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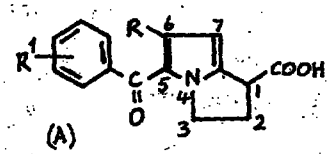
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(54) 1,2-DIHYDRO-3H-PYRROLO[1,2-a]PYRROLE-1-CARBOXYLIC ACID DERIVATIVES AND PROCESS FOR THE PRODUCTION THEREOF

(71) We, SYNTEX (U.S.A.) INC., a Corporation organised under the laws of the State of Delaware, United States of America, of 3401 Hillview Avenue, Palo Alto, California 94304, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to certain pyrrolo-pyrrole-1-carboxylic acid compounds and to a process for the production thereof.

More particularly, this invention relates to 5-aroyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acids represented by the formula



(A)

and the individual (l)-acid isomers and the (d)-acid isomers thereof and the pharmaceutically acceptable, non-toxic esters and salts thereof, wherein R represents hydrogen or a lower alkyl group having from 1 to 4 carbon atoms and R^1 represents hydrogen, a lower alkyl group having from 1 to 4 carbon atoms, a lower alkoxy group having from 1 to 4 carbon atoms, chloro, fluoro or bromo, the R^1 substituent being at the ortho, meta or para position of the aroyl group, to the method for the production thereof and to intermediates obtained thereby.

The compounds of the present invention as described above and more fully below, exclusive of the (d)-acid isomer and the derivatives thereof, exhibit anti-inflammatory, analgesic and antipyretic activities and thus are useful in the treatment of inflammation, pain and/or pyrexia in mammals, as described hereinafter in detail. They are also smooth muscle relaxants.

The term "pharmaceutically acceptable, non-toxic esters and salts" as used herein refers to "alkyl esters" in which the alkyl group is derived from hydrocarbons of branched or straight chain having from one to twelve carbon atoms and salts derived from pharmaceutically acceptable non-toxic inorganic and organic bases, respectively.

Typical alkyl ester groups are, for example, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, isoamyl, pentyl, isopentyl, hexyl, octyl, nonyl, isodecyl, 6-methyldecyl and dodecyl esters.

Salts derived from inorganic bases include sodium, potassium, lithium, ammonium, calcium, magnesium, ferrous zinc, copper, manganous aluminum, ferric 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,

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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, piperidine, tromethamine, dicyclohexylamine, choline and caffeine.

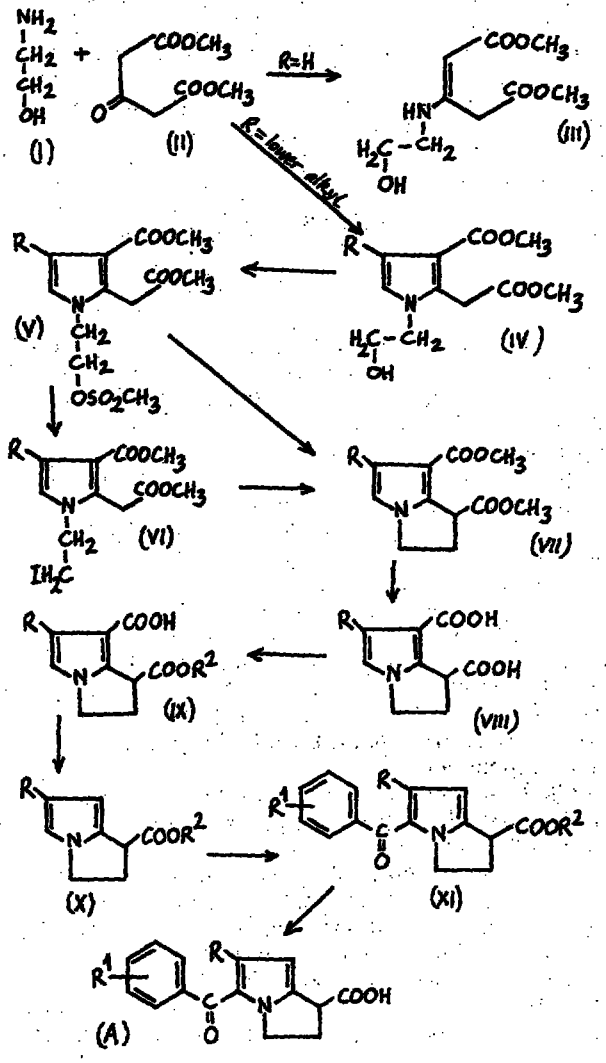
The compounds of Formulas (A) and (XI) depicted below exist as pairs of optical isomers (or enantiomorphs), i.e., a (dl) mixture. However, each optical isomer as well as the (dl) mixtures thereof are included within the present invention.

When the compounds of this invention are to be used to elicit a physiological response (e.g., anti-inflammatory, analgesic or antipyretic activity), i.e., they are to be used as medicinals, a preferred sub-grouping is that of the compounds of Formula (A) and the (l)-acid isomers thereof and the esters and pharmaceutically acceptable salts thereof.

A still further sub-grouping, for compounds to be used as medicinals, are the compounds of Formula (A) and the (l)-acid isomer of Formula (A) and the esters and pharmaceutically acceptable salts thereof wherein R and R^1 are both hydrogen.

The (d)-acid isomer of Formula (A) and the esters and pharmaceutically acceptable salts thereof are useful as intermediates for the preparation of the (dl)-acid of Formula (A), as described more fully below.

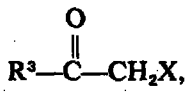
The (dl) compounds of the present invention can be prepared by a process illustrated by the following reaction sequence:



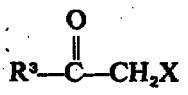
wherein R and R^1 have the above-indicated meaning and R^2 is a lower alkyl group of 1 to 4 carbon atoms, e.g., methyl, ethyl, isopropyl and n-butyl.

In practicing the process outlined above, for the preparation or the compound of Formula (IV) wherein R is hydrogen, equimolecular amounts of ethanolamine (I) and dimethyl 1,3-acetonedicarboxylate (II) are reacted at a temperature of from about 0° to about room temperature, to readily form a solution of the vinylamine of Formula (III), which is then treated, preferably in situ, in a suitable inert organic solvent, under anhydrous conditions, with 2-bromoacetaldehyde or 2-chloroacetaldehyde, at from about 40° to about 100°C for a period of time of from about 30 minutes to about 16 hours. Suitable solvents for this reaction are the aprotic solvents such as acetonitrile, tetrahydrofuran, dimethoxyethane, chloroform and dichloromethane. In the preferred embodiments, the reaction is conducted in acetonitrile solution, at reflux temperature for about 1 hour. The 2-bromo-(chloro)-acetaldehyde reagents are known compounds, or can be obtained by pyrolysis of the corresponding diethyl acetals in the presence of oxalic acid dihydrate.

To prepare the compounds of Formula (IV) wherein R is a lower alkyl group, preferably straight chain, having 1 to 4 carbon atoms, an aqueous mixture of ethanolamine (I) and dimethyl 1,3-acetonedicarboxylate (II) is treated with a compound of the formula



wherein X is bromo or chloro and R^3 is a lower alkyl group, preferably straight chain, of from 1 to 4 carbon atoms, and most preferably 1-bromoacetone, 1-bromo-2-butanone, 1-bromo-2-pentanone, and 1-bromo-2-hexanone, at from about 40° to about 100°C for a period of time from about 30 minutes to about 16 hours. In the preferred embodiment the reaction is conducted at a temperature of from about −10°C to about room temperature for from about 1 hour to about 6 hours. The



reagents are known compounds.

Esterification of compound (IV) with methanesulfonyl chloride in the presence of a tertiary amine, i.e., triethylamine or pyridine, optionally in the presence of a cosolvent such as dichloromethane, at a temperature of from about −10°C to about room temperature, for about 10 minutes to about 2 hours produces the corresponding mesylate of Formula (V), which is converted into the corresponding N-(2-iodoethyl)pyrrole of Formula (VI) by reaction with sodium iodide in acetonitrile solution, at reflux temperature for from about one to about ten hours.

Upon reaction of the iodoethyl compounds of Formula (VI) with sodium hydride in a suitable inert organic solvent such as dimethylformamide there are obtained dimethyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1,7-dicarboxylate and the 6-alkyl substituted derivatives thereof (VII). This cyclization is conducted under an inert atmosphere, i.e., under argon or nitrogen atmosphere, at temperatures of the order of from about 15° to about 40°C, for a period of time of from about 15 minutes to about 4 hours. Best results are obtained conducting the reaction at room temperature, for about 30 minutes when R is hydrogen.

Alternatively, the compounds of Formula (VII) can be prepared by direct cyclization of the mesylate (V), with sodium hydride in dimethylformamide solution, at from about −10°C to about room temperature, for from about 30 minutes to about 2 hours.

Basic hydrolysis of a compound of Formula (VII) with an alkali metal hydroxide or alkali metal carbonate, e.g., sodium hydroxide, potassium hydroxide, sodium carbonate or potassium carbonate in an aqueous lower aliphatic alcohol, e.g., methanol or ethanol, at a temperature of between room temperature and reflux, for from about 4 to about 24 hours, affords the corresponding free diacid of Formula (VIII), i.e., 1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1,7-dicarboxylic acid and the 6-alkyl derivatives thereof. The hydrolysis is preferably carried out using aqueous methanolic potassium hydroxide, at reflux temperature for about 10 hours.

The carboxylic acid group at the C-1 position in compound (VIII) is then

selectively esterified by treatment with a lower aliphatic alcohol, e.g., methanol, ethanol, isopropanol or n-butanol in the presence of hydrogen chloride, to produce the corresponding alkyl 1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate-7-carboxylic acid of Formula (IX). The reaction is conducted at a temperature of from about 0° to about 50°C., for about 1 to about 4 hours.

Decarboxylation of the monoesterified compounds (IX) to the corresponding compounds of Formula (X), the key intermediates in the process for obtaining the compounds of the present invention, is achieved by heating (IX) at an elevated temperature, of the order of from about 230° to about 280°C, for a period of time sufficient to complete the reaction. The course of the reaction can be followed by the rate of carbon dioxide evolution and t.l.c. analysis, decarboxylation being generally completed within from about 45 to about 90 minutes. The reaction product, namely, alkyl 1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate and the 6-alkyl derivatives thereof (X) can be purified by chromatographic techniques. Alternatively, and particularly for the decarboxylation of small batches of compound (IX), the reaction product (X) can be distilled directly from the reaction vessel.

