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SULFANILAMIDO PYRAZOLE COMPOUNDS

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6 Claims. (Cl. 260—239.9)

The present invention relates to sulfanilamidas and more particularly to sulfanilamido pyrazole compounds and to a process of making such compounds. The presinvention relates more specifically to 5-sulfanilamido-1,3-dialkyl or cycloalkyl pyrazole-1,2 compounds and to a process of making such compounds.

There have been known only a few sulfonamides of the pyrazole series. 5-sulfanilamido pyrazole-1,2 has been reported to have a good effect against pneumococci. 5-sulfanilamido-3-methyl pyrazole-1,2 and 5-sulfanilamido-3-methyl-1-phenyl-pyrazole-1,2 have also been described. Recently 5-sulfanilamido-1-phenyl pyrazole-1,2, i.e. a phenyl pyrazole compound which is unsubstituted in 3-position has been marketed. These known sulfanilamido pyrazole compounds, however, have a number of disadvantages. For instance, 5-sulfanilamido-3-methyl pyrazole-1,2 produces a rather low sulfonamide blood level, i.e., its adsorption by the musous membranes of the intestines is unsatisfactory so that it cannot be employed in the treatment of diseases which are ordinarily and successfully treated with sulfonamides such as pneumonia, angina, cystopyelitis, cholecystitis, and the like. 1-phenyl-5-sulfanilamido pyrazole-1,2 and 1-phenyl-3-methyl-5-sulfanilamido pyrazole-1,2 have a rather unsatisfactory effect upon Streptococcus infections as has been proved by tests with mice infected intraperitoneally with a highly pathogenic *Streptococcus pyrogenes Aronson* species.

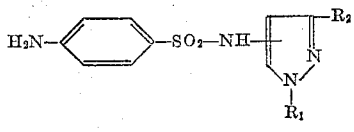
It is one object of the present invention to provide new sulfanilamido pyrazole compounds which are substituted by alkyl and/or cycloalkyl groups at least in 1-position, or in 1,3-position.

Another object of the present invention is to provide new and valuable pharmaceuticals which have a high chemotherapeutic activity against both Gram-positive and Gram-negative bacteria, which are highly soluble so that they are readily absorbed into the blood stream, and which provide a long-lasting high blood level.

A further object of the present invention is to provide a simple and effective process of making such compounds.

These and other objects of the present invention and advantageous features thereof will become apparent as the description proceeds.

It has been found that sulfanil amido pyrazoles of the formula



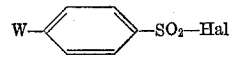
wherein

R_1 is selected from the group consisting of alkyl and cycloalkyl radicals, and

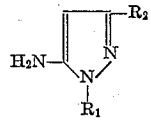
R_2 is selected from the group consisting of hydrogen, alkyl, and cycloalkyl radicals, the total number of carbon atoms in R_1 and R_2 ranging from 2 to 8,

are especially valuable sulfonamides. As stated above these new compounds have a very high activity against both Gram-positive and Gram-negative bacteria. Furthermore they produce long-lasting high blood levels in the body which property is great advantage for their therapeutical use. Due to their high solubility they are readily absorbed by the body. The corresponding acetylated compounds are also readily soluble so that there is no danger that these compounds will crystallize in the kidneys or in the urinary tract. This favorable combination of physico-chemical, bacteriostatic, and pharmocologica properties renders the new compounds especially valuable and provides a new group of compounds which are significantly superior to sulfonamides of the pyrazole series known heretofore.

The sulfanilamido pyrazoles according to the present invention can be obtained according to known processes. For instance, sulfonyl halides of the formula



wherein W is an amino group or a group convertible into an amino group, such as an acylamino or a nitro group, are reacted with amino pyrazole compounds of the formula

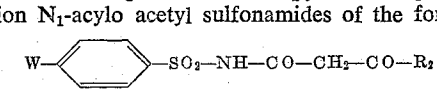


wherein R_1 and R_3 represent the same groups as indicated above.

