PATENT SPECIFICATION

646,597

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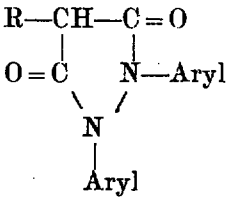
PROVISIONAL SPECIFICATION

Improvements in or relating to the Manufacture of Derivatives of 3:5-Dioxo-Pyrazolidine

I, LEONARD ELLWOOD JONES, Chartered Patent Agent, of 12, Church Street, Liverpool, in the County of Lancaster, Subject of the King of Great Britain, do hereby declare the nature of this invention, which has been communicated to me by J. R. Geigy S.A., a Swiss Company, of 213, Schwarzwaldalle, Basle, 16, Switzerland, to be as follows:—

The present invention is concerned with derivatives of 3:5-dioxo-pyrazolidine and with their manufacture. It is concerned more particularly with derivatives corresponding to the general formula



. . . (I)

or to its tautomeric forms, as well as with their salts with inorganic and organic bases. In this formula and throughout the specification R means a hydrocarbon or substituted hydrocarbon structure with 2 to 10 carbon atoms, bound to the pyrazolidine nucleus by a primary or secondary carbon atom, particularly a saturated or unsaturated aliphatic or cycloaliphatic, or a phenyl-substituted aliphatic hydrocarbon or substituted hydrocarbon radical, and Aryl means a phenyl radical, which may be either unsubstituted or substituted by halogen atoms, alkyl and/or alkoxy groups, such alkyl and alkoxy groups containing 1 to 3 carbon atoms.

The 3:5-dioxo-pyrazolidines of the invention can be made by allowing a reactive derivative of a monosubstituted malonic acid having the formula

$$R—CH(CO—X)_2 \quad . . . (II)$$

wherein X is a radical or atom which can split off from the acid derivative such as, e.g., halogen (acid halide), or an alkoxy group (acid ester), to react with a 1:2-diaryl hydrazine of the formula

$$Aryl—NH—NH—Aryl \quad . . . (III)$$

The reaction is suitably carried out in the presence of a condensing agent or an acid-binding medium, as described below.

A preferred method of manufacture consists in heating a dialkyl ester, above all the diethyl ester, of a monosubstituted malonic acid, with a diarylhydrazine in the presence of a metal alcoholate, e.g., sodium ethylate or potassium ter. butylate. This brings about ring-closure with the splitting off of two molecules of the alcohol, which it is convenient to distil off, at temperatures between 100 and 200° C.

As condensing agents there come into consideration such compounds as are suitable for the replacement of a movable hydrogen atom by a metal atom, such as alkali metals and active alkali compounds. As further examples may be mentioned metallic potassium, sodium methylate, sodium amide and phenyl lithium.

A number of other ways of carrying out the same process will now be described. These modifications consist in using other reactive derivatives, instead of a di-ester, of malonic acid of formula II, such as, for example, a dihalide, or an ester chloride.

Condensation of a diarylhydrazine of formula III with a malonic acid halide of formula II, e.g., the dichloride, takes place in a solvent which is indifferent to the acid halide, such as ether or benzene. In order to repress as far as possible the rearrangement of the diarylhydrazine by the hydrogen halide produced, it is

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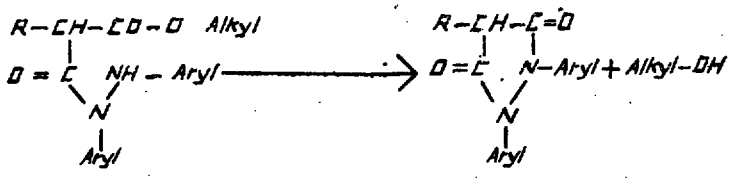
preferable to carry out the condensation in the presence of an acid-binding agent, preferably a tertiary organic base such as pyridine or dimethylaniline. In this case the reaction may take place even at low temperatures which may suitably be in the neighbourhood of 0° C.

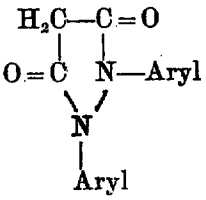
It is particularly easy to carry out the condensation in steps if unsymmetrical reactive derivatives of malonic acid (formula II) are used. For example, the ester-chloride Cl—CO—CH(R)—COO—Alkyl can be treated with a diarylhydrazine III to give firstly the acyl derivative IV, by allowing the components to react in the ratio of their molecular weights in ether or benzene in the presence of pyridine. Ring closure may then be brought about by heating with sodium ethylate:



(IV)

The 3:5-dioxo-pyrazolidines of the present invention can also be made by reacting an N-acyl derivative of a diarylhydrazine of formula III, e.g., N-acetylhydrazobenzene with the reactive derivative of a malonic acid of formula II, especially with a dialkyl ester. On heating with the condensing agents named, the acyl radical is split off, the ring closing to give the pyrazolidine derivative of formula I.

Another process for the production of the pyrazolidine derivative of formula I, can in some cases be of advantage, since it proceeds not from derivatives of substituted malonic acid (II) but directly from those of malonic acid itself, for example, from diethyl malonate. This method consists in introducing the radical R into the 4-position of a 1:2-diaryl-3:5-dioxo-pyrazolidine of formula V



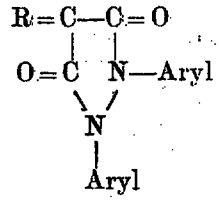
. . . (V)

According to this process the 3:5-dioxo-pyrazolidines of the present invention may be made by reacting the pyrazolidine derivative V or a salt thereof, preferably in the presence of an acid-binding agent, with a compound of the formula R—A, where A can mean Cl, Br. I, SO_4R or SO_3 Aryl.

The temperature necessary for the reaction depends on the reactivity of the compound R—A; it is well known, for example, that iodine compounds react more easily than bromine compounds. The setting-in of the reaction as well as its course can be easily followed by the formation of A ions. Generally speaking, temperatures between 0° C. and 100° C. are suitable.

The 3:5-dioxo-pyrazolidines of the present invention can also be made by introducing the group R by hydrogenating the diketopyrazolidine V in the presence of a carbonyl compound of the formula R=O, where R stands for a hydrocarbon or substituted hydrocarbon structure of 2 to 10 carbon atoms, the oxygen atom being bound by two valencies from one and the same carbon atom. In particular, R may be a saturated or unsaturated aliphatic or cycloaliphatic, or a phenyl substituted aliphatic hydrocarbon or substituted hydrocarbon radical. Because of its simplicity and the good yield this process is of special interest technically.

