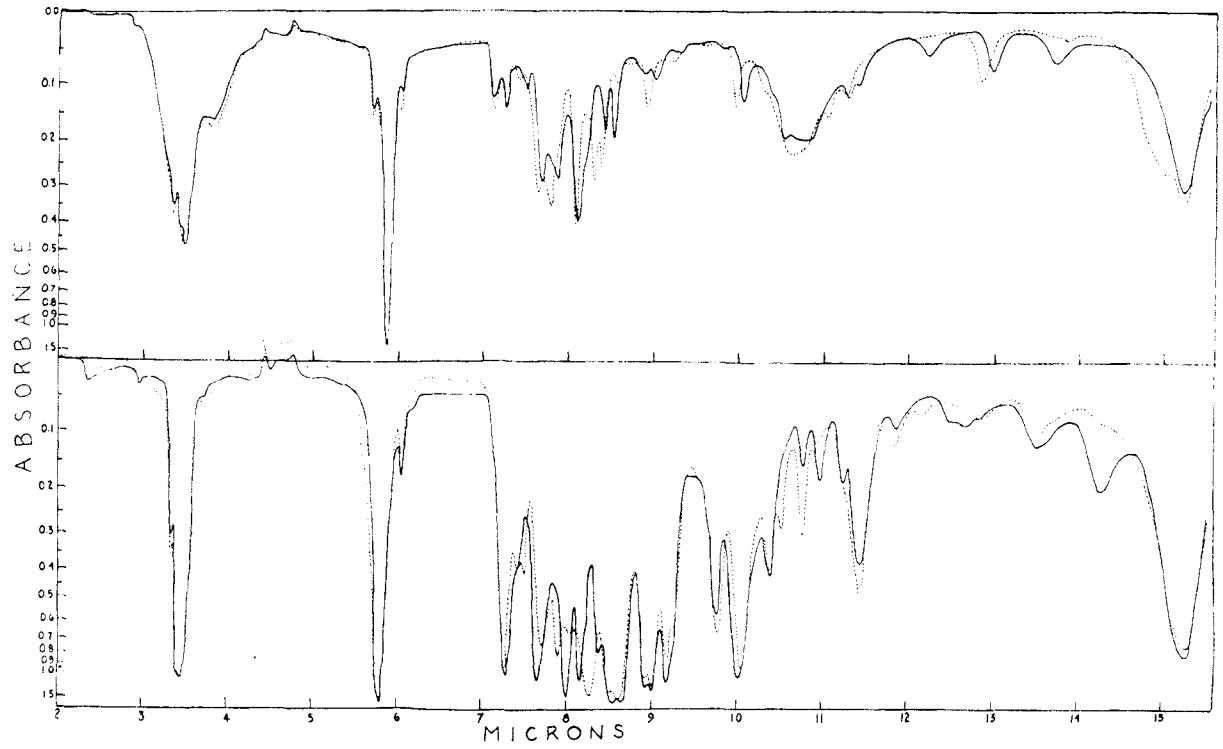

Fig. 1. Infrared spectra of 6-methyl-3-cyclohexene-1-carboxylic acid isomers (upper spectra) 10 mg./ml., and their *sec*-butyl esters (lower spectra) 50 mg./ml. in carbon disulfide. *Trans* isomers solid line, *cis* isomers broken line

Determination of cis-trans content of the sec-butyl esters by infrared spectroscopy. The infrared spectra of the acids and their *sec*-butyl esters are shown in Fig. 1. Two regions of the ester spectra exhibited absorbance differences that were adapted for analytical purposes. A *trans* peak appearing at 14.27 μ was measured by subtracting a background correction at 14.0 and 14.6 μ. A measure of *cis* absorption was obtained by subtracting the absorbance at 8.79 μ (an isosbestic point) from that at 8.27 μ. Several ester mixtures of known isomer content were prepared by careful esterification of known mixtures of the acid isomers and their spectra determined in the 2 regions. Although the absorbances did not follow Beer's law, this ideal was approached. Calibration curves made it possible to estimate isomer content, and in general the results obtained by the foregoing 2 procedures, which gave independent measures of *cis* and *trans* content, agreed within a few per cent.

