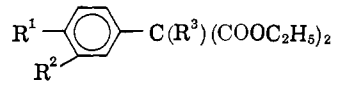
TABLE III

DIETHYL ARYLMALONATES AND ARYLCYANOALKYLMALONATES



R¹	R²	R³	B.p., ° C. (mm.)	Yield, %	Molecular formula	Calcd., % C	H	N	Found, % C	H	N
H	H	CH_2CN	115–116 (0.4)	63.5	$C_{15}H_{17}NO_4$	65.52	6.23	..	66.59	6.03	..
H	H	$CH(CH_3)CN$	140–142 (2)	34.6	$C_{16}H_{19}NO_4$	66.43	6.57	..	68.35	6.70	..
CH_3O	H	H	146–147 (1.0)	72	$C_{14}H_{18}O_5$	63.16	6.81	..	62.12	6.42	..
CH_3O	H	CH_2CN	160–170 (1.2)	39.2	$C_{16}H_{19}NO_5$	62.94	6.27	4.59	63.33	6.28	4.70
Cl	H	H	140–142 (1.0)	73	$C_{13}H_{15}ClO_4$	57.59	5.54	..	57.51	5.61	..
Cl	H	CH_2CN	155–160 (0.4)	42.2	$C_{15}H_{16}ClNO_4$	58.15	5.21	4.52	59.20	4.96	3.91
CH_3	CH_3	H	150–152 (2.2)	39.0	$C_{15}H_{20}O_4$	68.16	7.63	..	67.92	8.16	..
CH_3	CH_3	CH_2CN	150–170 (2.2)	43.0	$C_{17}H_{21}NO_4$	67.53	6.97	4.63	67.57	7.11	5.00
OCH_2O		H	174–175 (0.6)	81	$C_{14}H_{16}O_6$	59.98	5.75	..	59.74	5.31	..
OCH_2O		CH_2CN	157–160 (0.1)	32.0	$C_{16}H_{17}NO_6$	60.20	5.37	4.39	60.57	5.40	4.10

butyrate hydrochloride in 150 ml. of absolute ethanol was saturated at ice bath temperature with gaseous hydrogen chloride and then was stored at room temperature for 4 days. The crude crystalline precipitate, m.p. 158–159°, was isolated and recrystallized from ethanol to give 8 g. (90%) of product, m.p. 159–160°.

Synthesis and Pharmacological Study of New Piperazine Derivatives. I. Benzylpiperazines

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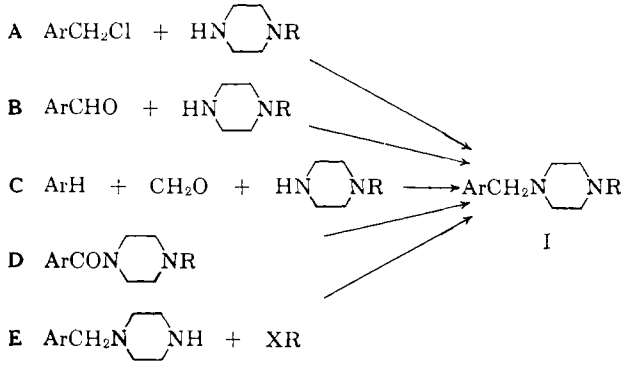
Twenty-three 1,4-disubstituted piperazines have been prepared, in which the 1-substituents are benzyl or its mono- or polyalkoxy-, or alkoxyhydroxy- derivatives, and the 4-substituents are phenyl, chloro- or methoxyphenyl, pyridyl, methylpyrazinyl, chloro- or methoxypyridazinyl. They have been studied systematically for potency against epinephrine and histamine on the isolated guinea pig seminal vesicle, in comparison with ergotamine and promethazine. Some compounds show potent activity against epinephrine, and all present very weak histaminolytic effects. The adrenergic blocking action observed *in vitro* was verified in anesthetized dogs.

