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Process for preparing amiloride and other new 6-substituted derivatives.
N- Amidino-3,5- diamino-6- substituted-2- pyrazinocarboxamides and a process for their synthesis.
SUMMARY AND BACKGROUND OF THE INVENTION

This invention relates to a novel process for preparing N-amidino-3,5-diamino-6-substituted-2-pyrazinecarboxamide particularly the N-amidino-3,5-diamino-6-chloro-2-pyrazinecarboxamide which is commercially known as amiloride. Also included are several novel N-amidino-3,5-diamino-6-substituted-2-pyrazinecarboxamides. These compounds are useful because they possess diuretic and naturetic properties. They differ from most of the known, effective diuretic agents, however, in that the compounds of this invention selectively enhance the excretion of sodium ions without causing an increase in excretion of potassium ions. The potassium loss, which is caused by known diuretics, often results in a severe muscular weakness. Since the compounds of this invention are essentially free of this potassium depletion, they have this decided advantage as diuretics. As diuretic agents, they can be used for the treatment of edema, hypertension and other diseases known to be responsive to this therapy.
In some instances it may be desirable to make a salt of these compounds, using a pharmaceutically acceptable acid, and these salts are to be considered as included in this invention and in the scope of the claims.

The products of this invention can be administered to man or animals in the form of pills, tablets, capsules, elixirs, injectable preparations and the like and can comprise one or more of the compounds of this invention as the only essential active ingredient of the pharmaceutical formulation or, as mentioned above, the novel compound(s) can be combined in pharmaceutical formulations with other diuretic agents or, indeed, other therapeutic agents.

The compounds of this invention are advantageously administered at a dosage range of from about 5 mg./day to about 750 mg./day or at a somewhat higher or lower dosage at the physician's discretion, preferably in subdivided amounts on a 2 to 4 times a day regimen.

Particular compounds which can be prepared according to the process of this invention are shown below in Formula I.

\[
\text{H}_2\text{N} \quad \text{CONH} \quad \text{NH}_2 \\
\text{X} \quad \text{CONHCNH}_2
\]

wherein X is Cl (this would be amiloride), CN, CH\textsubscript{3}S, CF\textsubscript{3}S or C\textsubscript{6}H\textsubscript{5}S.
The novel process used to prepare these compounds is depicted in the following flow sheet:

Generally the process shown as going from compound IV to II to I concerns the reaction of N-amidino-5-diamino-6-iodo (or 6-bromo)-2-pyrazine-carboxamide shown in Formula II and being described in the prior art particularly U.S. Patent 3,318,813 with \( \text{Cu} \ X \) salts wherein \( X \) is as previously defined.

This reaction can be run in a solvent, particularly an inert organic solvent and preferably hexamethylphosphonamide or dimethylformamide. The reaction temperature is not critical and the reaction can be run at anywhere from 25 - 100°C. The length of time the reaction is carried out is not critical either and can be run anywhere from 0.5 to 1 hour.
Isolation of the reaction product which is N-amidino-3,5-diamino-6-X-2-pyrazinecarboxamide from the reaction mixture is performed by methods known in the art such as by adding crushed ice and water to the reaction mixture to precipitate the desired product.

An alternative route to the compounds of this invention involves the reaction of CuX wherein X is as defined above with lower alkyl (methyl)-3,5-diamino-6-iodo-(or bromo)-pyrazinoate which in turn under similar reaction conditions as discussed for the first reaction above will provide lower alkyl-3,5-diamino-6-substituted pyrazinoate. This is shown in the above flow sheet as a reaction of IV to III. Compound IV is known from the literature particularly U. S. Patent 3,313,813. The lower alkyl 3,5-diamino-6-X-pyrazinoate (Compound III) can then be reacted with guanidine to yield the desired product Compound I. This latter reaction is preferably carried out under anhydrous conditions with or without a solvent such as methanol, ethanol, isopropyl alcohol or other solvents. The reaction may be carried out at room temperature or by heating on a steam bath for 1 minute to 2 hours or longer. The desired product usually is recovered from the cooled reaction mixture by trituration with water. Purification frequently is carried out by converting the product to a salt which can be recrystallized or the base can be regenerated by addition of aqueous alkali.

