Description

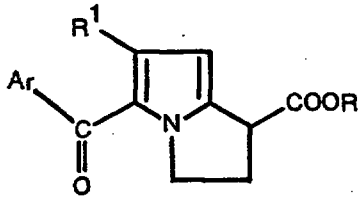
The present invention relates to a process for 5-aroylation of 1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic esters or nitriles. The aroylated esters or nitriles are then optionally converted to the corresponding acids or the pharmaceutically acceptable, non-toxic salts thereof which are useful as anti-inflammatory agents.

U.S. patents 4,087,539, 4,089,969, 4,232,038, 4,097,579 and 4,140,698; disclose a method for 5-aroylation of 1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic esters or nitriles to form first the corresponding 5-aroyl ester or nitrile, and then subsequent hydrolysis of that ester or nitrile to form the corresponding free carboxylic acids. In the method therein described, the aroyl moiety is supplied in the form of the dimethylamide, and the reaction is carried out in the presence of an inorganic acid halide and an inert solvent. The resulting intermediate complex is then hydrolyzed by base to the 5-aroyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic ester or nitrile; then stronger base or more vigorous conditions, followed by acidification, converts the ester or nitrile to acid. These previously disclosed processes have been unsatisfactory due to low yields and poor scalability.

Other methods of aroylation of the pyrrole nucleus, when not a part of the pyrrolopyrrole bicyclo system include reaction with an aroyl halide (U.S. 3,998,844) and with a 2-aryldithiolanium cation (U.S. 4,119,639). However, these methods suffer from the disadvantages of non-specificity as to the position aroylated and/or undue complexity and cost of reagent. In a manner more analogous to the previously described aroylation of pyrrolopyrroles using the aroyl dimethylamide, isolated pyrrole nuclei can be reasonably specifically aroylated using the corresponding aroyl morpholides, according to the description of White, J. and McGillivray, G.; *J. Org. Chem.* 42: 4247 (1977). Although these authors found that the morpholides were, in general, better reagents than the corresponding dimethylamides, they also found that alkyl (methyl) substitution at the ring nitrogen decreases the rate of reaction by a factor of 100 relative to the unsubstituted pyrrole when the morpholide is used. They attribute this decrease to steric factors related to the transition state. It is therefore implied that use of the morpholide would be disadvantageous for N-substituted pyrroles.

It is, therefore, quite surprising that substitution of the morpholide for the dimethylamide in the aroylation of the pyrrolopyrrole (which is, of course, substituted at the N-position of the pyrrole ring) enhances the rate of aroylation by a factor of approximately ten over the dimethylamide. The increase in rate is significant for reasons other than mere convenience because yields are enhanced in this process when reaction time is reduced. In addition, the morpholide reagent is intrinsically easier to handle than the dimethylamide.

According to the present invention there is provided a process for preparing a compound of the formula



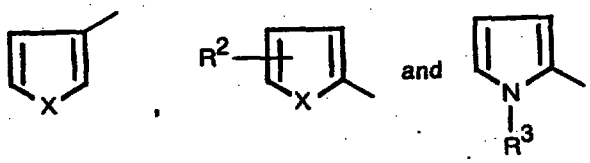
(III')

wherein

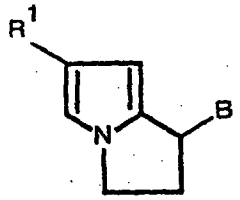
R is hydrogen or C_{1-6} alkyl;

R^1 is hydrogen or C_{1-6} alkyl; and

Ar is phenyl optionally substituted with one to three substituents selected from halogen, C_{1-6} alkyl or C_{1-6} alkoxy, or is selected from

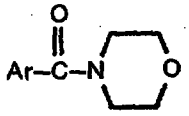


wherein X is O or S, R^2 is hydrogen, methyl, chloro or bromo; and R^3 is hydrogen or C_{1-6} alkyl; or the pharmaceutically acceptable salts thereof, which process comprises reacting a compound of the formula



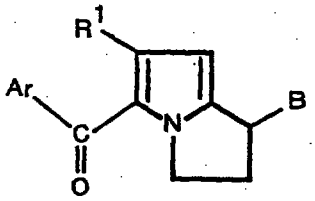
(I)

wherein B is —COOR or —CN and R^1 and R are as herein defined, with inorganic acid chloride and a compound of the formula



(A)

wherein Ar is as defined above, to afford a compound of formula VI



(VI)

wherein Ar, R^1 and B are as herein defined; optionally followed by conversion of the C_{1-6} alkyl ester of formula VI to a compound of formula III'; or followed by conversion of the nitrile of formula VI to a compound of formula III'; optionally followed by conversion of a salt of the compound of formula III' into the free acid by treatment with acid; or by conversion of a free acid of the compound of formula III' to a pharmaceutically acceptable salt by treatment with a pharmaceutically acceptable base.

Definitions

As used herein:

"Lower alkyl" means a saturated branched or unbranched hydrocarbon chain containing 1—6 carbons, such as for example, ethyl, n-hexyl, or t-butyl.

