

**ΚΥΠΡΙΑΚΟ ΓΡΑΦΕΙΟ ΔΙΠΛΩΜΑΤΩΝ
ΕΥΡΕΣΙΤΕΧΝΙΑΣ
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PUBLICATION NUMBER**

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Το έγγραφο που παρουσιάζεται πιο κάτω καταχωρήθηκε στο «Γραφείο Διπλωμάτων Ευρεσιτεχνίας» στην Αγγλία σύμφωνα με το Νόμο Κεφ. 266 πριν την 1^η Απριλίου 1998. Δημοσίευση έγινε μετέπειτα από το Γραφείο Διπλωμάτων Ευρεσιτεχνίας του Ηνωμένου Βασιλείου μόνο στην Αγγλική γλώσσα.

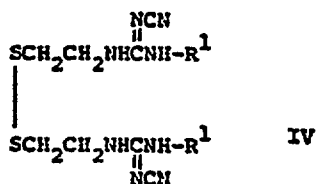
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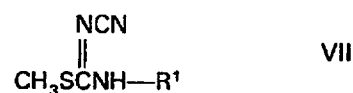
(54) N,N'-Bis[(N-cyano-N'-alkynyl)methanimidamidyl]cystamines

(57) Novel compounds of the formula:



wherein each R¹ is the same and is a straight or branched chain alkynyl

group containing from 3 to 9 carbon atoms, inclusive and acid addition salts thereof, which are useful intermediates in the preparation of anti-ulcer agents, may be prepared by reacting cystamine or an acid addition salt thereof with an N-cyano-N'-alkynyl-S-methylisothiourea of the formula



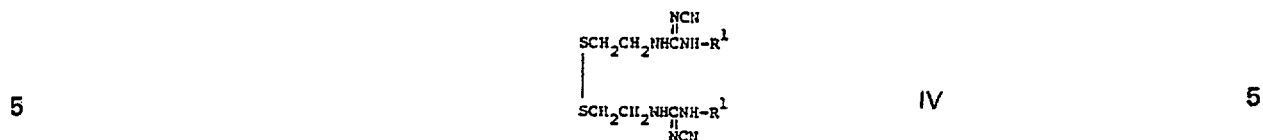
in which R¹ is as defined above.

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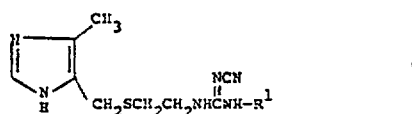
SPECIFICATION

Chemical compounds

This application relates to certain novel N,N'-bis[N-cyano-N'-alkynyl]methanimidamidyl]cystamines of the formula



wherein each R¹ is the same and is a straight or branched chain alkynyl group containing from 3 to 9 carbon atoms, inclusive, which are useful as intermediates in the preparation of anti-ulcer agents of the formula



10 wherein R¹ is as defined above. 10

The clinical objective in treatment of peptic ulcer disease is to decrease gastric acid secretion, based on the principle "no acid, no ulcer". Traditional peptic ulcer disease therapy involves control of diet and the use of antacids and anticholinergics.

15 There is evidence indicating that histamine may be the final common pathway for stimulation of gastric secretion. This effect of histamine is mediated via H₂ receptors and is not inhibited by the classical antihistamines, which are H₁ receptor blockers. A number of specific H₂ receptor blocking agents (H₂ receptor antagonists) are now known. These compounds inhibit basal acid secretion, as well as as secretion by other known gastric acid stimulants, and are useful in the treatment of peptic ulcers. 15

Burimamide (Va) was the first clinically effective

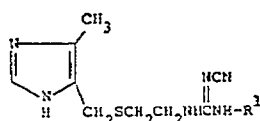


Va; R² = H, Z = CH₂, X = S Burimamide
b; R² = CH₃, Z = S, X = S Metiamide
c; R² = CH₃, Z = S, X = NCN Cimetidine

