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3,005,818

1-PHENYL-2,3-DIMETHYL-4-MORPHOLINO METHYL PYRAZOLONE-(5) COMPOUNDS

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3 Claims. (Cl. 260—247.2)

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.

The present application is a continuation-in-part of co-pending application Serial No. 717,332, now Patent No. 2,943,022, filed February 25, 1958, and being entitled "Substituted 1-phenyl-2,3-dimethyl-4-morpholino methyl pyrazolone-(5) compounds and process of making the same."

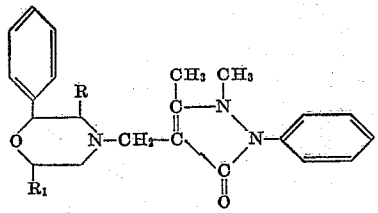
It is one object of the present invention to provide new and valuable analgesic agents which are far superior in their analgesic activity than any of the commonly used analgesic agents such as 1-phenyl-2,3-dimethyl-4-dimethylamino pyrazolone-(5), salicylic acid amide, aceto phenetidine, and others.

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-morpholine methyl pyrazolone-(5) compounds according to the present invention are compounds of the following formula



In said formula:

R indicates a lower alkyl radical with 1 to 5 carbon atoms arranged in a straight or branched chain, and

R_1 indicates hydrogen or a lower alkyl radical with 1 to 5 carbon atoms 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 or to 2-phenyl-3,6-dimethyl 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) or the hydrochloride of 1-phenyl-2,3-dimethyl-4-(2'-phenyl-3',6'-dimethyl 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.

When using optically active substituted morpholine compounds as the one reaction component, the corresponding optically active 1-phenyl-2,3-dimethyl-4-morpholino methyl pyrazolone compounds are obtained which cause rotation of the plane of polarized light in the same direction.

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
1 - phenyl - 2,3 - dimethyl - 4 - (2' - phenyl-3',6'-dimethyl morpholino methyl) pyrazolone-(5).HCl	59

It is evident that the new compounds have an analgestic activity which is twice as strong as that of the known pyrazolone derivative and about ten times as strong as that of salicyclic 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 pyrazolone, 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 or the 2-phenyl-3,6-dimethyl morhpolino methyl group.

The compounds which contain the 2-phenyl-3,6-di-(lower) alkyl morpholino methyl group have the same analgesic and antiphlogistic effect as the substances which contain the 2-phenyl-3-(lower) alkyl morpholino methyl group, but have the further advantage that their toxicity is only about half that of said 3-alkyl compounds. In addition thereto it has been found that by using the 3,6-dialkylated compounds a better hypnotic effect is obtained than with the 3-alkylated compounds.

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 coulld 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 in-

soluble 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 pyrozolone 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 is 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 hydrocholride of 1-phenyl-2,3-dimethyl-4-(2'-phenyl-3'-methyl morpholino 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

37.7 g. of the free base of 1-phenyl-2,3-dimethyl-4-(2'-phenyl-3'-methyl morpholino methyl) pyrazolone-(5) obtained according to Example 1 are dissolved in 50 cc. of methanol. 15.4 g. of gentisic acid are added thereto and the mixture is heated under reflux for one hour. 50 cc. of acetone are added to the reaction mixture, 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. 3.75 g. of 1-phenyl-2,3-dimethyl-4-(2'-phenyl-3'-methyl morpholino methyl) pyrazolone-(5) and, thereafter, 3.5 g. of salicylamide-O-sodium acetate are added thereto. The mixture is then filled up with distilled water to a volume of 25 cc. and the filtered solution is filled into ampoules of a capacity of 5 cc. each. The ampoules are sterilized according to customary methods.

Example 5

37.7 g. of 1-phenyl-2,3-dimethyl-4-(2'-phenyl-3'-methyl morpholino methyl) pyrazolone-(5) are reacted by following the procedure described in Example 3, with 19.5 g. 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 pyrazolone compound with salicylamide-O-acetic acid melts at a temperature between 112–113° C. (with decomposition). This salt is suitable for making tablets.

Example 6

38.2 g. of 2-phenyl-3,6-dimethyl morpholine are dissolved in 50 cc. of methanol. 20 cc. of an aqueous 40% formaldehyde solution are added thereto while cooling. 37.6 g. of 1-phenyl-2,3-dimethyl pyrazolone-(5) dissolved 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 reaction mixture is then adjusted to a pH between about 2 and 3. Stirring of the reaction mixture on a water bath is continued at 25–30° C. for two hours. The precipitated hydrochloride is recrystallized from a mixture of methanol and acetone.