"Lower alkoxy" means —OR wherein R is lower alkyl as herein defined.

"Halogen" means fluoro, chloro, bromo or iodo.

"Weak base" means a substance, which, when dissolved in water at 1 molar concentration generates a pH between 7 and 9. Examples of such weak bases are sodium acetate, sodium bicarbonate, ammonia and primary amines.

"Strong base" means a substance which, when dissolved in water at 1 molar concentration, generates a pH of greater than 10. Examples of such strong bases are sodium hydroxide, potassium hydroxide and sodium carbonate.

"Optionally substituted" phenyl means substitution in ortho, meta or para positions by one to three substituents selected from halogen, lower alkyl or lower alkoxy.

"Polar solvent" means either water, or methanol, ethanol or propanol, or aqueous mixture of these alcohols.

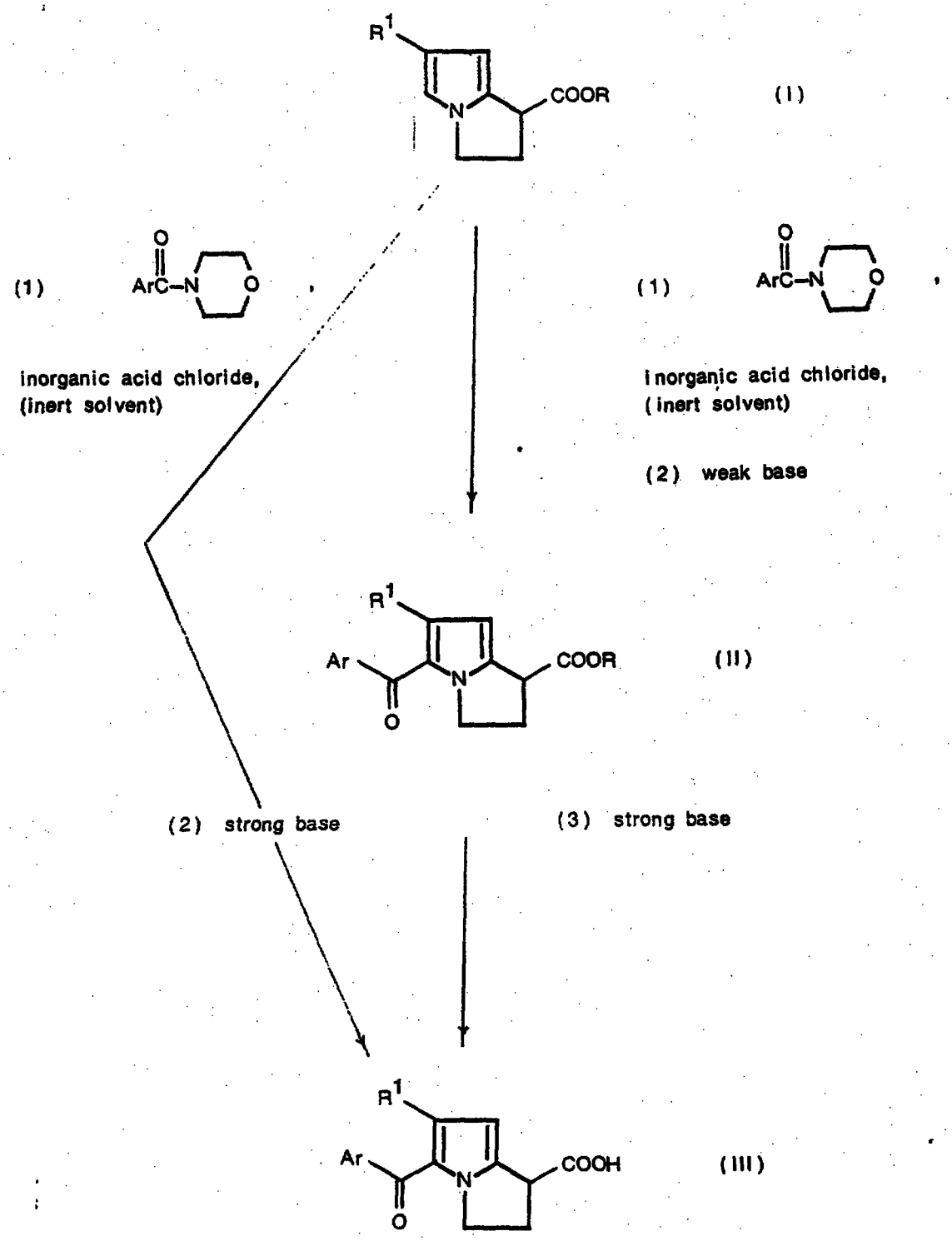
"Pharmaceutically acceptable, non-toxic salts" refers to salts derived from pharmaceutically acceptable, non-toxic inorganic and organic bases.

