"Imidazolylphenyl amidines"

This invention relates to new substituted imidazolylphenyl amidines, to processes for their preparation, and to pharmaceutical compositions containing them. The new compounds are H_2 receptor blocking agents and may be used as gastric acid secretion inhibitors and antiulcer agents.

The ineffectiveness of the ordinary antihistaminic drugs in blocking the stimulating effect of histamine on gastric secretion has prompted a search for histaminic antagonists. This effect of histamine, which is recognized as a powerful agonist of gastric secretion is mediated through H_2 receptors (Black, et al, Nature 236, 385, 1972) and is not inhibited by the classical antihistamines, H_1 receptor blockers (Ash and Schild, Brit. J. Pharmacol., 27, 427, 1966). Investigations in this direction culminated in the synthesis of a class of substances (G.J. Durant, et al, J. Med. Chem. 20, 901, 1977) typified by burimamide the first clinically effective H_2 receptor antagonist. Although burimamide was sufficiently selective pharmacologically it seemed to lack sufficient oral bioavailability. Metiamide a subsequently evaluated H_2 antagonist, proved more potent than burimamide and orally active in man. However, metiamide could not be introduced into therapy owing to its toxic side effects (agranulocytosis).

Cimetidine, a congener of metiamide bearing a cyanoguanidino instead of a thioureido group, proved as potent as metiamide as an H_2 antagonist but is devoid of the toxic side effects of metiamide.

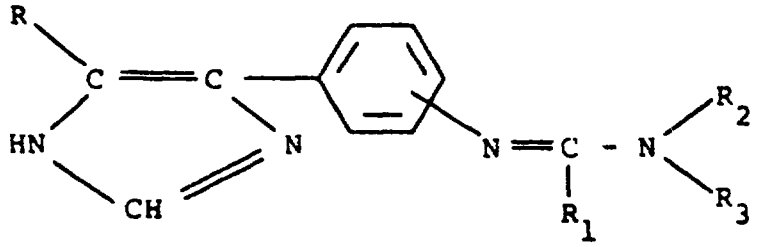
Cimetidine has been recently introduced into therapy as an antiulcer drug. Its half-life however is relatively short and administration of several daily doses of 200-300 mg tablets is required. This shortcoming has prompted further research in the

field of H_2 receptor blockers aimed at finding longer acting and/or more potent substances. Recently, two new H_2-receptor antagonists [ranitidine (AH 19065) and tiotidine (ICI 125,225)] have been reported possessing chemical features analogous to cimetidine, i.e. a linear methylthioethyl side-chain bearing neutral polar groups. The main chemical variation in the latter compounds with respect to cimetidine consists in the replacement of the imidazole ring by an aminoalkyl furan and a 2-guanidino-thiazole ring, respectively. Both ranitidine (Bradshaw, et al, Brit. J. Pharmacol. 66, 464 P, 1979) and tiotidine (T.O. Yellin, Life Sci., 25, 2001-9, 1979) have been reported to be more potent than cimetidine either as H_2 receptor antagonists in "in vitro" tests or as inhibitors of gastric acid secretion "in vivo".

We have now discovered that by substituting the linear side-chain, present in the classical as well as the two more recent H_2 receptor antagonists, with a phenyl ring possessing optionally substituted amidino groups, new substances endowed with potent H_2 - blocking activity, which inhibit gastric acid secretion, may be obtained.

The H_2 receptor antagonists besides being useful in blocking gastric secretion agents are potentially useful as therapeutically active agents in the treatment of inflammation [Yoshioka T., Monafo W.W, Ayvazian et al. (Am J.Surg. 136, 681 (1978)] and of cardiovascular disorders [Jerome P., Trzechiakowski and R. Levi [J. Pharmacol. Exp. Ther. 214, 629-634, (1980)]. In some conditions a combination of H_1 and H_2 antagonist activity would be useful [Barry L. Tepperman, Eugene D. Jacobson et al. (Life Sciences, vol. 24, 2301-2308 (1979)]. Some compounds disclosed herein show both these receptorial interactions.

According to one feature of the present invention there are provided compounds of general formula 1



(I)

in which R, R_1 and R_3, which may be the same or different, each represents a hydrogen atom or a C_{1-3} alkyl group, and R_2 represents a linear or branched alkyl, alkenyl or alkynyl group, a cyano group, a hydroxyl group, a substituted or unsubstituted cycloalkyl or cycloaliphatic alkyl group, a bicyclic cycloaliphatic group, an aralkyl or aryl group (optionally substituted by halogen, methyl, methoxy or methylenedioxy groups) or a substituted or unsubstituted heterocyclic group or an alkyl group substituted by a substituted or unsubstituted heterocyclic group, said heterocyclic groups optionally also containing a further heteroatom; tautomers thereof; and acid addition salts of the aforesaid compounds.

For pharmaceutical use, the acid addition salts refered to above will of course be physiologically compatible acid addition salts but ether acid addition salts may find use in the preparation of the compounds of formula I and their physiologically compatible acid addition salts. The term "acid addition salts" includes salts with inorganic and organic acids. Suitable physiologically compatible acid addition salts include, for example, salts formed with hydrochloric, maleic, fumaric, methanesulfonic, citric, tartaric or acetic acids.

It is to be understood that although in the formula I given above the double bond in the amidine radical and in the imidazole ring have been shown in a particular position, various other tautomeric forms are possible, and the present invention includes such tautomeric forms within its scope, both in terms of the compounds of the inventions and in terms of the manufacturing processes.

When in the compounds of formula I R, R_1 and/or

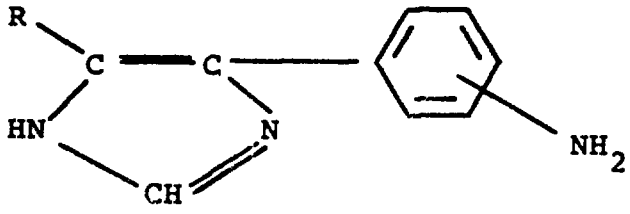
R_3 represent C_{1-3} alkyl groups these may, for example, be methyl groups. When R_2 represents a linear or branched alkyl group it may, for example be an alkyl group containing from 1 to 8 carbon atoms; when R_2 is a linear or branched alkenyl group it may, for example, be an alkenyl group containing from 2 to 5 carbon atoms; when R_2 represents a linear or branched alkynyl group it may, for example be an alkynyl group containing 3 or 4 carbon atoms; when R_2 is a bicyclic cycloaliphatic group it may, for example, be a norbornyl group; when R_2 represents an aralkyl group it may, for example, be a benzyl group; when R_2 represents an aryl group it may, for example, be a phenyl group optionally substitued by a halogen atom, e.g. chlorine; when R_2 represents substituted or unsubstituted cycloalkyl or cycloaliphatic alkyl groups they may, for example, contain from 3 to 6 carbon atoms; when R_2 represents a substituted or unsubstituted heterocyclic group or an alkyl group substituted by a substituted or unsubstituted heterocyclic group, the heterocyclic portion may, for example, be an unsaturated five-membered ring which may also contain a further heteroatom. In the above mentioned formula (I) the amidine radical may be in the ortho, meta or para position of the benzene ring.

Preferred compounds according to the present invention include those wherein the amidine radical is in the para position of the benzene ring, R, R_1 and R_3 all represent hydrogen atoms and R_2 is a hydroxyl, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, neopentyl, hexyl, heptyl, octyl, allyl, α-methylallyl, prenyl (i.e. 3-methyl-but-2-enyl), propargyl, α-methylpropargyl, cyano, norbornyl, benzyl, cyclopropyl, cyclopropylmethyl, dimethylcyclopropylmethyl, menthyl, cyclohexyl, cyclohexylmethyl, phenyl, p-chlorophenyl, p-methylphenyl, p-methoxyphenyl, methylenedioxyphenyl or 2-furylmethyl group and their physiologically compatible acid addition salts. Such compounds generally have better

activity and are therefore preferred as antiulcer agents and for treatment of disorders of the gastro-intestinal tract.

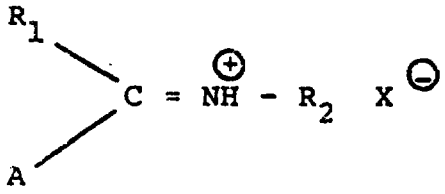
The compounds of general formula I as hereinbefore defined may, for example, be prepared by the following processes, which processes constitute further features of the present invention.

