

Patented Oct. 5, 1943

2,330,828

UNITED STATES PATENT OFFICE

2,330,828

SULPHAMIDO-BENZENE-AZO-PYRAZOLONE

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No Drawing. Application February 15, 1941, Serial No. 379,040

2 Claims. (Cl. 260-163)

The present invention relates to therapeutic pyrazolone derivatives, and it particularly relates to azo-pyrazolone derivatives effective against streptococci and pneumococci.

It is among the objects of the present invention to prepare novel azo-pyrazolone derivatives with enhanced therapeutic efficiency, which have improved bacteriostatic, analgesic and antiseptic action, and which may be readily excreted.

Another object is to provide azo-pyrazolone derivatives which are soluble, highly effective upon streptococcus and pneumococcus organisms and which do not cause nausea, headache and vomiting.

Still further objects and advantages will appear in the more detailed description set forth below, it being understood however that this more detailed description is given by way of illustration and explanation only, and not by way of limitation, since various changes therein may be made by those skilled in the art without departing from the scope and spirit of the present invention.

It has been found that benzene-azo-pyrazolones, and particularly sulphamido-benzene-azo-pyrazolones are quite effective from a therapeutic point of view and nevertheless do not give rise to any symptoms of nausea, headache and vomiting.

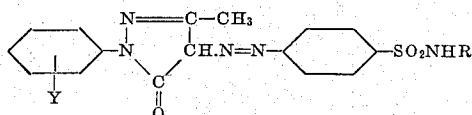
The preferred compounds which have been utilized are those which may be characterized by the following formula:



Where R^1 and R^3 are aryl nuclei and preferably benzene or phenyl nuclei and less preferably tolyl or xylol nuclei; where R^2 is preferably a heterocyclic nucleus, pyrazolone being preferred, and being much more satisfactory than thiazole, pyrimidine, uracil, pyridine or other monazine, diazine, triazine, or similar heterocyclic nuclei; where R^4 and R^5 are hydrogen, alkyl, aryl, a 2-pyridine radical, a 2-thiazole radical or a pyrimidine radical; and where Y is hydrogen, sulpho, ethoxy, methoxy, hydroxyl, or halogen, or



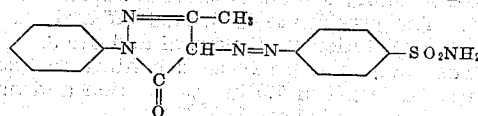
The preferred compounds have the formula:



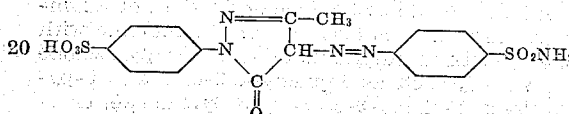
where Y represents H; SO_3H ; ethoxy; methoxy;

hydroxyl; or halogen; R represents a 2-pyridine radical, a 2-thiazole or a pyrimidine radical.

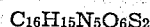
The preferred compound of the azo-pyrazolone series which has been found to be most satisfactory and effective is: 4-sulphamido-benzene-(1-azo-4)-1-phenyl-3-methyl-5-pyrazolone. This compound has the empirical formula $C_{16}H_{15}N_5O_3S$ and has the structural formula



Another compound which has been found to be quite effective is: 4-sulphamido-benzene-(1-azo-4)-1-phenyl-sulphonic acid)-3-methyl-5-pyrazolone, and has a structural formula



This compound has the empirical formula



These compounds are most satisfactorily made by combining together diazotized sulphanilamide and then slowly adding it to the solution of the pyrazolone in a weak alkali such as sodium carbonate, the solution being kept alkaline at all times.

The resultant compound will be precipitated or may be salted out and then is filtered and washed.

EXAMPLE I

Preparation of 4-sulphamido-benzene-(1-azo-4)-1-phenyl-3-methyl-5-pyrazolone

First 17.2 grams of sulphanilamide and 20 c. c. concentrated hydrochloric acid are dissolved, with warming, if necessary in 200 c. c. of water. This solution is cooled in ice and then diluted to one liter with water. Ice is then added and the mixture cooled to 0 to 10° C.

While stirring, a solution containing 7 grams of sodium nitrite is very slowly added. Any excess nitrous acid is destroyed by adding a small quantity of sulphamic acid.