Adrenolytic, sympatholytic, and antihistaminic properties have been described in 1-phenylpiperazine[1] and derivatives[2]: hypotensive, vasodilatator, and neuroleptic effects have also been reported in series of 1-aralkyl piperazines.[3]

A series of new benzyl piperazines (Table I) of type I has been prepared where Ar = phenyl, mono- or polyalkoxyphenyl, or alkoxyhydroxyphenyl and R = phenyl, chlorophenyl, methoxyphenyl, pyridyl, methylpyrazinyl, chloro- or methoxypyridazinyl.

These piperazine derivatives were obtained by five general methods according to the scheme



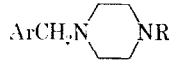
In method A, benzyl chlorides (whether isolated or not) were condensed with twice the theoretical amount

(1) (a) D. Bovet and F. Bovet-Nitti, "Médicaments du système nerveux végétatif," S. Karger, S. A., Bâle, 1948, p. 247; (b) L. W. Roth, *J. Pharmacol. Exptl. Therap.*, **110**, 157 (1954); (c) V. Prelog and G. J. Driza, *Collection Trav. Chim. Tchecoslov.*, **5**, 497 (1933).

(2) (a) E. Cerkovnikov and P. Stern, *Arkhiv. Kem.*, **18**, 12 (1946); (b) B. B. Morphis, L. W. Roth, and R. K. Richards, *Proc. Soc. Exptl. Biol. Med.*, **101**, 174 (1959); (c) D. F. Marsh and J. F. O'Leary, *Federation Proc.*, **12**, 348 (1953); (d) J. F. O'Leary, *Federation Proc.*, **12**, 355 (1953); (e) J. F. O'Leary, *Am. J. Med. Sci.*, **226**, 111 (1953); (f) J. E. Owen and T. Verhave, *J. Pharmacol. Exptl. Therap.*, **122**, 59A (1958); (g) I. H. Page, R. W. Wolford, and A. C. Corcoran, *Arch. Intern. Pharmacodyn.*, **119**, 214 (1959); (h) A. P. Swain and S. K. Naegele, *J. Am. Chem. Soc.*, **76**, 5091 (1954).

(3) (a) J. R. Boissier, C. Dumont, R. Ratouis, and J. Pagny, *Arch. Intern. Pharmacodyn.*, **133**, 29 (1961); (b) J. Mills, M. M. Boren, and N. R. Easton, Abstracts, 132nd National Meeting of the American Chemical Society, New York, N. Y., 1957, p. 11-O; (c) R. L. Moffitt and R. K. S. Lim, *Federation Proc.*, **15**, 461 (1956); (d) G. Quesnel, R. Chalaust, H. Schmitt, G. Kroneberg, and H. Schmitt, *Arch. Intern. Pharmacodyn.*, **128**, 17 (1960); (e) N. H. Schimmel and J. R. Beerm, *Antibiot. Med. Clin. Therapy*, **6**, 25 (1958); (f) G. Stille, W. Braun, and M. Walter, *Arzneimittel-Forsch.*, **7**, 225 (1957).

