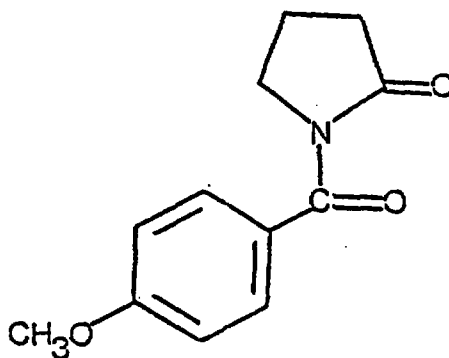


European Patent (UK) No. 5'143

1-Benzoyl-2-pyrrolidinone derivative, processes for its preparation and medicaments containing it

The present invention relates to the 1-(p-methoxybenzoyl)-2-pyrrolidinone which has the formula



and which is a novel compound with valuable pharmacodynamic properties.

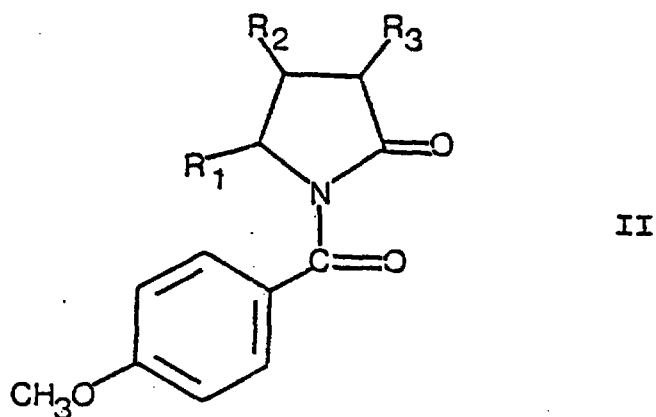
Objects of the present invention are 1-(p-methoxybenzoyl)-2-pyrrolidinone of formula I hereinbefore, the manufacture of this compound and medicaments containing 1-(p-methoxybenzoyl)-2-pyrrolidinone of formula I.

The 1-(p-methoxybenzoyl)-2-pyrrolidinone of formula I hereinbefore can be manufactured in accordance with the invention by

(a) appropriately acylating 2-pyrrolidinone in the 1-position, or

(b) methylating 1-(p-hydroxybenzoyl)-2-pyrrolidinone, or

(c) reducing a 2-pyrrolidinone derivative of the general formula



wherein one of R_1 and R_3 signifies hydrogen and the other together with R_2 signifies a second C-C bond,

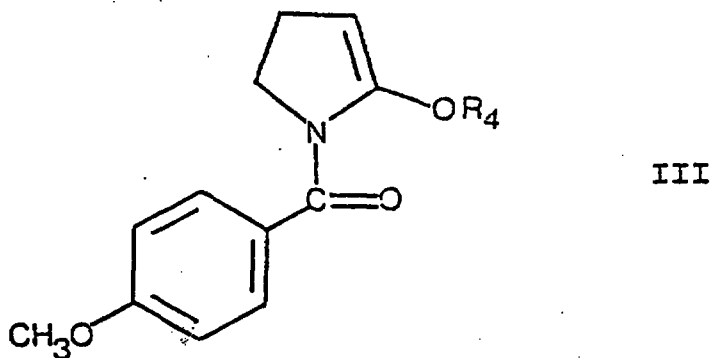
or a mixture of the two compounds falling under general formula II,

or

(d) cyclising 4-(p-methoxybenzoylamino)butyric acid,

or

(e) hydrolysing a compound of the general formula



wherein R_4 signifies lower alkyl.

According to a first embodiment of the process of the invention, the compound of formula I can thus be manufactured by appropriately acylating 2-pyrrolidinone in the 1-position, i.e. the hydrogen atom in the 1-position of 2-pyrrolidinone is replaced by a p-methoxybenzoyl group. This acylation can be carried out using methods which are generally known per se for such acylations. As the acylating agent there is used a derivative of p-methoxybenzoic acid which is sufficiently reactive, especially a reactive halide of this acid (preferably p-methoxybenzoyl chloride), a reactive ester of this acid, for example a polyhalophenyl ester (such as p-methoxybenzoic acid pentachlorophenyl ester) and the like.

