immersing them in a chlorine atmosphere for at least 10 min. After the immersion, air was blown across the plate to remove the unbound chlorine and the plates were sprayed with a 2% solution of potassium iodide containing thioline. Control runs showed that this procedure was specific for the urinary carbamates.

Bis(hydroxymethyl)dimethylsilane Dicarbamate (III).—A total of 1.5 g of III, mp 104–106°, was administered to three rats in a suspension of gum tragacanth. The urine was collected for 48 hr. Analysis for silicon indicated that approximately 70% of the administered dose was present in the urine. The urine was extracted continuously for 12 hr with ether. Removal of the ether under vacuum and crystallization of the resulting solid from water afforded 0.80 g (53%) of the unchanged dicarbamate, mp 99–101°, mmp (with III) 98.5–101°. The infrared spectrum of this material was identical with that of III.

(Hydroxymethyl)dimethyl-*n*-propylsilane Carbamate (IV).—A total of 7.8 g of IV was administered neat to 17 rats, and their urine was collected for 4 days. Analysis of the urine for silicon indicated that approximately 90% of the dosed silicon was present. The urine was extracted overnight with ethyl acetate. The solvent was removed under vacuum, and the residue was dissolved in acetone and filtered to remove the precipitated urea. Evaporation of the acetone afforded 5.3 g of a dark oil. Chromatography of the oil through 200 g of alumina, activity III, was carried out using the solvent scheme of chloroform–ether (1:1), 100 ml, and ether, 200 ml. Eighty fractions were collected. Tlc of these fractions indicated that only one carbamate (in fractions 43–78) was present. Combination of these fractions and crystallization from ether–petroleum ether (bp 30–60°) yielded 1.8 g (29%) of the dicarbamate disiloxane VI, mp 68–70°.

Anal. Calcd for $C_8H_{20}N_2O_5Si_2$: C, 34.25; H, 7.20; N, 9.99. Found: C, 34.43; H, 7.06; N, 9.82.

The nmr spectrum of VI in $CHCl_3$ showed a singlet at δ 0.3 ($SiCH_3$), a singlet at 3.8 ($SiCH_2OCONH_2$), and a broad band at 5.2 ($CONH_2$). The $CHCl_3$ proton was used as the internal standard. The two singlets showed an area ratio of 4:11. The significant bands in the infrared spectrum ($CHCl_3$) were 2.85, 2.95 (NH_2), 5.85, 6.25 ($CONH_2$), 7.95 ($SiCH_3$), and 9.5 μ (SiOSi). In another run, extraction of the urine with ether, followed by tlc analysis of the resulting oil, failed to reveal the presence of unaltered carbamate. Control runs indicated that this method could detect about 2% of the dosed amount.

Bis(hydroxymethyl)methyl-*n*-propylsilane Dicarbamate (Silameprobamate) (V).—Twelve grams of V was dosed to 62 rats and the urine was collected for 3 days. Silicon analysis at the end of this period indicated that approximately 80% of the ingested silica had been eliminated. The urine was extracted overnight with ethyl acetate. Removal of the ethyl acetate and the urea afforded 8.6 g of a dark oil. Chromatography of this material was carried out using 400 g of alumina, activity III. Sixty 10-ml fractions were collected, using the following solvent scheme: benzene–ethyl acetate (1:1), 150 ml; benzene–ethyl acetate (1:2), 50 ml; ethyl acetate, 50 ml; ethyl acetate–acetone (1:1), 50 ml; acetone, 50 ml; acetone–methanol (1:1), 50 ml; and methanol, 200 ml. Thin layer chromatography of the eluted fractions showed the presence of two carbamates: R_f 0.53 (minor component), appearing in fractions 19 and 20, and R_f 0.37 (major component), appearing in fractions 24–54.

The first component, R_f 0.53, 20 mg, was a white solid with mp 54–58°. The nmr spectrum of this material in $CHCl_3$ showed three bands: δ 0.30, singlet; 4.0, singlet; and 5.2, a broad band. The area ratio under the two singlets was 6:8.4. The infrared spectrum ($CHCl_3$) showed the significant peaks at 2.85, 3.0, 5.85, 6.3, and 7.95, and a broad band at 9.5 μ.

The second component, R_f 0.37, 2.3 g, was an oil. This material was combined and rechromatographed through alumina, activity IV, using ethyl acetate as solvent. The nmr of the eluted material, in D_2O showed a singlet at δ 0.2 (relative area, 3.0), three peaks (but not a triplet) at 1.0, 1.15, and 1.25 (combined area, 5.2), a singlet at 3.9, and a multiplet starting at 4.0 (combined area under the singlet and the multiplet, 5.0). The infrared spectrum (thin film) showed a broad and intense absorption in the 2.9-μ region and other significant bands appearing at 5.85, 6.25, 9.4 (sharp), and 7.95 μ. Using the Beckman IR-4 spectrophotometer and LiF optics, the broad band at 2.9 μ could not be resolved. The eluted oil gave a positive iodoform test and a positive ceric nitrate test but failed to yield a solid derivative with β-naphthyl isocyanate.

Anal. Calcd for $C_5H_{13}O_2N_2Si$: Si, 11.2. Found: Si, 10.5.

In another run, the urine was first extracted 12 hr with ether. Tlc analysis of the ether extract showed no evidence of silameprobamate. Control runs indicated that 10 mg of silameprobamate in 100 ml of urine (about 2% of the dose) could be detected.

Acknowledgment.—The authors are grateful to Mr. Lawrence Wendt for his aid in this project.

