Pyrazine Diuretics. I. N-Amidino-3-amino-6-halopyrazinecarboxamides

JOHN B. BICKING, JAMES W. MASON, OTTO W. WOLTERSDORF, JR., JAMES H. JONES, SARA F. KWONG, CHARLES M. ROBB, AND EDWARD J. CRAGOE, JR.

Merck Sharp and Dohme Research Laboratories, Division of Merck and Co., Inc., West Point, Pennsylvania

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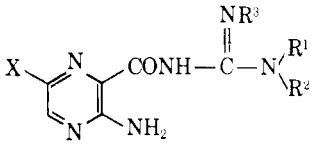
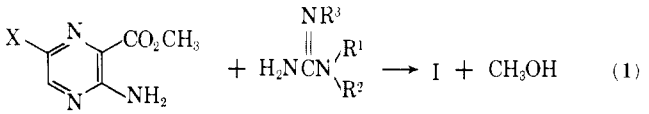
A series of N-amidino-3-amino-6-halopyrazinecarboxamides was prepared principally by the reaction of methyl 3-amino-6-halopyrazinecarboxylates with guanidine or substituted guanidines. A number of these compounds reverse the electrolyte excretion effects of deoxycorticosterone in the adrenalectomized rat and cause natriuresis in the intact rat and dog while leaving unaffected or even repressing K^+ excretion.

One objective of this laboratory is the development of improved diuretic agents. The increased urinary excretion of sodium bicarbonate produced by acetazolamide and of NaCl by the thiazide diuretics is accompanied by increased excretion of K^+ which can cause troublesome side effects in clinical use.[1] The discovery that certain N-amidino-3-aminopyrazinecarboxamides[2] possess saluretic activity while leaving unaffected or even repressing K^+ excretion gave promise that a clinically valuable diuretic without the most serious disadvantage of the sulfonamide diuretics could be developed from this class. More than 300 compounds were prepared and studied pharmacologically to define the structure–activity relationships in this class and to find an agent with an optimally attractive electrolyte excretion pattern. This first paper of a series reports the synthesis and diuretic activity of the N-amidino-3-amino-6-halopyrazinecarboxamides of general structure I.



I

Chemistry.—Most of the N-amidino-3-amino-6-halopyrazinecarboxamides were prepared by the reaction of methyl 3-amino-6-halopyrazinecarboxylates (II) with guanidine or substituted guanidines according to reaction 1 and are listed in Table I.

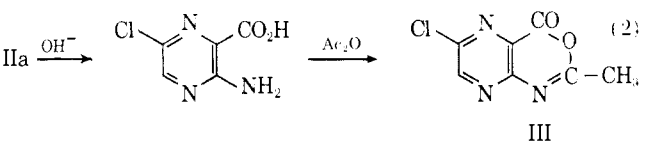


(1)

IIa, X = Cl
b, X = Br
c, X = I

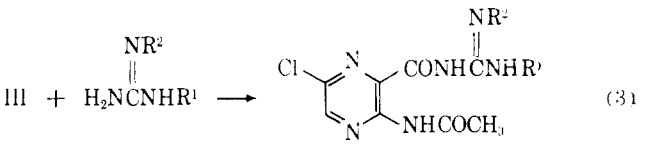
Preparation of the ester IIb by bromination of methyl 3-aminopyrazinecarboxylate[3] in acetic acid has been described by Ellingson and Henry.[4] Chlorination conducted analogously gave methyl 3-chloroamino-6-chloropyrazinecarboxylate which yielded IIa on treatment with a solution of sodium bisulfite. Iodination of methyl 3-aminopyrazinecarboxylate to obtain IIc was carried out by the method of Shepherd[5] for the iodination of 2-aminopyrimidine.

The esters II failed to react, however, with substituted guanidines of low basicity (*i.e.*, acylguanidines, 1,3-diphenylguanidine). The cyclic imino anhydride, 2-methyl-6-chloro-4H-pyrazino[2,3-*d*][1,3]oxazin-4-one (III), prepared by heating 3-amino-6-chloropyrazinecarboxylic acid with acetic anhydride (reaction 2), reacted readily with a number of guanidines which had failed to react with the esters II to give the N-amidino-3-acetamido-6-chloropyrazinecarboxamides (IV) (reaction 3) listed in Table II.



