Pyrazine Diuretics. III. 5- and 6-Alkyl, -Cycloalkyl, and -Aryl Derivatives of N-Amidino-3-aminopyrazinecarboxamides

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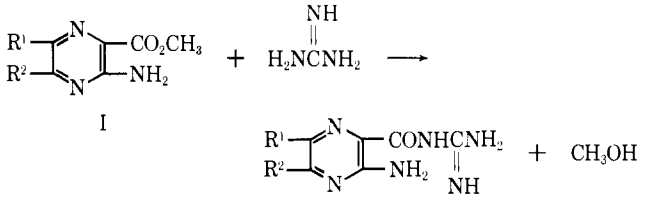
In the evaluation as diuretics of the N-amidino-3-aminopyrazinecarboxamides, a series of 5- and 6-alkyl, -cycloalkyl, and -aryl derivatives was synthesized and studied for effects on renal electrolyte excretion. Several compounds reverse the electrolyte excretion effects of deoxycorticosterone acetate in the adrenalectomized rat, the most highly active being N-amidino-3-amino-6-methylpyrazinecarboxamide.

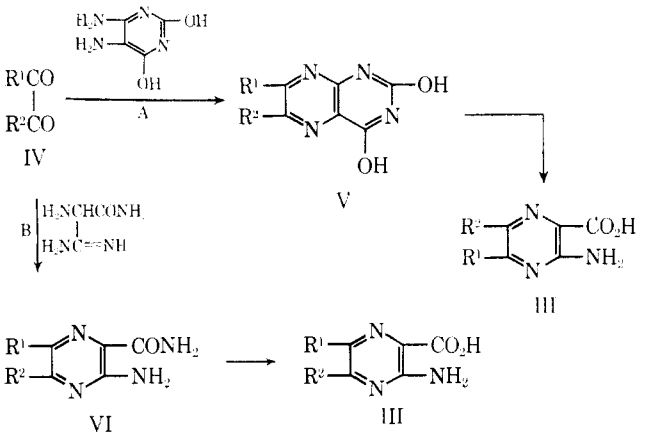
An extensive program of synthesis of N-amidino-3-aminopyrazinecarboxamides has been carried out in these laboratories since the discovery that certain compounds of this class possess saluretic and antikaliuretic activity in animals and man.[1,2] This paper is concerned with the synthesis and diuretic activity of N-amidino-3-aminopyrazinecarboxamides with alkyl, cycloalkyl, or aryl substituents at the 5 and 6 positions of the pyrazine ring and with several of their halogenated derivatives (II).



I II

Chemistry.—The substituted N-amidino-3-aminopyrazinecarboxamides (II) were prepared by the reaction of substituted methyl 3-aminopyrazinecarboxylates (I) (Table I) with guanidine and are listed in Table II.

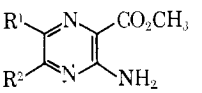
Chart I



The key intermediates for the synthesis of the esters (I) were the substituted 3-aminopyrazinecarboxylic acids (III) prepared by either of the two methods illustrated in Chart I. Substituted glyoxals or α-diketones (IV) were starting materials for both synthetic routes. Method A, that of Weijlard, *et al.*,[3] involved the reaction of IV with 4,5-diaminouracil followed by alkaline hydrolysis of the resulting lumazines (V). Method B, devised by Vogl and Taylor,[4] consisted of the reaction of IV with aminomalonamidamidine followed by alkaline hydrolysis of the resulting 3-aminopyrazinecarboxamides (VI). A convenient synthesis of aminomalonamidamidine dihydrochloride[5] involving catalytic hydrogenolysis of phenylazomalonamidami-

Table I

Methyl 5- and/or 6-Substituted 3-Aminopyrazinecarboxylates by Esterification with Methanol and HCl



Compd no.	R¹	R²	Reaction time, hr	Recrystn solvent[a]	Yield, %	Mp, °C	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Nitrogen, % Calcd	Nitrogen, % Found
2c[b]	H	CH_3	42	A	46	165–167	$C_7H_9N_3O_2$	50.29	50.05	5.43	5.35	25.14	24.88
3c	H	*c*-C_6H_{11}	46	C	31	173–174.5	$C_{12}H_{17}N_3O_2$	61.25	61.35	7.28	7.39	17.86	17.83
4c[c]	H	C_6H_5	44	B	98	231–232	$C_{12}H_{11}N_3O_2$					18.32	18.27
7c	CH_3	C_6H_5	21	C	93	163–164	$C_{13}H_{13}N_3O_2$	64.18	64.42	5.30	5.24	17.27	17.35
8c	C_6H_5	CH_3	21	C	99	162.5–163.5	$C_{13}H_{13}N_3O_2$	64.18	64.26	5.30	5.44	17.27	17.23
10c	C_2H_5	H	24	D	26	85–87.5	$C_8H_{11}N_3O_2$	53.03	53.11	6.12	6.16	23.19	23.26
11c	*c*-C_3H_5	H	3	C	15	112.5–114.5	$C_9H_{11}N_3O_2$	55.95	55.61	5.74	5.64		
12c	*c*-C_6H_{11}	H	6	E	53	126.5–128	$C_{12}H_{17}N_3O_2$	61.25	61.39	7.28	7.12	17.86	17.87
13c[d]	C_6H_5	H	42	C	66	140–141	$C_{12}H_{11}N_3O_2$	62.93	62.72	4.84	4.90	18.32	18.27
14c	*p*-ClC_6H_4	H	46	D	79	181.5–183.5	$C_{12}H_{10}ClN_3O_2$	54.66	54.37	3.82	3.69	15.94	15.92
15c	H	F_3C	19	C	97	195.5–196.5	$C_7H_6F_3N_3O_2$[e]	38.02	38.20	2.73	2.64	19.00	18.91
18c	$-(CH_2)_4-$		24	C	55	154–155	$C_{10}H_{13}N_3O_2$	57.95	58.02	6.32	6.33	20.28	20.46