Compounds Acting on the Central Nervous System. VII. Studies in 1-Pyridyl-4-substituted Piperazines. A New Class of Anticonvulsants

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A number of 1-pyridyl-4-substituted piperazines have been synthesized and evaluated for their pharmacological action. A number of 1-(3-amino-4-pyridyl)-4-phenylpiperazines have been shown to possess marked anticonvulsant and antireserpine properties. Their structure–activity relationship is discussed. In particular, 1-(3-amino-4-pyridyl)-4-(3-trifluoromethylphenyl)piperazine has shown promising anticonvulsant activity.

In a study reported earlier[1,2] it was found that the pattern of biological activity of 3,4- and 2,3-diaminopyridines was greatly changed when one of the amino groups was substituted by a β-arylalkyl- or β-azacycloalkane radical, and a number of new activities not associated with the parent compounds appeared in the resulting derivatives, which included hypotensive, antipyretic, anticonvulsant,[3] and antiinflammatory[4] activities. In continuation of this study of substituted diaminopyridines, making one of the amino groups part

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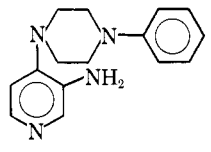
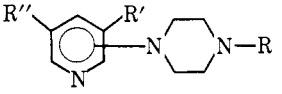
(3) P. C. Jain, V. Kapoor, N. Anand, A. Ahmad, G. K. Patnaik, and M. M. Vohra, International CNS Drugs Symposium, Hyderabad, India, 1966. G. S. Sidhu, I. K. Kacker, P. B. Sattur, G. Thyagarajan, and V. R. K. Parmahansa, Ed., Council of Scientific and Industrial Research, India, p 323.

(4) R. C. Sripal (unpublished data).

of a 4-arylpiperazine or piperidine ring as another variant of the substitution of the amino group seemed of interest, in view of the multitude of activities associated with 1-substituted 4-phenylpiperidine[5] and 4-phenylpiperazines.[6] Quite early in this study it was observed that 4-phenyl-1-(3-amino-4-pyridyl)piperazine[7] (I) had significant anticonvulsant, antireserpine, specific internuncial blocking, and weak, but definite, hypotensive, antipyretic, and anti-5-hydroxytryptamine activities. The novelty of this series for anticonvulsant activity added to the interest in them. In a study of the structure–activity relationship of this series systematic variations were introduced in different parts of the molecular architecture of I. The various types of compounds synthesized in this study are typified by the general formulas II–X.



I



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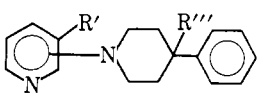
III, 4-pyridyl



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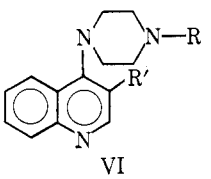
V, 4-pyridyl



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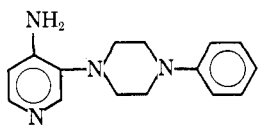

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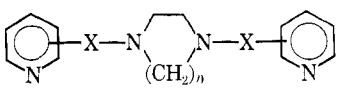
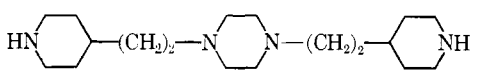


VIII, 2-pyridyl
IX, 4-pyridyl



X

R = CH_3, aryl, aralkyl
R′ = H, NO_2, NH_2
R″ = H, Br, NO_2, NH_2
R‴ = H, OH
n = 2, 3
X = CH_2CH_2, $CH(CH_3)$

The 4-arylpiperazines required in this study were prepared by the condensation of the appropriate anilines with bis-β-chloroethylamine hydrochloride[8] essentially according to the method of Prelog and Blazek.[9]

4-Aryl-1-(3-amino-2- or -4-pyridyl)piperazines (II and III), 1-(3-amino-2- or -4-pyridyl)-4-phenylpiperidines (IV and V), and 1-aryl-4-(3-amino-4-quinolyl)-piperazines (VI) were prepared by the condensation of the appropriate 2-chloro-3-nitro-,[10] 4-chloro-3-nitro-,[11] and 4-chloro-3-nitro-5-bromopyridines[12] and 4-chloro-3-nitroquinoline[13] with various arylpiperazines and arylpiperidines followed by reduction of the resulting nitro compounds. 1,4-Bis(aminopyridyl)piperazines were prepared by condensation of the appropriate halonitropyridines with 0.5 molar equiv of piperazines and 1 molar equiv of triethylamine followed by reduction of the resulting nitro compounds.

4-Aryl-1-(4-pyridyl)piperazines (III, R′ = R″ = H) were obtained by condensation of 4-chloropyridine N-oxide[14] with N-arylpiperazines in toluene followed by catalytic reduction of the resulting pyridine N-oxides.

1-(4-Amino-3-pyridyl)-4-phenylpiperazine (VII) was prepared by the condensation of 3-bromo-4-nitropyridine 1-oxide[15] with N-phenylpiperazine followed by catalytic reduction.

1,4-Bis(β-2- or -4-pyridyl)ethylpiperazines and homopiperazines (VIII and IX, X = $(CH_2)_2$; n = 2 or 3) were prepared by the pyridylethylation[16] of piperazine and homopiperazine with 2- and 4-vinylpyridine. 1,4-Bis(β-4-piperidylethyl)piperazine resulted from the catalytic reduction of the corresponding pyridine derivative (IX, X = $(CH_2)_2$; n = 2). 1,4-Bis(α-methyl-2- or -4-pyridylmethyl)piperazines (VIII and IX, n = 2; X = CH_3CH) were secured by the condensation[16] of 2- and 4-α-bromoethylpyridines[17] with piperazine.

