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PROCESS FOR THE PREPARATION OF 3-AMINOPYRAZINOYLUREAS

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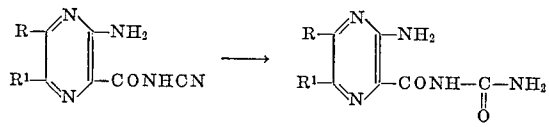
U.S. Cl. 260—250 13 Claims

ABSTRACT OF THE DISCLOSURE

A process is described for the preparation of pyrazinoylureas which comprises the hydrolysis of pyrazinoylcyanamides. The products are diuretic and/or saluretic agents.

This invention relates to processes for the preparation of pyrazinoylureas. More particularly it relates to a process for the preparation of (3-amino-5-R-6-R^1-pyrazinoyl) ureas from the corresponding pyrazinoylcyanamides. The process is depicted by the following equation:



I II

wherein R represents

(1) hydrogen,
(2) trifluoromethyl,
(3) lower cycloalkyl of from 3 to 6 carbon atoms such as cyclopropyl, cyclopentyl or cyclohexyl,
(4) mononuclear aryl, such as phenyl,
(5) lower alkyl, of from 1 to about 5 carbon atoms, either straight or branched chain, such as methyl, ethyl, propyl, butyl, or pentyl, or
(6) amino, of structure —NR^{3}R^4, wherein R^3 represents
  (a) hydrogen,
  (b) lower alkyl of from 1 to about 3 carbon atoms such as methyl, ethyl or propyl, and
R^4 represents
  (a) hydrogen,
  (b) amino,
  (c) lower cycloalkyl of from 3 to about 6 carbon atoms such as cyclopropyl, cyclopentyl or cyclohexyl,
  (d) mononuclear aryl such as phenyl,
  (e) lower alkenyl of from 3 to about 6 carbon atoms such as allyl,
  (f) lower alkyl of from 1 to about 5 carbon atoms either straight or branched chain, and either unsubstituted or substituted with such as
    (1) hydroxy,
    (2) amino,
    (3) di(lower alkyl) amino, wherein the lower alkyl groups have from 1 to about 3 carbon atoms such as methyl, ethyl, or propyl,
    (4) halo, such as fluoro or chloro,
    (5) mononuclear aryl, such as phenyl,
    (6) lower cycloalkyl of from 3 to about 6 carbon atoms, such as cyclopropyl, cyclopentyl, or cyclohexyl,
    (7) heterocyclic, such as pyridyl or furyl,
  and when R^3 and R^4 each represents lower alkyl, they can be linked together either directly or through a nitrogen atom to form with the nitrogen atom to which they are attached a heterocyclic ring such as pyrrolidinyl, hexahydro-1-azepinyl, or N-methyl piperazinyl;
R^1 represents
  (1) hydrogen,
  (2) halo, such as chloro, bromo or iodo,
  (3) lower alkyl of from 1 to about 3 carbon atoms, such as methyl, ethyl or propyl,
  (4) lower cycloalkyl of from 3 to about 6 carbon atoms, such as cyclopropyl, cyclopentyl or cyclohexyl,
  (5) mononuclear aryl, such as phenyl; and R and R^1 can be linked together to form a group such as

—CH=CH—CH=CH—, CH=CH—CCl=CH— or —$(CH_2)_4$—

The novel compounds of this invention possess diuretic and saluretic properties and can be administered in dosage forms known to be suitable for the administration of pyrazinoylguanidine type diuretic and saluretic agents either alone in the form of pills, capsules, tablets and the like or admixed with antihypertensive or other therapeutically effective compounds in a single dosage form. The compounds are effective in enhancing the excretion of sodium and chloride ions and are therefore useful natriuretic agents in the treatment of conditions resulting from an excessive accumulation of sodium chloride in the body. While the dosage of the compounds will vary from compound to compound, and also upon the age and condition of the patient, an average dosage of about 50 mg. or more or less of the novel compounds of this invention generally is effective in lowering the sodium chloride concentration of the blood. This dosage is well below their toxic dose and the compounds therefore are safe drugs for use in therapy of this type.

