Pyrazine Diuretics. VI. (Pyrazinecarboxamido)guanidines

KENNETH L. SHEPARD, JAMES W. MASON, OTTO W. WOLTERSDORF, JR., JAMES H. JONES, AND EDWARD J. CRAGOE, JR.

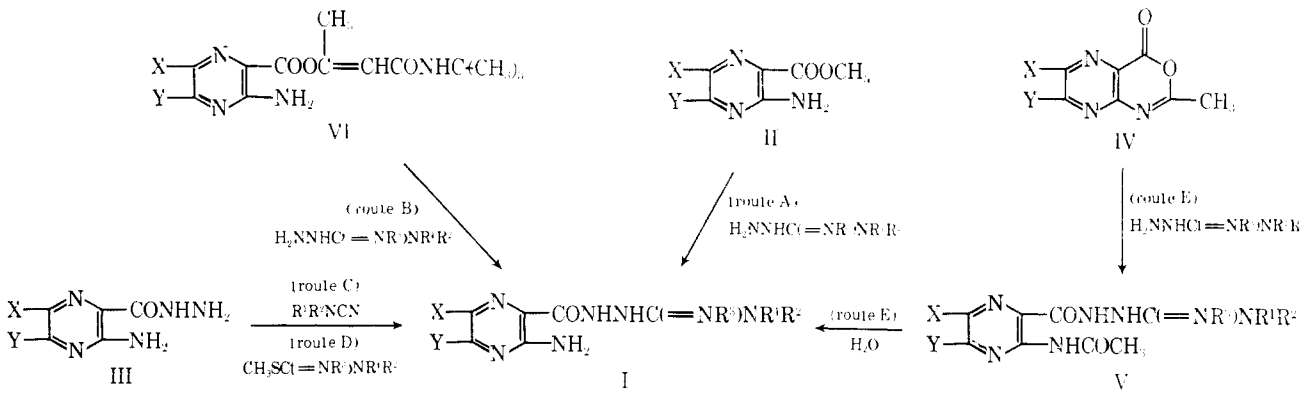
Merck Sharp & Dohme Research Laboratories, Division of Merck & Co., Inc., West Point, Pennsylvania

Received August 5, 1968

The synthesis of a series of (pyrazinecarboxamido)guanidines by a number of methods is described. These compounds, like their N-amidinopyrazinecarboxamide analogs, cause diuresis and saluresis in rats and dogs while potassium excretion is unaffected or repressed. Cyclization of a number of these compounds produced the analogous pyrazinyltriazoles which were generally less potent than the (pyrazinecarboxamido)guanidines.

In previous papers of this series[1] a number of N-amidinopyrazinecarboxamides have been shown to possess diuretic activity. Extension of this study has led to the synthesis of a variety of (pyrazinecarboxamido)guanidines of the type illustrated by I (see Table I). These compounds have been prepared by the general routes illustrated in Scheme I.

SCHEME I



The most general method for the preparation of these compounds involved the interaction of a methyl pyrazinecarboxylate (II) with the appropriate aminoguanidine (route A). Other methods of preparation were devised as alternate routes in those cases where the methyl ester gave poor results and for evidence in structure assignment to the products.

The highly reactive ester VI[2] (X = Cl, Y = NH_2) prepared from 3,5-diamino-6-chloropyrazinecarboxylic acid and N-*t*-butyl-5-methylisoxazolium perchlorate (Woodward's Reagent L), in general, gave better yields of products under less severe conditions than obtained with the methyl ester (route B).

Pyrazinecarboxylic acid esters were readily converted to the corresponding pyrazinecarboxylic acid hydrazides (III) by reaction with hydrazine. These compounds reacted with cyanamide or substituted cyanamides under acid catalysis to produce (pyrazinecarboxamido)guanidines (route C)[3] identical with those obtained by route A. The reaction of cyanamides with these hydrazides was relatively slow and required multiple additions of the cyanamide when aqueous acids were employed. The use of pyridine hydrochloride as the reaction medium (and catalyst) at 125°, however, afforded the desired derivatives in high yields in 1–2 hr.

The reaction of the hydrazides (III) with 2-methyl-2-thiopseudourea or its 3-substituted derivatives (route D) gave results similar to those obtained using route C.

