

PATENT SPECIFICATION

(11) 1338 169

NO DRAWINGS

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18X—197—277 1E4K4 1Q11D 1Q11G 1Q11J
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625 626 628 630 635 650 652 655 670 680 68X
694 702 703 70X 719 73X 747 750 753 754 758
75X 761 763 76X 76Y 771 78Y 790 79Y LJ
LZ MA MV QM QS QU RB RH RM SM UV

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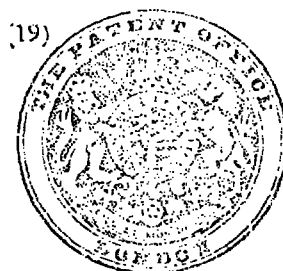
(71) We, SMITH KLINE & FRENCH LABORATORIES LIMITED, of Mundells, Welwyn Garden City, Herts., a British Company, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

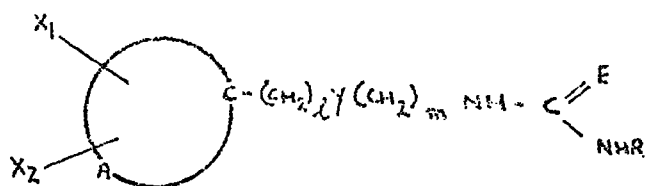
This invention relates to pharmacologically active compounds, to pharmaceutical compositions comprising these compounds and to processes for their preparation. The compounds of the invention can exist as the addition salts but, for convenience, reference will be made throughout this specification to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

It has for long been postulated that many of the physiologically active substances within the animal body, in the course of their activity, combine with certain specific sites known as receptors. Histamine is a compound which is believed to act in such a way but, since the actions of histamine fall into more than one type, it is believed that there is more than one type of histamine receptor. The type of action of histamine which is blocked by drugs commonly called "antihistamines" (of which mepyramine is a typical example) is believed to involve a receptor which has been designated by Ash and Schild (Brit. J. Pharmac. 1966, 27 427) as H—1. The substances of the present invention are distinguished by the fact that they act at histamine receptors other than the H—1 receptor. Thus they are of utility in inhibiting certain actions of histamine which are not inhibited by the above-mentioned "antihistamines". The substances of this invention may also be of utility as inhibitors of certain actions of gastrin.

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

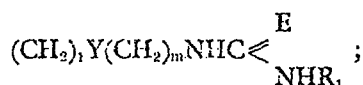
The compounds with which the present invention is concerned may be represented by the following general formula; in so far as tautomerism affects the compounds mentioned in this specification, the numbering of the nucleus has been modified accordingly:





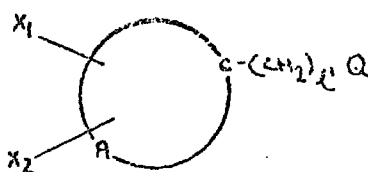
FORMULA I

wherein A is such that there is formed together with the carbon atom shown an unsaturated heterocyclic nucleus, preferably having five or six atoms, which nucleus comprises at least one nitrogen atom and may comprise further hetero atoms such as sulphur and oxygen, e.g. imidazole, pyridine, thiazole, oxazole, pyrazole, triazole, thiadiazole, pyrimidine, pyrazine or pyridazine; X₁ and X₂ which may be the same or different are hydrogen, lower alkyl, trifluoromethyl, hydroxyl, benzyl, halogen, amino,



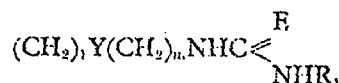
or X₁ may with X₂ and at least two of the atoms comprising A form a further ring e.g. a benzene ring, a pyrimidine ring or a partially unsaturated ring; l and m are integers from 0 to 4 provided that the sum of l and m is 3 or 4; Y is oxygen, sulphur or NH; E is oxygen, sulphur or, provided that A is not such that a pyridine ring is formed, NR₂; R₁ is hydrogen, lower alkyl such as methyl, acyl e.g. benzoyl, or dialkyl-aminoalkyl such as dimethylaminoethyl; and R₂ is hydrogen, nitro or cyano. Preferably A is such that the nitrogen atom is adjacent to the carbon atom shown and, more preferably, such that it forms with the said carbon atom an imidazole, thiazole or pyridine ring. Preferably X₁ is hydrogen, methyl, bromine, amino or hydroxyl and X₂ is hydrogen. One group of preferred compounds within the present invention is that wherein Y and E are sulphur, l is 1, m is 2 and R₁ is methyl. Specific compounds which are found to be particularly useful are N-methyl-N'-[2-((4-imidazolyl)methylthio)ethyl]-thiourea, N-methyl-N'-[2-((5-methyl-4-imidazolyl)methylthio)ethyl]thiourea, N-methyl-N'-[2-((5-bromo-4-imidazolyl)methylthio)ethyl]thiourea, N-methyl-N'-[2-((1-methyl-2-imidazolyl)methylthio)ethyl]thiourea, N-methyl-N'-[2-((2-imidazolyl)methylthio)ethyl]thiourea, N-methyl-N'-[2-((2-thiazolyl)methylthio)ethyl]thiourea, N-methyl-N'-[2-((3-hydroxy-2-pyridyl)methylthio)ethyl]thiourea, N-methyl-N'-[2-(5-amino-2-(1,3,4-thiadiazolyl)methylthio)ethyl]thiourea, N-methyl-N'-[2-(3-(1,2,4-triazolyl)methylthio)ethyl]thiourea and N-methyl-N'-[3-(2-thiazolyl)-thiopropyl]thiourea.

The compounds with which the present invention is concerned wherein Y is sulphur and l is 1 or 2 may be produced by processes which commence with a substance of the following general formula:

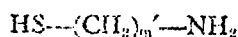


FORMULA II

wherein A, X₁ and X₂ have the same significance as in formula I except that X₁ and/or X₂ may not be



but may additionally be (CH₂)₁, Q; l' is 1 or 2 and Q is hydroxyl, halogen or methoxy. In the first stage of these processes, the compound of formula II is reacted with an amino-mercaptan of the following FORMULA III:

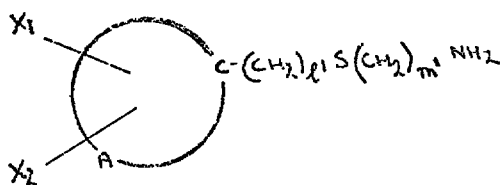


wherein m' is 2 or 3.

When Q is halogen, this reaction may be carried out under strongly basic conditions, for example in the presence of sodium ethoxide or sodium hydroxide. Since the substance of formula III is a primary amine it may be necessary to protect the amino group, for example by a phthalimido group which may subsequently be removed by acid hydrolysis or by hydrazinolysis. When Q is hydroxyl or halogen it is found that the reaction will take place under acidic conditions e.g. in the presence of a halogen acid such as 48% aqueous hydrogen bromide, or a halogen acid in the presence of glacial acetic acid. When Q is methoxy, the reaction will also take place in the presence of 48% hydrogen bromide.

When l is zero, the corresponding first stage of the reaction is between a nucleus directly substituted with a thiol or a thiene and, under acidic conditions with 3-amino-propanol or 4-aminobutanol or, under alkaline conditions, with a 3-haloethylamine or a 4-haloethylamine, the amino group being protected if required in the latter case e.g. by a phthalimido group.

The product produced by these processes is of the following formula IV, and may, of course, be in the form of the acid addition salt.



FORMULA IV.

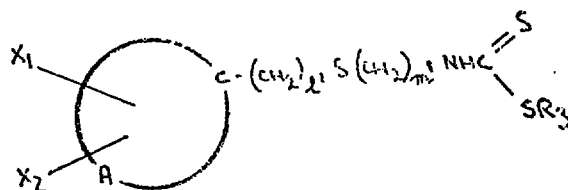
wherein A, X_1 and X_2 have the same significance as in formula II, except that X_1 and/or X_2 may additionally be $(CH_2)_nS(CH_2)_mNH_2$, Q being in this case $S(CH_2)_mNH_2$; l' is from 0—2 and m' is from 2 to 4, provided that $l'+m'$ are 3 or 4. The free base of formula IV may be obtained from the acid addition salt by treatment with an appropriate base e.g. an alkali metal alkoxide such as sodium ethoxide or an inorganic base such as potassium carbonate.

The compounds of Formula I, where R_1 is hydrogen, Y is sulphur and E is sulphur may be prepared from an amine of Formula IV by reaction with an acyl isothiocyanate in an appropriate solvent such as chloroform. Alkaline hydrolysis of these compounds, e.g. the benzoyl derivatives where R_1 is C_6H_5CO , with a reagent such as aqueous potassium hydroxide or aqueous potassium carbonate yields the compounds of formula I wherein R_1 is hydrogen and Y and E are sulphur.

Compounds of Formula I wherein R_1 is hydrogen, Y is sulphur and E is sulphur may alternatively be prepared directly from the amine of Formula IV by reaction at elevated temperature with the thiocyanate of ammonium or of a metal such as sodium or potassium.

The compounds of Formula I where R_1 is lower alkyl or dialkylaminoalkyl, Y is sulphur and E is sulphur may be prepared from the amine of Formula IV by reaction with an isothiocyanic ester of Formula $R_1N=C=S$ in an appropriate solvent such as chloroform, ethanol, isopropanol, acetonitrile or water.

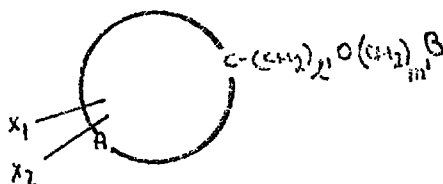
Alternatively the amine of Formula IV may be converted by reaction with carbon disulphide to the dithiocarbamic acid of the formula:



FORMULA V.

