1,045,544

PATENT SPECIFICATION

NO DRAWINGS

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Int. Cl.:—C 07 d 49/08

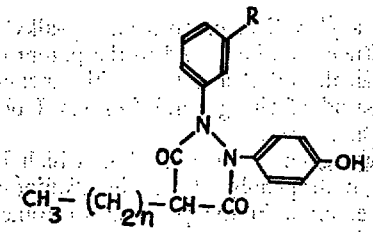
COMPLETE SPECIFICATION

New Derivatives of Pyrazolidines their production and use

We, J. R. GEIGY A.G. a body corporate organised according to the laws of Switzerland, of 215, Schwarzwaldallee, Basle, Switzerland, 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 concerns new derivatives of 1,2 - diphenyl - 3,5 - dioxo-pyrazolidine which have valuable pharmacological properties. 1,2 - Diphenyl - 3,5-dioxo - 4 - *n* - butyl - pyrazolidine, (phenylbutazone), as a medicament has attained great therapeutic importance in particular for the treatment of acute and chronic inflammatory diseases.

It has now been found that 4-substituted 1,2-diaryl-3,5-dioxo-pyrazolidines of the general formula I,



(I)

wherein R represents an alkyl radical having at most 3 carbon atoms, and

n represents 2—4,

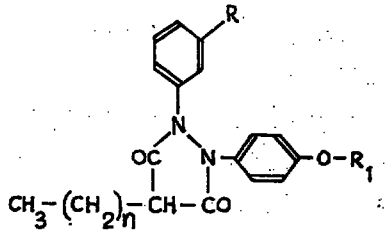
and their salts with inorganic and organic bases also possess valuable antiphlogistic properties. The compounds of the general formula I, e.g. 1-(*m*-tolyl)-2-(*p*-hydroxy-phenyl)-4-*n*-butyl-3,5-dioxo-pyrazolidine, are favourably distinguished from similar compounds with regard to side effects. They are also superior in their great intensity of action, therefore permitting dosages to be considerably decreased, and reducing the amount of foreign matter in the organism. This also facilitates the parenteral, in particular the intramuscular administration. In animal tests (rat) the previously mentioned 1-(*m*-tolyl)-2-(*p*-hydroxy-phenyl)-4-*n*-butyl-3,5-dioxo-pyrazolidine does not show any inhibiting action on the elimination of electrolytes stimulated by sulphonamide diuretics.

Furthermore, the strong inhibition of biosyntheses of sulphated polysaccharides such as chondroitin sulphuric acid in granulation tissue, as determined in animal experiments, is noteworthy.

The new compounds of general formula I are suitable, for example, for the treatment of rheumatic diseases, for which purposes they can be administered *per os* or rectally, or parenterally in the form of aqueous solutions of their salts, e.g. intramuscularly or intravenously.

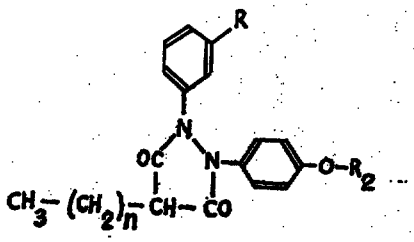
In the above general formula I, the substituent in the 4-position of the pyrazole ring is an *n*-propyl, *n*-butyl or *n*-pentyl radical corresponding to the meaning of n. R is a methyl, ethyl, *n*-propyl or isopropyl radical.

The new compounds of the general formula I are produced by treating a compound of the general formula II



(II)

wherein R_1 is an arylmethyl or diarylmethyl radical and R and n have the meanings given above, with catalytically activated hydrogen until substantially an equimolar amount of hydrogen has been taken up, or by subjecting a compound of the general formula III



(III)

wherein R_2 is a carboxylic acyl radical or an α-alkoxy-alkyl radical, whereby the alkyl radical of the alkoxy substituent can be bound to the parent chain in the form of a ring, e.g. a tetrahydropyranyl radical, and R and n have the meanings given above, to solvolysis. If desired, the compound of the general formula I obtained is converted into a salt with an inorganic or organic base.

