

PATENT SPECIFICATION

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COMPLETE SPECIFICATION

Novel 1-Amidino-3-Phenyl-Urea Derivatives, the preparation thereof and Compositions containing the same

We, THE WELLCOME FOUNDATION LIMITED, of 183—193 Euston Road, London, N.W.1, a company incorporated in England 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:—

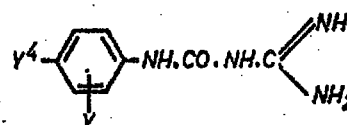
During the last 40 years, a number of safe and highly effective synthetic chemicals have been developed for use against malaria infections in humans. These chemicals include chloroquine [7 - chloro - 4 - (4 - diethylamino - 1 - methylbutylamino)quinoline], proguanil [1 - (p - chlorophenyl) - 5 - isopropylbiguanide], primaquine [8 - (4 - amino - 1 - methylbutylamino) - 6 - methoxyquinoline], and pyrimethamine [2,4 - diamino - 5 - (p - chlorophenyl) - 6 - ethylpyrimidine]. All are currently used for treating various forms of infection, but no single synthetic antimalarial drug is ideal for treatment and prophylaxis of all malaria infections. Resistance to these drugs by malaria parasites has now been reported from various parts of the world, and this has stimulated research into new types of antimalarial drugs to add to the armoury of the physician.

1 - (N - Alkylamidino) - 3 - phenylureas are a class of synthetic chemicals which were investigated in the late 1940's for antimalarial activity, and were found not worthy of further investigation. (Curd, F. H. S. *et al*, *J. Chem. Soc.*, 1949, 1732). Further 1 - amidino - 3 - phenylureas were investigated in 1960 by Urbanski, who indicated that of a large class of 1 - amidino - 3 - (monosubstituted - phenyl)ureas the highest activity against the

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malaria parasite *Plasmodium gallinaceum* in chicks was obtained with 1 - amidino - 3 - (4 - nitrophenyl)urea. [Skowronska-Serafin, B & Urbanski, T., *Tetrahedron*, 10, 12—25 (1906)].

It has now been found that amidinoureas of formula (I) also have activity against various malaria parasites in screening tests carried out with standard infections in laboratory animals.



(I)

In formula (I)

Y⁴ is a halogen when Y is a trihalomethyl, nitrile or nitro substituent at the 3- position or a halogen substituent at the 3- position or at both the 3- and 6- positions; or

Y⁴ is trihalomethyl or nitrile when Y is hydrogen or is a halogen or an alkyl substituent having 1 to 4 carbon atoms at the 2- or 3- position; or

Y⁴ is nitro when Y is a trihalomethyl or halogen substituent at the 3- position.

The positions are numbered with respect to the —NH.CO.NH.C(:NH).NH₂ group.

The preferred halogen atoms are chlorine, bromine and fluorine, but especially chlorine, and the preferred trihalomethyl group is trifluoromethyl. The preferred alkyl group is methyl.

The amidinoureas of formula (I) and their acid addition salts are active against *P. galinaceum* in chicks, and *P. vinckei* and *P.*

berghei in mice. Several have also been shown to be active against strains of *P. gallinaceum* resistant to pyrimethamine or a dihydrotriazine, and a strain of *P. berghei* resistant to chloroquine. The compounds of formula (I) are also more active against *P. gallinaceum*, and in many instances are also more active against *P. vinckei*, than the known 1-amidino-3-(4-nitrophenyl)urea, as is shown in the experimental results quoted below. Among the more active compounds of formula (I) against *P. vinckei* are those wherein Y⁴ is nitrile or trifluoromethyl when Y is hydrogen or is a halogen substituent in the 2- or 3- position; or wherein Y⁴ is a halogen when Y is a nitrile, nitro, halogen or trifluoromethyl substituent in the 3- position. These include

- 1 - Amidino - 3 - (4 - chloro - 3 - trifluoromethylphenyl)urea,
- 1 - Amidino - 3 - (2 - chloro - 4 - cyanophenyl)urea,
- 1 - Amidino - 3 - (3 - chloro - 4 - cyanophenyl)urea,
- 1 - Amidino - 3 - (3,4 - dichlorophenyl)urea,
- 1 - Amidino - 3 - (4 - chloro - 3 - cyanophenyl)urea,
- 1 - Amidino - 3 - (4 - trifluoromethylphenyl)urea

and acid addition salts thereof. Some of the compounds of formula (I) have also been found active against other protozoal infections.

The activities of the above compounds reside in the base, and the acid in the acid addition salts is of less importance, though it is preferably pharmacologically and pharmaceutically acceptable. For example, the acid may be hydrochloric, sulphuric, toluene-*p*-sulphonic, *p*-chlorobenzenesulphonic, maleic or tartaric acid. Ethanesulphonic and methanesulphonic acids are preferred since they provide salts having a higher solubility than most other salts.

The activity of the compounds of formula (I) against malaria parasites is illustrated by the results shown in Tables II and III, and comparative results for known amidinoureas are shown in Table I. In these Tables, the symbols have the following meanings:—

- 3+ 1% parasitaemia
- 2+ 1—30% parasitaemia
- 1+ 30—60% parasitaemia
- ± 60% parasitaemia but significantly lower than the controls
- No significant difference from the controls
- (T) Animals died

All percentages are estimated and recorded as in percentage of the untreated controls.

These results were obtained in the following manner.

P. gallinaceum

Heart blood from a chick previously infected with a normal or resistant strain of *Plasmodium gallinaceum* was introduced into a physiological solution of glucose saline containing sufficient heparin to prevent blood clotting. The volume of this mixture was adjusted to prepare an inoculum in which there were one million infected red blood cells per 0.2 ml. Chicks for test were then infected by introduction into the jugular vein of 0.2 ml. of the inoculum. The chicks were randomised, and then arranged in groups of five. They were given seven oral doses of a compound beginning on the afternoon of the day of infection, then twice a day for the following three days. On the fourth day blood smears were made from all the animals. These were stained and then examined. The parasitaemia of the test chicks was estimated and recorded as a percentage of the untreated controls. The results of these experiments using compounds of formula (I) against a normal laboratory strain of *P. gallinaceum* are shown in Table II, and it will be understood from a comparison with the results in Table I, that the compounds of formula (I) are all active against this parasite at a lower dose than the known compounds. Table III further shows that against a pyrimethamine-resistant strain and a Triazine-resistant strain (a strain resistant to 4,6 - diamino - 1 - (*p* - chlorophenyl) - 1,2 - dihydro - 2,2 - dimethyl - s - triazine) of *P. gallinaceum*, the compounds of formula (I) are also active at a lower dose than the known 4 - nitro-analogue.

P. vinckei

Heart blood from a mouse previously infected with *P. vinckei*, was introduced into physiological glucose saline containing sufficient heparin to prevent blood clotting. The volume of this mixture was adjusted to provide an inoculum containing one million parasitised red blood cells per 0.1 ml. Mice were infected with 0.1 ml. of the inoculum intraperitoneally, were randomised, and then arranged in groups of five. For the test they were given seven oral doses of a compound, beginning on the afternoon of the day of infection, then twice a day for the following three days. On the fourth day blood smears were made from all animals. These were stained and then examined. The parasitaemia of the mice was estimated and recorded as a percentage of the untreated controls.

The results of these experiments using compounds of formula (I) are shown in Table II, from which it will be understood that they have an activity greater than or equal to the known compounds cited in Table I.

Table III shows results of experiments using a chloroquine-resistant strain of *P. berghei* which were obtained in the same manner as

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those for *P. vinckei* except that the inoculum day as well as the fourth. Table III shows that compounds of formula (I) are active against this strain, and are more active than the known 4-nitro-analogue.