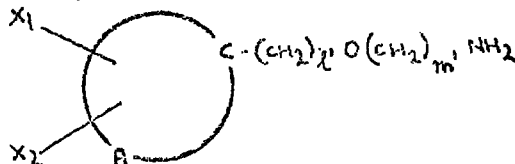
wherein, A, X₁, X₂, l' and m' have the same significance as in formula IV and R₂ is hydrogen and then methylated to yield the compound of formula V wherein R₂ is methyl. Finally, reaction of this methyl ester with an amine of formula R₁NH₂, wherein R₁ is lower alkyl yields the required compound.

In the case of compounds of formula I wherein Y is oxygen, the process for their production commences with a compound of formula VI (which may itself be formed by treatment with thionyl halide of the corresponding alcohol resulting from the reaction of a haloalkyl heterocyclic compound and the sodium salt of a diol):



FORMULA VI

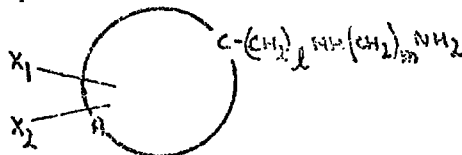
wherein A, X₁ and X₂ have the same significance as in formula I, l' and m' are from 1 to 3, l'+m' is 3 or 4 and B is halogen. This compound may be reacted with an alkali metal azide and the resulting product reduced e.g. by hydrogenation over a platinum dioxide catalyst to yield an amine of formula VII:



FORMULA VII.

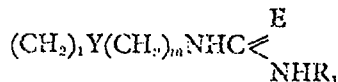
The compound of formula VII may be converted to the compounds of formula I wherein Y is oxygen and E is sulphur by methods analogous to those described hereinabove for the conversion of the compounds of formula IV to those of formula I wherein both Y and E are sulphur.

The compounds of formula I wherein Y is NH and E is sulphur are similarly formed from a compound of formula VIII.



FORMULA VIII.

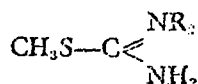
wherein A, X₁, X₂, l, m and R₂ have the same significance as in formula I, except that X₁ and X₂ may not be



but may additionally be (CH₂)_lY(CH₂)_mNH₂.

Compounds of formula I wherein E is oxygen may be formed from the amines of formula IV, formula VII or formula VIII by treatment thereof with an isocyanate of formula R₁NCO wherein R₁ is lower alkyl. The compounds of formula I wherein E is oxygen and R₁ is hydrogen may be obtained by reaction of the said amines with sodium or potassium cyanate.

Compounds of formula I wherein E is NR₂ may be prepared from the amines of formula IV, formula VII or formula VIII by treatment thereof with an isothiourea of formula IX.



FORMULA IX.

As stated above, the compounds represented by Formula I have been found to have pharmacological activity in the animal body as antagonists to certain actions of histamine which are not blocked by "antihistamines" such as mepyramine. For example, they have been found to inhibit selectively the histamine-stimulated secretion of gastric acid from the perfused stomachs of rats anaesthetised with urethane. Similarly, the action of these compounds may, in many cases, be demonstrated by their antagonism to the effects of histamine on other tissues which, according to the above-mentioned paper of Ash & Schild, are not H—1 receptors. Examples of such tissues are perfused isolated guinea-pig heart, isolated guinea-pig right atrium and isolated rat uterus. The compounds of the invention have also been found to inhibit the secretion of gastric acid stimulated by pentagastrin or by food. In addition to the above, the compounds of the invention also show some anti-inflammatory activity in conventional tests.

The level of activity found for the compositions comprising the thiourea derivatives of the present invention is illustrated by the effective dose range in the anaesthetised rat, as mentioned above of from 0.5 to 256 micromoles per kilogram. Many of the compounds of the present invention produce a 50% inhibition in this test at a dose of from 1 to 10 micromoles per kilogram. Similar results have been found in the dog and in man.

For therapeutic use, the pharmacologically active compounds of the present invention will normally be administered as a pharmaceutical composition comprising as the or an essential active ingredient at least one such compound in the basic form or in the form of an addition salt with a pharmaceutically acceptable acid and in association with a pharmaceutical carrier therefor.

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

The invention is illustrated but in no way limited by the following examples, wherein all temperatures are given in degrees Centigrade:

EXAMPLE 1.

N-Methyl-N'-[2-((4-imidazolyl)methylthio)ethyl]thiourea

(i) (a) A solution of 4(5)-hydroxymethylimidazole hydrochloride (67g.) and cysteamine hydrochloride (56.8g.) in aqueous hydrobromic acid (1 litre, 48%) was heated under reflux overnight. After cooling, the solution was evaporated to dryness and the residual solid washed with ethanol/ether to give 4(5)-[(2-aminoethyl)thiomethyl]-imidazole dihydrobromide (156g.), m.p. 178—179°.

(b) Phthalimidoethanethiol (2 g.) was added portionwise with stirring to a solution of sodium ethoxide (prepared from 0.23 g. of sodium) in ethanol (20 ml.) at 0° under a nitrogen atmosphere. After stirring at 0° for a further 2½ hours, the resulting yellow solution was cooled with an ice-salt bath and a solution of 4(5)-chloromethylimidazole hydrochloride (0.76 g.) in ethanol (5 ml.) was added dropwise over 10 minutes. After addition the mixture was stirred at room temperature overnight, then acidified with ethanolic hydrogen chloride and evaporated to dryness. Addition of water precipitated unreacted phthalimidoethanethiol (0.6 g.) which was removed by filtration. The filtrate was concentrated and basified with aqueous sodium bicarbonate solution to furnish a white precipitate which, on recrystallisation from aqueous ethanol, gave 4(5)-[(2-phthalimidoethyl)thiomethyl]imidazole (0.75 g.) m.p. 136—137°. A stirred mixture of this phthalimido derivative (0.62 g.) in aqueous hydrobromic acid (40 ml, 18%) was heated under reflux overnight. After cooling to 0°, the resulting clear solution was filtered and the filtrate evaporated to dryness. Recrystallisation of the residue from ethanol gave 4(5)-[(2-aminoethyl)thiomethyl]imidazole dihydrobromide (0.52 g.), m.p. 178—179°.

(c) A suspension of cysteamine hydrochloride (118—8 g.) in ethanol (200 ml., dried over molecular sieves) was added portionwise at 0° to a solution of sodium ethoxide (prepared from 48 g. of sodium) in ethanol (1 litre) under a nitrogen atmosphere. After stirring at 0°, for a further 2 hours, a solution of 4(5)-chloromethylimidazole hydrochloride (80 g.) in ethanol (400 ml.) was added dropwise over 45 minutes while the temperature was maintained at $-1^{\circ}\pm 2^{\circ}$. After addition, the mixture was stirred at room temperature overnight, filtered, and the filtrate acidified with concentrated hydrochloric acid. The solution was then evaporated to dryness, the residue dissolved in ethanol (1 litre) and a solution of excess picric acid in hot ethanol

added. The resulting crude picrate was dissolved in water (2.7 litres) and, after decantation from an insoluble oil, the solution was left to cool to give 4(5)-((2-aminoethyl)thiomethyl)imidazole dipicrate, m.p. 194—195°. Treatment of this picrate with aqueous hydrobromic acid followed by extraction with toluene gave the hydrobromide, m.p. 178—179°, after evaporation to dryness and recrystallisation of the crude residue from ethanol.

(ii) A solution of 4(5)-((2-aminoethyl)thiomethyl)imidazole dihydrobromide (10 g.) in water (25 ml.) was basified to pH 11 by the addition of a solution of potassium carbonate (8.7 g.) in water (25 ml.). The resulting solution was evaporated to dryness, extracted with isopropyl alcohol and the final traces of water removed by azeotropeing with isopropyl alcohol. The residual amine was extracted from the inorganic material with isopropyl alcohol, the extracts concentrated to about 70 ml. and a solution of methyl isothiocyanate (2.3 g.) in isopropyl alcohol (5 ml.) added. The reaction mixture was then heated under reflux for 1½ hours and, after cooling, evaporated to dryness. The residual oil was dissolved in acetone, the solution filtered to remove traces of inorganic material, and the filtrate concentrated to give N-methyl-N'-(2-(4-imidazolylmethylthio)ethyl)thiourea (4.1 g.), m.p. 96—98°. A sample, recrystallised from acetone, had m.p. 98—99°.

(Found: C, 41.8; H, 6.4; N, 24.4; S, 27.6. $C_6H_{11}N_4S_2$ requires: C, 41.7; H, 6.1; N, 24.3; S, 27.8).

EXAMPLE 2.

N-Methyl-N'-[2-((5-methyl-4-imidazolyl)methylthio)ethyl]thiourea

(i) (a) A solution of 4-hydroxymethyl-5-methylimidazole hydrochloride (30.0 g.) and cysteamine hydrochloride (23.0 g.) in acetic acid (200 ml.) was heated under reflux for 10 hours. Following cooling to 15—20°, the solid which crystallised was collected and washed with isopropyl alcohol to give 4-methyl-5-[(2-aminoethyl)thiomethyl]imidazole dihydrochloride (45.5 g.), m.p. 189—192°.

(b) A solution of 4-hydroxymethyl-5-methylimidazole hydrochloride (30.0 g.) and cysteamine hydrochloride (23.0 g.) in concentrated aqueous hydrochloric acid (450 ml.) was heated under reflux for 17 hours. Concentration followed by re-evaporation with water afforded a residue which was dissolved in isopropyl alcohol, concentrated to low bulk and cooled to afford 4-methyl-5-[(2-aminoethyl)thiomethyl]imidazole dihydrochloride (40.6 g.), m.p. 185—191°.

(c) A mixture of 4-hydroxymethyl-5-methylimidazole hydrochloride (15.0 g.), cysteamine hydrochloride (11.5 g.) and a solution of hydrogen bromide in acetic acid (18%, 225 ml.) was heated under reflux for 7 hours. Cooling afforded 4-methyl-5-[(2-aminoethyl)thiomethyl]imidazole dihydrobromide (21.6 g.), m.p. 208—211°.