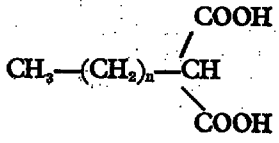
Starting materials of the general formula II in which R_1 is preferably the benzyl or benzhydryl radical, are hydrogenolysed e.g. in alkaline-aqueous solution or in an inert organic solvent, e.g. ethanol, in the presence of Raney nickel or a noble metal catalyst, e.g. palladium on charcoal. The hydrogenolysis can be performed at room temperature and atmospheric pressure; under more drastic conditions, the hydrogenation sometimes has to be broken off after the theoretical amount of hydrogen has been taken up in order to avoid side reactions.

Dilute hydrochloric acid in methanol is suitable, for example, for the solvolysis of starting materials of the general formula III wherein R_2 is an α-alkoxy-alkyl radical, e.g. a methoxy-methyl radical, an α-methoxy-ethyl radical, α-ethoxy-ethyl radical, α-*n*-butoxy-ethyl radical or a tetrahydropyranyl-(2) radical.

In addition, an α-alkoxy-alkyl radical R_2 can be split off, for example, by treatment with methanol or another low alkanol in the presence of an acid catalyst such as sulphuric acid, *p*-toluene sulphonic acid or by means of the mixture of acid phosphoric acid ester and polyphosphoric acid ester formed on adding phosphorus pentoxide to the alkanol, or of a Lewis acid, e.g. aluminium chloride or boron trifluoride, at room temperature or a moderately raised temperature.

Dilute sodium hydroxide solution, for example, can serve for the hydrolysis of starting material having an acyl radical, in particular an acetyl radical R_2. An acyl radical R_2 can be split off under anhydrous conditions, for example, by treatment of a corresponding compound of general formula III with methanolic ammonia solution.

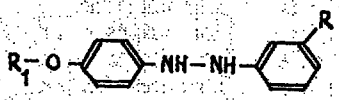
The starting materials of the general formulae II and III can be produced by various related methods, for example by condensing malonic acids of the general formula IV



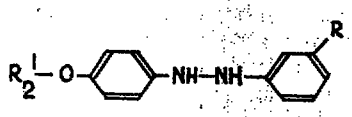
(IV)

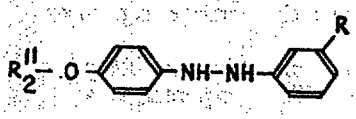
wherein n has the meaning given above, with hydrazobenzene derivatives of the general formula V, VI or VII,

(V)



(VI)





(VII)

wherein R_2' represents an α-alkoxy-alkyl radical, whereby the alkyl radical of the alkoxy substituent can be bound to the parent chain in the form of a ring, and

R_2'' represents a carboxylic acyl radical,

and R and R_1 have the meanings given above, the condensation being performed in the presence of N,N'-disubstituted carbodiimides, in particular N,N'-dicyclohexyl-carbodiimide in dioxan solution, also by condensing dihalides of malonic acids of the general formula IV with hydrazobenzene derivatives of the general formulae V or VII in the presence of acid binding agents, e.g. tertiary organic bases such as pyridine, dimethylaniline, triethylamine or tributylamine, in the presence or absence of additional organic solvents such as chloroform, diethyl ether or diisopropyl ether, this condensation being performed at temperatures from room temperature to the boiling temperature of the reaction medium.

