and dried to give 5.20 g (85%, mp 235–248°). Recrystallization from EtOH gave material with mp 249–251° dec. The uv spectral data are given in Table III. *Anal.* ($C_6H_7ClN_6O_2$) C, H, N.

Methyl 3-Hydroxy-6-chloropyrazinecarboxylate (XII).—A solution of $NaNO_2$ (7.0 g, 0.1 mole) in concentrated H_2SO_4 (75 ml) was added with stirring to a mixture of IIa (18.7 g, 0.10 mole) in concentrated H_2SO_4 (75 ml), and the resulting solution was stirred for 1 hr. The reaction mixture was poured over ice (500 g) and the resulting aqueous solution was extracted with four 250-ml portions of EtOAc. The EtOAc was dried ($MgSO_4$) and evaporated under reduced pressure to give 18.0 g (96%), mp 122–124°. Recrystallization from methylcyclohexane gave material with mp 127–129°. *Anal.* ($C_6H_3ClN_2O_3$) C, H, N.

Pyrazinyl-1H-1,2,4-triazoles (VIII).—The general procedures for the preparation of the (pyrazinecarboxamido)guanidines (I) applies as well to the preparation of the triazoles since, in most instances, a mixture of the two was obtained. This mixture was readily separated by taking advantage of the amphoteric properties of the triazoles. Routes B and E produced the least amount of VIII, undoubtedly due to the milder reaction conditions. Typical examples follow.

3-Amino-5-(3-amino-5-trifluoromethylpyrazinyl)-1H-1,2,4-triazole (VIIId).—Aminoguanidine hydrochloride (15.22 g, 0.137 mole) was added to a solution of Na (2.88 g, 0.125 g-atom) in MeOH (150 ml) and the mixture was stirred at room temperature for 1 hr. The mixture was filtered to remove NaCl and the filtrate was evaporated under reduced pressure to a thick paste. II (X = H, Y = CF_3, 5.52 g, 0.025 mole) was added and this mixture was heated on the steam bath for 2 min. H_2O (50 ml) was added and the mixture was filtered. This solid was Ik. The filtrate was neutralized with HOAc and the precipitate was filtered, washed (H_2O), and dried to give VIIId, 0.97 g.

3-Amino-5-(3-amino-6-chloropyrazinyl)-1H-1,2,4-triazole (VIIIa). Method F.—Ia (4.0 g, 0.0175 mole) was pulverized and placed in a large test tube. A stream of N_2 was admitted and the tube was heated to 290° for 30 min. After cooling, the product was dissolved in 5% HCl and clarified with Darco. This solution was made strongly basic with 10% NaOH and again treated with Darco. This solution, when neutralized with HOAc and cooled to 0°, gave VIIIa.

Method G.—X[1a] (0.5 g, 0.0016 mole) was dissolved in 5% HCl and warmed on the steam bath for 15 min. Neutralization of the cooled (0°) solution gave 0.20 g of VIIIa.

Pyrazine Diuretics. VII. N-Amidino-3-substituted Pyrazinecarboxamides

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The synthesis of a series of N-amidino-3-substituted pyrazinecarboxamides, principally by the reaction of a methyl 3-substituted pyrazinecarboxylate with guanidine, is described. The intermediate 3-substituted pyrazinecarboxylates were generally prepared by a nucleophilic displacement reaction involving the appropriate 3-bromopyrazinecarboxylates which in turn were prepared from the corresponding 3-aminopyrazinecarboxylates. When the 3 substituent was methoxy, mercapto, methylmercapto, or substituted amino the compounds were generally less active than their 3-amino analogs in the normal or adrenalectomized DOCA loaded rats. The 3-hydroxy compounds were exceptions since they were as potent as their 3-amino analogs in the latter test.

Certain N-amidino-3-aminopyrazinecarboxamides[1] possess interesting and useful diuretic properties; therefore, it was of interest to determine the effect of various substituents in the 3 position on the diuretic activity.