The substituent W is then converted into the amino group.

The "reciprocal" method, i.e. the reaction of the corresponding halogeno pyrazole compounds with sulfonyl amides or their alkali metal salts can also be employed but gives satisfactory results only in such cases where the halogen atom is sufficiently activated by adjacent substituents.

The new compounds according to the present invention may also advantageously be prepared by reacting suitable open-chain sulfonamides with substituted hydrazines to cause ring closure to the pyrazole ring. In this reaction N_1-acylo acetyl sulfonamides of the formula



wherein W and R_2 represent the same substituents as indicated above, are reacted with hydrazines of the formula

$$H_2N—NH—R_1$$

wherein R_1 represents the same substituent as indicated above, in acid medium. W is then converted into the amino group. The β-keto acylo sulfonamides used as starting materials for this ring-closure reaction are obtained by reacting the alkali metal salts of sulfonamides with phenyl esters of β-keto carboxylic acids according to a process of producing N_1-acyl sulfonamides described in German Patent No. 926,491. In order to make aceto acetyl sulfonamides it is also possible to use the diketene process as described in "Berichte," vol. 83, page 558 (1950).

The present invention is illustrated by the following examples but is, of course, not limited thereto.

EXAMPLE 1

5-Sulfanilamido-1,3-Dimethyl Pyrazole-1,2

126 cc. of anhydrous phosphoric acid are mixed with 32 g. of methyl hydrazine sulfate in an ice bath. After stirring for 30 minutes, 45 g. of acetyl sulfanilic acid aceto acetylamide (melting point: 205–207° C.) are added thereto at 10° C. Stirring at 10° C. is continued for one hour and 27 g. of phosphorus pentoxide are added while cooling with ice. The mixture gradually becomes viscous and is stirred for another 3 hours at 10° C. Thereafter, water and concentrated ammonia are added until the reaction of the mixture is only weakly acid. 5-acetyl sulfanilamido-1,3-dimethyl pyrazole is precipitated in a yield of 75.5%. Melting point: 199–200° C.

The acetyl compound is saponified by heating on a steam bath with 3 moles of 4 N sodium hydroxide solution. 5-sulfanilamido-1,3-dimethyl pyrazole is precipitated from the saponification mixture by the addition of dilute hydrochloric acid. Melting point: 213–215° C.; yield: 87% of the theoretical amount.

EXAMPLE 2

5-Sulfanilamido-3-Propyl-1-Methyl Pyrazole-1,2

0.15 mole of acetylsulfanilic acid butyro acetylamide (melting point: 177–180° C.) and 0.22 mole of methyl hydrazine sulfate are condensed under about the same conditions as described in Example 1. 5-acetyl sulfanilamido-3-propyl-1-methyl pyrazole having a melting point of 142–145° C. is obtained in a yield of 73%. This compound, on saponification, yields 5-sulfanilamido-3-propyl-1-methyl pyrazole having a melting point of 168–169° C. The yield is 88% of the theoretical yield.

EXAMPLE 3

5-Sulfanilamido-3-Methyl-1-Butyl Pyrazole-1,2

0.15 mole of acetyl sulfanilic acid aceto acetylamide is reacted with 0.18 mole of butyl hydrazine by following the procedure described in Example 1. 5-sulfanilamido-3-methyl-1-butyl pyrazole having a melting point of 173–175° C. is obtained in a yield of 70%. The corresponding acetyl compound has a melting point of 145–148° C.

EXAMPLE 4

5-Sulfanilamido-3-Methyl-1-Cyclohexyl Pyrazole-1,2

0.15 mole of acetyl sulfanilic acid aceto acetylamide is reacted with 0.18 mole of cyclohexyl hydrazine hydrochloride by following the procedure described in Example 1. The melting point of the resulting acetyl compound is 230–231° C. and the melting point of 5-sulfanilamido-3-methyl-1-cyclohexyl pyrazole-1,2 obtained there from by saponification is 220–223° C. The total yield is 69% of the theoretical amount.

