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COMPLETE SPECIFICATION

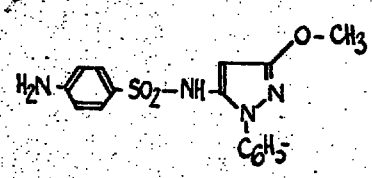
New Sulphonamides and process of making same

We, C. F. BOEHRINGER & SOEHNE G.M.B.H., a body corporate organised under the laws of Germany, of Mannheim-Waldhof, Germany, 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 new sulphonamides, namely 1-phenyl-3-methoxy-5-sulphanilamido-pyrazole-1,2 and the acid addition salts and acyl derivatives thereof, and with the production thereof.

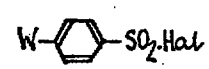
For a long time, only a few sulphonamides of the pyrazole series have been known, 5-sulphanilamido-pyrazole-1,2 (Dansk. Tidskr. Farmaci, *15*, 299/1941; Acta med. scand. *142*, 1/1943) has a good effect against pneumococci. 3-methyl-pyrazole-(1,2)-5-sulphanilamide is known from J.Chem.Soc. *1945*, 114, while the production of 5-sulphanilamido-3-methyl-1-phenylpyrazole-1,2 is described in ~~Schweiterische Meditinische Wocheaschrift~~, *1958*, 835. Recently, the 1-phenyl-pyrazole-(1,2)-5-sulphanilamide unsubstituted in the 3-position has become known (Helv., XLI, 307/1958).

We have now found that 1-phenyl-3-methoxy-5-sulphanilamido-pyrazole of the formula:



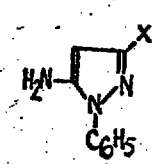
and the acid addition salts and acyl derivatives thereof are sulphonamides with specially valuable properties. These new compounds shew a very strong effectiveness against gram-positive and gram-negative bacteria; at the same time, they possess the property of forming high blood levels with a very long period of stay in the body, which is advantageous for their therapeutic application. As a result of the favourable solubility properties of the new compounds, a good absorption in the organism is also guaranteed. The corresponding acetyl compound is very soluble so that a danger of a crystallizing out of this elimination product in the kidneys and urinary ducts does not exist. This favourable combination of physico-chemical, bacteriological and pharmacological properties makes the new compounds particularly valuable medicaments which are clearly superior to the previously known sulphonamides of the pyrazole series.

The new 1-phenyl-3-methoxy-5-sulphanilamido-pyrazole can be produced by the methods known for the production of sulphonamides. The preferred process consists in reacting a sulphonyl halide of the general formula:



in which Hal is a halogen atom and W is an acyl-amino or nitro group convertible into an amino group by hydrolysis or reduction, respectively, with 1-phenyl-3-methoxy-5-amino-pyrazole whereupon W is, if necessary, converted into an amino group.

Instead of 1-phenyl-3-methoxy-5-amino-pyrazole, it is also possible to use for this reaction aminopyrazoles of the general formula:

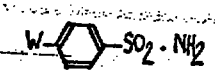


in which X is a hydroxyl group, a methoxy group or a benzyloxy group, the substituent

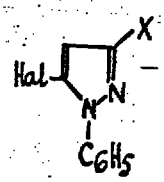
[*Price 3s. 6d.*]

X being subsequently etherified to a methoxy group, after conversion to a hydroxyl group, where necessary.

Furthermore, a sulphonamide of the general formula:



in which W has the same meaning as above, may be reacted with a 5-halo-pyrazole of the general formula:



in which Hal is a halogen atom and X is a methoxy group, a hydroxyl group or a benzyloxy group, and X, if necessary, subsequently converted into a methoxy group *via* a hydroxyl group. In this latter reaction, the sulphonamide can, if desired, be used in the form of an alkali metal salt.

If desired, the 1-phenyl-3-methoxy-5-sulphanilamido-pyrazole can then be converted into the corresponding acid addition salts of acyl derivatives by known methods.

The following Examples are given for the purpose of illustrating the present invention:

EXAMPLE 1.

45.1 g. 1-phenyl-3-methoxy-5-amino-pyrazole hydrochloride (m.p. 180°C.; produced from the corresponding hydroxy compound described in J.Am.Chem.Soc., *65*, 52/1943 by methylation by means of an ethereal diazomethane solution with the addition of methanol and subsequent precipitation with hydrogen chloride) and 98.1 g. acetyl-sulphanilyl chloride are suspended in 200 cc. absolute methylene dichloride. An approximately 20% solution of trimethylamine in dry benzene is then added dropwise, with stirring and under reflux, until the solution is exactly neutral. The reaction mixture is then boiled under reflux for 6 hours, the pH value being kept under constant control, further amounts of the trimethylamine solution being added, if necessary. After the addition of 200 cc. water, the organic solvents are distilled off in vacuo. The reaction mixture is then allowed to cool and the crystals which thereby precipitate are filtered off with suction. In this manner, 99.8 g. (86% of theory) 1-phenyl-3-methoxy-5-(bis-acetyl-sulphanilyl)-amino-pyrazole of m.p. 239—241°C. (from ethanol) are obtained.

This bis-sulphonyl compound is heated under reflux with 7.75 mol 10% sodium hydroxide solution until a clear solution is obtained (about 90 minutes). The reaction mixture is then heated for a further hour, clarified with animal charcoal, filtered and acidified with dilute hydrochloric acid. In this manner, 53.3 g. (90% of theory) 1-phenyl-3-methoxy-5-sulphanilamido-pyrazole of m.p. 154—156°C. (from ethanol) are obtained.