Experimental Section[18,19]

N-Arylpiperazines.—While most of the N-arylpiperazines were already known, some which were unknown were prepared by the general method outlined below and are described in Table I. A mixture of the appropriate aniline (0.3 mole) and bis(β-chloroethyl)amine hydrochloride (0.3 mole) in 1-butanol (200 ml) was refluxed for 24 hr. The reaction mixture was cooled and powdered anhydrous K_2CO_3 (0.15 mole) was added and refluxing continued for another 48 hr. The reaction mixture was filtered hot, the

TABLE I

N-PHENYLPIPERAZINES

No.	Phenyl substituent	Bp (mm) or mp, °C	% N Calcd	% N Found
1	*m*-CF_3[a]	HCl 232	10.5	10.48
2	*m*-CH_3O	HCl 173–174	12.2	12.38
		140–145 (bath) (0.25 mm)		
3	*p*-F	HCl 172	12.93	12.78
4	3,4-$(CH_3O)_2$	HCl 235–236	10.83	10.93
		78	12.6	12.5
5	2,4-$(CH_3O)_2$	HCl 194–196	10.83	10.62
		160–165 (bath) (0.5 mm)	12.6	12.93

[a] A. S. F. Ash, A. M. Creighton, and W. R. Wragg [(May and Baker Ltd.) British Patent 948,747 (Feb 5 1964); *Ch m. Abstr.*, **60**, 12029 (1964)] reported mp 250–253° for the hydrobromide.

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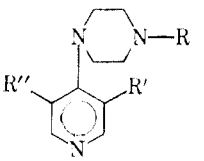
(18) The melting points were determined in a bath. The various compounds were checked routinely by ir and uv spectroscopy on Perkin-Elmer Infracord and Unicam spectrophotometers, respectively.

(19) The Roman numerals refer to the type of compounds, while the Arabic numerals refer to the specific compounds as they appear in the text.

TABLE II



No.	R	R′	R″	Mp, °C	Calcd, %			Found, %		
					C	D	N	C	D	N
6	4-C_5H_3N-(3-NO_2)	NO_2	H	252	50.99	4.24	25.45	51.21	4.53	25.54
7	4-C_5H_3N-(3-NH_2)	NH_2	H	2HCl >300	48.99	5.83	24.78	49.47	5.91	24.55
8	C_6H_5	NO_2	H	138–140	63.38	5.63	19.72	63.83	6.05	20.23
9	C_6H_5	NH_2	H	191	70.07	7.07	22.04	70.37	7.53	21.72
10	p-C_6H_4Cl	NO_2	H	169–170			17.58			18.07
11	p-C_6H_4Cl	NH_2	H	227–228			19.41			19.63
12	p-$C_6H_4CH_3$	NO_2	H	132–133			18.79			18.73
13	p-$C_6H_4CH_3$	NH_2	H	173–174			20.89			20.49
14	o-$C_6H_4CH_3$	NO_2	H	131			18.79			18.93
15	o-$C_6H_4CH_3$	NH_2	H	164–165			20.89			21.16
16	3,4-$C_6H_3(OCH_3)_2$	NO_2	H	133			16.25			16.78
17	3,4-$C_6H_3(OCH_3)_2$	NH_2	H	145–146			17.83			17.38
18	2,4-$C_6H_3(OCH_3)_2$	NO_2	H	142–143			16.25			16.11
19	2,4-$C_6H_3(OCH_3)_2$	NH_2	H	179			17.83			18.11
20	C_6H_5	H	H	·2HCl 235–236 dec	54.96	5.8	12.80	55.36	6.09	12.64
		(N-oxide)		·H_2O 73	65.9	6.98	15.31	65.30	7.07	14.82
21	C_6H_5	H	H	166	75.3	7.1	17.5	75.1	6.87	17.23
22	p-$C_6H_4OCH_3$	NO_2	H	155			17.8			18.0
23	p-$C_6H_4OCH_3$	NH_2	H	207	67.7	7.0	19.7	68.0	7.2	19.8
24	p-$C_6H_4NO_2$	NO_2	H	185			21.27			20.9
25	p-$C_6H_4NH_2$	NH_2	H	219			26.02			25.50
26	CH_3	NO_2	H	·2HCl 215–216	40.8	5.4	19.0	41.3	5.8	19.03
27	CH_3	NH_2	H	142	62.5	8.3	29.1	62.8	8.6	29.4
28	$CH_2C_6H_5$	NO_2	H	96–97			18.9			18.43
29	$CH_2C_6H_5$	NH_2	H	·3HCl 197 dec	51.3	6.14	14.9	51.82	5.68	15.05
30	m-$C_6H_4CF_3$	NO_2	H	107			15.90			15.90
31	m-$C_6H_4CF_3$	NH_2	H	146–147			17.3			17.18
32	m-$C_6H_4OCH_3$	NO_2	H	102–103			17.83			17.44
33	m-$C_6H_4OCH_3$	NH_2	H	179			19.7			19.26
34	m-C_6H_4Cl	NO_2	H	107			17.50			17.65
35	m-C_6H_4Cl	NH_2	H	110–111			19.4			19.16
36	o-$C_6H_4OCH_3$	NO_2	H	123–124			17.83			17.59
37	o-$C_6H_4OCH_3$	NH_2	H	184–185			19.72			19.38
38	p-$C_6H_4CH_3$	NO_2	Br	157–158			13.91			14.05
39	p-$C_6H_4CH_3$	NH_2	Br	183			16.13			15.72
40	p-$C_6H_4CH_3$	NO_2	NO_2	·2HCl 220–222			16.82			16.46
41	p-$C_6H_4CH_3$	NH_2	NH_2	·4HCl 214–215			16.31			16.12
42	p-C_6H_4F	NO_2	H	122			18.5			18.72
43	p-C_6H_4F	NH_2	H	218			20.59			20.2
44	p-$C_6H_4CH_3$	H	H	N-Oxide 120			15.6			15.2
45	p-$C_6H_4CH_3$	H	H	·2HCl·$2H_2O$ 228			11.7			11.63
46	C_6H_5	NO_2	Br	109			11.6			11.2
47	C_6H_5	NH_2	Br	175	54.0	5.1	16.78	54.37	5.52	16.64

filtrate was cooled, and the N-arylpiperazine hydrochlorides which separated were filtered and washed successively with 1-butanol and ether. The bases were liberated by making the aqueous solutions of the hydrochlorides strongly alkaline; yield 50–72%.