(2)

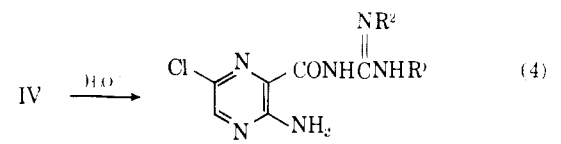
III



(3)

IV

Deacetylation of the compounds of type IV to give the N-amidino-3-amino-6-chloropyrazinecarboxamides listed in Table III was accomplished by treatment with hot dilute HCl. Under these conditions, however, N-(acetylamidino)-3-acetamido-6-chloropyrazinecarboxamide (**23**, prepared from III and acetylguanidine) underwent hydrolysis of both acetyl groups to give N-amidino-3-amino-6-chloropyrazinecarboxamide (**1**).



(4)

Some studies were made on the acylation of **1**. The reaction with acetyl chloride in pyridine under a variety of conditions yielded a diacetyl derivative as the only isolable product. Since this compound is not identical with **23**, it was assigned structure **29**. Benzoylation with benzoyl chloride in pyridine similarly yielded only a dibenzoyl derivative which, on this basis, was assumed to have a structure analogous to that of **29**.

(1) K. H. Beyer and J. E. Baer in "Progress in Drug Research," Vol. 2, E. Jucker, Ed., Interscience Publishers, Inc., New York, N. Y., 1960, pp. 9–69.

(2) N-Amidino-3-amino-6-bromopyrazinecarboxamide, the first compound of this series, was prepared in these laboratories by Dr. P. L. Southwick.

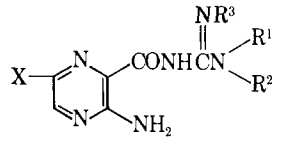
(3) R. C. Ellingson, R. L. Henry, and F. G. McDonald, *J. Am. Chem. Soc.*, **67**, 1711 (1945).

(4) R. C. Ellingson and R. L. Henry, *ibid.*, **71**, 2798 (1949).

(5) R. G. Shepherd, U. S. Patent 2,521,544 (1950).

TABLE I

N-AMIDINO-3-AMINO-6-HALOPYRAZINECARBOXAMIDES BY REACTION 1

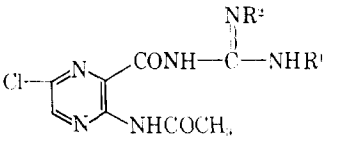


No.	X	R¹	R²	R³	Method	Recrystn. solvent[a]	Yield, %	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	DOCA inhib. score
1[b]	Cl	H	H	H	A	A	70	238 dec.	$C_6H_7ClN_6O$	33.58	33.60	3.29	3.39	39.16	39.04	+3
2	Cl	CH_3	H	CH_3	A	A	20	226–227 dec.	$C_8H_{11}ClN_6O$	39.59	39.53	4.57	4.66	34.63	34.54	+2
3	Cl	CH_3	CH_3	H	B, 45 min., 25°	A	65	198–199 dec.	$C_8H_{11}ClN_6O$	39.59	39.45	4.57	4.47	34.63	34.21	+3
4	Cl	CH_3	H	H	A	A	57	235–236 dec.	$C_7H_9ClN_6O$	36.77	36.83	3.97	3.92	36.76	36.63	+2
5	Cl	n-C_4H_9	n-C_4H_9	H	A	C	88	143.5–145	$C_{14}H_{23}ClN_6O$	51.45	51.71	7.09	7.28	25.72	25.92	+1
6	Cl	$-(CH_2)_5-$		H	A	A	71	219–220 dec.	$C_{11}H_{15}ClN_6O$	46.73	46.86	5.35	5.32	29.73	29.55	+1
7	Cl	H	$-(CH_2)_2-$		B, 25 min., reflux	A	72	225–226.5	$C_8H_9ClN_6O$	39.93	40.27	3.77	3.67	34.92	34.88	+1
8	Cl	H	$-(CH_2)_3-$		B, 1 hr., reflux	B	45	238.5	$C_9H_{11}ClN_6O$	42.44	42.46	4.35	4.28	33.00	33.01	±
9	Cl	C_6H_5	H	H	C	A	56	215–216	$C_{12}H_{11}ClN_6O$	49.57	49.48	3.82	3.85	28.91	28.98	+2
10	Cl	p-ClC_6H_4	H	H	C	A	58	227–228	$C_{12}H_{10}Cl_2N_6O$	44.32	44.30	3.10	3.13	25.85	26.05	±
11	Cl	$C_6H_5CH_2$	H	H	A	A	34	208–209	$C_{13}H_{13}ClN_6O$	51.23	51.66	4.30	4.53	27.58	27.53	+3
12	Cl	$C_6H_5CH_2CH_2$	H	H	A	A	33	214–215 dec.	$C_{14}H_{15}ClN_6O$	52.75	52.61	4.74	4.72	26.37	26.17	+2
13[c]	Cl	$HOCH_2CH_2$	H	H	A	D	59	196.5–197.5	$C_8H_{11}ClN_6O_2 \cdot HCl$	32.55	32.57	4.10	4.14	28.48	28.42	+3
14	Cl	$(CH_2)_7NCH_2CH_2$	H	H	B, 50 min., reflux	E	33	167–168	$C_{13}H_{24}ClN_7O$	50.91	51.27	6.84	6.64	27.71	27.68	±
15[d,e]	Br	H	H	H	A	A	78	234–235.5 dec.	$C_6H_7BrN_6O$	27.82	27.99	2.72	2.90	32.44	31.98	+2
16	Br	CH_3	CH_3	H	B, 16 hr., 25°	A	28	205.5–206.5 dec.	$C_8H_{11}BrN_6O$	33.46	33.47	3.86	3.81	29.27	29.25	+2
17	Br	H	$-(CH_2)_2-$		A	B	72	218 dec.	$C_8H_9BrN_6O$	33.70	33.95	3.18	3.20	29.45	29.75	+2
18	I	H	H	H	A	A	66	228–229 dec.	$C_6H_7IN_6O$[f]	23.54	23.68	2.31	2.27	27.46	27.19	+1
19[c,g]	Cl	$(CH_2)_2$	H	H	A	D	26	320 dec.	$C_{14}H_{16}Cl_2N_{12}O_2 \cdot HCl$	31.83	32.17	3.44	3.54	31.82	31.78	+1

