Chemical and Pharmacological Investigations of Some ω-Substituted Alkylamino-3-aminopyridines

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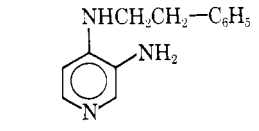
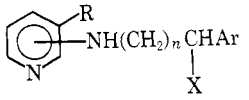
A number of 2- and 4-ω-substituted alkylamino-3-aminopyridines and -quinolines and corresponding imidazo and triazolo compounds have been synthesized and evaluated for their anticonvulsant and cardiovascular activities. 4-(3,4-Dihydroxy)phenethylamino-3-aminopyridine has been found to possess substantial hypotensive activity. At certain doses the compound potentiates the pressor response of epinephrine and blocks that of norepinephrine.

In a continued study on the synthesis and structure–activity relationships of substituted diaminopyridines,[1-3] the synthesis and pharmacological evaluation of a number of ω-substituted alkylamino-3-aminopyridines and -quinolines (II–VI), 1-β-arylethylimidazo- and -triazolo[4,5-*c*]pyridines and -quinolines (VII, VIII), and 6-substituted 3-β-arylethylimidazo[4,5-*b*]-pyridines (IX) is reported in this communication.

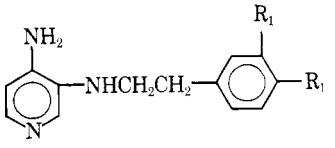
2- and 4-ω-arylalkylamino-3-aminopyridines (II and III, R = NH_2) were prepared by the condensation of 2- and 4-chloro-3-nitropyridine[4,5] with the appropriate arylethylamines followed by the reduction of the nitro compounds (II and III, R = NO_2) thus obtained.



I



II, 4-pyridyl
III, 2-pyridyl



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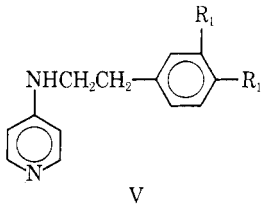
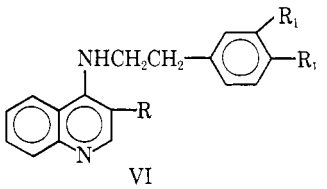
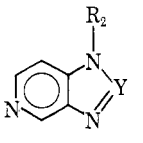


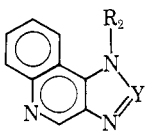
V



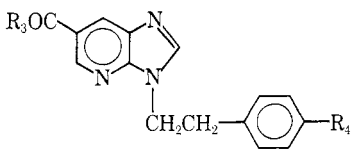
VI



VII



VIII



IX

3-Phenethylamino-4-aminopyridines (IV, R = $O-CH_3$) were obtained by the condensation of the phenethylamines with 3-bromo-4-nitropyridine N-oxide,[6] followed by Raney nickel reduction of the 4-nitropyridine 1-oxides so obtained. 4-Phenethylaminopyridines (V) were prepared by treating 4-aminopyridine with the appropriate phenylacetic acids[7] followed by $LiAlH_4$ reduction[8] of the resulting acetamidopyridines.

Various 3-amino-4-β-substituted ethylaminoquinolines (VI, R = NH_2) were prepared by condensing 3-nitro-4-chloroquinoline[9] with different β-substituted ethylamines followed by Raney nickel reduction of the resulting nitro compounds (VI, R = NO_2).

The hydroxyphenyl compounds were synthesized either through the corresponding methoxy derivatives by demethylation with HBr or from the benzyloxy compound by catalytic hydrogenation or treatment with 6 *N* HCl.

The arylalkylamines required in this work were known; however, the method of synthesis of a few of them had to be changed to improve the yields. Thus β-phenylethanolamine, which had been prepared earlier either by the reduction[10] of α-phenyl-β-nitroethanol or by acid hydrolysis[11] of N-β-hydroxyphenethylsuccinimide, was obtained in excellent yield by the alkaline hydrolysis[12] of the latter. Similarly, β-(1-naphthyl)ethylamine, which had been prepared earlier either by the sodium amalgam reduction of naphthylacetaldoxime[13] or by the Raney nickel reduction of 1-naphthylacetonitrile,[14] was obtained by the $LiAlH_4$ reduction of 1-naphthylacetamide[14] and β-(2-naphthyl)-

(1) M. M. Vohra, S. N. Pradhan, P. C. Jain, S. K. Chatterjee, and N. Anand, *J. Med. Chem.*, **8**, 296 (1965).

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

(3) P. C. Jain, V. Kapoor, N. Anand, A. Ahmad, and G. K. Patnaik, *J. Med. Chem.*, **10**, 812 (1967).

(4) Y. Ahmad and D. H. Hey, *J. Chem. Soc.*, 4516 (1954).

(5) S. Kruger and F. G. Mann, *ibid.*, 2755 (1955).

(6) J. M. Essery and K. Schofield, *ibid.*, 4953 (1960).

(7) Irwin Nesler and Co., British Patent 901,312 (July 18, 1962); *Chem. Abstr.*, **58**, 7914 (1963).