The 3:5-dioxo-pyrazolidines of the present invention can also be made by a variation of this method which consists in hydrogenating the condensation product VI derived from the dioxo-pyrazolidine V and the carbonyl compound R=O.



. . . (VI)

In both of the last two cases hydrogenation can be very conveniently carried out with hydrogen in the presence of a hydrogenation catalyst, such as finely divided nickel, platinum or palladium. Other reducing procedures, such as the use of sodium amalgam and water, offer no advantages over this method.

However, it must be noted in connection with this process, that when the radical R contains an aliphatic double bond it is difficult to avoid hydrogenating

it and the yield in such circumstances is usually unsatisfactory. On the other hand the corresponding saturated derivative can be easily prepared. Consequently the process is primarily suitable for the manufacture of those pyrazolidine derivatives of formula I in which the radical R contains no aliphatic double bonds.

The dioxo-pyrazolidines of formula V can be prepared by the methods known *per se* for the manufacture of 1:2-diphenyl - 3:5 - dioxo-pyrazolidine; the most suitable is the condensation of malonic ester with the corresponding diarylhydrazine of formula III in the presence of a metal alcoholate, e.g., sodium ethylate.

The substituted pyrazolidine derivatives of formula VI are derived from the unsubstituted parent compounds V by methods known *per se* (Bl. Chem. Soc. Japan, 1931, *6*, 1—9; 1932, *7*, 45-50).

Although most diaryl-dioxo-pyrazolidines of formula I have a noticeable analgesic and/or antipyretic effect, the extent of this action varies within the group of compounds named. In order to make the description more complete it may therefore be added that the compounds which have been tested and which have the best antipyretic and analgesic effect include 1:2-diphenyl-3:5-dioxo-4-alkyl-pyrazolidines, whose alkyl radical contains from 3 to 5 carbon atoms, particularly 4-*n*-butyl-, 4-*n*-propyl- and 4-isopropyl - 1:2 - diphenyl - 3:5 - dioxo-pyrazolidine. The 4-benzyl derivative also has a very good analgesic action, while antipyretic activity is especially well developed in the case of the 4-cyclohexyl derivative. Compounds with substituents in the phenyl radicals approximate to the corresponding parent compounds in activity, without surpassing them. For this reason the more readily available 1:2-diphenyl derivatives are generally to be preferred to those with substituted phenyl radicals. Here too, these compounds whose 4-alkyl radical contains 3—5 carbon atoms are the most valuable.

In contrast with the foregoing our researches show that 1:2-diphenyl-3:5-dioxo-pyrazolidine, which is the already known compound most nearly comparable to the pyrazolidines of formula I, possesses practically no analgesic or antipyretic activity.

The dioxo-pyrazolidine derivatives prepared according to the invention can also form salts with basic compounds. Alkali-metal salts are readily soluble in water, while the solubility of the alkaline earth metal salts is less and decreases with increasing atomic weight of the metal. The heavy metal salts are only slightly soluble in water, but salts with organic bases possess a high degree of solubility.

This property of salt-formation represents a great advantage of the compounds described as compared with other analgetic and antipyretic substances, particularly since the solutions of these salts are only weakly alkaline and are suitable for purposes of injection. For this purpose those salts with the less toxic cations should be used such as the sodium or magnesium salts or those of ethylenediamine, triethanolamine or trimethylamine.

To prepare the soluble salts, the free pyrazolidine of formula I is treated with an equimolecular quantity of a base containing the desired cation, e.g., with aqueous caustic soda, ethylenediamine, potassium hydroxide lye or sodium carbonate solution or with alcoholic caustic soda. It is best to employ stirring or shaking during the reaction. If an aqueous lye is used, then an excess of the pyrazolidine may be present, which, after the solution is neutral to phenolphthalein, can be removed by filtration.

The salt can be obtained in solid form when desired either by evaporation of the filtered solution or by adding a solvent in which the salt is insoluble, for example, by the addition of ether to an alcoholic solution of the sodium salt.

However, it is also possible to obtain the corresponding salt directly when using alkaline condensing agents, such as, for example, sodium ethylate.

The alkali salts are mostly in the form of colourless powders, usually of considerable stability in the air, which are readily soluble in water and alcohol. Their solutions do not turn phenolphthalein red.

The ~~difficultly~~ soluble salts can be also prepared by double decomposition of an alkali or ammonium salt of a pyrazolidine of formula I with a soluble alkaline earth or heavy metal salt, e.g., calcium chloride or silver nitrate. When working with a sufficiently concentrated solution the salts are obtained directly as precipitates. Alternatively they can be isolated by suitably concentrating or cooling the solution.

In the following examples a few methods of carrying out the manufacture as well as some of the compounds obtained are described in more detail. Parts are by weight, unless otherwise stated. The relationship of parts by weight to parts by volume is that of kilograms to litres.

Temperatures are in degrees Centigrade.

EXAMPLE 1.

7.6 Parts of sodium are dissolved in 190 parts by volume of absolute alcohol, 65 parts of diethyl-*n*-butyl malonate and 55 parts of hydrazobenzene are added. The alcohol is slowly distilled off and the reaction mixture heated for 12 hours at a bath temperature of 150°, finally *in vacuo*, until no more alcohol comes off.

The product is dissolved in water, clarified with a little animal charcoal and 15% hydrochloric acid is slowly added until an acid reaction to Congo red paper is produced. 1:2-diphenyl-3:5-dioxo-4-*n*-butyl-pyrazolidine separates as an oil, which rapidly becomes crystalline. It crystallises from alcohol as colourless needles with a melting point of 105°.

EXAMPLE 2.

The same compound, 1:2-diphenyl-3:5 - dioxo - 4 - *n* - butyl - pyrazolidine is obtained if the hydrazobenzene in Example 1 is replaced by 68 parts of N-acetyl-hydrazobenzene the method being otherwise the same. In this modification the coloured by-products formed are somewhat less than by the method of Example 1. The yield is good in this case too.

EXAMPLE 3.

19 Parts of *n*-butyl-malonyl-dichloride (b.p. 85° at 14 mm. pressure) are added dropwise to a mixture of 50 parts absolute pyridine and 200 parts by volume of absolute ether at about 0°. Next, 18 parts of hydrazobenzene, dissolved in 100 parts by volume of ether are added and the mixture stirred for two hours at room temperature. The solution is then shaken with 2 N hydrochloric acid to remove the pyridine, followed by 2 N sodium carbonate solution. The latter, which contains the sodium salt of 1:2-diphenyl-3:5-dioxo-4-*n*-butyl-pyrazolidine in solution is acidified with 10% hydrochloric acid, whereupon the free pyrazolidine derivative separates out.

