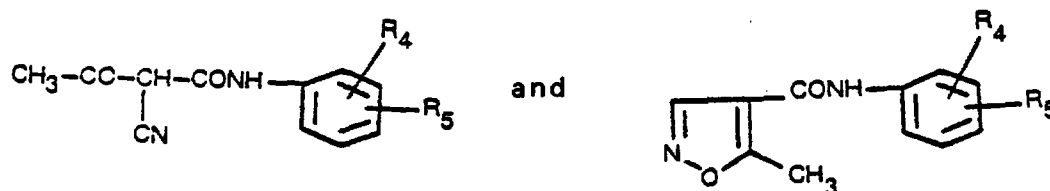


0,021,207

Description

According to Belgian Patents 842,688; 842,689; 849,343 and 861,500 or US Patent 4,061,767, "cyanoacetic acid anilides" and related "isoxazolylicarboxylic acid anilides" which are substituted in a particular manner, for example

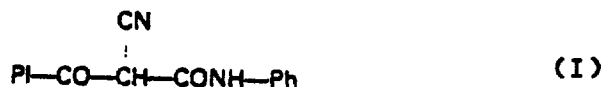
those of the formulae



are "non-ulcerogenic, anti-inflammatory and analgesic agents".

It has been found, surprisingly, that the pyrrole-propionitriles which are the subject of this patent offer marked therapeutic advantages compared with the known anilides mentioned, for example in respect of their spectrum of activity and tolerance. No pharmacological effects have been published for the analogous benzoyl compounds disclosed in J. Am. Chem. Soc., 35, 959 (1913).

The present invention relates to substituted β -oxo- α -phenylcarbamoylpyrrolepropionitriles of the general formula I



wherein PI denotes a 2-pyrrolyl or 3-pyrrolyl radical which is substituted in the 1-position by C_1-C_7 -alkyl or $\text{Ph}-\text{C}_1-\text{C}_7$ -alkyl and, in the remaining three positions, is

unsubstituted or substituted by one to three identical or different C_1-C_7 -alkyl groups and/or a carboxyl or carbo- C_1-C_7 -alkoxy group; and Ph denotes phenyl which is unsubstituted or substituted by one to three identical or different substituents belonging to the group comprising C_1-C_7 -alkyl, C_1-C_7 -alkoxy, C_1-C_7 -alkylthio, hydroxyl, halogen, trifluoromethyl, nitro, amino or C_1-C_7 -alkanoylamino; to these compounds in their enol form, enol C_1-C_7 -alkyl ethers or enol C_1-C_7 -alkanoyl esters thereof, or salts thereof with bases, in particular therapeutically usable salts thereof with bases, to processes for their preparation, pharmaceutical preparations containing these compounds and to these compounds for therapeutical use.

Both of the pyrrolyl and phenyl groups Pl and Ph mentioned are preferably C-unsubstituted. They can, however, also be substituted, especially by one or two identical or different substituents belonging to the group comprising C_1-C_7 -alkyl, for example methyl, ethyl, n-propyl, i-propyl, n-butyl or i-butyl. In addition, the radical Ph can also be substituted by C_1-C_7 -alkoxy, for example methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy or i-butoxy; C_1-C_7 -alkylthio, for example methylthio or ethylthio; hydroxyl; halogen, for example fluorine, chlorine or bromine; trifluoromethyl; nitro; or amino or C_1-C_7 -alkanoylamino, for example acetylamino or propionylamino. The radical Pl can also contain a carboxyl or carbo- C_1-C_7 -alkoxy group, for example carbo-methoxy or carboethoxy, especially in the 3-position or 4-position.

In the 1-position of the pyrrole ring the C_1-C_7 -alkyl or Ph- C_1-C_7 -alkyl groups are preferably methyl, but also ethyl, n-propyl, i-propyl, n-butyl, i-butyl, benzyl, 1-phenylethyl, 2-phenylethyl or 1-, 2- or 3-phenylpropyl. The last-mentioned radicals can be unsubstituted or substituted as indicated for Ph.

Amongst the C_1-C_7 -alkyl groups, those having not more than 4, in particular 1 or 2, carbon atoms are preferred.

The β -hydroxyl tautomeric compounds of the formula I

are sufficiently acid to form the said enol C₁-C₇-alkyl ethers, enol C₁-C₇-alkanoyl esters or salts with bases, in particular therapeutically usable salts with bases. These salts are derived from an alkali metal, alkaline earth metal, copper hydroxide or zinc hydroxide; ammonia, mono-, di- or tri-C₁-C₇-alkylamines or mono-, di- or tri-(hydroxy-C₁-C₇-alkyl)-amines, C₁-C₇-alkyleneamines or C₁-C₇-alkylenediamines. Examples of such salts are sodium, potassium, magnesium, ammonium, mono-, di- or tri-(methyl, ethyl or hydroxyethyl)-ammonium, pyrrolidinium, ethylenediammonium or morpholinium salts or various hydrates thereof.

The compounds of the invention exhibit valuable pharmacological properties, primarily anti-inflammatory and anti-arthritic effects. These can be demonstrated in in-vitro or in-vivo tests. In the latter, it is preferable to use mammals, for example rats, cats, guinea-pigs or dogs, as test objects. The compounds of the invention can be administered to the latter enterally, preferably orally, parenterally, for example subcutaneously or intravenously, or topically, for example in the form of solutions in water or oil or in the form of suspensions containing starch. The dose used can be within a range from 0.1 to 100 mg/kg/day, preferably 1 to 50 mg/kg/day and primarily 2 to 25 mg/kg/day. The tests chosen for the effects mentioned are either classical test methods, for example the Carrageenin paw oedema test or the adjuvans-arthritis test in rats, the synovitis test on dogs or the test in which the erythema induced by ultraviolet light is evaluated, or modern test methods. Examples of these are the neutral protease inhibition [described in Arthritis Rheum. 17, 47 (1974)] or the inhibition of leucocyte chemotaxis [N.Y. Acad. Sci., 256, 177 (1975)]. Further methods are the decrease in neutrophilic adherence [Amer. J. Med. 61, 597 (1976)] or the inhibition of prostaglandin (sic) synthetase, which test is described in Biochem. 10, 2372 (1971).

The following test method, which supplies relevant data is illustrative: male Charles River rats weighing

250-300 g are immunised by intradermal injections of 0.1 ml of Bacillus Calmette Guerin vaccine (BCG). After one week an injection of 10 ml of sterile 2% strength rice-starch solution is administered intraperitoneally to the test animals, in order to initiate the concentration of macrophages. On the eleventh day after immunisation, the animals are killed and peritoneal macrophages are collected by means of 20 ml of Gey's buffered salt solution containing heparin (25 units/ml). The cells are centrifuged for 10 minutes at 1000 revolutions/minute, washed at the same speed and for the same time with a further 50 ml of Gey's solution and then suspended in Gey's solution containing 0.1% of human serum albumin (fraction V, Sigma Co., pH = 7.1), in order to achieve a concentration of 2×10^6 cells/ml.

1×10^{-2} molar solutions in dimethylacetamide are prepared using the test substances. The dilutions below are made with Gey's solution and these are finally added to the above cell suspensions in order to achieve appropriate final concentrations of 10^{-4} , 10^{-5} , 10^{-6} and 10^{-7} mol. After the suspensions have been introduced into the upper section of modified Boyden chemotaxis chambers, the test substances mentioned remain together with the cells.

The chemotactic agent used is a rat serum which has been activated with the lipopolysaccharide of Escherichia coli (Difco) (1/10 dilution at pH = 7.1). This serum is introduced into the lower sections of the chambers mentioned. The section of the chamber containing the cells is separated from the chemotactic solution by a cellulose filter membrane having pores of 8 microns. The chambers are arranged in a three-fold replication and are incubated at 37°C for 5 hours. Cell suspensions containing no test compound are employed as a control of cell migration. After incubation, the filters are removed, fixed and dyed with iron haematoxylin by Weigert's method. Four sectors of the lower surface of the filter are examined under a microscope at a magnification of 320. The average number of neutrophils counted in these four fields is used as an index of the chemotactic

activity. Indomethacin and levamisol are also employed as reference compounds in this test method.

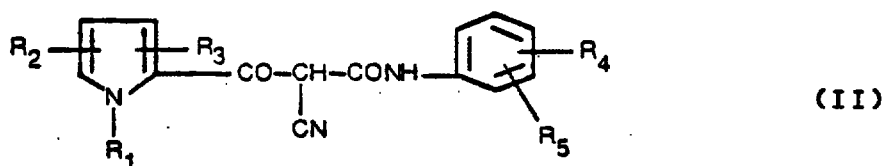
Thus, in the adjuvans-arthritis test, for example, 1-methyl- β -oxo- α -phenylcarbamoyl-2-pyrrolopropionitrile, a typical member of the compounds according to the invention, or the enol ethers or enol esters or salts mentioned or their related compounds of the formulae I and II are highly active in rats at peroral doses down to 2 mg/kg/day. The effect of these compounds on the in-vitro chemotactic activity of BCG-immunised macrophages is significant at concentrations down to 10^{-5} and 10^{-6} mol, and manifests itself in an increase in the chemotactic reaction of the macrophages. In contrast with this, indomethacin does not affect the chemotaxis of macrophages, whereas levamisol, a known immunopotentiator, produces an increased migration at final concentrations of 10^{-3} mol to 10^{-5} mol.

The above test methods demonstrate that the compounds according to the invention display a very good anti-inflammatory action, but also possess a different mechanism of action in comparison with the customary non-steroidal anti-inflammatory agents, since they also contain an active component similar to levamisol, as is also shown in the macrophages chemotaxis test. [Levamisol is an antirheumatic medicament which has an influence on diseases. (In this respect, reference is made to the journals "Arthritis and Rheumatism", 18, 385 (1975) and "The Lancet", 21st February 1976, page 393)]. The compounds of the present invention, which possess both the activity of the indomethacin type and also that of the levamisol type, are valuable anti-inflammatory and anti-arthritic agents, for example for the treatment or control of inflammatory arthritic and/or dermatopathological conditions. In addition, the new compounds can be employed as intermediate products for the preparation of other valuable formulations, in particular pharmacologically active formulations.

Preferred compounds are those of the formula I wherein Pl denotes 1-(C_1 - C_7 -alkyl or Ph- C_1 - C_7 -alkyl)-2-pyrrolyl or 1-(C_1 - C_7 -alkyl or Ph- C_1 - C_7 -alkyl)-3-pyrrolyl which or

unsubstituted in the remaining positions or is substituted by one or two C_1-C_7 -alkyl groups or by a carboxy- C_1-C_7 -alkoxy or carbo- C_1-C_7 -alkoxy group, and Ph represents phenyl which is unsubstituted or substituted by one or two identical or different substituents belonging to the group comprising C_1-C_7 -alkyl, C_1-C_7 -alkoxy, C_1-C_7 -alkylthio, hydroxyl, halogen, trifluoromethyl, nitro, amino and C_1-C_7 -alkanoyl-amino, enol C_1-C_7 -alkyl ethers or enol C_1-C_7 -alkanoyl esters thereof or salts thereof with bases, in particular therapeutically usable salts thereof with bases.

Compounds which should be singled out particularly are those of the general formula II



wherein R_1 denotes C_1-C_7 -alkyl, each of the symbols R_2 and R_3 represents hydrogen or C_1-C_7 -alkyl and each of the symbols R_4 and R_5 denotes hydrogen, C_1-C_7 -alkyl, C_1-C_7 -alkoxy, hydroxyl, halogen or trifluoromethyl, or salts thereof with bases, in particular therapeutically usable salts thereof with bases.

Compounds of the formula II which are also preferred are those wherein R_1 denotes alkyl having not more than 4 carbon atoms, each of the symbols R_2 and R_3 represents hydrogen and each of the symbols R_4 and R_5 denotes hydrogen, alkyl or alkoxy, in each case having not more than 4 carbon atoms, fluorine, chlorine or trifluoromethyl, or salts thereof with a base, in particular therapeutically usable salts thereof with bases.

Compounds of the general formula II which are particularly preferred are those wherein R_1 denotes methyl, each of the symbols R_2 and R_3 represents hydrogen and each of the symbols R_4 and R_5 denotes hydrogen, methyl, methoxy, fluorine, chlorine or trifluoromethyl, or sodium, potassium,

calcium, triethylammonium or trihydroxyethylammonium salts thereof, one of the symbols R_4 and R_5 which is other than hydrogen being preferably in the para-position.

