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PATENT SPECIFICATION

(11) 1 582 527

- (21) Application No. 53001/75 (22) Filed 29 Dec. 1975
(21) Application No. 48605/76 (22) Filed 22 Nov. 1976
(23) Complete Specification filed 25 March 1977
(44) Complete Specification published 7 Jan. 1981
(51) INT CL³ C07D 401/00; A61K 31/505; C07D 403/00, 405/00, 409/00, 413/00, 417/00; (C07D 401/00, 213/04, 215/02, 217/00, 233/54, 239/46); (C07D 403/00, 233/54, 237/06, 239/24); (C07D 403/00, 239/46, 241/10); (C07D 405/00, 233/54, 239/46, 307/34); (C07D 409/00, 233/54, 239/46, 333/04); (C07D 413/00, 233/54, 239/46, 263/30); (C07D 417/00, 213/04, 233/54, 275/00, 277/20, 285/04)



(52) Index at acceptance

C2C 1371 1380 1382 1410 1440 1470 1510 1530 1534 1535
1590 1600 1601 1620 200 213 215 220 22Y 246
247 250 251 252 253 254 255 256 25Y 28X 29X 29Y
304 305 30Y 311 313 314 31Y 321 322 326 32Y 332
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672 680 682 694 758 761 762 770 802 80Y AA BB BK
LF LK MB MC MD NB NG NL QS RM UL

(72) Inventors GRAHAM JOHN DURANT, CHARON ROBIN
GANELLIN and THOMAS HENRY BROWN

(54) PYRIMIDONE DERIVATIVES AND THIOPYRIMIDONE DERIVATIVES

(71) We, SMITH KLINE & FRENCH LABORATORIES LIMITED, of Mundells, Welwyn Garden City, Hertfordshire, England, 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:—

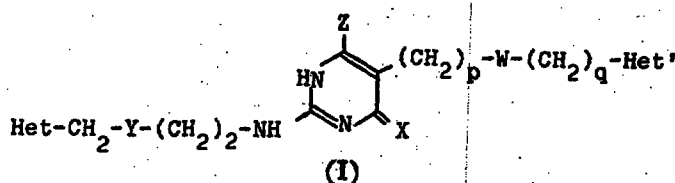
This invention relates to pyrimidone derivatives, to processes for preparing these compounds and to pharmaceutical compositions containing them.

Many physiologically active substances elicit their biological actions by interaction with specific sites known as receptors. Histamine is such a substance and has a number of biological actions. Those biological actions of histamine which are inhibited by drugs commonly called "anti-histamines" of which mepyramine, diphenhydramine and chlorpheniramine are examples, are mediated through histamine H₁-receptors (Ash and Schild, *Brit. J. Pharmac. Chemother.*, 27, 427, (1966)), and drugs with this activity are hereinafter referred to as histamine H₁-antagonists. However, other of the biological actions of histamine are not inhibited by histamine H₁-antagonists and actions of this type which are inhibited by a compound described by Black et al. (*Nature*, 236, 385, (1972)) and called burimade are mediated through receptors which are defined by Black et al. as histamine H₂-receptors. Thus histamine H₂-receptors may be defined as those histamine receptors which are not blocked by mepyramine but are blocked by burimamide. Compounds which block histamine H₂-receptors are referred to as histamine H₂-antagonists.

Blockade of histamine H₂-receptors is of utility in inhibiting the biological actions of histamine which are not inhibited by histamine H₁-antagonists. Histamine H₂-antagonists are therefore useful, for example, as inhibitors of gastric acid secretion, as anti-inflammatory agents and as agents which act on the cardiovascular system, for example, as inhibitors of the effects of histamine on blood pressure. In the treatment of certain conditions, for example, inflammation and in inhibiting the actions of histamine on blood pressure, a combination of histamine H₁- and H₂-antagonists is useful.

The compounds of this invention have both histamine H₁-antagonist and histamine H₂-antagonist activity, and are useful in the treatment of conditions wherein histamine H₂-antagonists are useful and conditions wherein a combination of histamine H₁- and H₂-antagonists are useful.

According to the present invention there is provided a compound of formula (I):—



and salts thereof where Het is a 2- or 4-imidazolyl group optionally substituted with lower alkyl, halogen, trifluoromethyl or hydroxymethyl; a 2-pyridyl group optionally substituted with lower alkyl, lower alkoxy, halogen, amino or hydroxy; a 2-thiazolyl group, a 3-isothiazolyl group optionally substituted with chlorine or bromine; a 3-(1,2,5)-thiadiazolyl group optionally substituted with chlorine or bromine; or 2-(5-amino,1,3,4-thiadiazolyl) group; Y is sulphur or methylene; Z is hydrogen or lower alkyl; X is oxygen or sulphur; W is methylene, oxygen or sulphur; p and q are such that their sum is from 1 to 4 when W is oxygen or sulphur, or from 0 to 4 when W is methylene; Het' is a 5 or 6 membered heteroaryl group optionally substituted with lower alkyl, lower alkoxy, or may have a phenyl group or substituted phenyl group fused to it.

When used herein lower alkyl and lower alkoxy mean such groups containing up to four carbon atoms.

When Het is a 2- or 4-imidazolyl or 2-pyridyl group substituted with lower alkyl, preferably the substituent is methyl.

When Het is a 2- or 4-imidazolyl or 2-pyridyl group substituted with halogen preferably the substituent is chlorine or bromine.

When Het is a 2-pyridyl group substituted with lower alkoxy preferably the substituent is methoxy.

Preferably Het is a 2-thiazolyl, 5-methyl-4-imidazolyl, 5-bromo-4-imidazolyl, 3-bromo-2-pyridyl, 3-chloro-2-pyridyl 3-methoxy-2-pyridyl or 3-hydroxy-2-pyridyl group.

Preferably Y is sulphur.

Preferably X is oxygen.

Preferably Z is hydrogen.

Preferably W is methylene and p and q are both 0.

By way of example Het' represents a pyridyl, furyl, thienyl, thiazolyl, oxazolyl, isothiazolyl, imidazolyl pyrazinyl, pyridazinyl, or pyrimidyl group optionally substituted with lower alkyl, lower alkoxy or may have a phenyl group or substituted phenyl group fused to it.

Preferably Het' is a 2-furyl, 2-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-thiazolyl, 2-imidazolyl, 2-pyrimidyl, 2-pyrazinyl or 4-pyridazinyl group, each of which are optionally substituted with lower alkyl or lower alkoxy.

More preferably Het' is a 2-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl or 2-thiazolyl group.

Most preferably Het' is a 3-pyridyl group.

Some specific compounds which fall within the scope of the present invention are:—

2 - [2 - (5-methyl-4-imidazolylmethylthio)ethylamino] - 5 - (4-pyridylmethyl)-4-pyrimidone

2 - [2 - (2-thiazolylmethylthio)ethylamino] - 5 - (4-pyridylmethyl) - 4-pyrimidone

2 - [2 - (3-bromo-2-pyridylmethylthio)ethylamino] - 5 - (4-pyridylmethyl)-4-pyrimidone

2 - [2 - (5-methyl-4-imidazolylmethylthio)ethylamino] - 5 - (2-thienylmethyl)-4-pyrimidone

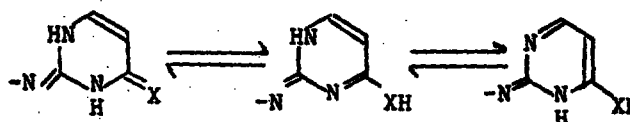
2 - [2 - (5-methyl-4-imidazolylmethylthio)ethylamino] - 5 - (2-pyridylmethyl)-4-pyrimidone

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- 2 - [2 - (5 - methyl - 4 - imidazolymethylthio)ethylamino] - 5 - (3 - pyridylmethyl) - 4 - pyrimidone
- 2 - [2 - (3 - bromo - 2 - pyridylmethylthio)ethylamino] - 5 - (2 - pyridylmethyl) - 4 - pyrimidone
- 5 2 - [2 - (5 - methyl - 4 - imidazolymethylthio)ethylamino] - 5 - (2 - thiazolylmethyl) - 4 - pyrimidone
- 2 - [2 - (2 - thiazolymethylthio)ethylamino] - 5 - (3 - pyridylmethyl) - 4 - pyrimidone
- 10 2 - [2 - (3 - bromo - 2 - pyridylmethylthio)ethylamino] - 5 - (3 - pyridylmethyl) - 4 - pyrimidone
- 2 - [4 - (3 - methoxy - 2 - pyridyl)butylamino] - 5 - (3 - pyridylmethyl) - 4 - pyrimidone
- and
- 15 2 - [4 - (3 - amino - 2 - pyridyl)butylamino] - 5 - (3 - pyridylmethyl) - 4 - pyrimidone

Examples of salts of compounds of formula (I) include in particular those with acids such that the addition salt is pharmaceutically acceptable, in particular, those with hydrochloric, hydrobromic, hydroiodic, sulphuric and maleic acids.