Acknowledgment. The suggestion that *cis-trans* isomerism may affect the attractive properties of the ester was made by H. L. Haller, Agricultural Research Service, U. S. Department of Agriculture. We also acknowledge the assistance received from S. A. Hall, S. I. Gertler, W. F. Barthel, and B. H. Alexander of the Entomology Research Division during various phases of this problem. David Henley, student trainee, performed most of the chromatographic analyses reported here.

BELTSVILLE, MD.

[CONTRIBUTION FROM THE LABORATORIES OF THE ORGANIC DIVISION OF THE CHEMISTRY DEPARTMENT AND PHARMACEUTICAL CHEMISTRY, COLLEGE OF PHARMACY, UNIVERSITY OF FLORIDA, GAINESVILLE, FLORIDA]

Derivatives of Piperazine. XXXIV. Some Reactions of Trimethylene Chlorobromide with 1-Arylpiperazines

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The variety of pharmacological activities shown by piperazine derivatives led to the syntheses of 38 new compounds by the reactions of trimethylene chlorobromide with various 1-arylpiperazines and other amines. The 1-arylpiperazines required for these syntheses were prepared by the method of Pollard *et al.*[1,2]

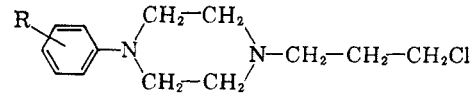
The compounds in Table I were prepared by the reaction of equimolar quantities of trimethylene

(1) C. B. Pollard and L. G. MacDowell, *J. Am. Chem. Soc.*, **56**, 2199 (1934).

(2) C. B. Pollard and T. H. Wicker, Jr., *J. Am. Chem. Soc.*, **76**, 1853 (1954).

TABLE I

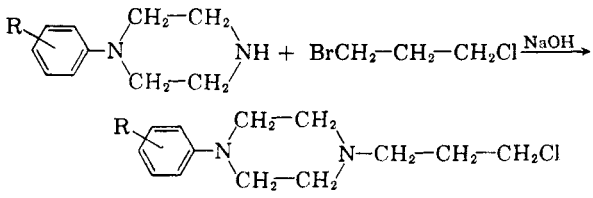
DATA CONCERNING COMPOUNDS HAVING THE GENERAL FORMULA



R	Yield, %	B.P., Mm.[a]	n_D^{25}	Empirical Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Chlorine Calcd.	Chlorine Found
H	53	132–138 0.5	1.5605	$C_{13}H_{19}ClN_2$	65.39	65.55	8.02	8.19	11.73	11.92	14.85	14.70
o-CH_3	43	143–151 1.2	1.5447	$C_{14}H_{21}ClN_2$	66.52	66.60	8.37	8.19	11.08	10.85	14.03	14.42
m-CH_3	46	152–159 0.8	1.5576	$C_{14}H_{21}ClN_2$	66.52	66.84	8.37	8.03	11.08	11.10	14.03	14.25
p-CH_3	40	148–150 0.5	—[b]	$C_{14}H_{21}ClN_2$	66.52	66.59	8.37	8.37	11.08	10.81	14.03	13.91
o-Cl	66	151–154 0.8	1.5594	$C_{13}H_{18}Cl_2N_2$	57.15	56.79	6.64	6.55	10.25	10.55	25.96	25.91
m-Cl	45	157–162 0.5	1.5715	$C_{13}H_{18}Cl_2N_2$	57.15	56.92	6.64	6.49	10.25	10.45	25.96	26.36
p-Cl	47	—[c]	—	$C_{13}H_{18}Cl_2N_2$	57.15	57.35	6.64	6.28	10.25	10.58	25.96	25.50

[a] All boiling points are uncorrected. [b] M.p. 35–36° (corr.). [c] M.p. 63–64° (corr.).

chlorobromide and the 1-arylpiperazine in the presence of sodium hydroxide.



