

PATENT SPECIFICATION

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(54) HETEROCYCLIC N-CYANO GUANIDINES

(71) We, SMITH KLINE & FRENCH LABORATORIES LIMITED, of Mundells, Welwyn Garden City, Hertfordshire, a British Company, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

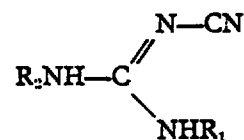
This invention relates to pharmacologically active compounds, in particular to pharmacologically active cyanoguanidines, to pharmaceutical compositions comprising these compounds and to processes for their preparation. The compounds of the invention can exist as their addition salts but, for convenience, reference will be made throughout this specification to the parent compounds.

It has long been postulated that many of the physiologically active substances within the animal body, in the course of their activity, combine with certain specific sites known as receptors. Histamine is a compound which is believed to act in such a way but, since the actions of histamine fall into more than one type, it is believed that there is more than one type of histamine receptor. The type of action of histamine which is blocked by drugs commonly called "antihistamines" (of which mepyramine is a typical example) is believed to involve a receptor which has been designated as H-1. A further group of substances has recently been described by Black et al (Nature 1972, 236, 385) which are distinguished by the fact that they act

at histamine receptors other than the H-1 receptor and these other receptors have been designated as H-2 receptors. This latter group of substances, to certain of which the present invention relates, are thus of utility in inhibiting certain actions of histamine which are not inhibited by the above-mentioned "antihistamines". The substances of this invention may also be of utility as inhibitors of certain actions of gastrin.

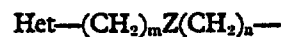
Throughout the present specification and claims, by the term "lower alkyl" we mean an alkyl group containing from 1 to 4 carbon atoms.

The cyanoguanidines with which the present invention is concerned may be represented by the following general formula:



I

wherein R₁ is hydrogen or lower alkyl such as methyl; and R₂ is a grouping of the structure shown in Formula II



wherein Het is an imidazole, pyridine, thiazole, isothiazole, oxazole, isoxazole, pyrazole, triazole, thiadiazole, pyrimidine, pyrazine or

pyridazine ring, which ring is optionally substituted by lower alkyl, trifluoromethyl, hydroxyl, halogen or amino; Z is sulphur, oxygen, NH or a methylene group and m and n are integers from 0 to 4 such that their sum is from 2 to 4.

It will be understood that the structure illustrated in Formula I is only one of several representations and that other tautomeric forms are also covered by the present invention.

In a preferred group of compounds R_1 is methyl or ethyl. R_2 is preferably



II

and is particularly preferably such that Het is imidazole, thiazole, isothiazole or pyridine and is optionally substituted by methyl, hydroxyl or halogen. Particularly useful specific compounds are

N - cyano - N' - methyl - N'' - [2 - ((4 - methyl - 5 - imidazolyl)methylthio)ethyl] guanidine,

N - cyano - N' - ethyl - N'' - [2 - ((4 - methyl - 5 - imidazolyl)methylthio)ethyl] guanidine,

N - cyano - N' - methyl - N'' - [2 - ((4 - bromo - 5 - imidazolyl)methylthio)ethyl] guanidine,

N - cyano - N' - methyl - N'' - [2 - ((2 - thiazolyl)methylthio)ethyl] guanidine,

N - cyano - N' - methyl - N'' - [2 - ((3 - isothiazolyl)methylthio)ethyl] guanidine,

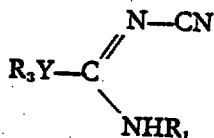
N - cyano - N' - methyl - N'' - [2 - ((3 - hydroxyl - 2 - pyridyl)methylthio)ethyl] guanidine, and

N - cyano - N' - methyl - N'' - [2 - ((3 - bromo - 2 - pyridyl)methylthio)ethyl] guanidine.

The compounds of the present invention may be produced from an amine of the formula



wherein R_2 has the same significance as in Formula I by reaction thereof with an isothiourea or isourea of Formula III:

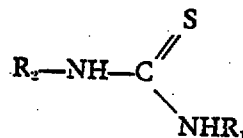


III

wherein R_1 has the same significance as in Formula I, Y is sulphur or oxygen (preferably sulphur) and R_3 is lower alkyl (preferably methyl), aryl or arylalkyl. This reaction may be carried out in the absence of a solvent but

preferably is carried out in a solvent such as acetonitrile.

Alternatively, for those compounds of Formula I wherein R_1 is lower alkyl, a thiourea of Formula IV



IV

wherein R_1 is lower alkyl and R_2 has the same significance as in Formula I may be reacted with a heavy metal salt of cyanamide such as the lead, mercury or cadmium salt. This process may be conveniently carried out in a solvent such as acetonitrile or dimethylformamide. In a modification of this process the thiourea of Formula IV is first reacted with a desulphurising agent such as a heavy metal salt or oxide and then treated with cyanamide.