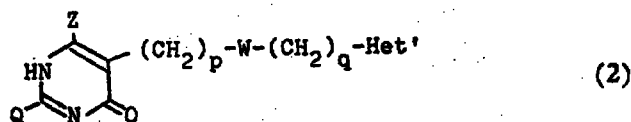
20 The compounds of formula (I) are shown and described as 4-pyrimidone and 4-thione derivatives and these derivatives exist in equilibrium with the corresponding 6-one and 6-thione tautomers. These compounds also exist to a lesser extent as the mercapto and hydroxy tautomers, and the pyrimidine ring may also exist in the following tautomeric forms:



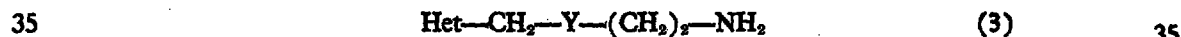
25 Certain Het and Het' may also exist in several tautomeric forms, and it will be understood that all these tautomeric forms are within the scope of the present invention.

Compounds of formula (I) and their salts may also exist in hydrate forms, it will be understood that these are also within the scope of this invention.

30 The compounds of formula (I) can be prepared by a process which comprises reacting an isocytosine of formula (2):—



wherein Z, W, p, q, and Het' are as defined with reference to formula (I) and Q is a grouping which is displaced by an amine, with an amine of formula (3):—

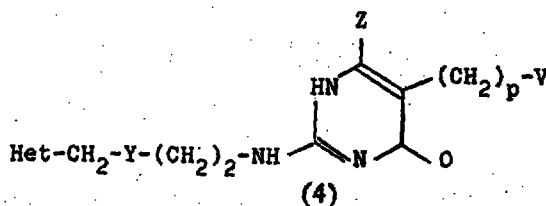


where Het and Y are as defined in formula (I).

In formula (2) Q is for example lower alkyl, benzylthio or halogen. Preferably Q is methylthio.

40 Preferably the reaction is carried out in the absence of a solvent at an elevated temperature, e.g., 150°C, or in the presence of a solvent, for example in refluxing pyridine.

Compounds of formula (I) wherein W is sulphur may alternatively be prepared by a process which comprises treating an isocytosine of formula (4):—



where Het, Y, Z and p are as defined in formula (I), and V is a mercapto, chloro or bromo group, with a compound of formula (5):—

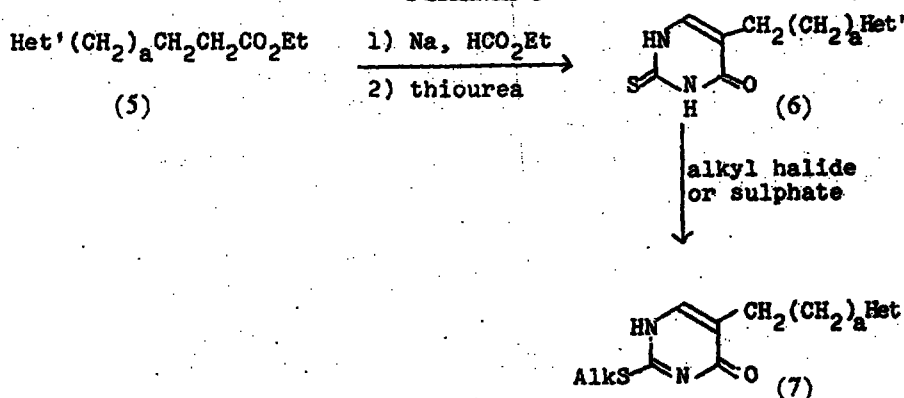


where Het' is as defined in formula (I), U is SH when V is chloro or bromo and U is chloro or bromo when V is mercapto, provided that when U is chloro or bromo q may only be 0 if U is an 'active' halogen (i.e. ortho or para to be a heterocyclic nitrogen atom).

Acid addition salts of compounds of formula (I) can be prepared by standard procedures for example by reacting the free base with an acid in a lower alkanol or by use of an ion exchange resin. Acid addition salts of compounds of formula (I) can also be interconverted using ion exchange resins.

The intermediates of formula (2) where W is methylene, Z is hydrogen and Q is loweralkylthio (shown as formula (7)) can be prepared according to Scheme 1:—

SCHEME 1



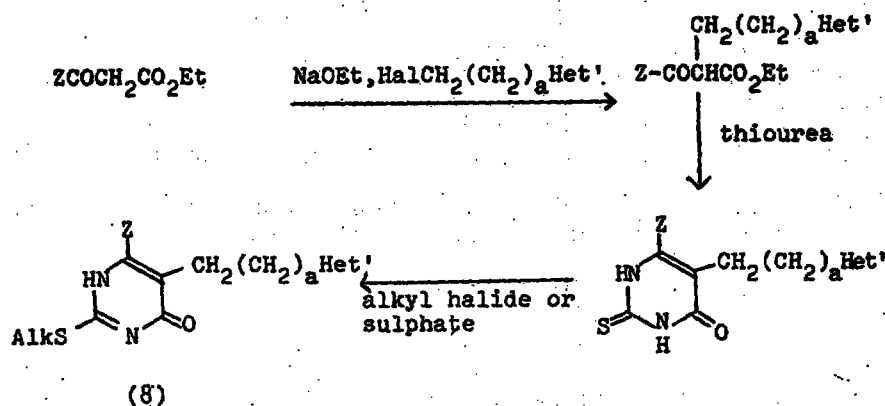
In this scheme Het' is as defined in formula (I), a is 0 to 4 and Alk is lower alkyl.

The esters of formula (5) can be prepared by general methods known to the art, for example compounds where a is 0 can be prepared by condensing an aldehyde Het'-CHO with malonic acid in the presence of pyridine and piperidine and hydrogenating and esterifying the product.

The intermediates of formula (2) where W is methylene, Z is lower alkyl, and Q is loweralkylthio (shown as formula (8)) can be prepared according to Scheme 2.

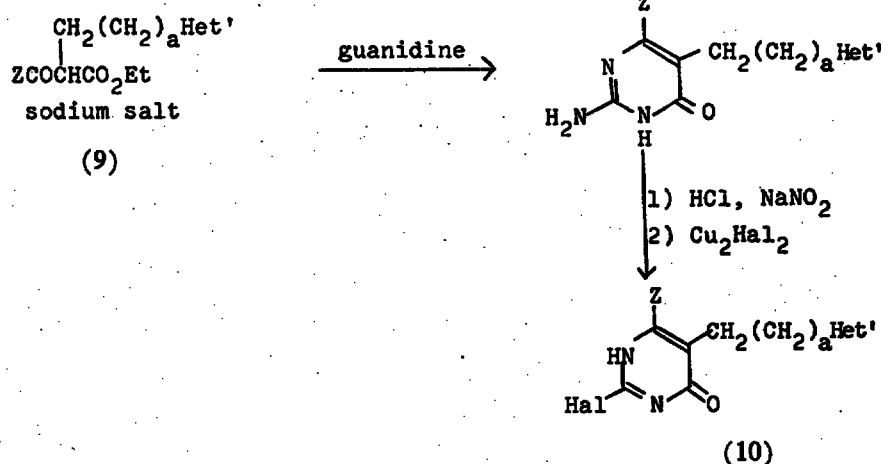
Het' is as defined in formula (I), a is 0 to 4, Hal is chlorine or bromine, and Alk is lower alkyl.

SCHEME 2



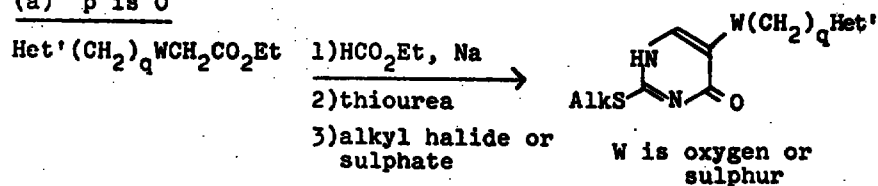
The intermediates of formula (2) where Q is halogen and W is methylene (shown as formula (10)) can be prepared according to Scheme 3 where Het' and Z are as defined in formula (I), a is 0 to 4 and Hal is chlorine or bromine.

