Synthesis and Structure–Activity Relationships of Some Aminopyridines, Imidazopyridines, and Triazolopyridines

M. M. VOHRA, S. N. PRADHAN,

Division of Pharmacology

P. C. JAIN, S. K. CHATTERJEE, AND NITYA ANAND[1]

Division of Medicinal Chemistry, Central Drug Research Institute, Lucknow, India

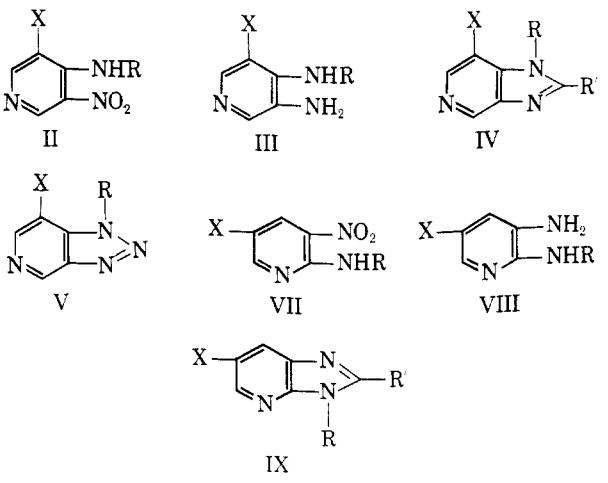
Revised Manuscript Received January 19, 1965

2- and 4-ω-substituted alkylamino-3-aminopyridines and the corresponding 5-nitro, bromo, amino, alkoxycarbonyl, and carboxamido derivatives and 3-substituted amino-4-aminopyridines have been synthesized and cyclized to the corresponding imidazo- and triazolo[4,5-*b*]- and -[4,5-*c*]pyridines. These compounds show diverse types of pharmacological activity. Their structure–activity relationship has been discussed.

Certain amino- and diaminopyridines prepared as intermediates in the synthesis of potential purine antagonists[2] were found to possess analeptic and pressor activities which were particularly marked in 2,3- and 3,4-diaminopyridines.[3] A survey of the literature[4] showed that a number of 2,3- and 3,4-diaminopyridines with substituents in the ring and also on the amino groups have been reported and cyclized to the corresponding imidazo and triazolopyridines, but except for Fastier[5] and Haxathausen,[6] who have described certain interesting biological properties of simple aminopyridines, the pharmacology of the isomeric diaminopyridines, substituted 2,3- and 3,4-diaminopyridines, and the corresponding imidazo and triazolopyridines has not been investigated, although the latter are isosteric with benzimidazoles. The latter have been shown to possess a wide spectrum of biological activities. This prompted the synthesis of a number of 2- and 4-ω-substituted alkylamino-3-aminopyridines carrying various substituents in the 5-position, of 3-substituted amino-4-aminopyridines, and also of the corresponding imidazo- and triazolo[4,5-*b*]- and -[4,5-*c*]pyridines. The synthesis and pharmacological evaluation of these compounds forms the subject matter of this paper. During the course of this work we came across three patents by the Ciba group, claiming analgetic activity for 2-benzylimidazopyridines[7] and analeptic activity for imidazopyridines[8] with dialkylamino–lower-alkylamino groups on the imidazole nitrogen.

Most of the aminopyridines required for this study were prepared by known methods, while new methods were developed for a few. Thus, 2,4-diaminopyridine had been prepared earlier by a Hofmann bromoamide degradation of 2,4-lutidinamide,[9] while in the present work it was found more convenient to synthesize it by ammonolysis of 2-chloro-4-aminopyridine, which in turn was prepared from 2-chloropyridine through its N-oxide,[10] by nitration[11] and reduction.[10] Similarly, it was found more expedient to synthesize 3,5-diaminopyridine by catalytic reduction of 2-chloro-3,5-dinitropyridine,[12] in preference to older methods[13] which were more laborious.

4-β-Substituted ethylamino-3-nitro-, -3,5-dinitro-, and -3-nitro-5-bromopyridines (II, X = H, NO_2, Br) were prepared from the corresponding 4-chloro compounds (I)[4e,14,15] by condensation[2b,4a,e,h] with the appropriate amines. The 3-nitro and 3,5-dinitro compounds thus obtained (II, X = H or NO_2) were reduced with Raney



(1) To whom all enquiries should be sent.

(2) (a) S. K. Chatterjee, M. M. Dhar, N. Anand, and M. L. Dhar, *J. Sci. Ind. Res.* (India), **19C**, 35 (1960); (b) P. C. Jain, S. K. Chatterjee, and N. Anand, *Indian J. Chem.*, **1**, 30 (1963).

(3) M. M. Vohra and S. N. Pradhan, *Arch. intern. Pharmacodyn.*, **150**, 413 (1964).

(4) (a) R. Weidenhagen and E. Weeden, *Chem. Ber.*, **71**, 2347 (1938); (b) R. Weidenhagen, G. Train, H. Wegner, and L. Nordstrom, *ibid.*, **75**, 1936 (1942); (c) J. P. English, J. H. Clarke, J. W. Claff, D. Seeger, and R. H. Ebel, *J. Am. Chem. Soc.*, **68**, 453 (1946); (d) J. R. Vaughan, Jr., J. Krapcho, and J. P. English, *ibid.*, **71**, 1885 (1949); (e) Von O. Bremer, *Ann. Chem.*, **529**, 290 (1937); (f) H. Graboyes and A. R. Day, *J. Am. Chem. Soc.*, **79**, 6421 (1957); (g) M. Israel and A. R. Day, *J. Org. Chem.*, **24**, 1455 (1959); (h) T. Takahashi, F. Yoneda, and R. Oishi, *Chem. Pharm. Bull.* (Tokyo), **7**, 602 (1959); *Chem. Abstr.*, **54**, 14246 (1960).

(5) F. N. Fastier, *Pharmacol. Rev.*, **14**, 37 (1962).

(6) E. Von Haxathausen, cited in ref. 5.

(7) K. N. Hoffmann, A. Hunger, J. Kebrle, and A. Rossi: (a) U. S. Patent 2,987,518 (June 6, 1961); *Chem. Abstr.*, **55**, 24795 (1961); (b) German Patent 1,120,454 (Dec. 1, 1959); *Chem. Abstr.*, **57**, 836 (1962).

(8) A. Hunger, J. Kebrle, A. Rossi, and K. N. Hoffmann, U. S. Patent 3,004,978 (Oct. 17, 1961); *Chem. Abstr.*, **56**, 4771 (1962).

(9) (a) Meyer and Tropsch, *Monatsh.*, **35**, 207 (1914); (b) J. Bernstein N. Stearns, M. Dexter, and W. A. Lott, *J. Am. Chem. Soc.*, **69**, 1147 (1947).

(10) H. J. den Hertog, C. R. Kolder, and W. P. Combe, *Rec. trav. chim.*, **70**, 591 (1951).

(11) G. C. Finger and L. D. Starr, *J. Am. Chem. Soc.*, **81**, 2674 (1959).

(12) E. Plazek, *Rec. trav. chim.*, **72**, 569 (1953).

(13) (a) H. Maier-Bode, *Chem. Ber.*, **69**, 1543 (1936); (b) C. Zwart and J. P. Wibaut, *Rec. trav. chim.*, **74**, 1062 (1955); (c) H. J. den Hertog and J. P. Wibaut, *ibid.*, **55**, 126 (1935).

(14) S. Kruger and F. G. Mann, *J. Chem. Soc.*, 2755 (1955).

(15) (a) M. Fujimato, *Pharm. Bull.* (Tokyo), **4**, 340 (1956); *Chem. Abstr.*, **51**, 9067 (1957); (b) E. Ochiai and K. Futaki, *J. Pharm. Soc. Japan*, **72**, 2745 (1952); *Chem. Abstr.*, **47**, 6417 (1953).

