

PATENT SPECIFICATION

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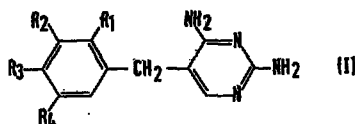
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(54) IMPROVEMENTS IN AND RELATING TO THE PRODUCTION OF BENZYL PYRIMIDINES

(71) We, PLANTEX LIMITED, of Ezor Hataasya Hehadash, Netanya, Israel, an Israeli Body Corporate, 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 relates to a process for the preparation of certain benzylpyrimidines of general formula (I) and to certain novel intermediates used in this process. These benzylpyrimidines have the general formula:



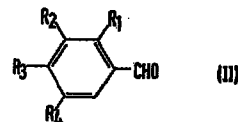
in which R₁ and R₂, which may be the same or different, are each a hydrogen or halogen atom or a lower alkyl or lower alkoxy group, and R₃ and R₄, which may be the same or different, are each a lower alkoxy group. Amongst the compounds of general formula (I) is 2,4 - diamino - 5 - (3',4',5' - trimethoxybenzyl)pyrimidine, which is commonly known as "trimethoprim". These compounds are antibacterial agents and are generally used in combination with antibacterial sulphonamides, such as sulphamethoxazole or sulphaminoxaline. The terms "lower alkyl" and "lower alkoxy" mean alkyl and alkoxy groups, respectively, having from 1 to 5 carbon atoms.

Various processes have been proposed for preparing these benzylpyrimidines, for example in U.K. specifications No. 875,562; No. 957,797; No. 1,128,224; No. 1,133,766; No. 1,142,654; No. 1,223,881; and No.

1,261,455, as well as German Offenlegungsschrift 2,003,578.

The present invention consists in a process for the preparation of benzylpyrimidines of general formula (I) (as hereinbefore defined), which comprises the steps:

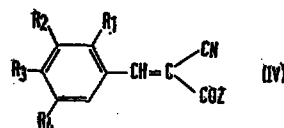
(a) reacting an aldehyde of general formula (II):



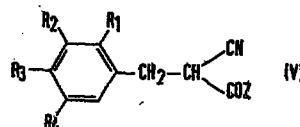
in the presence of a basic catalyst with a compound (a cyanoacetic acid or derivative thereof) of general formula (III):



in which Z is OH, OR or an unsubstituted or alkyl - substituted amino group (e.g. NH₂ or NHR), R being a lower alkyl group, to yield a compound of general formula (IV):



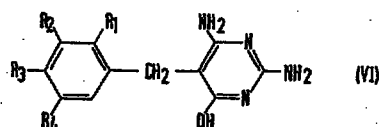
(b) catalytically hydrogenating said compound of general formula (IV) in an inert solvent to yield a compound of general formula (V):



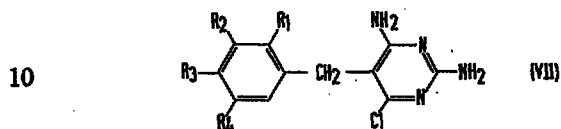
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(c) reacting said compound of general formula (V) with guanidine to yield a compound of general formula (VI):

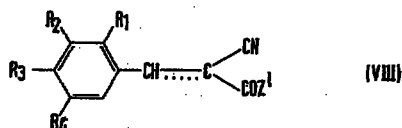


5 (d) reacting said compound of general formula (VI) with phosphorus oxychloride, optionally in the presence of a small amount of phosphorus pentachloride, to yield a compound of general formula (VII):



and; (e) catalytically hydrogenating said compound of general formula (VII) in a solvent to yield said compound of general formula (I).

15 The invention further consists in compounds of general formula (VIII):



in which R₁, R₂, R₃ and R₄ have the same meanings as in formula (I) and Z' is a hydroxy, an amino or an alkyl-substituted amino group, and C—C represents CH—CH or C=C, other than α-cyano-3,4,5-trimethoxycinnamic acid. The invention further consists in a process for the preparation of compounds of general formula (VIII), which comprises step (a), followed, when C—C is CH—CH, by step (b), as defined above.

