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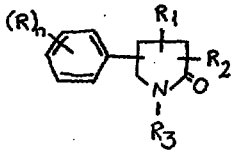
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(54) NEW DERIVATIVES OF 2-PYRROLIDINONE

(71) We, UCB formerly UCB (Union Chimique-Chemische Bedrijven) Société Anonyme, of 4 Chaussée de Charleroi, Saint-Gilles-lez-Bruxelles, Belgium, a Body Corporate organised under the laws of Belgium, 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 is concerned with new derivatives of 2-pyrrolidinone and with the preparation thereof and is also concerned with therapeutic compositions containing the new derivatives and with the use thereof in the therapeutic field.

The new derivatives according to the present invention are substituted phenyl - 2 - pyrrolidinones of the general formula:—



(I)

wherein R is a halogen atom, an alkyl, haloalkyl, alkenyl, alkynyl or alkoxy radical containing up to 5 carbon atoms or a nitro, amino or hydroxyl group; R_1 is an alkyl, alkenyl or alkynyl radical containing up to 5 carbon atoms or an aryl or aralkyl radical, the nucleus of which can be substituted, for example, by a halogen atom; R_2 is a hydrogen atom or an alkyl radical containing up to 5 carbon atoms, or an aryl radical; R_3 is a hydrogen atom, an alkyl, alkenyl or alkynyl radical containing up to 7 carbon atoms or a cycloalkyl or aralkyl radical; and n is 1, 2 or 3, as well as the *cis* and *trans* stereoisomers, racemates and optically-active isomers thereof.

We have found that the substituted phenyl-2-pyrrolidinones of the above general formula (I) possess very interesting therapeutic properties; in particular, they have a considerable action on the central nervous system. For example, they have a marked anxiolytic action, which has been demonstrated by pharmacological tests. We have also found that they have psychostimulant or anti-depressant properties and a protective effect against anoxic anoxia. From this latter property, it can be concluded that these compounds may be used, *inter alia*, in the treatment of the sequelae of cerebro-vascular insufficiencies and cranial traumata. These new compounds also have a low toxicity.

The new compounds of the present invention can be prepared by the methods which are known for obtaining 2-pyrrolidinones, for example, by one of the following processes:

a) cyclisation of a 4 - amino - butyric acid or of an alkyl ester thereof of the general formula

$$H(R_3)N—A—COOX,$$

wherein X is a hydrogen atom or an alkyl radical containing up to 4 carbon atoms and A is a trimethylene chain substituted by $(R)_n$-phenyl, R_1 and R_2 radicals; and R, R_1, R_2, R_3 and n having the same meanings as above.

The 4 - amino - butyric acid or the alkyl ester thereof used as starting material can be prepared, for example, when R_3 is a hydrogen atom and the methylene group in A adjacent to the nitrogen atom is unsubstituted, by subjecting an appropriate 3-cyanopropionic acid or an alkyl ester thereof of the general formula

$$NC—A'—COOX,$$

in which A' is an ethylene chain substituted

[Price 25p]

Price 33p

by $(R)_n$-phenyl, R_1 and R_2 radicals, X, R, R_1, R_2 and n having the same meanings as above, except that R and R_1 are not alkenyl or alkynyl radicals, to catalytic hydrogenation; when R_3 is a hydrogen atom, by subjecting an appropriate 4-nitrobutyric acid or an alkyl ester thereof of the general formula

$$O_2N—A—COOX,$$

in which A and X have the same meanings as above, except that R and R_1 are not alkenyl or alkynyl radicals, to catalytic reduction; when X is a hydrogen atom and at most one of the $(R)_n$-phenyl, R_1 and R_2 radicals is attached to the carbon atom of A adjacent to the nitrogen atom, by condensing an appropriate 4 - oxo - butyric acid of the general formula

$$O=A''.COOH,$$

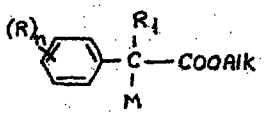
in which A'' is a propan - 1 - yl - 3 - ylidene radical substituted by $(R)_n$-phenyl, R_1 and R_2 radicals, R, R_1, R_2 and n having the same meanings as above, except that R and R_1 are not alkenyl or alkynyl radicals, with ammonia or a primary amine of the general formula

$$R_3NH_2,$$

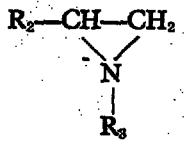
R_3 having the same meaning as above, followed by catalytic hydrogenation of the Schiff's base obtained; when X is a hydrogen atom and R_3 is a hydrogen atom and at most one of the $(R)_n$-phenyl, R_1 and R_2 radicals is attached to the carbon atom of A adjacent to the nitrogen atom, by condensation of an appropriate 4 - oxo - butyric acid of the general formula

$$O=A''.COOH,$$

in which A'' has the same meaning as above, with hydroxylamine and catalytic reduction of the resulting oxime, these reductions or hydrogenations being performed, for example, by reaction with hydrogen under increased pressure in the presence of palladium on carbon or of Raney nickel or cobalt as catalyst; or, in the case of the alkyl esters, in which the $(R)_n$-phenyl and R_1 radicals are attached to the carbon atom of A adjacent to the carboxylic group, by reaction of an alkali metal derivative of an alkyl 2 - [$(R)_n$ - phenyl] - 2 - R_1 - acetate of the general formula:—



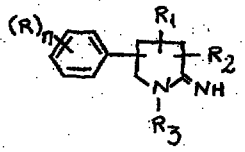
wherein Alk is an alkyl radical containing up to 4 carbon atoms, M is an alkali metal atom and R, R_1 and n have the same meanings as above, with an ethylene-imine of the general formula:—



wherein R_2 and R_3 have the same meanings as above.

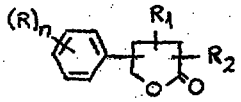
The 4 - amino - butyric acid or the alkyl ester thereof used as starting material can be prepared separately, optionally isolated and then cyclised. However, the starting material can also be prepared *in situ*, starting with the materials mentioned above, and cyclised directly, without isolating, to give a 2-pyrrolidinone according to the present invention.

b) hydrolysis of a 2 - imino - pyrrolidinone of the general formula:—



wherein R, R_1, R_2, R_3 and n have the same meanings as above;

c) reaction, at an elevated temperature, of a lactone of the general formula:—



wherein R, R_1, R_2 and n have the same meanings as above, with ammonia or a primary amine of general formula

$$R_3NH_2,$$

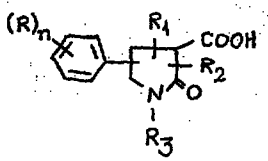
wherein R_3 has the same meaning as above;

d) cyclisation in the presence of an alkaline condensation agent, of a 4 - halogeno - butyramide of the general formula

$$Hal—A—CONH(R_3),$$

wherein Hal is a halogen atom and A a trimethylene chain substituted by $(R)_n$-phenyl, R_1 and R_2 radicals; and R, R_1, R_2, R_3 and n have the same meanings as above;

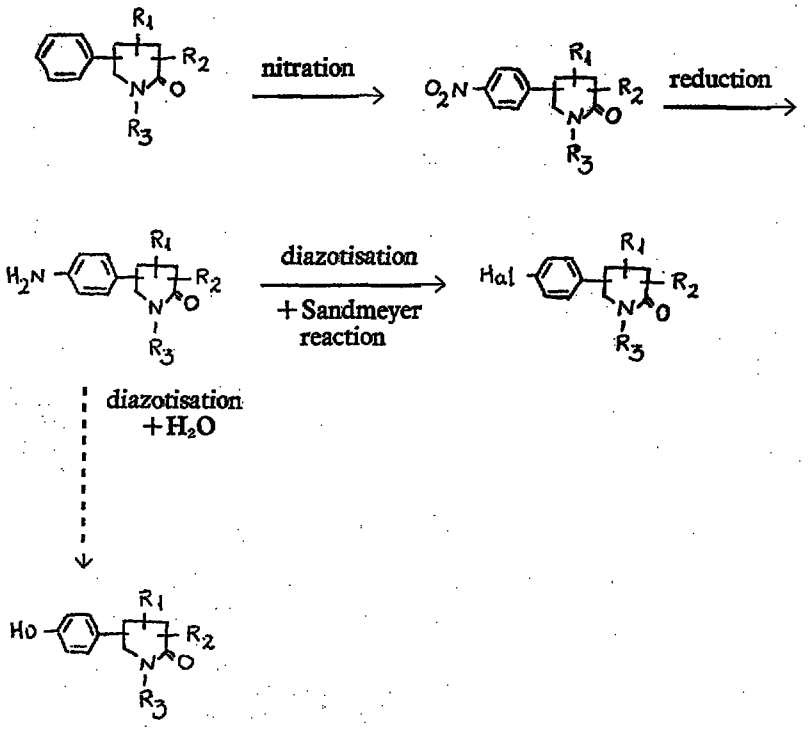
e) when at most one of the $(R)_n$-phenyl, R_1 and R_2 radicals is in the 3-position, decarboxylation, by heating, of a 2 - pyrrolidino - 3 - carboxylic acid of the general formula:—



wherein R, R_1, R_2, R_3 and n have the same meanings as above.