EXAMPLE 4.

1:2 - Diphenyl-3:5-dioxo-pyrazolidine (Ber. d. deutschen chem. Ges., 1940, *73*, 822) is heated for 5 hours on the boiling water-bath with five times its weight of cyclohexanone. The excess of cyclohexanone is then distilled off *in vacuo* and the residue recrystallised from alcohol. The 1:2 - diphenyl - 3:5 - dioxo-4-cyclohexylidene-pyrazolidine so obtained consists of yellow needles melting at 173°. If it is treated with hydrogen (at about 30 atmospheres pressure) in the presence of Raney nickel at 100°, then 1:2-diphenyl - 3:5 - dioxo - 4 - cyclohexyl-pyrazolidine is formed. The latter compound is difficultly soluble in alcohol and has a melting point of 177°.

If 1:2 - diphenyl - 3:5 - dioxo - 4-benzylidene-pyrazolidine (Bl. Chem. Soc. Japan, 1931, *6*, 8) is hydrogenated in a similar manner, then 1:2-diphenyl-3:5-dioxo-4-benzyl-pyrazolidine with a melting point of 136—138° is formed.

In the same way, 1:2-diphenyl-3:5-dioxo - 4 - (γ-phenyl-propyl)-pyrazolidine may be prepared from 1:2-diphenyl-3:5-dioxo-4-cinnamylidene-pyrazolidine (*loc. cit.*), 1:2-diphenyl-3:5-dioxo-4-(α-phenyl-ethyl)-pyrazolidine from 1:2-diphenyl-3:5 - dioxo - 4 - (α - phenyl-ethylidene)-pyrazolidine (Bl. Chem. Soc. Japan, 1931, *6*, 9), 1:2-diphenyl-3:5-dioxo-4-(*p* - methyl - benzyl) - pyrazolidine from 1:2 - diphenyl - 3:5 - dioxo - 4 - (*p*-methyl - benzal)-pyrazolidine (Bl. Chem. Soc. Japan, 1932, *7*, 45 *et seq.*), 1:2-diphenyl - 4 - (*p* - methoxy-benzyl) - 3:5-dioxo-pyrazolidine from 1:2-diphenyl-4-(*p* - methoxy - benzal) - 3:5-dioxo-pyrazolidine (*loc. cit.*), 1:2-diphenyl-4-piperonyl-3:5-dioxo-pyrazolidine from 1:2-diphenyl-4-piperonylidene - pyrazolidine (*loc. cit.*) and 1:2-diphenyl-3:5-dioxo-4-*n*-propyl-pyrazolidine (m.pt. 108—109°) from 1:2 - diphenyl - 3:5 - dioxo - 4-propylidene-pyrazolidine (*loc cit.*).

EXAMPLE 5.

1:2 - Diphenyl-3:5-dioxo-pyrazolidine is heated to boiling for 10 minutes with double its weight of cyclopentanone. On diluting the solution with alcohol and cooling, yellow crystals of 1:2-diphenyl-3:5 - dioxo - 4 - cyclopentylidene-pyrazolidine (m.pt. 153°) crystallise out. When the latter compound is hydrogenated in alcoholic solution at 50° in the presence of Raney nickel and at atmospheric pressure, 1:2 - diphenyl-3:5-dioxo-4-cyclopentyl-pyrazolidine, melting at 172°, is produced. It dissolves gradually on shaking with 2 N caustic soda lye with the formation of the sodium salt. It is soluble only with difficulty in alcohol.

EXAMPLE 6.

A solution of 160 parts of 1:2-diphenyl-3:5-dioxo-pyrazolidine and 120 parts of benzaldehyde in 500 parts by volume of alcohol is heated to 100° under 20 atmospheres of hydrogen in the presence of Raney nickel until the hydrogen is taken up only slowly and the solution becomes colourless. 1:2-Diphenyl - 3:5 - dioxo - 4 - benzyl-pyrazolidine crystallises from the hot, filtered solution.

EXAMPLE 7.

1:2 - Diphenyl - 3:5 - dioxo - pyrazolidine dissolved in 10 times the amount of acetone is hydrogenated at 100° under 20 atmospheres pressure of hydrogen in the presence of Raney nickel. On evaporating down the filtered acetone solution, 1:2 - diphenyl - 3:5 - dioxo - 4-isopropyl-pyrazolidine crystallises out in good yield. It melts at 143°.

EXAMPLE 8.

25 Parts of 1:2-diphenyl-3:5-dioxo-pyrazolidine are dissolved in 100 parts of 2 N caustic soda lye. 14 Parts of 1-bromo-butane are slowly dropped in, while stirring, and the mixture warmed to 70°. Undissolved oily fractions are removed by shaking with ether and the aqueous solution is then acidified with 10% hydrochloric acid. A precipitate of 1:2 - diphenyl - 3:5 - dioxo - 4 - butyl-pyrazolidine is obtained, melting at 105°.

Similarly, 1:2-diphenyl-3:5-dioxo-4-(*p*-chlorobenzyl)-pyrazolidine is obtained from 25 parts of 1:2-diphenyl-3:5-dioxo-pyrazolidine dissolved in 100 parts by volume of 2 N caustic soda lye by reacting with 16 parts of 4-chloro-benzyl chloride.

EXAMPLE 9.

To a sodium ethylate solution prepared from 23 parts of sodium and 500 parts by volume of absolute alcohol is added, while stirring, an equimolecular amount (308 parts) of 1:2-diphenyl-3:5-dioxo-4-*n*-butyl-pyrazolidine. The solution thus obtained, after filtration, if necessary, is evaporated to dryness *in vacuo*. The residue is triturated with absolute ether and filtered under suction. The sodium salt of 1:2-diphenyl-3:5-dioxo-4-*n*-butyl-pyrazolidine is left as a colourless powder which is readily soluble in water. The aqueous solution reacts weakly alkaline but is not, however, alkaline to phenol-phthalein.

The sodium salts of other 4-substituted 1:2-diphenyl - 3:5 - dioxo-pyrazolidines may be prepared similarly.

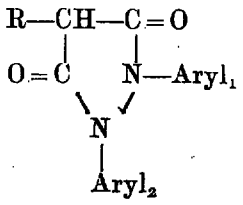
EXAMPLE 10.

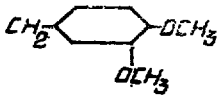
30 Parts of diethylamine are poured over 10 parts of 1:2-diphenyl-3:5-dioxo-4-*n*-butyl-pyrazolidine. The latter dissolves and, on rubbing, the salt separates out in crystalline form. The diethylamine salt of 1:2-diphenyl-3:5-dioxo-4-*n*-butyl-pyrazolidine thus obtained loses part of the base when exposed to the atmosphere.

