H_2SO_4 was immersed in an ice–salt bath and stirred vigorously for 5–10 min to effect rapid solution. Fuming HNO_3 (0.1 ml, d 1.5) was added from a microsyringe and the solution was stirred at 0–5° for 1 hr. The dark amber-colored solution was poured onto 50 g of ice, and the mixture was made basic by the addition of saturated Na_2CO_3 solution while the temperature was kept at or below 10°. The basic mixture containing a flocculent yellow precipitate was extracted with CH_2Cl_2. The combined extracts were washed twice with saturated NaCl, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The orange semisolid residue was crystallized from MeCN, giving 0.3 g (40%) of fine orange crystals of **18**, mp 252–254° dec. *Anal.* ($C_{20}H_{28}N_4O_3$) C, H, N.

d-**13-Amino-*N*-*n*-butyl-2,3,9,10-tetrahydrolysergamide (19).** A solution of 280 mg of **18** in 50 ml of absolute EtOH was hydrogenated at room temperature at 1.8 kg/cm² for 1.5 hr over 150 mg of 10% Pd/C. The catalyst was filtered off, the colorless filtrate was evaporated to dryness under vacuum, and the residue was recrystallized from Et_2O–MeOH giving 210 mg (82%) of **19**, mp 228–231° dec. *Anal.* ($C_{20}H_{30}N_4O$) C, H, N.

Preparation of 1-Substituted Lysergamides. Method C. 9,10-Dihydro-*N*-isopropyl-1-*n*-propyllysergamide (20b). A mixture of 730 mg (31.5 mg-atoms) of Na, 15 mg of $Fe(NO_3)_3 \cdot 9H_2O$, and 200 ml of liquid NH_3 was stirred until the blue color disappeared (40 min). **2e** (1 g, 3.2 mmol) was added and stirring was continued for 1 hr, with occasional addition of liquid NH_3 to keep the volume at 200 ml. Then a solution of 4.95 g (30 mmol) of *n*-propyl iodide in 25 ml of Et_2O was added dropwise during 20 min. After another 75 min of stirring, 1 g of NH_4Cl was added and the NH_3 was allowed to evaporate completely. The residue was shaken with a mixture of 100 ml of $CHCl_3$ and 400 ml of water. The $CHCl_3$ solution was dried ($CaSO_4$) and evaporated to dryness under vacuum. The residue was recrystallized from boiling Me_2CO (decolorizing C) to give 715 mg (62%) of **20b** as colorless crystals, mp 243–245°.

9,10-Dihydro-*N*-isopropyl-1-methoxymethyllysergamide (20c). A mixture of 92 mg (4 mg-atoms) of Na sand, 40 ml of dry THF, and 530 mg (4.13 mmol) of dry naphthalene was stirred for 4 hr at room temperature; the final color of the solution was dark green. The solution was cooled to 0° and 1.15 g (3.7 mmol) of **2e** dissolved in 25 ml of THF was added dropwise during 15 min. The resulting clear brown solution was heated to reflux and treated with 350 mg (4.35 mmol) of freshly distilled chloromethyl methyl ether in 10 ml of THF. The mixture was refluxed for 1 hr and stirred at room temperature overnight. The reaction mixture was shaken with 200 g of ice and 100 ml of $CHCl_3$. The organic phase was dried ($CaSO_4$) and concentrated, and the solid residue recrystallized twice from EtOAc–petroleum ether (bp 30–60°) giving 840 mg (64%) of **20c**, mp 237–239°.

Method D. 9,10-Dihydro-1-dimethylaminomethyl-*N*-isopropyllysergamide (20d). A mixture of 1.5 g (0.005 mol) of **2e**, 25 ml of AcOH, 15 ml of MeOH, and 25 ml of 32% aqueous dimethylamine was stirred at 50° while 12 ml of 40% aqueous formaldehyde was added. The mixture was then stirred at 65–75° for 1 hr, cooled, mixed with an equal volume of saturated aqueous NaCl, and made basic by the addition of K_2CO_3 to the cold solution. The mixture was extracted with $CHCl_3$ and the dried extract was evaporated to dryness. The residue was recrystallized three times from Me_2CO–*n*-hexane (decolorizing C) to give 850 mg (46%) of **20d** as an off-white powder, mp 201–203° dec.

Acknowledgments. The authors are indebted to Dr. Frederick C. Nachod who called our attention to the emetic properties of the lysergamides, Dr. Franklin J. Rosenberg for advice in pharmacology, Dr. S. P. Battista for assistance in emesis tests, and to Dr. Edward R. Atkinson for his assistance in the preparation of this manuscript.