(8) Irwin Nesler and Co., British Patent 901,311 (July 18, 1962); *Chem. Abstr.*, **58**, 7915 (1963).

(9) G. B. Bachman, D. E. Welton, G. L. Jenkins, and J. E. Christian, *J. Am. Chem. Soc.*, **69**, 365 (1947).

(10) (a) T. Kondo and F. Murayama, *J. Pharm. Soc. Japan*, **49**, 1198 (1929); *Chem. Abstr.*, **24**, 1631 (1930); (b) V. A. Darnow and M. Gellrich, *Ann.*, **594**, 177 (1955).

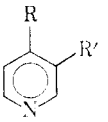
(11) H. J. Roth and A. Brandau, *Arch. Pharm.*, **292/64**, 761 (1959).

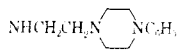
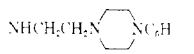
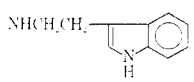
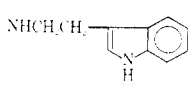
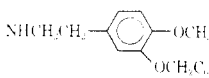
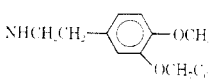
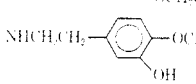
(12) G. A. Youngdale, G. W. Duncan, D. E. Emmert, and D. Lednicer, *J. Med. Chem.*, **9**, 155 (1966).

(13) F. Mayer, A. Sieglitz, E. Fisher, J. Hagen, R. Jung, W. Kinies, C. Kohl, F. Listman, W. Neugebauer, and T. Schulte, *Ber.*, **55B**, 1835 (1922).

(14) C. G. Skinner, W. Shive, R. G. Ham, D. C. Fitzerald, Jr., and R. E. Eakin, *J. Am. Chem. Soc.*, **78**, 5097 (1956).

TABLE I



No.	R	R′	Mp, °C	% calcd C	% calcd H	% calcd N	% found C	% found H	% found N
1	$NHCOCH_2C_6H_5$	H	Oil	73.5	5.66	13.2	73.70	5.93	13.1
2	$NHCH_2CH_2C_6H_5$	H	39[a]	78.7	7.07	14.14	78.13	7.27	13.85
3	$NHCOCH_2C_6H_3$-3,4-$(OCH_3)_2$	H	·HCl, 203–205[b]	58.3	5.5	9.07	58.08	6.13	9.02
4	$NHCH_2CH_2C_6H_3$-3,4-$(OCH_3)_2$	H	Oil			10.85			10.4
5	$NHCH_2CH_2C_6H_3$-3,4-$(OH)_2$	H	·HBr, 140	50.1	4.5	9.0	50.4	4.93	8.84
6	$NHCH_2CH_2CH_2C_6H_5$	NO_2	·HCl, 170–172[b]			14.3			14.10
7	$NHCH_2CH_2CH_2C_6H_5$	NH_2	·2HCl, 189–192[b]	56.00	6.3	14.0	56.38	6.48	14.50
8		NO_2	115–117[b]			21.4			20.79
9		NH_2	·3HCl, 250–252[b]	50.1	6.5	17.2	49.95	6.90	16.93
10	$NHCH_2CH_2C_{10}H_7$-α	NO_2	180[b]			14.03			14.08
11	$NHCH_2CH_2C_{10}H_7$-α	NH_2	·2HCl, 218[c]			12.2			11.8
12	$NHCH_2CH_2C_{10}H_7$-β	NO_2	114[b]	68.2	6.0	14.0	67.94	6.32	13.5
13	$NHCH_2CH_2C_{10}H_7$-β	NH_2	·HCl·H_2O, 243[c]	64.38	6.15	13.7	64.3	6.3	13.2
14		NO_2	193[b]	63.8	4.96	19.8	63.59	5.1	19.4
15		NH_2	·2HCl, 198[c]	55.5	5.6	17.2	56.09	5.9	17.28
16	$NHCH_2CH_2C_6H_3$-3,4-$(Cl)_2$	NO_2	189–190[b]			13.5			13.2
17	$NHCH_2CH_2C_6H_3$-3,4-$(Cl)_2$	NH_2	135–136[b]	55.5	4.6	14.9	55.78	4.58	14.93
			·2HCl, 274[c]	44.19	4.2	11.9	44.5	4.47	11.96
18	$NHCH_2CH_2C_6H_4$-4-OCH_3	NO_2	99[b]			15.3			15.85
19	$NHCH_2CH_2C_6H_4$-4-OCH_3	NH_2	·2HCl, 188–189[b]	53.1	6.01	13.29	53.12	6.08	13.93
20	$NHCH_2CH_2C_6H_4$-4-OH	NH_2	·2HBr, 217–218[b]	40.1	4.39	10.79	40.41	4.97	10.27
21	$NHCH_2CH_2C_6H_4$-3-OCH_3	NO_2	·HCl, 223 dec[b]			13.57			13.78
22	$NHCH_2CH_2C_6H_4$-3-OCH_3	NH_2	·2HCl, 185[b]	53.3	6.0	13.3	53.8	4.4	13.8
23	$NHCH_2CH_2C_6H_4$-3-OH	NH_2	·2HBr, 237[b]			10.74			10.9
24		NO_2	123[b]			11.09			10.68
25		NH_2	·2HCl, 177[c]	59.85	5.9	9.9	59.74	5.93	9.8
26		NH_2	·HCl·H_2O, 170[b]	53.5	6.3	13.3	54.06	6.52	13.25
27	$NHCH_2CHOHC_6H_5$	NO_2	174[d]			16.2			15.82
28	$NHCH_2CHOHC_6H_5$	NH_2	·2HCl, 178–179 dec[b]			13.90			13.74
29	NO_2	$HNCH_2CH_2C_6H_3$-3,4-$(OCH_3)_2$ (1-oxide)	184[b,e]	59.0	5.57	9.18	58.6	5.6	9.2
30	NH_2	$HNCH_2CH_2C_6H_3$-3,4-$(OCH_3)_2$	Oil	65.93	6.95	15.3	66.0	7.3	15.2
31	NH_2	$HNCH_2CH_2C_6H_3$-3,4-$(OH)_2$	·2HBr[f]			10.3			10.6