An advantageous method for the production of compounds of Formula I is by the reaction of an amine of Formula

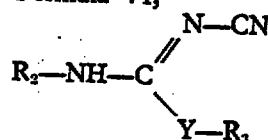


with a cyanodithioimidocarbonate or a cyanimidocarbonate of Formula V:



V

wherein R_3 is alkyl, preferably methyl and Y is sulphur or oxygen, preferably sulphur to give an N-cyanoisothiourea or N-cyanoisourea of Formula VI,

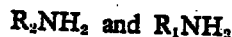


VI

wherein R_2 has the same significance as in Formula I and Y and R_3 have the same significance as in Formula V. Subsequent reaction of the compounds of Formula VI with



leads to the production of cyanoguanidines of Formula I. Both stages of this reaction may be carried out in a solvent such as ethanol or isopropyl alcohol. In a modification of this method, the compound of Formula V, which in the preferred case is dimethylcyanodithioimidocarbonate, may be reacted sequentially with



without isolation of the intermediate compound of Formula VI.

vent such
is of For-
1 thiourea 55

IV

has the
may be
cyanamide 60
ium salt.
ried out
dimethyl-
is process
it reacted 65
a heavy
ted with
produc-
is by the 70

a cyano-

75

V

ethyl and
sulphur
N-cyano-

80

VI

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ne signi-
reaction
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85

anidines
reaction
such as
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of For- 90
e is di-
y be re-

te com- 95

In an alternative method for the produc-
tion of those compounds of Formula I where-
in R_1 is hydrogen, the amine of Formula



- 5 may be reacted with a metal salt of dicyan-
amide of formula



- 10 wherein M is a metal e.g. an alkali metal
such as sodium in an appropriate solvent and
in the presence of one molar equivalent of a
strong acid per mole of dicyanamide salt.

The production of the starting material of
formula



- 15 is described in our U.K. Specifications Nos.
13305546 and 1338169. Methods for the
production of the thiourea of Formula IV
from R_2NH_2 are also described in these
specifications.

- 20 As stated above, the compounds repre-
sented by Formula I have been found to have
pharmacological activity in the animal body
as antagonists to certain actions of histamine
which are not blocked by "antihistamines"
25 such as mepyramine. For example, they have
been found to inhibit selectively the histamine-
stimulated secretion of gastric acid from the
perfused stomachs of rats anaesthetised with
urethane. Similarly, the action of these com-
pounds may, in many cases, be demonstrated
30 by their antagonism to the effects of hist-
amine on other tissues which, according to
the above-mentioned paper of Black et al.
are H-2 receptors.

- 35 Examples of such tissues are perfused iso-
lated guinea-pig heart, isolated guinea-pig
right atrium and isolated rat uterus. The
compounds of the invention have also been
found to inhibit the secretion of gastric acid
40 stimulated by pentagastrin or by food. In
addition to the above the compounds of the
invention also show some anti-inflammatory
activity in conventional tests.

- 45 The level of activity found for the com-
positions comprising the compounds of the
present invention is illustrated by the effec-
tive dose range in the anaesthetised rat, as
mentioned above of from 0.25 to 256 micro-
moles per kilogram, given intravenously.
50 Many of the compounds of the present in-
vention produce a 50% inhibition in this test
at a dose of from 1 to 10 micromoles per
kilogram. Similar results have been found in
the anaesthetised cat and in the dog.

- 55 The present invention also relates to a
pharmaceutical composition comprising a
compound of Formula I and a non-toxic
pharmaceutically acceptable diluent or carrier.

- 60 The pharmaceutical carrier employed may
be, for example, either a solid or liquid.

Exemplary of solid carriers are lactose, terra
alba, sucrose, talc, gelatin, agar, pectin, acacia,
magnesium stearate and stearic acid.
Exemplary of liquid carriers are syrup, peanut
oil, olive oil and water.

A wide variety of pharmaceutical forms
can be employed. Thus if a solid carrier is
used, the preparation can be tableted, placed
in a hard gelatin capsule in powder or pellet
form, or in the form of a troche or lozenge.
The amount of solid carrier will vary widely
but preferably will be from about 25 mg to
about 1 gm. If a liquid carrier is used, the
preparation may be in the form of a syrup,
emulsion, soft gelatin capsule, sterile inject-
able liquid such as an ampoule, or an aqueous
or nonaqueous liquid suspension.

The pharmaceutical compositions are pre-
pared by conventional techniques involving
procedures such as mixing, granulating and
compressing or dissolving the ingredients as
appropriate to the desired preparation.

The active ingredient will be present in the
composition in an effective amount to inhibit
histamine activity. The route of administra-
tion may be orally or parenterally.

Preferably, each dosage unit will contain
the active ingredient in an amount of from
about 50 mg to about 250 mg most prefer-
ably from about 100 mg to about 200 mg.

The active ingredient will preferably be
administered in equal doses one to three times
per day. The daily dosage regimen will pre-
ferably be from about 150 mg to about 750
mg most preferably from about 300 mg to
about 600 mg.

For therapeutic use, the pharmacologically
active compounds of the present invention
will normally be administered as a pharma-
ceutical composition comprising as the or an
essential active ingredient at least one such
compound in the basic form or in the form
of an addition salt with a pharmaceutically
acceptable acid and in association with a
pharmaceutical carrier therefore. Such addi-
105 tion salts include those with hydrochloric,
hydrobromic, hydriodic, sulphuric, picric and
maleic acids.

Other pharmacologically active compounds
may in certain cases be included in the
composition. Advantageously the compositions
will be made up in a dosage unit form
appropriate to the desired mode of administra-
tion, for example as a tablet, capsule, inject-
able solution or as a cream for topical
administration.

