PATENT SPECIFICATION

(11) 1 595 291

1 595 291

(21) Application No. 39066/76 (22) Filed 21 Sept. 1976
(23) Complete Specification filed 20 Sept. 1977
(44) Complete Specification published 12 Aug. 1981
(51) INT CL³ C07D 401/12 A61K 31/505 C07D 403/12 405/14 417/12 491/04 (C07D 401/12 213/04 217/14 239/46) (C07D 403/12) (C07D 405/14 233/54 317/50 319/18) (C07D 417/12 275/02 277/22 285/04) (C07D 491/04 213/69 317/28 319/12 321/00)
(52) Index at acceptance
C2C 1380 1382 1410 1440 1494 1504 1530 1531 1535 155X 1601 1693 200 213 214 215 21X 220 222 226 22Y 246 247 250 251 252 253 255 256 25Y 28X 29X 29Y 304 305 30Y 311 313 314 31Y 321 322 323 32Y 332 337 338 339 351 352 360 361 364 365 366 368 36Y 371 373 37X 37Y 388 40Y 440 453 45Y 461 462 463 464 491 509 50Y 553 610 612 613 614 620 621 623 624 625 628 630 633 634 644 650 652 658 65X 660 662 670 671 672 680 694 699 758 760 761 762 774 776 777 AA BB BE LH LK ML QS RM TY WB WC ZF ZL

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(54) PYRIMIDONE AND THIOPYRIMIDONE DERIVATIVES

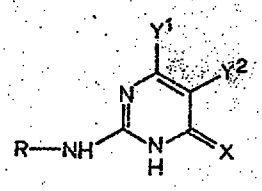
(71) We, SMITH KLINE & FRENCH LABORATORIES LIMITED of Mundells, Welwyn Garden City, Hertfordshire, a British Company, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following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

This invention relates certain pyrimidone derivatives to processes for their preparation 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 "antihistamines" of which mepyramine, diphenhydramine and chloropheniramine are examples, are mediated through histamine H_1-receptors (Ash and Schild, Brit. J. Pharmac. Chemother., *27*, 427, (1966)), and drugs with this activity are hereinafter referred to as histamine H_1-antagonists. However, other of the biological actions of histamine are not inhibited by histamine H_1-antagonists and actions of this type which are inhibited by a compound described by Black et al. (Nature, *236*, 385, (1972)) and called burimamide are medicated through receptors which are defined by Black et al. as histamine H_2-receptors. Thus histamine H_2-receptors may be defined as those histamine receptors which are not blocked by mepyramine but are blocked by buramimide. Compounds which block histamine H_2-receptors are referred to as histamine H_2-antagonists.

Blockade of histamine H_2-receptors is of utility in inhibiting the biological actions of histamine which are not inhibited by histamine H_1-antagonists. Histamine H_2-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 H_1- and H_2-antagonists is useful.

U.S. Patent 3,932,644, describes histamine H_2-antagonist compounds of formula (1):—



(1)

where R represents a group of in formula (2):—

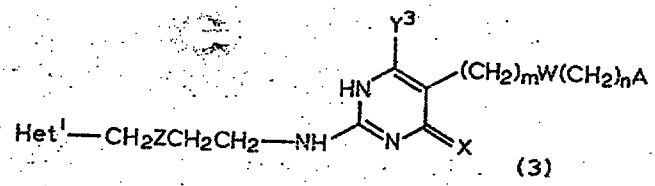
$$Het—CH_2Z(CH_2)_n—$$

(2)

where Het is a nitrogen-containing heterocyclic ring such as imidazole, pyridine, thiazole, isothiazole or thiadiazole, which ring is optionally substituted by lower alkyl, amino, hydroxy or halogen: Z is sulphur or a methylene group: and n is 2 or 3: X is oxygen or sulphur: Y^1 and Y^2, which may be the same or different, are hydrogen, lower alkyl, phenyl or benzyl.

We have now found a group of pyrimidone derivatives which have histamine H_1- as well as histamine H_2-antagonist activity. Thus the compounds of this invention can be used not only for treating conditions where histamine H_2-antagonists are useful but also for conditions where a combination of histamine H_1- and H_2-antagonists is useful.

Accordingly the present invention provides compounds of formula (3):—



(3)

and pharmaceutically acceptable acid addition salts thereof where Het' is a 2- or 4-imidazolyl group optionally substituted by lower alkyl, halogen, trifluoromethyl or hydroxymethyl, a 2-pyridyl group optionally substituted by lower alkyl, lower alkoxy, halogen, amino or hydroxy, a 2-pyridyl group which is disubstituted by lower alkoxy groups, or which has a phenyl, alicyclic or cyclic ether group containing two oxygen atoms fused to it, a 2-thiazolyl group, a 3-isothiazolyl group optionally substituted by chlorine or bromine, a 3 - (1,2,5) - thiadiazolyl group optionally substituted by chlorine or bromine, or a 2 - (5 - amino - 1,3,4 - thiadiazolyl) group; Z is sulphur or a methylene group; X is oxygen or sulphur, W is methylene, oxygen or sulphur; m and n 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: A is a 1- or 2-naphthyl group, a 2,3 - dihydro - 1,4 - benzodioxinyl or a 1,3 - benzodioxolyl group, a phenyl group substituted with one or more lower alkyl, lower alkoxy, halogen, arylalkoxy, hydroxy, lower alkoxy-lower alkoxy, trifluoromethyl, di(lower alkyl)amino, phenoxy, halophenoxy, lower alkoxyphenoxy, phenyl, halophenyl or lower alkoxyphenyl groups and when $—(CH_2)_mW(CH_2)_n—$ is not a methylene group, A is also phenyl; and Y^3 is hydrogen or lower alkyl.

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 of 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.

When A is a substituted phenyl group, typically the substituent is in the 3- or 4-position.

When A is a phenyl group substituted with aryloxy, preferably the aryloxy group is benzyloxy.

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 Z is sulphur.

Preferably X is oxygen.

Preferably Y^3 is hydrogen.

Preferably A is a phenyl group substituted by one or more lower alkoxy groups, or is a 2,3 - dihydro - 1,4 - benzodioxinyl or 1,3 - benzodioxolyl group, as compounds of formula (3) where A has these meanings have favourable solubility properties when compared to the general group of compounds of formula (3).

A preferred group of compounds is that where m and n are 0 and W is methylene.

Another preferred group of compounds is that where m is 0, n is 1 and W is oxygen.

Compound of formula (3) being basic from pharmaceutically acceptable acid addition salts. Examples of such salts include those with hydrochloric, hydrobromic, hydriodic, sulphuric and maleic acids.

Some specific preferred compounds of this invention are:—

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

2 - [2 - (2 - thiazolylmethylthio)ethylamino] - 5 - (4 - chlorobenzyl) - 4 - pyrimidone,

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

2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (4 - chlorobenzyl) - 6 - methyl - 4 - pyrimidone,

2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (3 - chlorobenzyl) - 4 - pyrimidone,

2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (3,4 - dichlorobenzyl) - 4 - pyrimidone,

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

2 - [2 - (5 - methyl - 4 - imidazolymethylthio)ethylamino] - 5 - (4 - methylbenzyl) - 4 - pyrimidone,

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

2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (2 - phenylethyl) - 6 - methyl - 4 - pyrimidone,

2 - [2 - (5 - methyl - 4 - imidazolymethylthio)ethylamino] - 5 - benzyloxy - 4 - pyrimidone,

2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (3 - methoxybenzyl) - 4 - pyrimidone,

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

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

2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (5 - (1,3 - benzodioxolyl)methyl) - 4 - pyrimidone,

2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (3 - ethoxybenzyl) - 4 - pyrimidone,

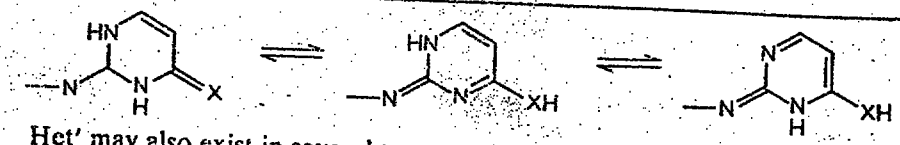
2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (3 - benzyloxybenzyl) - 4 - pyrimidone,

2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - [6 - (2,3 - dihydro - 1,4 - benzodioxinyl)methyl] - 4 - pyrimidone,

2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (1 - naphthylmethyl) - 4 - pyrimidone, and their pharmaceutically acceptable acid addition salts.

One specific salt within the scope of this invention is 2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - [5 - (1,3 - benzodioxolyl)methyl] - 4 - pyrimidone dihydrochloride.

The compounds of formula (3) are shown and described as 4-one 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 group may also exist in the following tautomeric forms:—

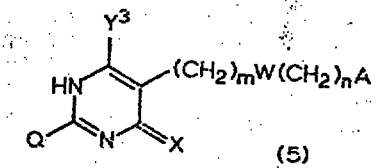


Het' may also exist in several tautomeric forms, and it will be understood that all these tautomeric forms are within the scope of the present invention.

The compounds of this invention can be prepared by reacting an amine of formula (4):—

$$Het'—CH_2ZCH_2CH_2NH_2$$
(4)

where Het' and Z are as defined in formula (3), with a compound of formula (5):—



(5)

where X, Y^3, m, W, n and A are as defined in formula (3) and Q is a reactive group which is displacable with an amine; and thereafter optionally coverting the compound of formula (3) so obtained into an acid addition salt.

Examples of groups Q are lower alkylthio, benzylthio and halogen. Preferably Q is lower alkylthio particularly methylthio.

Preferably this reaction is carried out in the absence of a solvent at about 150°C or in the presence of a solvent, for example pyridine at reflux temperature.

Compounds of formula (3) and the pharmaceutically acceptable salts where X is sulphur can be prepared by a process which comprises reacting the corresponding compound of formula (3) where X is oxygen with phosphorus pentasulphide, and thereafter optionally converting the product so obtained into an acid addition salt.

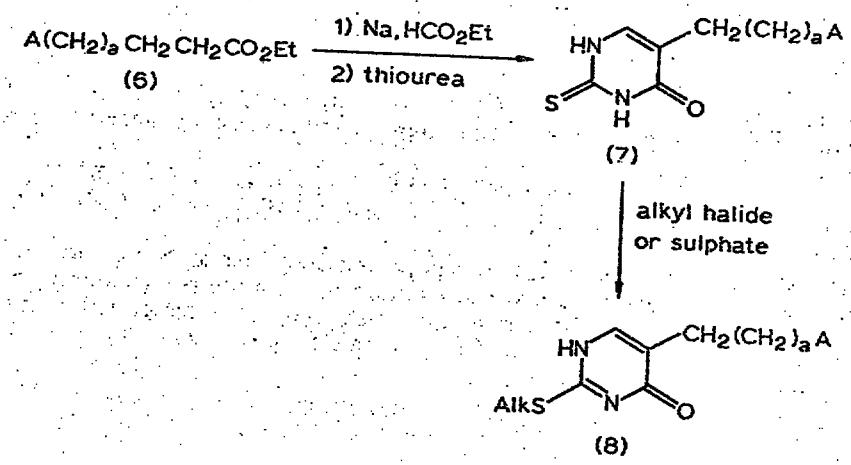
The reaction with phosphorus pentasulphide is generally carried out in the presence of a solvent for example pyridine.

Compounds of formula (3) where A is phenyl substituted with a hydroxy group can also be prepared by a process which comprises reacting a compound of formula (3) as previously defined where A is phenyl substituted with a methoxy group with boron tribromide and optionally converting the product so obtained into an acid addition salt.

Addition salts of compounds of formula (3) 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 (3) can be interconverted using an ion exchange resin.

The intermediates of formula (5) where W is methylene, Y^3 is hydrogen and Q is lower alkylthio (shown as formula (8)) can be prepared according to Scheme 1 where A is as defined in Formula 3 and a is 0 to 4 and Alk is lower alkyl.

Scheme 1.

