

L051006



PATENT SPECIFICATION

NO DRAWINGS

L051006

Date of Application and filing Complete Specification: June 16, 1965.

No. 25508/65.

Application made in Switzerland (No. 8084) on June 19, 1964.

Application made in Switzerland (No. 16252) on Dec. 16, 1964.

Complete Specification Published: Dec. 14, 1966.

© Crown Copyright 1966.

Index at acceptance:—C2 C(1E4K4, 1F2C4, 1F2D3, 1H1A1, 1H1C3, 1J1A6, 1J1A9, 1J1B, 1J1C3, 1J1E, 2A2, 2A5, 2B3A4, 2B3B, 2B3E, 2B3G1, 2B3G5, 2D43A, 2D43F, 2D43L, 2D43S4, 2R16, 3A13C6A, 3A13C9, 3A13C10H, B4D, B4M)

Int. Cl.:—C 07 d 51/42

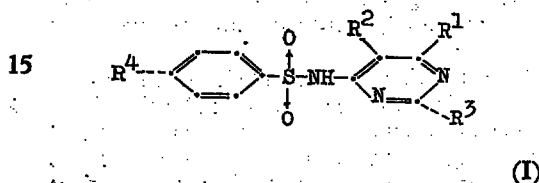
COMPLETE SPECIFICATION

Novel Sulphonamides and a process for the manufacture thereof

We, F. HOFFMANN - LA ROCHE & Co., AKTIENGESSELLSCHAFT, 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:—

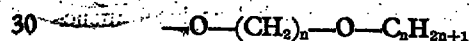
The present invention is concerned with novel sulphonamides and a process for the manufacture thereof.

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



wherein R¹ represents a lower alkoxy-alkoxy or lower hydroxy-alkoxy group, R² represents a lower-alkyl, lower-alkenyl, lower-cyclo-alkenyl, phenyl, substituted-phenyl, substituted lower-phenylalkyl, lower-alkoxy, lower alkoxy-alkyl or lower alkoxy-alkoxy group, R³ represents a lower alkoxy-alkoxy group and R⁴ represents a halogen atom or a lower-alkyl or lower-alkylthio group and wherein the broken lines denote that the substituents attached thereby are optional, and salts thereof.

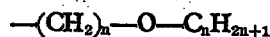
The term 'lower alkoxy-alkoxy' used herein denotes a group of the formula



in which *n* signifies a whole number of from [Price 4s. 6d.]

one to seven, preferably one, two or three. Such alkoxy-alkoxy groups are, for example, methoxy-methoxy, methoxy-ethoxy, methoxy-propoxy, methoxy-butoxy, methoxy-hexyloxy, ethoxy-methoxy, ethoxy-ethoxy, ethoxy-propoxy, ethoxy-butoxy and hexyloxy-ethoxy. The term 'lower hydroxy-alkoxy' denotes a group of the formula $-O-(CH_2)_n-OH$ in which *n* signifies a whole number of from one to seven, especially one, two or three. Such hydroxy-alkoxy groups are, for example, hydroxy-methoxy, hydroxy-ethoxy, hydroxy-propoxy, hydroxy-butoxy and hydroxy-hexyloxy. The term 'lower alkyl' when used alone or in conjunction with other groups (e.g. lower alkoxy) denotes a straight-chain or branched-chain alkyl group containing from one to seven carbon atoms such as methyl, ethyl, propyl, *iso*-propyl, butyl and hexyl. An alkyl group present as the R⁴ substituent contains from one to three carbon atoms; that is to say, the methyl, ethyl, propyl or *isopropyl* group. The term 'lower alkenyl' represents a straight-chain or branched-chain alkenyl group containing not more than seven carbon atoms such as allyl and the like. The term 'lower-cycloalkenyl' denotes a cyclo-alkenyl group containing from three to seven carbon atoms such as cyclopentenyl and cyclo-hexenyl. The terms 'substituted phenyl' and 'substituted lower-phenylalkyl' denote phenyl and lower-phenylalkyl groups in which the phenyl nucleus bears one or more of the following substituents: halogen atoms (e.g. bromine or chlorine atoms), hydroxy groups, lower alkyl and lower-alkoxy groups (especially those containing one, two or three carbon atoms), lower hydroxy-alkyl groups of the formula $-(CH_2)_n-OH$ in which *n* signifies a whole number from one to seven such as, for example, hydroxy-methyl, hydroxy-ethyl,

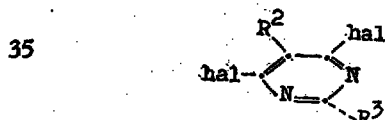
hydroxy-propyl and hydroxy-butyl, lower alkoxy-alkyl groups of the formula



- 5 in which n signifies a whole number from one to seven such as methoxy-methyl, methoxy-ethyl, methoxy-propyl, methoxy-butyl, methoxy-hexyl, ethoxy-methyl, ethoxy-ethyl, ethoxy-propyl, ethoxy-butyl, hexyloxy-methyl and hexyloxy-ethyl. Where R^2 represents substituted-phenyl or substituted lower-phenylalkyl, the *para*-position is the preferred point of substitution when only one substituent is present on the phenyl ring and the *meta*- and *para*-positions are preferred when two substituents are present. The term 'halogen' denotes iodine, bromine, chlorine and fluorine, but chlorine and bromine are preferred. The preferred 'lower-alkylthio' groups are those which contain from one to seven carbon atoms such as methylthio, ethylthio, propylthio and isopropylthio.