[a] Crystallized from hexane. [b] EtOH. [c] H_2O. [d] C_6H_6. [e] 3-(3,4-Dimethoxyphenethylamino)-4-nitropyridine 1-oxide, $C_{15}H_{17}N_3O_5$. [f] The product was hygroscopic and the melting point could not be determined.

ethylamine by reduction of 2-naphthylacetonitrile.[15] The synthesis of 3,4-dichlorophenethylamine by the reduction of the corresponding nitrile according to the method of Benington, *et al.*,[16] gave low yields. It was, therefore, prepared by $LiAlH_4$ reduction of 2-nitro-1-(3,4-dichlorophenyl)ethylene.[17] 1-Phenyl-4-(β-aminoethyl)piperazine, which has been prepared earlier[18] from β-N-morpholinoethylamine by ring opening with HBr to give β-bis(2-bromoethyl)aminoethylamine followed by ring closure with aniline, was prepared in good yields by the $LiAlH_4$ reduction of the corresponding nitrile;[19] the latter was obtained by the action of formaldehyde and KCN on N-phenylpiperazine.

1-ω-Substituted alkylimidazo- and -triazolo[4,5-*c*]-pyridines and -quinolines (VII and VIII) were prepared by the cyclization of the corresponding amino compounds with formic and nitrous acids, respectively.

3-(*p*-Dimethylaminophenethyl)-6-methoxycarbonylimidazo[4,5-*b*]pyridine on treatment with hydrazine hydrate gave the corresponding hydrazide which on reduction with Raney nickel gave 3-(*p*-dimethylaminophenethyl)-6-carbamoylimidazo[4,5-*b*]pyridine. 3-Phenethylimidazo[4,5-*b*]pyridine-6-carbonyl chloride[1] on treatment with morpholine gave the required morpholide and with β-diethylaminoethanol the required β-diethylaminoethyl ester.

Experimental Section[20]

The experimental conditions described below are typical of the general methods of synthesis followed in this work. Any variations in the methods are specifically mentioned.

(15) (a) N. B. Chapman and J. F. A. Williams, *J. Chem. Soc.*, 5044 (1952); (b) S. C. J. Olivier and J. Wit, *Rec. Trav. Chim.*, **57**, 90 (1938).

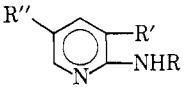
(16) F. Benington, R. D. Morin, and L. C. Clark, Jr., *J. Org. Chem.*, **25**, 2066 (1960).

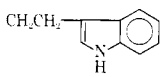
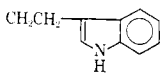
(17) G. B. Butler and M. E. Carter, *J. Am. Chem. Soc.*, **72**, 2302 (1950).

(18) E. Cerkovnikov and P. Stern, *Arhiv Kem.*, **18**, 12 (1946); *Chem. Abstr.*, **42**, 1941 (1948).

(19) C. B. Pollard and L. J. Hughes, *J. Am. Chem. Soc.*, **77**, 40 (1955).