[a] A, solution in dilute HCl, reprecipitation by dilute NaOH solution; B, acetonitrile; C, isopropyl alcohol; D, water; E, ethanol-water; F, isopropyl alcohol–dimethylformamide. [b] Hydrochloride, m.p. 286° dec. *Anal.* Calcd. for $C_6H_7ClN_6O \cdot HCl$: C, 28.70; H, 3.21; N, 33.47. Found: C, 28.89; H, 3.21; N, 33.72. [c] Isolated and purified as the hydrochloride. [d] Hydrochloride, m.p. 265° dec. *Anal.* Calcd. for $C_6H_7BrN_6O \cdot HCl$: C, 24.38; H, 2.73; Br, 27.03; Cl, 12.00. Found: C, 24.01; H, 3.13; Br, 26.73; Cl, 11.67. [e] See ref. 2. [f] *Anal.* Calcd.: I, 41.36. Found: I, 41.30. [g] Prepared from IIa and 1,2-diguanidinoethane.

TABLE II

N-AMIDINO-3-ACETAMIDO-6-CHLOROPYRAZINECARBOXAMIDES BY REACTION 3

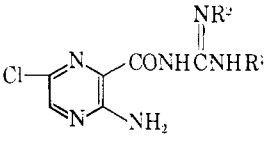


No.	R^1	R^2	M.p., °C.	Recrystn. solvent[a]	Yield, %	Formula	—Carbon, %— Calcd.	Found	—Hydrogen, %— Calcd.	Found	—Nitrogen, %— Calcd.	Found	DOCA inhib. score
20	$C_6H_5CH{=}N$	H	235.5 dec.	F	25	$C_{13}H_{13}ClN_7O_2$	50.07	49.82	3.92	3.90	27.26	27.10	±
21	$(CH_3)_2C{=}N$	H	192.5–193.5 dec.	C	39	$C_{11}H_{14}ClN_7O_2$	42.38	42.79	4.53	4.47	31.46	31.26	±
22	C_6H_5CO	H	194.5–196.5	F	36	$C_{13}H_{12}ClN_6O_4$	50.07	49.94	3.73	3.63	23.52	23.30	+1
23	CH_3CO	H	194.5–196.0	F	24	$C_{10}H_{11}ClN_6O_3$	40.21	40.28	3.71	3.60	28.14	28.03	±
24	C_6H_5	C_6H_5	211–212 dec.	F	52	$C_{26}H_{17}ClN_6O_2$	58.75	58.88	4.19	4.22	20.56	20.49	±

[a] See footnote *a*, Table I.

