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SUBSTITUTED 1-PHENYL-2,3-DIMETHYL-4-MORPHOLINO METHYL PYRAZOLONE-(5) COMPOUNDS AND PROCESS OF MAKING SAME

Harm Siemer, Konstanz, and Adolph Doppstadt, Konstanz-Litzelstetten, Germany, assignors to Ravensberg G.m.b.H., Chemische Fabrik, Konstanz, Germany, a corporation of Germany

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The present invention relates to valuable analgesic agents and more particularly to substituted 1-phenyl-2,3-dimethyl-4-morpholino methyl pyrazolone-(5) compounds and to a process of making same.

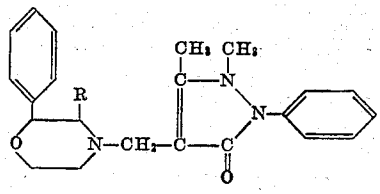
It is one object of the present invention to provide new and valuable analgesic agents which are far superior in their analgesic activity than any of the commonly used analgesic agents such as 1-phenyl-2,3-dimethyl-4-dimethylamino pyrazolone-(5), salicylic acid amide, aceto phenetidine, and others.

Another object of the present invention is to provide a new and simple process of producing such valuable analgesic 1-phenyl-2,3-dimethyl-4-morpholino methyl pyrazolone-(5) compounds.

A further object of the present invention is to provide valuable analgesic preparations such as tablets or injectable solutions containing, as active analgesic ingredient, said 1-phenyl-2,3-dimethyl-4-morpholino methyl pyrazolone-(5) compounds.

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

The new analgesic substituted 1-phenyl-2,3-dimethyl-4-morpholino methyl pyrazolone-(5) compounds according to the present invention are compounds of the following formula



In said formula R indicates a lower alkyl group with 1 to 5 carbon atoms arranged in a straight or branched chain.

Such new and valuable analgesic 1-phenyl-2,3-dimethyl-4-morpholino methyl pyrazolone compounds are produced in a surprisingly simple manner and in a good yield by adding to an alcoholic solution of the corresponding substituted morpholine compounds, for instance, to 2-phenyl-3-methyl morpholine, formaldehyde and an aqueous hydrochloric acid solution of 1-phenyl-2,3-dimethyl pyrazolone-(5) and stirring the mixture on the water bath at a temperature of 25–30° C., for several hours, preferably for 2 hours.

When proceeding in this manner, the hydrochlorides of the reaction products, such as the hydrochloride of 1-phenyl-2,3-dimethyl-4-(2'-phenyl-3'-methyl morpholino methyl) pyrazolone-(5) precipitate from the reaction solution and can be recrystallized from a mixture of alcohol and acetone, if required. Addition of alkali hydroxide solution to the aqueous solution of the hydrochlorides yields the corresponding bases which are obtained in solid form.

The new compounds have a high analgesic activity. The following table shows the results obtained on pharmacologically testing the new compound in comparison with well-known analgesic agents. The dose given is the mean therapeutic dose (AD_{50} II) determined according to the method of Wolff-Hardy by focusing rays of a strong light source on the blackened forehead of a test individual.

TABLE

Compound tested	AD_{50} II
1-Phenyl-2,3-dimethyl-4-dimethyl amino pyrazolone-(5)	120
Salicylic acid amide	540
Aceto phenetidine	500
1-Phenyl-2,3-dimethyl-4-(2'-phenyl-3'-methyl morpholino methyl) pyrazolone-(5).HCl	55

It is evident that the new compound has an analgesic activity which is twice as strong as that of the known pyrazolone derivative and about ten times as strong as that of salicylic acid amide or aceto phenetidine. When taking into consideration that the analgesic activity of 1-phenyl-2,3-dimethyl pyrazolone amounts to only one third of the activity of the tested compound 1-phenyl-2,3-dimethyl-4-dimethylamino pyrazalone, it follows that the analgesic activity of the first mentioned 1-phenyl-2,3-dimethyl pyrazolone is increased by about six times by introducing into its molecule the 2-phenyl-3-methyl morpholino methyl group.

The substituted 1-phenyl-2,3-dimethyl-4-morpholino methyl pyrazolone-(5) compounds according to the present invention, thus, possess a surprisingly high analgesic activity which could not be expected from their composition. Therefore, they represent new and valuable pharmaceutical compounds, especially in the form of their pharmaceutically acceptable acid addition salts. Solutions of the salts, especially solutions of salts with organic acids, are suitable for injection because they are well tolerated by the human body.

