

PATENT SPECIFICATION

NO DRAWINGS

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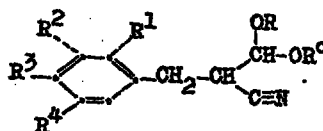
COMPLETE SPECIFICATION

Novel Acetals and a Process for the Manufacture and Conversion 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 acetals and a process for the manufacture thereof. The invention is also concerned with the conversion of these novel acetals into valuable pyrimidine derivatives.

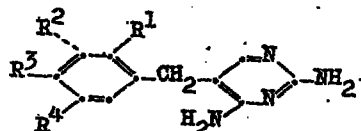
The novel acetals provided by the invention may be formulated thus:



(I)

wherein R¹ represents a chlorine atom or the methyl or methoxy group, R² represents a chlorine atom or the methoxy group, R³ and R⁴ each represent a lower-alkoxy group and R and R⁰ each represent a lower-alkyl group and wherein the broken lines denote that the substituents attached thereby are optional.

The novel acetals of formula I hereinbefore are useful in that they can be converted in a manner to be described hereinafter into pyrimidine derivatives of the general formula



(II)

wherein R¹, R², R³, R⁴ and the broken lines have the significance given earlier, which, in turn, are useful as antibacterial agents (particularly for topical application). The pyrimidine derivatives are also useful as antibacterial agents in combination with the antibacterial sulphonamides (e.g. sulphisoxazole, sulphamethoxazole, sulphadimethoxine and sulphaquinoxaline). For example, a typical adult dose of a combination of sulphisoxazole and a pyrimidine derivative of formula II for oral administration is

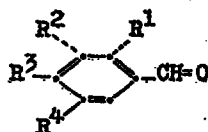
[Price 4s. 6d.] Price 25p

SEE DRAWING ATTACHED

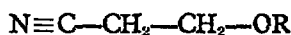
0.5 g of sulphisoxazole and 100 mg of a pyrimidine derivative of formula II in a unit dosage form (e.g. a tablet, capsule, aqueous suspension or troché) compounded with the usual pharmaceutical excipients. One especially useful class of pyrimidine derivatives of formula II comprises those in which R¹ (when present) represents the methyl group.

The most interesting novel acetals provided by the invention are those in which R¹, R³ and R⁴ each represent a methoxy group and R² is absent, those in which R¹ is absent and R², R³ and R⁴ each represent a methoxy group, those in which R¹ and R² are both absent and R³ and R⁴ each represent the methoxy group and those in which R¹ represents the methyl group, R² is absent and R³ and R⁴ each represent the methoxy group.

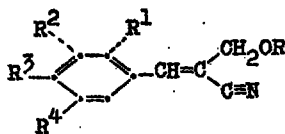
According to the process provided by the invention, the novel acetals provided by the invention are manufactured by reacting an aldehyde of the formula



(wherein R¹, R², R³, R⁴ and the broken lines have the significance given earlier) with a β -(lower alkoxy)-propionitrile of the formula



(wherein R represents a lower-alkyl group) in the presence of an alkali-metal lower-alkoxide and a lower-alkanol of the formula R⁰-OH (wherein R⁰ represents a lower-alkyl group) and treating the resulting compound of the general formula



(wherein R, R¹, R², R³, R⁴ and the broken lines have the significance given earlier) with a lower-alkanol of the formula R⁰-OH (wherein R⁰ has the significance given earlier) in the presence of an alkali-metal lower-alkoxide under substantially anhydrous conditions.

The aldehydes of formula III are in the main known compounds. Those aldehydes which may be novel can readily be prepared by known techniques; for example, by the VILSMEYER reaction [Methoden der Organischen Chemie, HOUBEN WEYL, 1954 volume Sauerstoffverbindungen II, Teil. 1, p. 29] or by the ROSENMUND method [Organic Syntheses, I.C., p. 1332]. The most interesting aldehyde starting materials of formula III are 2,4,5-trimethoxy-benzaldehyde, 3,4,5-trimethoxy-benzaldehyde, 3,4 - dimethoxy - benzaldehyde and 2 - methyl - 4,5 - dimethoxy - benzaldehyde.

The reaction of an aldehyde of formula III with a β -(lower alkoxy)-propionitrile of formula IV is carried out in the presence of an alkali-metal lower-alkoxide (e.g. sodium methoxide or potassium ethoxide) and a lower-alkanol of the formula R⁰-OH (e.g. methanol, ethanol or propanol). It is preferred to use sodium methoxide as the alkali-metal lower-alkoxide and methanol as the lower-alkanol. The temperature at which the reaction is carried out is not critical, but is generally within the range of from 60°C to 140°C. The reaction product obtained is a compound of formula V.