Condensation of a compound (X) with an amide of the formula



wherein R^1 has the above-indicated meaning, affords the corresponding alkyl 5-aroyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate (XI). This reaction can be conducted in an inert organic aprotic solvent and in the presence of phosphorous oxychloride, at reflux temperature for from about 1 to about 175 hours, under an inert atmosphere, followed by further reflux in the presence of sodium acetate, for from about 2 to about 10 hours. Alternatively, instead of phosphorous oxychloride other acid chlorides such as phosgene or oxalyl chloride may be used.

In the preferred embodiments, this condensation is carried out by adding a solution of compound (X) in a suitable solvent to a previously refluxed mixture of 1.1 to 5 molar equivalents of both the desired amide and phosphorous oxychloride in the same solvent, refluxing the reaction mixture thus obtained for from about 6 to about 72 hours under an argon atmosphere and thereafter adding thereto from about 3 to about 10 molar equivalents of sodium acetate, followed by an additional reflux period for from about 4 to about 6 hours.

Adequate solvents for this reaction are the halogenated hydrocarbons such as dichloromethane, 1,2-dichloroethane, chloroform and carbon tetrachloride, dimethoxyethane and tetrahydrofuran. The preferred solvent is 1,2-dichloroethane.

Representative of the N,N-dimethyl arylamides which can be used are:

N,N-dimethyl-benzamide,
N,N-dimethyl-o-toluamide,
N,N-dimethyl-m-toluamide,
N,N-dimethyl-p-toluamide,
N,N-dimethyl-p-ethyl-benzamide,
N,N-dimethyl-o-propyl-benzamide,
N,N-dimethyl-m-butyl-benzamide,
N,N-dimethyl-o-methoxy-benzamide,
N,N-dimethyl-m-methoxy-benzamide,
N,N-dimethyl-p-ethoxy-benzamide,
N,N-dimethyl-p-isopropoxy-benzamide,
N,N-dimethyl-o-chloro-benzamide,
N,N-dimethyl-m-chloro-benzamide,
N,N-dimethyl-p-chloro-benzamide,
N,N-dimethyl-o-fluoro-benzamide,
N,N-dimethyl-p-fluoro-benzamide,
N,N-dimethyl-m-bromo-benzamide, and
N,N-dimethyl-p-bromo-benzamide.

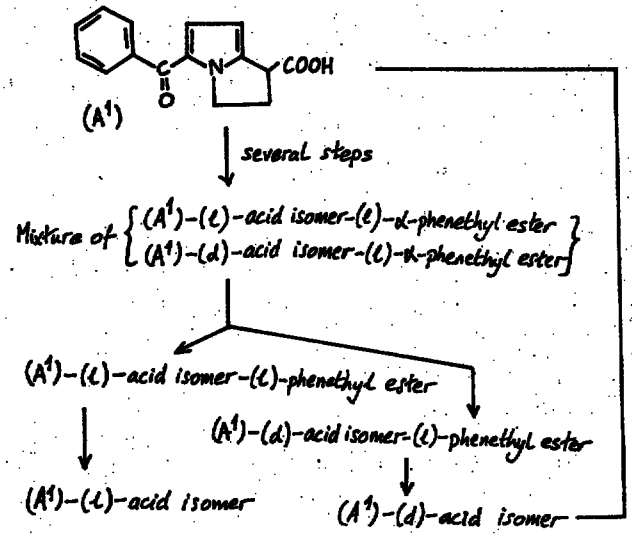
These amides are known, commercially available compounds or can be prepared in a conventional manner from the corresponding acids i.e., by conversion into the acid chlorides followed by treatment with dimethylamine.

Upon alkaline hydrolysis of the alkyl ester group in a compound of Formula (XI) there is obtained the corresponding free acid of Formula (A). This hydrolysis

is effected in a conventional manner, with an alkali metal hydroxide or alkali metal carbonate, e.g., sodium hydroxide, potassium hydroxide, sodium carbonate or potassium carbonate, in an aqueous lower aliphatic alcohol, e.g., methanol or ethanol at a temperature of from about room temperature to reflux, for from about 15 minutes to about 2 hours, under an inert atmosphere. In the preferred embodiments, this hydrolysis is effected with aqueous methanolic potassium carbonate, at reflux temperature for about 30 minutes.

The compounds of Formula (A) can be resolved, according to methods known in the art, to obtain the corresponding individual isomers thereof.

The (l)-acid isomers and (d)-acid isomers of the compounds of Formula (A) can be obtained by applying the known technique of high pressure liquid chromotography (HPLC) to the α-phenethyl diastereoisomeric esters of the compounds of Formula (A), followed by acid cleavage. Thus, for example, the compounds of Formula (A) wherein R and R¹ are both hydrogen can be subjected to further treatment in accordance with the following flow diagram:



A more detailed description of this procedure is set forth in Example 12B below.

The free acids of Formula (A) can be converted into other alkyl esters having from 1 to 12 carbon atoms by conventional methods, e.g., by treatment with (a) the alcohol corresponding to the desired ester in the presence of a strong mineral acid, (b) an ethereal diazoalkane or (c) the desired alkyl iodide in the presence of lithium carbonate. The (l)-acid isomers can be converted into their alkyl esters by the methods of (b) and (c) above.

The salt derivatives of the compounds of Formula (A) and the (l)-acid isomers thereof are prepared by treating these free acids with an appropriate amount of a 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, manganous hydroxide, aluminum hydroxide, ferric hydroxide, manganic hydroxide, isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, tromethamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, pyrines, 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 about 0°C. to about 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 (A) or the (l)-acid isomers thereof to base used are chosen to provide the ratio desired for any particular salt. For preparing, for example, the calcium salts or magnesium salts of the compounds of Formula (A) or the (l)-acid isomers thereof, the free acid starting material 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 (A) or the (l)-acid isomers thereof are prepared at least one-third molar equivalent of the pharmaceutically acceptable base are employed if a neutral salt product is desired.

In the preferred procedure, the calcium salts and magnesium salts of the compounds of Formula (A) and (l)-acid isomers thereof can be prepared by treating the corresponding sodium or potassium salts thereof with at least one-half molar equivalent of calcium chloride or magnesium chloride, respectively, in an aqueous solution, alone or in combination with an inert water-miscible organic solvent, at a temperature of from about 20°C to about 100°C. Preferably, the aluminum salts of the compounds hereof, can be prepared by treating the corresponding free acids with at least one-third molar equivalent of an aluminum alkoxide, such as aluminum triethoxide or aluminum tripropoxide in a hydrocarbon solvent, such as benzene, xylene, or cyclohexane, at a temperature of from about 20°C to about 115°C. Similar procedures can be used to prepare salts of inorganic bases which are not sufficiently soluble for easy reaction.

It is to be understood that isolation of the compounds described herein can be effected, if desired, by any suitable separation or purification procedure, such as, for example, extraction, filtration, evaporation, distillation, crystallization, thin-layer chromatography or column chromatography, high pressure liquid chromatography (HPLC) or a combination of these procedures. Illustrations of suitable separation and isolation procedures can be had by reference to the Examples herein below. However, other equivalent separation or isolation procedures could, of course, also be used.

While the (d)-acid isomers are not used as medicinal agents per se, they can, if desired, be converted to their pharmaceutically acceptable, non-toxic esters and salts thereof according to the methods described for the conversion of the (l)-acid isomers to their pharmaceutically acceptable, non-toxic esters and salts thereof.

The compounds of Formula (A) and the (l)-acid isomers thereof and the pharmaceutically acceptable non-toxic esters and salts thereof, are useful as anti-inflammatory agents, analgetic agents, platelet aggregation inhibitors, fibrinolytic agents, and as smooth muscle relaxants. These compounds can be used both prophylactically and therapeutically.

The compositions containing these compounds are thus useful in the treatment and elimination of inflammation such as inflammatory conditions of the muscular skeletal system, skeletal joints and other tissues, for example, in the treatment of inflammatory conditions such as rheumatism, concussion, laceration, arthritis, bone fractures, post-traumatic conditions, and gout. In those cases in which the above conditions include pain and pyrexia coupled with inflammation, the instant compounds are useful for the relief of these conditions as well as the inflammation.

Administration of the active compounds of Formula (A) or the (l)-acid isomers thereof and the pharmaceutically acceptable, non-toxic esters and salts thereof, in an appropriate pharmaceutical composition can be via any of the accepted modes of administration of agents for the treatment of inflammation, pain or pyrexia, or the prophylaxis thereof. Thus, administration can be for example, orally, parenterally or topically, in the form of solid, semi-solid or liquid dosage forms, such as, for example, tablets, suppositories, pills, capsules, powders, solutions, suspensions, emulsions, creams, lotions or ointments preferably in unit dosage forms suitable for simple administration of precise dosages. The compositions will include a conventional pharmaceutical carrier or excipient and an active compound of Formula (A) or the (l)-acid isomer thereof and the pharmaceutically acceptable non-toxic esters and salts thereof, and, in adidtion, may include other medicinal agents, pharmaceutical agents, carriers and adjuvants.

The preferred manner of administration, for the conditions detailed above, is oral using a convenient daily dosage regimen which can be adjusted according to the degree of affliction. Generally, a daily dose of from 25 mg. to 500 mg. of the active compound of Formula (A) or the (l)-acid isomer thereof and the pharmaceutically acceptable, non-toxic esters and salts thereof is used. Most conditions respond to treatment comprising a dosage level of the order of 0.5 mg. to 6 mg. per kilogram of body weight per day. For such oral administration, a pharmaceutically acceptable, non-toxic composition is formed by the incorporation of any of the normally employed excipients, such as, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccarine, talcum, cellulose, glucose, gelatin, sucrose and magnesium carbonate.

Such compositions take the form of solutions, suspensions, tablets, pills, capsules, powders or sustained release formulations.