References

(1) A. Hofmann in "Drugs Affecting the Nervous System," A. Burger, Ed., Marcel Dekker, New York, N. Y., 1968, Chapter 5.
(2) S. C. Wang and V. V. Glaviano, *J. Pharmacol. Exp. Ther.*, **111**, 329 (1954).
(3) A. Stoll and A. Hofmann, *Helv. Chim. Acta*, **26**, 944 (1943).
(4) A. Frey, U. S. Patent 3,084,164 (1963).
(5) R. P. Pioch, U. S. Patent 2,736,728 (1956).
(6) W. L. Garbrecht, *J. Org. Chem.*, **24**, 368 (1959).
(7) A. Stoll and A. Hofmann, *Helv. Chim. Acta*, **26**, 2070 (1943).
(8) A. Stoll, A. Hofmann, and Th. Petrzilka, *ibid.*, **29**, 635 (1946).
(9) R. C. Cookson, *Chem. Ind. (London)*, 337 (1953).
(10) A. Stoll, Th. Petrzilka, J. Rutschmann, A. Hofmann, and Hs. H. Gunthard, *Helv. Chim. Acta*, **37**, 2039 (1954).
(11) P. A. Stadler, A. J. Frey, F. Troxler, and A. Hofmann, *ibid.*, **47**, 756 (1964).
(12) A. Hofmann, P. Stadler, F. Troxler, A. Frey, and H. Ott, French Patent 1,298,156 (1962) and Swiss Patent 396,024 (1966).
(13) F. Troxler and A. Hofmann, *Helv. Chim. Acta*, **40**, 2160 (1957).
(14) T. B. Windholz and D. B. R. Johnston, *Tetrahedron Lett.*, 2555 (1967).
(15) F. Troxler and A. Hofmann, *Helv. Chim. Acta*, **40**, 1706 (1957).
(16) F. Troxler and A. Hofmann, *ibid.*, **40**, 1721 (1957).
(17) A. Hofmann and F. Troxler, British Patent 996,062 (1965).
(18) H. L. Borison and S. C. Wang, *Pharmacol. Rev.*, **5**, 193 (1953).
(19) H. W. van Urk, *Pharm. Weekbl.*, **66**, 473 (1929).
(20) M. I. Smith, *Pub. Health Rep.*, **45**, 1466 (1930).

6-Substituted 5-Chloro-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyrazin-2-ones with Hypotensive Activity

James H. Jones,* Wilbur J. Holtz, and Edward J. Cragoe, Jr.

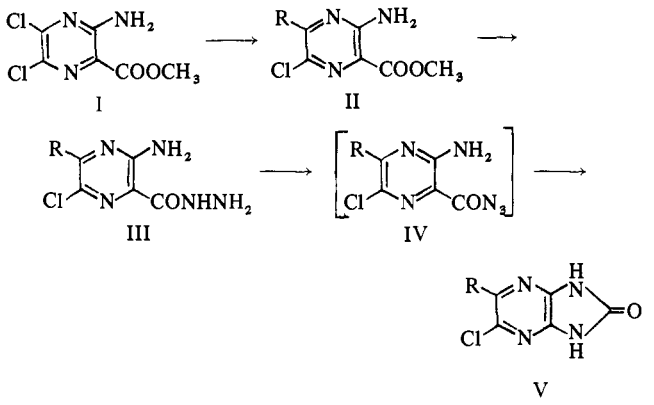
Merck Sharp and Dohme Research Laboratories, Division of Merck and Company, Inc., West Point, Pennsylvania 19486.
Received September 1, 1972

The thermal Curtius reaction of a 3-aminopyrazine-2-carboxylic acid azide proceeds with intramolecular cyclization to provide a versatile synthetic route to a wide variety of 1,3-dihydro-2*H*-imidazo[4,5-*b*]-pyrazin-2-ones. Many compounds in this series are potent hypotensive agents in animals; they are also inhibitors of the enyzme cyclic AMP phosphodiesterase *in vitro*.

Very few imidazo[4,5-*b*]pyrazines have been reported in the literature[1-3] and no good general method has been available for preparing compounds in this most interesting heterocyclic class. We have found that the Curtius reaction of a 3-aminopyrazine-2-carboxylic acid azide (Scheme I) proceeds with intramolecular cyclization to provide, in good yield, a wide variety of the subject compounds. We will report here only the 6-substituted 5-chloro-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyrazin-2-ones.† Most of these compounds are potent inhibitors[4] of cyclic AMP phosphodiesterase *in vitro*, and *in vivo* these compounds lower blood pressure because of peripheral vasodilatory properties. Most of the compounds also possess bronchodilatory and cardiac-stim-

†This tautomer most probably represents the true structure of the compounds and is named according to Chemical Abstracts nomenclature.

Scheme I

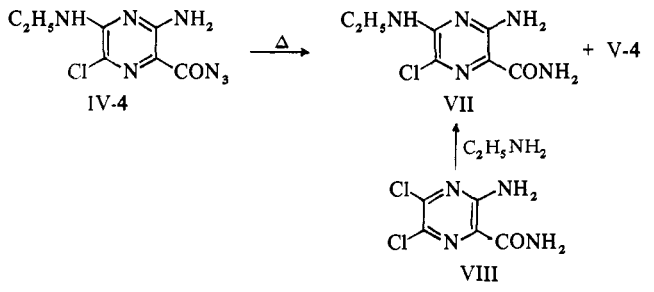


ulant properties. Only the hypotensive effects will be reported here as the details of the pharmacology are to be reported elsewhere.‡

Chemistry. Most of the 6-substituted 5-chloro-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyrazin-2-ones (V) were prepared by the thermal Curtius rearrangement of the appropriate pyrazinecarboxylic acid azide. We found 2-methoxyethanol to be the best solvent for these reactions. For the preparation of V-**44** (R = $Et_2NCH_2CH_2NH$), and similar compounds, by this rearrangement it was necessary to have a slight excess of acid (HCl or maleic) present in the 2-methoxyethanol, which then provided the acid salt of the desired product.

As indicated in Scheme II the preparation of V-**4** afforded

Scheme II



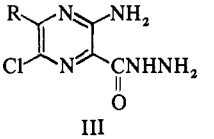
a by-product which was proved to be 3-amino-5-ethylamino-6-chloropyrazinamide (VII) by synthesis of this amide from 3-amino-5,6-dichloropyrazinamide (VIII). This is interesting because we believe this is the first time an amide has been isolated from a thermal Curtius rearrangement. We feel this indicates a finite existence for the nitrene[5] as an intermediate in this particular Curtius reaction. We have not investigated the extent of amide formation in the other Curtius reactions in this series.