4-Substituted 1-(3-Nitro-2- or -4-pyridyl)piperazines (II and III, R = CH_3, aryl; R′ = NO_2; R″ = H).—A solution of 2- or 4-chloro-3-nitropyridine (0.1 mole) in dry toluene (25 ml) was added under stirring to a solution of N-substituted piperazine (0.1 mole) and triethylamine (0.1 mole) in dry toluene (100 ml). The reaction mixture was heated with stirring at 80° for 2 hr, cooled, and filtered, the filtrate was extracted with 3 *N* HCl, the acid extract was made alkaline with NH_4OH, and the nitro compounds which separated were collected by filtration and crystallized from ethanol; yield 80–90% (Tables II and III).

4-Substituted 1-(3-Amino-2- or -4-pyridyl)piperazines (II and III, R = CH_3, aryl; R′ = NH_2; R″ = H).—The nitro compounds obtained above in ethanol (50 ml of ethanol/10 g of the compound) were reduced using Raney nickel catalyst at 4.5 atm pressure of H_2 and room temperature until absorption of H_2 was complete. If the amines were insoluble in ethanol enough tetrahydrofuran (THF) was added to dissolve them. The catalyst was removed by filtration and washed with THF, the solvent was removed, and the residue was crystallized from ethanol; yield 80–85% (Tables II and III).

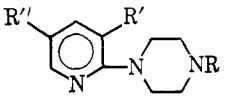
4-Aryl-1-(3-nitro-5-bromo-4-pyridyl)piperazines (II, R = aryl; R′ = NO_2; R″ = Br) were synthesized by the condensation of N-arylpiperazines with 4-chloro-3-nitro-5-bromopyridine by the method described above; yield 85% (Table II).

4-Aryl-1-(3-amino-5-bromo-4-pyridyl)piperazines (II, R = aryl; R′ = NH_2; R″ = Br) were prepared in 85–90% yield by the reduction of the corresponding nitro compounds by the method described earlier (Table II).

4-Phenyl- or 4-Phenyl-4-hydroxy-1-(3-nitro-2- or -4-pyridyl)-piperidines (IV and V, R″ = H, OH; R′ = NO_2) were prepared by the condensation of 4-phenyl- or 4-phenyl-4-hydroxypiperidines with 2- or 4-chloro-3-nitropyridine; yield 80–85% (Table IV).

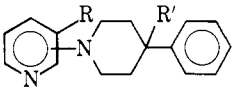
4-Phenyl- or 4-phenyl-4-hydroxy-1-(3-amino-2- or -4-pyridyl-piperidines (IV and V, R″ = H, OH; R′ = NH_2) were made by the reduction of the nitro compounds as in the case of piperazine derivatives (Table IV).

TABLE III



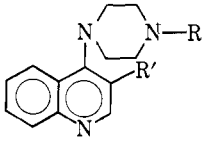
No.	R	R′	R″	Bp (mm) or mp, °C	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
48	2-C_5H_3N-3-NO_2	NO_2	H	201	50.99	4.24	25.45	51.48	4.63	25.64
49	2-C_5H_3N-3-NH_2	NH_2	H	226–228			31.11			31.13
				·2HCl >300	48.99	5.83	24.78	48.93	5.98	24.36
50	2-C_5H_3N-3,5-$(NO_2)_2$	NO_2	NO_2	259 dec	40.43	2.85	26.66	40.00	2.98	26.87
51	2-C_5H_3N-3,5-$(NH_2)_2$	NH_2	NH_2	·4HCl 278–282 dec			25.1			25.38
52	C_6H_5	NO_2	H	·HCl 218–220	56.1	5.3	17.46	56.4	5.72	17.92
53	C_6H_5	NH_2	H	167–168	70.07	7.07	22.04	70.2	7.37	22.13
54	p-C_6H_4Cl	NO_2	H	130	56.6	4.7	17.7	56.3	4.6	18.2
55	p-C_6H_4Cl	NH_2	H	127–128			19.44			19.23
56	CH_3	NO_2	H	·2HCl 215–216	40.8	5.4	19.0	41.2	5.8	19.03
57	CH_3	NH_2	H	210	62.5	8.3	29.1	62.8	8.6	29.4
58	p-$C_6H_4OCH_3$	NO_2	H	106	61.1	5.73	17.8	61.6	6.2	18.0
59	p-$C_6H_4OCH_3$	NH_2	H	125	67.7	7.0	19.7	67.8	7.4	19.4
60	p-$C_6H_5CH_3$	NO_2	H	223			16.74			16.5
61	p-$C_6H_5CH_3$	NH_2	H	154	71.6	7.46	20.89	71.48	7.66	21.00

TABLE IV



No.	Attachment to pyridine ring	R	R	Bp or mp, °C	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
62	4	NO_2	H	116	68.08	5.6	14.89	67.8	6.4	14.9
63	4	NH_2	H	173	75.8	7.5	16.6	76.0	7.7	16.74
64	4	NO_2	OH	142–143	64.2	5.68	14.0	64.5	6.2	13.7
65	4	NH_2	OH	131	71.3	7.0	15.78	70.92	7.24	15.80
66	2	NO_2	H	177	67.8	6.0	14.89	67.4	6.2	14.7
67	2	NH_2	H	201	75.8	7.5	16.6	75.8	7.44	16.38
68	2	NO_2	OH	82			14.0			13.9
69	2	NH_2	OH	187	71.3	7.0	15.78	71.35	7.22	15.28

