1,005,736

PATENT SPECIFICATION

NO DRAWINGS

1,005,736

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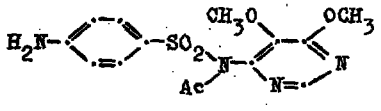
COMPLETE SPECIFICATION

Novel Sulphanilamido Pyrimidines and a process for the manufacture thereof

We, F. HOFFMANN-LA ROCHE & Co., Aktiengesellschaft, a Swiss Company, of 124—184 Grenzacherstrasse, Basle, Switzerland, 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:—

The present invention is concerned with novel sulphanilamido-pyrimidines, namely 4-(N^1 - acyl - sulphanilamido) - 5,6 - dimethoxy pyrimidines, and with a process for the manufacture thereof.

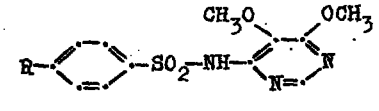
The novel sulphanilamido-pyrimidines of the invention have the formula:



wherein Ac represents an acyl residue [for example, the acyl residue of a straight or branched chain saturated or unsaturated aliphatic carboxylic acid having from one to eighteen carbon atoms (such as formic acid, acetic acid, propionic acid, butyric acid, lauric acid, palmitic acid, stearic acid, oleic acid), an aromatic carboxylic acid (such as benzoic acid) or an araliphatic carboxylic acid (such as a lower phenyl-alkanoic acid; phenyl-acetic acid for instance)]. They, especially the N^1-acetyl compound, are characterized by high antibacterial activity. Additionally, they possess a surprising advantage over the corresponding non-acylated compounds for *per os* applications (e.g. in the form of tablets or syrups). In particular, it has been discovered that they have much better taste characteristics. An additional surprising advantage over the corresponding non-acylated compounds is their significantly higher residence time in the organism.

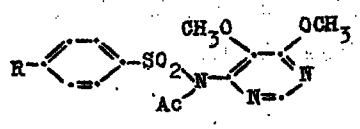
The compounds of this invention may be used as medicaments in the form of pharmaceutical preparations which contain them in admixture with a pharmaceutical organic or inorganic, solid or liquid carrier suitable for enteral (e.g. oral) or parenteral administration. For making up the preparations there may be employed substances which do not react with the compounds, such as water, gelatine, lactose, starches, magnesium stearate, talc, vegetable oils, gums, polyalkylene glycols, petroleum jelly or any other known compatible carrier used for the preparation of medicaments. The preparations may be in solid form (for example, as tablets, dragées, suppositories or capsules) or in liquid form (for example, as solutions, emulsions or suspensions). If desired, they may be sterilized and/or contain auxiliary substances, such as preserving agents, stabilizing agents, wetting or emulsifying agents, salts for varying the osmotic pressure or buffers. They may also contain other therapeutically useful substances.

The process of the invention is carried out by reacting a compound of the formula



wherein R is the nitro group or an arylazo, acylamino, alkoxycarbonylamino or aralkoxycarbonylamino group or a group of the formula —N=CH—R^1 in which R^1 signifies the phenyl group or an alkyl-substituted or alkoxy-substituted phenyl group with an acylating agent

(e.g. an acid halide, preferably the bromide or chloride, or with an acid anhydride) to form an N^1-acylated compound of the formula



wherein R and Ac have the same meanings as hitherto, and converting the R group therein into an amino group by reduction or hydrolysis as the case may require.

As will be evident from the foregoing, the R-groups are those which are convertible into an amino group by reduction or hydrolysis; that is to say, nitro, arylazo (e.g. phenylazo), groups of the general formula —N=CH—R^1 wherein R^1 signifies the phenyl group or an alkyl-substituted or alkoxy substituted phenyl group (e.g. the benzylideneamino group), an acylamino group (e.g. groups containing the aforementioned Ac group), an alkoxycarbonylamino or aralkoxycarbonylamino group (e.g. the ethoxycarbonylamino or benzyloxycarbonylamino group). In general, the preferred R-groups are those which can be reductively converted into the amino group (such as the nitro, phenyl-azo or benzylidene-amino group) since the N^1-acyl group remains intact. When using starting materials with a hydrolyzable R-group the R-group should be chosen such that it can be hydrolyzed with sufficient selectivity; that is to say, without simultaneous splitting off of the N^1-acyl group. One particularly suitable R-group in this respect is the benzylidene-amino group. As has been found, this group can be smoothly saponified to the amino group by gentle heating in aqueous-alcoholic medium without the N^1-acyl group also being split off.

For the reduction of R-groups which are convertible into the amino group in a reductive manner, catalytically activated hydrogen is particularly suitable. As catalysts there can be used, for example, noble metal catalysts such as palladium.