When 2-pyrrolidinone is acylated with p-methoxybenzoyl chloride, the acylation is conveniently carried out in the presence of an inert organic solvent and a base. Especially suitable solvents are ethers (e.g. diethyl ether, tetrahydrofuran, dioxan etc), aromatic hydrocarbons (e.g. toluene etc) or the like, and suitable bases are tertiary amines

(e.g. triethylamine or the like). The acylation can also be carried out in pyridine which simultaneously functions as the solvent and as the base. Neither the presence of a solvent nor the presence of a base is, however, imperative; it is quite possible to heat the starting materials together at about 80°-90°C for about one hour or to heat the starting materials at reflux for several hours in a suitable solvent (e.g. an ether, an aromatic hydrocarbon or the like).

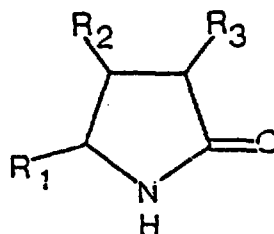
Furthermore, it is possible to treat 2-pyrrolidinone firstly with a base capable of abstracting the hydrogen atom on the nitrogen atom in the 1-position and then to react with p-methoxybenzoyl chloride. In this aspect the base which is used can be, for example, an alkali metal hydride (e.g. sodium hydride or the like) and the solvent can be an aromatic hydrocarbon (e.g. benzene), dimethylformamide or the like. It is also possible to use the 2-pyrrolidinone in the form of a reactive derivative in which a readily cleavable group, for example a readily cleavable metal-organic group, especially a trialkylsilyl group, is situated on the nitrogen atom in the 1-position. A preferred reactive derivative of this type is 1-trimethylsilyl-2-pyrrolidinone.

According to the second embodiment of the process of the invention the compound of formula I can be manufactured by methylating 1-(p-hydroxybenzoyl)-2-pyrrolidinone. This embodiment comprises the methylation of a phenolic hydroxyl group, and for this there can be used methods which are generally known

per se for such methylations of phenolic hydroxyl groups. Suitable methylating agents are, for example, dimethyl sulphate, methyl iodide or the like. When such methylating agents are used, the methylation is conveniently carried out in the presence of a base (e.g. sodium methylate, sodium hydride or the like) and in the presence of an organic solvent which is inert under the reaction conditions (e.g. dimethylformamide, an aromatic hydrocarbon such as benzene, toluene and the like). Diazomethane is also a suitable methylating agent. When diazomethane is used, the methylation is conveniently carried out in ethereal solution (e.g. in tetrahydrofuran, diethyl ether and the like or in mixtures of such ethers). The 1-(p-hydroxybenzoyl)-2-pyrrolidinone used as the starting material can be prepared, for example, by replacing the hydrogen atom on the nitrogen atom in the 1-position of 2-pyrrolidinone by a p-benzyloxybenzoyl group, for example using p-benzyloxybenzoyl chloride in an analogous manner to the methods described previously in connection with the first embodiment of the process, and debenzylating the resulting 1-(p-benzyloxybenzoyl)-2-pyrrolidinone according to methods known per se (e.g. by hydrogenation in the presence of a suitable catalyst such as palladium).

According to a further embodiment of the process of the invention, the compound of formula I can be manufactured by reducing a

2-pyrrolinone derivative of formula II hereinbefore or a mixture of the two compounds falling under the general formula II. In this embodiment there are used methods which are generally customary per se for such reductions. This reduction is preferably carried out using catalytically activated hydrogen in an organic solvent which is inert under the reaction conditions, palladium, platinum and the like coming into consideration as the hydrogenation catalysts and ethyl acetate, alcohols (e.g. methanol, ethanol or the like), ethers (e.g. tetrahydrofuran etc) coming into consideration, for example, as the solvent. The starting materials of formula II can be prepared, for example either by treating 5-oxo-3-pyrrolidinyl acetate or another suitable ester of 5-oxo-3-pyrrolidinol with trimethylchlorosilane or the like, reacting the resulting compound (e.g. 5-oxo-1-trimethylsilyl-3-pyrrolidinyl acetate) with a suitable p-methoxybenzoylating agent (e.g. p-methoxybenzoyl chloride) and treating the resulting product under mild conditions with a base (e.g. sodium bicarbonate), or by appropriately acylating in the 1-position a compound of the general formula



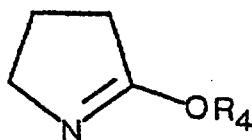
IV

, wherein R_1 , R_2 and R_3 have the significance given earlier,

or a mixture of the two compounds falling under formula IV.