Salts derived from inorganic bases include sodium, potassium, lithium, ammonium, calcium, magnesium, ferrous, zinc, copper, manganous, aluminum, ferric and manganic salts. Particularly preferred are the ammonium, potassium, sodium, calcium and magnesium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, tromethamine, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, N-ethylpiperidine and polyamine resins. Particularly preferred organic non-toxic bases are isopropylamine, diethylamine, ethanolamine, tromethamine, dicyclohexylamine, choline and caffeine.

Typical Process

The reactions which comprise the three alternative processes of the present invention as it relates to the starting material of formula I are shown in the Reaction Scheme I below:

REACTION SCHEME I



The compound of formula I is in all cases treated first with the aroyl morpholide in the presence of an inorganic acid halide. The aroyl morpholide is prepared essentially by the method of White (supra) in which the appropriate aroyl halide is reacted with an approximately equimolar amount of morpholine in the presence of triethylamine.

The resulting aroyl morpholide is mixed with an inorganic acid halide, such as $POCl_3$, POBr or SO_2Cl_2; preferably $POCl_3$. The relative amounts are not critical. Optionally an inert organic solvent such as ethane dichloride, chloroform, or carbon tetrachloride, but preferably methylene dichloride, may be included in

this mixture. The presence of the solvent, however, is not particularly advantageous in all cases. The mixture is agitated, preferably stirred, for about 0.5—36 hours, preferably 1—5 hours at about 30—50°; preferably 40—45°.

A solution of the pyrrolopyrrole substrate of formula I in an inert solvent, most preferably CH_2Cl_2, is then added to the above mixture. Again the ratio of reactants is not critical, but it is preferable that the molar amount of the substrate be slightly less than the molar amount of the minority reactant in the prepared morpholide/halide mixture. The resulting reaction mixture is kept at 30—70°, preferably 40—45° until the desired reaction has taken place; usually 1—8 hours, most usually 1.5—3 hours.

The entire procedure to this point is carried out in an inert atmosphere in order to exclude water. Any anhydrous gas could be used, but nitrogen is the most convenient choice. As the reaction is scaled up, the problem of water in the ambient air becomes smaller because of less proportional available surface area. However, it has been found prudent to use nitrogen as a matter of routine.

The intermediate formed at this point cannot conveniently be isolated, but must be hydrolyzed either to the ester of formula II, or to the free acid of formula III.

If it is desired to prepare a compound of formula III, a single step procedure is preferred. In this embodiment, the reaction mixture is poured into a solution in polar solvent, preferably aqueous, of a strong base, such as a mineral hydroxide or carbonate, preferably sodium hydroxide. A large excess of the base is used. The mixture is then kept at 30°—100°, preferably 40—60° until reaction is complete.

Alternatively, if the two-step procedure is to be used, or a compound of formula II is to be prepared, an amount of from 3 to 10 molar equivalents of sodium acetate or other weak base may be added directly to the reaction mixture, followed by an additional reaction time of 4—6 hours during which the mixture is refluxed. At the end of this period, the compound of formula II is produced.

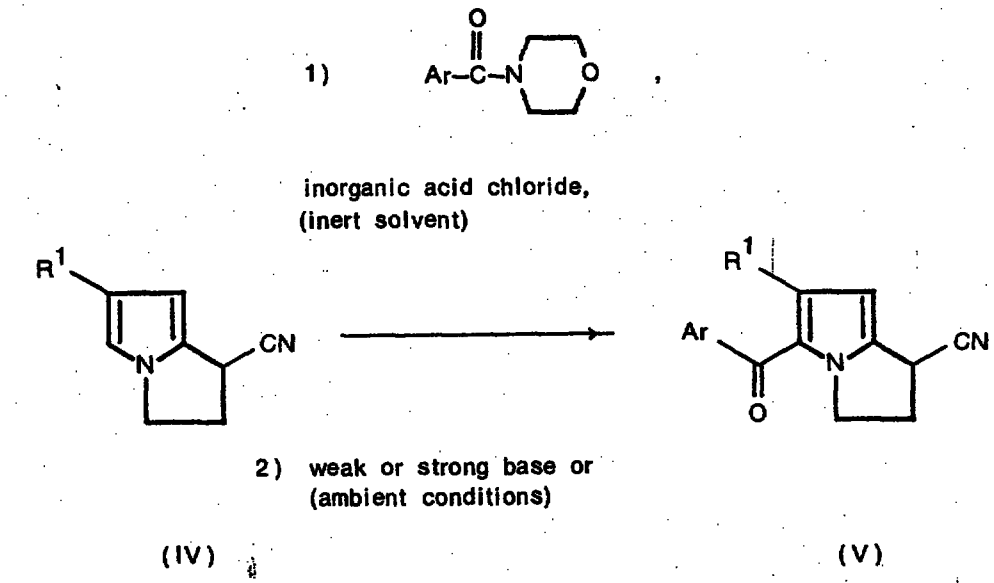
If subsequent conversion to the compound of formula III is desired, further hydrolysis is carried out in a conventional manner with an alkali metal hydroxide or carbonate in an aqueous or aqueous lower aliphatic alcohol (methanol, ethanol, etc.) solution. The temperature is about room temperature to reflux and the reaction time 15 minutes to 3 hours. Preferably, the hydrolysis is effected with aqueous methanolic potassium carbonate at reflux temperatures for about 30 minutes.