In order to prepare substituted phenyl - 2 - pyrrolidinones of general formula (I) in which R_3 is not a hydrogen atom, i.e. phenyl - 2 - pyrrolidinones substituted on the nitrogen atom, it is also possible, in accordance with conventional methods, to introduce a substituent on the cyclic nitrogen atom of a corresponding phenyl - 2 - pyrrolidinone in which the nitrogen atom is not substituted and has been obtained by one of the methods (a) to (e) above. Thus, it is possible, for example, to react an appropriate phenyl - 2 - pyrrolidinone with an R_3 halide in the presence of an alkaline condensation agent, R_3 being an alkyl, alkenyl or alkynyl radical containing up to 7 carbon atoms or a cycloalkyl or aralkyl radical.

In the particular case of substituted phenyl - 2 - pyrrolidinones of general formula (I) in which R is a nitro, amino or hydroxyl group or a halogen atom in the para-position, it is also possible to proceed in the following manner: an appropriately substituted phenyl - 2 - pyrrolidinone, the phenyl radical of which is not substituted, is nitrated by means of nitric acid, a mixture of concentrated nitric and sulphuric acids or some other appropriate nitration agent, in order to obtain the corresponding substituted *p* - nitrophenyl - 2 - pyrrolidinone (R=nitro). This nitro derivative is then optionally subjected to catalytic hydrogenation or chemical reduction and converted into the corresponding substituted *p* - aminophenyl - 2 - pyrrolidinone (R=amino). Finally, this amino derivative is optionally subjected to diazotisation in an aqueous medium with an alkali metal nitrite in the presence of a halohydric acid at a temperature of 0—5°C. in order to obtain the corresponding diazonium salt. This can be subjected to a Sandmeyer reaction in the presence of a cuprous halide or of copper powder to give the corresponding substituted *p* - halophenyl - 2 - pyrrolidinone (R=halogen), or it can also be converted into the corresponding substituted *p* - hydroxyphenyl - 2 - pyrrolidinone (R=hydroxyl) by heating an aqueous solution thereof. These different reactions can be represented by the following scheme:



wherein Hal is a halogen atom and R_1, R_2 and R_3 have the same meanings as above.

The phenyl - 2 - pyrrolidinones prepared by the foregoing methods are often obtained in the form of mixtures of the *cis* and *trans* stereoisomers. These mixtures can be separated into their *cis* and *trans* components by known methods, for example by fractional crystallisation or by column chromatography. Furthermore, the products may consist of racemic mixtures of the *d* and *l* - optically - active isomers. The mixtures can also be separated into the optically-active isomers by known methods.

Thus, the present invention also comprises the *cis* and *trans* stereoisomers and optically-

active (*d* and *l*) and racemic (*d,l*) forms of the substituted phenyl-pyrrolidinones of general formula (I).

To demonstrate the anxiolytic action of the compounds according to the present invention, the following test was performed:

Rats were subjected to a sequence of painful electric shocks on their paws at the rate of shocks lasting 3 seconds repeated every 30 seconds for 10 minutes. During this first sequence, it was found that the rats broke away before the end of the shock roughly 15 times out of 20 shocks.

On the other hand if the same animals were subjected to a sequence of shocks some hours later, paradoxically, instead of improving their performance (as in the course of a normal training) a reduction in the number of evasions was noted; the animals had become set and were less successful in getting away before the shocks ended. This behaviour was attributed to an anxiety state induced by the experimental situation.

Intraperitoneal administration of an anxiolytic product to the rats, before the second sequence was carried out, improved their performance (increased the number of escapes before the end of the shock and diminished the time elapsing before escape).

A group of rats which had been treated was compared with a reference group which had been injected with physiological serum under the same conditions.

The object was to discover the minimum dose of the anxiolytic product which would product an appreciable improvement in the performances of the rats in comparison with those of the reference rats.

The undermentioned compounds, designated with the leters A to T, which are in accordance with the present invention, were subjected to this test:

A. 4 - *p* - chlorophenyl - 5 - methyl - 2 - pyrrolidinone
B. 5 - (2,4 - dimethylphenyl) - 3 - methyl - 2 - pyrrolidinone
C. 4 - *p* chlorophenyl - 3 - ethyl - 2 - pyrrolidinone (*cis* isomer)
D. 4 - *p* - chlorophenyl - 3 - ethyl - 2 - pyrrolidinone (*trans* isomer)
E. 4 - *p* - chlorophenyl - 3 - methyl - 2 - pyrrolidinone (*cis* isomer)
F. 4 - *p* - chlorophenyl - 3 - methyl - 2 - pyrrolidinone (*trans* isomer)
G. 4 - *p* - chlorophenyl - 3 - phenyl - 2 - pyrrolidinone (*cis* isomer)
H. 4 - *p* - chlorophenyl - 3 - phenyl - 2 - pyrrolidinone (*trans* isomer)
I. 4 - *o* - chlorophenyl -3 - phenyl - 2 - pyrrolidinone
J. 4 - *p* - fluorophenyl - 3 - methyl - 2 - pyrrolidinone
K. 4 - *p* - chlorophenyl - N - methyl - 3 - phenyl - 2 - pyrrolidinone
L. 4 - *p* - fluorophenyl - 3 - phenyl - 2 - pyrrolidinone
M. 3 - *o* - chlorophenyl - 4 - *p* - chlorophenyl - 2 - pyrrolidinone
N. 4 - *p* - chlorophenyl - 4 - phenyl - 2 - pyrrolidinone
O. 4 - *p* - chlorophenyl - 3 - phenyl - N - benzyl - 2 - pyrrolidinone
P. 4 - *p* - chlorophenyl - 5 - ethyl - 3 - phenyl - 2 - pyrrolidinone
Q. 4 - *p* - chlorophenyl - 3 - phenyl - N - (2 - propynyl) - 2 - pyrrolidinone
R. 4 - *p* - chlorophenyl - 3 - phenyl - N - cyclopentyl - 2 - pyrrolidinone
S. 3 - allyl - 3 - *p* - chlorophenyl - 5 - phenyl - 2 - pyrrolidinone (isomer of m.p. 197—198°C.)
T. 3 - phenyl - 4 - *m* - trifluoromethylphenyl - 2 - pyrrolidinone.

In the following Table, the minimum dose (in mMol per kg.) with which an anxiolytic effect is observed, is given for each compound subjected to the test:

Compound	Dosage
A	0.10
B	0.10
C	0.18
D	0.10
E	0.032
F	0.024
G	0.0024
H	0.01
I	0.032
J	0.032
K	0.01
L	0.01
M	0.032
N	0.10
O	0.10
P	0.032
Q	0.032
R	0.032
S	0.032
T	0.01

Chlordiazepoxide (7 - chloro - 2 - methylamino - 5 - phenyl - 3H - 1,4 - benzodiazepine - 4 - oxide), which is a well-known anxiolytic, gave an anxiolytic result in this test at the minimum dose of 0.03 mmol/kg.

By comparison with this known anxiolytic, the products of the present invention have the advantage of not causing ataxia. Indeed, in the "Rotarod" test of N. W. Dunham and T. S. Miya (J. Amer. Pharm. Assoc. 46, (1957), 208—09), the efficacious dose (ED_{50}) for the rat is 8 mg/kg. in the case of chlordiazepoxide whereas it is 60 mg/kg. in the case of compound G.

Furthermore, the new compounds of the present invention are less toxic. Thus, the toxicity determined in rats by intraperitoneal administration (LD_{50}) is 520 mg/kg. for com-

pound A, 306 mg/kg. for compound F and 320 mg/kg. for compound G, whereas for chlordiazepoxide it is 240 mg/kg.

The present invention also provides pharmaceutical compositions comprising at least one compound according to the present invention, in admixture with a solid or liquid pharmaceutical diluent or carrier.

Thus, the new compounds according to the present invention may be administered *per os*, in the form of solid or liquid compositions comprising the usual excipients, or rectally, in the form of suppositories. In general, they are administered at doses of from 20 to 200 mg. once or twice per day, although variations occur depending on the weight and state of health of the subject to be treated, as well as the particular mode of administration chosen.