The synthesis of carboxamidoguanidines by the reaction of alkyl- and arylcarboxylic acid hydrazides with cyanamide or with 2-alkyl-2-thiopseudourea has been reported by Hogarth.[4] Atkinson and his associates.[5] and by Biemann and Bretschneider.[6]

The active acylating agent, 2-methyl-6-chloro-4H-pyrazino[2,3-*d*][1,3]oxazin-4-one (IV, X = Cl; Y = H), described in a previous paper,[1a] reacted with aminoguanidines to give (3-acetamido-6-chloropyrazinecarboxamido)guanidines (V, X = Cl; Y = H; route E). These compounds were rapidly deacetylated in cold dilute acid solution to yield the corresponding (3-amino-6-chloropyrazinecarboxamido)guanidines (I, X = Cl; Y = H).

In general, each of these routes gave, in addition to the desired (pyrazinecarboxamido)guanidines, the corresponding triazole derivatives VIII (see Table II). The two active acylating species VI and IV afforded less of this cyclic product, probably due to the milder conditions permitted by these highly reactive intermediates.

(1) (a) 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); (b) E. J. Cragoe, Jr., O. W. Woltersdorf, Jr., J. B. Bicking, S. F. Kwong, and J. H. Jones, *ibid.*, **10**, 66 (1967); (c) J. B. Bicking, C. M. Robb, S. F. Kwong, and E. J. Cragoe, Jr., *ibid.*, **10**, 598 (1967); (d) J. H. Jones, J. B. Bicking, and E. J. Cragoe, Jr., *ibid.*, **10**, 899 (1967); (e) J. H. Jones and E. J. Cragoe, Jr., *ibid.*, **11**, 322 (1968).

(2) This ester and its reactions with various nucleophiles will be the subject of a future communication.

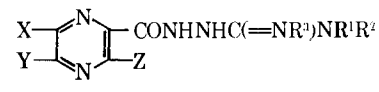
(3) We are indebted to Dr. L. M. Weinstock for his contributions in the development of this method.

(4) E. Hogarth, *J. Chem. Soc.*, 612 (1950).

(5) M. R. Atkinson, A. Komzack, E. A. Parkes, and J. B. Polya, *ibid.*, 1508 (1954).

(6) K. Biemann and H. Bretschneider, *Monatsh. Chem.*, **89**, 603 (1958).