The compounds of formula II or III may be isolated by conventional means, such as extraction into volatile solvents, precipitation and filtration, crystallization or chromatography; or combinations of such procedures. For compounds of formula III, the isolation is best carried out by neutralizing with acid, e.g. with HCl, and then extracting the neutralized free acid form of the compound into a volatile solvent, e.g. CH_2Cl_2, with subsequent conventional treatment to isolate pure product.

The pharmaceutically acceptable non-toxic salt derivatives of the compounds of Formula I are prepared by treating the free acids with an appropriate amount of pharmaceutically acceptable base. Representative pharmaceutically acceptable bases are sodium hydroxide, potassium hydroxide, lithium hydroxide, ammonium hydroxide, calcium hydroxide, magnesium hydroxide, ferrous hydroxide, zinc hydroxide, copper hydroxide, maganous hydroxide, aluminum hydroxide, ferric hydroxide, manganic hydroxide, isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylgluycamine, theobromine, purines, piperazine, piperidine, N-ethylpiperidine and polyamine resins. The reaction is conducted in water, alone or in combination with an inert, water-miscible organic solvent, at a temperature of from 0°C to 100°C, preferably at room temperature. Typical inert, water-miscible organic solvents include methanol, ethanol, isopropanol, butanol, acetone, dioxane or tetrahydrofuran. The molar ratio of compounds of formula I to base used are chosen to provide the ratio desired for any particular salt. For preparing, for example, the calcium salts or magnesium salts the free acid starting material of formula I can be treated with at least one-half molar equivalent of pharmaceutically acceptable base to yield a neutral salt. When the aluminum salts of the compounds of formula I are prepared, at least one-third molar equivalent of the pharmaceutically acceptable base are employed if a neutral salt product is desired.

The salt derivatives of the compounds of formula I can be reconverted to their respective free acids by acidifying said salts with an acid, preferably an inorganic acid, e.g., hydrochloric acid or sulfuric acid, at temperature of from 0°C to 50°C, preferably at room temperature.

The reaction which comprises the process of the invention as it relates to the starting material of formula IV is shown in Reaction Scheme II:



(IV) (V)

Treatment with the aroyl morpholide and inorganic acid chloride is carried out as outlined hereinabove. The subsequent treatment with base is effected by mixing this reaction mixture with a solution of either weak or strong base dissolved in a polar solvent such as water, ethanol or methanol, preferably water. Preferred bases are sodium acetate or sodium carbonate. The reaction is carried out without heating, at ambient temperature, and proceeds rapidly to completion, within 1—10 minutes.

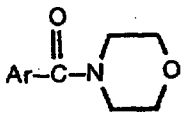
The resulting compound of formula V may be hydrolyzed to a compound of formula III by treatment with acid or base under more vigorous conditions. Procedures for this conversion are described in U.S. Patent 4,140,698 which is incorporated herein by reference.

Preferred Embodiments

In a preferred embodiment of the invention, $POCl_3$ and an aroyl morpholide in approximately equimolar ratio is used as the aroylating mixture. A preferred reaction temperature range is 40—45°.

The solvent of choice for the pyrrolopyrrole substrate is methylene chloride.

Preferred aroyl morpholides are those wherein Ar in the formula



(A)

is optionally substituted phenyl.

In a preferred embodiment of the hydrolysis procedure, to give a compound of formula III the reaction mixture containing inorganic acid halide, morpholide and substrate is added to an aqueous sodium hydroxide solution of 1—10 M.

Preferred compounds of formula I and IV for use in the invention are those wherein R^1 is methyl or hydrogen, and (for formula I) R is methyl.

The following examples are intended to illustrate the invention.

Example 1

Benzoylation of methyl 1,2-dihydro-3H-pyrrolo-[1,2-a]pyrrole-1-carboxylate with hydrolysis to the free acid.

A. Benzmorpholide (1.45 gm, 7.90 mmole), was placed in a 25 ml round bottom flask. $POCl_3$ (1.25 ml, 13.4 mmole) was added. This was stirred and heated in a 40° oil bath for 2.5 hours.

A solution of methyl 1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic ester (1.00 gm, 6.10 mmole) in 3.4 ml CH_2Cl_2 was added and heating was continued for 2 hours, at this time, thin layer chromatography (TLC) of the reaction mixture showed reaction to be complete.