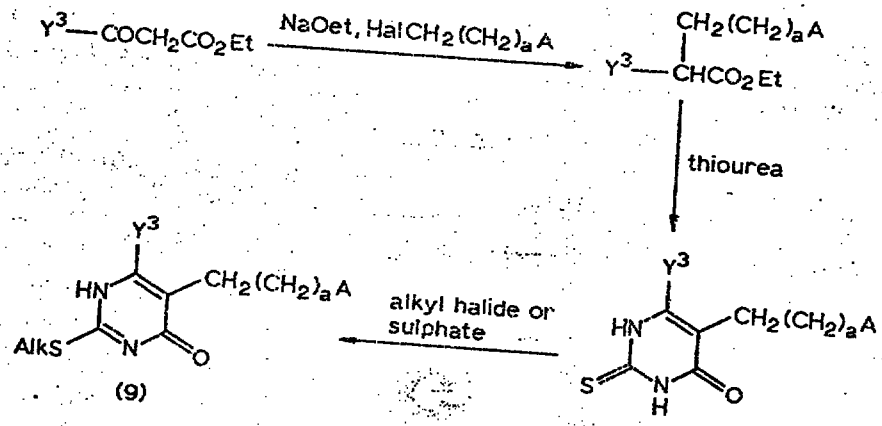


The esters of formula (6) where a is 0 can be prepared by condensing a substituted benzaldehyde with malonic acid, and hydrogenating and esterifying the product.

The intermediates of formula (5) where W is methylene, Y^3 is lower alkyl and Q is lower alkylthio (shown as formula (9)) may be prepared according to Scheme 2 where A is as defined in formula (3), a is 0 to 4, Hal is chlorine or bromine, and Alk is lower alkyl.

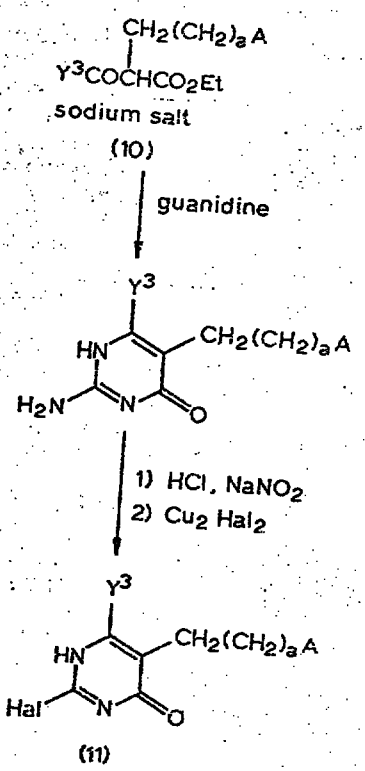
The compounds of formula (8) where a is 0 and A is 1,3 - benzodioxolyl or 2,3 - dihydro - 1,4 - benzodioxinyl, and a process for their preparation, are the subject of our Divisional Application No. 17903/80 (Serial No. 1595292).

Scheme 2.



The intermediates of formula (5) wherein Q is halogen (shown as formula 11) may be prepared according to Scheme 3 where A and Y^3 are as defined in formula (3), a is 0 to 4 and Hal is chlorine or bromine.

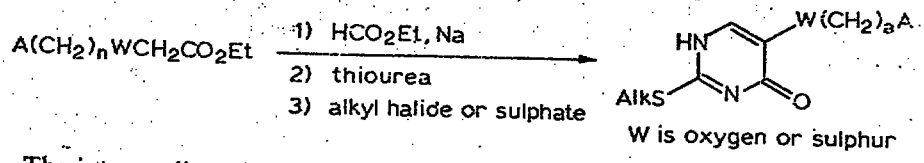
Scheme 3.



The compounds of formula (10) where Y^3 is hydrogen can be prepared from a compound of formula (6), sodium and ethyl formate, and the compounds of formula (10) where Y^3 is lower alkyl can be prepared as shown in Scheme 2.

The intermediates of formula (5) where W is oxygen or sulphur and m is 0 can be prepared as shown in Scheme 4 where A and n are as defined in formula (3) and Alk is lower alkyl.

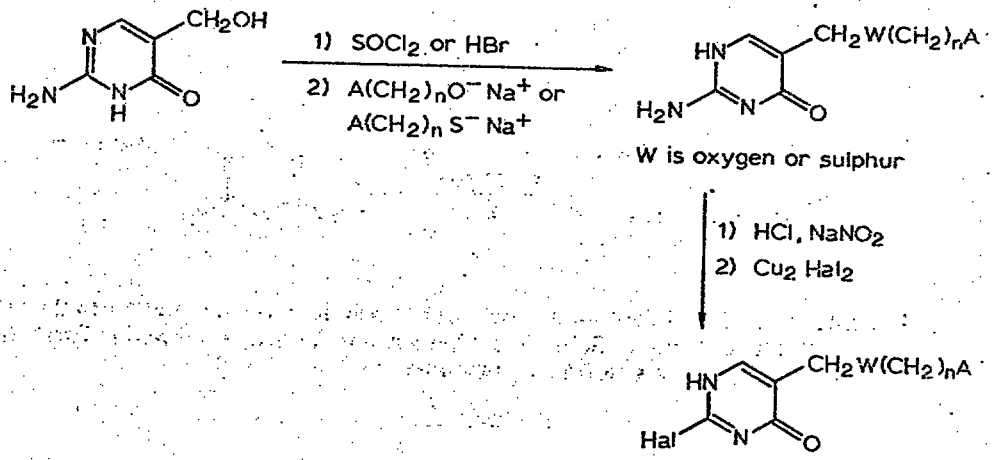
Scheme 4.



W is oxygen or sulphur

The intermediates of formula (5) where W is oxygen or sulphur and m is 1 can be prepared as shown in scheme 5 where A and m are as defined in formula (3) and Hal is halogen.

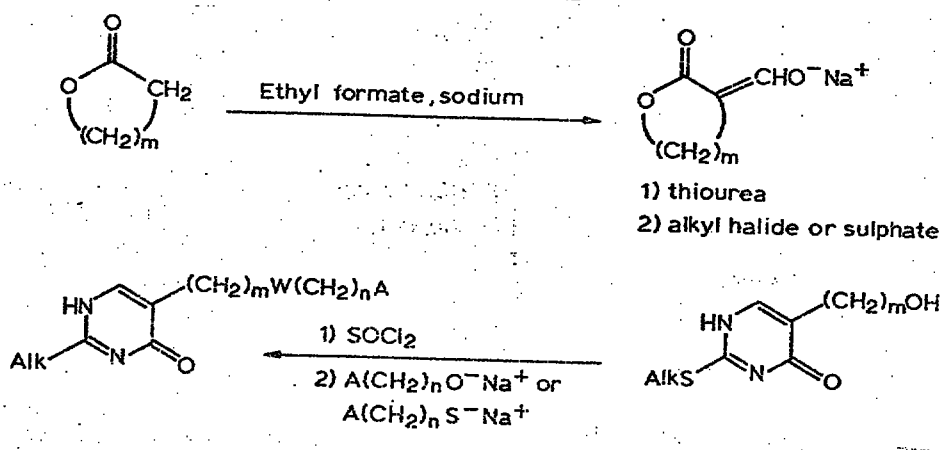
Scheme 5.



Alternatively, intermediates of formula (5) where W is oxygen or sulphur and m is 0 or 1 can be prepared from ethyl 4 - benzyloxybutyrate, or a similar protected derivative of ethyl 4 - hydroxybutyrate by a process analogous to that outlined in Scheme 1, followed successively by deprotection, treatment with thionyl chloride, and treatment with the sodium derivative of $A(CH_2)_nOH$ or $A(CH_2)_nSH$.

Intermediates of formula (5) where W is oxygen or sulphur and m is 2 to 4 can be prepared as shown in scheme 6 where A and n are as defined in formula (3) and Alk is lower alkyl.

Scheme 6.



The compounds of formula (3) block histamine H_2-receptors, that is they inhibit the biological actions of histamine which are not inhibited by histamine H_1-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 anaesthetized with urethane, at doses of from 0.5 to 16 micromoles per kilogram given intravenously. Many of the compounds of the present invention produce at least 50% inhibition in this test at a dose of from 1 to 10 micromoles per kilogram. This procedure is referred to in the above-mentioned paper of Ash and Schild. The activity of these compounds as histamine H_2-antagonists is also demonstrated by their ability to inhibit other actions of histamine which, according to the above-mentioned paper of Ash & Schild, are not mediated by histamine H_1-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 for example 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 about 500 micromoles/kg. of a compound of formula (3).

In 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 anaesthetised rat (which for many of the compounds of formula (3) is from 1 to 10 micromoles per kilogram) and the dose producing 50% inhibition of histamine-induced tachycardia in the isolated guinea pig atrium, (which for many of the compounds of formula (3), is below 10^{-5}M).

The compounds of formula (3) also block histamine H_1-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. They inhibit the histamine-stimulated contractions of the guinea pig ileum at doses of about 10^{-5} Molar.

For therapeutic use, the pharmacologically active compounds of the present invention will normally be administered in a pharmaceutical composition.

Accordingly the invention provides pharmaceutical compositions comprising a compound of formula (3) 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 can 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 (3) or pharmaceutically acceptable salts thereof will be present in the compositions in an effective amount to block histamine H_2-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 (3) or a pharmaceutically acceptable acid addition salt thereof calculated as the free base. These 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.

In use the compositions will preferably be administered once to six times daily. The daily dosage regimen will preferably be from 150 mg to 1500 mg of the compound of formula (3) 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-chlorobenzyl)-4-pyrimidone

(i) A solution of 5 - (4 - chlorobenzyl) - 2 - thiouracil (50.5 g), methyl iodide (28.4 g) and sodium hydroxide (8.2 g) in water (200 ml) and ethanol (400 ml) was stirred at 60° for 30 minutes then allowed to cool. The crystalline product was filtered and washed with water to give 5 - (4 - chlorobenzyl) - 2 - methylthio - 4 - pyrimidone (48.6 g), m.p. 193—194° (methanol/ethanol).

(ii) An intimate mixture of 5 - (4 - chlorobenzyl) - 2 - methylthio - 4 - pyrimidone (17.7 g) and 2 - (5 - methyl - 4 - imidazolylmethylthio) - ethylamine (11.4 g) was heated at 145—150° for 5 hours. After cooling, the reaction mixture was triturated with water to give the free base, which was separated by decantation and recrystallised from methanol to give 2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (4 - chlorobenzyl) - 4 - pyrimidone m.p. 204.5—206°.

(Found: C, 55.45; H, 5.2; N, 18.0; S, 8.3; Cl, 8.9; $C_{18}H_{22}ClN_5OS$ requires; C, 55.45; H, 5.2; N, 18.0; S, 8.2; Cl, 9.1%)

EXAMPLE 2

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

5 - (2 - Phenylethyl) - 2 - thiouracil (1.8 g) was converted into 5 - phenyl - ethyl - 2 - methylthio - 4 - pyrimidone (m.p. 160—161° ex ethanol) by the method described in Example 1(i). Reaction of this pyrimidone (1.55 g) with 2 - (5 - methyl - 4 - imidazolylmethylthio) - ethylamine (1.1 g) by the method described in Example 1(ii) gave an oil which was dissolved in 2N hydrochloric acid. the solution evaporated to dryness and the residue recrystallised from methanol to give 2 - [2 - (5 - methyl - 4 - imidazolylmethylthio) - ethylamino] - 5 - (2 - phenylethyl) - 4 - pyrimidone dihydrochloride, m.p. 214—218°.

(Found: C, 51.3; H, 5.6; N, 15.8; S, 7.1; Cl, 15.8; $C_{19}H_{23}N_5OS$. 2 HCl requires: C, 51.6; H, 5.7; N, 15.8; S, 7.25; Cl, 16.0%)

EXAMPLE 3

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

5 - (4 - Methylbenzyl) - 2 - thiouracil (4.65 g) was converted into 5 - (4 - methylbenzyl) - 2 - methylthio - 4 - pyrimidone (m.p. 208.5—211° ex methanol/ethanol) by the method described in Example 1(i). Reaction of this pyrimidone (1.6 g) with 2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamine (1.2 g) by the method described in Example 1(ii) and acidification with dilute ethanolic hydrogen chloride followed by evaporation to dryness and recrystallisation from ethanol gave 2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (4 - methylbenzyl) - 4 - pyrimidone dihydrochloride, m.p. 197—198.5°.