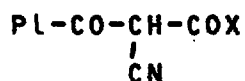
The compounds of the invention are prepared by methods which are in themselves known, for example

a) by subjecting compound (sic) of the formulae



to an addition reaction or

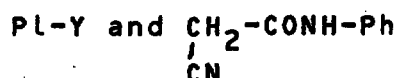
b) by subjecting compounds of the formulae



and $H-NH-Ph$,

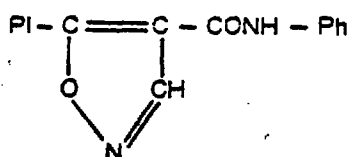
wherein X denotes C_1-C_7 -alkoxy, C_1-C_7 -alkanoyloxy or halogen to a condensation reaction or

c) subjecting compounds of the formulae



wherein Y denotes C_1-C_7 -alkoxycarbonyl, halogenocarbonyl or cyano to a condensation reaction and hydrolysing the resulting imines or

d) by isomerising a compound of the formula



by means of a strong base and, if desired, converting a resulting compound of the formula I into another compound of the invention, and/or, if desired, converting a resulting enol into an enol C_1-C_7 -alkyl ether or an enol C_1-C_7 -alkanoyl ester, and/or, if desired, converting a resulting enol into a salt with a base or a resulting enol salt into the free enol or into another salt with a base, and/or, if desired, resolving a resulting mixture of isomers into the individual isomers.

The addition reaction of the isocyanate in process a) is preferably carried out in accordance with the said

Belgian patents or in accordance with US Patent 3,905,997, that is to say in the absence or in the presence of an inorganic or organic base, for example sodium hydride, or in the presence or absence of a polar solvent, for example an ether, such as diethyl ether or tetrahydrofuran; and/or of an amide of sulphoxide, for example dimethylformamide or dimethyl sulphoxide, preferably at elevated temperatures, for example at approximately 150° if no base is used.

The process according to the invention is preferably carried out as follows: a suspension of the nitrile mentioned in an aromatic hydrocarbon, for example in warm toluene, is treated with a slight molar excess of an anhydrous tri-lower alkylamine, preferably triethylamine. 1 mol equivalent of phenyl isocyanate $\text{Ph-N}=\text{CO}$ or a solution thereof in a previously mentioned polar solvent, for example dimethyl sulphoxide, is then added to the mixture. The reaction mixture is stirred at room temperature for 2 to 12 hours and its volume is reduced by heating at not too high temperatures, for example up to 100°. The resulting precipitate is taken up in an alkanol, for example methanol, and the solution is treated with excess dilute aqueous acid, for example with 0.3-normal hydrochloric acid. The resulting crude product is separated off, washed with water, dried and triturated and/or recrystallised from suitable solvents. Solvents of this type are lower alkanols, lower alkanones, di-lower alkyl ethers and/or lower alkyl lower alkanoates, for example methanol, acetone, diethyl ether and/or ethyl acetate.

The amination in accordance with process b) is also carried out in a customary manner, preferably between room temperature and approximately 150°. The reaction is carried out either using equivalent amounts of the reactants, preferably if an ester is used, or using an excess of amine or in the presence of another base. Examples of bases of this type are tertiary amines, such as a tri-lower alkylamine or pyridine. These bases are employed when halide or anhydride starting materials are used for the neutralisation of the acid formed. The lower alkanol formed in the reaction of

ester starting materials is preferably distilled off together with the solvent, for example with an aromatic hydrocarbon, for example benzene, toluene or xylene.

The condensation reaction in process c) is preferably carried out using alkali metals, lower alkoxides thereof, or, in particular, hydrides thereof, for example sodium hydride, in the said polar solvents, preferably dimethylformamide or dimethyl sulphoxide. This condensation reaction is analogous to the preparation of the said nitrile starting materials for processes a) and b), and this condensation reaction is illustrated in the corresponding examples.

Finally, the isomerisation in process d) is carried out in the presence of strong inorganic or organic bases, for example alkali metal hydroxides or tri-lower alkylaralkylammonium hydroxides, for example trimethylbenzylammonium hydroxide.

The resulting compounds of the formula I can be converted into one another in a manner which is in itself known. Thus, for example, resulting enols can be etherified, preferably by means of diazoalkanes, or can be esterified, for example by means of C₁-C₇-alkanoic anhydrides. Therapeutically usable salts of the said enols can be prepared, for example, by means of aqueous alkali metal hydroxides, preferably in the presence of an ether or alcohol as solvent, for example a lower alkanol. The salts can be precipitated from the alcoholic solutions by means of the said ethers, for example diethyl ether or tetrahydrofuran. The reaction is carried out at moderate temperatures, for example below 100°. Resulting salts can, as mentioned above, be converted into the free compounds by treatment with acids. A nitro group in the Ph radical can also be converted into the amino group, for example by means of catalytically activated hydrogen, such as hydrogen in the presence of nickel or palladium catalysts. The amino group can be acylated either as described above or by means of C₁-C₇-alkanoyl halides or C₁-C₇-alkyl esters.

The starting materials are known or, insofar as they

are new, can be prepared in accordance with the processes described for analogous compounds, for example those which are described in the state of the art for the compounds mentioned there, or as illustrated in the examples.

Starting materials and end products which are mixtures of isomers can be separated into the individual isomers by methods which are in themselves known, for example by fractional distillation, crystallisation and/or chromatography.

The reactions described above are carried out in accordance with methods which are in themselves known, in the presence or absence of diluents, preferably in diluents which are inert towards the reagents and dissolve the latter, catalysts, condensation agents or neutralising agents, and/or in an inert atmosphere, with cooling, at room temperature or at elevated temperatures and at normal or elevated pressure.

The invention also relates to modifications of the present process according to which an intermediate product obtainable at any stage of the process is used as the starting material and the remaining process stages are carried out, or the process is discontinued at any stage, or according to which a starting material is formed under the reaction conditions, or wherein a starting material is used in the form of a salt or a reactive derivative, preferably an alkali metal salt or trialkylammonium salt. The isocyanates mentioned can also be prepared starting from corresponding acid azides, and mixed anhydrides can be prepared from corresponding acids and simple alkanolic anhydrides.

In the process of the present invention it is preferable to use starting materials which lead to the compounds described initially as particularly valuable, in particular compounds of the formula II.

The pharmacologically usable compounds of the present invention can be used for the preparation of pharmaceutical formulations which contain an effective amount of the active substance together with, or mixed with, excipients which are suitable for enteral or parenteral administration. It is

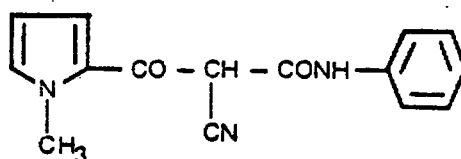
preferable to use tablets or gelatine capsules which contain the active compound together with diluents, for example lactose, dextrose, cane sugar, mannitol, sorbitol, cellulose and/or glycine, and lubricants, for example silica, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol; tablets also contain binders, for example magnesium aluminium silicate, starch paste, gelatine, tragacanth, methylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone, and, if desired, disintegrators, for example starches, agar or alginic acid or the sodium salt thereof, enzymes of the binders and/or effervescent mixtures or adsorbents, colorants, flavourings and sweeteners. Injectable formulations are preferably isotonic aqueous solutions or suspensions, and suppositories or topical lotions are primarily fatty emulsions or suspensions. The pharmacological formulations can be sterilised and/or contain auxiliaries, for example preservatives, stabilisers, wetting agents and/or emulsifiers, solubilisers, salts for regulating the osmotic pressure and/or buffers. The present pharmaceutical formulations which, if desired, can contain further pharmacologically valuable substances, are prepared in a manner which is in itself known, for example by means of conventional mixing, granulating or coating processes, and contain from 1% to 75%, in particular from 1% to 50%, of the active substance.

The examples which follow serve to illustrate the invention. Temperatures are quoted in degrees centigrade, and the data concerning parts relate to parts by weight. Unless defined otherwise, the evaporation of solvents is carried out under atmospheric pressure.

Example 1

10.7 g of phenyl isocyanate are added, with stirring, to a suspension of 12.9 g of 1-methyl- β -oxo-2-pyrrolepropionitrile in 150 ml of dry toluene and 10.1 g of anhydrous triethylamine. After the solid substances have dissolved, the dark red solution is kept for 30 minutes at room temperature, for 5 minutes on a steam bath and overnight at room

temperature. The mixture is evaporated on a steam bath, the residue is taken up in methanol, and the solution is poured into a mixture of 25 ml of 5-normal hydrochloric acid and 600 ml of water. The resulting pale brown crystals are separated off, washed with water, triturated with ethanol and recrystallised from about 2200 ml of methanol. This gives 1-methyl- β -oxo- α -phenylcarbamoyl-2-pyrrolepropionitrile of the formula



melting at 174-175°.

The starting material is prepared as follows: a solution of 28 g of 1-methylpyrrole-2-carboxylic acid in 20 ml of dimethylformamide is added, with stirring and cooling, to a suspension which has been prepared starting from 12 g of 50% strength sodium hydride in mineral oil by washing the sodium hydride with petroleum ether and suspending it in 50 ml of dimethylformamide. 30 ml of methyl iodide are then added to the reaction mixture and stirring is continued at room temperature. After the initial exothermic reaction has subsided, a further 10 ml of methyl iodide are added. The reaction mixture is allowed to stand overnight and is treated with water and extracted with diethyl ether. The extract is washed with aqueous sodium carbonate solution and water and is dried and evaporated. Methyl 1-methylpyrrole-2-carboxylate is obtained as an oil.

A solution of 28 g of the last-mentioned compound in 50 ml of acetonitrile is added, with stirring, to a suspension prepared from 19 g of 50% strength sodium hydride in mineral oil by washing the sodium hydride with petroleum ether and suspending it in 50 ml of dimethylformamide. After the exothermic reaction has subsided, the mixture is heated on a steam bath for 15 minutes, in the course of which a further reaction with vigorous effervescence takes place.

The viscous, red-brown suspension is diluted with a further 50 ml of dimethylformamide and allowed to stand overnight at room temperature. The mixture is then heated for a further 5 minutes on a steam bath and is then cooled and diluted with water. The aqueous solution is filtered, washed once with diethyl ether and acidified with hydrochloric acid. The resulting crystals are separated off, washed with water, dried, triturated with cold ethanol and recrystallised from ethanol. This gives 1-methyl- β -oxo-2-pyrrolepropionitrile, melting at 107-109^o.

Example 2

Treating 1-methyl- β -oxo- α -phenylcarbamoyl-2-pyrrolepropionitrile with equivalent amounts of concentrated aqueous solutions of sodium hydroxide, potassium hydroxide or calcium hydroxide, filtering the mixture and evaporating the filtrate to dryness gives the three corresponding metal salts. These appear to have no well-defined crystalline properties or melting points although they can be reprecipitated from ethanolic solution by adding diethyl ether. The salts are water-soluble and their infrared spectrum shows the following bands:

Na salt: 4.57; 6.17 and 6.29 μ ;

K salt: 4.58; 6.17 and 6.30 μ ;

Ca salt: 4.55; 6.13 and 6.23 μ .

In each case, the identical free compound (melting point 174-175^o) is recovered by acidifying the aqueous salt solution with hydrochloric acid.

Example 3

11.68 ml of triethanolamine in 25 ml of ethanol are added to a suspension of 21.4 g of 1-methyl- β -oxo- α -phenylcarbamoyl-2-pyrrolepropionitrile in 100 ml of absolute ethanol, and the mixture is heated until solution is complete. The solution is filtered while hot and allowed to cool to room temperature with stirring, the resulting suspension is cooled to 10^o and filtered, and the residue is washed with 25 ml of cold ethanol. This gives the corresponding tris-hydroxyethylammonium salt, melting at 115-117^o.

Example 4

3.8 g of 1-methyl- β -oxo- α -phenylcarbamoyl-2-pyrrolepropionitrile are added to 500 ml of ether containing diazomethane, the latter being prepared from 10.3 g of N-nitroso-N-methylurea by means of 35 ml of 45% strength aqueous potassium hydroxide solution and being dried over pellets of the latter. After the evolution of nitrogen has subsided, the solution is filtered and evaporated. The residue is triturated with diethyl ether and recrystallised from ethyl acetate. This gives the corresponding methyl enol ether, namely 1-methyl- β -methoxy- α -phenylcarbamoyl-2-pyrroleacrylonitrile, melting at 121-122^o.

Example 5

3.7 g of p-fluorophenyl isocyanate are added, with stirring, to a suspension of 4 g of 1-methyl- β -oxo-2-pyrrolepropionitrile in 70 ml of toluene and 3.2 g of triethylamine. The mixture is heated on a steam bath until the solid material has dissolved, and the red-brown solution is allowed to stand overnight at room temperature. The reaction mixture is evaporated on a steam bath, the residue is taken up in methanol, and the solution is poured into a mixture of 8 ml of 5-normal hydrochloric acid and 300 ml of water. The crystals precipitated are separated off, washed with water, dried, triturated with methanol and recrystallised from ethyl acetate. This gives 1-methyl- β -oxo- α -(p-fluorophenylcarbamoyl)-2-pyrrolepropionitrile, melting at 198-199^o.

