



PATENT SPECIFICATION

NO DRAWINGS

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Int. Cl.:—C 07 d 51/36

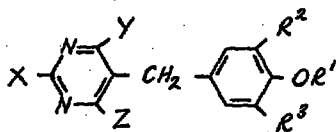
COMPLETE SPECIFICATION

5-Benzylpyrimidine Derivatives and Process for the preparation thereof

We, THE WELLCOME FOUNDATION LIMITED, of 183—193 Euston Road, London, N.W.1, a company incorporated in England do hereby declare this invention which was communicated from Burroughs Wellcome & Co., (USA) Inc., of 1 Scarsdale Road, Tuckahoe, New York 10707, a company incorporated in the State of Westchester, New York, United States of America 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 provides a novel method of preparing 5-benzylpyrimidines.

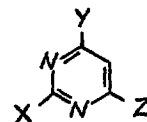
According to the present invention there is provided a method of preparing a 5-benzylpyrimidine of the formula (I)



(I)

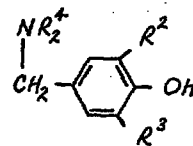
wherein X and Y are the same or different and each is an amino group or a hydroxyl group, Z is a hydrogen atom, an alkyl group containing not more than 4 carbon atoms, a hydroxyl group, or a substituted or unsubstituted amino group, the said substituted amino group including a cyclic amino group such as a piperidino group or a morpholino group, R¹ is a hydrogen atom or a saturated or unsaturated hydrocarbon radical which may be optionally substituted by halogen, and R² and R³ are the same or different and

each is a hydrogen atom or a halogen atom or an alkyl group or an alkoxy group, the said alkyl and alkoxy groups each containing not more than 4 carbon atoms, which method comprises reacting a compound of the formula (IV)



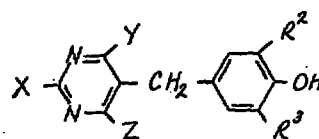
(IV)

wherein X, Y and Z are defined as above, with a Mannich base of the formula (II)



(II)

wherein R² and R³ are defined as above and NR₂⁺ is a dialkylamino group or a cyclic amino group, to produce a compound of the formula (III)



(III)

wherein X, Y, Z, R² and R³ are defined as above, which compound may optionally be reacted with a compound R¹Q, where Q is a reactive atom or group, for example halogen, and R¹ is a saturated or unsaturated hydrocarbon radical which may be optionally substituted by halogen, under basic conditions to produce a compound of formula (I).

The compounds of formula (I) are particularly valuable for their marked antibacterial action. For example, 2,4 - diamino - 5 - (3',4',5' - trimethoxybenzyl)pyrimidine, which is also known as Trimethoprim, is very active as an antibacterial compound and has demonstrated practical value. This type of compound and other methods of preparation thereof are described and claimed in U.K. Patent Specifications Nos. 734,801, 875,562, 920,412 and 957,797. Thus, the above method is preferred when Z is a hydrogen atom, R¹ is a methyl group and R² and R³ are each methoxy groups and is particularly preferred when Z, R¹, R² and R³ are so defined and X and Y are each primary amino groups.

An important sub-group of the compounds of formula (I) are those wherein X and Y are each primary amino groups, Z is a hydrogen atom, R¹ is a saturated or unsaturated hydrocarbon radical containing not more than 4 carbon atoms, and R² and R³ are defined as above.

The compounds of formula (III) above are novel and have been found to possess high antibacterial activity. Thus, the present invention also provides a compound of formula (III). Particularly important compounds of formula (III) are those wherein R² and R³ are each methoxy groups and Z is a hydrogen atom, and those wherein X and Y are each primary amino groups.

2,4 - Diamino - 5 - (3',5' - dimethoxy - 4' - hydroxybenzyl)pyrimidine is a preferred compound of formula (III), and has been found, in laboratory tests, to possess antibacterial activity similar to that of Trimethoprim. This compound of formula (III) has been found to be poorly absorbed from the digestive tract and thus it is particularly useful in treating bacterial infections of the digestive tract, such as bacterial dysenteries, and in topical application to surface infections.