A. Reaction of a compound of formula II



(II)

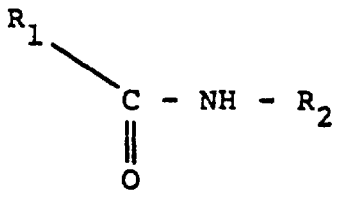
(wherein R is as hereinbefore defined) with a reactive derivative of a compound of formula III



(III)

where R_1 and R_2 are as hereinbefore defined, $X^{\ominus}$ represents the anion of an inorganic acid such as the chloride or fluoroborate ion, and A represents a benzoyloxy group, a C_{1-3} alkoxy group such as methoxy or ethoxy, or a chlorine atom. The compound of formula III may optionally be made to react as a base. Preferred temperatures are those between 0 and 100°C and preferably from 20 to 60° C. The reaction may, for example be carried out in the presence of an inert organic solvent such as, an alcohol having 1 to 3 carbon atoms such as methanol or ethanol or a halogenated hydrocarbon such as dichloromethane, dioxan or acetone.

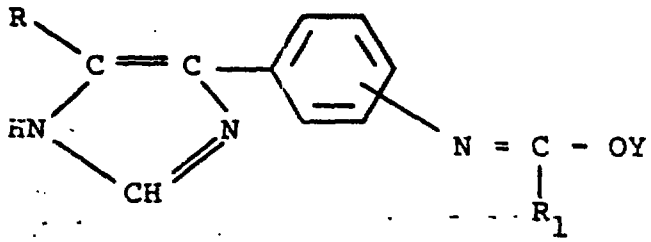
The compounds of formula III used as starting materials in the above process may be obtained by conventional methods, e.g by reacting a carboxamide of the formula IV



(IV)

(wherein R_1 and R_2 are as hereinbefore defined) with benzoyl chloride, triethyloxonium fluoroborate, ethyl chloroformate, phosphorous oxychloride or phosphorous pentachloride.

B. Reaction of a compound of formula V



(V)

wherein R and R_1 are as hereinbefore defined and Y represents a C_{1-3} alkyl group, such as methyl or ethyl, with an amine of formula VI

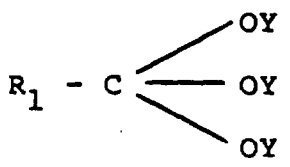
$$H_2N - R_2 \qquad (VI)$$

wherein R_2 is as hereinbefore defined.

The reaction is conveniently carried out in the presence of an inert organic solvent. Suitable solvents include, for example, alcohols such as methanol, ethanol, or dioxan.

The reaction may, however, be carried out in the absence of a solvent or an excess of the amine of formula VI may optionally be used as a solvent. Preferred temperatures are those between 20 and 80° C.

The compound of formula V may for example, be prepared <u>in situ</u>, by reacting an amine of formula II as hereinbefore defined with a compound of formula VII

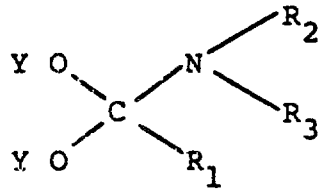


(VII)

where R_1 and Y are as hereinbefore defined, in the presence of an inorganic acid, for example sulfuric acid, as catalyst. Preferred temperatures are those between 60 and 120° C. After a few hours the amine of formula VI is added to the reaction mixture.

The compound of the general formula V used as starting material may be prepared by methods known in the literature, for example by reacting an amine of the formula II with a compound of formula VII in the absence of a solvent and distilling off the alcohol formed during the reaction.

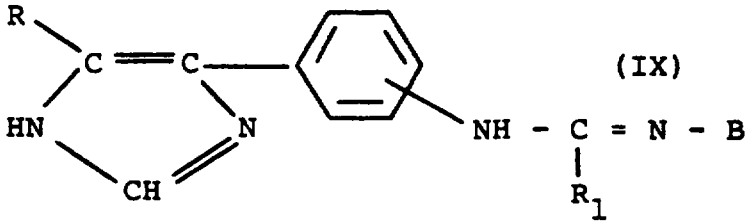
C. Reaction of a compound of formula VIII



(VIII)

wherein R_1, R_2, R_3 and Y are as hereinbefore defined, with an amine of formula II as hereinbefore defined. Preferred temperatures are those between 20 and 80° C. The alcohol formed during the reaction, is distilled off.

D. Reaction of a compound of formula IX

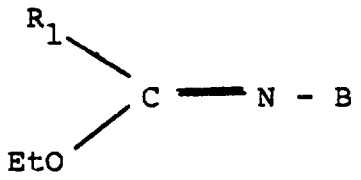


(IX)

(wherein R and R_1 are as hereinbefore defined and B represents a cyano, acetyl, carbethoxy or carbamyl group) with an amine of formula (VI) as hereinbefore defined.

The reaction may conveniently be performed in the presence of water or an inert organic solvent, for example an alcohol such as methanol or ethanol, formamide, dioxan or acetonitrile. Preferred temperatures are those between 10 and 50° C and preferably room temperature.

The compound of formula IX used as starting material in the above process may be prepared by processes that are known in the literature, for example, by reacting an amine of formula II as hereinbefore defined with a compound of formula X

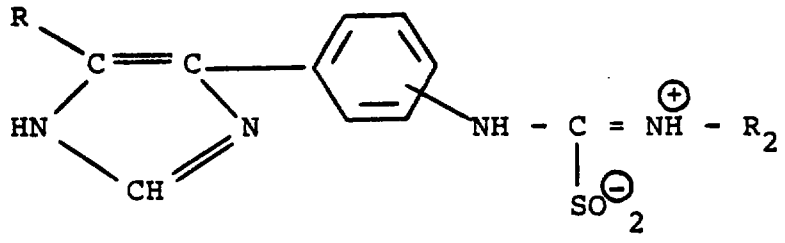


(X)

wherein R_1 and B are as hereinbefore defined. When in the compound of formula IX B represents a cyano group, the reaction may optionally be carried out in a single step by reacting an amine of formula II with cyanamide in the presence of a compound of formula VII, in which Y and R_1 are as hereinbefore defined.

The reaction may conveniently be carried out in the presence of a suitable inert organic solvent for example a lower alcohol, ethers, ethylacetate, acetonitrile or dioxan or without a solvent at a temperature of from 20 to 80° C. The compound of formula X may be prepared by conventional methods.

E. Reaction of a compound of formula XI

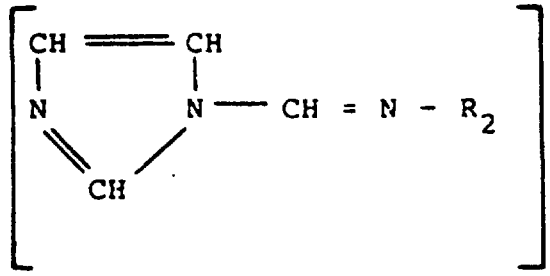


(XI)

(where R and R_2 are as hereinbefore defined) with a weak organic acid, for example formic, acetic or propionic acid.

The compound of formula XI may be obtained by conventional methods, for example by oxidizing the corresponding thiourea by means of hydrogen peroxide in the presence of a lower alcohol preferably at temperatures between 20 and 50°C.

F. To prepare a compound of formula I wherein R_1 and R_3 both represent hydrogen atoms: reaction in a single step of a compound of formula XII



(XII)

(wherein R_2 is as hereinbefore defined) (an intermediate obtained without isolation in situ from an isonitrile of formula $C\equiv N-R_2$ and imidazole in the presence of AgCl according to T. Saegusa et al. [Tetrah. Letters 1283 (1974)]) with an amine of formula II; or reaction of an amine of formula II with an isonitrile of formula $C\equiv N-R_2$ in the presence of CuCl. The reaction may be carried out without solvent, or in the presence of, for example ethanol or dioxan. Preferred temperatures are those between 100-150°C.

The compounds of formula I prepared according to the processes A to F may optionally be converted with inorganic or organic acids into physiologically compatible acid addition salts, for example by conventional methods such as by reacting the compounds as bases with a solution of the corresponding acids in a suitable solvent.

Particularly preferred acids include for example hydrochloric, maleic, fumaric and methanesulfonic acids. The salts thus obtained are normally soluble in water. The compounds of general formula I and their physiologically compatible acid addition salts are H_2 receptor blocking agents which inhibit gastric acid secretion.