[a] A, water; B, acetonitrile; C, methanol; D, isopropyl alcohol; E, ethanol. [b] Precursor acid: see ref 3. [c] Precursor acid: F. E. King and P. C. Spensley, *J. Chem. Soc.*, 2144 (1952). [d] Precursor acid: see ref 4. [e] *Anal.* Calcd: F, 25.77. Found: F, 25.84.

(1) 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).

(2) E. J. Cragoe, Jr., O. W. Woltersdorf, Jr., J. B. Bicking, S. F. Kwong, and J. H. Jones, *ibid.*, **10**, 66 (1967).

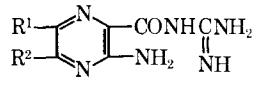
(3) J. Weijlard, M. Tishler, and A. E. Erickson, *J. Am. Chem. Soc.*, **67**, 802 (1945).

(4) O. Vogl and E. C. Taylor, *ibid.*, **81**, 2472 (1959).

(5) E. Shaw and D. W. Woolley, *J. Biol. Chem.*, **181**, 89 (1949).

TABLE II

5- AND/OR 6-SUBSTITUTED N-AMIDINO-3-AMINOPYRAZINECARBOXAMIDES



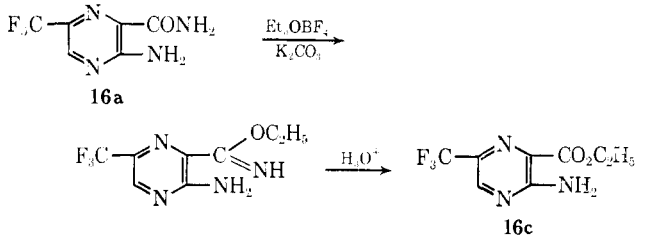
Compd no.	R¹	R²	Prepn method, time (min), temp	Recrystn solvent[a]	Yield, %	Mp, °C dec	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Nitrogen, % Calcd	Nitrogen, % Found	DOCA inhib. score[k]
1d[b,c]	H	H	B, 15, reflux	B	44	200–202	$C_6H_8N_6O$	40.00	40.24	4.48	4.59	46.65	46.70	0
2d	H	CH_3	A, 40, 60°	B	13	210	$C_7H_{10}N_6O$	43.29	43.70	5.19	5.28	43.28	43.50	±
3d	H	c-C_6H_{11}	A, 45, 25°	A	72	221–222	$C_{12}H_{18}N_6O$	54.94	55.04	6.92	6.68	32.04	31.54	0
4d	H	C_6H_5	B, 60, 55°	C	51	224–226	$C_{12}H_{12}N_6O$	56.24	56.56	4.72	5.01	32.80	32.44	±
5d[d,e]	C_6H_5	C_6H_5	A, 10, 95°	A	87	234.5–235.5	$C_{18}H_{16}N_6O$	65.04	64.59	4.85	4.62	25.29	24.88	±
6d[f]	CH_3	CH_3	B, 50, 50°	C	39	247	$C_8H_{12}N_6O$	46.14	45.90	5.81	5.98	40.36	40.37	±
7d	CH_3	C_6H_5	A, 5, 95°	A	77	212–213	$C_{13}H_{14}N_6O$	57.77	58.08	5.22	5.33	31.09	31.32	±
8d	C_6H_5	CH_3	A, 5, 95°	A	90	218–219	$C_{13}H_{14}N_6O$	57.77	57.94	5.22	5.06	31.09	30.73	+1
9d	CH_3	H	A, 60, 25°	A	89	218–219	$C_7H_{10}N_6O$	43.29	43.50	5.19	5.07	43.28	43.25	+2
10d	C_2H_5	H	A, 60, 25°	A	53	207.5–209.5	$C_8H_{12}N_6O$	46.14	46.47	5.81	5.69	40.36	40.34	±
11d	c-C_3H_5	H	A, 10, 95°	A	62	196.5–199	$C_9H_{12}N_6O$	49.08	49.35	5.49	5.49	38.16	37.94	±
12d	c-C_6H_{11}	H	A, 45, 25°	A	61	228–230	$C_{12}H_{18}N_6O$	54.94	55.25	6.92	6.83	32.04	31.78	0
13d	C_6H_5	H	B, 30, 55°	D	74	194.5–195.5	$C_{12}H_{12}N_6O$	56.24	56.63	4.72	5.03	32.80	32.99	+1
14d[g]	p-ClC_6H_4	H	A, 30, 25°	D	70	282–285	$C_{12}H_{11}ClN_6O \cdot HCl$	44.05	43.74	3.70	3.79	25.69	25.31	±
15d	H	F_3C	B, 15, reflux	A	26	222–223	$C_7H_7F_3N_6O$[h]	33.88	34.20	2.84	3.07	33.87	33.43	±
16d	F_3C	H	B, 3, reflux	A	57	230–232	$C_7H_7F_3N_6O$	33.88	33.74	2.84	3.09	33.87	33.98	±
17d[i,c]	–CH=CHCH=CH–		A, 5, 65°	A	56	211–213	$C_{10}H_{10}N_6O$	52.17	52.58	4.38	4.49	36.51	36.49	+1
18d[e]	–$(CH_2)_4$–		A, 5, 95°	A	25	220–221	$C_{10}H_{14}N_6O$	51.27	50.79	6.02	6.15	35.88	35.33	0
19d[g]	Br	CH_3	B, 45, 50°	D	68	290	$C_7H_9BrN_6O \cdot HCl$	27.16	27.31	3.26	3.32	27.15	26.89	±
20d	Br	C_6H_5	A, 60, 25°	A	66	234–236	$C_{12}H_{11}BrN_6O$	43.00	42.86	3.31	3.38	25.08	24.84	±
21d	C_6H_5	Cl	A, 60, 25°	A	69	214–216	$C_{12}H_{11}ClN_6O$	49.57	49.31	3.81	3.74	28.91	28.60	±
22d	C_6H_5	$(CH_3)_2N$	A, 10, 95°	A	67	205–206	$C_{14}H_{17}N_7O$	56.17	56.52	5.73	5.82	32.76	32.52	0
23d[j]	CH_3	$(CH_3)_2N$	A, 60, 60°	D	28	262	$C_9H_{15}N_7O \cdot 2HCl$	34.85	34.34	5.53	5.50	31.61	31.38	+1