The following examples illustrate but do not limit the preparation of the various compositions of the invention.
EXAMPLE 1
Preparation of N-Amidino-3,5-diamino-6-cyano-2-pyrazinecarboxamide

N-Amidino-3,5-diamino-6-iodo-2-pyrazine-carboxamide hydrochloride (3.50 g., 0.01 mole), cuprous cyanide (2.15 g., 0.024 mole) and hexa-methylphosphoramide (30 ml.) are combined and heated at 100°C for 15 minutes. After cooling to ambient temperature the reaction mixture is added to aqueous sodium cyanide solution (100 ml.), stirred at 25°C for 1/2 hour and the solid precipitate is collected by suction filtration, washed with water, then chloroform. On dissolving the product in boiling water (50 ml.), treating with 6N HCl and cooling one obtains 1.43 g. of N-amidino-3,5-diamino-6-cyano-2-pyrazinecarboxamide, m.p. > 350°C.

Elemental analysis for C<sub>7</sub>H<sub>8</sub>N<sub>8</sub>O·HCl·1/2 H<sub>2</sub>O:

Calc.: C, 31.65; H, 3.79; N, 42.18; Cl, 13.35;

Found: C, 31.36; H, 3.58; N, 41.26; Cl, 13.29.

EXAMPLE 2
Preparation of Methyl 3,5-diamino-6-cyano-2-pyrazinoate hemihydrate

Methyl 3,5-diamino-6-iodo-2-pyrazinoate (370 mg., 0.0012 mole), cuprous cyanide (215 mg., 0.0024 mole) and hexamethylphosphoramide (10 ml.) are combined and heated at 100°C for 15 minutes. After cooling to 25°C. the reaction mixture is added to aqueous sodium cyanide solution, stirred at 25°C. for 1 hour and extracted with CHCl<sub>3</sub>. The CHCl<sub>3</sub> layer was washed with dilute NaCN solution, then with H<sub>2</sub>O, and dried (MgSO<sub>4</sub>). After evaporation of the CHCl<sub>3</sub>, the residual oil was treated with hexane to give 75 mg. of methyl 3,5-diamino-2-pyrazinoate hemihydrate melting at 2
Elemental analysis for C$_7$H$_7$N$_5$O$_2$· 1/2 H$_2$O;
Calc.: C, 41.59; H, 3.99; N, 34.64;
Found: C, 42.81, H, 3.99; N, 34.09.

EXAMPLE 3
Preparation of N-Amidino-3,5-diamino-6-trifluoromethylthio-2-pyrazinecarboxamide

Step A.: Methyl 3,5-diamino-6-trifluoromethylthio-2-pyrazinoate
Methyl 3,5-diamino-6-iodo-2-pyrazinoate (3.70 g., 0.0012 mole), cuprous trifluoromethylmercaptide (5.0 g., 0.0025 mole) and hexamethylphosphoramide (100 ml.) are combined and heated at 100°C. for 15 minutes. The reaction mixture is added to crushed ice - H$_2$O and extracted with CHCl$_3$, the CHCl$_3$ layer washed with water, dried (MgSO$_4$) then concentrated to give an amber oil. The oil is dissolved in ether, extracted several times with H$_2$O, dried (MgSO$_4$) then concentrated to an oil which solidifies on trituration with butyl chloride to give 1.26 g. of methyl 3,5-diamino-6-trifluoromethylthio-2-pyrazinoate, m.p. 151-5°C.

Elemental analysis for C$_7$H$_7$F$_3$N$_4$O$_2$S:
Calc.: C, 31.35; H, 2.63; N, 20.89; S, 11.95;
Found: C, 31.04; H, 2.67; N, 19.65; S, 11.95.

Step B.: N-Amidino-3,5-diamino-6-trifluoromethylthio-2-pyrazinecarboxamide hydrate
Guanidine hydrochloride (3.34 g., 0.035 mole) is added to a solution of sodium methoxide (1.67 g., 0.032 mole) in methanol (20 ml.) with stirring at 25°C. After 15 minutes, methyl 3,5-diamino-6-trifluoromethylthio-2-pyrazinoate (1.85 g., 0.007 mole) is added, and the mixture is heated...
on a steam bath for 15 min. Crushed ice-$\text{H}_2\text{O}$ (20 ml.) is added to the reaction mixture to precipitate 390 mg. of N-amidino-3,5-diamino-6-trifluoromethylthio-2-pyrazinecarboxamide, m.p. 195°C.

Elemental analysis for $\text{C}_7\text{H}_8\text{F}_3\text{N}_7\text{O}_5\cdot \text{H}_2\text{O}$:
- Calc.: C, 26.84; H, 3.22; F, 18.19;
- Found: C, 27.09; H, 3.18; F, 17.49.

