[CONTRIBUTION FROM THE ORGANIC CHEMISTRY LABORATORIES OF THE UNIVERSITY OF FLORIDA]

Derivatives of Piperazine. XXIV. Synthesis of 1-Arylpiperazines and Amino Alcohol Derivatives

BY C. B. POLLARD AND THOMAS H. WICKER, JR.[1]

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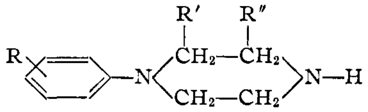
Eight 1-arylpiperazines have been prepared by the reaction of the mixed hydrochlorides of aromatic amines and diethanolamines. Derivatives of these piperazines were prepared by reaction with ethylene oxide, 1,2-epoxy-3-methoxypropane, acetic anhydride, benzoyl chloride and phenyl isothiocyanate.

Cerkovnikov and Stern reported the synthesis of a number of derivatives of 1-phenylpiperazine and the varying degree of physiological activity exhibited by these compounds.[2] These investigators found that several derivatives of 1-phenylpiperazine exhibited pronounced antihistaminic activity. This paper is concerned with the preparation of certain 1-arylpiperazines and several 2-hydroxyethyl derivatives for evaluation of physiological activity.

TABLE I

DATA CONCERNING 1-ARYLPIPERAZINES OF THE TYPE



Where R = N, Cl or CH_3; R′ = H or CH_3; and R″ = H or C_2H_5

Compound, piperazine	Molecular formula	Yield, %	B.p. °C.	B.p. Mm.	d^{25}_4	n^{25}_D	Nitrogen, % Calcd.	Nitrogen, % Found
1-(4-Tolyl)-	$C_{11}H_{16}N_2$	25.5	150.9–152.5	10	....	....	15.89	16.00
1-(3-Tolyl)-	$C_{11}H_{16}N_2$	22.8	154.2–156.2	10	1.0383	1.5744	15.89	15.67
1-(2-Tolyl)-	$C_{11}H_{16}N_2$	26.5	136.5–137.5	10	1.0261	1.5600	15.89	15.66
1-(4-Chlorophenyl)-	$C_{10}H_{13}N_2Cl$	52.3	155.7–157.2[a]	5	....	....	14.24	14.27
1-(3-Chlorophenyl)-	$C_{10}H_{13}N_2Cl$	38.4	157.2–158.2	5	1.1897	1.5985	14.24	14.15
1-(2-Chlorophenyl)-	$C_{10}H_{13}N_2Cl$	32.7	133.9–134.9	5	1.1763	1.5794	14.24	14.04
1-Phenyl-2-methyl-	$C_{11}H_{16}N_2$	30.7	138.5–140.5	10	1.0410	1.5723	15.89	15.95
1-Phenyl-3-ethyl-	$C_{12}H_{18}N_2$	20.3	147.8–149.8	10	1.0327	1.5635	14.72	14.66

[a] M.p. 71.5–73.5°.