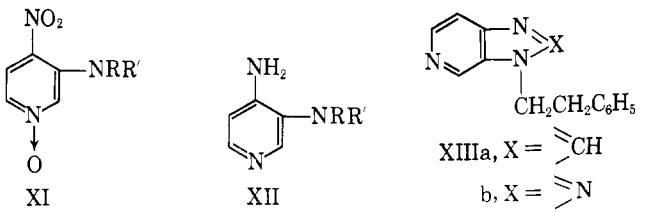
nickel catalyst to the corresponding amino compounds (III, X = H or NH_2). 4-Phenethylamino-3-nitro-5-bromopyridine was similarly reduced to the corresponding amine (III, X = Br; R = $CH_2CH_2C_6H_5$). However, when the same conditions were used for the reduction of 4-β-diethylaminoethylamino- and 4-β-(1-piperidyl)ethylamino-5-bromo-3-nitropyridines, reduction of the nitro group was accompanied by dehalogenation, and hydrobromides of the corresponding dehalogenated bases were obtained. This facile dehalogenation is obviously due to the high nucleophilicity of the tertiary nitrogen on the side chain of the ethylamino residue in the *ortho* position. The 4-β-aminoethylamino-5-bromo-3-nitropyridines were therefore reduced to the corresponding amino compounds with ammonium sulfide.[4f] 4-β-Substituted ethylamino-3,5-dinitropyridines (II, X = NO_2) were partially reduced to the 3-amino-5-nitro compounds (III, X = NO_2) using sodium hydrosulfide.[16] Attempted reduction with ammonium sulfide gave back the unchanged compound.

These 4-β-substituted ethylamino-3-aminopyridines gave the corresponding 1-β-substituted ethylimidazo-[4,5-*c*]pyridines (IV, R′ = H) on cyclization with formic acid[2,4e,d,f,h] while treatment with nitrous acid[4d-f] gave the corresponding triazolo[4,5-*c*]pyridines (V). Similarly, the reaction of 4-β-substituted ethylamino-3-aminopyridines (III, X = H) with carbon disulfide[4d,g] and urea[4d,g] gave the corresponding 2-mercapto- (IV, R′ = SH) and 2-oxoimidazo[4,5-*c*]pyridines (IV, R′ = OH). The corresponding 5-nitro compounds (III, X = NO_2), however, failed to react with CS_2 or urea under similar conditions.

2-ω-Substituted aminoalkylamino-3-nitro-, -3,5-dinitro-, -3-nitro-5-bromo-, or -3-nitro-5-alkoxy(or aralkyloxy)carbonylpyridines (VII) were synthesized from the corresponding 2-chloro-3-nitro-,[17] 3,5-dinitro-,[12] 3-nitro-5-methoxycarbonyl-,[18] and 3-nitro-5-bromopyridines[18a,19] (VI), respectively, by condensation with the various amines. 2-ω-Substituted alkylamino-3-nitro and the corresponding 5-methoxycarbonyl compounds (VII, X = H or $COOH_3$) were reduced to the corresponding amino compounds (VIII, X = H or $COOCH_3$) using Raney nickel, while the corresponding 3-nitro-5-bromo and 3,5-dinitro compounds (VII, X = Br and NO_2) were reduced to the corresponding 3-amino-5-bromo- and 3-amino-5-nitropyridines (VIII, X = Br or NO_2) with ammonium sulfide. The 5-benzyloxycarbonyl compounds were reduced with sodium dithionite.[4e] These substituted 2,3-diaminopyridines were cyclized to 3-substituted imidazo[4,5-*b*]pyridines (IX, R′ = H) and the corresponding 2-oxo- (IX, R′ = OH) and 2-mercaptoimidazo[4,5-*b*]pyridines (IX, R′ = SH) and 3-substituted triazolo[4,5-*b*]pyridines (X) as described above.

Attempts to prepare 3-β-substituted ethylimidazo-[4,5-*b*]pyridine-6-carboxamides (IX, R′ = H; X = $CONH_2$) from the corresponding methoxycarbonyl compounds by heating with alcoholic ammonia or diethylamine in sealed tubes at 120°, gave unchanged starting materials. In the case of 3-phenethyl-6-methoxycarbonylimidazo[4,5-*b*]pyridine, it was therefore first saponified with sodium hydroxide solution, and the carboxylic acid thus obtained was converted into its chloride which on treatment with ammonia or diethylamine gave the corresponding amides. The synthesis of the 3-β-diethylaminoethylimidazo[4,5-*b*]pyridine-6-carboxamide by this method proved difficult as the corresponding acid, due to its dipolar character, could not be satisfactorily isolated from the reaction mixture after hydrolysis. The preparation of the acid from the corresponding benzyl ester also proved unsatisfactory as the removal of the benzyl group by catalytic hydrogenation was unexpectedly difficult. This amide was eventually synthesized from the ester by conversion to the corresponding hydrazide followed by reduction with Raney nickel.[20]

The 3-substituted amino-4-aminopyridines (XII) were prepared from 3-bromo-4-nitropyridine 1-oxide[21] by condensation[22] with methanolic solutions of the



various amines followed by catalytic reduction with Raney nickel. 3-Phenethylamino-4-aminopyridine was cyclized to 3-phenethylimidazo- (XIIIa) and triazolo-[4,5-*c*]pyridine (XIIIb) with copper acetate–formalin[4a] and nitrous acid,[4e] respectively.

Experimental

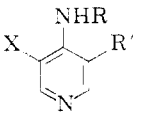
2,4-Diaminopyridine.—2-Chloropyridine (6.0 g.), glacial acetic acid (32 ml.), and 30% hydrogen peroxide (32 ml.) were heated at 55–60° for 8 days. The solvents were distilled under reduced pressure on a steam bath and the crude N-oxide so obtained was nitrated according to the method of Finger, *et al.*,[11] to give 2-chloro-4-nitropyridine 1-oxide in 50% yield, m.p. 150–151° (lit.[11] 153–153.5°).

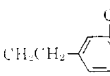
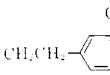
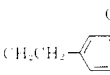
This pyridine 1-oxide (21.5 g.), reduced iron powder (20.0 g.), and glacial acetic acid (200 ml.) were gently warmed on the water bath when a vigorous reaction set in. After the reaction slowed down, the mixture was heated on the water bath for 1.5 hr. The reaction mixture was then cooled, diluted with water (200 ml.), and made basic with NaOH pellets under cooling. The hot solution was filtered, and the residue and the mother liquor were extracted with ether. The combined ether extracts were dried (Na_2SO_4), the ether was removed, and the 2-chloro-4-aminopyridine thus obtained was crystallized from benzene–hexane in 80% yield, m.p. 88–90° (lit.[23] 91–91.5°). The amine (0.5 g.), copper sulfate (0.1 g.), and concentrated NH_4OH (5 ml., sp. gr. 0.88) were heated in a sealed tube at 170–180° for 40 hr. The reaction mixture was evaporated to dryness, and the residue was made strongly alkaline and extracted with ether to give 2,4-diaminopyridine in 15% yield which was crystallized from benzene; m.p. 107° (lit.[9] m.p. 106–107°).

3,5-Diaminopyridine.—A solution of 2-chloro-3,5-dinitropyridine (1.0 g.) in ethyl acetate (50 ml.) was hydrogenated in presence of excess Raney nickel catalyst at a pressure of 2.46 kg./cm.^{2} The solution was filtered into concentrated HCl (1 ml.),

(16) W. W. Hartman and H. L. Silloway, *Org. Syn.*, **25**, 5 (1945).
(17) Y. Ahmed and D. H. Hey, *J. Chem. Soc.*, 4516 (1954).
(18) (a) A. H. Berrie, G. T. Newbold, and F. S. Spring, *ibid.*, 2590 (1951); (b) J. H. Boyer and W. Schoen, *J. Am. Chem. Soc.*, **78**, 423 (1956).
(19) E. V. Brown and H. T. Burke, *ibid.*, **77**, 6053 (1955).
(20) C. Ainsworth, *ibid.*, **76**, 5774 (1954).
(21) J. M. Essery and K. Schofield, *J. Chem. Soc.*, 4953 (1960).
(22) J. W. Clark-Lewis and R. P. Singh, *ibid.*, 2379 (1962).
(23) H. G. den Hertog, J. C. H. Schogt, J. Debruyn, and A. de Clark, *Rec. trav. chim.*, **69**, 673 (1950).