The following Examples are given for the purpose of illustrating the present invention:—

Example 1

4 - *p* - chlorophenyl - 3 - phenyl - 2 - pyrrolidinone

30 g. ethyl 4 - amino - 3 - *p* - chlorophenyl - 2 - phenyl - butyrate are heated for 15 minutes at 150°C. Liberation of ethanol is observed. The reaction medium is taken up in 120 ml. toluene and the resulting solution is filtered. After cooling the solution, the crystals formed are separated and recrystallised several times from toluene. 12 g 4 - *p* - chlorophenyl - 3 - phenyl - 2 - pyrrolidinone are obtained; m.p. 148—151°C. Nuclear magnetic resonance analysis shows that it is the *cis*-isomer.

By concentration and fractional crystallisation of the mother liquor, a small quantity of the *trans*-isomer is obtained; m.p. 130—135°C.

The ethyl 4 - amino - 3 - *p* - chlorophenyl - 2 - phenyl - butyrate used as starting material is prepared in the following way:

To 20 g. ethyl 3 - *p* - chlorophenyl - 3 - cyano - 2 - phenyl - propionate in 500 ml. ethanol, there is added an equimolecular solution of hydrochloric acid in ethanol. The resulting solution is hydrogenated in a Parr bomb with hydrogen at a pressure of 4 kg/cm² in the presence of 1.5 g. palladium on carbon (5%) at a temperature of about 40—50°C. until about 90% of the theoretical quantity of hydrogen has been absorbed (to prevent hydrogenolysis of the chlorine): this takes about 5 hours.

A precipitate is formed which is dissloved by the addition of a large volume of ethanol. The product is collected by filtering off the catalyst and concentrating the filtrate. After crystallisation, 10 g. ethyl 4 - amino - 3 - *p* - chlorophenyl - 2 - phenyl - butyrate hydrochloride are obtained; melting point 272—274°C. The corresponding base is then isolated by treating the hydrochloride with an equimolar quantity of sodium hydroxide in water, extracting the resulting aqueous solution with toluene and evaporating the solvent of the extract.

The preparation of ethyl 3 - *p* - chlorophenyl - 3 - cyano - 2 - phenyl - propionate is described in Example 2.

The following compounds is prepared in an analogous manner:

3 - p - Methylphenyl - 4 - phenyl - 2 - pyrrolidinone (m.p.: 123—125°C.; after recrystallisation from toluene-hexane (1:1)) was prepared by the cyclisation of ethyl 4 - amino - 2 - *p* - methylphenyl - 3 - phenyl - butyrate, which itself is obtained by the catalytic hydrogenation, in an acid medium, of ethyl 3 - cyano - 2 - *p* - methylphenyl - 3 - phenyl - propionate, which has a boiling point of 178—184°C./0.4 mm.Hg.

The melting point of ethyl 4 - amino - 2 - *p* - methylphenyl - 3 - phenyl - butyrate is 84—85°C., after recrystallisation from toluene-hexane (1:1) and melting point of the corresponding hydrochloride is 275—277°C., after recrystallisation from ethanol.

Example 2

4 - *p* - chlorophenyl - 3 - phenyl - 2 - pyrrolidinone

This Example shows a variant of the method described in Example 1 in which the starting material, ethyl 4 - amino - 3 - *p* - chlorophenyl - 2 - phenyl - butyrate, is formed *in situ* and cyclised directly to give 4 - *p* - chlorophenyl - 3 - phenyl - 2 - pyrrolidinone.

60 g. ethyl 3 - *p* - chlorophenyl - 3 - cyano - 2 - phenyl - propionate are dissolved in 300 ml. ethanol. The resulting solution is hydrogenated in an autoclave with hydrogen at a pressure of about 100 kg/cm², using 20 g. Raney nickel as catalyst. Heating is carried out for about 15 hours at 90—95°C. After filtration of the catalyst, the filtrate is evaporated to dryness and the residue is recrystallised from toluene. The yield is of the order of 50%. The melting point of the resulting 4 - *p* - chlorophenyl - 3 - phenyl - 2 - pyrrolidinone varies, according to the concentration of the two diastereoisomers. The two *cis* and *trans* isomers are prepared by fractional crystallisation from toluene and identified by nuclear magnetic resonance analysis. Melting point of the *cis* isomer; 148—151°C.; melting point of the *trans* isomer: 130—135°C.

The ethyl 3 - *p* - chlorophenyl - 3 - cyano - 2 - phenyl - propionate used as starting material is prepared as follows:

A mixture of 59 g. *p* - chlorophenyl - acetonitrile (0.39 mol), 87.5 g. ethyl 2 -

bromo - 2 - phenyl - acetate (0.36 mol), 150 ml. toluene and 75 ml. anhydrous dimethylformamide is heated to 60°C. To this is slowly added a suspension of 0.36 mol sodium hydride in 50 ml. toluene, while keeping the temperature at about 60°C. This addition takes about 5 hours. Heating is then continued for another 2 hours at 60—70°C.

The reaction mixture is left to cool, 100 ml. water are added, neutralisation is carried out by the addition of concentrated hydrochloric acid and the organic phase is decanted off. This is concentrated in a vacuum and then fractionally distilled in a vacuum. The fraction with a boiling point of 180—190°C./0.1 mm.Hg. (77 g.) is collected and recrystallised from a mixture of 25 ml. toluene and 150 ml. petroleum/hexane. 62 g. of product are obtained, with a melting point of 72—86°C.

The following compounds are prepared by the method described in Example 1 or 2; certain physical constants are also given for the 3-cyanopropionic acids involved in their syntheses:

4 - *p* - chlorophenyl - 3 - methyl - 2 - pyrrolidinone.
B.P.: 165—175°C./0.5 mm.Hg
M.P.: 149—151°C. (*cis* isomer)
M.P.: 129—133°C. (*trans* isomer) (separated by fractional crystallisation from toluene)
B.P. of ethyl 3 - *p* - chlorophenyl - 3 - cyano - 2 - methyl - propionate: 185°C./10 mm.Hg

4 - *p* - chlorophenyl - 3 - ethyl - 2 - pyrrolidinone.
B.P.: 160°C./0.22 mm.Hg
M.P.: 132—134°C. (*cis* isomer)
M.P.: 86—90°C. (*trans* isomer) (crystallised from toluene-hexane)
B.P. of ethyl 3 - *p* - chlorophenyl - 3 - cyano - 2 - ethyl - propionate: 145—155°C./0.03 mm. Hg

4 - *p* - *tert* - butylphenyl - 3 - methyl - 2 - pyrrolidinone.
B.P.: 175—177°C./0.2 mm.Hg
M.P.: 118—124°C. (recrystallised from toluene)
B.P. of ethyl 3 - *p* - *tert* - butylphenyl - 3 - cyano - 2 - methyl - propionate: 140—150°C./0.02 mm.Hg

4 - *o* - methylphenyl - 3 - methyl - 2 - pyrrolidinone.
B.P.: 140—150°C./0.001 mm.Hg
M.P.: 90— 92°C. (recrystallised from toluene-hexane)
B.P. of ethyl 3 - cyano - 2 - methyl - 3 - *o* - methylphenyl - propionate: 130—140°C./0.1 mm.Hg

4 - *o* - methoxyphenyl - 3 - methyl - 2 - pyrrolidinone.
M.P.: 93—103°C. (recrystallised from toluene-hexane)
B.P. of ethyl 3 - cyano - 3 - *o* - methoxyphenyl - 2 - methyl - propionate: 175—185°C./10 mm.Hg

4 - *p* - chlorophenyl - 3,3 - dimethyl - 2 - pyrrolidinone.
M.P.: 130—132°C. (recrystallised from toluene-hexane)
B.P. of ethyl 3 - *p* - chlorophenyl - 3 - cyano - 2,2 - dimethyl - propionate: 185—195°C./13 mm.Hg

4 - *o* - chlorophenyl - 3 - phenyl - 2 - pyrrolidinone.
M.P.: 121—123°C. (recrystallised from toluene)
B.P. of ethyl 3 - *o* - chlorophenyl - 3 - cyano - 2 - phenyl - propionate: 180—190°C./0.03 mm.Hg

4 - *o* - methylphenyl - 3 - phenyl - 2 - pyrrolidinone.
M.P.: 173—179°C. (recrystallised from toluene)
B.P. of ethyl 3 - cyano - 3 - *o* - methylphenyl - 2 - phenyl - propionate: 170—175°C./0.02 mm.Hg
M.P.: 103—120°C.