Example 6

A mixture of 1.1 g of 1-methyl- β -oxo- α -ethoxycarbonyl-2-pyrrolepropionitrile, 1.1 g of aniline and 60 ml of xylene is boiled under reflux for 4.5 hours. The reaction mixture is left to cool and to stand at room temperature overnight. The solution is then filtered and evaporated and the residue is recrystallised from methanol. This gives 1-methyl- β -oxo- α -phenylcarbamoyl-2-pyrrolepropionitrile, melting at 173-174^o. The product is identical with that of Example 1.

The starting material is prepared as follows: a

solution of 6 ml of thionyl chloride in 50 ml of diethyl ether is added in stages and with stirring to a solution of 10 g of 1-methylpyrrole-2-carboxylic acid in 650 ml of dry diethyl ether and 8.5 g of anhydrous triethylamine. The reaction mixture is filtered after 30 minutes, and the residue is washed with diethyl ether. The filtrate is evaporated to a smaller volume, filtered again and finally evaporated under reduced pressure. This gives the corresponding acid chloride.

A solution of the latter in 20 ml of ethylene glycol dimethyl ether is added slowly, with stirring and cooling, to a suspension of 7.3 g of 50% strength sodium hydride in mineral oil (washed with petroleum ether) in 50 ml of dimethylformamide and 20 g of ethyl cyanoacetate. The moderately exothermic reaction is accelerated by heating the mixture on a steam bath for a short time. The reaction mixture is allowed to stand overnight, treated with water, acidified with 5-normal hydrochloric acid and extracted with diethyl ether. The extract is washed with water, dried and evaporated, and the residue is triturated and recrystallised from diethyl ether. This gives 1-methyl- β -oxo- α -ethoxycarbonyl-2-pyrrolepropionitrile, melting at 74-77°.

The same product is obtained in the above stage of the reaction by acylation with the mixed anhydride, that is to say using an equivalent amount of ethyl chloroformate instead of thionyl chloride.

Example 7

A mixture of 5.7 g of 1-methyl- β -oxo- α -ethoxycarbonyl-2-pyrrolepropionitrile, 3.6 g of p-aminophenol and 300 ml of xylene is boiled under reflux for 2 hours and filtered while hot. The filtrate is cooled and the crystals obtained are separated off and recrystallised from methanol. This gives 1-methyl- β -oxo- α -(p-hydroxyphenylcarbamoyl)-2-pyrrolepropionitrile, melting at 182-184°.

Example 8

2.9 g of 1-benzyl- β -oxo-2-pyrrolepropionitrile in 30 ml of 1,2-dimethoxyethane, followed by 2.7 g of

p-chlorophenyl isocyanate, are added, with stirring, to a suspension of 0.8 g of 50% strength sodium hydride in mineral oil (washed with petroleum ether) in 10 ml of 1,2-dimethoxyethane. The reaction mixture is allowed to stand overnight at room temperature and is evaporated, the residue is taken up in water, and the solution is filtered and acidified with 5-normal hydrochloric acid. The resulting yellow precipitate is separated off, washed with water, triturated with methanol and recrystallised from ethyl acetate. This gives 1-benzyl- β -oxo- α -(p-chlorophenyl-carbamoyl)-2-pyrrolepropionitrile, melting at 214-215°.

The starting material is prepared as follows: 7.5 g of methyl pyrrole-2-carboxylate in 25 ml of dimethylformamide are added to a stirred suspension prepared from 3.4 g of 50% strength sodium hydride in mineral oil by washing the former with petroleum ether and suspending it in 20 ml of dimethylformamide. 8.5 ml of benzyl chloride are then added to the mixture, which is stirred overnight at room temperature. The reaction mixture is treated with water and extracted with diethyl ether, and the extract is washed with aqueous sodium hydroxide solution and water, dried and evaporated. Methyl 1-benzylpyrrole-2-carboxylate is obtained in the form of an oil. (After purification, a sample thereof melts at 31-32°).

A solution of 9.3 g of the last-mentioned compound in 15 ml of acetonitrile and 25 ml of dimethylformamide is added, with stirring, to a suspension prepared from 4 g of 50% strength sodium hydride in mineral oil by washing the former with petroleum ether and suspending it in 25 ml of dimethylformamide. The mixture is heated on a steam bath for 30 minutes, in the course of which a dark red solution is formed. This is allowed to stand overnight at room temperature, water is added, and the mixture is washed with diethyl ether and acidified with 5-normal hydrochloric acid. The resulting crystals are separated off, washed with water, dried, triturated with diethyl ether and recrystallised from methanol. This gives 1-benzyl- β -oxo-2-pyrrolepropionitrile,

melting at 119-120°.

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Example 9

28 g of potassium tert.-butoxide are added, with stirring and in an atmosphere of nitrogen, to a solution of 4 g of phenylcarbamoylacetonitrile in 50 ml of dimethylformamide. After 2 hours the resulting suspension is cooled to 5° and 4 g of 1-methylpyrrole-2-carboxylic acid chloride (US A 3,551,571) are added in the course of 10 minutes. The reaction mixture is stirred for 18 hours at room temperature and poured into 300 ml of ice-water, and the resulting precipitate is filtered off. It is washed with water, dried and recrystallised from ethanol. This gives 1-methyl- β -oxo- α -phenylcarbamoyl-2-pyrrolepropionitrile, melting at 172-174°. The product is identical with that of Example 1.

The starting material is prepared as follows: a solution of 113.7 g of N,N-dicyclohexylcarbodiimide in 500 ml of acetonitrile is added, in the course of 30 minutes and with stirring, in an atmosphere of nitrogen, to a mixture of 42.53 g of cyanoacetic acid, 46.56 g of aniline and 500 ml of acetonitrile. After 3 hours the resulting suspension is filtered, the residue is washed with 200 ml of acetonitrile, and the filtrates are evaporated. The residue is triturated with 500 ml of diethyl ether and 50 ml of ethyl acetate, filtered off and dried. This gives phenylcarbamoylacetonitrile, melting at 200-202°.

Example 10

913 g of anhydrous triethylamine, followed by 913 g of phenyl isocyanate, are added, with stirring and in an atmosphere of nitrogen, to a suspension of 1.135 g (sic) of 1-methyl- β -oxo-2-pyrrolepropionitrile in 17,000 ml of dry toluene. The resulting dark brown solution is stirred overnight at room temperature and is then evaporated at 60-70° / 10 mm Hg. The residue is taken up in 1400 ml of methanol, and the solution is treated with 1400 ml of 6-normal hydrochloric acid in 4200 ml of water. The suspension is cooled at 15-20° for 20 minutes and filtered, and the residue is washed with twice 1800 ml of water, twice 1000 ml of isopro-

panol and 13 times 1000 ml of diethyl ether. The crude residue is dried to constant weight at 60° and 5 mm Hg. 1960 g of this residue are dissolved at room temperature in 44,400 ml of methylene chloride. The solution is treated with 400 g of active charcoal and filtered, and the filtrate is evaporated. The residue is triturated with 12,000 ml of anhydrous ethanol, the suspension is filtered at 20° and the residue is washed with four times 1000 ml of anhydrous ethanol and dried at 60° and 5 mm Hg. This gives 1-methyl- β -oxo- α -phenyl-carbamoyl-2-pyrrolepropionitrile, melting at 172-174°. The product is identical with that of Examples 1, 6 or 9.

1801 g of the last-mentioned compound are suspended in 10,500 ml of anhydrous ethanol, and 1108 g of triethanolamine are added. The mixture is stirred and heated until the solid material has dissolved and is then cooled slowly to 20°. The resulting precipitate is filtered off, washed with twice 1000 ml of cold, anhydrous ethanol and dried at 45° and 0.1 mm Hg. This gives the corresponding tris-hydroxyethylammonium salt, melting at 115-117°. The salt is identical with that of Example 3.

The starting material is prepared as follows: a solution of 1325 g of 1-methylpyrrole-2-carboxylic acid in 2400 ml of dimethylformamide is added, with stirring and in a nitrogen atmosphere and with cooling by ice, to a suspension prepared from 568.5 g of 50% strength sodium hydride in mineral oil and 2400 ml of dimethylformamide. 1000 ml of dimethylformamide, followed by 4316 g of methyl iodide, are then added to the reaction mixture, with stirring and at a temperature below 88°. Stirring is continued overnight at room temperature, and the mixture is then cooled to 10° and 10,600 ml of water are added. The mixture is extracted with three times 5300 ml of diethyl ether, and the extract is washed with 5300 ml of 10% strength aqueous sodium carbonate solution and 5300 ml of water and is dried and evaporated. Methyl 1-methylpyrrole-2-carboxylate is obtained in the form of an oil.

A solution of 1604 g of the last-mentioned compound in 2650 ml of acetonitrile is added rapidly to a suspension prepared, with stirring and in a nitrogen atmosphere, from 1017 g of 50% strength sodium hydride in mineral oil and 2650 ml of dimethylformamide. The mixture is heated at 81° for 2 hours and is then cooled to 10° and, finally, 25,400 ml of water are added in the course of 15 minutes. The mixture is washed with three times 9000 ml of diethyl ether, stirred for 45 minutes at 10 mm Hg in order to remove the diethyl ether and acidified with 6400 ml of 6-normal hydrochloric acid. The resulting crystals are separated off, washed with four times 2400 ml of water and once with 2400 ... (sic) of isopropanol and dried at 60° and 5 mm Hg. This gives 1-methyl- β -oxo-2-pyrrolepropionitrile, melting at 106-108°.

Example 11

2.5 g of 1-methyl- β -oxo-2-pyrrolepropionitrile and 2.1 g of triethylamine are added, with stirring, to a filtered solution of 4.4 g of 2,6-dichlorophenyl isocyanate in 30 ml of toluene. The mixture is allowed to stand overnight at room temperature and is then filtered. The solid material is washed with toluene and diethyl ether and is taken up in 50 ml of methanol, and the solution is poured into a mixture of 6 ml of 5-normal hydrochloric acid and 300 ml of water. The crystals obtained are separated off, washed with water, dried, triturated with ethanol and recrystallised from methanol. This gives 1-methyl- β -oxo- α -(2,6-dichlorophenyl-carbamoyl)-2-pyrrolepropionitrile, melting at 196-199°.

Example 12

A suspension of 2 g of 1-methyl- β -oxo-2-pyrrolepropionitrile in 50 ml of toluene and 1.6 g of triethylamine is treated with 2.1 g of p-methoxyphenyl isocyanate. The mixture is warmed gently until the solid material has dissolved and is allowed to stand overnight at room temperature. It is then evaporated, and the residue is taken up in methanol, to which 10 ml of 10% strength aqueous sodium hydroxide solution and 250 ml of water are added. The alkaline solution

is filtered and acidified with 5-normal hydrochloric acid, and the resulting precipitate is separated off. The precipitate is washed with water, dried, triturated with a warm mixture of methanol and ethyl acetate, and recrystallised from ethyl acetate. This gives 1-methyl- β -oxo- α -(p-methoxyphenylcarbamoyl)-2-pyrrolepropionitrile, melting at 192-193°.

1-Methyl- β -oxo- α -(p-methylthiophenylcarbamoyl)-2-pyrrolepropionitrile is also prepared analogously, melting point 167-168°.

Example 13

A solution of 4.9 g of 1-methyl- β -oxo-2-pyrrolepropionitrile in 50 ml of toluene, 5 ml of dimethyl sulfoxide and 4 g of triethylamine is treated, with stirring, with a solution of 5.7 g of p-nitrophenyl isocyanate in the minimum amount of toluene. The reaction mixture is allowed to stand overnight and is evaporated, and the residue is taken up in methanol. The solution is filtered, diluted with water and 6 ml of triethylamine, and washed with ethyl acetate, and the wash liquor is extracted once with 5% strength aqueous sodium hydroxide solution. The combined aqueous solutions are acidified with 5-normal hydrochloric acid, and the resulting precipitate is separated off. It is washed with water, triturated with a mixture of methanol and ethanol and recrystallised from dimethylformamide. This gives 1-methyl- β -oxo- α -(p-nitrophenylcarbamoyl)-2-pyrrolepropionitrile, melting with decomposition at 245-250°.

A solution of 2 g of the last-mentioned compound in 220 ml of ethanol and 2 ml of triethylamine is hydrogenated for 50 minutes over 0.5 g of 10% strength palladium-on-charcoal at 3.5 atmospheres and room temperature. The filtered solution is evaporated, the residue is taken up in water, to which 1 ml of triethylamine is added, and the solution is washed with ethyl acetate and diethyl ether. The solution is acidified with 5-normal hydrochloric acid, and the precipitate is separated off, washed with water, dried and recrystallised from aqueous methanol. This gives 1-methyl- β -oxo-

α -(p-aminophenylcarbamoyl)-2-pyrrolepropionitrile, melting with decomposition at 193-195°.

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0.5 g of the last-mentioned compound is dissolved in 10 ml of acetic anhydride, and the solution is boiled under reflux for 10 minutes and evaporated. The residue is triturated with diethyl ether and recrystallised from methanol/ethyl acetate. This gives 1-methyl- β -acetoxy- α -(p-acetylaminophenylcarbamoyl)-2-pyrroleacrylonitrile, melting at 178-179°.