The analgesic compounds according to the present invention can be used in the form of their readily soluble salts with gentisic acid or ascorbic acid for preparing highly concentrated injectable solutions thereof. Such solutions are prepared, for instance, by dissolving the insoluble base, suspended in finely divided form in water, by the addition of the corresponding organic acid, whereby the pH-value is adjusted to a neutral or, respectively, weakly acid pH-value between about 6.0 and about 7.0. The gentisic acid salt of the new pyrazolone compound can also be prepared, for instance, by reacting equimolecular amounts of gentisic acid and the base in a mixture of methanol and acetone while heating. The resulting salt crystallizes on cooling. It is separated from the methanol-acetone mixture and is then dissolved in distilled water to form a solution of the desired concentration.

The following examples serve to illustrate the present invention without, however, limiting the same thereto.

Example 1

35.4 g. of 2-phenyl-3-methyl morpholine are dissolved in 50 cc. of methanol. 20 cc. of an aqueous 40% formaldehyde solution are added thereto while cooling. A solution of 37.6 g. of 1-phenyl-2,3-dimethyl pyrazolone-(5) in a mixture of 35 cc. of water and 20 cc. of concentrated hydrochloric acid are added at once to said reaction mixture. The pH-value of the resulting mixture is adjusted to a pH between about 2.0 and about 3.0 and the acid reaction mixture is then stirred on the water bath at a temperature of 25–30° C. for two hours. The precipitated hydrochloride is recrystallized from a mixture of methanol and acetone (1:1).

The melting point of the recrystallized hydrochloride of 1-phenyl-2,3-dimethyl-4-(2'-phenyl-3'-methyl mor-

pholino methyl) pyrazolone-(5) is 171–172° C. (with decomposition). Yield: 81.6%. The corresponding base is obtained by rendering alkaline the solution of said hydrochloride by the addition of sodium hydroxide solution, extraction by means of chloroform and evaporation of the extracting solvent. It has a melting point of 149–150° C.

Example 2

38.2 g. of 2-phenyl-3-ethyl morpholine are reacted with 37.6 g. of 1-phenyl-2,3-dimethyl pyrazolone-(5) by following the procedure described hereinabove in Example 1. The yield of 1-phenyl-2,3-dimethyl-4(2'-phenyl-3'-ethyl morpholino methyl) pyrazolone-(5) hydrochloride is 82.2%. The melting point of the hydrochloride is 174–175° C. (with decomposition) after recrystallization from a mixture of acetone and methanol (1:1).

Example 3

The free base of 1-phenyl-2,3-dimethyl-4-(2'-phenyl-3'-methyl morpholino methyl) pyrazolone-(5) obtained according to Example 1 is dissolved in methanol. An equimolecular amount of gentisic acid is added thereto and the mixture is heated under reflux for one hour. After cooling, an amount of acetone corresponding to the amount of methanol is added, whereupon the addition salt with gentisic acid crystallizes. It melts at 169–170° C. (with decomposition).

Example 4

1.575 g. of ascorbic acid and 0.425 g. of gluconic acid lactone are dissolved in 15 cc. of distilled water at a temperature of about 40° C. Thereto there are added 3.75 g. of 1-phenyl-2,3 - dimethyl - 4 - (2'-phenyl-3'-methyl-morpholino methyl)-pyrazolone-(5) and, subsequently, 3.5 g. of salicylamide-O-sodium acetate. The mixture is then filled up to a volume of 25 cc. with distilled water and the filtered solution is filled into ampoules of a capacity of 5 cc. The ampoules are sterilized according to customary methods.

Example 5

1-phenyl-2,3-dimethyl-4 - (2'-phenyl - 3' - methylmorpholinomethyl)-pyrazolone-(5)is reacted, in accordance with Example 3, with an equimolar amount of salicylamide-O-acetic acid. After cooling, the reaction solution is stirred with ether until it remains turbid and crystals precipitate on standing. The crystalline salt of the salicylamide-O-acetic acid melts at a temperature between 112° C. and 113° C. (with decomposition). This salt is suitable for making tablets.

In place of the 2-phenyl-3-methyl morpholine compound used in the preceding examples, there may be employed equimolecular amounts of other 2-phenyl morpholine compounds substituted in 3-position by a lower alkyl radical having a straight or branched chain, such as 2-phenyl-3-n-propyl morpholine, 2-phenyl-3-isopropyl morpholine, and the like, while otherwise the procedure is the same as given in said examples.

In place of the hydrochloride and the gentisic acid salt described in the preceding examples, there may be prepared other acid addition salts such as salts with inorganic acids, for instance, with sulfuric acid, phosphoric acid, hydrobromic acid, nitric acid, or with other organic acids, such as with tartaric acid, citric acid, malic acid, acetic acid, benzoic acid, salicylic acid, nicotinic acid, and others.

