Activated Esters of Substituted Pyrazinecarboxylic Acids (1)

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N-Amidino-3,5-diamino-6-chloropyrazinecarboxamide (**1**) has been shown to be an effective potassium sparing diuretic. Various carboxyl activating agents have been employed with 3-aminopyrazinecarboxylic acids in an effort to synthesize analogs of **1**. Stable enol esters were isolated from a number of such acids and *N*-*t*-butyl-5-methylisoxazolium perchlorate (**12**). Although strong bases in DMF or DMSO catalyze a competing destruction of the enol ester system, these esters are useful acylating agents for a variety of nucleophilic substrates in less polar media. Amides, esters, and thiol esters are produced in good yields under mild conditions from these activated esters.

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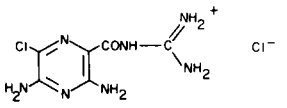
N-Amidino-3,5-diamino-6-chloropyrazinecarboxamide (**1**) has been shown to be a clinically effective potassium-sparing diuretic (2). A wide variety of analogs has been synthesized in an effort to define more clearly the structure-activity requirements (3). From these studies it was determined that substitution of the nuclear amino functions and/or the guanidine nitrogen atoms could be accomplished without concomitant loss of biological activity (3b). A program was designed to synthesize analogs of **1** with the major emphasis directed towards modification of the guanidine portion of the molecule. It became readily apparent that the requirement of an appropriate derivative of **5a** with sufficient acylating activity to react with a wide variety of nucleophilic substances constituted the major problem. We wish to report herein the results of our search for such an intermediate.



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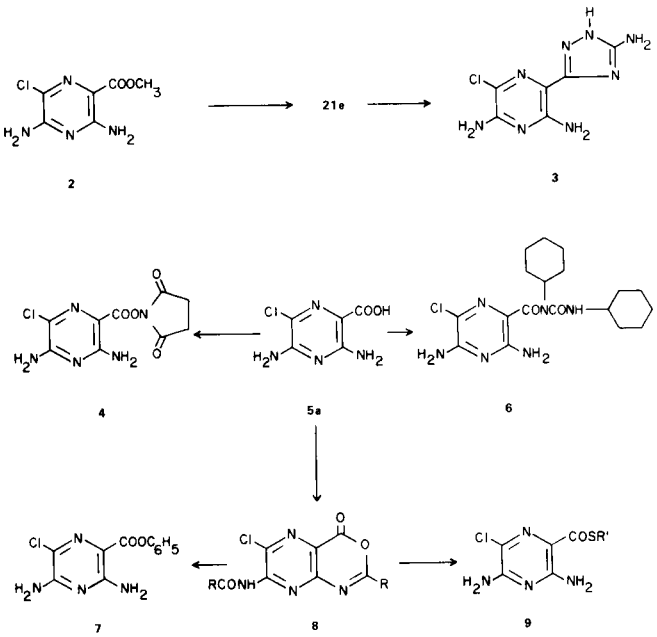
Although the methyl ester (**2**) was sufficiently reactive to condense with many guanidines, some aliphatic amines, and with hydrazine, it failed to condense with weak nitrogen bases (*i.e.*, 2-hydrazinopyrimidine, 2-amino-2-thiazoline) and afforded a plethora of side reactions with aminoguanidines. For example, most condensations between **2** and various aminoguanidines had to be performed under such rigorous conditions that the aminoguanidine decomposed prior to reaction. The acid hydrazide (**21f**) was produced from the liberated hydrazine. In other instances the interaction between the aminoguanidine and **2** was so slow and the conditions so vigorous that the desired pyrazinecarboxamidoguanidine (**21e**) underwent rapid cyclization to a pyrazinyltriazole (**3**) (3f).