The N-amidino-3-substituted pyrazinecarboxamides (IVa–p) examined in this study were prepared by the reaction of a methyl 3-substituted pyrazinecarboxylate (III) with guanidine according to the method described earlier[2] (see Scheme I). An exception to this method, noted in Scheme I, involves the synthesis of N-amidino-3-hydroxy-6-chloropyrazinecarboxamide (IVq) by the action of nitrous acid on the corresponding 3-amino analog (V). It is interesting to note that there is no attack on the guanidine moiety, even in the presence of excess nitrous acid.

The most useful method for the preparation of the intermediate methyl 3-substituted pyrazinecarboxylates (III) involved the nucleophilic displacement of the 3-halogen of the methyl 3-bromopyrazinecarboxylates (II). A wide variety of nucleophiles attack the 3-position halogen without affecting the halogen in the 6 position even when the reagent was present in excess. In an attempt to determine if displacement was occurring to any extent at the 6 position, methyl 3-bromo-6-chloropyrazinecarboxylate (IIb) was treated with NH_3 in DMSO. The progress of the reaction was checked readily by the periodic examination of a reaction mixture sample using tlc. The only product that could be detected, and eventually isolated in good yield, proved to be methyl 3-amino-6-chloropyrazinecarboxylate (Ib). Compounds IIId, e, and j were prepared by diazotization[3] of the appropriate methyl 3-aminopyrazinecarboxylate in concentrated H_2SO_4 followed by treatment of the diazonium salt with methanol or water to introduce a 3-methoxy or 3-hydroxy group. Methyl 6-bromo-3-methylaminopyrazinecarboxylate (IIIh) was prepared *via* 1,3-dimethyllumazine[4] which was hydrolyzed to 3-methylaminopyrazinecarboxylic acid,[5] then esterified, and, finally, brominated.

Ellingson and Henry[6] have reported the preparation of methyl 3-bromopyrazinecarboxylate (IIa) by diazotization of the 3-amino compound[7] (Ia) in 48% HBr containing Br_2. This method was readily adapted to the synthesis of compounds Ib–e by adding sufficient acetic acid to assure the dissolution of the ester in the reaction medium.

(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), paper I of this series.

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

(3) This method has been described by A. E. Erickson and P. E. Spoeri, *J. Am. Chem. Soc.*, **68**, 401 (1946).

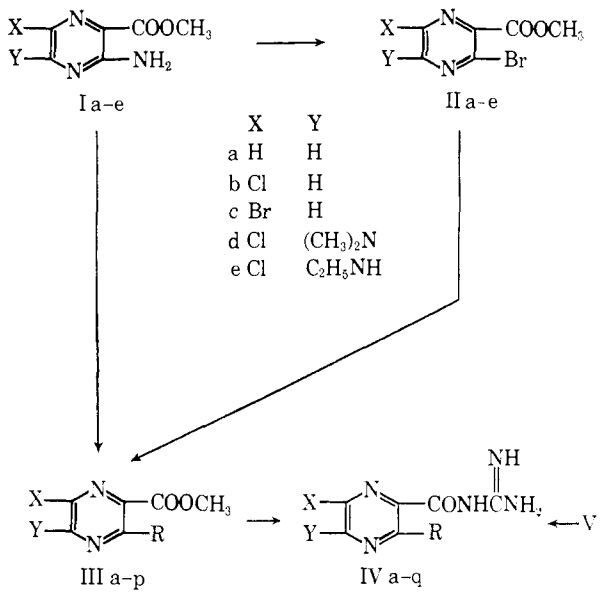
(4) A. Albert, D. J. Brown, and H. C. S. Wood, *J. Chem. Soc.*, 2066 (1956).

(5) D. J. Brown and N. W. Jacobsen, *ibid.*, 4413 (1961).

(6) R. C. Ellingson and R. L. Henry, *J. Am. Chem. Soc.*, **71**, 2800 (1949).