TABLE I

Activities of known 1-amidino-3-(monosubstituted-phenyl)ureas against *P. vinckei* in mice and *P. gallinaceum* in chicks

Prior Art Reference	Phenyl substitution	Activity against <i>P. vinckei</i> (Dose: mg./kg. $\times$ 7)				Activity against <i>P. gallinaceum</i> (Dose: mg./kg. $\times$ 7)			
		100	50	25	20	100	50	25	
Chem. Abs. 45, 1951, 10208	4-Methoxy-	1+	—						
Tetrahedron, 10, 1960, 12—25	4-Nitro-	3+	2+	+	—	3+	±	—	
Chem. Abs. 45, 1951, 10208	3-Chloro-	1+				—			
Tetrahedron, 10, 1960, 12—25	4-Chloro-	—				(T)			
Chem. Abs. 45, 1951, 10208	2-Chloro	(T)		—					

TABLE II

Activities of 1-amidino-3-(substituted-phenyl)ureas of formula (I) against *P. vinckei* in mice and *P. gallinaceum* in chicks

Example No.	Phenyl-substitution	Activity against <i>P. vinckei</i> (Dose: mg./kg. $\times$ 7)										Activity against <i>P. gallinaceum</i> (Dose: mg./kg. $\times$ 7)									
		100	50	25	20	15	12.5	10	7.5	6.15	5	100	50	30	25	15	12.5	10	6.25	7.5	2.5
7,9	4-Cyano-	3+	2+	1+	—							3+	2+	1+						±	—
2,15—19,26,28-30	3-Chloro-4-cyano-				3+			2+	1+		—					3+				2+	—
5	4-Cyano-3-methyl-	3+	—											3+		1+				—	
1	4-Chloro-2-cyano				3+	2+		1+	—							3+	2+	1+			—
8,24,25,27,31,32	3,4-Dichloro-				3+	2+	1+	—	—								3+	1+			—
4	2-Bromo-4-cyano-				3+	2+	1+	—	—												—
3	2-Chloro-4-cyano-				3+	2+	2+	±	—				3+	(T)	1+						—
6	4-cyano-2-methyl-				3+	1+	—							3+	2+						—
12	4-Trifluoromethyl-				3+	2+	1+	—								3+	1+				—
13	4-Chloro-3-nitro-				3+			—				(T)	3+								—
20	2,4,5-Trichloro-				3+	3+	2+					(T)			1+		—				—
14	4-Chloro-3-trifluoro-methyl-				3+	3+	3+					3+			3+		2+				—
23	3-Chloro-4-nitro-				3+	1+		—				3+	3+		3+		2+				—
21	4-Nitro-3-trifluoro-methyl-				3+	2+		—				(T)			2+						—
22	4-Cyano-3-fluoro-				3+	2+		—				3+			3+						—

23	5-Chloro-4-nitro-	3+	1+	—	3+	2+	—
21	4-Nitro-3-trifluoro-methyl-	3+	2+	—	(T)	2+	—
22	4-Cyano-3-fluoro-	3+	2+	—	3+	3+	—

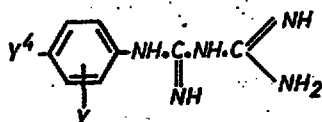
TABLE III
Activities of 1-amidino-3-(substituted-phenyl)ureas against resistant strains of *P. berghei* and *P. gallinaceum*

Compound or Phenyl substitution	Example No.	Activity against a Chloroquine-resistant strain of <i>P. berghei</i> (Dose: mg./kg. $\times$ 7)					Activity against a Pyrimethamine-resistant strain of <i>P. gallinaceum</i> (Dose: mg./kg. $\times$ 7)					Activity against a triazine*-resistant strain of <i>P. gallinaceum</i> (Dose: mg./kg. $\times$ 7)				
		100	50	25	12.5		20	10	5	20	10	5	20	10	5	
Chloroquine	—	—					/	/	/	/	/	/	/	/		
Pyrimethamine	—	/	/	/	/		$\pm$	—		/		/	/	/		
A triazine*	—	/	/	/	/		/	/	/			$\pm$	—			
4-NO ₂	—		$\pm$	—			—					—				
4-CN	7,9		1+	1+	—		2+	—				2+	—			
3-Cl, 4-CN	2,15-19, 26,28-30		2+	$\pm$	—		3+	+				3+	+	—		
2-Cl, 4-CN	3		2+	$\pm$	—											
4-CF ₃	12		1+	—			2+	—				2+	—			

*The triazine is 4,6-diamino-1-(*p*-chlorophenyl)-1,2-dihydro-2,2-dimethyl-*s*-triazine.

The compounds of formula (I) may be made by any known method for making compounds of analogous chemical structure, although some methods are preferred for the ease of preparation and adaption to a large scale.

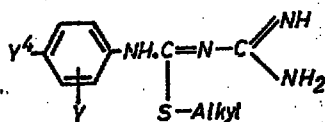
Thus a biguanide of formula (II)



(II)

may be converted to a compound of formula (I) by reaction with excess of nitrous acid, preferably at 0° to 20°C, or by hydrolysis with a strong aqueous acid, for example ethanesulphonic acid, methanesulphonic acid or hydrochloric acid, preferably between about 20° and 90°C. The biguanide starting materials may be made by a number of methods well documented in the literature (see, for example, "Chemistry of Carbon Compounds" Ed. E. H. Rodd, 1st edn. Vol III Part A, 1954 at p. 198 *et seq.*). In respect of the biguanides of formula (II) reference is made to Divisional Application No. 62879/69. Serial No. 1,194,836.

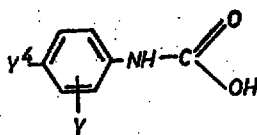
As another example, an *S*-alkyl-1-amidino-3-(substituted-phenyl) isothiourea of formula (IIa)



(IIa)

may be oxidised to a compound of formula (I), preferably using a peroxide, for example hydrogen peroxide, as an oxidising agent. The *S*-substituted-isothiurea starting material may be prepared from the corresponding 1-amidino-3-(substituted-phenyl)thiourea, which itself may be made by reaction of the appropriate isothiocyanate with guanidine.

Another type of method of preparing amidinoureas of formula (I) is by the reaction of guanidine with a reactive derivative of a substituted-phenylcarbamic acid of formula (III)

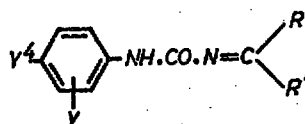


(III)

for example an isocyanate (the internal anhydride), or an urea (the amide). Other suitable reactive derivatives are alkyl esters (urethanes) preferably wherein the alkyl group is methyl or ethyl; for example the urethane may be preferably reacted with an anhydrous solution of guanidine base. A substituted-amide may also be used; for example, a suitable *N,N*-dialkyl-*N'*-arylcarbamide, where the alkyl groups are, for example, methyl or ethyl, may be fused with guanidine base to provide a compound of formula (I).

A further type of method for preparing the compounds of formula (I) comprises the reaction of an appropriately substituted aniline with dicyandiamide in the presence of at least twice the equivalent amount of a strong aqueous acid with respect to dicyandiamide. The acid may be, for example, hydrochloric acid, ethanesulphonic acid, methanesulphonic acid or an acid of similar strength. It will be appreciated by those skilled in the art that the amidinourea is formed via the corresponding biguanide, which is converted *in situ* to the amidinourea by the excess of acid. Of course if it is desired, for example for the purposes of characterisation or purification, the biguanide may be first isolated, (by using an equimolecular equivalent of acid in the reaction) and then converted to the amidinourea as described hereinbefore.

An amidinourea of formula (I) may also be made by ammonolysis of an *S*-alkylthiobiuret of formula (V)



(V)

in which R is the amino group and R' is an *S*-alkyl group having one to four carbon atoms. The preferred alkyl group is methyl. In formula (V), Y⁴ and Y have the same meaning as in formula (I); the preferred thiobiuret is an *S*-alkyl-1-(3-chloro-4-cyano-phenyl)-4-thiobiuret.