(Found: C, 51.9; H, 5.7; N, 15.9; S, 7.3; Cl, 15.4; $C_{19}H_{23}N_5OS$. 2HCl. requires: C, 51.6; H, 5.7; N, 15.8; S, 7.25; Cl, 16.0%).

In a similar manner 2 - [2 - (5 - methyl - 4 - imidazolylmethylthio) - ethylamino] - 5 - (3 - methylbenzyl) - 4 - pyrimidone dihydrochloride m.p. 203.5—205° (ex ethanol) may be prepared from 5 - (3 - methyl - benzyl) - 2 - thiouracil.

EXAMPLE 4

2-[2-(5-Methyl-4-imidazolylmethylthio)ethylamino]-5-(3-chlorobenzyl)-4-pyrimidone dihydrochloride

(i) Ethyl 3 - (3 - chlorophenyl)propionate (39.3 g) and ethyl formate (14.9 g) were added over a period of 6 hours to a stirred mixture of sodium wire (4.25 g) and dry ether (110 ml) cooled with an ice-salt bath. The mixture was stirred for 18 hours at room temperature and evaporated to dryness. The residue was refluxed for 7. hours with thiourea (14.05 g) and ethanol (100 ml). The mixture was evaporated to dryness and the residue was dissolved in water. Acetic acid was added until the mixture had pH 4. The white precipitate was filtered and washed to give 5 - (3 - chlorobenzyl) - 2 - thiouracil, m.p. 192—195° (ethanol).

(ii) 5 - (3 - Chlorobenzyl) - 2 - thiouracil (3.1 g) was converted into 5 - (3 - chlorobenzyl) - 2 - methylthio - 4 - pyrimidone, m.p. 178.5—180.5° (ethanol) by the method described in Example 1(i) and this latter compound (1.8 g) was reacted with 2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamine (1.14 g) as described in Example 1(ii) to give a residue which was treated with ethanolic hydrogen chloride to give 2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (3 - chlorobenzyl) - 4 - pyrimidone dihydrochloride, m.p. 212.5—216° (crystallized from ethanol).

(Found: C, 46.8; H, 4.7; N, 14.9; S, 6.9; Cl, 22.7. $C_{18}H_{20}ClN_5OS.2HCl$. requires: C, 46.7; H, 4.8; N, 15.1; S, 6.9; Cl, 23.0%)

EXAMPLE 5

2-(2-(5-Methyl-4-imidazolylmethylthio)ethylamino]-5-(3,4-dichlorobenzyl)-4-pyrimidone dihydrochloride

(i) Ethyl 3 - (3,4 - dichlorophenyl)propionate (48.9 g) was converted into 5 - (3,4 - dichlorobenzyl) - 2 - thiouracil m.p. 232.5—233.5° (ex methanol/ethanol) by the procedure of Example 4(i).

(ii) 5 - (3,4 - Dichlorobenzyl) - 2 - thiouracil (5.7 g) was converted into 5 - (3,4 - dichlorobenzyl) - 2 - methylthio - 4 - pyrimidone, m.p. 216—218° (acetic acid) by the procedure of Example 1(i).

(iii) 5 - (3,4 - Dichlorobenzyl) - 2 - methylthio - 4 - pyrimidone (2.1 g) was reacted with 2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamine (1.2 g) by the procedure of Example 3 to give 2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (3,4 - dichlorobenzyl) - 4 - pyrimidone dihydrochloride, m.p. 235.5—238.5° (aqueous methanol)

(Found: C, 43.3; H, 4.3; N, 13.8; S, 6.4; Cl, 27.8; $C_{18}H_{19}Cl_2N_5OS.2HCl$. requires; C, 43.5; H, 4.3; N, 14.1; S, 6.45; Cl, 28.5%).

EXAMPLE 6

2-[2-(2-thiazolylmethylthio)ethylamino]-5-(4-chlorobenzyl)-4-pyrimidone monohydrochloride

An intimate mixture of 5 - (4 - chlorobenzyl) - 2 - methylthio - 4 - pyrimidone (1.36 g) and 2 - (2 - thiazolylmethylthio)ethylamine (0.9 g) was heated at 130—135° for 3½ hours. After cooling the reaction mixture was treated with 2N hydrochloric acid. Evaporation to dryness followed by recrystallisation from isopropanol/methanol gave 2 - [2 - (2 - thiazolyl - methylthio) - ethylamino] - 5 - (4 - chlorobenzyl) - 4 - pyrimidone monohydrochloride, m.p. 172.5—174.5°.

(Found: C, 47.4; H, 4.3; N, 13.0; S, 14.7; Cl, 16.5; $C_{16}H_{18}Cl\ N_4OS_2.HCl$. requires; C, 47.55; H, 4.2; N, 13.05; S, 14.9; Cl, 16.5%).

EXAMPLE 7

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

An intimate mixture of 5 - (4 - methoxybenzyl) - 2 - methylthio - 4 - pyrimidone (3.0 g) and 2 - (5 - methyl - 4 - imidazolylmethylthio) - ethylamine (1.95 g) was heated at 135—140° with frequent stirring for 6 hours. After cooling, the reaction mixture was triturated with hot water, filtered, washed with dry ether and dissolved in propan-2-ol. The solution was acidified with dilute ethanolic hydrogen chloride, evaporated to dryness, and the residue recrystallised from ethanol to give 2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (4 - methoxybenzyl) - 4 - pyrimidone dihydrochloride m.p. 198—200°.

(Found: C, 49.0; H, 5.5; N, 15.0; S, 6.9; Cl, 14.7; $C_{18}H_{23}N_5O_2S.2HCl$ requires; C, 49.8; H, 5.5; N, 15.3; S, 7.0; Cl, 15.5%).

EXAMPLE 8

2-[2-(5-Methyl-4-imidazolylmethylthio)ethylamino]-5-(4-chlorobenzyl)-6-methyl-4-pyrimidone dihydrochloride

(i) 5 - (4 - Chlorobenzyl) - 6 - methyl - 2 - thiouracil was methylated with methyl iodide as described in Example 1(i) to give 5 - (4 - chlorobenzyl) - 6 - methyl - 2 - methylthio - 4 - pyrimidone (m.p. 248—251°).

(Found: C, 55.6; H, 4.7; N, 10.0; S, 11.4; $C_{13}H_{13}ClN_2OS$ requires; C, 55.3; H, 4.6; N, 9.9; S, 11.4%).

(ii) Reaction of 5 - (4 - chlorobenzyl) - 6 - methyl - 2 - methylthio - 4 - pyrimidone (1.95 g) with 2 - (5 - methyl - 4 - imidazolylmethylthio) - ethylamine

(1.19 g) by the method described in Example 1(ii) gave the title compound, m.p. 203—206.5°. (Crystallised from ethanol).

(Found: C, 47.7; H, 5.1; N, 14.4; S, 6.6; Cl, 21.3; $C_{19}H_{22}ClN_5OS.2HCl$ requires; C, 47.9; H, 5.1; N, 14.7; S, 6.7; Cl, 22.3%).

EXAMPLE 9

2-[2-(3-Bromo-2-pyridylmethylthio)ethylamino]-5-(4-chlorobenzyl)-4-pyrimidone monohydrochloride

5 - (4 - Chlorobenzyl) - 2 - methylthio - 4 - pyrimidone (1.2 g) was reacted with 2 - (3 - bromo - 2 - pyridylmethylthio)ethylamine (1.1 g) according to the procedure of Example 2. The reaction mixture was acidified with dilute ethanolic hydrogen chloride, evaporated to dryness and the residue recrystallised from ethanol/water to give 2 - [2 - (3 - bromo - 2 - pyridylmethylthio)ethylamino] - 5 - (4 - chlorobenzyl) - 4 - pyrimidone monohydrochloride, m.p. 215—218° (decomposes).

(Found: C, 45.4; H, 3.8; N, 11.1; S, 6.3; $C_{12}H_{18}Br\,Cl\,N_4OS.H$ requires: C, 45.4; H, 3.8; N, 11.2; S, 6.4%).

EXAMPLE 10

2-[2-(5-Methyl-4-imidazolylmethylthio)ethylamino]-5-(2-phenylethyl)-6-methyl-4-pyrimidone

(i) Ethyl α - (phenylethyl)acetoacetate (23.4 g) and thiourea (10.65 g) were added to a solution of sodium ethoxide in ethanol (100 ml) prepared from sodium (4.6 g). The mixture was refluxed for 5½ hours and evaporated to dryness. The solid residue was dissolved in water and acetic acid was added to pH 4. The white precipitate was filtered off and recrystallised from ethanol to give 5 - (2 - phenylethyl) - 6 - methyl - 2 - thiouracil m.p. 210—214°.

(ii) Substitution of 5 - (2 - phenylethyl) - 6 - methyl - 2 - thiouracil for 5 - (4 - chlorobenzyl) - 2 - thiouracil in the general procedure of Example 1 gave the title compound m.p. 222.5—224.5° (methanol)

(Found: C, 62.75; H, 6.5; N, 18.1; S, 8.3; $C_{20}H_{25}N_5OS$ requires; C, 62.6; H, 6.6; N, 18.2; S, 8.4%).

EXAMPLE 11

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

(i) Ethyl benzyloxyacetate (60.0 g) was converted into 5 - benzyloxy - 2 - thiouracil m.p. 240—241° (ex. acetonitrile/ethyl acetate, 1:1) by the procedure of Example 4(i).

(ii) 5 - Benzyloxy - 2 - thiouracil (10.0 g) was converted into 5 - benzyloxy - 2 - methylthio - 4 - pyrimidone m.p. 184—185° (ex methanol) by the procedure of Example 1(i).

(iii) 5 - Benzyloxy - 2 - methylthio - 4 - pyrimidone (4.10 g) was reacted with 2 - (5 - methyl - 4 - imidazolyl)ethylamine (2.83 g) by the procedure of Example 3 to give 2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - benzyloxy - 4 - pyrimidone dihydrochloride, m.p. 161—162° (ethanol).

EXAMPLE 12

2-[2-(5-Methyl-4-imidazolylmethylthio)ethylamino]-5-(3-methoxybenzyl)-4-pyrimidone dihydrochloride

5 - (3 - Methoxybenzyl) - 2 - thiouracil (16.1 g) was converted into 5 - (3 - methoxybenzyl) - 2 - methylthio - 4 - pyrimidone, m.p. 143—144°C (ex ethanol) by the procedure of Example 1(i).

5 - (3 - Methoxybenzyl) - 2 - methylthio - 4 - pyrimidone (3.0 g) was reacted with 2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamine (2.1 g) as described in Example 1(ii), to give a residue, which, on treatment with ethanolic hydrogen chloride gave 2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (3 - methoxybenzyl) - 4 - pyrimidone dihydrochloride, m.p. 173—175.5° (ex ethanol).

(Found: C, 49.6; H, 5.3; N, 15.1; S, 7.1; Cl, 15.8; $C_{19}H_{26}Cl_2N_5O_2S$ requires: C, 49.8; H, 5.5; N, 15.3; S, 7.0; Cl, 15.5%).

Treatment of this dihydrochloride with aqueous sodium bicarbonate, extraction of the mixture with ethyl acetate and evaporation of the organic extracts gives the free base which is converted into 2 - [2 - (5 - methyl - 4 -

imidazolylmethylthio) - ethylamino] - 5 - (3 - methoxybenzyl) - 4 - pyrimidone dihydrobromide by treatment with two equivalents of hydrobromic acid.

EXAMPLE 13

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

(i) Ethyl 3 - (2 - chlorophenyl)propionate (48.4 g) was converted into 5 - (2 - chlorobenzyl) - 2 - thiouracil m.p. 223—224° (ex methanol by the procedure described in Example 4(i).

(ii) 5 - (2 - Chlorobenzyl) - 2 - thiouracil (5.05 g) was converted into 5 - (2 - chlorobenzyl) - 2 - methylthio - 4 - pyrimidone, m.p. 171—173°C (ex ethanol) by the procedure of Example 1(i). 5 - (2 - Chlorobenzyl) - 2 - methylthio - 4 - pyrimidone (1.6 g) was reacted with 2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamine (1.03 g) as described in Example 1(ii), to give a residue, which on treatment with dilute ethanolic hydrogen chloride, gave 2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (2 - chlorobenzyl) - 4 - pyrimidone dihydrochloride, m.p. 215—219° (ex methanol-ethanol).