Particularly preferred compounds according to the present invention are the following:

N-Ethyl-N'-[4-(imidazol-4-yl)-phenyl]-formamidine (Compound 11)

N-Isopropyl-N'-[4-(imidazol-4-yl)-phenyl]-formamidine
(Compound 13)
N-Allyl-N'-[4-(imidazol-4-yl)-phenyl]-formamidine
(Compound 14)
N-n.Propyl-N'-[4-(imidazol-4-yl)-phenyl]-formamidine
(Compound 18)
N-sec.Butyl-N'-[4-(imidazol-4-yl)-phenyl]-formamidine
(Compound 19)
N-Isobutyl-N'-[4-(imidazol-4-yl)-phenyl]-formamidine
(Compound 20)
N-Prenyl-N'-[4-(imidazol-4-yl)-phenyl]-formamidine
(Compound 23)
N-Cyclopropylmethyl-N'-[4-(imidazol-4-yl)-phenyl]-
formamidine
(Compound 26)
N-Cyclopropyl-N'-[4-(imidazol-4-yl)-phenyl]-formamidine
(Compound 32)
N-(α-Methylallyl)-N'-[4-(imidazol-4-yl)-phenyl]-formamidine
(Compound 34)
N-Neopentyl-N'-[4-(imidazol-4-yl)-phenyl]-formamidine
(Compound 36)
N-(2,2-Dimethyl-cyclopropylmethyl)-N'-[4-(imidazol-
4-yl)-phenyl]-formamidine
(Compound 37)

The antagonistic activity of compounds according to the invention on histamine H_2 receptors may be demonstrated either in vitro or in vivo by their inhibition of H_2-dependent biological effects which include the histamine induced chronotropic effect and the histamine induced gastric secretion of acid respectively.

The positive chronotropic effect has been investigated in vitro in isolated guinea pig atria suspended in an organ bath (50 ml) containing oxygenated (O_2:95% -CO_2: 5%) Krebs - Henseleit solution (pH 7.4) maintained at 32°C. The myocardial preparation, loaded to 1 g isometric tension, is allowed to stabilize for 60 min., and then myocardial contractions are recorded through an isometric lever connected to a strain-

gauge coupler, and the instantaneous rate is monitored with a cardiotachymeter, and a heat-writing pen recorder. After control, responses (tachycardia) to histamine (10^{-6} g/ml) are obtained three times at 30 minute intervals, the test compounds are added to the bath to the desired final concentration, and the atria are again treated with histamine. The chronotropic response obtained in the presence of the antagonist is then compared to the control response to histamine and the percent reduction of the histamine H_2- evoked response is calculated. The average effective concentration (EC_{50}) of the H_2 antagonists is then calculated by the standard procedure according to D.R. Waud, Analysis of dose-response curves, in "Methods in Pharmacology" Vol. 3 Smooth muscle, Ed Daniel E.E. Paton, M., Plenum Press. New York (1975); Ash and Schild, Br. J. Pharmacol. Chemother. 27, 427-439, 1966.

The results are shown in Table 1.

TABLE 1

"In vitro" inhibitory activity in histamine induced tachycardia (guinea pig atria).

Compound	EC_{50} 10^{-8}M
11	30
13	9.2
14	9.3
18	4.4
19	15.0
20	6.5
23	7.4
26	4.8
32	37.9
34	16.8
36	12.1
37	50
CIMETIDINE	340.0

Some compounds of formula I have been found to effectively inhibit also the spasmodic action of histamine which is inhibited by classical H_1 antihistamines, such as diphenhydramine and pyrilamine, in the isolated guinea-pig ileum.

The ability of the test compounds to inhibit histamine induced gastric acid secretion, has been investigated in vivo after intravenous or intraduodenal administration in stomach perfused rats, according to Gosh and Shild (Br. J. Pharmacol, Chemother. 13, 54, 1958).

The preparation of the animals under general anaesthesia (urethane, 1 g. Kg^{-1} i.p.) and constant temperature, was achieved by inserting and tying in place polyethylene tubes (PE 50) in the aesophagus and in the pyloric-antral region. After the stomach was washed to remove remairs of food, continuous perfusion of the stomach was started with saline, 0.5 ml. min^{-1} (37°C), primed by a Jobling peristaltic pump. After 30 min. of perfusion adaptation, the stomach perfusate was collected at 30. min intervals, and titrated for acid content, expressed as µEq of NaOH 1 N. As control acid output became constant, intravenous perfusion of histamine (1 $mg.kg^{-1}hr^{-1}$) was started and maintained throughout the experimental period. After the acid secretion had reached a steady higher level, increasing doses of the test compounds were injected intravenously in order to obtain dose response functions. ED_{50} values were then calculated by standard procedures. The compounds tested by this procedure showed a very potent antisecretory activity when administered intravenously at or below 100 $\mu g/kg^{-1}$; the results are reported in the following table II:

TABLE II

"In vivo" antisecretory activity in histamine induced gastric secretion (stomach perfused rat).

Compound	ED_{50} mg/kg^{-1} (i.v.)*
11	0.02
13	0.0129
14	0.024
18	0.0111
19	0.0223
20	0.0259
23	0.0559
26	0.0235
32	0.0366
34	0.042
36	0.030
37	0.034
CIMETIDINE	0.560

* The values of activity are expressed taking the compound as a base.

The acute toxicity of the particularly preferred compounds of general formula I was approximately determined by oral administration of a single dose to groups of 5 Swiss mice pre-fasted for 18 hours. The resultant incidence of mortality after 14 days was evaluated. The results are reported in the following table, in which the values are expressed taking the compound as a base.

TABLE III

COMPOUND	No. Dead/No. Treated Mice
11	3/5 at 500 mg/kg
13	2/5 at 500 mg/kg
14	1/5 at 500 mg/kg
18	2/5 at 375 mg/kg
19	2/5 at 500 mg/kg
20	2/5 at 250 mg/kg
23	1/5 at 250 mg/kg
26	4/5 at 500 mg/kg
32	0/5 at 500 mg/kg
34	2/5 at 500 mg/kg
36	2/5 at 250 mg/kg
37	5/5 at 250 mg/kg

According to yet a further feature of the present invention there are provided pharmaceutical compositions comprising as active ingredient at least one compound of formula I, as hereinbefore defined, or a physiologically compatible acid addition salt thereof in association with a pharmaceutical carrier or excipient.

For pharmaceutical administration the compound of general formula I or its physiologically compatible acid addition salt may be incorporated into conventional pharmaceutical preparations in either solid or liquid form. The compositions may, for example, be presented in a form suitable for oral or parenteral administration. Preferred forms include, for example, capsules, plain tablets, coated tablets and vials.

The active ingredient may be incorporated in excipients or carriers conventionally used in pharmaceutical compositions such as for example talc, gum arabic, lactose, gelatine, magnesium stearate, corn starch and aqueous or non-aqueous vehicles, compositions may be formulated as dosage units, each dosage unit

being adapted to supply a fixed dose of the active ingredient. Each dosage unit may conveniently contain for example from 10 mg to 500 mg and preferably 20 mg to 150 mg, of active ingredient according to the invention.

The following non-limiting examples serve to illustrate the present invention.

(25)

Example 1

5-Methyl-4-(3-aminophenyl)-1-H-imidazole

5-Methyl-4-(3-nitrophenyl)-1-H-imidazole [R. Morgenstern, et al. Pharmazie 30, 103 (1975)] (84 g) dissolved in methanol was hydrogenated in the presence of Pd/C 5% (0.8 g) at atmospheric pressure and at room temperature. When the calculated amount of hydrogen had been taken up, the catalyst was filtered off and the solution was evaporated to dryness to afford 62.5 g of the desired compound. M.p. 198-199°C.

Analysis:

$C_{10}H_{11}N_3$:	found %	C 69.12;	H 6.43;	N 24.40
	calc. %	C 69.34;	H 6.40;	N 24.26.

Example 2

(a) 5-Methyl-4-(4-nitrophenyl)-1-H-imidazole

5-Methyl-4-phenyl-1-H-imidazole as a nitrate salt [R. Morgenstern, et al. Pharmazie 30, 103 (1975)] (50 g) was added in portions to 96% H_2SO_4 (100 ml). The thick solution so obtained was heated at 100°C for two hours, diluted with water (1000 ml) and again heated to 70° C for twenty hours. After cooling, the solution was neutralized with 30 % NaOH and 17% Na_2CO_3 aqueous solutions. The solid precipitated (a mixture of the o- and p-nitro derivatives) was filtered and converted into its nitrate salt by means of 30% nitric acid. The mixture of salts of the o- and p-nitro isomers so obtained was recrystallized from water to afford the pure para-isomer. Neutralization of an aqueous solution of the para-nitro derivative yielded 30 g of 5-methyl-4-(4-nitrophenyl)-1-H-imidazole as a base sufficiently pure to be used in the next step. M.p. 190-191°C.

Analysis:

$C_{10}H_9N_3O_2$:	found %	C 58.94;	H 4.42;	N 20.81.
	calc. %	C 59.10;	H 4.46;	N 20.68.