Melting point of 1-phenyl-2,3-dimethyl-4-(2'-phenyl-3', 6'-dimethyl morpholino methyl) pyrazolone-(5) hydrochloride: 135–137° C. (with decomposition). Yield 83.5%.

The corresponding base which is obtained by rendering alkaline the aqueous solution of the hydrochloride, extracting the alkaline solution with an organic solvent, such as chloroform, and evaporating the solvent from the extract, has a melting point of 132–133° C.

In place of the 2-phenyl-3-methyl morpholine or the 2-phenyl-3,6-dimethyl morpholine compounds used in the preceding examples, there may be employed equimolecular amounts of other substituted 2-phenyl compounds substituted in 3-position or in 3- and 6-positions by lower alkyl radicals having a straight or branched chain, such as 2-phenyl-3-n-propyl morpholine, 2-phenyl-3,6-di-n-propyl morpholine, 2-phenyl-3-isopropyl morpholine, 2-phenyl-3,6-diisopropyl 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 therapeutic administration the new 1-phenyl-2,3 - dimethyl - 4-(2' - phenyl-3'-lower alkyl morpholino methyl) pyrazolone-(5) compounds or 1-phenyl-2,3-dimethyl - 4 - (2'-phenyl-3',6'-di(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) or 1-phenyl - 2,3 - dimethyl-4-(2'-phenyl-3',6'-di-(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 4000 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 column 2, 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.

Clinical tests with the new compounds have confirmed the above given pharmacological tests and have shown that they have not only a surprisingly high analgesic effect but also a remarkable antiphlogistic-antiedematous effect. They produce complete freedom from pain within a few days of administration. They eliminate inflammation within a short period of time. They permit considerable reduction of the amounts of opiates to be administered. No toxic effects nor any disagreeable side-effects have been observed on administration of these compounds. They are well tolerated, especially by patients with a high sensitivity of the gastro-intestinal tract to drugs. No drug addiction has been observed.

The novel compounds are characterized by a very low toxicity as was proven by the pharmacological tests carried out with male mice in accordance with the method of Litchfield and Wilcoxon. In carrying out said tests, the testing substances were dissolved in a physiological solution of sodium chloride and the mice injected therewith subcutaneously. Each dose was dispensed in 0.5 cc. of

the solvent per 20 g. of mouse weight. The lethal dose LD_{50} was determined in a testing period of 24 hours.

TABLE

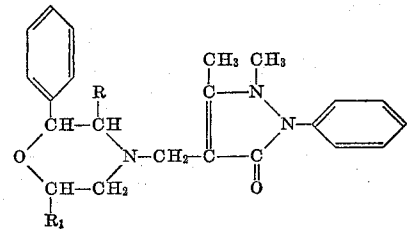
Compound tested:	LD_{50} mg./kg.
1 - phenyl-2,3-dimethyl--4-(2'-phenyl-3'-methyl morpholino methyl) pyrazolone-(5).HCl	95.4
1 - phenyl - 2,3-dimethyl-4-(2'-phenyl-3',6'-dimethyl morpholino methyl) pyrazolone-(5).HCl	199

We claim:

1. 1 - phenyl - 2,3-dimethyl-4-(2'-phenyl-3',6'-dimethyl morpholino methyl) pyrazolone-(5).

2. The hydrochloride of 1-phenyl-2,3-dimethyl-4-(2'-phenyl-3',6'-dimethyl morpholino methyl) pyrazolone-(5).

3. The 1-phenyl-2,3-dimethyl-4-morpholino methyl pyrazolone compound selected from the group consisting of the 1-phenyl-2,3-dimethyl-4-morpholino methyl pyrazolone compound of the formula



in which formula

R and R_1 indicate lower alkyl radicals with 1 to 5 carbon atoms,

and its non-toxic pharmaceutically acceptable acid addition salts.

References Cited in the file of this patent

UNITED STATES PATENTS

2,943,022 Siemer et al. ---------- June 28, 1960

UNITED STATES PATENT OFFICE

CERTIFICATE OF CORRECTION

Patent No. 3,005,818 October 24, 1961

Harm Siemer 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 2, line 48, for "morhpolino" read -- morpholino --; line 61, for "coulld" read -- could --; column 3, line 5, for "pyrozolone" read -- pyrazolone --; line 29, for "hydrocholride" read -- hydrochloride --.

Signed and sealed this 3rd day of April 1962.

(SEAL)
Attest:

ERNEST W. SWIDER
Attesting Officer

DAVID L. LADD
Commissioner of Patents