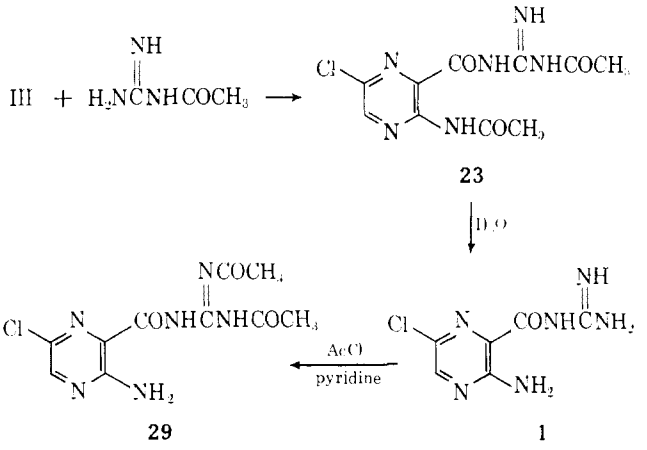
TABLE III

N-AMIDINO-3-AMINO-6-CHLOROPYRAZINECARBOXAMIDES BY REACTION 4

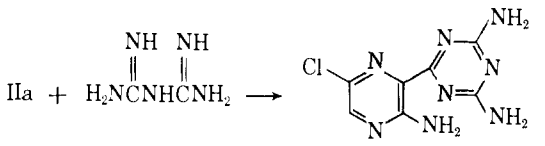


No.	R^1	R^2	M.p., °C.	Recrystn. solvent[a]	Yield, %	Formula	—Carbon, %— Calcd.	Found	Hydrogen, % Calcd.	Found	—Nitrogen, %— Calcd.	Found	DOCA inhib. score
25	$C_6H_5CH{=}N$	H	245–246	F	32	$C_{13}H_{12}ClN_7O$	49.13	49.29	3.81	3.76	30.86	30.61	±
26	$(CH_3)_2C{=}N$	H	202.5–204.5	C	33	$C_9H_{12}ClN_7O$	40.08	40.20	4.49	4.33	36.36	36.32	+2
27	C_6H_5CO	H	209.5–211.0	E	29	$C_{13}H_{10}ClN_6O_2$	48.99	48.93	3.48	3.36	26.37	26.38	±
28	C_6H_5	C_6H_5	224–226	F	76	$C_{25}H_{19}ClN_6O$	58.94	59.21	4.12	4.05	22.91	22.98	±

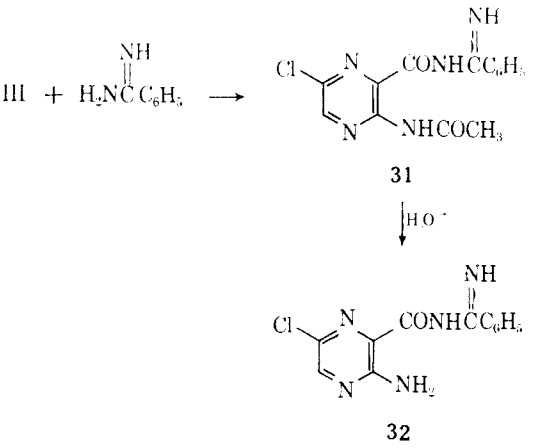
[a] See footnote *a*, Table I.



Acylation reactions similar to 1 and 3 were studied in which guanidine was replaced by biguanide and benzamidine. The ester IIa reacted typically[6] with biguanide to yield not the acylated biguanide but the product of its cyclization, 2-(2,4-diamino-6-*s*-triazinyl)-3-amino-6-chloropyrazine.



The imino anhydride III reacted with benzamidine to yield N-benzimido-3-acetamido-6-chloropyrazinecarboxamide (**31**). Hydrolysis in dilute acid gave the 3-amino compound **32**. Further reactions of III and related imino anhydrides will be reported in later papers in this series.



Pharmacology.—Members of the series of N-amidino-3-aminopyrazinecarboxamides, when administered orally to rats, produced a diuresis accompanied by a marked increase of Na^+ excretion and little or no increase, or even a decrease, in K^+ excretion. Such a pattern of electrolyte excretion is the reverse of that produced by the mineralocorticoids, aldosterone and deoxycorticosterone, which cause sodium retention and increased potassium excretion by the kidney. Thus, it appeared that the compounds might act, at least in part, by blocking the renal effects of the mineralocorticoids. Accordingly, the compounds were tested

(6) K. Rackmann, *Ann. Chem.*, **376**, 163 (1910).