(b) 5-Methyl-4-(4-aminophenyl)-1-H-imidazole

5-Methyl-4-(4-nitrophenyl)-1-H-imidazole (80 g) dissolved

in methanol was hydrogenated in the presence of Pd/C 5% (0.7 g) at atmospheric pressure and at room temperature. When the calculated amount of hydrogen had been taken up, the catalyst was filtered off and the solution was evaporated to dryness to afford 43 g of 5-methyl-4-(4-aminophenyl)-1-H-imidazole. M.p. 215-216°C.

Analysis:

$C_{10}H_{11}N_3$: found % C 69.12; H 6.29; N 24.15.
calc. % C 69.34; H 6.40; N 24.26.

Example 3

(a) N-[3-(Imidazol-4-yl)-phenyl acetimidate

A mixture of 4-(3-aminophenyl)-1-H-imidazole (15.9 g) [W. Schunack, et al, Arch. Pharm. 306,934 (1973)] and triethyl orthoacetate (18.17 g) was heated until the calculated amount of ethanol was distilled. The resulting solid was recrystallized from petroleum ether-diethyl ether (1:1 v/v) to give 21.6 g of N-[3-(imidazol-4-yl)-phenyl]-ethyl acetimidate. M.p. 126°-127°C.

Analysis:

$C_{13}H_{15}N_3O$: found % C 68.14; H 6.64; N 18.01.
calc. % C 68.10; H 6.59; N 18.33.

The following intermediates were prepared in a similar manner:

N-[3-(5-Methylimidazol-4-yl)-phenyl]-ethyl acetimidate was obtained starting from 5-Methyl-4-(3-amino-phenyl)-1-H-imidazole and triethylorthoacetate. M.p. 130-131°C (Et_2O).

Analysis:

$C_{14}H_{17}N_3O$: found % C 69.32; H 7.08; N 17.15.
calc. % C 69.11; H 7.04; N 17.27.

N-[4-(5-Methylimidazol-4-yl)-phenyl]-ethyl acetimidate was obtained starting from 5-Methyl-4-(4-amino-phenyl)-1-H-imidazole and triethylorthoacetate. M.p. 171-172° C (Et_2O).

Analysis:

$C_{14}H_{17}N_3O$: found % C 69.43; H 7.09; N 17.34.
calc. % C 69.11; H 7.04; N 17.27.

N-[4-(Imidazol-4-yl)-phenyl]-ethyl acetimidate was obtained starting from 4-(4-amino-phenyl)-1-H-imidazole [E. Balaban et al. J.Chem. Soc. 2701 (1925)] and triethylorthoacetate. M.p. 144-147°C (Et_2O).

Analysis:

$C_{13}H_{15}N_3O$	found %	C 68.21;	H 6.60;	N 18.14
	calc. %	C 68.10	H 6.59;	N 18.33

(b) N-Methyl-N'-[4-(imidazol-4-yl)-phenyl] acetamidine (Compound 1)

To a solution of N-[4-(imidazol-4-yl)-phenyl] ethyl-acetimidate (8.02 g) in ethanol (20 ml) three portions of 33% methylamine in ethanol (8 g each; 24 g total) were added in a period of six days. The solution was evaporated to dryness and the residue was dissolved in 10% hydrochloric acid. The acid solution was washed with ethyl acetate and basified to pH 10 with 10% NaOH. The solid which separated was collected by filtration and dried to give the title compound (5.5g). M.p. 226-227° C.

Anaylsis:

$C_{12}H_{14}N_4$	found %	C 67.53;	H 6.53;	N 25.98.
	calc. %	C 67.26;	H 6.59;	N 26.15.

Maleate salt. M.p. 170-171°C.

The following acetamidines were prepared in a similar manner, starting from the appropriate ethyl acetimidate as above described.

N-Methyl-N'-[3-(5-methylimidazol-4-yl)-phenyl]-acetamidine (Compound 2)

M.p. 201-202°C.

Analysis:

$C_{13}H_{16}N_4$	found %	C 67.77;	H 7.05;	N 24.18.
	calc. %	C 68.39:	H 7.06;	N 24.54.

Hydrochloride salt. M.p. 260-261°C.

N-Methyl-N'-[3-(imidazol-4-yl)-phenyl]acetamidine (Compound 3)

M.p. 117-120° C.

Analysis:

$C_{12}H_{14}N_4$	found %	C 66.86;	H 6.81;	N 25.82.
	calc. %	C 67.26;	H 6.59;	N 26.15.

Hydrochloride salt. M.p. 288-290°C.

N-Methyl-N'-[4-(5-Methylimidazol-4-yl)-phenyl]-acetamidine (Compound 4)

M.p. 223-226° C.

Analysis:

$C_{13}H_{16}N_4$	found %	C 68.45;	H 7.08;	N 24.36.
	calc. %	C 68.39;	H 7.06;	N 24.54.

Hydrochloride salt. M.p. 283-285°C.

Example 4

N-Methyl-N'-[4-(imidazol-4-yl)-phenyl]-formamidine (Compound 5)

To a solution of N-methylformamide (2.36 g) in anhydrous diethyl ether (10 ml) was slowly added at 0°C a solution of benzoyl chloride (5.62 g) in anhydrous diethyl ether (30 ml). After one hour stirring, the white solid which formed was filtered and immediately added to a suspension of 4-(4-aminophenyl)-1-H-imidazole (1.59 g) in dioxan (50 ml). The mixture was stirred overnight and then evaporated to dryness. The residue was taken up in water and the solution was basified to pH 10 with 10% NaOH and the product which separated was extracted with ethylacetate. The organic solution was dried ($MgSO_4$) and evaporated to dryness to give 0.75 g of the crude amidine which was recrystallized from acetone.

M.p. 189-190°C.

Analysis:

$C_{11}H_{12}N_4$	found %	C 65.55;	H 5.92;	N 27.56.
	calc. %	C 65.98;	H 6.04;	N 27.98.

Fumarate salt. M.p. 188-189°C.

Example 5

N-Methyl-N'-[4-(imidazol)-4-yl)-phenyl]-formamidine (Compound 5)

To a solution of N-methyl formamide (1.48 g) in 15 ml of dichloromethane, was slowly added at 0°C a solution of 4.78 g of triethyloxonium fluoroborate [H. Meerwein, Org. Synth. 46, 113 (1966)] in dichloromethane (25 ml). After six hr. stirring at room temperature, 4-(4-aminophenyl)-1-H-imidazole (2 g) in ethanol (10 ml) was added dropwise. The mixture was stirred overnight, and then evaporated to dryness. The fluoroborate salt of N-methyl-N'-[4(imidazol-4-yl)-phenyl]-formamidine was dissolved in water and the solution was basified to pH 10 with 10% NaOH. The product which crystallized off was collected by filtration to give 1.4 g of the title formamidine. M.p. 189-190°C.

The following compounds were prepared in a similar manner, starting from the appropriate imidazolylphenylamine and from the suitable N-substituted formamide:

N-tert-Butyl-N'-[4-(imidazol-4-yl)-phenyl]-formamidine (Compound 21)

Fumarate salt. M.p. 192-194°C (Ethanol).

Analysis:

$C_{22}H_{26}N_4O_8$	found %	C 55.94;	H 5.67;	N 11.68.
	calc. %	C 55.69;	H 5.52;	N 11.81.

N-Menthyl-N'-[4-(imidazol-4-yl)-phenyl]-formamidine (Compound 38)

Tartrate salt. M.p. 106-109° C.

Analysis:

$C_{28}H_{40}N_4O_{12}$	found %	C 53.99;	H 6.48;	N.8.94.
	calc. %	C 53.84;	H 6.45;	N 8.97.

Example 6

(a) N-Methyl-N'-[4-(imidazol-4-yl)-phenyl]-formamidine (Compound 5)

A suspension of 4-(4-aminophenyl)-1-H-imidazole (0.8 g) and ethyl N-methyl-formimidate hydrochloride (1.86 g) [F.H. Suydam, et al., J. Org. Chem. 34,292 (1969)] in

20 ml of anhydrous ethanol was stirred at room temperature for two days. The clear solution was evaporated to dryness, and the oily residue was dissolved in water. The solution so obtained was basified to pH 10 with 10% NaOH. Tbe product which separated was extracted with ethyl acetate, the organic solution was evaporated to dryness and the product obtained was purified through its hydrochloride salt to give 0.35 g of the title compound as a crystalline solid.M.p. 280-282°C. (ethanol).