[a] A, solution in dilute HCl, reprecipitation by dilute NaOH solution; B, ethanol; C, acetonitrile and H_2O; D, isopropyl alcohol. [b] Precursor methyl ester: R. C. Ellingson, R. L. Henry, and F. G. McDonald, *J. Am. Chem. Soc.*, **67**, 1711 (1945). [c] Prepared by Dr. J. H. Jones. [d] Precursor methyl ester: E. C. Taylor, Jr., *J. Am. Chem. Soc.*, **74**, 1951 (1952). [e] Prepared by Mr. O. W. Woltersdorf, Jr. [f] Precursor methyl ester: R. C. Ellingson and R. L. Henry, *J. Am. Chem. Soc.*, **70**, 1257 (1948). [g] Isolated and purified as the hydrochloride. [h] *Anal.* Calcd: F, 22.97. Found: F, 22.73. [i] Precursor methyl ester: A. H. Gowenlock, G. T. Newbold, and F. S. Spring, *J. Chem. Soc.*, 622 (1945). [j] Isolated and purified as the dihydrochloride. [k] The score is determined from the dose (micrograms per rat) necessary to produce a 50% reversal of the Na/K effects of a 12-μg dose of DOCA: +3 = 10–50 μg, +2 = 51–100, +1 = 101–800, ± = >800, and 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 rats weighed 130 ± 3 g.

dine hydrochloride[6] is described in the Experimental Section.[7]

Both method A or B theoretically can produce either or both of two isomeric aminopyrazinecarboxylic acids when substituted glyoxals or unsymmetrical α-diketones are used as starting materials. It has been established that methylglyoxal yields by method A, 3-amino-5-methylpyrazinecarboxylic acid (**2b**),[3] but by method B, 3-amino-6-methylpyrazinecarboxylic acid[4] (**9b**).[8] Nmr spectra[9] were obtained of the methyl esters of **2b** and **9b**, and the chemical shifts observed for the lone aromatic proton in each isomer were used for the assignment of structures to new aminopyrazinecarboxylic acids prepared in this study. Resonance of the 6-position proton of the methyl ester of **2b** appears at τ 2.19, of the 5-position proton of the methyl ester of **9b** at τ 1.80.