Amidinoureas of formula (I) in which the phenyl ring is substituted with a halogen atom or a nitrile group may also be prepared from the corresponding amino compound by diazotisation and subsequent reaction with a cyanide or halide of an alkali metal or a copper salt as provided by the Sandmeyer, Korner-Contardi, Gattermann and Angeli reactions. (See "Name Index of Organic Reactions", Gowan J. E. & Wheeler T. S., 1960, Longmans).

The product formed by any of the described

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reactions will be a 1 - amidino - 3 - (substituted - phenyl)urea, in the form of the base or an acid addition salt thereof, and may then be converted, as appropriate, into an acid addition salt, a salt of another acid or the base by reaction with an acid, a salt thereof or a base respectively, for example, in solution or on an ion exchange column. Thus, reaction of an acid addition salt with an alkali such as sodium hydroxide yields the 1 - amidino - 3 - (substituted - phenyl)urea base.

For treatment or prophylaxis of malaria, the compounds of formula (I) may be presented with an acceptable carrier therefor as pharmaceutical compositions. The carrier must of course be 'acceptable' in the sense of being compatible with the other ingredients of the composition and not deleterious to the recipient of the composition. The carrier may be a solid or a liquid, and is preferably formulated with a compound of formula (I) as a unit-dose composition, for example a tablet. Other pharmacologically active substances may also be present in compositions of the present invention. The amidinoureas of formula (I) may be incorporated in the compositions either in the form of a base or an acid addition salt thereof, and the composition formulated by any of the well-known techniques of pharmacy consisting basically of admixture of the components of the composition.

For oral administration, fine powders or granules of the compounds may contain diluents and dispersing and surface active agents, and may be presented in a draft in water or in a syrup; in capsules or cachets in the dry state or in an aqueous or non-aqueous suspension, when a suspending agent may also be included; in tablets, preferably made from granules of the active ingredient with a diluent, by compression with binders and lubricants; or in a suspension in water or a syrup or an oil or in a water/oil emulsion, when flavouring, preserving, suspending, thickening and emulsifying agents may also be included. The granules or the tablets may be coated, and the tablets may be scored.

For parenteral administration, the compounds may be presented in unit dose or multi-dose containers in aqueous or non-aqueous injection solutions which may contain antioxidants, buffers, bacteriostats and solutes which render the compounds isotonic with the blood; or in aqueous or non-aqueous suspensions when suspending agents and thickening agents may also be included; extemporaneous injection solutions and suspensions may be made from sterile powders, granules or tablets which may contain diluents, dispersing and surface active agents, binders and lubricants.

From experiments using the compounds of formula (I) in treating experimental infections of malaria in laboratory animals, it is estimated that a dose of from 1 to 100 mg./kg.

would be a therapeutic dose in man. Of course it is not possible to predict accurately the dose in view of differences between host and parasite susceptibility in the experimental animal and man.

The present invention therefore provides the compounds of formula (I), their acid addition salts and their preparation, and the above described compositions containing a compound of formula (I) and an acceptable carrier therefor, and the method of making such compositions by admixture of the components. The present invention also provides a process for the treatment or prophylaxis of malaria in a warm-blooded animal which comprises administering a compound of formula (I), preferably in an amount within the dose range from 1 to 100 mg./kg., to the host or potential host of the infection.

The following are Examples of this invention. All temperatures are in degrees Celsius.

EXAMPLE 1

4 - Chloro - 3 - cyanoaniline (6.1 g.), di-cyandiamide (3.7 g.), water (16 ml.) and concentrated hydrochloric acid (3.6 ml.) were heated under reflux for 30 minutes. With cooling a hydrochloride crystallised which was collected by filtration and washed with a little water. This crude salt was dried and recrystallised from alcohol. 4 - Chloro - 3 - cyanophenylbiguanide hydrochloride then separated as white needles (6.4 g.), m.p. 233° with effervescence. The base was obtained as small white needles when the solution of this salt was made alkaline with sodium hydroxide; recrystallised from alcohol, it formed colourless prisms, m.p. 202° with effervescence.

The biguanide base (3.2 g.) was dissolved in N-ethanesulphonic acid (32 ml.) and kept at 90° for 2 hours, during which period colourless crystals of 1 - amidino - 3 - (4 - chloro - 3 - cyanophenyl)urea ethanesulphonate separated. This salt was collected after cooling (2.8 g.), and was recrystallised from methanol (or water) and formed white needles, m.p. 219°. The base was obtained by treating an aqueous solution of the salt with sodium hydroxide. It formed white needles, m.p. 222°, which could be further purified by recrystallisation from alcohol. This substance was sparingly soluble in water.

EXAMPLE 2

In the manner described in Example 1, 3 - chloro - 4 - cyanoaniline was converted to 3 - chloro - 4 - cyanophenylbiguanide hydrochloride, which formed white matted needles from methanol, m.p. 258° with effervescence (the corresponding base formed white prisms from alcohol, m.p. 181°).

The biguanide (5 g.) was dissolved in 0.5N-ethanesulphonic acid (100 ml.) and the solu-

tion was kept at 90° for 2 hours. With cooling, a high yield of 1 - amidino - 3 - (3 - chloro - 4 - cyanophenyl)urea ethanesulphonate crystallised in white prisms, m.p. 224° (the corresponding base, crystallised from alcohol, had a m.p. 213°).

EXAMPLE 3

Dichloramine-T (6 g.) was added to a solution of 4-cyanoaniline (5.9 g.) in chloroform (59 ml.). After 4 hours the filtered solution was evaporated and the residue was lixiviated with N-NaOH. The undissolved crystalline material (6 g.) was 2 - chloro - 4 - cyanoaniline, m.p. 99—100°; after recrystallisation from aqueous alcohol it had a m.p. 102°.

2 - Chloro - 4 - cyanoaniline (4.2 g.), dicyandiamide (7.5 g.), concentrated hydrochloric acid (6.6 ml.) and water (15 ml.) were heated under reflux for 15 minutes. The crude hydrochloride that crystallised with cooling was separated, dried and heated with alcohol. The residue (4.1 g.) of 2 - chloro - 4 - cyanophenylbiguanide hydrochloride had a m.p. 243° with effervescence, and a m.p. of 244° after recrystallisation from water (the corresponding base formed white needles, m.p. 193° with effervescence).

When a solution of the biguanide (3.5 g.) in N-ethanesulphonic acid (35 ml.) was kept at 90° for 3 hours and then cooled, 1 - amidino - 3 - (2 - chloro - 4 - cyanophenyl)urea ethanesulphonate (4.4 g.) separated in colourless prisms, m.p. 211—214°; recrystallisation from methanol gave a product, m.p. 214° (the corresponding base formed white needles, m.p. 210° with effervescence).

EXAMPLE 4

2 - Bromo - 4 - cyanoaniline was converted in the manner described in Example 3 to 2 - bromo - 4 - cyanophenylbiguanide hydrochloride, m.p. 234° (the corresponding base, white needles, m.p. 200°). This biguanide was converted in the manner described in Example 3 to 1 - amidino - 3 - (2 - bromo - 4 - cyanophenyl)urea ethanesulphonate, which formed white prisms recrystallised from methanol, m.p. 210° (corresponding base formed white needles, m.p. 206° with effervescence).

EXAMPLE 5

4 - Cyano - 3 - methylaniline was converted in the manner described in Example 1 to 4 - cyano - 3 - methylphenylbiguanide hydrochloride, m.p. 232° after recrystallisation from water (the corresponding base had m.p. 172° after recrystallisation from alcohol). In the manner described in Example 1, this biguanide was converted into 1 - amidino - 3 - (4 - cyano - 3 - methylphenyl)urea ethanesulphonate, which formed white prisms on

recrystallisation from water, m.p. 232° (the corresponding base formed white leaflets after crystallisation from water, m.p. 200.5°).