Analysis:

$C_{11}H_{14}Cl_2N_4$	found %	C 47.98;	H 5.26;	Cl 25.78;	N.20.2
	calc. %	C 48.36;	H 5.17;	Cl 25.96;	N 20.5

(b) N-Phenyl-N'-[4-(imidazol-4-yl)-phenyl]-formamidine (Compound 30)

5 g of 4-(4-aminophenyl)-1-H-imidazole were added to a solution of ethyl N-phenyl-formimidate [Org. Synth., 35, 65 (1955)](4.6 g) in acetone (25 ml). After stirring for 4 hours at room temperature the solid which separated was filtered and dried under vacuum. The product was treated with acetone and acidified with glacial acetic acid. N-Phenyl-N'-[4-(imidazol-4-yl)]-formamidine crystallized as its acetate salt which was filtered to give 4.6 g of the title product. M.p. 123-124°C.

Analysis:

$C_{20}H_{22}N_4O_4$	found %	C 62.58;	H 5.72;	N 14.69.
	calc. %	C 62.81;	H 5.80;	N 14.65.

The following compounds were prepared in a similar manner, starting from the appropriate imidazolphenylamine and from the suitable ethyl formimidates:

N-3,4-Methylenedioxyphenyl-N'-[4-(imidazol-4-yl)-phenyl]-formamidine (Compound 39)

Fumarate salt. M.p. 140-141°C.

Analysis:

$C_{25}H_{22}N_4O_{10}$	found %	C 55.48;	H 4.15;	N 10.50.
	calc. %	C 55.76;	H 4.12;	N 10.41.

N-4-Chlorophenyl-N'-[4-(imidazol-4-yl)-phenyl]-formamidine (Compound 41)

Acetate salt. M.p. 78-79°C.

Analysis:

$C_{20}H_{21}ClN_4O_4$	found %	C 57.73; H 5.12; Cl 8.63; N 13.36.
	calc. %	C 57.62; H 5.08; Cl 8.50; N 13.44.

N-4-Tolyl-N'-[4-(imidazol-4-yl)-phenyl]-formamidine (Compound 42) Acetate salt. M.p. 91-92°C.

Analysis:

$C_{21}H_{24}N_4O_4$	found %	C 62.98; H 6.13; N 14.08.
	calc. %	C 63.62; H 6.10; N 14.13.

N-4-Anisyl-N'-[4-(imidazol-4-yl)-phenyl]-formamidine (Compound 43)

Fumarate salt. M.p. 131-132° C.

Analysis:

$C_{25}H_{24}N_4O_9$	found %	C 57.01; H 4.64; N 10.71
	calc. %	C 57.25; H 4.61; N 10.68.

N-(3,4-Dimethylisoxazol-5-yl)-N'-[4-(imidazol-4-yl)-phenyl]-formamidine (Compound 44)

M.p. 204-205°C.

Analysis:

$C_{15}H_{15}N_5O$	found %	C 63.91; H 5.40; N 24.85.
	calc. %	C 64.04; H 5.37; N 24.90.

Example 7

(a) N-Cyano-N'-[4-(imidazol-4-yl)-phenyl]-formamidine (Compound 6)

A solution of 4-(4-aminophenyl)-1-H-imidazole (25.3 g) and ethyl N-cyano formimidate (18.7 g) [K.R. Huffman et al., J. Org. Chem. 28, 1816, (1963)] in ethanol was stirred at room temperature overnight. The product which crystallized at the end of the reaction was collected by filtration, washed with cold ethanol to give 30.7 g of the title compound. M.p. 234-235° C.

Analysis:

$C_{11}H_{19}N_5$	found %	C 61.94% H 4.36; N 32.95.
	calc. %	C 62.55% H 4.30; N 33.16.

The following compounds were prepared in a similar manner starting from the appropriate imidazolyl phenyl amine.

N-Cyano-N'-[3-(imidazol-4-yl)-phenyl]-formamidine (Compound 7)

M.p. 206-207°C.

Analysis:

$C_{11}H_9N_5$	found %	C 62.60;	H 4.22;	N 32.84.
	calc. %	C 62.55;	H 4.30;	N 33.16.

N-Cyano-N'-[4-(5-methylimidazol-4-yl)-phenyl]-formamidine

M.p. 236-238°C.

Analysis:

$C_{12}H_{11}N_5$	found %	C 63.44;	H 5.04;	N 30.94.
	calc. %	C 63.98;	H 4.92;	N 31.09.

N-Cyano-N'-[3-(5-methylimidazol-4-yl)-phenyl]-formamidine

M.p. 221-223° C.

Analysis:

$C_{12}H_{11}N_5$	found %	C 63.96;	H 5.06;	N 30.82.
	calc. :	C 63.98;	H 4.92;	N 31.09.

(a') N-Cyano-N'-[4-(imidazol-4-yl)-phenyl]-formamidine. (Compound 6)

A mixture of 4-(p-aminophenyl)-1-H-imidazole (113.8 g), ethyl orthoformate (132.4 g) and cyanamide (30.7 g) was heated at 100°C for 20 minutes and stirred at room temperature for 3 hours. The solid was filtered and dried to give 130 g of the title compound. Mp. 236-238°C.

(b) N-Methyl-N'-[4-(imidazol-4-yl)-phenyl]-formamidine (Compound 5)

N-Cyano-N'-[4-(imidazol-4-yl)-phenyl]-formamidine (20 g) was added in one portion to 35% methylamine in water (70 ml). After few minutes, the solid N-methyl-N'-[4-(imidazol-4-yl)-phenyl]-formamidine separated out of the solution. This solid was filtered, washed with water and dried to give 13.45 g of the title product, which was recrystallized from acetone. M.p. 189-190°C.

Fumarate salt. M.p. 188°-189°C.

The following compounds were prepared in a similar manner, starting from the appropriate N-cyano formamidine derivatives.

N-Methyl-N'-[3-(imidazol-4-yl)-phenyl]-formamidine (Compound 8)

Maleate salt. M.p. 149-150° C. (ethanol).

Analysis:

$C_{19}H_{20}N_4O_8$	found %	C 51.93;	H 4.73;	N 13.15.
	calc. %	C 52.78;	H 4.66;	N 12.96.

N-Methyl-N'-[3-(5-methylimidazol-4-yl)-phenyl]-formamidine (Compound 9)

M.p. 180-181° C.

Analysis

$C_{12}H_{14}N_4$	found %	C 67.40;	H 6.67;	N 26.40
	calc. %	C 67.26;	H 6.59;	N 26.15.

N-Methyl-N'-[4-(5-methylimidazol-4-yl)-phenyl]-formamidine (Compound 10)

M.p. 225-226° C.

Analysis

$C_{12}H_{14}N_4$	found %	C 66.81;	H 6.70;	N 25.82.
	calc. %	C 67.26;	H 6.59;	N 26.15.

N-Ethyl-N'-[4-(imidazol-4-yl)-phenyl]-formamidine (Compound 11)

Hydrochloride salt. M.p. 253-254° C.

Analysis:

$C_{12}H_{16}Cl_2N_4$	found %	C 49.92;	H 5.70;	Cl 25.00;	N 19.56.
	calc. %	C 50.18;	H 5.61;	Cl 24.69;	N 19.51.

N-Butyl-N'-[4-(imidazol-4-yl)-phenyl]-formamidine (Compound 12)

Hydrochloride salt. M.p. 206-208° C.

Analysis:

$C_{14}H_{20}Cl_2N_4$	found %	C 53.48;	H 6.51;	Cl 22.63;	N 17.59.
	calc. %	C 53.34;	H 6.39;	Cl 22.49;	N 17.77.

N-Isopropyl-N'-[4-(imidazol-4-yl)-phenyl]-formamidine (Compound 13)

Fumarate salt. M.p. 130-133°C.

Analysis:

$C_{21}H_{24}N_4O_8$	found %	C 53.91;	H 5.30;	N 12.36.
	calc. %	C 54.78;	H 5.25;	N 12.17.

N-Allyl-N'-[4-(imidazol-4-yl)-phenyl]-formamidine (Compound 14) Maleate salt. M.p. 153-154°C

Analysis:

$C_{21}H_{22}N_4O_8$ found % C 54.85; H 4.71; N 11.93.
calc % C 55.02; H 4.84; N 12.22.

N-Hydroxy-N'-[4-(imidazol-4-yl)-phenyl]-formamidine (Compound 15)

Hydrochloride salt. M.p. 207-208°C.

Analysis:

$C_{10}H_{12}Cl_2N_4O$ found % C 43.70; H 4.34; Cl 25.48; N 20.45
calc. % C 43.65; H 4.39; Cl 25.76; N 20.36.