The 1-(3-chloropropyl)-4-phenylpiperazine was previously prepared by Bach *et al.*[3] from the corresponding propanol and phosphorus pentachloride. These authors obtained a product with a boiling range of 146–150° at 0.1 mm.

Table II contains data concerning compounds prepared by either of two methods. The bis compounds were synthesized by the reaction of 1-arylpiperazines and trimethylene chlorobromide in the molar ratio 2:1, in the presence of sodium carbonate. The other compounds in this table were prepared by refluxing the 1-(3-chloropropyl)-4-arylpiperaiznes, shown in Table I, with the various 1-arylpiperazines, in the presence of sodium carbonate.

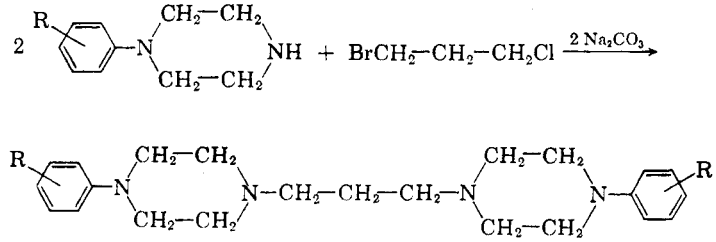
The compounds in Table III, with the exception of the carbazolyl derivative, were prepared by the reaction of the amine and 1-(3-chloropropyl)-4-phenylpiperazine in a molar ratio of 3:1. The carbazolyl compound was synthesized by first preparing the *N*-lithium salt of carbazole, by means of lithium amide in dimethylformamide,[4] and subsequent addition of 1-(3-chloropropyl)-4-phenylpiperazine.

All of the new compounds synthesized have been submitted for pharmacological testing.

EXPERIMENTAL

1-(3-Chloropropyl)-4-(3-tolyl)piperazine. To a solution of 0.5 mole (88.1 g.) of 1-(3-tolyl)piperazine in 100 ml. of acetone was added 75 ml. of a 25% solution of sodium hydroxide. Trimethylene chlorobromide (0.55 mole, 86.6 g.) was added carefully to minimize its mixing with the aqueous layer. The mixture was stirred slowly for 8 hr. with a magnetic stirrer. The organic phase was then separated and the solvent removed under vacuum. Fractional distillation of the resulting oil yielded 57.8 g. (46%) of the product boiling at 152–159° (0.8 mm.).

1,3-Bis[1-(4-phenyl)piperazinyl]propane. A solution of 0.2 mole (32.4 g.) of 1-phenylpiperazine and 0.1 mole (15.7 g.) of trimethylene chlorobromide in 75 ml. of ethanol was stirred until the mixture became almost solid. It was then allowed to stand overnight and 200 ml. of a 30% sodium carbonate solution was added. The alcohol was removed by



distillation and the mixture refluxed for 16 hr. After cooling to room temperature, the resulting solid was filtered and air dried. Recrystallization from hexane yielded 10 g. (27%) of the product, m.p. 104.5–105°.

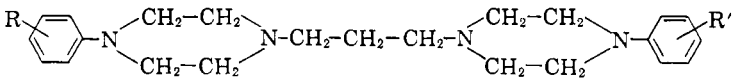
1-[1-(4-Phenyl)piperazinyl]-3-{1-[4-(3-tolyl)]piperazinyl}-propane. To 0.05 mole (12.6 g.) of 1-(3-chloropropyl)-4-(3-tolyl)piperazine was added 0.05 mole (8.1 g.) of 1-phenylpiperazine, 12 g. of sodium carbonate, and 40 ml. of water. The mixture was refluxed for 48 hr. and allowed to cool. The resulting solid was filtered and dried in vacuum. Recrystallization from hexane yielded 14.5 g. (77%) of the product, m.p. 70–72°.