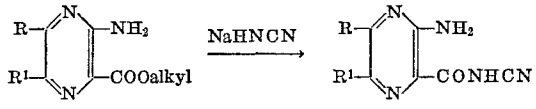
The previously known method for the preparation of pyrazinoylureas (i.e., by the reaction of the sodium salt of urea with a pyrazinoic acid ester) was found to be inoperative in many instances, e.g., wherein the pyrazine ring carried an amino or monosubstituted amino group in the 5-position. Since by analogy with the known pyrazinoylguanidines, the 5-amino compounds were expected to be the most active members of the pyrazinoylurea series it was important to discover a process for the preparation of these compounds that would be generally applicable to the entire series.

It was found that pyrazinoylcyanamides (I) are readily converted to the corresponding urea compounds (II) using mineral acid in either water or lower alkanol as the reaction medium.

The process of converting the pyrazinoylcyanamides (I) to the pyrazinoylureas (II) comprises suspending the starting material in dilute aqueous mineral acid such as hydrochloric, hydrobromic, sulfuric acid or the like of from 3 to about 10 N in strength preferably about 6 N, and agitating the suspension until conversion to the product is complete, that is, from one to about thirty hours at ambient temperature. The reaction can be conducted at temperatures between about 5° C. and 100° C., however temperatures below ambient prolong the reaction time unnecessarily, and higher temperatures lead to undesirable side reactions. When conversion is complete, the product is isolated by filtration and recrystallization.

Alternatively, the (pyrazinoyl)cyanamide is dissolved in a lower alkanol, such as methanol or ethanol containing about 10% (w./v.) of a hydrogen halide such as hydrogen chloride or hydrogen bromide at a temperature between about ambient and 50° C. The reaction product is separated and treated with water, dilute mineral acid or dilute alkali metal hydroxide at room temperature for about one hour. The product is collected and purified by recrystallization.

The pyrazinoylcyanamide starting materials (I) are prepared from esters of pyrazinoic acids, according to the following equation:



I

The process comprises dissolving cyanamide in an anhydrous lower alkanol, such as methanol, ethanol or propanol containing approximately an equivalent amount of an alkali metal such as sodium or potassium. After one-half to about one hour at a temperature between ambient and reflux, solid pyrazinoic acid ester is added and the mixture is refluxed for from 2 to about 24 hours, during which time a solid separates. This is collected by filtration dissolved in water and the solution is made slightly acid by addition of an acid such as hydrochloric, hydrobromic, sulfuric, acetic, propionic or the like. Purification by recrystallization provides the intermediate product (I).

The examples which follow demonstrate the preparation of pyrazinoylureas by the process of this invention as well as the preparation of the intermediate pyrazinoylcyanamides. It is to be understood that the invention is not limited to the reagents and conditions employed in the specific examples but extends to reasonable variations thereof cognizable in the art.

(A) PREPARATION OF PYRAZINOYL CYANAMIDES

Preparation 1A

(3,5 - diamino-6-chloropyrazinoyl)cyanamide.—Cyanamide (13.6 g., 0.324 mole) is dissolved in a solution of sodium (7.6 g., 0.324 mole) in absolute methanol (525 ml.). This solution is refluxed for one-half hour and methyl 3,5-diamino-6-chloropyrazinoate (22.0 g., 0.10 mole) is added. Refluxing is continued for twenty-four hours and the solid that separates during this time is collected by filtration. The solid is dissolved in warm water (750 ml.), treated with decolorizing carbon and filtered. The filtrate is acidified to congo red paper by the addition of dilute hydrochloric acid and the (3,5-diamino-6-chloropyrazinoyl)cyanamide that precipitates is collected and dried; yield 11.5 g. (50% yield), M.P. >330° C.

Analysis.—Calc. for $C_6H_5ClN_6O$ (percent): C, 33.89; H, 2.37; N, 39.53. Found (percent): C, 33.94; H, 2.50; N, 39.48.

Preparation 2A

(3-aminopyrazinoyl)cyanamide.—Cyanamide (5.04 g., 0.12 mole) is dissolved in a solution of sodium (2.76 g., 0.12 mole) in absolute methanol (150 ml.) and stirred for one-half hour at reflux temperature. Methyl 3-aminopyrazinoate (6.12 g., 0.04 mole) is added and the mixture is refluxed for two hours. The solid that separates is collected by filtration and dissolved in water (200 ml.). Acidification by the addition of glacial acetic acid (10 ml.) gives 4.96 g. (75%) of nearly white (3-aminopyrazinoyl)cyanamide, M.P. 225–235° C. (dec.). Reprecipitation of this solid from dilute ammonium hydroxide by the addition of glacial acetic acid gives material which undergoes gradual decomposition starting at 210° C.