N-n-Propyl-N'-[4-(imidazol-4-yl)-phenyl]-formamidine (Compound 18)

Hydrochloride salt. M.p. 220-221°C. (Ethanol).

Analysis

$C_{13}H_{18}Cl_2N_2$ found % C 51.13; H 6.10; Cl 23.30; N 18.51.
calc. % C 51.83; H 6.02; Cl 23.54; N 18.60.

N-sec Butyl-N'-[4-(imidazol-4-yl)-phenyl]-formamidine (Compound 19)

Hydrochloride salt. M.p. 196-197°C. (Ethanol).

Analysis

$C_{14}H_{20}Cl_2N_4$ found % C 52.97; H 6.51; Cl 22.08; N 17.44.
calc. % C 53.33; H 6.39; Cl 22.49; N 17.77.

N-Isobutyl-N'-[4-(imidazol-4-yl)-phenyl]-formamidine (Compound 20)

Hydrochloride salt. M.p. 238-240°C. (Ethanol)

Analysis:

$C_{14}H_{20}Cl_2N_4$ found % C 52.69; H 6.54; Cl 22.04; N 17.38.
calc % C 53.33; H 6.39; Cl 22.49; N 17.77

N-(1-Methyl)n.hexyl-N'-[4-(imidazol-4-yl)-phenyl]-formamidine (Compound 22) Maleate salt. M.p. 150-151°C. (Acetone)

Analysis

$C_{25}H_{32}N_4O_8$	found %	C 59.09; H 6.08; N 10.63.
	calc %	C 58.13; H 6.24; N 10.85.

N-Prenyl-N'-[4-(imidazol-4-yl)-phenyl]-formamidine (Compound 23). Fumarate salt. M.p. 174-175°C. (Ethanol).

Analysis

$C_{23}H_{26}N_4O_8$	found %	C 56.94; H 5.48; N 11.67.
	calc. %	C 56.78; H 5.39; N 11.52.

N-Propargyl-N'-[4-(imidazol-4-yl)-phenyl]-formamidine (Compound 24)

Methanesulfonate salt. M.p. 184-185°C. (Ethanol).

Analysis.

$C_{15}H_{20}N_4O_6S_2$	found %	C 42.75; H 4.93; N 13.20; S 15.29.
	calc. %	C 43.26; H 4.84; N 13.45; S 15.39.

N-n Hexyl-N'-[4-(imidazol-4-yl)-phenyl]-formamidine (Compound 25)

Hydrochloride salt M.p. >270°C. (Ethanol).

Analysis

$C_{16}H_{24}Cl_2N_4$	found %	C 55.35; H 7.00; Cl 20.39; N 16.00.
	calc. %	C 55.97; H 7.05; Cl 20.66; N 16.32.

N-Cyclopropylmethyl-N'-[4-(imidazol-4-yl)-phenyl]-formamidine (Compound 26)

Fumarate salt. M.p. 127-128°C.

Analysis

$C_{22}H_{24}N_4O_8$	found %	C 56.21; H 5.09; N 11.99.
	calc. %	C 55.93; H 5.12; N 11.86.

N-Bicyclo-[2,2,1]-Hept-2-yl-N'[4-(imidazol-4-yl)-phenyl]-formamidine (Compound 27) Maleate salt. M.p. 182-183°C.

Analysis

$C_{25}H_{28}N_4O_8$	found %	C 57.90; H 5.43; N 10.94.
	calc. %	C 58.58; H 5.51; N 10.93.

N-Furfuryl-N'-[4-(imidazol-4-yl)-phenyl]-formamidine (Compound 28)

Hydrochloride salt. M.p. 215-217°C (Ethanol).

Analysis:

$C_{15}H_{16}Cl_2N_4O$	found %	C 52.80; H 4.87; Cl 20.62; N 16.27.
	calc. %	C 53.11; H 4.75; Cl 20.90; N 16.52.

N-Cyclohexyl-N'-[4-(imidazol-4-yl)-phenyl]-formamidine (Compound 29)

Fumarate salt. M.p. 139-141°C. (Ethanol).

Analysis

$C_{24}H_{28}N_4O_8$	found %	C 57.89; H 5.68; N 10.99.
	calc. %	C 57.59; H 5.64. N 11.20.

N-Benzyl-N'-[4-(imidazol-4-yl)-phenyl]-formamidine (Compound 31)

Hydrochloride salt. M.p. 210-212°C. (Ethanol)

Analysis

$C_{17}H_{18}Cl_2N_4$	found %	C 57.91; H 5.29; Cl 19.94; N 15.87.
	calc. %	C 58.46; H 5.19; Cl 20.30; N 16.04.

N-Cyclopropyl-N'-[4-(imidazol-4-yl)-phenyl]-formamidine (Compound 32)

Fumarate salt. M.p. 185-186°C. (Ethanol).

Analysis

$C_{21}H_{22}N_4O_8$	found %	C 55.09; H 4.74; N 12.48.
	calc. %	C 55.02; H 4.84; N 12.22.

N-(α-Methylpropargyl)-N'-[4-(imidazol-4-yl)-phenyl]-formamidine (Compound 33)

Maleate salt. M.p. 188°C.

Analysis

$C_{22}H_{22}N_4O_8$ found % C 56.28; H 4.15; N 11.87.
calc. % C 56.16; H 4.17; N 11.91.

N-(α-Methylallyl)-N'-[4-(imidazol-4-yl)-phenyl]-formamidine (Compound 34) Maleate salt. M.p. 186°C.

Analysis

$C_{22}H_{24}N_4O_8$ found % C. 55.87; H 5.04; N 11 76.
calc. % C 55.93; H 5.12; N 11.86.

N-n.Octyl-N'-[4-(imidazol-4-yl)-phenyl]-formamidine (Compound 35) Fumarate salt. M.p. 152-153°C.

Analysis

$C_{26}H_{34}N_4O_8$ found % C 58.52; H 6.35; N 10.72.
calc. % C 58.85; H 6.46; N 10.56.

N-Neopentyl-N'-[4-(imidazol-4-yl)-phenyl]-formamidine (Compound 36) Fumarate salt. M.p. 251-252°C.

Analysis

$C_{23}H_{28}N_4O_8$ found % C 56.67; H 5.81; N 11.40.
calc. % C 56.55; H 5.78; N 11.47.

N-(2,2-Dimethyl-cyclopropylmethyl)-N'-[4-(imidazol-4-yl)-phenyl]-formamidine (Compound 37)

Hydrochloride salt. M.p. 246-248°C.

Analysis

$C_{16}H_{22}Cl_2N_4$ found % C 55.90; H 6.53; Cl 20.88; N 16.30.
calc. % C 56.30; H 6.50; Cl 20.78; N 16.42.

N-Cyclohexylmethyl-N'-[4-(imidazol-4-yl)-phenyl)-formamidine (Compound 40) Fumarate salt. M.p. 154-155°C.

Analysis

$C_{25}H_{30}N_4O_8$ found % C.57.79; H 5.91; N 10.75.
calc. % C 58.36; H 5.88; N 10.89.

Example 8

N,N-Dimethyl-N'-[4-(imidazol-4-yl)-phenyl]-formamidine (Compound 16)

A solution of 4-(4-aminophenyl)-1-H-imidazole (3.18 g) in N,N-dimethyl-formamide diethylacetal (8.82 g) was stirred at room temperature for two days. Addition of diethyl ether afforded precipitation of the formamidine (Compound 16) which was collected by filtration (3.9 g) M.p. 141-142°C.

Analysis

$C_{12}H_{14}N_4$ found % C 67.02; H 6.50; N 26.28.
calc. % C 67.26; H 6.59; N 26.15.

N,N-Dimethyl-N'-[4-(5-methylimidazol-4-yl)-phenyl]-formamidine (Compound 17) was prepared in a similar manner starting from 5-Methyl-4-(4-aminophenyl)-1-H-imidazole. M.p. 228-229°C.

Analysis

$C_{13}H_{16}N_4$ found % C 69.08; H 7.16; N 24.28.
calc. % C 68.39; H 7.06; N 24.54.

Example 9

N-Methyl-N'[4-(imidazol-4-yl)-phenyl]-formamidine (Compound 5

A mixture of 4-(4-aminophenyl)-1-H-imidazole (1.59 g) and triethyl orthoformate (2.22 g) was heated for 30 min. at 100°C in the presence of catalytic amounts of 96% H_2SO_4. A solution of methylamine 33% in ethanol (9.5 g) was then added dropwise to the cooled reaction mixture. The solution was stirred at room temperature for twenty hours and then evaporated to dryness. The residue obtained was dissolved in 10% hydrochloric acid and the acid solution was washed with ethyl acetate and then basified to pH10 with 10% NaOH. The

product which separated was extracted with ethyl acetate to give, after evaporation of the solvent, 0.45 g of the compound 5.
M.p. 188-189°C.