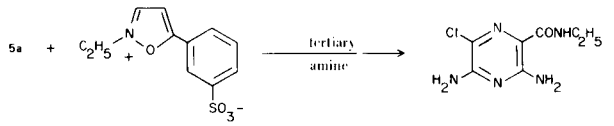


2 **3** **4** **5a** **6** **7** **8** **9**

The preparation of an acid chloride from **5a** failed,

although attempted under a variety of conditions. Even though the amino groups of **5a** are non-basic and essentially non-nucleophilic, **5a** resembles anthranilic acid in its resistance to acid chloride formation (4). The cyclic oxazinones (**8**, R = CH_3, C_3H_7-n) were prepared, but these extremely active acylating agents (5) were unstable to storage and yielded complex reactions on treatment with many amines (6). The oxazinones did undergo reaction with various thiols and phenols to give the corresponding thiol (**9**) and phenyl esters (**7**) upon subsequent careful hydrolysis. These latter derivatives, while somewhat more reactive than **2**, left much to be desired in terms of solubility and reactivity (6). Experiments conducted with **5a** and *N*-hydroxysuccinimide in the presence of dicyclohexylcarbodiimide produced the "active ester" **4**. Unfortunately, **4** was insoluble in most solvents and did not represent a great stride forward in reactivity (7). Other work with dicyclohexylcarbodiimide and **5a** generated the pyrazinoylurea (**6**) in the absence or presence of added amine with no evidence of amide formation (8).

The use of certain isoxazolium salts to generate "active esters" from amino acids for peptide synthesis has been reported (9,10). Recently, stable crystalline esters have been reported as products from acids and *N*-*t*-butyl-5-methylisoxazolium salts (11,12). We began an investigation of the reactions of **5a** with available isoxazolium salts to examine the potential usefulness of any such "active esters" formed.



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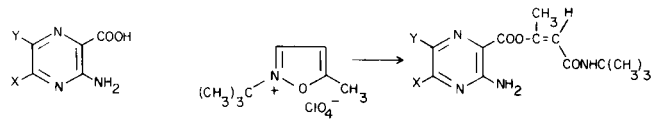
N-Ethyl-3,5-diamino-6-chloropyrazinecarboxamide (**11**) was the major product from the interaction of **5a**, as its triethylamine salt (DMSO), with *N*-ethyl-5-phenylisoxazolium-3′-sulfonate (**10**) and various amines. Apparently, rearrangement of the intermediate ester and subsequent cleavage occurred more readily than the desired acylation. Rearrangement of the enol esters derived from *N*-ethyl and *N*-methylisoxazolium salts is a well known disadvantage of these intermediates (9,10).



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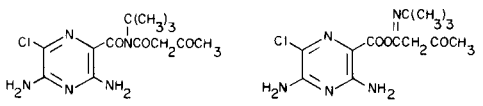
a. X = NH_2; Y = Cl
b. X = $N(CH_3)_2$; Y = Cl
c. X = NHC_2H_5; Y = Cl
d. X = H; Y = Cl
e. X = H; Y = H

12

13, X = NH_2; Y = Cl
14, X = $N(CH_3)_2$; Y = Cl
15, X = NHC_2H_5; Y = Cl
16, X = H; Y = Cl
17, X = H; Y = H

Utilization of *N*-*t*-butyl-5-methylisoxazolium perchlorate (**12**), a reagent devised to inhibit the spontaneous rearrangement of the enol esters derived from isoxazolium salts (11), with **5a** in the presence of triethylamine (DMF) produced a crystalline derivative. This material could be recrystallized from a variety of solvents (ethanol, 2-propanol, acetonitrile, toluene) without concomitant rearrangement or decomposition. The spectral properties of this product were consistent with the enol ester structure (**13**). Condensation of **12** with a number of other pyrazinecarboxylic acids in DMF or acetonitrile generated the corresponding enol esters (14-17). These derivatives, like **13**, were crystalline and stable to an assortment of boiling solvents.