The basic catalyst used in step (a) is preferably sodium or potassium hydroxide, a metal alkoxide or a secondary amine. This step may be performed in the absence of a solvent, but is preferably performed in an inert solvent, such as an alcohol, e.g. methanol, ethanol or isopropanol; an ether, e.g. dioxan or tetrahydrofuran; pyridine; or water. The step is preferably carried out at an elevated temperature, e.g. from 40 to 80°C. Preferred catalysts for the hydrogenation steps (b) and (e) are palladized or platinized charcoal. Suitable solvents include: ethyl acetate; alcohols, e.g. methanol, ethanol and isopropanol; and ethers, e.g. dioxan.

The condensation of the compound of

general formula (V) with guanidine in step (c) may be carried out without the use of a solvent, but we prefer to use an inert solvent, e.g. an alcohol, such as methanol, ethanol or isopropanol.

Steps (a) to (c) may be performed one after the other without any intermediate isolation of the compounds of general formulae (IV) and (V).

The starting materials for the process of the present invention are either known or may be produced by methods known *per se*.

The invention is further illustrated with reference to the following Examples.

Example 1

A mixture of 100 grams of 3,4,5-trimethoxybenzaldehyde and 58.8 grams of ethyl cyanoacetate in 250 cc of isopropanol containing 3 cc of a 10% sodium hydroxide solution was refluxed gently for 2 hours. The reaction mixture was then cooled to 0–5°C for 4 hours. The product was filtered by suction and washed with 40 cc of cold isopropanol. The crude material was dried at 50°C and used for further steps without purification. It melted at 80–82°C.

The yield of ethyl α-cyano-3,4,5-trimethoxycinnamate was 140 grams (94.5%).

Example 2

The procedure described in Example 1 was followed, except that 51 grams of methyl cyanoacetate were used in place of the ethyl cyanoacetate. The yield of methyl α-cyano-3,4,5-trimethoxycinnamate obtained was 130 grams (92%); melting point 114–115°C.

Example 3

The procedure described in Example 1 was repeated, except that 100 grams of 3,4-dimethoxybenzaldehyde and 69.5 grams of ethyl cyanoacetate were used. The product obtained was ethyl α-cyano-3,4-dimethoxycinnamate; melting point 153–154°C; yield 151 grams (96%).

Example 4

Example 1 was repeated, except that 100 grams of 3,4-dimethoxybenzaldehyde and 61 grams of methyl cyanoacetate were used. The product obtained was methyl α-cyano-3,4-dimethoxycinnamate; melting point 125–127°C; yield 142.5 grams (96%).

Example 5

A mixture of 100 grams of 3,4,5-trimethoxybenzaldehyde and 43.5 grams of cyanoacetic acid in 1 litre of water containing 21 grams of sodium hydroxide was stirred for 2 hours at 50°C. The clear solution obtained was cooled, 120 cc of 5N hydrochloric acid were added and, after additional cooling, the precipitate was filtered off and washed with 200 cc of water. The crude material was

dried at 80°C and used in a hydrogenation step without further purification. It melted at 221—224°C. The yield of α - cyano - 3,4,5 - trimethoxycinnamic acid was 126 grams (94%).

Example 6

100 grams of 3,4,5 - trimethoxybenzaldehyde and 44 grams of α - cyanoacetamide were dissolved in 300 cc of dry pyridine at 50°C. To this solution were added 10 cc of piperidine and the mixture was heated at 50°C, with stirring, for 2 hours. The reaction mixture was then cooled to room temperature, filtered off and the precipitate was washed on the filter with 50 cc of cold isopropanol. The product was dried at 80°C to yield 123.6 grams (92.5%) of α - cyano - 3,4,5 - trimethoxycinnamamide (melting point 192—194°C). This product was used in a hydrogenation step without further purification. A pure sample, recrystallized from isopropanol, melted at 193—195°C.

Example 7

The procedure described in Example 6 was repeated, except that 84.7 grams of 3,4 - dimethoxybenzaldehyde were used in place of the trimethoxybenzaldehyde. The product was dried at 80°C to obtain 111.2 grams (94%) of α - cyano - 3,4 - dimethoxycinnamamide (melting point 182—185°C). This product was used in a hydrogenation step without further purification. A pure sample, recrystallized from dimethylformamide had a melting point of 184—185°C.