TABLE I



No.	R	R′	X	B.p. (mm.) or m.p., °C.	% calcd. C	% calcd. H	% calcd. N	% found C	% found H	% found N
1	$CH_2CH_2NEt_2$	NO_2	H	110–115 (bath) (0.001)[a]	55.46	7.56	23.52	55.72	7.35	23.51
2	$CH_2CH_2NEt_2$	NH_2	H	145–150 (bath) (0.01)[b]	63.46	9.61	26.92	63.18	9.78	26.74
3	$CH_2CH_2NEt_2$	NO_2	NO_2	119[c]	46.6	6.00	24.73	46.92	6.37	24.5
4	$CH_2CH_2NEt_2$	NH_2	NO_2	82–83[c]	52.1	7.5	27.6	52.3	7.60	27.72
5	$CH_2CH_2NEt_2$	NH_2	NH_2	Picrate, 164–167[d]	...	...	24.78	...	...	24.56
6	$CH_2CH_2NEt_2$	NO_2	Br	82[c]	41.63	5.36	17.63	41.42	5.53	17.22
7	$CH_2CH_2NEt_2$	NH_2	Br	·2HCl, 208–209[e]	36.77	5.26	15.55	37.49	5.61	15.72
8	$CH_2CH_2NC_5H_{10}$	NO_2	H	79–81[c]	57.6	7.5	22.4	57.52	7.3	22.19
9	$CH_2CH_2NC_5H_{10}$	NH_2	H	72[f]	65.45	9.09	25.00	65.33	7.37	24.84
10	$CH_2CH_2NC_5H_{10}$	NO_2	NO_2	122[c]	48.98	5.69	23.7	49.57	6.22	24.06
11	$CH_2CH_2NC_5H_{10}$	NH_2	NO_2	137[c]	54.15	7.17	26.41	54.55	7.24	26.40
12	$CH_2CH_2NC_5H_{10}$	NH_2	NH_2	·3HCl, 234–236[c]	41.8	6.96	20.3	41.76	7.14	19.91
13	$CH_2CH_2NC_5H_{10}$	NO_2	Br	97–98[d]	43.76	5.16	17.02	44.02	5.36	16.84
14	$CH_2CH_2NC_5H_{10}$	NH_2	Br	·2HCl, 205–208[g]	38.7	5.61	15.08	39.2	5.91	15.17
15	$CH_2CH_2C_6H_5$	NO_2	H	82[c]	64.2	5.3	17.28	64.32	5.75	17.12
16	$CH_2CH_2C_6H_5$	NH_2	H	·HCl, 174–175[e]	62.65	6.39	16.83	62.72	6.66	16.73
17	$CH_2CH_2C_6H_5$	NO_2	NO_2	116–117[c]	54.2	4.1	19.4	54.5	4.5	19.2
18	$CH_2CH_2C_6H_5$	NH_2	NO_2	112[c]	60.4	5.48	21.7	60.75	5.4	21.53
19	$CH_2CH_2C_6H_5$	NO_2	Br	62[c]	48.44	3.76	13.0	48.18	3.47	12.95
20	$CH_2CH_2C_6H_5$	NH_2	Br	·HCl, 203–204[h]	47.58	4.53	12.8	47.83	4.92	12.99
21		NO_2	H	·HCl, 210–212 dec.[g]	...	...	12.37	...	...	12.98
22		NH_2	H	·2HCl 202– dec.[g]	...	...	12.13	...	...	12.50
23		NH_2	H	·2HBr 253–255 dec.[i]	...	...	10.31	...	...	9.98
24	$CH_3CHCH_2C_6H_5$	NO_2	H	49[f]	...	...	16.34	...	...	16.28
25	$CH_3CHCH_2C_6H_5$	NH_2	H	210–220 (bath) (0.001)	...	...	18.5	...	...	17.9

[a] Lit. b.p. 166° (1 mm.),[3] 141–143° (0.05 mm.).[8] [b] Lit. b.p. 181–185° (1 mm.),[3c] 155–160° (0.07 mm.).[8] [c] Crystallized from benzene–hexane. [d] Crystallized from aqueous ethanol. [e] Crystallized from ethanol–ether. [f] Crystallized from ether–hexane. [g] Crystallized from ethanol. [h] Crystallized from water. [i] Crystallized from hydrobromic acid.

and the catalyst was washed with hot alcohol. The filtrate on concentration gave 3,5-diaminopyridine dihydrochloride, which was crystallized from ethanol containing HCl; yield 0.43 g., m.p. >300°. The free base obtained from the dihydrochloride was crystallized from benzene: m.p. 110° (lit.[13,15a] m.p. 110–111°).

2- or 4-ω-(-Aminoalkylamino-3-nitropyridines (II and VII).—A solution of the 2- or 4-chloro-3-nitropyridine or its 5-substituted derivative (I or VI, 0.1 mole) in dry toluene (25 ml.) was added gradually with stirring to a solution of the appropriate amine (0.15 mole) in dry toluene (50 ml.). The reaction mixture was stirred at 70–75° for a further 2 hr., cooled, and filtered. The filtrate was washed with water and then extracted with 10% HCl, the acid layer was made basic with NH_4OH and extracted with $CHCl_3$. The chloroform extract was dried (Na_2SO_4), the solvent was removed, and the residue was purified through its hydrochloride and crystallized or distilled in a high vacuum. The different compounds thus obtained in yields of 75–95% are described in Tables I and II.

2- or 4-β-Arylethylamino-3-nitropyridines (II and VII).—The 2- or 4-chloro-3-nitropyridine and their 5-substituted derivatives (I or VI, 0.1 mole) were condensed with β-arylethylamine (0.2 mole) as described above. The reaction mixture was filtered, the filtrate was evaporated to dryness, and the residue was crystallized; yields varied from 75–97%. These compounds are described in Tables I and II.

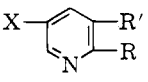
2- or 4-Substituted Amino-3-aminopyridines (III, X = H, NH_2; VIII, X = H, $COOCH_3$).—The appropriate nitro compounds were suspended in ethanol (10 ml./g.) and hydrogenated using Raney nickel catalyst at a pressure of 2.11 kg./cm.^{2} until the absorption of hydrogen ceased (*ca.* 30 min.). The catalyst was filtered and washed with hot ethanol, the filtrate was concentrated under reduced pressure, and the amines were isolated, either as free bases or as the hydrochlorides by adding a calculated quantity of ethanolic HCl to a concentrated solution of the amine in absolute ethanol when the hydrochloride separated out either on cooling or addition of dry ether, in yields of 65–90%. These compounds are described in Table I and II.

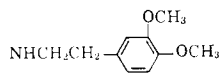
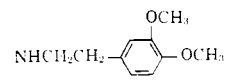
4-(3,4-Dihydroxyphenethylamino)-3-aminopyridine.—A mixture of 4-(3,4-dimethoxyphenethylamino)-3-aminopyridine dihydrochloride (6.5 g.) and 48% HBr (65 ml.) was refluxed for 8 hr. The hydrobromide of the amine separated on cooling; yield, 78%.

4-Phenethylamino-3-amino-5-bromopyridine.—4-Phenethylamino-3-nitro-5-bromopyridine was reduced using Raney nickel catalyst as described above; yield 92% (Table I).