SCHEME 3



The intermediates of formula (2) where W is oxygen or sulphur can be prepared by the following methods:—

(a) p is 0

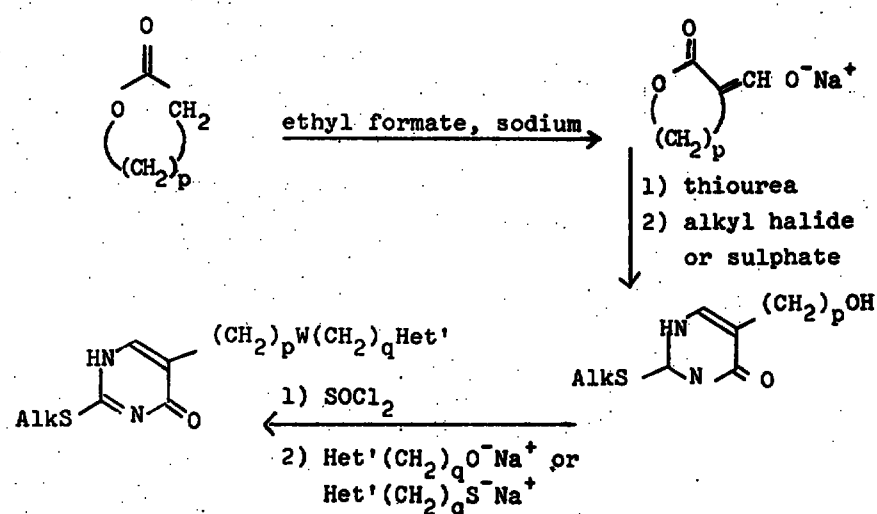


(b) p is 1

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These compounds can be prepared from ethyl 3-benzyloxypropionate, or a similar protected derivative of ethyl 3-hydroxypropionate, by a process analogous to that outlined in Scheme I, followed successively by deprotection, treatment with thionyl chloride, and treatment with the sodium derivative of Het'(CH₂)_qOH or Het'(CH₂)_qSH.

(c) p is 2 to 4



W is oxygen or sulphur

p is 2 to 4

Compounds of formula (I) where X is sulphur can be prepared by treating the compounds of formula (I) wherein X is oxygen with phosphorus pentasulphide in a solvent such as pyridine.

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The amines of formula (3) can be prepared by processes or by analogy with processes described in British Patent Specifications 1,305,547 and 1,338,169, and co-pending British Patent Applications 31968/75 and 31970/75 (Serial Nos. 1,565,647 and 1,564,502).

The compounds of formula (I) block histamine H₂-receptors, that is they inhibit the biological actions of histamine which are not inhibited by histamine H₁-antagonists such as mepyramine but are inhibited by burimamide. For example, the compounds of this invention have been found to inhibit histamine-stimulated secretion of gastric acid from the lumen-perfused stomachs of rats anaesthetised with urethane, at doses of from 0.5 to 16 micromoles per kilogram intravenously. This procedure is referred to in the above-mentioned paper of Ash and Schild. The activity of these compounds as histamine H₂-antagonists is also demonstrated by their ability to inhibit other actions of histamine which, according to the above mentioned paper of Ash and Schild, are not mediated by histamine H₁-receptors. For example, they inhibit the actions of histamine on the isolated guinea pig atrium and isolated rat uterus.

The compounds of this invention inhibit the basal secretion of gastric acid and also that stimulated by pentagastrin or by food.

In addition, the compounds of this invention show anti-inflammatory activity in conventional tests such as the rat paw oedema test, where the oedema is induced by an irritant, the rat paw volume is reduced by subcutaneous injection of doses of a compound of formula (I). In a conventional test, for example the measurement of blood pressure in the anaesthetised cat, the action of the compounds of this invention in inhibiting the vasodilator action of histamine can also be demonstrated. The level of activity of the compounds of this invention is illustrated by the effective dose producing 50% inhibition of gastric acid secretion in the anaesthetised rat (which for many of the compounds of formula (I) is from 1 to 10 micromoles per kilogram) and the dose producing 50% inhibition of histamine-induced tachycardia in the isolated guinea pig atrium.

The compounds of formula (I) also block histamine H₁-receptors, that is they inhibit the biological actions of histamine which are inhibited by mepyramine, diphenhydramine and chlorpheniramine. For example the compounds of this invention have been found to inhibit the action of histamine in the isolated guinea-pig ileum. For many of the compounds of formula (I) a dose of from 10⁻⁸ Molar inhibits the histamine-stimulated contractions of the guinea pig ileum.

For therapeutic use, the compounds of formula (I) and their pharmaceutically acceptable acid addition salts will normally be administered as a pharmaceutical composition.

Accordingly the invention also provides a pharmaceutical composition comprising a compound of formula (I) as defined above or a pharmaceutically acceptable acid addition salt thereof and a pharmaceutically acceptable carrier.

The compositions of this invention can be prepared in a form suitable for oral, parenteral or topical application by selection of an appropriate carrier.

The carrier employed can be a solid, for example lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate or stearic acid; or a liquid, for example, syrup, peanut oil, olive oil or water.

If a solid carrier is used, the composition can be tableted or encapsulated in powder or pellet form, in a hard gelatin shell or formed into a troche or lozenge. The amount of solid carrier can be varied widely but preferably will be from 25 mg to 1 g.

If a liquid carrier is used, the composition may be a syrup, emulsion, soft gelatin capsule, sterile injectable liquid dispensed in an ampoule, or an aqueous or non-aqueous liquid suspension.

The compound of formula (I) or pharmaceutically acceptable salts thereof will be present in the compositions in an effective amount to block histamine H₂-receptors.

Preferably the composition will be in unit dosage form for example, a tablet or capsule and each dosage unit will contain from 50 mg to 250 mg of a compound of formula (I) or a pharmaceutically acceptable acid addition salt thereof calculated as the free base. The pharmaceutical compositions can be prepared by conventional techniques involving procedures such as mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation.

Preferably administration will be once to six times daily. The daily dosage regimen will preferably be from 150 mg to 1500 mg of the compound of formula (I) or pharmaceutically acceptable acid addition salt calculated as the free base.

The following Examples in which all temperatures are in degrees centigrade illustrate the invention.

EXAMPLE 1.

2 - [2 - (5 - Methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (4 - pyridylmethyl) - 4 - pyrimidone trihydrochloride

- (i) Ethyl β -(4-pyridyl)propionate (43.45 g) and ethyl formate (19.6 g) were added over a period of 6 hours to a stirred mixture of sodium wire (5.6 g) and dry ether (150 ml) cooled by an ice-salt bath. The mixture was stirred for 18 hours at room temperature, evaporated to dryness and the residue treated with thiourea (18.45 g) and ethanol (130 ml) and refluxed for 7 hours. The mixture was evaporated to dryness and the residue dissolved in water and the solid product precipitated by adding glacial acid to pH4. The white solid was filtered and washed with ethanol to give 5 - (4 - pyridylmethyl) - 2 - thiouracil m.p. 320—324° (decomp).
- (ii) A solution of 5 - (4 - pyridylmethyl) - 2 - thiouracil (11.0 g), methyl iodide (7.2 g) and sodium hydroxide (2.1 g) in water (50 ml) and ethanol (100 ml) was stirred at 60° for 30 minutes, allowed to cool and filtered to give 5 - (4 - pyridylmethyl) - 2 - methylthio - 4 - pyrimidone m.p. 179—182° (ethanol).
- (iii) An intimate mixture of 5 - (4 - pyridylmethyl) - 2 - methylthio - 4 - pyrimidone (5.9 g) and 2 - (5 - methyl - 4 - imidazolylmethylthio) - ethylamine (4.3 g) was heated at 145—150° for 5 hours and allowed to cool. The residue was triturated with water, and treated with ethanolic hydrogen chloride to give the title compound m.p. 228—233° (Found: C, 43.6; H, 5.1; N, 17.6; S, 7.2; Cl, 21.95; $C_{17}H_{23}Cl_3N_6OS$ requires: C, 43.8; H, 5.0; N, 18.0; S, 6.9; Cl, 22.8%).

EXAMPLE 2.

2 - [2 - (2 - Thiazolylmethylthio)ethylamino] - 5 - (4 - pyridylmethyl) - 4 - pyrimidone trihydrochloride hemihydrate

- An intimate mixture of 5 - (4 - pyridylmethyl) - 2 - methylthio - 4 - pyrimidone (1.55 g) and 2 - (2 - thiazolylmethylthio)ethylamine (1.16 g) was heated at 135—140°C with frequent stirring. After cooling, the reaction mixture was triturated under water, acidified with dilute ethanolic hydrogen chloride, evaporated to dryness and the residue recrystallised from methanol to give the title compound m.p. 190—195° (Found: C, 40.3; H, 4.4; N, 14.5; S, 13.3; Cl, 21.7; $C_{18}H_{21}N_5OS_2 \cdot 3HCl \cdot \frac{1}{2}H_2O$ requires: C, 40.2; H, 4.4; N, 14.7; S, 13.4; Cl, 22.3%).

EXAMPLE 3.

2 - [2 - (3 - Bromo - 2 - pyridylmethylthio)ethylamino] - 5 - (4 - pyridylmethyl) - 4 - pyrimidone dihydrochloride

- 5 - (4 - Pyridylmethyl) - 2 - methylthio - 4 - pyrimidone (1.1 g) was reacted with 2 - (3 - bromo - 2 - pyridylmethylthio)ethylamine (1.15 g) according to the procedure of Example 2. The reaction mixture was triturated under hot water, acidified with dilute ethanolic hydrogen chloride, evaporated to dryness and the residue recrystallised from ethanol to give the title compound m.p. 211—215° (decomp). (Found: C, 42.65; H, 3.9; N, 13.9; S, 6.3; $C_{15}H_{18}BrN_5OS \cdot 2HCl$ requires: C, 42.8; H, 4.0; N, 13.9; S, 6.35%).