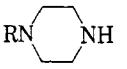
TABLE I



Compound	Ar	R	Method	Yield crystallized, %	Cryst.[a] solvent	M.p.,[b] °C., of amine or salt	Formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H	Pharmacological data[c] Adrenolytic activity EC_{50} μg./ml.[d]	Pharmacological data[c] Antihistaminic activity EC_{50} μg./ml.[d]	LD_{50} mg./kg mice i.p.[e]
I	C_6H_5[f]	C_6H_5	A	59	M–Et	214 (T)	$C_{17}H_{20}N_2 \cdot 2HCl$	62.77	6.82	62.1	6.8	>5	>5	
II	3-$CH_3OC_6H_4$	C_6H_5	A	50	AE	196 (T)	$C_{18}H_{22}N_2O \cdot 2HCl$	60.84	6.81	60.8	6.9	>5	>5	200
III	4-$CH_3OC_6H_4$	C_6H_5	A	72	AE–Et	224 (T)	$C_{18}H_{22}N_2O \cdot 2HCl$	60.84	6.81	60.8	7.0	2	4	>800
IV	2,5-$(CH_3O)_2C_6H_3$[g]	C_6H_5	A	60	E 96	119 (T)	$C_{19}H_{24}N_2O_2$	73.04	7.74	73.3	7.8	2	2	150
V	3,4-$(CH_3O)_2C_6H_3$	C_6H_5	A	85	M	74 (T)	$C_{19}H_{24}N_2O_2$	73.04	7.74	73.2	7.65	0.1	0.5	300
VI	3,4-$(CH_3O)_2C_6H_3$	C_6H_5	[h]	88	Ac	189 (T)	$C_{19}H_{24}N_2O_2 \cdot CH_3I$	..	..	..	..	>5	>5	150
VII	2,5-$(OH)(CH_3O)C_6H_3$	C_6H_5	C	50	E 96	121 (T)	$C_{18}H_{22}N_2O_2$	72.45	7.43	72.4	7.6	3	>5	>800
VIII	3,4-$(CH_3O)(OH)C_6H_3$	C_6H_5	B	15	E 96	139 (T)	$C_{18}H_{22}N_2O_2$	72.45	7.43	72.4	7.4	1	1	150
IX	3,4-$(OCH_2O)C_6H_3$	C_6H_5	A	85	M	94 (T)	$C_{18}H_{20}N_2O_2$	72.95	6.80	72.8	6.8	5	>5	75
X	3,4,5-$(CH_3O)_3C_6H_2$	C_6H_5	D	75	AE	271 (T)	$C_{20}H_{26}N_2O_3 \cdot HCl$	63.40	7.18	63.3	7.2	[i]	[i]	[i]
XI	3,4-$(CH_3O)_2C_6H_3$	2-ClC_6H_4	A	59	AE	79 (M)	$C_{19}H_{23}ClN_2O_2$	65.80	6.68	66.1	6.6	2	2	200
XII	3,4-$(CH_3O)_2C_6H_3$	3-ClC_6H_4	A	27	P	206 (M)	$C_{19}H_{23}ClN_2O_2 \cdot HCl$	59.53	6.31	59.8	6.3	1	0.2	100
XIII	3,4-$(CH_3O)_2C_6H_3$	4-ClC_6H_4	A	61	AE	102 (M)	$C_{19}H_{23}ClN_2O_2$	65.80	6.68	66.1	6.8	0.5	0.5	250
XIV	3,4-$(CH_3O)_2C_6H_3$	2-$CH_3OC_6H_4$	A	31	P	221 (M)	$C_{20}H_{26}N_2O_3 \cdot HCl$	63.39	7.18	63.2	7.2	0.02	1	150
XV	3,4-$(CH_3O)_2C_6H_3$	4-$CH_3OC_6H_4$	A	50	E 80	96 (M)	$C_{20}H_{26}N_2O_3$	70.15	7.65	69.9	7.6	1	1	150
XVI	C_6H_5	2-C_5H_4N[j]	A	73	M 50	61 (T)	$C_{16}H_{19}N_3$	75.85	7.56	75.9	7.4	>5	2	400
XVII	3,4-$(CH_3O)_2C_6H_3$	2-C_5H_4N	A	69	P	101 (T)	$C_{18}H_{23}N_3O_2$	68.98	7.39	68.6	7.4	0.05	5	300
XVIII	3,4-$(OCH_2O)C_6H_3$	2-C_5H_4N	A	83	P	87 (T)	$C_{17}H_{19}N_3O_2$	68.66	6.44	68.6	6.3	5	>5	600
XIX	C_6H_5	4-C_5H_4N[j]	E	72	H	102 (M)	$C_{16}H_{19}N_3$	75.85	7.56	75.8	7.4	>5	>5	25–50
XX	3,4-$(CH_3O)_2C_6H_3$	4-C_5H_4N	E	75	H	109 (M)	$C_{18}H_{23}N_3O_2$	68.97	7.40	69.2	7.3	>5	>5	100
XXI	3,4-$(CH_3O)_2C_6H_3$	2-$C_5H_5N_2$[k]	A	50	P	102 (T)	$C_{18}H_{24}N_4O_2$	65.83	7.37	65.8	7.5	>5	>5	150
XXII	3,4-$(CH_2O)_2C_6H_3$	3-$C_4H_2ClN_2$[l]	A	50	T-H	146 (M)	$C_{17}H_{21}ClN_4O_2$	58.53	6.07	58.3	6.15	>5	>5	200
XXIII	3,4-$(CH_3O)_2C_6H_3$	3-$C_5H_5N_2O$[m]	A	65	H	121 (M)	$C_{18}H_{24}N_4O_3$	62.77	7.02	62.9	7.0	2	>5	150