Example 8

100 grams of ethyl α - cyano - 3,4,5 - trimethoxycinnamate produced in Example 1 were dissolved in 800 cc of ethyl acetate containing 10 cc of a 10% sodium hydroxide solution. 7.5 grams of 5% palladized charcoal were added. The mixture was hydrogenated at atmospheric pressure until absorption of hydrogen had stopped, the catalyst was then removed and the solvent was evaporated under a vacuum. The residue was dissolved in 10 cc of isopropanol and the solution cooled at 0°C for 4 hours. The product was filtered off by suction, washed on the filter with 20 cc of cold isopropanol and dried in air to yield 93.5 grams (93%) of ethyl α - cyano - 3,4,5 - trimethoxy - dihydrocinnamate; melting point 61—62°C.

Example 9

100 grams of methyl α - cyano - 3,4,5 - trimethoxycinnamate, produced as in Example 2, were hydrogenated following the procedure described in Example 8. Crystallization of the product from 100 cc of isopropanol yielded 92.3 grams (92%) of methyl α - cyano - 3,4,5 - trimethoxydihydrocinnamate (melting point 89—91°C).

Example 10

100 grams of ethyl α - cyano - 3,4 - dimethoxycinnamate, produced in Example 3, were hydrogenated following the procedure described in Example 8. Crystallization of the product from isopropanol yielded 89 grams (89%) of ethyl α - cyano - 3,4 - dimethoxydihydrocinnamate (melting point 77—78°C).

Example 11

100 grams of methyl α - cyano - 3,4 - dimethoxycinnamate, produced in Example 4, were hydrogenated following the procedure described in Example 8. Crystallization of the product from isopropanol yielded 91 grams (91%) of methyl α - cyano - 3,4 - dimethoxydihydrocinnamate (melting point 80—81°C).

Example 12

100 grams of α - cyano - 3,4,5 - trimethoxycinnamic acid, obtained in Example 5, were dissolved in a solution of 16 grams of sodium hydroxide in 1 litre of water and then 7.5 grams of 5% palladized charcoal were added. The mixture was hydrogenated at atmospheric pressure until absorption of hydrogen had ceased. The catalyst was then removed and 175 cc of 10% hydrochloric acid were added. The precipitate was filtered off, washed with 200 cc of water and dried *in vacuo* at 50°C for 10 hours to yield 93.1 grams (93%) of α - cyano - 3,4,5 - trimethoxydihydrocinnamic acid (melting point 102—105°C). A pure sample, recrystallized from chloroform, melted at 104—105°C.

Example 13

100 grams of α - cyano - 3,4,5 - trimethoxycinnamamide, obtained in Example 6, were dissolved in 1 litre of a 9:1 mixture of dioxan; water and 7.5 grams of 5% palladized charcoal were added. The mixture was hydrogenated at atmospheric pressure until absorption of hydrogen had ceased. The catalyst was then removed and the solvent evaporated under a vacuum. The residue was crystallized from ethyl acetate to obtain, after drying at 60°C for 6 hours, 89.2 grams (89%) of α - cyano - 3,4,5 - trimethoxy - dihydrocinnamamide (melting point 128—130°C).

Example 14

100 grams of α - cyano - 3,4 - dimethoxycinnamamide, prepared in Example 7, were hydrogenated following the procedure described in Example 13. Crystallization of the product from dry ethanol yielded 90 grams (90%) of α - cyano - 3,4 - dimethoxy - dihydrocinnamamide (melting point 170—171°C).

Example 15

To a solution of 23 grams of sodium in 1 litre of dry methanol were added 90 grams of guanidine carbonate; the mixture was stirred for 15 minutes at room temperature.

The precipitated sodium carbonate was filtered off with suction over celite and the solids were washed with 200 cc of methanol. To this guanidine solution in methanol were added 146.5 grams of ethyl α - cyano - 3,4,5 - trimethoxy - dihydrocinnamate, prepared as described in Example 8.

The solution was refluxed for 6 hours and the methanol was distilled off *in vacuo*. The residue was dissolved in 300 cc of water and the product precipitated by the addition of 6N hydrochloric acid to pH 6. After allowing the mixture to cool at 0°C for 2 hours, the white solid was filtered off and washed with 40 cc of ice-cold water. The product was dried at 80°C under 5 mm Hg for 12 hours to yield 138.1 grams (90%) of colourless 2,4 - diamino - 5 - (3',4',5' - trimethoxybenzyl) - 6 - hydroxypyrimidine (melting point 275—276°C, molecular mass peak 306).