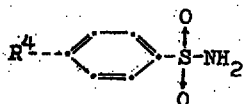
- 20 One interesting class of sulphonamides provided by the invention comprises those compounds of formula I in which R^1 represents a lower alkoxy-alkoxy group, R^2 represents a lower-alkyl, lower-alkenyl, phenyl, lower-alkoxy, lower alkoxy-alkyl or lower alkoxy-alkoxy group, R^3 is absent and R^4 (when present) represents a halogen atom or a lower-alkyl group, and salts thereof.

- 30 According to the process provided by the invention, the novel sulphonamides aforesaid are manufactured either by reacting a dihalo-pyrimidine of the formula



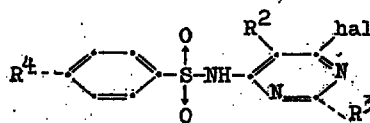
(II)

- (wherein R^2 , R^3 and the broken line have the significance given earlier and *hal* stands for a halogen atom, especially a bromine or chlorine atom) with an alkali-metal salt of a benzenesulphonic acid amide of the formula



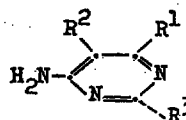
(III)

- 45 (wherein R^4 and the broken line have the significance given earlier) to give a compound of the formula



(IV)

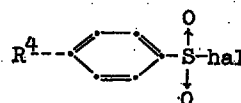
(wherein R^2 , R^3 , R^4 , *hal* and the broken lines have the significance given earlier) and replacing the 6-halogen atom therein by a lower alkoxy-alkoxy or lower hydroxy-alkoxy group by reaction with an appropriate metal-alcoholate in the presence of the corresponding alcohol or by condensing an amino-pyrimidine of the formula



55

(V)

(wherein R^1 , R^2 , R^3 and the broken line have the significance given earlier) with a benzene-sulphonyl halide of the formula



(VI)

(wherein R^4 , *hal* and the broken line have the significance given earlier) and, in either case where required, converting the product into a salt.

The reaction of the dihalo-pyrimidine of formula II with the alkali-metal salt of the amide of formula III is conveniently carried out using about 2 mol equivalents of the alkali-metal salt (e.g. the sodium or potassium salt) in the presence of a solvent or diluent such as N,N-dimethyl-formamide at temperatures within the approximate range of from 50° C to 120° C.

The 6-halogen atom of the reaction product of formula IV is then replaced by a lower alkoxy-alkoxy group or a lower hydroxy-alkoxy group. The replacement of the 6-halogen atom by a lower alkoxy-alkoxy or hydroxy-alkoxy group is effected by reacting the 6-halogeno compound of formula IV with the appropriate metal alcoholate in the presence of the corresponding alcohol. Suitable combinations of alcohols and metal alcoholates are, for example, (ethyleneglycol monoethyl ether)-sodium in ethyleneglycol mono-

ethyl ether and ethyleneglycol-sodium in ethyleneglycol. The alcoholysis can be carried out by heating the reaction mixture, preferably to a temperature of about 70°—120° C. Higher temperatures can also be used when the reaction is carried out under pressure.

The condensation of an amino-pyrimidine of formula V with a benzenesulphonyl halide can conveniently be carried out in a solvent such as an organic base (e.g. pyridine or the like). The condensation can suitably be carried out at room temperature although higher or lower temperatures can also be used.

The dihalo-pyrimidine starting materials of formula II, insofar as they are not known, can be obtained according to methods known *per se*; for example, by treating a R²-substituted malonic acid diamide with formamide or with a R²-substituted formamide in ethanol in the presence of sodium ethoxide and thereafter halogenating the product with a phosphorus oxyhalide in the presence of N,N-methyl-aniline.

The amino-pyrimidine starting materials of formula V can be obtained by reacting a 4,6-dihalo-5-R²-pyrimidine of formula II with liquid ammonia and subjecting the resulting 4-amino-5-R²-6-halo-pyrimidine to alcoholysis as described hereinbefore.

An especially interesting embodiment of the present process is that leading to the interesting sulphonamides mentioned hereinbefore and comprises *either* reacting a dihalo-pyrimidine of formula II in which R² represents a lower-alkyl, lower alkenyl, phenyl, lower-alkoxy, lower alkoxy-alkyl or lower alkoxy-alkoxy group and R³ is absent with an alkali-metal salt of a benzenesulphonic acid amide of formula III in which R⁴ (when present) represents a halogen atom or a lower-alkyl group and replacing the 6-halogen atom in the reaction product by a lower alkoxy-alkoxy group by reaction with an appropriate metal alcoholate in the presence of the corresponding alcohol *or* condensing an amino-pyrimidine of formula V in which R¹ represents a lower alkoxy-alkoxy group, R² has the significance given earlier in this paragraph and R³ is absent with a benzenesulphonyl halide of formula VI in which R⁴ (when present) represents a halogen atom or a lower alkyl group *and*, in either case where required, converting the product into a salt.

The compounds of formula I may be converted into salts with inorganic or organic bases such as alkali-metal hydroxides (e.g. sodium hydroxide or potassium hydroxide), alkaline-earth-metal hydroxides (e.g. calcium hydroxide), alkali carbonates, alkali bicarbonates, amines (e.g. methyl glucosamine or morpholine) or amino alcohols (e.g. ethanol amine). Salts in which the salt-forming moiety is a pharmaceutically acceptable base are the most interesting salts.