The invention is illustrated but in no way
limited by the following Examples:—

Example 1

N - cyano - N' - methyl - N'' - [2 - ((4 -
methyl - 5 - imidazolyl)methylthio)ethyl]
guanidine. 120

(a) A solution of 4 - methyl - 5 - [(2 -
aminoethyl)thiomethyl]imidazole (17.0 g) and

- N - cyano - N',S-dimethylisothiourca (11.2 g) in acetonitrile (500 ml) was heated under reflux for 24 hours. Following concentration, the residue was chromatographed on a column of silica gel with acetonitrile as eluant and the product obtained was finally recrystallised from acetonitrile-ether to yield N - cyano - N' - methyl - N'' - [2 - ((4 - methyl - 5 - imidazolyl)methylthio)ethyl]guanidine, m.p. 141—20°.
- (Found: C, 47.2; H, 6.4; N, 33.4; S, 12.4; $C_{10}H_{16}N_6S$ requires: C, 47.6; H, 6.4; N, 33.3; S, 12.7).
- (b) Lead cyanamide (3.0 g) was added to a solution of N - methyl - N' - [2 - (4 - methyl - 5 - imidazolyl)methylthio]ethyl]thiourea (2.44 g) in acetonitrile (50 ml). Dimethylformamide (20 ml) was added subsequently and the suspension was heated under reflux, with stirring, for 24 hours. Filtration, followed by concentration under reduced pressure and purification of the product by chromatography on a column of silica gel with acetonitrile as eluant and recrystallisation from the same solvent afforded N - cyano - N' - methyl - N'' - [2 - ((4 - methyl - 5 - imidazolyl)methylthio)ethyl]guanidine, m.p. 139—141°.
- (Found: C, 47.3; H, 6.6; N, 33.4; S, 12.6; $C_{10}H_{16}N_6S$ requires: C, 47.6; H, 6.4; N, 33.3; S, 12.7).
- (c) (i) A solution of 4 - methyl - 5 - ((2 - aminoethyl)thiomethyl)imidazole (23.4 g) in ethanol was added slowly to a solution of dimethylcyanodithioimidocarbonate (20.0 g) in ethanol, with stirring at room temperature. The mixture was set aside overnight at room temperature. Filtration afforded N - cyano - N' - [2 - ((4 - methyl - 5 - imidazolyl)methylthio)ethyl] - S - methylisothiourca (10.0 g), m.p. 148—150°. The filtrate was concentrated under reduced pressure and the mixture was triturated with cold water and the solid obtained, filtered off and recrystallised twice from isopropyl alcohol/ether to yield further product (27 g), m.p. 148—150°.
- (Found: C, 44.4; H, 5.6; N, 26.0; S, 24.3. $C_{10}H_{13}N_5S_2$ requires: C, 44.6; H, 5.6; N, 26.0; S, 23.8).
- (ii) A solution of methylamine in ethanol (33%, 75 ml) was added to a solution of N - cyano - N' - [2 - ((4 - methyl - 5 - imidazolyl)methylthio)ethyl] - S - methylisothiourca (10.1 g) in ethanol (30 ml). The reaction mixture was set aside at room temperature for 2.5 hours. Following concentration under reduced pressure, the residue was recrystallised twice from isopropyl alcohol/petroleum ether, affording N - cyano - N' - methyl - N'' - [2 - ((4 - methyl - 5 - imidazolyl)methylthio)ethyl]guanidine (8.6 g), m.p. 141—143°.
- (Found: C, 47.5; H, 6.3; N, 33.2; S, 12.9; $C_{10}H_{16}N_6S$ requires: C, 47.6; H, 6.4; N, 33.3; S, 12.7).
- (d) A solution of 4 - methyl - 5 - ((2 - aminoethyl)thiomethyl)imidazole (1.93 g) and dimethylcyanodithioimidocarbonate (1.65 g) in ethanol (33 ml) was allowed to stand overnight at room temperature. Ethanolic methylamine (33%, 22 ml) was added and the solution was then allowed to stand for 4 hours. Concentration and recrystallisation from isopropyl alcohol-ether yielded N - cyano - N' - methyl - N'' - [2 - ((4 - methyl - 5 - imidazolyl)methylthio)ethyl]guanidine (2.0 g), m.p. 139—140°.
- (Found: C, 47.5; H, 6.5; N, 33.3; S, 12.7; $C_{10}H_{16}N_6S$ requires: C, 47.6; H, 6.4; N, 33.3; S, 12.7).
- ### Example 2
- N - Cyano - N' - ethyl - N'' - [2 - ((4 - methyl - 5 - imidazolyl)methylthio)ethyl]guanidine
- (a) Anhydrous ethylamine (9.0 g) was added to a solution of N - cyano - N' - [2 - ((4 - methyl - 5 - imidazolyl)methylthio)ethyl] - S - methylisothiourca (Example 1 (C), 5.0 g) in ethanol. The solution was heated under reflux for 8 hours and concentrated under reduced pressure. The residue was dissolved in isopropyl alcohol, filtered, and diluted with water. The white solid obtained was recrystallised from isopropyl alcohol-ether to yield N - cyano - N' - ethyl - N'' - [2 - ((4 - methyl - 5 - imidazolyl)methylthio)ethyl]guanidine, m.p. 118—120°.
- (Found: C, 49.6; H, 6.8; N, 31.2; S, 11.7. $C_{11}H_{18}N_6S$ requires: C, 49.6; H, 6.8; N, 31.6; S, 12.0).
- (b) (i) A solution of 4 - methyl - 5 - ((2 - aminoethyl)thiomethyl)imidazole (6.9 g) and ethyl isothiocyanate (3.84 g) in ethanol was heated under reflux for 2 hours. Concentration followed by recrystallisation of the residue from aqueous ethanol gave N - ethyl - N' - [2 - ((4 - methyl - 5 - imidazolyl)methylthio)ethyl]thiourea (9.0 g), m.p. 140—141°.
- (Found: C, 46.5; H, 7.1; N, 21.7; S, 25.1. $C_{10}H_{14}N_4S_2$ requires: C, 46.5; N, 21.7; S, 24.8).
- (ii) Reaction of the thiourea with excess lead cyanamide by a procedure similar to that described in Example 1(b) afforded N - cyano - N' - ethyl - N'' - [2 - ((4 - methyl - 5 - imidazolyl)methylthio)ethyl]guanidine, comparable with that described in Example 2(a).
- ### Example 3
- N - Cyano - N' - (2 - ((4 - methyl - 5 - imidazolyl)methylthio)ethyl)guanidine
- A solution of N - cyano - N' - [2 - ((4 - methyl - 5 - imidazolyl)methylthio)ethyl] - S - methylisothiourca (2.69 g) in saturated ammoniacal ethanol (100 ml) was heated in