Once the identity and stability of these enol esters was confirmed, an investigation was initiated to determine their usefulness as acylating agents. A number of nitrogen bases were acylated with **13**, generated *in situ* in DMF or DMSO solution. It was observed, however, that strong bases produced very poor yields of the desired derivatives (13). For example, when sodium urea was added to a DMF solution of **13**, no pyrazinoylurea was found (tlc). Similarly, attempted conversion of **13** to the methyl ester (**2**) by treatment with sodium methoxide in DMF or DMSO solution (25°) produced no detectable (tlc) **2**. Careful work-up of this latter reaction yielded a new substance, **18** or **19** (14), albeit in low yield. Attempted preparation of the dimethylaminoethyl or *N*-methyl-4-piperidyl ester produced similar results. Rearrangement of enol esters derived from **12** heretofore have not been



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observed. Likewise, there have been no reports of treatment of such esters under these extreme basic conditions. Whereas **13** exhibited a pmr signal (d_6-DMSO) at 5.57 ppm for the vinylic proton, in addition to peaks for the methyl and *t*-butyl substituents, the rearrangement product exhibited no vinylic absorption.

Although no detectable reaction (tlc) occurred at 25°, when **13** was heated (90°, 24 hours) in DMF with triethylamine, the *t*-butyl amide (**20**) was the major isolated material. Formation of **20** is likely to have involved rearrangement of **13** to **18** followed by cleavage to **20** (15). It has been questioned whether the decreased tendency towards rearrangement of enol esters derived from **12** is the result of a large kinetic barrier, or the fact that the enol ester is the thermodynamically favored isomer (11,12). On the basis of these results, it would appear that there is a significant kinetic barrier to rearrangement, rather than **13** being the thermodynamically favored

isomer. Treatment of **13** with triethylamine in refluxing 2-propanol or DMF (90°, 72 hours) without triethylamine produced no detectable (tlc) quantities of **20**. Woodman has observed thermal conversion of an enol ester of this type to the corresponding *t*-butyl amide (16). It is likely that we are operating at less than the requisite temperature for thermal decomposition and require the combination of a highly polar basic medium to effect conversion to **20**. We have made no attempts to duplicate Woodman's thermal procedure, however. Therefore, we conclude that the competing rearrangement, and hence lower product yield, was a result of the high polarity and base enhancing properties of DMF and DMSO (17). Supportive evidence for this conclusion was obtained when **13** was treated with sodium methoxide in methanol. The methyl ester (**2**) was isolated in good yield with no evidence of the rearrangement product or the *t*-butyl amide (**20**) as contaminants. As a consequence, most subsequent reactions were performed with the isolated ester (**13**) in 2-propanol, tetrahydrofuran, or acetonitrile. The reactions with benzyl mercaptan and benzamidine were performed in aqueous sodium hydroxide solution. In general, the products derived from **13** were prepared under relatively mild conditions. The versatility of this reagent is indicated by the variety of products shown in Table I resulting from reaction with the appropriate nucleophile.

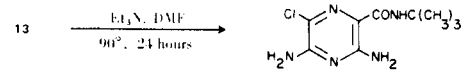
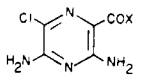