The compounds of formula I and the phar-

maceutically acceptable salts are useful as medicaments. More specifically, they are useful as blood-sugar depressants, particularly since such activity is unaccompanied by antibacterial activity. They can be used, for example, in the form of orally administerable pharmaceutical preparations which contain them in admixture with an organic or inorganic inert carrier material suitable for enteral application such as, for example, water, gelatin, lactose, starch, magnesium stearate, talc, vegetable oils, gums, polyalkylene glycols or petroleum jelly. The pharmaceutical preparations can be submitted in solid form (e.g. as tablets, dragées, suppositories or capsules) or in liquid form (e.g. as solutions, suspensions or emulsions). They may be sterilized and/or may contain additive materials such as preserving, stabilizing, wetting or emulsifying agents, salts for varying the osmotic pressure or buffers. They can also contain other therapeutically valuable materials.

The compounds of formula IV hereinbefore are novel and it will be appreciated that they also form part of this invention.

In order that the process provided by the invention may be more easily understood, and readily carried into effect, the following Examples are given by way of illustration.

EXAMPLE 1.

A) The preparation of the starting material.

4 - Amino - 5 - (2 - methoxy - ethyl) - 6 - chloro-pyrimidine of melting point 113°—114° C (from acetonitrile) was obtained by shaking 4,6 - dichloro - 5 - (2 - methoxy-ethyl) - pyrimidine with liquid ammonia in the autoclave at 20° C. It was reacted with (ethyleneglycol monoethyl ether)-sodium at 100° C to give 4 - amino - 5 - (2 - methoxy - ethyl) - 6 - (2 - ethoxy - ethoxy)-pyrimidine which melted at 66°—67° C when crystallized from butyl oxide.

B) The process

10 g of 4 - amino - 5 - (2 - methoxy-ethyl) - 6 - (2 - ethoxy - ethoxy) - pyrimidine were treated portionwise in 30 ml of absolute pyridine at 2°—3° C with stirring with 8.2 g of *paratoluene*-sulphonyl chloride. Stirring was continued for 32 hours at room temperature and the reaction solution was then evaporated *in vacuo* at 50° C. The residue was heated with dilute caustic soda at 50° C for 5 minutes and the solution was decolorised with carbon, filtered and the filtrate adjusted to pH 5 with acetic acid. The oily product which separated was taken up in ether and the ether solution was dried with sodium sulphate. The ether was distilled off and the residue was crystallized from butyl oxide to give 4 - (*paratoluene* - sulphonamido) - 5 - (2 - methoxy - ethyl) - 6 - (2 - ethoxy-ethoxy) - pyrimidine of melting point 79°—80° C.

EXAMPLE 2.

4 - (4 - chloro - benzenesulphonamido) - 5 - (2 - methoxy - ethyl) - 6 - (2 - ethoxy - ethoxy) - pyrimidine was prepared by a procedure analogous to that described in Example 1B using 25.5 g of 4 - amino - 5 - (2 - methoxy - ethyl) - 6 - (2 - ethoxy - ethoxy) - pyrimidine and 21 g of 4 - chloro - benzenesulphonyl chloride in 100 ml of absolute pyridine. The product melted at 68°—69° C after recrystallization from isopropyl ether.

EXAMPLE 3.

11.25 g of 4,6 - dichloro - 5 - phenyl - pyrimidine and 23 g of the sodium salt of *para*-toluene-sulphonamide in 80 ml of N,N-dimethyl-formamide were heated for 5 hours at 95° C. After evaporation of the resulting solution *in vacuo*, the residue was dissolved in water and adjusted to pH 6.8. The excess of *para*-toluene-sulphonamide which crystallized out was filtered off by suction and the solution was adjusted to pH 5 with acetic acid. The 4 - (*para*-toluene - sulphonamido) - 5 - phenyl - 6 - chloro - pyrimidine which crystallized out melted at 194°—195° C. This compound was heated at 100° C with (ethylene glycol monoethyl ether)-sodium in ethylene glycol monoethyl ether to give 4 - (*para*-toluene - sulphonamido) - 5 - phenyl - 6 - (2 - ethoxy - ethoxy) - pyrimidine which, when recrystallized from isopropyl ether, melted at 134°—136° C.

EXAMPLE 4.

A) The preparation of the starting material. 4,6 - Dichloro - 5 - phenyl - pyrimidine was shaken with liquid ammonia in the autoclave at 40° C. After evaporation of the ammonia, the residue was digested with water and solid 4 - amino - 5 - phenyl - 6 - chloro - pyrimidine was filtered off by suction. After crystallization from acetonitrile, this product melted at 194°—195° C. 4 - Amino - 5 - phenyl - 6 - (2 - ethoxy - ethoxy) - pyrimidine of melting point 103°—104° C was prepared from it by heating with sodium in ethyleneglycol monoethyl ether.

B) The process
16 g of 4 - amino - 5 - phenyl - 6 - (2 - ethoxy - ethoxy) - pyrimidine were heated for 16 hours at 100° C with 50 g of 4-chloro-benzenesulphonyl chloride in absolute pyridine. After evaporation of the pyridine *in vacuo*, the residue was treated at 60°—70° C for 6 hours with 3-N caustic soda. The solution was filtered with carbon and acidified. 4 - (4 - chloro - benzenesulphonamido) - 5 - phenyl - 6 - (2 - ethoxy - ethoxy) - pyrimidine which crystallized from acetonitrile and melted at 138°—140° C was thus obtained. The sodium salt (monohydrated) melted at 139°—141° C.

EXAMPLE 5.