The compounds of formula V are readily converted into the acetals of formula I by treatment with a lower-alkanol R⁰OH in the presence of an alkali-metal lower-alkoxide under substantially anhydrous conditions. The temperature at which this treatment is carried out is not critical and temperatures within the range of from 60°C to 140°C are also suitable here.

According to a further and additional step of the foregoing process, the novel acetals obtained thereby are converted into the pyrimidine derivatives of formula II hereinbefore by reaction with guanidine.

The reaction of a novel acetal of formula I with guanidine gives a pyrimidine derivative of formula II in almost quantitative yield.

The process and conversion provided by the present invention is of considerable significance since the yields of pyrimidine derivatives of formula II are surprisingly higher than those obtained according to known processes (for example, the processes described in United Kingdom Patent Specification no: 957,797).

Two of the pyrimidine derivatives of formula II hereinbefore, namely 2,4-diamino - 5 - (2,4,5 - trimethoxy - benzyl) - pyrimidine and 2,4 - diamino - 5 - (4,5 - dimethoxy - 2 - methyl - benzyl) - pyrimidine, are claimed *per se* in the specification of our copending Application for Letters Patent No. 58794/67 (now serial no: 1,132,086).

The following Examples illustrate the process and conversion provided by the invention.

EXAMPLE 1

A) The process:

6 g (0.26 mol) of sodium were dissolved with stirring and heating at reflux in 309 ml of methanol. 47.5 g (0.55 mol) of β -methoxy-propionitrile and 98 g (0.5 mol) of 3,4,5-trimethoxy-benzaldehyde were added and the mixture was heated at gentle reflux for 4 hours. The mixture was then chilled and 150 ml of water were added. The product crystallized rapidly. Crystallization was allowed to proceed at 5°—10°C with stirring for 1 hour. The product was filtered by suction and washed on the filter with 200 ml of 60% ice-cold methanol. The crude material was air-dried and used for further steps without purification. It melted at 78°—80°C. A pure sample recrystallized from methanol melted at 82°C. The yield of 3,4,5-trimethoxy-2'-methoxymethyl-cinnamionitrile was 92 g, corresponding to 70% of the theory.

19 g (0.83 mol) of sodium were dissolved in 300 ml of methanol. 106 g of 3,4,5 - trimethoxy - 2' - methoxymethyl - cinnamionitrile were added and the mixture was heated at gentle reflux for 24 hours. The solution (which had turned brown) was poured into 1 litre of water and the precipitated oil extracted repeatedly with benzene. The combined benzene layers (500—700 ml) were washed three times with 500 ml of water, the benzene was removed by evaporation in a vacuum on a water bath and the brown residual oil distilled *in vacuo* (boiling point 215°—225°C/11 mm). The clear, viscous oil consisting of 3,4,5 - trimethoxy - 2' - cyano - 2',3' - dihydro - cinnamaldehyde dimethyl acetal weighed 83 g (71% of the theory); $n_D^{25}=1.5230$. It solidified upon standing. A sample recrystallized from methanol melted at 69°—70°C and showed a large melting point depression when mixed with 3,4,5-trimethoxy-2' - methoxymethyl - cinnamionitrile; [$n_D^{25}=1.5190$ in its viscous oil form prior to crystallization setting in].

B) The conversion:

31.5 g (0.107 mol) of 3,4,5-trimethoxy-2'-cyano-2',3'-dihydro-cinnamaldehyde dimethyl acetal were heated at reflux for 2 hours with 200 ml of methanolic guanidine solution (containing 0.25 mol of guanidine). The methanol was completely distilled off while stirring the mixture, finally from a bath at 110°—120°C, until the residue solidified completely to a yellowish crystalline mass. After allowing to cool, it was slurried with 100 ml of water and collected by vacuum filtration and dried. The yield of 2,4-diamino - 5 - (3,4,5 - trimethoxy - benzyl) - pyrimidine amounted to 28 g (91% of the theory). The material showed the correct melting point of 199°—200°C but had, however, a yellowish discoloration.