(Found: C, 46.7; H, 4.9; N, 14.9; S, 6.8; Cl, 22.4; $C_{18}H_{22}Cl_3N_5OS$ requires: C, 46.7; H, 4.8; N, 15.1; S, 6.4; Cl, 23.0%).

EXAMPLE 14

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

(i) Ethyl 6-phenylhexanoate (43.5 g) was converted to 5 - (4 - phenylbutyl) - 2 - thiouracil, m.p. 177.5—181° (ex ethanol-water), as described in Example 4(i).

(ii) 5 - (4 - Phenylbutyl) - 2 - thiouracil (3.05 g) was converted into 5 - (4 - phenylbutyl) - 2 - methylthio - 4 - pyrimidone m.p. 146—149° (ex ethanol), by the procedure of Example 1(i). 5 - (4 - Phenylbutyl) - 2 - methylthio - 4 - pyrimidone (1.89 g) was reacted with 2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamine (1.18 g) as described in Example 1(ii) to give a residue, which on treatment with dilute ethanolic hydrogen chloride, gave 2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (4 - phenylbutyl) - 4 - pyrimidone dihydrochloride, m.p. 207—209.5° (ex ethanol)

(Found: C, 53.3; H, 6.2; N, 14.8; S, 6.8; Cl, 14.8. $C_{21}H_{29}Cl_2N_5OS$ requires: C, 53.6; H, 6.2; N, 14.9; S, 6.8; Cl, 15.1%).

EXAMPLE 15

2-[2-(5-Methyl-4-imidazolylmethylthio)ethylamino]-5-(5-(1,3-benzodioxolyl)-methyl)-4-pyrimidone dihydrochloride

(i) Ethyl 3 - (5 - (1,3 - benzodioxolyl)propionate (17.5 g) was converted into 5 - (5 - (1,3 - benzodioxolyl)methyl) - 2 - thiouracil m.p. 158—159° (ex ethanol/methanol, 1:1), by the procedure described in Example 4(i).

(ii) 5 - (5 - (1,3 - Benzodioxolyl)methyl) - 2 - thiouracil (2.9 g) was converted into 5 - (5 - (1,3 - benzodioxolyl)methyl) - 2 - methylthio - 4 - pyrimidone, m.p. 197—198° (ex acetonitrile) by the procedure of Example 1(i).

5 - (5(1,3 - Benzodioxolyl)methyl) - 2 - methylthio - 4 - pyrimidone (1.2 g) was reacted with 2 - (5 - methyl - 4 - imidazolylmethylthio) - ethylamine (0.77 g) as described in Example 1(ii), to give a residue, which, on treatment with ethanolic hydrogen chloride, gave the title product m.p. 230—232° (ex ethanol).

(Found: C, 48.5; H, 5.1; N, 14.5; S, 6.7; Cl, 14.7; $C_{19}H_{23}Cl_2N_5O_3S$ requires: C, 48.3; H, 4.9; N, 14.8; S, 6.8; Cl, 15.0%).

EXAMPLE 16

2-[2-(5-Methyl-4-imidazolylmethylthio)ethylamino]-5-(3-ethoxybenzyl)-4-pyrimidone dihydrochloride

5 - (3 - Ethoxybenzyl) - 2 - thiouracil (5.0 g) was converted into 5 - (3 - ethoxybenzyl) - 2 - methylthio - 4 - pyrimidone, m.p. 136—138°. (ex acetonitrile) by the procedure of Example 1(i). 5 - (3 - Ethoxybenzyl) - 2 - methylthio - 4 - pyrimidone (2.0 g) was reacted with 2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamine (1.25 g) as described in Example 1(ii), to give a residue which, on treatment with ethanolic hydrogen chloride gave 2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (3 - ethoxybenzyl) - 4 - pyrimidone dihydrochloride m.p. 176—178° (ex ethanol).

(Found: C, 50.6; H, 5.7; N, 14.7; S, 7.1; Cl, 14.7; $C_{20}H_{27}Cl_2N_5O_2S$ requires: C, 50.9; H, 5.8; N, 14.8; S, 6.8; Cl, 15.0%).

EXAMPLE 17

2-[2-(5-Methyl-4-imidazolylmethylthio)ethylamino]-5-(3-benzyloxybenzyl)-4-pyrimidone dihydrochloride

5 - (3 - Benzyloxybenzyl) - 2 - thiouracil (4.6 g) was converted into 5 - (3 - benzyloxybenzyl) - 2 - methylthio - 4 - pyrimidone, m.p. 176—178° (ex ethyl acetate), by the procedure of Example 1(i). 5 - (3 - Benzyloxybenzyl) - 2 - methylthio - 4 - pyrimidone (2.0 g) was reacted with 2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamine (1.0 g) as described in Example 1(ii), to give a residue which, on treatment with ethanolic hydrogen chloride gave 2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (3 - benzyloxybenzyl) - 4 - pyrimidone dihydrochloride m.p. 193—194° (ex ethanol/methanol, 1:1).

Found: C, 55.7; H, 5.4; N, 12.9; S, 6.0; Cl, 13.0; $C_{25}H_{29}Cl_2N_5O_2S$ requires: C, 56.2; H, 5.5; N, 13.1; S, 6.0; Cl, 13.3%).

EXAMPLE 18

2-[2-(5-Methyl-4-imidazolylmethylthio)ethylamino]-5-(1-naphthylmethyl)-4-pyrimidone dihydrochloride

5 - (1 - Naphthylmethyl) - 2 - thiouracil (6.7 g) was converted into 5 - (1 - naphthylmethyl) - 2 - methylthio - 4 - pyrimidone, m.p. 178—180° (ex methanol) by the procedure of Example 1(i). 5 - (1 - Naphthylmethyl) - 2 - methylthio - 4 - pyrimidone (0.4 g) was reacted with 2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamine (0.25 g) as described in Example 1(ii), to give a residue which, on treatment with ethanolic hydrogen chloride gave 2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (1 - naphthylmethyl) - 4 - pyrimidone dihydrochloride, m.p. 228—230° (ex ethanol).

(Found: C, 55.0; H, 5.3; N, 14.4; S, 6.6; Cl, 14.5; $C_{22}H_{25}ClN_5OS$ requires: C, 55.2; H, 5.3; N, 14.6; S, 6.7; Cl, 14.8%).

EXAMPLE 19

(i) Ethyl 3 - (3,4,5 - trimethoxyphenyl)propionate (82.4 g) was converted into 5 - (3,4,5 - trimethoxybenzyl) - 2 - thiouracil, m.p. 214—215°C (ex ethanol) by the procedure of Example 4(i).

(ii) 5 - (3,4,5 - Trimethoxybenzyl) - 2 - thiouracil (12.9 g) was converted into 5 - (3,4,5 - trimethoxybenzyl) - 2 - methylthio - 4 - pyrimidone, m.p. 158—159°C (ex ethanol) by the procedure of Example 1(i).

(iii) 5 - (3,4,5 - Trimethoxybenzyl) - 2 - methylthio - 4 - pyrimidone (2.39 g) was reacted with 2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamine (1.37 g) by the procedure of Example 3 to give 2 - [2 - (5 - methyl - 4 - imidazolylmethylthio) - ethylamino] - 5 - (3,4,5 - trimethoxybenzyl) - 4 - pyrimidone dihydrochloride, m.p. 170—174°C (ex ethanol).

Found: C, 48.5; H, 5.6; N, 13.5; S, 5.9; Cl, 13.7; $C_{21}H_{29}Cl_2N_5O_4S$ requires: C, 48.7; H, 5.6; N, 13.5; S, 6.2; Cl, 13.7%).

EXAMPLE 20

2 - [2 - (5 - Methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (4 - methoxybenzyl) - 4 - pyrimidone (1.5 g) was dissolved in pyridine (35 ml) and refluxed with phosphorus pentasulphide (0.87 g) for 7 hours. The pyridine was evaporated and the residue washed with boiling water. The residue was treated with 2NHCl and recrystallised to give 2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (4 - methoxybenzyl)pyrimid - 4 - thione dihydrochloride m.p. 202—206°C (ex 2N HCl)

(Found: C, 47.6; H, 5.3; N, 14.6; S, 13.2; Cl, 15.5 $C_{19}H_{25}N_5OS_2$ requires: C, 48.1; H, 5.3; N, 14.8; S, 13.5; Cl, 15.0%)

EXAMPLE 21

(i) 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)ethyl - amine
(k) 2 - (3 - hydroxy - 2 - pyridylmethylthio)ethyl - amine
(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
(q) 2 - (2 - thiazolylmethylthio)ethylamine

for 2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamine in the procedure of Example 7 leads to the production of:—

(a) 2 - [2 - (2 - imidazolylmethylthio)ethylamino] - 5 - (4 - methoxybenzyl) - 4 - pyrimidone
(b) 2 - [2 - (4 - imidazolylmethylthio)ethylamino] - 5 - (4 - methoxybenzyl) - 4 - pyrimidone
(c) 2 - [2 - (5 - bromo - 4 - imidazolylmethylthio)ethylamino] - 5 - (4 - methoxybenzyl) - 4 - pyrimidone
(d) 2 - [2 - (5 - trifluoromethyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (4 - methoxybenzyl) - 4 - pyrimidone
(e) 2 - [2 - (5 - hydroxymethyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (4 - methoxybenzyl) - 4 - pyrimidone
(f) 2 - [2 - (2 - pyridylmethylthio)ethylamino] - 5 - (4 - methoxybenzyl) - 4 - pyrimidone
(g) 2 - [2 - (3 - methyl - 2 - pyridylmethylthio)ethylamino] - 5 - (4 - methoxybenzyl) - 4 - pyrimidone
(h) 2 - [2 - (3 - methoxy - 2 - pyridylmethylthio)ethylamino] - 5 - (4 - methoxybenzyl) - 4 - pyrimidone
(i) 2 - [2 - (3 - chloro - 2 - pyridylmethylthio)ethylamino] - 5 - (4 - methoxybenzyl) - 4 - pyrimidone
(j) 2 - [2 - (3 - amino - 2 - pyridylmethylthio)ethylamino] - 5 - (4 - methoxybenzyl) - 4 - pyrimidone
(k) 2 - [2 - (3 - hydroxy - 2 - pyridylmethylthio)ethylamino] - 5 - (4 - methoxybenzyl) - 4 - pyrimidone
(l) 2 - [2 - (3 - isothiazolylmethylthio)ethylamino] - 5 - (4 - methoxybenzyl) - 4 - pyrimidone
(m) 2 - [2 - (4 - bromo - 3 - isothiazolylmethylthio)ethylamino] - 5 - (4 - methoxybenzyl) - 4 - pyrimidone
(n) 2 - [2 - (3 - (1,2,5) - thiadiazolylmethylthio)ethylamino] - 5 - (4 - methoxybenzyl) - 4 - pyrimidone
(o) 2 - [2 - (4 - chloro - 3 - (1,2,5) - thiadiazolylmethylthio)ethylamino] - 5 - (4 - methoxybenzyl) - 4 - pyrimidone
(p) 2 - [2 - (5 - amino - 2 - (1,3,4) - thiadiazolylmethylthio)ethylamino] - 5 - (4 - methoxybenzyl) - 4 - pyrimidone
(q) 2 - [2 - (2 - thiazolylmethylthio)ethylamino] - 5 - (4 - methoxybenzyl) - 4 - pyrimidone

(ii) Substitution of the above listed 4-pyrimidones for 2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (4 - methoxybenzyl) - 4 - pyrimidone in the procedure of Example 20 leads to the production of:—