4 - benzenesulphonamido - 5 - phenyl - 6 - chloro - pyrimidine [melting point, 207°—208° C; obtained by reaction of 54 g of 4,6 - dichloro - 5 - phenyl - pyrimidine and 86 g of the sodium salt of benzene-sulphonamide in 300 ml of N,N-dimethyl-formamide in a manner analogous to that described in Example 3 for the production of 4 - (*para*-toluene - sulphonamido) - 5 - phenyl - 6 - chloro - pyrimidine] was heated at 100° C with (ethylene glycol monoethyl ether)-sodium in ethylene glycol monoethyl ether. 4 - Benzenesulphonamido - 5 - phenyl - 6 - (2 - ethoxy - ethoxy) - pyrimidine was thus obtained and, when crystallized from ethanol, had a melting point of 134°—135° C. Under analogous conditions, using (ethyleneglycol monomethyl ether)-sodium in ethylene glycol monomethyl ether, 4 - benzenesulphonamido - 5 - phenyl - 6 - (2 - methoxy - ethoxy) - pyrimidine which, after crystallization from ethanol, melted at 126°—128° C was obtained; when (ethyleneglycol)-sodium in ethyleneglycol was used, 4 - benzenesulphonamido - 5 - phenyl - 6 - (2 - hydroxy - ethoxy) - pyrimidine which, after crystallization from acetonitrile, melted at 164°—166° C was obtained.

EXAMPLE 6.

4 - (4 - chloro - benzenesulphonamido) - 5 - phenyl - 6 - chloro - pyrimidine was obtained by reaction of 22.5 g of 4,6 - dichloro - 5 - phenyl - pyrimidine and 50 g of the sodium salt of 4-chloro-benzenesulphonamide in 160 ml of N,N-dimethyl-formamide in a manner analogous to that described in Example 3 for the production of 4 - (*para*-toluene - sulphonamido) - 5 - phenyl - 6 - chloro - pyrimidine. After crystallization from acetonitrile it had a melting point of 208°—209° C. Reaction with ethyleneglycol monomethyl ether and sodium in the manner of Example 5 gave 4 - (4 - chloro - benzenesulphonamido) - 5 - phenyl - 6 - (2 - methoxy - ethoxy) - pyrimidine which, when crystallized from ethanol, melted at 139°—141° C. Reaction with ethylene glycol and sodium gave 4 - (4 - chloro - benzenesulphonamido) - 5 - phenyl - 6 - (2 - hydroxy - ethoxy) - pyrimidine which, when crystallized from acetonitrile, melted at 189°—191° C; melting point of the sodium salt: >300° C.

EXAMPLE 7.

By a procedure analogous to that described in Example 3 for the production of 4 - (*para*-toluene - sulphonamido) - 5 - phenyl - 6 - chloro - pyrimidine, 49.7 g of 4,6 - dichloro - 5 - (2 - methoxy - ethyl) - pyrimidine were reacted with 86 g of the sodium salt of benzene sulphonamide in 380 ml of

N,N - dimethyl - formamide. The 4-benzenesulphonamido - 5 - (2 - methoxy-ethyl) - 6 - chloro - pyrimidine thus obtained has a melting point of 124°—125° C. It was reacted with ethyleneglycol mono-methyl ether and sodium to give 4-benzenesulphonamido - 5 - (2 - methoxy-ethyl) - 6 - (2 - methoxy - ethoxy) - pyrimidine which, when crystallized from acetonitrile/ether, melted at 79°—92° C. With ethyleneglycol monoethyl and sodium there was obtained 4 - benzenesulphonamido - 5 - (2 - methoxy - ethyl) - 6 - (2 - ethoxy-ethoxy) - pyrimidine which, when crystallized from ethanol, had a melting point of 92°—93° C.

EXAMPLE 8.

By a procedure analogous to that described in Example 3 for the production of 4-(*paratoluene* - sulphonamido) - 5 - phenyl-6 - chloro - pyrimidine, 20.7 g of 4,6-dichloro - 5 - (2 - methoxy - ethyl) - pyrimidine were reacted with 50 g of the sodium salt of 4 - chloro - benzenesulphonamide in 160 ml of N,N-dimethyl-formamide. 4-(4 - chloro - benzenesulphonamido) - 5 - (2-methoxy - ethyl) - 6 - chloro - pyrimidine thus obtained melted at 103°—104° C after crystallization from *isopropyl* ether. It was reacted with ethyleneglycol and sodium to give 4 - (4 - chloro - benzenesulphonamido)-5 - (2 - methoxy - ethyl) - 6 - (2 - hydroxy-ethoxy) - pyrimidine. From the uncrystallized oil there was prepared the calcium salt (melting point 303°—305° C when crystallized from acetonitrile) and the *dicyclohexyl* amine salt (melting point 132° C when crystallized from acetonitrile).

EXAMPLE 9.

By a procedure analogous to that described in Example 3 for the production of 4-(*paratoluene* - sulphonamido) - 5 - phenyl-6 - chloro - pyrimidine, 18 g of 4,6 - dichloro - 5 - (2 - methoxy - ethoxy) - pyrimidine and 24 g of the sodium salt of benzenesulphonamide were heated in 180 ml of N,N-dimethyl - formamide. The 4 - benzenesulphonamido - 5 - (2 - methoxy - ethoxy)-6 - chloro - pyrimidine thus obtained melted at 89°—90° C when crystallized from ethanol. It was heated with ethyleneglycol and sodium, to give 4 - benzenesulphonamido - 5 - (2 - methoxy - ethoxy) - 6 - (2-hydroxy - ethoxy) - pyrimidine which, when crystallized from ethanol, melted at 129° C.

EXAMPLE 10.