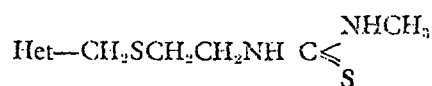
(ii) Potassium carbonate (7.75 g.) was added to a solution of 4-methyl-5-[(2-aminoethyl)thiomethyl]imidazole dihydrochloride (14.6 g.) in water (120 ml.). The solution was stored at room temperature for 15 minutes and methyl isothiocyanate (5.15 g.) was added. After heating under reflux for 30 minutes, the solution was slowly cooled to 5°.

The product (13.1 g.) was collected and re-crystallised from water to give N-methyl-N'-[2-((5-methyl-4-imidazolyl)methylthio)ethyl]thiourea, m.p. 150—152°.

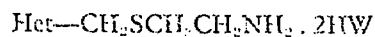
(Found: C, 44.5; H, 6.7; N, 23.0; S, 26.2. $C_7H_{16}N_4S_2$ requires: C, 44.2; H, 6.6; N, 22.9; S, 26.2.)

EXAMPLES 3—27.

By two-stage processes essentially similar to those described in Example 1 (i) and (ii) were produced thiourea compounds of the formula:



wherein Het has the significance as set out in the following table I. The solvent from which the product was crystallised and the melting point and elemental analysis data of the product are also set out in the table together with the melting point of the corresponding intermediate amine salt of formula:



wherein W is a picrate or bromide anion as indicated in the table.

The starting materials of formula:

Het-CH₂Q

wherein Q is hydroxyl, halogen or methoxy are all known compounds with the exception of those used in examples 3, 4 and 5, 14 and 26, the preparation of which is described hereinafter. In each case, the starting material was reacted with cysteamine hydrochloride in aqueous hydrobromic acid as described in Example 1 (i) (a). Where necessary, the resultant amine was purified by conversion to the picrate followed by treatment with hydrochloric or hydrobromic acid and removal of picric acid, thus yielding the corresponding hydrochloride or hydrobromide (as described in Example 1 (i) (c)).

Conversion of this hydrochloride or hydrobromide into the free base by the addition of potassium carbonate followed by concentration and extraction with isopropanol or ether/ethanol (3:1) yielded an extract which was reacted with methyl isothiocyanate in an appropriate solvent under conditions similar to those described in example 1 (ii). The resultant thiourea products, where crystallisable were recrystallised from a solvent as indicated in table 1.

Table 1

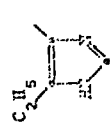
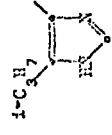
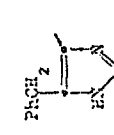
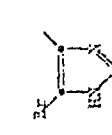
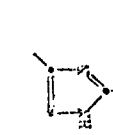
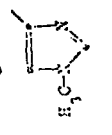
Ex. No.	Ret	Intermediate amide salt		Recryst. from	M.P. (°C)	Mol. Formula	Elemental Analysis										* * *
		W	M.P. (°C)				Found					Required					
							C	H	N	S	C	H	N	S			
3		bromide	-	aqueous ethanol	127-129	$C_{10}H_{13}N_4S_2$ 2 Picriclone	45.3	5.0	21.2	12.1	46.0	5.1	21.4	12.3	5-ethyl-4-imidazolyl		
4		picrate	170-172.5	isopropyl acetate/ether	85-89	$C_{11}H_{13}N_4S_2$	43.5	7.6	20.8	23.6	48.5	7.4	20.6	23.5	5-isopropyl-4-imidazolyl		
5		bromide	-	aqueous ethanol	131-133	$C_{15}H_{13}N_4S_2$	56.0	6.2	17.3	20.0	56.2	6.3	17.5	20.0	5-phenyl-4-imidazolyl		
6		bromide	180-181	acetone/ether	152-153	$C_8H_9BrN_4S_2$	32.1	4.4	18.1	20.4	31.1	4.2	18.1	20.7	5-bromo-4-imidazolyl		
7		bromide	181-2	water	119-122	$C_9H_{16}N_4S_2$	44.0	6.6	22.7	25.8	44.2	6.6	22.9	26.2	2-methyl-4-imidazolyl		
8		bromide	190-3	ethyl acetate/Ketone	111-115	$C_9H_{16}N_4S_2$	44.5	6.7	22.8	25.7	44.2	6.6	22.9	26.2	1-methyl-4-imidazolyl		

Table 1 Cont'd....

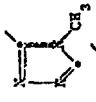
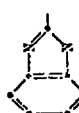
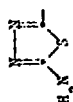
Ex. No.	Het	Intermediate amine salt		Recryst. from	M.P. (°C)	Molecular Formula	Product: N-methyl-N'-[2-(***)methylthio] ethyl] thiourea										***
		W	M.P. (°C)				Found					Required					
							C	H	N	S	C	H	N	S			
9		bromide	195-197	ethylacetate/petroleum ether	76-78	C ₈ H ₁₄ N ₂ S ₂	41.8	6.1	24.3	27.9	41.7	6.1	24.3	27.8	2-imidazolyl		
10		picrate	172-174	isopropyl acetate/ethanol	114-116	C ₉ H ₁₆ N ₂ S ₂	44.5	6.8	23.0	26.2	44.2	6.6	23.0	26.2	1-methyl-2-imidazolyl		
11		bromide	-	isopropyl acetate	105-107	C ₁₀ H ₁₈ N ₂ S ₂	46.4	6.8	21.6	24.3	46.5	7.0	21.7	24.8	1,5-dimethyl-2-imidazolyl		
12		bromide	-	water	96-98	C ₉ H ₁₅ ClN ₂ S ₂	38.6	5.3	19.9	22.6	38.8	5.4	20.1	23.0	5-chloro-1-methyl-2-imidazolyl		
13		bromide	177-179	ethanol/ether	97-99	C ₇ H ₁₃ S ₂	26.1	5.7	30.1	28.0	36.3	5.7	30.3	27.7	3-(1,2,4-triazolyl)		
14		bromide	175-177	water	154-155	C ₈ H ₁₅ N ₂ S ₂	39.3	6.0	28.7	26.2	39.2	6.2	28.5	26.1	4-methyl-3-(1,2,4-triazolyl)		
15		bromide	152-4	-	-	C ₈ H ₁₄ N ₂ S ₂	41.9	6.1	23.7		41.7	6.1	24.3		3-pyrazolyl		

Table I. Cont'd....

Product: N-methyl-N'-i2- (* * *)methylthio) ethyl thiourea																			
Ex. No.	Het	Intermediate amine salt		W	M.P. (°C)	Recryst. from	m.p. (°C)	Molecular Formula	Elemental Analysis										* * *
		Found	Required						Found				Required						
									C	H	N	S	C	H	N	S			
16		bromide	144-147.5	-	isopropyl acetate	114-116	$C_8H_{13}N_2S_3$	38.8	5.4	17.0	38.9	38.8	5.3	17.0	38.9	2-thiazolyl			
17		bromide	197-203	-	isopropyl acetate/isopropanol	78-80.5	$C_8H_{13}N_2S_3$	38.8	5.3	17.2	38.7	38.8	5.3	17.0	38.9	4-thiazolyl			
18		bromide	191-193	-	-	-	$C_{10}H_{15}N_2S_2$	49.4	6.3	17.3	26.2	49.8	6.3	17.4	26.6	2-pyridyl			
19		bromide	173-3	-	-	-	$C_{11}H_{17}N_2S_2$	51.4	6.5	16.2	24.8	51.7	6.7	16.5	25.1	3-methyl-2-pyridyl			
20		bromide	188-9	-	isopropyl acetate	82-83	$C_{11}H_{17}N_2S_2$	51.8	7.0	16.6	21.6	51.7	6.7	16.5	25.1	6-methyl-2-pyridyl			
21		bromide	185-7	-	methanol-ether	78-80°	$C_{10}H_{15}N_2S_2$	49.5	6.2	17.3	26.5	49.8	6.3	17.4	26.6	3-pyridyl			
22		bromide	236-8	-	-	-	$C_{10}H_{15}N_2S_2$	49.9	6.5	17.3	26.3	49.8	6.3	17.4	26.6	4-pyridyl			

Table 1 Cont'd....

Product: N-methyl-N'-[2-(***)(methylthio)ethyl] thiourea																	
Ex. No.	Het	Intermediate amine salt		Recryst. from	m.p. (°C)	Molecular Formula	Elemental Analysis										***
		W	m.p. (°C)				Found					Required					
							C	H	N	S	C	H	N	S			
23		bromide	231-2	water	130-133	C ₁₀ H ₁₅ NOS ₂	46.4	5.9	16.1	24.8	46.7	5.9	15.3	24.9	3-hydroxy-2-pyridyl		
24		picrate	145-8	acetone-ether	110-111	C ₉ H ₁₄ N ₂ S ₂	44.5	5.9	23.0	26.3	44.6	5.8	23.1	26.5	3-pyridazinyl		
25		bromide	242-5	isopropanol/isopropyl acetate	157-9	C ₁₂ H ₁₆ N ₂ S ₂	51.3	5.8	19.9	22.5	51.4	5.8	20.0	22.9	2-benzimidazolyl		
26		bromide	-	isopropyl acetate/ethyl acetate	105-6	C ₁₂ H ₂₀ N ₂ S ₂	50.7	7.1	19.6	22.3	50.7	7.1	19.7	22.5	5,6,7,8-tetrahydroimidazo[1,5-a]pyridyl		
27		bromide	229-232	aqueous ethanol	143-145	C ₇ H ₁₃ N ₂ S ₂	32.0	5.0	26.7	36.2	32.0	5.0	26.6	36.5	5-(2-amino-1,3,4-thiadiazolyl)		

Preparation of starting materials for Examples 3, 4 & 5, 11 & 26 :

(a) 4-Ethyl-5-hydroxymethylimidazole hydrochloride (Example 3)

Sulphuryl chloride (286 g.) was added dropwise to a solution of ethyl 3-oxopentanoate (300 g.) in chloroform (250 ml.) at 10—15°. Following addition the mixture was stirred overnight at room temperature, heated under reflux for 0.5 hours and cooled. After washing with water, sodium bicarbonate and water, the solution was dried (sodium sulphate), concentrated, and fractionated to yield ethyl 2-chloro-3-oxopentanoate, b.p. 94—96°/14 mm.

