-disubstituted piperazines has led to the development of the useful histaminic drug, Di-Paralene (II).[3] Consequently, a study was undertaken to determine the effect of branching on the antihistaminic activity of II.



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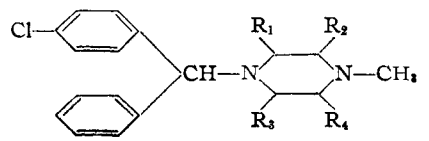

II, R_1, R_2, R_3, R_4 = H
III, R_1, R_3, R_4 = H; R_2 = CH_3
IV, R_1, R_4 = H; R_2, R_3 = CH_3
V, R_1, R_3 = H; R_2, R_4 = CH_3
VI, R_1, R_2 = H; R_3, R_4 = $CH_2CH_2CH_2CH_2$

The analogs III–VI were prepared from the corresponding C-substituted piperazines by the previously described procedure.[2a] This method

(1) Presented before the Medicinal Division of the American Chemical Society, Cleveland, April 9, 1951.

(2) (a) K. E. Hamlin, A. W. Weston, F. B. Fischer and R. J. Michaels, Jr., THIS JOURNAL, 71, 2731, 2734 (1949); (b) R. Baltzly, S. Du Breuil, W. S. Ide and E. Lorz, *J. Org. Chem.*, 14, 775 (1949).

(3) Di-Paralene is the Abbott Laboratories trade mark for Chlorcyclizine, 1-(*p*-chlorobenzhydryl)-4-methylpiperazine.