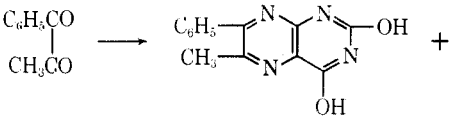
Cyclohexylglyoxal thus was shown to react analogously to methylglyoxal and yield, by method A, 3-amino-5-cyclohexylpyrazine carboxylic acid (singlet at τ 2.18) and, by method B, 3-amino-6-cyclohexylpyrazinecarboxylic acid (singlet at τ 1.82). When trifluoromethylglyoxal (prepared *in situ* by hydrolysis of 1,1,1-trifluoro-3,3-dibromoacetone)[10] reacted with aminomalonamidamidine, two isomeric 3-aminotrifluoromethylpyrazinecarboxamides were obtained. The nmr spectra of these isomers showed that the isomer of mp 193–195° had its most paramagnetic aromatic resonance as a single proton band at τ 1.79, whereas the isomer of mp 220–221° had the equivalent resonance at τ 1.38. The differential chemical shifts ($\Delta\delta$) for the three pairs of isomers reported here then are $-2.19 + 1.80 = -0.39$; $-2.18 + 1.82 = -0.36$; and $-1.79 + 1.38 = -0.41$. This is consistent with the conclusion that the most paramagnetic aromatic resonance arises from a 5-position proton and that the most diamagnetic aromatic resonance corresponds to a 6-position proton with the $\Delta\delta$ for an isomer pair being close to -0.40 τ units. Therefore, the isomer with mp 193–195° is 3-amino-5-trifluoromethylpyrazinecarboxamide (**15a**), and the isomer with mp 220–221° is 3-amino-6-trifluoromethylpyrazinecarboxamide (**16a**). Basic hydrolysis of the amide **15a** gave 3-amino-5-trifluoromethylpyrazinecarboxylic acid in high yield. A similar conversion of the amide **16a** to the acid was unsuccessful because the 6-trifluoromethyl group failed to survive under hydrolytic conditions.



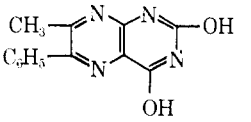
16a **16c**

Since the acid was unavailable, the necessary ester function was introduced by treatment of **16a** with the Meerwein reagent,[11] triethyloxonium fluoroborate, and hydrolysis of the resulting imino ether with dilute acid. Ethyl 3-amino-6-trifluoromethylpyrazinecarboxylate (**16c**) was obtained in 11% yield.

1-Phenyl-1,2-propanedione reacted with 4,5-diaminouracil (method A) to give isomeric lumazines, mp 281.5–282.5° dec and 254.5–255.5° dec. These compounds have been assigned arbitrarily the structures **7a** (6-methyl-7-phenyllumazine), and **8a** (6-phenyl-7-methyllumazine), respectively.



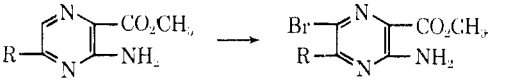
7a



8a

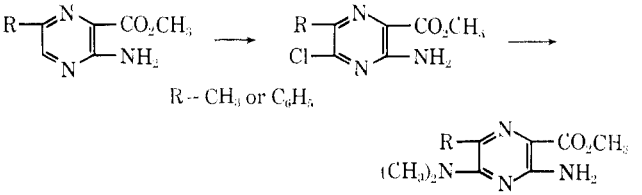
The methyl esters I were prepared, with one exception, by the reaction of the substituted 3-aminopyrazinecarboxylic acids with methanol in the presence of HCl. 6-Methyl-3-aminopyrazinecarboxylic acid was decarboxylated under these conditions. It was converted to the methyl ester by reaction of its sodium salt with dimethyl sulfate. The properties of the methyl esters are listed in Table I.

Some studies were made of the halogenation of methyl esters with unsubstituted positions on the pyrazine ring. Methyl 3-amino-5-methyl- and methyl 3-amino-5-phenylpyrazinecarboxylate were brominated at the 6 position by the action of bromine in acetic acid. Methyl 3-amino-6-methyl- and methyl 3-amino-6-phenylpyrazinecarboxylate were chlorinated at the



R = CH_3 or C_6H_5

5 position when stirred with sulfuryl chloride at room temperature. Halogen atoms at the 5 position of the methyl 3-aminopyrazinecarboxylates previously have been shown to be readily displaced by nucleophiles.[2] The 5-chloro esters reacted smoothly with dimethylamine in alcohol to yield the 5-dimethylamino esters.



R = CH_3 or C_6H_5

Structure-Activity Relationships.—The substituted N-amidino-3-aminopyrazinecarboxamides (II) were tested for deoxycorticosterone acetate (DOCA) inhibitory activity in adrenalectomized rats.[1,12] The

(6) L. H. Smith, Jr., and P. Yates, *J. Am. Chem. Soc.*, **76**, 6080 (1954).

(7) This process was developed and a large quantity of aminomalonamidamidine dihydrochloride was prepared by W. K. Russ, Jr., A. P. Sullivan, Jr., and R. Pospolita.

(8) Each sequence of reactions is assigned an arabic numeral. This numeral followed by the letter a designates the intermediate lumazine or pyrazinecarboxamide, by the letter b the pyrazinecarboxylic acid, by c the ester, and by d the N-amidinopyrazinecarboxamide.

(9) Nmr spectra were taken in DMSO with a Varian A-60 spectrometer. We are indebted to Drs. N. R. Trenner and B. Arison for taking and interpreting these spectra.

(10) R. Belcher, A. Sykes, and J. C. Tatlow, *J. Chem. Soc.*, 2393 (1957).

(11) H. Meerwein, E. Battenberg, H. Gold, E. Pfeil, and J. Willfang, *J. Prakt. Chem.*, **154**, 83 (1939).

(12) These assays were conducted by Drs. M. S. Glitzer and S. L. Steelman and their associates of these laboratories.

dose of each compound which will produce a 50% reversal of the electrolyte effects of a 12-μg dose of DOCA has been codified and the score is listed in Table II.