Table I



a. X = -NHNH-

b. X = -NH-

c. X = -NHNH-

d. X = -NHNHC(=NH)-SCH3

e. X = -NHNHC(=NH)-NH2

f. X = -NHNH2

g. X = -NHC(=NH)-NH2

h. X = -NHC(=NH)NHC(=NH)NHOCH2C6H5

i. X = -NH-C(=NH)-C6H5

j. X = -NH-

k. X = -NH-

l. X = -SCH2C6H5

m. X = -NHC6H5

n. X = -NHC(=NC6H5)NHC6H5

The position of acylation with many of these derivatives would appear to be open to question. However, consideration of the following factors supports the structural assignments. Neither 2-aminopyridine nor 3-amino-1,2,4-triazole underwent reaction with **13**, therefore the position of acylation with 2-hydrazinopyrimidine and 3,4,5-triamino-1,2,4-triazole appears to be as indicated (**21a**, **21b**, respectively). Although 2-amino-2-thiazoline condensed with **13** (*i.e.*, product **21j**), the position of acylation with 2-hydrazino-2-thiazoline should be as shown (**21c**). This conclusion is based on the fact that 3-methyl-3-thioisosemicarbazide forms **21d** as a result of interaction with **13**. The structure of **21d** was confirmed by an alternate synthesis. There is no question regarding the structure of the product from **13** and aminoguanidine, since this product (**21e**) was identical with an authentic sample whose structure had been previously established (3f). Guanidine also underwent smooth acylation with **13** to generate **21g**. Benzyloxybiguanide presented an unusual case in that the general reaction between an acylating species and a biguanide leads to formation of a triazine (18). The product (**21h**) was soluble in warm dilute acid, had spectral properties consistent with the assigned structure, and analyzed satisfactorily. The position of acylation with 2-amino-2-thiazoline and 2-amino-5-phenyloxazine is based on analogy with the reaction of other acylating agents with these type species (19). In general, the more reactive acylating agents, *i.e.*, acid chlorides, anhydrides, become attached to the *exo* nitrogen. Since the same product is derived from 2-amino-5-phenyl-2-oxazoline utilizing **13** or 3,5-diamino-6-chloropyrazinecarboxylic *N,N*-diphenylcarbamic anhydride (20), it follows that the structure of **21k** is as indicated.

Having demonstrated the versatile acylating properties of **13**, we explored other facets and limitations of its chemistry. *N,N'*-Diphenylguanidine underwent smooth reaction with **13** in refluxing acetonitrile, whereas reaction with **4** required fusion at 150-180° (7), and **2** was totally inert to reaction with this guanidine under all conditions employed. Aniline produced **21m** when refluxed with **13** in *n*-amyl alcohol; however, the yield was poor (10%). Condensations of **13-17** with a variety of extremely weak nucleophiles such as cyanamide, urea, cyano- and nitroguanidine, aminoheterocycles, and eneamines proved less satisfactory than with the stronger nucleophiles.

Although **13** satisfied most of our criteria, and is a most versatile acylating species, its poorer reactivity with these less nucleophilic substrates, and the occasional problem with rearrangement, prompted further investigation for a more potent acylating agent. The results of this search will be presented in a subsequent paper (20).

EXPERIMENTAL (21)

1,3-Dicyclohexyl-1-(3,5-diamino-6-chloropyrazinoyl)urea (**6**).

Dicyclohexylcarbodiimide (2.2 g., 0.011 mole) in 15 ml. of DMSO was added to a solution of **5a** (1.88 g., 0.01 mole) and 2-hydrazinopyrimidine (22) (1.1 g., 0.01 mole) in 35 ml. of DMSO. After 24 hours the solid that had separated was filtered, m.p. 205-215°, and the filtrate was diluted with water (250 ml.). The solid that precipitated was identical to that already isolated. The combined solids, 3.5 g., were recrystallized from ethanol, m.p. 218-220°. This material was identical with an authentic sample of **6** prepared by J. H. Jones of these laboratories.

N-Ethyl-3,5-diamino-6-chloropyrazinecarboxamide (**11**). (A) From Attempted Preparation of **21a** using **5a** and Woodward's Reagent K (**10**).

A mixture of **5a** (1.88 g., 0.01 mole), triethylamine (0.01 mole), and **10** (2.53 g., 0.01 mole) in DMSO (20 ml.) was stirred until complete solution was obtained (1-2 hours), followed by the addition of 2-hydrazinopyrimidine (22,23) (1.1 g., 0.01 mole). After 24 hours the solution was diluted with water (100 ml.) and chilled. Filtration and drying of the yellow solid produced 1.33 g., m.p. 200-205°. Recrystallization from benzene raised the m.p. to 205-206°. Pmr analysis (trifluoroacetic acid) showed the presence of an ethyl group as the only non-exchangeable protons.

Anal. Calcd. for $C_7H_{10}ClN_5O$: C, 38.98; H, 4.67. Found: C, 38.65; H, 4.60.

(B) From **13**.

Condensation of **13** and aqueous ethylamine in THF produced a material identical in every respect to that above.

N-*t*-Butyl-3-(3,5-diamino-6-chloropyrazinecarbonyloxy)crotonamide (**13**).