TABLE I

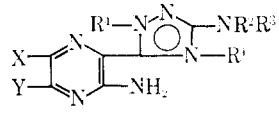


I

Compd I	X	Y	Z	R^1	R^2	R^3	Method of syn[a]	Recrystn solvent	Yield, %	Salt	Mp, °C	Formula[f]	DOCA inhib score[b]	Normal rate score[c]
a	Cl	H	NH_2	H	H	H	A-1	*i*-PrOH–H_2O	17	HCl	277–278	$C_6H_9Cl_2N_7O$	+3	+2
							C-1	*d*	66		333–334	$C_6H_8ClN_7O$		
							D		24					
							E		30					
b	H	H	NH_2	H	H	H	A-1	*i*-PrOH–H_2O	36	HCl	286–287	$C_6H_{10}ClN_7O$	±	0
c	Cl	H	NH_2	CH_3	H	H	A-1	*d*	20		263–265	$C_7H_{10}ClN_7O$	+3	+2
d	Cl	H	NH_2	CH_3	CH_3	H	C-1	*i*-PrOH–H_2O	8	HCl	279–280	$C_8H_{13}Cl_2N_7O$	±	±
							D		25					
e	Cl	H	NH_2	C_6H_5	H	H	A-1	H_2O	30	HCl	254–255	$C_{12}H_{13}Cl_2N_7O$	+2	+3
							E	*i*-PrOH–H_2O	10	HCl				
f	Cl	H	NH_2	$CH_2C_6H_5$	H	H	A-2	*i*-PrOH–H_2O	14	HCl	241–243	$C_{13}H_{15}Cl_2N_7O$	+2	+2
g	Cl	H	NH_2	CH_2CH_2OH	H	H	A-1	*i*-PrOH–H_2O	8	HCl	243–244	$C_8H_{13}Cl_2N_7O_2$	+3	+2
h	Cl	H	NH_2	NH_2	H	H	A-1	*i*-PrOH–H_2O	16	HCl	264–265	$C_6H_{10}Cl_2N_8O$	+4	+2
i	Br	H	NH_2	H	H	H	A-1	*i*-PrOH–H_2O	24	HCl	268–269	$C_6H_9BrClN_7O$	+3	+2
j	I	H	NH_2	H	H	H	A-1	H_2O	17	HCl	254–255	$C_6H_9ClIN_7O$	+1	+2
k	H	CF_3	NH_2	H	H	H	A-1	*i*-PrOH–H_2O	12	HCl	249–250	$C_7H_9ClF_3N_7O$	±	
l	Cl	NH_2	NH_2	H	H	H	A-2	*d*	21		281–282	$C_6H_9ClN_8O$	+4	+2
m	Cl	$N(CH_3)_2$	NH_2	H	H	H	A-2	*d*	26		220–221	$C_8H_{13}ClN_8O$	+4	+2
n	Cl	$NHCH(CH_3)_2$	NH_2	H	H	H	A-2	*i*-PrOH–H_2O	36	HCl	229–231	$C_9H_{16}Cl_2N_8O$	+3	
o	Cl	$NHCH_2CH{=}CH_2$	NH_2	H	H	H	A-2	*i*-PrOH–H_2O	10	HCl	182–183	$C_9H_{14}Cl_2N_8O$	+2	+1
p	Cl	H	$NHCOCH_3$	H	H	H	E		44		204–205	$C_8H_{10}ClN_7O_2$	+1	+2
q	Cl	H	OH	H	H	H	A-1[g]	*d*	69		259–260	$C_6H_7ClN_6O_2$	±	+2
r	Cl	NH_2	NH_2	CH_3	CH_3	H	C-2[e]	MeCN–H_2O	75		305–309	$C_8H_{13}ClN_8O$	+4	+2
s	Cl	NH_2	NH_2	$CH_2C_6H_5$	H	H	B-2	MeCN	6		244–247	$C_{13}H_{15}ClN_8O$	+4	+1
t	Cl	NH_2	NH_2	NH_2	H	H	B-1	*d*	70		196–200	$C_6H_{10}ClN_9O \cdot H_2O$	+4	±
u	Cl	NH_2	NH_2	$CH_2CH{=}CH_2$	$CH_2CH{=}CH_2$	H	C-2[e]	MeCN	66		281	$C_{12}H_{17}ClN_8O$	+4	+2
v	Cl	NH_2	NH_2	$C(CH_3)_3$	H	H	C-2[e]	MeCN	84		271–274	$C_{10}H_{17}ClN_8O$	+4	+2
w	Cl	NH_2	NH_2	H	$CH_2{-}{-}CH_2$		A-2	EtOH–H_2O	38		250–252	$C_8H_{11}ClN_8O$	+4	+2

[a] See the Experimental Section for the letter that corresponds to each synthetic method. [b] The DOCA inhibition score is the dose producing 50% reversal of the DOCA Na/K effect: +4 = <10 μg/rat, +3 = 51–100, +2 = 50–100, +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. Also, it will be noted that compounds inactive in this assay are active in the normal rat assay. [c] The activity[1d] is based on the increase of urinary electrolyte and volume over control values referred to standards: +3 = activity of hydrochlorothiazide, +2 = chlorothiazide, +1 and ± = compounds with activities between hydrochlorothiazide and chlorothiazide, 0 = controls. [d] Purified by dissolving in dilute HCl and precipitating with dilute NaOH. [e] Reaction temperature, 125°. [f] All compounds were analyzed for C, H, N, with the exception of Iq (C, H), and were within ±0.4% of the theoretical values except Ij (H: calcd, 2.54; found, 3.04) and In (C: calcd, 35.23; found, 34.54). [g] Also prepared from Ia, see Experimental Section.