Example 16

The procedure described in Example 15 was repeated, except that the ethyl ester was replaced by 139.5 grams of methyl α - cyano - 3,4,5 - trimethoxy - dihydrocinnamate, prepared as described in Example 9. The yield of product was 134 grams (87.5%) and the product had a melting point of 274—276°C and was identical with the compound obtained in Example 15.

Example 17

A mixture of 100 grams of ethyl α - cyano - 3,4,5 - trimethoxy - dihydrocinnamate, prepared as described in Example 8, and 50 grams of freshly prepared guanidine was heated at 110°C for 1 hour with occasional stirring. The reaction mixture was dissolved in 75 cc of hot water and the solution was filtered. The product was precipitated by adding sufficient 6N hydrochloric acid to the clear filtrate to raise its pH to 6. After allowing to cool at 0°C for 4 hours, the solid precipitated was filtered off and washed with 30 cc of ice-cold water. The product was dried at 80°C and 5 mm Hg for 12 hours, to obtain 95.5 grams (91%) of a compound having a melting point of 274—276°C, which was identical with the compound obtained in Example 15.

Example 18

The procedure described in Example 15 was repeated, except that the ethyl ester was replaced by 132 grams of α - cyano - 3,4,5 - trimethoxy - dihydrocinnamamide, produced as described in Example 13. The product obtained was identical with the compound obtained in Example 15 and was obtained in a yield of 136.5 grams (89%).

Example 19

The procedure described in Example 17 was repeated, except that the ethyl ester was

replaced by 100 grams of α - cyano - 3,4,5 - trimethoxy - dihydrocinnamamide, prepared as described in Example 13 and that 60 grams of freshly prepared guanidine were used. The product obtained was identical with that obtained in Example 15 and was obtained in a yield of 106.7 grams (92%).

Example 20

The procedure described in Example 15 was repeated, except that 131.5 grams of ethyl α - cyano - 3,4 - dimethoxy - dihydrocinnamate, prepared as described in Example 10, were used. The colourless crystalline product obtained was 2,4 - diamino - 5 - (3',4' - dimethoxybenzyl) - 6 - hydroxypyrimidine: melting point 268—270°C; yield 119 grams (86%); molecular mass peak 276.

Example 21

The procedure described in Example 17 was repeated, except that 100 grams of methyl α - cyano - 3,4 - dimethoxy - dihydrocinnamate, prepared as described in Example 11, and 60 grams of freshly prepared guanidine were used. The product obtained weighed 97 grams (92.5%) and had a melting point of 268—270°C and was identical with the compound obtained in Example 20.

Example 22

The procedure described in Example 15 was repeated, except that 50 grams of the product of Example 14, 10 grams of sodium and 38.5 grams of guanidine carbonate in 0.5 litre of dry methanol were used. The crystalline product, 2,4 - diamino - 5 - (3',4' - dimethoxybenzyl) - 6 - hydroxypyrimidine, had a melting point of 268—270°C and weighed 52 grams (87.5%).

Example 23

The procedure described in Example 17 was repeated, except that 100 grams of the product of Example 14 and 70 grams of freshly prepared guanidine were used. The product obtained, 2,4 - diamino - 5 - (3',4' - dimethoxybenzyl) - 6 - hydroxypyrimidine, had a melting point of 268—270°C and weighed 108 grams (91%).

Example 24

A mixture of 100 grams of 3,4,5 - trimethoxybenzaldehyde and 58.8 grams of ethyl α - cyanoacetate in 1 litre of ethanol containing 2 grams of sodium methoxide was refluxed for 2 hours. 11 grams of 5% palladized charcoal were added and the mixture was hydrogenated at atmospheric pressure until the absorption of hydrogen ceased. The catalyst was then removed and, to the solution obtained, were added 52 grams of sodium methoxide and 90 grams of guanidine carbonate. The solution was refluxed for 6 hours and the solvent then distilled off *in*

vacuo. The residue was dissolved in 300 cc of hot water, treated with 5 grams of charcoal, and filtered; the product was precipitated by the addition of sufficient 6N hydrochloric acid to bring the pH to 6.

- 5 After allowing the mixture to cool at 0°C for 2 hours, the white solid obtained was filtered off and washed with 40 cc of ice-cold water. The product was dried at 80°C under
10 5 mm Hg pressure for 12 hours to obtain 119 grams (76%) of colourless 2,4 - diamino - 5 - (3',4',5' - trimethoxybenzyl) - 6 - hydroxypyrimidine having a melting point of 274—276°C and identical with the product of
15 Example 15.