for deoxycorticosterone inhibitory activity by a method[7] based on that of Marcus, *et al.*[8] Saline-loaded, adrenalectomized Holtzmann rats weighing 130 ± 3 g. were injected subcutaneously with 12 γ of deoxycorticosterone acetate (DOCA), an amount sufficient to produce a maximal decrease in the urinary ratio of Na/K. The animals were then injected subcutaneously with the test compound and placed in metabolism cages, and 7-hr. samples of urine were collected. Analyses of the samples for Na^+ and K^+ concentrations gave values from which the urinary Na/K ratios could be calculated. The evidence of inhibition of the electrolyte effects of DOCA is a rise in Na/K ratio over that obtained with DOCA alone. The dose of each compound which will produce a 50% reversal of the DOCA effect is listed in Tables I, II, and III in the following codified form.

Dose producing 50% reversal of DOCA Na/K effect, γ/rat	DOCA inhibition score
<10	+4
10–50	+3
51–100	+2
101–800	+1
>800	±

The scores of the N-amidino-3-aminopyrazinecarboxamides should be compared with those determined for the aldosterone antagonist[9] spironolactone[10] (+1) and for 2.4.7-triamino-6-phenylpteridine[11] (+2).

N-Amidino-3-amino-6-chloropyrazinecarboxamide (**1**) is the most potent DOCA inhibitor of this series, producing a 50% reversal of the DOCA effect at 36 γ/rat. Substitution on the guanidine moiety generally lowered activity, the lowering being, very roughly, proportional to the bulk of the substituents. Only **3** with two methyl substituents, **11** with a benzyl, and **13** with a hydroxyethyl substituent were approximately equipotent with **1**. Replacement of the chlorine atom by bromine or iodine reduced activity. The acylation products of **1**, **29**, and **30** were weakly active (score ±).

The compounds of this series function as nonspecific inhibitors of the mineralocorticoids since, at a higher dose, the more highly active members not only completely reverse the electrolyte effects of DOCA but produce an added natriuresis and antikaliuresis thus giving urinary Na/K ratios greater than those found for adrenalectomized rats.

The diuretic and natriuretic activities in intact rats and dogs[12] closely parallel the DOCA inhibitory activities; compound **1** is most highly active in both species. At comparable doses, the compounds are generally more effective in the rat than in the dog. This activity in intact animals is, likewise, not characteristic of specific antagonists of the mineralocorticoids.

Experimental[13]

Many of the guanidines are commercially available. 1,3-Dimethylguanidine hydrochloride,[14] 1,1-pentamethyleneguanidine hydrochloride,[15] 2-amino-1,4,5,6-tetrahydropyrimidine dihydrochloride,[16] (2-hexahydro-1(2H)-azocinylethyl)guanidine sulfate,[17] phenylguanidine,[18] *p*-chlorophenylguanidine,[19] benzoylguanidine,[20] acetylguanidine,[20] benzylideneaminoguanidine,[21] and 1,2-diguanidinoethane dihydrochloride[22] were prepared by published procedures.

Benzylguanidine Hydrochloride.—A solution of benzylamine (80.3 g., 0.75 mole) and 2-methyl-2-pseudothiuronium sulfate (69.5 g., 0.25 mole) in 200 ml. of water was kept at room temperature for 18 hr. The benzylguanidine sulfate which separated was collected, dissolved in 200 ml. of boiling water, and a saturated aqueous solution of $BaCl_2 \cdot 2H_2O$ (48.8 g., 0.2 mole) was added. The $BaSO_4$ was filtered off, the filtrate was evaporated to dryness at reduced pressure, and the residue was recrystallized from aqueous ethanol to yield 51.5 g. (55%) of product, m.p. 175–178°.

Anal. Calcd. for $C_8H_{11}N_3 \cdot HCl$: N, 22.62. Found: N, 22.45.

Phenethylguanidine hydrochloride prepared analogously was used directly without purification, m.p. 135–137°.

(2-Hydroxyethyl)guanidine Sulfate.—A solution of 2-methyl-2-pseudothiuronium sulfate (13.9 g., 0.05 mole) in ethanolamine (9.2 g., 0.15 mole) was heated for 20 min. at 100°. The solution was evaporated at reduced pressure, and the syrupy residue stirred with ethanol to obtain a crystalline solid which was recrystallized from aqueous ethanol to yield 12.5 g. (41%) of product, m.p. 127–135° (hygroscopic).

Anal. Calcd. for $C_6H_{20}N_6O_6S$: C, 23.68; H, 6.63; N, 27.62. Found: C, 23.91; H, 6.48; N, 27.39.