TABLE II

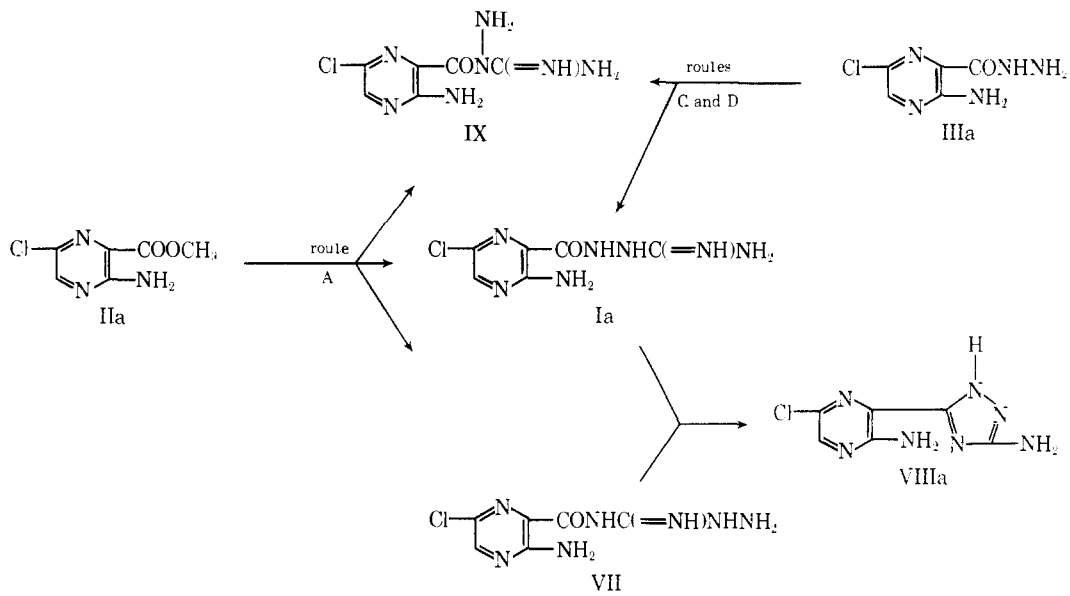


VIII

Compd VIII	X	Y	R^1	R^2	R^3	R^4	Synth method[a]	Recryst solvent	Yield, %	Salt	Mp, °C	Formula[c]	Normal rat assay[b]
a	Cl	H	H	H	H		F	[e]	46		333–334	$C_6H_5ClN_7$	±
							G	[e]	59		333–334		
b	Cl	H	CH_3	CH_3	H		A	2-PrOH–H_2O	43	HCl	317–318	$C_8H_{10}Cl_2N_7$	±
c	Cl	H	CH_3	CH_3	CH_3		A	MeCN–EtOH	19		178–180	$C_9H_{12}ClN_7$	+1
d	H	CF_3	H	H	H		A	2-PrOH	16		316–318	$C_7H_6F_3N_7$	±
e	Cl	NH_2	H	CH_3	H		A	MeCN	18		261–265	$C_7H_8ClN_8$	+2
f	Cl	NH_2	H	C_6H_5	H		A	MeCN–EtOH	17		319–320	$C_{12}H_{10}ClN_8$	±
g	Cl	NH_2	H	H	H		A	MeCN–H_2O	23		295–297	$C_6H_5ClN_8$	+3
h	Cl	NH_2	H	$CH_2CH{=}CH_2$	$CH_2CH{=}CH_2$		C-2[d]	MeCN–H_2O	23		286–288	$C_{12}H_{15}ClN_8$	±
i	Cl	NH_2		H	H	$(CH_2)_2C_6H_5$	A-1	EtOH	80		211.5–212.5	$C_{14}H_{16}ClN_8$	+1

[a] See the Experimental Section for the letter that corresponds to each synthetic method. [b] See footnote *b*, Table I. [c] Purified by dissolving in dilute aqueous HCl and precipitating with dilute NaOH. [d] A reaction temperature of 175° was used. [e] All compounds were analyzed for C, H, N, with the exception of VIIIe (C, H), and were within ±0.4% of the theoretical values.

SCHEME II

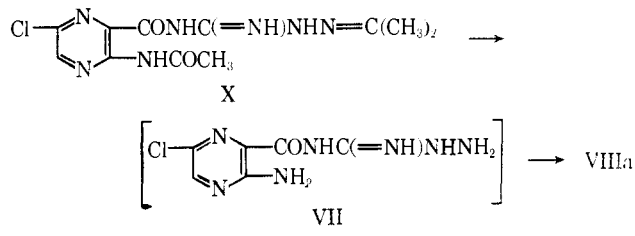


When route C was employed, using pyridine hydrochloride as a solvent (C-2), it was especially easy to adjust the reaction conditions to produce either the (pyrazinecarboxamido)guanidine or the pyrazinyltriazole as the major product by regulating the reaction temperature. Temperatures greater than 130°, especially in the range of 150–175°, gave predominantly the triazoles, whereas temperatures less than 130° gave high yields of the (pyrazinecarboxamido)guanidines.