Example 25

- A mixture of 100 g of 2,4 - diamino - 5 - (3',4',5' - trimethoxybenzyl) - 6 - hydroxypyrimidine, 500 cc of phosphorus oxychloride and 10 grams of phosphorus pentachloride was heated at 100°C for 3 hours. About 70% of the phosphorus oxychloride was removed by vacuum distillation and the residual syrup was poured, while still warm,
20 onto 1 kg of crushed ice. A solid precipitate was obtained from the solution. After allowing this to cool for 4 hours at 0°C, the precipitate was filtered off and washed with 100 cc of ice-cold water. The solid was
25 triturated with a dilute solution of sodium bicarbonate, filtered off and washed with 50 cc of ice-cold water. The product was crystallized from dimethylformamide to give 93.2 grams (88%) of 2,4 - diamino - 5 - (3',4',5' - trimethoxybenzyl) - 6 - chloropyrimidine:
30 melting point 226—227°C; molecular mass peak 325.

Example 26

- The chlorination of 100 grams of 2,4 - diamino - 5 - (3',4' - dimethoxybenzyl) - 6 - hydroxypyrimidine was conducted following the procedure described in Example 25. The product was crystallized from a mixture of dimethylformamide and methanol to yield
40 91.8 grams (86%) of 2,4 - diamino - 5 - (3',4' - dimethoxybenzyl) - 6 - chloropyrimidine: melting point 277—278°C; molecular mass peak 295.

Example 27

- 50 A suspension of 50 grams of 2,4 - diamino - 5 - (3',4',5' - trimethoxybenzyl) - 6 - chloropyrimidine in 350 cc of 50% acetic acid was hydrogenated with 4 grams of 5% palladized charcoal at 1.5 atmospheres until absorption
55 of hydrogen had ceased. The catalyst was then removed and the solvent evaporated under vacuum. The residue was dissolved in 200 cc of water and the product precipitated by the addition of sufficient 20% sodium
60 hydroxide solution to raise the pH to 9. The solid was filtered off, washed with 200 cc of distilled water and dried at 80°C under 5 mm Hg pressure for 6 hours to obtain 37.5

grams (94%) of 2,4 - diamino - 5 - (3',4',5' - trimethoxybenzyl) - 6 - chloropyrimidine (trimethoprim): melting point 200—202°C; molecular mass peak 290.

Example 28

50 grams of 2,4 - diamino - (3',4' - dimethoxybenzyl) - 6 - chloropyrimidine were hydrogenated exactly as described in Example 27. The colourless crystalline product, 2,4 - diamino - 5 - (3',4' - dimethoxybenzyl) - pyrimidine (diaveridine), had a melting point of 232—233°C and weighed 41 grams (93%).

The compounds of formula (I) produced by the process of the invention are useful antibacterial agents and thus the invention further provides a pharmaceutical composition comprising a compound of formula (I) when produced by the process of the invention in admixture with a pharmaceutically acceptable carrier or diluent. The composition is preferably administered in tablet form.

These compounds also, as has previously been mentioned, show a strong potentiative effect when administered in combination with antibacterial sulphonamides. Thus, the invention still further provides a pharmaceutical composition comprising a compound of general formula (I) when produced by the process of the invention in admixture with an antibacterial sulphonamide, particularly a sulphamethoxazole or a sulphaquinoxaline.

WHAT WE CLAIM IS:—

1. A process for the preparation of benzylpyrimidines of general formula (I), as hereinbefore defined, which comprises the steps:
 - (a) reacting an aldehyde of general formula (II), as hereinbefore defined, in the presence of a basic catalyst with a compound of general formula (III), as hereinbefore defined, to yield a compound of general formula (IV), as hereinbefore defined,
 - (b) catalytically hydrogenating said compound of general formula (IV) in an inert solvent to yield a compound of general formula (V), as hereinbefore defined,
 - (c) reacting said compound of general formula (V) with guanidine to yield a compound of general formula (VI), as hereinbefore defined,
 - (d) reacting the compound of general formula (VI) with phosphorus oxychloride to yield a compound of general formula (VII), as hereinbefore defined, and
 - (e) catalytically hydrogenating said compound of general formula (VII) in a solvent to yield said compound of general formula (I).
2. Compounds of general formula (VIII), as hereinbefore defined.
3. α - Cyano - 3,4,5 - trimethoxy - dihydrocinnamic acid.
4. α - Cyano - 3,4,5 - trimethoxy - cinnamamide.

vacuo. The residue was dissolved in 300 cc of hot water, treated with 5 grams of charcoal, and filtered; the product was precipitated by the addition of sufficient 6N hydrochloric acid to bring the pH to 6.