; H, 6.4; 65

5 - ((2 - 1.65 g) and 70
and over-
c methyl-
the solu-
4 hours.
from iso-
no - N' -
yl - 5 -
c (2.0 g),

33.3; S,
; H, 6.4; 80

2 - ((4 -
hio)ethyl]

g) was
N' - [2 -
ethylthio)
xample 1
was heated
concentrated
was dis-
solved, and
obtained
alcohol-
yl - N'' -
ethylthio)

31.2; S,
; H, 6.8; 100

yl - 5 -
ole (6.9 g)
n ethanol
rs. Con-
on of the
- ethyl -
imidazolyl)

p. 140—
21.7; S,
; N, 7.0;

th excess
ar to that
d N -
methyl -
guanidine,
Example

120

110

115

120

120

125

125

a pressure vessel for 16 hours at 95°. Follow-
ing concentration, the residue was chromato-
graphed on a column of silica gel with ethyl
acetate as eluant and finally recrystallised
from acetonitrile to give N - cyano - N' -
(2 - ((4 - methyl - 5 - imidazolyl)methylthio)
ethyl)guanidine (0.9 g), m.p. 125—127°.
(Found: C, 45.2; H, 5.9; N, 35.1; S,
13.3. C₁₁H₁₃N₄S requires: C, 45.4; H, 5.9;
N, 35.3; S, 13.5).

Example 4

N - Cyano - N' - [2 - ((3 - hydroxy - 2 -
pyridyl)methylthio)ethyl] - N'' - methyl
guanidine

15 (i) The reaction of dimethylcyanodithio-
imidocarbonate (6.0 g) with 2 - ((2 - amino-
ethyl)thiomethyl) - 3 - hydroxypyridine (7.5 g)
by the procedure described in Example 1(c)
afforded N - cyano - N' - [2 - ((3 - hydroxy -
2 - pyridyl)methylthio)ethyl] - S - methyl-
isothiourea (4.85 g), m.p. 192—194°. Recry-
stallisation from aqueous ethanol gave fine
needles, m.p. 196—198°.

(Found: C, 46.6; H, 5.0; N, 19.8; S,
22.7. C₁₁H₁₄N₄OS₂ requires: C, 46.8; N,
19.8; S, 22.7).

20 (ii) The reaction of N - cyano - N' - [2 -
(3 - hydroxy - 2 - pyridyl)methylthio)ethyl] -
S - methylisothiourea (4.8 g) with excess
methylamine according to the procedure de-
scribed in Example 1(c) followed by chromato-
graphy of the product on a column of silica
gel with ethylacetate containing 15% iso-
propyl alcohol as eluant and recrystallisation
from isopropyl alcohol-petroleum ether gave
N - cyano - N' - [2 - ((3 - hydroxy - 2 -
pyridyl)methylthio)ethyl] - N'' - methyl-
guanidine (2.4 g), m.p. 146—148°.

(Found: C, 49.6; H, 5.7; N, 26.2; S,
11.9. C₁₁H₁₃N₅OS requires: C, 49.8; H, 5.7;
N, 26.4; S, 12.1).

Example 5

N - Cyano - N' - (2 - ((4 - bromo - 5 -
imidazolyl)methylthio)ethyl) - N'' - methyl
guanidine

45 The sequential reaction of dimethylcyano-
dithioimidocarbonate (0.99 g) with 4 -
bromo - 5 - ((2 - aminoethyl)thiomethyl)
imidazole (1.6 g) and excess methylamine by
the procedure described in Example 1(d)
afforded N - cyano - N' - (2 - ((4 - bromo -
5 - imidazolyl)methylthio)ethyl) - N'' -
methyl guanidine (1.45 g), m.p. 144—146°
(from nitromethane).

(Found: C, 34.3; H, 4.2; N, 26.7; S,
10.1. C₁₁H₁₃BrN₄S requires: C, 34.1; H, 4.1;
N, 26.5; S, 10.2).

Example 6

N - Cyano - N' - methyl - N'' - [2 - (2 -
thiazolyl)methylthio)ethyl]guanidine

60 (a) Reaction of 2 - ((2 - aminoethyl)thio-
methyl)thiazole (from the dihydrobromide

20.2 g) with N - cyano - N',S - dimethyl-
isothiourea (7.75 g) by a procedure similar
to that described in Example 1(a) afforded
N - cyano - N' - methyl - N'' - [2 -
(2 - thiazolyl)methylthio)ethyl]guanidine, m.p.
120—122.5°, following chromatography on
silica gel with acetonitrile as eluant, and re-
crystallisation from isopropyl alcohol.

(Found: C, 42.3; H, 5.1; N, 27.2; S,
25.3. C₁₁H₁₃N₅S₂ requires: C, 42.3; H, 5.1;
N, 27.4; S, 25.1).