EXAMPLE 6

4 - Cyano - 2 - methylaniline was converted in the manner described in Example 1 to 4 - cyano - 2 - methylphenylbiguanide hydrochloride which separated from water in white needles, m.p. 256° (the corresponding base: white prisms after separation from alcohol, m.p. 183° with effervescence). This biguanide was then converted in the manner described in Example 1 to 1 - amidino - 3 - (4 - cyano - 2 - methylphenyl)urea ethanesulphonate which crystallised from methanol in white needles, m.p. 204° (the corresponding base: white needles after separation from water, m.p. 171°).

EXAMPLE 7

To a solution of 4-cyanoaniline (5.9 g.) in acetone (60 ml.) were added anhydrous sodium carbonate (5.3 g.) and ethyl chloroformate (5.5 g.). The mixture was heated under reflux for 3 hours and then filtered. The filtrate was evaporated to dryness and the residue was crystallised from aqueous alcohol. The product, *p*-cyanophenylurethane, formed pale yellow prisms (7.4 g.), m.p. 115.5°.

Guanidine hydrochloride (2.9 g.) was added to a solution of sodium (0.7 g.) in ethanol (60 ml.). *p*-Cyanophenylurethane (4.9 g.) was then added and the mixture was heated under reflux for 4 hours and filtered hot. The residue left after evaporation of the filtrate was lixiviated with aqueous alcohol (20 ml. alcohol, 10 ml. water). The undissolved crystalline residue of crude 1 - amidino - 3 - *p*-cyanophenylurea (1.5 g.), m.p. ca. 199°, was purified by recrystallisation from N-ethanesulphonic acid as the ethanesulphonate, m.p. 219—220°, identical with the product described in Example 9.

EXAMPLE 8

In the manner described in Example 1, 3,4-dichloroaniline was converted to 3,4-dichlorophenylbiguanide hydrochloride, which formed white needles, m.p. 230°, from water (the corresponding base: white leaflets after separation from alcohol, m.p. 154°). This biguanide was converted in the manner of Example 1 to 1 - amidino - 3 - (3,4 - dichlorophenyl)urea ethanesulphonate, which gave white prisms from water, m.p. 224° (the corresponding base: hydrated white needles after separation from water, m.p. 95—98°).

EXAMPLE 9

p-Cyanoaniline (11.8 g.) was dissolved in 2N-hydrochloric acid (50 ml.) at 90° and the solution was stirred as dicyandiamide (8.4 g.) was added. The mixture was heated under reflux for 30 minutes, the product, *p*-cyano-

n.p. 232° (the white leaflets after 200°).

was converted in Example 1 to 4-cyanophenylbiguanide hydrochloride in white effervescent base: from alcohol, This biguanide inner described 3 - (4 - cyano - ethanesulphonate) which white needles, base: white in water, m.p.

ine (5.9 g.) in hydrous sodium chloroformate under reflux. The filtrate and the residue alcohol. The formed pale 5.5°.

g.) was added in ethanol (60 g.) was then heated under reflux. The residue: filtrate was 20 ml. alcohol, red crystalline 3 - p - cyano - 99°, was purified N-ethanesulphonate, m.p. product de-

Example 1, red to 3,4-dichloride, which 10°, from water leaflets after 154°. This manner of 3 - (3,4 - dionate, which n.p. 224° (the white needles p. 95-98°).

s dissolved in it 90° and the amide (8.4 g.) heated under reflux, p-cyano-

phenylbiguanide hydrochloride, separating meanwhile. After cooling, this salt (20 g.) was collected and washed with water, m.p. 277° with decomposition.

5 Metathesis of this salt with silver ethanesulphonate in water furnished a solution of p-cyanophenylbiguanide ethanesulphonate, evaporation of which gave the crystalline salt. Recrystallisation from alcohol gave white leaflets, m.p. 209-211°.

10 A solution of p-cyanophenylbiguanide ethanesulphonate (13.5 g.) in ethanesulphonic acid (120 ml.) at room temperature slowly deposited colourless prisms of 1 - amidino - 3 - (4 - cyanophenyl)urea ethanesulphonate, m.p. 218-219° with effervescence. A yield of 50% was obtained in 7 days but longer standing gave 80%.

20 A solution of the urea ethanesulphonate salt in hot water was made alkaline with 10N-sodium hydroxide and the base crystallised

in white prismatic needles, m.p. 205° with effervescence.

A solution of p-cyanophenylbiguanide ethanesulphonate (10 g.) in ethanesulphonic acid (500 ml.) was treated dropwise with a concentrated aqueous solution of sodium nitrite (20 g.). The flocculent precipitate that first formed redissolved, and effervescence followed as precipitation ensued. After 2 hours the solid was collected and washed with cold water. It was dissolved in hot water and 10N-sodium hydroxide was added. 1 - Amidino - 3 - (4 - cyanophenyl)urea separated as rather discoloured prismatic needles, m.p. 205° with effervescence.

EXAMPLES 10 AND 11

Tablets of 1 - amidino - 3 - (2 - chloro - 4 - cyanophenyl)urea ethanesulphonate were prepared from the following ingredients:

	Example 11	Example 12
Amidinourea ethanesulphonate	100 mg.	200 mg.
Lactose B.P.	125 mg.	100 mg.
Starch B.P.	60 mg.	75 mg.
Magnesium stearate B.P.	5 mg.	10 mg.

45 The tablets of Example 10 were prepared by moist granulation and compression using a 10% gelatin solution as a granulating agent; and those of Example 11 using an alcoholic solution of polyvinylpyrrolidone.

EXAMPLE 12

50 p-Aminobenzotrifluoride hydrochloride (7.92 g.), dicyandiamide (10.08 g.), concentrated hydrochloric acid (7.04 ml.) and water (20 ml.) were heated under reflux for 15 minutes and the resulting solution was cooled and made alkaline. The base separated as an oil which slowly solidified and was extracted with ether. 55 The extract was dried with anhydrous sodium sulphate and evaporated, and the residue was heated at 90° in solution in N-ethanesulphonic acid (100 ml.). After 2 hours the reaction mixture was cooled and the crystalline product was collected (6.5 g.). Recrystallisation from methanol afforded 1 - amidino - 3 - p - trifluoromethylphenylurea ethanesulphonate, m.p. 222°, as white prisms (the base crystallised from water in white leaflets, m.p. 173°).

EXAMPLE 13

65 4 - Chloro - 3 - nitroaniline (6.8 g.), dicyandiamide (5.04 g.) and 4N-HCl (15 ml.) were heated under reflux for 15 minutes and

the reaction mixture was filtered while hot from a small residue. The filtrate was made alkaline, and the crude basic material that separated was collected and lixiviated with cold 0.2N-acetic acid (total of 300 ml.). The undissolved residue (2.3 g.) was crystallised from alcohol and gave buff prisms of the sparingly-soluble acetate of 1 - amidino - 3 - (4 - chloro - 3 - nitrophenyl)urea, m.p. 175.5° with effervescence. The acetic acid extract was made alkaline and the precipitated base was crystallised from aqueous alcohol, affording brown prisms (6.5 g.) of 4 - chloro - 3 - nitro - phenylbiguanide, m.p. 164°. This biguanide was converted in the manner described in Example 1 into 1 - amidino - 3 - (4 - chloro - 3 - nitrophenyl)urea ethanesulphonate which crystallised from methanol in pale yellow prisms, m.p. 214-215°. The base crystallised from alcohol in yellow needles, m.p. 213° with effervescence.

EXAMPLE 14

90 2 - Chloro - 5 - nitrobenzotrifluoride (J. Org. Chem., 1957, 22, 300) (22.5 g.) was added dropwise with stirring to a solution of stannous chloride dihydrate (67.8 g.) in ethanol (325 ml.) and concentrated hydrochloric acid (60 ml.). After the addition, the solution was

heated on the steam-bath for 30 minutes. Alcohol was distilled off and the residue was poured into excess of 10N-NaOH. The basic oil thus liberated was collected in ether, dried with anhydrous sodium sulphate, and distilled.