The azides IV in this study were prepared from the corresponding pyrazinoic acid hydrazides. Usually the reaction was carried out in dilute hydrochloric acid by adding aqueous sodium nitrite and the azide precipitated from the solution at once (method 4A). These azides were isolated and dried; however, when attempting to take their melting points they detonated sharply; for this reason they were not purified further. The azides of certain compounds (*i.e.*, III-**44** and similar compounds) were prepared in 2-methoxyethanol containing a slight excess of HCl by adding isoamyl nitrite. The resulting azide was used *in situ*.

The pyrazinoic acid hydrazides (Table I) were prepared from the corresponding esters by the procedure described

‡L. S. Watson, unpublished results.

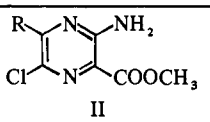
Table I[f]



No.	% yield	Recrystn solvent	Mp, °C	Formula[g] (analyses)
1[a]				
2[a]				
3[d]	90	AcOH	230-231	$C_8H_{11}ClN_6O_2$ (mono Ac)
4	96	*i*-PrOH	168-170	$C_7H_{11}ClN_6O$
5	98	EtOH	171-173	$C_8H_{13}ClN_6O$
6	98	EtOH-H_2O	132-134	$C_8H_{13}ClN_6O$
7	80	EtOH	158-160	$C_8H_{11}ClN_6O$
8	98	EtOH	166-168	$C_9H_{15}ClN_6O$
9	62	EtOH	192-193	$C_9H_{15}ClN_6O$
10	83	EtOH	181-182	$C_9H_{13}ClN_6O$
11	77	EtOH	143-145	$C_{10}H_{15}ClN_6O$
12	88	EtOH	151-154	$C_8H_{13}ClN_6O_2$
13	90	EtOH	184-185	$C_7H_{11}ClN_6O_2$
14	95	EtOH	194-195	$C_{11}H_{11}ClN_6O$
15	96	*i*-PrOH	158-160	$C_{12}H_{12}Cl_2N_6O$
16[a]				
17	87	*i*-PrOH	141-143	$C_9H_{15}ClN_6O$
18	96	EtOH-H_2O	134-136	$C_8H_{13}ClN_6O$
19	68	EtOH	133-136	$C_9H_{15}ClN_6O$
20	80	EtOH	122-125	$C_8H_{13}ClN_6O_2$
21	70	NaOH-AcOH	>300	$C_5H_6ClN_5O_2$
22[b]	79	CH_3CN	228-230 dec	$C_6H_8ClN_5O_2$
23	77	DMF	218-220	$C_5H_6ClN_5OS$ (N)
24	98	$MeOCH_2CH_2OH$	240-242	$C_6H_8ClN_5OS$
25	91	EtOH	196-199	$C_7H_{10}ClN_5OS$
26	89	EtOH	166-168	$C_8H_{12}ClN_5OS$
27	40	EtOH	265-267	$C_{10}H_{16}ClN_5OS \cdot HCl$
28	81	EtOH-H_2O	200-203	$C_7H_{10}ClN_5O_2S$
29[c]	76	EtOH	150-153	$C_9H_{12}ClN_5O_3S$
30[c]	93	$MeOCH_2CH_2OH$	248-250 dec	$C_7H_7ClN_6OS$
31[c]	88	CH_3NO_2	195-197	$C_{13}H_{12}ClN_5O_2S$
32[c]	80	EtOH	190-200 dec	$C_9H_{13}ClN_7OS$
33	80	HCl-NH_4OH	245-248	$C_9H_{14}ClN_7O_2$
34[e]				
35	45	C_6H_5	161-162	$C_{10}H_{16}ClN_7O_2$
36[e]				
37	70	*i*-PrOH	175-176	$C_{11}H_{18}ClN_7O_2$
38	43	EtOH	220-222	$C_{10}H_{16}ClN_7O_2$
39	78	EtOH	163-165	$C_8H_{14}ClN_7O$
40	59	C_6H_6	114-115	$C_9H_{16}ClN_7O$
41	40	EtOAc	129-130	$C_{10}H_{18}ClN_7O$
42	85	EtOH	161-163	$C_9H_{16}ClN_7O$
43	56	C_6H_6	113-115	$C_{11}H_{20}ClN_7O$
44	91	Cyclohexane	95-97	$C_{11}H_{20}ClN_7O$
45	68	Cyclohexane	87-88	$C_{12}H_{22}ClN_7O$
46	62	BuCl	77-78	$C_{11}H_{20}ClN_7O$
47	60	AcOEt	116-118	$C_{12}H_{22}ClN_7O$
48	70	EtOH	189-190	$C_{10}H_{16}ClN_7O$ (C, H)
49	84	CH_3CN	168-170	$C_{11}H_{18}ClN_7O$
50	54	EtOH	190-192	$C_9H_{13}ClN_6O_2$
51	91	C_6H_6	120-121	$C_{11}H_{18}ClN_7O$
52	89	EtOH	183-184	$C_{12}H_{20}ClN_7O_2$
53	61	EtOH	167-169	$C_{13}H_{23}ClN_8O$
54	92	EtOH	213-214	$C_{11}H_{12}ClN_7O$
55	93	EtOH	191-192	$C_{11}H_{12}ClN_7O$
56	69	EtOH	208-210	$C_{11}H_{12}ClN_7O$
57	58	EtOH	137-138	$C_{12}H_{14}ClN_7O$
58	61	EtOH	230-232	$C_{12}H_{14}ClN_7O$
59	67	C_6H_6	109-111	$C_{13}H_{16}ClN_7O$
60	69	C_6H_6	124-125	$C_{12}H_{14}ClN_7O$
61	71	H_2O	300 dec	$C_6H_9ClN_8O \cdot 2HCl$ (C, H)
62[e]				

[a]See footnote ‡. [b]Prepared by method 3C. [c]Prepared by method 3B. [d]The rest of these hydrazides were prepared by method 3A with the exceptions noted. [e]The corresponding hydrazide was not prepared. [f]The corresponding R groups are listed in Table III. [g]All compounds were analyzed for C, H, and N, and analyses were found within limits.