(7) R. C. Ellingson, R. L. Henry, and F. G. McDonald, *ibid.*, **67**, 1711 (1945).

Scheme I



	X	Y	R
a	H	H	HS
b	Cl	H	$(CH_3)_2NCH_2CH_2NH$
c	Cl	H	HS
d	Cl	H	CH_3O
e	Cl	$(CH_3)_2N$	HO
f	Br	H	$C_5H_{10}N$
g	Br	H	$(CH_3)_2N$
h	Br	H	CH_3NH
i	Br	H	CH_3S
j	Br	H	HO
k	Cl	H	p-$ClC_6H_4CH_2NH$
l	Cl	H	p-$CH_3OC_6H_4CH_2NH$
m	Cl	C_2H_5NH	$CH_2{=}CHCH_2NH$
n	Cl	C_2H_5NH	$CH_3OCH_2CH_2NH$
o	Cl	$(CH_3)_2N$	C_2H_5NH
p	Cl	$(CH_3)_2N$	$HOCH_2CH_2NH$
q	Cl	H	HO (*via* V)

Structure–Activity Relationships.—The N-amidino-3-substituted pyrazinecarboxamides (IV) that were prepared in this study were assayed[8] for their ability to inhibit the decrease in the urinary ratio of Na/K produced by desoxycorticosterone acetate (DOCA) using the adrenalectomized rat according to the method described previously.[1,7] The compounds were routinely administered subcutaneously but similar results were obtained when intraperitoneal or oral routes were used. The activity scores, which are presented in Table I, are in accordance with the scoring system described earlier.[1,7]

Using this assay as the criterion of evaluation it can be seen that substitution of the 3-amino nitrogen of N-amidino-3-amino-6-bromopyrazinecarboxamide (VI) (**15** in paper I[1] scored +2) results in reduction of activity. Furthermore, the larger groups have a greater effect than the smaller ones; thus, IVf is less

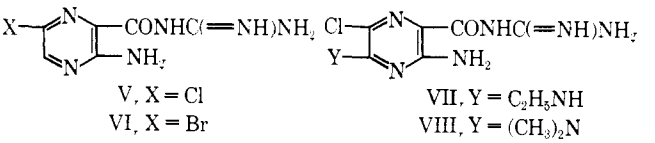
Table I

Biological Results

IV	Rat DOCA-inhibn score[a]	Normal rat score[b]
a	±	+1
b	+1	0
c	±	0
d	0	±
e	0	+1
f	±	0
g	+1	0
h	+2	+1
i	±	±
j	0	+3
k	±	0
l	±	0
m	+4	+1
n	+1	+1
o	+3	+2
p	±	+2
q	±	+3

[a] The DOCA-inhibition score[7] is the dose producing 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. Compounds which scored 0 were tested only at a maximum dose of 800 μg/rat; thus, the possibility exists that activity would be observed at higher doses. [b] Activity[10] based on increase of urinary electrolyte and volume over control values referred to standards: +3 = activity of hydrochlorothiazide, +2 = chlorothiazide, 0 = controls. Compounds with activities between chlorothiazide and controls are scored +1 or ±.

active than IVg and h. Similarly, a considerable reduction in activity is observed upon substitution of the 3-amino group of N-amidino-3-amino-6-chloropyrazinecarboxamide (V) (**1** in paper I[1] scored +3) with relatively large groups (IVb, k, and l). On the other hand substitution of the 3-amino nitrogen of the more potent 5-amino series, *i.e.*, N-amidino-3-amino-5-ethylamino- (or dimethylamino-) 6-chloropyrazinecarboxamide (VII and VIII) (IIa-3 and IIa-14 in paper II[2] scored +3), with groups such as allyl or ethyl (IVm and o) produced compounds with potencies equal to or greater than their parents. Substituents bearing hydroxy or alkoxy groups were detrimental to activity (IVp and n).