Analysis.—Calc. for $C_6H_5N_5O$ (percent): C, 44.17; H, 3.09; N, 42.93. Found (percent): C, 44.11; H, 3.26; N, 42.91.

Preparation 3A

(3-amino - 6 - chloropyrazinoyl)cyanamide.—Sodium (1.9 g., 0.081 moles) is dissolved in absolute methanol (125 ml.) and cyanamide (3.4 g., 0.081 moles) is added. The resulting solution is refluxed with stirring for one-half hour. Methyl 3-amino-6-chloropyrazinoate (5.00 g., 0.027 moles) is added and the reaction mixture is refluxed for another two hours. The precipitated solid is then collected by filtration, dissolved in water (200 ml.), and the resulting solution is acidified with 6 N hydrochloric acid (5 ml.). The yellow solid which precipitates is collected and dried; yield 3.5 g. (67%), M.P. 180–183° C. (dec.) with effervescence. Recrystallization from toluene yields yellow crystals of (3-amino-6-chloropyrazinoyl)cyanamide, M.P. 182–184° C. (dec.) with effervescence.

Analysis.—Calc. for $C_6H_4ClN_5O$ (percent): C, 36.47; H, 2.04; N, 35.45. Found (percent): C, 36.80; H, 2.25; N, 35.37.

Preparation 4A

(3 - amino-5-dimethylamino-6-chloropyrazinoyl)cyanamide.—Cyanamide (5.04 g., 0.12 mole) is dissolved in a solution of sodium (2.76 g., 0.12 mole) in absolute methanol (150 ml.) and stirred for one-half hour at room temperature. Methyl 3-amino-5-dimethylamino-6-chloropyrazinoate (9.22 g., 0.04 mole) is added and the solution refluxed for twenty-four hours. The solid that separates is collected by filtration and dissolved in water (100 ml.). The solution is acidified by the addition of glacial acetic acid and the solid that precipitates is collected and dried; yield 2.67 g. (28%), M.P. 193–197° C. (dec.). Recrystallization from isopropyl alcohol gives yellow needles of (3-amino-5-dimethylamino - 6 - chloropyrazinoyl)cyanamide, M.P. 194–196° C. (dec.).

Analysis.—Calc. for $C_8H_9ClN_6O$ (percent): C, 39.92; H, 3.77; N, 34.92. Found (percent): C, 40.27; H, 3.90; N, 34.96.

Preparation 5A

(3-amino - 5 - ethylamino - 6 - chloropyrazinoyl)cyanamide.—Sodium (2.76 g., 0.12 mole) is dissolved in absolute methanol (150 ml.) and cyanamide (5.04 g., 0.12 mole) is added. The resulting solution is stirred at room temperature for one-half hour. Methyl 3-amino-5-ethylamino-6-chloropyrazinoate (9.24 g., 0.04 mole) is added and the reaction mixture is refluxed with stirring for twenty-one hours. The methanol is evaporated under reduced pressure, the residue is taken up in water (200 ml.), filtered, and the filtrate is acidified with 6 N hydrochloric acid (21 ml.). The yellow solid which precipitates is collected and dried, yield 7.0 g. (73%), M.P. >300° C. Recrystallization from acetonitrile gives light yellow (3-amino-5-ethylamino-6-chloropyrazinoyl)cyanamide, melting at >300° C.

Analysis.—Calc. for $C_8H_9ClN_8O$ (percent): C, 39.92; H, 3.77; N, 34.92. Found (percent): C, 40.11; H, 3.90; N, 34.90.

Preparation 6A

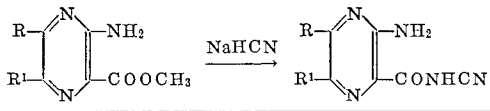
(3-amino-5-methylamino - 6 - chloropyrazinoyl)cyanamide.—Cyanamide (12.6 g., 0.30 mole) is dissolved in a solution of sodium (6.9 g., 0.30 mole) in absolute methanol (750 ml.) and stirred for one-half hour at room temperature. Methyl 3-amino-5-methylamino-6-chloropyrazinoate (21.7 g., 0.10 mole) is added and the resulting solution is refluxed overnight. The solvent is evaporated under reduced pressure. The residue is diluted with water (500 ml.), some insoluble material is filtered off and the filtrate is acidified with dilute hydrochloric acid (50 ml.). The solid that precipitates is collected and dried, yield 3.75 g., M.P., gradual decomposition beyond 150° C. Recrystallization from acetonitrile gives (3-amino-5-methylamino-6-chloropyrazinoyl)cyanamide, M.P. >300° C.