Alternative method: 10 Parts of 1:2-diphenyl - 3:5 - dioxo - 4 - *n* - butyl-pyrazolidine are dissolved in 50 parts of hot absolute alcohol and about 40 parts of diethylamine are then added. The diethylamine salt of 1:2-diphenyl-3:5-dioxo-4-*n*-butyl-pyrazolidine is precipitated out by adding absolute ether, filtered off under suction and washed with ethereal diethylamine solution.

The methods described in the above examples can be applied, as will be clear to those skilled in the art, for the production of other 4-substituted 1:2-diphenyl-3:5-dioxo-pyrazolidines. For example, in addition to those given above, the following compounds may be prepared:

General formula:



$Aryl_1$	$Aryl_2$	R	Melting point.
C_6H_5	C_6H_5	CH_3	114—116°
C_6H_5	C_6H_5	C_2H_5	108°
C_6H_5	C_6H_5	$CH_2—CH=CH_2$	135°
C_6H_5	C_6H_5	iso-C_4H_9	127—128°
C_6H_5	C_6H_5	$CH_2—CH=CH—CH_3$	128°
C_6H_5	C_6H_5	n-C_5H_{11}	104—105°
C_6H_5	C_6H_5	iso-C_5H_{11}	137°.
C_6H_5	C_6H_5	$CH(CH_3)—CH_2—CH(CH_3)_2$	107—108°
C_6H_5	C_6H_5		133°
$C_6H_4—CH_3(p)$	$C_6H_4—CH_3(p)$	iso-C_3H_7	167°
$C_6H_4—CH_3(p)$	$C_6H_4—CH_3(p)$	n-C_4H_9	133°
$C_6H_4—Cl(p)$	C_6H_5	n-C_4H_9	132°
$C_6H_4—Cl(p)$	$C_6H_4—Cl(p)$	n-C_4H_9	132°
$C_6H_4—OCH_3(p)$	$C_6H_4—OCH_3(p)$	n-C_4H_9	198°
$C_6H_4—OC_2H_5(p)$	C_6H_5	n-C_4H_9	81.5°

Dated this 9th day of April, 1948.

W. P. THOMPSON & CO.,
12, Church Street, Liverpool, 1,
Chartered Patent Agents.

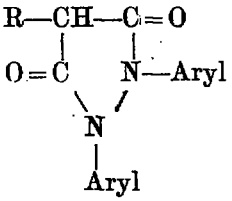
COMPLETE SPECIFICATION

Improvements in or relating to the Manufacture of Derivatives of 3:5-Dioxo-Pyrazolidine

I, LEONARD ELLWOOD JONES, Chartered Patent Agent, of 12, Church Street, Liverpool, in the County of Lancaster, Subject of the King of Great Britain, do hereby declare the nature of this invention, which has been communicated to me by J. R. Geigy S.A., a Swiss Company, of 213, Schwarzwaldalle, Basle, 16, Switzerland, and in what manner the same is to be performed, to be particularly described and ascertained in and by the following statement:—

The present invention is concerned with derivatives of 3:5-dioxo-pyrazolidine and with their manufacture. It is concerned more particularly with derivatives corre-

sponding to the general formula



. . . (I)

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wherein X is a radical or atom which can split off from the acid derivative such as, e.g., halogen (acid halide), or an alkoxy group (acid ester), to react with a 1:2-diaryl hydrazine of the formula

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The reaction is suitably carried out in the presence of a condensing agent or an acid-binding medium, as described below.

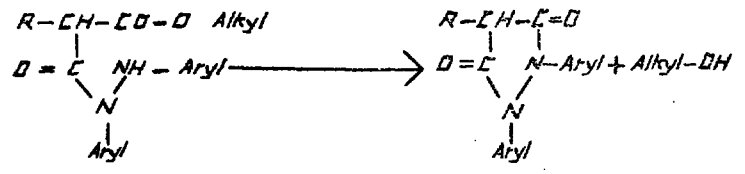
A preferred method of manufacture consists in heating a dialkyl ester, above all the diethyl ester, of a mono-substituted malonic acid, with a diaryl hydrazine in the presence of a metal alcoholate, e.g., sodium ethylate or potassium ter. butylate. This brings about ring-closure with the splitting off of two molecules of the alcohol, which it is convenient to distil off, at temperatures between 100 and 200° C.

As condensing agents there come into consideration such compounds as are suitable for the replacement of a movable hydrogen atom by a metal atom, such as alkali metals and active alkali compounds. As further examples may be mentioned metallic potassium, sodium methylate, sodium amide and phenyl lithium.

A number of other ways of carrying out the same process will now be described. These modifications consist in using other reactive derivatives, instead of a di-ester, of malonic acid of formula II, such as, for example, a di-halide, or an ester chloride.

Condensation of a diarylhydrazine of formula III with a malonic acid halide of formula II, e.g., the dichloride, takes place in a solvent which is indifferent to the acid halide, such as ether or benzene. In order to repress as far as possible the re-arrangement of the diarylhydrazine by the hydrogen halide produced, it is preferable to carry out the condensation in the presence of an acid-binding agent, preferably a tertiary organic base, such as pyridine or dimethyl-aniline. In this case the reaction may take place even at low temperatures which may suitably be in the neighbourhood of 0° C.

It is particularly easy to carry out the condensation in steps if unsymmetrical reactive derivatives of malonic acid (formula II) are used. For example, the ester-chloride Cl—CO—CH(R)—COO—Alkyl can be treated with a diaryl-hydrazine III to give firstly the acyl derivative IV, by allowing the components to react in the ratio of their molecular weights in ether or benzene in the presence of pyridine. Ring closure may then be brought about by heating with sodium ethylate:



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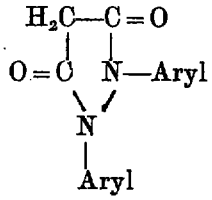
the pyrazolidine derivative of formula I, can in some cases be of advantage since it proceeds not from derivatives of substituted malonic acid (II), but directly from those of malonic acid itself, for example, from diethyl malonate. This method consists in introducing the radical R into the 4-position of a 1:2-diaryl-3:5-dioxo-pyrazolidine of formula V.



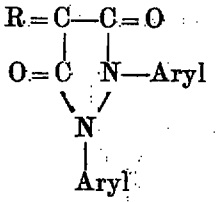
. . . (V)

According to this process the 3:5-dioxo-pyrazolidines of the present invention may be made by reacting the pyrazolidine derivative V or a salt thereof, preferably in the presence of an acid-binding agent, with a compound of the formula R—A, where A can mean Cl, Br, I, SO_4R or SO_3 Aryl.