TABLE II

CHARACTERIZATION DERIVATIVES OF 1-ARYLPIPERAZINES

Derivative, piperazine	Molecular formula	M.p., °C.	Nitrogen, % Calcd.	Nitrogen, % Found
1-Acetyl-4-(4-tolyl)-	$C_{13}H_{18}N_2O$	109.5–110.5	12.83	12.99
1-Acetyl-4-(3-tolyl)-	$C_{13}H_{18}N_2O$	46.7–48.2	12.83	12.76
1-Acetyl-4-(2-tolyl)-	$C_{13}H_{18}N_2O$	55.9– 57.9	12.83	12.90
1-Acetyl-4-(4-chlorophenyl)-	$C_{12}H_{15}N_2OCl$	99.5–101.5	11.73	11.88
1-Acetyl-4-(3-chlorophenyl)-	$C_{12}H_{15}N_2OCl$	42.2– 44.2	11.73	11.70
1-Acetyl-4-(2-chlorophenyl)-	$C_{12}H_{15}N_2OCl$	65.5– 67	11.73	11.86
1-Acetyl-3-methyl-4-phenyl-	$C_{13}H_{18}N_2O$	57.4– 59.4	12.83	12.95
1-Benzoyl-4-(4-tolyl)- monohydrochloride	$C_{18}H_{20}N_2O \cdot HCl$	201.6–203.6	8.84[a]	8.85
1-Benzoyl-4-(3-tolyl)- monohydrochloride	$C_{18}H_{20}N_2O \cdot HCl$	202.6–204.6 d.	8.84[a]	8.73
1-Benzoyl-4-(2-tolyl)-	$C_{18}H_{20}N_2O$	122.5–123.5	9.99	10.13
1-Benzoyl-4-(4-chlorophenyl)-	$C_{17}H_{17}N_2OCl$	128.0–129.5	9.31	9.11
1-Benzoyl-4-(3-chlorophenyl)- monohydrochloride	$C_{17}H_{17}N_2OCl \cdot HCl$	158.3–159.8	8.31[a]	8.50
1-Benzoyl-4-(2-chlorophenyl)-	$C_{17}H_{17}N_2OCl$	130.5–132	9.31	9.43
1-(N-Phenylthiocarbamyl)-3-methyl-4-phenyl-	$C_{18}H_{21}N_3S$	156.2–157.2	13.49	13.65
1-(N-Phenylthiocarbamyl)-2-ethyl-4-phenyl-	$C_{19}H_{23}N_3S$	184–185.5	12.91	12.99

[a] Calculated for the monohydrochloride.

The synthesis of 1-phenylpiperazine was reported by Prelog and Driza who prepared it by refluxing bis-(2-chloroethyl)-amine with a solution of aniline in methanol for sixteen hours.[3] Pollard and MacDowell have reported another method of synthesis whereby the hydrochlorides of diethanolamine and aniline in stoichiometric quantities were heated at about 240° for a period of eight hours.[4] The reaction between salts of bis-(2-haloethyl)-amines and aromatic amines has been used by Prelog and Blažek to give several additional 1-arylpiperazines.[5] Pollard and Bain have reported that

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[1] This paper is abstracted from a portion of a dissertation submitted by Thomas H. Wicker, Jr., to the Graduate Council of the University of Florida in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June, 1951.

[2] E. Cerkovnikov and P. Stern, *Arkiv Kemi*, **18**, 12 (1946).

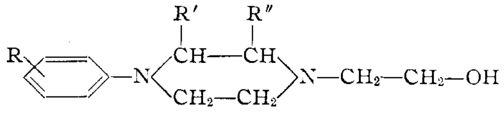
(3) V. Prelog and G. J. Driza, *Collection Czechoslov. Chem. Communications*, **5**, 497 (1933).

(4) C. B. Pollard and L. G. MacDowell, THIS JOURNAL, **56**, 2199 (1934).

(5) V. Prelog and Z. Blažek, *Collection Czechoslov. Chem. Communications*, **6**, 211 (1934).

TABLE III

DATA ON COMPOUNDS OF THE TYPE



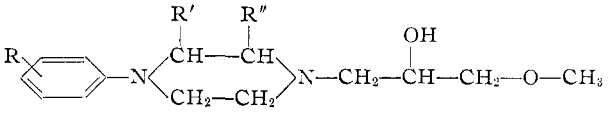
Where R = H, Cl or CH_3; R′ = H or CH_3; and R″ = H or C_2H_5