4 - Chloro - 3 - trifluoromethylaniline was obtained, m.p. 118—120°/17 mm. Hg.; refractive index n_D^{17} 1.5150. The product crystallised and had m.p. 38—39°.

10 This aniline (5.9 g.), dicyandiamide (5.5 g.) and 4N-HCl (15 ml.) were heated under reflux for 15 minutes. With cooling a crystalline hydrochloride separated (6 g.) which, on recrystallisation from water gave white leaflets

15 of 4 - chloro - 3 - trifluoromethylphenylbiguanide hydrochloride, m.p. 210—211°. A solution of the base of this biguanide (3.5 g.) in normal methanesulphonic acid was heated to 95° and after 25 minutes crystals began to separate. After 2.5 hours the reaction mixture was cooled, and the crude product collected and recrystallised from methanol. 1 - Amidino - 3 - (4 - chloro - 3 - trifluoromethyl)phenylurea methanesulphonate crystallised as white needles, m.p. 239—240° with decomposition.

EXAMPLE 15

3 - Chloro - 4 - cyanoaniline (15.2 g.), dicyandiamide (16.8 g.) and 4N-hydrochloric acid (50 ml.) were heated under reflux until solid began to separate. The reaction mixture was then kept at 100° for 30 minutes, cooled and filtered. The solid was dried, and heated with alcohol (200 ml.). After cooling, the residual solid (23 g.) was collected, washed with alcohol and dried. This substance, 3 - chloro - 4 - cyanophenylbiguanide hydrochloride, m.p. 257—258° with decomposition, was dissolved in boiling water (300 ml.) and the solution was made alkaline with 10N-sodium hydroxide.

40 After cooling, the biguanide base was collected and washed with water, m.p. 174—175° with effervescence, pure enough for the next step.

The base (16.4 g.) was dissolved in N-ethanesulphonic acid (164 ml.) and the solution was kept at 100° for 2 hours and then cooled. The crystalline 1 - amidino - 3 - (3 - chloro - 4 - cyanophenyl)urea ethanesulphonate thus obtained had m.p. 223—224° with effervescence. Recrystallisation from water or methanol gave colourless prisms of similar melting-decomposition properties. This salt was dissolved in hot water and the solution was made alkaline (10N-sodium hydroxide).

55 The base separated in white leaflets, m.p. 212—213° with effervescence, little changed by recrystallisation from alcohol.

EXAMPLE 16

3 - Chloro - 4 - cyanoaniline (1.52 g.), di-

60 cyandiamide (0.84 g.) and N-ethanesulphonic acid (20 ml.) were heated at 100° for 2 hours. After cooling, the solid product was collected by filtration, dried, and then heated with alcohol. After cooling, the undissolved solid was collected and washed with alcohol. The crystalline residue, m.p. 223° with decomposition, was identical with the ethanesulphonate of Example 2.

When N-ethanesulphonic acid was replaced by N-methanesulphonic acid, the corresponding methanesulphonate, m.p. 249—250° with decomposition, was produced.

EXAMPLE 17

3 - Chloro - 4 - cyanoaniline (1.52 g.), dicyandiamide (1.68 g.) and N-hydrochloric acid (30 ml.) were heated under reflux for 15 minutes. Some decolourising charcoal was added, followed by filtration at the boiling point. The filtrate deposited white needles of 1 - amidino - 3 - (3 - chloro - 4 - cyanophenyl)urea hydrochloride, which decomposed about 250°.

The same product was obtained when 3 - chloro - 4 - cyanophenylbiguanide was heated for a short period under reflux with dilute hydrochloric acid.

EXAMPLE 18

1 - Amidino - 3 - (3 - chloro - 4 - cyanophenyl)urea ethanesulphonate (1.74 g.) was dissolved in boiling methanol (150 ml.) and the solution was treated with a solution of dry sodium embonate (1.08 g.) in methanol (50 ml.) and water (50 ml.). The solution was heated under reflux and in a few moments 1 - amidino - 3 - (3 - chloro - 4 - cyanophenyl)urea embonate crystallised. It was collected by filtration and washed with water, m.p. 195° with effervescence.

EXAMPLE 19

Methyl 3 - chloro - 4 - cyanophenyl - carbamate, m.p. 136°, was prepared from 3 - chloro - 4 - cyanoaniline by the method of Example 7. This substance (4.5 g.) was heated under reflux for 4 hours with a solution of guanidine (from 2.5 g. of the hydrochloride) in ethanol. With cooling, crystalline solid (0.5 g.) separated, evaporation giving a second crop (0.9 g.). This crude base was purified by dissolving it in the calculated amount of hot aqueous ethanesulphonic acid. With cooling there separated 1 - amidino - 3 - (3 - chloro - 4 - cyanophenyl)urea ethanesulphonate, m.p. 223—224° with decomposition, from which the base, m.p. 211.5° with decomposition, was obtained. These products were identical with those of Example 15.

ethanesulphonic
for 2 hours.
was collected
heated with
dissolved solid
alcohol. The
decomposition
ethanesulphonate

was replaced
corresponding
-250° with

1.52 g.),
hydrochloric
efflux for 15
minutes was
the boiling
needles of
4 - cyano-
decomposed

1 when 3 -
was heated
with dilute

4 - cyano-
74 g.) was
10 ml.) and
solution of dry
ethanol (50
ml.) was
with moments
4 - cyano-
It was col-
with water,

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acid. With
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products were

EXAMPLE 20

2,4,5-Trichloroaniline (9.8 g.), dicyandiamide (8.4 g.) and 4N-hydrochloric acid (50 ml.) were heated at 100° for 2 hours and then steam-distilled to remove unchanged trichloroaniline. The liquid in the still was treated with charcoal and then made alkaline (10N-sodium hydroxide). Crude 1 - amidino - 3 - (2,4,5 - trichlorophenyl)urea was thus precipitated. It was purified as the methanesulphonate by crystallising from the calculated amount of dilute aqueous methanesulphonic acid, this salt forming white silky needles which began to decompose about 236°. The base was crystallised from aqueous alcohol and formed white silky needles of a monohydrate, m.p. 180.5° with effervescence.

EXAMPLE 21

4 - Nitro - 3 - trifluoromethylaniline (6.18 g.), dicyandiamide (7.54 g.) and 4N-hydrochloric acid (22.5 ml.) were heated under reflux for 10 minutes to provide a clear solution. The solution was made alkaline (10N-sodium hydroxide) and the precipitate that formed was collected and washed with water. The crude base was extracted with hot 2N-acetic acid (50 ml.) and the extract was made alkaline (10N-sodium hydroxide), thus precipitating 4 - nitro - 3 - trifluoromethyl - phenylbiguanide, which gave orange prisms from alcohol, m.p. 149—150°.

Reaction of this biguanide (4.8 g.) with normal methanesulphonic acid by the method of Example 14 gave 1 - amidino - 3 - (4 - nitro - 3 - trifluoromethylphenyl)urea methanesulphonate in yellow needles, m.p. 245° with decomposition; the base, on crystallisation from aqueous alcohol, formed pale yellow silky needles, m.p. 202° with effervescence.

EXAMPLE 22

The procedure of Example 15 was applied to 4 - cyano - 3 - fluoroaniline. The biguanide hydrochloride separated from the reaction mixture and had m.p. 274° with decomposition; the base formed white plates, m.p. 169.5° with effervescence.

1 - Amidino - 3 - (4 - cyano - 3 - fluoro-phenyl)urea methanesulphonate crystallised from water in white prisms, m.p. 241—242° with effervescence; the base had m.p. 205—206° with effervescence.