Replacement of the amino group of V by SH (IVc) or the amino group of VI by SCH_3 (IVi) produced a marked reduction in activity. Similar decreases in activity were seen when the amino group of VI, V, or VIII was replaced by OH (IVj, q, and e) or OCH_3 (IVd).

The compounds recorded in Table I also were tested in normal rats using the intraperitoneal route of administration.[9] The assay and the scoring system have been described previously.[10] The relative activities obtained in this test generally paralleled those observed

[8] Drs. M. S. Glitzer and S. L. Steelman and their associates supplied part of these data; the remainder was supplied by Dr. J. E. Baer and his associates.

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

[10] J. H. Jones, J. B. Bicking, and E. J. Cragoe, Jr., *J. Med. Chem.*, **10**, 890 (1967).

in the DOCA-inhibition assay. The exceptions were the 3-hydroxy compounds (IVe, j, and q) which were markedly more active (comparable to their amino analogs V, VI, and VII) and IVm which was considerably less active in the normal rat assay than in the DOCA-inhibition assay.

Experimental Section[11]

Details of the syntheses of the new compounds are presented. Where several compounds of one type have been prepared by a particular method, only one example is given. Pertinent data regarding each compound are recorded in Table II.

Method 1. Methyl 3-bromopyrazinecarboxylates (II). Methyl 3-Bromo-6-chloropyrazinecarboxylate (IIb).—A suspension of Ib (18.7 g, 0.1 mole) in a solution of 48% HBr (114 ml) and AcOH (30 ml) was cooled to 0°, stirred, and treated with a solution of Br_2 (15 ml) in AcOH (30 ml) over a period of 45 min. Then a solution of $NaNO_2$ (17.4 g, 0.1 mole) in H_2O (39 ml) was added while maintaining the temperature at 0°. Stirring was continued for 30 min and then the excess Br_2 was destroyed by the dropwise addition of a 30% aqueous solution of $NaHSO_3$ (150 ml). The product, which separated, was recovered by filtration, washed well with cold H_2O, dried, and recrystallized.

Method 2. Methyl 3-Substituted Pyrazinecarboxylates (III). Method 2A. Methyl 3-(2-Dimethylaminoethylamino)-6-chloropyrazinecarboxylate (IIIb).—To 2-dimethylaminoethylamine (3.4 g, 0.04 mole) in DMSO (20 ml) was added IIb (5.0 g, 0.92 mole), the solution was stirred at room temperature for 1.5 hr, then poured into H_2O (100 ml), and the product which separated was removed by filtration, dried, and purified by recrystallization.

For the synthesis of related compounds, the pure liquid or gaseous amine was used.

Method 2B. Methyl 3-Mercapto-6-chloropyrazinecarboxylate (IIIc).—A suspension of $Na_2S \cdot 9H_2O$ (4.8 g, 0.02 mole) and S (5.0 g, 0.156 g-atom) in EtOH (40 ml) was refluxed for 30 min and cooled. Then IIb (5.0 g, 0.01 mole) was added and the solution was stirred at ambient temperature for 1.5 hr. The reaction mixture was poured into H_2O (100 ml), the precipitated S was removed by filtration, and the filtrate was acidified with HCl to precipitate the product which was removed by filtration and purified by crystallization.

Method 2C. Methyl 3-Methylmercapto-6-bromopyrazinecarboxylate (IIIi).—CH_3SH gas (1.28 g, 0.026 mole) was dissolved in a solution of MeOH (75 ml) containing 20% NaOH (5.3 ml, 0.026 mole). IIc (7.8 g, 0.026 mole) was added and the reaction mixture was stirred at ambient temperature for 1 hr, then poured into H_2O (100 ml). The precipitated product was purified by recrystallization.