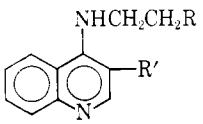
Table II



No.	R	R′	R″	Mp, °C	% calcd C	% calcd H	% calcd N	% found C	% found H	% found N
32	$CH_2CH_2C_6H_3$-3,4-$(CH_3)_2$	NO_2	H	98–99[a]			15.49			15.73
33	$CH_2CH_2C_6H_3$-3,4-$(CH_3)_2$	NH_2	H	·HCl, 168[b]			15.1			15.13
34	$CH_2CH_2C_6H_3$-3,4-$(OCH_3)_2$	NO_2	H	110[a]	59.4	5.6	13.86	60.0	5.9	13.7
35	$CH_2CH_2C_6H_3$-3,4-$(OCH_3)_2$	NH_2	H	·HCl·H_2O, 162–164	56.15	6.65	13.05	56.2	6.8	12.8
36	$CH_2CH_2C_6H_3$-3,4-$(OH)_2$	NH_2	H	·2HBr, 174	38.32	4.4	10.31	38.7	5.0	10.8
37	$CH_2CH_2C_{10}H_7$-α	NO_2	H	102[a]	69.6	5.1	14.3	69.75	5.5	14.26
38	$CH_2CH_2C_{10}H_7$-α	NH_2	H	·HCl, 175[a]	68.5	6.05		67.92	6.28	
39		NO_2	H	161[a]			19.8			20.4
40		NH_2	H	·2HCl, 240[c]			18.61			18.3
41	$CH_2CHOHC_6H_5$	NO_2	H	90–92[d]			16.2			15.92
42	$CH_2CHOHC_6H_5$	NH_2	H	·2HCl, 157–158[a]			13.90			14.00
43	$CH_2CHOHC_6H_5$	H	NO_2	137–138[d]			16.2			16.57
44	$CH_2CHOHC_6H_5$	H	NH_2	·2HCl, 179–180[a]			13.90			14.45
45	$CH_2CH_2C_6H_4$-4-(NMe_2)	NO_2	CO_2Me	110[a]	59.3	5.8	16.28	59.63	5.78	15.90
46	$CH_2CH_2C_6H_4$-4-(NMe_2)	NH_2	CO_2Me	134–135[a]	64.98	7.00	17.83	65.38	7.12	17.76

[a] Crystallized from EtOH. [b] EtOH–Et_2O. [c] H_2O. [d] C_6H_6.

Table III



No.	R	R	Mp, °C	% N Calcd	% N Found
47	NC_5H_{10}	NO_2	126[a]	18.66	18.95
48	NC_5H_{10}	NH_2	·2HCl,[b] 245–246	16.3	15.8
49	C_6H_5	NO_2	132[c]	14.33	14.04
50	C_6H_5	NH_2	·2HCl,[c] 208–209	12.53	12.2
51	C_6H_4-3,4-$(OCH_3)_2$	NO_2	160[c]	11.89	11.55
52	C_6H_3-3,4-$(OCH_3)_2$	NH_2	·HCl,[c] 162–163	11.69	11.47
53	C_6H_3-3,4-$(OH)_2$	NH_2	·2HBr,[d,e] 250	9.19	9.48

[a] Crystallized from C_6H_6–hexane. [b] EtOH–Et_2O. [c] EtOH. [d] Aqueous HBr. [e] *Anal.* Calcd: C, 44.63; H, 4.1. Found: C, 44.61; H, 4.15.

4- or 2-(ω-Arylalkyl)amino-3-nitropyridines and -quinolines (II, III, VI, R = NO_2).—A solution of the appropriate chloronitropyridine or -quinoline (0.1 mole) in dry toluene or $CHCl_3$ (30 ml), depending on their solubility, was added gradually to a solution of the appropriate amine (0.1 mole) and triethylamine (0.15 mole) in dry toluene (50 ml) with stirring. After the addition was complete, the reaction mixture was stirred at 70–80° for 2 hr, cooled, and filtered. The filtrate was washed (H_2O) and dried, the solvent was removed, and the residue was either crystallized as a free base or purified through its hydrochloride; yield 70–95% (Tables I–III).

4- or 2-(ω-Arylalkyl)amino-3-aminopyridines and -quinolines (II, III, VI, R = NH_2).—A mixture of the nitro compound and ethanol was reduced with H_2 using Raney nickel catalyst at a pressure of 3.5 atm and room temperature until H_2 absorption ceased. The catalyst was removed by filtration and washed with hot EtOH, the filtrate was concentrated under reduced pressure, and the amine was isolated either as the free base or as the hydrochloride by adding the calculated quantity of ethanolic HCl to a concentrated solution of the amine in absolute EtOH, when the hydrochloride separated, either on cooling or on adding dry ether; yield 85–95% (Tables I–III).

Hydroxyphenethylamino-3-aminopyridines and -quinolines.—A solution of the appropriate methoxyphenethylamino-3-aminopyridine or -quinoline hydrochlorides (5.0 g) in HBr (50 ml of 48%) was refluxed for 6 hr. If the product separated on cooling it was filtered and washed (dry EtOH, Et_2O), otherwise the reaction mixture was evaporated to dryness under reduced pressure and the residue crystallized from EtOH; yields 85–90% (Tables I–III).

4-(4-Methoxy-3-hydroxy)phenethylamino-3-aminopyridine.—A suspension of 4-(4-methoxy-3-benzyloxy)phenethylamino-3-aminopyridine dihydrochloride (0.5 g) in 6 *N* HCl (20 ml) was refluxed for 4 hr. The reaction mixture was cooled, made strongly alkaline with 10% NaOH solution, and filtered to remove some unchanged product. The filtrate was neutralized with 3 *N* AcOH and the amine so obtained was dissolved in absolute EtOH and converted to its hydrochloride by adding ethanolic HCl; yield 75% (Table I).

3-(3,4-Dimethoxyphenethyl)amino-4-nitropyridine 1-Oxide.—A solution of 3-bromo-4-nitropyridine 1-oxide (10.9 g, 0.05 mole) and 3,4-dimethoxyphenethylamine (18.1 g, 0.1 mole) in absolute MeOH (150 ml) was refluxed for 4 hr. MeOH was distilled under reduced pressure and the residue crystallized from absolute EtOH, yield 36% (Table I).

