1,005,737

PATENT SPECIFICATION

NO DRAWINGS

1,005,737

Date of Application and filing Complete Specification: Jan. 31, 1964.
No. 13175/65.
Application made in Switzerland (No. 1585) on Feb. 8, 1963.
(Divided out of No. 1,005,736.)
Complete Specification Published: Sept. 29, 1965.
© Crown Copyright 1965.

Index at acceptance:—C2 C(2D43B, 2D43F, 2D43G, 2D43H, 2D43J, 2D43S4, 2D43Z1)
Int. Cl.:—C 07 d

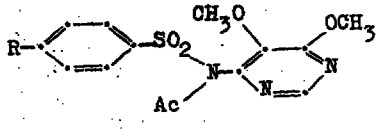
COMPLETE SPECIFICATION

Novel Pyrimidine Derivatives and a process for the preparation 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:—

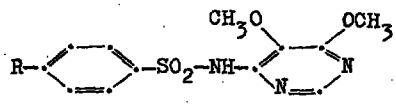
The present invention is concerned with novel pyrimidine derivatives and a process for the preparation thereof.

The novel derivatives provided by the invention are compounds of the general formula



wherein R represents 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 and 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 are useful in that they can be readily converted by hydrolysis or reduction into the sulphanilamido-pyrimidines which form the subject of our copending application for Letters Patent No. 4126/64 (now serial No. 1,005,736).

According to the process provided by the invention, the novel derivatives aforesaid are prepared by reacting a compound of the formula



, wherein R has the significance given earlier, with an acylating agent (e.g. with an acid halide, preferably the bromide or chloride, or with an acid anhydride).

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 alkoxycarbonyl-amino or aralkoxycarbonylamino group (e.g. the ethoxycarbonylamino or benzyloxy-carbonylamino 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 is preferably 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 groups also being split off.

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

[Price 4s. 6d.]

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 following Examples are illustrative of the process provided by the invention:

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 equivalents 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.

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.

EXAMPLE 2.

A) The preparation of the starting material.

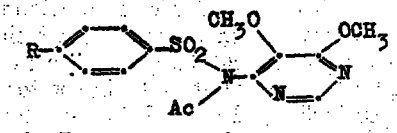
The 4^1-benzylideneamino compound used as the starting material can be obtained as follows: 124 g of 4 - sulphanilamido - 5,6-dimethoxy - pyrimidine are treated in 480 ml of absolute ethanol and 30°C with 120 ml of benzaldehyde. The mixture is heated up to 60°C in the course of one hour, treated with 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.

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.

WHAT WE CLAIM IS:—

1) Compounds of the formula



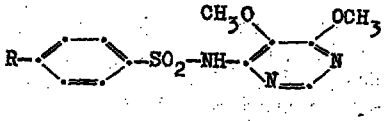
wherein R represents the nitro group or an arylazo, acylamino, alkoxycarbonylamino or aralkoxycarbonylamino group or a group of the formula —N=CH—R^1 in which R^1 signifies the phenyl group or an alkyl-substituted or alkoxyl-substituted phenyl group and Ac represents an acyl residue.

2) Compounds as formulated in claim 1, wherein Ac represents an acyl residue 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 - 4^1 - nitro - benezenesulphonamido) - 5,6 - dimethoxy - pyrimidine.

4) 4 - (N^1 - acetyl - 4^1 - benzylideneamino-benzenesulphonamido) - 5,6 - dimethoxy-pyrimidine.

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



, wherein R has the significance given in claim 1, with an acylating agent.

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

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

8) A process for the preparation of the

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 following Examples are illustrative of the process provided by the invention:

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 equivalents 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.

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.

EXAMPLE 2.

A) The preparation of the starting material.

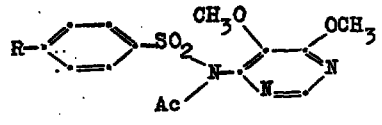
The 4^1-benzylideneamino compound used as the starting material can be obtained as follows: 124 g of 4 - sulphanilamido - 5,6-dimethoxy - pyrimidine are treated in 480 ml of absolute ethanol and 30°C with 120 ml of benzaldehyde. The mixture is heated up to 60°C in the course of one hour, treated with 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.

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.

WHAT WE CLAIM IS:—

1) Compounds of the formula



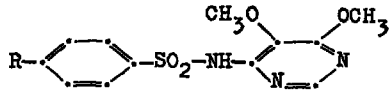
wherein R represents the nitro group or an arylazo, acylamino, alkoxycarbonylamino or aralkoxycarbonylamino group or a group of the formula —N=CH—R^1 in which R^1 signifies the phenyl group or an alkyl-substituted or alkoxyl-substituted phenyl group and Ac represents an acyl residue.

2) Compounds as formulated in claim 1, wherein Ac represents an acyl residue 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 - 4^1 - nitro - benezenesulphonamido) - 5,6 - dimethoxy - pyrimidine.

4) 4 - (N^1 - acetyl - 4^1 - benzylideneamino-benzenesulphonamido) - 5,6 - dimethoxy-pyrimidine.

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



, wherein R has the significance given in claim 1, with an acylating agent.

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

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

8) A process for the preparation of the

* C L M S *

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

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

W. D. WHITAKER,
Patent Agent,
for F. Hoffmann-La Roche & Co.,
Aktiengesellschaft.

Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press (Leamington) Ltd.—1965. Published by The Patent Office, 25 Southampton Buildings, London, W.C.2, from which copies may be obtained.