The active compounds of Formula (A) or the (l)-acid isomers thereof and the pharmaceutically acceptable, non-toxic esters and salts thereof, may be formulated into a suppository using, for example, polyalkylene glycols, for example, polypropylene glycol, as the carrier. Liquid pharmaceutically administerable compositions can, for example, be prepared by dissolving, dispersing, etc. an active compound, as described above, and optional pharmaceutical adjuvants in a carrier, such as, for example, water, saline, aqueous dextrose, glycerol or ethanol, to thereby form a solution or suspension. If desired, the pharmaceutical composition to be administered may also contain minor amounts of non-toxic auxiliary substances such as wetting or emulsifying agents and pH buffering agents such as for example, sodium acetate, sorbitan monolaurate and triethanolamine oleate.

Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pennsylvania, 14th. Edition, 1970. The composition to be administered will, in any event, contain a quantity of the active compound(s) in a pharmaceutically effective amount for relief of the particular condition being treating in accordance with the teachings of this invention.

The compounds of Formula (A) and the (l)-acid isomers thereof and the non-toxic, pharmaceutically acceptable esters and salts thereof, described above, are also uterine smooth muscle relaxants and thus are useful as agents for maintaining the pregnancy of pregnant mammals, for the benefit of the mother and/or fetus, until termination of the pregnancy is considered, from a medical point of view, to be favorable, or more favorable, for the mother and/or the fetus. It should be understood, however, that in certain instances, for example where parturition has already begun (i.e., the mother is experiencing uterine contractions, especially near full term), that administration of the compounds herein described may not maintain the pregnant state for an indefinite period of time. Rather, in such instances, the pregnancy will, most probably, be slightly "prolonged", a factor which may be advantageous to either the mother and/or the fetus.

In particular, the compounds of Formula (A) and the (l)-acid isomers thereof and the pharmaceutically acceptable, non-toxic esters and salts thereof, are used as agents for delaying the onset of, or for postponing, parturition. As used in this application, the phrase "to delay the onset of parturition" is intended to cover that delay in parturition caused by the administration of the compounds of Formula (A) or the (l)-acid isomers thereof and the pharmaceutically acceptable, non-toxic esters and salts thereof, at any time before uterine muscle contractions have begun. Thus, it is intended that the aforementioned phrase cover abortion prevention early in pregnancy (i.e., before the fetus is "viable") as well as delaying premature parturition, a term which sometimes is used with reference to that premature labor experienced later in the pregnancy when the fetus is considered to be "viable". In either case, the agents are administered, as prophylactic agents in that such administration tends to prevent the onset of parturition. This administration is particularly useful in the treatment of women having a history of spontaneous abortion, miscarriage or premature delivery (i.e., delivery prior to full term). Such administration is also useful where there are clinical indications that the pregnancy might be terminated prior to that time and is considered favorable to the mother and/or fetus.

With respect to animals, this treatment can also be utilized to synchronize the deliveries from a group of pregnant animals to happen at or about the same time, or to happen at or about a desired time and/or place, when the births can be handled with greater facility.

As used in this application, the phrase "postponing parturition" is intended to cover that delay in parturition caused by the administration of the compounds of Formula (A) or the (l)-acid isomers thereof and the pharmaceutically acceptable, non-toxic esters and salts thereof after uterine muscle contractions have begun. The condition of the patient, including the time within the gestation period when the contractions have begun, the severity of the contractions and how long the contractions have taken place will affect the results achieved with the administration of the compounds hereof. For example, the effect can be to reduce the intensity and/or the duration of the contractions (the actual act of parturition being "prolonged"), or to stop the contractions altogether. In either case, the effect will be to prolong the gestation period although, depending upon the conditions of

the patient as described above, the effect may either be slight or, under appropriate circumstances, somewhat greater. Such administration may be to prevent spontaneous abortion, to cause the delivery to be more easily accomplished and/or less painful to the mother, or to occur at a more appropriate time and/or place.

In all cases, administration of the compounds of Formula (A) or the (l)-acid isomers thereof and the pharmaceutically acceptable, non-toxic esters and salts thereof, for the purposes set forth herein should be consistent with best and/or accepted medical (or veterinary) practices so as to maximize the benefits to the mother and the fetus. For example, administration should not be continued so long past full term that the fetus dies in utero.

In the practice of the methods of the present invention, a therapeutically effective amount of a compound of Formula (A) or the (l)-acid isomers thereof and the pharmaceutically acceptable, non-toxic esters and salts thereof, or a pharmaceutical composition containing same, is administered to the pregnant mammal via any of the usual and acceptable methods known in the art. The compound can be administered either singly or in combination with another compound or compounds, as defined above, or other pharmaceutical agents, carriers, adjuvants, etc. Such compound(s) or compositions can be administered orally, parenterally, either in the form of solid, semi-solid, or liquid dosage forms. Typically, administration is by a pharmaceutical composition containing the pharmaceutically active compound and one or more pharmaceutical carriers or adjuvants.

The administerable pharmaceutical composition may take the form of oral tablets, vaginal or uterine tablets or suppositories, pills, capsules, liquid solutions, or suspensions, preferably in unit dosage forms suitable for simple administration of precise dosages. Conventional non-toxic solid carriers include, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, talcum, cellulose, glucose, gelatin, sucrose and magnesium carbonate. The active compound as defined above may be formulated as suppositories using, for example, polyalkylene glycols, for example, polypropylene glycol, as the carrier. Liquid pharmaceutically administerable compositions can, for example, be prepared by dissolving, dispersing, etc. an active compound as defined above and optional pharmaceutical adjuvants in a carrier, such as, for example, water, saline, aqueous dextrose, glycerol or ethanol, to thereby form a solution or suspension. If desired, the pharmaceutical composition to be administered may also contain minor amounts of non-toxic auxiliary substances such as wetting or emulsifying agents and pH buffering agents for example, sodium acetate, sorbitan monolaurate, triethanolamine oleate. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pennsylvania, 14th Edition, 1970. The composition or formulation to be administered will, in any event, contain a quantity of the active compound(s) in an amount effective to delay the onset of parturition or to postpone parturition if uterine contractions have already begun. Generally a daily dose of from 0.5 mg. to about 25 mg. of the active compound per kilogram of body weight will be administered, with administration being a single daily dose or up to three or four smaller dosages regularly given throughout the day. The amount of active compound administered will, of course, depend on its relative activity.

The following Examples illustrative the invention but are not intended to limit its scope. The abbreviation t.l.c. refers to thin-layer chromatography and all mixture ratios used with regard to liquids refer to volume ratios. Also where necessary, examples are repeated to prepare additional material for subsequent examples; and unless otherwise specified the reactions are carried out at room temperature (20°C to 30°C). Examples 1 to 5, 13A and 13B, 17 and 18 relate to intermediate steps in preparing compounds of the invention.

EXAMPLE 1

A 250 ml. 3-necked round bottomed flask containing a magnetic stirring bar and fitted with a calcium chloride filled drying tube is connected directly (via one of the outer necks) by means of a receiver adapter and short (3") water condenser to the acetal pyrolysis apparatus. This latter apparatus consists of a 100 ml. round bottom flask [previously charged with 15.6 g. of oxalic acid dihydrate and 11.82 g. of bromoacetaldehyde diethyl acetal, prepared from vinyl acetate, as described by P. Z. Bedoukian, J. Am. Chem. Soc. 66, 651 (1944)], topped with a 6" Vigreux column, bearing a thermometer, connected to the above mentioned condenser.

The 3-necked flask is charged with 3.36 g. of ethanolamine cooled in an ice bath at 0°—10°C and treated dropwise, with stirring, with 8.7 g. of dimethyl 1,3-acetonedicarboxylate. Methyl 3-carbomethoxymethyl-3(2'-hydroxyethyl) amino acrylate (III) forms immediately. When the addition is completed, the ice bath is removed and 100 ml. of dry acetonitrile is added. The pyrolysis part of the apparatus is placed in an oil bath and the temperature thereof is raised to 150—160°C. The bromoacetaldehyde solution which forms is distilled (b.p. 80—83°C/580 mm) directly into the magnetically stirred solution of the vinylamine (III). When the distillation temperature drops below 80°C, the pyrolysis apparatus is disconnected and replaced by a reflux condenser fitted with a drying tube containing calcium chloride. The solution is heated at reflux temperature for 1 hour, the solvent is removed under reduced pressure and then 200 ml. of methanol and 20 g. of silica gel are added to the residue. This mixture is evaporated to dryness in vacuum and placed on top of a column of 200 g. of silica gel packed in hexane. The column is then eluted with hexane:ethyl acetate (80:20; 500 ml.) and hexane:ethyl acetate (1:1, 9×500 ml.). Fractions 2 and 3 contain less polar impurities and dimethyl 1,3-acetonedicarboxylate; fractions 4—8 afford 4.1 g. of methyl N-(2-hydroxyethyl)-3-carbomethoxypyrrole-2-acetate (IV, R=H), which upon recrystallization from ether-hexane has a melting point of 52—54°C.

EXAMPLE 2

To a stirred solution of 4.1 g. of methyl N-(2-hydroxyethyl)-3-carbomethoxypyrrole-2-acetate in 35 ml. of dry dichloromethane cooled to −10°C, are added 2.65 ml. of triethylamine and thereafter, in a dropwise fashion, 1.46 ml. of methanesulfonyl chloride, maintaining the temperature of the reaction mixture at −10° to −5°C. The course of the reaction is followed by t.l.c. analysis using chloroform:acetone (90:10). When the reaction appears to be complete (about 30 minutes after the addition of the methanesulfonyl chloride is terminated) there is added slowly 10 ml. of water. The organic phase is separated, washed with water (3×30 ml.), dried over sodium sulfate and evaporated under reduced pressure. Crystallization of the residue from dichloromethanehexane affords 4.75 g. (77.7%) of methyl N-(2-mesyloxyethyl)-3-carbomethoxypyrrole-2-acetate (V, R=H), m.p. 99—101°C.