4 - *p* - methylphenyl - 3 - phenyl - 2 - pyrrolidinone.
M.P.: 135—137°C. (recrystallised from toluene)
B.P.: of ethyl 3 - cyano - 3 - *p* - methylphenyl - 2 - phenyl - propionate: 178—182°C./0.1 mm.Hg
M.P.: 129—133°C. (recrystallised from toluene)

3,4 - bis - *p* - chlorophenyl - 2 - pyrrolidinone.
M.P.: 152—156°C. (recrystallised from toluene)
B.P. of ethyl 2,3 - bis - *p* - chlorophenyl - 3 - cyano - propionate: 195—205° C./0.05 mm.Hg

3 - *p* - chlorophenyl - 4 - phenyl - 2 - pyrrolidinone.
M.P.: 95—108°C. (recrystallised from toluene)
B.P. of ethyl 2 - *p* - chlorophenyl - 3 - cyano - 3 - phenyl - propionate: 175—185°C./0.1 mm.Hg

4 - *p* - methoxyphenyl - 3 - phenyl - 2 - pyrrolidinone.
M.P.: 137—141°C. (recrystallised from toluene-hexane)
B.P. of ethyl 3 - cyano - 3 - *p* - methoxyphenyl - 2 - phenyl - propionate: 170—175°C./0.001 mm.Hg

3 - methyl - 4 - *p* - methylphenyl - 2 - pyrrolidinone.
B.P.: 145—152°C./0.1 mm.Hg
M.P.: 92—130°C. (recrystallised from toluene-hexane)
B.P. of ethyl 3 - cyano - 2 - methyl - 3 - *p* - methylphenyl - propionate: 175—176°C./10 mm.Hg

4 - *p* - fluorophenyl - 3 - methyl - 2 - pyrrolidinone.
B.P.: 158—165°C./0.1 mm.Hg
M.P.: 90—118°C. (recrystallised from toluene-hexane)
B.P. of ethyl 3 - cyano - 3 - *p* - fluorophenyl - 2 - methyl - propionate: 167—168°C./10 mm.Hg

4 - *o* - methoxyphenyl - 3 - phenyl - 2 - pyrrolidinone.
M.P.: 134—138°C. (recrystallised from toluene-hexane)
B.P. of ethyl 3 - cyano - 3 - *o* - methoxyphenyl - 2 - phenyl - propionate: 165—170°C./0.001 mm.Hg

4 - *m* - chlorophenyl - 3 - phenyl - 2 - pyrrolidinone.
M.P.: 122—126°C. (recrystallised from absolute ethanol)
B.P. of ethyl 3 - *m* - chlorophenyl - 3 - cyano - 2 - phenyl - propionate: 165—170°C./0.001 mm.Hg

4 - *p* - fluorophenyl - 3 - phenyl - 2 - pyrrolidinone.
M.P.: 164—170°C. (recrystallised from toluene)
B.P. of ethyl 3 - cyano - 3 - *p* - fluorophenyl - 2 - phenyl - propionate: 160—163°C./0.001 mm.Hg

4 - *m* - methylphenyl - 3 - phenyl - 2 - pyrrolidinone.
M.P.: 104—106°C. (recrystallised from toluene-hexane)
B.P. of ethyl 3 - cyano - 3 - *m* - methylphenyl - 2 - phenyl - propionate: 170—180°C./0.1 mm.Hg

3 - *o* - chlorophenyl - 4 - *p* - chlorophenyl - 2 - pyrrolidinone.
M.P.: 110—116°C. (recrystallised from toluene-hexane)
B.P. of ethyl 2 - *o* - chlorophenyl - 3 - *p* - chlorophenyl - 3 - cyano - propionate: 170—180°C./0.025 mm.Hg

4 - *m* - fluorophenyl - 3 - phenyl - 2 - pyrrolidinone.
M.P.: 170—171°C. (recrystallised from ethanol)
B.P. of ethyl 3 - cyano - 3 - *m* - fluorophenyl - 2 - phenyl - propionate: 150—160°C./0.001 mm. Hg

4 - *p* - chlorophenyl - 4 - methyl - 3 - phenyl - 2 - pyrrolidinone.
M.P.: 154—156°C. (recrystallised from toluene)
M.P. of ethyl 3 - *p* - chlorophenyl - 3 - cyano - 2 - phenyl - butyrate: 126—128°C. (recrystallised from ethanol)

4 - *o* - fluorophenyl - 3 - phenyl - 2 - pyrrolidinone.
M.P.: 127—128°C. (recrystallised from toluene)
B.P. of ethyl 3 - cyano - 3 - *o* - fluorophenyl - 2 - phenyl - propionate: 145—155°C./0.001 mm.Hg

3 - phenyl - 4 - *m* - trifluoromethylphenyl - 2 - pyrrolidinone.
M.P.: 112—113°C. (recrystallised from hexane)
B.P. of ethyl 3 - cyano - 2 - phenyl - 3 - *m* - trifluoromethylphenyl - propionate: 178—183°C./1 mm.Hg

4 - *p* - chlorophenyl - 4 - phenyl - 2 - pyrrolidinone.
M.P.: 145—146°C. (recrystallised from ethanol)
B.P. of ethyl 3 - *p* - chlorophenyl - 3 - cyano - 3 - phenyl - propionate: 170°C./0.2 mm.Hg

Example 3

5 - (2,4 - dimethylphenyl) - 3 - methyl - 2 - pyrrolidinone

This product is obtained by the cyclisation of 4 - amino - 4 - (2,4 - dimethylphenyl) - 2 - methyl - butyric acid, formed *in situ* by the catalytic hydrogenation of the Schiff's base obtained by the reaction of ammonia with 4 - (2,4 - dimethylphenyl) - 2 - methyl - 4 - oxo - butyric acid.

50 g. 4 - (2,4 - dimethylphenyl) - 2 - methyl - 4 - oxo - butyric acid, dissolved in 500 ml. methanol saturated with ammonia, are hydrogenated in an autoclave with hydrogen at a pressure of 120 kg/cm², using 20 g. Raney nickel as catalyst. Heating is carried out progressively to 190°C. and this temperature is maintained until absorption of hydrogen is ended, i.e. for about 20 hours.

After filtering off the catalyst, the solvent is evaporated and the residue is crystallised from toluene. The yield of 5 - (2,4 - dimethylphenyl) - 3 - methyl - 2 - pyrrolidinone is 40%. Melting point: 117—123°C.

Example 4

4 - *p* - chlorophenyl - 5 - methyl - 2 - pyrrolidinone

This product is obtained by the cyclisation of ethyl 4 - amino - 3 - *p* - chlorophenyl - pentanoate, formed *in situ* by the catalytic hydrogenation of the corresponding 4-nitro derivative.

50 g. ethyl 3 - *p* - chlorophenyl - 4 - nitropentanoate, dissolved in 200 ml. ethanol, are hydrogenated in an autoclave with hydrogen at a pressure of 100 kg/cm², using 10 g. Raney nickel as catalyst, at a temperature of 100°C. for about 15 hours.

After the reaction is finished, the catalyst is filtered off, the solvent is evaporated and the residue subjected to fractional distillation in a vacuum.

Yield: 40%; B.P.: 172—178°C./0.1 mm. Hg; M.P.: 114—120°C. (after recrystallisation from toluene-hexane (1:1)).

The ethyl 3 - *p* - chlorophenyl - 4 - nitropentanoate used as starting material is prepared by the method described by J. Colonge and J. M. Pouchol (Bull. Soc. Chim. Fr. 1962, 596—8).

A mixture of 150 g. (2 mol) nitroethane, 105 g. (0.5 mol) ethyl *p*-chlorocinnamate and 6.6 g. "Triton" B (35% solution of trimethylbenzyl-ammonium hydroxide in methanol) is heated for 20 hours at 80°C. ("Triton" is a Registered Trade Mark). After the reaction is finished, toluene is added, washing is carried out with a saturated solution of sodium chloride and the organic solution is dried and evaporated to dryness and the residue is distilled. Yield: 80%; B.P.: 150—155°C./0.3 mm.Hg.

The following compounds were prepared by the same method:—

4 - *p* - Chlorophenyl - 5,5 - dimethyl - 2 - pyrrolidinone.
B.P.: 175—185°C./0.001 mm.Hg
M.P.: 151—154°C. (recrystallised from ethyl acetate)

The ethyl 3 - *p* - chlorophenyl - 4 - methyl - 4 - nitropentanoate used for this synthesis is obtained from 2-nitropropane, ethyl *p*-chlorocinnamate and Triton B. B.P.: 160—170°C./0.6 mm.Hg.