(b) The sequential reaction of dimethyl-
cyanodithioimidocarbonate (5.5 g) with 2 -
[(2 - aminoethyl)thiomethyl]thiazole (from
the dihydrobromide) (12.0 g) and excess
methylamine by the procedure described in
Example 1(d) afforded N - cyano - N' -
methyl - N'' - [2 - (2 - thiazolyl)methyl-
thio)ethyl]guanidine (8.46 g), m.p. 121—123°
(from isopropyl alcohol).

Example 7

N - Cyano - N' - methyl - N'' - [4 - (2 -
thiazolyl)butyl]guanidine

85 Reaction of 2 - (4 - aminobutyl)thiazole
(from the dihydrochloride, 13.8 g) with N -
cyano - N',S - dimethylisothiourea (7.75 g)
by a procedure similar to that described in
Example 1(a) afforded N - cyano - N' -
methyl - N'' - [4 - (2 - thiazolyl)butyl]
guanidine, m.p. 87—89.5°, following chro-
matography on silica gel with acetonitrile
as eluant and recrystallisation from isopropyl
alcohol-isopropyl acetate.

(Found: C, 50.7; H, 6.5; N, 29.8; S,
13.5. C₁₁H₁₅N₄S requires: C, 50.6; H, 6.5;
N, 29.5; S, 13.5).

Example 8

N - Cyano - N' - methyl - N'' - [3 - ((4 -
methyl - 5 - imidazolyl)methylthio)propyl]
guanidine

100 (i) A solution of homocysteamine hydro-
chloride (22.0 g) and 4 - hydroxymethyl -
5 - methylimidazole hydrochloride (25.6 g)
in aqueous hydrobromic acid (500 ml) was
heated under reflux for one hour. Concen-
tration under reduced pressure, followed by
recrystallisation from methanol-isopropyl
alcohol afforded 4 - methyl - 5 - [(3 - amino-
propyl)thiomethyl]imidazole dihydrobromide
(24.5 g), m.p. 200.5—202—5°.

(ii) The reaction of 4 - methyl - 5 - [(3 -
aminopropyl)thiomethyl]imidazole (from the
dihydrobromide, 20.0 g) with methylisothio-
cyanate (4.5 g) in isopropyl alcohol afforded
N - methyl - N' - [3 - ((4 - methyl - 5 -
imidazolyl)methylthio)propyl]thiourea, m.p.
104.5—105.5° (from methyl ethyl ketone).

(Found: C, 46.6; H, 7.0; N, 21.7; S,
24.6. C₁₁H₁₅N₄S₂ requires: C, 46.5; H, 7.0;
N, 21.7; S, 24.8).

(iii) The reaction of N - methyl - N' -
[3 - ((4 - methyl - 5 - imidazolyl)methylthio)
propyl]thiourea (5.9 g) with lead cyanamide

65

70

75

80

85

90

95

100

105

110

115

120

125

- (17.5 g) by a procedure similar to that described in Example 1(b) afforded N - cyano - N' - methyl - N'' - [3 - ((4 - methyl - 5 - imidazolyl)methylthio)propyl]guanidine (0.91 g), m.p. 156—158°, following chromatography on silica gel with successive elution by chloroform-ethylacetate (1:1), ethyl acetate and ethyl acetate-isopropyl alcohol (5:1) and final recrystallisation from isopropyl alcohol-ether.

(Found: C, 49.5; H, 7.0; S, 12.0. $C_{11}H_{13}N_6S$ requires: C, 49.6; H, 6.8; S, 12.0).

Example 9

- 15 N - Cyano - N' - methyl - N'' - (2 - ((4 - imidazolyl)methylthio)ethyl)guanidine
Lead cyanamide (24.7 g) was added to a solution of N - methyl - N' - [2 - ((4 - imidazolyl)methylthio)ethyl]thiourea (11.5 g) in acetonitrile (250 ml) containing dimethylformamide. The stirred suspension was heated under reflux for 48 hours. Filtration followed by concentration under reduced pressure and purification of the product on a column of silica gel with ethyl acetate-isopropyl alcohol (2:1) as eluant gave N - cyano - N' - methyl - N'' - (2 - (4 - imidazolylmethylthio)ethyl)guanidine (3.7 g), m.p. 138—140° (from acetonitrile).
- 20 (Found: C, 45.7; H, 5.9; N, 35.5; S, 13.5. $C_8H_{11}N_5S$ requires: C, 45.4; H, 5.9; N, 35.3; S, 13.5).

Example 10

- 35 N - Cyano - N' - methyl - N'' - [4 - (4 - imidazolyl)butyl]guanidine
Lead cyanamide (30 g) was added to a solution of N - methyl - N' - (4 - (4 - imidazolyl)butyl)thiourea (21.2 g) in acetonitrile (500 ml) containing dimethylformamide (50 ml).
The suspension was stirred under reflux for 24 hours, fresh lead cyanamide (15 g) was added and the suspension was then stirred under reflux for an additional 24 hours. Following filtration and concentration the product was chromatographed on a column of silica gel with isopropyl alcohol as eluant to give N - cyano - N' - methyl - N'' - [4 - (4 - imidazolyl)butyl]guanidine (9.4 g), m.p. 147—148° (from water).
- 50 (Found: C, 54.2; H, 7.2; N, 37.7. $C_{16}H_{21}N_7$ requires: C, 54.5; H, 7.3; N, 38.2).

Example 11

- 55 N - Cyano - N' - methyl - N'' - (3 - (4 - imidazolyl)propyl)guanidine
The reaction of N - methyl - N' - (3 - (4 - imidazolyl)propyl)thiourea (7.0 g) with lead cyanamide (21.8 g) under conditions similar to those described in Example 10 afforded N - cyano - N' - methyl - N'' - (3 - (4 - imidazolyl)propyl)guanidine (1.5 g, m.p.