A) The preparation of the starting material—99 g of 2 - (2 - methoxy - ethoxy)-malonic acid dimethyl ester of boiling point 187°—190°/18 mm in 600 ml of concentrated ammonia were stirred for 16 hours at room temperature. The diamide, which

melted at 154°—155° C after recrystallization from ethanol, was obtained after evaporation *in vacuo*. 43.8 g of the 2-(2 - methoxy - ethoxy) - malonic acid diamide thus obtained with a solution of 15.7 g of sodium in 400 ml of absolute ethanol and 15.7 g of formamide were boiled at reflux for 3 hours. After distilling off 200 ml of ethanol, the disodium salt of the resulting 4,6 - dihydroxy - 5 - (2 - methoxy - ethoxy)-pyrimidine was filtered off by suction in the hot state, dried and heated for 3 hours with 230 ml of phosphorous oxychloride and 22 ml of N,N - dimethyl - aniline at a bath temperature of 130° C. The greater part of the phosphorous oxychloride was evaporated off *in vacuo*, the residue was treated with ice-water and the 4,6 - dichloro - 5 - (2-methoxy ethoxy) - pyrimidine thus obtained was extracted with methylene chloride. The compound distilled at 98°—100° C/0.1 mm.

B) The process.

By a procedure analogous to that described in Example 3 for the production of 4-(*paratoluene* - sulphonamido) - 5 - phenyl-6 - chloro - pyrimidine, 18 g of 4,6 - dichloro - 5 - (2 - methoxy - ethoxy) - pyrimidine were reacted with 29.4 g of the sodium salt of 4-chloro-benzenesulphonamide in 180 ml of N,N - dimethyl - formamide. The 4 - (4 - chloro - benzenesulphonamido) - 5 - (2 - methoxy - ethoxy) - 6 - chloro - pyrimidine thus obtained melted at 147°—149° C when crystallized from ethanol. It was treated with ethyleneglycol and sodium to give 4 - (4 - chloro - benzenesulphonamido)-5 - (2 - methoxy - ethoxy) - 6 - (2 - hydroxy-ethoxy) - pyrimidine which had a melting point of 123° C when crystallized from ethanol.

EXAMPLE 11.

By a procedure analogous to that described in Example 3 for the production of 4-(*paratoluene* - sulphonamido) - 5 - phenyl-6 - chloro - pyrimidine, 12.8 g of 4,6-dichloro - 5 - phenyl - 2 - methoxy - pyrimidine were heated with 25 g of the sodium salt of 4 - chloro - benzenesulphonamide in 80 ml of N,N - dimethyl - formamide. The 4 - (4 - chloro - benzenesulphonamido)-5 - phenyl - 2 - methoxy - 6 - chloro - pyrimidine thus obtained melted at 190°—191° C when crystallized from acetonitrile. It was heated with ethylene with ethylene glycol monoethyl ether and sodium to give 4 - (4 - chloro - benzenesulphonamido) - 5-phenyl - 2,6 - bis(2 - methoxy - ethoxy)-pyrimidine which melted at 137° C when crystallized from acetonitrile. With ethyleneglycol monoethyl ether and sodium, there was obtained 4 - (4 - chloro - benzenesulphonamido) - 5 - phenyl - 2,6 - bis(2-ethoxy - ethoxy) - pyrimidine which melted

at 133°—135° C when crystallized from acetonitrile.

EXAMPLE 12.

By a procedure analogous to that described in Example 3 for the production of 4-(*paratoluene* - sulphonamido) - 5 - phenyl - 6 - chloro - pyrimidine, 22.5 g of 4,6-dichloro - 5 - phenyl - pyrimidine were reacted with 48 g of the sodium salt of 4 - methylthio - benzenesulphonamide in 160 ml of N,N - dimethyl - formamide to give 4 - (4 - methylthio - benzenesulphonamido) - 5 - phenyl - 6 - chloro - pyrimidine which melted at 229°—231° C when crystallized from acetonitrile. When treated with ethyleneglycol and sodium this compound gave 4 - (4 - methylthio - benzenesulphonamido) - 5 - phenyl - 6 - (2 - hydroxy - ethoxy) - pyrimidine of melting point 174°—176° C (from acetonitrile), and when treated with ethyleneglycol monoethyl ether and sodium gave 4 - (4 - methylthio - benzenesulphonamido) - 5 - phenyl - 6 - (2 - methoxy - ethoxy) - pyrimidine of melting point 145°—147° C (from acetonitrile).

EXAMPLE 13.

By a procedure analogous to that described in Example 3 for the production of 4-(*paratoluene* - sulphonamido) - 5 - phenyl - 6 - chloro - pyrimidine, 4 - (4 - methylthio - benzenesulphonamido) - 5 - (2 - methoxy - ethyl) - 6 - chloro - pyrimidine (melting point 145°—146° C after crystallization from acetonitrile) was prepared from 12.5 g of 4,6 - dichloro - 5 - (2 - methoxy - ethyl) - pyrimidine and 31.5 g of the sodium salt of 4 - methylthio - benzenesulphonamide in 145 ml of N,N - dimethyl - formamide. When treated with ethyleneglycol and sodium it gave 4 - (4 - methylthio - benzenesulphonamido) - 5 - (2 - methoxy - ethyl) - 6 - (2 - hydroxy - ethoxy) - pyrimidine of melting point 105°—106° C (from acetonitrile).

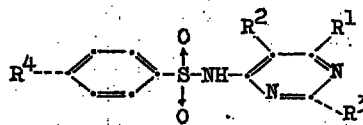
The following Examples illustrate pharmaceutical preparations containing the novel derivatives provided by the invention.

A. Tablets each containing 500.00 mg of 4 - (4 - chloro - benzenesulphonamido) - 5 - (2 - methoxy - ethyl) - 6 - (2 - ethoxy - ethoxy) - pyrimidine, 90.00 mg of lactose, 125.60 mg of corn starch, 1.44 mg of magnesium stearate and 12.96 mg of talc and having a total weight of 730.00 mg were prepared in a manner known *per se*.