EXAMPLE 3

A solution of 785 mg. of methyl N-(2-mesyloxyethyl)-3-carbomethoxypyrrole-2-acetate and 1.83 g. of sodium iodide in 10 ml. of acetonitrile is refluxed for 1 hour. The cooled reaction mixture is evaporated to dryness under reduced pressure and the residue is triturated with water. The insoluble material is separated by filtration and air dried, thus obtaining 840 mg. (97%) of methyl N-(2-iodoethyl)-3-carbomethoxypyrrole-2-acetate (Vi, R=H), m.p. 137—138°C.

EXAMPLE 4

A solution of 1 g. of methyl N-(2-iodoethyl)-3-carbomethoxypyrrole-2-acetate in 5 ml. of dry dimethylformamide is stirred, under an atmosphere of argon, with 137 mg. of 50% sodium hydride in mineral oil. The reaction mixture is maintained for 30 minutes at room temperature and then quenched with 100 ml. of water. The product is extracted with ethyl acetate (3×50 ml.), the combined extracts are washed with water, dried over magnesium sulfate and evaporated to dryness. Chromatography of the residue on 20 g. of silica gel, using hexane:ethyl acetate (4:1) as eluant, affords 500 mg. (80%) of dimethyl 1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1,7-dicarboxylate (VII, R=H) m.p. 70—71°C.

A solution of 1.80 g. of dimethyl 1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1,7-dicarboxylate in 20 ml. of methanol is treated with a solution of 4.48 g. of potassium hydroxide in 20 ml. of water, and the reaction mixture is refluxed for 6 hours. The cooled solution is evaporated to dryness and the residue is treated with 50 ml. of saturated sodium chloride solution. The resultant solution is acidified with 6 N hydrochloric acid and extracted with ethyl acetate (3×50 ml.). The combined extracts are dried over magnesium sulfate and evaporated to dryness under reduced pressure, to yield 1.51 g. (95%) of 1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1,7-dicarboxylic acid (VIII, R=H), m.p. 220°C, with decomposition.

EXAMPLE 5

A solution of 1.34 g. of 1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1,7-dicarboxylic acid in 50 ml. of isopropanol, cooled in an ice bath is saturated with gaseous hydrogen chloride, maintaining the temperature of the reaction mixture below

50°C. The ice bath is then removed and the reaction mixture is stirred for 1.5 hours at room temperature, and evaporated to dryness under reduced pressure; 10 ml. of benzene is added to the residue and the solution is evaporated under vacuum once again, repeating this process a total of three times to completely remove the excess hydrogen chloride, thus obtaining 1.58 g. (96%) of isopropyl 1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate-7-carboxylic acid (IX, R=H, R^2=iC_3H_7), which upon crystallization from methanol-ethyl acetate has a melting point of 144—145°C.

In a similar manner but substituting methanol, ethanol, propanol and n-butanol for isopropanol in the above procedure there are respectively obtained:
methyl 1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate-7-carboxylic acid,
ethyl 1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate-7-carboxylic acid,
propyl 1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate-7-carboxylic acid, and
butyl 1,2-dihydro-3H-pyrrolo[1,2-a]-yrrole-1-carboxylate-7-carboxylic acid.

EXAMPLE 6

1.054 g. of isopropyl 1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate-7-carboxylic acid is heated to 240—250°C in a dry 10 ml. round bottomed flask, distilling directly the reaction product from the reaction vessel. In this manner there is obtained 745 mg. (87%) of isopropyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate (X, R=H, R^2=iC_3H_7), a pale yellow oil, having the following physical constants:

U.V.: λ_{max}^{MeOH} 215 nm (ϵ 6020);
I.R.: $\nu_{max}^{CHCl_3}$ 1725 cm^{-1};
N.M.R.: $\delta_{TMS}^{CDCl_3}$ 1.22 (d, J=7 Hz, 6 H), 2.40—2.90 (m, 2H), 3.60—4.20 (m, 2 H), 4.65—5.2 (m, 1 H), 5.73—5.92 (m, 1 H), 6.10 (t, J=3 Hz, 1 H), 6.43—6.53 ppm. (m, 1 H).

EXAMPLE 7

A 100 ml. 3-necked round bottomed flask equipped with a condenser, nitrogen inlet tube and a gas bubbler is charged with 5.0 g. of isopropyl 1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate-7-carboxylic acid. The apparatus is thoroughly flushed with nitrogen and then the nitrogen flow is stopped. The apparatus is immersed in an oil bath heated at 270°C and the reaction is followed by the rate of carbon dioxide evolution (gas bubbler) and by t.l.c. on silica gel, using benzene:dioxan:acetic acid (90:10:1) as developing solvent. After 45 minutes the reaction is almost complete. After one hour, the vessel is removed from the oil bath and the contents of the reaction flask are transferred to a round bottomed flask with 500 ml. of acetone. The solvent is removed under reduced pressure, and the residue is purified by column chromatography on 100 g. of silica gel. The fractions eluted with hexane:benzene (70:30) and hexane:benzene (50:50) afford 2.77 g. (68%) of isopropyl 1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate (X, R=H, R^2=iC_3H_7), an oil, whose physical constants are identical to those obtained in Example 6.

EXAMPLE 8

A solution of 179 mg. of N,N-dimethyl-p-toluamide and 0.11 ml. of phosphorous oxychloride in 2 ml. of 1,2-dichloroethane is refluxed for 30 minutes. To this solution is added a solution of 193 mg. of isopropyl 1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate in 2 ml. of 1,2-dichloroethane. The reaction mixture is refluxed under an argon atmosphere for 8 hours, treated with 405 mg. of sodium acetate and refluxed for a further 5 hours. The resultant mixture is then evaporated to dryness and the residue is chromatographed on 12 g. of silica gel, eluting with hexane:ethyl acetate (3:1), thus obtaining 208 mg. (66%) of isopropyl 5-p-toluoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate (XI, R=H, R^1=p-CH_3, R^2=iC_3H_7), an oil, having the following physical constants:

U.V.: λ_{max}^{MeOH} 256, 312 nm, (ϵ 8700, 19500);
I.R.: ν_{max}^{film} 1735, 1620, 1605 cm^{-1};
N.M.R.: $\delta_{TMS}^{CDCl_3}$ 1.23 (d, J=7 Hz, 6 H), 2.38 (s, 3 H), 2.5—3.0 (m, 2 H), 3.75—4.10 (m, 1 H), 4.2—4.60 (m, 2 H), 4.85—5.20 (m, 1 H), 5.95 (d, J=4 Hz, 1 H), 6.70 (d, J=4 Hz, 1 H), 7.10 (d, J=8 Hz, 2 H), 7.60 ppm (d, J=8 Hz, 2 H).

EXAMPLE 9

A solution of 336 mg. of isopropyl 5-p-toluoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate in 10 ml. of methanol is treated with a solution of 690 mg.

of potassium carbonate in 5 ml. of water. The reaction mixture is refluxed under nitrogen atmosphere for 30 minutes, cooled, and evaporated to dryness. The residue is taken up in 10 ml. of 10% aqueous hydrochloric acid and 50 ml. of water and the resultant mixture extracted with ethyl acetate (2×50 ml.). The combined extracts are dried over magnesium sulfate and evaporated to dryness under reduced pressure. Crystallization of the residue from ethyl acetate-hexane affords 238 mg. (89%) of 5-p-toluoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid [(A), R=H, R¹=p-CH_3], m.p. 182—183°C.

EXAMPLE 10

A solution of 250 mg. of isopropyl 5-p-toluoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate in 8 ml. of methanol is treated under an atmosphere of nitrogen, with a solution of 200 mg. of sodium hydroxide in 1 ml. of water, maintaining the reaction mixture at room temperature for 1.5 hours. The methanol is then removed under reduced pressure and the basic solution which remains is diluted with 5 ml. of water and extracted with ether to remove any unsaponifiable product. The aqueous solution is acidified with 10% hydrochloric acid and extracted three times with ethyl acetate. The combined extracts are dried and evaporated to dryness under reduced pressure, and the residue crystallized from ethyl acetate-hexane, to give 5-p-toluoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid, identical to the product obtained in Example 9.

EXAMPLE 11

By following the methods of Example 6 or 7, the remaining compounds obtained in Example 5 are converted respectively into:

methyl 1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate,
ethyl 1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate,
propyl 1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate, and
butyl 1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate.

Upon condensation of these compounds with N,N-dimethyl-p-toluamide, in accordance with the method of Example 8 there are respectively obtained:

methyl 5-p-toluoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate,
ethyl 5-p-toluoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate,
propyl 5-p-toluoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate, and
butyl 5-p-toluoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate.

EXAMPLE 12A

Following the procedure of Example 8 using 1.1 to 5 molar equivalents of N,N-dimethyl-benzamide,

N,N-dimethyl-o-toluamide,
N,N-dimethyl-m-toluamide,
N,N-dimethyl-p-ethyl-benzamide,
N,N-dimethyl-o-propyl-benzamide,
N,N-dimethyl-m-butyl-benzamide,
N,N-dimethyl-o-methoxy-benzamide,
N,N-dimethyl-p-methoxy-benzamide,
N,N-dimethyl-p-ethoxy-benzamide,
N,N-dimethyl-p-isopropoxy-benzamide,
N,N-dimethyl-o-chloro-benzamide,
N,N-dimethyl-m-chloro-benzamide,
N,N-dimethyl-p-chloro-benzamide,
N,N-dimethyl-o-fluoro-benzamide,
N,N-dimethyl-p-fluoro-benzamide,
N,N-dimethyl-m-bromo-benzamide, and
N,N-dimethyl-p-bromo-benzamide,

in place of N,N-dimethyl-p-toluamide, and monitoring the course of the reaction by t.l.c., there are obtained respectively:

isopropyl 5-benzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate, a light yellow oil, having the following physical constants:

U.V.: λ_{max}^{MeOH} 245, 311 nm (ε 7230, 17800);
I.R. $\upsilon_{max}^{CHCl_3}$ 1735, 1620 cm^{-1};
N.M.R.: $\delta_{TMS}^{CDCl_3}$ 1.24 [d, 6 H, $(CH_3)_2CH$], 2.50—3.13 (m, 2 H; H-2); 3.97 (dd, 1 H, H-1), 4.18—4.70 (m, 2 H, H-3), 5.00 (sept., 1 H, $(CH_3)_2CH$), 6.00 (d, 1 H, H-7), 6.86 (d, 1 H, H-6), 7.10—7.90 ppm (m, 5H, phenyl protons); M.S.: m/e 297 (M^+),

isopropyl 5-o-toluoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate, an oil, having the following physical constants:
U.V.: λ_{max}^{MeOH} 252, 303 nm (ε 4460, 19100);
I.R.: $\upsilon_{max}^{CHCl_3}$ 1735, 1620 cm^{-1};
N.M.R.: $\delta_{TMS}^{CDCl_3}$ 1.18 [d, 6 H, $(CH_3)_2CH$], 2.28 (s, 3 H-, o-CH_3), 2.50—3.13 (m, 2 H, H-2), 3.92 (dd, 1 H, H-1), 4.17—4.70 (m, 2 H, H-3), 4.98 [sept. 1 H, $(CH_3)_2CH$], 5.92 (d, 1 H, H-7), 6.43 (d, 1 H, H-6), 6.97—7.45 ppm (m, 4 H, phenyl protons).

isopropyl 5-m-toluoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate, an oil, having the following physical constants:
U.V.: λ_{max}^{MeOH} 250—251, 310—312 nm (ε 6460, 17400);
I.R.: $\upsilon_{max}^{CHCl_3}$ 1735, 1620 cm^{-1};
N.M.R.: $\delta_{TMS}^{CDCl_3}$ 1.25 [d, 6 H, $(CH_3)_2CH$], 2.27 (s, 3 H, CH_3), 2.52—3.13 (m, 2 H, H-2), 3.92 (dd, 1 H, H-1), 4.13—4.70 (m, 2 H, H-3), 4.95 [sept. 1 H, $(CH_3)_2CH$], 5.95 (d, 1 H, H-7), 6.67 (d, 1 H, H-6), 7.03—7.57 ppm. (m, 4 H; phenyl protons),

isopropyl 5-p-ethylbenzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate,

isopropyl 5-o-propylbenzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate,

isopropyl 5-m-butylbenzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate,

isopropyl 5-o-methoxybenzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate,

isopropyl 5-p-methoxybenzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate, having the following physical constants:
U.V. λ_{max}^{MeOH} 218, 270—284 (shoulder), 314 nm (ε 9780, 9320, 22400);
I.R. $\upsilon_{max}^{CHCl_3}$ 1730, 1605 cm^{-1};
N.M.R. $\delta_{TMS}^{CDCl_3}$ 1.24 [d, 6 H, J=6 Hz; $(CH_3)_2CH$—], 2.50—3.10 (m, 2 H; H-2), 3.78 (s, 3 H; CH_3O), 3.93 (dd, 1 H, J_{AX}=6 Hz, J_{BX}=7 Hz; H-1), 4.13—4.60 (m, 2 H; H-3), 4.95 [sept., 1 H, J=6 Hz; $(CH_3)_2CH$], 5.95 (s, 1 H, J=4 Hz; H-7), 6.68 (d, 1 H, J=4 Hz; H-6), 6.70—7.90 ppm. (m, 4 H; phenyl protons); M.S. m/e 327 (M^+).

isopropyl 5-p-ethoxybenzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate, m.p. 94—95°C.,

isopropyl 5-p-isopropoxybenzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate,

isopropyl 5-o-chlorobenzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate, an oil, having the following physical constants:
U.V.: λ_{max}^{MeOH} 251, 306 nm (ε 5750, 16600);
I.R.: $\upsilon_{max}^{CHCl_3}$ 1735, 1625 cm^{-1};
N.M.R.: $\delta_{TMS}^{CDCl_3}$ 1.22 [d, 6 H, $(CH_3)_2CH$], 2.55—3.05 (m, 2 H; H-2), 3.97 (dd, 1 H, H-1), 4.17—4.70 (m, 2 H, H-3), 4.97 [sept., 1 H, $(CH_3)_2CH$], [5.93 (d, 2/3 H), 6.00 (d, 1/3 H) H-7], [6.42 (d, 2/3 H), 6.67 (d, 1/3 H), H-6], 7.07—7.80 ppm (m, 4 H; phenyl protons),

isopropyl 5-m-chlorobenzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate, an oil, having the following physical constants:
U.V.: λ_{max}^{MeOH} 241, 313 nm (ε 6600, 15100);
I.R.: $\upsilon_{max}^{CHCl_3}$ 1735, 1620, 1570 cm^{-1};
N.M.R.: $\delta_{TMS}^{CDCl_3}$ 1.27 [d, 6 H, $(CH_3)_2CH$], 2.50—3.18 (m, 2 H, H-2), 3.93 (dd, 1 H, H-1), 4.10—4.63 (m, 2 H, H-3), 4.98 [sept., 1 H, $(CH_3)_2CH$], 5.98 (d, 1 H, H-7), 6.67 (d, 1 H, H-6), 7.07—7.78 ppm. (m, 4 H, phenyl protons); M.S.: m/e 331—333 (M^+),

isopropyl 5-p-chlorobenzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate, m.p. 80.5—81°C.,

isopropyl 5-o-fluorobenzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate,

isopropyl 5-p-fluorobenzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate, m.p. 72—72.5°C.,

isopropyl 5-m-bromobenzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate, and

isopropyl 5-p-bromobenzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate.

Upon hydrolysis of the isopropyl ester group, in accordance with the methods of Examples 9 or 10, there are obtained the corresponding free acids, namely:

5-benzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid, m.p. 160—161°C.,

5-o-toluoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid, an oil, having the following physical constants:

U.V.: λ_{max}^{MeOH} 253, 307 nm (ε 3310, 16980);

I.R.: $\nu_{max}^{CHCl_3}$ 1720, 1620 cm^{-1};

N.M.R.: $\delta_{TMS}^{CDCl_3}$ 2.32 (s, 3 H, CH_3), 2.53—3.03 (m, 2 H, H-2), 3.97 (dd, 1 H, H-1), 4.17—4.67 (m, 2 H, H-3), 6.92 (d, 1 H, H-7), 6.40 (d, 1 H, H-6), 6.83—7.37 (m, 4 H, phenyl protons), 8.60 ppm. (b.s, 1 H, COOH),

5-m-toluoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid,

5-p-ethylbenzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid,

5-o-propylbenzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid,

5-m-butylbenzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid,

5-o-methoxybenzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid,

5-p-methoxybenzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid, m.p. 187—187.5°C.,

5-p-ethoxybenzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid, m.p. 169.5—170°C.,

5-p-isopropoxybenzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid,

5-o-chlorobenzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid, having the following physical constants:

U.V.: λ_{max}^{MeOH} 250, 307.5 nm (ε 4360, 17400);

I.R.: $\nu_{max}^{CHCCl_3}$ 1715, 1620 cm^{-1};

N.M.R.: $\delta_{TMS}^{CDCl_3}$ 2.60—3.15 (m, 2 H; H-2), 4.02 (dd, 1 H, J_{AX}=6 Hz, J_{BX}=7 Hz; H-1), 4.20—4.70 (m, 2 H; H-3), 5.98 (d, 1 H, J=4 Hz; H-7), 6.42 (d, 1 H, J=4 Hz; H-6), 7.00—7.77 (m 4 H; phenyl protons), 8.67 ppm [s, (br), 1 H; COO*H*],

5-m-chlorobenzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid, m.p. 180—181°C.,

5-p-chlorobenzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid, m.p. 201.5—202.5°C.,

5-o-fluorobenzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid,

5-p-fluorobenzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid, m.p. 179.5—180.5°C.,

5-m-bromobenzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid, and

5-p-bromobenzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid.

EXAMPLE 12 B

To a solution of 300 mg. of 5-benzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid in 25 ml. of dry benzene, 0.58 g. of trifluoroacetic anhydride is added. The mixture is stirred at room temperature for 10 minutes and the resulting solution is cooled to 0—5°C and 1.4 g. of dry triethylamine is added, followed immediately by the addition of 0.5 g. of (l)-α-phenyl ethyl alcohol. The thus-obtained reaction solution is stirred at room temperature for 15 minutes and poured into 20 ml. of water containing 1 ml. of triethylamine, followed by extraction with ethyl acetate. The ethyl acetate extract is dried over sodium sulfate, followed by removal of the solvent and excess (l)-α-phenyl ethyl alcohol under vacuum to yield 0.42 g. of a mixture of (l)-5-benzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid (l)-α-phenethyl ester and (d)-5-benzoyl-1,2-dihydro-3H-pyrrolo[1,2-α]pyrrole-1-carboxylic acid-(l)-α-phenethyl ester which is separated by high pressure liquid chromatography (using 4% EtOAc/hexane on a 11 mm.×50 cm., 10 μm. Lichrosorb (Trade Mark) S1-60 column) to give 180 mg. of a more polar ester (α_D^{MeOH} −145.7°) and 178 mg. of a less polar ester (α_D^{MeOH} +128.6°).

148 mg. of the more polar ester is dissolved in 8 ml. of dry benzene. The solution is cooled to 15—20°C and 5 ml. of trifluoroacetic acid is added and the solution stirred at room temperature for 1 hour and 10 minutes. The reaction solution is poured into 60 ml. of dry benzene and the solvents are removed under vacuum and at ambient temperature. Purification is effected by high pressure liquid chromatography (using a column as that described above, except that 35% EtOAc/hexane in 1/2% acetic acid is substituted for 4% EtOAc/hexane) to give 63 mg. (l)-5-benzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid having an $\alpha_D^{CHCl_3}$ −153.7°, and a melting point of 153—155°C.

Similarly, cleavage of the less polar ester, according to the method described

above for the cleavage of the more polar ester, yields 85 mg. of (d)5-benzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid having an $\alpha_D^{CHCl_3}$ +155.1°, and a melting point of 154—156°C. The thus-obtained (d)-acid isomer may, if desired, be racemized (and recycled), according to methods known in the art.

Similarly other (dl) compounds may be converted to their respective (l)-isomers and (d)-isomers.