According to a further embodiment of the process of the invention, the compound of formula I can be manufactured by cyclising 4-(p-methoxybenzoylamino)butyric acid. In this cyclisation one mol of water is cleaved off, and there are therefore used for this embodiment methods which are generally customary per se for such dehydrating cyclisations, i.e. heating and/or treatment with a water-cleaving agent such as polyphosphoric acid, phosphorus pentachloride, thionyl chloride and the like. Depending on the method used, it can be of advantage to carry out the dehydrating cyclisation in an inert organic solvent, for example in an aromatic hydrocarbon (e.g. toluene or the like), in an ether (e.g. tetrahydrofuran or the like), in a halogenated hydrocarbon (e.g. chloroform or the like) etc. The 4-(p-methoxybenzoylamino)butyric acid can be prepared, for example, by appropriately acylating 4-aminobutyric acid (e.g. using p-methoxybenzoyl chloride in the presence of an acid-binding agent such as sodium hydroxide).

Finally, the compound of formula I can be manufactured according to the invention by hydrolysing a compound of formula III hereinfore. The compounds of formula III can be prepared, for example, by treating a compound of the general formula



, wherein R_4 has the significance given earlier,

with p-methoxybenzoyl chloride, the resulting compound of formula III not being isolated but being hydrolysed to give the compound of formula I. In the manufacture of the compound of formula I from a compound of formula V via a compound of formula III it is a question of the manufacture of a N-acylated lactam via a N-acylated enol ether, and such methods are known per se. The manufacture of the N-acylated enol ether from the compound of formula V and p-methoxybenzoyl chloride is carried out in a suitable organic solvent (e.g. benzene or the like) and, if necessary, in the presence of a strong base (e.g. an alkali metal hydride such as lithium hydride). Depending on the reaction conditions in the preparation of the N-acylated enol ether and its hydrolysis, there can be obtained besides the desired N-acylated lactam (i.e. the compound of formula I) in varying amounts also the corresponding amidoalkyl ester which results from ring-opening. Where the preparation of the compound of formula III is carried out in a water-immiscible solvent, then in the hydrolysis the formation of the desired product (i.e. the compound of formula I) predominates. As mentioned earlier, the compound of formula III is not isolated, but is hydrolysed in situ, whereby the hydrolysis can be carried out in a manner

known per se by addition of water, aqueous alkali (e.g. lithium hydroxide solution) or aqueous acid (e.g. aqueous hydrochloric acid).

As mentioned earlier, the 1-(p-methoxybenzoyl)-2-pyrrolidinone of formula I is a novel compound having valuable pharmacodynamic properties. The compound of formula I has only a very low toxicity and it has been shown that, in the animal experiments described hereinafter, it is capable of counteracting cerebral insufficiency produced experimentally in various ways.

A) POSTHYPERCAPNIC "AVOIDANCE" ACQUISITION

The test apparatus is a "shuttle box" having a 10 cm high hurdle in the middle and an electrifiable grid floor. A loudspeaker is mounted in the soundproof chamber. One or three hours after administration, by injection, of a control or test preparation, untrained rats (120-150 g; 10 per group) are placed for 12 seconds in a pure carbon dioxide environment. A third group of 10 rats is treated neither with the test preparation nor with carbon dioxide. Three minutes after treatment with carbon dioxide the rats of all three groups must learn a conditioned and unconditioned reflex in the "shuttle box" in the following programme: 10 seconds silence - 5 seconds noise ("avoidance response") - 15 seconds noise + foot-shock ("escape response"); six times in succession. For each of the six individual experiments

the reaction time (time until the rat jumps over the hurdle) of each rat is measured and the statistical significance of the differences between the various groups is calculated by means of the Rang test.

An "active" dosage of a test preparation is that dosage which shows a significant activity during the six individual experiments; thereby the animals treated with the test preparation and carbon dioxide must learn significantly better than the animals treated only with carbon dioxide and equally well as the animals treated neither with the test preparation nor with carbon dioxide.