A mixture of ethyl 2-chloro-3-oxopentanoate (178 g.) freshly distilled formamide (450 g.) and water (38 ml.) was heated at 140—148° and then cooled and added to dilute hydrochloric acid. After decanting from insoluble material, the solution was basified with ammonium hydroxide to give a solid which, following recrystallisation from aqueous ethanol and ethanol-ethyl acetate, yielded 4-ethyl-5-carbethoxyimidazole (29 g.) m.p. 170—172°. This ester (14.0 g.) was reduced with lithium aluminium hydride (4.6 g.) in tetrahydrofuran and then treated with hydrogen chloride to give 4-ethyl-5-hydroxymethylimidazole hydrochloride (10.6 g.) m.p. 141—143° (from isopropyl alcohol-ether)

(b) 4-Isopropyl-5-hydroxymethylimidazole hydrochloride (Example 4)

A solution of sodium nitrite (43.8 g.) in water (92 ml.) was added dropwise, with stirring, to a solution of ethyl isobutyrylacetate (100.3 g.) in acetic acid (80 ml.) at 0°. After stirring at 0° for 30 minutes then at room temperature for 3 hours, water (100 ml.) was added and the mixture extracted with ether. The extracts were washed with water, saturated sodium bicarbonate solution and water. After drying (CaSO₄), the solution was evaporated to give ethyl 2-oximino-4-methyl-3-oxopentanoate (112 g.) as a crude oil.

A solution of this oximinoketone (219 g.) in ethanol (230 ml.) was added to a suspension of pre-reduced palladised charcoal (10 g., 10%) in ethanol (1 lit.) and saturated ethanolic hydrogen chloride (512 ml.) and the mixture hydrogenated at room temperature and pressure until the theoretical amount of hydrogen was taken up. The mixture was filtered, the filtrate concentrated and ethyl acetate added to give ethyl 2-amino-4-methyl-3-oxopentanoate hydrochloride (230.6 g.) m.p. 129—131° (dec.). This aminoketone (50.5 g.) was dissolved in redistilled formamide (180 ml.) and the solution heated at 120° for two hours, 130° for one hour, and finally at 140° for two hours. After cooling, the mixture was filtered and the crystalline product washed with water to give ethyl 4-isopropyl-5-carbethoxyimidazole (22 g.) m.p. 177—178°.

This ester (108 g.) was placed in a soxhlet and reduced with lithium aluminium hydride (34.5 g.) in tetrahydrofuran to give 4-hydroxymethyl-5-isopropylimidazole (62.3 g.) m.p. 121—123°.

(c) 4-Benzyl-5-hydroxymethylimidazole hydrochloride (Example 5)

Reaction of ethyl 3-oxo-4-phenylbutyrate (10.3 g.) with sodium nitrite followed by reduction of the crude ethyl 2-oximino-3-oxo-4-phenylbutyrate (10.8 g.) as described in the previous section, (b), gave ethyl 2-amino-3-oxo-4-phenylbutyrate hydrochloride (8.5 g.) m.p. 150—153°. An analytical sample, recrystallised from ethanol/ethyl acetate, had m.p. 154—155°.

Reaction of this aminoketone (160 g.) with formamide (480 ml.) by the method described in the previous section, (b), gave 4-benzyl-5-carbethoxyimidazole (75 g.) m.p. 168.5—169.5°. Reduction of this ester (30 g.) with lithium aluminium hydride (6.4 g.) in tetrahydrofuran (600 ml.), followed by addition of water, filtration and acidification of the filtrate with ethanolic hydrogen chloride, gave 4-benzyl-5-hydroxymethylimidazole hydrochloride (22.9 g.), m.p. 149—151°, after concentration and addition of ethyl acetate.

(d) 4-Methyl-3-hydroxymethyl-1,2,4-triazole (Example 14)

Ethoxyacetyl chloride (57 g.) was added slowly to a stirred solution of 4-methylthiosemicarbazide (53.5 g.) in dry pyridine (500 ml.) at 0—5°. The mixture was allowed to attain room temperature and stirring was continued for 18 hours. Following concentration under reduced pressure the residue was treated with a solution of sodium (21.4 g.) in ethanol (500 ml.) and the mixture was heated under reflux for 24 hours. Following concentration and acidification with hydrochloric acid a solid was obtained. After partial concentration the solid was collected and recrystallised from ethyl acetate to give 3-ethoxymethyl-4-methyl-1,2,4-triazoline-5-thione (53 g.), m.p. 137—138°.

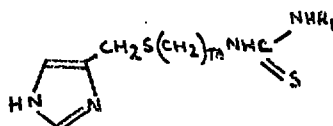
The thione (44 g.) was desulphurised by slow addition to a solution prepared from nitric acid (75 ml.) water (150 ml.) and sodium nitrite (1.5 g.) at 15—20°. Following subsequent basification with sodium carbonate and concentration the residue was extracted with ethanol-ether 1:1 and distilled to afford 3-ethoxymethyl-4-methyl-1,2,4-triazole (30 g.) b.p. 154—156°/0.05 mm. The above compound (15 g.) dissolved in 48% aqueous hydrobromic acid (150 ml.) was heated under reflux for 24 hours, concentrated to dryness and the residue obtained was used directly in the reaction with cysteamine hydrochloride and hydrobromic acid.

(e) 3-Hydroxymethyl-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine (Example 26)

A solution of 1.58 molar n-butyl lithium in n-hexane (49 ml.) was added over 0.5 hour to a stirred solution of 5,6,7,8-tetrahydroimidazo[1,5-a]pyridine (8.9 g.) in dry ether at -60° under nitrogen. After 3 hours, gaseous formaldehyde generated by the thermal condensation of paraformaldehyde (6.9 g.) was passed into the red solution. The mixture was allowed to warm to room temperature overnight, acidified with hydrochloric acid and extracted with chloroform. The aqueous layer was basified with an excess of saturated sodium carbonate solution and extracted with chloroform. Concentration and recrystallisation of the residue from ethanol-ethyl acetate-petroleum ether afforded 3-hydroxymethyl-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine (7.7 g.) m.p. 188—199°.

Examples 28—30.

Two stage processes as described in examples 3—27 were used for the production of compounds of the following formula.



Wherein R₁ has the significance as set out in table II. In each case the intermediate amine was of the formula:

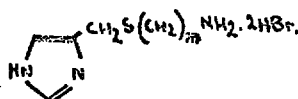


Table II shows the values for *m* and R₁ and recrystallisation solvent, melting point and elemental analysis for each product.

Table 2

Ex. No.	Product: N-(*)*) - N'-(4-imidazolylmethylthio)*)*) thiourea														
	R ₁	Recrystallised from.	m.p. (°C)	Molecular formula	Elemental Analysis										
					Found				Required						
					C	H	N	S	C	H	N	S			
28	CH ₃	water	118-120	C ₉ H ₁₆ N ₄ S ₂	44.0	6.7	22.9	25.7	44.2	6.6	22.9	26.2	methyl	3	propyl
29	C ₂ H ₅	water	128-129	C ₉ H ₁₈ N ₄ S ₂	44.2	6.9	23.2	26.4	44.2	6.6	22.9	26.2	ethyl	2	ethyl
30	CH ₂ CH ₂ N(CH ₃) ₂	isopropyl acetate/ether	97-99.5	C ₁₁ H ₂₁ N ₄ S ₂	46.2	7.6	24.7	22.2	46.0	7.4	24.4	22.3	2 di-ethyl-amino-ethyl	2	ethyl

5

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N₂

Example 31.

N-Methyl-N'-(2-(2-(4-imidazolyl)ethyl)thioethyl)thiourea dihydroiodide.

(i) A solution of 4(5)-(2-chloroethyl)imidazole hydrochloride (13.6 g.) and cysteamine hydrochloride (9.3 g.) in distilled water (100 ml.) was added over 30 minutes to a stirred solution of potassium hydroxide (15.8 g., 85%) in water (40 ml.) at room temperature under a nitrogen atmosphere. After addition the solution was heated for 4 hours at 50°. From time to time it was necessary to add a few drops of potassium hydroxide solution to prevent the pH of the reaction mixture falling below 11. The reaction mixture was then acidified with 2N hydrochloric acid, evaporated to dryness under reduced pressure and the final traces of water removed by azeotropeing with n-propanol. The residue was extracted several times with isopropyl alcohol and the combined extracts added to a hot solution of picric acid in isopropyl alcohol. On cooling, this gave 4(5)-(2-(2-aminoethyl)thioethyl)imidazole dipicrate (42.3 g.) m.p. 225—226°.