Table II



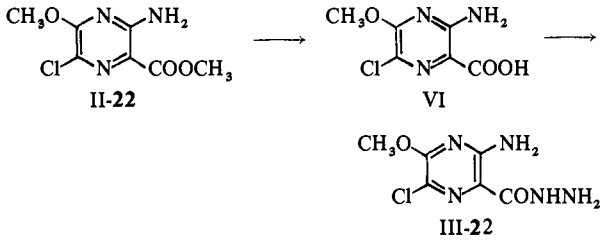
II

No.	R[f]	% yield	Recrystn solvent	Mp, °C	Formula[g]
1-28[a]					
9-32[b]					
33		57	CH_3CN	208-210 dec	$C_{10}H_{14}ClN_5O_3$
34[b]					
35[c]					
36[b]					
37[c]					
38[d]		27	C_6H_6	180-182	$C_{11}H_{16}ClN_5O_3$
39	P[e]$CH_2CH_2N(CH_3)$-	57	EtOH	166-168	$C_{17}H_{16}ClN_5O_4$
40	$PCH_2CH_2N(C_2H_5)$-	78	EtOAc	173-175	$C_{18}H_{18}ClN_5O_4$
41	$PCH_2CH_2N[CH(CH_3)_2]$-	40	C_6H_6	169-170	$C_{19}H_{20}ClN_5O_4$
42[a]					
43		50	EtOH	223-224	$C_{12}H_{20}ClN_5O_2 \cdot HCl$
44		82	Cyclohexane	114-116	$C_{12}H_{20}ClN_5O_2$
45		74	*i*-PrOH	157-158	$C_{13}H_{22}ClN_5O_2 \cdot C_4H_4O_4$
46		69	*i*-PrOH	203-204	$C_{12}H_{20}ClN_5O_2 \cdot HCl$
47		50	Cyclohexane	51-54	$C_{13}H_{22}ClN_5O_2$
48[a]					
49		94	BuCl	143-145	$C_{12}H_{18}ClN_5O_2$
50		88	EtOH	196-198	$C_{10}H_{13}ClN_4O_3$
51		58	C_6H_6-cyclohexane	121-122	$C_{12}H_{18}ClN_5O_2$
52		86	C_6H_6	158-160	$C_{13}H_{20}ClN_5O_3$
53		71	EtOAc	148-149	$C_{14}H_{23}ClN_6O_2$
54		89	C_6H_6	199-201	$C_{12}H_{12}ClN_5O_2$
55		92	C_6H_6	170-171	$C_{12}H_{12}ClN_5O_2$
56		75	C_6H_6	154-156	$C_{12}H_{12}ClN_5O_2$
57		82	C_6H_6	114-115	$C_{13}H_{14}ClN_5O_2$
58		62	EtOAc	192-194	$C_{13}H_{14}ClN_5O_2$
59		77	C_6H_6	120-122	$C_{14}H_{16}ClN_5O_2$
60		53	C_6H_6	110-113	$C_{13}H_{14}ClN_5O_2$
61	$CH_3CONHC(=NH)NH$-	56	CH_3CN	246-248	$C_9H_{11}ClN_6O_3$
62[b]					

[a]Reference 7. [b]No corresponding ester prepared. [c]Ester used without purification. [d]The rest of these esters were prepared by method 2. [e]P stands for phthalimido. [f]The corresponding R groups are listed in Table III. [g]All compounds were analyzed for C, H, and N and analyses were found within limits.

previously.[6] It was necessary to convert the ester II-22 to the corresponding acid (Scheme III) because of the labile 5-

Scheme III



II-22 VI III-22

methoxy group. Using *N-tert*-butyl-5-methylisoxazolium perchlorate as the condensing agent, this acid VI afforded the desired hydrazide III-22 under very mild conditions. The sodium salt of 3-amino-5-mercapto-6-chloropyrazinoic acid hydrazide (III-23) reacted with the appropriate halo compounds to afford the 5-(*R,S*)-hydrazides III-29-32.

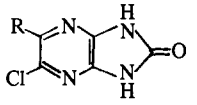
Many of the esters (Table II) used in this study have been described,[7] and the others reported here were prepared by the same method using DMSO as the solvent.

The procedure of Tkaczynski[8] was used to prepare 1-methyl-1-acetylethylenediamine and 1-ethyl-1-acetylethylenediamine. These amines afforded the imidazopyrazines V-36 and V-37 when carried through the reaction sequence shown in Scheme I. The isomeric imidazopyrazines V-39 and V-40 were prepared starting with the amines *N*-(2-methylaminoethyl)phthalimide and *N*-(2-ethylaminoethyl)-phthalimide. The phthalimide group was removed by the hydrazine during the preparation of the hydrazides from the esters prepared from these amines.