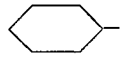
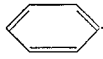
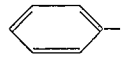
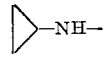
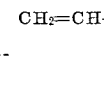
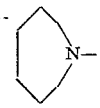
Analysis.—Calc. for $C_7H_7ClN_6O$ (percent): C, 37.09; H, 3.11; N, 37.08. Found (percent): C, 37.35; H, 2.96; N, 36.96.

Employing the method substantially as described in Preparations 1A to 6A but substituting for the pyrazinoic esters used therein, equivalent quantities of the methyl 3-amino-5-R-6-R^1-pyrazinoates described in Table I, there are produced the (3-amino-5-R-6-R^1-pyrazinoyl)cyana-

mides, also described in Table I, according to the reaction scheme illustrated therein.

TABLE I



Preparation:	R	R¹
7A	CH_3—	Br—
8A	NH_2—	I—
9A	C_6H_5NH—	Cl—
10A	NH_2—	H—
11A	$C_6H_5CH_2NH$—	H—
12A	CF_3—	H—
13A	$(CH_3)_2N$—	CH_3—
14A		H—
15A	H	
16A	H	
17A		Br—
18A	$(CH_3)_2N$—	
19A	—$(CH_2)_4$—	
20A	—CH=CH—CCl=CH—	
21A	$CH_3(CH_2)_2NH$—	Cl—
22A	$(CH_3)_2CHNH$—	Cl—
23A	$(CH_3)_3CNH$—	Cl—
24A		Cl—
25A		Cl—
26A		Cl—
27A		Cl—
28A	$CF_3CH_2CH_2NH$—	Cl—
29A	$HO(CH_2)_2NH$—	Cl—
30A	$H_2N(CH_2)_2NH$—	Cl—
31A	$(CH_3)_2N(CH_2)_2NH$—	Cl—
32A		Cl—
33A		Cl—
34A		Cl—
35A		Cl—
36A		Cl—
37A		Cl—
38A		Cl—
39A		Cl—

(B) PREPARATION OF PYRAZINOYLUREAS

Example 1B

(3,5-diamino-6-chloropyrazinoyl)urea.—(3,5-diamino-6-chloropyrazinoyl)cyanamide (0.50 g.), from Preparation 1A, is suspended in dilute hydrochloric acid (10 ml., 6 N) and this mixture is stirred at room temperature for twenty-four hours. The (3,5-diamino-6-chloropyrazinoyl)-urea that precipitates is collected by filtration, washed with water and dried to yield 0.22 g., M.P. >300° C. Further purification is accomplished by recrystallization from methyl alcohol, M.P. >300° C.

Analysis.—Calc. for $C_6H_7ClN_6O_2$ (percent): C, 31.24; H, 3.06; N, 36.44. Found (percent): C, 31.25; H, 3.36; N, 36.28.

Example 1B (Alternate)

(3,5-diamino-6-chloropyrazinoyl)urea.—(3,5-diamino-6-chloropyrazinoyl)cyanamide (1.0 g.), from Preparation 1A, is dissolved in a solution of methanol (50 ml.) containing hydrogen chloride (5 g.) and stirred at room temperature. The solid that separates is collected and suspended in dilute hydrochloric acid (60 ml., 0.4 N) and stirred at room temperature for one hour. The solid is collected, washed with water and dried to yield 0.68 g. of (3,5-diamino-6-chloropyrazinoyl)urea, M.P. >300° C. Purification is effected by recrystallization from a mixture of water and dimethylformamide.

Analysis.—Calc. for $C_6H_7ClN_6O_2$ (percent): C, 31.24; H, 3.06. Found (percent): C, 31.22; H, 3.14.

Example 2B

(3-aminopyrazinoyl)urea.—A mixture of (3-aminopyrazinoyl)cyanamide (from Preparation 2A) (2.0 g., 0.011 mole) and 6 N hydrochloric acid (40 ml.) is stirred at room temperature for four hours. Water (150 ml.) is added and the solution is evaporated under reduced pressure to a volume of 30–40 ml. The solid that separates on standing is filtered and dried. Recrystallization from water gives (3-aminopyrazinoyl)urea with M.P. 193–6° C.

