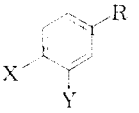
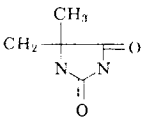
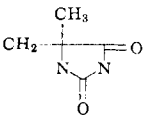
TABLE II



No.	X	Y	R	Yield, %	Mp or bp (mm), °C	Cryst solvent	Formula	Calcd, %: C	H	N	Found, %: C	H	N
1	CH_3	H		20	222–223	60% EtOH	$C_7H_8N_2O_2$	56.0	6.17	12.8	55.8	6.18	12.7
2	F	H		62	212–213.5	60% EtOH	$C_6H_5FN_2O_2$	59.5	4.00	12.6	59.3	4.00	12.5
3	F[a]	F	CH_2Br	57	59–61 (3.5)		[b]						
4	F	Cl	CH_2Br	72	63–65 (0.55)		[b]						
5	F	Br	CH_2Br	50	130 (0.5)		$C_7H_5BrFNO_2$	36.0	2.15	34.2[c]	35.8	2.39	34.3[c]
6	H	Br	$CH_2C(NHAc)(COOEt)_2$	66	97–99	EtOH	$C_{16}H_{20}BrNO_5$	49.8	5.22	3.63	49.9	5.31	3.56
7	F	F	$CH_2C(NHAc)(COOEt)_2$	41	145–146	EtOH	$C_{16}H_{19}F_2NO_5$	56.0	5.58	4.08	55.9	5.67	4.33
8	F	Cl	$CH_2C(NHAc)(COOEt)_2$	38	128	EtOH	$C_{16}H_{19}ClFNO_5$	53.4	5.32	3.90	53.6	5.34	4.01
9	F	Br	$CH_2C(NHAc)(COOEt)_2$	30	118–119.5	EtOH	$C_{16}H_{19}BrFNO_5$	47.5	4.74	3.47	47.4	4.47	3.51
10	CH_3	H	$CH_2C(CH_3)(NH_3^+Cl^-)COOH$	41	252–254	50% EtOH	$C_5H_{10}NO_2 \cdot HCl$	57.5	7.02	6.10	57.4	7.16	6.22
11	F	H	$CH_2C(CH_3)(NH_2)COOH$	43	265–268	Water	$C_5H_8FNO_2$	60.9	6.14	7.10	61.1	6.26	7.20
12	H	Br	$CH_2CH(NH_2)COOH$	61	226–228	50% EtOH	$C_5H_8BrNO_2$	44.1	4.13	5.74	44.1	4.10	5.69
13	F	F	$CH_2CH(NH_3^+Cl^-)COOH$	79	211–212		$C_5H_6F_2NO_2 \cdot HCl$	45.5	4.24	5.89	45.3	4.39	5.85
14	F	Cl	$CH_2CH(NH_3^+Cl^-)COOH$	85	202–204.5		$C_5H_6ClFNO_2 \cdot HCl$	42.5	3.97	5.51	42.8	4.12	5.30
15	F	Br	$CH_2CH(NH_2)COOH$	42	164.5–165.5	Water	$C_5H_6BrFNO_2$	41.2	3.16	5.35	41.4	3.17	5.29

[a] Prepared from 3,4-difluorotoluene: D. Robertson, *J. Org. Chem.*, **24**, 2051 (1959). [b] Compounds were found to be unstable and were used immediately in the next reaction. [c] Bromine analysis.

pounds **13** and **14** were obtained as the hydrochloride directly from the chilled acid solutions and did not require recrystallization.

3,4-Dihydro-6,7-dihydroxycoumarin (3,4-Dihydroesculetin).—To a suspension of 100 mg of PtO_2 in 10 ml of absolute ethanol was added 691 mg (3.98 mmoles) of esculetin. The mixture was hydrogenated at room temperature (22°) and atmospheric pressure, taking up 1 equiv of hydrogen in 4 hr. The catalyst was filtered off and the filtrate was evaporated *in vacuo* to dryness. Recrystallization of the residue from ethanol yielded 353 mg (60%) of white crystals, mp 204–206°. A second crop of 140 mg (20%) was obtained from the mother liquors: mp 200–203°; λ_{max}^{EtOH} 228 mμ (ε 12,000), 257 (5300), 300 (5300), 350 (9700).

Anal. Calcd for $C_9H_8O_4$: C, 60.0; H, 4.48. Found: C, 59.8; H, 4.49.

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Pyrazine Diuretics. II. N-Amidino-3-amino-5-substituted 6-Halopyrazinecarboxamides

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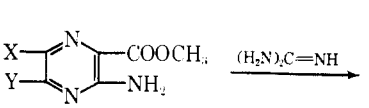
Received July 14, 1966

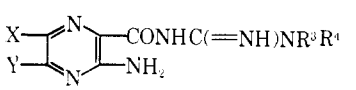
The synthesis of a series of N-amidino-3-amino-5-substituted 6-halopyrazinecarboxamides is described. In rats and dogs, these compounds cause diuresis and saluresis while potassium excretion is unaffected or repressed. Compounds with a variety of 5 substituents including hydroxy, alkoxy, mercapto, alkylmercapto, amino, and substituted amino were prepared. The latter two types embrace compounds with the highest activity. Several routes for the synthesis of methyl 3-amino-5,6-dichloropyrazinoate, a key intermediate, are presented.

The unique effect of the N-amidino-3-amino-6-halopyrazinecarboxamides[1] on renal electrolyte excretion prompted a thorough structure–activity study of this series and its congeners. It is the purpose of this paper to report the investigation of N-amidino-3-amino-6-halopyrazinecarboxamides (II) bearing various substituents at the 5 position and on one nitrogen of the amidino group.

Chemistry.—In general, the target compounds (II) were prepared by the interaction of the appropriate



I



II

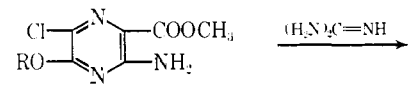
ester (I) with a guanidine. The reaction was usually carried out by heating the ester with a methanolic solution of the guanidine. Satisfactory results were achieved with guanidine itself and a variety of esters in-

(1) Paper I in this series: J. B. Bicking, J. W. Mason, O. W. Woltersdorf, Jr., J. H. Jones, S. F. Kwong, C. M. Robb, and E. J. Cragoe, Jr., *J. Med. Chem.*, **8**, 638 (1965).

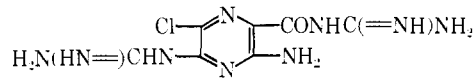
cluding those where the 5 substituent, Y, is amino, substituted amino, hydroxy, alkoxy, mercapto, or methylmercapto and where the 6 substituent, X, is chloro or hydrogen.

N-Substituted amidinopyrazinecarboxamides were prepared by the reaction of a number of mono- and 1,1-disubstituted guanidines with a few selected esters. Theoretically, a monosubstituted guanidine (*e.g.*, methylguanidine) could give rise to either or both of two isomeric products: (a) II (where R^3 = H and R^4 = CH_3) or (b) the isomer in which the acyl and methyl groups are attached to the same nitrogen atom. That the former structure (a) is the more likely one is based on the following arguments: (1) an unequivocal synthesis of N-(methylamidino)benzamide has been reported[2] and it has been shown to be identical with the compound prepared from methylguanidine and ethyl benzoate[3] or benzoyl chloride;[2] (2) no reaction occurred

SCHEME I



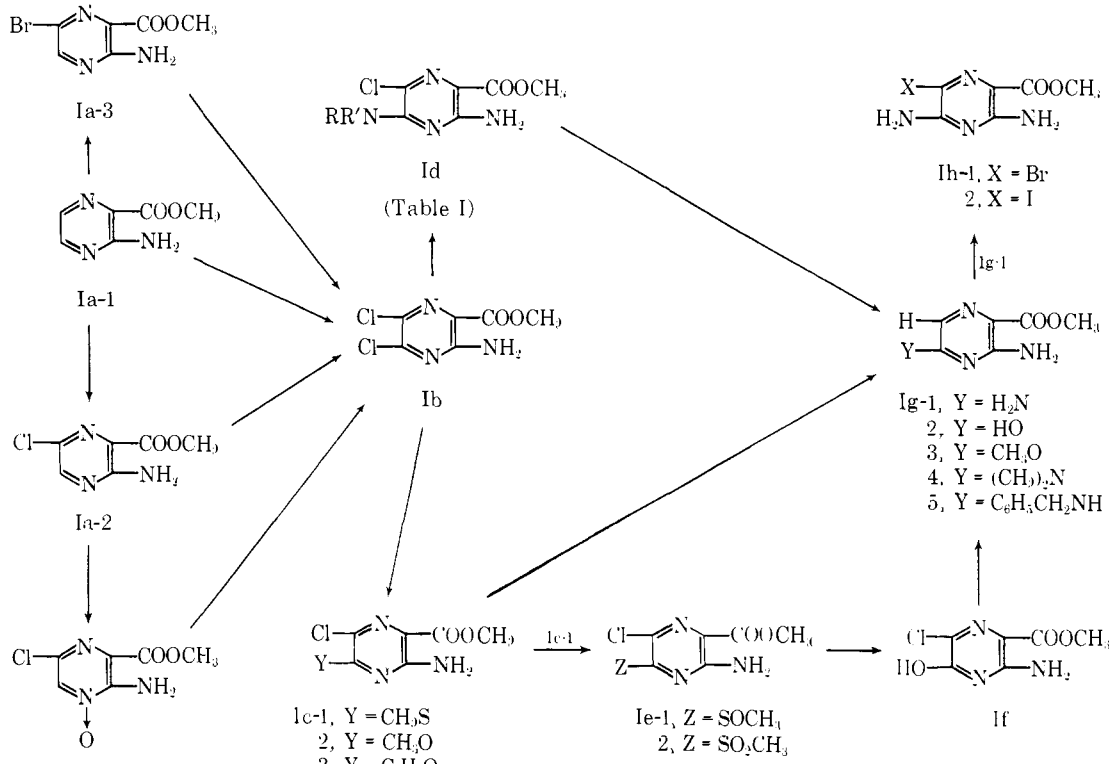
Ic-4, R = C_6H_5
5, R = $(CH_3)_2NCH_2CH_2$



IIa-48

An alternate synthesis of N-amidino-3-amino-5-dimethylamino-6-chloropyrazinecarboxamide (IIa-14) was devised which might have broader application (Scheme III). Treatment of methyl 3-amino-5,6-dichloropyrazinecarboxylate (Ib) with guanidine afforded the acylguanidine (IIc-82) which reacted with

SCHEME II



with 1,2,3-trimethylguanidine and selected esters of type I; and (3) steric and statistical probability considerations favor this structure.