Three isomeric structures are theoretically possible from the interaction of an aminoguanidine with a pyrazinecarboxylic acid ester, as illustrated by the reaction of aminoguanidine with methyl 3-amino-6-chloropyrazinecarboxylate (IIa) (see Scheme II), which could yield Ia, VII, and/or IX.

Consideration of the following facts permitted the assignment of structure I to the compounds of this series. Employment of the four synthetic routes (A, C, D, and E), illustrated in Scheme I, in the instance where X = Cl and Y = R^1 = R^2 = R^3 = H

SCHEME III



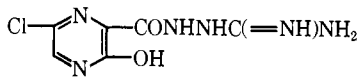
led to the same substance. It may be seen from Scheme II that routes C and D, involving 3-amino-6-chloropyrazinecarboxylic acid hydrazide (IIIa) and either cyanamide or 2-methyl-2-thiopseudourea could not have produced VII; therefore, this compound is eliminated from further consideration. The facile cyclization of Ia to 3-amino-5-(3-amino-6-chloropyrazinyl)-1H-1,2,4-triazole (VIIIa) provided the final evidence for structure Ia since IX could not undergo such a cyclization. Only the (pyrazinecarboxamido)guani-

dine structure (Ia) satisfied the data. Some of the features of this structure proof are analogous to those reported for other acylaminoguanidines.[4-6]

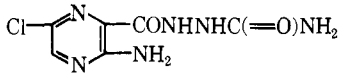
An attempt was made to prepare one of the isomeric substances, 1-amino-3-(3-amino-6-chloropyrazinecarbonyl)guanidine (VII), by the route outlined in Scheme III. However, hydrolysis of the isopropylidene intermediate (X),[1a] even under extremely mild conditions, produced VIIIa.

Assignment of the triazole structure to VIIIa is based upon its amphoteric properties, its elemental analysis, and the two modes of its synthesis (Schemes II and III). Indeed, it has been impossible to isolate many acylaminoguanidines because they undergo a rapid cyclization to the corresponding triazoles.[7,8] Other 1,2,4-triazoles isolated in this study are listed in Table II.

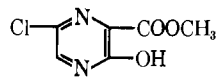
Treatment of Ia with nitrous acid produced (3-hydroxy-6-chloropyrazinecarboxamido)guanidine (Iq). This structure was initially assigned to the product on the following evidence. First, the product was amphoteric in nature; secondly, it was different from XI, an isomer and possible product, as shown by a direct comparison of absorption and infrared spectra. The structure was conclusively established by synthesis of Iq from XII and aminoguanidine according to method A-1.



Iq



XI



XII

Structure–Activity Relationships.—The (pyrazinecarboxamido)guanidines synthesized during this investigation were assayed for their deoxycorticosterone acetate (DOCA)-inhibitory activity using the adrenalectomized rat according to the method described previously.[1a,b] The compounds were routinely administered subcutaneously but similar results were obtained when intraperitoneal or oral routes were used. A scoring system identical with that already described[1a] was used and the results are tabulated in Table I.[9]

The structure–activity relationships in this series generally parallel those found in the N-amidinopyrazinecarboxamides.[1] The parent compound (Ib) and its 5-trifluoromethyl derivative (Ik) were only weakly active. However, introduction of a 6-chloro substituent gave a compound (Ia) with marked activity. Replacing the 6-chloro substituent with bromo (Ii) diminished the activity only slightly but with iodo (Ij) the activity was considerably lower.

Introduction of substituents on the terminal nitrogen atoms of the aminoguanidine moiety of compound Ia usually gave compounds with less activity (Id–f) or, at best, with equal activity (Ic and g). However, the compound with an amino group in this position (Ih) exhibited a substantial increase in activity.

Significantly increased activity was obtained by the introduction of a 5-amino (Il) or substituted-amino function (Im–o). The 5-amino derivative Il appears to be the most active member of the entire series. The presence of alkyl substituents on the nitrogen atom at the 5 position tended to reduce activity approximately in proportion to the size of the substituent. Substitution on the terminal nitrogen atoms of compound Il produced no significant changes in activity (Ir–w). Replacement of the 3-amino group of Ia by hydroxyl markedly reduced activity.

Each of the compounds recorded in Table I was tested intraperitoneally in normal rats.[10] In general, the relative activities paralleled those obtained in the DOCA-inhibition assay. The exceptions were the 3-OH compound (Iq), which was relatively more active, and Il and its derivatives, which were less active in the normal rat assay than in the DOCA-inhibition assay.