The only highly active (+2) compound of this series is N-amidino-3-amino-6-methylpyrazinecarboxamide (**9d**), which is equipotent with the analogous 6-bromo compound[1] but less active than the 6-chloro analog[1] (+3). The strong dependence of DOCA inhibitory activity on structure is seen in the marked reduction in activity when the methyl group of **9d** is replaced by hydrogen or ethyl or shifted to the 5 position of the pyrazine ring.

Substitution of the 5 position of **9d** or of the analogous 6-bromo compound with methyl (to give **6d** and **19d**, respectively) reduced inhibitory activity markedly.

N-Amidino-3-amino-6-phenylpyrazinecarboxamide (**13d**) is less active than **9d** but is still approximately equipotent with the DOCA antagonist spironolactone.[13] Here again, a shift of the phenyl group to the 5 position reduced activity.

Substitution of the 5 position of **9d** with dimethylamino (to give **23d**) reduced activity. In contrast, a similar substitution in the N-amidino-3-amino-6-halopyrazinecarboxamide series enhanced DOCA inhibitory activity.[2]

Experimental Section[14,15]

7-Cyclohexyllumazine (3a).—Cyclohexylglyoxal hemihydrate (14.9 g, 0.1 mole) was added to a suspension of 5,6-diaminouracil hydrochloride (17.9 g, 0.1 mole) in 250 ml of H_2O and the mixture was stirred and heated 1 hr at 100°. The solid precipitate obtained upon cooling was collected, dissolved in hot dilute NaOH, and reprecipitated by acidification of the solution with HCl. Recrystallization from aqueous acetic acid gave 7.5 g (30%) of product, mp 217–227°. A sample recrystallized from aqueous acetic acid had mp 229–231°.

Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 58.52; H, 5.73; N, 22.75. Found: C, 58.59; H, 5.52; N, 23.02.

6- (or 7-) Methyl-7- (or 6-) phenyllumazine (7a) and 6- (or 7-) Phenyl-7- (or 6-) methyllumazine (8a).—A mixture of 4,5-diaminouracil hydrochloride (103.6 g, 0.58 mole), 1-phenyl-1,2-propanedione (103.7 g, 0.7 mole), H_2O (1500 ml), and concentrated NH_4OH (300 ml) was stirred and heated 1 hr at 90°. The mixture then was cooled and neutralized with acetic acid to precipitate a yellow solid, mp 202–223° dec. Recrystallization from acetic acid gave a crop of crystals, mp 276–279° dec. The filtrate on standing yielded a second crop, mp 250–253°.

Recrystallization of the high-melting product from acetic acid gave 82.4 g (56%) of crystalline product, mp 281.5–282.5° dec, designated as **7a**.

Anal. Calcd for $C_{13}H_{10}N_4O_2$: C, 61.41; H, 3.96; N, 22.04. Found: C, 61.78; H, 3.91; N, 22.08.

Recrystallization of the low-melting product from acetic acid gave 32 g (22%) of crystals, mp 254.5–255.5° dec, designated as **8a**.

Anal. Calcd for $C_{13}H_{10}N_4O_2$: C, 61.41; H, 3.96; N, 22.04. Found: C, 61.79; H, 4.09; N, 22.14.

6,7,8,9-Tetrahydroalloxazine (18a).—5,6-Diaminouracil hydrochloride (76 g, 0.428 mole), 1,2-cyclohexanedione (57 g, 0.51 mole), and $NaHCO_3$ (57 g, 0.68 mole) were added to water (2 l.), and the solution was heated 0.5 hr on a steam bath. The solution was cooled, filtered, and adjusted to pH 2 by addition of 5% HCl. The precipitated product weighed 104 g (90%), mp 329.5–330.5°. A sample recrystallized from aqueous ethanol had mp 331.5–332.5°.

Anal. Calcd for $C_{10}H_{10}N_4O_2$: C, 55.04; H, 4.62; N, 25.68. Found: C, 55.29; H, 4.70, N, 25.58.

Aminomalonamidamidine Dihydrochloride.—Phenylazomalonamidamidine hydrochloride[6] (530 g, 2.19 moles) suspended in H_2O (3.66 l.) with 269 g of 5% Pt–C catalyst was hydrogenated at room temperature under an initial pressure of 2.8 kg/cm² of hydrogen. The theoretical 4.38 moles of hydrogen was absorbed in 6 hr. The catalyst was removed by filtration, the filtrate was extracted with five 2-l. portions of ether, and the aqueous solution was concentrated by distillation at 2–4 mm to 300 ml. Concentrated HCl (325 ml) and then isopropyl alcohol (2.92 l.) were added to cause the product to precipitate as an oil which soon crystallized. There was obtained 275 g (66%) of product, mp 217° dec.

3-Amino-6-ethylpyrazinecarboxamide (10a).—Aminomalonamidamidine dihydrochloride (52.5 g, 0.28 mole) was added to a solution of ethylglyoxal (28.8 g, 0.335 mole) in H_2O (450 ml) at 5°. Concentrated NH_4OH (65 ml) was added to make the solution basic. After 20 hr at 25°, the precipitated product was collected and recrystallized from isopropyl alcohol to obtain 17.5 g (38%) of **10a**, mp 160–167°. A sample recrystallized from isopropyl alcohol has mp 165.5–168.5°.