When the 5-phenoxy-6-chloro (Ic-4) and the 5-(2-dimethylaminoethoxy)-6-chloro (Ic-5) esters were heated with guanidine in 2-propanol, replacement of the 5 substituent with a guanidino group occurred with the formation of IIa-48 (Scheme I). The 5-methylsulfinyl-6-chloro (Ie-1) and 5-mesyl-6-chloro (Ie-2) esters (see Scheme II) reacted with guanidine to give compounds (II) with the expected properties, but lack of stability prevented isolation of pure samples.

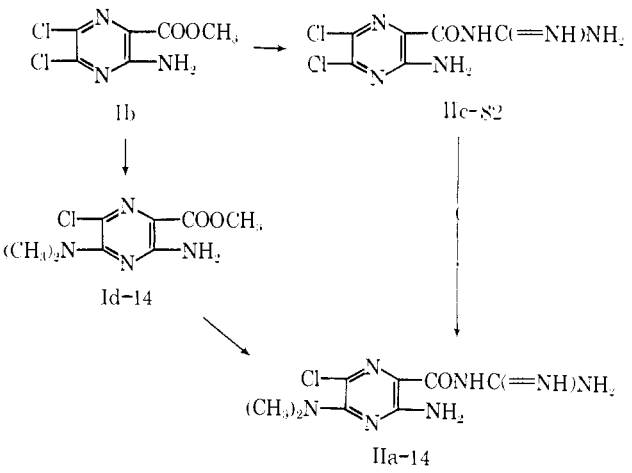
dimethylamine in dimethylformamide to give (IIa-14). The product was identical with that obtained from Id-14 and guanidine.

The intermediate esters were prepared by the methods outlined in Scheme II. A key intermediate for these syntheses was Ib which was first made[4] from methyl 3-aminopyrazinecarboxylate (Ia-1) and sulfuryl chloride. As expected, methyl 3-amino-6-chloropyrazinecarboxylate (Ia-2) and sulfuryl chloride gave the same product (Ib). With methyl 3-amino-6-bromopyrazinecarboxylate (Ia-3) replacement of the bromine

(2) I. Greenwald, *J. Am. Chem. Soc.*, **47**, 1443 (1929).
(3) W. Traube and K. Gorniak, *Z. Angew. Chem.*, **42**, 379 (1929).

(4) R. J. Tull, J. ten Broeke, and E. J. Cragoe, Jr., are responsible for the original synthesis of this compound and Dr. J. van de Kamp and his colleagues adapted the method for the preparation of the larger amounts of the material required in this study.

SCHEME III

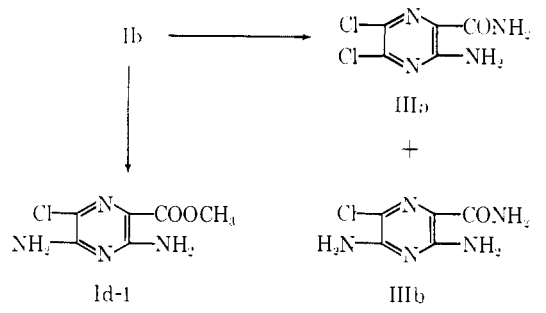


atom with chlorine occurred resulting in the formation of Ib. The conversion of Ia-2 to the 4-oxide (Ia-4) and subsequently to Ib by treatment with phosphoryl chloride also has been accomplished[5] (see Scheme II).

Although the 6-halogen atom of Ia-2, Ia-3, and Ib is inert, the nucleophilic displacement of the 5-chloro atom of Ib occurs readily. Thus, refluxing a 2-propanol solution of Ib with a variety of primary or secondary amines produced the corresponding 5-amino derivative (Id).

The reaction of Ib with liquid ammonia in an autoclave at room temperature produced a mixture of equal parts of 3-amino-5,6-dichloropyrazinecarboxamide (IIIa) and the corresponding 5-amino compound (IIIb) (Scheme IV). When higher temperatures were em-

SCHEME IV



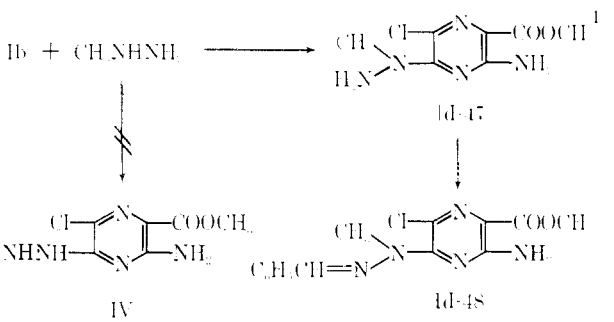
ployed, only IIIb was isolated. However, when the reaction was conducted in a highly polar solvent such as dimethyl sulfoxide, dimethylformamide, dimethyl sulfone, or sulfolane, the desired ester, methyl 3,5-diamino-6-chloropyrazinecarboxylate (Id-1) (Table I) was produced in good yields.

The reaction of Ib with aromatic amines gave the best results when a mixture of the amine and the amine hydrochloride was used.

Methylhydrazine theoretically could react with Ib to produce either (or both) of two isomers (Id-47 and IV). However, it was proved that the product was the 5-(1-methylhydrazino) compound (Id-47) by demonstrating that it reacted with benzaldehyde to produce the hydrazone (Id-48) (Scheme V). Similarly, Carmi, *et al.*,[6] found that 2-haloalkanoic acids reacted with

(5) J. H. Jones, to be published.
(6) A. Carmi, G. Pollak, and H. Yellin, *J. Org. Chem.*, **25**, 41 (1960).

SCHEME V

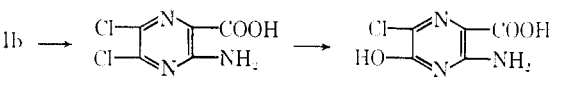


methylhydrazine to yield the corresponding 2-(1-methylhydrazino)alkanoic acids.

Treatment of Ib with the sodium salt of the appropriate mercaptan, alkanol, etc., provided the 5-methylthio, -methoxy, -ethoxy, -phenoxy, -(2-dimethylaminoethoxy), and -mercapto esters (Ic-1–6) (see Table II). It should be noted that with sodium ethoxide, transesterification occurred with the formation of the ethyl ester of the 5-ethoxy compound (Ic-3).

The reaction of Ib with sodium hydroxide under a variety of conditions gave, upon acidification, either 3-amino-5,6-dichloropyrazinecarboxylic acid (Va) and or the 5-hydroxy derivative (Vb) (Scheme VI). Un-

SCHEME VI



fortunately, the esterification of Vb to If was unsuccessful; therefore, an alternate route to If was devised. Oxidation of methyl 3-amino-5-methylthio-6-chloropyrazinecarboxylate (Ic-1) with hydrogen peroxide gave the corresponding sulfoxide (Ic-1) or sulfone (Ic-2) depending upon the reaction conditions. It was found that the sulfoxide (Ic-1) could be hydrolyzed readily to the 5-hydroxy ester (If) by heating in aqueous acetic acid.

Catalytic hydrogenolysis of the methyl 3-amino-6-chloropyrazinoates bearing a 5-amino, -hydroxy, -methoxy, -dimethylamino, or -benzylamino was accomplished in good yields with the formation of the corresponding dechloro compound (Ig-1–5). Optimum reaction conditions consisted of using 5% palladium-on-charcoal catalyst in methanol in the presence of magnesium oxide. Inexplicably, the 5-methylamino ester (Id-2) failed to react under these conditions.

We have presented only *a priori* evidence that it is the 5-chloro atom of Ib which is involved in the nucleophilic displacement reactions. However, the unequivocal synthesis of 3-amino-6-dimethylaminopyrazinecarboxylic acid (VI) has been accomplished[5] and comparison of VI with VII derived from the saponification of Ig-4 reveals that these compounds are not identical but isomeric. Thus, it is the 5-chloro atom that was replaced in the reaction of Ib with dimethylamine to give Ig-4. The halogenation of methyl 3-amino-6-methyl- (and 6-phenyl-) pyrazinecarboxylate to the

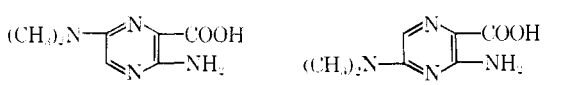
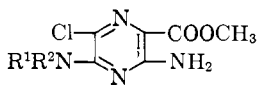