Example 10

(a) N-Methyl-N'-[4-(imidazol-4-yl)-phenyl]-thiourea

A solution of 4-(4-aminophenyl)-1-H-imidazole (2.3g) and methyl isothiocyanate (1.15 g) in 30 ml of ethanol was refluxed for 0.5 hour and evaporated to dryness. The oily base so obtained was purified by conversion into the corresponding hydrochloride salt by bubbling hydrogen chloride through it, in isopropanol. The desired thiourea was obtained as a white solid (2 g) M.p. 210-211°C.
Analysis:

$C_{11}H_{13}ClN_4S$ found % C 49.23; H 4.98; Cl 13.20; N 20.64; S 11.72.
calc. % C 49.15; H 4.87; Cl 13.19; N 20.84; S 11.92.

(b) N-Methyl-N'-[4-(imidazol-4-yl)-phenyl]-formamidine sulfinic acid

Hydrogen peroxide (31%, 1.08 g) was added dropwise in 30 min. to a stirred, ice-cooled solution of N-methyl-N'-[4-(imidazol-4-yl)-phenyl] thiourea (1.16 g) in 5 ml of methanol. After two hr. stirring the mixture was evaporated to dryness and the residue so obtained was crystallized from ethanol to afford 0.95 g of the desired compound.
Analysis:

$C_{11}H_{12}N_4O_2S$ found % C 50.17; H 4.55; N 21.41; S 12.04.
calc. % C 49.98; H 4.57; N 21.20; S 12.12.

Acetate salt. M.p. 194-195°C (acetone).

(c) N-Methyl-N'-[4-(imidazol-4-yl)-phenyl]-formamidine (Compound 5)

N-Methyl-N'-[4-(imidazol-4-yl)-phenyl]-formamidine sulfinic acid (0.9 g) was dissolved in 15 ml of glacial acetic acid and refluxed for one hr. The concentrated solution was basified to pH 10 with 10% NaOH and extracted with ethyl acetate. The organic solution

was evaporated to dryness to afford 0.3 g of N-methyl-N'-[4-(imidazol-4-yl)-phenyl]-formamidine. M.p. 187-189°C.

Example 11

N-t. Butyl-N'-[4-(imidazol-4-yl)-phenyl]-formamidine (Compound 21)

A mixture of 4-(p-aminophenyl)-1-H-imidazole (2.3 g), t-butylisonitrile (1.25 g), AgCl (0.2 g) and imidazole (0.11g) was heated at 100°C for 13 hours. The thick reaction mixture was treated with 10% HCl and ethyl acetate. The acid solution was taken to pH 6.5 with 10% NaOH, treated with charcoal, filtered and completely basified. The layer which separated was extracted with ethyl acetate. After drying, the organic solution was evaporated to give 0.38 g of the title compound. Fumarate salt.
M.p. 192-194°C.

Example 12

N-Cyclohexyl-N'-[4-(imidazol-4-yl)-phenyl]-formamidine (Compound 29)

A mixture of 4-(p-aminophenyl)-1-H-imidazole (1.59 g) cyclohexyl isonitrile (1.2 g) and CuCl (0.99 g) was heated at 150°C for 3 hours. The thick reaction mixture was extracted into methanol. The methanol solution after treated with charcoal was evaporated to dryness and extracted into ethyl acetate and 10% hydrochloric acid. The acid solution was basified to pH 7.5 with 17% Na_2CO_3 and extracted into ethyl acetate. The organic solution was evaporated to dryness. The residue, after recrystallization from acetone gave 0.25 g of the title product. M.p. 220-221°C.
Fumarate salt. M.p. 139-141°C.

(41)

Example 13

Tablets. One tablet contains:

-active ingredient	50 mg
-lactose	217 mg
-corn starch	30 mg
-magnesium stearate	3 mg

Example 14

Capsules. One capsule contains

- active ingredient	50 mg
- corn starch	170 mg
- magnesium stearate	2 mg

Example 15

Vials. One vial contains

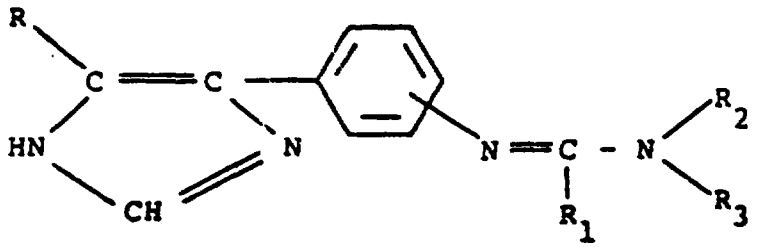
- active ingredient	50 mg
- water for injection q.s.	5 ml

* C L M S *

(42)

CLAIMS

1. Compounds of general formula I



(I)

[wherein R, R_1 and R_3, which may be the same or different, each represents a hydrogen atom or a C_{1-3} alkyl group, and R_2 represents a linear or branched alkyl, alkenyl or alkynyl group, a cyano group, a hydroxyl group, a substituted or unsubstitued cycloalkyl or cycloaliphatic alkyl group, a bicyclic cycloaliphatic group, an aralkyl or aryl group (optionally substitued by a halogen atom or by methyl, methoxy or methylenedioxy groups), or a substituted or unsubstituted heterocyclic group or an alkyl group substituted by a substituted or unsubstituted heterocyclic group, said heterocyclic groups optionally also containing a further heteroatom], tautomers thereof and acid addition salts of the aforesaid compounds.

2. Physiologically compatible acid addition salts of compounds of formula I as defined in claim 1.

3. Salts as claimed in claim 2 formed with hydrochloric, fumaric, methanesulfonic or maleic acid.

4. Compounds as claimed in any one of the preceding claims wherein R, R_1 and R_3 each represents a hydrogen atom.

5. Compounds as claimed in any one of the preceding claims wherein the amidine radical is in the para position of the benzene ring.

6. Compounds as claimed in any one of the preceeding claims wherein R_2 represents a hydroxyl, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, neopentyl, hexyl, heptyl, octyl, allyl, α-methylallyl, prenyl (i.e. 3-methylbut-2-enyl), propargyl, α-methylpropargyl, cyano, norbornyl, benzyl, cyclopropyl, cyclopropylmethyl, dimethylcyclopropylmethyl,

menthyl, cyclohexyl, cyclohexylmethyl, phenyl, p-chlorophenyl, p-methylphenyl, p-methoxyphenyl, methylene-dioxyphenyl or 2-furylmethyl group.

7. N-Ethyl-N'-[4-(imidazol-4-yl)-phenyl]-formamidine.

8. N-Isopropyl-N'-[4-(imidazol-4-yl)-phenyl]-formamidine.

9. N-Allyl-N'-[4-(imidazol-4-yl)-phenyl]-formamidine.

10. N-n-Propyl-N'-[4-(imidazol-4-yl)phenyl]-formamidine.

11. N-sec.Butyl-N'-[4-(imidazol-4-yl)phenyl]-formamidine.

12. N-Isobutyl-N'-[4-(imidazol-4-yl)phenyl]-formamidine,

13. N-Prenyl-N'-[4-(imidazol-4-yl)-phenyl]-formamidine.

14. N-Cyclopropylmethyl-N'-[4-(imidazol-4-yl)-phenyl]-formamidine.

15. N-Cyclopropyl-N'-[4-(imidazol-4-yl)-phenyl]-formamidine.

16. N-(α-Methylallyl)-N'-[4-(imidazol-4-yl)-phenyl]-formamidine.

17. N-Neopentyl-N'-[4-(imidazol-4-yl)-phenyl]-formamidine.

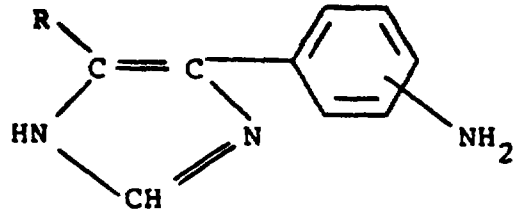
18. N-(2,2-Dimethyl-cyclopropylmethyl)-N'-[4-(imidazol-4-yl)-phenyl]-formamidine.

19. Physiologically compatible acid addition salts of compounds as claimed in claim 7 to 18.

20. Compounds as claimed in claim 1 other than those claimed in claims 7 to 18, as herein specifically described in any one of the Examples.