EXAMPLE 13A

A 250 ml. 3-necked round bottomed flask containing a magnetic stirring bar and fitted with a calcium chloride filled drying tube, is charged with a 3.36 g. of ethanolamine, cooled in an ice bath at 0°—10°C and treated dropwise, with stirring, with 8.7 g. of dimethyl 1,3-acetonedicarboxylate. Methyl 3-carbomethoxymethyl-3-(2'-hydroxyethyl)amino acrylate (III) forms immediately. When the addition is completed, the ice bath is removed and 80 ml. of dry acetonitrile is added. The reaction mixture is then treated dropwise with 6.75 g. of bromoacetaldehyde in 20 ml. of acetonitrile and thereafter heated at reflux temperature for 2 hours. The solvent is then removed under reduced pressure and 200 ml. of methanol and 20 g. of silica gel are added to the residue. This mixture is evaporated to dryness in vacuum and placed on top of a column of 200 g. of silica gel packed in hexane, eluting the column with hexane:ethyl acetate mixtures. The fractions eluted with hexane:ethyl acetate (1:1) afford methyl N-(2-hydroxyethyl)-3-carbomethoxypyrrole-2-acetate (IV, R=H) identical to the product obtained in Example 1.

EXAMPLE 13B

To a solution of 6 ml. of ethanolamine in 5 ml. of water there is added 1.74 g. of dimethyl 1,3-acetonedicarboxylate. The resultant mixture is rapidly cooled to −10°C and treated dropwise, over a 15 minute period, with stirring, with 1.67 ml. of 1-bromoacetone, whilst maintaining the reaction mixture at a temperature not higher than 40°C. When the addition is completed the dark reaction mixture is stirred for an additional hour at room temperature, and then poured into a mixture of hydrochloric acid-ice, saturated with solid sodium chloride and extracted with ethyl acetate (3×100 ml.). The combined organic extract is washed with cold water to neutrality, dried with anhydrous sodium sulfate and evaporated to dryness under reduced pressure. Chromatography of the residue on 30 g. of silica gel, using hexane:ethyl acetate (70:30) as eluant, affords 890 mg. of crystalline methyl N-(2-hydroxyethyl)-3-carbomethoxy-4-methylpyrrole-2-acetate which upon recrystallization from methylene chloride-hexane melts at 78°C and has the following analysis:

Calculated for $C_{12}H_{17}NO_5$: C, 56.45; H, 6.71.
Found: C, 56.41; H, 6.73.

In a similar manner but using a stoichiometric equivalent of 1-bromo-2-butanone, 1-bromo-2-pentanone, and 1-bromo-2-hexanone in place of 1-bromoacetone there are respectively obtained:

methyl N-(2-hydroxyethyl)-3-carbomethoxy-4-ethylpyrrole-2-acetate,
methyl N-(2-hydroxyethyl)-3-carbomethoxy-4-propylpyrrole-2-acetate, and
methyl N-(2-hydroxyethyl)-3-carbomethoxy-4-butylpyrrole-2-acetate.

EXAMPLE 14

By following the methods of Examples 2, 3, 4, 5 and 7 methyl N-(2-hydroxyethyl)-3-carbomethoxy-4-methylpyrrole-2-acetate (IV, R=CH_3) is converted successively into:

methyl N-(2-mesyloxyethyl)-3-carbomethoxy-4-methylpyrrole-2-acetate,
methyl N-(2-iodoethyl)-3-carbomethoxymethyl-4-methylpyrrole-2-acetate,
dimethyl 1,2-dihydro-6-methyl-3H-pyrrolo[1,2-a]pyrrole-1,7-dicarboxylate,
1,2-dihydro-6-methyl-3H-pyrrolo[1,2-a]pyrrole-1,7-dicarboxylic acid,
isopropyl 1,2-dihydro-6-methyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate-7-carboxylic acid, and
isopropyl 1,2-dihydro-6-methyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate (X, R=CH_3, R^2=iC_3H_7).

In a similar manner substituting methyl N-(2-hydroxyethyl)-3-carbomethoxy-4-ethylpyrrole-2-acetate, methyl N-(2-hydroxyethyl)-3-carbomethoxy-4-propylpyrrole-2-acetate and methyl N-(2-hydroxyethyl)-3-carbomethoxy-4-butylpyrrole-2-acetate for methyl N-(2-hydroxyethyl)-3-carbomethoxy-4-methylpyrrole-2-acetate there are respectively obtained as final products:

isopropyl 1,2-dihydro-6-ethyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate,

isopropyl 1,2-dihydro-6-propyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate, and
isopropyl 1,2-dihydro-6-butyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate.

EXAMPLE 15

In accordance with the method of Example 8, isopropyl 1,2-dihydro-6-methyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate is condensed with N,N-dimethyl-p-toluamide, to produce isopropyl-5-toluoyl-1,2-dihydro-6-methyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate (XI, R=CH_3, R^1=p-CH_3, R^2=iC_3H_7).

In a similar manner but using the N,N-dimethyl arylamides listed in Example 12A in place of N,N-dimethyl-p-toluamide, there are respectively obtained:

isopropyl 5-benzoyl-1,2-dihydro-6-methyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate,

isopropyl-5-o-toluoyl-1,2-dihydro-6-methyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate,

isopropyl 5-m-toluoyl-1,2-dihydro-6-methyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate,

isopropyl 5-p-ethylbenzoyl-1,2-dihydro-6-methyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate,

isopropyl 5-o-propylbenzoyl-1,2-dihydro-6-methyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate,

isopropyl 5-m-butylbenzoyl-1,2-dihydro-6-methyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate,

isopropyl 5-o-methoxybenzoyl-1,2-dihydro-6-methyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate,

isopropyl 5-p-methoxybenzoyl-1,2-dihydro-6-methyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate,

isopropyl 5-p-ethoxybenzoyl-1,2-dihydro-6-methyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate,

isopropyl 5-p-isopropoxybenzoyl-1,2-dihydro-6-methyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate,

isopropyl 5-o-chlorobenzoyl-1,2-dihydro-6-methyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate,

isopropyl 5-m-chlorobenzoyl-1,2-dihydro-6-methyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate,

isopropyl 5-p-chlorobenzoyl-1,2-dihydro-6-methyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate,

isopropyl 5-o-fluorobenzoyl-1,2-dihydro-6-methyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate,

isopropyl 5-p-fluorobenzoyl-1,2-dihydro-6-methyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate, having the following physical constants:

U.V.: λ_{max} 250, 315 nm (ε 6170, 14,100);
I.R.: $\upsilon_{max}^{CHCl_3}$ 1734, 1605, 1593 cm^{-1};
N.M.R.: $\delta_{TMS}^{CDCl_3}$ 1.25 (d, 6 H, J=6 Hz; ester CH_3), 1.83 (s, 3 H; ring CH_3), 2.49—3.00 (m, 2H; CH_2), 3.90 (t, 1 H, ΣJ=7.4 Hz; CHCO), 4.10—4.23 (m, 2 H; N—CH_2), 4.98 (sept., 1 H, J=6 Hz; ester CH), 5.94 (s, 1 H, H-3), 7.00 (t, 2 H, J_{ortho}=8.4 Hz, J_{HF}=8 Hz; H-3′, 5′), 7.55 (q, 2 H, J_{ortho}=8.4 Hz, J_{HF}=5.5 Hz; H-2, 6′); M.S. m/e, 1%, 329, 25 M^+ 242, 100 M^+—$CO_2CH(CH_3)_2$, 123, 36 F—C_6H_4CO,

isopropyl 5-m-bromobenzoyl-1,2-dihydro-6-methyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate, and

isopropyl 5-p-bromobenzoyl-1,2-dihydro-6-methyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate.

Likewise, the remaining final compounds obtained in Example 14 are converted into the corresponding 5-aroyl substituted derivatives. Representative compounds thus obtained are:

isopropyl 5-benzoyl-1,2-dihydro-6-ethyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate,

isopropyl 5-benzoyl-1,2-dihydro-6-propyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate,

isopropyl 5-benzoyl-1,2-dihydro-6-butyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate,

isopropyl 5-p-toluoyl-1,2-dihydro-6-ethyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate,

isopropyl 5-p-ethylbenzoyl-1,2-dihydro-6-propyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate,

isopropyl 5-o-methoxybenzoyl-1,2-dihydro-6-butyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate,
isopropyl 5-p-ethoxybenzoyl-1,2-dihydro-6-ethyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate,
isopropyl 5-o-chlorobenzoyl-1,2-dihydro-6-propyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate,
isopropyl 5-m-chlorobenzoyl-1,2-dihydro-6-butyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate,
isopropyl 5-o-fluorobenzoyl-1,2-dihydro-6-ethyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate,
isopropyl 5-p-fluorobenzoyl-1,2-dihydro-6-propyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate, and
isopropyl 5-p-bromobenzoyl-1,2-dihydro-6-butyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate.

EXAMPLE 16

A solution of 500 mg. of isopropyl 5-p-toluoyl-1,2-dihydro-6-methyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate in 15 ml. of methanol is treated with a solution of 1.05 g. of potassium carbonate in 8 ml. of water. The reaction mixture is refluxed under nitrogen atmosphere for 30 minutes, cooled, and evaporated to dryness. The residue is taken up in 10 ml. of 10% aqueous hydrochloric acid and 50 ml. of water and the resultant mixture extracted with ethyl acetate (3×50 ml.). The combined extracts are dried over magnesium sulfate and evaporated to dryness under reduced pressure, to give 5-p-toluoyl-1,2-dihydro-6-methyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid [(A), R=CH_3, R^1=p-CH_3].