Analysis.—Calc. for $C_6H_7N_5O_2$ (percent): C, 39.78; H, 3.89; N, 38.66. Found (percent): C, 39.65; H, 3.67; N, 38.80.

Example 3B

(3-amino-6-chloropyrazinoyl)urea.—A mixture of (3-amino-6-chloropyrazinoyl)cyanamide (from Preparation 3A) (2.0 g., 0.01 mole) and 6 N hydrochloric acid (40 ml.) is stirred at room temperature for six hours. Water (150 ml.) is added and the solid is collected and dried, 1.08 g., M.P. 210–15° C. resolidifies and melts with decomposition at 240° C. Recrystallization from acetonitrile gives (3-amino-6-chloropyrazinoyl)urea with M.P. unchanged.

Analysis.—Calc. for $C_6H_6ClN_5O_2$ (percent): C, 33.42; H, 2.80; N, 32.48. Found (percent): C, 33.72; H, 2.90; N, 32.62.

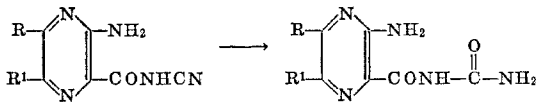
Example 4B

(3-amino-5-dimethylamino-6-chloropyrazinoyl)urea.—A mixture of (3-amino-5-dimethylamino-6-chloropyrazinoyl)cyanamide (from Preparation 4A) (2.0 g., 0.0083 mole) and 6 N hydrochloric acid (40 ml.) is stirred at room temperature for four and one-half hours. Water (150 ml.) is added and the solid that separates is collected and dried, 1.13 g., M.P. 204–10° C. (dec.). Recrystallization from methanol gives (3-amino-5-dimethylamino-6-chloropyrazinoyl)urea melting at 210–14° C.

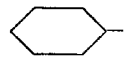
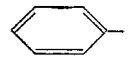
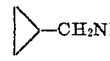
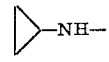
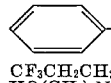
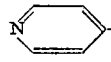
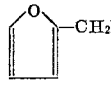
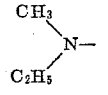
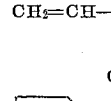
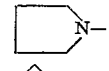
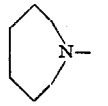
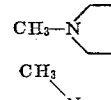
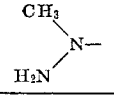
Analysis.—Calc. for $C_8H_{11}ClN_6O_2$ (percent): C, 37.14; H, 4.29; N, 32.49. Found (percent): C, 37.01; H, 4.41; N, 32.48.

Employing the method of Example 1B or 1B (alternate) but substituting for the (3,5-diamino-6-chloropyrazinoyl) cyanamide used therein, equivalent amounts of the pyrazinoylcyanamides described in Table II, there are produced the pyrazinoylureas also described in Table II according to the reaction scheme illustrated therein.

TABLE II

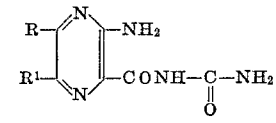


I II

Example	Starting material from preparation	R	R¹
5B	5A	C_2H_5NH—	Cl—
6B	6A	CH_3NH—	Cl—
7B	7A	CH_3—	Br—
8B	8A	NH_2—	I—
9B	9A	C_6H_5NH—	Cl—
10B	10A	NH_2—	H—
11B	11A	$C_6H_5CH_2NH$—	H—
12B	12A	CF_3—	H—
13B	13A	$(CH_3)_2N$—	CH_3—
14B	14A		H—
15B	15A	H	
16B	16A	H	
17B	17A		Br—
18B	18A	$(CH_3)_2N$—	
19B	19A	—$(CH_2)_4$—	
20B	20A	—CH=CH—CCl=CH—	
21B	21A	$CH_3(CH_2)_2NH$—	Cl—
22B	22A	$(CH_3)_2CHNH$—	Cl—
23B	23A	$(CH_3)_3CNH$—	Cl—
24B	24A		Cl—
25B	25A		Cl—
26B	26A		Cl—
27B	27A		Cl—
28B	28A	$CF_3CH_2CH_2NH$—	Cl—
29B	29A	$HO(CH_2)_2NH$—	Cl—
30B	30A	$H_2N(CH_2)_2NH$—	Cl—
31B	31A	$(CH_3)_2N(CH_2)_2NH$—	Cl—
32B	32A		Cl—
33B	33A		Cl—
34B	34A		Cl—
35B	35A		Cl—
36B	36A		Cl—
37B	37A		Cl—
38B	38A		Cl—
39B	39A		Cl—