EXAMPLE 23

The procedure of Example 21 was applied to 3 - chloro - 4 - nitroaniline. The biguanide crystallised from alcohol in yellow leaflets, m.p. 178°, and 1 - amidino - 3 - (3 - chloro - 4 - nitrophenyl)urea methanesulphonate from water in yellow prisms, m.p. 241° with decomposition.

EXAMPLE 24

A solution of guanidine was obtained by reaction of a solution of sodium ethoxide in ethanol (15 ml.) with an equivalent of guanidine hydrochloride (2.1 g.). After removal of sodium chloride by filtration, 1 - (3,4 - dichlorophenyl)urea (4.1 g.) was added and the solution was evaporated to dryness. The residue was heated at 130° for 3 hours during which time ammonia was evolved. The residue was then extracted with warm decinormal ethanesulphonic acid. The extract was made alkaline, on which white wool-like crystals of 1 - amidino - 3 - (3,4 - dichlorophenyl)urea separated. Recrystallisation from aqueous alcohol gave the hydrate, m.p. 95—98°, alone or in admixture with the product of Example 8. This identity was confirmed by thin-layer chromatography using silica gel.

EXAMPLE 25

A solution of guanidine was obtained by reaction of a solution of sodium ethoxide in ethanol (115 ml.) with an equivalent of guanidine hydrochloride (2.1 g.). After removal of sodium chloride by filtration, 1 - (3,4 - dichlorophenyl) - 3,3 - diethylurea (5.2 g.) was added, and the solution was evaporated to dryness. The residue was heated at 120° for 2½ hours, diethylamine being freely evolved. The melt was extracted with hot decinormal ethanesulphonic acid (200 ml.) in which most dissolved, and, with cooling, white needles of 1 - amidino - 3 - (3,4 - dichlorophenyl)urea ethanesulphonate separated, recrystallisation of which, from ethanol, gave white prisms, m.p. 222° undepressed by admixture with the corresponding product of Example 8.

EXAMPLE 26

3 - Chloro - 4 - cyanophenyl isocyanate, m.p. 84—86°, was prepared from 3 - chloro - 4 - cyanoaniline by a method described in *J. Amer. Chem. Soc.*, 1938, 60, 2675. A solution of the isocyanate (7 g.) in dry dioxan (50 ml.) was treated dropwise with stirring with a solution of diethylamine (2.75 g.) in dry dioxan (25 ml.). The solution was stirred for 30 minutes after the addition and then evaporated to dryness. The residue was crystallised from aqueous alcohol, forming fawn leaflets (8.4 g.), m.p. 110—111°, of 1 - (3 - chloro - 4 - cyanophenyl) - 3,3 - diethylurea.

This urea (5.3 g.) was reacted with guanidine base by the method of Example 24 and crude 1 - amidino - 3 - (3 - chloro - 4 - cyanophenyl)urea ethanesulphonate was thus obtained. Recrystallisation from methanol gave characteristic crystals of this salt, m.p. 223—224°, not depressed by admixture with the corresponding product of Example 15.

EXAMPLE 27

Sliced sodium (0.75 g.) was added to acetone (40 ml.) and the warm suspension that resulted was treated with guanidine thiocyanate (4.43 g.). 3,4-Dichlorophenyl isothiocyanate (5.1 g.) was added and the mixture was heated under reflux for 5 minutes and then poured on to ice. The precipitated product was collected and crystallised from methanol, forming colourless plates (2.8 g.), m.p. 168.5° with vigorous effervescence. This substance, 1-amidino - 3 - (3,4 - dichlorophenyl)thiourea (1 g.), was heated under reflux in methanolic solution (20 ml.) with methyl iodide (1 ml.) for 30 minutes. Evaporation of the solution and addition of alkali precipitated 1-amidino - 3 - (3,4 - dichlorophenyl) - S - methylisothiourea, which on crystallisation from methanol formed colourless rhombs, m.p. 165—166° with effervescence. This substance (600 mg.) was added portionwise to 100-volume hydrogen peroxide. After the vigorous reaction had subsided the product was collected and dissolved in boiling water, there being a slight residue. Addition of alkali to the solution precipitated 1 - amidino - 3 - (3,4 - dichlorophenyl)urea, which was characterised as the ethanesulphonate, m.p. 223—224° with effervescence, and identical with the product of Example 8.

EXAMPLE 28

Reaction of 3 - chloro - 4 - cyanoaniline and thiophosgene afforded a good yield of 3 - chloro - 4 - cyanophenyl isothiocyanate which crystallised from cyclohexane in fawn prisms, m.p. 77.5°, and which was converted by the methods of Example 27 successively into 1-amidino - 3 - (3 - chloro - 4 - cyanophenyl)thiourea, white prisms, m.p. 199.5° with effervescence, and 1 - amidino - 3 - (3 - chloro - 4 - cyanophenyl) - S - methylisothiourea, white needles, m.p. 165° with effervescence. The last-named was similarly oxidised by hydrogen peroxide, affording 1-amidino - 3 - (3 - chloro - 4 - cyanophenyl)urea, m.p. 212° with effervescence, identical with the product of Example 15.

EXAMPLE 29

Pyridine (10 ml.), 4N-HCl (2.5 ml.) and benzene (10 ml.) were heated under reflux in a Dean and Stark apparatus until no more water was collected. Benzene was then distilled off and to the residue was added 3 - chloro - 4 - cyanoaniline (1.52 g.) and dicyandiamide (0.92g.). The mixture was heated under reflux for 2½ hours and during this time solid separated. After cooling, the solid was collected by filtration and washed with alcohol. It had m.p. 258° and was 3 - chloro - 4 - cyanophenylbiguanide hydrochloride, the base from which was converted to 1 - amidino - 3 -

(3 - chloro - 4 - cyanophenyl)urea ethanesulphonate by the method of Example 15.

EXAMPLE 30

1 - Amidino - 3 - (3 - chloro - 4 - nitrophenyl)urea methanesulphonate (6.2 g. Example 23), crystalline stannous chloride (13.6 g.), and N-HCl (54 ml.) were heated to effect solution. With cooling, crude 1 - amidino - 3 - (4 - amino - 3 - chlorophenyl)urea dihydrochloride separated, which was recrystallised from water, forming white leaflets (2.7 g.) which began to decompose about 200° and became black at 220°. A solution of this salt (0.45 g.) in water (12.5 ml.) was diazotised with sodium nitrite (0.11 g.), and the resulting solution was added to a solution at 95° prepared from crystalline cuprous sulphate (0.4 g.), potassium cyanide (0.5 g.) and water (5 ml.). After effervescence had subsided (30 minutes) the reaction mixture was cooled and filtered. The solid was extracted with hot water and the extract was made alkaline. The brownish base thus precipitated behaved as 1 - amidino - 3 - (3 - chloro - 4 - cyanophenyl)urea on a thin layer chromatogram showing a spot which had the characteristic blue fluorescence in ultra-violet light and which gave no colour with Ehrlich's reagents. It was purified as the ethanesulphonate, m.p. 224°.

EXAMPLE 31

3,4-Dichlorophenyl isocyanate (3.7 g.) and thiourea (1.5 g.) were mixed and heated at 100° for 3 hours. The solid product was crystallised from methanol and formed white needles (2.5 g.), m.p. 219° with effervescence, of 1 - (3,4 - dichlorophenyl) - 4 - thiobiuret. This substance (1 g.) was heated under reflux with methanol (25 ml.) and methyl iodide (1 ml.) until a clear solution was obtained. The solution was concentrated to half bulk and added to a saturated solution (10 ml.) of ammonia in methanol. After 48 hours the solution was evaporated and the residual gum was extracted with decinormal ethanesulphonic acid. The extract was concentrated and left to crystallise. The first crop, which melted at 217—219° with effervescence, was recrystallised from ethanol. Colourless plates separated, m.p. 223—224° with effervescence, of 1 - amidino - 3 - (3,4 - dichlorophenyl)urea ethanesulphonate.