EXAMPLE 4.

2 - [2 - (5 - Methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (2 - thienylmethyl) - 4 - pyrimidone dihydrochloride

- (i) Ethyl 2-thienylpropionate (33.3 g), ethyl formate (14.1 g) and sodium (4.2 g) were reacted together in ether (120 ml), the mixture being cooled with an ice-salt bath. The ether was removed by evaporation, and the residue was refluxed with thiourea (13.8 g) and ethanol (100 ml). The ethanol was removed by evaporation and the residue was dissolved in water, and acetic acid was added to precipitate 5 - (2 - thienylmethyl) - 2 - thiouracil (38%) m.p. 212—215° (ethanol).
- (ii) 5 - (2 - Thienylmethyl) - 2 - thiouracil (4.5 g) was warmed at 65° with a mixture of methyl iodide (2.8 g), sodium hydroxide (0.8 g), water (75 ml) and ethanol (150 ml) to give 5 - (2 - thienylmethyl) - 2 - methylthio - 4 - pyrimidone (89%) m.p. 170.5—171.5° (ethanol).

- (iii) An intimate mixture of 5 - (2 - thienylmethyl) - 2 - methylthio - 4 - pyrimidone (1.43 g) and 2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamine (1.03 g) was heated at 100° for 6 hours. The cooled residue was washed with water and treated with dilute ethanolic HCl to give the title compound in 40% yield, m.p. 172—176° (ethanol-acetonitrile). The dihydrochloride was passed down an ion-exchange column of IRA 400 eluting with 1N hydrobromic acid, and the eluate was evaporated to dryness and recrystallised from ethanol-acetonitrile to give the corresponding dihydrobromide m.p. 199—203°.
(Found: C, 36.7; H, 4.2; N, 13.5; S, 12.1; Br, 30.6; $C_{16}H_{19}N_5OS_2 \cdot 2HBr$ requires C, 36.7; H, 4.0; N, 13.4; S, 12.2; Br, 30.5%)

EXAMPLE 5.

2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (2 - pyridylmethyl) - 4 - pyrimidone trihydrochloride hemihydrate

- (i) Ethyl β - (2 - pyridyl) - propionate (19.24 g) and ethyl formate (8.5 g) were added over a period of 1½ hours to a stirred mixture of sodium wire (2.5 g) and dry ether (80 ml) cooled by a carbon dioxide bath. The mixture was stirred for 21 hours at room temperature, evaporated to dryness and the residue was treated with thiourea (8.2 g) and ethanol (70 ml), and refluxed for 7½ hours. The mixture was evaporated to dryness and the residue was dissolved in water and glacial acid was added to pH 5. The white precipitate was filtered off, washed with water and recrystallised from water-acetic acid to give 5 - (2 - pyridylmethyl) - 2 - thiouracil, m.p. 262—7° (decomp.).
- (ii) A solution of 5 - (2 - pyridylmethyl) - 2 - thiouracil (6.6 g), methyl iodide (4.3 g) and sodium hydroxide (2.5 g) in water (100 ml) and ethanol (100 ml) was stirred at 70°C for 30 minutes, allowed to cool and glacial acetic acid added to pH 5. The solution was partially evaporated and cooled in an ice-bath. The precipitate was filtered off and recrystallised from ethanol to give 5 - (2 - pyridylmethyl) - 2 - methylthio - 4 - pyrimidone, m.p. 195—197.5°
- (iii) An intimate mixture of 5 - (2 - pyridylmethyl) - 2 - methylthio - 4 - pyrimidone (4.7 g) and 2 - (5 - methyl - 4 - imidazolylmethylthio) - ethylamine (3.4 g) was heated at 130—135° for 7 hours. The cooled residue was triturated with hot water and treated with dilute ethanolic HCl to give the title compound m.p. 207—210° (aqueous ethanol)
(Found: C, 42.8; H, 4.9; N, 17.8; S, 6.9; Cl, 21.8; $C_{17}H_{20}N_6OS \cdot 3HCl \cdot \frac{1}{2}H_2O$ requires: C, 43.0; H, 5.1; N, 17.7; S, 6.8; Cl, 22.4%)

EXAMPLE 6.

2 - -2 - (5 - Methyl - 4 - imidazolylmethylthio) - ethylamino] - 5 - (3 - pyridylmethyl) - 4 - pyrimidone trihydrochloride

- (i) Ethyl β - (3 - pyridyl) - propionate (38.9 g) and ethyl formate (17.0 g) were added over a period of 2½ hours to a stirred mixture of sodium wire (5.0 g) and dry ether (150 ml) cooled by an ice bath. The mixture was stirred for 22 hours at room temperature, evaporated to dryness and the residue was treated with thiourea (16.5 g) and ethanol (130 ml) and refluxed for 8 hours. The mixture was evaporated to dryness and the residue was dissolved in water and acetic acid added to pH 5 to give 5 - (3 - pyridylmethyl) - 2 - thiouracil, m.p. 271—4° (decomp.) (acetic acid-water).
- (ii) A solution of 5 - (3 - pyridylmethyl) - 2 - thiouracil (11.0 g), methyl iodide (7.1 g) and sodium hydroxide (4.2 g) in water (150 ml) and ethanol (150 ml) was stirred at 65° for 40 minutes, allowed to cool and acetic acid was added to pH 5. The solution was partially evaporated, cooled and filtered to give 5 - (3 - pyridylmethyl) - 2 - methylthio - 4 - pyrimidone, m.p. 247—9° (ex. ethanol-acetic acid).
- (iii) An intimate mixture of 5 - (3 - pyridylmethyl) - 2 - methylthio - 4 - pyrimidone (6.55 g) and 2 - (5 - methyl - 4 - imidazolylmethylthio) - ethylamine (4.8 g) was heated at 130—135° for 7 hours. The cool mixture was triturated with hot water and treated with dilute ethanolic HCl to give the title compound m.p. 237—241° (ethanol-water)
(Found: C, 43.7; H, 5.2; N, 17.4; S, 6.5; Cl— 22.0. $C_{17}H_{20}N_6OS \cdot 3HCl$ requires C, 43.8; H, 5.0; N, 18.0; S, 6.9; Cl, 22.8%)

EXAMPLE 7.

2 - [2 - (3 - Bromo - 2 - pyridylmethylthio) - ethylamino] - 5 - (2 - pyridylmethyl) - 4 - pyrimidone trihydrobromide

An intimate mixture of 5 - (2 - pyridylmethyl) - 2 - methylthio - 4 - pyrimidone (1.5 g) and 2 - (3 - bromo - 2 - pyridylmethylthio) - ethylamine (1.6 g) was heated at 130° for 6 hours. After cooling, the residue was triturated with hot water and treated with dilute hydrobromic acid to give the title compound, in 44.5% yield, m.p. 225—230° (decomp.) (ex methanol-water).

(Found: C, 32.1; H, 3.1; N, 10.5; S, 4.8; Br⁻ 35.0%. C₁₆H₁₈BrN₅OS · 3HBr requires C, 32.0; H, 3.1; N, 10.4; S, 4.8; Br⁻ 35.5%)

EXAMPLE 8.

2 - [2 - (5 - methyl - 4 - imidazolylmethylthio) - ethylamino] - 5 - (2 - thiazolmethyl) - 4 - pyrimidone trihydrochloride

(i) A solution of 2-thiazoleacrylic acid (26.76 g) and concentrated sulphuric acid (10 ml) in ethanol (150 ml) was refluxed for 18 hours. The solution was partially evaporated and dissolved in water. This solution was extracted with ether and the ethereal extracts were evaporated to give ethyl 2-thiazoleacrylate.

(ii) Ethyl 2-thiazoleacrylate (14.8 g) was dissolved in ethanol (170 ml) and hydrogenated at 40° and a pressure of 50 psi using 10% Palladium on charcoal to give ethyl 2-thiazolepropionate.

(iii) Ethyl 2-thiazolepropionate (14.2 g) and ethyl formate (5.9 g) were added over a period of 2½ hours to a stirred mixture of sodium wire (1.8 g) and dry ether (65 ml) cooled by an ice-bath. The mixture was stirred for 21 hours at room temperature, evaporated to dryness and the residue was treated with thiourea (5.8 g) and ethanol (60 ml) and refluxed for 9 hours. The solid product was obtained according to the procedure of Example 5(i) to give 5-(2-thiazole-methyl)-2-thiouracil, m.p. 275—280° (decomp.) (ex acetic acid).