4 - *p* - chlorophenyl - 5 - ethyl - 3 - phenyl - 2 - pyrrolidinone.
M.P.: 133—138°C. (recrystallised from toluene)

The ethyl 3 - *p* - chlorophenyl - 4 - nitro - 2 - phenyl - hexanoate used in this preparation is obtained by reaction of 1 - *p* - chlorophenyl - 2 - nitro - 1 - butene with the sodium derivative of ethyl phenylacetate. M.P.: 118—120°C. (recrystallised from ethanol).

Example 5

3 - allyl - 3 - *p* - chlorophenyl - 2 - pyrrolidinone

This product is obtained by the cyclisation of ethyl 2 - allyl - 4 - amino - 2 - *p* - chlorophenyl - butyrate, formed *in situ* by the reaction of ethylene-imine with the sodium derivative of ethyl 2 - allyl - 2 - *p* - chlorophenyl - acetate.

To a suspension of 12 g. (0.5 mol) sodium hydride in 100 ml. dimethylformamide, there is added rapidly, at a temperature of about 50°C., 0.25 mol ethyl 2 - allyl - 2 - *p* - chlorophenyl - acetate (B.P.: 95—96°C./0.01 mm.Hg). After the sodium derivative is formed, the reaction mixture is cooled to about —50°C. and to it are added 11 g. (0.25 mol) ethylene-imine, dissolved in 100 ml. dimethylformamide. The mixture is allowed to return to ambient temperature, an exothermic reaction taking place (internal temperature about 27°C. for a bath temperature around 17°C.). This internal temperature is maintained for about 2 hours, after which heating is carried out at about 65—70° C. for 1 hour to complete the reaction.

After cooling, 400 ml. water are added to the mixture which is then extracted with toluene. The toluene extract is washed with a little dilute hydrochloric acid (1N) and then with water, whereafter it is dried over anhydrous sodium sulphate. It is then evaporated in a vacuum and the residue is crystallised from a mixture of ethyl acetate-hexane (1:3). In this way, 25.4 g. 3 - allyl - 3 - *p* - chlorophenyl - 2 - pyrrolidinone are obtained. M.P.: 101—102°C.

As a variation of the method, it is also possible to introduce the sodium derivative of ethyl 2 - allyl - 2 - *p* - chlorophenyl acetate into a cold solution of ethylene-imine in dimethylformamide, without the yield and quality of the resulting product being affected.

The following compounds are prepared in the same way:—

3 - allyl - 3 - *p* - methylphenyl - 2 - pyrrolidinone (M.P.: 74—75°C.) starting from ethyl 2 - allyl - 2 - *p* - methyl - phenyl - acetate (B.P.: 136—137°C./17 mm.Hg) and ethylene-imine;

3 - allyl - 3 - *p* - methoxyphenyl - 2 - pyrrolidinone (M.P.: 87—88°C.) starting from ethyl 2 - allyl - 2 - *p* - methoxyphenyl - acetate (B.P.: 142—145°C./16 mm.Hg) and ethylene-imine;

3 - allyl - 3 - *o* - methylphenyl - 2 - pyrrolidinone (M.P.: 132—133°C.) starting from ethyl 2 - allyl - 2 - *o* - methylphenyl - acetate (B.P.: 132—133°C./13 mm.Hg) and ethylene-imine.

3 - allyl - 3 - *p* - chlorophenyl - 5 - phenyl - 2 - pyrrolidinone

This last compound was obtained as follows:

To a solution of 47.7 g. (0.2 mol) ethyl 2 - *p* - chlorophenyl - 4 - pentanoate in 200 ml. anhydrous dimethylformamide, there is added simultaneously, by means of two drop-

ping funnels, 7.32 g. (0.2 mol) of a suspension of sodium hydride in anhydrous ethyl ether and 23.8 g. (0.2 mol) 2 - phenyl - ethylene - imine, the addition being regulated as a function of the evolution of hydrogen, the temperature being kept below 25°C. The mixture is then heated for one hour at 40°C. and then, while agitating vigorously, the reaction is left to continue for 12 hours at ambient temperature.

50 ml. toluene are added and the solution is then treated several times with water. The organic phase is recanted and dried. By concentration and fractional recrystallisation, 20 g. 3 - allyl - 3 - *p* - chlorophenyl - 5 - phenyl - 2 - pyrrolidinone are separated; m.p.: 197—198°C. (recrystallised from ethanol). By distillation of the mother liquor at 190—200°C. under 0.1 mm.Hg pressure and recrystallisation of the distillate from a mixture of hexane-toluene (1:1), about 10 g. of a stereoisomer are separated; m.p.: 116—122°C.

These two stereoisomers have different UV, IR and NMR spectra but their mass spectra are identical. However, it has not been possible to attribute a relative configuration to them.

Example 6

3 - methyl - 4 - *p* - nitrophenyl - 2 - pyrrolidinone

A mixture of 116 g. 3 - methyl - 4 - phenyl - 2 - pyrrolidinone in 330 g. concentrated sulphuric acid is cooled to about 0—5°C. Nitration thereof is carried out by adding to it progressively, while maintaining the same temperature, a mixture of 62 g. fuming nitric acid and 62 g. concentrated sulphuric acid. The reaction mixture is then stirred for 3 hours, after which it is poured into 4 kg. of a mixture of water and ice. Stirring is continued for another 30 minutes and then the precipitate is filtered off and washed several times with water. The separated product is recrystallised twice from boiling absolute ethanol. 60 g. 3 - methyl - 4 - *p* - nitrophenyl - 2 - pyrrolidinone are obtained; m.p.: 236—237°C.

Example 7

4 - *p* - aminophenyl - 3 - methyl - 2 - pyrrolidinone

45 g. of the 3 - methyl - 4 - *p* - nitrophenyl - 2 - pyrrolidinone prepared in Example 6 are dissolved in 3 litres absolute ethanol and hydrogenated at 100°C. with hydrogen at a pressure of 90 kg/cm², in the presence of 5 g. Raney nickel as catalyst. When the hydrogen absorption is finished, the catalyst is filtered off and the filtrate is evaporated to dryness. The residue is recrystallised twice from ethanol. 30 g. 4 - *p* - aminophenyl - 3 - methyl - 2 - pyrrolidinone are obtained; m.p. 190—194°C.

Example 8

4 - *p* - bromophenyl - 3 - methyl - 2 - pyrrolidinone

13 g. (0.0684 mol) of the 4 - *p* - aminophenyl - 3 - methyl - 2 - pyrrolidinone prepared in Example 7, in 40 ml. 40% hydrobromic acid (0.2236 mol), are cooled to 0°C. Diazotisation is carried out by adding, at about 0—5°C., in small amounts, a solution of 6.1 g. sodium nitrate in 20 ml. water. 1 g. electrolytic copper is then added carefully and the mixture is heated to 80°C. for 30 minutes. After cooling, the reaction mixture is extracted with toluene and the toluene phase is dried and evaporated to dryness. The residue is recrystallised from toluene-hexane (1:1). 5 g. 4 - *p* - bromophenyl - 3 - methyl - 2 - pyrrolidinone are obtained; m.p. 127—130°C.

Example 9

4 - *p* - chlorophenyl - N - methyl - 3 - phenyl - 2 - pyrrolidinone

A suspension of 0.115 mol sodium hydride in toluene is added slowly, keeping the temperature between 30 and 40°C., to a solution of 27.15 g. (0.1 mol) 4 - *p* - chlorophenyl - 3 - phenyl - 2 - pyrrolidinone (mixture of the *cis* and *trans* isomers mentioned in Example 2) in a mixture of 70 ml. toluene and 35 ml. dimethylformamide. The mixture is stirred for 30 minutes at 40°C. To this there is then added very slowly 22.7 g. (0.16 mol) methyl iodide, keeping the temperature at around 40°C. After the addition, the temperature is kept for a further 3 hours at 40° C. The solvents are evaporated in a vacuum and the residue is taken up with toluene. The toluene solution is washed twice water, dried and concentrated in a vacuum. The residue is recrystallised twice from toluene-hexane (1:1). 19.7 g. 4 - *p* - chlorophenyl - N - methyl - 3 - phenyl - 2 - pyrrolidinone are obtained; m.p.: 111—112.5°C.