Example 14

A mixture of 2.1 g of 1-ethyl- β -oxo-2-pyrrolepropionitrile, 25 ml of toluene and 1.6 g of triethylamine is treated, with stirring, with 1.6 g of phenyl isocyanate. The mixture is allowed to stand overnight at room temperature and is then evaporated and dissolved in methanol. The solution is poured into 300 ml of water containing 5 ml of 5-normal hydrochloric acid, and the precipitate is separated off and dissolved in 5% strength aqueous sodium hydroxide solution. The solution is filtered, the filtrate is acidified again and the solid material is separated off, washed with water, dried and recrystallised from ethanol. This gives 1-ethyl- β -oxo- α -phenylcarbamoyl-2-pyrrolepropionitrile, melting at 144-145°.

The starting material is prepared as follows: 20 g of methyl pyrrole-2-carboxylate in 50 ml of dimethylformamide is added in stages, with stirring and cooling by ice, to a suspension prepared from 9.1 g of 50% strength sodium hydride in mineral oil by washing the sodium hydride with petroleum ether and suspending it in 50 ml of dimethylformamide. When the material has dissolved, 25 ml of ethyl bromide are added and the reaction mixture is warmed gently in order to initiate the exothermic reaction. When the latter subsides, a further 5 ml of ethyl bromide are added and the mixture is allowed to stand overnight. It is treated with water and extracted with diethyl ether. The extract is washed with water, dried, filtered and evaporated. Methyl 1-ethylpyrrole-2-carboxylate is obtained in the form of an

oil.

A solution of 10 g of the last-mentioned compound in 25 ml of acetonitrile and 25 ml of dimethylformamide is added to a suspension in 15 ml of dimethylformamide of 5.5 g of 50% strength sodium hydride (washed with petroleum ether), and the mixture is heated for 15 minutes on a steam bath, with stirring. It is allowed to stand overnight, water is added and the mixture is filtered and acidified with 5-normal hydrochloric acid. The precipitate is separated off, washed with water and recrystallised from ethanol. This gives 1-ethyl- β -oxo-2-pyrrolepropionitrile, melting at 77-79°.

Example 15

1.6 g of phenyl isocyanate are added, with stirring, to a solution of 2.5 g of 1-isobutyl- β -oxo-2-pyrrolepropionitrile in 30 ml of toluene and 1.6 g of triethylamine. The mixture is allowed to stand overnight and is filtered and the residue is dissolved in 5% strength aqueous sodium hydroxide solution. The solution is filtered, acidified with 5-normal hydrochloric acid and extracted with a mixture of diethyl ether and ethyl acetate. The organic solution is washed with water, dried and evaporated. The residue is triturated with ethanol and recrystallised from methanol. This gives 1-isobutyl- β -oxo- α -phenylcarbamoyl-2-pyrrolepropionitrile, melting at 134-136°.

The starting material is prepared as follows: 13 g of methyl pyrrole-2-carboxylate are added, with stirring, to a suspension prepared from 5.5 g of 50% strength sodium hydride in mineral oil by washing the sodium hydride with petroleum ether and suspending it in 70 ml of dimethylformamide. 40 g of isobutyl bromide are then added to the mixture, and it is heated for 10 minutes on a steam bath, with stirring. The reaction mixture is allowed to stand overnight and is then treated with water and extracted with diethyl ether. The extract is washed with water, dried and evaporated. This gives methyl 1-isobutylpyrrole-2-carboxylate in the form of an oil.

A solution of 10 g of the last-mentioned compound in

15 ml of acetonitrile is added, with stirring, to a suspension prepared from 5 g of 50% strength sodium hydride in mineral oil by washing the sodium hydride with petroleum ether and suspending it in 25 ml of dimethylformamide. After the effervescent reaction has subsided, the mixture is heated on a steam bath for 30 minutes. The sodium hydride is applied (sic) during this time. The mixture is allowed to stand overnight at room temperature, water is added to it and it is acidified with 5-normal hydrochloric acid. The mixture is extracted with diethyl ether, and the extract is washed with water, dried and evaporated. 1-Isobutyl- β -oxo-2-pyrrolepropionitrile is obtained in the form of an oil.

Example 16

0.8 g of phenyl isocyanate is added, with stirring, to a solution of 1.6 g of 1,3,5-trimethyl-4-ethoxycarbonyl- β -oxo-2-pyrrolepropionitrile in 30 ml of dry toluene and 0.8 g of anhydrous triethylamine. The mixture is heated on a steam bath for 10 minutes and is allowed to stand overnight at room temperature. It is then evaporated, the residue is taken up in methanol and the solution is treated with 2 ml of 5-normal hydrochloric acid and 200 ml of water. The resulting crystals are separated off, washed with water, triturated with a mixture of methanol and ethanol and recrystallised from methanol. This gives 1,3,5-trimethyl-4-ethoxycarbonyl- β -oxo- α -phenylcarbamoyl-2-pyrrolepropionitrile, melting at 164-166°.

1,3,5-Trimethyl-4-ethoxycarbonyl- β -oxo- α -(p-fluorophenylcarbamoyl)-2-pyrrolepropionitrile, melting point 178-179°, and 1,3,5-trimethyl-4-ethoxycarbonyl- β -oxo- α -(p-chlorophenylcarbamoyl)-2-pyrrolepropionitrile, melting point 238-241° (with decomposition), are also prepared analogously.

The starting material is prepared as follows: 16 g of diethyl 3,5-dimethylpyrrole-2,4-dicarboxylate in 25 ml of dimethylformamide are added in portions and with stirring to a suspension of 3.6 g of 50% strength sodium hydride in mineral oil (washed with petroleum ether) and 50 ml of dimethylformamide. After the sodium hydride has been consumed,

40 ml of methyl iodide are added to the mixture, which is allowed to stand overnight at room temperature. The mixture is then treated with water and the solid material obtained is separated off and dried in the air in order to remove the excess methyl iodide. The solid material is washed with water, dried and recrystallised from ethanol. This gives diethyl 1,3,5-trimethylpyrrole-2,4-dicarboxylate.

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A solution of 13.9 g of the last-mentioned compound in 30 ml of acetonitrile and 30 ml of dimethylformamide is added, with stirring, to a suspension prepared from 5.5 g of 50% strength sodium hydride in mineral oil (washed with petroleum ether) and suspending (sic) in 60 ml of dimethylformamide. The mixture is heated on a steam bath for 15 minutes, and the resulting solution is allowed to stand overnight. The mixture is then treated with water, and the aqueous solution is filtered and acidified with 5-normal hydrochloric acid. The precipitate is separated off, washed with water, triturated with ethanol and recrystallised from ethanol. This gives 1,3,5-trimethyl-4-ethoxycarbonyl- β -oxo-2-pyrrolepropionitrile, melting at 105-107°.

Example 17

A solution of 0.3 g of 5-(1-methyl-2-pyrrolyl)-4-phenylcarbamoyleisoxazole in 10 ml of 5% strength aqueous sodium hydroxide solution and the minimum amount of ethanol is heated on a steam bath for 5 minutes. The solution is then filtered and acidified with 5-normal hydrochloric acid. The resulting crystals are separated off, washed with water and triturated with methanol. This gives 1-methyl- β -oxo- α -phenylcarbamoyle-2-pyrrolepropionitrile, melting at 170-172°. The product is identical with that of Examples 1, 6, 9 or 10.

The starting material is prepared as follows: 28 g of anhydrous aluminium chloride are added in portions, with stirring and cooling at 10-15°, to a solution of 17 g of 1-methylpyrrole in 400 ml of 1,2-dichloroethane. 27 g of malonic acid ethyl ester-chloride in 50 ml of dichloroethane are then added in such portions that the temperature remains between 10 and 15°. The mixture is stirred for 3.5 hours,

and its temperature is then allowed to rise slowly to 32°. The reaction mixture is allowed to stand overnight at room temperature, treated with water and extracted by shaking. The organic layer is separated off, washed twice with water, dried and evaporated. The dark brown oil obtained as the residue is distilled, and the fraction boiling at 105-112° / 0.25 mm Hg is collected. This gives ethyl 1-methyl- β -oxo-2-pyrrolepropionate.

A mixture of 3.6 g of the last-mentioned compound and 3.9 g of N,N'-diphenylformamidine is heated at 145-165° for 2.5 hours. The resulting brittle, glassy mass is pulverised, triturated with diethyl ether and recrystallised from ethanol/ethyl acetate. This gives 1-methyl- β -oxo- α -anilinomethylene-2-pyrrolepropionanilide, melting at 178-180°.

A mixture of 1.4 g of the last-mentioned compound, 1.1 g of hydroxylamine hydrochloride, 1.2 g of pyridine and 150 ml of ethanol is boiled under reflux for 7 hours. The reaction mixture is allowed to stand overnight, is filtered and evaporated, and the residue is treated with water. After standing, the resulting orange-coloured oil becomes crystalline. The precipitate is separated off, washed with water and recrystallised from ethanol. This gives 5-(1-methyl-2-pyrrolyl)-4-phenylcarbamoylisoxazole, melting at 100-103°.

Example 18

0.75 g of phenyl isocyanate is added, with stirring, to a suspension of 1 g of 1,3,5-trimethyl- β -oxo-2-pyrrolepropionitrile in 30 ml of dry toluene and 0.7 g of anhydrous triethylamine. The mixture is heated for 5 minutes on a steam bath and is allowed to stand overnight at room temperature. The mixture is filtered, the residue is taken up in methanol, and the solution is acidified with 1-normal hydrochloric acid. The resulting precipitate is separated off, dissolved in 1-normal aqueous sodium hydroxide solution, reprecipitated with 5-normal hydrochloric acid and washed with water. This gives 1,3,5-trimethyl- β -oxo- α -phenylcarbamoyl-2-pyrrolepropionitrile, melting at 172-174°.

The starting material is prepared as follows: a

mixture of 11.9 g of diethyl 1,3,5-trimethylpyrrole-2,4-dicarboxylate and 50 ml of concentrated sulphuric acid is heated on a steam bath for one hour. The resulting solution is poured onto ice, and the precipitate is separated off and washed with water. It is then taken up in aqueous sodium carbonate solution, the solution is filtered and the filtrate is acidified with 5-normal hydrochloric acid. The resulting precipitate is separated off, washed with water, dried and recrystallised from ethanol. This gives 1,3,5-trimethyl-2-carboethoxypyrrole-4-carboxylic acid, melting with decomposition at 197-198°.

7.5 g of the last-mentioned compound are heated under reflux at 235-240° for 15 minutes and are then cooled. The residue is taken up in petroleum ether, and the solution is filtered and evaporated. This gives ethyl 1,3,5-trimethylpyrrole-2-carboxylate, melting at 38-40°. (The product is described in US Patent 2,479,972 as having a boiling point of 102-108°/3-4 mm Hg).

A solution of 4 g of the last-mentioned compound in 10 ml of acetonitrile is added, with stirring, to a suspension prepared from 2 g of 50% strength sodium hydride in mineral oil (washed with petroleum ether) and suspending (sic) in 15 ml of dimethylformamide. The mixture is heated on a waterbath for 25 minutes and is allowed to stand for 3 hours at room temperature. Water is added to the mixture, and the aqueous solution is extracted with diethyl ether and acidified with 5-normal hydrochloric acid. The crystals are separated off, washed with water, dried and recrystallised from ethanol to which active charcoal has been added. This gives 1,3,5-trimethyl- β -oxo-2-pyrrolepropionitrile, melting at 106-107°.

1,3,5-Trimethyl- β -oxo- α -(p-fluorophenylcarbamoyl)-2-pyrrolepropionitrile, which, after recrystallisation from 1:1 methanol/ethanol, melts at 184-186°, is also obtained analogously.

Example 19

A suspension of 1 g of 1,2,5-trimethyl- β -oxo-3-

pyrrolepropionitrile in 40 ml of toluene and 0.7 g of triethylamine is treated with 0.75 g of phenyl isocyanate and is heated on a waterbath for 5 minutes, until the solid material has dissolved. The mixture is allowed to stand overnight, the resulting precipitate is separated off and taken up in methanol, and the solution is added to a mixture of 3 ml of 5-normal hydrochloric acid and 250 ml of water. The crude product is separated off, washed with water and dissolved in 5% strength aqueous sodium hydroxide solution, the solution is filtered and the alkaline filtrate is acidified with 5-normal hydrochloric acid. The precipitate is separated off, washed with water, dried in the air and recrystallised from ethanol. This gives 1,2,5-trimethyl- β -oxo- α -phenylcarbamoyl-3-pyrrolepropionitrile, melting at 158-160°.

Crude 1,2,5-trimethyl- β -oxo- α -(p-fluorophenylcarbamoyl)-3-pyrrolepropionitrile is also obtained analogously. It is dissolved in aqueous sodium bicarbonate solution, precipitated with 5-normal hydrochloric acid and recrystallised from ethanol. Melting point 171-172°.