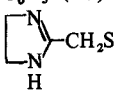
Structure-Activity Relationships. All the compounds in this series were evaluated for hypotensive activity§ in a standard cardiovascular dog assay. All data were obtained from anesthetized (vinbarbital), vagotomized mongrel dogs. Blood pressure was measured through an indwelling, left carotid artery catheter. All compounds were injected intravenously through an indwelling catheter (right femoral vein), the test dose being 20 mg/kg. Two animals were used at this dose; the pressure was monitored for 120 min and the average decrease over this period was used in assigning the numerical evaluations. The numerical evaluation of each test was based on the following scale related to the decrease in blood pressure measured in millimeters of mercury: ± = 0-19, 1 = 20-29, 2 = 30-39, 3 = 40-49, 4 = >50. The results of the cardiovascular assay are recorded in Table III. From this table it can be seen that small monoalkylamino or dialkylamino substituents in the 6 position (*i.e.*, V-4,6,17) afford compounds with potent hypotensive activity. Compounds with excellent activity were obtained also when the 6 substituent was monoalkyl- or dialkylaminoethylamino (*i.e.*, V-36,37,42). A third class of quite active compounds was found when the 6 substituent was pyridylalkylamino, such as V-54-56. For certain compounds in each of these

§Dr. L. S. Watson and his associates conducted these studies and supplied the data.

Table III



V

Inhib[b] C-AMP-PPD, %	Hypotensive score	No.	R	% yield	Recrystn solvent	Mp, °C	Formula[a]	Synthetic method
0	±	**1**	H	93	EtOAc	280 dec	$C_5H_3ClN_4O$	4a
29	±	**2**	NH_2	78	H_2O	>300	$C_5H_4ClN_5O$	4a
45	4	3	CH_3NH	22	EtOAc	>280	$C_6H_6ClN_5O$	4a
70	4	4	C_2H_5NH	34	EtOH-H_2O	248-249	$C_7H_8ClN_5O$	4a
70	4	5	C_3H_7NH	41	EtOAc	215-216	$C_8H_{10}ClN_5O$	4a
71	4	**6**	$(CH_3)_2CHNH$	42	CH_3CN	249 dec	$C_8H_{10}ClN_5O$	4a
46	3	7	$CH_2{=}CHCH_2NH$	56	CH_3CN	284-285	$C_8H_8ClN_5O$	4a
57	3	8	n-C_4H_9NH	15	Et_2O	195-198	$C_9H_{12}ClN_5O$	4a
	±	9	$(CH_3)_2CNH$	10	C_6H_6	235	$C_9H_{12}ClN_5O$	4a
50	3	10	c-C_4H_8N	19	EtOAc	228 dec	$C_9H_{10}ClN_5O$	4a
62	4	**11**	c-C_5H_9-NH	30	CH_3CN	256-257	$C_{10}H_{12}ClN_5O$	4a
25	3	**12**	$CH_3OCH_2CH_2NH$	39	EtOH	229-231	$C_8H_{10}ClN_5O_2$	4a
20	2	**13**	$HOCH_2CH_2NH$	32	EtOH	250-251	$C_7H_8ClN_5O_2$	4a
	1	**14**	C_6H_5NH	17	EtOAc	257	$C_{11}H_8ClN_5O$	4a
0	±	**15**	p-$ClC_6H_4CH_2NH$	29	$MeOCH_2CH_2OH$	270-272	$C_{12}H_9Cl_2N_5O$	4a
23	3	**16**	$(CH_3)_2N$	35	EtOH	222-224 dec	$C_7H_8ClN_5O$	4a
60	4	**17**	$(C_2H_5)_2N$	56	EtOAc	207-208 dec	$C_9H_{12}ClN_5O$	4a
32	4	**18**	$C_2H_5N(CH_3)$	63	EtOAc	203-205	$C_8H_{10}ClN_5O$	4a
31	2	**19**	$C_3H_7N(CH_3)$	19	EtOAc	177-178	$C_9H_{12}ClN_5O$	4a
	±	**20**	$HOCH_2CH_2N(CH_3)$	60	EtOH	188-190	$C_8H_{10}ClN_5O_2$	4a
	0	**21**	HO	27	EtOH	>300	$C_5H_3ClN_4O_2$	4a
	1	**22**	CH_3O	70	EtOH	315 dec	$C_6H_5ClN_4O_2$	4a
	2	**23**	HS	58	NH_4OH-HCl	300	$C_5H_3ClN_4OS \cdot 0.5H_2O$	4a
21	2	**24**	CH_3S	44	EtOH	308 dec	$C_6H_5ClN_4OS$	4a
	1	**25**[a]	C_2H_5S	54	EtOAc	256-258	$C_7H_7ClN_4OS$	4a
23	±	**26**	C_3H_7S	60	EtOH	244-246	$C_8H_9ClN_4OS$	4a
0	0	**27**	$C_5H_{11}S$	36	EtOH	232-233	$C_{10}H_{13}ClN_4OS$	4a
	±	**28**	$HOCH_2CH_2S$	74	EtOH	236-238	$C_7H_7ClN_4O_2S$	4a
	0↑	**29**	$C_2H_5OOCCH_2S$	68	EtOAc	206-208	$C_9H_9ClN_4O_3S$	4a
	0↑	**30**	$NCCH_2S$	87	CH_3CN	250-252	$C_7H_4ClN_5OS$	4a
	0↑	31	$C_6H_5C(=O)CH_2S$	75	CH_3CN	245-247	$C_{13}H_9ClN_4O_2S$	4a
	0↑	32		48	H_2O	292-293	$C_9H_9ClN_6OS \cdot HCl \cdot 0.5H_2O$	4a
	2	33	$CH_3CONHCH_2CH_2NH$	50	H_2O	235-238 dec	$C_9H_{11}ClN_6O_2$	4a
10	3	34	$NH_2CH_2CH_2NH$	79	H_2O	>300	$C_7H_9ClN_6O \cdot HCl$	4c
	1	**35**	$CH_3CON(CH_3)CH_2CH_2NH$	62	MeOH-H_2O	227-228	$C_{10}H_{13}ClN_6O_2$	4a
0	3	**36**	$CH_3NHCH_2CH_2NH$	21	EtOH	247-248	$C_8H_{11}ClN_6O \cdot HCl$	4c
c	3	37	$C_2H_5NHCH_2CH_2NH$	25	$MeOCH_2CH_2OH$	247-248	$C_9H_{13}ClN_6O \cdot HCl$	4c
c	1	**38**	$CH_3CONHCH_2CH_2CH_2NH$	31	EtOH	222-223	$C_{10}H_{13}ClN_6O_2$	4a
c	3	**39**	$NH_2CH_2CH_2N(CH_3)$	59	EtOH-H_2O	304-306 dec	$C_8H_{11}ClN_6O \cdot HCl$	4b
c	1	**40**	$NH_2CH_2CH_2N(C_2H_5)$	80	*i*-PrOH-H_2O	281-282	$C_9H_{13}ClN_6O \cdot HCl$	4b
c	0	**41**	$NH_2CH_2CH_2N[CH(CH_3)_2]$	38	EtOH-H_2O	274-276	$C_{10}H_{15}ClN_6O \cdot HCl$	4b
19	3	**42**	$(CH_3)_2NCH_2CH_2NH$	35	EtOH	219-220	$C_9H_{13}ClN_6O$	4b