20 g of the product were added with stirring to 30 ml of 3-N aqueous sulphuric acid at 60°C. The solution was chilled with stirring to 5°—10°C. The crystalline sulphate was collected by vacuum filtration and washed on the filter twice with 10 ml of cold 3-N aqueous sulphuric acid each time. From the filtrate there were recovered 1.3 g (6.5%) of discoloured material melting at 195°—196°C (which could be added to subsequent purification batches). The sulphate on the filter was dissolved in 200 ml of hot water, the solution charcoaled hot, filtered and the product precipitated from the clear colourless filtrate by the gradual addition under chilling of a solution of 20 g of sodium hydroxide in 40 ml of water. The precipitate was filtered by suction and washed thoroughly with water on the filter. 17.5 g (88%) of white material showed the correct melting point of 200°—201°C.

EXAMPLE 2

A) The process:

166 g (1 mol) of veratraldehyde, 95 g (1.1 mol) of β -methoxy-propionitrile and the methanolic sodium methylate solution obtained by dissolving 11 g of sodium in

400 ml of absolute methanol were heated at reflux with stirring for 4 hours. Upon chilling to 0°C and seeding, the solution crystallized. The crystals were filtered by suction and washed on the filter with 200 ml of ice-cold 60% methanol. The air-dried 3,4 - dimethoxy - 2' - methoxymethyl - cinnamionitrile weighed 147 g. By diluting the filtrate with water, benzene extraction and vacuum distillation (boiling point=190°—208°C/12 mm), a second crop of 35 g was recovered, raising the yield to 77.5%. A sample recrystallized from methanol for characterization and analysis melted at 75°C; $[n_D^{25}=1.5862$ in its viscous oil form prior to crystallisation setting in].

180 g (0.775 mol) of 3,4 - dimethoxy - 2' - methoxymethyl - cinnamionitrile and the methanolic sodium methylate solution obtained by dissolving 37 g (1.6 mol) of sodium in 600 ml of absolute methanol were heated at reflux with stirring for 24 hours. The brown solution was diluted with 1.5 litres of water and the precipitated oil extracted with 500 ml of benzene. The benzene layer was washed repeatedly with water containing a small amount of acetic acid and the benzene evaporated in a vacuum. The residue, 3,4 - dimethoxy - 2' - cyano - 2',3' - dihydro - cinnamaldehyde dimethyl acetal, distilled at 205°—210°C as a colourless oil, which solidified in the receiver upon standing. The yield of 152 g corresponded to 74.5% of the theory. A sample for characterization of the compound and analysis was recrystallized from methanol; melting point=50°—51°C; $[n_D^{25}=1.5235$ in its viscous oil form prior to crystallisation setting in]

B) The conversion:

26.5 g (0.1 mol) of 3,4-dimethoxy-2'-cyano-2',3'-dihydro-cinnamaldehyde dimethyl acetal were heated at reflux with 250 ml of 1-N methanolic guanidine solution for 2 hours and then the solvent was distilled off completely within 2 hours. The crystalline residue was slurried with 100 ml of water and washed on the filter with a little alcohol and ether. The yield of 24.5 g corresponded to 95.5% of the theory. The product, 2,4 - diamino - 5 - (3,4 - dimethoxy - benzyl) - pyrimidine, showed the correct melting point of 233°C.

EXAMPLE 3

A) The process:

90 g (0.5 mol) of 4,5 - dimethoxy - 2 - methyl - benzaldehyde, 50 g (0.59 mol) of β -methoxy-propionitrile and the methanolic sodium methylate solution obtained by dissolving 5.5 g of sodium in 150 ml of methanol were heated at reflux with stirring for 4 hours. The solution was poured into 1 litre of water and extracted with benzene. The benzene layer was washed with water, the solvent evaporated *in vacuo* on a water-bath and the residue distilled at 200°—208°C/12 mm. 4,5 - Dimethoxy - 2 - methyl - 2' - methoxymethyl - cinnamionitrile was obtained as a yellowish oil which solidified upon standing. The yield of 103 g corresponded to 83% of the theory. A sample recrystallized from methanol melted at 68°—69°C; $[n_D^{25}=1.5823$ in its viscous oil form prior to crystallisation setting in]. 283 g (1.145 mol) of 4,5 - dimethoxy - 2 - methyl - 2' - methoxymethyl - cinnamionitrile were heated at reflux for 24 hours with the methanolic sodium methylate solution obtained by dissolving 53 g of sodium (2.29 mol) in 800 ml of absolute methanol. The brown solution was poured into 1.5 litres of water and the precipitated oil extracted with benzene. The benzene layer was washed repeatedly with water containing a small amount of acetic acid. The benzene was evaporated in a vacuum on a water-bath and the residue distilled at 205°—211°C/12 mm. The colourless distillate solidified upon standing. The yield of 250 g of 4,5 - dimethoxy - 2 - methyl - 2' - cyano - 2',3' - dihydro - cinnamaldehyde dimethyl acetal corresponded to 78% of the theory. A sample recrystallized from methanol melted at 60°—61°C; $[n_D^{24}=1.5228$ in its viscous oil form prior to crystallisation setting in].