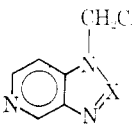
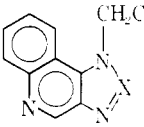
3-(3,4-Dimethoxyphenethyl)amino-4-aminopyridine.—3-(3,4-Dimethoxyphenethyl)amino-4-nitropyridine 1-oxide was hydrogenated using Raney nickel catalyst. It was worked up in the usual manner and purified by chromatography over alumina, using $CHCl_3$ as the eluent. Removal of the solvent gave the product as a thick oil; yield 90% (Table I).

4-Arylacetamidopyridines.—A mixture of 4-aminopyridine (0.1 mole), the appropriate phenylacetic acid (0.1 mole), and *p*-toluenesulfonic acid (500 mg) in xylene (60 ml) was refluxed using a Dean–Stark separator until no more water separated. The reaction mixture was cooled and extracted with 4 *N* HCl, and the acid layer was basified with NH_4OH and extracted with EtOAc–C_6H_6 (1:3). The organic layer was dried and the solvent was removed. The residue was washed repeatedly (hot H_2O) to remove any unreacted 4-aminopyridine, dried, and converted to the hydrochloride in absolute ethanolic HCl; yield 20% (Table I).

4-β-Arylethylaminopyridine (V, R = H or OCH_3).—A solution of the above amide (2.72 g) in ether (20 ml) was added dropwise to a suspension of $LiAlH_4$ (1.14 g) in ether (100 ml) with stirring at such a rate that a gentle reflux was maintained. After the addition, stirring and refluxing was continued for an additional 2 hr and the product was worked up in the normal manner. The product was purified by chromatographing over alumina using $CHCl_3$ as the eluent; yield 77% (Table I).

(20) (a) The melting points were determined in an H_2SO_4 bath and are uncorrected. (b) All reaction products were routinely checked by ir and uv spectroscopy on Perkin-Elmer Infracord and Unicam spectrophotometers, respectively. (c) Roman numerals refer to the type of compound, while arabic numerals refer to their number in the tables.

TABLE IV

No.	R	X	Mp, °C	% calcd C	% calcd H	% calcd N	% found C	% found H	% found N
									
54		CH	·3HCl, 273–274	51.9	5.7	16.8	52.3	5.98	16.43
55	$CH_2C_6H_5$	CH	·HCl, 197–199			15.3			14.98
56	$CH_2C_6H_5$	N	55–57	70.6	5.9	23.5	70.93	5.64	23.51
			HCl, 180–181	59.8	4.99	21.45	59.41	5.37	20.93
									
57	NC_5H_{10}	CH	·2HCl, 282			15.9			15.64
58	C_6H_5	N	97	74.4	5.1	20.43	74.12	4.88	20.1

Imidazo[4,5-*c*]pyridines and -quinolines (VII and VIII, Y = CH).—A solution of the appropriate 4-substituted amino-3-aminopyridine or -quinoline in formic acid (98–100%) was refluxed for 20 hr. Excess formic acid was removed under reduced pressure, and the residue was taken up in a little water and made alkaline with NH_4OH. The oily product so obtained was extracted ($CHCl_3$), the extract was dried (Na_2SO_4), the solvent was removed, and the syrupy residue was dissolved in a little absolute EtOH and treated with ethanolic HCl, when the hydrochloride separated and was filtered and recrystallized from absolute EtOH; yield 90–95% (Table IV).

Triazolo[4,5-*c*]pyridines and -quinolines (VII and VIII, Y = N).—A solution of $NaNO_2$ (10%) in H_2O was added with stirring to a suspension of the appropriate 4-substituted amino-3-aminopyridine or -quinoline (6.0 g) in 3 *N* HCl (100 ml). After the addition was over, the reaction mixture was stirred for another 1.5 hr below 10° and the triazole thus separated was filtered, washed (H_2O), dried, and crystallized from benzene–hexane; yield 70–85% (Table IV).

β-Phenethanolamine.—A suspension of N-(β-hydroxy-β-phenethyl)succinimide (70 g) in NaOH [400 g in H_2O (400 ml) and EtOH (1200 ml)] was gently refluxed when the compound gradually went into solution. After some time the sodium salt of the partially hydrolyzed amide separated. More water (*ca.* 400 ml) was added to dissolve this salt and refluxing was continued for a further 24 hr. The reaction mixture was concentrated under reduced pressure, and the oily layer was separated. The aqueous layer was extracted with ether (four 100-ml portions), the ether extracts were combined with the organic layer and dried (Na_2SO_4), the solvent was removed, and the residue was treated with ethanolic HCl, followed by ether when the amine·HCl separated out; yield 95%, mp 215–216° (lit.[21] 210–212° dec).

β-(1-Naphthyl)ethylamine.—A suspension of 1-naphthylacetamide (6.4 g) in dry THF (25 ml) was added to a suspension of $LiAlH_4$ (2.5 g) in dry THF (70 ml) with stirring and worked up as usual, bp 174–176° (12 mm) [lit.[13,14] bp 170–173° (16 mm)], yield 4.7 g.