Prepared as previously described using **5a** and **12** in DMF (3f); nmr (d_6-DMSO): 1.20, s, 9H (-C(CH_3)); 2.00, s, 3H (-C(=CH_3)-C<); 5.57, s, 1H (-C(=CH_3)-C<$_H$); 7.12, s (broad), 3H (-NH_2, -CONH-); 7.34, s (broad), 2H (-NH_2). Ir: 1695 cm^{-1} (-COO-C(=CH_3)-C<); 1670 cm^{-1} (-CONH-).

N-*t*-Butyl-3-(3-amino-5-dimethylamino-6-chloropyrazinecarbonyloxy)crotonamide (**14**).

Preparation similar to **13** using **5b** (24) and **12** in acetonitrile (98% yield), m.p. 154-155° dec.

Anal. Calcd. for $C_{15}H_{22}ClN_5O_3$: C, 50.63; H, 6.23; N, 19.68. Found: C, 50.37; H, 6.25; N, 19.70.

N-*t*-Butyl-3-(3-amino-5-ethylamino-6-chloropyrazinecarbonyloxy)-crotonamide (**15**).

Prepared from **5c** (24) and **12** in acetonitrile (97% yield), m.p. 144-146.5° (butyl chloride).

Anal. Calcd. for $C_{15}H_{22}ClN_5O_3$: C, 50.63; H, 6.23; N, 19.68. Found: C, 50.60; H, 6.23; N, 19.60.

N-*t*-Butyl-3-(3-amino-6-chloropyrazinecarbonyloxy)crotonamide (**16**).

Prepared from **5d** (3a) and **12** in acetonitrile (quantitative), m.p. 143-145° (butyl chloride).

Anal. Calcd. for $C_{13}H_{17}ClN_4O_3$: C, 49.92; H, 5.48; N, 17.91. Found: C, 50.21; H, 5.67; N, 17.51.

N-*t*-Butyl-3-(3-aminopyrazinecarbonyloxy)crotonamide (**17**).

Prepared from **5e** and **12** in acetonitrile (80% yield), m.p. 133-135° (butyl chloride); nmr (deuteriochloroform): 1.28, s, 9H (-C(CH_3)$_3$); 2.18, s, 3H (-O-C(=CH_3)-C<); 5.59, s (broad), 1H (>C=C<$_H$); 6.67, s (broad), 1H (-CONH-); 6.92, s (broad), 2H (-NH_2); 8.02, d, 1H (6-H); 8.30, d, 1H (5-H).

Anal. Calcd. for $C_{13}H_{18}N_4O_3$: C, 56.10; H, 6.52; N, 20.13. Found: C, 56.15; H, 6.52; N, 20.05.

Rearrangement Product (**18** or **19**).

A mixture of sodium hydride (0.40 g., 0.01 mole, 51.8% oil dispersion) and *N*-methyl-4-piperidinol (1.15 g., 0.01 mole) in DMSO (7 ml.) was stirred until hydrogen evolution ceased. The enol ester **13** (3.27 g., 0.01 mole) was added and stirring was continued for 0.5 hour. The reaction mixture was diluted with cold water (50 ml.) and the *p*H of the solution carefully adjusted to 6.0-6.5. The yellow solid that separated was filtered quickly, washed with water and dried, 1.1 g., m.p. 200-210°. Repeated recrystallization from 2-propanol followed by acetonitrile raised the m.p. to 221-224° dec.; nmr (d_6-DMSO): 1.47, s, 9H (-C(CH_3)$_3$); 2.04, s, 3H (-COCH_3) accompanied by small singlets at 2.10 and 2.17 (enol forms?); ir: 1730-1710 cm^{-1}; 1680 cm^{-1}.

Anal. Calcd. for $C_{13}H_{18}ClN_5O_3$: C, 47.63; H, 5.53; N, 21.37. Found: C, 47.73; H, 5.37; N, 21.55.