4-Substituted Amino-3-amino-5-nitropyridines (III, X = NO_2).—Sodium hydrosulfide (115 ml.), prepared by saturating a 12% NaOH solution with H_2S at 0°, and NH_4Cl (100 ml. of 20% solution) were added simultaneously under vigorous stirring to a suspension of the 4-substituted amino-3,5-dinitropyridines (17.0 g.) in ethanol (250 ml.) and NH_4OH (30 ml., sp. gr. 0.88). The reaction mixtures became warm and the nitro compounds gradually went into solution. Stirring was continued for 2 hr., and the dark red reaction mixtures were acidified with concentrated HCl and filtered. The filtrates were concentrated under reduced pressure and made basic with concentrated NH_4OH, and the products so obtained were extracted with $CHCl_3$. The

TABLE II



No.	R	R′	X	B.p. (mm.) or m.p., °C.	% calcd. C	% calcd. H	% calcd. N	% found C	% found H	% found N
49	Cl	NO_2	$COOCH_2C_6H_5$	86[a]	53.33	3.06	9.57	53.23	3.36	9.65
50	$NHCH_2CH_2NEt_2$	NO_2	H	100 (bath) (0.001)[b]	55.5	7.5	23.5	55.9	7.7	23.6
51	$NHCH_2CH_2NEt_2$	NO_2	NO_2	66[c,d]	46.6	6.0	24.7	46.9	5.72	24.3
52	$NHCH_2CH_2NEt_2$	NO_2	$COOCH_3$	59[a]	...	...	18.91	...	...	18.98
53[e]	$NHCH_2CH_2NEt_2$	NH_2	H	110 (bath) (0.001)	63.46	9.61	26.92	63.70	9.53	27.11
54	$NHCH_2CH_2NEt_2$	NH_2	NO_2	83[f,g]	51.9	7.8	27.3	52.2	7.5	27.6
55	$NHCH_2CH_2NEt_2$	NH_2	$COOCH_3$	34[d]	...	...	21.06	...	...	20.85
56	$NHCH_2CH_2NEt_2$	NO_2	Br	57–59[d]	...	...	17.66	...	...	17.98
57	$NHCH_2CH_2NC_5H_{10}$	NO_2	H	120 (bath) (0.001)	57.6	7.2	22.4	58.0	7.36	22.3
58	$NHCH_2CH_2NC_5H_{10}$	NO_2	NO_2	97[h]	48.98	5.69	23.7	48.53	5.26	23.42
59	$NHCH_2CH_2NC_5H_{10}$	NH_2	H	94[a]	65.5	9.1	25.4	65.6	9.5	25.7
60	$NHCH_2CH_2NC_5H_{10}$	NH_2	NO_2	118[h]	54.34	7.1	26.4	54.0	7.2	26.8
61	$NHCH_2CH_2C_6H_5$	NO_2	H	85[i]	64.2	5.35	17.28	64.5	5.6	17.4
62	$NHCH_2CH_2C_6H_5$	NO_2	NO_2	120–122[i]	54.8	4.4	19.44	54.3	4.2	19.6
63	$NHCH_2CH_2C_6H_5$	NO_2	$COOCH_3$	102[h]	...	...	13.93	...	...	14.01
64	$NHCH_2CH_2C_6H_5$	NO_2	$COOCH_2C_6H_5$	91[g]	66.81	5.04	11.14	66.62	5.31	11.27
65	$NHCH_2CH_2C_6H_5$	NH_2	H	·HCl, 144[i]	62.5	6.4	16.8	62.9	6.6	17.01
66	$NHCH_2CH_2C_6H_5$	NH_2	NO_2	136[i]	60.11	5.7	21.4	60.4	5.4	21.7
67	$NHCH_2CH_2C_6H_5$	NH_2	$COOCH_3$	105[g]	...	...	15.48	...	...	15.31
68	$NHCH_2CHOHCH_2NEt_2$	NO_2	NO_2	73–75[d]	...	...	22.36	...	...	22.06
69	$NHCH_2CHOHCH_2NEt_2$	NH_2	NO_2	135–137[h]	...	...	24.73	...	...	24.82
70		NO_2	NO_2	130[j]	...	...	16.00	...	...	15.54
71		NH_2	NO_2	174–176[j]	...	...	17.61	...	...	17.52
72	$NHCH(CH_3)CH_2C_6H_5$	NO_2	NO_2	116[i]	...	...	18.54	...	...	18.13
73	$NHCH(CH_3)CH_2C_6H_5$	NH_2	NO_2	·HCl, 208–211[k]	...	...	18.15	...	...	18.06

[a] Crystallized from hexane. [b] Lit.[8] b.p. 120° (0.05 mm.). [c] Lit.[8] m.p. 66°. [d] Crystallized from ether–hexane. [e] Reported earlier[8] but boiling point was not described. [f] Lit.[8] m.p. 83°. [g] Crystallized from benzene–hexane. [h] Crystallized from aqueous ethanol. [i] Crystallized from ethanol. [j] Crystallized from benzene. [k] Crystallized from water.

chloroform extracts were dried (Na_2SO_4) and evaporated, and the amines were purified through their hydrochlorides. Yields of various amines varied from 65–80% (Table I).

2-Substituted Amino-3-amino-5-nitropyridines (VIII, X = NO_2).—Solutions of the nitro compounds (8.4 g.) in ethanol 120 ml.) and NH_4OH (40 ml., sp. gr. 0.88) were heated to 70°, and H_2S gas was passed until saturation. The dark red solutions so obtained were evaporated to dryness under reduced pressure, the residue was extracted with HCl (charcoal) and made basic with NH_4OH, and the liberated amine was extracted with chloroform. The amines were purified by repeatedly dissolving in acid and precipitating with a base, and finally crystallized either as free bases or as hydrochlorides; they were obained in yields of 65–80% (Table II).

4-β-*t*-Aminoethylamino-3-amino-5-bromopyridines (III, X = Br; R = $CH_2CH_2N<$).—These were prepared from the corresponding nitro compounds by reduction with ammonium sulfide as described above in yields of 70–75% (Table I).

Imidazo[4,5-*b*]- and -[4,5-*c*]pyridines (IV and IX, R′ = H).—The diaminopyridines (III and VIII) were refluxed with 98–100% formic acid for periods varying from 5–20 hr. The formic acid was removed under reduced pressure, and the residue was taken up in a little water and made basic with NH_4OH. The products were either filtered and crystallized or extracted with chloroform, the extracts were dried (Na_2SO_4), the solvents were removed under reduced pressure, and the products were isolated as the free bases or as hydrochlorides, in yields from 75–95%. (Table III and IV).

2-Oxoimidazo[4,5-*b*]- and -[4,5-*c*]pyridines (IV and IX, R′ = OH).—2- or 4-Substituted amino-3-aminopyridines (III and VIII) were fused with urea at 160–170°. After the evolution of ammonia had slowed down, the melt was cooled and extracted with absolute ethanol (charcoal), the alcoholic extract was concentrated, and the products were isolated as hydrochlorides by treatment with ethanolic HCl; yields 45–50% (Table III and IV).

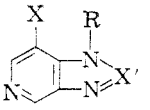
2-Mercaptoimidazo[4,5-*b*]- and -[4,5-*c*]pyridines (IV and IX, R′ = SH).—A solution of the 2- or 4-substituted amino-3-aminopyridine (III and VIII) in methanol and CS_2 was refluxed for 20 hr. The solvent was evaporated under reduced pressure and the residue was crystallized from ethanol; yields 80–90% (Table III and IV).

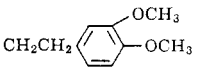
Triazolo[4,5-*b*]- and -[4,5-*c*]pyridines (V and X).—A 5% aqueous solution of sodium nitrite was added to a vigorously stirred solution of the diaminopyridine (III and VIII) in 10% HCl cooled to 0°, until the reaction mixture gave a test for nitrous acid. Stirring was continued at this temperature for a further 1.5 hr. In cases where a solid separated, it was filtered and crystallized; otherwise the solution was evaporated to dryness *in vacuo*, the residue was dissolved in a little water and made basic with NH_4OH, and the free base was worked up as usual; yields 85–100% (Table III and IV).