The reaction mxiture was added carefully to a solution of NaOH (3.09 gm, 77.3 mmole) in 10 ml H_2O, allowing the CH_2Cl_2 to boil off, and the mixture heated to 50°. More NaOH (1.30 gm, 32.5 mmole) was added. TLC 15 minutes later showed complete hydrolysis. The mixture was cooled and extracted with 2 × 10 ml CH_2Cl_2. The aqueous layer was acidified by the addition of 3.30 ml (39.6 mmole) conc. HCl. A milk formed. This was extracted with 5 × 10 ml CH_2Cl_2. Extract numbers 1—4 were dried (Na_2SO_4) and charcoaled (Darco 660), then evaporated to a tan solid, which was a mixture of all benzoyl isomers. This solid was dissolved in 10 ml 2-propanol and hexane (10 ml) was added. A crystalline solid formed slowly.

(14)

The first crop had a weight of 0.90 gm (58.5%) and was pure (by TLC) 5-benzoyl 1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid, m.p. 160—161°C. A second crop (0.35 g, 23%), which was contaminated by other isomers, formed on evaporation the supernatant to 2 ml of 2-propanol and adding 2 ml hexane.

B. In a manner similar to that in Part A, and substituting for benzmorpholide
p-methoxybenzmorpholide,
4-chlorobenzmorpholide,
3-methylbenzmorpholide,
2-furanoylmorpholide,
2-thenoylmorpholide,
3-thenoylmorpholide,
3-ethyl-2-thenoylmorpholide,
4-n-butyl-2-furanoylmorpholide,
2-pyrroylmorpholide, or
1-methylpyrroylmorpholide,
one obtains
5-(p-methoxybenzoyl)-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid, m.p. 187—187.5°C;
5-(4-chlorobenzoyl)-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid, m.p. 202.5—202.5°C;
5-(3-methylbenzoyl)-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid;
5-(2-furanoyl)-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid;
5-(2-thenoyl)-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid, m.p. 166°C;
5-(3-thenoyl)-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid;
5-(3-ethyl-2-thenoyl)-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid;
5-(4-n-butyl-2-furanoyl)-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid;
5-(2-pyrroyl)-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid; or
5-(1-methylpyrroyl)-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid.

C. In a manner similar to that in Part A, but substituting for methyl 1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate, the corresponding 6-alkyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylates and the appropriate benzmorpholides, one obtains
5-(4-methoxybenzoyl)-6-methyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid, m.p. 182°C;
5-(4-chlorobenzoyl)-6-methyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid, m.p. 204°C;
5-(4-fluorobenzoyl)-6-ethyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid; m.p. 196°C.

Example 2

Benzoylation of methyl 1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate

Benzmorpholide, (15.23 gm. 79.67 mmole) was dissolved in 15.3 ml CH_2Cl_2. $POCl_2$ (6.87 ml, 76 mmole) was added. This was heated in a 42° oil bath overnight. A solution of the methyl 1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic ester, 10.0 gm, 61 mmole) in 15 ml CH_2Cl_2 was added. Heating was continued at 42° bath for 1.5 hours.

The reaction was shown to be complete by TLC. The resulting light brown solution was transferred with a 10 ml CH_2Cl_2 wash to a separatory funnel. The funnel was placed on a 500 ml 3 neck flask, which was also equipped with a reflux condenser and mechanical stirrer. H_2O (67 ml) and NaOH (24.9 gm, 0.62 mole) were placed in the flask. The reaction mixture was added dropwise to the NaOH solution over 45 minutes with stirring and allowing the CH_2Cl_2 to reflux in the condenser. After the addition was complete the mixture was stirred at ambient temperature for 30 minutes. The hydrolysis was shown to be complete by TLC.

In the isolation procedure for the product, 6N HCl (40 ml) was added. The lower organic layer was removed, and pH of upper aqueous phase was shown to be 8—9 (paper). The aqueous layer was then extracted with 2×30 ml CH_2Cl_2, which removed a small amount of product. The aqueous layer was then acidified to pH 2—3 (paper) by the addition of 18 ml 6N HCl. A milk was formed, which was extracted with CH_2Cl_2 (1×60 ml, 2×30 ml), to extract the majority of the product.

The extracts from the acidified aqueous CH_2Cl_2 were combined, washed with 2×30 ml H_2O, dried (Na_2SO_4) and evaporated to a solid (11.4 gm). This was dissolved in 50 ml CH_2Cl_2 and hexane (50 ml) was added, and a solid crystallized overnight.

The above extracts from the neutral (pH 8—9) mixture were combined and extracted with 2×25 ml 1N NaOH. The NaOH solutions were then combined, washed with 25 ml CH_2Cl_2 and acidified with 9 ml 6H HCl. A milk formed, which was extracted with 2×25 ml CH_2Cl_2. The CH_2Cl_2 was dried (Na_2SO_4) and evaporated to a solid (3.1 gm). The solid was then dissolved in 15 ml CH_2Cl_2, 15 ml hexane was added, and the mixture allowed to crystallize overnight. Both crystal crops were shown to be pure 5-benzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid, m.p. 160—161°C by TLC.

wt. from acid CH_2Cl_2's = 7.80 gm (50.5%)
wt. from neutral CH_2Cl_2's = 2.30 gm(14.9%)

65.4% total yield.