β-(2-Naphthyl)ethylamine was prepared by reduction of 2-naphthylacetonitrile (15.0 g) in dry THF (20 ml) with $LiAlH_4$ (10.2 g) in dry ether (250 ml) and the reaction mixture was worked up as usual; yield 8.2 g, bp 165–167° (10 mm), HCl mp 262° dec [lit.[13] bp 160–165° (15 mm)].

3,4-Dichlorophenethylamine was prepared by reduction of 1-(3,4-dichlorophenyl)-2-nitroethylene (8.8 g) and $LiAlH_4$ (4.4 g) in ether. The amine was isolated as its hydrochloride, yield 6.0 g, mp 175–176° (lit.[16] mp 178–179°).

1-Phenyl-4-cyanomethylpiperazine.—Powdered sodium metabisulfite (50.0 g) was added to a solution of CH_2O (22 ml of 37–40%) in H_2O (50 ml). The reaction mixture was kept at 55–60° for 0.5 hr, and N-phenylpiperazine (40.5 g) was added, followed by a saturated aqueous solution of KCN (17.0 g). The reaction mixture was stirred for another 2 hr, the organic layer was separated, the aqueous layer was extracted ($CHCl_3$), the mixed organic phase was dried (Na_2SO_4), and $CHCl_3$ was evaporated. The brown syrupy residue was repeatedly extracted with boiling hexane, the hexane solution cooled when the nitrile separated which was collected by filtration. An additional quantity of slightly impure product was obtained on concentrating the mother liquor, yield 35.0 g, mp 65° (lit.[22] mp 65–66.5°).

1-Phenyl-4-(β-aminoethyl)piperazine.—The above nitrile (31.0 g) was reduced by $LiAlH_4$ in dry THF and worked up as usual; yield 22.5 g, bp 115–117° (1×10^{-3} mm) [lit.[18] bp 175–178° (0.5 mm)].

3-Phenethyl-6-N-morpholinocarbonylimidazo[4,5-*b*]pyridine.—Morpholine (1.74 g) was added to a solution of 3-phenethylimidazo[4,5-*b*]pyridine-6-carbonyl chloride[1] (from 2.8 g of the acid[1]) in dry benzene, the reaction mixture was kept at room temperature for 1 hr, the morpholine hydrochloride which separated was removed by filtration, the filtrate was concentrated under reduced pressure, and the product thus obtained was crystallized from benzene–hexane; yield 2.2 g (Table V).

3-Phenethyl-6-β-diethylaminoethoxycarbonylimidazo[4,5-*b*]pyridine was prepared by treating the acid chloride with diethylaminoethanol as above and the product was isolated as a hydrochloride, yield 1.37 g (Table V).

3-(*p*-Dimethylaminophenethyl)imidazo[4,5-*b*]pyridine-6-carboxhydrazide.—Hydrazine hydrate (5 ml, 99–100%) was added to a solution of the above ester (2.3 g) in absolute EtOH (10 ml) and the reaction mixture was refluxed for 14 hr. EtOH was removed under reduced pressure and the residue was crystallized from MeOH; yield 2.3 g (Table V).

3-(*p*-Dimethylaminophenethyl)amino-6-carbamoylimidazo-[4,5-*b*]pyridine.—The above hydrazide (2.1 g) in absolute EtOH (210 ml) was refluxed with Raney nickel catalyst (21.0 g wet) for 24 hr. The catalyst was removed by filtration and washed (hot EtOH), the filtrate was evaporated to dryness under reduced pressure, and the residue crystallized from EtOH; yield 1.6 g (Table V).

Pharmacological Methods.—The compounds were tested for their acute toxicity, gross behavioral effects, and anticonvulsant activity against maximum electroshock seizures (MES)[23] in mice. Effects on blood pressure, respiration, and nictitating membrane contraction were studied in anesthetized cats according to the standard methods.[24] 4-(3,4-Dihydroxyphenethyl)amino-3-aminopyridine (**66**, Table VI) was further studied for its selective effect on the α- and β-adrenergic receptors in cat blood pressure, isolated guinea pig auricle,[25] and seminal vesicle preparation.[26]

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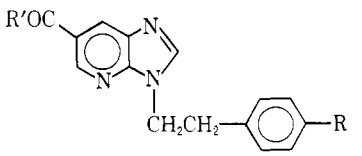
Table V



No.	R	R′	Mp, °C	% calcd C	% calcd H	% calcd N	% found C	% found H	% found N
69	H	NC_5H_8O	111–112			16.66			16.80
60	H	$OCH_2CH_2NEt_2$	·HCl, 166–167			13.91			13.68
61	NMe_2	NH_2	129	66.01	6.11	22.65	65.66	6.47	22.89
62	NMe_2	$NHNH_2$	188	62.96	6.7	25.92	63.29	6.53	25.84
63	NMe_2	OMe	119	66.66	6.17	17.28	66.92	6.51	17.13