Selected compounds were tested parenterally and orally in dogs and, although the effects were not as pronounced in this species as in rats, the qualitative activity in respect to electrolyte excretion (*i.e.*, saluresis, diuresis with potassium ion unaffected or repressed) and relative activities parallel those observed in the rat assays.

These compounds, like those in the N-amidinopyrazinecarboxamide series,[1a-d] may be classified as nonspecific inhibitors of the mineralocorticoids since, at high doses, the active compounds not only completely reverse the electrolyte effects of DOCA, but produce added natriuresis and antikaluresis giving urinary Na/K ratios several fold greater than those found for adrenalectomized rats.

Selected compounds in this series have been tested in the clinic.[11] The results obtained with Il are especially noteworthy in that they are quite comparable with those reported for amiloride.

Cyclization of the (pyrazinecarboxamido)guanidines (I) to the corresponding 1,2,4-triazoles (VIII) essentially abolished DOCA-inhibitory activity except for compound VIIIg, which retained some activity (+1). More meaningful data were obtained for these compounds using the normal rat assay. The results are recorded in Table II.

The 5-trifluoromethyl compound (VIIId), the 6-chloro compound (VIIIa), and its methyl-substituted derivatives (VIIIb and c) had only weak activity. Maximal activity was found with the 5-amino-6-chloro compound (VIIIg). Substitution of the triazole ring nitrogen (R^4) (VIIIi) or its amino nitrogen (R^2 of R^3) (VIIIe, f, and h) reduced activity.

Experimental Section[12]

Intermediates.—Aminoguanidine bicarbonate, available commercially, was converted to the hydrochloride salt by treatment with concentrated HCl.[13] 1-Methyl-3-aminoguanidine hydri-

(7) E. Lieber and G. B. L. Smith, *Chem. Rev.*, **25**, 213 (1939).

(8) F. Kurzer and L. E. A. Godfrey, *Angew. Chem. Intern. Ed. Engl.*, **2**, 459 (1963).

(9) Drs. M. S. Glitzer, S. L. Steelman, and their associates supplied part of these data; the remainder was supplied by Dr. J. E. Baer and his associates.

(10) Dr. J. E. Baer and his associates conducted these studies using procedures which have been described previously.

(11) These studies were conducted by Dr. E. L. Foltz and his staff.

(12) Melting points were taken in open capillaries and are corrected values. K. B. Streeter, Y. C. Lee, and their staff supplied the analytical data.

(13) J. Thiele, *Ann. Chem.*, **270**, 24 (1892).

odide,[14] 1,1-dimethyl-3-aminoguanidine hydriodide,[15] 1,1,2-trimethyl-3-aminoguanidine hydriodide,[15] 1-phenyl-3-aminoguanidine hydriodide,[15] 1-benzyl-3-aminoguanidine hydriodide,[15] 2-hydrazino-2-imidazoline hydriodide,[15] and 1,3-diaminoguanidine hydriodide[16] were prepared by published procedures. Dimethylcyanamide, diallylcyanamide, and *t*-butylcyanamide are commercially available.

The methyl pyrazinecarboxylates and the 2-methyl-6-chloro-4H-pyrazino[2,3-*d*][1,3]oxazin-4-one have been described in earlier papers in this series.[1]

1-(2-Hydroxyethyl)-3-aminoguanidine Hydriodide.—Ethanolamine (6.5 g, 0.11 mole) was added to a refluxing solution of 3-methyl-3-thioisosemicarbazide hydriodide (23 g, 0.10 mole) in MeOH (100 ml). This mixture was refluxed for 2 hr and the resulting solution was used directly in method A to prepare compound Ig (Table I).

3-Amino-6-chloropyrazinecarboxylic Acid Hydrazide (IIIa).—Anhydrous NH_2NH_2 (32 g, 1.0 mole) was added to a refluxing solution of IIa (94 g, 0.50 mole) in EtOH (2.2 l.) and the mixture refluxed for 2 hr. The precipitated product was filtered, washed with EtOH, and dried to give 94 g, mp 218–220°. *Anal.* ($C_5H_6ClN_5O$) C, H, N.