B) "PASSIVE AVOIDANCE" TEST WITH ELECTROSHOCK AMNESIA

The test apparatus is a Skinner box having an electrifiable grid floor and a grey quadrangular platform in one corner. Untrained male rats weighing 100-120 g are placed on the grey platform. Each time when they climb down on to the grid floor they receive an electric shock. After 3-5 experiments, the rats exhibit a so-called "passive avoidance response", i.e. refusal to climb down from the platform. Immediately after acquisition of the refusal three groups each of 20 rats are formed. One group receives an electric shock (45 mA, 2 seconds) between the ears and a i.p. sodium chloride injection. The second group receives an electric shock between the ears and a i.p. injection of the test preparation. The third group receives only sodium chloride. After three hours, each rat

is placed once on the platform and the retention time (maximum 60 seconds) is measured. The significant activity of the test preparation in comparison to the two control groups is calculated by means of the Rang test.

An "active" dosage of a test preparation is that dosage which exhibits a significant protective activity against the electric shock (the animals treated with an active dosage of a test preparation and electric shock exhibit a long retention time just as the animals not treated with electric shock, whereas the animals treated with sodium chloride and electric shock exhibit a short retention time).

C) INHIBITION OF THE HALOPERIDOL-INDUCED "KNOCK OUT" IN
A "CONTINUOUS AVOIDANCE" PROGRAMME WITH SQUIRREL
MONKEYS

Male, untrained squirrel monkeys (*Saimiri sciureus*), each weighing 0.6 to 1.2 kg, housed individually, are trained in a two-lever Skinner box in the following "continuous avoidance" programme: "avoidance-shock" - interval 40 seconds; "shock-shock" - interval 20 seconds; foot-shock maximum 5 seconds. Monkeys having a normal basic performance receive haloperidol 1.0 mg/kg p.o. to determine the "knock-out" time (blocking of "avoidance" and "escape"). Monkeys having stable "knock-out" times are selected for the evaluation of test preparations as potential cerebral insufficiency improvers. The test preparations can be injected at various times before the treatment with haloperidol.

An "active" dosage of a test preparation is that dosage which, upon administration before the treatment with haloperidol, brings about a significant delay in the "knock-out" time in a three hours test.

D) ANTI-ANOXIA TEST

Male rats weighing 300-350 g are used for this test. The animals are tracheotomised under halothane anaesthesia and an epidural cortical electrode is placed in each. After completion of this operation, the anaesthesia is discontinued, all wounds and pressure points are infiltrated with xylocaine, d-tubocurarine is infused and the animal is artificially ventilated. The EEG is recorded continuously during the entire duration of the test. Anoxias are carried out at hourly intervals by ventilating the animal with 99.9% nitrogen until an isoelectric EEG is attained. After a period of 30 seconds with isoelectric EEG, the animal is again ventilated with normal room air.

As the test parameters there are defined:

1. "survival time": Time up to the attainment of an isoelectric EEG under nitrogen ventilation.
= ST
2. "recovery time": Time between further ventilation with room air and first electrical activity from the cortex.
= RT

The test preparations are administered 60 or 120 minutes before the first anoxia. The ST and RT values of treated rats are compared with placebo-treated controls by means of the Rang test. A lengthening of ST and/or shortening of RT is regarded as the protective activity against an anoxia.

An "active" dosage of a test preparation is that dosage which displays a significant protective activity.

In the previously described tests, the 1-(p-methoxybenzoyl)-2-pyrrolidinone, which has a very low acute toxicity [LD 50 > 5000 mg/kg p.o. (mice)], already exhibits a significant activity at the following dosages:

Test	Minimum active dosage
A	10 mg/kg i.p. (after 1 hr.)
	30 mg/kg p.o. (after 1 hr.)
B	50 mg/kg i.p.
C	1 mg/kg i.p.
	0.1 mg/kg p.o.
D	20 mg/kg i.p.

The 1-(p-methoxybenzoyl)-2-pyrrolidinone of formula I can be used as a medicament, for example in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered orally, for example in the form of tablets, coated tablets, dragées, hard gelatin capsules, soft gelatin capsules, solutions, emulsions or suspensions.