B. Tablets each containing 500.00 mg of the sodium salt of 4 - (4 - chloro - benzenesulphonamido) - 5 - phenyl - 6 - (2 - hydroxy - ethoxy) - pyrimidine, 215.40 mg of corn starch, 1.46 mg of magnesium stearate and 13.14 mg of talc and having a total weight of 730.00 mg were prepared in a manner known *per se*.

WHAT WE CLAIM IS:—

1) Compounds of the formula



wherein R¹ represents a lower alkoxy-alkoxy or lower hydroxy-alkoxy group, R² represents a lower-alkyl, lower-alkenyl, lower-*cyclo*-alkenyl, phenyl, substituted-phenyl, substituted lower-phenylalkyl, lower-alkoxy, lower alkoxy-alkyl or lower alkoxy-alkoxy group, R³ represents a lower alkoxy-alkoxy group and R⁴ represents a halogen atom or a lower-alkyl or lower-alkylthio group and wherein the broken lines denote that the substituents attached thereby are optional, and salts thereof.

2) Compounds as formulated in claim 1, wherein R¹ represents a lower alkoxy-alkoxy group, R² represents a lower - alkyl, lower - alkenyl, phenyl, lower - alkoxy, lower alkoxy - alkyl or lower alkoxy - alkoxy group, R³ is absent from R⁴ (when present) represents a halogen atom or a lower - alkyl group, and salts thereof.

3) Salts as set forth in claim 1 or claim 2, wherein the salt-forming moiety is a pharmaceutically acceptable base.

4) 4 - (*paratoluene* - sulphonamido) - 5 - (2 - methoxy - ethyl) - 6 - (2 - ethoxy - ethoxy) - pyrimidine.

5) 4 - (4 - chloro - benzenesulphonamido) - 5 - (2 - methoxy - ethyl) - 6 - (2 - ethoxy - ethoxy) - pyrimidine.

6) 4 - (*paratoluene* - sulphonamido) - 5 - phenyl - 6 - (2 - ethoxy - ethoxy) - pyrimidine.

7) 4 - (4 - chloro - benzenesulphonamido) - 5 - phenyl - 6 - (2 - ethoxy - ethoxy) - pyrimidine.

8) 4 - benzenesulphonamido - 5 - phenyl - 6 - (2 - ethoxy - ethoxy) - pyrimidine.

9) 4 - benzenesulphonamido - 5 - phenyl - 6 - (2 - methoxy - ethoxy) - pyrimidine.

10) 4 - benzenesulphonamido - 5 - phenyl - 6 - (2 - hydroxy - ethoxy) - pyrimidine.

11) 4 - (4 - chloro - benzenesulphonamido) - 5 - phenyl - 6 - (2 - methoxy - ethoxy) - pyrimidine.

12) 4 - (4 - chloro - benzenesulphonamido) - 5 - phenyl - 6 - (2 - hydroxy - ethoxy) - pyrimidine.

13) 4 - benzenesulphonamido - 5 - (2 - methoxy - ethyl) - 6 - (2 - methoxy - ethoxy) - pyrimidine.

14) 4 - benzenesulphonamido - 5 - (2 - methoxyethyl) - 6 - (2 - ethoxy - ethoxy) - pyrimidine.

15) 4 - (4 - chloro - benzenesulphon-

at 133°—135° C when crystallized from acetonitrile.

EXAMPLE 12.

By a procedure analogous to that described in Example 3 for the production of 4-(*paratoluene* - sulphonamido) - 5 - phenyl - 6 - chloro - pyrimidine, 22.5 g of 4,6-dichloro - 5 - phenyl - pyrimidine were reacted with 48 g of the sodium salt of 4 - methylthio - benzenesulphonamide in 160 ml of N,N - dimethyl - formamide to give 4 - (4 - methylthio - benzenesulphonamido) - 5 - phenyl - 6 - chloro - pyrimidine which melted at 229°—231° C when crystallized from acetonitrile. When treated with ethyleneglycol and sodium this compound gave 4 - (4 - methylthio - benzenesulphonamido) - 5 - phenyl - 6 - (2-hydroxy - ethoxy) - pyrimidine of melting point 174°—176° C (from acetonitrile), and when treated with ethyleneglycol monoethyl ether and sodium gave 4 - (4 - methylthio - benzenesulphonamido) - 5 - phenyl - 6 - (2-methoxy - ethoxy) - pyrimidine of melting point 145°—147° C (from acetonitrile).

EXAMPLE 13.

By a procedure analogous to that described in Example 3 for the production of 4-(*paratoluene* - sulphonamido) - 5 - phenyl - 6 - chloro - pyrimidine, 4 - (4 - methylthio - benzenesulphonamido) - 5 - (2 - methoxy - ethyl) - 6 - chloro - pyrimidine (melting point 145°—146° C after crystallization from acetonitrile) was prepared from 12.5 g of 4,6 - dichloro - 5 - (2 - methoxy - ethyl) - pyrimidine and 31.5 g of the sodium salt of 4 - methylthio - benzenesulphonamide in 145 ml of N,N - dimethyl - formamide. When treated with ethyleneglycol and sodium it gave 4 - (4 - methylthio - benzenesulphonamido) - 5 - (2 - methoxy - ethyl) - 6 - (2-hydroxy - ethoxy) - pyrimidine of melting point 105°—106° C (from acetonitrile).

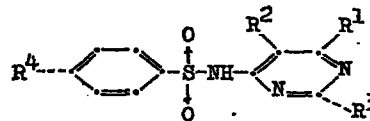
The following Examples illustrate pharmaceutical preparations containing the novel derivatives provided by the invention.