Example 3

Aroylation of 1,2-dihydro-3H-pyrrole[1,2-a]pyrrole-1-nitrile

Benzmorpholide (5.67 kg, 29.7 mole) was mixed with stirring with $POCl_3$ (4.88 l, 52.4 moles) under an atmosphere of nitrogen. The mixture was heated to 40°—43° for 6 hours.

The mixture was washed into a larger vessel with 1 liter methylene chloride, and mixed with a solution of 1,2-dihydro-3H-pyrrole[1,2-a]pyrrole-1-nitrile (3.238 kg, 24.5 moles) in 17.2 l of methylene chloride, all under nitrogen. The reaction mixture was brought to 42° and agitated under nitrogen overnight.

The mixture was then added to a solution of Na_2CO_3 (18.5 kg) in 60 l water. The temperature was kept at 40°C for one-half hour, and then the mixture was cooled to 21°C.

Addition of both water and methylene chloride resulted in layer separation: When an initial total of 60 l water failed to result in separation, 80 l of the mixture was removed and treated with 20 l water and 20 l CH_2Cl_2. The layers were separated, the aqueous layer washed twice with 10 l portions of CH_2Cl_2. The remaining mixture (after the removal of the 80 l above) was treated with 40 l water and 20 l CH_2Cl_2; the layers separated, the aqueous layer was washed with the previously used CH_2Cl_2 washes. All organic fractions were then combined.

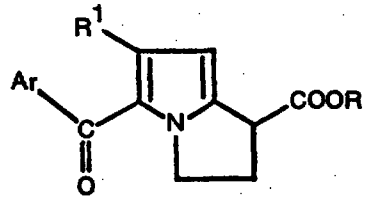
The solvent was removed by distillation and the resulting product cleaned up by adsorption of impurities onto silica gel. The silica gel was eluted for product with methylene chloride, which was then removed by distillation during replacement by methanol.

The product, 5-benzoyl-1,2-dihydro-3H-pyrrole[1,2-a]pyrrole-1-nitrile crystallized from methanol to give 3.47 kg or 60% yield.

In a manner analogous to that set forth hereinabove, but using instead of benzmorpholide, 2-thenoylmorphilide, 5-(2-thenoyl)-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-nitrile, m.p. 106—107.5°C is obtained.

Claims

1. A process for preparing a compound of the formula



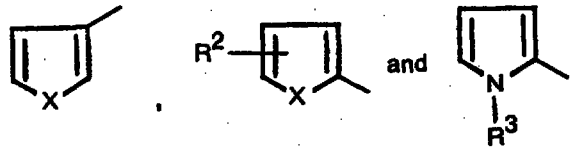
(III')

wherein

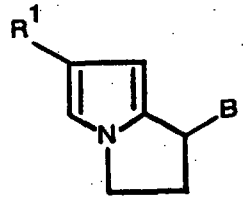
R is hydrogen or C_{1-6} alkyl;

R^1 is hydrogen or C_{1-6} alkyl; and

Ar is phenyl optionally substituted with one to three substituents selected from halogen, C_{1-6} alkyl or C_{1-6} alkoxy, or is selected from



wherein X is O or S, R^2 is hydrogen, methyl, chloro or bromo; and R^3 is hydrogen or C_{1-6} alkyl; or the pharmaceutically acceptable salts thereof, which process comprises reacting a compound of the formula



(I)

wherein B is —COOR or —CN and R^1 and R are as herein defined, with inorganic acid chloride and a compound of the formula

Example 3

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The mixture was then added to a solution of Na_2CO_3 (18.5 kg) in 60 l water. The temperature was kept at 40°C for one-half hour, and then the mixture was cooled to 21°C.

Addition of both water and methylene chloride resulted in layer separation: When an initial total of 60 l water failed to result in separation, 80 l of the mixture was removed and treated with 20 l water and 20 l CH_2Cl_2. The layers were separated, the aqueous layer washed twice with 10 l portions of CH_2Cl_2. The remaining mixture (after the removal of the 80 l above) was treated with 40 l water and 20 l CH_2Cl_2; the layers separated, the aqueous layer was washed with the previously used CH_2Cl_2 washes. All organic fractions were then combined.

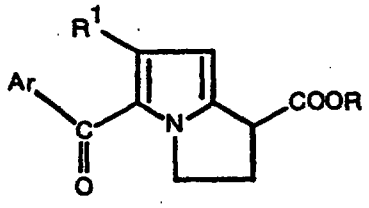
The solvent was removed by distillation and the resulting product cleaned up by adsorption of impurities onto silica gel. The silica gel was eluted for product with methylene chloride, which was then removed by distillation during replacement by methanol.

The product, 5-benzoyl-1,2-dihydro-3H-pyrrole[1,2-a]pyrrole-1-nitrile crystallized from methanol to give 3.47 kg or 60% yield.

In a manner analogous to that set forth hereinabove, but using instead of benzmorpholide, 2-thenoylmorphilide, 5-(2-thenoyl)-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-nitrile, m.p. 106—107.5°C is obtained.