The reaction between the compound of formula (IV) and the compound of formula (II) usually requires a moderately elevated temperature, e.g., at least 130°C. Above about 200°C, excessive decomposition may take place, and so the preferred temperature range for this reaction is 130°C to 200°C. Furthermore, this reaction preferably takes place in the presence of at least one equivalent of a base such as methoxide ion. A solvent is also desirable for this reaction and the solvent selected should ideally fulfil the following requirements:—

(i) the solvent should have a boiling point above or in the preferred temperature range of 130°C to 200°C so that the use of pressure apparatus may be avoided;

(ii) the solvent should be capable of dissolving the reactants and

(iii) the solvent should not react chemically with the reactants. Glycols fulfil the above requirements and ethylene glycol, propylene glycol, trimethylene glycol and glycerol are all suitable. Ethylene glycol (b.p. 198—200°C) is inexpensive and is preferred in practice. This reaction may be run in an inert atmosphere, for example nitrogen, though this is not an essential condition. The inert atmosphere serves to entrain and remove the compound NR₂⁴H, where NR₂⁴ is as hereinbefore defined, which is formed during the reaction and eliminated. Thus the precise nature of the group NR₂⁴ is not critical, though most frequently, for reasons of convenience, it is dimethylamino.

A compound of formula (III) may be presented for antibacterial use in association with a pharmaceutically acceptable carrier. The compound may advantageously be presented in discrete units, such as tablets, capsules, cachets, ampoules or suppositories, each containing a predetermined amount of the compound. The compound may also be presented as a powder or granules, as a solution or suspension in an aqueous, non-aqueous or emulsified liquid, or as an ointment. For parenteral use, the formulations of this invention may be made by any of the methods of pharmacy, and may include one or more of the following accessory ingredients: diluents, solutes, buffers, flavouring, binding, dispersing, surface-active, thickening, lubricating and coating materials, preservatives, antioxidants, bacteriostats, suppository and ointment bases, and any other acceptable excipients.

According to the present invention, there is provided:

(a) a method of preparing a compound of the formula (I) comprising the reaction as defined herein,

(b) a compound of formula (III) as defined herein,

(c) a pharmaceutical composition comprising a compound of formula (III) as active ingredient in admixture with a pharmaceutically acceptable carrier,

(d) a method of preparing a pharmaceutical composition comprising the admixture of a compound of formula (III) with a pharmaceutically acceptable carrier.

The following examples illustrate the invention:—

EXAMPLE 1

Preparation of 2,6 - dimethoxy - 4 - (N,N - dimethylaminomethyl)phenol

2,6-Dimethoxyphenol (92 g.) was slowly added to a mixture of 2N hydrochloric acid (315 ml.), 25% aqueous dimethylamine (150

ml.) and 37% aqueous formaldehyde solution (81 g.). An exothermic reaction occurred, and the mixture turned purple. Additional 35% aqueous dimethylamine (50 ml.) was added and the solution was permitted to stand overnight. The product was isolated by evaporation of the solvent. The resultant tan solid was washed well with ether, followed by recrystallisation from ethanol. This produced 2,6 - dimethoxy - 4 - (N,N - dimethylaminomethyl)phenol hydrochloride as white crystals melting at 224—224.2°C (dec).

Preparation of 2,4 - diamino - 5 - (3',5' - dimethoxy - 4' - hydroxybenzyl)pyrimidine
A mixture of 2,4-diaminopyrimidine (3.3 g.), 2,6 - dimethoxy - 4 - (N,N - dimethylaminomethyl)phenol hydrochloride (7.43 g.), sodium methoxide (1.62 g.) and ethylene glycol (40 ml.) was heated under nitrogen in an oil bath at 150°C for four hours, during which time dimethylamine was evolved. The solvent was removed, and the residual material was then recrystallised twice from dimethylformamide, which yielded 2,4 - diamino - 5 - (3',5' - dimethoxy - 4' - hydroxybenzyl)pyrimidine as white crystals decomposing at 265—270°C.