**EXAMPLE 4**

**Step A.: Methyl 3,5-diamino-6-trifluoromethylthio-2-pyrazinoate**

Methyl 3,5-diamino-6-trifluoromethylthio-2-pyrazinoate is prepared from methyl 3,5-diamino-6-iodo-2-pyrazinoate following essentially the same procedure described in Example 3, Step A except that dimethylformamide is used as the solvent.

**EXAMPLE 5**

**Step A.: Methyl 3,5-diamino-6-trifluoromethylthio-2-pyrazinoate**

Methyl 3,5-diamino-6-trifluoromethylthio-2-pyrazinoate is prepared from methyl 3,5-diamino-6-iodo-2-pyrazinate following essentially the same procedure described in Example 3, Step A except that bis(trifluoromethylthio)-mercury and copper are used to generate cuprous trifluoromethylthiomercaptide in situ.

**EXAMPLE 6**

**Step A.: N-Amidino-3,5-diamino-6-trifluoromethylthio-2-pyrazinecarboxamide**

N-Amidino-3,5-diamino-6-trifluoromethylthio-2-pyrazinecarboxamide is prepared from
N-amidino-3,5-diamino-6-iodo-2-pyrazinecarboxamide hydrochloride by essentially the same procedure described in Example 1 using trifluoromethylthiocupper in place of cuprous cyanide.

EXAMPLE 7
Preparation of N-Amidino-3,5-diamino-6-methylthio-2-
pyrazinecarboxamidehydrochloridehydrate

Step A.: Methyl 3,5-diamino-6-methylthio-
pyrazinoate

A solution of methyl 3,5-diamino-6-iodo-
pyrazinoate (14 g., 0.048 mole) and cuprous methyl-
mercaptide (12 g., 0.108 mole) in hexamethylphos-
phoramide (100 ml.) is heated on a steam bath with
stirring for 1-1/2 hours, poured into ice water
(0.5 l) extracted with chloroform, washed with water,
dried over MgSO₄ and evaporated at reduced pressure.
Treatment of the residue with hexane gives 2.0 g. of
methyl 3,5-diamino-6-methylthiopyrazinoate which
melts at 158-60°C. after purification by chromato-
graphy on silica gel; eluent 50% benzene-ethyl
acetate.

Elemental analysis for C₇H₁₀N₄O₂S:
Calc.: C, 39.25; H, 4.70; N, 26.16;
Found: C, 40.16; H, 4.93; N, 26.58.

Step B.: N-Amidino-3,5-diamino-6-methylthio-
-2-pyrazinecarboxamide hydrochloride
hydrate

Guanidine hydrochloride (1.5 g., 0.016
mole) is added to a solution of sodium methoxide
(0.75 g., 0.014 mole) in methanol (25 ml.), stirred
for five minutes and filtered free of sodium
chloride. The guanidine solution is evaporated to 5 ml. then treated with methyl 3,5-diamino-6-methylthiopyrazinoate (0.6 g., 0.0028 mole) heated on a steam bath for five minutes, treated with water (10 ml.) and acidified with hydrochloric acid to give 0.6 g. of N-amidino-3,5-diamino-6-methylthio-2-pyrazinecarboxamide hydrochloride hydrate which melts at 170°C.

Elemental analysis for C_7H_11N_7O_S·HCl·H_2O:
Calculated: C, 28.42; H, 4.77; N, 33.15; Cl, 11.98;
Found: C, 28.62; H, 4.44; N, 32.91; Cl, 12.11.

**EXAMPLE 8**

Preparation of N-Amidino-3,5-diamino-6-phenylthio-2-pyrazinecarboxamide hemihydrate

**Step A.:** Methyl 3,5-diamino-6-phenylthio-pyrazinoate

A mixture of methyl 3,5-diamino-6-iodopyrazinoate (3.5 g., 0.012 mole) and cuprous phenyl-mercaptide (2.3 g., 0.013 mole) in hexamethylphosphoramidine (18 ml.) is heated on a steam bath for ten minutes and filtered. The filtrate is poured into 300 ml. of water, and the methyl 3,5-diamino-6-phenylthio-pyrazinoate which separates melts at 210°C. after recrystallization from 2-propanol.