The following compounds are prepared by the same method:

4 - *p* - chlorophenyl - 3 - methyl - N - methyl - 2 - pyrrolidinone.
B.P.: 140°C./0.1 mm.Hg Yield: 87%

4 - *p* - chlorophenyl - 3 - phenyl - N - allyl - 2 - pyrrolidinone.
B.P.: 200—204°C./0.001 mm.Hg

4 - *p* - chlorophenyl - 3 - phenyl - N - *n* - butyl - 2 - pyrrolidinone.
B.P.: 204—206°C./0.001 mm.Hg

4 - *p* - chlorophenyl - 3 - phenyl - N - *n* - hexyl - 2 - pyrrolidinone.
B.P.: 206—208°C./0.001 mm.Hg

By the same method, by reacting 4 - *p* - chlorophenyl - 3 - phenyl - 2 - pyrrolidinone

with 3-bromopropyne, bromocyclopentane and benzyl chloride, respectively, there are obtained:

4 - *p* - chlorophenyl - 3 - phenyl - N - (2 - propynyl) - 2 - pyrrolidinone.
Oil purified by chromatography on silica.

Analysis for $C_{19}H_{16}ClNO$:
calculated: C 73.7% H 5.2% N 4.52% Cl 11.5%
found: C 73.1% H 5.1% N 4.50% Cl 11.3%

4 - *p* - chlorophenyl - 3 - phenyl - N - cyclopentyl - 2 - pyrrolidinone.
M.P.: 102—105°C. (recrystallised from toluene-hexane and then from ethanol).

4 - *p* - chlorophenyl - 3 - phenyl - N - benzyl - 2 - pyrrolidinone.
Oil purified by chromatography on silica.

Analysis for $C_{23}H_{20}ClNO$:
calculated: C 76.4% H 5.52% N 3.90% Cl 9.82%
found: C 76.4% H 5.50% N 3.80% Cl 9.20%

Example 10

3 - ethyl - 4 - *p* - methylphenyl - 2 - pyrrolidinone

5 g. 3 - carboxy - 3 - ethyl - 4 - *p* - methylphenyl - 2 - pyrrolidinone are decarboxylated by heating in a vacuum at melting temperature, i.e. about 165°C., until the evolution of carbon dioxide has ceased (a few minutes). The resin obtained is recrystallised from isopropyl ether. M.P.: 105°C.

The 3 - carboxy - 3 - ethyl - 4 - *p* - methylphenyl - 2 - pyrrolidinone was prepared, starting with *p*-tolualdehyde, according to the synthesis used by C. F. Koelsch and C. H. Stratton (J.A.C.S. 66, (1944), 1883—4) to prepare the corresponding 4-phenyl derivative.

In the course of the synthesis of the 3 - carboxy - 3 - ethyl - 4 - *p* - methylphenyl - 2 - pyrrolidinone, the following compounds were prepared:

diethyl *p* - methyl - benzal - malonate. B.P: 133—135°C./0.005 mm.Hg

ethyl 2 - carbethoxy - 3 - cyano - 3 - *p* - methylphenyl - propionate. B.P. 135—136° C./0.001 mm.Hg

3 - carbethoxy - 4 - *p* - methylphenyl - 2 - pyrrolidinone. M.P.: 76°C. (recrystallised from benzene-hexane (3:2))

3 - carbethoxy - 3 - ethyl - 4 - *p* - methylphenyl - 2 - pyrrolidinone. M.P.: 86—87°C. (recrystallised from benzene-hexane (1:2))

3 - carboxy - 3 - ethyl - 4 - *p* - methylphenyl - 2 - pyrrolidinone. After recrystallisation from ethanol-water (1:1). M.P.: 165°C. (decomposition).

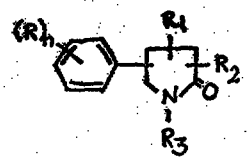
4 - *p* - chlorophenyl - 5 - phenyl - 2 - pyrrolidinone

12 g. 3 - carboxy - 4 - *p* - chlorophenyl - 5 - phenyl - 2 - pyrrolidinone in 200 ml. xylene are refluxed until the evolution of carbon dioxide has ceased (about 20 minutes). The solution is cooled, 200 ml. hexane are added and the reaction product crystallises out. 8 g. 4 - *p* - chlorophenyl - 5 - phenyl - 2 - pyrrolidinone are obtained; m.p. 159—160°C.

The 3 - carboxy - 4 - *p* - chlorophenyl - 5 - phenyl - 2 - pyrrolidinone (after recrystallisation from ethanol, m.p.: 184°C. (decomposition)) was prepared by condensing 1 - *p* - chlorophenyl - 2 - nitro - 2 - phenyl - ethylene with the sodium derivative of diethyl malonate, reduction of the ethyl 2 - carbethoxy - 3 - *p* - chlorophenyl - 4 - nitro - 4 - phenyl - butanoate (M.P.: 148—149°C. (recrystallised from ethanol)) obtained by means of hydrogen under increased pressure in the presence of Raney cobalt and hydrolysis of the resulting 3 - carbethoxy - 4 - *p* - chlorophenyl - 5 - phenyl - 2 - pyrrolidinone (m.p.: 198°C. (recrystallised from toluene)).

WHAT WE CLAIM IS:—

1. Substituted phenyl - 2 - pyrrolidinones of the general formula:—



wherein R is a halogen atom, an alkyl, haloalkyl, alkenyl, alkynyl or alkoxy radical having up to 5 carbon atoms, or a nitro, amino or hydroxyl group; R_1 is an alkyl, alkenyl or alkynyl radical having up to 5 carbon atoms, or an aryl or aralkyl radical or a ring-substituted derivative thereof; R_2 is a hydrogen atom, an alkyl radical having up to 5 carbon atoms or an aryl radical; R_3 is a hydrogen atom, an alkyl, alkenyl or alkynyl radical having up to 7 carbon atoms, or a cycloalkyl or aralkyl radical and *n* is 1, 2 or 3; and the *cis* and *trans* stereoisomers, racemates and optically-active isomers thereof.

2. 4 - *p* - chlorophenyl - 5 - methyl - 2 - pyrrolidinone.

* C L M S *

with 3-bromopropyne, bromocyclopentane and benzyl chloride, respectively, there are obtained:

4 - *p* - chlorophenyl - 3 - phenyl - N - (2 - propynyl) - 2 - pyrrolidinone.
Oil purified by chromatography on silica.

Analysis for $C_{19}H_{16}ClNO$:
calculated: C 73.7% H 5.2% N 4.52% Cl 11.5%
found: C 73.1% H 5.1% N 4.50% Cl 11.3%

4 - *p* - chlorophenyl - 3 - phenyl - N - cyclopentyl - 2 - pyrrolidinone.
M.P.: 102—105°C. (recrystallised from toluene-hexane and then from ethanol).

4 - *p* - chlorophenyl - 3 - phenyl - N - benzyl - 2 - pyrrolidinone.
Oil purified by chromatography on silica.

Analysis for $C_{23}H_{20}ClNO$:
calculated: C 76.4% H 5.52% N 3.90% Cl 9.82%
found: C 76.4% H 5.50% N 3.80% Cl 9.20%

Example 10

3 - ethyl - 4 - *p* - methylphenyl - 2 - pyrrolidinone

5 g. 3 - carboxy - 3 - ethyl - 4 - *p* - methylphenyl - 2 - pyrrolidinone are decarboxylated by heating in a vacuum at melting temperature, i.e. about 165°C., until the evolution of carbon dioxide has ceased (a few minutes). The resin obtained is recrystallised from isopropyl ether. M.P.: 105°C.

The 3 - carboxy - 3 - ethyl - 4 - *p* - methylphenyl - 2 - pyrrolidinone was prepared, starting with *p*-tolualdehyde, according to the synthesis used by C. F. Koelsch and C. H. Stratton (J.A.C.S. 66, (1944), 1883—4) to prepare the corresponding 4-phenyl derivative.

In the course of the synthesis of the 3 - carboxy - 3 - ethyl - 4 - *p* - methylphenyl - 2 - pyrrolidinone, the following compounds were prepared:

diethyl *p* - methyl - benzal - malonate. B.P: 133—135°C./0.005 mm.Hg

ethyl 2 - carbethoxy - 3 - cyano - 3 - *p* - methylphenyl - propionate. B.P. 135—136° C./0.001 mm.Hg

3 - carbethoxy - 4 - *p* - methylphenyl - 2 - pyrrolidinone. M.P.: 76°C. (recrystallised from benzene-hexane (3:2))

3 - carbethoxy - 3 - ethyl - 4 - *p* - methylphenyl - 2 - pyrrolidinone. M.P.: 86—87°C. (recrystallised from benzene-hexane (1:2))

3 - carboxy - 3 - ethyl - 4 - *p* - methylphenyl - 2 - pyrrolidinone. After recrystallisation from ethanol-water (1:1). M.P.: 165°C. (decomposition).