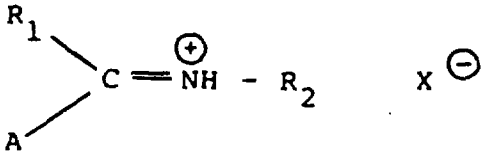
21. Hydrochloric, fumaric, methanesulfonic or maleic acid addition salts of compounds as claimed in claims 7 to 18.

22. A process for the preparation of compounds as claimed in claim 1 which comprises reacting a compound of formula II



(II)

(wherein R is as defined in claim 1) with a compound of formula III



(III)

in which R_1 and R_2 are as defined in claim 1, $X^{\ominus}$ represents the anion of an inorganic acid and A represents a benzyloxy group, a C_{1-3} alkoxy group or a chlorine atom.

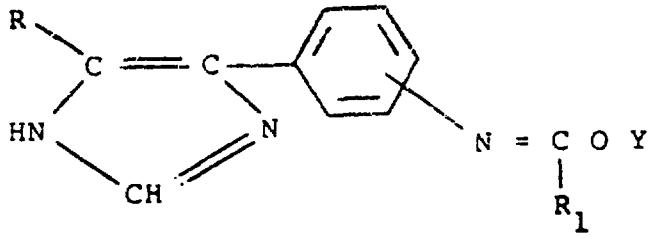
23. A modification of the process as claimed in claim 22 in which a compound of formula III as defined in claim 22 is reacted in the form of a base.

24. A process as claimed in claim 22 or claim 23 in which the reaction is carried out in the presence of an inert organic solvent.

25. A process as claimed in claim 24 in which the inert organic solvent comprises ethanol, dioxan or acetone.

26. A process as claimed in any one of claims 22 to 25 in which the reaction is carried out at a temperature of from 20 to 60° C.

27. A process for the preparation of compounds as claimed in claim 1, which comprises reacting a compound of formula V



(V)

(wherein R and R_1 are as defined in claim 1 and Y represents a C_{1-3} alkyl group) with an amine of formula VI

$$H_2N - R_2 \qquad (VI)$$

where R_2 is as defined in claim 1.

28. A process as claimed in claim 27 in which the reaction is carried out in an inert organic solvent.

29. A process as claimed in claim 28 in which the inert organic solvent is ethanol.

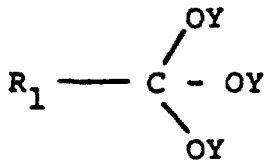
30. A process as claimed in any one of claims 27 to 29 in which the reaction temperature is from 20 to 80°C.

31. A process as claimed in claim 27 in which the

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compound of formula V is prepared in situ by reacting an amine of formula II as defined in claim 22 with a compound of formula VII



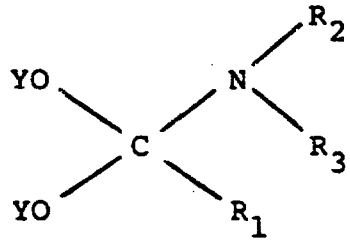
(VII)

(where R_1 and Y are as defined in claim 1 and claim 27 respectively) in the presence of a catalyst and is further reacted, without isolation, with an amine of formula VI as defined in claim 27.

32. A process as claimed in claim 31 in which the catalyst is sulfuric acid.

33. A process as claimed in claim 31 or claim 32 in which the reaction is carried out at a temperature of from 60° to 120° C.

34. A process for the preparation of compounds as claimed in claim 1 which comprises reacting a compound of formula VIII

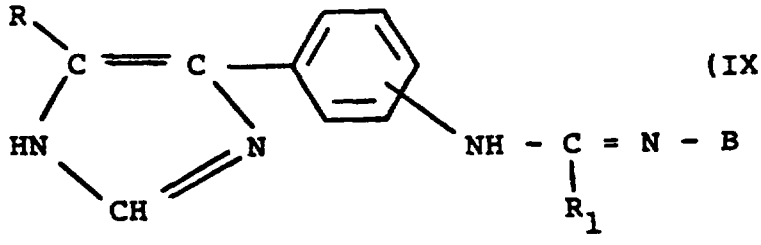


(VIII)

(wherein R_1, R_2 and R_3 are as defined in claim 1 and Y is as defined in claim 27) with an amine of formula II as defined in claim 22.

35. A process as claimed in claim 34 in which the reaction is carried out at a temperature of from 20 to 80° C.

36. A process for the preparation of compounds as claimed in claim 1 which comprises reacting a compound of formula IX



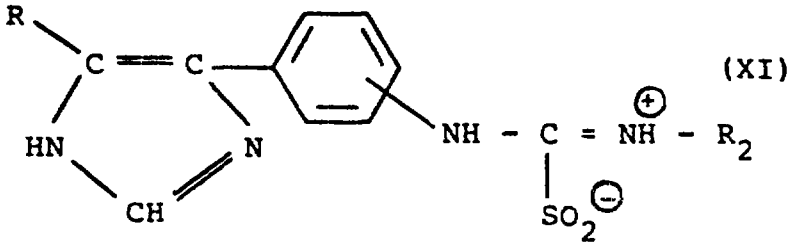
(IX)

(wherein R and R_1 are as defined in claim 1 and B represents a cyano, acetyl, carbethoxy or carbamyl group) with an amine of formula VI as defined in claim 27.

37. A process as claimed in claim 36 in which the reaction is carried out in the presence of water.

38. A process as claimed in claim 36 or claim 37 in which the reaction is effected at room temperature.

39. A process for the preparation of compounds of general formula I as claimed in claim 1 which comprises reacting a compound of formula XI

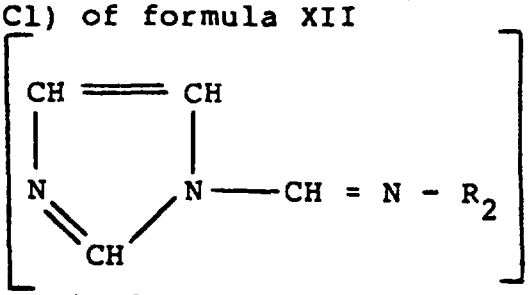


(XI)

(wherein R and R_2 are as defined in claim 1) with a weak organic acid.

40. A process as claimed in claim 39 in which the said weak organic acid is formic, acetic or propionic acid.

41. A process for the preparation of compounds as claimed in claim 1, wherein R_1 and R_3 both represent hydrogen atoms, which comprises reacting a compound, not isolated, (obtained in situ by reaction of an isonitrile of formula $C\equiv N - R_2$ and imidazole in the presence of AgCl) of formula XII



(XII)

(wherein R_2 is as defined in claim 1) with an amine of formula II, as defined in claim 22.

42. A modification of the process as claimed in claim 41, in which an amine of formula II, as defined in claim 22, is directly reacted with an isonitrile of formula $C\equiv N - R_2$, wherein R_2 is as defined in claim 1, in the presence of CuCl.

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43. A process as claimed in claim 41 or claim 42 in which the reaction is carried out without solvent or in the presence of an inert organic solvent.

44. A process as claimed in claim 43, in which the inert organic solvent comprises ethanol or dioxan.

45. A process as claimed in any one of claims 41 to 44 in which the reaction temperature is between 100-150° C.

46. A process as claimed in any one of claims 22 to 45 wherein a compound of formula I initially obtained is subsequently converted into an acid addition salt thereof or an acid addition salt of a compound of formula I initially obtained is subsequently converted into a compound of formula I,

47. A process for the preparation of compounds as claimed in claim 1 substantially as herein described in any one of Examples 1 to 12.

48. Compounds as claimed in claim 1 whenever prepared by a process as claimed in any one of claims 22-47.

49. Pharmaceutical compositions comprising as active ingredient at least one compound of formula I as defined in claim 1 or a tautomer or physiologically compatible acid addition salt thereof, in association with a pharmaceutical carrier or excipient.

50. Compositions as claimed in claim 49 in a form suitable for oral or parenteral administration.

51. Compositions as claimed in claim 49 or claim 50 in the form of plain tablets, coated tablets, capsules or vials.

52. Compositions as claimed in any one of claims 49 to 51 in the form of dosage units.

53. Compositions as claimed in claim 52 wherein each dosage unit contains from 10 to 500 mg of active ingredient.

54. Compositions as claimed in claim 53 wherein each dosage unit contains from 20 to 150 mg of active ingredient.

55. Pharmaceutical compositions as claimed in claim 49 substantially as herein described.

56. Pharmaceutical compositions substantially as herein described in any one of examples 13-15.

57. Compounds of general formula I as claimed in claim 1 or tautomers thereof, or physiologically compatible acid addition salts thereof for use in a method of treatment of patients suffering from ulcers and/or disorders of the gastro-intestinal tract.

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