By the usual acetylation (e.g. using acetyl chloride and pyridine), 1-phenyl-3-methoxy-5-acetyl-sulphanilamido-pyrazole can be produced from this compound; m.p. 105—108°C. (from ethanol/water).

It is also possible to perform the above described reaction using the free 1-phenyl-3-methoxy-5-aminopyrazole (m.p. 65—67°C.). Instead of trimethylamine, other tertiary amines may be used as condensation catalysts, such as dimethyl-ethylamine or pyridine. An especially preferred condensation method consists in passing gaseous trimethylamine into a suspension of the reactants in absolute ethylene chloride.

EXAMPLE 2.

7 g. 1-phenyl-3-benzyloxy-5-aminopyrazole (produced by the reaction of the potassium salt of 1-phenyl-3-hydroxy-5-aminopyrazole with benzyl chloride in dimethyl formamide at 50°C.; m.p. 82—83.5°C. from alcohol) and 13.5 g. acetyl sulphanilic acid chloride are suspended in 150 ml. absolute ethylene chloride and gaseous trimethylamine passed in until the pH value of the solution is 8. Stirring is continued for one hour, while controlling the pH value, the clear solution obtained is then mixed with water and the crystals which thereby separate are filtered off. 15 g. (86% of theory) 1-phenyl-3-benzyloxy-5-(bis-acetyl-sulphanilyl) aminopyrazole of m.p. 102°C. (decomposes) are obtained.

In order to split off the benzyl radical, the compound is dissolved in methanol/dioxan and hydrogenated with hydrogen in the presence of a palladium catalyst. 1-phenyl-3-hydroxy-5-(bis-acetyl-sulphanilyl)-aminopyrazole of m.p. 227°C. (decomposes) crystallizes out of the solution by concentration in a vacuum.

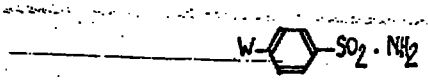
The crude product is suspended in methanol/dimethyl acetamide and admixed with an ethereal diazo-methane solution until a yellow coloration remains. In this way, a rapid solution and a vigorous evolution of nitrogen take place. Excess diazomethane is removed with glacial acetic acid, the solution is concentrated in a vacuum and the residue is diluted with water, whereby crystallization occurs. The resultant 1-phenyl-3-methoxy-5-(bis-acetyl-sulphanilyl)-aminopyrazole is saponified in the manner described in Example 1. The hydrolysis product is, after recrystallization, identical to the 1-phenyl-3-methoxy-5-sulphanilamido-pyrazole produced according to Example 1.

WHAT WE CLAIM IS:—

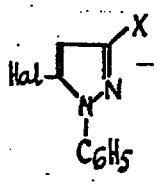
1. 1-phenyl-3-methoxy-5-sulphanilamido-pyrazole-1,2 and the acid addition

X being subsequently etherified to a methoxy group, after conversion to a hydroxyl group, where necessary.

Furthermore, a sulphonamide of the general formula:



in which W has the same meaning as above, may be reacted with a 5-halo-pyrazole of the general formula:



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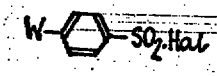
WHAT WE CLAIM IS:—

1. 1-phenyl-3-methoxy-5-sulphanilamido-pyrazole-1,2 and the acid addition

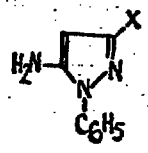
salts and the acyl derivatives thereof.

2. 1 - phenyl - 3 - methoxy - 5 - acetyl-sulphanilamido - pyrazole - 1,2.

3. Process for the production of 1 - phenyl-3 - methoxy - 5 - sulphanilamido - pyrazole-2, wherein a sulphonyl halide of the general formula:

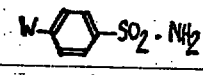


in which W is an acyl amino or nitro group convertible into an amino group by hydrolysis or reduction, respectively, and Hal is a halogen atom, is condensed with a 5-aminopyrazole of the general formula:

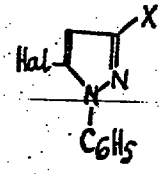


in which X is a methoxy group, a hydroxyl group or a benzyloxy group, and, if necessary, the substituent W and the substituent X converted into an amino group and a methoxy group, respectively.

4. Process for the production of 1-phenyl-3-methoxy - 5 - sulphanilamido - pyrazole - 1,2, wherein a sulphonamide of the general formula:



in which W is an acyl amino or nitro group convertible into an amino group by hydrolysis or reduction, respectively, or an alkali metal salt of such a sulphonamide, is condensed with a 5-halo-pyrazole of the general formula:



in which X is a methoxy, a hydroxyl group or a benzyloxy group, and, if necessary, the substituent W and the substituent X converted into an amino group and a methoxy group, respectively.

5. Process for the production of 1-phenyl-3-methoxy-5-sulphanilamido-pyrazole-1,2, substantially as hereinbefore described and with reference to either of the specific Examples.

6. 1-phenyl-3-methoxy-5-sulphanilamido-pyrazole-1,2, whenever prepared by the process according to any of claims 3 to 5.

CARPMAELS & RANSFORD,
Agents for the Applicants,
24, Southampton Buildings, London, W.C.2.

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