1,1-Dibutylguanidine Hydrochloride.—Dibutylamine (71.5 g., 0.55 mole) was added to a mixture of 41 ml. of concentrated HCl and 125 ml. of water to give a solution of pH 9.2. While the solution was held at 100°, a 50% aqueous solution of cyanamide (65.1 g., 0.775 mole) was added during 3 hr. After 1 additional hr. at 100°, the solution was evaporated at reduced pressure. The residual salt was dissolved in 100 ml. of water, 50 ml. of 40% NaOH solution was added, and CO_2 was bubbled in to precipitate the bicarbonate salt of 1,1-dibutylguanidine. This salt was dissolved in 100 ml. of warm water, 1 equiv. of concentrated HCl was added, and the solution was chilled to precipitate 88.8 g. (77%) of the product, m.p. 101–106°. A sample recrystallized from water melted at 104.5–106°.

Anal. Calcd. for $C_9H_{21}N_3 \cdot HCl$: C, 52.03; H, 10.67; N, 20.23. Found: C, 52.11; H, 10.20; N, 20.17.

Isopropylideneaminoguanidine.—The reaction of acetone with aminoguanidine hydrochloride was carried out by the method of Finnegan, *et al.*[23] The reaction solution was made strongly basic by addition of 40% NaOH solution to precipitate isopropylideneaminoguanidine which was recrystallized from a cyclohexane–isopropyl alcohol mixture. The product, m.p. 104–109°, was obtained in 86% yield.[24]

Anal. Calcd. for $C_4H_{10}N_4$: N, 49.09. Found: N, 49.50.

Methyl 3-Amino-6-chloropyrazinecarboxylate (IIa).—A mixture of methyl 3-aminopyrazinecarboxylate[3] (90 g., 0.588 mole), 750 ml. of acetic acid, and 3180 ml. of water was heated to 41° to obtain a solution. The solution then was placed in an ice bath

(7) The method was developed and assays conducted by Drs. M. S. Glitzer and S. L. Steelman and their associates of these laboratories. A report in greater detail on their studies on these compounds will appear elsewhere.

(8) F. Marcus, L. P. Romanoff, and G. Pincus, *Endocrinology*, **50**, 286 (1952).

(9) G. W. Liddle, *Metab. Clin. Exptl.*, **10**, 1021 (1961).

(10) C. M. Kagawa, *Endocrinology*, **67**, 125 (1960).

(11) (a) V. D. Wiebelhaus, J. Weinstock, F. T. Brennan, G. Sosnowski, and T. J. Larsen, *Federation Proc.*, **20**, 409 (1961); (b) A. P. Crosley, Jr., L. M. Ronquillo, W. H. Strickland, and F. Alexander, *Ann. Internal Med.*, **56**, 241 (1962).

(12) We are indebted to Dr. J. E. Baer and his associates for these studies.

(13) Melting points were taken in open capillaries and are corrected.

(14) R. Kitawaki, *Nippon Kagaku Zasshi*, **78**, 1435 (1957).

(15) R. A. B. Bannard, A. A. Casselman, W. F. Cockburn, and G. M. Brown, *Can. J. Chem.*, **36**, 1541 (1958).

(16) V. H. Smith and B. E. Christensen, *J. Org. Chem.*, **20**, 829 (1955).

(17) R. P. Mull, M. E. Egbert, and M. R. Dapero, *ibid.*, **25**, 1953 (1960).

(18) R. H. McKee, *Am. Chem. J.*, **26**, 221 (1901).

(19) A. F. Crowther, F. H. S. Curd, and F. L. Rose, *J. Chem. Soc.*, 586 (1948).

(20) W. Traube, *Chem. Ber.*, **43**, 3586 (1910).

(21) J. Thiele, *Ann. Chem.*, **270**, 1 (1892).

(22) K. Sugino, K. Shirai, and K. Aoyagi, *Bull. Chem. Soc. Japan*, **17**, 126 (1942).

(23) W. G. Finnegan, R. A. Henry, and G. B. L. Smith, *J. Am. Chem. Soc.*, **74**, 2981 (1952).

(24) *Cf.* F. Baiocchi, *et al.*, *J. Med. Chem.*, **6**, 431 (1963).

while chlorine was passed in during 25 min. so that a weight gain of about 140 g. occurred. The temperature dropped to 20° during the reaction. The voluminous white precipitate of **methyl 3-chloroamino-6-chloropyrazinecarboxylate** was collected and washed with ice water. A sample recrystallized from acetic acid melted at 142° dec.