The temperature necessary for the reaction depends on the reactivity of the compound R—A; it is well known, for example, that iodine compounds react more easily than bromine compounds. The setting-in of the reaction as well as its course can be easily followed by the formation of A ions. Generally speaking, temperatures between 0° C. and 100° C. are suitable.

The 3:5-dioxo-pyrazolidines of the present invention can also be made by introducing the group R by hydrogenating the diketopyrazolidine V in the presence of a carbonyl compound of the formula R=O, where R stands for a hydrocarbon or substituted hydrocarbon structure of 2 to 10 carbon atoms, the oxygen atom being bound by two valencies from one and the same carbon atom. In particular, R may be a saturated or unsaturated aliphatic or cycloaliphatic, or a phenyl substituted aliphatic hydrocarbon or substituted hydrocarbon radical. Because of its simplicity and the good yield this process is of special interest technically.

The 3:5-dioxo-pyrazolidines of the present invention can also be made by a variation of this method which consists in hydrogenating the condensation product VI derived from the dioxo-pyrazolidine V and the carbonyl compound R=O.



. . . (VI)

In both of the last two cases hydrogenation can be very conveniently carried out with hydrogen in the presence of a hydrogenation catalyst, such as finely divided nickel, platinum or palladium. Other reducing procedures, such as the use of sodium amalgam and water, offer no advantages over this method.

However, it must be noted in connection with this process, that when the radical R contains an aliphatic double bond, it is difficult to avoid hydrogenating it and the yield in such circumstances is usually unsatisfactory. On the other hand, the corresponding saturated derivative can be easily prepared. Consequently, the process is primarily suitable for the manufacture of those pyrazolidine derivatives of formula I in which the radical R contains no aliphatic double bonds.

The dioxopyrazolidines of formula V can be prepared by the methods known *per se* for the manufacture of 1:2-diphenyl-3:5-dioxo-pyrazolidine; the most suitable is the condensation of malonic ester with the corresponding diarylhydrazine of formula III in the presence of a metal alcoholate, e.g., sodium ethylate.

The substituted pyrazolidine derivatives of formula VI are derived from the unsubstituted parent compounds V by methods known *per se* (Bl. Chem. Soc. Japan, 1931, *6*, 1—9, 1932, *7*, 45—50).

Although most diaryl-dioxo-pyrazolidines of formula I have a noticeable analgesic and/or antipyretic effect, the extent of this action varies within the group of compounds named. In order to make the description more complete it may, therefore, be added that the compounds which have been tested and which have the best antipyretic and analgesic effect include 1:2-diphenyl-3:5-dioxo-4-alkyl-pyrazolidines, whose alkyl radical contains from 3 to 5 carbon atoms, particularly 4-*n*-butyl-, 4-*n*-propyl and 4-isopropyl-1:2-diphenyl-3:5-dioxo-pyrazolidine. The 4-benzyl derivative also has a very good analgesic action, while antipyretic activity is

especially well developed in the case of the 4-cyclohexyl derivative. Compounds with substituents in the phenyl radicals approximate to the corresponding parent compounds in activity, without surpassing them. For this reason the more readily available 1:2-diphenyl derivatives are generally to be preferred to those with substituted phenyl radicals. Here too, these compounds whose 4-alkyl radical contains 3—5 carbon atoms are the most valuable.

In contrast with the foregoing, our researches show that 1:2-diphenyl-3:5-dioxo-pyrazolidine, which is the already known compound most nearly comparable to the pyrazolidines of formula I, possesses practically no analgesic or antipyretic activity.

The dioxo-pyrazolidine derivatives prepared according to the invention can also form salts with basic compounds. Alkali-metal salts are readily soluble in water, while the solubility of the alkaline earth metal salts is less and decreases with increasing atomic weight of the metal. The heavy metal salts are only slightly soluble in water, but salts with organic bases possess a high degree of solubility.

This property of salt-formation represents a great advantage of the compounds described as compared with other analgetic and antipyretic substances, particularly since the solutions of these salts are only weakly alkaline and are suitable for purposes of injection. For this purpose, those salts with the less toxic cations should be used such as the sodium or magnesium salts, or those of ethylenediamine, triethanolamine or trimethylamine.

To prepare the soluble salts, the free pyrazolidine of formula I, is treated with an equimolecular quantity of a base containing the desired cation, e.g., with aqueous caustic soda, ethylenediamine, potassium hydroxide lye or sodium carbonate solution, or with alcoholic caustic soda. It is best to employ stirring or shaking during the reaction. If an aqueous lye is used, then an excess of the pyrazolidine may be present, which, after the solution is neutral to phenolphthalein, can be removed by filtration.

The salt can be obtained in solid form when desired either by evaporation of the filtered solution or by adding a solvent in which the salt is insoluble, for example, by the addition of ether to an alcoholic solution of the sodium salt.

However, it is also possible to obtain the corresponding salt directly when using alkaline condensing agents, such as, for example, sodium ethylate.

The alkali salts are mostly in the form of colourless powders, usually of considerable stability in the air, which are readily soluble in water and alcohol. Their solutions do not turn phenolphthalein red.

The difficultly soluble salts can be also prepared by double decomposition of an alkali or ammonium salt of a pyrazolidine of formula I, with a soluble alkaline earth or heavy metal salt, e.g., calcium chloride or silver nitrate. When working with a sufficiently concentrated solution the salts are obtained directly as precipitates. Alternatively, they can be isolated by suitably concentrating or cooling the solution.

In the following Examples a few methods of carrying out the manufacture as well as some of the compounds obtained are described in more detail. Parts are by weight, unless otherwise stated. The relationship of parts by weight to parts by volume is that of kilograms to litres. Temperatures are in degrees Centigrade.

EXAMPLE 1.

7.6 Parts of sodium are dissolved in 190 parts by volume of absolute alcohol, 65 parts of diethyl-*n*-butyl malonate and 55 parts of hydrazobenzene are added. The alcohol is slowly distilled off and the reaction mixture heated for 12 hours at a bath temperature of 150°, finally *in vacuo*, until no more alcohol comes off.

The product is dissolved in water, clarified with a little animal charcoal and 15% hydrochloric acid is slowly added until an acid reaction to Congo red paper is produced. 1:2-diphenyl-3:5-dioxo-4-*n*-butyl-pyrazolidine separates as an oil, which rapidly becomes crystalline. It crystallises from alcohol as colourless needles with a melting point of 105°.