Method 2D. Methyl 3-Methoxy-6-chloropyrazinecarboxylate (IIId).—To a solution of Ib (18.7 g, 0.1 mole) in concentrated H_2SO_4 (75 ml) maintained at 0–5° was added a solution of $NaNO_2$ (9.0 g, 0.13 mole) in concentrated H_2SO_4 (75 ml) and the reaction mixture was stirred at 5–10° for an additional 30 min. The reaction mixture was carefully added to MeOH (1 l.), refluxed for 1.5 hr, then concentrated *in vacuo* to 500 ml and poured onto ice (1500 g). The aqueous solution was extracted with $CHCl_3$ (three 300-ml portions), then the organic phase was washed with 2% NaOH (three 200-ml portions), dried, and evaporated *in vacuo* to an oil which was purified by recrystallization.

Method 2E. Methyl 3-Hydroxy-6-bromopyrazinecarboxylate (IIIj).—Diazotization was carried out exactly as described in method 2D using Ic (4.6 g, 0.02 mole), concentrated H_2SO_4 (30 ml), and $NaNO_2$ (1.4 g, 0.02 mole). Then the reaction mixture was poured directly onto ice (200 g). The resulting mixture was extracted with $CHCl_3$ (two 200-ml portions), the $CHCl_3$ layer was extracted with 2% NaOH (two 100-ml portions), and the aqueous phase was acidified with HCl which precipitated the product. The crude material was purified by recrystallization.

Method 2F. Methyl 3-Methylamino-6-bromopyrazinecarboxylate (IIIh).—1,3-Dimethyllumizine[4] was hydrolyzed using aqueous NaOH (10%) to give 3-methylaminopyrazinecarboxylic acid[5] which, in turn, was esterified using MeOH saturated with HCl. The ester was not purified but brominated directly by the procedure of Ellingson and Henry[6] and the product was purified by crystallization.

Method 3. The preparation of the **N-amidinopyrazinecarboxamides (IVa–p)** was carried out exactly as described previously.[2]

Method 4. N-Amidino-3-hydroxy-6-chloropyrazinecarboxamide (IVq).—Compound V (6.42 g, 0.03 mole) was dissolved in H_2O (300 ml) by the addition of methanesulfonic acid (7.2 g, 0.075 mole), then stirred and cooled to 5–10°. A solution of $NaNO_2$ (2.01 g, 0.033 mole) in H_2O (20 ml) was added dropwise over a period of 1 hr. The reaction mixture then was stirred at room temperature for 30 min, heated to 60°, and filtered, and the filtrate was neutralized with NaOH to pH 7 which caused the product to separate. The product was removed by filtration and purified by reprecipitation.

Method 5. Methyl 3-Amino-6-chloropyrazinecarboxylate (Ib) from Methyl 3-Bromo-6-chloropyrazinecarboxylate (IIb).—A solution of IIb (1.0 g, 3 mmoles) in DMSO (3 ml) was stirred and heated on the steam bath while a stream of NH_3 was admitted over a period of 30 min. Addition of H_2O (15 ml) afforded a solid that was recrystallized from H_2O to yield 0.65 g (91%) of Ib melting 158–160°. Mixture melting point with authentic Ib was not depressed; the ir spectra of the compounds were identical.

TABLE II

METHYL 3-BROMOPYRAZINECARBOXYLATES (II), METHYL 3-SUBSTITUTED PYRAZINECARBOXYLATES (III), AND N-AMIDINO-3-SUBSTITUTED PYRAZINECARBOXAMIDES (IV)