H₂ receptor antagonist. It inhibits gastric secretion in animals and man, but oral absorption is poor. 25
Metiamide (Vb), a subsequently evaluated H₂ antagonist, is more potent than burimamide and is orally active in man. Clinical utility was limited, however, owing to toxicity (agranulocytosis). Cimetidine (Vc) is as effective an H₂ antagonist as metiamide, without producing agranulocytosis, and has recently been marketed as an anti-ulcer drug. The half-life of cimetidine is relatively short, thereby necessitating a therapeutic regimen of multi daily doses of 200—300 mg. tablets. There is thus a need for anti-ulcer 30 agents which are longer acting and/or more potent than cimetidine.

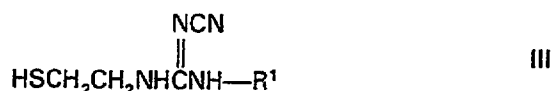
Reviews on the development of H₂ antagonists, including those discussed in the preceding paragraph, may be found in C. R. Ganellin, *et al.*, Federation Proceedings, 35, 1924 (1976), in Drugs of the Future, 1, 13 (1976), and in references cited therein.

Our co-pending application No. 23611/78 describes and claims novel histamine H₂ receptor 35 antagonists of the formula



wherein R¹ is a straight or branched chain alkynyl group containing from 3 to 9 carbon atoms, inclusive, and nontoxic, pharmaceutically acceptable salts thereof, which are effective inhibitors of gastric secretion in animals, including man, and which are useful in the treatment of peptic ulcer disease.

40 Our United States Patent No. 4158013 discloses and claims novel intermediates of the formula: 40

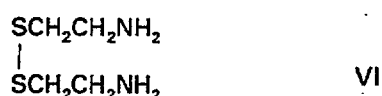


wherein R¹ is as described above, and a novel process for the preparation of anti-ulcer compounds of Formula I by reacting a compound of Formula III with a compound of the formula



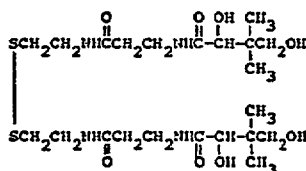
5 wherein X is a conventional leaving group, and wherein the compound of Formula II preferably is in the form of an acid addition salt. **5**

Cystamine (VI) is a known compound, being described



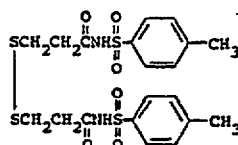
for example, on page 363 of The Merck Index, ninth edition (1976), as compound 2775.

10 Pantethine, a derivative of cystamine having the formula 10



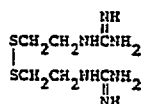
is described in The Merck Index, ninth edition (1976) as compound 6817.

The compound N,N'-bis(p-tolylsulfonylcarbonyl)cystamine having the formula

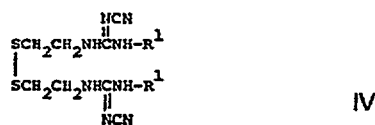


15 is listed in the Alfred Bader Chemicals Library of Rare Chemicals, Aldrich Chemical Company, Inc. (1971) by structure on page 114 and by name on page 275. 15

The Journal of The American Chemical Society, 79, 5663—6 (1957) discloses guanidinoethyldisulfide [N,N'-bis(quanyl) cystamine], having the formula

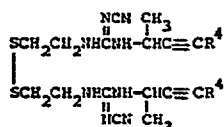


20 In its broadest aspect, this invention relates to novel N, N'-bis[(N-cyano-N'-alkynyl)meth- 20
animidamidyl]-cystamines of the formula



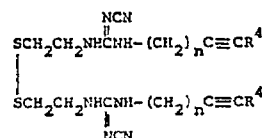
wherein each R¹ is the same and is a straight or branched chain alkynyl group containing from 3 to 9 carbon atoms, inclusive, and acid addition salts thereof.