(iv) A solution of 5 - (2 - thiazolemethyl) - 2 - thiouracil (4.8 g) methyl iodide (3.0 g) and sodium hydroxide (0.9 g) in water (75 ml) and ethanol (150 ml) was stirred at 70° for 30 minutes. The solid product was obtained according to the procedure of Example 5(ii), giving 5 - (2 - thiazolemethyl) - 2 - methylthio - 4 - pyrimidone, m.p. 181—182.5° (ex ethanol).

(v) An intimate mixture of 5 - (2 - thiazolemethyl) - 2 - methylthio - 4 - pyrimidone (1.4 g) and 2 - (5 - methyl - 4 - imidazolylmethylthio) - ethylamine (1.0 g) was heated at 145—150°C for 6 hours. The cooled residue was triturated with hot water and treated with dilute ethanolic HCl to give the title compound m.p. 208—211° (ex. ethanol water)

(Found: C, 38.9; H, 4.7; N, 17.9; S, 13.5; Cl, 21.6. C₁₈H₁₈N₆OS₂ · 3HCl requires C, 38.2; H, 4.5; N, 17.8; S, 13.6; Cl, 22.5%)

EXAMPLE 9.

2 - [2 - (2 - Thiazolylmethylthio) - ethylamino] - 5 - (3 - pyridylmethyl-4 - pyrimidone trihydrobromide

5 - (3 - Pyridylmethyl) - 2 - methylthio - 4 - pyrimidone (1.74 g) was reacted with 2 - (2 - thiazolylmethylthio) - ethylamine (1.30 g) according to the procedure in Example 2. The reaction mixture was triturated in hot water and treated with dilute hydrobromic acid to give the title compound, m.p. 229—233.5° (ex. methanol-water).

(Found: C, 32.1; H, 3.4; N, 11.7; S, 10.3; Br⁻, 39.9; C₁₈H₁₇N₅OS₂ · 3HBr requires: C, 31.9; H, 3.4; N, 11.6; S, 10.7; Br⁻ 39.8%)

EXAMPLE 10.

2 - [2 - (3 - Bromo - 2 - pyridylmethylthio) - ethylamino] - 5 - (3 - pyridylmethyl) - 4 - pyrimidone trihydrobromide

5 - (3 - Pyridylmethyl) - 2 - methylthio - 4 - pyrimidone (1.27 g) was reacted with 2 - (3 - bromo - 2 - pyridylmethylthio) - ethylamine (1.35 g) according to the procedure in Example 2. The reaction mixture was triturated with hot water and treated with dilute hydrobromic acid to give the title compound, m.p. 217—220.5° (ex-methanol)

(Found: C, 32.1; H, 3.2; N, 10.2; S, 4.5; Br, 47.5. C₁₈H₁₈BrN₅OS · 3HBr requires: C, 32.0; H, 3.1; N, 10.4; S, 4.8; Br, 47.4%)

EXAMPLE 11.

- Substitution of (a) ethyl β -(2-methoxy-3-pyridyl)propionate
 (b) ethyl β -(3-methoxy-2-pyridyl)propionate
 (c) ethyl β -(3,4-dimethoxy-2-pyridyl)propionate
 (d) ethyl β -(4-isoquinolyl)propionate

for ethyl β -(4-pyridyl)propionate in the procedure of Example 1 leads to the production of

- (a) 2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (2 - methoxy-3 - pyridylmethyl) - 4 - pyrimidone
 (b) 2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (3 - methoxy-2 - pyridylmethyl) - 4 - pyrimidone
 (c) 2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (3,4 - dimethoxy - 2 - pyridylmethyl) - 4 - pyrimidone
 (d) 2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (4 - isoquinolylmethyl) - 4 - pyrimidone

The starting materials may be made from the corresponding heterocyclic carboxaldehyde by condensation with malonic acid and subsequent hydrogenation and esterification.

EXAMPLE 12.

- Substitution of: (a) 2-(2-imidazolylmethylthio)ethylamine
 (b) 2-(4-imidazolylmethylthio)ethylamine
 (c) 2-(5-bromo-4-imidazolylmethylthio)ethylamine
 (d) 2-(5-trifluoromethyl-4-imidazolylmethylthio)ethylamine
 (e) 2-(5-hydroxymethyl-4-imidazolylmethylthio)ethylamine
 (f) 2-(2-pyridylmethylthio)ethylamine
 (g) 2-(3-methyl-2-pyridylmethylthio)ethylamine
 (h) 2-(3-methoxy-2-pyridylmethylthio)ethylamine
 (i) 2-(3-chloro-2-pyridylmethylthio)ethylamine
 (j) 2-(3-amino-2-pyridylmethylthio)ethylamine
 (k) 2-(3-hydroxy-2-pyridylmethylthio)ethylamine
 (l) 2-(3-isothiazolylmethylthio)ethylamine
 (m) 2-(4-bromo-3-isothiazolylmethylthio)ethylamine
 (n) 2-(3-(1,2,5)-thiadiazolylmethylthio)ethylamine
 (o) 2-(4-chloro-3-(1,2,5)-thiadiazolylmethylthio)ethylamine
 (p) 2-(5-amino-2-(1,3,4)-thiadiazolylmethylthio)ethylamine

for 2-(5-methyl-4-imidazolylmethylthio)ethylamine in the procedure of Example 6 leads to the production of:—

- (a) 2 - [2 - (2 - imidazolylmethylthio)ethylamino] - 5 - (3 - pyridylmethyl) - 4 - pyrimidone
 (b) 2 - [2 - (4 - imidazolylmethylthio)ethylamino] - 5 - (3 - pyridylmethyl) - 4 - pyrimidone
 (c) 2 - [2 - (5 - bromo - 4 - imidazolylmethylthio)ethylamino] - 5 - (3 - (pyridylmethyl) - 4 - pyrimidone
 (d) 2 - [2 - (5 - trifluoromethyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (3 - pyridylmethyl) - 4 - pyrimidone
 (e) 2 - [2 - (5 - hydroxymethyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (3 - pyridylmethyl) - 4 - pyrimidone
 (f) 2 - [2 - (2 - pyridylmethylthio)ethylamino] - 5 - (3 - pyridylmethyl) - 4 - pyrimidone
 (g) 2 - [2 - (3 - methyl - 2 - pyridylmethylthio)ethylamino] - 5 - (3 - pyridylmethyl) - 4 - pyrimidone
 (h) 2 - [2 - (3 - methoxy - 2 - pyridylmethylthio)ethylamino] - 5 - (3 - pyridylmethyl) - 4 - pyrimidone
 (i) 2 - [2 - (3 - chloro - 2 - pyridylmethylthio)ethylamino] - 5 - (3 - pyridylmethyl) - 4 - pyrimidone
 (j) 2 - [2 - (3 - amino - 2 - pyridylmethylthio)ethylamino] - 5 - (3 - pyridylmethyl) - 4 - pyrimidone

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11		1,582,527	11
	(k)	2 - [2 - (3 - hydroxy - 2 - pyridylmethylthio)ethylamino] - 5 - (3 - pyridylmethyl) - 4 - pyrimidone	
	(l)	2 - [2 - (3 - isothiazolylmethylthio)ethylamino] - 5 - (3 - pyridylmethyl) - 4 - pyrimidone	
5	(m)	2 - [2 - (4 - bromo - 3 - isothiazolylmethylthio)ethylamino] - 5 - (3 - pyridylmethyl) - 4 - pyrimidone	5
	(n)	2 - [2 - (3 - (1,2,5) - thiadiazolylmethylthio)ethylamino] - 5 - (3 - pyridylmethyl) - 4 - pyrimidone	
10	(o)	2 - [2 - (4 - chloro - 3 - (1,2,5) - thiadiazolylmethylthio)ethylamino] - 5 - (3 - pyridylmethyl) - 4 - pyrimidone	
	(p)	2 - [2 - (5 - amino - 2 - (1,3,4) - thiadiazolylmethylthio)ethylamino] - 5 - (3 - pyridylmethyl) - 4 - pyrimidone	10

EXAMPLE 13.