TABLE I



Id

No.	R^1	R^2	% yield[a]	Recrystn solvent[b]	Mp, °C	Formula	—Carbon, %— Calcd	Found	—Hydrogen, %— Calcd	Found	—Nitrogen, %— Calcd	Found
1[c]	H	H	91	A	212–213	$C_6H_7ClN_4O_2$	35.57	35.80	3.48	3.38	27.65	28.01
2	CH_3	H	88	P	221–222	$C_7H_9ClN_4O_2$	38.81	38.74	4.19	4.22	25.86	25.49
3	C_2H_5	H	89	P	149–150	$C_8H_{11}ClN_4O_2$	41.66	42.11	4.81	5.05	24.29	24.24
4	C_3H_7	H	75	P	138–140	$C_9H_{13}ClN_4O_2$	44.18	44.21	5.36	5.39	22.90	22.89
5	$(CH_3)_2CH$	H	70	P	125.5–126.5	$C_9H_{13}ClN_4O_2$	44.18	43.82	5.36	5.18	22.90	22.62
6	C_4H_9	H	91	P	140–142	$C_{10}H_{15}ClN_4O_2$	46.42	46.39	5.84	5.77	21.66	21.67
7	$(CH_3)_2CHCH_2$	H	51	P	113.5–115.5	$C_{10}H_{15}ClN_4O_2$	46.42	46.34	5.84	5.80	21.66	21.64
8	$C_2H_5CH(CH_3)$	H	75	P	106–108	$C_{10}H_{15}ClN_4O_2$	46.42	46.46	5.84	6.04	21.66	21.65
9	$(CH_3)_3C$	H	38	D-W	98–108	$C_{10}H_{15}ClN_4O_2$	46.42	46.31	5.84	5.72	21.66	21.25
10	C_5H_{11}	H	72	C	100.5–102.5	$C_{11}H_{17}ClN_4O_2$	48.44	48.27	6.28	6.09	20.54	20.45
11	$C_3H_7CH(CH_3)$	H	40	PE	74.5–75.5	$C_{11}H_{17}ClN_4O_2$	48.44	48.65	6.28	6.50	20.54	20.57
12	$(C_2H_5)_2CH$	H	81	He	82.5–84.5	$C_{11}H_{17}ClN_4O_2$	48.44	47.96	6.28	5.70	20.54	20.40
13	C_6H_{13}	H	70	P	72.5–75.5	$C_{12}H_{19}ClN_4O_2$	50.25	50.27	6.68	6.60	19.54	19.45
14	CH_3	CH_3	97	M	145.5–146.5	$C_8H_{11}ClN_4O_2$	41.66	41.73	4.81	4.52	24.29	24.24
15	CH_3	C_2H_5	73	P	102–104	$C_9H_{13}ClN_4O_2$	44.18	44.16	5.36	5.24	22.90	22.81
16	CH_3	C_3H_7	58	P	83.5–85.5	$C_{10}H_{15}ClN_4O_2$	46.42	46.55	5.84	5.75	21.66	21.70
17	CH_3	$(CH_3)_2CH$	78	P	75.5–77.5	$C_{10}H_{15}ClN_4O_2$	46.42	46.70	5.84	5.97	21.66	21.46
18	CH_3	C_4H_9	74	P	59.5–61.5	$C_{11}H_{17}ClN_4O_2$	48.44	48.60	6.28	6.22	20.54	20.54
19	C_2H_5	C_2H_5	54	PE	99–101	$C_{10}H_{15}ClN_4O_2$	46.42	46.75	5.84	5.79	21.66	21.45
20	C_2H_5	C_3H_7	65	PE	80.5–83.5	$C_{11}H_{17}ClN_4O_2$	48.44	48.39	6.28	6.37	20.54	20.40
21	C_2H_5	$(CH_3)_2CH$	75[d]	...		$C_{11}H_{17}ClN_4O_2$						
22	C_2H_5	C_4H_9	91	PE	77.5–79.5	$C_{12}H_{19}ClN_4O_2$	50.25	49.81	6.68	6.28	19.54	19.45
23	C_3H_7	C_4H_9	59	PE	45.5–47.5	$C_{13}H_{21}ClN_4O_2$	51.91	52.00	7.04	6.94	18.63	18.54
24	$-(CH_2)_4-$		95	P	168–171	$C_{10}H_{13}ClN_4O_2$	46.78	47.01	5.10	4.95	21.83	21.86
25	$-(CH_2)_6-$		75	P	109–111	$C_{12}H_{17}ClN_4O_2$	50.61	50.54	6.02	5.79	19.68	19.60
26	$CH_2=CHCH_2$	H	69	P	105–106.5	$C_9H_{11}ClN_4O_2$	44.54	44.46	4.57	4.61	23.09	23.12
27	$CH_2=CHCH_2$	CH_3	70	P	90.5–92	$C_{10}H_{13}ClN_4O_2$	46.78	46.85	5.10	5.08	21.83	21.73
28	$CH_2=CHCH_2$	C_2H_5	54	P-W	43.5–45.5	$C_{11}H_{15}ClN_4O_2$	48.80	48.70	5.58	5.40	20.70	20.44
29		H	98	P	167–169	$C_9H_{11}ClN_4O_2$	44.54	44.63	4.57	4.52	23.09	23.09
30		H	78	P	132–133	$C_{10}H_{13}ClN_4O_2$	46.78	46.93	5.10	5.18	21.83	21.92
31		H	98	P	119.5–121.5	$C_{11}H_{15}ClN_4O_2$	48.80	48.91	5.58	5.39	20.70	20.59
32	$C_6H_5CH_2$	H	64	M	157–158	$C_{13}H_{13}ClN_4O_2$	53.34	53.46	4.48	4.46	19.14	19.22
33	$4\text{-}CH_3C_6H_4CH_2$	H	66	P	112.5–114.5	$C_{14}H_{15}ClN_4O_2$	54.81	55.24	4.93	4.99	18.27	18.20
34	$2\text{-}FC_6H_4CH_2$	H	84	P	171–174	$C_{13}H_{12}ClFN_4O_2$	50.25	50.05	3.89	4.08	18.03	18.06
35	$4\text{-}ClC_6H_4CH_2$	H	93[d]	...	137–138	$C_{13}H_{12}Cl_2N_4O_2$						
36	$C_6H_5CH_2CH_2$	H	59	P	115–119	$C_{14}H_{15}ClN_4O_2$	54.81	55.25	4.93	4.88	18.27	18.13
37		H	81	P	148–149	$C_{11}H_{11}ClN_4O_3$	46.73	46.14	3.92	4.08	19.82	19.57
38	CF_3CH_2	H	97	W	153–154	$C_8H_8ClF_3N_4O_2$	33.76	34.10	2.83	3.08	19.69	19.57
39	$CF_3CH_2CH_2$	H	76	P-W	124.5–125.5	$C_9H_{10}ClF_3N_4O_2$	36.19	36.46	3.37	3.22	18.76	18.70
40	$HOCH_2CH_2$	H	100[d]	...	155–157	$C_8H_{11}ClN_4O_3$						
41	$(CH_3)_2NCH_2CH_2$	H	40	M[e]	257	$C_{10}H_{18}Cl_2N_4O_7$	38.72	39.25	5.52	5.55	22.58	22.33
42	$HOCH_2(CHOH)_4CH_2$[h]	H	60[d]	...	172–175	$C_{12}H_{19}ClN_4O_7$						
43[f]	C_6H_5	H	71	P	171.5–174	$C_{12}H_{11}ClN_4O_2$	51.71	51.33	3.98	4.12	20.10	20.30
44[f]	$4\text{-}ClC_6H_4$	H	89	A	206.5–207.5	$C_{12}H_{10}Cl_2N_4O_2$	46.02	45.96	3.22	3.10	17.89	17.86
45	CH_3	CH_3O	68	P	144–146	$C_8H_{11}ClN_4O_3$	38.95	38.41	4.50	4.33	22.72	20.50
46	$-CH_2CH_2N(CH_3)CH_2CH_2-$		88	P	186–188	$C_{11}H_{16}ClN_5O_2$	46.23	46.36	5.64	5.49	24.51	24.02
47	CH_3	NH_2	67	E	136.5–138.5	$C_7H_{10}ClN_5O_2$	36.29	36.54	4.35	4.08	30.23	30.82
48[g]	CH_3	$C_6H_5CH=N$	...	...	179.5–180.5	$C_{14}H_{14}ClN_5O_2$	52.58	52.25	4.41	4.39	21.90	21.72

[a] The compounds in this table were prepared by method B-3 in the Experimental Section unless otherwise specified. [b] A, acetonitrile; C, cyclohexane; D, dimethylformamide; E, ethanol; He, hexane; M, methanol; P, 2-propanol; PE, petroleum ether (Merck's Benzin, bp 30–60°); W, water; Et, ethyl acetate; Ac, acetic acid; S, dilute methanesulfonic acid; H, dilute HCl; N, dilute NaOH; H-N, Ac-N, and S-N indicate that the compound was purified by dissolving in the indicated dilute acid and precipitating with dilute NaOH. [c] This compound was prepared by method B-2. [d] This compound was used in the next step without purification. [e] Isolated as the hydrochloride salt. [f] This compound was prepared by method B-4. [g] This compound was prepared by method B-5. [h] Derived from D-glucamine.

corresponding 5-halo derivatives and the easy nucleophilic displacement of the halogen atom also has been accomplished.[7]

Bromination of methyl 3,5-diaminopyrazinecarboxylate (Ig-1) afforded the 6-bromo derivative (Ih-1). Analogously, with iodine and mercuric acetate in aqueous dioxane the 6-iodo compound (Ih-2) was obtained.

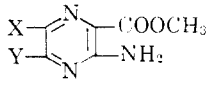
Structure–Activity Relationships.—Each of the N-amidino-3-amino-5-substituted 6-halopyrazinecarboxamides (II) synthesized were assayed for their deoxycorticosterone acetate (DOCA)-inhibitory activity using the adrenalectomized rat according to the method described earlier.[1,8] The compounds routinely were administered subcutaneously, but similar results were obtained with representative compounds when the oral or intraperitoneal routes were employed. A scoring system[9] similar to that already described[1] was used and the results are recorded in Tables III–V.

(7) J. B. Bicking, to be published.

(8) M. S. Glitzer and S. L. Steelman, *Nature*, **212**, 191 (1966).

(9) See footnote *g*, Table III, for a description of this system.