Furthermore, the starting materials of the general formula II as well as some of those of the general formula III can be produced by condensing dialkyl esters of malonic acids of the general formula IV with hydrazobenzene derivatives of the general formula V or VI in the presence of alkaline condensing agents, or by condensing alkyl ester halides of malonic acids of the general formula IV with hydrazobenzene derivatives of the general formula V or VI in the presence of acid binding agents and treating the reaction products immediately obtained with alkaline condensing agents. The condensation of malonic acid dialkyl esters with hydrazobenzene derivatives is preferably performed in organic solvents such as benzene, toluene, xylene, butanol or dibutyl ester, at raised temperatures, e.g. between 80—160°, the alcohol liberated being continuously distilled off. In this reaction, generally those alkaline condensing agents are suitable which are capable of replacing a mobile hydrogen atom by a metal atom, e.g. alkali metals or their alcoholates, amides, hydrides and metal organic compounds such as sodium, potassium, lithium, sodium ethylate, potassium ethylate, sodamide, lithium hydride, phenyl lithium and butyl lithium. The acid binding agents mentioned previously can serve for the reaction of alkyl ester halides with hydrazobenzene derivatives and then the alkaline condensing agents mentioned above can be used. In this reaction, however, the ring may sometimes be closed under milder conditions than when the malonic acid dialkyl esters are used.

Finally, it is also possible to produce starting materials of the general formula II and III by introducing, by known methods, an *n*-alkyl radical having 2 to 4 carbon atoms in the 4-position of analogous pyrazolidine compounds which are unsubstituted in this position. For this purpose, for example, corresponding 4-unsubstituted compounds are condensed with propionaldehyde, butyraldehyde or valeraldehyde or with corresponding unsaturated aldehydes such as crotonaldehyde, e.g. by boiling in glacial acetic acid, and the 4-alkylidene or 4-alkenylidene compounds obtained are hydrogenated to form starting materials of the general formulae II and III. This hydrogenation of the semicyclic double bond and of any extracyclic double bond present can sometimes be performed simultaneously with the hydrogenloysis; however, this method of introducing the 4-substituent is not limited to compounds having an arylmethyl or diarylmethyl radical R_1.

The new compounds of the general formula I form fairly easily to easily soluble monobasic salts with alkali metal hydroxides. Solutions thereof can be produced by dissolving the new compounds in the calculated amount of alkali lye, i.e. in solutions of

lithium, sodium or potassium hydroxide. The new compounds are also soluble in alkali metal carbonate solutions.

The new compounds according to the invention or their alkali metal salts or salts with organic bases e.g. dimethylaminoethanol, diethylaminoethanol or piperazine, can be converted into pharmaceuticals by combining them with suitable pharmaceutical carriers. The solutions of the alkali metal salts of the new compounds mentioned above have a weakly alkaline reaction and are well suited for injection purposes. The pharmaceuticals can also be capsules, powders, tablets and other forms suitable for oral administration and can be produced, e.g. by mixing the active substances, i.e. the new 1,2-diaryl-4-alkyl-3,5-dioxo-pyrazolidines with pharmaceutical carriers such as starch, lactose, stearic acid, talcum, and magnesium stearate. They can also be worked up, however, with semi-solid substances having a suitable melting range, e.g. cocoa butter, to form suppositories.

The following Examples ~~illustrate~~ the production of the new compounds but are by no means the only methods of production. The temperatures are in degrees Centigrade.

EXAMPLE 1

a) 125 g of sodium hydroxide are dissolved in 3 litres of methanol. After adding 302 g of *p*-benzyloxy-*m'*-methyl-azobenzene (M.P. 81°) 200 g of zinc dust are added in five equal portions at reflux temperature under an atmosphere of nitrogen, the addition being made within 30 minutes while stirring. The reaction mixture is then stirred for about 15 minutes, i.e. until it is no longer yellowish coloured. It is then filtered, and the filtrate is concentrated at 11 Torr to about half its volume. The residue contains the crude *p*-benzyloxy-*m'*-methyl-hydrazobenzene.