The administration can, however, also be carried out by the rectal route (e.g. in the form of suppositories) or by the parenteral route (e.g. in the form of injection solutions).

For the manufacture of tablets, coated tablets, dragées and hard gelatin capsules, the 1-(p-methoxybenzoyl)-2-pyrrolidinone can be processed with pharmaceutical inert, inorganic or organic excipients. As such excipients there can be used, for example, for tablets, dragées and hard gelatin capsules lactose, maize starch or derivatives thereof, talc, stearic acid or salts thereof etc.

Suitable excipients for soft gelatin capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols etc.

Suitable excipients for the manufacture of solutions and syrups are, for example, water, polyols, saccharose, invert sugar, glucose and the like.

Suitable excipients for injection solutions are, for example, water, alcohols, polyols, glycerine, vegetable oils etc.

Suitable excipients for suppositories are, for example, natural or hardened oils, waxes, fats, semi-liquid or liquid polyols and the like.

Moreover, the pharmaceutical preparations can contain preserving agents, solubilising agents, stabilising agents, wetting agents, emulsifying agents, sweetening agents, colouring agents, flavouring agents, salts for varying the osmotic pressure, buffers, coating agents or antioxidants. The pharmaceutical preparations can also contain other therapeutically valuable substances.

The 1-(p-methoxybenzoyl)-2-pyrrolidinone of formula I is suitable for use in the control or prevention of cerebral insufficiency or in the improvement of intellectual capacity, for example in the case of cerebral seizure, in geriatrics, in alcoholism etc. The dosage can vary within wide limits and is, of course, fitted to the individual requirements in each particular case. In general, in the case of oral administration a daily dosage of about 10 mg to 2500 mg of 1-(p-methoxybenzoyl)-2-pyrrolidinone may be appropriate, although the upper limit can be readily exceeded when this is shown to be indicated having regard to the low toxicity of the 1-(p-methoxybenzoyl)-2-pyrrolidinone.

In the following Examples which are given by way of illustration of the present invention and are in no way intended to limit its extent, all temperatures are indicated in degrees Centigrade.

Example 1

40.0 g of p-methoxybenzoyl chloride, 25.0 g of 2-pyrrolidinone and 110 ml of absolute diethyl ether are treated at between 0° and 10° while stirring with 52.5 ml of triethylamine. The mixture is stirred at room temperature for a further 30 minutes and at reflux for 3 hours, then cooled down and treated at 2° with cold water. The insoluble constituents are filtered off under suction and washed with water and diethyl ether. The thus-obtained solid substance is recrystallised from alcohol after drying over phosphorus pentoxide. There is obtained 1-(p-methoxybenzoyl)-2-pyrrolidinone which melts at 121°-122°.

Example 2

20.2 g of the sodium salt of 2-pyrrolidinone (prepared using sodium hydride) suspended in 270 ml of dimethylformamide are added in four portions at -10° to a solution of 37.0 g of p-methoxybenzoyl chloride in 50 ml of dimethylformamide. Subsequently, the mixture is stirred at room temperature for 1 hour and then at 40° for 4 hours. The solvent is evaporated and the residue is treated with diethyl ether and with cold sodium bicarbonate solution.

The insoluble crystalline constituents are filtered off, washed with water and diethyl ether and dried in vacuo over phosphorus pentoxide. There is obtained 1-(p-methoxybenzoyl)-2-pyrrolidinone of melting point 120°-121° .

Example 3

20 g of p-methoxybenzoyl chloride and 20 g of 2-pyrrolidinone are boiled at reflux in 20 ml of diethyl ether for 16 hours and then diethyl ether, ice and 2-N aqueous ammonia are added to the mixture. The insoluble constituents are filtered off and washed ion-free with diethyl ether and water. The filter cake is dried and there is obtained 1-(p-methoxybenzoyl)-2-pyrrolidinone of melting point 119.5°-120.5° .

Example 4

The procedure described in Example 3 is followed, but the starting materials are heated in 20 ml of toluene instead of diethyl ether. The resulting 1-(p-methoxybenzoyl)-2-pyrrolidinone melts at 117°-118° .