EXAMPLE 2.

The same compound, 1:2-diphenyl-3:5-dioxo-4-*n*-butyl-pyrazolidine is obtained if the hydrazobenzene in Example 1 is replaced by 68 parts of N-acetyl-hydrazobenzene the method being otherwise the same. In this modification, the coloured by-products formed are somewhat less than by the method of Example 1. The yield is good in this case too.

EXAMPLE 3.

19 Parts of *n*-butyl-malonyl-dichloride (b.p. 85° at 14 mm. pressure) are added dropwise to a mixture of 50 parts absolute pyridine and 200 parts by volume of absolute ether at about 0°. Next, 18 parts of hydrazobenzene, dissolved in 100 parts by volume of ether are added and the mixture stirred for two hours at room temperature. The solution is then

shaken with 2 N hydrochloric acid to remove the pyridine, followed by 2 N sodium carbonate solution. The latter, which contains the sodium salt of 1:2-diphenyl - 3:5 - dioxo - 4 - *n* - butyl-pyrazolidine in solution is acidified with 10% hydrochloric acid, whereupon the free pyrazolidine derivatives separates out.

EXAMPLE 4.

1:2 - Diphenyl - 3:5 - dioxo - pyrazolidine (Ber. d. deutschen chem. Ges., 1940, *73*, 822) is heated for 5 hours on the boiling water-bath with five times its weight of cyclohexanone. The excess of cyclohexanone is then distilled off *in vacuo*, and the residue recrystallised from alcohol. The 1:2-diphenyl-3:5-dioxo-4-cyclohexylidene-pyrazolidine so obtained consists of yellow needles melting at 173°. If it is treated with hydrogen (at about 30 atmospheres pressure) in the presence of Raney nickel at 100°, then 1:2-diphenyl-3:5-dioxo-4-cyclohexyl-pyrazolidine is formed. The latter compound is difficultly soluble in alcohol and has a melting point of 177°.

If 1:2 - diphenyl - 3:5 - dioxo - 4-benzylidene-pyrazolidine (Bl. Chem. Soc. Japan, 1931, *6*, 8), is hydrogenated in a similar manner, then 1:2-diphenyl-3:5-dioxo-4-benzyl-pyrazolidine with a melting point of 136—138° is formed.

In the same way, 1:2-diphenyl-3:5-dioxo - 4 - (γ - phenyl - propyl) - pyrazolidine may be prepared from 1:2-diphenyl - 3:5 - dioxo - 4 - cinnamylidene-pyrazolidine (*loc. cit.*), 1:2-diphenyl-3:5 - dioxo - 4 - (α - phenylethyl)-pyrazolidine from 1:2-diphenyl-3:5-dioxo - 4 - (α - phenyl - ethylidene)-pyrazolidine (Bl. Chem. Soc. Japan, 1931, *6*, 9), 1:2-diphenyl-3:5-dioxo-4-(*p*-methyl-benzyl)-pyrazolidine from 1:2-diphenyl - 3:5 - dioxo - 4 - (*p* - methyl-benzal)-pyrazolidine (Bl. Chem. Soc. Japan, 1932, *7*, 45 *et seq.*), 1:2-diphenyl-4 - (*p* - methoxy - benzyl) - 3:5 - dioxo-pyrazolidine from 1:2-diphenyl-4-(*p*-methoxy - benzal) - 3:5 - dioxo - pyrazolidine (*loc. cit.*), 1:2 - diphenyl - 4 - piperonyl-3:5-dioxo-pyrazolidine from 1:2 - diphenyl - 4 - piperonylidene-pyrazolidine (*loc. cit.*) and 1:2-diphenyl-3:5 - dioxo - 4 - *n* - propyl - pyrazolidine (m.pt. 108—109°) from 1:2-diphenyl-3:5 - dioxo - 4 - propylidene - pyrazolidine (*loc. cit.*).

EXAMPLE 5.

1:2 - Diphenyl - 3:5 - dioxo - pyrazolidine is heated to boiling for 10 minutes with double its weight of cyclopentanone. On diluting the solution with alcohol and cooling, yellow crystals of 1:2-diphenyl - 3:5 - dioxo - 4 - cyclopentylidene-pyrazolidine (m.pt. 153°) crystallise out. When the latter compound is hydrogenated in alcoholic solution at 50° in the presence of Raney nickel and at atmospheric pressure, 1:2-diphenyl - 3:5 - dioxo - 4 - cyclo - pentyl-pyrazolidine, melting at 172° is produced. It dissolves gradually on shaking with 2 N caustic soda lye with the formation of the sodium salt. It is soluble only with difficulty in alcohol.

EXAMPLE 6.

A solution of 160 parts of 1:2-diphenyl-3:5-dioxo-pyrazolidine and 120 parts of benzaldehyde in 500 parts by volume of alcohol is heated to 100° under 20 atmospheres of hydrogen in the presence of Raney nickel until the hydrogen is taken up only slowly and the solution becomes colourless. 1:2-Diphenyl - 3:5 - dioxo - 4 - benzyl-pyrazolidine crystallises from the hot, filtered, solution.

EXAMPLE 7.

1:2 - Diphenyl - 3:5 - dioxo-pyrazolidine dissolved in 10 times the amount of acetone is hydrogenated at 100° under 20 atmospheres pressure of hydrogen in the presence of Raney nickel. On evaporating down the filtered acetone solution, 1:2 - diphenyl - 3:5-dioxo-4-isopropyl-pyrazolidine crystallises out in good yield. It melts at 143°.

EXAMPLE 8.

25 Parts of 1:2-diphenyl-3:5-dioxo-pyrazolidine are dissolved in 100 parts of 2 N caustic soda lye. 14 Parts of 1-bromo-butane are slowly dropped in, while stirring, and the mixture warmed at 70°. Undissolved oily fractions are removed by shaking with ether and the aqueous solution is then acidified with 10% hydrochloric acid. A precipitate of 1:2 - diphenyl - 3:5 - dioxo - 4 - butyl-pyrazolidine is obtained, melting at 105°.

Similarly, 1:2-diphenyl-3:5-dioxo-4-(*p*-chlorobenzyl)-pyrazolidine is obtained from 25 parts of 1:2-diphenyl-3:5-dioxo-pyrazolidine dissolved in 100 parts by volume of 2N caustic soda lye by reacting with 16 parts of 4-chloro-benzyl chloride.

EXAMPLE 9.