The starting material is prepared as follows: a solution of 7.6 g of ethyl 1,2,5-trimethylpyrrole-3-carboxylate [Ber. 56, 2374 (1923), melting point after recrystallisation from methanol 65-66°] in 20 ml of acetonitrile is added to a suspension of 4 g of 50% strength sodium hydride in mineral oil and 11 ml of dimethylformamide. The mixture is heated on a steam bath for 20 minutes, with stirring, and the resulting suspension is allowed to cool to room temperature in the course of 90 minutes. The suspension is poured into 200 ml of ice water, the alkaline aqueous solution is filtered and the filtrate is acidified with 18% strength hydrochloric acid, with cooling by ice. The precipitate is separated off, washed with water, dried in the air, triturated with diethyl ether and recrystallised from methanol. This gives 1,2,5-trimethyl- β -oxo-3-pyrrolepropionitrile, melting at 140-141°.

Example 20

Starting from equivalent amounts of corresponding

starting materials, the following compounds of the formula II wherein $R_2 = R_3 = H$ are also prepared in accordance with the processes of the preceding examples, in particular in accordance with Examples 1, 4, 8 and 10:

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No.	R_1	R_4	R_5	Recrystallised from	M.p., °C
1	CH ₃	2-CH ₃	6-CH ₃	Ethanol	170-171
2	CH ₃	3-F	H	Ethyl acetate	191-192
3	CH ₃	3-Cl	H	Ethyl acetate	192-193
4	CH ₃	4-Cl	H	Ethyl acetate	205-207
5	CH ₃	3-CF ₃	H	Methanol	185-186
6	CH ₃	2-F	4-F	Methanol	136-138
7	CH ₃	4-F	3-Cl	Ethyl acetate	215-216
8	CH ₃	2-Cl	4-Cl	Ethyl acetate	160-162
9	CH ₃	3-Cl	4-Cl	Dimethylformamide	217-219
10	Benzyl	4-F	H	Ethyl acetate	188-189
11	Benzyl	4-F	H	Ethyl acetate	203-204
12	C ₂ H ₅	4-F	H	Methanol	156-157
13	C ₂ H ₅	4-Cl	H	Ethanol	160-161
14	i-Butyl	4-F	H	Methanol	162-163

Example 21

Preparation of 10,000 tablets each containing 100 mg of active substance:

Ingredients:

Trishydroxyethylammonium-1-methyl- β -oxo- α -phenylcarbamoyl-2-pyrrolepropionitrile	1000 g
Lactose	2535 g
Maize starch	125 g
Polyethylene glycol 6000	150 g
Talc powder	150 g
Magnesium stearate	40 g
Purified water	q.s.

Process:

All the pulverulent ingredients are sieved using a sieve of 0.6 mm mesh width. The active compound is then mixed with the lactose, the talc, the magnesium stearate and half of the starch in a suitable mixer. The other half of

the starch is suspended in 65 ml of water, and the suspension is added to a boiling solution of polyethylene glycol in 260 ml of water. The resulting paste is added to the powders, and the mixture is granulated, if necessary with the addition of a further amount of water. The granules are dried overnight at 35°, forced through a sieve of 1.2 mm mesh width and compressed to give tablets of 10.3 mm diameter, having a breaking groove.

Tablets containing another compound illustrated in the preceding examples are prepared analogously.

Example 22

Preparation of 1000 capsules each containing 25 mg of active substance:

Process (sic) :

1-Methyl- β -oxo- α -(p-fluorophenyl-carbamoyl)-2-pyrrolepropionitrile	25 g
Lactose	207 g
Maize starch	80 g
Magnesium stearate	3 g

Process:

All the pulverulent ingredients are sieved using a sieve of 0.6 mm mesh width. The active compound is then homogenised in a suitable mixer, first with the magnesium stearate and subsequently with the lactose and the starch. No. 2 capsules are filled with 315 mg of the mixture in each case, using a filling machine.

Capsules containing 25-100 mg of other compounds mentioned and illustrated, in particular those of the formula II, or of alkali metal, zinc, tri-lower alkylammonium or trishydroxyethylammonium salts thereof, are prepared analogously.



Patent Claims for the contracting States: BE CH DE FR GB
IT LI LU NL SE

1. Substituted β -oxo- α -phenylcarbamoylpyrrolepropionitriles of the general formula I

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wherein PI denotes a 2-pyrrolyl or 3-pyrrolyl radical which is substituted in the 1-position by C_1-C_7 -alkyl or $\text{Ph}-\text{C}_1-\text{C}_7$ -alkyl and in the remaining three positions is unsubstituted or substituted by one to three identical or different C_1-C_7 -alkyl groups and/or a carboxyl or carbo- C_1-C_7 -alkoxy group; and Ph denotes phenyl which is unsubstituted or substituted by one to three identical or different substituents belonging to the group C_1-C_7 -alkyl, C_1-C_7 -alkoxy, C_1-C_7 -alkylthio, hydroxyl, halogen, trifluoromethyl, nitro, amino or C_1-C_7 -alkanoylamino; these compounds in their enol form, enol C_1-C_7 -alkyl ethers or enol C_1-C_7 -alkanoyl esters thereof or salts thereof with bases.

2. Compounds according to claim 1, formula I wherein PI denotes 1-(C_1-C_7 -alkyl or $\text{Ph}-\text{C}_1-\text{C}_7$ -alkyl)-2-pyrrolyl or 1-(C_1-C_7 -alkyl or $\text{Ph}-\text{C}_1-\text{C}_7$ -alkyl)-3-pyrrolyl which, in the remaining positions, is unsubstituted or substituted by one or two C_1-C_7 -alkyl groups or a carboxyl or carbo- C_1-C_7 -alkoxy group, and Ph represents phenyl which is unsubstituted or substituted by one or two identical or different substituents belonging to the group C_1-C_7 -alkyl, C_1-C_7 -alkoxy, C_1-C_7 -alkylthio, hydroxyl, halogen, trifluoromethyl, nitro, amino and C_1-C_7 -alkanoylamino, enol- C_1-C_7 -alkyl ethers or enol C_1-C_7 -alkanoyl esters thereof or salts thereof with bases.

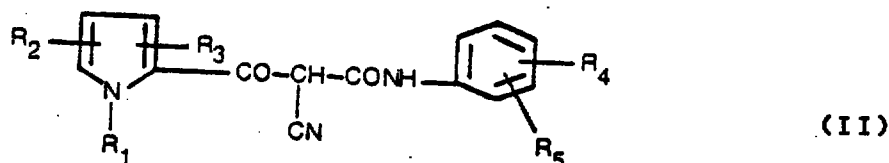
3. Compounds according to claim 1, formula I wherein PI denotes a 2-pyrrolyl or 3-pyrrolyl radical which is substituted in the 1-position by C_1-C_7 -alkyl or $\text{Ph}-\text{C}_1-\text{C}_7$ -alkyl and, in the remaining three positions, is unsubstituted or substituted by one to three identical or different C_1-C_7 -alkyl groups; and Ph denotes phenyl which is unsubstituted



or substituted by one to three identical or different substituents belonging to the group C_1-C_7 -alkyl, C_1-C_7 -alkoxy, C_1-C_7 -alkylthio, hydroxyl, halogen, trifluoromethyl, nitro or amino, enol C_1-C_7 -alkyl ethers thereof or salts thereof with bases.

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4. Compounds according to claim 1, which correspond to the general formula II



wherein R_1 denotes C_1-C_7 -alkyl, each of the symbols R_2 and R_3 represents hydrogen or C_1-C_7 -alkyl and each of the symbols R_4 and R_5 denotes hydrogen, C_1-C_7 -alkyl, C_1-C_7 -alkoxy, hydroxyl, halogen or trifluoromethyl, or salts thereof with bases.

5. Compounds according to claim 1, which correspond to the formula II illustrated in claim 4 wherein R_1 denotes alkyl having not more than 4 carbon atoms, each of the symbols R_2 and R_3 represents hydrogen and each of the symbols R_4 and R_5 denotes hydrogen, alkyl or alkoxy, in each case having not more than 4 carbon atoms, fluorine, chlorine or trifluoromethyl, or salts thereof with bases.

6. Compounds according to claim 1, which correspond to the formula II illustrated in claim 4 wherein R_1 denotes methyl, each of the symbols R_2 and R_3 represents hydrogen and each of the symbols R_4 and R_5 denotes hydrogen, methyl, methoxy, fluorine, chlorine or trifluoromethyl, or salts thereof with bases.

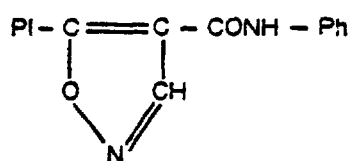
7. 1-Methyl- β -oxo- α -phenylcarbamoyl-2-pyrrolepropionitrile and salts thereof with bases.

8. 1-Methyl- β -oxo- α -(p-fluorophenylcarbamoyl)-2-pyrrolepropionitrile and salts thereof with bases.

9. Compounds according to claim 1 having an anti-inflammatory and anti-arthritic action.



10. Compounds according to claim 3 having an anti-inflammatory and anti-arthritic action.
11. Pharmaceutical formulations containing compounds according to one of claims 1, 2 and 9, only those of the salts which can be used therapeutically being suitable.
12. Pharmaceutical formulations containing compounds according to one of claims 3 to 8 and 10, only those of the salts which can be used therapeutically being suitable.
13. The use of compounds of claims 1, 2 and 9 for the preparation of pharmaceutical formulations.
14. The use of compounds of claims 3 to 8 and 10 for the preparation of pharmaceutical formulations.
15. The compounds of claims 1, 2 and 9 for use in a process for the therapeutical treatment of a human or animal body.
16. The compounds of claims 3 to 8 and 10 for use in a process for the therapeutical treatment of a human or animal body.
17. Process for the preparation of substituted β -oxo- α -phenylcarbamoylpyrrolepropionitriles defined in claim 1, characterised in that
 - a) compound (sic) of the formulae
$$\text{PL-CO-CH}_2\text{-CN and OC=N-Ph}$$
are subjected to an addition reaction, or
 - b) compounds of the formula
$$\begin{array}{c} \text{PL-CO-CH-COX} \\ | \\ \text{CN} \end{array}$$
and H-NH-Phwherein X denotes $\text{C}_1\text{-C}_7\text{-alkoxy}$, $\text{C}_1\text{-C}_7\text{-alkanoyloxy}$ or halogen are subjected to a condensation reaction, or
 - c) compounds of the formulae
$$\text{PL-Y and } \begin{array}{c} \text{CH}_2\text{-CONH-Ph} \\ | \\ \text{CN} \end{array}$$
wherein Y denotes $\text{C}_1\text{-C}_7\text{-alkoxycarbonyl}$, halogenocarbonyl or cyano are subjected to a condensation reaction and the resulting imines are hydrolysed, or
 - d) a compound of the formula



is isomerised by means of a strong base, and, if desired, a resulting compound of the formula I is converted into another compound of the invention, and/or, if desired, a resulting enol is converted into an enol $\text{C}_1\text{-C}_7$ -alkyl ether or enol $\text{C}_1\text{-C}_7$ -alkanoyl ester, and/or, if desired, a resulting enol is converted into a salt with a base or a resulting enol salt is converted into the free enol or into another salt with a base, and/or, if desired, a resulting mixture of isomers is separated into the individual isomers.

18. The compounds obtainable by the process of claim 17.



Patent claims for the contracting State: AT

1. Process for the preparation of substituted β -oxo- α -phenylcarbamoylpyrrolepropionitriles of the general formula I



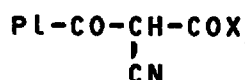
wherein Pl denotes a 2-pyrrolyl or 3-pyrrolyl radical which is substituted in the 1-position by $\text{C}_1\text{-C}_7\text{-alkyl}$ or $\text{Ph-C}_1\text{-C}_7\text{-alkyl}$ and in the remaining three positions is unsubstituted or substituted by one to three identical or different $\text{C}_1\text{-C}_7\text{-alkyl}$ groups and/or a carboxyl or carbo- $\text{C}_1\text{-C}_7\text{-alkoxy}$ group; and Ph denotes phenyl which is unsubstituted or substituted by one to three identical or different substituents belonging to the group $\text{C}_1\text{-C}_7\text{-alkyl}$, $\text{C}_1\text{-C}_7\text{-alkoxy}$, $\text{C}_1\text{-C}_7\text{-alkylthio}$, hydroxyl, halogen, trifluoromethyl, nitro amino or $\text{C}_1\text{-C}_7\text{-alkanoylamino}$; of these compounds in their enol form, enol $\text{C}_1\text{-C}_7\text{-alkyl}$ ethers or enol $\text{C}_1\text{-C}_7\text{-alkanoyl}$ esters thereof or salts thereof with bases, characterised in that

a) compounds of the formulae



are subjected to an addition reaction, or

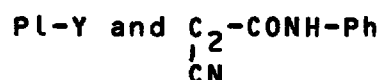
b) compounds of the formulae



and H-NH-Ph

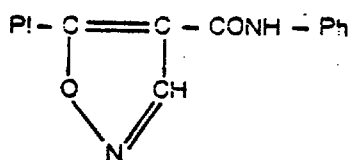
wherein X denotes $\text{C}_1\text{-C}_7\text{-alkoxy}$, $\text{C}_1\text{-C}_7\text{-alkanoyloxy}$ or halogen are subjected to a condensation reaction, or

c) compounds of the formulae



wherein Y denotes $\text{C}_1\text{-C}_7\text{-alkoxycarbonyl}$, halogenocarbonyl or cyano are subjected to a condensation reaction and the resulting imines are hydrolysed, or

d) a compound of the formula



is isomerised by means of a strong base, and, if desired, a resulting compound of the formula I is converted into another compound of the invention, and/or, if desired, a resulting enol is converted into an enol $\text{C}_1\text{-C}_7$ -alkyl ether or enol $\text{C}_1\text{-C}_7$ -alkanoyl ester, and/or, if desired, a resulting enol is converted into a salt with a base or a resulting enol salt is converted into the free enol or into another salt with a base, and/or, if desired, a resulting mixture of isomers is separated into the individual isomers.