25 In a preferred embodiment the compounds of Formula IV have the structure



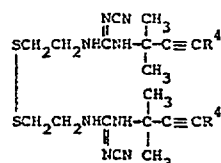
wherein each R⁴ is the same and is hydrogen or methyl, or an acid addition salt thereof.

In another preferred embodiment the compounds of Formula IV have the structure



wherein each R⁴ is the same and is hydrogen or methyl, and n is an integer of from 1 to 6 inclusive, or an acid addition salt thereof.

In yet another preferred embodiment the compounds of Formula IV have the structure



wherein each R⁴ is the same and is hydrogen or methyl, or an acid addition salt thereof.

In a more preferred embodiment the compound of Formula IV is N,N'-bis[([N-cyano-N'-(2-butyn-1-yl)]methanimidamidyl)cystamine, or an acid addition salt thereof.

In another more preferred embodiment the compound of Formula IV is N,N'-bis[([N-cyano-N'-(3-butyn-1-yl)]methanimidamidyl)cystamine, or an acid addition salt thereof.

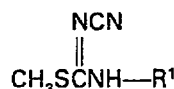
In another more preferred embodiment the compound of Formula IV is N,N'-bis[([N-cyano-N'-(4-pentyn-1-yl)]methanimidamidyl)cystamine, or an acid addition salt thereof.

In still another more preferred embodiment the compound of Formula IV is N,N'-bis[([N-cyano-N'-(2-methyl-3-butyn-2-yl)]methanimidamidyl)cystamine, or an acid addition salt thereof.

In yet another more preferred embodiment the compound of Formula IV is N,N'-bis[([N-cyano-N'-(3-butyn-2-yl)]methanimidamidyl)cystamine, or an acid addition salt thereof.

In the most preferred embodiment the compound of Formula IV is N,N'-bis[([N-cyano-N'-propargyl]methanimidamidyl)cystamine, or an acid additional salt thereof.

The compounds of Formula IV may be prepared by reacting cystamine (VI) or an acid addition salt thereof, with an N-cyano-N'-alkynyl-S-methylisothiourea of the formula



in which R¹ is as defined above, or an acid addition salt thereof, in a ratio of about 2 moles of compound VII per mole of Compound VI, in an inert organic solvent. Suitable inert organic solvents include, for example, (lower)alkanols, acetonitrile, DMF, DMSO, acetone and the like. We normally prefer to conduct the reaction in DMF.

The reaction temperature is not critical; the reaction may be conducted at temperatures of from about 0° to about 200°. At low temperatures the reaction is slow, while high temperatures normally lead to less pure products due to decomposition and the formation of side-products. We normally prefer to conduct the reaction at room temperature.

When reacting Compound VI with an N-cyano-N'-alkynyl-S-methylisothiourea of Formula VII to produce a compound of Formula IV it has been found desirable to conduct the reaction in the presence of a small amount of hydroquinone and to bubble nitrogen through the reaction mixture. These reaction conditions were found to produce compounds of Formula IV in higher yield and of higher purity. The nitrogen sweep is believed to remove the methyl mercaptan produced in the reaction and thereby avoid secondary reactions arising from the addition of methyl mercaptan to the carbon-carbon triple bond. It is believed that the hydroquinone prevents the formation of free radicals and secondary reactions arising from their presence.

The acid addition salts of compounds disclosed herein, including compounds of Formula IV, are intended to include salts of a compound of such compounds with any conventional inorganic or organic acid, e.g. hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric, maleic, fumaric, succinic, oxalic, acetic, propionic, tartaric, citric, camphorsulfonic, and the like. The acid addition salts are prepared by conventional methods.