After allowing the mixture to cool at 0°C for 2 hours, the white solid obtained was filtered off and washed with 40 cc of ice-cold water. The product was dried at 80°C under 5 mm Hg pressure for 12 hours to obtain 119 grams (76%) of colourless 2,4 - diamino - 5 - (3',4',5' - trimethoxybenzyl) - 6 - hydroxypyrimidine having a melting point of 274—276°C and identical with the product of Example 15.

Example 25

A mixture of 100 g of 2,4 - diamino - 5 - (3',4',5' - trimethoxybenzyl) - 6 - hydroxypyrimidine, 500 cc of phosphorus oxychloride and 10 grams of phosphorus pentachloride was heated at 100°C for 3 hours. About 70% of the phosphorus oxychloride was removed by vacuum distillation and the residual syrup was poured, while still warm, onto 1 kg. of crushed ice. A solid precipitate was obtained from the solution. After allowing this to cool for 4 hours at 0°C, the precipitate was filtered off and washed with 100 cc of ice-cold water. The solid was triturated with a dilute solution of sodium bicarbonate, filtered off and washed with 50 cc of ice-cold water. The product was crystallized from dimethylformamide to give 93.2 grams (88%) of 2,4 - diamino - 5 - (3',4',5' - trimethoxybenzyl) - 6 - chloropyrimidine: melting point 226—227°C; molecular mass peak 325.

Example 26

The chlorination of 100 grams of 2,4 - diamino - 5 - (3',4' - dimethoxybenzyl) - 6 - hydroxypyrimidine was conducted following the procedure described in Example 25. The product was crystallized from a mixture of dimethylformamide and methanol to yield 91.8 grams (86%) of 2,4 - diamino - 5 - (3',4' - dimethoxybenzyl) - 6 - chloropyrimidine: melting point 277—278°C; molecular mass peak 295.

Example 27

A suspension of 50 grams of 2,4 - diamino - 5 - (3',4',5' - trimethoxybenzyl) - 6 - chloropyrimidine in 350 cc of 50% acetic acid was hydrogenated with 4 grams of 5% palladized charcoal at 1.5 atmospheres until absorption of hydrogen had ceased. The catalyst was then removed and the solvent evaporated under vacuum. The residue was dissolved in 200 cc of water and the product precipitated by the addition of sufficient 20% sodium hydroxide solution to raise the pH to 9. The solid was filtered off, washed with 200 cc of distilled water and dried at 80°C under 5 mm Hg pressure for 6 hours to obtain 37.5

grams (94%) of 2,4 - diamino - 5 - (3',4',5' - trimethoxybenzyl) - pyrimidine (trimethoprim): melting point 200—202°C; molecular mass peak 290.

Example 28

50 grams of 2,4 - diamino - (3',4' - dimethoxybenzyl) - 6 - chloropyrimidine were hydrogenated exactly as described in Example 27. The colourless crystalline product, 2,4 - diamino - 5 - (3',4' - dimethoxybenzyl) - pyrimidine (diaveridine), had a melting point of 232—233°C and weighed 41 grams (93%).

The compounds of formula (I) produced by the process of the invention are useful antibacterial agents and thus the invention further provides a pharmaceutical composition comprising a compound of formula (I) when produced by the process of the invention in admixture with a pharmaceutically acceptable carrier or diluent. The composition is preferably administered in tablet form.

These compounds also, as has previously been mentioned, show a strong potentiative effect when administered in combination with antibacterial sulphonamides. Thus, the invention still further provides a pharmaceutical composition comprising a compound of general formula (I) when produced by the process of the invention in admixture with an antibacterial sulphonamide, particularly a sulphamethoxazole or a sulphaquinoxaline.