Example 5

10 g of 2-pyrrolidinone and 10 g of p-methoxybenzoyl chloride are heated at 80°-90° (internal temperature) in the absence of a solvent for 1 hour. The mixture is then

left to cool down and is worked-up as described in Example 3. After recrystallisation from alcohol, there is obtained 1-(p-methoxybenzoyl)-2-pyrrolidinone of melting point 120°-121° .

5

Example 6

24.4 g of p-methoxybenzoyl chloride and 22.5 g of 1-trimethylsilyl-2-pyrrolidinone are mixed and the mixture is stirred at room temperature for 10 minutes. Then, the resulting trimethylchlorosilane is distilled off under
10 reduced pressure in an oil bath at 80° . The residue is triturated with 100 ml of diethyl ether. The mixture is filtered and the filter cake is recrystallised from ethanol. There is obtained 1-(p-methoxybenzoyl)-2-pyrrolidinone of melting point 120°-121° .

15

Example 7

7.0 g of the sodium salt of 2-pyrrolidinone (prepared using sodium hydride) suspended in 120 ml of dimethylformamide are added at -10° to a solution of 20.0 g of p-methoxybenzoic acid pentachlorophenyl ester in 100 ml of
20 dimethylformamide. Subsequently, the mixture is stirred at room temperature for 1 hour and at 55° for 8 hours. The solvent is evaporated, the residue is treated with cold aqueous acetic acid solution and the mixture is extracted with ethyl acetate. The organic phase is washed with cold

sodium bicarbonate solution and water, dried over sodium sulphate, filtered and evaporated. The residue is taken up in ethanol and stirred in an ice bath. The separated crystals are filtered off and there is obtained 1-(p-methoxybenzoyl)-2-pyrrolidinone of melting point 119°-120° .

Example 8

15.9 g of p-benzyloxybenzoyl chloride, 500 ml of absolute diethyl ether and 6.3 ml of 2-pyrrolidinone are treated with 13.4 ml of triethylamine at 0° to 10° while stirring. The mixture is stirred at reflux for 9 hours, then cooled down and treated at 0° with cold water and ethyl acetate. The organic phase is washed with water, dried over sodium sulphate and evaporated. The residue is triturated with diethyl ether and the insoluble constituents are chromatographed over silica gel (particle size 0.2-0.5 mm). The constituents elutable with methylene chloride are triturated with diethyl ether. The insoluble constituents are filtered off and there is obtained 1-(p-benzyloxybenzoyl)-2-pyrrolidinone of melting point 115°-117° .

2.0 g of 1-(p-benzyloxybenzoyl)-2-pyrrolidinone are hydrogenated in 20 ml of absolute tetrahydrofuran and 20 ml of absolute methanol over 300 mg of palladium/carbon (5%) under atmospheric pressure and at room temperature. The catalyst is filtered off, the filtrate is concentrated and

the residue is triturated with diethyl ether. After filtration, there is obtained 1-(p-hydroxybenzoyl)-2-pyrrolidinone of melting point 179°-182° .

150 mg of 1-(p-hydroxybenzoyl)-2-pyrrolidinone are dissolved in 7 ml of absolute tetrahydrofuran and then ethereal diazomethane solution is added. The solvents are distilled off, the residue is triturated with diethyl ether and the mixture is filtered. There is obtained 1-(p-methoxybenzoyl)-2-pyrrolidinone which melts at 117.5°-119° after sublimation.

Example 9

10.0 g of 5-oxo-3-pyrrolidinyl acetate and 8.82 ml of trimethylchlorosilane are dissolved in 100 ml of absolute tetrahydrofuran and then 9.65 ml of triethylamine are added at -5° to 0° . The temperature is held at -5° to 0° for 1 hour, the mixture is then filtered under an argon atmosphere, the filtrate is evaporated and the residue is distilled in vacuo. There is obtained 5-oxo-1-trimethylsilyl-3-pyrrolidinyl acetate of boiling point 110° /0.07 mmHg.

12.5 g of 5-oxo-1-trimethylsilyl-3-pyrrolidinyl acetate are placed in 30 ml of absolute tetrahydrofuran and then 9.90 g of p-methoxybenzoyl chloride dissolved in 10 ml of absolute tetrahydrofuran are added dropwise at 0°-10° .