TABLE II

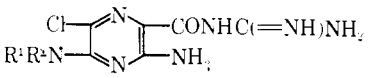


1

Code	5-Y	6-X	Synthetic method[a]	% yield	Recrystn solvent[b]	Mp, °C	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Nitrogen, % Calcd	Nitrogen, % Found
1c	Cl	Cl	B-1	80	A	233–234	$C_6H_3Cl_2N_5O_2$[c]	32.16	32.83	2.27	2.35	18.93	19.12
1c-1	C_7H_5S	Cl	C-1	60	M	214–216	$C_{13}H_9ClN_5O_2S$	35.98	36.21	3.15	3.33	17.98	17.91
1c-2	C_7H_5O	Cl	C-2	92	A	255–257	$C_{13}H_9ClN_5O_4$	38.63	39.00	3.71	3.82	19.31	18.76
1c-3	C_7H_5O[d]	Cl	C-3	92	P	124–125	$C_{15}H_{13}ClN_5O_5$	41.00	41.11	4.92	4.69	17.11	17.28
1c-4	C_6H_5O	Cl	C-4	82	P–D	188–189	$C_{12}H_{10}ClN_5O_3$	51.53	51.73	3.60	3.70	15.02	14.96
1c-5	$(CH_3)_2NCH_2CH_2O$	Cl	C-5	70	P	134–136	$C_{10}H_{13}ClN_6O_3$	43.72	43.96	5.50	5.33	20.40	20.30
1c-6	HS	Cl	C-6	89	N–Ar	207–208	$C_6H_6ClN_5O_2S$	32.81	32.31	2.75	2.90	19.13	19.13
1c-1	C_7H_5SO	Cl	C-7	74	M–Et–D	237.5–240.5	$C_{13}H_9ClN_5O_3S$	33.67	33.79	3.23	3.15	16.83	16.72
1c-2	$C_7H_5SO_2$	Cl	C-8	61	P–D	206.5–209	$C_{13}H_9ClN_5O_4S$	31.64	32.27	3.63	3.19	15.82	15.93
1f	HO	Cl	C-9	61	M–D	245 dec	$C_6H_6ClN_5O_3$	35.39	35.69	2.98	2.83	20.69	20.57
1g-1	H_2N	H	C-10	85	P–W	252–254	$C_6H_8N_6O_2$	42.85	43.15	4.80	4.76	33.32	33.11
1g-2	HO	H	C-10	65	M–W	260 dec	$C_6H_7N_5O_3$	42.60	42.79	4.17	4.29	24.85	24.88
1g-3	CH_3O	H	C-10	72	M	205.5–207.5	$C_7H_9N_5O_3$	45.90	45.32	4.95	4.78	22.94	22.79
1g-4	$(CH_3)_2N$	H	C-10	38	M	242.5–243.5	$C_8H_{12}N_6O_2$	48.97	49.05	6.17	5.91	28.56	28.62
1g-5	$C_6H_5CH_2NH$	H	C-10	62	M	189.5–191.5	$C_{13}H_{14}N_6O_2$	60.45	60.66	5.46	5.72	21.70	21.62
1b-1	H_2N	Br	C-11	11	P	217.5–219.5	$C_6H_7BrN_6O_2$	29.17	29.51	2.86	3.02	22.68	22.56
1b-2	H_2N	I	C-12	12	P–D	200–202	$C_6H_7IN_6O_2$	24.50	24.81	2.40	2.46	19.05	18.76

[a] The numbers and letters refer to those used in the Experimental Section. [b] See ref *b* in Table I for a code to the solvents used. [c] *Anal.* Calcd: Cl, 31.94. Found: Cl, 31.94. [d] Transesterification occurred during the reaction with the formation of the ethyl ester.

Early in the study it was found that N-amidino-3-amino-5-substituted amino-6-chloropyrazinecarboxamides (IIa) exhibited a high order of activity in this test. Thus, a study of the effect of substituents on the 5-amino group was made (Table III). Maximal activity was obtained with the parent 5-amino compound (IIa-1), which produced 50% reversal of DOCA at 2.5 μg./rat (spironolactone requires 400 μg./rat). Compounds



IIa

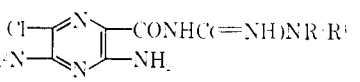
where R^2 = H and R^1 = methyl, ethyl, propyl, isopropyl, or butyl (2–6) were nearly as potent as the parent. However, those having a branched butyl (7–9) or a higher alkyl substituent (10–13) were markedly less active.

The 5-dialkylamino compounds (14–23) had activities as great or greater than the 5-alkylamino analogs, and it was generally beneficial to have the total mass of the substituent divided between two (R^1 and R^2) rather than in a single group. Thus, the dimethylamino derivative (14) is more potent than the methylamino (2), and the N-ethyl-N-butylamino (22) is much more active than the hexylamino compound (13). Joining R^1 and R^2 to form a ring (24 and 25) affords compounds considerably less potent than their dialkyl counterparts (19 and 22).

Allyl (26–28) and cycloalkyl (29–31) substituents gave results comparable to the analogous alkyl derivatives. The benzyl (32), substituted benzyl (33–35), and phenethyl (36) derivatives exhibited only weak activity, but the furfuryl compound (37) was relatively potent. The ω-polyfluoroalkyl (38 and 39), ω-hydroxyalkyl (40), polyhydroxyalkyl (42), and ω-aminoalkyl (41) derivatives which were studied exhibited little activity.

The introduction of a phenyl substituent (43) produced a compound with moderate activity, but the *p*-chlorophenyl analog (44) was nearly devoid of activity. The compounds in which the amino group bore a methoxy (45), amino (*i.e.*, hydrazino, 46), or amidino (*i.e.*, guanidino, 48) substituent or where two alkyl groups were joined through a nitrogen atom to form a ring (piperazine, 47) generally exhibited a low order of activity.

The effect of substituting the terminal guanidino nitrogen (R^3 and R^4) of compounds of type IIb was studied (see Table IV). The high potency of the parent 5-amino compound (IIa-1) is maintained upon introduction of a variety of alkyl, substituted alkyl, or aryl substituents (49–64) at R^3 or similar substituents at both R^3 and R^4 (65–68). Some diminution of activity is noted with bulkier groups (57, 58, 60, and 67).



IIb

The potency of the 5-isopropylamino compound (5) is actually increased in the introduction of a methyl, 2-hydroxyethyl, or benzyl group at R^3 or a methyl at both R^3 and R^4 (69–72). Several other 5-alkyl- and dialkylamino derivatives where R^3 = R^4 = CH_3 (73–79) received activity scores about the same as the analogs where R^3 = R^4 = H (26, 30, 6, 14, 15, 17, and 19), respectively.

Analogs of N-amidino-3,5-diamino-6-chloropyrazinecarboxamide (IIa-1) in which the chlorine is replaced by bromine (80) or by iodine (81) are very active, although somewhat less than the chloro compound (Table V).

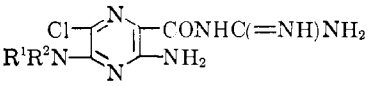
Compounds of type IIc where X is Cl and Y is chloro, hydroxy, methoxy, ethoxy, mercapto, or methylthio (82–87) are much less potent than the 5-amino series (IIa).

None of the five compounds in which the 6-chloro atom (X) was replaced by hydrogen (88–92) showed appreciable activity. This is not surprising in the case where Y is benzylamino (90), hydroxy (91), or methoxy (92); however, for the amino (88) and dimethylamino (89) compounds, it represents a marked difference from the 6-chloro analogs (1 and 14).

Each of the compounds recorded in Tables III–V also were tested intraperitoneally in normal rats and intravenously in dogs.[10] The compounds were active as measured by these assays and, in general, the relative

[10] Dr. J. E. Baer and his associates conducted these studies.