15	(i)	Reaction of 2 - chloro - 3 - nitropyridine with 2 - (2 - cyanoethyl)malonic acid diethyl ester and sodium hydride in tetrahydrofuran gives 3 - (3 - nitro - 2 - pyridyl) - 1,1 - bis - (carbethoxy) - butyronitrile, m.p. 93.5—94.5°, which after alkaline hydrolysis and acidification gives 2 - (3 - cyanopropyl) - 3 - nitropyridine hydrochloride 142—145.5°. Reduction with hydrogen and palladium on charcoal gives 3 - amino - 2 - (3 - cyanopropyl)pyridine, and treatment of this with sodium nitrite and sulphuric acid and subsequent warming gives 2 - (3 - cyanopropyl) - 3 - hydroxypyridine. Methylation with methyl iodide and sodium ethoxide in dimethylsulphoxide and subsequent reduction with lithium aluminium hydride gives 4 - (3 - methoxy - 2 - pyridyl)butylamine. Reduction of 3 - amino - 2 - (3 - cyanopropyl) - [3 - hydroxy]pyridine with lithium aluminium hydride gives 4 - (3 - amino - 2 - pyridyl)butylamine. Diazotisation of 4 - (3 - amino - 2 - pyridyl)butylamine at pH 1 and treatment with cuprous chloride or cuprous bromide gives 4 - (3 - chloro - 2 - pyridyl)butylamine and 4 - (3 - bromo - 2 - pyridyl)butylamine, respectively.	15
20			20
25			25
30	(ii)	Substitution of (a) 4-(4-imidazolyl)butylamine (b) 4-(3-methoxy-2-pyridyl)butylamine (c) 4-(3-chloro-2-pyridyl)butylamine (d) 4-(3-bromo-2-pyridyl)butylamine (e) 4-(3-amino-2-pyridyl)butylamine	30

35		for 2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamine in the procedure of Example 6 leads to the production of:	35
	(a)	2 - [4 - (4 - imidazolyl)butylamino] - 5 - (3 - pyridylmethyl) - 4 - pyrimidone	
	(b)	2 - [4 - (3 - methoxy - 2 - pyridyl)butylamino] - 5 - (3 - pyridylmethyl) - 4 - pyrimidone	
40	(c)	2 - [4 - (3 - chloro - 2 - pyridyl)butylamino] - 5 - (3 - pyridylmethyl) - 4 - pyrimidone	40
	(d)	2 - [4 - (3 - bromo - 2 - pyridyl)butylamino] - 5 - (3 - pyridylmethyl) - 4 - pyrimidone	
	(e)	2 - [4 - (3 - amino - 2 - pyridyl)butylamino] - 5 - (3 - pyridylmethyl) - 4 - pyrimidone	

EXAMPLE 14.

45		Reaction of ethyl acetoacetate with sodium ethoxide and 3-(chloromethyl)-pyridine gives ethyl α - (3 - pyridylmethyl)acetoacetate which gives 5 - (3 - pyridylmethyl) - 6 - methyl - 2 - thiouracil when treated with thiourea and sodium ethoxide. Substitution of 5 - (3 - pyridylmethyl) - 6 - methyl - 2 - thiouracil for 5 - (4 - pyridylmethyl) - 2 - thiouracil in the general procedure of Example 1 gives 2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (3 - pyridylmethyl) - 6 - methyl - 4 - pyrimidone. 2 - [2 - (5 - Methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (3 - pyridylmethyl) - 6 - propyl - 4 - pyrimidone may be prepared in a similar manner starting with ethyl butyroacetate.	45
50			50

EXAMPLE 15.

55		Treatment of 2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (3 - pyridylmethyl) - 4 - pyrimidone with phosphorus pentasulphide in hot pyridine	55
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leads to the production of 2 - [2 - (5 - methyl - 4 - imidazolymethylthio)ethylamino] - 5 - (3 - pyridylmethoxy)pyrimid - 4 - thione

EXAMPLE 16.

- (i) Butyrolactone is treated with sodium and ethyl formate, and the product is successively treated with thiourea and methyl iodide to give 5 - (2 - hydroxyethyl) - 2 - methylthio - 4 - pyrimidone.
- (ii) 5 - (2 - Hydroxyethyl) - 2 - methylthio - 4 - pyrimidone is treated with thionyl chloride and the product is reacted with the sodium derivative of (a) 3-(hydroxymethyl)pyridine and (b) 3-(mercaptomethyl)pyridine to give:
- (a) 5 - (2 - (3 - pyridylmethoxy)ethyl) - 2 - methylthio - 4 - pyrimidone
- (b) 5 - (2 - (3 - pyridylmethylthio)ethyl) - 2 - methylthio - 4 - pyrimidone
- (iii) substitution of:
- (a) 5 - (2 - (3 - pyridylmethoxy)ethyl) - 2 - methylthio - 4 - pyrimidone
- (b) 5 - (2 - (3 - pyridylmethylthio)ethyl) - 2 - methylthio - 4 - pyrimidone
- for 5 - (3 - pyridylmethyl) - 2 - methylthio - 4 - pyrimidone in the general procedure of Example 6 leads to the production of:
- (a) 2 - [2 - (5 - methyl - 4 - imidazolymethylthio)ethylamino] - 5 - (2 - (3 - pyridylmethoxy)ethyl) - 4 - pyrimidone
- (b) 2 - [2 - (5 - methyl - 4 - imidazolymethylthio)ethylamino] - 5 - (2 - (3 - pyridylmethylthio)ethyl) - 4 - pyrimidone
- (iv) substitution of:
- (a) 3-hydroxypyridine and
- (b) 3-mercaptopyridine for
- 3-(hydroxymethyl)pyridine in procedure (ii) and (iii) above leads to the production of:
- (a) 2 - [2 - (5 - methyl - 4 - imidazolymethylthio)ethylamino] - 5 - (2 - (3 - pyridyloxy)ethyl) - 4 - pyrimidone
- (b) 2 - [2 - (5 - methyl - 4 - imidazolymethylthio)ethylamino] - 5 - (2 - (3 - pyridylthio)ethyl) - 4 - pyrimidone
- (v) substitution of:
- (a) 3-(2-hydroxyethyl)pyridine and
- (b) 3-(2-mercaptoethyl)pyridine for
- 3-(hydroxymethyl)pyridine in procedure (ii) and (iii) above leads to the preparation of
- (a) 2 - [2 - (5 - methyl - 4 - imidazolymethylthio)ethylamino] - 5 - (2 - (2 - (3 - pyridyl)ethoxy)ethyl) - 4 - pyrimidone
- (b) 2 - [2 - (5 - methyl - 4 - imidazolymethylthio)ethylamino] - 5 - (2 - (2 - (3 - pyridyl)ethylthio)ethyl) - 4 - pyrimidone
- (vi) substitution of valerolactone for butyrolactone in procedure (i) (ii) and (iii) above leads to the production of
- (a) 2 - [2 - (5 - methyl - 4 - imidazolymethylthio)ethylamino] - 5 - (3 - (3 - pyridylmethoxy)propyl) - 4 - pyrimidone
- (b) 2 - [2 - (5 - methyl - 4 - imidazolymethylthio)ethylamino] - 5 - (3 - (3 - pyridylmethylthio)propyl) - 4 - pyrimidone

EXAMPLE 17.

Ethyl 3-pyridylmethoxyacetate is converted into 5 - (3 - pyridylmethoxy) - 2 - thiouracil by the general procedure of Example 1 (i). Substitution of 5 - (3 - pyridylmethoxy) - 2 - thiouracil for 5 - (4 - pyridylmethyl) - 2 - thiouracil in the general procedure of Example 1 gives 2 - [2 - (5 - methyl - 4 - imidazolymethylthio)ethylamino] - 5 - (3 - pyridylmethoxy) - 4 - pyrimidone.

2 - [2 - (5 - Methyl - 4 - imidazolymethylthio)ethylamino] - 5 - (3 - (3 - pyridylpropoxy) - 4 - pyrimidone and 2 - [2 - (5 - methyl - 4 - imidazolymethylthio)ethylamino] - 5 - (3 - (3 - pyridyl)propylthio) - 4 - pyrimidone may be pre-

pared in a similar manner starting with ethyl 3 - (3 - pyridyl)propoxyacetate and ethyl 3 - (3 - pyridyl)propylthioglycolate, respectively.

EXAMPLE 18.

Substitution of (a) ethyl β -(2-furyl)propionate
(b) ethyl β -(5-oxazolyl)propionate
(c) ethyl β -(3-isothiazolyl)propionate
(d) ethyl β -(2-pyrimidyl)propionate
(e) ethyl β -(5-pyrimidyl)propionate
(f) ethyl β -(2-pyrazinyl)propionate
(g) ethyl β -(4-pyridazyl)propionate

for ethyl β - (4 - pyridyl)propionate in the procedure of Example 1 leads to the production of

- (a) 2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (2 - furyl-methyl) - 4 - pyrimidone
(b) 2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (2 - oxazolyl-methyl) - 4 - pyrimidone
(c) 2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (3 - isothiazolylmethyl) - 4 - pyrimidone
(d) 2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (2 - pyrimidylmethyl) - 4 - pyrimidone
(e) 2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (5 - pyrimidylmethyl) - 4 - pyrimidone
(f) 2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (2 - pyrazinylmethyl) - 4 - pyrimidone
(g) 2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (4 - pyridazylmethyl) - 4 - pyrimidone

The starting materials (b) to (g) above may be prepared by condensing the corresponding heterocyclic carboxaldehyde with malonic acid, and hydrogenating and esterifying the product.

EXAMPLE 19.