2-Phenethylimidazo[4,5-*b*]pyridine-6-carboxylic Acid.—3-Phenethyl-6-methoxycarbonylimidazo[4,5-*b*]pyridine (1.5 g.) was refluxed for 2 hr. with 20% NaOH solution (25 ml.) and the reaction mixture was cooled and acidified to pH 4–5 with HCl. The acid which separated was filtered, washed with water, and crystallized from aqueous ethanol; yield 95% (Table IV).

3-Phenethylimidazo[4,5-*b*]pyridine-6-carboxamide.—The acid (0.4 g.) was refluxed with oxalyl chloride (2.0 ml.) in dry benzene (10 ml.) for 4 hr. The solvent was removed *in vacuo*, and the residue repeatedly was distilled with dry benzene to remove traces of oxalyl chloride. The acid chloride was obtained as a brown crystalline solid. This was dissolved in benzene and a

TABLE III



No.	R	X	X′	B.p. (mm.) or m.p., °C.	% calcd. C	% calcd. H	% calcd. N	% found C	% found H	% found N
26[a]	$CH_2CH_2NEt_2$	H	CH	·2HCl, 219–221[b,c]	49.48	6.87	19.48	49.71	7.18	19.05
				·HCl, 179–181[d]	...	...	22.03	...	...	21.74
27[e]	$CH_2CH_2NEt_2$	NO_2	CH	35[f]	54.71	6.46	26.6	55.18	6.92	26.17
28[a]	$CH_2CH_2NEt_2$	Br	CH	·2HCl, 211–212[e]	38.89	5.13	15.13	38.42	5.51	15.32
29	$CH_2CH_2NEt_2$	H	N	130–135 (bath) (0.005)[g]	60.27	7.7	31.96	60.54	8.00	31.59
30	$CH_2CH_2NEt_2$	NO_2	N	145–150 (bath) (0.0003)	50.0	6.06	31.8	50.4	6.34	31.63
31	$CH_2CH_2NEt_2$	Br	N	·2HCl, 187–189[e]	35.57	4.85	19.13	35.93	4.79	19.05
32[a]	$CH_2CH_2NC_5H_{10}$	H	CH	73–74[f]	68.6	8.6	24.3	68.52	8.32	24.6
33[h]	$CH_2CH_2NC_5H_{10}$	H	COH	237–239[e]	...	...	21.21	...	...	20.98
34	$CH_2CH_2NC_5H_{10}$	H	CSH	215–216[e]	59.54	6.86	21.4	59.72	6.91	21.19
35[e]	$CH_2CH_2NC_5H_{10}$	NO_2	CH	88–90[f]	56.7	6.2	25.0	56.94	6.31	24.9
36[a]	$CH_2CH_2NC_5H_{10}$	Br	CH	·HCl, 261–263[e]	43.89	5.06	15.75	43.37	5.01	15.61
37	$CH_2CH_2NC_5H_{10}$	H	N	85–87[f]	62.38	7.35	30.30	62.52	7.23	29.91
38	$CH_2CH_2NC_5H_{10}$	NO_2	N	67–68[f]	52.1	5.7	30.4	51.94	5.89	30.25
39	$CH_2CH_2NC_5H_{10}$	Br	N	·HCl, 222–224[e]	37.59	4.64	18.27	37.98	4.93	17.92
40[a,h]	$CH_2CH_2C_6H_5$	H	CH	121–122[i]	69.70	6.22	17.4	69.3	6.39	17.02
				·HCl, 202–204[e]	64.74	5.43	16.14	65.02	5.44	16.22
41	$CH_2CH_2C_6H_5$	H	COH	·HCl, 258–260[e]	60.98	5.08	15.2	60.63	5.32	15.61
42	$CH_2CH_2C_6H_5$	H	CSH	260[e]	65.88	5.09	16.4	65.83	5.42	16.32
43[e]	$CH_2CH_2C_6H_5$	NO_2	CH	122–123[e]	62.75	4.4	20.9	63.15	4.27	20.71
44[a]	$CH_2CH_2C_6H_5$	Br	CH	85–86[f]	55.62	3.97	13.90	55.84	4.24	13.86
45	$CH_2CH_2C_6H_5$	H	N	79–80[e]	69.6	5.3	25.0	69.90	5.33	24.79
46	$CH_2CH_2C_6H_5$	NO_2	N	169–170[f]	57.97	4.08	26.02	58.1	4.12	25.72
47	$CH_2CH_2C_6H_5$	Br	N	131–132[e]	51.45	3.61	18.50	51.62	3.61	18.61
48		H	N	115[f]	...	...	19.36	...	...	18.98

[a] Reaction time of 15–20 hr. [b] Lit.[8] m.p. 225–226. [c] Crystallized from ethanol. [d] Crystallized from ethanol–ether. [e] Reaction time of 3 hr. [f] Crystallized from ether–hexane. [g] Lit.[4e] b.p. 147° (1 mm.). [h] Crystallized as monohydrate. [i] Crystallized from benzene–hexane.

stream of dry NH_3 was passed through the solution, and the amide so obtained was filtered, washed with water, and crystallized from aqueous ethanol; yield 75% (Table IV).

N,N-Diethyl-3-phenethylimidazo[4,5-*b*]pyridine-6-carboxamide.—Diethylamine was added to a benzene solution of the acid chloride prepared as described above. The solution was filtered, the filtrate was evaporated to dryness, and the residue was crystallized from ether–petroleum ether; yield 95% (Table IV).

2-Phenethylamino-5-benzyloxycarbonyl-3-nitropyridine.—6-Chloro-5-nitronicotinoyl chloride,[18] prepared from 6-hydroxy-5-nitronicotinic acid (1.0 g.),[16] was dissolved in dry benzene (10 ml.); benzyl alcohol (1.0 ml.) was added and the mixture was kept for 15 min. Benzene was removed under reduced pressure, and the residue was triturated with cold ethanol, filtered, and crystallized from hexane. It was then condensed with phenethylamine as described above for the methoxycarbonyl compound; yield 65%.

3-Phenethyl-6-benzyloxycarbonylimidazo[4,5-*b*]pyridine.—The above nitro compound (0.5 g.) was suspended in ethanol (10 ml.) and reduced with sodium dithionite by warming on the water bath. The reaction mixture was evaporated to dryness *in vacuo*, and the residue was extracted with chloroform. Removal of the chloroform gave a sirup (0.3 g.) which was refluxed with 98–100% formic acid (5 ml.) for 15 hr. and worked up as usual; yield 50%.

3-β-Diethylaminoethylimidazo[4,5-*b*]pyridine-6-carboxhydrazide.—A solution of 3-β-diethylaminoethyl-6-methoxycarbonylimidazo[4,5-*b*]pyridine (0.6 g.) in absolute ethanol (5 ml.) and hydrazine hydrate (1 ml. of 99–100%) was refluxed for 15 hr. The reaction mixture was evaporated to dryness *in vacuo*, and the residue was crystallized from ethanol–ether; yield 95% (Table IV).

3-β-Diethylaminoethylimidazo[4,5-*b*]pyridine-6-carboxamide. The above hydrazide (0.3 g.) in ethanol (30 ml.) was refluxed in the presence of moist Raney nickel catalyst (3.0 g.) for 24 hr. The catalyst was filtered, the filtrate was evaporated to dryness *in vacuo*, and the residue was crystallized from ethanol–ether; yield 65% (Table IV).