[a] Ac, acetone; AE, absolute ethanol; E 96, 96% ethanol; E 80, 80% ethanol; Et, ether; H, heptane; M, methanol; M 50, 50% methanol; P, 2-propanol; T, toluene. [b] Uncorrected melting points, (T) capillary tube; (M) Kofler hot stage microscope. [c] Compounds prepared as bases were dissolved in dilute acetic acid. [d] EC_{50} is the concentration which inhibited the normal contraction of either adrenaline (2 μg./ml.) and histamine (2 μg./ml.) by 50%. Note: > means that the compound was inactive up to the concentration of 5 μg./ml. [e] Acute toxicity determined by intraperitoneal injection of increasing doses (25, 50, 100, 200, 400, and 800 mg./kg.) to pairs of mice according to W. G. Smith, in "Progress in Medicinal Chemistry," G. P. Ellis and G. B. West, Ed., Butterworths, London, 1961, p. 1. The LD_{50} is approximately the dose killing one out of two mice or the average of the two successive doses for which mortalities of 0/2 and 2/2 have been observed. [f] V. Prelog and Z. Blazek, *Collection Trav. Chim. Tchecoslov.*, 6, 549 (1934), reported m.p. 228° for monohydrochloride salt. [g] From 2,5-dimethoxybenzyl chloride used in benzene solution, K. Hejno and Z. Arnold, *Chem. Listy*, **47**, 601 (1953). [h] From V and CH_3I in acetone, recrystallized from acetone; I, calcd.: 27.93; found: 28.0. [i] Not experimented with because of its low solubility. [j] C_5H_4N: pyridyl. [k] $C_5H_5N_2$: 3-methylpyrazinyl. [l] $C_4H_2ClN_2$: 6-chloropyridazinyl. [m] $C_5H_5N_2O$: 6-methoxypyridazinyl.

TABLE II[g]



Compound	R	Yield, %	B.p., C. (mm.)[a]	M.p., °C.[b]	Formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H
XXIV	2-$C_5H_5N_2$[c]	62	115–117 (0.3)		$C_9H_{14}N_4$	60.65	7.92	60.6	7.9
XXV	3-$C_4H_2ClN_2$[d]	54		101	$C_8H_{11}ClN_4$	48.36	5.59	48.5	5.6
XXVI	3-$C_5H_5N_2O$[e]	60		82	$C_9H_{14}N_4O$	55.65	7.26	55.6	7.5
XXVII	3,4-$(CH_3O)_2C_6H_3CH_2$[f]	70	135–140 (0.5)	56	$C_{13}H_{20}N_2O_2$	66.07	8.53	65.8	8.6