TABLE III



IIa

No.	R^1	R^2	% yield[a]	Recrystn solvent[b]	Mp, °C	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Nitrogen, % Calcd	Nitrogen, % Found	Chlorine, % Calcd	Chlorine, % Found	DOCA inhib score[g]
1	H	H	93	H-N	240.5–241.5	$C_6H_8ClN_7O$	31.38	31.59	3.51	3.43	42.70	42.85	15.44	15.42	+4
2	CH_3	H	89	H-N	238–239	$C_7H_{10}ClN_7O$	34.50	34.19	4.14	4.28	40.24	39.02	14.55	14.56	+3
3	C_2H_5	H	63	H-N	217–218	$C_8H_{12}ClN_7O$	37.29	37.35	4.69	4.73	38.05	38.05	13.76	13.76	+3
4	C_3H_7	H	93	M-W	221–222	$C_9H_{14}ClN_7O$	39.78	39.75	5.19	5.28	36.09	35.89	13.05	13.05	+3
5	$(CH_3)_2CH$	H	75	M-W	215	$C_9H_{14}ClN_7O$	39.78	39.80	5.19	5.13	36.09	35.77	13.05	12.97	+3
6	C_4H_9	H	65	P	219.5	$C_{10}H_{16}ClN_7O$	42.03	42.26	5.64	5.65	34.32	33.95	12.41	12.47	+3
7	$(CH_3)_2CHCH_2$	H	76	M-W	221	$C_{10}H_{16}ClN_7O$	42.03	41.81	5.64	5.31	34.32	34.32	12.41	12.35	+1
8	$C_2H_5CH(CH_3)$	H	74	M-W	208–209	$C_{10}H_{16}ClN_7O$	42.03	42.02	5.64	5.64	34.32	34.16	12.41	12.40	+1
9	$(CH_3)_3C$	H	84	M-W	222–223	$C_{10}H_{16}ClN_7O$	42.03	42.20	5.64	5.59	34.32	34.00	12.41	12.27	±
10	C_5H_{11}	H	70	P	215–216	$C_{11}H_{18}ClN_7O$	44.07	44.01	6.05	5.88	32.70	32.66	11.83	11.85	+1
11	$C_3H_7CH(CH_3)$	H	89	P	186.5–188.5	$C_{11}H_{18}ClN_7O$	44.07	44.34	6.05	5.81	32.70	32.41	11.83	11.75	+1
12	$(C_2H_5)_2CH$	H	82	P	209–211	$C_{11}H_{18}ClN_7O$	44.07	44.02	6.05	5.95	32.70	32.59	11.83	11.81	±
13	C_6H_{13}	H	100	M-W	194.5–196.5	$C_{12}H_{20}ClN_7O$	45.93	45.95	6.42	6.42	31.25	31.03	11.30	11.20	±
14	CH_3	CH_3	93	H-N	216–217	$C_8H_{12}ClN_7O$	37.29	37.24	4.69	4.49	38.05	37.83	13.76	13.78	+3
15	CH_3	C_2H_5	92	H-N	229–230	$C_9H_{14}ClN_7O$	39.78	39.99	5.19	5.18	36.09	35.83	13.05	13.15	+4
16	CH_3	C_3H_7	97	M-W	214–215	$C_{10}H_{16}ClN_7O$	42.03	42.31	5.64	5.94	34.32	34.40	12.41	12.56	+4
17	CH_3	$(CH_3)_2CH$	70	M-W	207–208	$C_{10}H_{16}ClN_7O$	42.03	42.40	5.64	5.70	34.32	34.05	12.41	12.45	+4
18	CH_3	C_4H_9	95	M-W	208–209	$C_{11}H_{18}ClN_7O$	44.07	44.34	6.05	6.08	32.70	32.38	11.83	11.94	+3
19	C_2H_5	C_2H_5	75	E-W	215	$C_{10}H_{16}ClN_7O$	42.03	42.00	5.64	5.52	34.32	34.14	12.41	12.21	+3
20	C_2H_5	C_3H_7	92	A	224–225	$C_{11}H_{18}ClN_7O$	44.07	44.25	6.05	6.03	32.70	32.63	11.83	11.82	+3
21	C_2H_5	$(CH_3)_2CH$	70	A	207–208	$C_{11}H_{18}ClN_7O$	44.07	43.91	6.05	5.82	32.70	32.58	11.83	11.68	+3
22	C_2H_5	C_4H_9	98	P	200.5–201.5	$C_{12}H_{20}ClN_7O$	45.93	46.06	6.42	6.49	31.25	31.02	11.30	11.34	+3
23	C_3H_7	C_4H_9	84	P	215–217	$C_{13}H_{22}ClN_7O$	47.62	47.60	6.76	6.77	29.91	29.44	10.82	10.93	+1
24	$-(CH_2)_4-$		90	H-N	244.5–245.5	$C_{10}H_{14}ClN_7O$	42.33	42.34	4.97	4.87	34.56	34.11	12.50	12.71	+1
25	$-(CH_2)_6-$		49	E	224–225	$C_{12}H_{18}ClN_7O$	46.22	46.55	5.82	5.85	31.45	31.41	11.37	11.18	±
26	$CH_2=CHCH_2$	H	84	M-W	213–214	$C_9H_{12}ClN_7O$	40.08	40.41	4.48	4.44	36.36	36.07	13.15	13.25	+4
27	$CH_2=CHCH_2$	CH_3	95	M-W	207–208	$C_{10}H_{14}ClN_7O$	42.33	42.59	4.97	4.92	34.56	34.17	12.50	12.38	+3
28	$CH_2=CHCH_2$	C_2H_5	92	P-W	208–209	$C_{11}H_{16}ClN_7O$	44.37	44.51	5.42	5.43	32.93	32.58	11.91	11.84	+3
29		H	85	H-N	213–215	$C_8H_{12}ClN_7O$	40.08	40.24	4.48	4.43	36.36	36.34	13.15	13.31	+3
30		H	95	M-W	220–221.5	$C_{10}H_{14}ClN_7O$	42.33	42.57	4.97	5.14	34.56	34.47	12.50	12.57	+4
31		H	65	Ac-N	219–220	$C_{11}H_{16}ClN_7O$	44.37	44.36	5.42	5.54	32.93	33.01	11.91	11.97	±
32	$C_6H_5CH_2$	H	44	H-N	206–209	$C_{13}H_{14}ClN_7O$	48.83	48.83	4.41	4.49	30.67	30.44	...	...	+1
33	$4\text{-}CH_3C_6H_4CH_2$	H	57	A	216–217	$C_{14}H_{16}ClN_7O$	50.37	50.16	4.83	4.77	29.38	29.31	10.62	10.58	+1
34	$2\text{-}FC_6H_4CH_2$	H	100	A	206–208	$C_{13}H_{13}ClFN_7O$	46.22	46.40	3.88	3.82	29.03	28.82	10.50	11.40	+1
35	$4\text{-}ClC_6H_4CH_2$	H	96	H-N	225–226	$C_{13}H_{13}Cl_2N_7O$	44.08	44.01	3.70	3.95	27.68	27.69	20.02	20.10	±
36	$C_6H_5CH_2CH_4$	H	57	P-W[c]	199–202	$C_{14}H_{16}ClN_7O \cdot HCl$	45.41	45.20	4.63	4.71	26.48	25.94	...	...	±
37		H	92	E	217–218	$C_{11}H_{12}ClN_7O_2$	42.65	42.80	3.91	3.89	31.66	31.37	11.45	11.50	+3
38	CF_3CH_2	H	77	A	232–233	$C_8H_9ClF_3N_7O$	30.83	30.82	2.91	3.13	31.46	31.27	11.38	11.26	+1
39	$CF_3CH_2CH_2$	H	65	A	221–222.5	$C_9H_{11}ClF_3N_7O$	33.19	33.57	3.40	3.64	30.11	29.92	10.89	10.86	+2
40	$HOCH_2CH_2$	H	63	H[c]	272–273	$C_8H_{12}ClN_7O_2 \cdot HCl$	30.98	31.40	3.90	4.30	31.61	31.38	22.86	22.61	+1
41	$(CH_3)_2NCH_2CH_2$	H	98	H-N	192.5–194.5	$C_{10}H_{17}ClN_8O$	39.93	39.83	5.70	5.72	37.26	37.63	11.79	11.65	±
42	$HOCH_2(CHOH)_4\text{-}CH_2$[e]	H	68	D-W	223–224	$C_{12}H_{20}ClN_7O_6$	36.59	36.54	5.12	5.15	24.90	24.34	9.00	9.01	±
43	C_6H_5	H	95	E	248.5–250.5	$C_{12}H_{12}ClN_7O$	47.15	47.13	3.96	4.09	32.07	31.65	11.60	11.70	+2
44	$4\text{-}ClC_6H_4$	H	95	S-N	276–278	$C_{12}H_{11}Cl_2N_7O$	42.36	42.08	3.26	3.48	28.82	28.23	20.83	20.32	±
45	CH_3	CH_3O	85	H-N	203.5–204.5	$C_8H_{12}ClN_7O_2$	35.11	35.23	4.42	4.28	35.83	36.05	12.95	13.03	+2
46	CH_3	NH_2	92	H-N	234	$C_7H_{11}ClN_8O$	32.50	32.85	4.29	4.65	43.32	42.08	13.71	13.88	+1
47	$-CH_2CH_2N(CH_3)CH_2CH_2-$		74	H[d,f]	299–300	$C_{11}H_{17}ClN_8O \cdot 2HCl$	34.25	33.91	4.97	5.08	29.05	29.45	27.58	27.09	0
48	$NH_2C(=NH)$	H	38	H[d]	>340	$C_7H_{10}ClN_9O \cdot 2HCl$	24.40	24.62	3.51	3.57	36.58	36.41	30.87	30.52	0

[a] The compounds are prepared by method D-1 unless otherwise specified. [b] See footnote *b*, Table I. [c] Isolated as the hydrochloride salt. [d] Isolated as the dihydrochloride salt. [e] Derived from D-glucamine. [f] Prepared by method D-2. [g] The DOCA inhibition score is the dose (in micrograms per rat) producing 50% reversal of the DOCA Na/K effect: +4 = <10 μg/rat, +3 = 10–50, +2 = 51–100, +1 = 101–800, ± = >800, 0 = no activity at 800 μg. Although no statistically significant activity was noted at the last dose, the possibility of activity at higher doses exists. Furthermore, most of the compounds which scored zero in this test were active diuretics in the normal rat assay. The animals weighed 130 ± 3 g; thus, the dose in milligrams per kilogram is approximately 0.008 times the microgram per rat value.

potency of individual members of the series paralleled those recorded in the adrenalectomized rat test. Representative compounds were assayed in these two tests using the oral route of administration and found to be active.

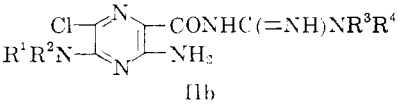
By each assay procedure, diuresis and saluresis is noted, while potassium ion excretion is either unaffected or repressed. The effects observed in rats are somewhat more pronounced than in dogs when equivalent doses are used.

Several members of this series have been tested in combination with certain other diuretics and found to produce additive or synergistic effects on saluresis while reversing the kaluresis caused by the other agent.

Selected compounds from this series are presently undergoing clinical trial.[11] The observations in humans appear to correlate quite well with the animal studies.

(11) Preliminary reports include: N. W. Moukheibir and W. M. Kirkendall, *Clin. Res.*, **13**, 25 (1965); T. B. Reynolds and H. C. Pelle, *ibid.*, **14**, 184 (1966); R. J. Sperber and S. Fisch, *ibid.*, **14**, 262 (1966).