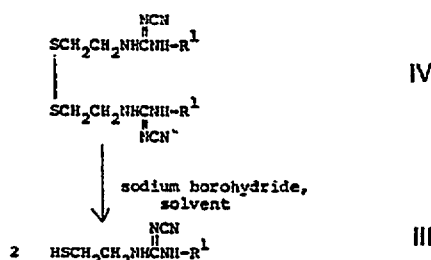
As used herein the term "(lower)alkanol" means a straight or branched chain aliphatic alcohol containing from 1 to 6 carbon atoms. The abbreviations DMF and DMSO represent dimethylformamide and dimethylsulfoxide, respectively. All temperatures herein are given in degrees centigrade. Celite is a registered trademark of the Johns-Manville Products Corporation for diatomaceous earth.

Preparation of Starting Materials

The N-cyano-N'-alkynyl-S-methylisothiourea starting materials of Formula VII utilized herein may be prepared by reacting dimethyl cyanodithioiminocarbonate with about an equimolar amount of the appropriate alkynylamine, as described in co-pending application No. 23611/78.

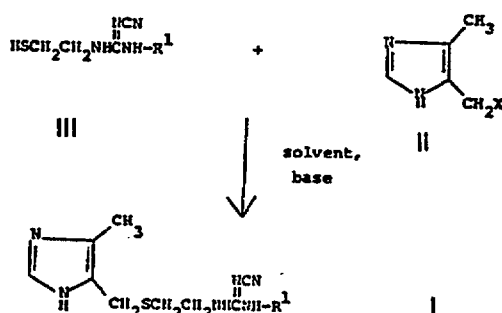
The dimethyl cyanodithioiminocarbonate which is used as a starting material for the preparation of the N-cyano-N'-alkynyl-S-methylisothioureas may itself be prepared by procedures described in J. Org. Chem., 32, 1566 (1967). The alkynylamine starting materials are either commercially available or may be prepared by methods described in Bull. Soc. Chim. Fr., 490 (1958); Bull. Soc. Chim. Fr., 592 (1967) and Annales de Chimie (Paris), 3, 656 (1958).

The compounds of Formula IV may be converted to compounds of Formula III by the general procedure for the reduction of disulfides to thiols, as described by J. J. D'Amico in J. Org. Chem., 26, 3436 (1961), as shown in the following reaction scheme:



wherein R^1 is as described above.

The compounds of Formula III may subsequently be converted to the anti-ulcer agents of Formula I by the process described in our United States Patent No. 4,158,013, as shown in the following reaction scheme.



in which R^1 and X are as described above. The reduction of compounds of Formula IV to compounds of Formula III, and the subsequent reaction of compounds of Formula III with a compound of Formula II to produce anti-ulcer agents of Formula I are further described in the following Illustrative Procedures.

Illustrative Procedure 1

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

A. N-Cyano-N'-propargyl-N''-(2-mercaptoethyl)-guanidine

To a solution of 0.082 g (0.226 m mole) of N,N'-bis[(N-cyano-N'-propargyl)methanimidamidyl]cystamine in 4 ml ethanol was added a solution of 0.082 g sodium borohydride in 2 ml ethanol and the mixture was stirred at room temperature for 1.5 hours. Acetic acid (1 ml) was added to decompose excess borohydride, the solution was poured into an 8% solution of sodium bicarbonate in water (50 ml) and extracted with chloroform (3 x 15 ml). The chloroform solution, after drying (Na_2SO_4), was evaporated to dryness to give 0.056 g of the title product as a syrup. I.R. (nujol): 3410 and 3270 (NH), 2540 (SH), 2160 ($\text{C}\equiv\text{N}$), 1590 ($\text{C}=\text{N}$) cm^{-1} ; n.m.r. (CDCl_3 - CH_3OD) δ , 4.21 (NH), 4.03 (d, 2H, $\text{CH}_2\text{C}\equiv\text{C}$, $J=2.5$ Hz), 3.43 (m, 2H, CH_2N), 2.73 (m, 2H, SCH_2), 2.45 (t, 1H, $\text{C}\equiv\text{CH}$, $J=2.5$ Hz).