EXAMPLE 32

Sodium (0.7 g.) was dissolved in acetone (40 ml.) and to the resulting suspension was added guanidine thiocyanate (3.5 g.). 3,4-Dichlorophenyl isocyanate (3.75 g.) was added with shaking to the clear solution that was formed. After one hour the solution was poured into water. An amorphous precipitate formed and was separated and extracted with

urea ethane-
sample 1"

- 4 - nitro- 65
(6.2 g. Ex-
chloride (13.6
ated to effect
- amidino -
urea dihydro- 70
recrystallised
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at 200° and
of this salt
is diazotised
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ation at 95°
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rmed white
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(10 ml.) of
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in acetone 115
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5 g.). 3,4-
was added
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olution was 120
precipitate
racted with

decinormal ethanesulphonic acid (200 ml.), but much remained undissolved. The extract was concentrated to small bulk until a crude crystalline product separated. Recrystallisation of this material from ethanol furnished colourless plates of 1 - amidino - 3 - (3,4 - dichlorophenyl)urea ethanesulphonate, m.p. 223—224°.

EXAMPLE 33

- 10 A tablet of 1 - amidino - 3 - (3 - chloro - 4 - cyanophenyl)urea base was prepared from the following ingredients:—

Amidinourea	100.0 mg.
Lactose, B.P.	100.0 mg.
15 Starch Maize, B.P.	50.0 mg.
Magnesium Stearate, B.P.	2.5 mg.
Gelatin, B.P., in solution	8.0 mg.
	260.5 mg.

- 20 The amidinourea was mixed with the lactose and starch maize, and the resulting mass granulated with a 10% solution of gelatin in aqueous alcohol. The granules were sifted through a mesh, 1,000 μ (16 # B.S.S.) and dried at 37°C. The dried granules were sifted through a mesh 1,000 μ (16 # B.S.S.), admixed with the magnesium stearate, and compressed on a 9.4 m.m. die.

EXAMPLE 34

- 30 A syrup suspension containing 25 mg./ml. of 1 - amidino - 3 - (3 - chloro - 4 - cyanophenyl)urea base was prepared from the following ingredients.

Amidinourea (in fine powder)	0.5 g.
Sucrose, B.P.	50.0 g.
35 Glycerin, B.P.	15.0 g.
Sodium carboxymethyl cellulose, medium viscosity	0.65 g.
Methyl Hydroxybenzoate, B.P.	0.1 g.
Sodium Benzoate, B.P.	0.1 g.
40 Sodium Saccharin, B.P.	0.1 g.
Tartrazine, B.P.C. 1954	5.0 mg.
Banana Flavour (Synthetic)	0.1 ml.
Purified Water, B.P.	100.0 ml.

- 45 A liquid vehicle was prepared from all the components, except the amidinourea, using $\frac{3}{4}$ volume of water. The amidinourea was then suspended in this vehicle and the density adjusted to 25 mg./ml.

EXAMPLE 35

- 50 An injection suspension of 1 - amidino - 3 - (3 - chloro - 4 - cyanophenyl)urea base was prepared from the following to provide 20 mg. of the compound per ml.

Amidinourea	20.0 g.	
Polyoxyethylene sorbitan mono-oleate	0.2 g.	55
Methyl Hydroxybenzoate, B.P.	1.0 g.	
Water for Injection, B.P. to	1,000.0 ml.	

The methyl hydroxybenzoate was dissolved in the water at 80°, cooled, the polyoxyethylene monooleate added, and the solution made up to standard volume to provide the vehicle. The amidinourea was sterilized by gamma-irradiation and ball-milled with the sterile vehicle until the majority of the particles were less than 10 μ .

EXAMPLE 36

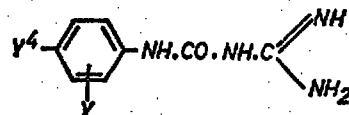
An injection solution of 1 - amidino - 3 - (3 - chloro - 4 - cyanophenyl)urea base was prepared from the following:— 70

Amidinourea	2.00 g.
Propylene glycol, B.P.	70.00 ml.
Alcohol (95%), B.P. to	100.00 ml.

The amidinourea was dissolved in the solvents and the solution sterilised by filtration. 75

WHAT WE CLAIM IS:—

1. An amidinourea of the formula

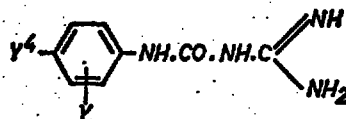


or an acid addition salt thereof wherein Y' is a halogen when Y is a trihalomethyl, nitrile or nitro substituent at the 3- position or a halogen substituent at the 3- position or at both the 3- and 6- positions; or

Y' is trihalomethyl or nitrile when Y is hydrogen or is a halogen or an alkyl substituent having 1 to 4 carbon atoms at the 2- or 3- position; or

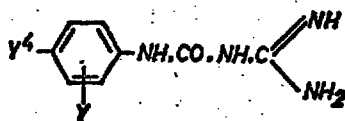
Y' is nitro when Y is a trihalomethyl or halogen substituent at the 3- position.

2. An amidinourea of the formula 90



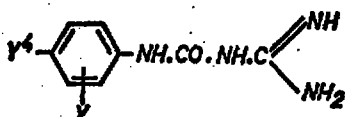
or an acid addition salt thereof wherein Y' is nitrile or trifluoromethyl when Y is hydrogen or is a halogen substituent in the 2- or 3- position; or Y' is a halogen when Y is a nitrile, nitro, halogen or trifluoromethyl substituent in the 3- position.

3. An amidinourea of the formula 95



or an acid addition salt thereof wherein Y^4 is nitrile and Y is hydrogen or is a halogen substituent in the 2- or 3- position.

- 5 4. An amidinourea of the formula



or an acid addition salt thereof wherein Y^4 is a halogen and Y is a halogen, nitrile or nitro substituent in the 3- position.

- 10 5. An amidinourea or an acid addition salt thereof as claimed in any of claims 1 to 4 wherein the halogen substituents are chlorine.

6. An amidinourea or an acid addition salt thereof as claimed in any of claims 1 to 4 wherein the halogen substituents are bromine or fluorine.

7. An amidinourea or an acid addition salt thereof as claimed in claim 1 wherein the trihalomethyl substituent is trifluoromethyl.

- 20 8. An amidinourea or an acid addition salt thereof as claimed in claim 1 wherein the alkyl substituent is methyl.

9. 1 - Amidino - 3 - (4 - chloro - 3 - cyanophenyl)urea.

- 25 10. 1 - Amidino - 3 - (3 - chloro - 4 - cyanophenyl)urea.

11. 1 - Amidino - 3 - (3,4 - dichlorophenyl)urea.

- 30 12. 1 - Amidino - 3 - (2 - chloro - 4 - cyanophenyl)urea.

13. 1 - Amidino - 3 - (1 - trifluoromethylphenyl)urea.

14. 1 - Amidino - 3 - (4 - chloro - 3 - nitrophenyl)urea.

- 35 15. 1 - Amidino - 3 - (4 - chloro - 3 - trifluoromethylphenyl)urea.

16. 1 - Amidino - 3 - (4 - cyanophenyl)urea.

17. 1 - Amidino - 3 - (4 - cyano - 3 - methylphenyl)urea.

- 40 18. 1 - Amidino - 3 - (2 - bromo - 4 - cyanophenyl)urea.

19. 1 - Amidino - 3 - (4 - cyano - 2 - methylphenyl)urea.

- 45 20. 1 - Amidino - 3 - (2,4,5 - trichlorophenyl)urea.

21. 1 - Amidino - 3 - (3 - chloro - 4 - nitrophenyl)urea.

22. 1 - Amidino - 3 - (4 - nitro - 3 - trifluoromethylphenyl)urea.

- 50 23. 1 - Amidino - 3 - (4 - cyano - 3 - fluorophenyl)urea.