TABLE IV



IIb

No.	R^1	R^2	R^3	R^4	%, yield[a]	Recrystn solvent[b]	Mp, °C
49	H	H	CH_3	H	100	D-W	254.5
50	H	H	$HOCH_2CH_2$	H	37	H[c]	228–229 dec
51	H	H	$C_6H_5CH_2$	H	52	P-W	215–216 dec
52	H	H	$2\text{-}ClC_6H_4CH_2$	H	39	H-N	220–223 dec
53	H	H	$4\text{-}ClC_6H_4CH_2$	H	46	H-N	204–206 dec
54	H	H	$4\text{-}FC_6H_4CH_2$	H	38	P	216–219.5 dec
55	H	H	$4\text{-}CH_3C_6H_4CH_2$	H	27	H-N	210–212 dec
56	H	H	$4\text{-}CH_3OC_6H_4CH_2$	H	27	H-N	175.5–179.5 dec
57	H	H	$2,4\text{-}Cl_2C_6H_3CH_2$	H	34	P-W	267.5–270.5 dec
58	H	H	$3,4\text{-}Cl_2C_6H_3CH_2$	H	47	P	216–219 dec
59	H	H	$2,4\text{-}(CH_3)_2C_6H_3CH_2$	H	59	P	220–222 dec
60	H	H		H	38	D-P	243.5–245.5 dec
61	H	H	$C_6H_5CH(CH_3)$	H	37	P-W	152–160
62	H	H	$C_6H_5CH_2CH_2$	H	46	H-N	219–221.5 dec
63	H	H		H	19	H[d]	280.5–283.5 dec
64	H	H	C_6H_5	H	20	S[e]	272 dec
65	H	H	CH_3	CH_3	28	H[f]	277 dec
66[g]	H	H	C_2H_5	C_2H_5	89	H-N	265
67[g]	H	H	C_3H_9	C_3H_9	72	P	149–151
68	H	H	$C_6H_5CH_2$	CH_3	35	P-W	274.5 dec
69	$(CH_3)_2CH$	H	CH_3	H	30	P	216.5–219
70	$(CH_3)_2CH$	H	CH_3	CH_3	35	P	238.5–240
71	$(CH_3)_2CH$	H	$HOCH_2CH_2$	H	46	H[h]	185–186 dec
72	$(CH_3)_2CH$	H	$C_6H_5CH_2$	H	46	P	200.5–204.5
73	$CH_2{=}CHCH_2$	H	CH_3	CH_3	39	P	212.5–214.5
74		H	CH_3	CH_3	3	P	196–197
75	C_4H_9	H	CH_3	CH_3	17	P	187.5
76	CH_3	CH_3	CH_3	CH_3	69	M	219
77	CH_3	C_2H_5	CH_3	CH_3	49	E	217–218
78	CH_3	$(CH_3)_2CH$	CH_3	CH_3	61	P	209–211
79	C_2H_5	C_2H_5	CH_3	CH_3	40	E	212–214

[a] Prepared by method D-1 unless otherwise specified. [b] See footnote *b*, Table I. [c] This compound was isolated as the hydrochloride salt. [d] This compound was isolated as the dihydrochloride salt. [e] This compound was isolated as the methanesulfonate salt. [f] This

Experimental Section[12,13]

A. Intermediates. 1. Amines.—3,3,3-Trifluoropropylamine[14] was prepared by the method of Raash.[15] All other amines used in this study were commercially available.

2. Guanidinium Chlorides.—The sources of guanidinium chloride and of the 2-hydroxyethyl, phenyl, benzyl, phenethyl, and 1,1-dibutyl derivatives have been described.[1] *p*-Chloro-,[16] *p*-fluoro-,[16] 2,4-dichloro-,[17] and 3,4-dichlorobenzylguanidinium chloride[18] and 1,1-diethylguanidinium chloride[19] have been described elsewhere. The sulfate salts of *o*-chlorobenzyl-,[20] *p*-methoxybenzyl-,[16] *p*-methylbenzyl-, α-methylbenzyl-,[21] 2,4-dimethylbenzyl-, 1-naphthylmethyl-, 3-pyridylmethyl-,[22] and 1-benzyl-1-methylguanidine[23] were prepared by the 2-methyl-2-pseudothiuronium sulfate procedure and were converted to their hydrochloride salts according to the method already described.[1] The physical properties of these hydrochlorides are given in Table VI.

Methyl- and 1,1-dimethylguanidinium sulfate, which are commercially available, were used *per se* without conversion to the chlorides.

B. Methyl 3-Amino-5-substituted Amino-6-chloropyrazinoates (Table I). 1. Methyl 3-Amino-5,6-dichloropyrazinecarboxylate[4] (Ib). Route a.—Under anhydrous conditions, a suspension of Ia-1[1] (765 g, 5 moles) in benzene (5 l.) was stirred and treated dropwise with sulfuryl chloride (1.99 l., 3318 g, 24.58 moles) over a period of 30 min after which stirring was continued for 1 hr. During this period, the temperature rose to 50° and then began to subside. The mixture was heated cautiously to reflux, refluxed for 5 hr, and then stirred overnight at room temperature. The solvent and excess SO_2Cl_2 were removed by distillation, and the dark red residue was chilled to 6°. The crystals that separated were removed by filtration, washed first with cold (8°) benzene (two 100-ml portions) then with petro-

(12) All melting points were taken in open capillary tubes and are corrected values.

(13) K. B. Streeter, Y. C. Lee, and their staff supplied the analytical data reported here.

(14) Dr. W. H. Jones is responsible for this preparation.

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Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Nitrogen, % Calcd	Nitrogen, % Found	Chlorine, % Calcd	Chlorine, % Found	DOCA Inhib score[i]
$C_7H_{10}ClN_7O$	34.50	34.63	4.14	4.04	40.24	39.91	...	...	+4
$C_8H_{12}ClN_7O_2 \cdot HCl$	30.98	30.56	4.22	4.51	31.62	31.36	...	...	+4
$C_{13}H_{14}ClN_7O$	48.83	48.89	4.41	4.62	30.67	30.56	...	...	+4
$C_{13}H_{13}Cl_2N_7O$	44.08	44.12	3.70	3.91	27.68	27.18	...	...	+4
$C_{13}H_{13}Cl_2N_7O$	44.08	44.27	3.70	3.95	27.68	27.73	...	...	+3
$C_{13}H_{13}ClFN_7O$	46.23	46.34	3.88	3.89	29.03	28.76	...	...	+4
$C_{14}H_{16}ClN_7O$	50.37	50.34	4.83	4.76	29.38	29.07	...	...	+4
$C_{14}H_{16}ClN_7O_2$	48.07	48.02	4.61	4.69	28.03	27.55	...	...	+4
$C_{13}H_{12}Cl_3N_7O \cdot HCl$	36.73	36.75	3.08	3.24	23.07	22.88	...	...	+3
$C_{13}H_{12}Cl_3N_7O$	40.17	39.95	3.11	3.06	25.23	24.91	...	...	+3
$C_{15}H_{18}ClN_7O$	51.80	52.08	5.21	5.23	28.19	27.88	...	...	+4
$C_{17}H_{16}ClN_7O$	55.21	55.50	4.36	4.58	26.51	26.38	...	...	+3
$C_{14}H_{16}ClN_7O$	50.37	50.22	4.83	4.62	29.38	29.14	...	..	+4
$C_{14}H_{16}ClN_7O$	50.37	50.67	4.83	4.86	29.38	29.08	...	...	+4
$C_{12}H_{13}ClN_8O \cdot 2HCl$	36.61	36.89	3.84	4.12	28.47	28.14	...	...	+4
$C_{12}H_{12}ClN_7O \cdot CH_3SO_3H$	38.85	39.05	4.01	4.12	24.40	24.32	...	...	+3
$C_8H_{12}ClN_7O \cdot HCl \cdot H_2O$	30.78	30.74	4.84	5.00	31.41	31.41	22.72	22.88	+4
$C_{10}H_{16}ClN_7O$	42.03	42.02	5.64	5.45	34.32	34.14	12.41	12.49	+4
$C_{14}H_{24}ClN_7O$	49.19	49.01	7.08	6.94	28.68	28.86	10.37	10.43	+3
$C_{14}H_{16}ClN_7O \cdot HCl$	45.41	45.22	4.63	4.48	26.48	26.16	...	...	+4
$C_{10}H_{16}ClN_7O$	42.03	42.28	5.64	5.53	34.32	34.14	...	...	+4
$C_{11}H_{18}ClN_7O$	44.07	44.35	6.05	6.04	32.70	32.62	11.83	11.67	+4
$C_{11}H_{18}ClN_7O_2 \cdot HCl \cdot 0.5H_2O$	36.57	36.55	5.58	5.28	27.15	27.23	...	...	+4
$C_{16}H_{20}ClN_7O$	53.11	53.59	5.57	5.31	27.10	26.69	...	...	+4
$C_{11}H_{16}ClN_7O$	44.37	44.50	5.42	5.25	32.93	32.76	11.91	11.85	+4
$C_{12}H_{18}ClN_7O$	46.22	46.40	5.82	6.14	31.45	31.34	...	...	+3
$C_{12}H_{20}ClN_7O$	45.93	45.95	6.42	6.50	31.25	30.81	...	...	+4
$C_{10}H_{16}ClN_7O$	42.03	41.97	5.64	5.63	34.32	34.13	12.41	12.26	+3
$C_{11}H_{18}ClN_7O$	44.07	44.17	6.05	5.81	32.70	32.73	11.83	11.86	+3
$C_{12}H_{20}ClN_7O$	45.93	45.88	6.42	6.36	31.25	31.06	11.30	11.09	+4
$C_{12}H_{20}ClN_7O$	45.93	46.03	6.42	6.11	31.25	31.14	11.30	11.35	+4

compound was isolated as the hydrochloride hydrate salt. [g] We are indebted to Mr. C. M. Robb for the preparation of this compound. [h] This compound was isolated as the hydrochloride hemihydrate salt. [i] See footnote *g*, Table III.

leum ether (bp 30–60°) (300 ml), and dried yielding 888 g of red crystalline Ib, mp 228–230°. The crude product was dissolved in boiling acetonitrile (56 l.) and passed through a heated (70–80°) column of decolorizing charcoal (444 g). The column was washed with hot solvent (25 l.) and the combined eluate was concentrated *in vacuo* (to about 6 l.) and chilled. The yield of yellow crystalline Ib was 724 g (66%). Additional recrystallizations from acetonitrile gave pure material (See Table II).