Preparation of 2,4 - diamino - 5 - (3',4',5' - trimethoxybenzyl)pyrimidine
Methyl iodide (1.42 g.) was added to a solution of 2,4 - diamino - 5 - (3',5' - dimethoxy - 4' - hydroxybenzyl)pyrimidine (2.76 g.) in 40% aqueous methanol (35 ml.) plus a 3.2 N methanolic solution of potassium hydroxide (4.5 ml.). The mixture was allowed to stand in a stoppered flask at room temperature for 72 hours, after which the solvent was removed, and the residue extracted with water to remove impurities. Recrystallisation from ethanol yielded crystals of 2,4 - diamino - 5 - (3',4',5' - trimethoxybenzyl)pyrimidine, melting at 197—199°C, and identical in all respects with the product prepared by other synthetic routes (B. Roth, E. A. Falco, G. H. Hitchings and S. R. M. Bushby, *J. Med. Pharm. Chem.*, 5, 1103, (1962)).

EXAMPLE 2

Preparation of 2 - amino - 4 - hydroxy - 5 - (3',5' - dimethoxy - 4' - hydroxybenzyl) - pyrimidine
A mixture of isocytosine (12.1 g.), 2,6 - dimethoxy - 4 - dimethylaminomethylphenol hydrochloride (27 g.), sodium methylate (5.9 g.) and ethylene glycol (110 ml.) was heated at 150°C for two hours. Nitrogen was swept through the solution, and the dimethylamine which was evolved was collected in acid. The reaction was stopped when approximately 90% of the theoretical amount of dimethylamine had been collected. The mixture was cooled, and poured into water. The resultant precipitate was isolated and washed well with

water, after which it was dried. The solid was extracted several times with hot ethanol. Upon chilling, the extracts deposited crystalline precipitates, which were combined. This material was extracted with dilute hydrochloric acid. Neutralisation of the acid solution yielded a light grey solid, which was recrystallised several times from ethanol containing a little methyl Cellosolve (Registered Trade Mark), followed by crystallisation from an acetone-water mixture (60:40 by volume). There was thus produced 2 - amino - 4 - hydroxy - 5 - (3',5' - dimethoxy - 4' - hydroxybenzyl)pyrimidine as a hydrate which sintered and became frothy at 150°C. This was then methylated with methyl iodide, using the procedure of Example 1, to produce 2 - amino - 4 - hydroxy - 5 - (3',4',5' - trimethoxybenzyl)pyrimidine, which was then chlorinated and aminated according to the procedure described by B. Roth, E. A. Falco, G. H. Hitchings and S. R. M. Bushby (*J. Med. Pharm. Chem.*, 5, 1103 (1962)) to produce 2,4 - diamino - 5 - (3',4',5' - trimethoxybenzyl)pyrimidine. This melted at 197—199°C, and was otherwise identical with the product of Example 1.

EXAMPLE 3

Preparation of 5 - (3',5' - dimethoxy - 4' - hydroxybenzyl)uracil

A mixture of uracil (22.4 g.), 2,6 - dimethoxy - 4 - dimethylaminomethylphenol hydrochloride (49.5 g.), sodium methylate (11.9 g.) and ethylene glycol (300 ml.) was heated at 150°C for 4 hours under nitrogen. Most of the solvent was removed under vacuum. The residue was taken up in ethanol, neutralised with concentrated hydrochloric acid, and poured into an excess of diethyl ether. The resultant off-white precipitate was isolated and purified by recrystallisation from methyl cellosolve. There was thus obtained 5 - (3',5' - dimethoxy - 4' - hydroxybenzyl)uracil, which melted at 241—242°C dec.

EXAMPLE 4

Preparation of 2,4,6 - triamino - 5 - (3',5' - dimethoxy - 4' - hydroxybenzyl)pyrimidine

A mixture of 2,4,6 - triaminopyrimidine (2.5 g.), 2,6 - dimethoxy - 4 - dimethylaminomethylphenol hydrochloride (4.95 g.) sodium methylate (1.1 g.) and ethylene glycol (70 ml.) was heated for two hours under nitrogen in an oil bath at 150°C. During this time, more than 92% of the theoretical amount of dimethylamine was evolved. A white precipitate formed in the solution. After chilling, the precipitate was isolated and washed well with water. It was then recrystallised from dimethylformamide, followed by conversion to the hydrochloride by adding an equivalent amount of concentrated hydrochloric acid to an ethanol solution thereof, followed by the addition of a little diethyl ether. After re-

- crystallisation from an ethyl cellosolve-diethyl ether mixture, the white product, 2,4,6 - tri-amino - 5 - (3',5' - dimethoxy - 4' - hydroxybenzyl)pyrimidine hydrochloride, decomposed between 287—289°C.