Table VI

Pharmacological Activity of 2- and 4-Arylethylamino-3-aminopyridines

Pyridine derivatives	Approx LD_{50} (mice), mg/kg ip	Gross effects[a]	Anti-MES[b] (mice) at 0.25LD_{50} ip % block	Cardiovascular act. Dose, mg/kg iv (animal)	Cardiovascular act. Effect on blood pressure[c]	Cardiovascular act. Effect on pressor response at epinephrine[d]	Remarks
4-(Phenethyl)amino-3-amino- (**64**)[e,f]	150	Depressant	40	5 (cat)	−72 (T)	↑	
4-γ-(Phenylpropyl)amino-3-amino- (**7**)	58	...	0	6 (dog)	0	0	
4-(3,4-Dimethoxyphenethyl)amino-3-amino- (**65**)[f]	250	...	0	2.5 (cat)	−10 (T)	↑	
4-(3,4-Dihydroxyphenethyl)amino-3-amino- (**66**)[f]	150	Mixed	0	2.5 (cat)	+40 (T)	↑	[g]
				10 (cat)	−65 (P)	↑	
4-(4-Hydroxyphenethyl)amino-3-amino- (**20**)	200	Stimulant	0	3 (dog)	0	0	
				5 (cat)	−20 (T)	↑	
4-(3-Hydroxyphenethyl)amino-3-amino- (**23**)	...	...	...	5 (cat)	0	0	
4-(4-Methoxyphenethyl)amino-3-amino- (**19**)	150	Depressant	20	3 (dog)	0	↑	
2-(3,4-Dimethylphenethyl)amino-3-amino- (**33**)	100	Stimulant	...	2.5 (cat)	+20 (P)	0	
4-(3,4-Dichlorophenethyl)amino-3-amino- (**17**)	100	Depressant	...	3 (dog)	0	↑	
4-β-Hydroxyphenethylamino-3-amino- (**28**)	250	Depressant	0	5 (cat)	0	↑	
4-(2-Naphthylethyl)amino-3-amino- (**13**)	100	Depressant	...	3 (cat)	0	↑	Mild resp stim
4-(3-Indolylethyl)amino-3-amino- (**15**)	80	Depressant	...	5 (cat)	+20 (T)	0	
4-(3,4-Dihydroxyphenethyl)amino- (**5**)	...	...	...	2 (cat)	−32 (T)	0	NM[h] ↑
4-(3,4-Dihydroxyphenethyl)amino-3-aminoquinoline- (**53**)	...	...	...	10 (cat)	−40 (P)	↑	NM ↑, histamine ↑
3-(3,4-Dihydroxyphenethyl)amino-4-amino- (**31**)	150	Mixed	0	2.5 (cat)	+40 (P)	↑	NM ↑
2-(3,4-Dihydroxyphenethyl)amino-3-amino- (**36**)	>800	Depressant	0	3 (dog)	0	0	
2-(3,4-Dimethoxyphenethyl)amino-3-amino- (**35**)	>400	Depressant	40	3 (dog)	0	0	
4-Phenethylamino- (**2**)	20	Stimulant	60	2.5 (cat)	+60 (P)	↓	NM ↑
2-(3-Indolylethyl)amino-3-amino- (**40**)	250	Depressant	...	...	...	...	

[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 siezures (48 ma, 0.2 sec), was tested in groups of five mice. [c] Millimeter rise (+) and fall (−) (T = transient and P = persistent) from normal for 10 min or above, respectively. [d] ↑ = increase and ↓ = decrease. [e] The numbers in parentheses refer to the serial numbers of compounds in Tables I–V. [f] Compounds **64–66** have been synthesized earlier.[1] [g] Potentiates epinephrine but antagonizes the pressor response of norepinephrine and antagonizes the depressor effect of isoproterenol. [h] Nictitating membrane contraction.

Results and Discussion

The results of pharmacological activity of some of the selected compounds are given in Table VI. The only significant pharmacological activity of this series of compounds was the hypotensive activity of 4-(3,4-dihydroxyphenethyl)amino-3-aminopyridine (**66**). In dogs at 3 mg/kg iv it produced a fall in blood pressure of about 20–30% which lasted for 2.5 hr. However, when administrered intraduodenally, it had no effect on blood pressure, thus indicating that it was not absorbed from the gastrointestinal tract. In the cat at 2.5 mg/kg iv it had only a direct sympathomimetic effect evidenced by a sharp rise in blood pressure with marked tachycardia which was blocked by phentolamine but not by cocaine. At a higher dose (10–12 mg/kg iv) the initial transient rise in blood pressure was followed by a persistent (about 60 min) hypotensive response. At this dose it potentiated the pressor effect of epinephrine but antagonized the effect of norepinephrine, ephedrine, tyramine, amphetamine, and the pressure effect of isoproterenol (Table VII). The epinephrine reversal produced by phentolamine was also abolished at this dose and it completed the partial block of norepinephrine produced by phentolamine on isolated guinea pig auricle. A concentration of 6×10^{-6} g/ml blocked the effect of isoproterenol but had no effect on norepinephrine. However, at a higher dose it also blocked the effects of both epinephrine and norepinephrine. Antagonism to isoproterenol at a lower dose than antagonism to norepinephrine in guinea pig auricle preparation would suggest that **66** has a stronger blocking action on the β-receptors than on the α-receptors. The same conclusion is also suggested by the selective augmentation of the pressor response of epinephrine and antagonism to that of norepinephrine in the cat blood pressure study. Thus, when the β-receptors are completely blocked and α-receptors only partially, there would be a depression in the norepinephrine response and an augmentation of the pressor response of epinephrine.