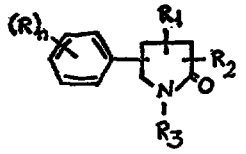
4 - *p* - chlorophenyl - 5 - phenyl - 2 - pyrrolidinone

12 g. 3 - carboxy - 4 - *p* - chlorophenyl - 5 - phenyl - 2 - pyrrolidinone in 200 ml. xylene are refluxed until the evolution of carbon dioxide has ceased (about 20 minutes). The solution is cooled, 200 ml. hexane are added and the reaction product crystallises out. 8 g. 4 - *p* - chlorophenyl - 5 - phenyl - 2 - pyrrolidinone are obtained; m.p. 159—160°C.

The 3 - carboxy - 4 - *p* - chlorophenyl - 5 - phenyl - 2 - pyrrolidinone (after recrystallisation from ethanol, m.p.: 184°C. (decomposition)) was prepared by condensing 1 - *p* - chlorophenyl - 2 - nitro - 2 - phenyl - ethylene with the sodium derivative of diethyl malonate, reduction of the ethyl 2 - carbethoxy - 3 - *p* - chlorophenyl - 4 - nitro - 4 - phenyl - butanoate (M.P.: 148—149°C. (recrystallised from ethanol)) obtained by means of hydrogen under increased pressure in the presence of Raney cobalt and hydrolysis of the resulting 3 - carbethoxy - 4 - *p* - chlorophenyl - 5 - phenyl - 2 - pyrrolidinone (m.p.: 198°C. (recrystallised from toluene)).

WHAT WE CLAIM IS:—

1. Substituted phenyl - 2 - pyrrolidinones of the general formula:—



wherein R is a halogen atom, an alkyl, haloalkyl, alkenyl, alkynyl or alkoxy radical having up to 5 carbon atoms, or a nitro, amino or hydroxyl group; R_1 is an alkyl, alkenyl or alkynyl radical having up to 5 carbon atoms, or an aryl or aralkyl radical or a ring-substituted derivative thereof; R_2 is a hydrogen atom, an alkyl radical having up to 5 carbon atoms or an aryl radical; R_3 is a hydrogen atom, an alkyl, alkenyl or alkynyl radical having up to 7 carbon atoms, or a cycloalkyl or aralkyl radical and *n* is 1, 2 or 3; and the *cis* and *trans* stereoisomers, racemates and optically-active isomers thereof.

2. 4 - *p* - chlorophenyl - 5 - methyl - 2 - pyrrolidinone.

3. 5 - (2,4 - dimethylphenyl) - 3 - methyl - 2 - pyrrolidinone.

4. 4 - *p* - chlorophenyl - 3 - ethyl - 2 - pyrrolidinone (*cis* isomer).

5. 4 - *p* - chlorophenyl - 3 - ethyl - 2 - pyrrolidinone (*trans* isomer).

6. 4 - *p* - chlorophenyl - 3 - methyl - 2 - pyrrolidinone (*cis* isomer).

7. 4 - *p* - chlorophenyl - 3 - methyl - 2 - pyrrolidinone (*trans* isomer).

8. 4 - *p* - Chlorophenyl - 3 - phenyl - 2 - pyrrolidinone (*cis* isomer).

9. 4 - *p* - Chlorophenyl - 3 - phenyl - 2 - pyrrolidinone (*trans* isomer).

10. 4 - *o* - Chlorophenyl - 3 - phenyl - 2 - pyrrolidinone.

11. 4 - *p* - Fluorophenyl - 3 - methyl - 2 - pyrrolidinone.

12. 4 - *p* - Chlorophenyl - N - methyl - 3 - phenyl - 2 - pyrrolidinone.

13. 4 - *p* - Fluorophenyl - 3 - phenyl - 2 - pyrrolidinone.

14. 3 - *o* - Chlorophenyl - 4 - *p* - chlorophenyl - 2 - pyrrolidinone.

15. 3 - *p* - Methyl - phenyl - 4 - phenyl - 2 - pyrrolidinone.

16. 4 - *p* - *tert.* - Butyl - phenyl - 3 - methyl - 2 - pyrrolidinone.

17. 4 - *o* - Methyl - phenyl - 3 - methyl - 2 - pyrrolidinone.

18. 4 - *o* - Methoxy - phenyl - 3 - methyl - 2 - pyrrolidinone.

19. 4 - *p* - Chlorophenyl - 3,3 - dimethyl - 2 - pyrrolidinone.

20. 4 - *o* - Methyl - phenyl - 3 - phenyl - 2 - pyrrolidinone.

21. 4 - *p* - Methyl - phenyl - 3 - phenyl - 2 - pyrrolidinone.

22. 3,4 - bis - *p* - Chlorophenyl - 2 - pyrrolidinone.

23. 3 - *p* - Chlorophenyl - 4 - phenyl - 2 - pyrrolidinone.

24. 4 - *p* - Methoxy - phenyl - 3 - phenyl - 2 - pyrrolidinone.

25. 3 - Methyl - 4 - *p* - methylphenyl - 2 - pyrrolidinone.

26. 4 - *o* - Methoxy - phenyl - 3 - phenyl - 2 - pyrrolidinone.

27. 4 - *m* - Chlorophenyl - 3 - phenyl - 2 - pyrrolidinone.

28. 4 - *m* - Methyl - phenyl - 3 - phenyl - 2 - pyrrolidinone.

29. 4 - *m* - Fluorophenyl - 3 - phenyl - 2 - pyrrolidinone.

30. 4 - *p* - Chlorophenyl - 4 - methyl - 3 - phenyl - 2 - pyrrolidinone.

31. 4 - *o* - Fluorophenyl - 3 - phenyl - 2 - pyrrolidinone.

32. 4 - *p* - Chlorophenyl - 5,5 - dimethyl - 2 - pyrrolidinone.

33. 3 - Allyl - 3 - *p* - chlorophenyl - 2 - pyrrolidinone.

34. 3 - Allyl - 3 - *p* - methyl - phenyl - 2 - pyrrolidinone.

35. 3 - Allyl - 3 - *p* - methoxy - phenyl - 2 - pyrrolidinone.

36. 3 - Allyl - 3 - *o* - methyl - phenyl - 2 - pyrrolidinone.

37. 3 - Methyl - 4 - *p* - nitrophenyl - 2 - pyrrolidinone.

38. 4 - *p* - Aminophenyl - 3 - methyl - 2 - pyrrolidinone.

39. 4 - *p* - Bromophenyl - 3 - methyl - 2 - pyrrolidinone.

40. 4 - *p* - Chlorophenyl - 3 - methyl - N - methyl - 2 - pyrrolidinone.

41. 4 - *p* - Chlorophenyl - 3 - phenyl - N - allyl - 2 - pyrrolidinone.

42. 4 - *p* - Chlorophenyl - 3 - phenyl - N - *n* - butyl - 2 - pyrrolidinone.

43. 4 - *p* - Chlorophenyl - 3 - phenyl - N - *n* - hexyl - 2 - pyrrolidinone.

44. 3 - Ethyl - 4 - *p* - methyl - phenyl - 2 - pyrrolidinone.

45. 4 - *p* - Chlorophenyl - 5 - phenyl - 2 - pyrrolidinone.

46. 4 - *p* - Chlorophenyl - 4 - phenyl - 2 - pyrrolidinone.

47. 4 - *p* - Chlorophenyl - 3 - phenyl - N - benzyl - 2 - pyrrolidinone.

48. 4 - *p* - Chlorophenyl - 5 - ethyl - 3 - phenyl - 2 - pyrrolidinone.

49. 4 - *p* - Chlorophenyl - 3 - phenyl - N - (2 - propynyl) - 2 - pyrrolidinone.

50. 4 - *p* - Chlorophenyl - 3 - phenyl - N - cyclopentyl - 2 - pyrrolidinone.

51. 3 - Allyl - 3 - *p* - chlorophenyl - 5 - phenyl - 2 - pyrrolidinone (isomer of m.p. 197—198°C.).

52. 3 - Allyl - 3 - *p* - chlorophenyl - 5 - phenyl - 2 - pyrrolidinone (isomer of m.p. 116—122°C.).

53. 3 - Phenyl - 4 - *m* - trifluoromethylphenyl - 2 - pyrrolidinone.