2. Process according to claim 1, characterised in that the reaction a) is carried out in the presence of a base or at an elevated temperature.

3. Process according to claim 1, characterised in that the reaction b) is carried out at an elevated temperature.

4. Process according to claim 1, characterised in that the reaction c) is carried out in the presence of an alkali metal alkoxide or hydride.

5. Process according to claim 1, characterised in that the reaction d) is carried out in the presence of a strong inorganic or organic base.

6. Process according to claim 1, characterised in that, in a resulting compound containing a nitro group as a substituent in the radical Ph, this group is reduced to the amino group.

7. Process according to one of claims 1 to 6, characterised in that, in a resulting compound containing the amino group as a substituent in the radical Ph, this group is acylated to give a $\text{C}_1\text{-C}_7$ -alkanoyl amino group.

8. Process according to one of claims 1 to 7, characterised in that compounds of the formula I illustrated in claim 1 wherein Pl denotes 1-($\text{C}_1\text{-C}_7$ -alkyl or Ph- $\text{C}_1\text{-C}_7$ -alkyl)-2-pyrrolyl or 1-($\text{C}_1\text{-C}_7$ -alkyl or Ph- $\text{C}_1\text{-C}_7$ -alkyl)-3-pyrrolyl



which in the remaining positions is unsubstituted or substituted by one or two C_1-C_7 -alkyl groups or a carboxyl or carbo- C_1-C_7 -alkoxy group, and Ph represents phenyl which is unsubstituted or substituted by one or two identical or different substituents belonging to the group C_1-C_7 -alkyl, C_1-C_7 -alkoxy, C_1-C_7 -alkylthio, hydroxyl, halogen, trifluoromethyl, nitro, amino and C_1-C_7 -alkanoylamino, enol C_1-C_7 -alkyl ethers or enol C_1-C_7 -alkanoyl esters thereof or salts thereof with bases are prepared.

9. Process according to claim 1 for the preparation of new substituted β -oxo- α -phenylcarbamoylpyrrolepropionitriles of the formula I illustrated in claim 1, wherein Pl denotes a 2-pyrrolyl or 3-pyrrolyl radical which is substituted in the 1-position by C_1-C_7 -alkyl or Ph- C_1-C_7 -alkyl and, in the remaining three positions, is unsubstituted or substituted by one to three identical or different C_1-C_7 -alkyl groups; and Ph denotes phenyl which is unsubstituted or substituted by one to three identical or different substituents belonging to the group C_1-C_7 -alkyl, C_1-C_7 -alkoxy, C_1-C_7 -alkylthio, hydroxyl, halogen, trifluoromethyl, nitro or amino; enol C_1-C_7 -alkyl ethers thereof or salts thereof with bases, characterised in that

- a) starting materials of the formulae indicated in claim 1 are subjected to an addition reaction, or
- b) starting materials of the formulae indicated in claim 1 are subjected to a condensation reaction or
- c) starting materials of the formulae indicated in claim 1 are subjected to a condensation reaction and the resulting imines are hydrolysed, or
- d) compounds of the formula indicated in claim 1 are isomerised by means of a strong base, and, if desired, a resulting compound of the formula I is converted into another compound of the invention, and/or, if desired, a resulting enol is converted into an enol C_1-C_7 -alkyl ether, and/or, if desired, a resulting enol is converted into a salt with a base or a resulting enol salt is converted into the free

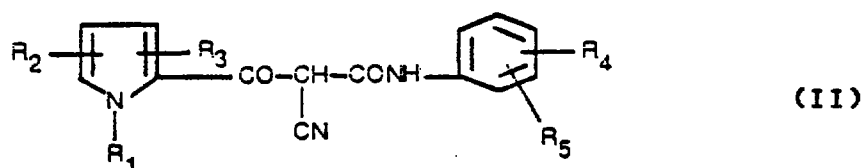


enol or into another salt with a base, and/or, if desired, a resulting mixture of isomers is separated into the individual isomers.

10. Process according to claim 9, characterised in that the reactions a), b), c) and d) are carried out in accordance with claims 2, 3, 4 and 5, respectively.

11. Process according to one of claims 9 and 10, characterised in that, in a resulting compound containing a nitro group as a substituent in the radical Ph, this group is reduced to the amino group.

12. Process according to one of claims 9 and 10, characterised in that compounds of the general formula II



wherein R_1 denotes C_1 - C_7 -alkyl, each of the symbols R_2 and R_3 represents hydrogen or C_1 - C_7 -alkyl and each of the symbols R_4 and R_5 denotes hydrogen, C_1 - C_7 -alkyl, C_1 - C_7 -alkoxy, hydroxyl, halogen or trifluoromethyl, or salts thereof with bases, are prepared.

13. Process according to one of claims 9 and 10, characterised in that compounds of the formula II illustrated in claim 12 wherein R_1 denotes alkyl having not more than 4 carbon atoms, each of the symbols R_2 and R_3 represents hydrogen and each of the symbols R_4 and R_5 denotes hydrogen, alkyl or alkoxy each of which has not more than 4 carbon atoms, fluorine, chlorine or trifluoromethyl, or salts thereof with bases, are prepared.

14. Process according to one of claims 9 and 10, characterised in that compounds of the formula II illustrated in claim 12 wherein R_1 denotes methyl, each of the symbols R_2 and R_3 represents hydrogen and each of the symbols R_4 and R_5 denotes hydrogen, methyl, methoxy, fluorine, chlorine or trifluoromethyl, or salts thereof with bases, are prepared.

15. Process according to one of claims 9 and 10,



- 38 -

characterised in that 1-methyl- β -oxo- α -(phenylcarbamoyl)-2-pyrrolepropionitrile and salts thereof with bases are prepared.

16. Process according to one of claims 9 and 10, characterised in that 1-methyl- β -oxo- α -(p-fluorophenylcarbamoyl)-2-pyrrolepropionitrile and salts thereof with bases are prepared.

17. Process for the preparation of a pharmaceutical formulation, characterised in that an active compound, according to the invention, according to one of claims 1 to 8, is processed together with a pharmaceutical excipient.

18. Process for the preparation of a pharmaceutical formulation, characterised in that an active compound, according to the invention, according to one of claims 9 to 16, is processed together with a pharmaceutical excipient.



Claims for the Contracting States: DE GB FR CH LI IT NL BE SE LU (as printed)

1. A substituted β -oxo- α -phenylcarbamoylpyrrolepropionitrile of the general formula I

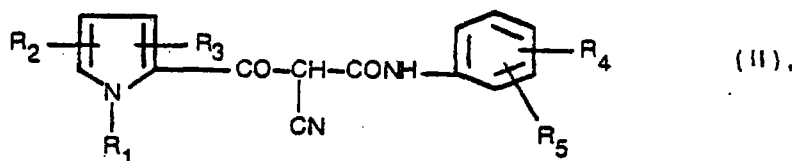


wherein PI is 2- or 3-pyrrolyl substituted in the 1-position by C_1-C_7 alkyl or $\text{Ph}-\text{C}_1-\text{C}_7$ alkyl, and unsubstituted in the remaining 3 positions or substituted therein by one to three identical or different C_1-C_7 alkyl groups and/or by one carboxy or C_1-C_7 carbalkoxy group; and Ph is phenyl which is unsubstituted or substituted by one to three identical or different members selected from C_1-C_7 alkyl, C_1-C_7 alkoxy, C_1-C_7 alkylthio, hydroxy, halogen, trifluoromethyl, nitro, amino or C_1-C_7 alkanoylamino; this compound in its enol form, a C_1-C_7 alkyl enol ether or a C_1-C_7 alkanoyl enol ester thereof, or a salt thereof with a base.

2. A compound according to claim 1 of the formula I, wherein PI is 1-(C_1-C_7 alkyl or $\text{Ph}-\text{C}_1-\text{C}_7$ alkyl)-2- or -3-pyrrolyl which is unsubstituted in the remaining positions or substituted therein by one or two C_1-C_7 alkyl groups, or by one carboxy or C_1-C_7 carbalkoxy group; Ph is phenyl or phenyl which is substituted by one or two identical or different members selected from C_1-C_7 alkyl, C_1-C_7 alkoxy, C_1-C_7 alkylthio, hydroxy, halogen, trifluoromethyl, nitro, amino and C_1-C_7 alkanoylamino; or a C_1-C_7 alkyl enol ether or a C_1-C_7 alkanoyl enol ester thereof, or a salt thereof with a base.

3. A compound according to claim 1 of the formula I, wherein PI is 2- or 3-pyrrolyl substituted in the 1-position by C_1-C_7 alkyl or $\text{Ph}-\text{C}_1-\text{C}_7$ alkyl, and unsubstituted in the remaining 3 positions or substituted therein by one to three identical or different C_1-C_7 alkyl groups; and Ph is phenyl which is unsubstituted or substituted by one to three identical or different members selected from C_1-C_7 alkyl, C_1-C_7 alkoxy, C_1-C_7 alkylthio, hydroxy, halogen, trifluoromethyl, nitro or amino; or a C_1-C_7 alkyl enol ether thereof, or a salt thereof with a base.

4. A compound according to claim 1 of the general formula II



wherein R_1 is C_1-C_7 alkyl; each of R_2 and R_3 is hydrogen or C_1-C_7 alkyl; and each of R_4 and R_5 is hydrogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, hydroxy, halogen or trifluoromethyl; or a salt thereof with a base.

5. A compound according to claim 1 of the formula II as indicated in claim 4, wherein R_1 is alkyl of not more than 4 carbon atoms; each of R_2 and R_3 is hydrogen; and each of R_4 and R_5 is hydrogen, alkyl or alkoxy of not more than 4 carbon atoms each, fluoro, chloro or trifluoromethyl, or a salt thereof with a base.

6. A compound according to claim 1 of the formula II as indicated in claim 4, wherein R_1 is methyl; each of R_2 and R_3 is hydrogen; and each of R_4 and R_5 is hydrogen, methyl, methoxy, fluoro, chloro or trifluoromethyl, or a salt thereof with a base.

7. 1-Methyl- β -oxo- α -phenylcarbamoyl-2-pyrrolepropionitrile, or a salt thereof with a base.

8. 1-Methyl- β -oxo- α -(p-fluorophenylcarbamoyl)-2-pyrrolepropionitrile, or a salt thereof with a base.

9. A compound according to claim 1 having antiinflammatory and antiarthritic activity.

10. A compound according to claim 3 having antiinflammatory and antiarthritic activity.

11. A pharmaceutical composition containing a compound as claimed in any one of claims 1, 2 or 9, or a therapeutically acceptable salt thereof.

12. A pharmaceutical composition containing a compound as claimed in any one of claims 3 to 8 or 10, or a therapeutically acceptable salt thereof.

13. Use of a compound as claimed in any one of claims 1, 2 or 9 for the preparation of a pharmaceutical composition.

14. Use of a compound as claimed in any one of claims 3 to 8 or 10 for the preparation of a pharmaceutical composition.

15. Use of a compound as claimed in any one of claims 1, 2 or 9 in a therapeutic method of treating the human or animal body.

16. Use of a compound as claimed in any one of claims 3 to 8 or 10 in a therapeutic method of treating the human or animal body.