In a similar manner, or alternatively by the hydrolysis method of Example 10, the remaining isopropyl ester compounds obtained in Example 15 are converted into the corresponding free acids, namely:
5-benzoyl-1,2-dihydro-6-methyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid,
5-o-toluoyl-1,2-dihydro-6-methyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid,
5-m-toluoyl-1,2-dihydro-6-methyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid,
5-p-ethylbenzoyl-1,2-dihydro-6-methyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid,
5-o-propylbenzoyl-1,2-dihydro-6-methyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid,
5-m-butylbenzoyl-1,2-dihydro-6-methyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid,
5-o-methoxybenzoyl-1,2-dihydro-6-methyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid,
5-p-methoxybenzoyl-1,2-dihydro-6-methyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid,
5-p-ethoxybenzoyl-1,2-dihydro-6-methyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid,
5-p-isopropoxybenzoyl-1,2-dihydro-6-methyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid,
5-o-chlorobenzoyl-1,2-dihydro-6-methyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid,
5-m-chlorobenzoyl-1,2-dihydro-6-methyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid,
5-p-chlorobenzoyl-1,2-dihydro-6-methyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid,
5-o-fluorobenzoyl-1,2-dihydro-6-methyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid,
5-p-fluorobenzoyl-1,2-dihydro-6-methyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid, m.p. 204°C.,
5-m-bromobenzoyl-1,2-dihydro-6-methyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid,
5-p-bromobenzoyl-1,2-dihydro-6-methyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid,
5-benzoyl-1,2-dihydro-6-ethyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid,
5-benzoyl-1,2-dihydro-6-propyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid,
5-benzoyl-1,2-dihydro-6-butyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid,
5-p-toluoyl-1,2-dihydro-6-ethyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid,
5-p-ethylbenzoyl-1,2-dihydro-6-propyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid,

5-o-methoxybenzoyl-1,2-dihydro-6-butyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid,

5-p-ethoxybenzoyl-1,2-dihydro-6-ethyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid,

5-o-chlorobenzoyl-1,2-dihydro-6-propyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid,

5-m-chlorobenzoyl-1,2-dihydro-6-butyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid,

5-o-fluorobenzoyl-1,2-dihydro-6-ethyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid,

5-p-fluorobenzoyl-1,2-dihydro-6-propyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid, and

5-p-bromobenzoyl-1,2-dihydro-6-butyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid.

EXAMPLE 17

710 mg. of a 50% suspension of sodium hydride in mineral oil is washed with anhydrous hexane under an atmosphere of nitrogen, and then suspended in 50 ml. of dimethylformamide. The suspension is cooled to −5°C and 4.5 g. of methyl N-(2-mesyloxymethyl)-3-carbomethoxypyrrole-2-acetate are added, stirring the reaction mixture at −5° to 0°C for 1 hour. It is then poured into iced sodium chloride solution and extracted several times with benzene. the combined extracts are washed with water, dried and evaporated to dryness under reduced pressure. The solid residue is crystallized from ether, thus obtaining dimethyl 1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1,7-dicarboxylate (VII, R=H) identical to the product obtained in Example 4.

EXAMPLE 18

To a 250 ml. of 3-necked round bottomed flask, fitted with a dry nitrogen inlet-outlet valve, a magnetic stirrer bar, and a pressure equalized addition funnel, containing 10.08 g. of ethanolamine, there is added dropwise, with stirring, 26.1 g. of dimethyl 1,3-acetonedicarboxylate over a period of 30 minutes whilst maintaining the temperature below 30°C. The methyl 3-carbomethoxymethyl-3-(2'-hydroxyethyl)-aminoacrylate (III) which is formed is diluted with 20 ml. of acetonitrile and chloroacetaldehyde, previously prepared by heating a mixture of 27.4 g. of chloroacetaldehyde diethyl acetal with 46.8 g. of oxalic acid dihydrate at 150° to 160°C, is added with stirring over a 2 minute period. The reaction mixture is refluxed for 5 to 10 minutes, after which time the reaction is found to be complete, as measured by t.l.c. analysis using acetone-chloroform (10:90) as eluant. The solvent is removed under reduced pressure and to the residue is added 250 ml. of benzene and 250 ml. of heptane, and distillation is then carried out under reduced pressure. The oily residue remaining, following distillation, is suspended in 50 ml. of methylene chloride and 20 g. of silica gel is added thereto. The methylene chloride mixture is poured onto a column containing 200 g. of silica gel made up in ethyl acetate:hexane (20:80). The column is first eluted with 6 liters of ethyl acetate:hexane (20:80) and then with 4 liters of ethyl acetate:hexane (50:50). Those fractions eluted with ethyl acetate:hexane (50:50) are combined and concentrated to give 12.8 g. of an oil which is triturated with 20 ml. of petroleum ether (30°—60°C), followed by removal of the solvent under reduced pressure to yield 11.89 g. (32.9% of theory) of methyl N-(2'-hydroxyethyl)-3-carbomethoxypyrrole-2-acetate (IV, R=H) having a melting point of 51—54°C, the same product obtained in Example 1.

EXAMPLE 19

A solution of 200 mg. of 5-benzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid in 5 ml. of dichloromethane is treated with an excess of ethereal diazomethane, and the reaction mixture is maintained at room temperature for 30 minutes. The solvents and excess reagent are eliminated under reduced pressure and the residue crystallized from ethyl acetate-methanol, to yield methyl 5-benzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate.

Likewise but using diazoethane and diazopropane in place of diazomethane there are respectively obtained ethyl 5-benzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate and propyl 5-benzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate.

In a similar manner, the remaining free acids obtained in Examples 12A (and 12B) and the acids of Example 16 are converted into the corresponding methyl, ethyl and propyl esters.

EXAMPLE 20

A solution of 300 mg. of 5-p-toluoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid in 5 ml. of isoamyl alcohol is saturated with hydrogen chloride. After 24 hours, the excess alcohol is distilled off in vacuo and the residue purified by chromatography on alumina, to yield isoamyl 5-p-toluoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate.

Likewise other esters, e.g., pentyl, hexyl, octyl, nonyl and dodecyl, of 5-p-toluoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid are obtained by substituting other alcohols, e.g., pentyl, hexyl, octyl, nonyl and dodecyl alcohol for isoamyl alcohol.

By the same method the free acid compounds obtained in Examples 12A and 16 are esterified with the appropriate alcohol thus obtaining the corresponding esters, e.g.,

isoamyl 5-benzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate,
pentyl 5-m-toluoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate,
hexyl 5-p-ethylbenzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate,
isoamyl 5-o-propylbenzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate,
octyl 5-p-methoxybenzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate,
nonyl 5-p-isopropoxybenzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate,
dodecyl 5-o-chlorobenzyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate,
isoamyl 5-m-chlorobenzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate,
dodecyl 5-o-fluorobenzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate,
hexyl 5-p-fluorobenzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate,
nonyl 5-p-bromobenzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate,
isoamyl 5-benzoyl-1,2-dihydro-6-methyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate,
hexyl 5-p-ethylbenzoyl-1,2-dihydro-6-methyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate,
nonyl 5-o-methoxybenzoyl-1,2-dihydro-6-methyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate,
dodecyl 5-o-fluorobenzoyl-1,2-dihydro-6-methyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate,
nonyl 5-benzoyl-1,2-dihydro-6-ethyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate,
isoamyl 5-p-ethoxybenzoyl-1,2-dihydro-6-ethyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate,
pentyl 5-p-fluorobenzoyl)1,2-dihydro-6-propyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate,
hexyl 5-m-chlorobenzoyl-1,2-dihydro-6-butyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate, and
dodecyl 5-p-bromobenzoyl-1,2-dihydro-6-butyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate.

EXAMPLE 21

To a solution of 300 mg. of 5-p-toluoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid in 5 ml. of methanol is added 1 molar equivalent of sodium hydroxide, in the form of a 0.1 N solution. The solvent is then evaporated under reduced pressure and the residue taken up in 2 ml of methanol, followed by precipitation with ether, to yield crude sodium 5-p-toluoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate which can be crystallized from ethyl acetate-hexane.

Likewise other salts, e.g., ammonium and potassium of 5-p-toluoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid are prepared by substituting ammonium hydroxide and potassium hydroxide for sodium hydroxide.

In a similar manner, the 5-substituted-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid compounds obtained in Examples 12A (and 12B) and 16 can be converted into the corresponding sodium, potassium and ammonium salts. Representative compounds thus obtained are:

sodium 5-o-toluoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate,
sodium 5-benzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate,

sodium (l)-5-benzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate,
potassium 5-p-ethylbenzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate,
potassium 5-o-butylbenzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate,
sodium 5-p-methoxybenzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate,
ammonium 5-p-chlorobenzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate,
ammonium 5-o-fluorobenzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate,
potassium 5-p-bromobenzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate,
sodium 5-benzoyl-1,2-dihydro-6-ethyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate,
potassium 5-toluoyl-1,2-dihydro-6-methyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate,
ammonium 5-o-methoxybenzoyl-1,2-dihydro-6-methyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate,
sodium 5-p-fluorobenzoyl-1,2-dihydro-6-propyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate, and
potassium 5-m-chlorobenzoyl-1,2-dihydro-6-butyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate.

EXAMPLE 22

To a solution of 175 mg. of 5-p-toluoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid in 5 ml. of methanol is added 1 molar equivalent of potassium hydroxide, in the form of 0.1 N solution, thus yielding a solution containing potassium 5-p-toluoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate. A solution of 40 mg. of calcium carbonate dissolved in the minimum amount of 1 N hydrochloric acid necessary to effect solution of the calcium carbonate, is buffered with 100 mg. of solid ammonium chloride, followed by the further addition of 5 ml. of water. The thus obtained buffered calcium solution is then added to the solution of potassium 5-p-toluoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate and the precipitate which forms is collected by filtration, washed with water and air dried, to yield calcium 5-p-toluoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate.

Likewise, magnesium 5-p-toluoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate is prepared by substituting magnesium carbonate for calcium carbonate.

Similarly, by substituting 5-benzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid,
(l)-5-benzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid,
5-p-chlorobenzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid,
5-o-methoxybenzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid,
5-p-methoxybenzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid,
5-benzoyl-1,2-dihydro-6-methyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid, and
5-o-fluorobenzoyl-1,2-dihydro-6-ethyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid for
5-p-toluoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid there are obtained the corresponding calcium and magnesium salts.

EXAMPLE 23

To a solution of 200 mg. of 5-p-toluoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid in 5 ml. of methanol is added 1 molar equivalent of potassium hydroxide in the form of a 0.1 N solution. The solvent is stripped and the residue is dissolved in 5 ml. of water. The thus obtained aqueous solution of potassium 5-p-toluoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate is added to a solution of 150 mg. of cupric nitrate trihydrate in 5 ml. of water. The formed precipitate is collected, washed with water and air dried, thus obtaining copper 5-p-toluoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate.