Route b.—Under anhydrous conditions, Ia-2[1] (9.35 g, 0.05 mole) was treated dropwise with stirring with SO_2Cl_2 (10 ml) during a 10-min period. After 45 min, gas was evolved, the mixture became red, and heat was evolved. After standing overnight at room temperature, the mixture was heated at 70° for 1 hr. The excess SO_2Cl_2 was removed by evaporation at reduced pressure and the residue (11.2 g) was recrystallized from acetonitrile (300 ml) (using decolorizing charcoal) to give 4.2 g (38%) of Ib. Subsequent recrystallization gave pure material.

Route c.—Upon heating a mixture of Ia-3[1] (34.8 g, 0.15 mole) and SO_2Cl_2 (89 ml) for 1 min on a steam bath, a vigorous reaction occurred. The reaction vessel was cooled and then allowed to stand for 20 hr. The product was isolated and purified as described for method b to yield 4 g (12%) of pure Ib.

Route d.—The synthesis of Ib from Ia-4 will be reported in a later paper.

2. Methyl 3,5-Diamino-6-chloropyrazinecarboxylate (Id-1).—A solution of Ib (100 g, 0.45 mole) in dry dimethyl sulfoxide (DMSO) (1 l.) was maintained at 65–70° and dry NH_3 was admitted below the surface with stirring over a period of 45 min. The solution was cooled to 10° while the procedure was continued for another 1.25 hr. The yellow reaction mixture was poured into cold water (2 l.) and the light yellow solid that separated was removed by filtration, thoroughly washed with water, and dried. The yield was 82.5 g (91%). Recrystallization from acetonitrile gave pure material. Similar results were obtained when the reaction was carried out in other highly polar solvents such as DMF, dimethyl sulfone (liquid), or sulfolane.

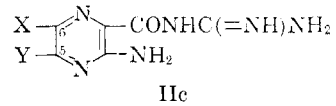
When the reaction was carried out in an autoclave using liquid ammonia at room temperature for 24 hr, a mixture (approximately 1:1) of IIIa, mp 291.5–293.5° (from DMF), and IIIb, mp 218.5–220.5° (from methanol), was obtained. At 60° complete conversion to IIIb occurred.

Anal. Calcd for $C_5H_4Cl_2N_4O$ (IIIa): C, 29.07; H, 1.95; N, 27.06. Found: C, 29.58; H, 1.87; N, 27.36.

Anal. Calcd for $C_5H_6ClN_5O$ (IIIb): C, 32.01; H, 3.22; N, 37.33; Cl, 18.90. Found: C, 32.36; H, 3.00; N, 37.50; Cl, 18.84.

3. Methyl 3-Amino-5-dimethylamino-6-chloropyrazinecarboxylate (Id-14).—A suspension of Ib (178 g, 0.8 mole) in 2-propanol (1.1 l.) was stirred while dimethylamine (200 g, 4.44 moles) in 2-propanol (2 l.) was added, and then the mixture was refluxed for 1 hr. The solution was cooled in an ice bath and the crystalline product that separated was removed by filtration and dried. The yield was 177.2 g (97%); for purification, the product was recrystallized from methanol.

TABLE V



IIc

No.	5-Y	6-X	% yield[a]	Recrystn solvent[b]	Mp, °C	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Nitrogen, % Calcd	Nitrogen, % Found	Chlorine, % Calcd	Chlorine, % Found	DOCA inhib score[c]
80	NH_2	Br	52	H-N	232.5–235.5 dec	$C_6H_8BrN_7O$	26.20	26.34	2.90	3.00	35.77	35.20	...	...	+3
81	NH_2	I	43	H-P[d]	273.5–274.5 dec	$C_6H_8IN_7O \cdot HCl$	20.15	20.10	2.54	2.63	27.42	27.24	...	...	+3
82	Cl	Cl	72	H[e]	259–261	$C_6H_6Cl_2N_6O \cdot HCl$	25.24	25.50	2.47	2.91	29.43	29.17	...	...	0
83	HO	Cl	67	H[e]	>300	$C_6H_7ClN_6O_2Cl \cdot HCl$	26.98	27.57	3.02	2.98	31.47	31.25	...	...	+
84	CH_3O	Cl	90	H[e]	257	$C_7H_9ClN_6O_2 \cdot HCl$	29.91	30.18	3.59	3.51	29.90	29.94	25.23	25.10	+
85	C_2H_5O	Cl	81	H-N	215–216	$C_8H_{11}ClN_6O$	37.15	36.96	4.29	4.31	32.49	32.12	13.71	13.79	0
86	HS	Cl	100	H-N	236.5	$C_6H_7ClN_6OS$	29.21	29.38	2.86	2.79	34.07	34.42	14.37	14.46	+
87	CH_3S	Cl	100	D-W	234.5–236.5	$C_7H_9ClN_6OS$	32.25	32.85	3.48	3.47	32.24	31.82	13.60	13.72	+0
88	H_2N	H	9	H-N	200.5–203.5 dec	$C_6H_9N_7O$	36.92	36.97	4.65	4.42	50.24	49.87	...	...	1+
89	$(CH_3)_2N$	H	45	P-W	224–225 dec	$C_8H_{13}N_7O$	43.04	43.18	5.87	5.73	43.93	43.63	...	...	+
90	$C_6H_5CH_2NH$	H	75	P-W[e]	231–233 dec	$C_{13}H_{15}N_7O \cdot HCl$	48.52	48.68	5.01	5.04	30.47	30.48	...	...	+
91	HO	H	10	W[e]	>310	$C_7H_8N_6O_2 \cdot HCl$	30.98	31.07	3.90	3.87	36.13	35.93	...	...	0
92	CH_3O	H	51	W[e]	229–230 dec	$C_7H_{10}N_6O_2 \cdot HCl$	34.08	34.00	4.49	4.71	34.08	33.80	...	...	+

[a] Prepared by method D-1 unless otherwise specified. [b] See footnote *b*, Table I. [c] Isolated as the hydrochloride salt. [d] See footnote *g*, Table III.

TABLE VI

SUBSTITUTED GUANIDINIUM CHLORIDES

Substituent	Yield,[a] %	Mp,[b] °C	Recrystn solvent	Formula	Nitrogen, % Calcd	Nitrogen, % Found
o-Chlorobenzyl	71	131–136	AcOEt	$C_8H_{11}Cl_2N_3$	19.09	19.01
p-Methoxybenzyl	69	132–137	EtOH	$C_9H_{14}ClN_3O$	19.48	19.20
p-Methylbenzyl	28	153–155	*i*-PrOH	$C_9H_{14}ClN_3$	21.04	20.95
α-Methylbenzyl	52	122.5–130.5	No recrystn	$C_9H_{13}ClN_3$	21.04	20.73
2,4-Dimethylbenzyl	52	105–115	EtOH–Et_2O	$C_{10}H_{16}ClN_3$	19.66	19.47
1-Naphthylmethyl	73	188.5–195.5	No recrystn	$C_{12}H_{14}ClN_3$	17.83	17.46
3-Pyridylmethyl	89	133.5–138.5	No recrystn	$C_7H_{11}ClN_4$	30.02	29.50
1-Benzyl-1-methyl	32	122.5–125.5	EtOH–AcOEt	$C_9H_{14}ClN_3$	21.04	20.88

[a] Based on 2-methyl-2-pseudothiouronium sulfate. [b] Hygroscopic.

Unless otherwise noted, each of the esters recorded in Table I was prepared using a procedure similar to that described above wherein the appropriate amine was substituted for dimethylamine.

4. Methyl 3-Amino-5-(*p*-chloroanilino)-6-chloropyrazinecarboxylate (Id-44).—Under anhydrous conditions, Ib (11.1 g, 0.05 mole), *p*-chloroaniline (19.7 g, 0.155 mole), *p*-chloroaniline hydrochloride (17.9 g, 0.11 mole), and 2-propanol (500 ml) were stirred and refluxed for 24 hr. The product which separated upon cooling was removed by filtration and dried; yield 13.9 g (89%). Purification was effected by recrystallization from acetonitrile.

Using aniline and aniline hydrochloride for *p*-chloroaniline and *p*-chloroaniline hydrochloride in the above procedure gave a 71% yield of Id-43.

5. Methyl 3-amino-5-(1-methyl-2-benzylidenehydrazino)-6-chloropyrazinecarboxylate (Id-48) was prepared for the structure proof of Id-47. Compound Id-47 (100 mg) was dissolved in warm ethanol (2 ml), benzaldehyde (2 drops) was added, and the solution was cooled. The crystals that separated were removed by filtration, washed with water, and dried.

C. **Methyl 3-Amino-5- (and 5,6-di-) substituted Pyrazinecarboxylates (Table II). 1. Methyl 3-Amino-5-methylthio-6-chloropyrazinecarboxylate (Ic-1).**—A solution of methyl mercaptan (10 g, 0.18 mole) in 20% aqueous NaOH (17 ml) and methanol (100 ml) was added during 10 min to a boiling mixture of Ib (17.7 g, 0.08 mole) and methanol (1 l.). The mixture was refluxed for an additional 15 min and cooled, and the product (12 g) was separated by filtration, dried, and recrystallized.

2. Methyl 3-Amino-5-methoxy-6-chloropyrazinecarboxylate (Ic-2).—A boiling solution of Ib (1.1 g, 0.003 mole) in anhydrous methanol (200 ml) was treated with a solution of sodium methoxide prepared from Na (115 mg, 0.005 g-atom) in anhydrous methanol (20 ml). The product (1 g) which separated upon cooling was removed by filtration, washed with water and then methanol, and finally dried and recrystallized.