b) 2000 ml of benzene and 1000 ml of water are added to the residue obtained according to a). The organic phase is separated, dried over sodium sulphate and poured into a reaction vessel. After distilling off about 1500 ml of benzene, a sodium ethylate solution prepared from 23 g of sodium and 400 ml of abs. ethanol and then adding 216 g of *n*-butyl malonic acid diethyl ester is added and then 500 ml of xylene are poured in. The reaction mixture is then heated for 12 hours at a bath temperature of 130—140° in a vessel fitted with a sloping condenser, whereupon the solvent and liberated ethanol pass over. After cooling, the reaction mixture is stirred at 5° with 1500 ml of ice water until a two-phase solution is attained. The aqueous phase is extracted twice with 500 ml of ether each time and then made acid to congo red paper while stirring vigorously with hydrochloric acid. The crystals obtained are washed neutral with water and recrystallised from ethanol. The 1-(*m*-tolyl)-2-(*p*-benzyloxy-phenyl)-4-*n*-butyl-3,5-dioxo-pyrazolidine so obtained melts at 120°.

c) 96 g of 1-(*m*-tolyl)-2-(*p*-benzyloxy-phenyl)-4-*n*-butyl-3,5-dioxo-pyrazolidine are dissolved in a solution of 18 g of sodium hydroxide in 500 ml of water and hydrogenated at room temperature and atmospheric pressure in the presence of 30 g of Raney nickel. The hydrogen take-up ceases after 9 hours, after it has attained about 93% of the theoretical. The catalyst is filtered off, the filtrate is extracted twice with ether and then made acid to congo red paper with concentrated hydrochloric acid. The precipitated reaction product is taken up in ethyl acetate. After washing with water and thoroughly drying over sodium sulphate, the ethyl acetate solution is concentrated in vacuo and as much petroleum ether as possible is added without the solution becoming permanently cloudy. The 1-(*m*-tolyl)-2-(*p*-hydroxyphenyl)-4-*n*-butyl-3,5-dioxo-pyrazolidine gradually crystallises out. It melts at 113°. 5 g (0.0141 mole) of this product is dissolved in 14.1 ml of aqueous sodium hydroxide solution. Distilled water is added to diminish the concentration of the sodium salt of 1-(*m*-tolyl)-2-(*p*-hydroxy-phenyl)-4-*n*-butyl-3,5-dioxo-pyrazolidine, e.g. ad 100 ml to obtain a solution applicable for pharmacological testing.

EXAMPLE 2.

25 g of *m*-methyl-*p'*-acetoxy-hydrazobenzene are dissolved in a mixture of 17.6 g of pyridine and 200 ml of chloroform. At 0—5°, a solution of 19.7 g of *n*-butyl malonic acid dichloride in 100 mol of chloroform is added dropwise while stirring. The reaction mixture is left to stand for 12 hours at room temperature and is then poured onto ice. The organic phase is separated, extracted at 0—5° with dilute hydrochloric acid and then twice with 500 ml of sodium carbonate solution each time.

These extracts are made acid to congo red paper, the oil which precipitates is dissolved in ethyl acetate, the solution is dried with sodium sulphate and concentrated at 11 Torr. The 1-(*m*-tolyl)-2-(*p*-acetoxy-phenyl)-3,5-dioxo-4-*n*-butyl-pyrazolidine is an oil, so that it is hydrolysed without further purification. The residue (about 30 g) is dissolved in 300 ml of 2N sodium hydroxide solution and heated for 30 minutes at 90—

95°. The solution is filtered with charcoal and, after covering with 300 ml of ethyl acetate, it is made acid to congo red paper with concentrated hydrochloric acid. The organic phase is worked up as described in Example 1 to obtain 1-(*m*-tolyl)-2-(*p*-hydroxyphenyl)-3,5-dioxo-4-*n*-butyl-pyrazolidine.