A. Tablets each containing 500.00 mg of 4 - (4 - chloro - benzenesulphonamido) - 5 - (2 - methoxy - ethyl) - 6 - (2 - ethoxy - ethoxy) - pyrimidine, 90.00 mg of lactose, 125.60 mg of corn starch, 1.44 mg of magnesium stearate and 12.96 mg of talc and having a total weight of 730.00 mg were prepared in a manner known *per se*.

B. Tablets each containing 500.00 mg of the sodium salt of 4 - (4 - chloro - benzenesulphonamido) - 5 - phenyl - 6 - (2 - hydroxy - ethoxy) - pyrimidine, 215.40 mg of corn starch, 1.46 mg of magnesium stearate and 13.14 mg of talc and having a total weight of 730.00 mg were prepared in a manner known *per se*.

WHAT WE CLAIM IS:—

1) Compounds of the formula



wherein R¹ represents a lower alkoxy-alkoxy or lower hydroxy-alkoxy group, R² represents a lower-alkyl, lower-alkenyl, lower-cyclo-alkenyl, phenyl, substituted-phenyl, substituted lower-phenylalkyl, lower-alkoxy, lower alkoxy-alkyl or lower alkoxy-alkoxy group, R³ represents a lower alkoxy-alkoxy group and R⁴ represents a halogen atom or a lower-alkyl or lower-alkylthio group and wherein the broken lines denote that the substituents attached thereby are optional, and salts thereof.

2) Compounds as formulated in claim 1, wherein R¹ represents a lower alkoxy-alkoxy group, R² represents a lower - alkyl, lower - alkenyl, phenyl, lower - alkoxy, lower alkoxy - alkyl or lower alkoxy - alkoxy group, R³ is absent from R⁴ (when present) represents a halogen atom or a lower - alkyl group, and salts thereof.

3) Salts as set forth in claim 1 or claim 2, wherein the salt-forming moiety is a pharmaceutically acceptable base.

4) 4 - (*paratoluene* - sulphonamido) - 5 - (2 - methoxy - ethyl) - 6 - (2 - ethoxy - ethoxy) - pyrimidine.

5) 4 - (4 - chloro - benzenesulphonamido) - 5 - (2 - methoxy - ethyl) - 6 - (2 - ethoxy - ethoxy) - pyrimidine.

6) 4 - (*paratoluene* - sulphonamido) - 5 - phenyl - 6 - (2 - ethoxy - ethoxy) - pyrimidine.

7) 4 - (4 - chloro - benzenesulphonamido) - 5 - phenyl - 6 - (2 - ethoxy - ethoxy) - pyrimidine.

8) 4 - benzenesulphonamido - 5 - phenyl - 6 - (2 - ethoxy - ethoxy) - pyrimidine.

9) 4 - benzenesulphonamido - 5 - phenyl - 6 - (2 - methoxy - ethoxy) - pyrimidine.

10) 4 - benzenesulphonamido - 5 - phenyl - 6 - (2 - hydroxy - ethoxy) - pyrimidine.

11) 4 - (4 - chloro - benzenesulphonamido) - 5 - phenyl - 6 - (2 - methoxy - ethoxy) - pyrimidine.

12) 4 - (4 - chloro - benzenesulphonamido) - 5 - phenyl - 6 - (2 - hydroxy - ethoxy) - pyrimidine.

13) 4 - benzenesulphonamido - 5 - (2 - methoxy - ethyl) - 6 - (2 - methoxy - ethoxy) - pyrimidine.

14) 4 - benzenesulphonamido - 5 - (2 - methoxyethyl) - 6 - (2 - ethoxy - ethoxy) - pyrimidine.

15) 4 - (4 - chloro - benzenesulphon-





1,051,006

7

amido) - 5 - (2 - methoxy - ethyl) - 6 - (2 - hydroxy - ethoxy) - pyrimidine.

16) 4 - benzenesulphonamido - 5 - (2 - methoxy - ethoxy) - 6 - (2 - hydroxy - ethoxy) - pyrimidine.

17) 4 - (4 - chloro - benzenesulphonamido) - 5 - (2 - methoxy - ethoxy) - 6 - (2 - hydroxy - ethoxy) - pyrimidine.

18) 4 - (4 - chloro - benzenesulphonamido) - 5 - phenyl - 2,6 - bis(2 - methoxy - ethoxy) - pyrimidine.

19) 4 - (4 - chloro - benzenesulphonamido) - 5 - phenyl - 2,6 - bis(2 - ethoxy - ethoxy) - pyrimidine.

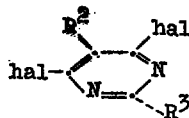
20) 4 - (4 - methylthio - benzenesulphonamido) - 5 - phenyl - 6 - (2 - hydroxy - ethoxy) - pyrimidine.

21) 4 - (4 - methylthio - benzenesulphonamido) - 5 - phenyl - 6 - (2 - methoxy - ethoxy) - pyrimidine.

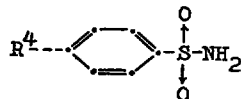
22) 4 - (4 - methylthio - benzenesulphonamido) - 5 - (2 - methoxy - ethyl) - 6 - (2 - hydroxy - ethoxy) - pyrimidine.

23) A pharmaceutical preparation comprising a compound as formulated in claim 1 or a pharmaceutically acceptable salt thereof in admixture with a compatible pharmaceutical carrier.