Then 17.4 grams of 1-phenyl-3-methyl-5-pyrazolone are dissolved in 400 c. c. H_2O with the addition of 40 grams anhydrous sodium carbonate and cooled to 0 to 10° C. The solution of diazotized sulphanilamide prepared above is then slowly added to the cold solution of 1-phenyl-3-

methyl-5-pyrazolone while rapidly stirring. Care is taken to keep the solution alkaline, more sodium carbonate being added if necessary.

The reaction mixture is let stand for one or two hours, and the precipitate formed is filtered, washed with water until neutral, and then dried.

The resultant compound has a molecular weight of about 357, an orange yellow color, is insoluble in water but soluble in alcohol, acetone and benzene and has a melting point of about 263° C.

EXAMPLE II

Preparation of the sodium salt of 4-sulphamido-benzene-(1-azo-4) - 1 - (4 - phenyl-sulphonic acid) - 3-methyl-5-pyrazolone

First 25.3 grams of 1-(4-sulphophenyl)-3-methyl-5-pyrazolone are dissolved in 400 c. c. water containing 40 grams of Na₂CO₃ and cooled to 0 to 10° C. with ice.

The solution of diazotized sulphanilamide is then very slowly added to this solution while rapidly stirring. The solution is kept alkaline at all times and is then permitted to stand for two hours. The sodium salt thus produced is more soluble than the compound produced in Example I.

If the sodium salt is not completely precipitated upon standing, sodium chloride is added to salt it out. The precipitate is filtered off and washed with salt solution until neutral and dried.

The compound produced according to Example II has a pH of 7.0 in 1% solution and has a melting point of above 350° C.

Where in Example II the benzene group attached to the one position of the pyrazolone contains a sulpho group, this sulpho group may be readily converted into a sulphamido group.

Instead of the pyrazolone derivatives of Examples I and II, it is also possible to combine with the diazotized sulphanilamide other pyrazolone derivatives such as 1-phenyl-2,3-dimethyl-5-pyrazolone, 1-phenyl-3-carboxy-5-pyrazolone, or 1-(4-sulphophenyl)-3-carboxy-5-pyrazolone.

It is also possible to treat any one of these pyrazolone derivatives or the pyrazolone derivatives of Examples I and II with nitrous acid to form a derivative having a —NOH group at the 4 position which then may be reduced to form an amino group. This amino group may be diazotized and coupled with the same or a different pyrazolone derivative to give a sulphamido-pyrazolone-azo-pyrazolone compound of great value.

In some instances it may also be desired to re-

place one or both of the nitrogen atoms of the azo linkage with arsenic atoms. This may be done in the same manner as it is possible to prepare arseno-sulphanilamide. In preparing arseno-sulphanilamide, the sulphanilamide is diazotized and then treated with sodium arsenite to replace the amino group with an arseno group. Finally upon reduction the two benzene nuclei will be linked together with the arseno group being at 4 position in respect to the sulphamido group.

The sulphamido-azo-pyrazolones of the present application avoid the toxic symptoms usually associated with sulphanilamide derivatives, and there is a marked elimination of the tendency to nausea, vomiting, headache, hematuria, due to renal calculi and toxic dermatoses. These sulphamido-azo-pyrazolone derivatives also have most satisfactory analgesic and antipyretic effect. For intravenous injection the sodium salt may be utilized with a dosage from 5 to 7½ grains, while the oral dose may be 1 gram of 15 grains at morning and 1 gram of 15 grains at night. The sulphamido-azo-pyrazolone derivative has a high bacteriostatic and bacteriocidal action against mono- and diplo-coccus organisms. When used intravenously, the sodium salt as, for example, produced where Example II is used at a pH of 6 to 8 and may be buffered in isotonic solutions.

Although not preferred, the sulphamido-azo-pyrazolone may be combined with nicotinic acid, thiamin chloride, ascorbic acid, and other water soluble vitamins as well as with methylene blue.

Many other changes could be effected in the particular features of sulphamido-benzene-azo-pyrazolone and methods of making the same disclosed, and in specific details thereof, without substantially departing from the invention intended to be defined in the claims, the specific description herein merely serving to illustrate certain elements by which, in one embodiment, the spirit of the invention may be effectuated.

What is claimed is:

1. A therapeutic agent comprising a sulphonated sulphamido-benzene-azo-pyrazolone, the benzene being unsubstituted in the 2, 3, 5 and 6 positions.

2. A therapeutic agent comprising 4-sulphamido-benzene-(1-azo-4)-1-(4-phenyl-sulphonic acid)-3-methyl-5-pyrazolone, the benzene being unsubstituted in the 2, 3, 5 and 6 positions.

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