EXAMPLE 5

- Preparation of 2,4 - diamino - 6 - piperidino - 5 - (3',5' - dimethoxy - 4' - hydroxybenzyl)pyrimidine
- 2,4 - Diamino - 6 - piperidinopyrimidine was treated in the manner described in Example 4 to produce 2,4 - diamino - 6 - piperidino - 5 - (3',5' - dimethoxy - 4' - hydroxybenzyl)pyrimidine.

EXAMPLE 6

- Preparation of 5 - (3',5' - dimethoxy - 4' - hydroxybenzyl) - 6 - methyluracil
- 6-Methyluracil was treated in the manner described in Example 3, to produce 5 - (3',5' - dimethoxy - 4' - hydroxybenzyl) - 6 - methyluracil.

EXAMPLE 7

- Preparation of 2,4 - diamino - 5 - (3',5' - dimethoxy - 4' - hydroxybenzyl) - 6 - hydroxypyrimidine
- 2,4 - Diamino - 6 - hydroxypyrimidine was treated in the manner of Example 4, to produce 2,4 - diamino - 5 - (3',5' - dimethoxy - 4' - hydroxybenzyl) - 6 - hydroxypyrimidine.

EXAMPLE 8

Tablet

- A mixture of 2,4 - diamino - 5 - (3',5' - dimethoxy - 4' - hydroxybenzyl)pyrimidine (50 mg.), lactose B.P. (100 mg.), starch B.P. (20 mg.), polyvinylpyrrolidone (2 mg.) and magnesium stearate B.P. (3 mg.) was made into a tablet by a process of moist granulation and compression.

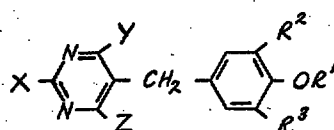
EXAMPLE 9

Topical Preparation

- 2,4 - Diamino - 5 - (3',5' - dimethoxy - 4' - hydroxybenzyl)pyrimidine was incorporated into white soft paraffin so that the former constituted 2% by weight of the mixture. A sterile preparation of this formula is suitable for ophthalmic use.

WHAT WE CLAIM IS:—

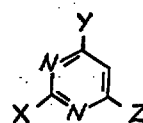
1. A method of preparing a compound of the formula (I)



(I)

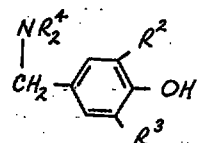
wherein X and Y are the same or different and each is an amino group or a hydroxyl group, Z is a hydrogen atom, an alkyl group

containing not more than 4 carbon atoms, a hydroxyl group, or a substituted or unsubstituted amino group, the said substituted amino group including a cyclic amino group R¹ is a hydrogen atom or a saturated or unsaturated hydrocarbon radical which may be optionally substituted by halogen, and R² and R³ are the same or different and each is a hydrogen atom or a halogen atom or an alkyl group or an alkoxy group, the said alkyl and alkoxy groups each containing not more than 4 carbon atoms, which method comprises reacting a compound of the formula (IV)



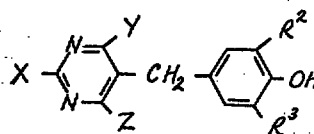
(IV)

wherein X, Y and Z are defined as above, with a Mannich base of the formula (II)



(II)

wherein R² and R³ are defined as above and NR₂' is a dialkylamino or a cyclic amino group, to produce a compound of formula (III)



(III)

wherein X, Y, Z, R² and R³ are defined as above, which compound may optionally be reacted with a compound R¹Q, where Q is a reactive atom or group and R¹ is a saturated or unsaturated hydrocarbon radical which may be optionally substituted by halogen, under basic conditions to produce a compound of formula (I).