Substituents	Molecular formula	Yield, %	M.p. or b.p. (mm.) °C.	Nitrogen, % Calcd.	Nitrogen, % Found	Other data
1-(4-Tolyl)-	$C_{13}H_{20}N_2O$	35.5	51.5– 52.5	12.72	12.67	
1-(3-Tolyl)-	$C_{13}H_{20}N_2O$	31.8	67 – 68.5	12.72	12.65	
1-(2-Tolyl)-	$C_{13}H_{20}N_2O$	65.6	146–149 (1.5)	9.56[a]	9.58	Di-HCl m.p. 175.1–176.6°
1-(4-Chlorophenyl)-	$C_{12}H_{17}N_2OCl$	81.2	107–108.5	11.64	11.86	
1-(3-Chlorophenyl)-	$C_{12}H_{17}N_2OCl$	33	97.5–98.5	11.64	11.63	
1-(2-Chlorophenyl)-	$C_{12}H_{17}N_2OCl$	55	166–169 (2.3)	10.11[b]	10.26	Mono-HCl m.p. 154.2–155.7°
1-Phenyl-2-methyl-	$C_{13}H_{20}N_2O$	74	167–172 (1)	9.56[a]	9.53	Di-HCl m.p. 235.2–236.5°
1-Phenyl-3-ethyl-	$C_{14}H_{22}N_2O$	67	156–158.2 (2.2)	11.95	11.73	

[a] Calculated for dihydrochloride. [b] Calculated for monohydrochloride.

TABLE IV

DATA ON COMPOUNDS OF THE TYPE



Where R = H, Cl or CH_3; R′ = H or CH_3; and R″ = H or C_2H_5

(2-Hydroxy-3-methoxypropyl)-piperazine	Yield, %	Molecular formula	M.p., °C.	Nitrogen, % Calcd.	Nitrogen, % Found
1-(4-Tolyl)-4-	61	$C_{15}H_{24}N_2O_2$	77.5–79	10.59	10.45
1-(3-Tolyl)-4-	44.6	$C_{15}H_{24}N_2O_2$	56.5–57.5	10.59	10.40
1-(2-Tolyl)-4-	46.7	$C_{15}H_{24}N_2O_2$	38–39	10.59	10.51
1-(4-Chlorophenyl)-4-	47.5	$C_{14}H_{21}N_2O_2Cl$	78–79.5	9.84	9.56
1-(3-Chlorophenyl)-4-	34.4	$C_{14}H_{21}N_2O_2Cl$	58.8–59.8	9.84	9.81
1-(2-Chlorophenyl)-4-	70.4	$C_{14}H_{21}N_2O_2Cl$	90–91.5	9.84	9.59
1-Phenyl-2-methyl-4-	56	$C_{15}H_{24}N_2O_2$	......[a]	10.59	10.39

[a] B.p. 151.5–153.5° (0.3 mm.).

C-substituted piperazines could not be prepared conveniently from arylamines and diisopropanolamine.[6]

An adaptation of the ring closure described by Pollard and MacDowell[4] was used to prepare eight 1-arylpiperazines which are described in Table I. With the exception of 1-(4-tolyl)-piperazine[5] and 1-(2-tolyl)-piperazine,[5] the compounds described are new to the literature. Characterization derivatives for these piperazines are reported in Table II.

The amino alcohols resulting from the reaction of 1-arylpiperazines with ethylene oxide are reported in Table III. Derivatives prepared by reaction between 1-arylpiperazines and 1,2-epoxy-3-methoxypropane are reported in Table IV.

Experimental

Intermediates.—The aromatic amines diethanolamine and ethylene oxide were commercial products and were used without further purification. N-(2-Hydroxyethyl)-1-amino-2-propanol and N-(2-hydroxyethyl)-2-amino-1-butanol were prepared as described by Cottle and co-workers.[7] The preparation of 1,2-epoxy-3-methoxypropane has been described by Flores-Gallardo and Pollard.[8]

Syntheses.—An outline of the method of synthesis for one compound of each type is given in detailed form.