EXAMPLE 5

5-Sulfanilamido-3-Cyclohexyl-1-Methyl Pyrazole-1,2

20 g. of 1-methyl-3-cyclohexyl-5-amino pyrazole-1,2 (melting point: 169–172° C.), prepared by reacting hexahydrobenzoyl acetonitrile with methyl hydrazine sulfate in aqueous-alcoholic solution, are dissolved in 90 cc. of pyridine. To this solution 28.6 g. of acetyl sulfanilyl chloride are added in small portions whereby the temperature rises spontaneously. The reaction mixture is heated for one hour on a steam bath and is then poured into a mixture of 2 N hydrochloric acid and ice. The precipitated crystals are filtered off by suction and washed until neutral. They consist of 5-acetyl sulfanilamido-3-cyclohexyl-1-methyl pyrazole which has a melting point of 235–236° C. The yield is 85%.

Said acetyl compound is saponified by refluxing it with 150 cc. of 2 N sodium hydroxide solution for one and a half hours. After decolorizing with animal charcoal, the solution is acidified with 5 N acetic acid and the precipitated crystals are filtered off by suction and washed until neutral. 5-sulfanilamido-3-cyclohexyl-1-methyl pyrazole is obtained in a yield of 70%. It melts at 181–194° C. and, after recrystallization from ethanol, at 183–184° C.

EXAMPLE 6

5-Sulfanilamido-1,3-Dimethyl-Pyrazole-1,2

0.12 mole of acetyl sulfanilyl chloride is reacted with 0.1 mole of 1,3-dimethyl-5-amino pyrazole-1,2 (melting point: 78–79° C.) by following the procedure described in Example 5. 1,3-dimethyl-5-amino pyrazole-1,3 is obtained by reacting diacetonitrile with methyl hydrazine sulfate. 5-sulfanilamido-1,3-dimethyl pyrazole having a melting point of 213–215° C. is obtained in a yield of 50%. The melting point of the acetyl compound is 198–200° C.

EXAMPLE 7

5-Sulfanilamido-3-Ethyl-1-Methyl Pyrazole-1,2

0.1 mole of 1-methyl-3-ethyl-5-amino pyrazole-1,2 (melting point: 71–74° C.), prepared from propionyl acetonitrile and methyl hydrazine sulfate, is reacted with 0.11 moles of acetyl sulfanilyl chloride as described in Example 5. The resulting acetyl compound has a melting point of 157–159° C. On saponification, 5-sulfanilamido-3-ethyl-1-methyl pyrazole is obtained in a total yield of 55%; it has a melting point of 174–176° C.

EXAMPLE 8

5-Sulfanilamido-3-Isopropyl-1-Methyl Pyrazole-1,2

0.1 mole of 1-methyl-3-isopropyl-5-amino pyrazole-1,2 (melting point: 109–112° C.), prepared from isobutyroyl acetonitrile and methyl hydrazine sulfate, is reacted with 0.12 mole of acetyl sulfanilyl chloride by following the procedure described in Example 5. Thereby, 5-acetyl-sulfanilamido-3-isopropyl-1-methyl pyrazole-1,2 of the melting point 149–152° C. is obtained in a yield of 55%. On saponification, the corresponding sulfanilamido pyrazole of the melting point 160–163° C. is obtained in a yield of 85%.

The following compounds are obtained by proceeding as indicated in the attached table (see column 5).

The following starting materials are produced as described hereinafter:

(*a*) 1-methyl-3-butyl-5-amino pyrazole is prepared by reacting valeroyl acetonitrile with methyl hydrazine sulfate. It is an oil which was found to be of uniform composition on paper chromatographic investigation.

(*b*) 1,3-diethyl-5-amino pyrazole is prepared by reacting propionyl acetonitrile and ethyl hydrazine sulfate. Its melting point is 60–66° C.