TABLE V



No.	R	R′	Mp, °C	% N Calcd	% N Found
70	C_6H_5	NO_2	149–150	16.7	16.27
71	C_6H_5	NH_2	170	18.4	18.03
72	m-$C_6H_4CF_3$	NO_2	154–155	13.93	13.99
73	m-$C_6H_4CF_3$	NH_2	138–139	15.0	14.8
74	2,4-$C_6H_3(OCH_3)_2$	NO_2	145–146	14.2	14.43
75	2,4-$C_6H_3(OCH_3)_2$	NH_2	105–106	15.65	15.7

4-Aryl-1-(3-nitro-4-quinolyl)piperazines (VI, R′ = NO_2) were obtained by the condensation of 4-chloro-3-nitroquinoline with N-arylpiperazines by the method described earlier; yield 85–90% (Table V).

4-Aryl-1-(3-amino-4-quinolyl)piperazines (VI, R′ = NH_2) were synthesized by the reduction of the corresponding nitro compounds as described above (Table V).

Bis-1,4-(3-nitro-2- or -4-pyridyl)piperazines (II, R = substituted pyridyl; R′ = NO_2; R″ = H, NO_2).—A solution of piperazine (0.08 mole) in dry $CHCl_3$ (10 ml) was added under stirring to a solution of the chloronitropyridine (0.16 mole) in dry toluene (150 ml) and triethylamine (0.16 mole). The reaction mixture was further stirred at room temperature for 30 min and then heated on the steam bath for 3 hr and cooled. The product which had separated was filtered and washed thoroughly with water to remove $Et_3N \cdot HCl$, and the nitro compounds thus obtained were crystallized from pyridine–water; yield 90–95% (Tables II and III).

Bis-1,4-(3-amino-2- or -4-pyridyl)piperazines (II, R = substituted pyridyl; R′ = NH_2; R″ = H, NH_2).—The above nitro compounds in 95% ethanol were reduced using Pd–C (10%) catalyst at a pressure of 4.5 atm of H_2 and room temperature. When the absorption of H_2 ceased (*ca.* 2.5 hr), the reaction mixtures were filtered, and the precipitate was extracted repeatedly with 3 *N* HCl and mixed with the ethanolic filtrate, when the hydrochlorides of the amino compounds separated, which were crystallized from 6 *N* HCl; yield 75–80% (Table II and III).

1-Arylpiperazinyl-4-pyridine 1-Oxides.—A mixture of 4-chloropyridine 1-oxide (0.01 mole) and N-arylpiperazines (0.02 mole) in dry toluene (15 ml) was refluxed gently for 4 hr, when a solid separated out. It was collected by filtration, dried, and dissolved in water and the aqueous solution was made alkaline with 2 *N* NaOH. The syrupy product which separated was extracted (CH_2Cl_2), the extract was dried (Na_2SO_4), the solvent was removed *in vacuo*, and the residue was converted to its hydrochloride; yield 40% (Table II).

4-Aryl-1-(4-pyridyl)piperazine (II, R = aryl; R′ = R″ = H).—The above N-oxides in ethanol were deoxygenated with H_2 over Raney nickel catalyst; yield 75–86% (Table II).

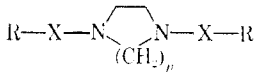
4-Phenyl-1-(4-nitro-3-pyridyl 1-oxide)piperazine (83).—A solution of 3-bromo-4-nitropyridine 1-oxide (0.1 mole) in absolute methanol (250 ml) and N-phenylpiperazine (0.2 mole) was gently refluxed on the steam bath for 45 min. The compound crystallized on cooling; a second crop was obtained by concentrating the filtrate. It was crystallized from ethanol; yield 65%, mp 168°.

Anal. Calcd for $C_{15}H_{16}N_4O_3$: C, 60.00; H, 5.33. Found: C, 60.32; H, 5.68.

4-Phenyl-1-(4-amino-3-pyridyl)piperazine (VII, 84).—The nitro compound **83** was reduced as in other cases to give the required amino compound, which crystallized from aqueous ethanol; yield 70%, mp 174–176°.

Anal. Calcd for $C_{15}H_{18}N_4$: C, 70.07; H, 7.07; N, 22.04. Found: C, 70.34; H, 7.29; N, 22.63.

TABLE VI



No.	R	X	n	Mp, °C	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
76	2-C_5H_4N	$(CH_2)_2$	2	97–98	73.4	7.4	19.03	73.3	7.23	19.13
77	2-C_5H_4N	$(CH_2)_2$	3	Syrup			18.18			18.16
78	4-C_5H_4N	$(CH_2)_2$	2	92	73.4	7.4	19.03	73.28	7.56	18.77
79	4-C_5H_4N	$(CH_2)_2$	3	Syrup			18.18			17.86
80	2-C_5H_4N	$CH(CH_3)$	2	112	72.97	8.1	18.9	73.2	8.4	19.06
81	4-C_5H_4N	$CH(CH_3)$	2	185–186			18.9			18.5
82	4-C_5H_4N	$-(CH_2)_2-$	2	$\cdot H_2O$ 122	64.00	16.34	11.65	64.4	16.70	11.65

Bis-1,4-(β-2- or -4-pyridylethyl)piperazines or -homopiperazines (VIII and IX, X = $(CH_2)_2$; n = 2 or 3).—A mixture of 2- or 4-vinylpyridine (0.11 mole), glacial acetic acid (0.1 mole), and anhydrous piperazine or homopiperazine (0.05 mole) in ethanol (75 ml) was refluxed for 16 hr. The reaction mixture was evaporated under reduced pressure and the residue was made alkaline with 2 *N* NaOH. The piperazine derivatives separated as solids on cooling which were filtered, washed with water, and crystallized from benzene–hexane. The homopiperazine derivatives were thick oils, which were taken up in $CHCl_3$, the extracts were dried (Na_2SO_4), and the products were purified by chromatography on alumina using $CHCl_3$ as the eluent; yields 80–85% (Table VI).