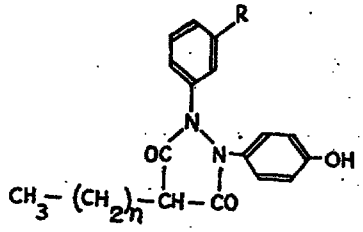
EXAMPLE 3

16 g of *n*-butyl malonic acid are dissolved in 500 ml of abs. dioxan, 30 g of *m*-methyl-*p'*-[tetrahydropyranyl-(α)-oxy]-hydrazobenzene are added and 45 g of dicyclohexyl carbodiimide are added all at once to the solution. The reaction mixture is left to stand overnight at room temperature. The precipitated dicyclohexyl urea is filtered off under suction and the filtrate is concentrated at 11 Torr. The residue is dissolved in 1000 ml of ethyl acetate and the solution is extracted twice with 500 ml of 1N sodium carbonate solution each time. The pH of the extracts is adjusted to 5 with acetic acid, and the oil which separates is dissolved in ethyl acetate. The solution obtained is dried with sodium sulphate and concentrated at 11 Torr. The 1-(*m*-tolyl)-2-[*p*-(tetrahydropyranyl-(α)-oxy)-phenyl]-3,5-dioxo-4-*n*-butyl-pyrazolidine cannot be crystallised so that is hydrolysed direct. 4.2 g are dissolved in 84 ml of methanol, 8.4 ml of 1N hydrochloric acid are added and the mixture is refluxed for 30 minutes. 8.4 ml of 1N sodium hydroxide solution are added at room temperature and the mixture is concentrated at 11 Torr. The residue is distributed between ethyl acetate and water. The organic phase is dried over sodium sulphate and concentrated. 1-(*m*-tolyl)-2-(*p*-hydroxyphenyl)-3,5-dioxo-4-*n*-butyl-pyrazolidine is recrystallised as described in Example 1.

In an analogous manner 1-(*m*-tolyl)-2-(*p*-hydroxyphenyl)-3,5-dioxo-4-*n*-propyl-pyrazolidine, M.P. 125° and 1-(*m*-tolyl)-2-(*p*-hydroxyphenyl)-3,5-dioxo-4-*n*-amyl-pyrazolidine, M.P. 71°, are obtained, as described in Examples 1 to 3.

WHAT WE CLAIM IS:—

1. Compounds of the formula I



(I)

wherein R is an alkyl radical having at most 3 carbon atoms, and n is an integer from 2 to 4, and non-toxic salts thereof with an inorganic or organic base.

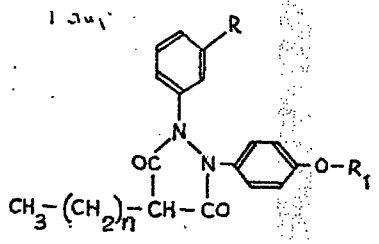
2. Alkali metal salts of compounds of the formula I defined in claim 1.

3. Sodium salts of compounds of the formula I defined in claim 1.

4. 1-(*m*-tolyl)-2-(*p*-hydroxyphenyl)-3,5-dioxo-4-*n*-butyl-pyrazolidine.

5. The sodium salt of 1-(*m*-tolyl)-2-(*p*-hydroxyphenyl)-3,5-dioxo-4-*n*-butyl-pyrazolidine.

6. A process of producing the compounds claimed in claim 1 which comprises treating a compound of the general formula II



(II)

wherein R_1 represents an arylmethyl or diarylmethyl radical, and R and n have the meanings given in claim 1, with catalytically activated hydrogen until substantially an equimolar amount of hydrogen has been taken up, and if desired, converting the compound of the general formula I obtained into a salt with an inorganic or organic base.

95°. The solution is filtered with charcoal and, after covering with 300 ml of ethyl acetate, it is made acid to congo red paper with concentrated hydrochloric acid. The organic phase is worked up as described in Example 1 to obtain 1-(*m*-tolyl)-2-(*p*-hydroxyphenyl)-3,5-dioxo-4-*n*-butyl-pyrazolidine.

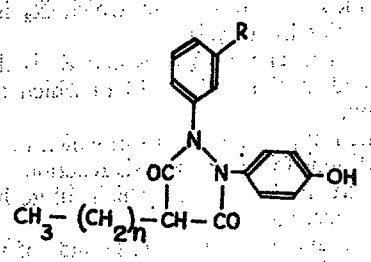
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In an analogous manner 1-(*m*-tolyl)-2-(*p*-hydroxyphenyl)-3,5-dioxo-4-*n*-propyl-pyrazolidine, M.P. 125° and 1-(*m*-tolyl)-2-(*p*-hydroxyphenyl)-3,5-dioxo-4-*n*-amyl-pyrazolidine, M.P. 71°, are obtained, as described in Examples 1 to 3.