3. Ethyl 3-Amino-5-ethoxy-6-chloropyrazinecarboxylate (Ic-3).—A boiling solution of Ib (2.2 g, 0.01 mole) in absolute ethanol (200 ml) was treated with a $NaOC_2H_5$ solution prepared from Na (230 mg, 0.01 g-atom) and ethanol (20 ml). The mixture was refluxed for 15 min and then concentrated at reduced pressure to 30 ml. Water (30 ml) was added and the product that separated was removed by filtration and recrystallized.

4. Methyl 3-Amino-5-phenoxy-6-chloropyrazinecarboxylate (Ic-4).—Phenol (15 g, 0.16 mole) was melted and treated with 10 *N* NaOH (2.5 ml, 0.025 mole), then Ib (4.4 g, 0.02 mole) was added, and the mixture was heated on a steam bath for 15 min. After cooling, the product which separated was removed by filtration, washed with water, dried, and recrystallized.

5. Methyl 3-Amino-5-(2-dimethylaminoethoxy)-6-chloropyrazinecarboxylate (Ic-5).—A solution of Ib (11.1 g, 0.05 mole) in 2-dimethylaminoethanol (55 ml) was heated on a steam bath for 35 min. After cooling overnight, the solution was diluted with water, and the product which separated was removed by filtration, washed with water, dried, and recrystallized.

6. Methyl 3-Amino-5-mercapto-6-chloropyrazinoate (Ic-6).—A mixture of sodium sulfide nonahydrate (9.6 g, 0.4 mole), sulfur (10 g), and absolute ethanol (80 ml) was refluxed for 30 min and cooled to 25°. After the addition of Ib (8.9 g, 0.04 mole), the solution was stirred at 25° for 1 hr, filtered, and acidified with acetic acid. The product that separated was removed by filtration and purified by dissolving in NaOH solution and precipitating with acetic acid.

7. Methyl 3-Amino-5-methylsulfinyl-6-chloropyrazinecarboxylate (Ie-1).—A mixture of Ic-1 (23.4 g, 0.1 mole), 30% aqueous H_2O_2 (35 ml), and acetic acid (300 ml) was stirred for 18 hr at room temperature. The solid then was removed by filtration, washed with acetic acid, dried, and recrystallized.

8. Methyl 3-Amino-5-mesyl-6-chloropyrazinecarboxylate (Ie-2).—A suspension of Ic-1 (7.0 g, 0.03 mole) in acetic acid (90 ml) and 30% aqueous H_2O_2 (10 ml) was stirred at room temperature. After 60 hr, more 30% H_2O_2 (2 ml) was added, and stirring was continued for a total reaction time of 160 hr. The solid was removed by filtration, washed with acetic acid, dried, and recrystallized.

9. Methyl 3-Amino-5-hydroxy-6-chloropyrazinoate (If).—A mixture of Ie-1 (7.5 g, 0.03 mole), acetic acid (75 ml), and water (12 ml) was heated on a steam bath for 3 hr. The product grad-

ually crystallized from the reaction mixture during the heating period and continued after cooling. This material was separated by filtration, dried, and recrystallized.

Attempts to convert Ib to If by heating with NaOH solutions led to the formation of Va or Vb depending upon the reaction conditions. Esterification of Vb to If was unsuccessful.

10. 3-Amino-5,6-dichloropyrazinecarboxylic Acid (Va).—Compound Ib (1.8 g, 0.0081 mole) was refluxed with a solution of NaOH (648 mg, 0.324 mole) in water (120 ml) for 10 min. The hot solution was filtered and acidified with HCl to give 1.5 g (91%) of Va, mp 228.5° dec.

Anal. Calcd for $C_5H_3Cl_2N_3O_2$: C, 28.87; H, 1.44; Cl, 34.09. Found: C, 29.30; H, 1.65; Cl, 33.44.

11. 3-Amino-5-hydroxy-6-chloropyrazinecarboxylic Acid (Vb).—A mixture of Ib (4.0 g, 0.018 mole) and 5% NaOH solution (55 ml, 0.688 mole) was stirred and heated on a steam bath for 2.5 hr. The resulting solution was cooled and acidified with HCl. The precipitate was removed by filtration, washed with water, dried, and recrystallized twice from aqueous ethanol to give 400 mg (12%) of Vb, mp 210° dec.

Anal. Calcd for $C_5H_4ClN_3O_3$: C, 31.68; H, 2.13; N, 22.17. Found: C, 31.64; H, 2.22; N, 22.27.

12. Methyl 3,5-Diaminopyrazinecarboxylate (Ig-1).—A mixture of Id-1 (14.2 g, 0.07 mole), 5% Pd-C catalyst (9 g), MgO (4.0 g, 0.1 mole), and methanol (250 ml) was shaken in an atmosphere of hydrogen for 18 hr at room temperature at an initial pressure of 2.1 kg/cm². The pressure drop indicated an absorption of 0.07 mole of hydrogen. The mixture was filtered, and the solids were extracted with a boiling solution of 2-propanol (500 ml) and water (250 ml). The methanol filtrate and the 2-propanol–water extract were united and concentrated to a volume of 100 ml and cooled. The product which precipitated weighed 10 g (85%) and was purified by recrystallization.

Four other esters, Ig-2,3,4,5, were prepared by a procedure similar to Ig-1 above, wherein the appropriate ester was substituted for Id-1; the data are recorded in Table II.

13. Methyl 3,5-Diamino-6-bromopyrazinecarboxylate (Ih-1).—A solution of bromine (2.1 g, 0.013 mole) in acetic acid (10 ml) was added to a suspension of Ig-1 (2.0 g, 0.012 mole) in acetic acid (25 ml) at 50°. The mixture was stirred for 10 min at room temperature and the crystalline product that separated was collected on a filter. After recrystallization, the yield was 1.2 g (41%).

14. Methyl 3,5-Diamino-6-iodopyrazinecarboxylate (Ih-2).—A suspension of Ig-1 (1.7 g., 0.01 mole) in water (30 ml) was heated to 70°, then mercuric acetate (3.2 g, 0.01 mole) and a solution of iodine (2.5 g, 0.01 mole) in warm dioxane (20 ml) were added quickly. The mixture was stirred and heated on a steam bath for 5 min, then allowed to cool to room temperature and treated with an aqueous solution of KI (50 ml containing 7.5 g of KI). The red solution quickly deposited a crystalline product which was separated by filtration, dried, and recrystallized.

D. N-Amidino-3-amino-5-substituted Pyrazinecarboxamides. Route a. 1. N-Amidino-3-amino-5-dimethylamino-6-chloropyrazinecarboxamide (IIa-14).—Under anhydrous conditions, Na (5.75 g, 0.25 g-atom) was dissolved in dry methanol (150 ml) and the resulting solution was treated with dry guanidine hydrochloride (26.3 g, 0.275 mole) and stirred for 10 min. The NaCl which formed was removed by filtration under anhydrous conditions and the filtrate was concentrated *in vacuo* to 30 ml. The residue was treated with Id-14 (11.5 g, 0.05 mole), heated for 1 min on a steam bath, and then kept at room temperature for 1 hr. The product that separated was removed by filtration and washed well with water. This material was suspended in water dissolved by the addition of a little HCl and precipitated by the addition of dilute NaOH solution. After filtration and washing with water, the product was dried; mp 216–217°.

By substituting the appropriate ester for Id-14 and the desired guanidine hydrochloride for guanidine hydrochloride itself, the above method was used for the synthesis of each of the compounds which appear in Tables III–V. With methylguanidine and dimethylguanidine, the sulfate salts were used instead of the hydrochlorides. These required heating with sodium methoxide in methanol for 45 min to assure complete conversion to the free guanidine. In some cases it was convenient to isolate the products as the hydrochloride salts using a procedure analogous to the following one.

2. N-Amidino-3-amino-5-dimethylamino-6-chloropyrazinecarboxamide Hydrochloride.—A suspension of IIa-14 (2.0 g, 0.0775 mole) in water (70 ml) was treated with sufficient HCl to effect solution. After filtration, concentrated HCl (5 ml) was added to the filtrate and the crystalline product which separated was removed by filtration and dried, yield 2.2 g (97%). Recrystallization from a mixture of water (50 ml) and concentrated HCl (3 ml) gave pure material, mp 298° dec.

Anal. Calcd for $C_8H_{13}Cl_2N_7O$: C, 32.66; H, 4.45; N, 33.33; Cl, 24.11. Found: C, 33.03; H, 4.43; N, 33.10; Cl, 23.80.

Route b. Step 1. N-Amidino-3-amino-5,6-dichloropyrazinecarboxamide Hydrochloride (IIc-82).—Sodium (920 mg, 0.04 g-atom) was dissolved in 2-propanol (50 ml) under anhydrous conditions, guanidine hydrochloride was added (3.85 g, 0.04 mole) and, after stirring for 30 min, the mixture was filtered. To the filtrate was added Ib (4.44 g, 0.02 mole), and the mixture was refluxed for 15 min and then cooled to 10°. The solid that separated was removed by filtration, dried, and recrystallized from a mixture of water (50 ml) and 6 *N* HCl (3 ml).

Step 2. N-Amidino-3-amino-5-dimethylamino-6-chloropyrazinecarboxamide.—To a solution of IIc-82 (100 mg) in DMF (5 ml) was added 25% aqueous dimethylamine (1 ml). The mixture was heated for 1 hr on a steam bath and then diluted with water (25 ml). The product that separated was removed by filtration and purified by reprecipitation; mp 216–217°.

3. N-Amidino-3-amino-5-guanidino-6-chloropyrazinecarboxamide Dihydrochloride (IIa-48).—A solution of guanidine in 2-propanol was prepared by dissolving sodium (2.3 g, 0.1 g-atom) in 2-propanol (80 ml) and adding guanidine hydrochloride (9.6 g, 0.1 mole). Compound Ic-5 (4.7 g, 0.017 mole) was added and the mixture was refluxed for 30 min. After cooling in ice, the product was separated by filtration and converted to the hydrochloride by recrystallization from dilute HCl. Similar results were obtained when Ic-5 was replaced by Ic-4.