Bis-1,4-(α-methyl-2-pyridylmethyl)piperazine (VIII, X = $CH(CH_3)$; n = 2).—A mixture of 2-α-bromoethylpyridine (15.5 g), anhydrous piperazine (3.8 g), and triethylamine (8.5 ml) in dry toluene (150 ml) was refluxed for 14 hr. The reaction mixture was cooled and filtered and the solvent was removed under reduced pressure. The crude product was precipitated by adding petroleum ether (bp 40–60°) to the benzene solution of the residue. The product was collected by filtration and crystallized from petroleum ether; yield 33% (Table VI).

Bis-1,4-(α-methyl-4-pyridylmethyl)piperazine (IX, X = $CH(CH_3)$; n = 2).—4-Ethylpyridine was brominated with *N*-bromosuccinimide essentially according to the method of Walker[17] for 2-ethylpyridine. The crude 4-α-bromoethylpyridine was condensed with piperazine in benzene as described above without any purification on account of its instability. The product was crystallized from benzene–petroleum ether; yield 30% (Table VI).

Bis-1,4-(β-4-piperidylethyl)piperazine (X).—A solution of bis-1,4-(β-4-pyridylethyl)piperazine hydrochloride (6.0 g) in aqueous ethanol was reduced with H_2 at 4 atm pressure at 65–70° using 5% Rh–C catalyst until the uptake of H_2 ceased. After removal of the catalyst by filtration, the solution was concentrated under reduced pressure, the residue was made alkaline, and the product was crystallized from benzene; yield 65% (Table VI).

Pharmacological Screening Methods.—These compounds were tested for their acute toxicity and gross observation effects in mice. The action of compounds on cardiovascular system was studied at a dose of 2.5–10 mg/kg iv in anesthetized cats or dogs. In addition the compounds were evaluated for the following specific activities at $0.25LD_{50}$ in mice.

Anticonvulsant Test.—The effect of compounds against supramaximal electroshock seizure (48 ma, 0.2 sec) in mice was tested according to the methods of Swinyard, *et al.*[20] A few compounds were also tested against pentylenetetrazole (100 mg/kg sc) and strychnine sulfate (1.5 mg/kg sc) induced seizures. Five animals were used in each group.

Antireserpine Test.—The effect of compounds on reserpine-induced hypothermia, ptosis, and sedation was studied in mice by injecting the test compounds intraperitoneally 3 hr and 45 min after the administration of reserpine (2.5 mg/kg ip) and compared with that of the control group at different intervals.

Effects on locomotor activity of the control and treated groups of mice were tested in activity cages and recorded photoelectrically.[21]

Antiamphetamine Test.—The effect of amphetamine toxicity in aggregated mice was studied according to the method of Burn and Hobbs.[22]

Effect on conditioned avoidance response (CAR) in rats was studied according to the method of Cook and Weidley.[23]

Effect on Somatic Reflexes.—Some compounds were tested for their effect on patellar and flexor reflexes according to the method of Witkin, *et al.*,[24] and DeSalva and Oester.[25]

Results and Discussion

Of the various activities shown by 4-phenyl-1-(3-amino-4-pyridyl)piperazine (**1**), its anticonvulsant and antireserpine activities were most prominent and the different homologs and analogs were therefore tested particularly for these activities. Pharmacological screening data for various compounds are given in Tables VII and VIII.

It was found that the replacement of N^4 of the piperazine ring by a CH or C(OH) in the corresponding 4-(4-phenyl-1-piperidyl)- and 4-(4-phenyl-4-hydroxy-1-piperidyl)-3-aminopyridines (**2**, **3**) led to a considerable diminution of these activities. Similarly, replacement of the phenyl residue by a methyl or benzyl radical (**4**, **5**) caused a complete loss of these activities. These observations would show that the presence of $PhN(C-C)_2$ is a specific structural requirement for these activities.

Next, the effect of the substituents in the two aryl rings was studied. The corresponding 3-deamino compound **6** had greatly reduced anticonvulsant and antireserpine activities. The corresponding 3-nitro compound was also completely devoid of these activities. Substitution of the pyridine ring by an additional bromine residue at position 5 (**7**) caused a complete disappearance of these activities. The position of attachment of the arylpiperazine to the pyridine ring was found to have an important bearing on its activity. Thus, if the position of attachment of the arylpiperazine and the amino radicals was interchanged as in 1-(4-amino-3-pyridyl)-4-phenylpiperazine (**8**), the central stimulant and the anticonvulsant activities were considerably reduced. On the other hand, if the arylpiperazine residue was attached to position 2 of the pyridine ring as in 1-(3-amino-2-pyridyl)-4-phenylpiperazine (**9**), it showed a depressant action in the gross behavior of mice and it was devoid of any anticonvulsant action. This depressant action was enhanced by replacing N^4 of the piperazine residue by a C(OH) group as in 1-(3-amino-2-pyridyl)-4-hydroxy-4-phenylpiperidine (**13**). One compound was made

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(21) G. D. Davis, *Am. J. Physiol.*, **188**, 619 (1957).