(a) 2 - [2 - (2 - imidazolylmethylthio)ethylamino] - 5 - (4 - methoxybenzyl)pyrimid - 4 - thione
(b) 2 - [2 - (4 - imidazolylmethylthio)ethylamino] - 5 - (4 - methoxybenzyl)pyrimid - 4 - thione
(c) 2 - [2 - (5 - bromo - 4 - imidazolylmethylthio)ethylamino] - 5 - (4 - methoxybenzyl)pyrimid - 4 - thione
(d) 2 - [2 - (5 - trifluoromethyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (4 - methoxybenzyl)pyrimid - 4 - thione
(e) 2 - [2 - (5 - hydroxymethyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (4 - methoxybenzyl)pyrimid - 4 - thione
(f) 2 - [2 - (2 - pyridylmethylthio)ethylamino] - 5 - (4 - methoxybenzyl)pyrimid - 4 - thione
(g) 2 - [2 - (3 - methyl - 2 - pyridylmethylthio)ethylamino] - 5 - (4 - methoxybenzyl)pyrimid - 4 - thione
(h) 2 - [2 - (3 - methoxy - 2 - pyridylmethylthio)ethylamino] - 5 - (4 - methoxybenzyl)pyrimid - 4 - thione

(i) 2 - [2 - (3 - chloro - 2 - pyridylmethylthio)ethylamino] - 5 - (4 - methoxybenzyl)pyrimid - 4 - thione
(j) 2 - [2 - (3 - amino - 2 - pyridylmethylthio)ethylamino] - 5 - (4 - methoxybenzyl)pyrimid - 4 - thione
(k) 2 - [2 - (3 - hydroxy - 2 - pyridylmethylthio)ethylamino] - 5 - (4 - methoxybenzyl)pyrimid - 4 - thione
(l) 2 - [2 - (3 - isothiazolylmethylthio)ethylamino] - 5 - (4 - methoxybenzyl)pyrimid - 4 - thione
(m) 2 - [2 - (4 - bromo - 3 - isothiazolylmethylthio)ethylamino] - 5 - (4 - methoxybenzyl)pyrimid - 4 - thione
(n) 2 - [2 - (3 - (1,2,5) - thiadiazolylmethylthio)ethylamino] - 5 - (4 - methoxybenzyl)pyrimid - 4 - thione
(o) 2 - [2 - (4 - chloro - 3 - (1,2,5) - thiadiazolylmethylthio)ethylamino] - 5 - (4 - methoxybenzyl)pyrimid - 4 - thione
(p) 2 - [2 - (5 - amino - 2 - (1,3,4) - thiadiazolymethylthio)ethylamino] - 5 - (4 - methoxybenzyl)pyrimid - 4 - thione
(q) 2 - [2 - (2 - thiazolylmethylthio)ethylamino] - 5 - (4 - methoxybenzyl)pyrimid - 4 - thione

(iii) Substitution of the above-listed amines for 2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamine in the procedure of Example 2 leads to the production of:—

(a) 2 - [2 - (2 - imidazolylmethylthio)ethylamino] - 5 - (2 - phenylethyl) - 4 - pyrimidone
(b) 2 - [2 - (4 - imidazolylmethylthio)ethylamino] - 5 - (2 - phenylethyl) - 4 - pyrimidone
(c) 2 - [2 - (5 - bromo - 4 - imidazolylmethylthio)ethylamino] - 5 - (2 - phenylethyl) - 4 - pyrimidone
(d) 2 - [2 - (5 - trifluoromethyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (2 - phenylethyl) - 4 - pyrimidone;
(e) 2 - [2 - (5 - hydroxymethyl - 4 - imidazolylmethylthio)ethyl - amino] - 5 - (2 - phenylethyl) - 4 - pyrimidone
(f) 2 - [2 - (2 - pyridylmethylthio)ethylamino] - 5 - (2 - phenylethyl) - 4 - pyrimidone
(g) 2 - [2 - (3 - methyl - 2 - pyridylmethylthio)ethylamino] - 5 - (2 - phenylethyl) - 4 - pyrimidone
(h) 2 - [2 - (3 - methoxy - 2 - pyridylmethylthio)ethylamino] - 5 - (2 - phenylethyl) - 4 - pyrimidone
(i) 2 - [2 - (3 - chloro - 2 - pyridylmethylthio)ethylamino] - 5 - (2 - phenylethyl) - 4 - pyrimidone
(j) 2 - [2 - (3 - amino - 2 - pyridylmethylthio)ethylamino] - 5 - (2 - phenylethyl) - 4 - pyrimidone
(k) 2 - [2 - (3 - hydroxy - 2 - pyridylmethylthio)ethylamino] - 5 - (2 - phenylethyl) - 4 - pyrimidone
(l) 2 - [2 - (3 - isothiazolylmethylthio)ethylamino] - 5 - (2 - phenylethyl) - 4 - pyrimidone
(m) 2 - [2 - (4 - bromo - 3 - isothiazolylmethylthio)ethylamino] - 5 - (2 - phenylethyl) - 4 - pyrimidone
(n) 2 - [2 - (3 - (1,2,5) - thiadiazolylmethylthio)ethylamino] - 5 - (2 - phenylethyl) - 4 - pyrimidone
(o) 2 - [2 - (4 - chloro - 3 - (1,2,5) - thiadiazolylmethylthio)ethylamino] - 5 - (2 - phenylethyl) - 4 - pyrimidone
(p) 2 - [2 - (5 - amino - 2 - (1,3,4) - thiadiazolylmethylthio)ethylamino] - 5 - (2 - phenylethyl) - 4 - pyrimidone
(q) 2 - [2 - (2 - thiazolylmethylthio)ethylamino] - 5 - (2 - phenylethyl) - 4 - pyrimidone

(iv) Substitution of the above listed amines for 2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamine in the procedure of Example 11 leads to the production of:—

(a) 2 - [2 - (2 - imidazolylmethylthio)ethylamino] - 5 - benzyloxy - 4 - pyrimidone
(b) 2 - [2 - (4 - imidazolylmethylthio)ethylamino] - 5 - benzyloxy - 4 - pyrimidone

(c) 2 - [2 - (5 - bromo - 4 - imidazolylmethylthio)ethylamino] - 5 - benzyloxy - 4 - pyrimidone
(d) 2 - [2 - (5 - trifluoromethyl - 4 - imidazolylmethylthio)ethylamino] - 5 - benzyloxy - 4 - pyrimidone
(e) 2 - [2 - (5 - hydroxymethyl - 4 - imidazolylmethylthio)ethylamino] - 5 - benzyloxy - 4 - pyrimidone
(f) 2 - [2 - (2 - pyridylmethylthio)ethylamino] - 5 - benzyloxy - 4 - pyrimidone
(g) 2 - [2 - (3 - methyl - 2 - pyridylmethylthio)ethylamino] - 5 - benzyloxy - 4 - pyrimidone
(h) 2 - [2 - (3 - methoxy - 2 - pyridylmethylthio)ethylamino] - 5 - benzyloxy - 4 - pyrimidone
(i) 2 - [2 - (3 - chloro - 2 - pyridylmethylthio)ethylamino] - 5 - benzyloxy - 4 - pyrimidone
(j) 2 - [2 - (3 - amino - 2 - pyridylmethylthio)ethylamino] - 5 - benzyloxy - 4 - pyrimidone
(k) 2 - [2 - (3 - hydroxy - 2 - pyridylmethylthio)ethylamino] - 5 - benzyloxy - 4 - pyrimidone
(l) 2 - [2 - (3 - isothiazolylmethylthio)ethylamino] - 5 - benzyloxy - 4 - pyrimidone
(m) 2 - [2 - (4 - bromo - 3 - isothiazolylmethylthio)ethylamino] - 5 - benzyloxy - 4 - pyrimidone
(n) 2 - [2 - (3 - (1,2,5) - thiadiazolylmethylthio)ethylamino] - 5 - benzyloxy - 4 - pyrimidone
(o) 2 - [2 - (4 - chloro - 3 - (1,2,5) - thiadiazolylmethylthio)ethylamino] - 5 - benzyloxy - 4 - pyrimidone
(p) 2 - [2 - (5 - amino - 2 - (1,3,4) - thiadiazolylmethylthio)ethylamino] - 5 - benzyloxy - 4 - pyrimidone
(q) 2 - [2 - (2 - thiazolylmethylthio)ethylamino] - 5 - benzyloxy - 4 - pyrimidone

(v) Substitution of the above-listed amines for 2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamine in the procedure of Example 12 leads to the production of:—

(a) 2 - [2 - (2 - imidazolylmethylthio)ethylamino] - 5 - (3 - methoxybenzyl) - 4 - pyrimidone
(b) 2 - [2 - (4 - imidazolylmethylthio)ethylamino] - 5 - (3 - methoxybenzyl) - 4 - pyrimidone
(c) 2 - [2 - (5 - bromo - 4 - imidazolylmethylthio)ethylamino] - 5 - (3 - methoxybenzyl) - 4 - pyrimidone
(d) 2 - [2 - (5 - trifluoromethyl - 4 - imidazolylmethylthio) - ethylamino - 5 - (3 - methoxybenzyl) - 4 - pyrimidone
(e) 2 - [2 - (5 - hydroxymethyl - 4 - imidazolylmethylthio) - ethylamino] - 5 - (3 - methoxybenzyl) - 4 - pyrimidone
(f) 2[2 - (2 - pyridylmethylthio)ethylamino] - 5 - (3 - methoxybenzyl) - 4 - pyrimidone
(g) 2 - [2 - (3 - methyl - 2 - pyridylmethylthio)ethylamino] - 5 - (3 - methoxybenzyl) - 4 - pyrimidone
(h) 2 - [2 - (3 - methoxy - 2 - pyridylmethylthio)ethylamino] - 5 - (3 - methoxybenzyl) - 4 - pyrimidone
(i) 2 - [2 - (3 - chloro - 2 - pyridylmethylthio)ethylamino] - 5 - (3 - methoxybenzyl) - 4 - pyrimidone
(j) 2 - [2 - (3 - amino - 2 - pyridylmethylthio)ethylamino] - 5 - (3 - methoxybenzyl) - 4 - pyrimidone
(k) 2 - [2 - (3 - hydroxy - 2 - pyridylmethylthio)ethylamino] - 5 - (3 - methoxybenzyl) - 4 - pyrimidone
(l) 2 - [2 - (3 - isothiazolylmethylthio)ethylamino] - 5 - (3 - methoxybenzyl) - 4 - pyrimidone
(m) 2 - [2 - (4 - bromo - 3 - isothiazolylmethylthio)ethylamino] - 5 - (3 - methoxybenzyl) - 4 - pyrimidone
(n) 2 - [2 - (3 - (1,2,5) - thiadiazolylmethylthio)ethylamino] - 5 - (3 - methoxybenzyl) - 4 - pyrimidone
(o) 2 - [2 - (4 - chloro - 3 - (1,2,5) - thiadiazolylmethylthio)ethylamino] - 5 - (3 - methoxybenzyl) - 4 - pyrimidone

(p) 2 - [2 - (5 - amino - 2 - (1,3,4) - thiadiazolylmethylthio)ethylamino] - 5 - (3 - methoxybenzyl) - 4 - pyrimidone
(q) 2 - [2 - (2 - thiazolylmethylthio)ethylamino] - 5 - (3 - methoxybenzyl) - 4 - pyrimidone

(vi) 2 - (4 - chloro - 3 - (1,2,5) - thiadiazolylmethylthio)ethylamine can be prepared by the following route:—
3 - Methyl(1,2,5)thiadiazole is chlorinated for 4 days in acetonitrile at 25° to give 4 - chloro - 3 - methyl(1,2,5)thiadiazole (oil) which is treated with N-bromosuccinimide in carbon tetrachloride to give 3 - bromomethyl - 4 - chloro(1,2,5)thiadiazole (oil), the 100 MHz n.m.r. in $CDCl_3$ had singlet at 4.66δ. 3 - Bromomethyl - 4 - chloro(1,2,5)thiadiazole was treated with cysteamine and sodium ethoxide in ethanol to give 2 - (4 - chloro - 3(1,2,5)thiadiazolylmethylthio)ethylamine (oil). A 60 MHz n.m.r. spectrum ($CDCl_3$) gave a singlet at 3.91 attributed to the Het—CH_2—S protons.

EXAMPLE 22

Substitution of 4 - (4 - imidazolyl)butylamine for 2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamine in the procedure of Example 12 leads to the production of 2 - [4 - (4 - imidazolyl) - butylamino] - 5 - (3 - methoxybenzyl) - 4 - pyrimidone, m.p. 193—194°.