The treatment of the starting compound with the acylating agent can be effected in accordance with known methods for acylating amino groups. Usually, the reaction is undertaken in the presence of acid-binding agents such as inorganic or organic bases (especially tertiary amines such as pyridine, etc.). By using acyl halides as the acylating agents, the metal salts (such as the alkali-metal salts or, preferably, the silver salt) of the starting compound can be employed. Moreover, the reaction can be undertaken either with or without the use of organic solvents or diluents (such as dioxane, benzene, acetone etc.).

The intermediate N^1-acylated compounds of the third formula hereinbefore and that step of the present process leading thereto are claimed in the specification of our copending Application for Letters Patent No. 13175/65 (now Serial No. 1,005,737).

The following Examples are illustrative of the process:

EXAMPLE 1

A) *The preparation of the starting material.*

The 4 - (4^1 - nitro - benzenesulphonamido)-5,6 - dimethoxy - pyrimidine used as the starting material can be obtained either by reacting 4 - amino - 5,6 - dimethoxy - pyrimidine with 2 molar equivalents of *p* - nitro-benzenesulphonyl chloride and hydrolysing the resulting 4 - (bis 4^1 - nitro - benzenesulphonamido) - 5,6 - dimethoxy - pyrimidine or by reacting 4,6 - dichloro - 5 - methoxy - pyrimidine with 2 molar equivalent of sodium *p*-nitro-benzenesulphonamide and treating the resulting 4 - (4^1 - nitro - benzenesulphonamido) - 5 - methoxy - 6 - chloro - pyrimidine with sodium methylate.

B) *The Process.*

a) 33 g of 4 - (4^1 - nitro - benzenesulphonamido) - 5,6 - dimethoxy - pyrimidine are heated on a steam-bath for 3 hours in 70 ml of absolute pyridine with 33 ml of acetic acid anhydride. The solution is then evaporated under reduced pressure, the residue treated with ethanol and the crystalline portion filtered with suction. The so-obtained 4-(N^1-acetyl - 4^1 - nitro - benzenesulphonamido)-5,6 - dimethoxy - pyrimidine melts at 160°—161°C after recrystallization from acetonitrile. Yield: 94% of theory.

b) 13 g of the foregoing N^1-acetyl compound are hydrogenated at room temperature and atmospheric pressure in 450 ml of glacial acetic using 13 g of palladium/carbon (5% palladium) as catalyst. The calculated amount of hydrogen is taken up within 2 hours. After filtration, the solution is evaporated under reduced pressure, the residue treated with absolute alcohol and, after crystallization is complete, the 4 - (N^1 - acetyl - sulphanilamido)-5,6 - dimethoxy - pyrimidine obtained is filtered with suction. The yield is practically quantitative. Melting point: 201°—203°C (from acetonitrile).

EXAMPLE 2

A) *The preparation of the starting material.*

The 4^1 - benzylideneamino compound used as the starting material can be obtained as follows: 124 g of 4-sulphanilamido-5,6-dimethoxy-pyrimidine are treated in 480 ml of absolute ethanol at 30°C with 120 ml of benzaldehyde. The mixture is heated up to 60°C in the course of one hour, treated with 250 ml of benzene and subsequently boiled at reflux for 20 minutes. The solution, which is cooled down somewhat, is evaporated under reduced pressure and the residue brought to crystallization with 100 ml of absolute ethanol. There

are thus obtained 153 g (96% of theory) of 4 - (4^1 - benzylideneamino - benzenesulphonamido) - 5,6 - dimethoxy - pyrimidine of melting point 179°—181°C.

B) *The process*

a) 153 g of 4 - (4^1 - benzylideneamino-benzenesulphonamido) - 5,6 - dimethoxy - pyrimidine are heated at 55°C for 0.25 hours while stirring in 300 ml of absolute pyridine with 180 ml of acetic acid anhydride. At 55°C (bath temperature) ca 360—370 ml of the solvent are distilled off under reduced pressure. The residue is treated with 200 ml of absolute ethanol with ice-cooling and stirring. The mixture is stirred for 0.5 hours at 20°—25°C and for 1 hour at 5°C. Thereafter, the crystalline portion is filtered with suction. There are obtained 157 g (92% of theory) of 4-(N^1-acetyl-4^1-benzylideneamino-benzenesulphonamido) - 5,6 - dimethoxy - pyrimidine of melting point 145—146°C.

b) 1200 ml of 80% ethanol are heated to 55°C and, in the course of 0.25 hours 157 g of the N^1-acetyl compound obtained as described in a) are introduced. After all has dissolved at 75°C, the solution is boiled at reflux for a further 10 minutes. After cooling the solution to 5°C and allowing it to stand (1.5 hours), the 4 - (N^1 - acetyl - sulphanilamido) - 5,6 - dimethoxy - pyrimidine obtained is filtered with suction. Melting point: 201°—203°C. Yield 97%.