(22) J. H. Burn and R. Hobbs, *Arch. Intern. Pharmacodyn.*, **113**, 299 (1958).

(23) L. Cook and E. Weidley, *Ann. N. Y. Acad. Sci.*, **66**, 740 (1957).

(24) L. B. Witkin, P. Spicaletta, and A. J. Plummer, *Arch. Intern. Pharmacodyn.*, **124**, 105 (1960).

(25) S. J. DeSalva and Y. T. Oester, *ibid.*, **124**, 255 (1960).

TABLE VII

PHARMACOLOGICAL ACTIVITY OF 1-PYRIDYL-4-SUBSTITUTED PIPERAZINES

No.	Piperazine derivatives	Approx LD_{50} (mice), mg/kg ip	Gross effects[a] (mice)	Anti-MES[b] % block (mice)	Antireserpine activity (mice) Anti-hypothermia[d]	Anti-ptosis[e]	Anti-sedation	Cardiovascular activity[c] (cats) Effect on BP[f] at 2.5 mg/kg iv	Adrenaline[g]	Remarks
1	1-Phenyl-1-(3-amino-4-pyridyl)-	100	Stimulant	80	4+	4+	4+	−50 (P)	↓	Mild antipyretic and antiinflammatory, blocked polysynaptic reflexes.
2	4-Phenyl-1-(3-amino-4-pyridyl)-piperidine	100	Mixed	40	0[h]	0	0	0	0	
3	4-Phenyl-4-hydroxy-1-(3-amino-4-pyridyl)piperidine	50	Stimulant	60	+	+	+	−60 (T)	0	Mild antipyretic.
4	4-Methyl-1-(3-amino-4-pyridyl)-	288	Stimulant	0	0	0	0	+10 (T)	0	Mild antipyretic.
5	4-Benzyl-1-(3-amino-4-pyridyl)-	80	Stimulant	40	+	+	+	0	0	
6	4-Phenyl-1-(4-pyridyl)-	25	Stimulant	60	+	+	+	−30 (P)	↑	
7	4-Phenyl-1-(3-amino-5-bromo-4-pyridyl)-	200	Stimulant	0	...[i]	...	...	0	0	
8	4-Phenyl-1-(4-amino-3-pyridyl)-	50	Stimulant	20	0	+	+	+30 (P)	↑	
9	4-Phenyl-1-(3-amino-2-pyridyl)-	150	Depressant	20	0	0	0	−40 (T)	0	
10	4-(*p*-Methoxyphenyl)-1-(3-amino-2-pyridyl)-	660	Depressant	60	+	+	0	+40 (T)	↑	Mild antipyretic.
11	4-Methyl-1-(3-amino-2-pyridyl)-	50	Stimulant	20	0	0	0	0	0	Ganglion blocking at 10^{-6}.
12	4-Phenyl-1-(3-amino-2-pyridyl)-piperidine	100	...	0	0	0	0	0	0	Anti-5-HT and ganglion blocking on isolated guinea pig ileum at 10^{-6}.
13	4-Phenyl-4-hydroxy-1-(3-amino-2-pyridyl)piperidine	100	Depressant	60	Enhances reserpine-induced depression			0	0	Mild diuresis, no anti-amphetamine action.
14	4-Phenyl-1-(3-amino-4-quinolyl)-	800	0	0	0	...	...	...	..	
15	4-(*m*-Trifluoromethylpheny1)-1-(3-amino-4-quinolyl)-	800	0	0	0	...	...	...	..	
16	4-(*o*-Methoxyphenyl)-1-(3-amino-4-pyridyl)-	116	Mixed	0	...	...	...	−30 (P)	0	Moderate anti-5-HT on isolated guinea pig ileum.
17	4-(*p*-Methoxyphenyl)-1-(3-amino-4-pyridyl)-	100	Stimulant	60	3+	3+	3+	0	0	
18	4-(2,4-Dimethoxyphenyl)-1-(3-amino-4-pyridyl)-	40	Stimulant	20	0	+	+	0	0	
19	4-(3,4-Dimethoxyphenyl)-1-(3-amino-4-pyridyl)-	40	Stimulant	20	0	+	0	0	0	Marked antipyretic.
20	4-(*p*-Chlorophenyl)-1-(3-amino-4-pyridyl)-	80	Depressant	100	2+	3+	2+	0	0	Marked antipyretic and mild antiinflammatory.
21	4-(*m*-Methoxyphenyl)-1-(3-amino-4-pyridyl)-	40	Stimulant	60	+	+	+	0	0	
22	4-(*m*-Chlorophenyl)-1-(3-amino-4-pyridyl)-	80	Stimulant	100	+	2+	+	−16 (T)	0	
23	4-(*m*-Trifluoromethylphenyl)-1-(3-amino-4-pyridyl)-	100	Stimulant	100	+	+	+	−20 (T)	0	Anti-5-HT in isolated guinea pig ileum, locomotor activity reduced.
24	4-(*p*-Tolyl)-1-(3-amino-4-pyridyl)-	125	Mixed	60	2+	3+	2+	0	0	Marked antipyretic and diuretic action.
25	4-(*p*-Tolyl)-1-(3-amino-5-bromo-4-pyridyl)-	800	Depressant	20	0	+	0	...	..	
26	Bis-1,4-(β-2-pyridylethyl)-	80	Depressant	20	0	0	0	0	0	Moderate antipyretic, antiinflammatory, antiamphetamine CAR block, spontaneous locomotor activity reduced.
27	Bis-1,4-(β-4-pyridylethyl)-	100	Depressant	0	...	...	...	...	0	
28	Bis-1,4-(β-2-pyridylethyl)homopiperazine	150	Depressant	0	...	...	...	...	0	Moderate anti-5-HT in isolated guinea pig ileum and ganglion blocking.
29	Bis-1,4-(β-4-pyridylethyl)homopiperazine	40	Depressant	0	...	...	...	0	0	
30	Bis-1,4-(α-methyl-2-pyridyl)-methyl-	150	Depressant	0	...	...	...	0	0	
31	4-(*p*-Tolyl)-1-(3-amino-2-pyridyl)-	200	Depressant	0	0	0	0	0	0	Mild diuretic.
32	4-(*p*-Tolyl)-1-(4-pyridyl)-	67	Stimulant	0	0	0	0	0	0	Mild anti-5-HT and ganglion blocking in isolated guinea pig ileum.
33	4-(*p*-Tolyl)-1-(3,5-diamino-4-pyridyl)-	82	Stimulant	0	0	0	0	−25 (P)	0	