This product, without further purification was used in step B.

B. N-Cyano-N'-[2-[(4-methyl-5-imidazolyl)methylthio]ethyl]-N''-propargylguanidine

A solution of 0.029 g (0.16 m mole) of the product of step A, in 1 ml ethanol containing 0.42 m mole sodium ethoxide, was placed under a nitrogen atmosphere and cooled to 4°C with stirring. After 5 minutes, 0.035 g (0.21 m mole) of solid 4-methyl-5-chloromethylimidazole was added. The mixture

- was stirred for 40 minutes, poured into brine (30 ml) and then extracted with chloroform (3 x 15 ml). After drying (Na_2SO_4), the solvent was removed by evaporation. The residue was purified by thin layer chromatography on silica gel plates using a methanol-chloroform (1:4) solvent system to give 0.022 g (50%) of the title compound as a syrup which crystallized on standing at room temperature. Trituration with chloroform gave the crystalline product, m.p. 147—149°C. I.R. (nujol): 3360 (NH), 3300 ($\text{C}\equiv\text{CH}$), 2160 ($\text{C}\equiv\text{N}$), 1600 and 1585 ($\text{C}=\text{N}$) cm^{-1} ; n.m.r. (acetone D_6): δ 8.53 (1H, NH), 7.68 (s, 1H), 7.00 (1H, NH), 4.13 (q, 2H, $J = 2.5$ Hz), 3.73 (s, 2H), 3.53 (m, 2H), 2.73 (m, 3H), 2.21 (s, 3H).

Illustrative Procedure 2

- The general procedure of Illustrative Procedure 1 is repeated except that the N,N'-bis[(N-cyano-N'-propargyl)methanimidamidyl]cystamine utilized therein is replaced by

- N,N'-bis[(N-cyano-N'-(2-butyne-1-yl))methanimidamidyl]cystamine,
 N,N'-bis[(N-cyano-N'-(3-butyne-1-yl))methanimidamidyl]cystamine,
 N,N'-bis[(N-cyano-N'-(4-pentyne-1-yl))methanimidamidyl]cystamine,
 N,N'-bis[(N-cyano-N'-(2-methyl-3-butyne-2-yl))methanimidamidyl]cystamine and
 N,N'-bis[(N-cyano-N'-(3-butyne-2-yl))methanimidamidyl]cystamine, respectively,

and there is thereby produced

- N-cyano-N'-[2-[(4-methyl-5-imidazolyl)methylthio]ethyl]-N''-(2-butyne-1-yl)guanidine,
 N-cyano-N'-[2-[(4-methyl-5-imidazolyl)methylthio]ethyl]-N''-(3-butyne-1-yl)guanidine,
 N-cyano-N'-[2-[(4-methyl-5-imidazolyl)methylthio]ethyl]-N''-(4-pentyne-1-yl)guanidine,
 N-cyano-N'-[2-[(4-methyl-5-imidazolyl)methylthio]ethyl]-N''-(2-methyl-3-butyne-2-yl)guanidine and
 N-cyano-N'-[2-[(4-methyl-5-imidazolyl)methylthio]ethyl]-N''-(3-butyne-2-yl)guanidine, respectively.

This invention is illustrated by, but in no way limited to, the following Examples.

Example 1.