2. A method according to claim 1 wherein X and Y are each primary amino groups, Z is a hydrogen atom, and R¹ is a saturated or unsaturated hydrocarbon radical containing not more than 4 carbon atoms.

3. A method according to claim 1 wherein Z is a hydrogen atom, R¹ is a methyl group and R² and R³ are each methoxy groups.

4. A method according to any of the

crystallisation from an ethyl cellosolve-diethyl ether mixture, the white product, 2,4,6 - tri-amino - 5 - (3',5' - dimethoxy - 4' - hydroxybenzyl)pyrimidine hydrochloride, decomposed between 287—289°C.

EXAMPLE 5

Preparation of 2,4 - diamino - 6 - piperidino - 5 - (3',5' - dimethoxy - 4' - hydroxybenzyl)pyrimidine

2,4 - Diamino - 6 - piperidinopyrimidine was treated in the manner described in Example 4 to produce 2,4 - diamino - 6 - piperidino - 5 - (3',5' - dimethoxy - 4' - hydroxybenzyl)pyrimidine.

EXAMPLE 6

Preparation of 5 - (3',5' - dimethoxy - 4' - hydroxybenzyl) - 6 - methyluracil

6-Methyluracil was treated in the manner described in Example 3, to produce 5 - (3',5' - dimethoxy - 4' - hydroxybenzyl) - 6 - methyluracil.

EXAMPLE 7

Preparation of 2,4 - diamino - 5 - (3',5' - dimethoxy - 4' - hydroxybenzyl) - 6 - hydroxypyrimidine

2,4 - Diamino - 6 - hydroxypyrimidine was treated in the manner of Example 4, to produce 2,4 - diamino - 5 - (3',5' - dimethoxy - 4' - hydroxybenzyl) - 6 - hydroxypyrimidine.

EXAMPLE 8

Tablet

A mixture of 2,4 - diamino - 5 - (3',5' - dimethoxy - 4' - hydroxybenzyl)pyrimidine (50 mg.), lactose B.P. (100 mg.), starch B.P. (20 mg.), polyvinylpyrrolidone (2 mg.) and magnesium stearate B.P. (3 mg.) was made into a tablet by a process of moist granulation and compression.

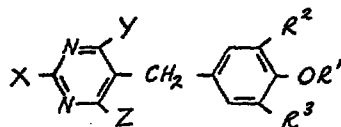
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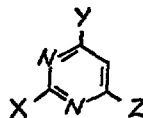
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(I)

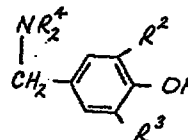
wherein X and Y are the same or different and each is an amino group or a hydroxyl group, Z is a hydrogen atom, an alkyl group

containing not more than 4 carbon atoms, a hydroxyl group, or a substituted or unsubstituted amino group, the said substituted amino group including a cyclic amino group. R¹ is a hydrogen atom or a saturated or unsaturated hydrocarbon radical which may be optionally substituted by halogen, and R² and R³ are the same or different and each is a hydrogen atom or a halogen atom or an alkyl group or an alkoxy group, the said alkyl and alkoxy groups each containing not more than 4 carbon atoms, which method comprises reacting a compound of the formula (IV)



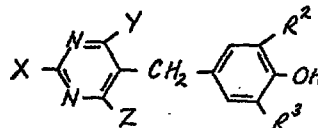
(IV)

wherein X, Y and Z are defined as above, with a Mannich base of the formula (II)



(II)

wherein R² and R³ are defined as above and NR₂⁴ is a dialkylamino or a cyclic amino group, to produce a compound of formula (III)



(III)

wherein X, Y, Z, R² and R³ are defined as above, which compound may optionally be reacted with a compound R¹Q, where Q is a reactive atom or group and R¹ is a saturated or unsaturated hydrocarbon radical which may be optionally substituted by halogen, under basic conditions to produce a compound of formula (I).

2. A method according to claim 1 wherein X and Y are each primary amino groups, Z is a hydrogen atom, and R¹ is a saturated or unsaturated hydrocarbon radical containing not more than 4 carbon atoms.

3. A method according to claim 1 wherein Z is a hydrogen atom, R¹ is a methyl group and R² and R³ are each methoxy groups.

4. A method according to any of the