(ii) This dipicrate was converted to the dihydrochloride by addition of concentrated hydrochloric acid (200 ml.) followed by extraction with toluene (5 × 50 ml.). The aqueous solution was evaporated to dryness, the residue dissolved in water and the solution basified by the addition of aqueous potassium carbonate solution. This mixture was then evaporated to dryness and the residue extracted with n-propanol to give the crude base of 4(5)-(2-(2-aminoethyl)thioethyl)imidazole on removal of the n-propanol. A solution of this base (3.3 g.) and methyl isothiocyanate (1.9 g.) in ethanol (15 ml.) was heated under reflux for 30 minutes. After cooling the solution was evaporated to dryness and the residue chromatographed on silica gel. Elution with ethyl acetate/methanol (3:2) and evaporation of the appropriate middle fractions gave an oily residue, which was acidified with aqueous hydriodic acid (64%). Decantation several times with ether gave a yellow precipitate which, on washing with acetonitrile and then ether gave N-methyl-N'-(2-(2-(4-imidazolyl)ethyl)thioethyl)thiourea dihydroiodide, m.p. 143—145°, as an off-white solid. (Found: C, 21.6; H, 3.1; N, 11.1; S, 12.9; I, 50.7.

$C_9H_{16}N_4S_2 \cdot 2HI$ requires: C, 21.6; H, 3.6; N, 11.2; S, 12.8; I, 50.7).

Example 32.

N-(2-(4-imidazolylmethylthio)ethyl)thiourea.

(i) A solution of 4(5)-(2-aminoethyl)thiomethylimidazole (6.0 g.) and benzoyl isothiocyanate (6.0 g.) in chloroform (150 ml.) was heated under reflux for one hour. Concentration followed by recrystallisation from ethyl acetate-isopropyl acetate afforded N-benzoyl-N'-(2-(4-imidazolylmethylthio)ethyl)thiourea (7.5 g.). An analytically pure sample (from aqueous isopropyl alcohol) m.p. 126—128°.

(ii) The benzoyl thiourea (6.0 g.) was added to a solution of potassium carbonate (1.4 g.) in water (80 ml.), at 60°. The solution was maintained at this temperature for one hour, concentrated to low bulk and acidified with hydrochloric acid. Benzoic acid was removed by filtration and the filtrate was basified with potassium carbonate and concentrated under reduced pressure. Following extraction with isopropyl alcohol and concentration, the product was crystallised from isopropyl acetate. Recrystallisation from water gave N-(2-(4-imidazolylmethylthio)ethyl)thiourea (2.5 g.) m.p. 135—7°.

(Found: C, 38.9; H, 5.5; N, 26.1; S, 29.6 $C_8H_{12}N_4S_2$ requires: C, 38.9; N, 25.6; S, 29.6;

Example 33.

N-[(2-(4-methyl-5-imidazolyl)methylthio)ethyl]thiourea.

(a) The reaction of 4-methyl-5-((2-aminoethyl)thiomethyl)imidazole (5.0 g.) and benzoyl isothiocyanate (23.8 g.) by the procedure described in Example 32 (i) afforded N-benzoyl-N'-(2-(4-methyl-5-imidazolyl)methylthio)ethyl]thiourea (24 g.), m.p. 138—140° (from isopropyl alcohol-ethylacetate-ether). An analytically pure sample obtained by recrystallisation from aqueous isopropyl alcohol had m.p. 165—6°.

(b) The crude benzoyl thiourea (22 g.) was hydrolysed with potassium carbonate by the procedure described in Example 32 (ii) to afford N-[(2-(4-methyl-5-imidazolyl)methylthio)ethyl]thiourea (7.5 g.). Further recrystallisation from water, followed by isopropyl alcohol-ether gave the pure product (3.8 g.) m.p. 110—112°.

(Found: C, 41.9; H, 6.3; N, 24.5; S, 28.0; $C_8H_{14}N_4S_2$ requires C, 41.7; H, 6.1; N, 24.3; S, 27.8).

Example 34.

4,5-bis-(2-(N-Methylthioureido)ethylthiomethyl)imidazole.

(i) The reaction of 4,5-dihydroxymethylimidazole hydrochloride (1.6 g.) with cysteamine hydrochloride (2.2 g.) by the procedure described in Example 1 (i) (a) afforded 4,5-bis-((2-aminoethyl)thiomethyl) imidazole trihydrobromide (3.8 g.), m.p. 233—236°.

(ii) The reaction of 4,5-bis-((2-aminoethyl)thiomethyl imidazole (1.2 g.) with methyl isothiocyanate (1.5 g.) by the procedure described in Example 1 (ii) afforded 4,5-bis-(2-(N-methylthioureido)ethylthiomethyl) imidazole (1.1 g.) m.p. 154—155° (from isopropyl alcohol—isopropyl acetate).

(Found: C, 39.8; H, 6.2; N, 21.5; S, 32.5. $C_{13}H_{24}N_6S_4$ requires: C, 39.8; H, 6.2; N, 21.4; S, 32.7.

Example 35.

3,5-bis-(2-(N-Methylthioureido)ethylthiomethyl)-1,2,4, triazole.

(i) The reaction of 3,5-dihydroxymethyl-1,2,4-triazole (9.0g.; obtained from 1,2,4 triazole and excess formaldehyde at elevated temperatures) with cysteamine hydrochloride (17.3 g.) by the procedure described in Example 1 (i) (a) afforded 3,5-bis-((2-aminoethyl)thiomethyl)-1,2,4-triazole trihydrobromide (4.7 g.), m.p. 214—215°.

(ii) The reaction of 3,5-bis-((2-aminoethyl)thiomethyl)-1,2,4-triazole (from 6.5 g. trihydrobromide) with methylisothiocyanate (1.92 g.) afforded the bis-thiourea which was purified by passage through a column of silica gel with ethanol as eluant. Trituration with isopropyl acetate, followed by recrystallisation from ethanol-ether afforded 3,5-bis-(2-(N-methylthioureido)ethylthiomethyl)-1,2,4-triazole (0.9 g.) m.p. 133—135°.

(Found: C, 35.7; H, 5.9; N, 24.6; $C_{12}H_{23}N_5S_4 \cdot 0.5 H_2O$ requires: C, 35.8; H, 6.1; N, 24.3).

Example 36.

N-Methyl-N'-(3-(2-imidazolylthio)propyl)thiourea.

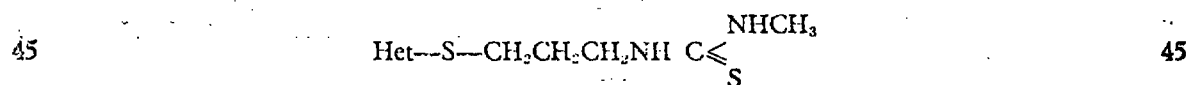
(i) A solution of 2-mercaptoimidazole (2 g.) and 3-aminopropanol (1.14 ml.) in hydrobromic acid (48%, 25 ml.) was heated under reflux for 25 hours. The reaction mixture was evaporated to dryness and the oily residual solid recrystallised twice from ethanol/ether to give 2-(3-aminopropylmercapto) imidazole dihydrobromide (3.55 g.) m.p. 160—162°.

(ii) This amine dihydrobromide (7 g.) was converted to the free base and reacted with methyl isothiocyanate (1.75 g.), by the method described in Example 1 (ii), to give a crude yellow solid after evaporation of the reaction mixture. This crude product was washed with acetone/isopropyl acetate (1:1) and recrystallised from water to give N-methyl-N'-(3-(2-imidazolylthio)propyl)thiourea (3.46 g.) m.p. 139—141°.

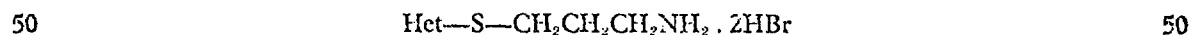
(Found: C, 41.5; H, 6.1; N, 24.1; S, 27.7. $C_8H_{14}N_4S_2$ requires: C, 41.7; H, 6.1; N, 24.3; S, 27.8).

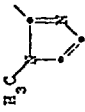
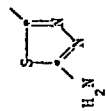
Examples 37—40.

The two stage process described in Example 36 (i) and (ii) was used to produce thiourea compounds of the formula:



wherein Het has the significance as set out in the following Table 3. The solvent from which the product was crystallised and the melting point and elemental analysis data for the product are also set out in the table together with the melting point of corresponding intermediate amine salt of formula:



Ex. No.	Het	Intermediate Dihydrobromide m.p. (°C)	Recryst. from	m.p. (°C)	Molecular Formula	Product: N-methyl-N'-[(3- (* * *)thio)propyl] thiourea										* * *
						Elemental Analysis										
						Found					Required					
						C	H	N	S	C	H	N	S			
37		164-166	water	109-111	C ₉ H ₁₆ N ₄ S ₂	44.5	6.5	23.1	26.3	44.2	6.6	22.9	26.2	1-methyl-2-imidazolyl		
38		175-178	water	67-68	C ₈ H ₁₃ N ₃ S ₃	38.6	5.3	16.9	38.9	38.8	5.3	17.0	38.9	2-thiazolyl		
39		186-188	ethanol-ether	40-42°	C ₁₀ H ₁₅ N ₃ S ₂ .HCl	43.4	6.0	15.1	23.0	43.2	5.8	15.1	23.1	2-pyridyl		
40		185-188	ethanol-ether	109-110°	C ₇ H ₁₃ N ₅ S ₃	31.5	5.0	26.2	36.1	31.9	5.0	26.6	36.5	5-amino-2-(1,3,4-thiadiazolyl)		

Example 41.

N-Methyl-N'-[3-(2-oxazolyl)thiopropyl]thiourea.

(i) Hydrochloric acid (90 ml.) was added to potassium thiocyanate in ethanol (1.8 l.) with stirring. Following filtration from inorganic material, glycollaldehyde (35.9 g.) was added and the resulting solution was heated under reflux for 24 hours. Concentration, followed by cooling afforded a white solid, which following recrystallisation from ethanol afforded oxazole-2-thiol (30 g.), m.p. 143—4.