155—156°) following chromatography on silica gel with ethyl acetate-isopropyl alcohol (2:1) as eluant and recrystallisation from water.

(Found: C, 52.0; H, 6.7; N, 40.8. $C_9H_{11}N_5$ requires: C, 52.4; H, 6.8; N, 40.8).

Example 12

N - Cyano - N' - methyl - N'' - (2 - ((3 - isothiazolyl)methylthio)ethyl)guanidine

- (a) The reaction of N - methyl - N' - (2 - ((3 - isothiazolyl)methylthio)ethyl)thiourea (17.7 g) with lead cyanamide (52.6 g) under conditions similar to those described in Example 10 afforded N - cyano - N' - methyl - N'' - (2 - ((3 - isothiazolyl)methylthio)ethyl)guanidine, in a crystalline form m.p. 63—64°, following chromatography on silica gel with ethyl acetate as eluant and recrystallisation from isopropyl acetate-ether. Further recrystallisation from isopropyl acetate afforded the cyanoguanidine in a crystalline form, m.p. 91—92°.

(Found: C, 42.6; H, 5.2; N, 27.4; S, 25.4. $C_8H_{10}N_4S_2$ requires: C, 42.3; H, 5.1; N, 27.4; S, 25.1).

- (b) (i) The reaction of dimethylcyanodithioimidocarbonate (1.50 g) with 3((2 - aminoethyl)thiomethyl)isothiazole (1.70 g) by the procedure described in Example 1(c) afforded N - cyano - N' - [2 - ((3 - isothiazolyl)methylthio)ethyl] - S - methylisothiourea. Recrystallisation from isopropyl acetate afforded 0.68 g, m.p. 85—87°.

(Found: C, 39.7; H, 4.4; N, 20.6; S, 35.4. $C_8H_{12}N_4S_3$ requires: C, 39.7; H, 4.4; N, 20.6; S, 35.3).

- (ii) The reaction of N - cyano - N' - [2 - (3 - isothiazolylmethylthio)ethyl] - S - methylisothiourea (0.27 g) with excess methylamine according to the procedure described in Example 1(c) and recrystallisation of the product from isopropyl acetate afforded N - cyano - N' - methyl - N'' - [2 - ((3 - isothiazolyl)methylthio)ethyl]guanidine (0.12 g), m.p. 91—93°.

(Found: C, 42.4; H, 5.1; N, 27.3; S, 25.2. $C_8H_{11}N_5S_2$ requires: C, 42.3; H, 5.1; N, 27.4; S, 25.1).

Example 13

N - Cyano - N' - [2 - ((4 - methyl - 5 - imidazolyl)methylthio)ethyl] - N'' - propylguanidine

- A solution of N - cyano - N' - [2 - ((4 - methyl - 5 - imidazolyl)methylthio)ethyl] - S - methylisothiourea (2.69 g) and n-propylamine (1.1 g) in ethanol (50 ml) was heated under reflux for 6 hours. Concentration, followed by chromatographic purification on a column of silica gel with ethyl acetate-isopropyl alcohol (4:1) as eluant and final recrystallisation from aqueous isopropyl alcohol afforded N - cyano - N' - [2 - ((4 - methyl -

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N, 40.8).

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; H, 5.1;

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ropyl ace-

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; H, 4.4;

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(0.12 g),

27.3; S,
; H, 5.1;

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- propyl

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final re-

l alcohol
methyl -

5 - imidazolyl)methylthio)ethyl] - N'' - pro-
pylguanidine (2.0 g) m.p. 108°—110°.

(Found: C, 51.4; N, 7.4; S, 30.0; S, 11.4. C₁₂H₂₀N₆S requires: C, 51.4; H, 7.2; N, 30.0; S, 11.4).

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Example 14

N - Cyano - N' - [2 - ((3 - bromo - 2 -
pyridyl)methylthio)ethyl] - N'' - methyl
guanidine

10

(a) A solution sodium nitrite (2.38 g) in
water (10 ml) was added dropwise to a
stirred mixture of 3 - amino - 2 - hydroxy-
methylpyridine (4.8 g) in aqueous hydro-
bromic acid (48%, 10 ml) and water (5 ml)
at 0—5°C. This solution of the diazonium
salt was added to a hot solution of cuprous
bromide (2.5 g) in 60% hydrobromic acid
and following cessation of nitrogen evolution
the mixture was heated on the steam bath for
0.5 hours, diluted with water and saturated
with hydrogen sulphide. Filtration, concen-
tration to low bulk and extraction with chloro-
form yielded 3 - bromo - 2 - hydroxymethyl-
pyridine (4.8 g). This was dissolved in

15

aqueous hydrobromic acid (48%, 50 ml),
cysteamine hydrochloride (3.22 g) added and
the solution obtained was heated under re-
flux for 6 hours. Concentration, followed by
recrystallisation from aqueous ethanol afforded
2 - ((2 - aminoethyl) - thiomethyl) - 3 -
bromopyridine dihydrobromide (6.1 g), m.p.
252—254°.

20

Found: C, 23.7; H, 3.4; N, 6.7; S, 7.9.
C₈H₁₁BrN₂S. 2HBr requires: C, 23.5; H,
3.2; N, 6.9; S, 7.8.