Treatment of 1 - (4 - methoxybenzyl) - 2 - imidazole carboxaldehyde with malonic acid in the presence of pyridine and piperidine gives 2 - [1 - (4 - methoxybenzyl)imidazolyl]acrylic acid. Substitution of 2 - [1 - (4 - methoxybenzyl)imidazolyl]acrylic acid for 2-thiazoleacrylic acid in the procedure of Example 8 and removal of the benzyl protecting group from the product with anisole and hydrogen bromide in acetic acid gives 2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (2 - imidazolylmethyl) - 4 - pyrimidone.

EXAMPLE 20.

Pharmaceutical composition:—

Ingredients	Amounts
2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)-ethylamino] - 5 - (3 - pyridylmethyl) - 4-pyrimidone trihydrochloride	75 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 21.

Pharmaceutical composition:—

Ingredients	Amounts
2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (3 - pyridylmethyl) - 4-pyrimidone trihydrochloride	100 mg
Lactose	100 mg

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

Similarly, the other compounds of Formula I may be formulated into pharmaceutical compositions by the procedures of Examples 20 and 21.

The pharmaceutical compositions prepared as in the foregoing examples are administered to a subject within the dose ranges given hereabove to block histamine H_2 -receptors.

EXAMPLE 22.

2 - [2 - (5 - methyl - 4 - imidazolylmethylthio) - ethylamino] - 5 - (3 - quinolylmethyl) - 4 - pyrimidone trihydrochloride

(i) A solution of 3-quinolineacrylic acid (63.71 g) and concentrated sulphuric acid (25 ml) in ethanol (350 ml) was refluxed for 18 hours. The product was obtained according to the procedure of Example 8 (i), giving ethyl 3-quinolineacrylate, m.p. 86.5—88° (Ex ethanol-water).

(Found: C, 73.8; H, 5.8; N, 6.0; $C_{14}H_{13}NO_2$ requires: C, 74.0; H, 5.8; N, 6.2%)

(ii) 3-quinolineacrylate (51.68 g) was dissolved in ethanol (170 ml) and hydrogenated at 37° and a pressure of 50 psi using 10% Palladium on charcoal to give ethyl 3-quinolinepropionate.

(iii) Ethyl 3-quinolinepropionate (47.99 g) and ethyl formate (16.3 g) were added over a period of 3 hours to a stirred mixture of sodium wire (4.8 g) and dry ether (150 ml) cooled by an ice-bath. The mixture was stirred for 20 hours at room temperature, evaporated to dryness and the residue was treated with thiourea (15.9 g) and ethanol (130 ml) and refluxed for 7 hours. The mixture evaporated to dryness and the residue was dissolved in water and acetic acid added to pH 4. The mixture was filtered to give 5 - (3 - quinolinemethyl) - 2-thiouracil, m.p. 281—6° (decomp.) (ex. acetic acid-water).

(iv) A solution of 5 - (3 - quinolinemethyl) - 2 - thiouracil (17.51 g), methyl iodide (9.2 g) and sodium hydroxide (5.4 g) in water (200 ml) and ethanol (200 ml) was stirred at 75° for 1 hour, allowed to cool and acetic acid added to pH 4 to give 5 - (3 - quinolinemethyl) - 2 - methylthio - 4 - pyrimidone, m.p. 215.5—218° (ex. ethanol).

(v) An intimate mixture of 5 - (3 - quinolinemethyl) - 2 - methylthio - 4 - pyrimidone (2.1 g) and 2 - (5 - methyl - 4 - imidazolylmethylthio) - ethylamine (1.3 g) was heated at 150—5° for 6 hours. The cooled mixture was triturated with hot water and treated with dilute ethanolic HCl to give the title compound, m.p. 184—9° (ex. ethanol-water).

EXAMPLE 23.

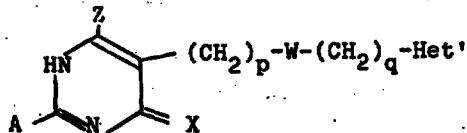
2 - [2 - (2 - thiazolylmethylthio)ethylamino] - 5 - (3 - quinolylmethyl) - 4 - pyrimidone trihydrochloride

An intimate mixture of 5 - (3 - quinolinemethyl) - 2 - methylthio - 4 - pyrimidone (2.0 g) and 2 - (2 - thiazolylmethylthio) - ethylamine (1.2 g) was heated at 145° for 4 hours. After cooling the residue was triturated with hot water and treated with dilute ethanolic HCl to give the title compound, m.p. 217.5—221.5° (ex. ethanol-water).

(Found: C, 45.9; H, 4.3; N, 13.3; S, 12.2; Cl, 19.7. $C_{20}H_{19}N_5OS_2 \cdot 3HCl$ requires: C, 46.3; H, 4.3; N, 13.5; S, 12.4; Cl, 20.5%)

WHAT WE CLAIM IS:—

1. A compound of the formula:—



where X is oxygen or sulphur, A is $Het-CH_2-Y(CH_2)_2-NH-$ where Het is a 2- or 4-imidazolyl group optionally substituted with lower alkyl, halogen, trifluoromethyl or hydroxymethyl; a 2-pyridyl group optionally substituted with lower alkyl, lower alkoxy, halogen, amino or hydroxy; a 2-thiazolyl group; a 3-isothiazolyl group optionally substituted with chlorine or bromine; a 3 - (1,2,5) - thiadiazolyl group optionally substituted with chlorine or bromine, or a 2 - (5 - amino - 1,3,4 - thiadiazolyl) group; Y is sulphur or methylene and A is also lower alkylthio, benzylthio or halogen when X is oxygen; Z is hydrogen or lower alkyl; X is oxygen or sulphur;

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The ingredients are screened, mixed and filled into a hard gelatin capsule. Similarly, the other compounds of Formula I may be formulated into pharmaceutical compositions by the procedures of Examples 20 and 21.

The pharmaceutical compositions prepared as in the foregoing examples are administered to a subject within the dose ranges given hereabove to block histamine H_2 -receptors.

EXAMPLE 22.

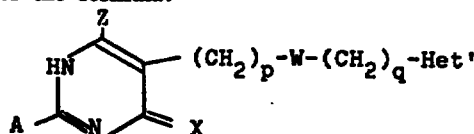
- 2 - [2 - (5 - methyl - 4 - imidazolylmethylthio) - ethylamino] - 5 - (3 - quinolylmethyl) - 4 - pyrimidone trihydrochloride
- (i) A solution of 3-quinolineacrylic acid (63.71 g) and concentrated sulphuric acid (25 ml) in ethanol (350 ml) was refluxed for 18 hours. The product was obtained according to the procedure of Example 8 (i), giving ethyl 3-quinolineacrylate, m.p. 86.5—88° (Ex ethanol-water). (Found: C, 73.8; H, 5.8; N, 6.0; $C_{14}H_{13}NO_2$ requires: C, 74.0; H, 5.8; N, 6.2%)
- (ii) 3-quinolineacrylate (51.68 g) was dissolved in ethanol (170 ml) and hydrogenated at 37° and a pressure of 50 psi using 10% Palladium on charcoal to give ethyl 3-quinolinepropionate.
- (iii) Ethyl 3-quinolinepropionate (47.99 g) and ethyl formate (16.3 g) were added over a period of 3 hours to a stirred mixture of sodium wire (4.8 g) and dry ether (150 ml) cooled by an ice-bath. The mixture was stirred for 20 hours at room temperature, evaporated to dryness and the residue was treated with thiourea (15.9 g) and ethanol (130 ml) and refluxed for 7 hours. The mixture evaporated to dryness and the residue was dissolved in water and acetic acid added to pH 4. The mixture was filtered to give 5 - (3 - quinolinemethyl) - 2 - thiouracil, m.p. 281—6° (decomp.) (ex. acetic acid-water).
- (iv) A solution of 5 - (3 - quinolinemethyl) - 2 - thiouracil (17.51 g), methyl iodide (9.2 g) and sodium hydroxide (5.4 g) in water (200 ml) and ethanol (200 ml) was stirred at 75° for 1 hour, allowed to cool and acetic acid added to pH 4 to give 5 - (3 - quinolinemethyl) - 2 - methylthio - 4 - pyrimidone, m.p. 215.5—218° (ex. ethanol).
- (v) An intimate mixture of 5 - (3 - quinolinemethyl) - 2 - methylthio - 4 - pyrimidone (2.1 g) and 2 - (5 - methyl - 4 - imidazolylmethylthio) - ethylamine (1.3 g) was heated at 150—5° for 6 hours. The cooled mixture was triturated with hot water and treated with dilute ethanolic HCl to give the title compound, m.p. 184—9° (ex. ethanol-water).

EXAMPLE 23.