- N,N'-bis[(N-Cyano-N'-propargyl)methanimidamidyl]cystamine
 Cystamine hydrochloride (2.25 g, 10 m moles) (Aldrich Chemical Co. Ltd) was treated with 1 N aqueous sodium hydroxide (20 ml) to liberate the base and then evaporated to dryness. The residue was stirred with 2-propanol and the suspension filtered through a bed of Celite filter aid to remove the inorganic salts. The filtrate was evaporated to dryness to give cystamine free base as an oil. This oil was dissolved in 5 ml DMF and added to a solution of 3.06 g (20 m moles) of N-cyano-N'-propargyl-S-methylisothiurea and 0.11 g hydroquinone in 5 ml DMF, and the reaction mixture was allowed to stand at room temperature for 16 hours while nitrogen was bubbled through the solution. The reaction mixture was diluted with ethyl acetate saturated with water (150 ml) and washed first with water saturated with ethyl acetate (2 x 100 ml) and then with brine (100 ml). After drying over sodium sulfate, the solvent was removed by evaporation. The solid residue was triturated with carbon tetrachloride (50 ml), filtered and washed with carbon tetrachloride (50 ml) to give 2.68 g of the title product, m.p. 134—136°C. Extraction of the sodium sulfate drying agent with methanol (150 ml) afforded an additional 0.41 g of the title product, thus increasing the yield to 3.09 g (85.5%). I.R. (nujol), 3290 ($\text{C}\equiv\text{CH}$), 3270 (NH), 2160 ($\text{C}\equiv\text{N}$), 1595 and 1580 ($\text{C}=\text{N}$) cm^{-1} ; n.m.r. (CD_3OD): δ 4.00 (d, 4H, $\text{N}-\text{CH}_2\text{C}\equiv\text{CH}$, $J=2.6$ Hz), 3.60 (m, 4H, CH_2N), 2.90 (m, 4H, $-\text{SCH}_2-$), 2.66 (t, 2H, $\text{C}\equiv\text{CH}$, $J=2.5$ Hz).
- Anal. Calc'd for $\text{C}_{14}\text{H}_{18}\text{N}_8\text{S}_2$: C, 46.38; H, 5.00; N, 30.91; S, 17.69
 Found: C, 46.12; H, 4.91; N, 31.21; S, 17.41

Example 2.

N,N'-bis[(N-Cyano-N'-(2-butyne-1-yl))methanimidamidyl]cystamine

- The general procedure of Example 1 is repeated except that the N-cyano-N'-propargyl-S-methylisothiurea utilized therein is replaced by an equimolar amount of N-cyano-N'-(2-butyne-1-yl)-S-methylisothiurea, and the title product is thereby produced.

Example 3.

N,N'-bis[(N-Cyano-N'-(3-butyne-1-yl))methanimidamidyl]cystamine

- The general procedure of Example 1 is repeated except that the N-cyano-N'-propargyl-S-methylisothiurea utilized therein is replaced by an equimolar amount of N-cyano-N'-(3-butyne-1-yl)-S-methylisothiurea, and the title product is thereby produced.

Example 4.

N,N'-bis[(N-Cyano-N'-(4-pentyne-1-yl))methanimidamidyl]cystamine

- The general procedure of Example 1 is repeated except that the N-cyano-N'-propargyl-S-methylisothiurea utilized therein is replaced by an equimolar amount of N-cyano-N'-(4-pentyne-1-yl)-S-

methylisothiourea, and the title product is thereby produced.

Example 5.

N,N'-bis[[N-Cyano-N'-(2-methyl-3-butyn-2-yl)]methanimidamidyl]cystamine

- 5 The general procedure of Example 1 is repeated except that the N-cyano-N'-propargyl-S-methylisothiourea utilized therein is replaced by an equimolar amount of N-cyano-N'-(2-methyl-3-butyn-2-yl)-S-methylisothiourea-cystamine, and the title product is thereby produced. 5

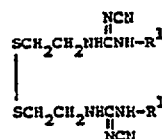
Example 6.