The pharmacological screening results of various analogs of **66** shows that substituents in the phenyl and the pyridine rings and the position of attachment of the phenylalkyl chain have a marked effect on the pharmacological activity. Removal of the 3-hydroxy group as in **20** greatly reduced the hypotensive activity, while removing the 4-hydroxy group (**23**) completely abolished this activity. Similarly, introduction

TABLE VII

EFFECT OF COMPOUND 66 AND INTERACTIONS WITH EPINEPHRINE, NOREPINEPHRINE, ISOPROTERENOL, TYRAMINE, EPHEDRINE, AND AMPHETAMINE ON CAT BLOOD PRESSURE AND NICTITATING MEMBRANE (NM) CONTRACTION TO PREGANGLIONIC CERVICAL SYMPATHETIC NERVE STIMULATION

Expt no.	Dose, mg/kg iv	Response[a] (min)	Change[b] in the responses of: Norepinephrine	Isoproterenol	Epinephrine	Tyramine	Ephedrine	Amphetamine	NM
1	2.5	+40 (5)	0	−10	+16	...	...	...	+20
2	5.0	+80 (2)	−29	−33	...	...	...	...	0
		−50 (2)							
3	10.0	+84 (2)							
		−40 (50)	−100	...	+25	−100	...	...	...
4	10.0	+60 (2)							
		−100 (>60)	−50	−75	0	...	...	−50	...
5	10.0	+70 (2)							
		−60 (>60)	−50	...	+50	...	−50	...	...
6	12.0	+70 (2)							
		−70 (60)	−100	−100	+66	...	−100	...	...

[a] Millimeter rise (+) or fall (−). [b] % augmentation (+) or antagonism (−).

of monomethoxy (**19**), dimethoxy (**65**), or chloro (**17**) groups in place of the hydroxy function, as also the substitution of a β-naphthyl (**13**) or indolyl (**15**) residue in place of the dihydroxyphenyl group led to a complete loss of this activity. The corresponding 3-deamino compound (**5**) also had greatly reduced activity. 4-(3,4-Dihydroxyphenethyl)amino-3-aminoquinoline (**53**), however, showed significant hypotensive activity. In the corresponding 2-(3,4-dihydroxyphenethyl)amino-3-aminopyridine (**36**) there was a complete loss of the hypotensive activity, while the 3-(3,4-dihydroxyphenethyl)amino-4-aminopyridine (**31**) showed vasopresser activity.

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Silicon-Containing Barbiturates

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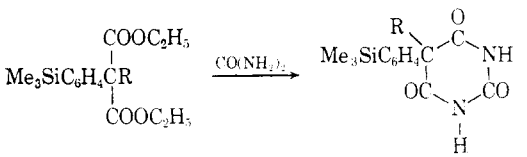
Three 5-(*p*-trimethylsilylphenyl)barbiturates and one related thiobarbiturate were prepared starting from *p*-trimethylsilylphenylacetic acid, which was converted to diethyl alkyl-*p*-trimethylsilylphenylmalonates and condensed with urea or thiourea. Preliminary pharmacological evaluation of these barbiturates, as well as of two 5-(*p*-trimethylsilylbenzyl)barbiturates, showed them to have low sedative activity. Some of the compounds showed anticonvulsant activity.

Recently, work was reported on the preparation and biological evaluation of some silicon-containing analogs of biologically active organic compounds.[1] This interest was aroused by the fact that, although silicon is the main constituent of the earth's crust, it only rarely appears in living organisms.[2] Spirobarbiturates containing silicon in a cyclohexyl ring have been prepared and found to have narcotic activity.[3] Several silicon-containing barbituric acids having a trimethylsilylmethyl group have also been synthesized.[4] We have recently prepared 5-(*p*-trimethylsilylbenzyl)barbiturates,[5] and we wish now to report the synthesis of 5-(*p*-trimethylsilylphenyl)barbiturates and their preliminary pharmacological evaluation.

The barbiturates were prepared from *p*-trimethylsilylphenylacetic acid,[6] which was converted to the ethyl ester under mild conditions.[7] The ethyl ester was condensed with diethyl carbonate in the presence of sodium ethoxide[8] to yield diethyl *p*-trimethylsilylphenylmalonate. This was treated, in absolute ethanol in the presence of sodium ethoxide, with ethyl iodide or allyl bromide yielding diethyl *p*-trimethylsilylphenylethyl- or -allylmalonate, respectively. Condensation of the malonate derivatives with urea or thiourea in absolute ethanol in the presence of sodium ethoxide yielded the silicon-containing barbiturates (Table I).



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