(3) F. L. Bach, Jr., H. J. Brabander, and S. Kushner, *J. Am. Chem. Soc.*, **79**, 2221 (1957).

(4) R. F. Parcell, unpublished material.

TABLE II

DATA CONCERNING COMPOUNDS HAVING THE GENERAL FORMULA

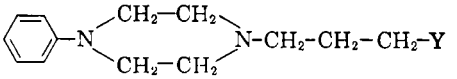


R	R′	Yield, %	M.P. (Corr.)	Empirical Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Chlorine Calcd.	Chlorine Found
H	H	27	104.5–105	$C_{23}H_{32}N_4$	75.78	75.73	8.85	8.70	15.37	15.05	—	—
H	*o*-CH_3	59	60.5–62	$C_{24}H_{34}N_4$	76.15	75.75	9.05	8.87	14.80	14.84	—	—
H	*m*-CH_3	77	70–72	$C_{24}H_{34}N_4$	76.15	76.27	9.05	8.91	14.80	15.00	—	—
H	*p*-CH_3	80	103–104	$C_{24}H_{34}N_4$	76.15	76.02	9.05	9.05	14.80	14.95	—	—
H	*o*-Cl	63	69–71	$C_{23}H_{31}ClN_4$	69.24	68.59	7.83	8.00	14.04	13.75	8.89	9.17
H	*m*-Cl	70	63–65.5	$C_{23}H_{31}ClN_4$	69.24	69.15	7.83	7.73	14.04	13.73	8.89	8.79
H	*p*-Cl	66	119.5–120.5	$C_{23}H_{31}ClN_4$	69.24	69.52	7.83	7.71	14.04	13.92	8.89	8.73
o-CH_3	*o*-CH_3	58	—[a]	$C_{25}H_{36}N_4$	76.48	76.22	9.24	9.22	14.27	14.65	—	—
o-CH_3	*m*-CH_3	65	—[b]	$C_{25}H_{36}N_4$	76.48	76.56	9.24	8.92	14.27	14.46	—	—
o-CH_3	*p*-CH_3	54	59–60.5	$C_{25}H_{36}N_4$	76.48	76.52	9.24	9.25	14.27	14.15	—	—
o-CH_3	*o*-Cl	52	—[c]	$C_{24}H_{33}ClN_4$	69.79	69.93	8.05	7.90	13.57	13.74	8.59	8.43
o-CH_3	*m*-Cl	53	—[d]	$C_{24}H_{33}ClN_4$	69.79	69.86	8.05	8 06	13.57	13.85	8.59	8.42
o-CH_3	*p*-Cl	74	85.5–86	$C_{24}H_{33}ClN_4$	69.79	69.55	8.05	8.05	13.57	13.83	8.59	8.80
m-CH_3	*m*-CH_3	44	59–61	$C_{25}H_{36}N_4$	76.48	76.24	9.24	9.21	14.27	14.34	—	—
m-CH_3	*p*-CH_3	62	61–63	$C_{25}H_{36}N_4$	76.48	76.32	9.24	9.18	14.27	14.47	—	—
m-CH_3	*o*-Cl	46	—[e]	$C_{24}H_{33}ClN_4$	69.79	69.30	8.05	7.86	13.57	13.09	8.59	8.62
m-CH_3	*m*-Cl	62	53–56	$C_{24}H_{33}ClN_4$	69.79	69.74	8.05	7.68	13.57	13.64	8.59	8.44
m-CH_3	*p*-Cl	85	88–90	$C_{24}H_{33}ClN_4$	69.79	69.22	8.05	7.72	13.57	13.47	8.59	8.31
p-CH_3	*p*-CH_3	62	148–149	$C_{25}H_{36}N_4$	76.48	76.69	9.24	9.20	14.27	14.17	—	—
p-CH_3	*o*-Cl	72	76–77.5	$C_{24}H_{33}ClN_4$	69.79	69.48	8.05	7.69	13.57	13.86	8.59	8.30
p-CH_3	*m*-Cl	65	77–78	$C_{24}H_{33}ClN_4$	69.79	69.79	8.05	8.04	13.57	13.55	8.59	8.87
p-CH_3	*p*-Cl	70	157–158	$C_{24}H_{33}ClN_4$	69.79	70.04	8.05	8.03	13.57	13.32	8.59	8.42
o-Cl	*o*-Cl	58	82–83	$C_{23}H_{30}Cl_2N_4$	63.73	63.77	6.98	6.91	12.93	12.90	16.36	16.16
o-Cl	*m*-Cl	67	—[f]	$C_{23}H_{30}Cl_2N_4$	63.73	63.26	6.98	6.91	12.93	13.01	16.36	16.64
o-Cl	*p*-Cl	74	75–76	$C_{23}H_{30}Cl_2N_4$	63.73	63.62	6.98	6.52	12.93	12.93	16.36	16.72
m-Cl	*m*-Cl	34	69–70	$C_{23}H_{30}Cl_2N_4$	63.73	63.66	6.98	7.13	12.93	12.81	16.36	16.09
m-Cl	*p*-Cl	63	84–86	$C_{23}H_{30}Cl_2N_4$	63.73	63.15	6.98	7.07	12.93	12.95	16.36	16.75
p-Cl	*p*-Cl	85	172–173	$C_{23}H_{30}Cl_2N_4$	63.73	63.78	6.98	6.70	12.93	12.84	16.36	16.28