25

(b) Sequential reaction of dimethylcyanodi-
thioimidocarbonate with 2 - ((2 - amino-
ethyl)thiomethyl) - 3 - bromopyridine and ex-
cess methylamine by the procedure described
in Example 1(d) followed by chromatographic
purification on a column of silica gel with
elution by ethyl acetate and final recrystal-
lisation from ethyl acetate-petroleum ether
gave N - cyano - N' - [2 - ((3 - bromo - 2 -
pyridyl)methylthio)ethyl] - N'' - methyl-
guanidine m.p. 114—116°.

30

Found: C, 40.6; H, 4.4; N, 21.4; S, 9.8.
C₁₁H₁₄BrN₃S requires: C, 40.3; H, 4.3; N,
21.3; S, 9.8.

35

(b) Sequential reaction of dimethylcyanodi-
thioimidocarbonate with 2 - ((2 - amino-
ethyl)thiomethyl) - 3 - bromopyridine and ex-
cess methylamine by the procedure described
in Example 1(d) followed by chromatographic
purification on a column of silica gel with
elution by ethyl acetate and final recrystal-
lisation from ethyl acetate-petroleum ether
gave N - cyano - N' - [2 - ((3 - bromo - 2 -
pyridyl)methylthio)ethyl] - N'' - methyl-
guanidine m.p. 114—116°.

40

Found: C, 40.6; H, 4.4; N, 21.4; S, 9.8.
C₁₁H₁₄BrN₃S requires: C, 40.3; H, 4.3; N,
21.3; S, 9.8.

45

(b) Sequential reaction of dimethylcyanodi-
thioimidocarbonate with 2 - ((2 - amino-
ethyl)thiomethyl) - 3 - bromopyridine and ex-
cess methylamine by the procedure described
in Example 1(d) followed by chromatographic
purification on a column of silica gel with
elution by ethyl acetate and final recrystal-
lisation from ethyl acetate-petroleum ether
afforded N - cyano - N' - [2 - ((3 - bromo - 2 -
pyridyl)methylthio)ethyl] - N'' - ethyl-
guanidine, m.p. 123—124°.

50

Example 15

N - Cyano - N' - [2 - ((3 - bromo - 2 -
pyridyl) - methylthio)ethyl] - N'' - ethyl-
guanidine

55

Sequential reaction of dimethylcyanodithio-
imidocarbonate with 2 - ((2 - aminoethyl)
thiomethyl) - 3 - bromopyridine and excess
ethylamine, followed by chromatographic
purification on a column of silica gel with
elution by ethyl acetate and final recrystal-
lisation from ethyl acetate-petroleum ether
afforded N - cyano - N' - [2 - ((3 - bromo - 2 -
pyridyl)methylthio)ethyl] - N'' - ethyl-
guanidine, m.p. 123—124°.

60

Found: C, 42.2; H, 4.7; N, 20.5; S, 9.4.
C₁₂H₁₆BrN₃S requires: C, 42.1; H, 4.7; N,
20.5; S, 9.4. 65

Example 16

Treatment of the following amines:

- (a) 2 - [(2 - aminoethyl)thiomethyl]oxa- 70
zole
- (b) 3 - [(2 - aminoethyl)thiomethyl]iso-
oxazole
- (c) 3 - [2 - aminoethyl]thiomethyl]pyra-
zole
- (d) 3 - [(2 - aminoethyl)thiomethyl] - 1,2, 75
4 - triazole
- (e) 5 - amino - 2 - [(2 - aminoethyl)thio-
methyl] - 1,3,4 - thiazole
- (f) 2 - [(2 - aminoethyl)thiomethyl]pyri- 80
midine
- (g) 2 - [(2 - aminoethyl)thiomethyl]pyra-
zine
- (h) 3 - [(2 - aminoethyl)thiomethyl]pyri-
dazine
- (i) 1 - methyl - 2 - [(2 - aminoethyl)thio- 85
methyl]imidazole
- (j) 2 - [(2 - aminoethyl)thiomethyl]imida-
zole
- (k) 5 - trifluoromethyl - 4 - [(2 - amino-
ethyl)thiomethyl] - imidazole 90
- (l) 4 - (- aminoethoxymethyl)imidazole
- (m) 2 - (3 - aminopropylamino)pyridine

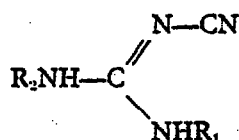
with dimethylcyanodithioimidocarbonate and
then with methylamine according to a pro-
cedure similar to that described in Example
1(c) or Example 1(d) results in the produc-
tion of the following products 95

- (a) N - cyano - N' - methyl - N'' - [2 -
((2 - oxazolyl)methylthio)ethyl]guani- 100
dine
- (b) N - cyano - N' - methyl - N'' - [2 -
((3 - isoxazolyl)methylthio)ethyl]guani-
dine.
- (c) N - cyano - N' - methyl - N'' - [2 -
((3 - pyrazolyl)methylthio)ethyl]guani- 105
dine.
- (d) N - cyano - N' - methyl - N'' - [2 -
((3 - (1,2,4 - triazolyl)methylthio)ethyl]
guanidine.
- (e) N - cyano - N' - methyl - N'' - [2 - 110
(5 - amino - 2 - (1,3,4 - thiadiazolyl)
methylthio)ethyl]guanidine.
- (f) N - cyano - N' - methyl - N'' - [2 -
((2 - pyrimidinyl)methylthio)ethyl]
guanidine. 115
- (g) N - cyano - N' - methyl - N'' - [2 -
((2 - pyrazolyl)methylthio)ethyl]guani-
dine.
- (h) N - cyano - N' - methyl - N'' - [2 -
((3 - pyridazinyl)methylthio)ethyl] 120
guanidine.
- (i) N - cyano - N' - methyl - N'' - [2 -
((1 - methyl - 2 - imidazolyl)methyl-
thio)ethyl]guanidine.