The mixture is stirred at room temperature for 1 hour and at 70° for 1 hour and is then evaporated. The residue is dissolved in ethyl acetate and the ethyl acetate solution is washed with sodium chloride and sodium bicarbonate solution, dried over sodium sulphate and evaporated. 20 ml of tetrahydrofuran and 20 ml of saturated sodium bicarbonate solution are added to the residual viscous oil and the mixture obtained is then stirred at room temperature for 18 hours. The solvent mixture is decanted off and the residue is partitioned between water and methylene chloride. The organic phase is separated, dried over sodium sulphate and evaporated. The residual brown oil is chromatographed over silica gel (particle size 0.2-0.5 mm). The 1-(p-methoxybenzoyl)pyrrolin-2-one, which is eluted with benzene/diethyl ether (1:1) is recrystallised from alcohol and then has a melting point of 148°-150°.

150 mg of 1-(p-methoxybenzoyl)pyrrolin-2-one are dissolved in 100 ml of ethyl acetate and hydrogenated over 30 mg of 5% palladium/carbon with hydrogen at atmospheric pressure and room temperature. After filtering off the catalyst and evaporating the solvent, there is obtained 1-(p-methoxybenzoyl)-2-pyrrolidinone.

Example 10

10.2 g of p-methoxybenzoyl chloride are added at 30° in one portion while stirring well to 30.9 g of 4-amino-

butyric acid, 24.0 g of sodium hydroxide and 300 ml of ion-free water. After 2 hours, the mixture is acidified with 75 ml of concentrated hydrochloric acid at a temperature below 10° . The precipitate is filtered off, washed ion-free with water, dried in a drying oven at 65° over phosphorus pentoxide and then recrystallised from 45 ml of acetone/low-boiling petroleum ether (3:1). There is obtained 4-(p-methoxybenzoylamino)butyric acid of melting point 120.5°-122° . . .

10 g of phosphorus pentoxide and 6 ml of orthophosphoric acid (at least 85%) are warmed with one another. 2.0 g of 4-(p-methoxybenzoylamino)butyric acid are added at room temperature to the resulting solution. The mixture is warmed to 50° for 60 minutes, subsequently treated with ice and extracted with ethyl acetate. The organic phase is washed firstly with cold water, then with cold sodium bicarbonate solution and finally again with water and dried over sodium sulphate. The residue is triturated with diethyl ether and there is obtained 1-(p-methoxybenzoyl)-2-pyrrolidinone of melting point 120°-122° .

Example 11

20.0 g of 4-(p-methoxybenzoylamino)butyric acid, 50 ml of toluene and 9.2 ml of thionyl chloride are heated at reflux for 2 hours and then the mixture is treated with decolorising charcoal and evaporated. The residue is dis-

solved in methylene chloride and chromatographed over neutral aluminium oxide. The 1-(p-methoxybenzoyl)-2-pyrrolidinone, which is eluted with methylene chloride, is recrystallised from alcohol and has a melting point of 119°-120°.

Example 12

276 mg of lithium hydride (98%), 40 ml of benzene and 4.2 g of 2-methoxypyrroline are boiled at reflux for 2 hours under nitrogen and while stirring well. After cooling to 25°, 6.6 g of p-methoxybenzoyl chloride dissolved in 25 ml of benzene are added and the resulting mixture is stirred under reflux for 2 hours and at room temperature for 16 hours. 100 ml of ethyl acetate followed by 3.0 g of lithium hydroxide (98%) dissolved in 25 ml of water are added to the mixture at room temperature within 15 minutes. The organic phase is washed neutral with water, dried over sodium sulphate and evaporated under reduced pressure. After recrystallisation from ethanol, there is obtained 1-(p-methoxybenzoyl)-2-pyrrolidinone of melting point 119°-120°.

Example 13

4.2 g of 2-methoxypyrroline are dissolved in 25 ml of benzene and treated at room temperature with 6.6 g of p-methoxybenzoyl chloride dissolved in 30 ml of benzene.