2	43	$(CH_3)_2NCH_2CH_2CH_2CH_2NH$	13	EtOH–H_2O	278–279	$C_{11}H_{17}ClN_6O\cdot H_2O$	4b
2	44	$(C_2H_5)_2NCH_2CH_2NH$	60	EtOH	276–278	$C_{11}H_{17}ClN_6O\cdot HCl$	4b
0	45	$C_4H_9N(CH_3)CH_2CH_2NH$	47	*i*-PrOH–H_2O	257–258	$C_{12}H_{16}ClN_6O\cdot HCl$	4b
1	46	$(CH_3)_2NCH_2CH_2CH_2N(CH_3)$	50	*i*-PrOH–H_2O	229–230	$C_{11}H_{17}ClN_6O\cdot HCl\cdot 0.5H_2O$	4b
0	47	$(C_2H_5)_2NCH_2CH_2N(CH_3)$	80	*i*-PrOH–H_2O	244 dec	$C_{12}H_{19}ClN_6O\cdot HCl$	4b
10	48	CH_3-c-$N(CH_2CH_2)_2N$	10	MeOCH$_2$CH$_2$OH	275 dec	$C_{10}H_{13}ClN_6O$	4b
0	49	C_2H_5-c-$N(CH_2CH_2)_2N$	34	H_2O	307 dec	$C_{11}H_{15}ClN_6O\cdot HCl$	4b
1	50	c-$O(CH_2CH_2)_2N$	17	EtOAc	272–273	$C_9H_{10}ClN_5O_2$	4b
1	51	c-C_4H_8N-CH_2CH_2NH	10	EtOH–H_2O	148–149	$C_{11}H_{15}ClN_6O\cdot C_4H_4O_4\cdot H_2O$ (C, H)	4b
±	52	c-$O(CH_2CH_2)_2N$-CH_2CH_2NH	13	EtOH–H_2O	158–160	$C_{12}H_{17}ClN_6O_2\cdot C_4H_4O_4\cdot 0.5H_2O$	4b
3	53	CH_3-c-$N(CH_2CH_2)_2N$-$CH_2CH_2CH_2NH$	27	EtOH–H_2O	244–245	$C_{13}H_{20}ClN_7O$	4b
28	54	C_5H_5N-*o*-CH_2NH	45	EtOH–H_2O	280	$C_{11}H_9ClN_6O\cdot HCl$	4b
68	55	C_5H_4N-*m*-CH_2NH	36	MeOH–H_2O	271–272	$C_{11}H_9ClN_6O\cdot HCl\cdot H_2O$	4b
68	56	C_5H_4N-*p*-CH_2NH	29	EtOH	291–293	$C_{11}H_{10}Cl_2N_6O$	4b
3	57	C_5H_4N-*o*-CH_2CH_2NH	48	EtOAc	235–236	$C_{12}H_{11}ClN_6O$	4b
1	58	C_5H_4N-*p*-CH_2CH_2NH	22	*i*-PrOH–H_2O	256–257	$C_{12}H_{11}ClN_6O\cdot HCl$	4b
3	59	C_5H_4N-*o*-$CH_2CH_2N(CH_3)$	35	EtOH–H_2O	251–252	$C_{13}H_{13}ClN_6O\cdot HCl$	4b
3	60	C_5H_5N-*o*-$CH_2N(CH_3)$	25	*i*-PrOH–H_2O	255–256	$C_{12}H_{11}ClN_6O\cdot HCl$	4b
10	61	$NH_2C(=NH)NH$	59	H_2O	>300	$C_6H_6ClN_7O\cdot HCl$	4b
0	62	$CH_3CON(C_2H_5)$	42	CH_3CN	286–288 dec	$C_9H_{10}ClN_5O_2$	6

[a] All compounds were analyzed for C, H, and N, and analyses were found within limits. [b] See footnote *b*, Table IV. [c] These compounds were very weak inhibitors by this protocol; thus only a few were tested.

three classes we have recorded in Table III the values of the per cent inhibition of the enzyme cyclic-AMP phosphodiesterase.[4] The compounds were tested at $1 \times 10^{-3} M$ concentration and the value is an average of two tests at that concentration. We feel these values correlate fairly well with the hypotensive scores with the exception of compounds such as V-**34**,**36**,**42**. Why these compounds with basic side chains are such weak inhibitors in this protocol is uncertain since they do share the other properties of the compounds in this series except, of course, for the cardiac stimulant properties.