N,N'-bis[[N-Cyano-N'-(3-butyn-2-yl)]methanimidamidyl]cystamine

- 10 The general procedure of Example 1 is repeated except that the N-cyano-N'-propargyl-S-methylisothiourea utilized therein is replaced by an equimolar amount of N-cyano-N'-(3-butyn-2-yl)-S-methylisothiourea, and the title product is thereby produced. 10

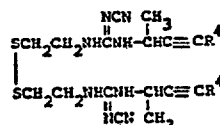
CLAIMS

1. A compound of the formula:



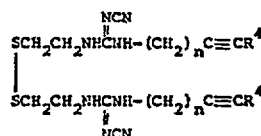
- 15 in which each R¹ is the same and is a straight or branched chain alkynyl group containing from 3 to 9 carbon atoms, or an acid addition salt thereof. 15

2. A compound as claimed in claim 1 having the formula:



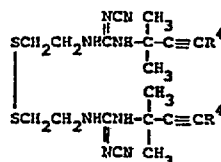
wherein each R⁴ is the same and is hydrogen or methyl, or an acid addition salt thereof.

- 20 3. A compound as claimed in claim 1 having the formula: 20



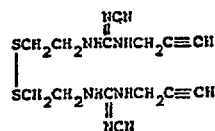
wherein each R⁴ is the same and is hydrogen or methyl, and n is an integer of from 1 to 6 inclusive, or an acid addition salt thereof.

4. A compound as claimed in claim 1 having the formula:



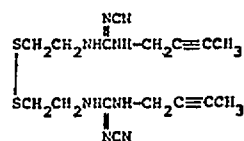
wherein each R⁴ is the same and is hydrogen or methyl, or an acid addition salt thereof.

5. A compound as claimed in claim 1 of the formula:



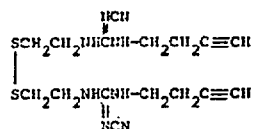
or an acid addition salt thereof.

- 30 6. A compound as claimed in claim 1 of the formula: 30



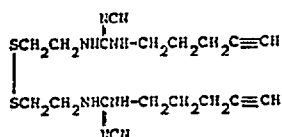
or an acid addition salt thereof.

7. A compound as claimed in claim 1 of the formula:



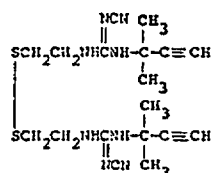
5 or an acid addition salt thereof.

8. A compound as claimed in claim 1 of the formula:



or an acid addition salt thereof.

9. A compound as claimed in claim 1 of the formula:

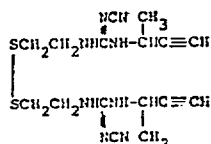


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or an acid addition salt thereof.

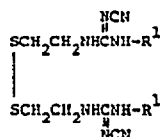
10. A compound as claimed in claim 1 of the formula:



or an acid addition salt thereof.

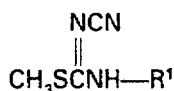
15 11. A process for the preparation of a compound of the formula:

15



IV

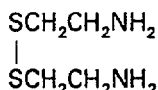
in which each R¹ is the same and is a straight or branched chain alkynyl group containing from 3 to 9 carbon atoms, or an acid addition salt thereof, which process comprises reacting in an inert organic solvent a compound of the formula:



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20

with a compound of the formula:



VI

or an acid addition salt thereof in which R¹ is as defined above, in a ratio of about 2 moles of compound VII per mole of compound VI, and if desired, converting the resulting compound of formula IV basic form or an acid addition salt thereof to the corresponding acid addition salt in free base form.

- 5 12. A process as claimed in claim 11 which is carried out in the presence of hydroquinone and in which nitrogen gas is bubbled through the reaction mixture. 5
13. A process as claimed in claim 11 or claim 12 wherein the reaction is conducted at a temperature within the range of from 0 to 200°C.
14. A process as claimed in claim 13 wherein the reaction is conducted at ambient temperature.
- 10 15. A process as claimed in any one of claims 11 to 13 wherein the inert solvent is a (lower)alkanol, acetonitrile, DMF, DMSO, or acetone. 10
16. A process as claimed in claim 11 substantially as hereinbefore described with reference to any one of the Examples.
17. A compound as claimed in claim 1 whenever prepared by a process as claimed in any one of claims 11 to 16.

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