[a] B.p. 236–240° at 0.3 mm. (uncorr.), n_D^{25} 1.5707. [b] B.p. 246–250° at 0.6 mm. (uncorr.), n_D^{25} 1.5779. [c] B.p. 248–252° at 0.7 mm. (uncorr.), n_D^{25} 1.5805. [d] B.p. 258–263° at 0.75 mm. (uncorr.), n_D^{25} 1.5879. [e] B.p. 260–262° at 0.7 mm. (uncorr.), n_D^{25} 1.5875. [f] B.p. 286–292° at 1.1 mm. (uncorr.), n_D^{25} 1.5977.

TABLE III

DATA CONCERNING COMPOUNDS HAVING THE GENERAL FORMULA



Y	Yield, %	M.P. or B.P. (Mm.)[a]	n_D^{25}	Empirical Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
$C_4H_{10}N$- (Diethylamino)	44	164–169 (0.1)	1.5330	$C_{17}H_{29}N_3$	74.13	73.50	10.61	10.61	15.26	15.30
$C_5H_{10}N$- (1-Piperidyl)	20	148–150 (0.075) 46–47	—	$C_{18}H_{29}N_3$	75.22	75.24	10.17	9.62	14.62	14.65
C_4H_8NO- (4-Morpholinyl)	52	170–172 (0.08)	1.5513	$C_{17}H_{27}N_3O$	70.55	69.92	9.41	9.52	14.52	14.42
$C_{12}H_8N$- (9-Carbazolyl)	32	130.5–131.5	—	$C_{25}H_{27}N_3$	81.26	81.65	7.37	6.98	11.37	11.30

[a] All melting points are corrected, boiling points are not.

1-[3-(Diethylamino)propyl]-4-phenylpiperazine. To 0.1 mole (23.9 g.) of 1-(3-chloropropyl)-4-phenylpiperazine in 25 ml. of ethanol was added 0.3 mole (21.9 g.) of diethylamine. The mixture was refluxed for 8 hr., cooled, and the diethylamine hydrochloride filtered. After removal of the solvent and excess diethylamine under vacuum, the resulting oil was distilled. Fractional distillation yielded 12.2 g. (44%) of the product boiling at 164–169° (0.1 mm.).