No.	Syn method[a]	Recrystn solvent	% yield	Mp, °C	Formula[d]
IIa[c]					
IIb	1	Petr ether	56	38–40	$C_5H_4BrClN_2O_2$
IIc	1	EtOH–H_2O	60	66–68	$C_5H_4Br_2N_2O_2$
IId	1	Cyclohexane	51	98–99	$C_8H_9BrClN_3O_2$
IIe	1	C_6H_6	60	160–162	$C_8H_9BrClN_3O_2$
IIIa	2B	*b*	48	124–125	$C_8H_8N_2O_2S$[b]
IIIb	2A	*i*-PrOH	33	116–118	$C_{10}H_{16}ClN_4O_2$[e]
IIIc	2B	EtOH	87	80–82	$C_8H_8ClN_2O_2S$[f]
IIId	2D	EtOH·H_2O	13	45	$C_7H_7ClN_2O_3$[b]
IIIe	2E	MeOH	35	140–141	$C_8H_{10}ClN_3O_3$
IIIf	2A	EtOH·H_2O	73	88–90	$C_{11}H_{14}BrN_3O_2$
IIIg	2A	EtOH·H_2O	77	80–82	$C_8H_{10}BrN_3O_2$
IIIh	2F	*i*-rPOH	75	181–183	$C_7H_8BrN_3O_2$
IIIi	2C	EtOH	80	135–136	$C_7H_7BrN_2O_2S$
IIIj	2E	Hexane	75	120.5–121.5	$C_6H_5BrN_2O_3$
IIIk	2A	EtOH	67	152–154	$C_{13}H_{11}Cl_2N_3O_2$
IIIl	2A	EtOH	98	105–106	$C_{14}H_{14}ClN_3O_3$
IIIm	2A	*i*-PrOH	78	100–102	$C_{11}H_{16}ClN_4O_2$
IIIn	2A	Hexane	68	89–90	$C_{11}H_{17}ClN_4O_3$
IIIo	2A	Cyclohexane	92	93–95	$C_{10}H_{16}ClN_4O_2$
IIIp	2A	BuCl	88	103–105	$C_{10}H_{16}ClN_4O_3$
IVa	3	EtOH·H_2O	33	244–246 dec	$(C_6H_7N_5OS \cdot HCl)_2 \cdot H_2O$
IVb	3	HCl–NaOH	16	210–212 dec	$C_{10}H_{16}ClN_7O$
IVc	3	HCl–NaOH	54	260 dec	$(C_6H_6ClN_5OS)_2 \cdot H_2O$
IVd	3	Dil HCl	47	214–216 dec	$C_7H_8ClN_5O_2 \cdot HCl$
IVe	3	Dil HCl	20	231.5–233.5 dec	$C_8H_{11}ClN_6O_2 \cdot HCl$
IVf	3	HCl–NaOH	81	220–222 dec	$C_{11}H_{16}BrN_6O$
IVg	3	HCl–NaOH	30	216–218 dec	$C_8H_{11}BrN_6O$
IVh	3	HCl–NaOH	50	230–232 dec	$C_7H_9BrN_6O$
IVi	3	H_2O	55	275–278 dec	$C_7H_8BrN_6OS \cdot HCl$
IVj	3	EtOH–H_2O	75	>290	$C_6H_6BrN_5O_2 \cdot HCl$
IVk	3	EtOH–H_2O	40	245–248 dec	$C_{13}H_{12}Cl_2N_6O \cdot HCl$
IVl	3	EtOH–H_2O	43	200–202 dec	$C_{14}H_{16}ClN_6O_2 \cdot HCl$
IVm	3	H_2O	97	132–135	$C_{11}H_{16}ClN_7O \cdot HCl$
IVn	3	MeOH	80	219–220	$C_{11}H_{15}ClN_7O_2$
IVo	3	H_2O	67	241–242	$C_{10}H_{16}ClN_7O \cdot HCl$
IVp	3	H_2O	75	242–244	$C_{10}H_{16}ClN_7O \cdot HCl \cdot H_2O$
IVq	4	HCl–NaOH	81	257–259 dec	$C_6H_5ClN_6O_2$

[a] See the Experimental Section for the number and letter that corresponds to each experimental method. [b] This material was used in the next step without further purification. [c] Dr. J. B. Bicking is responsible for this preparation. [d] All compounds were analyzed for C, H, N, except for IIIa and IIId. The analytical results for the elements were within ±0.4% of the theoretical values except where indicated. [e] C: calcd, 46.42; found, 45.95. [f] C: calcd, 35.21; found, 35.62.

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