(ii) 3-Bromopropylphthalimide (13.4 g.) was added to a stirred solution of sodium ethoxide (from 1.15 g. sodium) and oxazole-2-thiol (5.1 g.) in ethanol (100 ml.). The resultant solution was heated under reflux for 2.5 hours and concentrated under reduced pressure. The residue was triturated with water (100 ml.) to afford 2-(3-phthalimido propylthio)oxazole (14 g.) m.p. 101. Recrystallisation from ethanol gave the pure oxazole, m.p. 102—3.

(iii) Hydrazine hydrate (5.3 g.) was added carefully to a solution of 2-(3-phthalimidopropylthio)oxazole (10 g.) in ethanol (173 ml.) with stirring. The solution was then heated under reflux for 25 minutes. After cooling, and filtration from phthalhydrazide, the filtrate was concentrated under reduced pressure and the residue was re-evaporated with ethanol to yield crude 2-(3-aminopropylthio)oxazole which was washed twice with ether and dissolved in ethanol (60 ml.). Methyl isothiocyanate (2.54 g.) was added and the solution was heated under reflux for 30 minutes. Following cooling and filtration from insoluble material, the filtrate was concentrated to an oil which was chromatographed on a column of silica gel with ethyl acetate as eluent. The product obtained crystallised from ethanol-ether-*n*-hexane to give N-methyl-N'-[3-(2-oxazolyl)thiopropyl]thiourea (2.4 g.), m.p. 43—45°. (Found: C, 41.7; H, 5.9; N, 18.3; S, 27.5. $C_8H_{13}N_3OS_2$ requires: C, 41.5; H, 5.7; N, 18.2; S, 27.7).

Example 42.

N-Methyl-N'-[3-(4-methyl-2-oxazolyl)thiopropyl]thiourea.

(i) The reaction of 4-methyloxazole-2-thiol (5.8 g.) with 3-bromopropylphthalimide (13.4 g.), using the conditions described in Example 41 afforded 4-methyl-2-(3-phthalimidopropylthio)oxazole (14 g.) m.p. 92—93° (ethanol-ether).

(ii) Treatment of the phthalimide compound (3.0 g.) with hydrazine (1.53 g.) followed by reaction of the product directly with methylisothiocyanate (0.73 g.) using the conditions described in Example 41 afforded N-methyl-N'-[3-(4-methyl-2-oxazolyl)thiopropyl]thiourea (1.0 g.), m.p. 73—74° (from ethanol-ether-*n*-hexane).

(Found: C, 44.0; H, 6.2; N, 17.1; S, 25.9. $C_9H_{13}N_3OS_2$ requires: C, 44.1; H, 6.2; N, 17.1; S, 26.1).

Example 43.

N-Methyl-N'-[2-(4-imidazolylmethoxy)ethyl]thiourea.

(i) A stirred suspension of 4-(2-chloroethoxy methyl)imidazole hydrochloride (14.7 g.) sodium azide (9.8 g.) in dry dimethylformamide (103 ml.) was maintained at 95° for 5 hours and then set aside overnight at room temperature. Following dilution with water and filtration, the filtrate was concentrated and the residue purified by chromatography on a dry column of alumina using ethanol. The product was basified with potassium carbonate (6.5 g.) in water (3 ml.) and the anhydrous residue was extracted with isopropyl alcohol (3 × 50 ml.). Concentration of the extracts afforded 4-(2-azidoethoxymethyl)imidazole (7.2 g.). Hydrogenation of the azido compound (7.2 g.) in isopropyl alcohol (142 ml.) over platinum oxide catalyst (3.0 g.) gave 4-(2-aminoethoxy methyl)imidazole (6.48 g.). A sample of the monopicate monohydrochloride had m.p. 139—140° (from nitromethane).

(Found: C, 35.4; H, 3.8; N, 20.5; Cl, 8.8. $C_{12}H_{15}ClN_4O_3$ requires: C, 35.4; H, 3.7; N, 20.7; Cl, 8.7).

(ii) 4-(2-Aminoethoxymethyl)imidazole (2.24 g.) was caused to react with methylisothiocyanate (1.21 g.) in isopropyl alcohol (25 ml.) in the usual way. The crude product was purified by chromatography on a column of silica gel with ethyl acetate as eluant and subsequently on a dry column of alumina, using chloroform. The final product was recrystallised from ethyl acetate to give N-methyl-N'-[2-(4-imidazolylmethoxy)ethyl]thiourea (0.80 g.), m.p. 96—98°.

(Found: C, 44.6; H, 6.5; N, 26.0; S, 14.7; $C_8H_{14}N_4OS$ requires: C, 44.8; H, 6.6; N, 26.2; S, 15.0.)

Example 44.

N-Methyl-N'-[3-(2-pyridylamino)propyl]thiourea.

A solution of 2-(3-aminopropylamino)pyridine (2.74 g.) and methyl isothiocyanate (1.46 g.) in isopropyl alcohol (50 ml.) was stirred at room temperature for 16 hours.

Concentration, followed by trituration of the residue under methyl ethyl ketone gave the crude product which was recrystallised from aqueous ethanol to give N-methyl-N'-[3-(2-pyridylamino)propyl]thiourea (2.45 g.), m.p. 134—135.5°.

(Found: C, 53.4; H, 7.2; N, 25.0; S, 14.3. $C_{10}H_{16}N_4S$ requires: C, 53.5; H, 7.2; N, 25.0; S, 14.3).

Example 45.

N-Methyl-N'-[2-((4-methyl-5-imidazolyl)methylthio)ethyl]urea.

A mixture of 4-methyl-5-((2-aminoethyl)thiomethyl)imidazole (5.1 g.) and methyl isocyanate (2.0 g.) in acetonitrile was heated for 18 hours in a pressure vessel at 100°. After cooling, the solid obtained was collected and recrystallised from isopropyl alcohol-acetonitrile to give N-methyl-N'-[2-((4-methyl-5-imidazolyl)methylthio)ethyl]urea (4.0 g.) m.p. 158—159°.

(Found: C, 47.4; H, 7.1; N, 24.5; S, 14.1. $C_9H_{16}N_4OS$ requires: C, 47.3; H, 7.1; N, 24.5; S, 14.0).

Example 46.

2-[(4-Imidazolyl)methylthio]ethylguanidine sulphate.

A solution of 4-((2-aminoethyl)thiomethyl)imidazole (5.8 g.) and S-methyl isothiuronium sulphate (4.8 g.) in water (50 ml.) was heated under reflux for 3 hours. Following concentration to low bulk and acidification with dilute sulphuric acid, ethanol was added. The product obtained was recrystallised from aqueous methanol to give 2-[(4-imidazolyl)methylthio]ethylguanidine sulphate (5.2 g.), m.p. 211—213°.

(Found: C, 28.1; H, 5.1; N, 23.3; S, 21.3. $C_7H_{13}N_5S \cdot H_2SO_4$ requires: C, 28.3; H, 5.1; N, 23.6; S, 21.6).

Example 47.

N-(2-[(4-methyl-5-imidazolyl)methylthio]ethyl)-N'-nitroguanidine.

A solution of 4-methyl-5-(2-aminoethyl thiomethyl)imidazole (1.7 g.) and S-methyl-N-nitrosothiourea (1.45 g.) in methanol (35 ml.) was heated at 50—60° for 2.5 hours and then set aside at room temperature for 48 hours. The crystalline product was filtered off and recrystallised from methanol to give N-(2-[(4-methyl-5-imidazolyl)methylthio]ethyl)-N'-nitroguanidine, m.p. 184—186°.

(Found: C, 37.5; H, 5.7; N, 32.5; S, 12.5. $C_8H_{14}N_6O_2S$ requires: C, 37.2; H, 5.5; N, 32.5; S, 12.4).

Example 48.

N-Methyl-N'-[2-(5-thiazolyl)methylthio]ethyl]thiourea.

(i) The reaction of 5-hydroxymethylthiazole (2.01 g.) with cysteamine hydrochloride (1.99 g.) in aqueous hydrobromic acid by the method described in Example 1 (i) gave 5-((2-aminoethyl)thiomethyl)thiazole dihydrobromide (4.85 g.) m.p. 191—4° (from methanol).

(ii) The reaction of 5-((2-aminoethyl)thiomethyl)thiazole (2.24 g.) with methyl isothiocyanate (0.94 g.) in ethanol (10 ml.) gave a thiourea which was purified by chromatography on a column of silica gel with ethyl acetate as eluant. Recrystallisation from isopropyl acetate-methyl ethyl ketone-ether gave N-methyl-N'-[2-(5-thiazolyl)methylthio]ethyl]thiourea (2.1 g.) m.p. 86—88°.

(Found: C, 38.6; H, 5.4; N, 16.9; S, 38.6. $C_6H_{12}N_3S_2$ requires: C, 38.8; H, 5.3; N, 17.0; S, 38.9).

Example 49.

N-Methyl-N'-[2-(2-pyridyl)methylthio]ethyl]urea.

The reaction of 2-[(2-aminoethyl)thiomethyl]pyridine (7.0 g.) with methyl isocyanate (2.7 g.) by the method described in Example 45 gave N-methyl-N'-[2-(2-pyridyl)methylthio]ethyl]urea, m.p. 63—66° (from acetonitrile/ether).

Example 50.

N-methyl-N'-[2-(1,4-dimethyl-2-imidazolyl)methylthio]ethyl]thiourea.

(i) The reaction of 1,4-dimethylimidazole (5.65 g.) with n-butyl lithium followed by treatment with formaldehyde according to the method described for the preparation of 3-hydroxymethyl-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine (used for Example 26) gave 1,4-dimethyl-2-hydroxymethylimidazole (2.71 g.), m.p. 125—126° (ethyl acetate-petroleum ether).

(ii) The reaction of 1,4-dimethyl-2-hydroxymethylimidazole (2.5 g.) with cysteamine hydrochloride (2.5 g.) in aqueous hydrobromic acid by the method described in Example 1 (i) (a) gave 1,4-dimethyl-2-[(2-aminoethyl)thiomethyl]imidazole dihydrobromide (6.2 g.), m.p. 161—163° (from isopropyl alcohol-methanol).