[a] Uncorrected. [b] Uncorrected, determined with a Kofler hot stage microscope. [c] $C_5H_5N_2$: 3-methylpyrazinyl monohydrochloride salt crystallized from 2-propanol, m.p. 198°. *Anal.* Calcd. for $C_9H_{14}N_4 \cdot HCl$: C, 50.34; H, 7.04; Cl, 16.51. Found: C, 51.0; H, 7.1; Cl, 16.5. [d] $C_4H_2ClN_2$: 6-chloropyridazinyl Cl: calcd., 17.85; found, 18.0. [e] $C_5H_5N_2O$: 6-methoxypyridazinyl. [f] From 3,4-dimethoxybenzyl chloride[9] and piperazine according to the procedure reported for 1-benzylpiperazine.[4e] The dihydrochloride salt has been reported.[3d] [g] Purities of all distilled monosubstituted piperazines were determined by gas chromatography using a Prolabo apparatus with a thermal conductivity detector (column: 4 m. long, 6 mm. diameter, packed with C 22 firebrick coated with 20% by weight of Rhodorsil silicone oil, temperature: 240°, carrier gas: hydrogen). Retention time: 8 to 10 min. With compounds prepared from anilines, chromatograms showed a trace of these materials even after 3 rectifications (retention time: about 2 min.).

of N-monosubstituted piperazine in a solvent in which the N-monosubstituted piperazinium chloride obtained was insoluble. In method B, condensation of an aldehyde with an amine and hydrogenation under pressure over Raney nickel catalyst were performed in one step. In method C, the well known Mannich procedure was followed. In method D, the intermediate amide (from the reaction of an acid chloride with an amine) was reduced using lithium aluminum hydride. Method E (used only in case of a fairly mobile halogen atom in the RX compound) was essentially the same as method A.

Several N-monosubstituted piperazines were prepared according to previously reported procedures.[4] In Table II, descriptive and analytical data are listed for additional compounds of this type. Synthetic details for these derivatives are given in the Experimental part.

The adrenolytic and antihistaminic activities were studied on the isolated guinea pig seminal vesicle according to the method of Stone and Loew.[5] The results are presented in Table I. For comparative purposes, in the same conditions, EC_{50} for ergotamine against epinephrine was found 0.02 μg./ml. and EC_{50} for promethazine against histamine 0.001 μg./ml. Compounds V, XIV, and XVII had the most potent inhibitory effect against epinephrine. All the compounds presented rather weak and easily reversible histaminolytic effects.

The adrenergic blocking effect observed *in vitro* has been confirmed on anesthetized bilaterally vagotomized and atropinized dogs. Blood pressure was recorded from the carotid artery. The intravenous injection of V, XIV, and XVII produced suppression of hypertensive response to epinephrine respectively at 5 mg./kg. for V, and 0.5–1 mg./kg. for XIV and XVII. Higher doses provoked reversal of epinephrine hypertension.

Experimental

1-(3-Methyl-2-pyrazinyl)piperazine (XXIV).—A mixture of 43 g. (0.5 mole) of anhydrous piperazine, 32 g. (0.25 mole) of 2-chloro-3-methylpyrazine,[6] 26.5 g. (0.25 mole) of anhydrous sodium carbonate, and 150 ml. of 1-pentanol was refluxed for 5 hr. with stirring. After cooling, separation of salts and distillation of the organic phase gave XXIV. **Bis 1,4-(3-methyl-2-pyrazinyl)-piperazine** was obtained by crystallization from methanol of the distillation tailings, m.p. 178°.

Anal. Calcd. for $C_{14}H_{18}N_6$: C, 62.20; H, 6.71. Found: C, 62.15; H, 7.0.

1-(6-Chloro-3-pyridazinyl)piperazine (XXV).—A solution of 149 g. (1 mole) of 3,6-dichloropyridazine,[7] 505 g. (2.6 moles) of piperazine hexahydrate, 225 ml. of acetone, 200 ml. of water, and 18 ml. of hydrochloric acid (sp. gr. 1.19) was slowly heated while a rather violent starting of the reaction was observed, and then refluxed for 3 hr. After cooling, 5% of insoluble **bis 1,4-(6-chloro-3-pyridazinyl)piperazine** was separated; m. p. 352° (from dimethylformamide).