Elemental analysis for C_{12}H_{12}N_4O_2S:
Calculated: N, 20.28; H, 4.38;
Found: N, 20.17; H, 4.40
Step B.: N-Amidino-3,5-diamino-6-phenylthio-2-pyrazinecarboxamide hemihydrate

Guanidine hydrochloride (5.2 g., 0.055 mole) is added to a solution of sodium methoxide (2.7 g., 0.50 mole) in methanol (40 ml) stirred for five minutes and filtered free of sodium chloride. The guanidine solution is evaporated to a volume of 20 ml. then treated with methyl 3,5-diamino-6-phenylthio-pyrazinoate (2.5 g., 0.009 mole), heated on a steam bath for ten minutes then poured into water (200 ml.) to give 2.2 g. N-amidino-3,5-diamino-6-phenylthio-2-pyrazinecarboxamide hemihydrate which melts at 238°C. after being washed with methanol.

Elemental analysis for C₁₂H₁₃N₇O·1/2 H₂O:
Calc.: C, 46.14; H, 4.52; N, 31.39;
Found: C, 46.15; H, 4.59; N, 31.41.

EXAMPLE 9
Preparation of N-Amidino-3,5-diamino-6-chloro-2-pyrazinecarboxamide

N-Amidino-3,5-diamino-6-iodo-2-pyrazinecarboxamide (1.61 g., 0.005 mole), cuprous chloride (1.19 g., 0.012 mole) and hexamethylphosphoramide (15 ml.) are heated at 100°C for 10 minutes. The mixture is cooled to 25°C. then added to aqueous sodium cyanide solution and extracted with CHCl₃. On evaporating the CHCl₃ and triturating the oily residue with hexane there is obtained N-amidino-3,5-diamino-6-chloro-2-pyrazinecarboxamide, m.p. 241°C.

Elemental analysis for C₆H₈ClN₇O:
Calc.: C, 31.38; H, 3.51; N, 42.70; Cl, 15.44;
Found: C, 31.59; H, 3.43; N, 42.85; Cl, 15.42.
1 WHAT IS CLAIMED IS:

1. A compound of the formula:

\[
\begin{array}{c}
\text{H}_2\text{N} \\
\text{X} \\
\text{N} \\
\text{H} \\
\text{N} \\
\text{X} \\
\text{CONHCNH}_2
\end{array}
\]

wherein X is CN, CH$_3$S, CF$_3$S or C$_6$H$_5$S.

2. A process for preparing compounds of the formula:

\[
\begin{array}{c}
\text{H}_2\text{N} \\
\text{X} \\
\text{N} \\
\text{H} \\
\text{N} \\
\text{X} \\
\text{CONHCNH}_2 \\
\text{Y}
\end{array}
\]

wherein X is Cl, CN, CH$_3$S, CF$_3$S or C$_6$H$_5$S

which comprises reacting a compound of the formula:

\[
\begin{array}{c}
\text{H}_2\text{N} \\
\text{Y} \\
\text{N} \\
\text{H} \\
\text{N} \\
\text{Y} \\
\text{CONHCNH}_2
\end{array}
\]

with CuX

wherein X is as previously defined and Y is I or Br.
1. A process of claim 2 wherein the reaction is carried out in the solvent hexamethylphosphoramide or dimethylformamide at 25 - 100°C.

4. A process for preparing compounds of the formula

\[ \text{H}_2\text{N} \begin{array}{c} \text{N} \\ \text{NH}_2 \end{array} \begin{array}{c} \text{N} \\ \text{X} \end{array} \begin{array}{c} \text{NH} \\ \text{CONH-CN-H}_2 \end{array} \]

which comprises

a) reacting a compound of the formula:

\[ \text{H}_2\text{N} \begin{array}{c} \text{N} \\ \text{NH}_2 \end{array} \begin{array}{c} \text{Y} \\ \text{CO}_2\text{CH}_3 \end{array} \]

with CuX

wherein X is Cl, CN, CH\(_3\)S, CF\(_3\)S or C\(_6\)H\(_5\)S and Y is I or Br to produce a compound of the formula:

\[ \text{H}_2\text{N} \begin{array}{c} \text{N} \\ \text{NH}_2 \end{array} \begin{array}{c} \text{X} \\ \text{CO}_2\text{CH}_3 \end{array} \]

wherein X is as previously defined and

b) reacting the product of step a) with guanidine to yield the desired compounds.
5. A process of claim 4 wherein the reaction of step a) is carried out in the presence of hexamethylphosphoramide or dimethylformamide at 25-100°C.
<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document with indication, where appropriate, of relevant passages</th>
<th>Relevant to claim</th>
<th>CLASSIFICATION OF THE APPLICATION (Int.Cl.)</th>
</tr>
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| X        | US - A - 3 305 552 (MERCK)  
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The present search report has been drawn up for all claims.

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