24. An acid addition salt of an amidinourea defined in any of claims 9 to 23.

25. An ethanesulphonic acid addition salt of

an amidinourea defined in any of claims 9 to 23. 55

26. A methanesulphonic acid addition salt of an amidinourea defined in any of claims 9 to 23.

27. A hydrochloric acid addition salt of an amidinourea defined in any of claims 9 to 23. 60

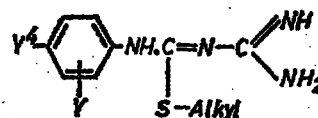
28. 1 - Amidino - 3 - (3 - chloro - 4 - cyanophenyl)urea ethanesulphonate.

29. 1 - Amidino - 3 - (3 - chloro - 4 - cyanophenyl)urea methanesulphonate. 65

30. 1 - Amidino - 3 - (3 - chloro - 4 - cyanophenyl)urea hydrochloride.

31. 1 - Amidino - 3 - (3 - chloro - 4 - cyanophenyl)urea embonate. 10

32. A method of preparing an amidinourea or an acid addition salt thereof claimed in any of claims 1 to 31 comprising the selective oxidation of the S-alkyl group of a compound of the formula 70

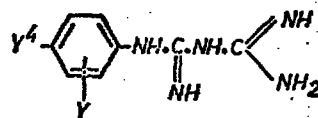


wherein Y^4 and Y are as defined in any of claims 1 to 31, followed by optional conversion of the product to an acid addition salt thereof. 75

33. A method as claimed in claim 32 wherein the oxidation is performed using hydrogen peroxide. 80

34. A method as claimed in either claim 32 or 33 wherein Y^4 is nitrile and Y is a chlorine substituent at the 3- position.

35. A method of preparing an amidinourea or an acid addition salt thereof claimed in any of claims 1 to 31 comprising the reaction of a biguanide of the formula 85



wherein Y^4 and Y are as defined in any of claims 1 to 31, with an excess of nitrous acid, or with a hydrolysing agent. 90

36. A method as claimed in claim 35 wherein the hydrolysing agent is a strong aqueous acid. 95

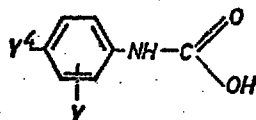
37. A method as claimed in claim 36 wherein the strong aqueous acid is ethanesulphonic acid, methanesulphonic acid or hydrochloric acid.

38. A method as claimed in any of claims 35 to 37 wherein the biguanide is 3 - chloro - 4 - cyanophenylbiguanide. 100

39. A method of preparing an amidinourea or an acid addition salt thereof claimed in any of claims 1 to 31 comprising the reaction 105

of claim 9 to 55
 addition salt of
 of claims 9
 on salt of an 60
 aims 9 to 23.
 chloro - 4 -
 te.
 chloro - 4 -
 ate. 65
 chloro - 4 -
 amidinourea 70
 aimed in any
 the selective
 a compound
 H
 H₂ 75
 d in any of
 ul conversion
 salt thereof.
 n 32 where-
 ng hydrogen 80
 er claim 32
 is a chlorine
 amidinourea 85
 claimed in
 the reaction
 H
 H₂
 l in any of 90
 itrous acid,
 claim 35
 s a strong 95
 claim 36
 s ethanesul-
 l or hydro-
 y of claims 100
 3 - chloro -
 midinourea
 claimed in
 he reaction 105

of guanidine with a reactive derivative of a substituted-phenylcarbamic acid of the formula



5 wherein Y⁴ and Y are as defined in any of claims 1 to 31, followed by optional conversion of the product to an acid addition salt thereof.
 10 40. A method as claimed in claim 39 wherein the derivative is an alkyl ester of the acid.

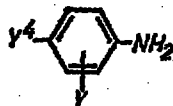
41. A method as claimed in claim 39 wherein the derivative is an N,N-dialkylamide of the acid.

15 42. A method as claimed in either claim 40 or 41 wherein the alkyl groups are methyl or ethyl.

43. A method as claimed in any of claims 39 to 42 wherein the guanidine is in the form of its base.

20 44. A method as claimed in any of claims 39 to 43 wherein the derivative is one of 3 - chloro - 4 - cyanophenylcarbamic acid.

25 45. A method of preparing an amidinourea or an acid addition salt thereof as claimed in any of claims 1 to 31 comprising the reaction of an aniline of the formula



30 with dicyandiamide in the presence of at least twice the equivalent amount of a strong aqueous acid with respect to the dicyandiamide.

46. A method as claimed in claim 45 wherein the acid is ethanesulphonic acid, methanesulphonic acid or hydrochloric acid.

35 47. A method as claimed in any of claims 45 or 46 wherein the aniline is 3 - chloro - 4 - cyanoaniline.

40 48. A method for preparing an amidinourea or an acid addition salt thereof as claimed in any of claims 1 to 31 comprising the ammonolysis of an S-alkylthiobiuret of the formula



45 wherein Y⁴ and Y are as defined in any of claims 1 to 31 and the alkyl group has one to four carbon atoms, followed by optional conversion of the product to an acid addition salt thereof.

49. A method as claimed in claim 48 wherein the alkyl group is methyl.

50. A method as claimed in either claim 48 or 49 wherein the thiobiuret is an S - alkyl - 1 - (3 - chloro - 4 - cyanophenyl) - 4 - thiobiuret.

51. An amidinourea or an acid addition salt thereof as defined in any of claims 1 to 31 when prepared by a method claimed in any of claims 32 to 50.

52. A pharmaceutical composition comprising an amidinourea or an acid addition salt thereof as defined in any of claims 1 to 31 in association with an acceptable carrier therefor.

53. A composition as claimed in claim 52 wherein the carrier is a solid.

54. A composition as claimed in claim 52 wherein the carrier is a liquid.

55. A composition as claimed in any of claims 52 to 54 in unit dosage form.

56. A tablet comprising an amidinourea or an acid addition salt thereof as defined in any of claims 1 to 31 and an acceptable carrier therefor.

57. A capsule comprising an amidinourea or an acid addition salt thereof as defined in any of claims 1 to 31 and an acceptable carrier therefor.

58. A solution in a liquid carrier of an amidinourea or an acid addition salt thereof as defined in any of claims 1 to 31, suitable for oral administration.

59. A suspension in a liquid carrier of an amidinourea or an addition salt thereof as defined in any of claims 1 to 31, suitable for oral administration.

60. A sterile injectable fluid comprising an amidinourea or an acid addition salt thereof as claimed in any of claims 1 to 31, in a liquid carrier suitable for parenteral administration.

61. A composition as claimed in any of claims 52 to 60 wherein the amidinourea is 1 - amidino - 3 - (3 - chloro - 4 - cyanophenyl)urea or an acid addition salt thereof.

62. A tablet comprising 1 - amidino - 3 - (3 - chloro - 4 - cyanophenyl)urea or an acid addition salt thereof and an acceptable carrier therefor.

63. A method of preparing a pharmaceutical composition as defined in any of claims 52 to 62 comprising admixture of the amidinourea or an addition salt thereof with an acceptable carrier therefor.

64. A method for preparing a tablet of 1 - amidino - 3 - (3 - chloro - 4 - cyanophenyl)urea or an acid addition salt thereof comprising moist granulation of the compound and an acceptable carrier therefor followed by compression of the dry granules into a tablet.

65. A method of preparing an amidinourea as defined in any of claims 1 to 31 substantially as hereinbefore described with particular reference to Examples 1 to 9 and 12 to 32.

66. A pharmaceutical composition comprising an amidinourea as defined in any of claims

1 to 31 and an acceptable carrier therefor substantially as hereinbefore described with particular reference to Examples 10, 11 and 33 to 36.

- 5 67. A method of preparing a pharmaceutical composition comprising an amidinourea as de-

finied in any of claims 1 to 31 and an acceptable carrier therefor substantially as hereinbefore described with particular reference to Examples 10, 11 and 33 to 36.

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