Anal. Calcd for $C_7H_{10}N_4O$: N, 33.72. Found: N, 33.83.

3-Amino-6-cyclopropylpyrazinecarboxamide (11a) was prepared analogously from cyclopropylglyoxal in 33% yield and has mp 185.5–187.5° (from isopropyl alcohol).

Anal. Calcd for $C_8H_{10}N_4O$: C, 53.92; H, 5.66. Found: C, 53.83; H, 5.43.

3-Amino-6-cyclohexylpyrazinecarboxamide (12a) was prepared analogously from cyclohexylglyoxal hemihydrate in 27% yield and has mp 185.5–187° (from ethanol).

Anal. Calcd for $C_{11}H_{16}N_4O$: C, 59.98; H, 7.32; N, 25.44. Found: C, 60.07; H, 7.39; N, 25.22.

3-Amino-6-*p*-chlorophenylpyrazinecarboxamide (14a) was prepared analogously from *p*-chlorophenylglyoxal monohydrate in 38% yield and has mp 246.5–248.5° (from 95% ethanol).

Anal. Calcd for $C_{11}H_9ClN_4O$: C, 53.13; H, 3.65; N, 22.53. Found: C, 52.83; H, 3.68; N, 22.33.

3-Amino-5-trifluoromethylpyrazinecarboxamide (15a) and 3-Amino-6-trifluoromethylpyrazinecarboxamide (16a).—A mixture of 1,1,1-trifluoro-3,3-dibromoacetone[16] (97.8 g, 0.363 mole), sodium acetate trihydrate (98.6 g, 0.725 mole), and 300 ml of H_2O was heated, with stirring, to 100° during 20 min. After 5 min at 100°, the solution was rapidly chilled to 0° and added to a solution of aminomalonamidamidine dihydrochloride (68.5 g, 0.363 mole) in 720 ml of H_2O at 0°. The pH of the solution was adjusted to 8–9 by addition of about 140 ml of concentrated NH_4OH and maintained at 8–9 during the reaction by additional small portions of the base. The mixture was stirred 20 hr at 25°. The green solid precipitate was collected and extracted with two 200-ml portions of boiling acetonitrile. The combined extracts were evaporated *in vacuo*. The residual brown solid was recrystallized from acetic acid to yield 20 g (27%) of yellow crystals of **15a**, mp 193–195°. A sample of **15a** recrystallized from acetic acid had mp 195–196°.

Anal. Calcd for $C_6H_5F_3N_4O$: C, 34.96; H, 2.44; F, 27.65; N, 27.18. Found: C, 35.39; H, 2.71; F, 27.53; N, 27.19.

The acetic acid mother liquor from the recrystallization of **15a** was diluted with H_2O to precipitate 7.1 g of a light yellow solid, mp 211–214°. Recrystallization from aqueous acetic acid gave **16a**, mp 220–221°.

Anal. Calcd for $C_6H_5F_3N_4O$: C, 34.96; H, 2.44; F, 27.65; N, 27.18. Found: C, 35.26; H, 2.75; F, 27.24; N, 26.89.

3-Amino-6-ethylpyrazinecarboxylic Acid (10b).—A mixture of **10a** (24.4 g, 0.147 mole) and 200 ml of 10% NaOH solution was stirred and heated on a steam bath for 30 min. When the resulting solution was chilled, the sodium salt of **10b** precipitated. The salt was collected and dissolved in hot water, and the solution was acidified to congo red with HCl to precipitate 22.8 g (93%) of **10b**, mp 149–152°, which was esterified without further purification or analysis.

3-Amino-6-cyclopropylpyrazinecarboxylic acid (11b) was prepared by the analogous hydrolysis of **11a** in 61% crude yield, mp 169–172°.

3-Amino-6-cyclohexylpyrazinecarboxylic acid (12b) was prepared by the analogous hydrolysis of **12a** in 80% crude yield, mp 125–135°. A sample purified by repeated dissolution in dilute aqueous NaOH and precipitation by acidification with HCl had mp 138.5–139.5°.

Anal. Calcd for $C_{11}H_{15}N_3O_2$: C, 59.71; H, 6.83; N, 18.99. Found: C, 59.43; H, 6.78; N, 18.92.

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

(14) Melting points were taken in open capillary tubes and are corrected.

(15) Microanalytical data were obtained by Mr. K. B. Streeter, Mr. Y. C. Lee, and their staff.

(16) E. T. McBee and T. M. Burton, *J. Am. Chem. Soc.*, **74**, 3902 (1952).

3-Amino-6-*p*-chlorophenylpyrazinecarboxylic Acid (14b).—A mixture of **14a** (17.5 g, 0.071 mole) and 5% NaOH solution (1.2 l.) was heated and stirred 5.5 hr on a steam bath and then cooled to precipitate the sodium salt of **14b**. The salt was dissolved in boiling water and the solution was acidified with HCl. The precipitated product was recrystallized from acetic acid to obtain 10.5 g (60%) of **14b**, mp 207–213°. A sample recrystallized from acetic acid had mp 213–215°.