EXAMPLE 23

Treatment of ethyl butyroacetate with sodium ethoxide and 4-methoxybenzyl chloride gives ethyl α - (4 - methoxybenzyl) - butyroacetate which is refluxed with thiourea and sodium ethoxide to give 5 - (4 - methoxybenzyl) - 6 - propyl - 2 - thiouracil. Substitution of 5 - (4 - methoxybenzyl) - 6 - propyl - 2 - thiouracil for 5 - (4 - chlorobenzyl) - 2 - thiouracil in the general procedure of Example 1 gives 5 - (4 - methoxybenzyl) - 2 - methylthio - 6 - propyl - 4 - pyrimidone and 2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (4 - methoxybenzyl) - 6 - propyl - 4 - pyrimidone.

EXAMPLE 24

Substitution of
(a) ethyl 3 - (2 - naphthyl)propionate
(b) ethyl 3 - (4 - trifluoromethylphenyl)propionate
(c) ethyl 3 - (4 - dimethylaminophenyl)propionate
(d) ethyl 3 - (4 - phenoxyphenyl)propionate
(e) ethyl 3 - (4 - (4 - chlorophenoxy)phenyl) - propionate
(f) ethyl 3 - (4 - (4 - methoxyphenoxy)phenyl - propionate
(g) ethyl 3 - (4 - biphenylyl)propionate
(h) ethyl 3 - (4' - chloro - 4 - biphenylyl)propionate
(i) ethyl 3 - (4' - methoxy - 4 - biphenylyl)propionate

for ethyl 3 - (3 - chlorophenyl)propionate in the procedure of Example 4 leads to the production of:

(a) 5 - (2 - naphthylmethyl) - 2 - methylthio - 4 - pyrimidone
(b) 5 - (4 - trifluoromethylbenzyl) - 2 - methylthio - 4 - pyrimidone
(c) 5 - (4 - dimethylaminobenzyl) - 2 - methylthio - 4 - pyrimidone
(d) 5 - (4 - phenoxybenzyl) - 2 - methylthio - 4 - pyrimidone
(e) 5 - (4 - (4 - chlorophenoxy)benzyl) - 2 - methylthio - 4 - pyrimidone
(f) 5 - (4 - (4 - methoxyphenoxy)benzyl) - 2 - methylthio - 4 - pyrimidone
(g) 5 - (4 - phenylbenzyl) - 2 - methylthio - 4 - pyrimidone
(h) 5 - (4 - (4 - chlorophenyl)benzyl) - 2 - methylthio - 4 - pyrimidone
(i) 5 - (4 - (4 - methoxyphenyl)benzyl) - 2 - methylthio - 4 - pyrimidone

and

(a) 2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (2 - naphthylmethyl) - 4 - pyrimidone
(b) 2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (4 - trifluoromethylbenzyl) - 4 - pyrimidone
(c) 2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (4 - dimethylaminobenzyl) - 4 - pyrimidone
(d) 2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (4 - phenoxybenzyl) - 4 - pyrimidone
(e) 2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (4 - (4 - chlorophenoxy)benzyl) - 4 - pyrimidone

(f) 2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (4 - (4 - methoxyphenoxy)benzyl) - 4 - pyrimidone
(g) 2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (4 - phenylbenzyl) - 4 - pyrimidone
(h) 2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - 4 - (4 - chlorophenyl)benzyl) - 4 - pyrimidone
(i) 2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - 4 - (4 - methoxyphenyl)benzyl)) - 4 - pyrimidone

EXAMPLE 25

Treatment of 2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (3 - benzyloxybenzyl) - 4 - pyrimidone with hydrogen bromide in acetic acid leads to the production of
2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (3 - hydroxybenzyl) - 4 - pyrimidone.

EXAMPLE 26

(a) 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.
(b) 5 - (2 - Hydroxyethyl) - 2 - methylthio - 4 - pyrimidone is treated with thionyl chloride and the product is reacted with the sodium derivative of (1) 4 - methoxybenzyl alcohol and (2) 4 - methoxybenzyl mercaptan, to give:
1. 5 - (2 - (4 - methoxybenzyloxy)ethyl) - 2 - methylthio - 4 - pyrimidone
2. 5 - (2 - (4 - methoxybenzylthio)ethyl) - 2 - methylthio - 4 - pyrimidone
(c) substitution of:
1. 5 - (2 - (4 - methoxybenzyloxy)ethyl) - 2 - methylthio - 4 - pyrimidone
2. 5 - (2 - (4 - methoxybenzylthio)ethyl) - 2 - methylthio - 4 - pyrimidone

for 5 - (4 - chlorobenzyl) - 2 - methylthio - 4 - pyrimidone in the general procedure of Example 1(ii) leads to the production of:
1. 2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (2 - (4 - methoxybenzyloxy)ethyl) - 4 - pyrimidone
2. 2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (2 - (4 - methoxybenzylthio)ethyl) - 4 - pyrimidone

(d) substitution of (1) phenol and (2) thiophenol for p-methoxybenzyl alcohol in procedure (bii) and (c) above leads to the production of:
1. 2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (2 - phenoxyethyl) - 4 - pyrimidone
2. 2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (2 - phenylthioethyl) - 4 - pyrimidone

(e) substitution of (1) 2-phenylethanol and (2) 2 - phenyl - ethyl mercaptan for p-methoxybenzyl alcohol in procedure (bii) and (c) above leads to the production of
1. 2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (2 - (2 - phenylethoxy)ethyl) - 4 - pyrimidone
2. 2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (2 - (2 - phenylethylthio)ethyl - 4 - pyrimidone

(f) substitution of caprolactone for butyrolactone in procedure (a) (bii) and (c) above leads to the production of
1. 2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (3 - (4 - methoxybenzyloxy)propyl) - 4 - pyrimidone
2. 2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (3 - (4 - methoxybenzylthio)propyl) - 4 - pyrimidone.

EXAMPLE 27

Substitution of
(a) ethyl 3-phenylpropoxyacetate
(b) ethyl 3-phenylpropylthioglycolate for ethyl benzyloxyacetate in the procedure of Example 11 results in the preparation of:
(a) 5 - (3 - phenylpropoxy) - 2 - methylthio - 4 - pyrimidone
(b) 5 - (3 - phenylpropylthio) - 2 - methylthio - 4 - pyrimidone and
(a) 2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (3 - phenylpropoxy) - 4 - pyrimidone
(b) 2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (3 - phenylpropylthio) - 4 - pyrimidone.

EXAMPLE 28

Substitution of

(a) 5 - [3 - (2 - (4 - methoxyphenyl)ethoxy)benzyl] - 2 - thiouracil

(b) 5 - [3 - (3 - chlorobenzyloxy)benzyl] - 2 - thiouracil

for 5 - (3 - benzyloxybenzyl) - 2 - thiouracil in the general procedure of Example 17 leads to the production of:

(a) 5 - [3 - (2 - (4 - methoxyphenyl)ethoxy)benzyl] - 2 - methylthio - 4 - pyrimidone

(b) 5 - [3 - (3 - chlorobenzyloxy)benzyl] - 2 - methylthio - 4 - pyrimidone

and

(a) 2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - [3 - (2 - (4 - methoxyphenyl)ethoxy)benzyl] - 4 - pyrimidone

(b) 2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - [3 - (3 - chlorobenzyloxy)benzyl] - 4 - pyrimidone.

EXAMPLE 29

Substitution of ethyl 3 - (3 - bromophenyl)propionate for ethyl 3 - (3 - chlorophenyl)propionate in the procedure of Example 4 leads to the production of:

5 - (3 - bromobenzyl) - 2 - methylthio - 4 - pyrimidone and

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

EXAMPLE 30

Treatment of ethyl 3 - (3 - hydroxyphenyl)propionate with dimethoxymethane and substitution of the product for ethyl 3 - (3 - chlorophenyl)propionate in the procedure of Example 4 leads to the production of 5 - [3 - (methoxymethoxy)benzyl] - 2 - methylthio - 4 - pyrimidone and 2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - [3 - (methoxymethoxy)benzyl] - 4 - pyrimidone. Treatment of this product with hydrochloric acid gives 2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (3 - hydroxybenzyl) - 4 - pyrimidone.

EXAMPLE 31

Pharmaceutical composition:—

Ingredients	Amounts
2 - [2 - (5 - methyl - 4 - imidazolylmethylthio) - ethylamino] - 5 - (3 - methoxybenzyl) - 4 - pyrimidone dihydrochloride	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 32

Pharmaceutical composition:—

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

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

Similarly, the other compounds of Formula 3 may be formulated into pharmaceutical compositions by the procedures of Examples 31 and 32.

The pharmaceutical compositions prepared as in the foregoing examples are administered to a subject within the dose ranges given hereabove to block histamine H_1- and H_2-receptors.

EXAMPLE 33

(i) Ethyl 3 - (2 - methoxyphenyl)propionate (65.0 g) was converted into 5 - (2 - methoxybenzyl) - 2 - thiouracil, m.p. 192—193°C (ex. ethanol/H_2O, 1:1) by the procedure of Example 4(i).

(ii) 5 - (2 - Methoxybenzyl) - 2 - thiouracil (9.0 g) was converted into 5 - (2 - methoxybenzyl) - 2 - methylthio - 4 - pyrimidone, m.p. 163—166°C (ex. ethanol) by the procedure of Example 1(i).

(iii) 5 - (2 - Methoxybenzyl) - 2 - methylthio - 4 - pyrimidone (2.00 g) was reacted with 2 - (5 - methyl - 4 - imidazolylmethylthio) - ethylamine (1.37 g) by the procedure of Example 1(ii) to give a 2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (2 - methoxybenzyl) - 4 - pyrimidone, m.p. 163—167°C (ex ethanol).

(Found: C, 58.4; H, 6.1; N, 17.6; S, 8.2; $C_{19}H_{23}N_5O_2S$ requires: C, 59.2; H, 6.0; N, 18.2; S, 8.3%)

EXAMPLE 34

(i) Ethyl 3 - (3,4 - dimethoxyphenyl)propionate (37.5 g) was converted into 5 - (3,4 - dimethoxybenzyl) - 2 - thiouracil, m.p. 236—237°C (ex ethanol) by the procedure of Example 4(i).

(ii) 5 - (3,4 - Dimethoxybenzyl) - 2 - thiouracil (7.3 g) was converted to 5 - (3,4 - dimethoxybenzyl) - 2 - methylthio - 4 - pyrimidone, m.p. 199—200°C (ex ethanol) by the procedure of Example 1(i).

(iii) 5 - (3,4 - Dimethoxybenzyl) - 2 - methylthio - 4 - pyrimidone (1.3 g) was reacted with 2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamine (0.76 g) by the procedure of Example 3 to give 2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (3,4 - dimethoxybenzyl) - 4 - pyrimidone dihydrochloride, m.p. 226—230°C, (ex methanol).

(Found: C, 48.1; H, 5.5; N, 14.0; S, 6.4; Cl, 14.2; $C_{20}H_{27}Cl_2N_5O_3S$ requires: C, 49.2; H, 5.6; N, 14.3; S, 6.6; Cl, 14.5%).

EXAMPLE 35

(i) Ethyl 3 - (3 - trifluoromethylphenyl)propionate (90.0 g) was converted to 5 - (3 - trifluromethylbenzyl) - 2 - thiouracil, m.p. 217—219°C (ex ethanol/methanol) by the procedure of Example 4 (i).

(ii) 5 - (3 - trifluoromethylbenzyl) - 2 - thiouracil (40.13 g) was converted into 5 - (3 - trifluoromethylbenzyl) - 2 - methylthio - 4 - pyrimidone, m.p. 187—189°C (ex ethanol) by the procedure of Example 1(i).