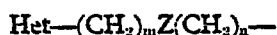
- (j) N - cyano - N' - methyl - N'' - [2 - ((2 - imidazolyl)methylthio)ethyl]guanidine.
- 5 (k) N - cyano - N' - methyl - N'' - [2 - ((5 - trifluoromethyl - 4 - imidazolyl)methylthio)ethyl]guanidine.
- (l) N - cyano - N' - methyl - N'' - [2 - ((4 - imidazolyl)methoxy)ethyl]guanidine.
- 10 (m) N - cyano - N' - methyl - N'' - [3 - (2 - pyridylamino)propyl]guanidine.
- ((3 - hydroxyl - 2 - pyridyl)methylthio)ethyl]guanidine.
14. N - Cyano - N' - methyl - N'' - [2 - ((3 - bromo - 2 - pyridyl)methylthio)ethyl] 60 guanidine.
15. A process for the production of a compound according to claim 1 in which an amine of the formula
- $$R_2NH_2$$
- 65

WHAT WE CLAIM IS:—

1. A compound of the formula



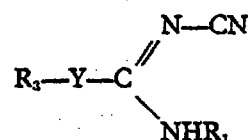
- 15 wherein R_1 is hydrogen or lower alkyl; and R_2 is a grouping of the structure.



- wherein Het is an imidazole, pyridine, thiazole, isothiazole, oxazole, isoxazole, pyrazole, triazole, thiadiazole, pyrimidine, pyrazine or pyridazine ring, which ring is optionally substituted by lower alkyl, trifluoromethyl, hydroxy, halogen or amino, Z is sulphur, oxygen, NH or a methylene group; and m and n are integers from 0 to 4 such that their sum is from 2 to 4.
- 20
2. A compound according to claim 1 wherein R_1 is methyl or ethyl.
3. A compound according to claim 1 or claim 2 wherein m is 1 and n is 2.
- 25 4. A compound according to any one of the preceding claims wherein Z is sulphur.
5. A compound according to any one of claims 1 to 3 wherein Z is methylene.
- 35 6. A compound according to any one of the preceding claims wherein Het is imidazole, thiazole or isothiazole and is optionally substituted by methyl, hydroxyl or halogen.
- 40 7. A compound according to any one of the preceding claims wherein Het is pyridine and is optionally substituted by methyl, hydroxyl or halogen.

8. N - Cyano - N' - methyl - N'' - [2 - ((4 - methyl - 5 - imidazolyl)methylthio)ethyl]guanidine.
- 45 9. N - Cyano - N' - ethyl - N'' - [2 - ((4 - methyl - 5 - imidazolyl)methylthio)ethyl]guanidine.
10. N - Cyano - N' - methyl - N'' - [2 - ((4 - bromo - 5 - imidazolyl)methylthio)ethyl]guanidine.
- 50 11. N - Cyano - N' - methyl - N'' - [2 - ((2 - thiazolyl)methylthio)ethyl]guanidine.
12. N - Cyano - N' - methyl - N'' - [2 - ((3 - isothiazolyl)methylthio)ethyl]guanidine.
- 55 13. N - Cyano - N' - methyl - N'' - [2 -

wherein R_2 has the same significance as in claim 1 is reacted with a compound of the formula



- wherein R_1 has the same significance as in claim 1; Y is sulphur or oxygen; and R_3 is lower alkyl, aryl or arylalkyl.
- 70

16. A process according to claim 15 wherein Y is sulphur and R_3 is methyl.

17. A process according to claim 15 as hereinbefore described in Example 1(a).

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18. A process for the production of a compound according to claim 1 in which an amine of the formula



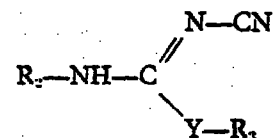
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wherein R_2 has the same significance as in claim 1 is reacted with a compound of the formula



wherein R_3 is alkyl and Y is sulphur or oxygen to give a compound of the formula

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wherein R_2 , R_3 and Y have the above significance which compound is then reacted with an amine of formula

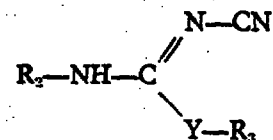
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wherein R_1 has the same significance as in claim 1.

19. A process according to claim 18 wherein the intermediate compound of formula

95



is not isolated.

(thio)ethyl]
N'' - [2 -
(thio)ethyl] 60
of a com-
which an
65

20. A process according to claim 18 or claim 19 wherein Y is sulphur and R₃ is methyl.

21. A process according to claim 18 as hereinbefore described in any one of Examples 1(c), 1(d), 2(a), 3 to 5, 6(b), 12(b) and 13.

22. A compound according to claim 1 whenever produced by a process according to any one of claims 15 to 21.

23. Pharmaceutical compositions comprising a compound according to claim 1 or a non-toxic acid addition salt thereof in association with a pharmaceutically acceptable diluent or carrier.

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Agent for the Applicants.

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PATENTS ACT 1949

SPECIFICATION NO. 1397436

The following corrections were allowed under Section 76 on 12 October 1976

Page 7, line 117 *delete* pyrazolyl *insert* pyrazinyl

Attention is also directed to the following printers error:-

Page 7, line 78 *delete* thiazole *insert* thiadiazole

THE PATENT OFFICE
10 November 1976

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SPECIFICATION No. 1,397,436
Slip No. 2

Page 3, line 16, *for* 13305546 *read* 1305546
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7th July, 1978