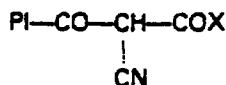
17. A process for the preparation of a substituted β -oxo- α -phenylcarbamoylpyrrolepropionitrile as defined in claim 1, which comprises

- a) adding compounds of formulae





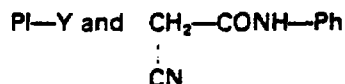
b) condensing compounds of the formulae



and $\text{R}-\text{NH}-\text{Ph}$,

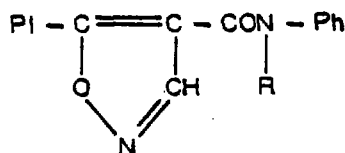
wherein X is C_1-C_7 alkoxy, C_1-C_7 alkanoyloxy or halogen, or

c) condensing compounds of formulae



wherein Y is C_1-C_7 alkoxycarbonyl, halocarbonyl or cyano and hydrolysing the resultant imines, or

d) isomerizing compounds of the formula



with a strong base and, if desired, converting a resultant compound of formula I into another compound of the invention, and/or, if desired, converting a resultant enol into a C_1-C_7 alkyl enol ether or a C_1-C_7 alkanoyl enol ester, and/or, if desired, converting a resultant enol into a salt with a base, or a resultant enol salt into the free enol or into another salt with a base, and/or, if desired, resolving a mixture of isomers obtained into the individual isomers.

18. A compound obtainable according to the process of claim 17.

Claims for the Contracting State: AT (as printed)

1. A process for the preparation of a substituted β -oxo- α -phenylcarbamoylpyrrolepropionitrile of the general formula I

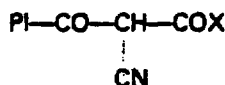


wherein PI is 2- or 3-pyrrolyl substituted in the 1-position by C_1-C_7 alkyl or $\text{Ph}-\text{C}_1-\text{C}_7$ alkyl, and unsubstituted in the remaining 3 positions or substituted therein by one to three identical or different C_1-C_7 alkyl groups and/or by one carboxy or C_1-C_7 carbalkoxy group; and Ph is phenyl which is unsubstituted or substituted by one to three identical or different members selected from C_1-C_7 alkyl, C_1-C_7 alkoxy, C_1-C_7 alkylthio, hydroxy, halogen, trifluoromethyl, nitro, amino or C_1-C_7 alkanoylamino; of this compound in its enol form, a C_1-C_7 alkyl enol ether or a C_1-C_7 alkanoyl enol ester thereof, or a salt thereof with a base, which process comprises

a) adding compounds of formulae



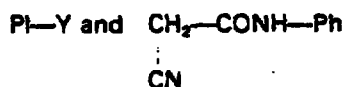
b) condensing compounds of the formulae



and $\text{R}-\text{NH}-\text{Ph}$,

wherein X is C_1-C_7 alkoxy, C_1-C_7 alkanoyloxy or halogen, or

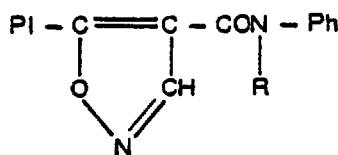
c) condensing compounds of formulae



wherein Y is C_1-C_7 alkoxycarbonyl, halocarbonyl or cyano and hydrolysing the resultant imines, or



d) isomerizing compounds of the formula



with a strong base and, if desired, converting a resultant compound of formula I into another compound of the invention, and/or, if desired, converting a resultant enol into a C₁-C₇alkyl enol ether or a C₁-C₇alkanoyl enol ester, and/or, if desired, converting a resultant enol into a salt with a base, or a resultant enol salt into the free enol or into another salt with a base, and/or, if desired, resolving a mixture of isomers obtained into the individual isomers.

2. A process according to claim 1, wherein the reaction a) is carried out in the presence of a base or at elevated temperature.

3. A process according to claim 1, wherein the reaction b) is carried out at elevated temperature.

4. A process according to claim 1, wherein the reaction c) is carried out in the presence of an alkali metal alkoxide or hydride.

5. A process according to claim 1, wherein the reaction d) is carried out in the presence of a strong inorganic or organic base.

6. A process according to claim 1, wherein in a resultant compound having a nitro group as substituent in the Ph radical, said group is reduced to the amino group.

7. A process according to any one of claims 1 to 6, wherein in a resultant compound having the amino group as substituent in the Ph radical, said group is acylated to a C₁-C₇alkanoylamino group.

8. A process according to any one of claims 1 to 7, which process comprises preparing a compound of the formula I as indicated in claim 1, wherein PI is a 1-(C₁-C₇alkyl or Ph-C₁-C₇alkyl)-2- or -3-pyrrolyl which is unsubstituted in the remaining positions or substituted therein by one or two C₁-C₇alkyl groups, or by one carboxy or C₁-C₇carbalkoxy group; Ph is phenyl or phenyl which is substituted by one or two identical or different members selected from C₁-C₇alkyl, C₁-C₇alkoxy, C₁-C₇alkylthio, hydroxy, halogen, trifluoromethyl, nitro, amino and C₁-C₇alkanoylamino; or a C₁-C₇alkyl enol ether or a C₁-C₇alkanoyl enol ester thereof, or a salt thereof with a base.

9. A process according to claim 1 for the preparation of a novel substituted β-oxo-α-phenylcarbamoyl-pyrrolepropionitrile of the formula I as indicated in claim 1, wherein PI is 2- or 3-pyrrolyl substituted in the 1-position by C₁-C₇alkyl or Ph-C₁-C₇alkyl, and unsubstituted in the remaining 3 positions or substituted therein by one to three identical or different C₁-C₇alkyl groups; and Ph is phenyl which is unsubstituted or substituted by one to three identical or different members selected from C₁-C₇alkyl, C₁-C₇alkoxy, C₁-C₇alkylthio, hydroxy, halogen, trifluoromethyl, nitro or amino; or a C₁-C₇alkyl enol ether thereof, or a salt thereof with a base, which process comprises

a) adding starting materials of the formulae as indicated in claim 1, or

b) condensing starting materials of the formulae as indicated in claim 1, or

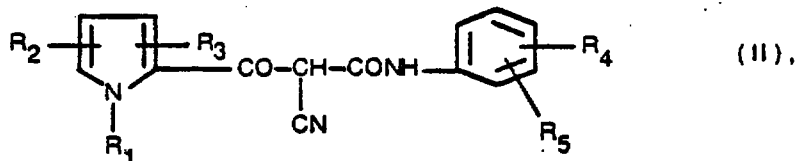
c) condensing starting materials of the formulae as indicated in claim 1 and hydrolysing the resultant imines, or

d) isomerizing compounds of the formula as indicated in claim 1 with a strong base and, if desired, converting a resultant compound of formula I into another compound of the invention, and/or, if desired, converting a resultant enol into a C₁-C₇alkyl enol ether, and/or, if desired, converting a resultant enol into a salt with a base, or a resultant enol salt into the free enol or into another salt with a base, and/or, if desired, resolving a mixture of isomers obtained into the individual isomers.

10. A process according to claim 9, wherein the reactions a), b), c) and d) are carried out in accordance with any one of claims 2, 3, 4 and 5.

11. A process according to either claim 9 or claim 10, wherein in a resultant compound having a nitro group as substituent in the Ph radical, said group is reduced to the amino group.

12. A process according to either claim 9 or claim 10, which process comprises preparing a compound of the general formula II



wherein R₁ is C₁-C₇alkyl; each of R₂ and R₃ is hydrogen or C₁-C₇alkyl; and each of R₄ and R₅ is hydrogen, C₁-C₇alkyl, C₁-C₇alkoxy, hydroxy, halogen or trifluoromethyl; or a salt thereof with a base.

13. A process according to either claim 9 or claim 10, which process comprises preparing a compound of formula II as indicated in claim 12, wherein R₁ is alkyl of not more than 4 carbon atoms; each of R₂ and R₃



is hydrogen; and each of R_4 and R_5 is hydrogen, alkyl or alkoxy of not more than 4 carbon atoms each, fluoro, chloro or trifluoromethyl, or a salt thereof with a base.

14. A process according to either claim 9 or claim 10, which process comprises preparing a compound of the formula II as indicated in claim 12, wherein R_1 is methyl; each of R_2 and R_3 is hydrogen; and each of R_4 and R_5 is hydrogen, methyl, methoxy, fluoro, chloro or trifluoromethyl, or a salt thereof with a base.

15. A process according to either claim 9 or claim 10, which process comprises preparing 1-methyl- β -oxo- α -phenylcarbamoyl-2-pyrrolepropionitrile, or a salt thereof with a base.

16. A process according to either claim 9 or claim 10, which process comprises preparing 1-methyl- β -oxo- α -(p-fluorophenylcarbamoyl)-2-pyrrolepropionitrile, or a salt thereof with a base.

17. A process for the preparation of a pharmaceutical composition, which process comprises combining a compound of the invention according to any one of claims 1 to 8 with a pharmaceutical carrier.

18. A process for the preparation of a pharmaceutical composition, which process comprises combining a compound of the invention according to any one of claims 9 to 16 with a pharmaceutical carrier.

Revendications pour les Etats contractants: DE GB FR CH LI IT NL BE SE LU (as printed)

1. Bêta-oxo-alpha-phénylcarbamoyl-pyrrolopropionitriles substituées de formule générale I

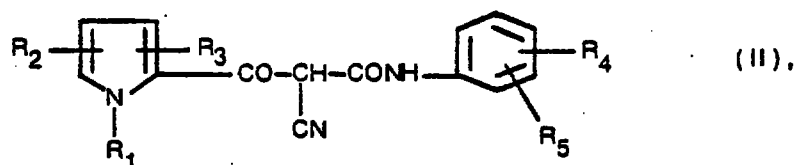


dans laquelle PI représente un reste 2- ou 3-pyrrolyle qui est substitué en position 1 par un groupe alkyle en C_1-C_7 , ou phényl-alkyle en C_1-C_7 , et est non substitué dans les trois autres positions ou est substitué par 1 à 3 groupes alkyle en C_1-C_7 , identiques ou différents et/ou un groupe carboxy ou carbo-alcoxy en C_1-C_7 ; et Ph représente le groupe phényle non substitué ou portant un à trois substituants identiques ou différents choisis parmi les groupes alkyle en C_1-C_7 , alkylthio en C_1-C_7 , hydroxy, les halogènes, les groupes trifluorométhyle, nitro, amino ou alcanoylamino en C_1-C_7 ; ces composés sous leur forme énol, leurs éthers alkaliqes en C_1-C_7 , 7 d'énols ou leurs esters alcanoyliques en C_1-C_7 , d'énols ou leurs sels de bases.

2. Composés selon la rev. 1, de formule I, dans laquelle PI représente un groupe 1-(alkyle en C_1-C_7 , ou Ph-alkyle en C_1-C_7)-2- ou -3-pyrrolyle non substitué dans les autres positions ou substitué par un ou deux groupes alkyle en C_1-C_7 , un ou groupe carboxy ou carboalcoxy en C_1-C_7 , Ph représente le groupe phényle non substitué ou portant un ou deux substituants identiques ou différents choisis parmi les groupes alkyle en C_1-C_7 , alcoxy en C_1-C_7 , alkylthio en C_1-C_7 , hydroxy, les halogènes, les groupes trifluorométhyle, nitro, amino et alcanoylamino en C_1-C_7 , leurs éthers alkylques en C_1-C_7 , d'énols ou leurs esters alcanoyliques en C_1-C_7 , d'énols ou leurs sels de bases.

3. Composés selon la rev. 1, de formule I dans laquelle PI représente un groupe 2- ou 3-pyrrolyle substitué en position 1 par un groupe alkyle en C_1-C_7 , ou Ph-alkyle en C_1-C_7 , et non substitué dans les trois autres positions ou portant un à trois substituants alkyle en C_1-C_7 , identiques ou différents; et Ph représente le groupe phényle non substitué ou portant un à trois substituants identiques ou différents choisis parmi les groupes alkyle en C_1-C_7 , alcoxy en C_1-C_7 , alkylthio en C_1-C_7 , hydroxy, les halogènes, les groupes trifluorométhyle, nitro ou amino, leurs éthers alkylques en C_1-C_7 , d'énols ou leurs sels de bases.

4. Composés selon la rev. 1 répondant à la formule générale II



dans laquelle R_1 représente un groupe alkyle en C_1-C_7 , chacun des symboles R_2 et R_3 représente l'hydrogène ou un groupe alkyle en C_1-C_7 , et chacun des symboles R_4 et R_5 représente l'hydrogène, un groupe alkyle en C_1-C_7 , alcoxy en C_1-C_7 , hydroxy, un halogène ou un groupe trifluorométhyle, ou leurs sels de bases.

5. Composés selon la revendication 1, répondant à la formule II de la rev. 4, dans laquelle R_1 représente un groupe alkyle à 4 atomes de carbone au maximum, chacun des symboles R_2 et R_3 représente l'hydrogène et chacun des symboles R_4 et R_5 représente l'hydrogène, un groupe alkyle ou alcoxy contenant chacun 4 atomes de carbone au maximum, le fluor, le chlore ou un groupe trifluorométhyle, ou leurs sels de bases.