(iii) The reaction of 1,4-dimethyl-2-[(2-aminoethyl)thiomethyl]imidazole (derived from the 6.2g. dihydrobromide) with methyl isothiocyanate (1.34g.) in ethanol (50 ml.) followed by chromatography on a column of silica gel with ethyl acetate-ethanol (9:1) as eluent gave N-methyl-N'-[2-(1,4-dimethyl-2-imidazolyl)methylthio]ethyl]thiourea (2.1 g.).

(Found: C, 46.8; H, 6.9; N, 21.5; S, 24.9. $C_{10}H_{18}N_4S_2$ requires: C, 46.5; H, 7.0; N, 21.7; S, 24.8).

Example 51.

N-Methyl-N'-[2-(4-trifluoromethyl-5-imidazolyl)methylthio]ethyl]thiourea.

A mixture of ethyl 2-chloro-4,4,4-trifluorobutyrate (65.7g.), distilled formamide (135g.) and water (11 ml.) was heated at 128—130° for 1.5 hours. After cooling, an equal volume of ice-cold water was added to give 4-trifluoromethyl-5-carbethoxyimidazole, m.p. 184—186° (from aqueous methanol).

Reduction of the ester (9.4g.) with lithium aluminium hydride (2.4g.) in tetrahydrofuran gave 5-hydroxymethyl-4-trifluoromethylimidazole, isolated as its picrate, m.p. 135.5—137.5° (from aqueous isopropyl alcohol).

The picrate (5.3g.) was dissolved in 48% aqueous hydrobromic acid and extracted with toluene to remove picric acid. Cysteamine hydrochloride (1.52g.) was added to the aqueous phase and the acidic solution heated under reflux for 12 hours. Concentration and trituration of the residue with ethanol-ether gave 4-trifluoromethyl-5-[(2-aminoethyl)thiomethyl]imidazole dihydrobromide (3.2g.), m.p. 179—182°. Basification followed by treatment with methyl isothiocyanate gave N-methyl-N'-[2-(4-trifluoromethyl-5-imidazolyl)methylthio]ethyl]thiourea.

Example 52.

N-Methyl-N'-[2-(2-pyrimidyl)methylthio]ethyl]thiourea.

A mixture of 5-bromo-2-hydroxymethylpyrimidine (5.6g.) and magnesium oxide (5.6g.) in water/ethanol (2:1) was submitted to hydrogenolysis over 10% palladised charcoal for 0.5 hours. Filtration, concentration and ether extraction from an aqueous solution of the residue afforded 2-hydroxymethylpyrimidine (1.85 g.) as a mobile liquid.

The reaction of 2-hydroxymethylpyrimidine with cysteamine, followed by further reaction of the product with methyl isothiocyanate, according to the methods described in Examples 1 and 2 gave N-methyl-N'-[2-(2-pyrimidyl)methylthio]ethyl]thiourea.

Example 53.

N-Methyl-N'-[2-(2-pyrazinyl)methylthio]ethyl]thiourea.

(i) 2-chloromethylpyrazine (6.4 g) was added over 20 minutes to a solution freshly prepared from sodium (0.23 g) in ethanol (50 ml) to which cysteamine hydrochloride (5.7 g) had been added gradually at 0° and stirred at this temperature for 2 hours. The suspension finally obtained was stirred at room temperature overnight, acidified with hydrochloric acid (pH 5) and concentrated under reduced pressure. The dry residue was extracted with ethanol and the extracts filtered and concentrated to give the crude product. Extraction with isopropyl alcohol, with the removal of some polymeric material and the addition of ether gave a cream coloured solid (3.5 g), which was recrystallised from ethanol-ether to furnish 2-[(2-aminoethyl)thiomethyl]pyrazine hydrochloride m.p. 144—146°.

(ii) The amine hydrochloride (1.6 g) was concentrated into the free base using potassium carbonate and reacted with methyl isothiocyanate (0.61 g) in ethanol in the usual way. Recrystallisation from ethanol furnished N-methyl-N'-[2-(2-pyrazinyl)methylthio]ethyl]thiourea (0.88 g) m.p. 99.5—100.5°.

(Found: C, 44.6; H, 5.9; N, 22.8; S, 26.5. $C_8H_{14}N_4S$ requires: C, 44.6; H, 5.8; N, 23.1; S, 26.5).

Example 54.

N-[(2-(4-methyl-5-imidazolyl)methylthio)ethyl]urea.

A solution of 4-methyl-5-[(2-aminoethyl)thiomethyl]imidazole dihydrobromide (3.33 g), potassium cyanate (0.81 g) and potassium carbonate (0.69 g) in water (30 ml) was heated at 80—90° for 3 hours. Concentration under reduced pressure and extraction of the residue with n-propanol gave the crude product which was chromatographed on a column of silica gel with ethylacetate-ethanol (5:1) as eluant. Recrystallisation from isopropyl alcohol-ether and finally from acetonitrile furnished N-[(2-(4-methyl-5-imidazolyl)methylthio)ethyl]urea (0.8 g), m.p. 148—149°.

(Found: C, 44.6; H, 6.5; N, 25.7; S, 15.0. $C_8H_{14}N_4OS$ requires: C, 44.8; H, 6.6; N, 26.1; S, 15.0).

Example 55.

N-Methyl-N'-[2-(2-amino-4-thiazolyl)methylthio]ethyl]thiourea.

(i) A mixture of 2-amino-4-chloromethylthiazole hydrochloride (9.0 g) and cysteamine hydrochloride (5.53 g) in acetic acid (100 ml) was heated under reflux for 18 hours. The crude product obtained after concentration was treated with picric acid in ethanol to afford 2-amino-4-[(2-aminoethyl)thiomethyl]thiazole dipicrate, m.p. approximately 200—210° (from ethanol).

(ii) The picrate was converted into the free base by addition of hydrochloric acid, removal of picric acid by toluene extraction, basification with potassium carbonate and extraction of the aqueous residue with ethanol-ether. Reaction of the base (1.89 g) with methyl isothiocyanate (0.73 g) in ethanol (10 ml) in the usual way gave the crude thiourea. Chromatography on a column of silica gel with ethyl acetate as eluant, followed by recrystallisation from isopropyl alcohol-isopropyl acetate gave N-methyl-N'-[2-(2-amino-4-thiazolyl)methylthio]ethyl]thiourea (1.0 g), m.p. 136—140°.

(Found: C, 37.1; H, 5.5; N, 20.8; S, 36.3 C₉H₁₄N₄S₂ requires: C, 36.6; H, 5.4; N, 21.3; S, 36.7).

Example 56.

N-Methyl-N'-[3-(4-imidazolyl methoxy)propyl]thiourea.

(i) Sodium (13.5 g) was added over 3 hours to propane-1,3-diol (450 ml) under nitrogen at 70° with stirring. This solution was added over 20 minutes to a stirred solution of 4-chloromethylimidazole hydrochloride (50.0 g) under nitrogen at 40—60°. Subsequent heating at 60—65° for 3 hours followed by overnight cooling, filtration and concentration gave 4-(3-hydroxypropoxy)methylimidazole. Subsequent reaction with thionyl chloride gave 4-(3-chloropropoxy)methylimidazole hydrochloride (38.3 g).

(ii) The reaction of this chloride (36.2 g) with sodium azide (22.4 g) in dry dimethylformamide at 95° for 3 hours followed by 'dry-column' chromatography on aluminium with ethanol as eluant gave 4-(3-azidopropoxy)methylimidazole which was further purified by the same method using chloroform as eluant. The azide (2.95 g) in ethanol (200 ml) was hydrogenated over platinum oxide catalyst to give 4-(3-amino-propoxy)methylimidazole (2.42 g).

(iii) Reaction of the amine (2.42 g) with methylisothiocyanate (1.25 g) in ethanol at room temperature for 65 hours followed by chromatography of the product on a column of silica gel with ethyl acetate as eluant gave N-methyl-N'-[3-(4-imidazolyl-methoxy)propyl]thiourea (0.49 g) as a low melting solid.

Example 57.

Ingredients

Amounts

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

150 mg.

Sucrose

75 mg.

Starch

25 mg.

Talc

5 mg.

Stearic acid

2 mg.

The ingredients are screened, mixed and filled into a hard gelatin capsule.

Example 58.

Ingredients

Amounts

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

200 mg.

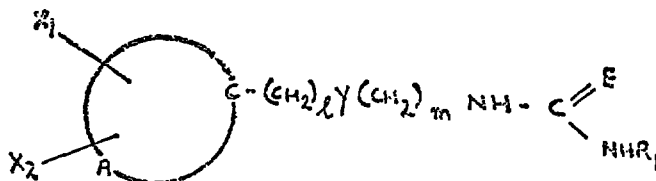
Lactose

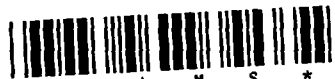
100 mg.

The ingredients are screened, mixed and filled into a hard gelatin capsule.

WHAT WE CLAIM IS:—

1. A compound of the following general formula:





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Example 55.

N-Methyl-N'-[2-(2-amino-4-thiazolyl)methylthio]ethyl]thiourea.

(i) A mixture of 2-amino-4-chloromethylthiazole hydrochloride (9.0 g) and cysteamine hydrochloride (5.53 g) in acetic acid (100 ml) was heated under reflux for 18 hours. The crude product obtained after concentration was treated with picric acid in ethanol to afford 2-amino-4-[(2-aminocetyl)thiomethyl]thiazole dipicrate, m.p. approximately 200—210° (from ethanol).