To a sodium ethylate solution prepared from 23 parts of sodium and 500 parts by volume of absolute alcohol is added, while stirring, an equimolecular amount (308 parts) of 1:2-diphenyl-3:5-dioxo-4-*n*-butyl-pyrazolidine. The solution thus obtained, after filtration, if necessary, is evaporated to dryness *in vacuo*. The residue is triturated with absolute ether and filtered under suction. The sodium salt of 1:2-diphenyl-3:5-dioxo-4-*n*-butyl-

pyrazolidine is left as a colourless powder which is readily soluble in water. The aqueous solution reacts weakly alkaline but is not, however, alkaline to phenolphthalein.

The sodium salts of other 4-substituted 1:2 - diphenyl - 3:5 - dioxo - pyrazolidines may be prepared similarly.

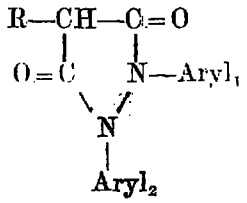
EXAMPLE 10.

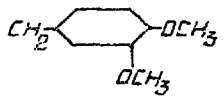
30 Parts of diethylamine are poured over 10 parts of 1:2-diphenyl-3:5-dioxo-4-*n*-butyl-pyrazolidine. The latter dissolves and, on rubbing, the salt separates out in crystalline form. The diethylamine salt of 1:2-diphenyl-3:5-dioxo-4-*n*-butyl-pyrazolidine thus obtained loses part of the base when exposed to the atmosphere.

Alternative method: 10 Parts of 1:2-diphenyl - 3:5 - dioxo - 4 - *n* - butyl-pyrazolidine are dissolved in 50 parts of hot absolute alcohol and about 40 parts of diethylamine are then added. The diethylamine salt of 1:2-diphenyl-3:5-dioxo-4-*n*-butyl-pyrazolidine is precipitated out by adding absolute ether, filtered off under suction and washed with ethereal diethylamine solution.

The methods described in the above Examples can be applied, as will be clear to those skilled in the art, for the production of other 4-substituted 1:2-diphenyl-3:5-dioxo-pyrazolidines. For example, in addition to those given above, the following compounds may be prepared:—

General formula:

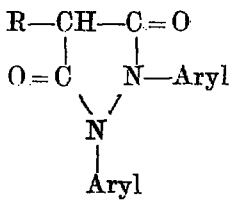


$Aryl_1$	$Aryl_2$	R	Melting point.
C_6H_5	C_6H_5	CH_3	114—116°
C_6H_5	C_6H_5	C_2H_5	108°
C_6H_5	C_6H_5	$CH_2—CH=CH_2$	135°
C_6H_5	C_6H_5	iso-C_4H_9	127—128°
C_6H_5	C_6H_5	$CH_2—CH=CH—CH_3$	128°
C_6H_5	C_6H_5	*n*-C_5H_{11}	104—105°
C_6H_5	C_6H_5	iso-C_5H_{11}	137°
C_6H_5	C_6H_5	$CH(CH_2)—CH_2—CH(CH_3)_2$	107—108°
C_6H_5	C_6H_5		133°
C_6H_5	C_6H_5	$CH_3—CH—CH_2—CH_3$	116°
C_6H_5	C_6H_5	*n*-C_7H_{15}	95°
$C_6H_4—CH_3(p)$	$C_6H_4—CH_3(p)$	iso-C_3H_7	167°
$C_6H_4—CH_3(p)$	$C_6H_4—CH_3(p)$	*n*-C_4H_9	133°
$C_6H_4—Cl(p)$	C_6H_5	*n*-C_4H_9	132°
$C_6H_4—Cl(p)$	$C_6H_4—Cl(p)$	*n*-C_4H_9	132°
$C_6H_4—OCH_3(p)$	$C_6H_4—OCH_3(p)$	*n*-C_4H_9	198°
$C_6H_4—OC_2H_5(p)$	C_6H_5	*n*-C_4H_9	81.5°

When the expression " functional reactive derivative of a monosubstituted malonic acid " is used in the specification and claims, it is intended to mean a compound of the formula R—CH(CO—X)$_2$; and when the expression " functional reactive derivative of an unsubstituted malonic acid " is used in the specification and claims, it is intended to mean a compound of the formula $CH_2(CO—X)_2$, wherein R means a hydrocarbon or substituted hydrocarbon structure with 2 to 10 carbon atoms, bound to the pyrazolidine nucleus by a primary or secondary carbon atom, particularly a saturated or unsaturated aliphatic or cycloaliphatic, or a phenyl-substituted aliphatic hydrocarbon or substituted hydrocarbon radical and X is a radical or atom which can split off from the acid derivative. Thus, the compound may be for example, a di-ester, a di-halide, or an ester halide.

Having now particularly described and ascertained the nature of the said invention and in what manner the same is to be performed, as communicated to me by my foreign correspondents, I declare that what I claim is:—

1. New 3:5 - dioxo - pyrazolidines having the general formula:—



wherein R means a hydrocarbon or substituted hydrocarbon structure with 2 to 10 carbon atoms, bound to the pyrazolidine nucleus by a primary or secondary carbon atom, particularly a saturated or unsaturated aliphatic, or cycloaliphatic or a phenyl-substituted aliphatic hydrocarbon or substituted hydrocarbon radical, and Aryl means a phenyl radical, which may be either unsubstituted or substituted by halogen atoms, alkyl and/or alkoxy groups, such alkyl and alkoxy groups containing 1 to 3 carbon atoms, and their salts, whenever prepared or produced by the processes herein particularly described and ascertained.

2. Process for the manufacture of the new 3:5-dioxo-pyrazolidines defined in claim 1, which comprises reacting, preferably in the presence of a condensing agent such as a compound suitable for the replacement of a movable hydrogen atom by a metal atom or in the presence of an acid-binding agent, a functional reactive derivative of a monosubstituted malonic acid with a 1:2-diaryl hydrazine of the formula:—

Aryl—NY—NY—Aryl,

wherein Aryl has the meaning hereinbefore given, and Y represents either a hydrogen atom or an acyl radical.

3. Process for the manufacture of the new 3:5-dioxo-pyrazolidines defined in claim 1 which comprises reacting, preferably in the presence of an acid-binding agent, 1:2-diaryl - 3:5 - dioxo-pyrazolidine, or a salt thereof, with a compound of the formula R—A wherein, A means chlorine, bromine, iodine, SO_4R or SO_3 Aryl and—R and Aryl have the meanings hereinbefore given.

4. Process for the manufacture of the new 3:5-dioxo-pyrazolidines defined in claim 1 which comprises hydrogenating 1:2 - diaryl - 3:5 - dioxo - pyrazolidine in the presence of a carbonyl compound of the formula R=O, wherein R has the meaning hereinbefore given and wherein the oxygen atom is bound by two valencies from one and the same carbon atom.