6. Composés selon la rev. 1, répondant à la formule II de la rev. 4 dans laquelle R_1 représente un groupe méthyle, chacun des symboles R_2 et R_3 représente l'hydrogène et chacun des symboles R_4 et R_5 représente



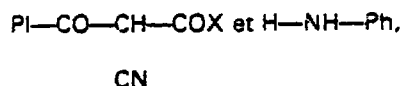
l'hydrogène, un groupe méthyle, méthoxy, le fluor, le chlore ou un groupe trifluorométhyle, ou leurs sels de bases.

7. Le 1-méthyl-bêta-oxo-alpha-phénylcarbamoyl-2-pyrrolopropionitrile et ses sels de bases.
8. Le 1-méthyl-bêta-oxo-alpha-(p-fluorophénylcarbamoyl)-2-pyrrolopropionitrile et ses sels de bases.
9. Composés à activité anti-inflammatoire et anti-arthritique selon la rev. 1.
10. Composés à activité anti-inflammatoire et anti-arthritique selon la rev. 3.
11. Compositions pharmaceutiques contenant des composés selon l'une des rev. 1, 2 et 9, les sels étant uniquement ceux qui conviennent pour l'usage pharmaceutique.
12. Compositions pharmaceutiques contenant des composés selon l'une des rev. 3 à 8 et 10, les sels étant uniquement ceux qui conviennent pour l'usage pharmaceutique.
13. Utilisation de composés selon les rev. 1, 2 et 9, pour la préparation de compositions pharmaceutiques.
14. Utilisation de composés selon les rev. 3 à 8 et 10, pour la préparation de compositions pharmaceutiques.
15. Les composés des rev. 1, 2 et 9, pour l'utilisation dans un procédé pour le traitement thérapeutique de l'organisme humain ou animal.
16. Les composés des rev. 3 à 8 et 10, pour l'utilisation dans un procédé pour le traitement thérapeutique de l'organisme humain ou animal.
17. Procédé de préparation des bêta-oxo-alpha-phénylcarbamoyl-pyrrolopropionitrile substitués définis dans la rev. 1, caractérisé en ce que:
 - a) on fixe par addition les composés de formule



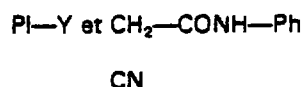
ou bien

b) on condense des composés de formules



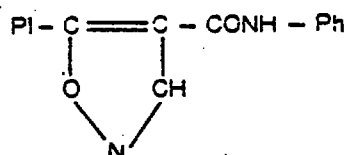
dans lesquelles X représente un groupe alcoxy en C_1-C_7 , alcanoyloxy en C_1-C_7 , ou un halogène, ou bien

c) on condense des composés de formules



dans lesquelles Y représente un groupe (alcoxy en C_1-C_7)-carbonyle, halogénocarbonyle ou cyano, et on hydrolyse les imines obtenues, ou bien

d) on isomérisé des composés de formule

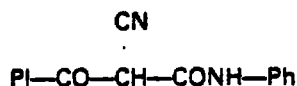


à l'aide d'une base forte, et si on le désire, on convertit un composé obtenu répondant à la formule I en un autre composé de l'invention et/ou, si on le désire, on convertit un émol obtenu en un éther alkyle en C_1-C_7 , d'émol ou un ester alcanoylique en C_1-C_7 , d'émol et/ou, si on le désire, on convertit un émol obtenu en un sel d'une base ou un sel d'émol obtenu en l'émol libre ou en un autre sel d'une base et/ou, si on le désire, on sépare un mélange d'isomères obtenu en les isomères individuels.

18. Les composés obtenus par le procédé de la rev. 17.

Revendications pour l'Etat contractant: AT (as printed)

1. Procédé de préparation de bêta-oxo-alpha-phénylcarbamoyl-pyrrolopropionitriles de formule générale I



(I),

dans laquelle PI représente un groupe 2- ou 3-pyrrolyle substitué en position 1 par un groupe alkyle en C_1-C_7 , ou Ph-alkyle en C_1-C_7 , et non substitué dans les trois autres positions ou substitué par un à trois

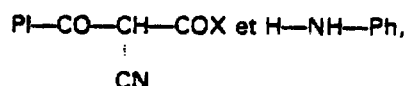


groupes alkyle en C_1-C_7 , identiques ou différents et/ou un groupe carboxy ou carbo-alcoxy en C_1-C_7 ; et Ph représente le groupe phényle non substitué ou portant un à trois substituants identiques ou différents choisis parmi les groupes alkyle en C_1-C_7 , alcoxy en C_1-C_7 , alkylthio en C_1-C_7 , hydroxy, les halogènes, les groupes trifluorométhyle, nitro, amino ou alcanoylamino en C_1-C_7 , de ces composés sous leur forme d'énols, de leurs éthers alkyls en C_1-C_7 , d'énols ou de leurs esters alcanoyliques en C_1-C_7 , d'énols ou de leurs sels de bases, caractérisé en ce que:

a) on fixe par addition les composés de formules

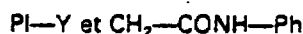


b) on condense les composés de formules



dans lesquelles X représente un groupe alcoxy en C_1-C_7 , alcanoyloxy en C_1-C_7 ou un halogène, ou bien

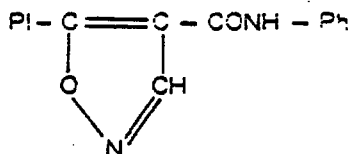
c) on condense les composés de formules



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dans lesquelles Y représente un groupe (alcoxy en C_1-C_7)-carbonyle, halogénocarbonyle ou cyano, et on hydrolyse les imines obtenues, ou bien

d) on isomérise les composés de formule



à l'aide d'une base forte, et si on le désire, on convertit un composé obtenu répondant à la formule I en un autre composé de l'invention et/ou, si on le désire, on convertit un énoï obtenu en un éther alkyls en C_1-C_7 , d'énol ou un ester alcanoyliques en C_1-C_7 , d'énol et/ou, si on le désire, on convertit un énoï obtenu en un sel d'une base ou un sel d'énol obtenu en l'énol libre ou en un autre sel de base et/ou, si on le désire, on sépare un mélange d'isomères obtenu en les isomères individuels.

2. Procédé selon la rev. 1, caractérisé en ce que la réaction a) est effectuée en présence d'une base ou à température élevée.

3. Procédé selon la rev. 1, caractérisé en ce que la réaction b) est effectuée à température élevée.

4. Procédé selon la rev. 1, caractérisé en ce que la réaction c) est effectuée en présence d'un alcoolate ou d'un hydrure de métal alcalin.

5. Procédé selon la revendication 1, caractérisé en ce que la réaction d) est effectuée en présence d'une base minérale ou organique forte.

6. Procédé selon la rev. 1, caractérisé en ce que dans un composé obtenu dans lequel le groupe Ph porte en tant que substituant un groupe nitro, on réduit ce groupe en groupe amino.

7. Procédé selon l'une des rev. 1 à 6, caractérisé en ce que, dans un composé obtenu dans lequel le groupe Ph porte en tant que substituant le groupe amino, on acyle ce groupe en un groupe alcanoylamino en C_1-C_7 .

8. Procédé selon l'une des rev. 1 à 7, caractérisé en ce que l'on prépare des composés de formule I de la rev. 1 dans laquelle PI représente un groupe 1-(alkyle en C_1-C_7 ou Ph-alkyle en C_1-C_7)-2 ou -3-pyrrolyle non substitué dans les autres positions ou substitué par un ou deux groupes alkyle en C_1-C_7 ou par un groupe carboxy ou carbo-alcoxy en C_1-C_7 , Ph représente le groupe phényle non substitué ou portant un ou deux substituants identiques ou différents choisis parmi les groupes alkyle en C_1-C_7 , alcoxy en C_1-C_7 , alkylthio en C_1-C_7 , hydroxy, les halogènes, les groupes trifluorométhyle, nitro, amino et alcanoylamino en C_1-C_7 , leurs éthers alkyls en C_1-C_7 , d'énols ou leurs esters alcanoyliques en C_1-C_7 , d'énols ou leurs sels de bases.

9. Procédé selon la rev. 1, pour la préparation des nouveaux bêta-oxo-alpha-phénylcarbonyl-pyrrolo-propionitriles substitués de formule I de la rev. 1 dans laquelle PI représente un groupe 2- ou 3-pyrrolyle substitué en position 1 par un groupe alkyle en C_1-C_7 ou Ph-alkyle en C_1-C_7 et non substitué dans les trois autres positions ou substitué par un à trois groupes alkyle en C_1-C_7 , identiques ou différents; et Ph représente le groupe phényle non substitué ou portant un à trois substituants identiques ou différents choisis parmi les groupes alkyle en C_1-C_7 , alcoxy en C_1-C_7 , alkylthio en C_1-C_7 , hydroxy, les halogènes,



les groupes trifluorométhyle, nitro ou amino; de leurs éthers alkyliques en C₁-C₇, d'énols ou de leurs sels de bases, caractérisés en ce que:

a) on fixe par addition des composés de départ répondant aux formules indiquées dans la rev. 1, ou bien

b) on condense des produits de départ répondant aux formules indiquées dans la rev. 1,

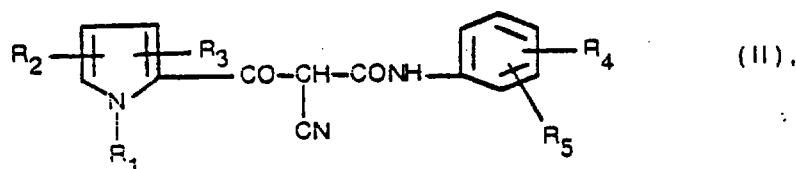
c) on condense des produits de départ répondant aux formules indiquées dans la rev. 1, et on hydrolyse les imines obtenues, ou bien

d) on isomérisé des composés répondant à la formule indiquée dans la rev. 1 à l'aide d'une base forte, et, si on le désire, on convertit un composé obtenu répondant à la formule I en un autre composé de l'invention et/ou, si on le désire, on convertit un émol obtenu en un éther alkylique en C₁-C₇, d'émol, et/ou, si on le désire, on convertit un émol obtenu en un sel de base ou un sel d'émol obtenu en l'émol libre ou en un autre sel de base, et/ou, si on le désire, on sépare un mélange d'isomères obtenu en les isomères individuels.

10. Procédé selon la rev. 9, caractérisé en ce que l'on effectue les réactions a), b), c) et d) selon les rev. respectives 2, 3, 4 et 5.

11. Procédé selon l'une des rev. 9 et 10, caractérisé en ce que, dans un composé obtenu dans lequel le groupe Ph porte en tant que substituant un groupe nitro, on réduit ce groupe en un groupe amino.

12. Procédé selon l'une des rev. 9 et 10, caractérisé en ce que l'on prépare les composé de formule générale II



dans laquelle R₁ représente un groupe alkyle en C₁-C₇, chacun des symboles R₂ et R₃ représente l'hydrogène ou un groupe alkyle en C₁-C₇ et chacun des symboles R₄ et R₅ représente l'hydrogène, un groupe alkyle en C₁-C₇, alcoxy en C₁-C₇, hydroxy, un halogène ou un groupe trifluorométhyle, ou leurs sels de bases.

13. Procédé selon l'une des rev. 9 et 10, caractérisé en ce que l'on prépare des composés de formule II de la rev. 12, dans laquelle R₁ représente un groupe alkyle à 4 atomes de carbone au maximum, chacun des symboles R₂ et R₃ représente l'hydrogène et chacun des symboles R₄ et R₅ l'hydrogène, un groupe alkyle ou alcoxy ayant chacun 4 atomes de carbone au maximum, le fluor, le chlore ou un groupe trifluorométhyle, ou leurs sels de bases.

14. Procédé selon l'une des rev. 9 et 10, caractérisé en ce que l'on prépare des composés de formule II de la rev. 12, dans laquelle R₁ représente un groupe méthyle, chacun des symboles R₂ et R₃ l'hydrogène et chacun des symboles R₄ et R₅ l'hydrogène, un groupe méthyle, méthoxy, le fluor, le chlore ou un groupe trifluorométhyle, ou leurs sels de bases.

15. Procédé selon l'une des rev. 9 et 10, caractérisé en ce que l'on prépare le 1-méthyl-béta-oxo-alpha-phénylcarbamoyl-2-pyrrolopropionitrile et ses sels de bases.

16. Procédé selon l'une des rev. 9 et 10, caractérisé en ce que l'on prépare le 1-méthyl-béta-oxo-alpha-(p-fluorophénylcarbamoyl)-2-pyrrolopropionitrile et ses sels de bases.

17. Procédé de préparation d'une composition pharmaceutique, caractérisé en ce que l'on utilise à cet effet une substance active selon l'invention selon l'une des rev. 1 à 8, et un véhicule pharmaceutique.

18. Procédé de préparation d'une composition pharmaceutique caractérisé en ce que l'on utilise à cet effet une substance active selon l'invention selon l'une des rev. 9 à 16, et un véhicule pharmaceutique.