3-Substituted Amino-4-nitropyridine 1-Oxides (XI).—A solution of 3-bromo-4-nitropyridine 1-oxide (3.3 g.) in absolute methanol (70 ml.) and the appropriate amine (2 mole equiv. of phenethylamine, 1.5 mole equiv. of β-diethylaminoethylamine, and excess dimethylamine) was heated on the steam bath for 45 min. The solution was evaporated to dryness under reduced pressure, and the residue crystallized from absolute ethanol (charcoal). Thus 3-dimethylamino 4-nitropyridine 1-oxide (**99**) was obtained in 45% yield, m.p. 145°.

Anal. Calcd. for $C_7H_9N_3O_2$: N, 22.9. Found: N, 23.04.

3-Phenethylamino-4-nitropyridine 1-oxide (100) was obtained in 30% yield, m.p. 172°.

Anal. Calcd. for $C_{13}H_{13}N_3O_3$: N, 16.21. Found: N, 16.22.

3-β-Diethylaminoethylamino-4-nitropyridine 1-oxide (101) was obtained in 10% yield, m.p. 89°.

Anal. Calcd. for $C_{11}H_{18}N_4O_3$: N, 22.1. Found: N, 21.97.

3-Substituted Amino-4-aminopyridines (XII).—The nitropyridine 1-oxides (XI) were hydrogenated at a pressure of 2.46 kg./cm.^{2} using Raney nickel as catalyst; yield 79–85%. Thus 3-dimethylamino-4-aminopyridine hydrochloride (**102**) crystallized from ethanol; m.p. 245°.

Anal. Calcd. for $C_7H_{11}N_3 \cdot HCl$: N, 24.2. Found: N, 23.76.

3-Phenethylamino-4-aminopyridine (103) crystallized from benzene; m.p. 125°.

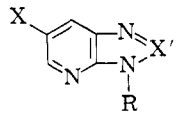
Anal. Calcd. for $C_{13}H_{15}N_3$: N, 19.71. Found: N, 19.32.

3-β-Diethylaminoethylamino-4-aminopyridine dihydrochloride (104) crystallized from ethanol; m.p. 103°

Anal. Calcd. for $C_{11}H_{20}N_4 \cdot 2HCl \cdot H_2O$: C, 44.14; H, 8.02; N, 18.73. Found: C, 43.75; H, 8.31; N, 18.53.

3-Phenethylimidazo[4,5-*c*]pyridine (105).—3-Phenethylamino-4-aminopyridine (0.57 g.), water (20 ml.), copper acetate (1.1

TABLE IV



No.	R	X	X′	B.p. (mm.) or m.p., °C.	% calcd. C	% calcd. H	% calcd. N	% found C	% found H	% found N
74[a]	$CH_2CH_2NEt_2$	H	CH	110 (bath) (0.001)[b]	66.1	8.25	25.7	66.42	8.37	25.42
75[c]	$CH_2CH_2NEt_2$	NO_2	CH	62[d,e]	52.8	6.22	25.64	53.0	6.4	25.6
76	$CH_2CH_2NEt_2$	NO_2	COH	·2HCl, 236[f,g]	...	...	22.18	...	...	22.17
77	$CH_2CH_2NEt_2$	NO_2	CSH	185–187[h,g]	...	...	23.72	...	...	23.41
78	$CH_2CH_2NEt_2$	NH_2	CH	Sirup	...	...	30.04	...	...	30.34
79[a]	$CH_2CH_2NEt_2$	Br	CH	Picrate, 147–149[i]	...	...	18.66	...	...	19.03
80[a]	$CH_2CH_2NEt_2$	$COOCH_3$	CH	41[e]	...	...	20.9	...	...	20.67
81	$CH_2CH_2NEt_2$	H	N	·HCl, 132[j]	51.66	7.04	27.4	51.96	6.94	27.08
82	$CH_2CH_2NEt_2$	NO_2	N	·HCl, 165–167[j]	43.92	5.65	27.95	43.66	5.80	28.75
83[a]	$CH_2CH_2NC_5H_{10}$	H	CH	·HCl, 165[j]	...	...	21.1	...	...	20.89
84[c]	$CH_2CH_2NC_5H_{10}$	NO_2	CH	107[e]	...	...	25.45	...	...	25.57
85	$CH_2CH_2NC_5H_{10}$	H	N	·HCl, 218–219[j]	53.83	6.70	25.40	53.41	6.25	25.72
86	$CH_2CH_2NC_5H_{10}$	NO_2	N	104[k]	52.17	5.79	30.43	52.35	5.92	30.18
87[a]	$CH_2CH_2C_6H_5$	H	CH	73[k]	75.1	5.8	18.75	75.1	6.0	18.5
88[c]	$CH_2CH_2C_6H_5$	NO_2	CH	107–108[k]	62.7	4.4	20.89	63.00	4.1	20.79
89[a]	$CH_2CH_2C_6H_5$	$COOCH_3$	CH	103[k]	...	...	14.9	...	...	14.7
90	$CH_2CH_2C_6H_5$	H	N	68[e]	70.76	5.35	24.50	70.53	5.77	24.66
91	$CH_2CH_2C_6H_5$	NO_2	N	137–138[k]	57.99	4.09	26.02	58.09	4.32	25.83
92[a]	$CH_2CH_2C_6H_5$	$COOCH_2C_6H_5$	CH	164[l]	73.66	5.26	11.76	73.37	5.51	11.52
93[c]	$CH_2CHOHCH_2NEt_2$	NO_2	CH	79–81[e]	...	...	23.88	...	...	23.22
94	$CH_2CH_2C_6H_5$	COOH	CH	222–225 dec.[i]	67.41	4.86	15.72	67.53	4.70	15.85
95	$CH_2CH_2C_6H_5$	$CONH_2$	CH	194–197[i]	...	...	21.05	...	...	20.93
96	$CH_2CH_2C_6H_5$	$CONEt_2$	CH	108–110[e]	68.68	6.62	16.86	68.48	6.99	16.78
97	$CH_2CH_2NEt_2$	$CONHNH_2$	CH	145–146[j]	56.5	7.2	30.4	56.21	7.77	29.98
98	$CH_2CH_2NEt_2$	$CONH_2$	CH	197–199[j]	...	...	26.82	...	...	26.63

[a] Reaction time of 15–20 hr. [b] Lit.[8] b.p. 125° (0.07 mm.). [c] Reaction time of 2–3 hr. [d] Lit.[8] m.p. 66–67°. [e] Crystallized from ether–hexane. [f] Lit.[8] m.p. 240°. [g] Crystallized from ethanol. [h] Lit.[8] m.p. 191–192°. [i] Crystallized from aqueous ethanol. [j] Crystallized from ethanol–ether. [k] Crystallized from benzene–hexane. [l] Crystallized from hexane.

g.), and formalin (0.4 ml.) were refluxed for 5 hr. The reaction mixture was cooled, acidified with concentrated HCl, and freed of copper ions by passing in H_2S, and the compound was isolated as its hydrochloride; m.p. 184–187°, yield 50%.

Anal. Calcd. for $C_{14}H_{13}N_3 \cdot HCl$: N, 16.21. Found: N, 16.2

3-Phenethyltriazolo[4,5-*c*]pyridine (106).—3-Phenethylamino-4-aminopyridine (0.5 g.) was treated with nitrous acid by the method described above and the triazole was crystallized from benzene–hexane; m.p. 119–120°, yield 75%.

Anal. Calcd. for $C_{13}H_{12}N_4$: C, 69.64; H, 5.35; N, 25.0. Found: C, 69.84; H, 5.72; N, 25.51.

Pharmacological Methods.—Acute toxidity, gross observational effects, antagonism to sodium pentobarbital (60 mg./kg. i.p.), pentylenetetrazole (60 or 90 mg./kg. s.c.), and electroshock were studied in male mice at 0.5–0.25 LD_{50}. The actions on blood pressure, respiration, superior cervical ganglia, and salivation were studied in anesthetized cats by administering 2–5 mg./kg. i.v.