This product was the major material obtained (some 3,5-diamino-6-chloropyrazinecarboxylic acid was also present in all runs) when methanol or dimethylaminoethanol was substituted for *N*-methyl-4-piperidinol in DMSO or DMF. However, when **13** was treated with one equivalent of sodium methoxide in methanol, **2** (80%) was the only product isolated.

Isolation of *N*-*t*-Butyl-3,5-diamino-6-chloropyrazinecarboxamide (**20**) from **13** with Triethylamine and DMF.

A solution of **13** (3.27 g., 0.01 mole) and triethylamine (0.02 mole) in DMF (20 ml.) was stirred for 24 hours (25°). Tlc examination, fluorescent silica, benzene (1):ethyl acetate (1), indicated no change. The solution was heated to 90° (oil bath) for 24 hours. Tlc probes at intervals indicated the appearance of **20** after 1-2 hours. Dilution of the cooled reaction mixture with water (100 ml.) provided 1.0 g., m.p. 205-218°, after filtration. Recrystallization from acetonitrile-water raised the m.p. to 219-221°.

Anal. Calcd. for $C_9H_{14}ClN_5O$: C, 44.35; H, 5.79; N, 28.74. Found: C, 44.53; H, 5.62; N, 28.47.

N-(2-Pyrimidinylamino)-3,5-diamino-6-chloropyrazinecarboxamide Hydrate (**21a**).

To a solution of **5a** (1.9 g., 0.01 mole) and triethylamine (0.01 mole) in DMF (20 ml.) was added **12** (2.4 g., 0.01 mole). After 10 minutes, 2-hydrazinopyrimidine (22) (4.4 g., 0.04 mole) was added followed by warming on the steam bath for 4 hours. Dilution of the cooled reaction mixture with water (200 ml.) gave 2.3 g., m.p. 257-260°. Recrystallization from 80% aqueous acetonitrile produced material of m.p. 262-263°.

Anal. Calcd. for $C_9H_9ClN_8O \cdot H_2O$: C, 36.19; H, 3.71; N, 37.52. Found: C, 36.18; H, 3.75; N, 37.74.

3,5-Diamino-4-(3,5-diamino-6-chloropyrazinecarboxamido)-4*H*-1,2,4-triazole Hemihydrate (**21b**).

3,4,5-Triamino-4*H*-1,2,4-triazole (25) (3.06 g., 0.03 mole) was substituted for 2-hydrazinopyrimidine in the above procedure and the solution heated on the steam bath for 16 hours. Work-up as described above gave 1.5 g. of brown solid, m.p. 275-278° dec.

after recrystallization from water.

Anal. Calcd. for $C_7H_9ClN_{10}O \cdot \frac{1}{2}H_2O$: C, 28.63; H, 3.43; N, 47.40. Found: C, 28.58; H, 3.37; N, 47.45.

2-(3,5-Diamino-6-chloropyrazinecarboxamido)amino-2-thiazoline (**21c**).

2-Hydrazino-2-thiazoline hydrobromide (26) (8.7 g., 0.044 mole) was added to a refluxing solution of sodium (0.92 g., 0.04 mole) in 2-propanol (500 ml.) and refluxing was continued for 0.75 hour. The ester (**13**, 6.54 g., 0.02 mole) was added and the mixture refluxed for 20 hours. The mixture was filtered while hot and the filtrate was evaporated to dryness *in vacuo*. The residue was slurried with water (100 ml.) and filtered to give 4.05 g., m.p. 217-223° dec. Two recrystallizations from aqueous acetonitrile followed by reprecipitation from dilute methanesulfonic acid by the addition of 6*N* aqueous ammonia gave m.p. 243-245° dec.

Anal. Calcd. for $C_8H_{10}ClN_7OS$: C, 33.39; H, 3.50; N, 34.08. Found: C, 33.50; H, 3.90; N, 34.01.

1-(3,5-Diamino-6-chloropyrazinoyl)-3-methyl-3-thioisosemicarbazide (**21d**).