Anal. Calcd. for $C_{12}H_{12}Cl_2N_6$: C, 46.31; H, 3.89; Cl, 22.79. Found: C, 46.4; H, 3.6; Cl, 23.0.

Acetone was removed from the filtrate by vacuum distillation. The aqueous phase was extracted 3 times with chloroform. The dried chloroform layer was concentrated and the residue crystallized from an acetone–petroleum ether mixture to give XXV.

1-(6-Methoxy-3-pyridazinyl)piperazine (XXVI).—1-(6-Chloro-3-pyridazinyl)piperazine (49.6 g., 0.25 mole) was dissolved in a sodium methoxide solution prepared from 8.5 g. of sodium in 300 ml. of methanol and heated in an autoclave at 130–140° for 4 hr. Water (20 ml.) was added to the mixture, salts were separated, and methanol was evaporated *in vacuo;* the residue was extracted with chloroform, the extracts were concentrated, and the solid was recrystallized from heptane.

Method A. 1-(3,4-Dimethoxybenzyl)-4-phenylpiperazine (V).—A solution of 93.25 g. (0.5 mole) of 3,4-dimethoxybenzyl chloride[8] and 162 g. (1 mole) of 1-phenylpiperazine in 800 ml. of anhydrous xylene was heated under reflux for 3 hr. After cooling and separation of about 100 g. (0.5 mole) of 1-phenylpiperazine hydrochloride, the solvent was evaporated *in vacuo* and crude V was crystallized.

1-(3,4-Dimethoxybenzyl)-4-(2-methoxyphenyl)piperazine Hydrochloride (XIV).—Following the same procedure, 1-(3,4-dimethoxybenzyl)-4-(2-methoxyphenyl)piperazine was obtained as an oil after concentration of the xylene phase. To a solution of 36 g. (0.105 mole) of this base in 50 ml. of absolute ethanol was added 0.1 mole of 2 *N* absolute ethanolic hydrogen chloride. After standing overnight at 0°, crude (XIV) was separated by filtration and recrystallized.

Method B. 1-(3-Methoxy-4-hydroxybenzyl)-4-phenylpiperazine (VIII).—A mixture of 30.4 g. (0.2 mole) of vanillin, 35.6 g. (0.22 mole) of 1-phenylpiperazine, and 200 ml. of ethanol was heated for 3 hr. at 110° in a 1-l. autoclave, under an hydrogen initial pressure of 80 kg. at 20°, over about 6 g. of Raney nickel catalyst. After cooling the catalyst was removed and the alcoholic solution was concentrated to about 80 ml. and allowed to stand for 24 hr. at 0°. Crude VIII was collected and recrystallized.

(4) (a) 1-Phenylpiperazine, K. Fujii, K. Tomino, and H. Watanabe, *J. Pharm. Soc. Japan*, **74**, 1052 (1954); (b) chlorophenylpiperazines, C. B. Pollard and T. H. Wicker, *J. Am. Chem. Soc.*, **76**, 1853 (1954); (c) methoxyphenylpiperazines, C. B. Pollard and J. B. Christie, *J. Org. Chem.*, **23**, 1333 (1958); (d) 1-(2-pyridyl)piperazine, K. L. Howard, H. W. Stewart, E. A. Conroy, and J. J. Denton, *ibid.*, **18**, 1484 (1953); (e) 1-benzylpiperazine, R. Baltzly, J. S. Buck, E. Lorz, and W. Schon, *J. Am. Chem. Soc.*, **66**, 244 (1944).

(5) C. A. Stone and E. R. Loew, *J. Pharmacol. Exptl. Therap.*, **106**, 226 (1952).

(6) G. Karmas and P. E. Spoerri, *J. Am. Chem. Soc.*, **74**, 1580 (1952).