Results and Discussion

Pharmacological data for some of the selected compounds are described in Table V. Among the aminopyridines the vasopressor action and barbiturate antagonism were most marked in 4-aminopyridine; these effects were accompanied by marked increase in secretions, thus indicating the possibility of involvement of the autonomic nervous system. 2-Aminopyridine was somewhat less active, while 3-aminopyridine was the least active of the aminopyridines. Introduction of an additional amino group in position 3 of 2- and 4-aminopyridines further increased the intensity and duration of their action on blood pressure and barbiturate antagonism. Introduction of an amino or a methyl group in position 5 or 6 of 2-aminopyridine reduced the magnitude of activity without affecting its pattern. In 3-aminopyridine, introduction of an amino group at position 5 increased the analeptic activity without altering the magnitude of the pressor action, thus indicating that the two actions may be independent of each other and showing the possibilities of their dissociation. However, in 2,4-diaminopyridine both these activities are completely abolished. This appears to be due either to the competition between 2- and 4-amino groups for the same sites on the bioreceptor or perhaps to the binding of the molecule at the "sites of loss." Introduction of a bromo or nitro group in position 5 or an amino group in position 6 in 2,3-diaminopyridine completely abolished these activities, and 2,3,6-triaminopyridine even showed a mild vasodepressor and anticonvulsant response of an antiextensor type.

Substitution of either of the amino groups in 2,3- or 3,4-diaminopyridines markedly altered their activity. With small alkyl substituents (mono and dimethyl) a certain amount of residual pressor and analeptic effects could still be noticed, but, with bigger substituents, these actions were abolished and in certain cases even the pattern completely changed. Thus 4-phenethylamino-3-aminopyridine produced ptosis and mild ataxia, blocked the extensor convulsions, and had a marked vasodepressor action. Branching of the alkyl chain of this 4-phenethylaminopyridine did not alter its anticonvulsant activity as shown by the activity of its

TABLE V

PHARMACOLOGICAL RESULTS

No.	Pyridine derivative	Approx. LD_{50} (mice) i.p., mg./kg.	Gross observations (mice)	Effect on barbiturate hypnosis (mice) Dose, mg./kg.	Effect on barbiturate hypnosis (mice) %[a]	Cardiovascular effects (cats) Dose, mg./kg.	Cardiovascular effects (cats) B.P., mm.[b] (min.)	Cardiovascular effects (cats) Resp.[c]	Cardiovascular effects (cats) N.M.[c,d]	Cardiovascular effects (cats) Salivation[c]	Remarks[e]
1	2-Amino	35	Hyperreflexia, slight motor activity, tonic convul.	10 20	−40 0	2	+37 (15)	0	0	+	Thick and mucoid saliva
2	3-Amino	28	Hyperreflexia, tremors, tonic convul.	6 15	−10 0	2	+15 (10)	0	0	0	...
3	4-Amino	10	Hyperreflexia, quiet, tonic convul., salivation ++	2.5 5	−60 −50	2	+31 (20–40)	++	+++	++	Profuse and watery saliva
4	2,3-Diamino	25	Hyperreflexia, irritation, piloerection, tail raising, tonic convul.	5 12	−56 0	2	+25 (20 30)	+	+	+	Thick and mucoid saliva
5	3,4-Diamino	20	Hyperreflexia, irritation, piloerection, tail raising, tonic convul., salivation	5 10	−42 −64	2	+51 (30–50)	++	+++	+++	Profuse and watery saliva
6	2,4-Diamino	>200	Quiet and markedly relaxed, incoordinated movements	50 100	0 0	2	+10 (7)	0	0	0	
7	2,5-Diamino	50	Hyperreflexia, irritation, tonic convulsions	12.5 25	−14 −40	2	+20 (20)	0	+	±	
8	2,6-Diamino	100	Alert, slight increase in random movements and tail raising followed by depression, clonic convul., secretions ±	40 20	−41 0	2	+20 (15 30)	0	+	+	
9	3,5-Diamino	200	Alert, tail raising, hyperreflexia	150 100	−30 −35	2	+10 (10)	0	0	0	
10	2,3,6-Triamino	200	Quiet but moved away freely, cyanosis respiratory failure	50 100	0 0	2	−20 (10)	0	0	0	Blocked pentylenetetrazole-induced extensor convul.
11	3,4-Diamino-5-bromo	100	Markedly alert, irritation, fight, squeaking noise, tail raising followed by depression, tonic convul.	50	0	4	0	0	0	0	
12	3,4-Diamino-5-nitro[f]	>800	Slightly alert, piloerection, later depressed	500	0	2	−20 (2)	0	0	0	
13	4-Amino-3-phenethylamino	100	Quiet, labored respiration, irritation, preconvul. jumping, clonic convul., decrease in locomotor activity	50	0	2	+10 (3)	0	0	0	Blocked pentylenetetrazole-induced extensor convul.
14	3-Amino-4-phenethylamino	150	Ptosis, marked depression, mild ataxia, clonic convul.	80	0	5	−72 (5)	0	0	0	Blocked electroshock-induced convul.
15	3-Amino-4-(α-methylphenethylamino)	80	Quiet, ataxia, death due to resp. failure	50	0	5	−25 (2)	0	0	0	Blocked pentylenetetrazole-induced tonic convul.
16	3-Amino-4-(3,4-dimethoxyphenethylamino)	250	Marked depression, hypothermia 3°F., anoxic convul., death	100	+40	2.5	−10 (2)	0	0	0	Did not block pentylenetetrazole-induced extensor convul.
17	3-Amino-4-(3,4-dihydroxyphenethylamino)	150	Quiet, piloerection, cyanosis, gasping, death due to respiratory failure	50	−15	2.5	+30 (4)	0	0	0	Did not block pentylenetetrazole-induced extensor convul.

18	3-Amino-4-(β-diethylaminoethylamino)	>500	Quiet, piloerection, labored respiration	200	0	5	−36 (2)	0	0	0	
19	3-Amino-4-(β-piperidylethylamino)	150	Depression, increased secretions, mild ataxia, decrease in locomotor activity	100	0	2	−20 (3)	0	0	0	
20	3,5-Diamino-4-(β-piperidylethylamino)	500	Slight motor activity, high doses produce depression, salivation	200	0	5	−20 (3)	0	0	0	Diuretic action
21	3-Amino-5-nitro-4-(β-piperidylethylamino)	100	Quiet, salivation, tonic convul., decrease in locomotor activity	50	0	4	−26 (2)	0	0	0	Potentiated pentylenetetrazole-convul.
22	3-Amino-5-bromo-4-(β-piperidylethylamino)	150	Sit-like patches, ptosis, pseudo-sedation, clonic convul., death	50	0	4	−10 (5)	0	0	0	
23	3-Amino-2-phenylethylamino[f]	>500	Marked depression, ataxia, ptosis, decrease in locomotor activity	100	0	3	0	0	0	0	
24	3-Amino-5-bromo-4-phenylethylamino	>350	Slightly active, tail raising, later depressed	100	0	4	+20 (5)	0	0	0	
25	3-Amino-5-nitro-2-phenylethylamino[f]	>800	Active, restless, piloerection, later depressed, locomotor activity reduced	100	0	4	+30 (10)	0	0	0	Antagonizes reserpine ptosis
26	3-Amino-5-nitro-4-phenylethylamino[f]	>800	Quiet, gasping and convul., locomotor activity reduced	400	0	2	−40 (2)	0	0	0	
27	3,5-Diamino-4-phenylethylamino	150	Hyperreflexia, no clear cut convul., death due to respiratory failure	80	0	5	−50 (5)	0	0	0	
28	3-(β-Diethylaminoethyl)imidazo[4,5-*b*]	100	Quiet, quick resp., tonic convul.	50	−46	3	0	0	0	0	Potentiated pentylenetetrazole-induced convul.
29	3-(β-Diethylaminoethyl)-6-nitroimidazo-[4,5-*b*]	100	Alert, hyperreflexia, slight motor activity followed by depression, tonic convul.	50	−41	3	−15 (5)	0	0	0	Potentiated pentylenetetrazole-induced convul.
30	3-(β-Diethylaminoethyl)-2-hydroxy-6-nitroimidazo[4,5-*b*]	>200	Depression, piloerection, sit-like patches	50	−15	2	0	0	0	0	Potentiated pentylenetetrazole-induced convul.
31	3-Phenethylimidazo[4,5-*b*][f]	>400	Depression	100	+50	3	0	0	0	0	
32	3-(β-Diethylaminoethyl)-6-methoxy carboxylimidazo[4,5-*b*]	150	Quiet, slightly depressed, quick resp., piloerection, tonic convul.	50	−40	4	+25 (10)	+	+	0	
33	3-(β-Diethylaminoethyl)imidazo[4,5-*b*]-pyridine-6-carboxylic acid	500	Quiet, hyperreflexia, pseudo-sedation	200	0	4	0	0	0	0	
34	3-Phenethyl-6-methoxycarboxylimidazo-[4,5-*b*][f]	>500	...	...	...	7.5	0	++	0	0	Rate and amplitude of resp. increased and lasted for more than 60 min.
35	3-Phenylethylimidazo[4,5-*b*]pyridine-6-carboxylic acid	200	Depression, slight hypothermia	100	0	7.5	+13 (3)	0	0	0	
36	3-Phenylethylimidazo[4,5-*b*]pyridine-6-carboxamide[d]	>500	...	...	...	7.5	−25 (2)	+++	0	0	Rate and amplitude of resp. increased, and lasted for more than 90 min.
37	N,N-Diethyl-3-phenethylimidazo[4,5-*b*]-pyridine-6-carboxamide[f]	500	...	...	...	7.5	−40 (7)	+++	0	0	Rate and amplitude of resp. increased and lasted for more than 60 min.
38	1-Phenethyltriazolo[4,5-*c*]	>400	Marked depression, increased salivation	150	+60	2	0	0	0	0	Produced hypothermia and enhanced the effect of reserpine and chlorpromazine and affects CAR