3-Methyl-3-thioisosemicarbazide hydroiodide (5.12 g., 0.022 mole) was added to a refluxing solution of sodium (0.46 g., 0.02 mole) in 2-propanol (100 ml.). After 5 minutes a solution of **13** (3.27 g., 0.01 mole) in THF (90 ml.) was added and refluxing continued for two hours. The mixture was chilled; the solid collected, washed with water and dried, 0.30 g., m.p. > 300°. This material was identical with a sample prepared by an alternate procedure (27).

1-(3,5-Diamino-6-chloropyrazinecarboxamido)guanidine (**21e**).

Aminoguanidine hydrochloride (28) (5.5 g., 0.05 mole) was added to a hot solution of sodium (1.0 g., 0.044 mole) in 2-propanol (200 ml.). This mixture was refluxed 1 hour, **13** (6.54 g., 0.02 mole) was added, and refluxing was continued for another hour. The cooled reaction mixture was filtered and the yellow solid was washed successively with water and 2-propanol, 3.45 g. (70%), m.p. 278-280° dec., which was identical with a previously prepared sample of **21e** (3f).

A preparation from **13** (0.01 mole) generated *in situ* in DMF produced **21e** in less than 10% yield.

3,5-Diamino-6-chloropyrazinecarboxylic Acid Hydrazide (**21f**).

A solution of hydrazine (5 ml.) and **13** (6.54 g., 0.02 mole) in THF (200 ml.) was warmed on the steam bath for 2 hours. Removal of the solvent *in vacuo* and recrystallization of the residue from DMF-water gave **21f** identical in all respects with a previously prepared sample (3f).

N-Amidino-3,5-diamino-6-chloropyrazinecarboxamide (**21g**).

Using guanidine hydrochloride (4.75 g., 0.05 mole) and the procedure described for **21e**, **21g**, 2.8 g. (61%), m.p. 239-241° was isolated, identical with a previously prepared sample (3b).

Another preparation from **13** (0.01 mole) generated *in situ* in DMF produced crude **21g** in 36% yield.

1-(3,5-Diamino-6-chloropyrazinoyl)-5-benzyloxybiguanide (**21h**).

A solution of **13** (3.27 g., 0.01 mole) and benzyloxybiguanide (29) (3.30 g., 0.016 mole) in THF (90 ml.) was refluxed for 24 hours. Removal of the solvent *in vacuo* gave 2.90 g., m.p. 180-191°. Recrystallization from acetonitrile raised the m.p. to 198-199°.

Anal. Calcd. for $C_{14}H_{16}ClN_9O_2$: C, 44.50; H, 4.27; N, 33.37. Found: C, 44.68; H, 4.32; N, 33.90.

N-Benzimido-3,5-diamino-6-chloropyrazinecarboxamide (**21i**).

A solution of benzamidine hydrochloride (5.6 g., 0.036 mole) and sodium hydroxide (1.2 g., 0.03 mole) in water (30 ml.) was stirred for 2 minutes and **13** (3.27 g., 0.01 mole) was added. This mixture was stirred for two hours (25°) and filtered. Recrystallization of the filtered solid from acetonitrile followed by ethanol produced light tan needles, 0.83 g., m.p. 221-224° dec.

Anal. Calcd. for $C_{12}H_{11}ClN_6O$: C, 49.57; H, 3.81; N, 28.91. Found: C, 49.95; H, 3.90; N, 29.12.

N-(2-Thiazolin-2-yl)-3,5-diamino-6-chloropyrazinecarboxamide Hydrochloride Hemihydrate (**21j**).

A mixture of 2-amino-2-thiazoline (4.08 g., 0.04 mole) and **13** (3.27 g., 0.01 mole) in THF (90 ml.) was refluxed for 24 hours. The solvent was removed *in vacuo* and the residue dissolved in dilute methanesulfonic acid (1.4 ml. of 6*N* acid diluted to 50 ml.). Addition of concentrated hydrochloric acid (5 ml.) precipitated the product as its hydrochloride salt, 0.86 g., m.p. > 340°.

Anal. Calcd. for $C_8H_9ClN_6OS \cdot HCl \cdot 0.5H_2O$: C, 30.19; H, 3.49; N, 26.41. Found: C, 30.35; H, 3.64; N, 26.22.