1-(4-Chlorophenyl)-piperazine.—A mixture of 280.6 g. (2.2 moles) of *p*-chloroaniline and 210.3 g. (2 moles) of diethanolamine was carefully neutralized with 375 ml. of concentrated hydrochloric acid (37% HCl, sp. gr. 1.19), and heating of the flask was then regulated so that water distilled continuously. When approximately the theoretical quantity of water had been collected in the arm of an attached distilling trap and had been removed the reaction mass was neutralized with 180 g. of sodium hydroxide dissolved in 300 ml. of water. The oily layer which separated was first distilled under water-pump vacuum to remove low-boiling materials. 1-(4-Chlorophenyl)-piperazine was collected at 155.7–157.2° at 5 mm. The yield was 205 g. (or 52.3%).

1-Benzoyl-4-(4-chlorophenyl)-piperazine.—This derivative was prepared by shaking a slight excess of benzoyl chloride with 1-(4-chlorophenyl)-piperazine in a flask in the presence of an excess of 10% sodium hydroxide solution. Recrystallization was from ethanol.

1-Acetyl-4-(4-chlorophenyl)-piperazine.—This derivative was prepared by refluxing 1-(4-chlorophenyl)-piperazine with a threefold excess of acetic anhydride for thirty minutes. The reaction mixture was poured into 100 ml. of ice-water and then was neutralized with solid sodium carbonate. The solid product was recrystallized from ethanol.

All other acetyl derivatives except 1-acetyl-4-(4-tolyl)-piperazine were separated as oils and were taken up in ether. The ethereal solutions were dried over anhydrous potassium carbonate and the ether was removed on the steam-bath. Recrystallization of the residues was from heptane. 1-Acetyl-4-(4-tolyl)-piperazine was recrystallized from water.

1-(4-Chlorophenyl)-4-(2-hydroxy-3-methoxypropyl)-piperazine.—To a solution of 19.66 g. (0.1 mole) of 1-(4-chlorophenyl)-piperazine in 100 ml. of methanol, 8.8 g. (0.1 mole) of 1,2-epoxy-3-methoxypropane was added over a period of 15 minutes. After the addition had been completed the hot mixture was then refluxed for three hours, methanol was removed under water-pump vacuum and the residue was cooled. The solid which separated was recrystallized from boiling heptane and yielded 13.5 g. (47.5%) of product. The compound, which was dried over solid potassium hydroxide in a vacuum desiccator, melts at 78–79.5°.

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(6) J. P. Bain and C. B. Pollard, THIS JOURNAL, **61**, 2704 (1939).

(7) D. L. Cottle, A. E. Jeltsch, T. H. Stoudt and D. R. Walters, *J. Org. Chem.*, **11**, 286 (1946).

(8) H. Flores-Gallardo and C. B. Pollard, *ibid.*, **12**, 831 (1947).

1-(4-Chlorophenyl)-4-(2-hydroxyethyl)-piperazine.—A slight excess over 0.1 mole (4.405 g.) of ethylene oxide was introduced near the bottom of a solution of 19.66 g. (0.1 mole) of 1-(4-chlorophenyl)-piperazine in 100 ml. of methanol in a manner that did not permit boiling. No external heating of the ethylene oxide was necessary. After addition of the ethylene oxide had been completed the mixture was stirred several hours at room temperature, and finally the methanol was evaporated on the steam-bath. The residue was solid after cooling, and recrystallization from heptane gave 19.5 g. (or 81.2% yield) of 1-(4-chlorophenyl)-4-(2-hydroxyethyl)-piperazine.

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GAINESVILLE, FLORIDA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, INSTITUTE OF POLYMER RESEARCH, POLYTECHNIC INSTITUTE OF BROOKLYN]

The Ultraviolet Absorption Spectra of Substituted Aminotriazines

BY C. G. OVERBERGER AND SEYMOUR L. SHAPIRO[1]

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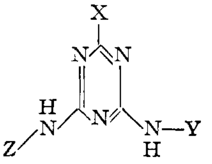
The ultraviolet absorption spectra for a representative number of aminotriazines have been obtained and the results compared with known spectra. The data are interpreted on the basis of individual structure and current theory.