In Table IV are recorded the bronchodilatory activity, phosphodiesterase inhibitory activity, and the hypotensive score for three representative compounds from this series, as well as for theophylline. Table IV shows that our compounds are quite active in these tests. Additionally, it was found that compound V-**42** has no cardiac stimulant properties *in vivo* at doses that cause marked hypotension or considerable bronchodilation. It should be noted that V-**42** scored below theophylline in the phosphodiesterase assay. This compound shows rather remarkable specificity since compounds V-**4**, V-**54**, and theophylline all exhibit pronounced cardiac stimulant properties. Several of these compounds were tested by the oral route in dogs and primates and the hypotensive properties were also evident by this test procedure.‡

Experimental Section#

Details of the synthesis of the new compounds are presented. Where several compounds of one type have been prepared by a particular method, only one example is given. Pertinent data regarding each compound is recorded in Tables I–III.

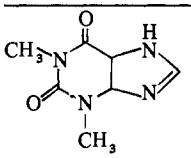
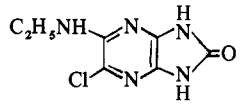
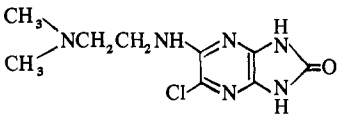
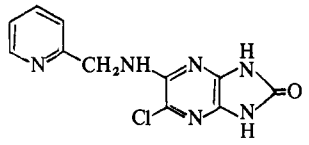
Method 1. Amines. A. Most of the amines used in this study were commercially available. **B.** The amines used to prepare II-35 and II-37 were synthesized by the procedure of Tkaczynski.[8] **C. *N*-(2-Methylaminoethyl)phthalimide Hydrochloride** (used to prepare II-39). An intimate mixture of phthalimide (2.9 g, 0.02 mol) and *N*-methylethylenediamine (1.64 g, 0.02 mol) was heated on the steam bath for 3 hr and then at 130° for 1 hr. The resulting solid was dissolved in hot EtOH and filtered, and to the filtrate was added a solution of 8 *N* EtOH–HCl (3 ml) which precipitated the product. Recrystallization from EtOH yielded 1.6 g (33%), mp 246°.[9] **D. *N*-(2-Ethylaminoethyl)phthalimide hydrochloride (IX)** (used for II-40) was prepared by the above procedure in 65% yield, mp 232–234° (from *i*-PrOH). *Anal.* ($C_{12}H_{15}ClN_2O_2$) C, H, N. **E. *N*-(2-Ethylaminoethyl)phthalimide hydrochloride** (used for II-**40**) was prepared by the above procedure in 67% yield, mp 192–193° (from *i*-PrOH). *Anal.* ($C_{13}H_{17}ClN_2O_2$) C, H, N.

Method 2. Methyl 3-Amino-5-substituted 6-Chloropyrazinoates (II). These esters were prepared by the procedure reported previously[7] using I, the appropriate amine, and DMSO as the solvent.

Method 3. 3-Amino-5-substituted 6-Chloropyrazinoic Acid Hydrazides (III). A. Most of these hydrazides were prepared by essentially the procedure described in our paper[6] using 64% hydrazine and alcohol as solvent. **B.** The synthesis of compounds III-**29**–**32** is exemplified by the preparation of **3-amino-5-ethoxycarbonylmethylmercapto-6-chloropyrazinoic acid hydrazide** (III-**29**). Compound III-**23** (2.1 g, 0.01 mol) was dissolved in EtOH–H_2O (40 ml, 1:1) containing 5% NaOH (10 ml) and then ethyl bromoacetate (1.67 g, 0.01 mol) was added. Stirring at room temperature for 1.5 hr afforded a pale yellow solid that was recovered by filtration, washed with water, dried, and recrystallized. For the preparation of compounds III-**30**–**32** the appropriate halo compound was substituted for ethyl bromoacetate. **C. 3-Amino-5-methoxy-6-chloropyrazinoic Acid Hydrazide (III-22). Step 1. 3-Amino-5-methoxy-6-chloropyrazinoic Acid (VI).** To a water (200 ml) solution of KOH (1.2 g, 0.021 mol) heated to boiling was added II-**22** (4.3 g, 0.02 mol); boiling was continued an additional 10 min and then the reaction was filtered. The cooled filtrate was acidified (dilute HCl) which precipitated the product: yield 3.0 g (75%); mp 222–224° dec (from

#Mr. K. B. Streeter, Mr. Y. C. Lee, and their staff have provided the analytical data. The melting points are corrected (open capillaries).

Table IV

	ED_{50},[a] mg/kg	Inhib[b] C-AMP-PPD, %	Hypotensive score
 Theophylline	51.0	23	
 V-4	1.8	70	+4
 V-42	1.6	19	+3
 V-54	2.4	28	+3

[a] Histamine-induced bronchoconstriction in dog. The test procedure involved anesthetized dogs under forced respiration while intrapulmonary pressure changes were recorded automatically. Standard intravenous doses of histamine were used to obtain control responses; the test compound was given intravenously 2 min prior to a subsequent challenge. Doses were given in increasing increments to obtain a dose-response curve and the ED_{50} was extrapolated from the graph. Dr. N. N. Share and Mr. R. A. Hall supplied these data. [b] Inhibition of cyclic AMP phosphodiesterase from steer heart.[4] Compounds tested at $1 \times 10^{-3} M$ concentration. Dr. L. Mandel and his associates supplied these data.