The benzylidene residue can also be split off as follows: 10 g of 4 - (N^1 - acetyl - 4^1-benzylideneamino - benzenesulphonamido)-5,6-dimethoxy-pyrimidine are dissolved in 800 ml of methanol and hydrogenated in the presence of 5 g of palladium/carbon (5%) as catalyst at room temperature and atmospheric pressure. The theoretical amount of hydrogen is taken up after 2 hours. The resulting mixture is filtered from the catalyst, the filtrate evaporated under reduced pressure to a volume of *ca* 30 ml and the crystalline portion obtained is filtered with suction. There are thus obtained 6 g of 4 - (N^1 - acetyl - sulphanilamido) - 5,6-dimethoxy - pyrimidine of melting point 201°—203°C.

Tablets and suspensions containing 4-(N^1-acetyl - sulphanilamido) - 5,6 - dimethoxy - pyrimidine may be prepared with the following compositions:

(a) *Tablets*:

Active substance	500 mg
Lactose	35 mg
Gelatine	3 mg
Corn starch	40 mg
Talc	20 mg
Magnesium stearate	2 mg
Total weight	600 mg

(b) *Suspension for injection*:

Active substance	400 mg
Polyvinyl-pyrrolidone	200 mg
Sodium phosphate $2H_2O$ primary	1.45 mg
Sodium phosphate anhydrous secondary	1.00 mg
Methyl *p*-hydroxy-benzoate/ propyl p-hydroxy-benzoate	1.00 ml
Redistilled water *ad*	1.00 ml

WHAT WE CLAIM IS:—

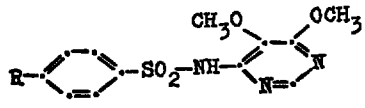
1) 4 - (N^1 - acyl - sulphanilamido) - 5,6-dimethoxy-pyrimidines.

2) Pyrimidines as set forth in claim 1, wherein the acyl residue is derived from a straight or branched chain saturated or unsaturated aliphatic carboxylic acid having from one to eighteen carbon atoms or from an aromatic or araliphatic carboxylic acid.

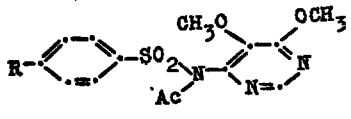
3) 4 - (N^1 - acetyl - sulphanilamido) - 5,6-dimethoxy-pyrimidine.

4) A pharmaceutical preparation comprising a compound as claimed in claim 1 in admixture with a compatible pharmaceutical carrier.

5) A process for the manufacture of the compounds claimed in claim 1, which process comprises reacting a compound of the formula



wherein R is the nitro group or an arylazo, acylamino, alkoxycarbonylamino or aralkoxycarbonylamino group or a group of the formula —N=CH—R^1 in which R^1 is the phenyl group or an alkyl-substituted or alkoxy-substituted phenyl group, with an acylating agent to form an N^1-acylated compound of the formula



wherein R has the same meaning as given earlier in this claim and Ac represents an acyl residue, and converting the R group therein into an amino group by reduction or hydrolysis as the case may require.

6) A process in accordance with claim 5, wherein an acetylating agent is used as the acylating agent.

7) A process in accordance with claim 5 or claim 6, wherein the R-group in the starting material is the nitro or benzylideneamino group.

8) A process for the manufacture of the

are thus obtained 153 g (96% of theory) of 4 - (4^1 - benzylideneamino - benzenesulphonamido) - 5,6 - dimethoxy - pyrimidine of melting point 179°—181°C.

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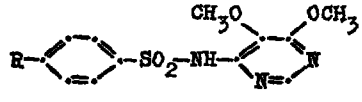
1) 4 - (N^1 - acyl - sulphanilamido) - 5,6-dimethoxy-pyrimidines.

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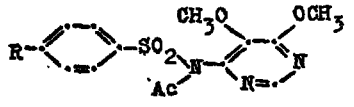
3) 4 - (N^1 - acetyl - sulphanilamido) - 5,6-dimethoxy-pyrimidine.

4) A pharmaceutical preparation comprising a compound as claimed in claim 1 in admixture with a compatible pharmaceutical carrier.

5) A process for the manufacture of the compounds claimed in claim 1, which process comprises reacting a compound of the formula



wherein R is the nitro group or an arylazo, acylamino, alkoxycarbonylamino or aralkoxycarbonylamino group or a group of the formula —N=CH—R^1 in which R^1 is the phenyl group or an alkyl-substituted or alkoxy-substituted phenyl group, with an acylating agent to form an N^1-acylated compound of the formula



wherein R has the same meaning as given earlier in this claim and Ac represents an acyl residue, and converting the R group therein into an amino group by reduction or hydrolysis as the case may require.

6) A process in accordance with claim 5, wherein an acetylating agent is used as the acylating agent.

7) A process in accordance with claim 5 or claim 6, wherein the R-group in the starting material is the nitro or benzylideneamino group.

8) A process for the manufacture of the

* C L M S *

compounds in claim 1, substantially as described with reference to the Examples.

9) Compounds as claimed in claim 1, when manufactured by the process claimed in any one of claims 5 to 8 inclusive.

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