- 2 - [2 - (2 - thiazolylmethylthio)ethylamino] - 5 - (3 - quinolylmethyl) - 4 - pyrimidone trihydrochloride
- An intimate mixture of 5 - (3 - quinolinemethyl) - 2 - methylthio - 4 - pyrimidone (2.0 g) and 2 - (2 - thiazolylmethylthio) - ethylamine (1.2 g) was heated at 145° for 4 hours. After cooling the residue was triturated with hot water and treated with dilute ethanolic HCl to give the title compound, m.p. 217.5—221.5° (ex. ethanol-water). (Found: C, 45.9; H, 4.3; N, 13.3; S, 12.2; Cl, 19.7. $C_{20}H_{19}N_5OS_2 \cdot 3HCl$ requires: C, 46.3; H, 4.3; N, 13.5; S, 12.4; Cl, 20.5%)

WHAT WE CLAIM IS:—

1. A compound of the formula:—



where X is oxygen or sulphur, A is Het—CH₂Y(CH₂)₂—NH— where Het is a 2- or 4-imidazolyl group optionally substituted with lower alkyl, halogen, trifluoromethyl or hydroxymethyl; a 2-pyridyl group optionally substituted with lower alkyl, lower alkoxy, halogen, amino or hydroxy; a 2-thiazolyl group; a 3-isothiazolyl group optionally substituted with chlorine or bromine; a 3 - (1,2,5) - thiadiazolyl group optionally substituted with chlorine or bromine, or a 2 - (5 - amino - 1,3,4 - thiadiazolyl) group; Y is sulphur or methylene and A is also lower alkylthio, benzylthio or halogen when X is oxygen; Z is hydrogen or lower alkyl; X is oxygen or sulphur;



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W is methylene, oxygen or sulphur; p and q are such that their sum is from 1 to 4 when W is oxygen or sulphur, or from 0 to 4 when W is methylene; Het' is a 5 or 6 membered heteroaryl group optionally substituted by lower alkyl, lower alkoxy, or may have a phenyl group or substituted phenyl group fused to it.

5 2. A compound according to claim 1 where Het' is a pyridyl, furyl, thienyl, thiazolyl, oxazolyl, isothiazolyl, imidazolyl, pyrazinyl, pyridazinyl or pyrimidyl group, optionally substituted by lower alkyl, lower alkoxy, or may have a phenyl group or substituted phenyl group fused to it.

10 3. A compound according to claim 2 where Het' is a 2-furyl, 2-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-thiazolyl, 2-imidazolyl, 2-pyrimidyl, 2-pyrazinyl or 4-pyridazyl group, optionally substituted with lower alkyl or lower alkoxy.

4. A compound according to claim 3 where Het' is a 2-furyl, 2-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-thiazolyl, 2-imidazolyl, 2-pyrimidyl, 2-pyrazinyl, or 4-pyridazyl group optionally substituted with lower alkyl.

15 5. A compound according to claim 4 where Het' is a 2-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl or 2-thiazolyl group.

6. A compound according to claim 5 where Het' is a 3-pyridyl group.

7. A compound according to any one of claims 1 to 6 where Z is hydrogen.

20 8. A compound according to any one of claims 1 to 7 where W is methylene and p and q are both 0.

9. A compound according to any one of claims 1 to 8 where X is oxygen.

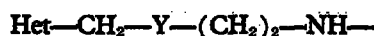
10. A compound according to claim 9 where A is lower alkylthio, benzylthio or halogen.

25 11. A compound according to claim 10 where A is methylthio.

12. 5 - (4 - pyridylmethyl) - 2 - methylthio - 4 - pyrimidone.

13. 5 - (3 - pyridylmethyl) - 2 - methylthio - 4 - pyrimidone.

14. A compound as claimed in any one of claims 1 to 9 where A is:—



and acid addition salts thereof.

30 15. A compound according to claim 14 where Het is a 2-thiazolyl, 5-methyl-4-imidazolyl, 5-bromo-4-imidazolyl, 3-bromo-2-pyridyl, 3-chloro-2-pyridyl, 3-methoxy-2-pyridyl or 3-hydroxy-2-pyridyl group.

16. A compound according to any one of claims 14 or 15 where Y is sulphur.

35 17. 2 - [2 - (5 - Methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (4 - pyridylmethyl) - 4 - pyrimidone.

18. 2 - [2 - (2 - Thiazolylmethylthio)ethylamino] - 5 - (4 - pyridylmethyl) - 4 - pyrimidone.

19. 2 - [2 - (3 - Bromo - 2 - pyridylmethylthio)ethylamino] - 5 - (4 - pyridylmethyl) - 4 - pyrimidone.

40 20. 2 - [2 - (5 - Methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (2 - thienylmethyl) - 4 - pyrimidone.

21. 2 - [2 - (5 - Methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (2 - pyridylmethyl) - 4 - pyrimidone.

45 22. 2 - [2 - (5 - Methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (3 - pyridylmethyl) - 4 - pyrimidone.

23. 2 - [2 - (3 - Bromo - 2 - pyridylmethylthio)ethylamino] - 5 - (2 - pyridylmethyl) - 4 - pyrimidone.

24. 2 - [2 - (5 - Methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (2 - thiazolylmethyl) - 4 - pyrimidone.

50 25. 2 - [2 - (2 - Thiazolylmethylthio)ethylamino] - 5 - (3 - pyridylmethyl) - 4 - pyrimidone.

26. 2 - [2 - (3 - Bromo - 2 - pyridylmethylthio)ethylamino] - 5 - (3 - pyridylmethyl) - 4 - pyrimidone.

55 27. 2 - [4 - (3 - Methoxy - 2 - pyridyl)butylamino] - 5 - (3 - pyridylmethyl) - 4 - pyrimidone.

28. 2 - [4 - (3 - Amino - 2 - pyridyl)butylamino] - 5 - (3 - pyridylmethyl) - 4 - pyrimidone.

29. A pharmaceutically acceptable acid addition salt of a compound according to any one of claims 14 to 28.

60 30. A process for preparing a compound according to claim 1 where A is $\text{Het}-\text{CH}_2\text{Y}(\text{CH}_2)_2-\text{NH}-$ and X is oxygen, which comprises reacting an isocytosine of formula:—

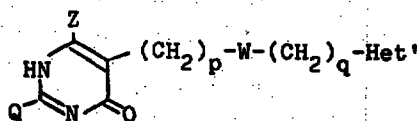


* C L M S *

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where Z, W, p, q, and Het' are as defined in claim 1 and Q is a group which is displaceable by an amine, with an amine of formula:—



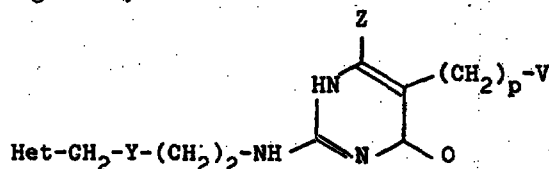
where Het and Y are as defined in claim 1, and thereafter optionally converting the compound so obtained into a salt.

31. A process according to claim 30 where Q is lower alkylthio, benzylthio or halogen.

32. A process according to claim 31 where Q is methylthio.

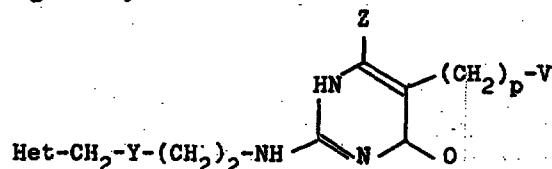
33. A process for preparing a compound as claimed in claim 14 where X is oxygen and W is sulphur which comprises either

a) reacting an isocytosine of formula:—



where Het, Y, Z and p are as defined in claim 1 and V is mercapto, with a compound of formula $\text{U}(\text{CH}_2)_q \text{Het}'$ where q and Het' are as defined in claim 1, and U is chloro or bromo, provided that q may be 0 only if U is an 'active' halogen; or

b) reacting an isocytosine of formula:—



where Het, Y, Z and p are as defined in claim 1 and V is chloro or bromo with a compound of formula $\text{U}(\text{CH}_2)_q \text{Het}'$ where q and Het' are as defined in claim 1 and U is mercapto, and thereafter optionally converting the compound so obtained into a salt.

34. A process for preparing a compound according to claim 14 where X is sulphur which comprises reacting a corresponding compound where X is oxygen with phosphorus pentasulphide and thereafter optionally converting the compound so obtained into a salt.

35. A compound according to claim 14 where X is oxygen whenever prepared by a process according to any one of claims 30 to 33.

36. A compound according to claim 14 where X is sulphur whenever prepared by a process according to claim 34.

37. A process for preparing a compound according to claim 14 substantially as hereinbefore illustrated in any one of Examples 1 to 5.

38. A process for preparing a compound according to claim 14 substantially as hereinbefore illustrated in any one of Examples 1 to 19, 22 and 23.

39. A compound according to claim 14 whenever prepared by a process according to any one of claims 30 to 33, 34, and 35.

40. A pharmaceutical composition comprising a compound according to any one of claims 14 to 29, 35, 36 or 39, or a pharmaceutically acceptable acid addition salt thereof and a pharmaceutically acceptable carrier.

41. A pharmaceutical composition substantially as hereinbefore illustrated in Example 20 or 21.

G. H. HARGREAVES,
Agent for the Applicants.