EtOH). *Anal.* ($C_6H_6ClN_3O_3$) C, H, N. **Step 2. 3-Amino-5-methoxy-6-chloropyrazinoic Acid Hydrazide (III-22).** The acid VI (2.0 g, 0.01 mol) was dissolved in DMF by the addition of triethylamine (2.5 g, excess). To the solution was added *N-tert*-butyl-5-methylisoxazolium perchlorate (2.39 g, 0.01 mol) and the reaction was allowed to stand at room temperature for 24 hr and then poured into water which caused the ester to separate. The yield was 2.7 g (79%), mp 155–156° (from BuCl); however, the compound was not analyzed. This ester (1.7 g, 0.005 mol) was dissolved in THF (10 ml) and 64% hydrazine (0.3 ml) was added dropwise. The product separated at once; it was recovered by filtration, dried, and recrystallized.

Method 4. 6-Substituted 5-Chloro-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyrazin-2-ones (V). A. 6-Ethylamino-5-chloro-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyrazin-2-one (V-4). To a stirred solution of III-4 (11.5 g, 0.05 mol) in 1 *N* HCl (250 ml) was added a solution of $NaNO_2$ (3.5 g, 0.05 mol) in H_2O (20 ml) over a period of 15 min. 3-Amino-5-ethylamino-6-chloropyrazinoic acid azide separated immediately; it was recovered by filtration and dried. Because of the explosive nature of the azides, no purification was attempted in most cases. The crude azide was dissolved in methoxyethanol (200 ml), stirred, and heated on the steam bath. At 90°, an exothermic reaction occurred; heating was stopped and mild cooling used to keep the reaction temperature below 110°. After the exothermic reaction, steam heating was continued for 30 min and then the solvent was removed *in vacuo*. Water was added to the resulting black residue and a tan solid separated which was recovered by filtration, dried, and recrystallized. **B. 6-(2-Diethylaminoethylamino)-5-chloro-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyrazin-3-one Hydrochloride (V-44).** To a stirred solution of III-44 (21.0 g, 0.07 mol) in methoxyethanol (250 ml) containing 8 *N* EtOH–HCl (25 ml) was added isoamyl nitrite (8.2 g, 0.07 mol) over a period of 15 min. The reaction was stirred at room temperature an additional 15 min and then heated on the steam bath for 1.5 hr. The solvent was removed *in vacuo* and the residue washed out with EtOH, dried, and recrystallized. **C. 6-(2-Aminoethylamino-5-chloro-1,3-dihydro-2*H*-imidazo[4,5-*b*]-pyrazin-2-one Hydrochloride (V-34).** Compound V-33 (2.7 g, 0.01 mol) was suspended in 4 *N* HCl (75 ml), stirred, and heated on the steam bath for 2 hr. After about 30 min a solution was obtained and toward the end of the heating period the product began to separate. The reaction was then cooled; the product was recovered by filtration and recrystallized.

Method 5. 3-Amino-5-ethylamino-6-chloropyrazinamide (VII). Crude V-4 (8 g) was dissolved in dioxane (200 ml) and the solution passed over an alumina chromatography column. Continued elution with dioxane removed a pale yellow band leaving V-4 still at the top of the column. Evaporation of the solvent afforded crude VII, yield 2.0 g (25%), mp 190°. Recrystallization from 2-propanol gave material melting at 195–198°. *Anal.* ($C_7H_{10}ClN_5O$) C, H, N. The identity of this compound was established by its preparation from 3-amino-5,6-dichloropyrazinamide (VIII)[7] according to the following procedure. To a stirred solution of VIII (2.0 g, 0.01 mol) in DMSO (25 ml) was added (70%) ethylamine (3 ml); the reaction was stirred at room temperature for 1 hr, heated on the steam bath for 30 min, and then poured into water (150 ml). The resulting solid was recovered by filtration and dried, yielding 2.0 g (93%), mp 195–198°. Recrystallization from 2-propanol did not improve this melting point. A mixture melting point with the product above was not depressed, melting at 195–198°. The ir spectra of these samples were identical in all respects.

Method 6. 6-(*N*-Ethylacetamido)-5-chloro-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyrazin-2-one (V-62). Compound V-4 (1.0 g, 0.0047 mol) was suspended in isopropenyl acetate (40 ml), concentrated H_2SO_4 (2 drops) was added, and the reaction was heated on the steam bath for 15 min. The cooled reaction was filtered to recover the product which was purified by recrystallization. The position of the acetyl group was clearly established by inspection of the nmr spectra of the compound.

References

(1) E. Schipper and A. R. Day, *J. Amer. Chem. Soc.*, **74**, 350 (1952).
(2) F. R. Muehlmann and A. R. Day, *ibid.*, 78, 242 (1956).
(3) R. H. Martin and Z. Tarasiezsha, *Bull. Soc. Chim. Belg.*, 66, 136 (1959).
(4) L. R. Mandel, *Biochem. Pharmacol.*, **20**, 3413 (1971).
(5) G. L'Abbé, *Chem. Rev.*, **69** (3), 345 (1969).
(6) K. L. Shepard, J. W. Mason, O. W. Woltersdorf, Jr., J. H. Jones, and E. J. Cragoe, Jr., *J. Med. Chem.*, **12**, 280 (1969).
(7) E. J. Cragoe, Jr., O. W. Woltersdorf, Jr., J. B. Bicking, S. F. Kwong, and J. H. Jones, *ibid.*, **10**, 66 (1967).
(8) T. Tkaczynski, *Acta, Polon. Pharm.*, **19**, 277 (1962); *Chem. Abstr.*, 59, 6239 (1963).
(9) P. C. Jocelyn, *J. Chem. Soc.*, 3305 (1957).