For therapeutical administration the new 1-phenyl-2,3-dimethyl-4-(2'-phenyl-3'-lower alkyl morpholino methyl) pyrazolone-(5) compounds or their acid addition salts and preferably their salts with gentisic acid or ascorbic acid are incorporated into pharmaceutical excipients and are used, for instance, in the form of tablets, dragees, capsules, pills, suppositories, sirups, and the like preparations. Such tablets and other preparations contain at least 15% of the active ingredient. Its percentage in the preparation may be varied and is preferably between about 15% and about 60% of the weight of the tablet or preparation. It is, of course, also possible to use greater amounts of the active ingredient although with such greater amounts administration of a suitable dosage becomes more difficult. Preferred preparations according to the present invention are prepared in such a manner that a dosage unit form of tablet and the like preparation contains between about 50 mg. and about 250 mg. of an acid addition salt of 1-phenyl-2,3-dimethyl-4-(2'-phenyl-3'-lower alkyl morpholino methyl) pyrazolone-(5).

When preparing tablets, pills, dragees, and the like shaped solid preparations for oral administration, the commonly used diluting agents, binders, lubricants, and other tableting adjuvants are employed such as sugar, dextrose, lactose, starch, methyl cellulose, yeast extract, agar, tragacanth, and as lubricants stearic acid, magnesium stearate, and others.

Injectable solutions of the new analgesic compounds according to the present invention are prepared as described hereinabove in Example 3.

The effective daily dose for an adult person is between about 100 mg. and about 800 mg. The preferred daily dose is about 400 mg. The dose is preferably given subdivided in 4 doses in intervals of 2 hours to 3 hours. Of course, larger or smaller doses may also be given if they are required.

With respect to the Wolff-Hardy method for determining the therapeutic dose as mentioned in columne 2, lines 2–6, it may be mentioned that the prolongation of the reaction time in seconds subsequent to administration (30 to 45 minutes) was taken as the criterion concerning the analgesic activity of the substances tested. In this connection a prolongation of the reaction time by 8 seconds represents the analgesic stage II. In carrying out the tests, the preparations were injected in mice weighing from 20 g. to 25 g.

We claim:

1. 1-phenyl-2,3-dimethyl-4-(2'-phenyl-3'-methyl morpholino methyl) pyrazolone-(5).

2. 1-phenyl-2,3-dimethyl-4-(2' - phenyl - 3' - ethyl morpholino methyl) pyrazolone-(5).

3. The gentisic acid salt of 1-phenyl-2,3-dimethyl-4-(2'-phenyl-3'-methyl morpholino methyl) pyrazolone-(5).

4. The hydrochloride of 1-phenyl-2,3-dimethyl-4-(2'-phenyl-3'-methyl morpholino methyl) pyrazolone-(5).

5. The hydrochloride of 1-phenyl-2,3-dimethyl-4-(2'-phenyl-3'-ethyl morpholino methyl) pyrazolone-(5).

6. A substituted 1-phenyl-2,3-dimethyl-4-morpholino methyl pyrazolone-(5) compound selected from the group consisting of 1-phenyl-2,3-dimethyl-4-(2'-phenyl-3'-lower alkyl morpholino methyl) pyrazolone-(5) and its non-toxic pharmaceutically acceptable acid addition salts.

7. In the process of producing 1-phenyl-2,3-dimethyl-4-morpholino methyl pyrazolone-(5) compounds selected from the group consisting of 1-phenyl-2,3-dimethyl-4-(2'-phenyl-3'-lower alkyl morpholino methyl) pyrazolone-(5) and its non-toxic, pharmaceutically acceptable acid addition salts, the step which comprises gently heating an alcoholic solution of 2-phenyl-3-lower alkyl morpholine and formaldehyde with an aqueous acid solution of 1-phenyl-2,3-dimethyl pyrazolone-(5) at a pH between about 2.0 and about 3.0 and separating the precipitated acid addition salt of the reaction product from the reaction mixture.

8. An analgesic composition comprising, as analgesic ingredient, not less than 15% of 1-phenyl-2,3-dimethyl-4-(2'-phenyl-3'-lower alkyl morpholino methyl) pyrazolone-(5) and a significant amount of a pharmaceutical carrier.

9. An injectable analgesic composition comprising, as analgesic ingredient, not less than 10% of the water soluble acid addition salt of 1-phenyl-2,3-dimethyl-4-(2'-phen-

yl-3'-lower alkyl morpholino methyl) pyrazolone-(5) dissolved in water.

10. The process of alleviating pain comprising administering to persons suffering from pain a composition comprising not less than 0.1% of a 1-phenyl-2,3-dimethyl-4-morpholino methyl pyrazolone-(5) compound selected

from the group consisting of 1-phenyl-2,3-dimethyl-4-(2'-phenyl-3'-lower alkyl morpholino methyl) pyrazolone-(5) and its non-toxic, pharmaceutically acceptable acid addition salt.

No references cited.