Anal. Calcd. for $C_6H_5Cl_2N_3O_2$: C, 32.46; H, 2.27; Cl (total), 31.94; Cl (active), 15.97; N, 18.93. Found: C, 32.82; H, 2.34; Cl (total), 32.09; Cl (active), 16.06; N, 18.90.

The chloramine was stirred with a solution of 150 g. of sodium bisulfite in 900 ml. of water for 1.5 hr. at 25°. The light yellow methyl 3-amino-6-chloropyrazinecarboxylate was collected, washed with water and isopropyl alcohol, and air dried. There was obtained 60 g. (55%) of product, m.p. 159–161°. Recrystallization from ethanol did not raise the melting point.

Anal. Calcd. for $C_6H_6ClN_3O_2$: C, 38.42; H, 3.22; Cl, 18.90; N, 22.40. Found: C, 38.81; H, 3.54; Cl, 18.39; N, 22.83.

Methyl 3-Amino-6-iodopyrazinecarboxylate (IIc).—A mixture of methyl 3-aminopyrazinecarboxylate[3] (30.6 g., 0.2 mole), mercuric acetate (39.8 g., 0.125 mole), and 500 ml. of water was stirred and heated on a steam bath while a solution of iodine (50.8 g., 0.2 mole) in 250 ml. of warm dioxane was rapidly added and for 40 min. thereafter. The mixture was poured into 600 ml. of a 15% solution of KI in water. The precipitated solid was recrystallized from acetic acid to yield 13.5 g. (24%) of product, m.p. 200–202°.

Anal. Calcd. for $C_6H_6IN_3O_2$: C, 25.82; H, 2.17; I, 45.48; N, 15.06. Found: C, 26.18; H, 2.14; I, 45.89; N, 14.81.

3-Amino-6-chloropyrazinecarboxylic Acid.—A mixture of methyl 3-amino-6-chloropyrazinecarboxylate (150 g., 0.8 mole) and 800 ml. of 10% aqueous NaOH solution was stirred and heated 1.5 hr. on a steam bath. The resulting solution was cooled, the precipitated sodium salt was collected and dissolved in 2400 ml. of boiling water, and the solution was acidified to precipitate 127 g. (92%) of product, m.p. 173.5–175.5° dec. A sample recrystallized from methanol melted at 177–178° dec.

Anal. Calcd. for $C_5H_4ClN_3O_2$: C, 34.60; H, 2.32; N, 24.21. Found: C, 34.93; H, 2.55; N, 24.21.

2-Methyl-6-chloro-4H-pyrazino[2,3-*d*][1,3]oxazin-4-one (III).—A solution of 3-amino-6-chloropyrazinecarboxylic acid (127 g., 0.73 mole) in 550 ml. of acetic anhydride was heated for 1 hr. on a steam bath and then chilled. The precipitated product was washed with ethyl acetate and dried *in vacuo* to yield 97 g. (67%), m.p. 155–158° dec. A sample recrystallized for analysis from ethyl acetate melted at 158–160° dec.

Anal. Calcd. for $C_7H_4ClN_3O_2$: C, 42.55; H, 2.04; N, 21.27. Found: C, 42.59; H, 2.14; N, 21.19.

General Methods for N-Amidino-3-amino-6-halopyrazinecarboxamides (Table I).—The guanidine salt (0.1 mole) was added to a solution of sodium methoxide prepared by dissolving Na (0.1 g.-atom) in 100 ml. of methanol. In method A, the methanol was removed by vacuum distillation, the methyl 3-amino-6-halopyrazinecarboxylate (0.02 mole) was added, and the mixture was heated 15 min. on a steam bath. The mixture was cooled and stirred with 100 ml. of water, and the solid product was collected. In method B, the methyl 3-amino-6-halopyrazinecarboxylate (0.02 mole) was added directly to the solution of guanidine in methanol, and the reaction was conducted at the temperature and for the time specified in Table I. The reaction mixture was then cooled and the solid product which separated was collected and washed with water.

In method C, a mixture of arylguanidine (0.1 mole) and methyl 3-amino-6-chloropyrazinecarboxylate (IIa) (0.02 mole) was heated 15 min. on a steam bath. The reaction mixture was dissolved in dilute HCl, and the solution was filtered and basified with dilute NaOH solution to precipitate the product.

The N-amidino-3-amino-6-halopyrazinecarboxamides were purified by recrystallization from the solvents specified in Table I, or by dissolution in dilute HCl and reprecipitation by basification of the solution with dilute NaOH solution.