B) The conversion:

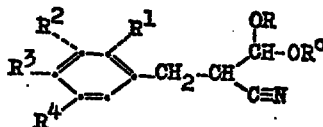
55 g (0.2 mol) of 4,5 - dimethoxy - 2 - methyl - 2' - cyano - 2',3' - dihydro - cinnamaldehyde dimethyl acetal were heated at reflux with 250 ml of a 1 molar methanolic guanidine solution for 2 hours and then the solvent was distilled off completely. The crystalline residue of 2,4-diamino-5-(4,5-dimethoxy-2-methylbenzyl)-pyrimidine was slurried with 100 ml of water, filtered by suction and washed with a little ice-cold alcohol and ether. The yield of 47 g corresponded to 86% of the theory. The material melted at 233°C. After recrystallization of 1 g of material from 30 ml of alcohol, the melting point remained unchanged.

The terms 'lower alkyl' and 'lower alkoxy' are used in the foregoing description

and in the claims appended hereto to mean straight- and branched-chain alkyl and alkoxy groups containing from 1 to 7 carbon atoms (e.g. methyl, ethyl, propyl, *iso*-propyl, butyl, hexyl, heptyl, methoxy, ethoxy, propoxy, *isopropoxy*, butoxy, hexyloxy, heptyloxy).

WHAT WE CLAIM IS:—

1. Acetals of the formula



wherein R¹ represents a chlorine atom or the methyl or methoxy group, R² represents a chlorine atom or the methoxy group, R³ and R⁴ each represent a lower-alkoxy group and R and R⁰ each represent a lower-alkyl group and wherein the broken lines denote that the substituents attached thereby are optional.

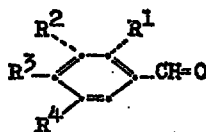
2. An acetal of the formula given in claim 1, wherein R¹, R³ and R⁴ each represent a methoxy group and R² is absent.

3. An acetal of the formula given in claim 1, wherein R¹ is absent and R², R³ and R⁴ each represent a methoxy group.

4. An acetal of the formula given in claim 1, wherein R¹ and R² are both absent and R³ and R⁴ each represent a methoxy group.

5. An acetal of the formula given in claim 1, wherein R¹ represents the methyl group, R² is absent and R³ and R⁴ each represent the methoxy group.

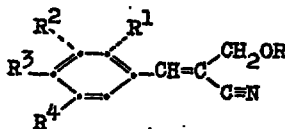
6. A process for the manufacture of the acetals claimed in claim 1, which process comprises reacting an aldehyde of the formula



(wherein R¹, R², R³, R⁴ and the broken lines have the significance given in claim 1) with a β-(lower alkoxy)-propionitrile of the formula



(wherein R represents a lower-alkyl group) in the presence of an alkalimetal lower-alkoxide and a lower-alkanol of the formula R⁰-OH (wherein R⁰ represents a lower-alkyl group) and treating the resulting compound of the general formula



(wherein R, R¹, R², R³, R⁴ and the broken lines have the significance given in claim 1) with a lower-alkanol of the formula R⁰-OH (wherein R⁰ has the significance given earlier in this claim) in the presence of an alkali-metal lower-alkoxide under substantially anhydrous conditions.

7. A process as set forth in claim 6, wherein 2,4,5-trimethoxy-benzaldehyde is used as the aldehyde starting material.

8. A process as set forth in claim 6, wherein 3,4,5-trimethoxy-benzaldehyde, 3,4-dimethoxy-benzaldehyde or 4,5-dimethoxy-2-methyl-benzaldehyde is used as the aldehyde starting material.

9. A process as set forth in claim 6, claim 7 or claim 8, wherein sodium methoxide is used as the alkali-metal lower-alkoxide and methanol is used as the lower-alkanol.