3,5-Diamino-6-chloropyrazinecarboxylic Acid Hydrazide (IIIb).—A mixture of II (X = Cl, Y = NH_2) (10.15 g, 0.05 mole), anhydrous NH_2NH_2 (5 ml), and absolute EtOH (200 ml) was refluxed for 20 hr. The reaction mixture was cooled and the product was filtered and dried, 8.5 g (84%). After recrystallization from DMF–H_2O the melting point was 266–268°. *Anal.* ($C_5H_7ClN_6O$) C, H.

3,5-Diamino-6-chloropyrazinecarboxylic Acid.—A mixture of finely ground II (X = Cl, Y = NH_2) (101.31 g, 0.50 mole), *i*-PrOH (1875 ml), and 5% aqueous NaOH solution (625 ml) was refluxed, with vigorous stirring, for 1 hr. H_2O (7500 ml) was added to the cooled reaction mixture and the resulting clear solution was made acid to congo red paper by the addition of concentrated HCl. The light yellow solid that separated was removed by filtration and dried, yield 92.8 g (98%), mp 230–231° dec. After recrystallization from DMSO–H_2O, the melting point was 272° dec. *Anal.* ($C_5H_5ClN_4O_2$) C, H, N.

N-*t*-Butyl-3-(3,5-diamino-6-chloropyrazinecarbonyloxy)crotonamide (VI, X = Cl; Y = NH_2).—A mixture of 3,5-diamino-6-chloropyrazinecarboxylic acid (1.90 g, 0.01 mole) and $(C_2H_5)_3N$ (1.0 g, 0.01 mole) in DMF (20 ml) was stirred at room temperature until complete solution was obtained (about 10 min). N-*t*-Butyl-5-methylisoxazolium perchlorate (2.40 g, 0.01 mole) was added and the resulting solution was stirred for 2 hr. The reaction mixture was diluted with H_2O (100 ml) and the yellow solid was removed by filtration and dried; the yield was 2.85 g (87%), mp 171–176°. Recrystallization from MeCN gave material that melted at 187–189°, resolidified, and remelted above 230° with decomposition. *Anal.* ($C_{13}H_{18}ClN_5O_3$) C, H, N.

General Methods for the Preparation of (3-Aminopyrazinecarboxamido)guanidines. Each method is illustrated by a specific example.

Method A-1. (3-Amino-6-chloropyrazinecarboxamido)guanidine (Ia).—Aminoguanidine hydrochloride (0.1 mole) was added to a solution of Na (0.1 g-atom) in MeOH (200 ml). IIa (0.025 mole) was added and the mixture was concentrated to approximately 60 ml by evaporation under reduced pressure. The solid obtained was filtered, washed well (H_2O), dried, and purified to give Ia.

Method A-2. (3,5-Diamino-6-chloropyrazinecarboxamido)guanidine (Ib).—Aminoguanidine hydrochloride (0.1 mole) and II (X = Cl, Y = NH_2) (0.05 mole) were dissolved in refluxing EtOH (500 ml). A solution of Na (0.10 g-atom) in EtOH (100 ml) was introduced and the mixture was refluxed for 22 hr. The yellow solid was filtered, washed (EtOH, H_2O), and purified to give Ib.

Method B. 1-(3,5-Diamino-6-chloropyrazinecarboxamido)-3-aminoguanidine (Ic).—Na (0.022 g-atom) was dissolved in refluxing *i*-PrOH (100 ml). 1,3-Diaminoguanidine hydriodide (0.024 mole) was added, the mixture refluxed for 1 hr, VI (X = Cl, Y = NH_2, 0.01 mole) was added, and the mixture refluxed for an additional 1 hr. The cooled reaction mixture was filtered, and the solid was washed well with H_2O and purified to give Ic.

The ester VI (X = Cl, Y = NH_2, 0.01 mole) could be generated as described above in DMF and used *in situ*. Thus, Is is prepared as follows. 1-Benzyl-3-aminoguanidine hydriodide (0.039 mole) was mixed with a solution of Na (0.039 g-atom) in EtOH (100 ml), this was added to a DMF solution of VI (X = Cl, Y = NH_2) generated as described earlier, and the mixture was warmed on a steam bath for 3 hr. Removal of the solvent under reduced pressure and addition of H_2O gave Is.

Method C-1. 1-(3-Amino-6-chloropyrazinecarboxamido)-3,3-dimethylguanidine (Id).—A paste of IIIa (0.05 mole) and EtOH (200 ml) was treated with 10% HCl (10 ml) and refluxed. A solution of dimethylcyanamide (0.055 mole) in EtOH (25 ml) was added and refluxing continued for 17 hr. Dimethylcyanamide (0.055 mole) and concentrated HCl (5 ml) were added and refluxing continued for 4 hr. The solution was cooled and neutralized with concentrated NH_4OH (20 ml), and the yellow precipitate was collected, dried, and purified to give Id.