1-[3-(9-Carbazolyl)propyl]-4-phenylpiperazine. A suspension of 0.1 mole (16.7 g.) of carbazole in 35 ml. of dimethylformamide was vigorously stirred while 0.105 mole (2.4 g.) of lithium amide was added. The addition caused the temperature to rise to 60°. When the temperature began to fall, heating was started. The mixture was maintained at 80–90° for 30 min., while partial vacuum was applied. When the mixture had cooled to 65°, 0.11 mole (26.3 g.) of 1-(3-

chloropropyl)-4-phenylpiperazine was added. Heating was resumed and the temperature was kept at 100–110° for 3 hr. After the mixture had cooled to 60°, it was poured, with stirring, into 600 ml. of ice and water. The solid was filtered, triturated with 100 ml. of water, and then dried under vacuum. Recrystallization from ethanol yielded 11.9 g. (32%) of the product, m.p. 130.5–131.5°.

The lithium amide was obtained from the Lithium Corp. of America and the trimethylene chlorobromide from the Dow Chemical Co. The amines were purchased from the Fisher Scientific Co. and were used without further purification.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, KANSAS STATE UNIVERSITY]

The pK_a's of Aromatic Sulfinic Acids[1]

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Received July 25, 1958

The pK_a's of six aromatic sulfinic acids have been determined by means of potentiometric titration and found to be in the vicinity of 1.8 to 2.0.

During the course of research in the laboratory of the first author, the occasion arose to determine the neutral equivalent of *p*-nitrobenzenesulfinic acid.[3] The results from this determination not only yielded the desired neutral equivalent but also indicated that the acidic group being titrated was weaker than benzenesulfinic acid.[4–7] This observation suggested that the ionization constants of aromatic sulfinic acids be reinvestigated and accordingly such a program was undertaken.

Six aromatic sulfinic acids were selected for this study: benzene-, *p*-toluene-, *p*-chlorobenzene-, *p*-bromobenzene, *m*- and *p*-nitrobenzenesulfinic acids. Each of these was prepared from the corresponding sulfonyl chloride by reduction. The identity and purity of each compound was established by means of melting point and neutral equivalent determinations (Table I).

TABLE I

MELTING POINTS AND NEUTRAL EQUIVALENTS OF SULFINIC ACIDS

Sulfinic Acid	M.P., °C. Obsd.	M.P., °C. Lit.	Neut. Equiv. Obsd.	Neut. Equiv. Theor.
Benzene	81.5–83	84[7] 85[8,9]	144.6	142.2
p-Toluene	84–85	84[10] 84–85[11] 86–87[8,9,12]	160.1	156.2
p-Chlorobenzene	98.5–99.5	93–94[13] 98–99[10] 99[14] 100–102[15]	179.7	176.7
p-Bromobenzene	113–114	114[10] 114–115[13] 115[16]	229.8	221.1
m-Nitrobenzene	94.5–96	95–96[17] 98[18]	190.4	187.2
p-Nitrobenzene	s. 125 m. 152–154	s. 136[19,20] m. 159[19] 160[20] 120[21,22]	195.5	187.2

(1) Supported in part by the Faculty Research Fund, Kansas State University and National Science Foundation Grant No. P-2670.

As a means of comparing the values obtained for benzenesulfinic acid with the values reported earlier in the literature two methods of sample preparation (A and B) were used. In method A the samples were dried *in vacuo* prior to use, while in method B the samples were used immediately after preparation. The pK_a's and other data related to the potentiometric titrations are given in Table II.

With the exception of the value of 1.29 which Rumpf and Sadet report[7] for benzesulfinic acid there is reasonable agreement among the values reported in Table II and the earlier literature. Loven, for example, has reported that the dissociation

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(2) Present address, Department of Chemistry, Southern Illinois University, Carbondale, Ill.

(3) Unpublished data taken by Harry A. Smith, deceased.

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