Anal. Calcd for $C_{11}H_8ClN_3O_2$: C, 52.92; H, 3.23; N, 16.83. Found: C, 52.69; H, 3.19; N, 16.89.

3-Amino-5-trifluoromethylpyrazinecarboxylic Acid (15b).—A mixture of **15a** (18.5 g, 0.09 mole) and 5% NaOH solution (740 ml) was heated 10 min on a steam bath. The resulting solution was chilled and acidified to congo red with 6 *N* HCl to precipitate 17.8 g (95%) of **15b**, mp 185–186° dec.

Anal. Calcd for $C_6H_4F_3N_3O_2$: C, 34.79; H, 1.95; N, 20.29. Found: C, 35.10; H, 1.95; N, 20.23.

3-Amino-5-cyclohexylpyrazinecarboxylic Acid (3b).—A solution of **3a** (18.5 g, 0.075 mole) and NaOH (9.0 g, 0.225 mole) in H_2O (90 ml) was heated 17 hr at 165° in a sealed autoclave. The resulting mixture was added to 200 ml of H_2O and filtered, and the filtrate was acidified with HCl to precipitate the crude acid which was recrystallized from isopropyl alcohol to obtain 8.0 g (48%) of **3b**, mp 182.5–183.5°.

Anal. Calcd for $C_{10}H_{15}N_3O_2$: C, 59.71; H, 6.83; N, 18.99. Found: C, 59.99; H, 6.56; N, 18.98.

3-Amino-5- (or 6-) phenyl-6- (or 5-) methylpyrazinecarboxylic Acid (7b).—A solution of **7a** (40.7 g, 0.16 mole) and NaOH (14.9 g, 0.372 mole) in H_2O (185 ml) was heated 3.5 hr at 170°. The solution was cooled to precipitate the sodium salt of **7b**. The salt was dissolved in 600 ml of boiling H_2O and the solution was acidified with acetic acid to precipitate 29.6 g (81%) of **7b**, mp 193.5–194.5°. The melting point after recrystallization from acetic acid was unchanged.

Anal. Calcd for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.97; H, 4.68; N, 18.46.

3-Amino-5- (or 6-) methyl-6- (or 5-) phenylpyrazinecarboxylic Acid (8b).—The analogous hydrolysis of **8a** gave 19.1 g (69%) of **8b**, mp 155–156° (from aqueous ethanol).

Anal. Calcd for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.95; H, 4.80; N, 18.54.

3-Amino-5,6,7,8-tetrahydroquinoxaline-2-carboxylic Acid (18b).—A solution of **18a** (45 g, 0.206 mole) and NaOH (45 g, 1.125 moles) in H_2O (375 ml) was heated 20 hr at 170°. The mixture was cooled, diluted with 100 ml of water and filtered, and the filtrate was acidified with 6 *N* hydrochloric acid to pH 2 to precipitate the crude acid. Recrystallization from aqueous ethanol gave 14 g (35%) of **18b**, mp 174.5°.

Anal. Calcd for $C_9H_{11}N_3O_2$: C, 55.95; H, 5.74; N, 21.75. Found: C, 55.77; H, 5.67; N, 21.73.

Methyl 5- and/or 6-Substituted 3-Aminopyrazinecarboxylates. General Method for Table I.—The 5- and/or 6-substituted 3-aminopyrazinecarboxylic acid (0.1 mole) was stirred with a solution of HCl (300 g) in methanol (1 l.) at 25° for the time specified in Table I. The mixture was then concentrated by vacuum distillation to about one-quarter volume, poured into 750 ml of H_2O, and made basic by the addition of solid $NaHCO_3$, and the precipitated ester was collected and recrystallized.

Methyl 3-Amino-6-methylpyrazinecarboxylate (9c).—The sodium salt of 3-amino-6-methylpyrazinecarboxylic acid was prepared by dissolving the acid[4] in hot 5% NaOH and chilling to precipitate the salt which was collected and air dried. A mixture of the salt (97 g, 0.55 mole), $(CH_3)_2SO_4$ (77 g, 0.61 mole), and 700 ml of methanol was stirred 19 hr at 25°. The resulting near solution was filtered, and the filtrate was evaporated to dryness by vacuum distillation. The residue was stirred with 200 ml of saturated $NaHCO_3$ solution. The insoluble product was collected, washed with water, and dried. There was obtained 18 g (20%) of **9c**, mp 138.5–140.5°. A sample was recrystallized from benzene with unchanged melting point.

Anal. Calcd for $C_7H_9N_3O_2$: C, 50.29; H, 5.43; N, 25.14. Found: C, 50.45; H, 5.49; N, 25.02.

Ethyl 3-Amino-6-trifluoromethylpyrazinecarboxylate (16c).—A hot solution of the amide **16a** (2.0 g, 0.0097 mole) in ethylene chloride (350 ml) was added to a solution of triethyloxonium fluoroborate (20.0 g, 0.105 mole) in ethylene chloride (350 ml). After 3 hr, the ethylene chloride was evaporated *in vacuo*. The residual oil was stirred with a 5 *N* K_2CO_3 solution (40 ml) for 3 min; H_2O (50 ml) was added, and the imino ether was taken up in ether and then extracted into 1 *N* H_2SO_4 solution (100 ml). After 3 hr, the product was extracted with ether, dried ($MgSO_4$), and distilled at reduced pressure. The distilled product solidified and was recrystallized from hexane to yield 250 mg (11%) of the ester, mp 91.5–93.5°.