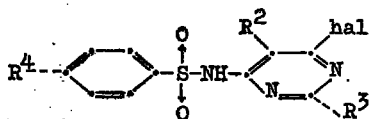
24) A process for the manufacture of the sulphonamides claimed in claim 1, which process comprises *either* reacting a dihalo-pyrimidine of the formula



(wherein R^2 , R^3 and the broken line have the significance given in claim 1 and *hal* stands for a halogen atom) with an alkali-metal salt of a benzenesulphonic acid amide of the formula

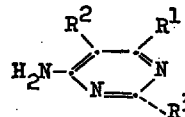


(wherein R^4 and the broken line have the significance given in claim 1) to give a compound of the formula

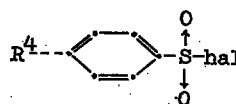


(wherein R^2 , R^3 , R^4 and the broken line have the significance given in claim 1 and *hal* has the significance given earlier in this claim) and replacing the 6-halogen atom therein by a lower-alkoxy-alkoxy or lower hydroxy-alkoxy group by reaction with an appropriate

metal-alcoholate in the presence of the corresponding alcohol *or* condensing an amino-pyrimidine of the formula



(wherein R^1 , R^2 , R^3 and the broken line have the significance given in claim 1) with a benzenesulphonyl halide of the formula



(wherein R^4 and the broken line have the significance given in claim 1 and *hal* has the significance given earlier in this claim) and, in either case when required, converting the product into a salt.

25) A process as set forth in claim 24, wherein a dihalo-pyrimidine in which R^2 represents a lower-alkyl, lower alkenyl, phenyl, lower-alkoxy, lower alkoxy-alkyl or lower alkoxy-alkoxy group and R^3 is absent is reacted with an alkali-metal salt of a benzenesulphonic acid amide in which R^4 (when present) represents a halogen atom or a lower-alkyl group and the 6-halogen atom of the reaction product is replaced by a lower alkoxy-alkoxy group by reaction with an appropriate metal-alcoholate in the presence of the corresponding alcohol *or* wherein an amino-pyrimidine in which R^1 represents a lower alkoxy-alkoxy group and R^2 and R^3 have the significance given earlier in this claim is condensed with a benzenesulphonyl halide in which R^4 (when present) represents a halogen atom or a lower-alkyl group.

26) A process as set forth in claim 24 or claim 25, wherein the product is converted into a salt with a pharmaceutically acceptable base.

27) A process as set forth in claim 24, in claim 25 or in claim 26, wherein a dihalo-pyrimidine in which R^2 represents a phenyl, 2-methoxy-ethyl or 2-methoxy-ethoxy group and R^3 is absent is reacted with an alkali-metal salt of a benzenesulphonic acid amide in which R^4 (when present) represents a chlorine atom or the methyl or methylthio group and the 6-halogen atom of the reaction product is replaced by a 2-hydroxy-ethoxy, 2-methoxy-ethoxy or 2-ethoxy-ethoxy group by reaction with an appropriate metal alcoholate in the presence of the corresponding alcohol *or* wherein an amino-pyrimidine in which R^1 represents a 2-hydroxy-ethoxy, 2-methoxy-ethoxy or 2-ethoxy-ethoxy group is condensed with a benzenesulphonyl halide in

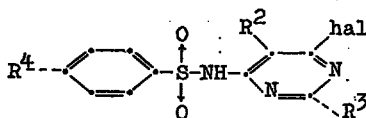
which R⁴ (when present) represents a chlorine atom or the methyl or methylthio group.

28) A process as set forth in claim 27, wherein a 4,6-dihalo-5-phenyl-pyrimidine is reacted with an alkali-metal salt of 4-chloro-benzenesulphonic acid amide and the 6-halogen atom of the reaction product is replaced by the 2-hydroxy-ethoxy group by reaction with (ethyleneglycol)-sodium in ethyleneglycol or wherein 4-amino-5-phenyl-6-(2-hydroxy-ethoxy)-pyrimidine is condensed with a 4-chloro-benzenesulphonyl halide.

29) A process for the manufacture of the sulphonamides set forth in claim 1, substantially as described with reference to Examples 1 to 13.

30) Sulphonamides as set forth in claim 1, when manufactured by the process set forth in any one of claims 24 to 29 inclusive.

31) Compounds of the formula



wherein R², R³, R⁴ and the broken lines have the significance given in claim 1 and *hal* has the significance given in claim 24.

32) Compounds as formulated in claim 31

wherein *hal* stands for a chlorine or bromine atom.

33) 4-(*paratoluene* - sulphonamido) - 5-phenyl - 6-chloro - pyrimidine.

34) 4-benzenesulphonamido - 5-phenyl - 6-chloro - pyrimidine.

35) 4-(4-chloro - benzenesulphonamido) - 5-phenyl - 6-chloro - pyrimidine.

36) 4-benzenesulphonamido - 5-(2-methoxy - ethyl) - 6-chloro - pyrimidine.

37) 4-(4-chloro - benzenesulphonamido) - 5-(2-methoxy - ethyl) - 6-chloro - pyrimidine.

38) 4-benzenesulphonamido - 5-(2-methoxy - ethoxy) - 6-chloro - pyrimidine.

39) 4-(4-chloro - benzenesulphonamido) - 5-(2-methoxy - ethoxy) - 6-chloro - pyrimidine.

40) 4-(4-chloro - benzenesulphonamido) - 5-phenyl - 2-methoxy - 6-chloro - pyrimidine.

41) 4-(4-methylthio - benzenesulphonamido) - 5-phenyl - 6-chloro - pyrimidine.

42) 4-(4-methylthio - benzenesulphonamido) - 5-(2-methoxy - ethyl) - 6-chloro-pyrimidine.

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.—1966. Published by The Patent Office, 25 Southampton Buildings, London, W.C.2, from which copies may be obtained.