In place of methyl hydrazine, butyl hydrazine, and cyclohexyl hydrazine as used as the one reaction component and of acetyl sulfanilic acid aceto acetamide and of acetyl sulfanilic acid butyro acetamide as the other reaction component in Examples 1 to 4, there may, of course, be used equimolecular amounts of other alkyl and cycloalkyl hydrazines and of other acetyl sulfanilic acid acylo acetamides while otherwise the procedure is followed as described in said examples.

Likewise, other alkyl and/or cycloalkyl substituted 5-amino pyrazole-1,2 compounds than those used in Examples 5 to 8 may be employed as the one reaction component while otherwise the procedure is about the same.

Of course, many changes and variations in the reaction components, in the reaction conditions, temperature and duration, in the methods of working up the reaction products, of saponifying the resulting acetyl sulfanilamido compounds, and of isolating and purifying the valuable new sulfanilamido pyrazole compounds may be made by those skilled in the art in accordance with the

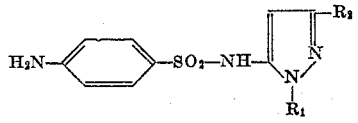
principles set forth herein and in the claims annexed hereto.

Ex. No.	Starting components		According to Example	Resulting sulfanilamido pyrazole compound	Melting point of the—	
	Sulfanilic acid compound	Hydrazine or pyrazole			Sulfanilamide, ° C.	Acetyl compound, ° C.
9	Acetyl sulfanilyl chloride	1-methyl-3-butyl-5-amiuo pyrazole (*a*) [1]	5	1-methyl-3-n-butyl	150–152	195–197
10	do	1,3-diethyl-5-amino pyrazole (*b*) [1]	5	1,3-diethyl	140–144	131–134
11	Acetyl sulfanilic acid butyro acetyl-amide.	Ethyl hydrazine sulfate	1	1-ethyl-3-propyl	140–141	144–147
12	Acetyl sulfanilic acid aceto acetyl-amide.	Propyl hydrazine	1	1-propyl-3-methyl	193–195	148–152
13	do	Isopropyl hydrazine hydrochloride	1	1-isopropyl-3-methyl	176–178	169–170
14	do	Ethyl hydrazine sulfate	1	1-ethyl-3-methyl	166–168	148–152

[1] See previous text.

We claim:

1. 1,3-dimethyl-5-sulfanilamido pyrazole-1,2.
2. 1-methyl-3-propyl-5-sulfanilamido pyrazole-1,2.
3. 1-ethyl-3-methyl-5-sulfanilamido pyrazole-1,2.
4. 1,3-diethyl-5-sulfanilamido pyrazole-1,2.
5. 1-propyl-3-methyl-5-sulfanilamido pyrazole-1,2.
6. A 5-sulfanilamido pyrazole-1,2 compound of the formula



wherein

R_1 is the member selected from the group consisting of alkyl with 1 to 4 carbon atoms and cyclohexyl, and

R_2 is the member selected from the group consisting of hydrogen, alkyl with 1 to 4 carbon atoms, and cyclohexyl,

said members R_1 and R_2 together having between 2 carbon atoms and 8 carbon atoms.

References Cited in the file of this patent

Okeda et al.: J. Pharm. Soc. Japan, vol. 76, pages 521–4 (1956).

UNITED STATES PATENT OFFICE

CERTIFICATE OF CORRECTION

Patent No. 3,028,382 April 3, 1962

Johann Daniel Achelis et al.

It is hereby certified that error appears in the above numbered patent requiring correction and that the said Letters Patent should read as corrected below.

Column 1, line 10, for "sulfanilamidas" read -- sulfanilamides --; line 28, for "musous" read -- mucous --; column 2, lines 13 and 14, for "pharmocologica" read -- pharmocological --; column 4, line 6, for "194° C." read -- 184° C. --.

Signed and sealed this 17th day of July 1962.

(SEAL)
Attest:

ERNEST W. SWIDER
Attesting Officer

DAVID L. LADD
Commissioner of Patents