[a] Stimulant implies alertness, Straub phenomenon, excitement, hyperreflexia, preconvulsiveness and convulsions, while depressant implies reduced spontaneous motor activity, ataxia, loss of righting reflex. [b] MES = maximal electroshock seizures. [c] T = transient and P = persistent (change from normal for 10 min or above) fall (−) and rise (+) in blood pressure (mm). [d] Compared to control, + = slight reduction in fall of body temperature, 2+ = no significant fall in body temperature, 3+ = slight rise in body temperature, 4+ = marked rise in body temperature. [e] Each + means 25% counteraction of ptosis compared to control. [f] BP = blood pressure. [g] ↓ = counteraction, ↑ = potentiation. [h] 0 = no effect. [i] Not done.

TABLE VIII

ANTICONVULSANT ACTIVITY OF SOME 4-ARYL-1-(3-AMINO-4-PYRIDYL)PIPERAZINES

Compd.[a]	Dose,[b] mg./kg.	Addl-MES % block	Antipentylene tetrazole % block of tonic convul.	Antistrychnine % block of tonic clonic	Remarks
1	40 ip	100	100	100	No protection against death, the survival time was doubled, somatic reflexes inhibited.
	20 ip	60	40	40	
	10 ip	20	20	...	
20	20 ip	100	100	0	No protection against death.
	10 ip	80	80	...	
	20 oral	50	...	...	
22	20 ip	100	100	0	No protection against death.
	10 ip	80	80	...	
	20 oral	60	...	...	
	10 orad	20	...	...	
23[c]	20 ip	100	100	0	No protection against death, survival time prolonged, no effect on somatic reflexes.
	10 ip	80	80	...	
	7.5 ip	50	...	...	
	20 oral	90	90	0	
	15 oral	70	...	...	
	10 oral	30	...	...	
Diphenylhydantoin sodium[c]	15 ip	80	...	...	No protection against death, survival time prolonged.
	10 ip	40	...	...	
	20 oral	90	80	0	
	15 oral	70	...	...	
	10 oral	30	...	...	

[a] Numbers refer to compound in Table VII. [b] Five and ten mice were used for intraperitoneal and oral routes, respectively. [c] ED_{50} for 23 and diphenylhydantoin sodium was calculated to be 12.6 and 12.2 mg./kg. (oral), respectively.

with a bolder change in which the pyridine moiety was replaced by a quinoline (**14**, **15**) residue. This compound had neither anticonvulsant nor antireserpine activities.

Substituents in the phenyl ring were also found to have a profound effect on the biological activity. In general, substituents in 2 and 4 position of the phenyl group as in the 2- and 4-methoxyphenyl (**16**, **17**), 2,4-dimethoxyphenyl (**18**), and 3,4-dimethoxyphenylpiperazinyl (**19**) compounds had greatly reduced activities with the exception of 1-(3-amino-4-pyridyl)-4-(*p*-chlorophenyl)piperazine (**20**) which was almost as active as the prototype as an anticonvulsant with somewhat reduced antireserpine activity. Thus, there was some dissociation of antireserpine and anticonvulsant activities in this compound. Substitution in the *meta* position led to a greater dissociation of these activities. The corresponding 4-(3-amino-4-pyridyl)-1-(*m*-trifluoromethylphenyl)piperazine (**23**) showed very weak antireserpine activity while the anticonvulsant activity was more marked than its prototype. This compound has been compared with diphenylhydantoin sodium as an anticonvulsant. It has practically the same order of activity[26] against chemo- and electroshock-induced seizures in mice with a better safety margin (Table VIII).

The methoxy- and methyl-substituted phenyl compounds showed significant diuretic actions, which was more marked in the *p*-tolyl (**24**) and 2,4-dimethoxyphenyl (**18**) derivatives. Introduction of a bromo or amino group in position 5 of the pyridine nucleus as in 1-(5-bromo-3-amino-4-pyridyl)-4-(*p*-tolyl)piperazine and 1-(3,5-diamino-4-pyridyl)-4-(*p*-tolyl)piperazine and the removal of 3-amino group as in 1-(4-pyridyl)-4-(*p*-tolyl)piperazine resulted in the disappearance of this diuretic activity.

The other interesting activity was the antipyretic and tranquilizing activity of 1,4-bis-β-(2-pyridyl)-ethylpiperazine (**26**). This compound caused reduction in locomotor activity, decreased amphetamine toxicity in aggregated mice, and caused a specific blockade of the CAR. The over-all pattern of activity was not altered when the attachment of the piperazinoethyl residue to the pyridine ring was changed to position 4 (**27**), although the order of activity was somewhat reduced. The change to a homopiperazine analog (**28**, **29**) caused almost a complete abolition of the activity. The piperazine ring thus seems essential for this activity.

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(26) A. Ahmad, unpublished work.