In three previous papers,[2] the synthesis and properties of a number of substituted aminotriazines has been reported. It was of interest to establish the relationship between their structure and their ultraviolet absorption spectra.

The general structure of the compounds reported here may be represented by A. A summary of the published spectra for related compounds is given in Table I.

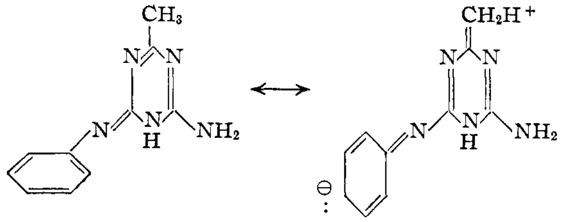


A

The spectra of compounds obtained in this work are reported in Table II.

Substitution of an anilino group for an amino group (1 and I) results in a considerable increase in the intensity of absorption and a significant bathochromic shift of the maximum band. A comparison of compounds 1 and 2 indicates that there is a hyperchromic and hypsochromic effect when the phenyl group is attached directly to the triazine ring. The introduction of a phenyl group on a triazine (compare 1 and 2) shows no bathochromic effect.

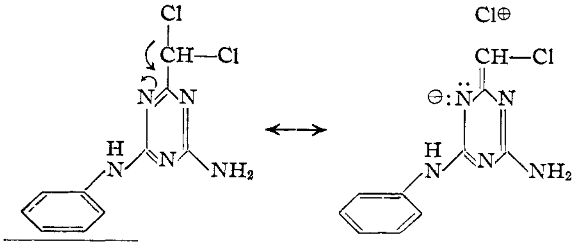
O'Shaughnessy and Rodebush[3] found in a study of the absorption spectra of substituted biphenyls, that *para* methyl substituents gave significant bathochromic shifts and increased absorption at the maximum. Inspection of the data for compounds 1 and 7 shows that, in the formoguanamine structure, the substitution of methyl for hydrogen results in very little change of spectra. On the other hand, when IV and VIII are compared with I, there are pronounced spectral changes with bathochromic shifts and increased intensities. The relatively low absorption of 11 and 12 and the insignificant contribution of a methyl group in 7 as compared to 1 indicate that the phenyl group is probably involved in the excited state as indicated



The availability of only two hydrogens on the α-carbon atom in VIII compared to IV is indicated by the lower intensities for VIII. The introduction of a p-bromo group on the phenyl ring results in a bathochromic shift and increased intensities. (Compare III and I and IX and VIII.) This is probably due to excited states in which the bromine atom is contributing to the stabilization of the above electron distributions.[4]

If halogen is placed on the α-carbon atom as in V, VI, VII and X, a pronounced hypsochromic shift is obtained. The order of intensity of absorption is 3Cl > Br = 2Cl > Cl. Thus one bromine and two chlorines result in an intensity similar to the unsubstituted methyl group (Fig. 1).

This is of interest since the excited states involving electron release from the halogen may play a significant role.



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[1] A portion of a thesis by Seymour L. Shapiro submitted to the Polytechnic Institute of Brooklyn in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

[2] (a) C. G. Overberger and S. L. Shapiro, THIS JOURNAL, **76**, 93 (1954); (b) S. L. Shapiro and C. G. Overberger, *ibid.*, **76**, 97 (1954); (c) C. G. Overberger and S. L. Shapiro, *ibid.*, **76**, 1061 (1954).

[3] M. T. O'Shaughnessy and W. H. Rodebush, *ibid.*, **62**, 2906 (1940). For a discussion of bathochromic shifts resulting from methyl substitution in conjugated systems, see V. A. Crawford, *J. Chem. Soc.*, 2061 (1953).

[4] L. Doub and J. M. Vandenbelt, THIS JOURNAL, **69**, 2714 (1947).