WHAT WE CLAIM IS:—

1. A process for the preparation of benzylpyrimidines of general formula (I), as hereinbefore defined, which comprises the steps:

(a) reacting an aldehyde of general formula (II), as hereinbefore defined, in the presence of a basic catalyst with a compound of general formula (III), as hereinbefore defined, to yield a compound of general formula (IV), as hereinbefore defined,

(b) catalytically hydrogenating said compound of general formula (IV) in an inert solvent to yield a compound of general formula (V), as hereinbefore defined,

(c) reacting said compound of general formula (V) with guanidine to yield a compound of general formula (VI), as hereinbefore defined,

(d) reacting the compound of general formula (VI) with phosphorus oxychloride to yield a compound of general formula (VII), as hereinbefore defined, and

(e) catalytically hydrogenating said compound of general formula (VII) in a solvent to yield said compound of general formula (I).

2. Compounds of general formula (VIII), as hereinbefore defined.

3. α - Cyano - 3,4,5 - trimethoxy - dihydrocinnamic acid.

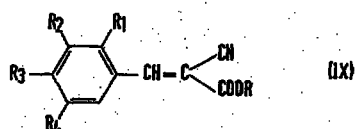
4. α - Cyano - 3,4,5 - trimethoxy - cinnamamide.



5. α - Cyano - 3,4,5 - trimethoxy - dihydrocinnamamide.

6. α - Cyano - 3,4 - dimethoxy - dihydrocinnamamide.

5. 7. A process for the preparation of a compound of general formula:



- 10 in which R is a lower alkyl group and R₁, R₂, R₃, and R₄ are as defined in formula (I), which comprises the step: (a) reacting an aldehyde of general formula (II), as hereinbefore defined, in the presence of a basic catalyst with a compound of general formula NC—CH₂—COOR.

- 15 8. A process according to claim 7, in which said basic catalyst is sodium or potassium hydroxide, a metal alkoxide or a secondary amine.

- 20 9. A process according to claim 7 or claim 8, effected in the presence of an inert solvent.

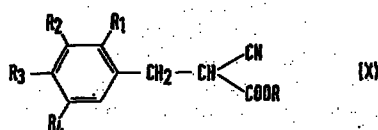
10. A process according to claim 9, in which said solvent is an alcohol, or an ether.

- 25 11. A process according to any one of claims 7 to 10, in which R₁ is a hydrogen atom and R₂, R₃, and R₄ are each methoxy groups.

- 30 12. A process according to any one of claims 7 to 10, in which R₁ and R₂ are each hydrogen atoms and R₃ and R₄ are each methoxy groups.

13. A compound of formula (IX) when produced by a process according to any one of claims 7 to 12.

- 35 14. A process for the preparation of a compound of general formula:



- 40 which comprises the step: (b) catalytically hydrogenating a compound of formula (IX) according to claim 13, in the presence of a solvent.

15. A process according to claim 14, in which the hydrogenation catalyst is palladized or platinized charcoal.

- 45 16. A process according to claim 14 or claim 15, in which the solvent in step (b) is ethyl acetate, an alcohol or an ether.

17. A compound of general formula (X) when prepared by a process according to any one of claims 14 to 16.

- 50 18. A process for the preparation of a compound of formula (VI), as hereinbefore defined, which comprises the step: (c) reacting a compound of formula (X) according to claim 17 with guanidine.

19. A process according to claim 18, effected in the presence of a solvent.

20. A process according to claim 19, effected in alcoholic solution.

21. A process according to claim 18, effected in the absence of a solvent.

22. A process according to any one of claims 18 to 21, in which steps (a) to (c) are performed one after the other without isolation of said compounds of general formulae (IX) and (X).

23. A compound of general formula (VI) when prepared by a process according to any one of claims 18 to 22.

24. A process for the preparation of a compound of general formula (VII), as hereinbefore defined, which comprises the step: (d) reacting a compound of general formula (VI) according to claim 23 with phosphorus oxychloride.

25. A process according to claim 24, effected in the presence of a minor amount of phosphorus pentachloride.

26. A compound of formula (VII) when prepared by a process according to claim 24 or claim 25.

27. A process for the preparation of a compound of general formula (I), as hereinbefore defined, which comprises catalytically hydrogenating a compound of general formula (VII) according to claim 26, in the presence of an inert solvent.