(iii) 5 - (3 - trifluoromethylbenzyl) - 2 - methylthio - 4 - pyrimidone (2.5 g) was reacted with 2 - (5 - methyl - 4 - imidazolyl - methylthio)ethylamine (1.43 g) by the procedure of Example 3 to give 2 - [2 - (5 - methyl - 4 - imidazolylmethylthio) - ethylamino] - 5 - (3 - trifluoromethylbenzyl) - 4 - pyrimidone dihydrochloride, m.p. 174—176°C (ex Propan-2-ol)

(Found: C, 45.8; H, 4.4; N, 14.0; S, 6.6; Cl, 13.9; $C_{18}H_{22}Cl_2F_3N_5OS$ requires: C, 46.0; H, 4.5; N, 14.1; S, 6.5; Cl, 14.3%).

EXAMPLE 36

2 - [2 - (5 - Methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (3 - methoxybenzyl) - 4 - pyrimidone (2.35 g) was suspended in dry dichloromethane (30 ml) and boron tribromide (6.49 g) carefully added. The mixture was stirred in a dry atomosphere overnight. Careful addition of water (30 ml) was followed by separation of the two phases. The aqueous phase was treated in $NaHCO_3$ which precipitated a tacky solid which was repeatedly washed with water until it became solid, when it was filtered and dried. Treatment with ethanolic HCl gave 2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (3 - hydroxybenzyl) - 4 - pyrimidone dihydrochloride, m.p. 142—144° (ex. ethanol)

(Found: C, 48.5; H, 5.2; N, 15.7; S, 7.3; Cl, 15.8; $C_{18}H_{23}Cl_2N_5O_2S$ requires: C, 48.7; H, 5.2; N, 15.8; S, 7.2; Cl, 16.0%)

EXAMPLE 37

2 - [2 - (5 - Methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (4 - methoxybenzyl) - 4 - pyrimidone (5.66 g) was reacted with boron tribromide (14.73 g) using the procedure of Example 36 to give 2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (4 - hydroxybenzyl) - 4 - pyrimidone dihydrochloride, m.p. 207—210°C (ex ethanol)

(Found: C, 48.4; H, 5.1; N, 15.5; S, 7.2; Cl, 15.4 $C_{18}H_{23}Cl_2N_5O_2S$ requires: C, 48.7; H, 5.2; N, 15.8; S, 7.2; Cl, 16.0%)

EXAMPLE 38

(a) Ethyl 3 - (6 - (2,3 - dihydro - 1,4 - benzodioxinyl))propionate was prepared by esterifying 3 - (6 - (2,3 - dihydro - 1,4 - benzodioxinyl) - prop - 2 -

enoic acid with ethanol in the presence of toluene and sulphuric acid, and hydrogenating the product using palladium-on-charcoal catalyst.

(b) Ethyl 3 - (6 - (2,3 - dihydro - 1,4 - benzodioxinyl))propionate was converted into 5 - (6 - (2,3 - dihydro - 1,4 - benzodioxinyl)methyl) - 2 - thiouracil, m.p. 294—296° (ex 2 - methoxyethanol/ethanol, 2:1) by the procedure of Example 4(i), and the latter compound was converted into 5 - (6 - (2,3 - dihydro - 1,4 - benzodioxinyl)methyl) - 2 - methylthio - 4 - pyrimidone, m.p. 200—201°C (ex methanol) by the procedure of Example 1(i).

(c) 5 - (6 - (2,3 - dihydro - 1,4 - benzodioxinyl)methyl) - 2 - methylthio - 4 - pyrimidone (1.50 g) was reacted with 2 - (5 - methyl - 4 - imidazolyl - methylthio)ethylamine (0.94 g) by the procedure of Example 3 to give 2 - [2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - [6 - (2,3 - dihydro - 1,4 - benzodioxinyl)methyl] - 4 - pyrimidone which was dissolved in dilute hydrobromic acid to give the dihydrobromide, m.p. 210—214°C (ex ethanol)

(Found: C, 41.9; H, 4.4; N, 11.9; S, 5.3; Br^-, 27.5 $C_{20}H_{25}Br_2N_5O_3S$ requires: C, 41.8; H, 4.4; N, 12.2; S, 5.6; Br^-, 27.8%)

EXAMPLE 39

5 - (3 - Methoxybenzyl) - 2 - methylthio - 4 - pyrimidone (2.79 g) was reacted with 2 - (2 - thiazolylmethylthio)ethylamine (1.86 g) by the procedure of Example 6 to give 2 - [2 - (2 - thiazolylmethylthio) - ethylamino] - 5 - (3 - methoxybenzyl) - 4 - pyrimidone hemihydrochloride m.p. 104—106°C (ex Propan-2-ol)

(Found: C, 52.9; H, 5.2; N, 13.6; S, 15.5; Cl, 4.6; $C_{18}H_{20}N_4O_2S_2 . \frac{1}{2}$ HCl requires: C, 53.2; H, 5.1; N, 13.8; S, 15.8; Cl, 4.4%)

EXAMPLE 40

3 - Fluoro - 2 - methyl - 4 - nitropyridine N-oxide is treated with an excess of sodium methoxide and the product is heated in acetic anhydride and deacetylated to give 2 - hydroxymethyl - 3,4 - dimethoxy - pyridine. 2 - Hydroxymethyl - 3,4 - dimethoxypyridine is treated with thionyl chloride and the product is treated with cysteamine to give 2 - (3,4 - dimethoxy - 2 - pyridylmethylthio)ethylamine.

Substitution of 2 - (3,4 - dimethoxy - 2 - pyridylmethylthio)ethylamine for 2 - (5 - methyl - 4 - imidazolylmethylthio)ethylamine in the procedure of Example 7 leads to the production of 2 - [2 - (3,4 - dimethoxy - 2 - pyridylmethylthio)ethylamino] - 5 - (4 - methoxybenzyl) - 4 - pyrimidone.

EXAMPLE 41

(i) 4 - Nitro - 3 - methoxy - 2 - methylpyridine N-oxide is heated in acetic anhydride and the purified product is deacetylated and reduced with hydrogen and palladium on charcoal to give 4 - amino - 2 - hydroxymethyl - 3 - methoxypyridine.

(ii) 4 - Amino - 2 - hydroxymethyl - 3 - methoxypyridine is diazotised in dilute sulphuric acid with sodium nitrite and the diazonium compound is warmed to give 4 - hydroxy - 2 - hydroxymethyl - 3 - methoxy - pyridine which may be demethylated with hydrobromic acid.

(iii) Alkylation of 3,4 - dihydroxy - 2 - hydroxymethylpyridine with pelleted sodium hydroxide and

(a) Dibromomethane
(b) 1,2-Dibromoethane
(c) 1,4-Dibromobutane

leads to the production of (a) 4-hydroxymethyl(1,3 - dioxolo[4,5 - c]pyridine)
(b) 2,3 - Dihydro - 5 - hydroxymethyl - (p - dioxino[2,3 - c]pyridine)
(c) 2,3,4,5 - Tetrahydro - 7 - hydroxymethyl - (1,4 - dioxocino[2,3 - c] - pyridine) which may be converted into

(a) 2 - [2 - (4 - (1,3 - dioxolo[4,5 - c]pyridyl)methylthio)ethylamino] - 5 - (4 - methoxybenzyl) - 4 - pyrimidone.
(b) 2 - [2 - (5 - (2,3 - dihydro - p - dioxino[2,3 - c]pyridyl)methylthio) - ethylamino] - 5 - (4 - methoxybenzyl) - 4 - pyrimidone.
(c) 2 - [2 - (7 - (2,3,4,5 - tetrahydro - 1,4 - dioxocino[2,3 - c]pyridyl) - methylthio)ethylamino] - 5 - (4 - methoxybenzyl) - 4 - pyrimidone, by successive treatment with thionyl chloride and cysteamine and substitution of the resultant amine for 2 - (5 - methyl - 4 - imidazolyl - methylthio)ethylamine in the procedure of Example 7.

EXAMPLE 42

Treatment of

(a) 1-hydroxymethylisoquinoline

(b) 5,6,7,8 - tetrahydro - 1 - hydroxymethylisoquinoline with cysteamine in hydrogen bromide gives

(a) 2 - (1 - isoquinolylmethylthio)ethylamine

(b) 2 - (5,6,7,8 - tetrahydro - 1 - isoquinolylmethylthio) - ethylamine which, when substituted for 2 - (5 - methyl - 4 - imidazolylmethylthio) - ethylamine in the procedure of Example 7 gives:—

(a) 2 - [2 - (1 - isoquinolylmethylthio)ethylamino] - 5 - (4 - methoxy - benzyl) - 4 - pyrimidone

(b) 2 - [2 - (1 - (5,6,7,8 - tetrahydroisoquinolyl)methylthio)ethylamino] - 5 - (4 - methoxybenzyl) - 4 - pyrimidone.

EXAMPLE 43

Alkylation of

(a) 5 - (3 - methoxybenzyl) - 2 - thiouracil

(b) 5 - (5 - (1,3 - benzodioxolyl)methyl) - 2 - thiouracil

(c) 5 - (6 - (2,3 - dihydro - 1,4 - benzodioxinyl) - methyl) - 2 - thiouracil with benzyl chloride and sodium hydroxide gives

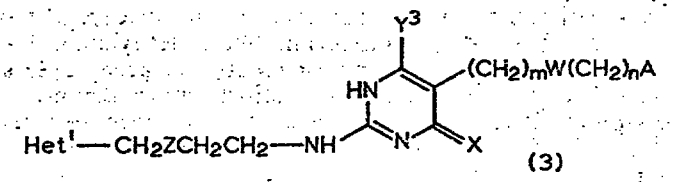
(a) 5 - (3 - methoxybenzyl) - 2 - benzylthio - 4 - pyrimidone

(b) 5 - (5 - (1,3 - benzodioxolyl)methyl) - 2 - benzylthio - 4 - pyrimidone

(c) 5 - (6 - (2,3 - dihydro - 1,4 - benzodioxinyl)methyl) - 2 - benzylthio - 4 - pyrimidone

WHAT WE CLAIM IS:—

1. A compound of the formula (3):—



(3)

where Het' is a 2- or 4-imidazolyl group optionally substituted by lower alkyl, halogen, trifluoromethyl or hydroxymethyl, a 2-pyridyl group optionally substituted by lower alkyl, lower alkoxy, halogen, amino or hydroxy, a 2-pyridyl group which is disubstituted by lower alkoxy groups, or which has a phenyl, alicyclic or cyclic ether group containing two oxygen atoms fused to it, a 2-thiazolyl group, a 3-isothiazolyl group optionally substituted by chlorine or bromine, a 3 - (1,2,5) - thiadiazolyl group optionally substituted by chlorine or bromine, or a 2 - (5 - amino - 1,3,4 - thiadiazolyl) group: Z is sulphur or a methylene group; X is oxygen or sulphur; W is methylene, oxygen or sulphur; m and n 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; A is a 1- or 2-naphthyl group, a 2,3 - dihydro - 1,4 - benzodioxinyl or a 1,3 - benzodioxolyl group, a phenyl group substituted with one or more lower alkyl, lower alkoxy, halogen, arylalkoxy, hydroxy, lower alkoxy-lower alkoxy, trifluoromethyl, di(lower alkyl)amino, phenoxy, halophenoxy, alkoxyphenoxy, phenyl, halophenyl or alkoxyphenyl groups and when $-(CH_2)_mW(CH_2)_n-$ is not a methylene group, A may also be phenyl; and Y^3 is hydrogen or lower alkyl; and pharmaceutically acceptable acid addition salts thereof.

2. A compound as claimed in claim 1 where Het' is a 2- or 4-imidazolyl group optionally substituted by lower alkyl, halogen, trifluoromethyl or hydroxymethyl, a 2-pyridyl group optionally substituted by lower alkyl, lower alkoxy, halogen, amino or hydroxy, a 2-thiazolyl group, a 3-isothiazolyl group optionally substituted by chlorine or bromine, a 3 - (1,2,5) - thiadiazolyl group optionally substituted by chlorine or bromine, or a 2 - (5 - amino - 1,3,4 - thiadiazolyl)group.

3. A compound as claimed in claim 2 where A is a phenyl group substituted with one or more lower alkyl, lower alkoxy, halogen, hydroxy, trifluoromethyl, di(lower alkyl)amino, phenoxy, halophenoxy, phenyl, or halophenyl groups, or when $-(CH_2)_mW(CH_2)_n-$ is not a methylene group A may be phenyl.