WHAT WE CLAIM IS:—

1. Compounds of the formula I



(I)

wherein R is an alkyl radical having at most 3 carbon atoms, and n is an integer from 2 to 4, and non-toxic salts thereof with an inorganic or organic base.

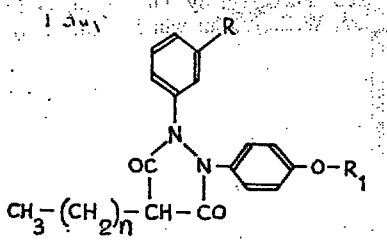
2. Alkali metal salts of compounds of the formula I defined in claim 1.

3. Sodium salts of compounds of the formula I defined in claim 1.

4. 1-(*m*-tolyl)-2-(*p*-hydroxyphenyl)-3,5-dioxo-4-*n*-butyl-pyrazolidine.

5. The sodium salt of 1-(*m*-tolyl)-2-(*p*-hydroxyphenyl)-3,5-dioxo-4-*n*-butyl-pyrazolidine.

6. A process of producing the compounds claimed in claim 1 which comprises treating a compound of the general formula II



(II)

wherein R_1 represents an arylmethyl or diarylmethyl radical, and R and n have the meanings given in claim 1, with catalytically activated hydrogen until substantially an equimolar amount of hydrogen has been taken up, and if desired, converting the compound of the general formula I obtained into a salt with an inorganic or organic base.

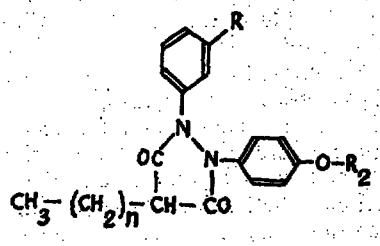
7. A process as claimed in claim 6 in which R_1 is the benzyl radical and the compound of general formula II is treated with catalytically activated hydrogen in the presence of Raney nickel.

8. A process as claimed in claim 7 in which the hydrogenolysis is performed in an alkaline aqueous solution or in an inert organic solvent.

9. A process as claimed in claim 6 in which a noble metal catalyst is used.

10. A process as claimed in claim 9 in which said noble metal catalyst comprises palladium on charcoal.

11. A process of producing the compounds claimed in claim 1 which comprises subjecting a compound of the general formula III



wherein R_2 represents a carboxylic acyl radical or an α-alkoxyalkyl radical, whereby the alkyl radical of the alkoxy substituent can be bound to the parent chain in the form of a ring, and R and n have the meanings given in claim 1, to solvolysis, and if desired, converting the compound obtained of the general formula I into a salt with an inorganic or organic base.

12. A process as claimed in claim 11 in which R_2 is an acyl radical and the solvolysis is performed by alkaline hydrolysis.

13. A process as claimed in claim 12 in which R_2 is the acetyl group.

14. A process as claimed in claim 12 or 13 in which dilute sodium hydroxide is used for the solvolysis reaction.

15. A process as claimed in claim 12 or 13 in which methanolic ammonia solution is used under anhydrous conditions for the solvolysis reaction.

16. A process as claimed in claim 11 in which dilute hydrochloric acid in methanol is used for the solvolysis reaction.

17. A process for the production of the compounds of the general formula I substantially as hereinbefore described with reference to and as illustrated in any of the foregoing Examples.

18. Compounds of the general formula I as defined in claim 1 and non-toxic salts thereof with inorganic or organic bases as hereinbefore described in any of the foregoing Examples.

19. A pharmaceutical composition comprising as active agent a compound of the general formula I as defined in claim 1 or a non-toxic salt thereof derived from an inorganic or organic base, together with a pharmaceutical carrier.

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