(7) R. H. Mizzoni and P. E. Spoerri, *ibid.*, **73**, 1873 (1951).

(8) M. Tiffeneau, *Bull. soc. chim. France*, **9**, 930 (1911).

Method C. 1-(2-Hydroxy-5-methoxybenzyl)-4-phenylpiperazine (VII).—To an ice-cold mixture of 24.8 g. (0.2 mole) of 1-hydroxy-4-methoxybenzene and 32.4 g. (0.2 mole) of 1-phenylpiperazine in 90 ml. of ethanol and 50 ml. of water was added 20 ml. of 30% aqueous formaldehyde solution. After stirring for 48 hr. at room temperature, crystalline VII was filtered and recrystallized.

Method D. 1-(3,4,5-Trimethoxybenzyl)-4-phenylpiperazine Hydrochloride (X).—A solution of 23.05 g. (0.1 mole) of 3,4,5-trimethoxybenzoyl chloride and 16.2 g. (0.1 mole) of 1-phenylpiperazine in 150 ml. of anhydrous chloroform was refluxed for 2 hr. and evaporated to dryness to give a solid which was recrystallized from a chloroform–toluene mixture (1:1) to give **1-(3,4,5-trimethoxybenzoyl)-4-phenylpiperazine hydrochloride** in 60% yield; m.p. 216°.

Anal. Calcd. for $C_{20}H_{25}ClN_2O_4$: C, 61.13; H, 6.41; Cl, 9.03. Found: C, 60.9; H, 6.4; Cl, 9.4.

The hydrochloride was converted quantitatively to the free base by alkalinization of an aqueous solution and recrystallization from isopropyl ether; m.p. 134–135°.

Anal. Calcd. for $C_{20}H_{24}N_2O_4$: C, 67.39; H, 6.79. Found: C, 67.7; H, 6.75.

This base was also prepared by mixing a solution of 4.6 g. (0.02 mole) of 3,4,5-trimethoxybenzoyl chloride in 10 ml. of anhydrous chloroform with a solution of 3.24 g. (0.02 mole) of 1-phenylpiperazine and of 1.6 g. of pyridine in 10 ml. of anhydrous chloroform. After standing for 5 days at room temperature and washing twice with 20 ml. of water, the chloroform was removed *in vacuo*. The crystalline residue was recrystallized from isopropyl ether to give the amide in 50% yield, m.p. and mixture m.p. with the above sample 134–136°.

A solution of 35.6 g. (0.1 mole) of the above amide in anhydrous ether was reduced with 0.1 mole of lithium aluminum hydride in anhydrous ether to give **1-(3,4,5-trimethoxybenzyl)-4-phenylpiperazine** in 75% yield, b.p. 180–185° (0.1 mm.).

Anal. Calcd. for $C_{20}H_{26}N_2O_3$: C, 70.15; H, 7.65. Found: C, 70.2; H, 7.65.

To a solution of 17.1 g. (0.05 mole) of this disubstituted piperazine in 50 ml. of anhydrous chloroform was added a solution of 0.11 mole of 2 *N* absolute ethanolic hydrogen chloride. The solvent was evaporated *in vacuo* to give impure 1-(3,4,5-trimethoxybenzyl)-4-phenyl piperazine dihydrochloride which was added to 200 ml. of water, boiled under reflux until completely dissolved, and filtered hot. On cooling, pure crystalline monohydrochloride salt (X) was deposited,[9] m.p. 270°. Recrystallization from absolute ethanol gave an analytical sample; sublimation was observed on a hot stage microscope at 218–220°.

Method E. 1-Benzyl-4-(4-pyridyl)piperazine (XIX).—A solution of 88 g. (0.5 mole) of 1-benzylpiperazine, 28.4 g. (0.25 mole) of 4-chloropyridine,[10] and 200 ml. of anhydrous xylene was refluxed for 20 hr. After cooling, 1-benzylpiperazine hydrochloride was separated and the xylene was evaporated to dryness to give XIX which was recrystallized.