No.	Pyridine derivative	Approx. LD_{50} (mice) i.p., mg./kg.	Effect on barbiturate hypnosis (mice) Dose, mg./kg.	%	Cardiovascular effects (cats) Dose, mg./kg.	B.P., mm.[b] (min.)	Resp.[c]	N.M.[d]	Salivation[e]	Remarks[a]
39	1-Phenethyl-7-nitrotriazolo[4,5-*c*][f]	>800	500	0	4	−80 (7)	0	0	0	MAO of brain and liver inhibited 28 and 63%, respectively
40	1-(β-Piperidylethyl)triazolo[4,5-*c*]	150	100	+40	2	0	0	0	0	Potentiated pentylenetetrazole-induced convul.
41	1-(β-Piperidylethyl)-7-nitrotriazolo[4,5-*c*]	200	50	0	4	+10 (2)	0	0	0	Slight stimulation followed by depression, tonic convul., death
42	1-(β-Diethylaminoethyl)-7-nitrotriazolo-[4,5-*c*]	500	100	+40	2	+12 (2)	0	0	0	Potentiated pentylenetetrazole-induced convul.
43	1-(β-Piperidylethyl)imidazo[4,5-*c*]	150	50	+50	2	0	0	0	0	Potentiated pentylenetetrazole-induced convul. and no effect on CAR
44	1-(β-Piperidylethyl)-7-nitroimidazo[4,5-*c*]	75	50	0	4	−20 (3)	+	0	0	
45	1-(β-Piperidylethyl)-2-mercaptoimidazo-[4,5-*c*]	200	50	0	4	−20 (2)	+	+	+	Potentiated pentylenetetrazole-induced convul.
46	1-(β-Phenylethyl)imidazo[4,5-*c*]	150	80	+40	5	−50 (3)	0	0	0	
47	1-(β-Phenylethyl)-7-nitroimidazo[4,5-*c*][f]	>800	500	0	4	−44 (1)	0	0	0	

[a] % decrease (−) or increase (+) in barbiturate sleeping time with respect to controls. [b] + = raised blood pressure, − = lowered blood pressure. [c] 0 = no effect, ± = 10%, + = 10–25%, ++ = 25–50%, and +++ = 50% effect. [d] Nictitating membrane; + signs denote amplitude of contraction. [e] All the compounds were tested for effect on pentylenetetrazole-induced clonic and extensor convulsions. Only those compounds which modified the convulsions are mentioned. [f] Insoluble compounds, administered *per os*.

α-methyl analog (**15**), while the introduction of 3,4-dimethoxy (**16**) or dihydroxy groups (**17**) in the phenyl ring abolished this anticonvulsant activity. The dihydroxy compound showed vasopressor action of short duration, while the dimethoxy compound did not have much effect on blood pressure; however, it markedly potentiated barbiturate hypnosis. The corresponding 3-*l*-aminoethylamino-3-aminopyridines and their 5-*nitro-*, *bromo*, *or amino* derivatives did *not* possess these activities. Introduction of a nitro or bromo group in phenethylamino compounds conferred vasopressor action as shown in 2-phenethylamino-3-amino-5-nitropyridine and 4-phenethylamino-3-amino-5-bromopyridine; the former in addition also antagonized reserpine-induced ptosis in mice. 4-β-Piperidylethylamino-3,5-diaminopyridine, however, showed mild diuretic action.

In imidazo[4,5-*b*]pyridines, the β-*l*-aminoethyl residue at position 3 conferred a stimulant and analeptic activity, which was particularly marked in 3-β-diethylaminoethylimidazo[4,5-*b*]pyridine. Introduction of a nitro (**29**) and a methoxycarbonyl (**32**) group in position 6 of this compound did not appreciably enhance the analeptic activity. However, the methoxycarbonyl compound in addition to its analeptic action possessed vasopressor and respiratory stimulant actions. This respiratory stimulant action was more marked in the corresponding 3-phenethyl-6-carboxamide (**36**), where it persisted for as long as 90 *min*. Introduction of an amino or bromo group in position 6 or a mercapto or hydroxyl group in position 2 of 3-β-diethylaminoethylimidazo[4,5-*b*]pyridine abolished analeptic activity. The corresponding triazolo[4,5-*b*]pyridines did not show this analeptic action.

1-Phenethyl- and 1-β-*l*-aminoethylimidazo- or -triazolo[4,5-*c*]pyridines on the other hand, showed a general depressant action, which was quite pronounced in 1-phenethyltriazolo[4,5-*c*]pyridine and 1-β-piperidylethylimidazo[4,5-*c*]pyridine. These two compounds showed marked potentiation of barbiturate hypnosis and also potentiated the action of reserpine and chlorpromazine. The phenethyl compound (**38**) at a dose of 100 mg./kg. blocked 50% of the conditioned avoidance response (CAR) in rats,[24] the piperidylethyl compound (**43**), however, did not affect the CAR. Introduction of a mercapto or hydroxyl group at position 2, and a bromo or nitro group at position 7 of these imidazo- and triazolopyridines did not confer any significant activity.

A group of workers[5] have claimed analeptic activity for lower-alkyl 3-β-*l*-aminoimidazo[4,5-*b*]pyridines and the isomeric 1-substituted imidazo[4,5-*c*]pyridines, especially for 3-β-diethylaminoethyl-6-nitroimidazo-[4,5-*b*]pyridine (**29**). Although our study agrees with the claimed analeptic activity of the latter, it shows that the corresponding imidazo- and triazolo[4,5-*c*]pyridines have a depressant action.

Acknowledgment.—We would like to express our thanks to Dr. M. L. Dhar, Director, for his interest in this work, to Mr. J. Saran and his associates for microanalysis, and to Riker Laboratories, Inc., Northridge, Calif., for a generous gift of chemicals.

(24) A. Ahmad and M. M. Vohra, unpublished work.