The **hydrochloride salts** were prepared by dissolving the N-amidino-3-amino-6-halopyrazinecarboxamides in dilute HCl and then adding concentrated HCl which caused the salts to precipitate. They were purified by recrystallization from water.

2-(2,4-Diamino-6-*s*-triazinyl)-3-amino-6-chloropyrazine.—A mixture of IIa (4.7 g., 0.025 mole), biguanide (2.5 g., 0.025 mole), sodium methoxide (1.3 g., 0.025 mole), and 40 ml. of methanol was stirred 20 hr. at room temperature. The solid present was collected, dissolved in 100 ml. of a 5% solution of methanesulfonic acid in water, and reprecipitated by basification with NaOH solution to obtain 5.4 g. (90%) of product with m.p. >360°.

Anal. Calcd. for $C_7H_7ClN_8$: C, 35.23; H, 2.96; Cl, 14.86; N, 46.96. Found: C, 35.69; H, 3.25; Cl, 14.49; N, 46.97.

General Procedure for N-Amidino-3-acetamido-6-chloropyrazinecarboxamides (Table II).—The substituted guanidine (0.1 mole) was added to a refluxing solution of 6-chloro-2-methyl-4H-pyrazino[2,3-*d*][1,3]oxazin-4-one (0.075 mole) in 250 ml. of ethyl acetate. Refluxing was continued for 10 min. The product which precipitated was collected and recrystallized from the solvent specified in Table II.

General Procedure for N-Amidino-3-amino-6-chloropyrazinecarboxamides (Table III).—A mixture of the N-amidino-3-acetamido-6-chloropyrazinecarboxamide (0.02 mole), 60 ml. of 5% HCl and sufficient acetic acid to give a solution were heated 10 min. on a steam bath. The solution was cooled and made basic by the addition of 5% NaOH solution to precipitate the product which was recrystallized from the solvent specified in Table III.

N-(N,N'-Diacetylamidino)-3-amino-6-chloropyrazinecarboxamide (29).—Acetyl chloride (1.9 g., 0.024 mole) was added dropwise during 5 min. to a suspension of compound **1** (2.2 g., 0.01 mole) in 15 ml. of pyridine. The mixture was heated 5 min. at 100°, cooled, and diluted with 50 ml. of water. The product precipitated and was recrystallized from an isopropyl alcohol and dimethylformamide mixture to yield 0.3 g., m.p. 187.5–188.5°.

Anal. Calcd. for $C_{10}H_{11}ClN_6O_4$: C, 40.21; H, 3.71; N, 28.14. Found: C, 40.51; H, 3.94; N, 28.06.

N-(N,N'-Dibenzoylamidino)-3-amino-6-chloropyrazinecarboxamide (30) was prepared analogously in 40% yield using benzoyl chloride and had m.p. 215–217° (from isopropyl alcohol–dimethylformamide).

Anal. Calcd. for $C_{20}H_{15}ClN_6O_3$: C, 56.81; H, 3.58; N, 19.88. Found: C, 56.74; H, 3.44; N, 19.92.

N-Benzimido-3-acetamido-6-chloropyrazinecarboxamide (31).—Benzamidine hydrochloride (2.8 g., 0.018 mole) was added to a solution of NaOH (0.6 g., 0.015 mole) in 15 ml. of water. 6-Chloro-2-methyl-4H-pyrazino[2,3-*d*][1,3]oxazin-4-one (2.0 g., 0.01 mole) was then added, and the mixture was stirred vigorously for 20 min. The solid which formed was collected and recrystallized from an isopropyl alcohol–dimethylformamide mixture to yield 1.1 g. (35%) of product, m.p. 196.5–197.5° dec.

Anal. Calcd. for $C_{14}H_{12}ClN_5O_2$: C, 52.92; H, 3.81; N, 22.05. Found: C, 53.05; H, 3.92; N, 21.89.

N-Benzimido-3-amino-6-chloropyrazinecarboxamide (32).—A solution of **31** (2.0 g., 0.0063 mole) in 20 ml. of 5% HCl was kept 3.5 hr. at room temperature. The solution was made basic with NaOH solution and the precipitated product was recrystallized from an isopropyl alcohol–dimethylformamide mixture to yield 0.4 g. (23%), m.p. 179.5–180.5°.

Anal. Calcd. for $C_{12}H_{10}ClN_5O$: C, 52.27; H, 3.66; N, 25.40. Found: C, 52.21; H, 3.80; N, 25.19.

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