4. A compound as claimed in claim 2 or claim 3 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.

EXAMPLE 42

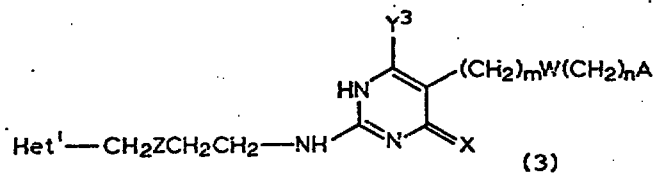
Treatment of
(a) 1-hydroxymethylisoquinoline
(b) 5,6,7,8 - tetrahydro - 1 - hydroxymethylisoquinoline with cysteamine in hydrogen bromide gives
(a) 2 - (1 - isoquinolylmethylthio)ethylamine
(b) 2 - (5,6,7,8 - tetrahydro - 1 - isoquinolylmethylthio) - ethylamine which, when substituted for 2 - (5 - methyl - 4 - imidazolylmethylthio) - ethylamine in the procedure of Example 7 gives:—
(a) 2 - [2 - (1 - isoquinolylmethylthio)ethylamino] - 5 - (4 - methoxy - benzyl) - 4 - pyrimidone
(b) 2 - [2 - (1 - (5,6,7,8 - tetrahydroisoquinolyl)methylthio)ethylamino] - 5 - (4 - methoxybenzyl) - 4 - pyrimidone.

EXAMPLE 43

Alkylation of
(a) 5 - (3 - methoxybenzyl) - 2 - thiouracil
(b) 5 - (5 - (1,3 - benzodioxolyl)methyl) - 2 - thiouracil
(c) 5 - (6 - (2,3 - dihydro - 1,4 - benzodioxinyl) - methyl) - 2 - thiouracil with benzyl chloride and sodium hydroxide gives
(a) 5 - (3 - methoxybenzyl) - 2 - benzylthio - 4 - pyrimidone
(b) 5 - (5 - (1,3 - benzodioxolyl)methyl) - 2 - benzylthio - 4 - pyrimidone
(c) 5 - (6 - (2,3 - dihydro - 1,4 - benzodioxinyl)methyl) - 2 - benzylthio - 4 - pyrimidone

WHAT WE CLAIM IS:—

1. A compound of the formula (3):—



(3)

where Het' is a 2- or 4-imidazolyl group optionally substituted by lower alkyl, halogen, trifluoromethyl or hydroxymethyl, a 2-pyridyl group optionally substituted by lower alkyl, lower alkoxy, halogen, amino or hydroxy, a 2-pyridyl group which is disubstituted by lower alkoxy groups, or which has a phenyl, alicyclic or cyclic ether group containing two oxygen atoms fused to it, a 2-thiazolyl group, a 3-isothiazolyl group optionally substituted by chlorine or bromine, a 3 - (1,2,5) - thiadiazolyl group optionally substituted by chlorine or bromine, or a 2 - (5 - amino - 1,3,4 - thiadiazolyl) group: Z is sulphur or a methylene group: X is oxygen or sulphur: W is methylene, oxygen or sulphur; m and n 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; A is a 1- or 2-naphthyl group, a 2,3 - dihydro - 1,4 - benzodioxinyl or a 1,3 - benzodioxolyl group, a phenyl group substituted with one or more lower alkyl, lower alkoxy, halogen, arylalkoxy, hydroxy, lower alkoxy-lower alkoxy, trifluoromethyl, di(lower alkyl)amino, phenoxy, halophenoxy, alkoxyphenoxy, phenyl, halophenyl or alkoxyphenyl groups and when $-(CH_2)_mW(CH_2)_n-$ is not a methylene group, A may also be phenyl; and Y^3 is hydrogen or lower alkyl; and pharmaceutically acceptable acid addition salts thereof.

2. A compound as claimed in claim 1 where Het' is a 2- or 4-imidazolyl group optionally substituted by lower alkyl, halogen, trifluoromethyl or hydroxymethyl, a 2-pyridyl group optionally substituted by lower alkyl, lower alkoxy, halogen, amino or hydroxy, a 2-thiazolyl group, a 3-isothiazolyl group optionally substituted by chlorine or bromine, a 3 - (1,2,5) - thiadiazolyl group optionally substituted by chlorine or bromine, or a 2 - (5 - amino - 1,3,4 - thiadiazolyl)group.

3. A compound as claimed in claim 2 where A is a phenyl group substituted with one or more lower alkyl, lower alkoxy, halogen, hydroxy, trifluoromethyl, di(lower alkyl)amino, phenoxy, halophenoxy, phenyl, or halophenyl groups, or when $-(CH_2)_mW(CH_2)_n-$ is not a methylene group A may be phenyl.

4. A compound as claimed in claim 2 or claim 3 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.

5. A compound as claimed in any one of claims 2 to 4 where Z is sulphur.
6. A compound as claimed in any one of claims 2 to 5 where X is oxygen.
7. A compound as claimed in any one of claims 2 to 6 where Y^3 is hydrogen.
8. A compound as claimed in any one of claims 2 to 7 where A is a phenyl group substituted by one or more lower alkoxy groups.
9. A compound as claimed in any one of claims 2 to 7 where A is a 2,3 - dihydro - 1,4 - benzodioxinyl or 1,3 - benzodioxolyl group.
10. A compound as claimed in any one of claims 2 to 9 where m and n are 0 and W is methylene.
11. A compound as claimed in any one of claims 2 to 9 where m is 0, n is 1 and W is oxygen.
12. A compound as claimed in claim 1 or claim 2 where Y^3 is hydrogen, m and n are 0, W is methylene and A is a 2,3 - dihydrobenzodioxinyl or 1,3-benzodioxolyl group or a phenyl group substituted with one or more lower alkoxy groups.
13. A compound as claimed in any of claims 1 to 12 where A is a substituted phenyl group, the substituents being in position 3 and/or 4.
14. 2 - [2 - (5 - Methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (4 - chlorobenzyl) - 4 - pyrimidone and its pharmaceutically acceptable salts.
15. 2 - [2 - (2 - Thiazolylmethylthio)ethylamino] - 5 - (4 - chlorobenzyl) - 4 - pyrimidone and its pharmaceutically acceptable salts.
16. 2 - [2 - (3 - Bromo - 2 - pyridylmethylthio)ethylamino] - 5 - (4 - chlorobenzyl) - 4 - pyrimidone and its pharmaceutically acceptable salts.
17. 2 - [2 - (5 - Methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (4 - chlorobenzyl) - 6 - methyl - 4 - pyrimidone and its pharmaceutically acceptable salts.
18. 2 - [2 - (5 - Methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (3 - chlorobenzyl) - 4 - pyrimidone and its pharmaceutically acceptable salts.
19. 2 - [2 - (5 - Methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (3,4 - dichlorobenzyl) - 4 - pyrimidone and its pharmaceutically acceptable salts.
20. 2 - [2 - (5 - Methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (4 - methoxybenzyl) - 4 - pyrimidone and its pharmaceutically acceptable salts.
21. 2 - [2 - (5 - Methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (4 - methylbenzyl) - 4 - pyrimidone and its pharmaceutically acceptable salts.
22. 2 - [2 - (5 - Methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (2 - phenylethyl) - 4 - pyrimidone and its pharmaceutically acceptable salts.
23. 2 - [2 - (5 - Methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (2 - phenylethyl) - 6 - methyl - 4 - pyrimidone and its pharmaceutically acceptable salts.
24. 2 - [2 - (5 - Methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - benzyloxy - 4 - pyrimidone and its pharmaceutically acceptable salts.
25. 2 - [2 - (5 - Methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (3 - methoxybenzyl) - 4 - pyrimidone and its pharmaceutically acceptable salts.
26. 2 - [2 - (5 - Methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (2 - chlorobenzyl) - 4 - pyrimidone and its pharmaceutically acceptable salts.
27. 2 - [2 - (5 - Methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (4 - phenylbutyl) - 4 - pyrimidone and its pharmaceutically acceptable salts.
28. 2 - [2 - (5 - Methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (5 - (1,3 - benzodioxolyl)methyl) - 4 - pyrimidone and its pharmaceutically acceptable salts.
29. 2 - [2 - (5 - Methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (3 - ethoxy - benzyl) - 4 - pyrimidone and its pharmaceutically acceptable salts.
30. 2 - [2 - (5 - Methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (3 - benzyloxybenzyl) - 4 - pyrimidone and its pharmaceutically acceptable salts.
31. 2 - [2 - (5 - Methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (1 - naphthylmethyl) - 4 - pyrimidone and its pharmaceutically acceptable salts.
32. 2 - [2 - (5 - Methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - [6 - (2,3 - dihydro - 1,4 - benzodioxinyl)methyl] - 4 - pyrimidone and its pharmaceutically acceptable salts.
33. 2 - [2 - (5 - Methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - [5 - (1,3 - benzodioxolyl)methyl] - 4 - pyrimidone dihydrochloride.
34. A pharmaceutical composition comprising a compound as claimed in anyone of claims 1 to 33 in combination with a pharmaceutically acceptable carrier.
35. A pharmaceutical composition comprising a compound as claimed in claim 2 in combination with a pharmaceutically acceptable carrier.

36. A pharmaceutical composition comprising a compound as claimed in claim 28 in combination with a pharmaceutically acceptable carrier.

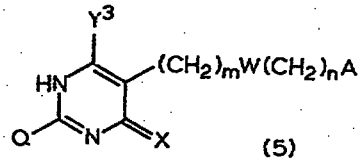
37. A pharmaceutical composition comprising the compound claimed in claim 33 in combination with a pharmaceutically acceptable carrier.

38. A composition as claimed in anyone of claims 34 to 37 in the form of a sterile liquid suitable for injection.

39. A process for preparing a compound as claimed in claim 1 which comprises reacting an amine of the formula (4):—

$$Het'—CH_2ZCH_2CH_2NH_2 \quad (4)$$

where Het' and Z are as defined in claim 1, with a compound of the formula (5):—



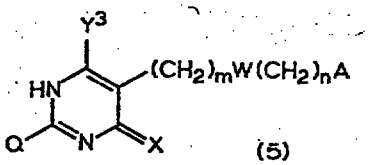
(5)

where X, Y^3, m, W, n, and A are as defined in claim 1 and Q is a reactive group which is displacable with an amine, and thereafter optionally converting the compound of formula (3) so obtained into an acid addition salt.

40. A process for preparing a compound as claimed in claim 2 which comprises reacting an amine of the formula (4):—

$$Het'—CH_2ZCH_2CH_2NH_2 \quad (4)$$

where Het' and Z are as defined in claim 2, with a compound of the formula (5):—



(5)

where X, Y^3, m, W and n are as defined in claim 1, A is defined in claim 2 and Q is a reactive group which is displacable with an amine, and thereafter optionally converting the compound of formula (3) so obtained into an acid addition salt.

41. A process as claimed in claim 39 or claim 40 where Q is benzylthio, lower alkylthio or halogen.

42. A process according to claim 39 or claim 40 where Q is methylthio.

43. A process for preparing a compound as claimed in claim 1 where X is sulphur which comprises reacting a compound of formula (3) as defined in claim 1 where X is oxygen with phosphorus pentasulphide and optionally converting the product into so obtained an acid addition salt.

44. A process for preparing a compound as claimed in claim 1 where A is phenyl substituted with a hydroxy group which comprises reacting a compound of formula (3) as defined in claim 1 where A is phenyl substituted with a methoxy group with boron tribromide and optionally converting the product so obtained into an acid addition salt.

45. A process as claimed in claim 39 or 40 substantially as described in anyone of Examples 1 to 19, 21(i), 21(iii), 21(iv), 21(v), 22 to 30, 33 to 35, and 38 to 42 herein.

46. A process as claimed in claim 43 substantially as described in anyone of Examples 20 or 21(ii) herein.

47. A process as claimed in claim 44 substantially as described in anyone of Examples 36 or 37 herein.

48. A compound as claimed in claim 1 or claim 2 whenever prepared by a process as claimed in anyone of claims 39 to 47.

49. A pharmaceutical composition substantially as described in Examples 31 and 32 herein.

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Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1981
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.