28. A process according to claim 27, in which the hydrogenation catalyst is palladized or platinized charcoal.

29. A process according to claim 27 or claim 28, in which said inert solvent is ethyl acetate, an alcohol or an ether.

30. A compound of general formula (I) when prepared by a process according to any one of claims 27 to 29.

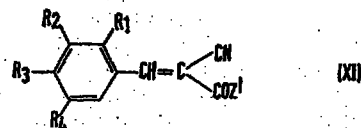
31. Trimethoprim when prepared by a process according to any one of claims 27 to 29.

32. Diaveridine when prepared by a process according to any one of claims 27 to 29.

33. A pharmaceutical composition comprising a compound of general formula (I) according to claim 30 in admixture with a pharmaceutically acceptable carrier or diluent.

34. A pharmaceutical composition comprising a compound of general formula (I) according to claim 30 in admixture with an antibacterial sulphonamethoxazole or sulphaquinoxaline.

35. A process for the preparation of a compound of general formula:



in which R_1 , R_2 , R_3 , and R_4 are as defined in formula (I) and Z' is a hydroxy, an amino, or an alkyl-substituted amino group, which comprises the step: (a) reacting an aldehyde of general formula (II), as hereinbefore defined, in the presence of a basic catalyst with a compound of general formula $NC-CH_2-COZ'$.

36. A process according to claim 35, in which said basic catalyst is sodium or potassium hydroxide, a metal alkoxide or a secondary amine.

37. A process according to claim 35 or claim 36, effected in the presence of an inert solvent.

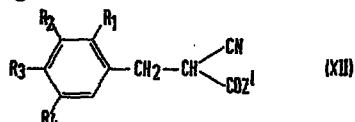
38. A process according to claim 37, in which said solvent is an alcohol, an ether, pyridine or water.

39. A process according to any one of claims 35 to 38, in which R_1 is a hydrogen atom and R_2 , R_3 , and R_4 are each methoxy groups.

40. A process according to any one of claims 35 to 38, in which R_1 and R_2 are each hydrogen atoms and R_3 and R_4 are each methoxy groups.

41. A compound of formula (XI) when produced by a process according to any one of claims 35 to 40.

42. A process for the preparation of a compound of general formula:



which comprises the step: (b) catalytically hydrogenating a compound of formula (XI) according to claim 41, in the presence of a solvent.

43. A process according to claim 42, in which the hydrogenation catalyst is palladized or platinized charcoal.

44. A process according to claim 42 or claim 43, in which the solvent in step (b) is ethyl acetate, an alcohol or an ether.

45. A compound of general formula (XII) when prepared by a process according to any one of claims 42 to 44.

46. A process for the preparation of a compound of formula (VI), as hereinbefore defined, which comprises the step: (c) reacting a compound of formula (XII) according to claim 45 with guanidine.

47. A process according to claim 46, effected in the presence of a solvent.

48. A process according to claim 47, effected in alcoholic solution.

49. A process according to claim 46, effected in the absence of a solvent.

50. A process according to any one of claims 46 to 49, in which steps (a) to (c) are performed one after the other without isolation of said compounds of general formulae (XI) and (XII).

51. A compound of general formula (VI) when prepared by a process according to any one of claims 46 to 50.

52. A process for the preparation of a compound of general formula (VII), as hereinbefore defined, which comprises the step: (d) reacting a compound of general formula (VI) according to claim 51 with phosphorus oxychloride.

53. A process according to claim 52, effected in the presence of a minor amount of phosphorus pentachloride.

54. A compound of formula (VII) when prepared by a process according to claim 52 or claim 53.

55. A process for the preparation of a compound of general formula (I), as hereinbefore defined, which comprises catalytically hydrogenating a compound of general formula (VII) according to claim 54, in the presence of an inert solvent.

56. A process according to claim 55, in which the hydrogenation catalyst is palladized or platinized charcoal.

57. A process according to claim 55 or claim 56, in which said inert solvent is ethyl acetate, an alcohol or an ether.

58. A compound of general formula (I) when prepared by a process according to any one of claims 55 to 57.

59. Trimethoprim when prepared by a process according to any one of claims 55 to 57.

60. Diaveridine when prepared by a process according to any one of claims 55 to 57.

61. A pharmaceutical composition comprising a compound of general formula (I) according to claim 58 in admixture with a pharmaceutically acceptable carrier or diluent.

62. A pharmaceutical composition comprising a compound of general formula (I) according to claim 58 in admixture with an antibacterial sulphamethoxazole or sulphamethoxazole.

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