N-(5-Phenyl-2-oxazolin-2-yl)-3,5-diamino-6-chloropyrazinecarboxamide (**21k**).

A solution of 2-amino-5-phenyl-2-oxazoline (30) (2.96 g., 0.02 mole) and **13** (3.27 g., 0.01 mole) in THF (100 ml.) was refluxed for 18 hours. The solid that precipitated was collected and recrystallized from warm DMF by the addition of acetonitrile, 2.45 g., m.p. 210-211°.

Anal. Calcd. for $C_{14}H_{13}ClN_6O_3$: C, 50.53; H, 3.94; N, 25.26. Found: C, 50.58; H, 4.03; N, 25.38.

Benzyl 3,5-Diamino-6-chloropyrazinethiolcarboxylate (**21l**).

Benzyl mercaptan (0.15 ml.) was added to a mixture of sodium hydroxide (0.08 g., 0.002 mole), water (0.5 ml.) and acetonitrile (3.5 ml.) followed by the addition of **13** (0.327 g., 0.001 mole). The mixture was stirred for 2 hours, diluted with water (6 ml.) and the yellow solid collected, 0.25 g., m.p. 137-142°. Recrystallization from acetonitrile raised the m.p. to 145-146.5°.

Anal. Calcd. for $C_{12}H_{11}ClN_4OS$: C, 48.89; H, 3.76; N, 19.01. Found: C, 48.98; H, 3.54; N, 18.85.

N-Phenyl-3,5-diamino-6-chloropyrazinecarboxamide (**21m**).

A mixture of aniline (4.65 g., 0.05 mole), **13** (3.27 g., 0.01 mole) and *n*-amyl alcohol (20 ml.) was heated to reflux for 24 hours. The mixture was filtered while hot to remove some **5a** and the filtrate was stripped to an oil under reduced pressure. The oil was dissolved in methylene chloride (50 ml.), extracted with 1*N* hydrochloric acid (2 x 20 ml.) and dried (magnesium sulfate). Removal of the solvent and addition of butyl chloride to the residue produced off-white crystals, m.p. 192-196°. The analytical sample had m.p. 198-202° (cyclohexane).

Anal. Calcd. for $C_{11}H_{10}ClN_5O$: C, 50.10; H, 3.82; N, 26.56. Found: C, 49.98; H, 3.84; N, 26.39.

N-(1,2-Diphenylamidino)-3,5-diamino-6-chloropyrazinecarboxamide (**21n**).

A mixture of **13** (3.27 g., 0.01 mole) and *N,N'*-diphenylguanidine (4.22 g., 0.01 mole) in acetonitrile (200 ml.) was refluxed for 48 hours. The solid that was collected, 2.2 g., m.p. 232-234°, was identical with a previously prepared sample (7).

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(13) See, for example, reference 3f where 1-benzyl-3-(3,5-diamino-6-chloropyrazinecarboxamido)guanidine was isolated in 6% yield by this method.

(14) Although the available evidence similarly supports either **18** or **19** as the structure of the rearrangement product, the fact that enol esters of this type (**13**) undergo any rearrangement at all, even under these severe conditions, somewhat limits their use.

(15) In direct analogy with Woodman and Davidson (12), we find that the *t*-butylamide is a by-product of the synthesis of these enol esters. We are also in agreement with their findings that the *t*-butylamide is *not* produced by rearrangement of the enol ester under the conditions of its synthesis. The amide (**20**) is removed below the limits of detection (tlc) before this base catalyzed rearrangement of **13** is attempted.

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(21) Melting points were taken in open capillaries (Thomas Hoover apparatus) and are corrected values. Nmr spectra were taken on a Varian A-60A spectrometer and chemical shift values are expressed in δ units (ppm) from tetramethylsilane used as an internal standard. Infrared spectra were taken as potassium bromide discs on a Perkin-Elmer Model 137 spectrophotometer. K. B. Streeter, Y. C. Lee and their staff supplied the analytical data.

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