Method C-2. 1-(3,5-Diamino-6-chloropyrazinecarboxamido)-3,3-diallylguanidine (Ie).—A mixture of IIIb (0.025 mole), diallylcyanamide (0.06 mole), and pyridine hydrochloride (10 g) was heated at 125 ± 5° for 1–2 hr. The cooled melt was dissolved in H_2O (200 ml) and made alkaline by the addition of 20% NaOH solution. The precipitate which formed was collected, dried, and purified to give Ie.

Method D. Compound Ia.—Two solutions were prepared. (1) Under N_2, a solution of IIIa (0.03 mole) in DMSO (50 ml) was heated on a steam bath. (2) 2-Methyl-2-thiopseudourea (0.050 mole) was added to a solution of $NaOCH_3$ (0.049 mole) in DMSO (150 ml). The thiopseudourea solution was added to the hydrazide solution and the mixture was heated on a steam bath for 20 hr. A second charge of the thiopseudourea in DMSO, prepared as above, was added and the whole was heated on a steam bath another 24 hr. The DMSO was removed under reduced pressure, the residue was dissolved in 2% HCl (100 ml) and clarified with Darco, and this solution was rendered alkaline with 10% NaOH solution. The resulting precipitate was collected, dried, and purified to give Ia.

Method E. Compound Ia.—Aminoguanidine hydrochloride (0.045 mole) was added to a solution of Na (0.044 g-atom) in EtOH (125 ml). 2-Methyl-6-chloro-4H-pyrazino[2,3-*d*][1,3]-oxazin-4-one (0.03 mole) was dissolved in boiling EtOAc (125 ml). The two solutions were united producing an immediate yellow precipitate of the corresponding 3-acetamido derivative (V, X = Cl, Y = H). The acetyl group was removed by heating the product with 10% HCl (5 ml) for 15 min, clarifying with Darco, and precipitating the product by the addition of dilute NaOH to give Ia.

As noted in Table I some of the (3-aminopyrazinecarboxamido)guanidines were converted to their hydrochloride salts by dissolving in 6 *N* HCl and chilling and removing the precipitate by filtration.

(3-Hydroxy-6-chloropyrazinecarboxamido)guanidine (Ig). Ia·HCl (5.0 g, 0.02 mole) was dissolved in H_2O (50 ml) and cooled to 0°, and $MeSO_3H$ (2 ml) was added. With the temperature maintained below 5°, $NaNO_2$ (1.50 g, 0.022 mole) dissolved in H_2O (10 ml) was added slowly with stirring. This addition required 15 min. The mixture was allowed to stand 2 hr as it warmed to room temperature, was neutralized with dilute NaOH, and cooled to 0°. The precipitated yellow solid was purified to give Ig. The uv spectral data are given in Table III.

TABLE III

ULTRAVIOLET SPECTRA

Compd	Solvent	λ_{max}, mμ	ε
Ig	0.1 *N* HCl	375, 240	7650, 10,000
	0.1 *N* NaOH	364, 246	12,000, 11,800
XI	0.1 *N* HCl	370, 255.5	7531, 15,645
	0.1 *N* NaOH	367, 232.5	10,179, 13,605

1-(3-Amino-6-chloropyrazinoyl)semicarbazide (XI).—A mixture of IIIa (0.027 mole) and KNCO (0.054 mole) in a solution of 5 ml of concentrated HCl in 50 ml of H_2O was heated on the steam bath for 2 hr. The solid was collected, washed with H_2O

(14) G. W. Kirsten and G. B. L. Smith, *J. Am. Chem. Soc.*, **58**, 809 (1936).

(15) W. G. Finnegan, R. A. Henry, and E. Lieber, *J. Org. Chem.*, **18**, 779 (1953).

(16) G. I. Keim, R. A. Henry, and G. B. L. Smith, *J. Am. Chem. Soc.*, **72**, 4911 (1950).

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.* ($C_6H_5ClN_2O_3$) 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

JAMES H. JONES, WILBUR J. HOLTZ, AND EDWARD J. CRAGOE, JR.

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

Received October 2, 1968

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. Spoerri, *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).