Claims

1. A process for preparing a compound of the formula



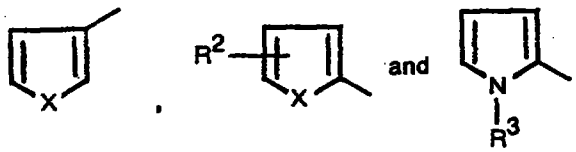
(III')

wherein

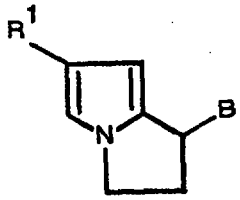
R is hydrogen or C_{1-6} alkyl;

R^1 is hydrogen or C_{1-6} alkyl; and

Ar is phenyl optionally substituted with one to three substituents selected from halogen, C_{1-6} alkyl or C_{1-6} alkoxy, or is selected from

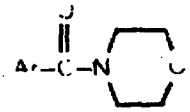


wherein X is O or S, R^2 is hydrogen, methyl, chloro or bromo; and R^3 is hydrogen or C_{1-6} alkyl; or the pharmaceutically acceptable salts thereof, which process comprises reacting a compound of the formula



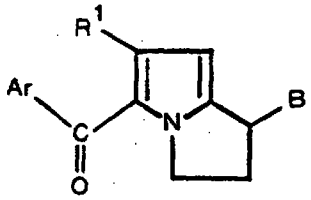
(I)

wherein B is —COOR or —CN and R^1 and R are as herein defined, with inorganic acid chloride and a compound of the formula



(A)

wherein Ar is as defined above, to afford a compound of formula VI



(VI)

wherein Ar, R^1 and B are as herein defined, optionally followed by conversion of the C_{1-6} alkyl ester of formula VI to a compound of formula III'; or followed by conversion of the nitrile of formula VI to a compound of formula III', optionally followed by conversion of a salt of the compound of formula III' into the free acid by treatment with acid; or by conversion of a free acid of the compound of formula III' to a pharmaceutically acceptable salt by treatment with a pharmaceutically acceptable base.

2. The process of claim 1 wherein the compound of formula VI is treated with a weak base, or water and a strong base.

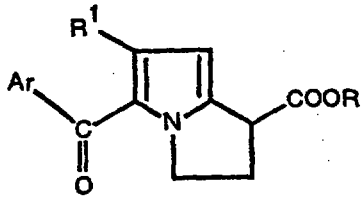
3. The process of claim 1 wherein the compound of formula VI wherein B is —COOR is treated with water and a weak base, followed by treatment with a solution of strong base in a plar solvent.

4. The process of claim 1 wherein the compound of formula VI wherein B is —CN is treated with a solution of a base in a polar solvent.

5. The process of claim 1 wherein the compound of formula VI wherein B is —CN is converted to a compound of formula VI, wherein B is —COOH, using an acid or a base.

Patentansprüche

1. Ein Verfahren zur Herstellung einer Verbindung der Formel



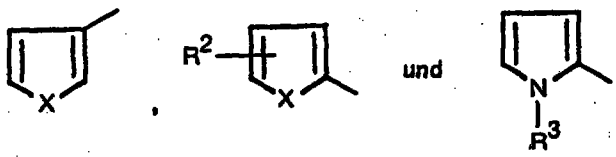
(III')

worin

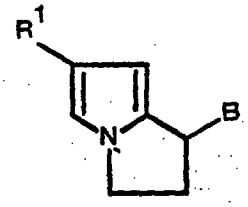
R Wasserstoff oder C_{1-6}-Alkyl bedeutet;

R^1 Wasserstoff oder C_{1-6}-Alkyl bedeutet; und

Ar Phenyl bedeutet, das gegebenenfalls mit einem bis drei Substituenten, ausgewählt unter Halogen, C_{1-6}-Alkyl oder C_{1-6}-Alkoxy, substituiert ist, oder ausgewählt ist unter

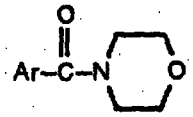


worin X für Sauerstoff oder Schwefel steht, R^2 Wasserstoff, Methyl, Chlor oder Brom bedeutet; und R^3 Wasserstoff oder C_{1-6}-Alkyl darstellt; oder der pharmazeutisch annehmbaren Salze hievon, welches Verfahren ein Umsetzen einer Verbindung der Formel



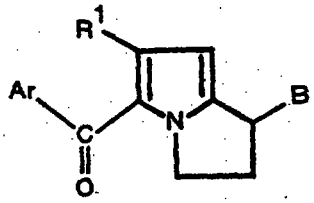
(I)

worin B für —COOR oder —CN steht und R^1 und R wie vorstehend definiert sind, mit einem anorganischen Säurechlorid und einer Verbindung der Formel



(A)

worin Ar wie vorstehend definiert ist, zu einer Verbindung der Formel VI



(VI)

umfaßt, worin Ar, R^1 und B wie vorstehend definiert sind; gegebenenfalls gefolgt von einer Umwandlung des C_{1-6}-Alkylesters der Formel VI zu einer Verbindung der Formel III'; oder gefolgt von einer Umwandlung des Nitrils der Formel VI zu einer Verbindung der Formel III'; gegebenenfalls gefolgt von einer Umwandlung eines Salzes der Verbindung der Formel III' in die freie Säure durch Behandlung mit einer Säure; oder von einer Umwandlung einer freien Säure der Verbindung der Formel III' in ein pharmazeutisch annehmbares Salz durch Behandlung mit einer pharmazeutisch annehmbaren Base.