(9) Such a hydrolysis of dihydrochloride to monohydrochloride salts by boiling water was observed in some other N,N'-disubstituted piperazines when one of the substituents was a phenyl or a substituted phenyl group.

(10) J. P. Wibaut and F. W. Broekman, *Rec. trav. chim.*, **58**, 885 (1939).

Substituted 2,3-Dihydro-1,5-benzothiazepin-4(5H)-ones and 3,4-Dihydro-2-phenyl-(2H)-1,6-benzothiazocin-5(6H)-ones

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The synthesis of substituted 2,3-dihydro-1,5-benzothiazepin-4(5H)-ones and their alkylation is described. The preparation of 3,4-dihydro-2-phenyl-2H-1,6-benzothiazocin-5(6H)-one and 6-(2-dimethylaminoethyl)-3,4-dihydro-2-phenyl-2H-1,6-benzothiazocin-5(6H)-one hydrochloride is also reported. Three of these compounds were found to be highly effective in calming rats with lesions in the septal area of the brain.

In extension of our studies on substituted 2-phenyl-1,4-benzothiazin-3(4H)-ones,[1] we have prepared a number of related 2,3-dihydro-1,5-benzothiazepin-4(5H)-ones (Table II) and 3,4-dihydro-2-phenyl-2H-1,6-benzothiazocin-5(6H)-ones.

The intermediate 2,3-dihydro-1,5-benzothiazepin-4(5H)-ones (Table I) were obtained by heating 2-aminobenzenethiol (or 2-amino-4-chlorobenzenethiol) with the appropriate cinnamic, phenylcrotonic, or furanacrylic acid according to a procedure used for the preparation of 2,3-dihydro-2-methyl-1,5-benzothiazepin-4(5H)-one and the 2-phenyl analog.[2]

The compounds listed in Table II were obtained by addition of a slurry of the appropriate 1,5-benzothiazepin-4(5H)-one in toluene to a slurry of sodamide in toluene; the resulting solution was treated with the corresponding basically-substituted alkyl chloride and the mixture maintained usually at 60–65° for 3 hr. The yield in this alkylation reaction is dependent on the stability of the benzothiazepin-4(5H)-one to ring cleavage under the reaction conditions and the reactivity of the alkyl halide. The alkylation of 2,3-dihydro-2-phenyl-1,5-benzothiazepin-4(5H)-one with 2-dimethylaminoethyl chloride gave a 50% yield of purified product (**3**, Table II); whereas the reaction with the less reactive 3-dimethylaminopropyl chloride gave only a 9% yield of **6** and 65% of 2′-(3-dimethylaminopropylthio)cinnamanilide.[3] The formation of the latter product was not surprising since treatment of 2,3-dihydro-2-phenyl-1,5-benzothiazepin-4(5H)-one with 10% potassium hydroxide was reported to yield 2′-mercaptocinnamanilide.[2]

Because of the low reactivity of 2-(N-benzyl-N-methylamino)ethyl chloride under the above conditions, the corresponding bromide was used in the reaction with 2,3-dihydro-2-phenyl-1,5-benzothiazepin-4(5H)-one to give **5**.

The homologous 8-membered ring system, 3,4-dihydro-2-phenyl-1,6-benzothiazocin-5(6H)-one, was prepared as shown on the following page.

(1) J. Krapcho, A. Szabo, and J. Williams, *J. Med. Chem.*, **6**, 214 (1963).

(2) W. H. Mills and J. B. Whitworth, *J. Chem. Soc.*, 2738 (1927).

(3) An alternate synthesis of 2′-(3-dimethylaminopropylthio)cinnamanilide and the biological activity of this compound has been reported by J. Krapcho, B. Rubin, A. M. Drungis, E. R. Spitzmiller, C. F. Turk, J. Williams, B. N. Craver, and J. Fried, *J. Med. Chem.*, **6**, 219 (1963).