54. Process for the preparation of phenyl - 2 - pyrrolidinones according to claim 1, which comprises cyclising a 4 - amino - butyric acid or an alkyl ester thereof of the general formula

$$H(R_8)N—A—COOX,$$

in which X is a hydrogen atom or an alkyl radical containing up to 4 carbon atoms and A is a trimethylene chain substituted by $(R)_n$-phenyl, R_1 and R_2 radicals; and R, R_1, R_2, R_3 and *n* have the same meanings as in claim 1.

55. Process according to claim 54, wherein the 4 - amino - butyric acid or alkyl ester thereof is prepared *in situ*.

56. Process according to claim 54 or 55, wherein the 4 - amino - butyric acid or the alkyl ester thereof, in which R_3 is a hydrogen atom and the methylene group in A adjacent to the nitrogen atom is unsubstituted, is obtained by subjecting a 3 - cyano - propionic acid or an alkyl ester thereof of the general formula

$$NC—A'—COOX,$$

in which A′ is an ethylene chain substituted by $(R)_n$-phenyl, R_1 and R_2 radicals, X, R, R_1, R_2 and n having the same meanings as in claim 54, except that R and R_1 are not alkenyl or alkynyl radicals, to catalytic hydrogenation.

57. Process according to claim 54 or 55, wherein the 4 - amino - butyric acid or the alkyl ester thereof, in which R_3 is a hydrogen atom, is obtained by subjecting a 4 - nitro - butyric acid or an alkyl ester thereof of the general formula

$$O_2N—A—COOX,$$

in which A and X have the same meanings as in claim 54, except that R and R_1 are not alkenyl or alkynyl radicals, to catalytic reduction.

58. Process according to claim 54 or 55, wherein the 4 - amino - butyric acid, wherein at most one of the $(R)_n$-phenyl, R_1 and R_2 radicals is attached to the carbon atom of A adjacent to the nitrogen atom, is obtained by condensing a 4 - oxo - butyric acid of the general formula

$$O=A''.COOH,$$

in which A″ is a propan - 1 - yl - 3 - ylidene radical substituted by $(R)_n$-phenyl, R_1 and R_2 radicals, R, R_1, R_2 and n having the same meanings as in claim 1, except that R and R_1 are not alkenyl or alkynyl radicals, with a nitrogen compound of the formula

$$R_3NH_2,$$

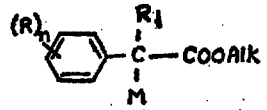
R_3 having the same meaning as in claim 1, followed by catalytic hydrogenation of the Schiff's base obtained.

59. Process according to claim 54 or 55, wherein the 4 - amino - butyric acid, wherein R_3 is a hydrogen atom and at most one of the $(R)_n$-phenyl, R_1 and R_2 radicals is attached to the carbon atom of A adjacent to the nitrogen atom, is obtained by condensing a 4 - oxo - butyric acid of the general formula

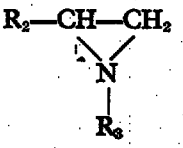
$$O=A''.COOH,$$

in which A″ has the same meaning as in claim 58, with hydroxylamine and catalytic reduction of the resulting oxime.

60. Process according to claim 54 or 55, wherein the alkyl ester of the 4 - amino - butyric acid, in which the $(R)_n$-phenyl and R_1 radicals are attached to the carbon atom of A adjacent to the carboxylic group, is obtained by reacting an alkali metal derivative of the alkyl 2 - [$(R)_n$ - phenyl] - 2 - R_1 - acetate of the general formula:—

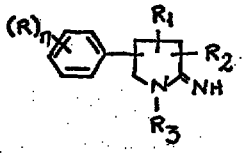


in which Alk is an alkyl radical containing up to 4 carbon atoms, M is an alkali metal atom and R, R_1 and n have the same meanings as in claim 1, with an ethylene-imine of the general formula:—



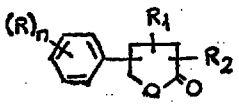
in which R_2 and R_3 have the same meanings as in claim 1.

61. Process for the preparation of phenyl - 2 - pyrrolidinones according to claim 1, which comprises hydrolysing a 2 - imino - pyrrolidinone of the general formula:—



wherein R, R_1, R_2, R_3 and n have the same meanings as in claim 1.

62. Process for the preparation of phenyl - 2 - pyrrolidinones according to claim 1, which comprises reacting, at an elevated temperature, a lactone of the general formula:—



wherein R, R_1, R_2 and n have the same meanings as in claim 1, with a nitrogen compound of the formula

$$R_3NH_2,$$

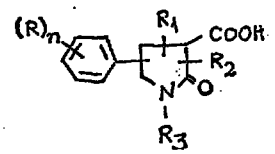
in which R_3 has the same meaning as in claim 1.

63. Process for the preparation of phenyl - 2 - pyrrolidinones according to claim 1, which comprises cyclising, in the presence of an alkaline condensation agent, a halogeno-butyramide of the general formula

$$Hal—A—CONH(R_3),$$

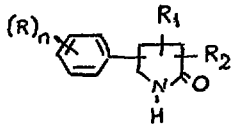
in which Hal is a halogen atom and A is a trimethylene chain substituted by $(R)_n$-phenyl, R_1 and R_2 radicals; and R, R_1, R_2, R_3 and n have the same meanings as in claim 1.

64. Process for the preparation of phenyl - 2 - pyrrolidinones according to claim 1, wherein at most one of the $(R)_n$-phenyl, R_1 and R_2 radicals is in the 3-position, which comprises subjecting to thermal decarboxylation a 2 - pyrrolidinone - 3 - carboxylic acid of the general formula:—



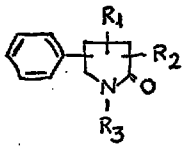
in which R, R_1, R_2, R_3 and n have the same meanings as in claim 1.

65. Process for the preparation of phenyl - 2 - pyrrolidinones according to claim 1 in which R_3 is an alkyl, alkenyl or alkynyl radical having up to 7 carbon atoms or a cycloalkyl or aralkyl radical, which comprises reacting a phenyl - 2 - pyrrolidinone of the general formula:—



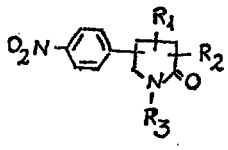
in which R, R_1, R_2 and n have the same meanings as in claim 1, with an R_3 . halide, in which R_3 has the same meaning as in claim 1, in the presence of an alkaline condensation agent.

66. Process for the preparation of phenyl - 2 - pyrrolidinones according to claim 1 in which R is a nitro group in the *para*-position, which comprises nitrating a phenyl - 2 - pyrrolidinone of the general formula:—



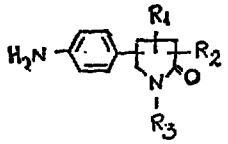
in which R_1, R_2 and R_3 have the same meanings as in claim 1.

67. Process for the preparation of phenyl - 2 - pyrrolidinones according to claim 1 in which R is an amino group in the *para*-position, which comprises reducing a *p* - nitro - phenyl - 2 - pyrrolidinone of the general formula:—



in which R_1, R_2 and R_3 have the same meanings as in claim 1.

68. Process for the preparation of phenyl - 2 - pyrrolidinones according to claim 1 in which R is a halogen atom in the *para*-position, which comprises subjecting to diazotisation in an aqueous medium with an alkali metal nitrite in the presence of a halohydric acid at 0—5°C., a *p* - amino - phenyl - 2 - pyrrolidinone of the general formula:—



in which R_1, R_2 and R_3 have the same meanings as in claim 1, and subjecting the diazonium salt thus obtained to a Sandmeyer reaction in the presence of copper powder or of a cuprous halide.

69. Process for the preparation of phenyl - 2 - pyrrolidinones according to claim 1 in which R is a hydroxyl group in the *para*-position, which comprises subjecting to diazotisation in an aqueous medium with an alkali metal nitrite in the presence of halohydric acid at 0—5°C., a *p* - amino - phenyl - 2 - pyrrolidinone of the general formula given in claim 68, and heating the aqueous solution of the diazonium salt thus obtained.

70. Process according to claims 54—69, wherein the compounds which are obtained in the form of stereoisomer mixtures are separated into the *cis* and *trans* components thereof.

71. Process according to any of claims 54—69, wherein the compounds which are obtained in the form of racemates are separated into the optically-active isomers thereof.

72. Process for the preparation of phenyl - 2 - pyrrolidinones according to claim 1, substantially as hereinbefore described and exemplified.

73. Phenyl - 2 - pyrrolidinones according to claim 1, whenever prepared by the process according to any of claims 54—72.

74. Pharmaceutical compositions, comprising at least one phenyl - 2 - pyrrolidinone according to claim 1, in admixture with a solid or liquid pharmaceutical diluent or carrier.

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