Anal. Calcd for $C_8H_8F_3N_3O_2$: C, 40.86; H, 3.43; N, 17.87. Found: C, 41.51; H, 3.87; N, 17.45.

Methyl 3-Amino-5-methyl-6-bromopyrazinecarboxylate (19c).—A solution of bromine (4.2 g, 0.026 mole) in 3 ml of acetic acid was added during 20 min to a solution of methyl 3-amino-5-methylpyrazinecarboxylate (**2c**) (4.2 g, 0.025 mole) in acetic acid (15 ml). The solution was poured into 150 ml of H_2O. The precipitated product was recrystallized twice from acetic acid to yield 3.6 g (59%) of **19c**, mp 179–181°.

Anal. Calcd for $C_7H_8BrN_3O_2$: C, 34.16; H, 3.28; N, 17.08. Found: C, 34.42; H, 3.26; N, 17.00.

Methyl 3-Amino-5-phenyl-6-bromopyrazinecarboxylate (20c).—A solution of bromine (11.2 g, 0.07 mole), and methyl 3-amino-5-phenylpyrazinecarboxylate (**4c**) (10.5 g, 0.046 mole) in acetic acid (700 ml) was heated at 85° for 21 hr. The solution was poured into 2 l. of water, and the precipitated product was recrystallized from acetic acid to yield 10.5 g (74%) of **20c**, mp 217–221°.

Anal. Calcd for $C_{12}H_{11}BrN_3O$: C, 43.00; H, 3.31; N, 25.08. Found: C, 42.86; H, 3.38; N, 24.84.

Methyl 3-Amino-5-chloro-6-phenylpyrazinecarboxylate (21c).—A mixture of methyl 3-amino-6-phenylpyrazinecarboxylate (**13c**) (28.6 g, 0.125 mole) and SO_2Cl_2 (90 ml) was stirred 1.5 hr at 25°. Excess SO_2Cl_2 was removed by vacuum distillation. The residue was suspended in 200 ml of H_2O and the mixture was neutralized with $NaHCO_3$. The insoluble product was recrystallized from acetic acid to obtain 15 g (45%) of **21c**, mp 184–190°. A sample recrystallized repeatedly from acetic acid had mp 187.5–191.5°.

Anal. Calcd for $C_{12}H_{10}ClN_3O_2$: C, 54.66; H, 3.82; N, 15.94. Found: C, 54.58; H, 3.59; N, 15.98.

Methyl 3-amino-5-chloro-6-methylpyrazinecarboxylate was prepared analogously from **9c** in 41% yield and had mp 176–178.5° (from ethyl acetate).

Methyl 3-Amino-5-dimethylamino-6-phenylpyrazinecarboxylate (22c).—A mixture of **21c** (2.6 g, 0.01 mole), dimethylamine (8 g), and methanol (40 ml) was stirred at 25° for 16 hr. The solid product was recrystallized from methanol to obtain 1.4 g (52%) of **22c**, mp 167.5–169.5°.

Anal. Calcd for $C_{14}H_{16}N_4O_2$: C, 61.75; H, 5.92; N, 20.58. Found: C, 61.92; H, 6.06; N, 20.48.

Methyl 3-Amino-5-dimethylamino-6-methylpyrazinecarboxylate (23c).—A solution of methyl 3-amino-5-chloro-6-methylpyrazinecarboxylate (3.3 g, 0.0164 mole), and dimethylamine (6 g) in isopropyl alcohol (25 ml) was kept at 25° for 1 hr and then evaporated. The residue was recrystallized from benzene–cyclohexane to obtain 2.9 g (84%) of **23c**, mp 108.5–110.5°.

Anal. Calcd for $C_9H_{14}N_4O_2$: N, 26.65. Found: N, 26.70.

5- and/or 6-Substituted N-Amidino-3-aminopyrazinecarboxamides. General Methods for Table II.—Guanidine hydrochloride (0.1 mole) was added to a solution of sodium methoxide prepared by dissolving sodium (0.1 g-atom) in methanol (100 ml). In method A, the methanol was removed by vacuum distillation, the methyl 5- and/or 6- substituted 3-aminopyrazinecarboxylate (0.02 mole) was added, and the reaction was conducted at the temperature and for the time specified in Table II. The mixture was cooled and stirred with 100 ml of water, and the solid product was collected. In method B, the ester (0.02 mole) was added directly to the solution of guanidine in methanol and the mixture was heated at the temperature and for the time specified in Table II. The reaction mixture then was cooled and the solid product which separated was collected and washed with water.

The substituted N-amidino-3-aminopyrazinecarboxamides were purified by recrystallization from the solvents specified in Table II, 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 substituted N-amidino-3-aminopyrazinecarboxamides in dilute HCl, and then adding concentrated HCl to cause the salts to precipitate. They were purified by recrystallization as specified in Table II.