(ii) The picrate was converted into the free base by addition of hydrochloric acid, removal of picric acid by toluene extraction, basification with potassium carbonate and extraction of the aqueous residue with ethanol-ether. Reaction of the base (1.89 g) with methyl isothiocyanate (0.73 g) in ethanol (10 ml) in the usual way gave the crude thiourea. Chromatography on a column of silica gel with ethyl acetate as eluant, followed by recrystallisation from isopropyl alcohol-isopropyl acetate gave N-methyl-N'-[2-(2-amino-4-thiazolyl)methylthio]ethyl]thiourea (1.0 g), m.p. 136—140°.

(Found: C, 37.1; H, 5.5; N, 20.8; S, 36.3 C₈H₁₄N₄S₂ requires: C, 36.6; H, 5.4; N, 21.3; S, 36.7).

Example 56.

N-Methyl-N'-[3-(4-imidazolyl methoxy)propyl]thiourea.

(i) Sodium (13.5 g) was added over 3 hours to propane-1,3-diol (450 ml) under nitrogen at 70° with stirring. This solution was added over 20 minutes to a stirred solution of 4-chloromethylimidazole hydrochloride (50.0 g) under nitrogen at 40—60°. Subsequent heating at 60—65° for 3 hours followed by overnight cooling, filtration and concentration gave 4-(3-hydroxypropoxy)methylimidazole. Subsequent reaction with thionyl chloride gave 4-(3-chloropropoxy)methylimidazole hydrochloride (38.3 g).

(ii) The reaction of this chloride (36.2 g) with sodium azide (22.4 g) in dry dimethylformamide at 95° for 3 hours followed by 'dry-column' chromatography on aluminium with ethanol as eluant gave 4-(3-azidopropoxy)methylimidazole which was further purified by the same method using chloroform as eluant. The azide (2.95 g) in ethanol (200 ml) was hydrogenated over platinum oxide catalyst to give 4-(3-amino-propoxy)methyl imidazole (2.42 g).

(iii) Reaction of the amine (2.42 g) with methylisothiocyanate (1.25 g) in ethanol at room temperature for 65 hours followed by chromatography of the product on a column of silica gel with ethyl acetate as eluant gave N-methyl-N'-[3-(4-imidazolyl-methoxy)propyl]thiourea (0.49 g) as a low melting solid.

Example 57.

Ingredients	Amounts
N-methyl-N'-[2-((5-methyl-4-imidazolyl)methylthio)ethyl]thiourea	150 mg.
Sucrose	75 mg.
Starch	25 mg.
Talc	5 mg.
Stearic acid	2 mg.

The ingredients are screened, mixed and filled into a hard gelatin capsule.

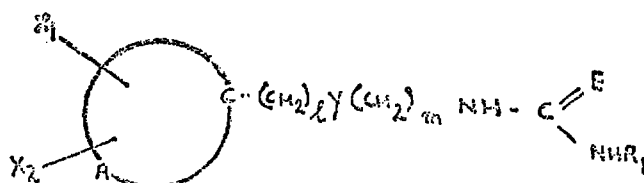
Example 58.

Ingredients	Amounts
N-methyl-N'-[2-((2-thiazolyl)methylthio)ethyl]thiourea	200 mg.
Lactose	100 mg.

The ingredients are screened, mixed and filled into a hard gelatin capsule.

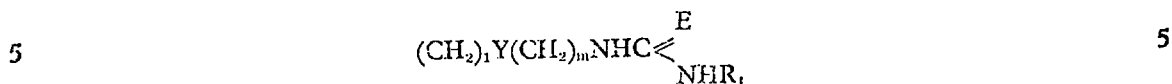
WHAT WE CLAIM IS:—

1. A compound of the following general formula:





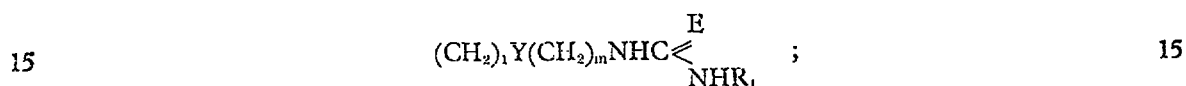
wherein A is such that there is formed together with the carbon atom shown an unsaturated heterocyclic nucleus, which comprises at least one nitrogen atom and may comprise further hetero atoms; X₁ and X₂, which may be the same or different, are hydrogen, lower alkyl, trifluoromethyl, hydroxyl, benzyl, halogen, amino,



the atoms comprising A form a further ring; *l* and *m* are integers from 0 to 4, provided that the sum of *l* and *m* is 3 or 4; Y is oxygen, sulphur or NH; E is oxygen, sulphur or, provided that A may not be such that a pyridine ring is formed, NR₂; R₁ is hydrogen, lower alkyl, acyl or dialkylaminoalkyl; and R₂ is hydrogen, nitro or cyano.

10 2. A compound according to claim 1 wherein said unsaturated heterocyclic basic nucleus contains 5 or 6 atoms and the nitrogen atom is adjacent to the carbon atom shown. 10

3. A compound according to claim 2 wherein X₁ and X₂, which may be the same or different, are hydrogen, lower alkyl, benzyl, halogen or



l is an integer from 0 to 4; *m* is an integer from 2 to 4; and E is oxygen or sulphur.

4. A compound according to claim 3 where X₁ and X₂, which may be the same or different, are hydrogen, lower alkyl, benzyl or halogen; and *l* is an integer from 1 to 4.

5. A compound according to claim 1 or claim 2 where X₁ is hydrogen, methyl, bromo, amino or hydroxyl and X₂ is hydrogen. 20

6. A compound according to any one of the preceding claims wherein said unsaturated heterocyclic nucleus is imidazole, pyridine, thiazole, oxazole, pyrazole, triazole, thiodiazole, pyrimidine, pyrazine or pyridazine. 10

7. A compound according to claim 6 wherein said unsaturated heterocyclic nucleus is imidazole, thiazole or pyridine. 25

8. A compound according to any one of the preceding claims wherein *l* is 1 and *m* is 2.

9. A compound according to any one of the preceding claims wherein Y is sulphur and E is sulphur.

10. A compound according to any one of the preceding claims wherein R₁ is methyl. 30

11. N-Methyl-N'-[2-(4-imidazolylmethylthio)ethyl]thiourea.

12. N-Methyl-N'-[2-((5-methyl-4-imidazolyl)methylthio)ethyl]thiourea.

13. N-Methyl-N'-[2-((5-bromo-4-imidazolyl)methylthio)ethyl]thiourea.

14. N-Methyl-N'-[2-((1-methyl-2-imidazolyl)methylthio)ethyl]thiourea. 35

15. N-Methyl-N'-[2-((2-imidazolyl)methylthio)ethyl]thiourea.

16. N-Methyl-N'-[2-((2-thiazolyl)methylthio)ethyl]thiourea.

17. N-Methyl-N'-[2-((3-hydroxy-2-pyridyl)methylthio)ethyl]thiourea.

18. N-Methyl-N'-[2-((5-amino-2-(1,3,4)-thiadiazolyl)methylthio)ethyl]thiourea.

19. N-Methyl-N'-[2-((3-(1,2,4)-triazolyl)methylthio)ethyl]thiourea. 40

20. N-Methyl-N'-[3-(2-thiazolyl)thiopropyl]thiourea.

21. Pharmaceutical compositions comprising as the or an active constituent a compound according to any one of the preceding claims together with a non-toxic pharmaceutically acceptable diluent or carrier.

22. A process for the production of a compound according to claim 1 as hereinbefore described in any one of examples 1, 2 and 31. 45

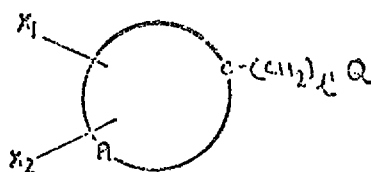
23. A process for the production of a compound according to claim 1 as hereinbefore described in any one of examples 3 to 6, 9, 10, 13, 16 to 18, 25, 28 to 30, 32 and 34 to 36.

24. A process for the production of a compound according to claim 1 as hereinbefore described in any one of examples 7, 8, 11, 12, 14, 15, 19 to 24, 26, 27, 33 and 37 to 49. 50

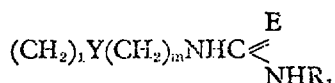
25. A process for the production of a compound according to claim 1 wherein Y is sulphur, E is sulphur, *l* is 1 or 2, and R₁ is lower alkyl or dialkylaminoalkyl wherein a substance of the following general formula: 55



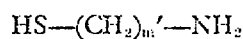
1,338,169



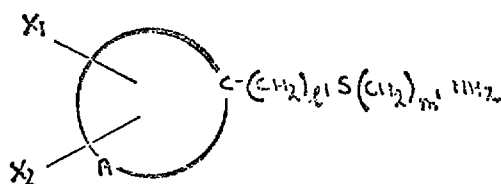
in which A, X₁ and X₂ have the same significance as in the formula set out in claim 1 except that X₁ and/or X₂ may not be



but may additionally be (CH₂)₂'Q; l' is 1 or 2; and Q is hydroxyl, halogen or methoxy is reacted with an aminomercaptan of the formula:



in which m' is 2 or 3 to give a product of the formula:



which is then reacted with an isothiocyanic ester of the formula:



wherein R₁ is lower alkyl or dialkylaminoalkyl.

R. A. A. HURST,
Agent for the Applicants.

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which copies may be obtained.

ERRATA

SPECIFICATION No. 1,338,169

Page 1, Heading, (72) Inventors for GANIL-
LIN read GANELLIN

Page 3, line 41, insert FORMULA V below
Formula

Page 4, line 1, delete FORMULA V

Page 4, line 38, insert FORMULA IX below
Formula

Page 5, line 1, delete FORMULA IX

Page 22, line 6, before the insert or X₁ may
with X₂ and at least two of

Page 22, line 23, for thiodiazole read thia-
diazole

THE PATENT OFFICE
21th December, 1973