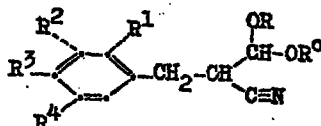


and in the claims appended hereto to mean straight- and branched-chain alkyl and alkoxy groups containing from 1 to 7 carbon atoms (e.g. methyl, ethyl, propyl, *iso*-propyl, butyl, hexyl, heptyl, methoxy, ethoxy, propoxy, *isopropoxy*, butoxy, hexyloxy, heptyloxy).

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WHAT WE CLAIM IS:—

1. Acetals of the formula



wherein R¹ represents a chlorine atom or the methyl or methoxy group, R² represents a chlorine atom or the methoxy group, R³ and R⁴ each represent a lower-alkoxy group and R and R⁰ each represent a lower-alkyl group and wherein the broken lines denote that the substituents attached thereby are optional.

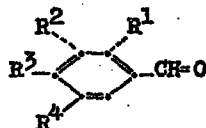
2. An acetal of the formula given in claim 1, wherein R¹, R³ and R⁴ each represent a methoxy group and R² is absent.

3. An acetal of the formula given in claim 1, wherein R¹ is absent and R², R³ and R⁴ each represent a methoxy group.

4. An acetal of the formula given in claim 1, wherein R¹ and R² are both absent and R³ and R⁴ each represent a methoxy group.

5. An acetal of the formula given in claim 1, wherein R¹ represents the methyl group, R² is absent and R³ and R⁴ each represent the methoxy group.

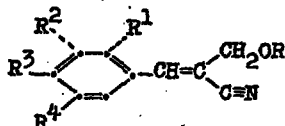
6. A process for the manufacture of the acetals claimed in claim 1, which process comprises reacting an aldehyde of the formula



(wherein R¹, R², R³, R⁴ and the broken lines have the significance given in claim 1) with a β-(lower alkoxy)-propionitrile of the formula



(wherein R represents a lower-alkyl group) in the presence of an alkalimetal lower-alkoxide and a lower-alkanol of the formula R⁰-OH (wherein R⁰ represents a lower-alkyl group) and treating the resulting compound of the general formula



(wherein R, R¹, R², R³, R⁴ and the broken lines have the significance given in claim 1) with a lower-alkanol of the formula R⁰-OH (wherein R⁰ has the significance given earlier in this claim) in the presence of an alkali-metal lower-alkoxide under substantially anhydrous conditions.

7. A process as set forth in claim 6, wherein 2,4,5-trimethoxy-benzaldehyde is used as the aldehyde starting material.

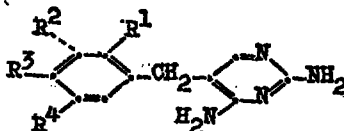
8. A process as set forth in claim 6, wherein 3,4,5-trimethoxy-benzaldehyde, 3,4-dimethoxy-benzaldehyde or 4,5-dimethoxy-2-methyl-benzaldehyde is used as the aldehyde starting material.

9. A process as set forth in claim 6, claim 7 or claim 8, wherein sodium methoxide is used as the alkali-metal lower-alkoxide and methanol is used as the lower-alkanol.

10. A process for the manufacture of the acetals formulated in claim 1, substantially as described with reference to part A of the Examples.

11. Acetals as claimed in claim 1, when manufactured by the process claimed in any one of claims 6 to 10 inclusive.

12. A process as set forth in any one of claims 6 to 10 inclusive which includes the further and additional step of converting the product of the process claimed in any one of said claims into a pyrimidine derivative of the general formula



wherein R^1 , R^2 , R^3 , R^4 and the broken lines have the significance given in claim 1, by reaction with guanidine.

13. A process for the manufacture of the pyrimidine derivatives formulated in claim 12, substantially as described with reference to part B of the Examples.

14. Pyrimidine derivatives as formulated in claim 12, when manufactured by the process claimed in claim 12 or claim 13.

W. D. WHITAKER,

Patent Agent,

for: F. HOFFMANN-LA ROCHE & Co.,

Aktiengesellschaft.

Reference has been directed in pursuance of Section 9, subsection (1) of the Patents Act, 1949, to patent Nos. 734,801; 875,562; 920,412 and 957,797.

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ERRATA

SPECIFICATION No. 1,133,766

Page 3, line 2, for "quantitive" read "quantitative"

Page 5, line 26, for "alkalimetal" read "alkali-metal"

THE PATENT OFFICE
1st January 1969