2. Das Verfahren nach Anspruch 1, worin die Verbindung der Formel VI mit einer schwachen Base oder mit Wasser und einer starken Base behandelt wird.

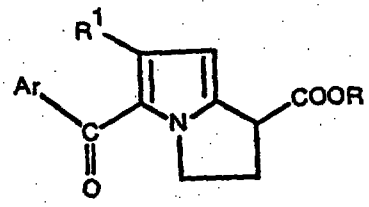
3. Das Verfahren nach Anspruch 1, worin eine Verbindung der Formel VI, worin B für —COOR steht, mit Wasser und einer schwachen Base behandelt wird, gefolgt von einer Behandlung mit einer Lösung einer starken Base in einem polaren Lösungsmittel.

4. Das Verfahren nach Anspruch 1, worin eine Verbindung der Formel VI, worin B für —CN steht, mit einer Lösung einer Base in einem polaren Lösungsmittel behandelt wird.

5. Das Verfahren nach Anspruch 1, worin eine Verbindung der Formel VI, worin B für —CN steht, unter Verwendung einer Säure oder einer Base in eine Verbindung der Formel VI übergeführt wird, worin B für —COOH steht.

Revendications

1. Procédé de production d'un composé de formule



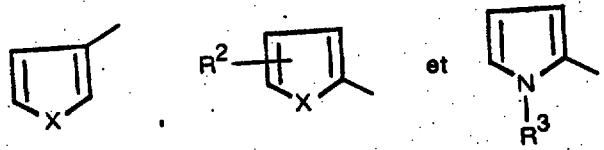
(III')

dans laquelle

R est l'hydrogène ou un groupe alkyle en C_1—C_6;

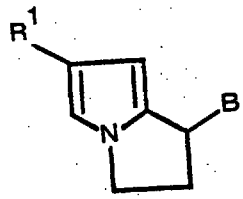
R^1 est l'hydrogène ou un groupe alkyle en C_1—C_6; et

Ar est un groupe phényle éventuellement substitué avec un à trois substituants choisis entre un halogène, un groupe alkyle en C_1—C_6 ou un groupe alkoxy en C_1—C_6 ou est choisi entre des groupes



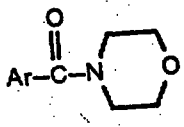
dans lesquels X est O ou S, R^2 est l'hydrogène ou un radical méthyle, chloro ou bromo; et R^3 est l'hydrogène ou un groupe alkyle en C_1—C_6; ou de leurs sels pharmaceutiquement acceptables,

procédé qui consiste à faire réagir un composé de formule



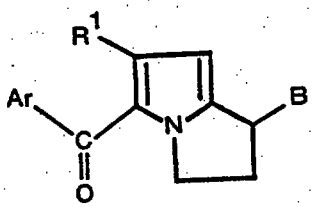
(I)

dans laquelle B représente —COOR ou —CN et R^1 et R ont les définitions données ci-dessus, avec un chlorure d'acide inorganique et un composé de formule



(A)

dans laquelle Ar a la définition donnée ci-dessus, pour offrir un composé de formule VI



(VI)

dans laquelle Ar, R^1 et B ont les définitions données ci-dessus; la réaction étant éventuellement suivie d'une transformation de l'ester alkylique en C_1—C_6 de formule VI en un composé de formule III'; ou suivie de la transformation du nitrile de formule VI en un composé de formule III'; éventuellement suivie de la transformation d'un sel du composé de formule III' en l'acide libre par traitement avec un acide; ou de la transformation d'un acide libre du composé de formule III' en un sel pharmaceutiquement acceptable par traitement avec une base pharmaceutiquement acceptable.

2. Procédé suivant la revendication 1, dans lequel le composé de formule VI est triaté avec une base faible, ou de l'eau et une base forte.

3. Procédé suivant la revendication 1, dans lequel un composé de formule VI, dans laquelle B représente —COOR, est traité avec de l'eau et une base faible, puis traité avec une solution d'une base forte dans un solvant polaire.

4. Procédé suivant la revendication 1, dans lequel un composé de formule VI, où B représente —CN, est traité avec une solution d'un base dans un solvant polaire.

5. Procédé suivant la revendication 1, dans lequel un composé de formule VI, où B représente —CN, est converti en un composé de formule VI dans laquelle B représente —COOH, en utilisant un acide ou une base.