The mixture is stirred at room temperature for 60 minutes and at reflux for 4 hours. 30 ml of benzene are then added and the mixture is boiled at reflux for a further 24 hours. The volatile constituents are distilled off, the residue is taken up in ethanol, the mixture is concentrated, the residue is triturated with diethyl ether, filtered and the filter cake is taken up in ethyl acetate. The ethyl acetate solution is washed with sodium bicarbonate solution and water, dried over sodium sulphate and concentrated. The residue is sublimed in vacuo and there is obtained 1-(p-methoxybenzoyl)-2-pyrrolidinone of melting point 119°-120° .

Example 14

1-(p-Methoxybenzoyl)-2-pyrrolidinone is used as the active substance for the manufacture of tablets of the following composition:

	<u>Per tablet</u>
Active substance (finely ground)	100 mg
Lactose (powdered)	150 mg
Maize starch (white)	230 mg
Polyvinylpyrrolidone	15 mg
Magnesium stearate	5 mg
	500 mg

The finely ground active substance, the powdered lactose and a part of the white maize starch are mixed with

one another. The mixture is sieved, then moistened with a solution of polyvinylpyrrolidone in water, kneaded, moist granulated and dried. The granulate, the rest of the maize starch and the magnesium stearate are sieved and mixed with one another. The mixture is pressed to tablets of suitable form and size.

Example 15

1-(p-Methoxybenzoyl)-2-pyrrolidinone is used as the active substance for the manufacture of tablets of the following composition:

	<u>Per tablet</u>
Active substance (finely ground)	100 mg
Maize starch (white)	160 mg
Lactose	50 mg
Microcrystalline cellulose	40 mg
Polyvinylpyrrolidone	20 mg
Sodium carboxymethyl starch	23 mg
Magnesium stearate	2 mg
	395 mg

The finely ground active substance, a part of the white maize starch, the lactose, the microcrystalline cellulose and the polyvinylpyrrolidone are mixed with one another. The mixture is sieved and converted with the rest of the white maize starch and water into a granulate which is dried and sieved. The sodium carboxymethyl starch and

the magnesium stearate are then added thereto, mixed and the mixture is pressed to tablets of suitable size, the tablets having a break-bar.

Example 16

1-(p-Methoxybenzoyl)-2-pyrrolidinone is used as the active substance for the manufacture of tablets of the following composition:

	<u>Per tablet</u>
Active substance (finely ground)	500 mg
Maize starch (white)	270 mg
Lactose	80 mg
Microcrystalline cellulose	70 mg
Polyvinylpyrrolidone	35 mg
Sodium carboxymethyl starch	40 mg
Magnesium stearate	5 mg
	1000 mg

The finely ground active substance, a part of the white maize starch, the lactose, the microcrystalline cellulose and the polyvinylpyrrolidone are mixed with one another. The mixture is sieved and converted with the rest of the white maize starch and water into a granulate, which is dried and sieved. The sodium carboxymethyl starch and the magnesium stearate are then added thereto, mixed and the mixture is pressed to tablets of suitable size, the tablets having a break-bar.

Example 17

1-(p-Methoxybenzoyl)-2-pyrrolidinone is used as the active substance for the manufacture of duplex ampoules of the following composition:

Active substance solution

Active substance		100 mg
Polyethyleneglycol	ad	5 ml

Diluent

Water for injection		5 ml
---------------------	--	------

Prior to the injection the diluent is added to the content of the active substance ampoule. There are obtained 10 ml of a ready-for-use injection solution containing 100 mg of active substance.

Example 18

1-(p-Methoxybenzoyl)-2-pyrrolidinone is used as the active substance for the manufacture of duplex ampoules of the following composition:

Active substance solution

Active substance		100 mg
Glycofurol	ad	3.5 ml

Diluent

Sodium chloride		67.5 mg
Water for injection	ad	7.5 ml

Prior to the injection the diluent is added to the content of the active substance ampoule. There are obtained 10 ml of a ready-for-use injection solution containing 100 mg of active substance.

Example 19

1-(p-Methoxybenzoyl)-2-pyrrolidinone is used as the active substance for the manufacture of duplex ampoules of the following composition:

Active substance solution

Active substance		100 mg
Polyethyleneglycol		1.5 ml
Glycofurol	ad	4 ml

Diluent

Water for injection		6 ml
---------------------	--	------

Prior to the injection the diluent is added to the content of the active substance ampoule. There are obtained 10 ml of a ready-for-use injection solution containing 100 mg of active substance.