What is claimed is:

1. A process for the preparation of (3-amino-5-R-6-R¹-pyrazinoyl)urea of formula



wherein R is a member selected from the group consisting of

(1) hydrogen,
(2) trifluoromethyl,
(3) lower cycloalkyl,
(4) phenyl,
(5) lower alkyl,
(6) —NR^3R^4 wherein R^3 is a member selected from the group consisting of
  (a) hydrogen, and
  (b) lower alkyl;
  R^4 is a member selected from the group consisting of
  (a) hydrogen,
  (b) amino,
  (c) lower cycloalkyl,
  (d) phenyl,
  (e) lower alkenyl,
  (f) lower alkyl,
  (g) hydroxy-lower alkyl,
  (h) amino-lower alkyl,
  (i) di(lower alkyl)amino-lower alkyl,
  (j) halo-lower alkyl,
  (k) phenyl-lower alkyl,
  (l) lower cycloalkyl,
  (m) pyridyl-lower alkyl, and
  (n) furyl-lower alkyl,
  and when R^3 and R^4 each represents lower alkyl, they can be linked together directly to form a 5 to 7 membered heterocyclic ring with the nitrogen to which they are attached, and when R^3 and R^4 each represents lower alkyl, they can be linked together through a nitrogen atom to form a piperazine ring with the nitrogen atom to which they are attached;

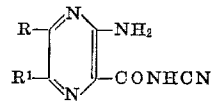
R^1 is a member selected from the group consisting of

(1) hydrogen,
(2) halo,
(3) lower alkyl,
(4) lower cycloalkyl, and
(5) phenyl;

R and R^1 can be linked together to form a member selected from the group consisting of

—CH=CH—CH=CH—, —CH=CH—CCl=CH—

and —$(CH_2)_4$— which comprises the treatment of a (3-amino-5-R-6-R¹-pyrazinoyl)cyanamide of formula



with a mineral acid in a solvent selected from (a) water, and (b) lower alkanol, wherein R and R^1 have the meanings assigned above.

2. The process as claimed in claim **1**, wherein the (3-amino-5-R-6-R¹-pyrazinoyl)cyanamide is treated with aqueous mineral acid.

3. The process as claimed in claim **1**, wherein the (3-amino-5-R-6-R¹-pyrazinoyl)cyanamide is treated with a mineral acid in lower alkanol.

4. The process as claimed in claim **1**, wherein R is hydrogen and R^1 is chloro to yield (3-amino-6-chloropyrazinoyl)urea.

5. The process as claimed in claim **1** wherein R is —NR^3R^4, and R^1 is chloro to yield (3-amino-5-NR^3R^4-6-chloropyrazinoyl)urea wherein R^3 and R^4 have the meaning assigned in claim **1**.

6. The process as claimed in claim 5 wherein R^3 and R^4 are both hydrogen to yield (3,5-diamino-6-chloropyrazinoyl)urea.

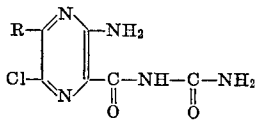
7. The process as claimed in claim 5 wherein R^3 is hydrogen, and R^4 is lower alkyl, to yield (3-amino-5-lower alkylamino-6-chloropyrazinoyl)urea.

8. The process as claimed in claim 5, wherein R^3 is hydrogen and R^4 is methyl, to yield (3-amino-5-methylamino-6-chloropyrazinoyl)urea.

9. The process as claimed in claim 5 wherein R^3 and R^4 are lower alkyl to yield [3-amino-5-di-(lower alkyl)-amino-6-chloropyrazinoyl]urea.

10. The process as claimed in claim 5 wherein R^3 and R^4 are each methyl to yield (3-amino-5-dimethylamino-6-chloropyrazinoyl)urea.

11. A compound of formula



wherein R is amino or mono(lower alkyl)amino.

12. A compound according to claim 11, wherein R is mono(lower alkyl)amino.

13. Crystalline 3,5 - diamino - 6 - chloropyrazinoylurea having a melting point greater than 300° C.

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NICHOLAS S. RIZZO, Primary Examiner

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