5. Process for the manufacture of the new 3:5-dioxo-pyrazolidines defined in claim 1 which comprises condensing 1:2-diaryl - 3:5 - dioxo-pyrazolidine with a carbonyl compound of the formula R=O wherein, R has the meaning hereinbefore given and wherein the oxygen atom is bound by two valencies from one and the same carbon atom, and subsequently hydrogenating the condensation product.

6. Process as claimed in claim 4 or 5 in which R represents a saturated or unsaturated aliphatic radical.

7. Process as claimed in claim 3, 4, 5 or 6 in which the 1:3-diaryl-3:5-dioxo-pyrazolidine is obtained by reacting a functional reactive derivative of an unsubstituted malonic acid with a 1:2-diaryl hydrazine of the formula:—

Aryl—NY—NY—Aryl

wherein Aryl and Y have the meanings hereinbefore given.

8. Process as claimed in any of claims 2—7 in which the new 3:5-dioxo-pyrazolidines defined in claim 1 are reacted with organic or inorganic bases to form salts thereof.

9. Process for the manufacture of the new 3:5-dioxo-pyrazolidines defined in claim 1, and their salts, substantially as herein described.

10. 1:2 - Diphenyl - 4 - propyl - 3:5-dioxo-pyrazolidine and salts thereof with bases, whenever prepared according to the processes defined in claims 2 to 8.

When the expression "functional reactive derivative of a monosubstituted malonic acid" is used in the specification and claims, it is intended to mean a compound of the formula $R—CH(CO—X)_2$; and when the expression "functional reactive derivative of an unsubstituted malonic acid" is used in the specification and claims, it is intended to mean a compound of the formula $CH_2(CO—X)_2$, wherein R means a hydrocarbon or substituted hydrocarbon structure with 2 to 10 carbon atoms, bound to the pyrazolidine nucleus by a primary or secondary carbon atom, particularly a saturated or unsaturated aliphatic or cycloaliphatic, or a phenyl-substituted aliphatic hydrocarbon or substituted hydrocarbon radical and X is a radical or atom which can split off from the acid derivative. Thus, the compound may be for example, a di-ester, a di-halide, or an ester halide.

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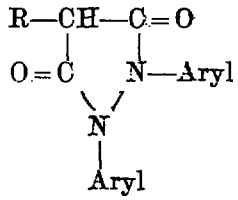

wherein R means a hydrocarbon or substituted hydrocarbon structure with 2 to 10 carbon atoms, bound to the pyrazolidine nucleus by a primary or secondary carbon atom, particularly a saturated or unsaturated aliphatic, or cycloaliphatic or a phenyl-substituted aliphatic hydrocarbon or substituted hydrocarbon radical, and Aryl means a phenyl radical, which may be either unsubstituted or substituted by halogen atoms, alkyl and/or alkoxy groups, such alkyl and alkoxy groups containing 1 to 3 carbon atoms, and their salts, whenever prepared or produced by the processes herein particularly described and ascertained.

2. Process for the manufacture of the new 3:5-dioxo-pyrazolidines defined in claim 1, which comprises reacting, preferably in the presence of a condensing agent such as a compound suitable for the replacement of a movable hydrogen atom by a metal atom or in the presence of an acid-binding agent, a functional reactive derivative of a monosubstituted malonic acid with a 1:2-diaryl hydrazine of the formula:—

$$Aryl—NY—NY—Aryl,$$

wherein Aryl has the meaning hereinbefore given, and Y represents either a hydrogen atom or an acyl radical.

3. Process for the manufacture of the new 3:5-dioxo-pyrazolidines defined in claim 1 which comprises reacting, preferably in the presence of an acid-binding agent, 1:2-diaryl - 3:5 - dioxo-pyrazolidine, or a salt thereof, with a compound of the formula R—A wherein, A means chlorine, bromine, iodine, SO_4R or SO_3 Aryl and—R and Aryl have the meanings hereinbefore given.

4. Process for the manufacture of the new 3:5-dioxo-pyrazolidines defined in claim 1 which comprises hydrogenating 1:2 - diaryl - 3:5 - dioxo - pyrazolidine in the presence of a carbonyl compound of the formula R=O, wherein R has the meaning hereinbefore given and wherein the oxygen atom is bound by two valencies from one and the same carbon atom.

5. Process for the manufacture of the new 3:5-dioxo-pyrazolidines defined in claim 1 which comprises condensing 1:2-diaryl - 3:5 - dioxo-pyrazolidine with a carbonyl compound of the formula R=O wherein, R has the meaning hereinbefore given and wherein the oxygen atom is bound by two valencies from one and the same carbon atom, and subsequently hydrogenating the condensation product.

6. Process as claimed in claim 4 or 5 in which R represents a saturated or unsaturated aliphatic radical.

7. Process as claimed in claim 3, 4, 5 or 6 in which the 1:3-diaryl-3:5-dioxo-pyrazolidine is obtained by reacting a functional reactive derivative of an unsubstituted malonic acid with a 1:2-diaryl hydrazine of the formula:—

$$Aryl—NY—NY—Aryl$$

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8. Process as claimed in any of claims 2—7 in which the new 3:5-dioxo-pyrazolidines defined in claim 1 are reacted with organic or inorganic bases to form salts thereof.

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10. 1:2 - Diphenyl - 4 - propyl - 3:5-dioxo-pyrazolidine and salts thereof with bases, whenever prepared according to the processes defined in claims 2 to 8.

* C L M S *

11. 1:2 - Diphenyl-4-iso-propyl 3:5-dioxo-pyrazolidine and salts thereof with bases, whenever prepared according to the processes defined in claims 2 to 8.

12. 1:2 - Diphenyl - 4 - butyl - 3:5-dioxo-pyrazolidine and salts thereof with bases, whenever prepared according to the processes defined in claims 2 to 8.

13. 1:2 - Diphenyl - 4 - *n* - butyl - 3:5-dioxo-pyrazolidine and salts thereof with bases, whenever prepared according to the processes defined in claims 2 to 8.

14. 1:2-Diphenyl - 4 - benzyl - 3:5-dioxo-pyrazolidine and salts thereof with bases, whenever prepared according to the processes defined in claims 2 to 8.

15. 1:2 - Diphenyl - 4 - cyclohexyl-3:5-dioxo-pyrazolidine and salts thereof with bases, whenever prepared according to the processes defined in claims 2 to 8.

Dated this 23rd day of February, 1949.

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