In a similar manner the free acid compounds obtained in Examples 12A (and 12B) and 16 can be converted into the corresponding copper salts.

EXAMPLE 24

A solution of 200 mg. of 5-p-toluoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-

carboxylic acid in 15 ml. of hot benzene is treated with 60 mg. of isopropylamine. The solution is allowed to cool to room temperature and the product filtered off, washed with ether and dried to yield the isopropylamine salt of 5-p-toluoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid.

Likewise other amine salts, e.g., diethylamine, ethanolamine, piperidine, tromethamine, choline and caffeine salts of 5-p-toluoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid are prepared by substituted each of the respective amines for isopropylamine.

In similar manner the free acid compounds obtained in Examples 12A (and 12B) and 16 can be converted into the corresponding isopropylamine, diethylamine, ethanolamine, piperidine, tromethamine, choline and caffeine salts.

EXAMPLE 25

A solution of 770 mg. of 5-o-toluoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid in 10 ml. of benzene is treated with 580 mg. of dicyclohexylamine. The reaction mixture is stirred for 10 minutes, and the solid which forms is separated by filtration and washed with anhydrous ether thus obtained 965 mg. of the dicyclohexylamine salt of 5-o-toluoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid, m.p. 161—163°C.

In a similar manner the remaining free acid compounds obtained in Examples 12A (and 12B) and the compounds of Examples 9 and 16 can be converted into the corresponding dicyclohexylamine salts, e.g., the dicylcohexylamine salt of 5-o-chlorobenzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid, m.p. 173—175°C.

EXAMPLE 26

Ingredients	Quantity per tablet, mgs.
5-benzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid	25
cornstarch	20
lactose, spray-dried	153
magnesium stearate	2

The above ingredients are thoroughly mixed and pressed into single scored tablets.

EXAMPLE 27

Ingredients	Quantity per tablet, mgs.
5-benzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid	200
cornstarch	50
lactose	145
magnesium stearate	5

The above ingredients are mixed intimately and pressed into single scored tablets.

100 mg. of (l)-5-benzoyl-1,2-hydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid is substituted for the 200 mg. of the (dl) compound of the above composition.

EXAMPLE 28

Ingredients	Quantity per capsules, mgs.
sodium 5-benzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate	108
lactose	15
cornstarch	25
magnesium stearate	2

The above ingredients are mixed and introduced into a hard-shell gelatin capsule.

EXAMPLE 29

Ingredients	Quantity per capsule, mgs.
calcium 5-benzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate	115
lactose	93
cornstarch	40
magnesium stearate	2

The above ingredients are mixed and introduced into a hard-sheel gelatin capsule.

EXAMPLE 30

Ingredients	Quantity per tablet, mgs.
isopropylammonium 5-benzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate	245
cornstarch	75
lactose	175
magnesium stearate	5

The above ingredients are mixed intimately and pressed into single scored tablets.

EXAMPLE 31

Ingredients	Quantity per capsule, mgs.
methyl 5-benzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate	25
lactose	125

The above ingredients are mixed and introduced into a No. 1 hard-shell gelatin capsule.

EXAMPLE 32

Ingredients	Quantity per tablet, mgs.
5-benzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid	300
sucrose	300

The above ingredients are thoroughly mixed and processed into single scored tablets, one tablet being administered every three to four hours.

EXAMPLE 33

Ingredients	Quantity per tablet, mgs.
isoamyl 5-benzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate	254
cornstarch	50
lactose	190
magnesium stearate	6

The above ingredients are mixed intimately and pressed into single scored tablets.

EXAMPLE 34

Ingredients	Quantity per capsule, mgs.
5-benzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid	100
lactose	148
dextrose	2

The above ingredients are mixed and introduced into a hard-shell gelatin capsule.

50 mg. of (l)-5-benzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid is substituted for the 100 mg. of the (dl) compound of the above composition.

Example 35

Ingredients	Quantity per capsule, mgs.
methyl 5-benzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate	158
lactose	92

The above ingredients are mixed and introduced into a hard-shell gelatin capsule.

EXAMPLE 36

Ingredients	Quantity per tablet, mgs.
isoamyl 5-benzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate	127
lactose	91
cornstarch	25
magnesium stearate	2
gelatin	5

The above ingredients are mixed and pressed into single scored tablets.

EXAMPLE 37

Ingredients	Quantity per tablet, mgs.
calcium 5-benzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate	230
cornstarch (paste)	40
cornstarch	50
magnesium stearate	2
lactose	178

The above ingredients are thoroughly mixed and pressed into single scored tablets.

EXAMPLE 38

Ingredients	Quantity per tablet, mgs.
sodium 5-benzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate	217
cornstarch	50
magnesium stearate	2
gelatin	226
lactose	5

The above ingredients are mixed intimately and pressed into single scored tablets.

EXAMPLE 39

Ingredients	Quantity per capsule, mgs.
isopropylammonium 5-benzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate	122
cornstarch	30
lactose	98

The above ingredients are mixed and introduced into a hard-shell gelatin capsule.

EXAMPLE 40

Ingredients	Quantity per capsule, mgs.
isoamyl 5-benzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate	32
lactose	101
cornstarch	15
magnesium stearate	2

The above ingredients are mixed and introduced into a hard-shell gelatin capsule.

EXAMPLE 41

An injectable preparation buffered to a pH of 7 is prepared having the following composition:

5-benzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid	0.2 g
K_2HPO_4 buffer (0.4 M solution)	2 ml.
KOH (1 N)	q.s. to pH 7
water (distilled sterile)	q.s. to 20 ml.

0.1 g. of (l)-5-benzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid is substituted for the 0.2 g. of the (dl) compound of the above composition.

EXAMPLE 42

A suppository totaling 2.8 grams is prepared having the following composition:

5-benzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid	25 mg.
Witepsol H-15 (Trade Mark) (triglycerides of saturated vegetable fatty acids; a product of Riches-Nelson, Inc., New York, N.Y.)	balance

12.5 mg. of (l)-5-benzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid is substituted for the 25 mg. of the (dl) compound of the above composition.

EXAMPLE 43

An oral suspension for pediatric use is prepared having the following composition:

5-benzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid	0.1 g.
fumaric acid	0.5 g.
sodium chloride	2.0 g.
methyl paraben	0.1 g.
granulated sugar	25.5 g.
sorbitol (70% solution)	12.85 g.
Veegum K (Vanderbilt Co. Trade Mark)	1.0 g.
flavoring	0.035 ml.
colorings	0.5 mg.
distilled water	q.s. to 100 ml.

0.05 g. of (l)-5-benzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid is substituted for the 0.1 g. of the (dl) compound of the above composition.

EXAMPLES 44—45

Powdered top dressings for veterinary use are prepared having the following compositions:

	Ex. 44	Ex. 45
5-benzoyl-1,2-dihydro-3H-pyrrol[1,2-a]pyrrole-1-carboxylic acid	0.1 g.	1.2 g.
sucrose	5.7 g.	3.7 g.
polyvinyl pyrrolidone	0.3 g.	0.3 g.

0.05 g. of (l)-5-benzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid is substituted for the 0.1 g. of the (dl) compound of the composition of Example 44.

0.6 g. of (l)-5-benzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid is substituted for the 1.2 g. of the (dl) compound of the composition of Example 45.

EXAMPLE 46

Biodata

A. Mouse Analgesic (Anti-writhing) Assay

Protocol: The test material is administered orally by gavage in an aqueous vehicle at time 0 to 18—20 gram male Swiss-Webster mice. Twenty minutes later 0.25 ml. of a 0.02% solution of phenylquinone is injected intraperitoneally. This solution induces writhing. The animals are then observed during the next 10 minutes for writhing.

End point: The total number of mice that writhe and the average number of writhes per mouse.

Using the above protocol it is determined that 5-benzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid has approximately 430 times the analgetic acitivity of aspirin; and

(l)-5-(benzoyl)-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid has approximately 700 times the analgetic acitivity of aspirin.

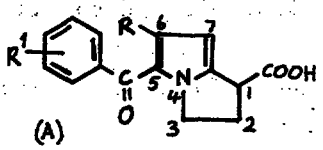
B. Mouse Acute Oral Toxicity (LD_{50})

Protocol: The test material is suspended in an aqueous carboxymethyl cellulose suspending vehicle. Concentrations are adjusted so that doses can be given in volumes of 10 ml./kg. body weight. Five groups (comprising six Swiss-Webster male mice in each group) of mice are used. A single oral dose, by stomach tube, per kilogram of body weight, of either 200 mg., 400 mg., 800 mg., or 1200 mg. of 5-(benzoyl)-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid is administered to the mice. (The fifth group is used as a control). After administration the mice are observed for a three week period.

Using the above protocol, the acute oral LD_{50} of 5-(benzoyl)-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid is approximately 200 mg./kg.

WHAT WE CLAIM IS:—

1. A compound of the general formula:



(A)

or a pharmaceutically acceptable, non-toxic ester or salt thereof, wherein R represents hydrogen or a lower alkyl group having from 1 to 4 carbon atoms and R^1 represents hydrogen, a lower alkyl group having from 1 to 4 carbon atoms, a lower alkoxy group having from 1 to 4 carbon atoms, chloro, fluoro or bromo, the R^1 substitution being at the ortho, meta or para positions of the aroyl group.

2. A compound of Claim 1, wherein R is hydrogen.

3. A compound of Claim 1, wherein R is methyl.

4. The carboxylic acid compound of Claim 2, wherein R^1 is hydrogen, 5-benzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid.

5. The isopropyl ester of the compound of Claim 4, isopropyl 5-benzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate.

6. The carboxylic acid compound of Claim 2, wherein R^1 is o-methyl, 5-o-toluoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid.

7. The isopropyl ester of the compound of Claim 6, isopropyl 5-o-toluoyl-1,2-dihydro-3H-pyrrole[1,2-a]pyrrole-1-carboxylate.

8. The carboxylic acid compound of Claim 2, wherein R^1 is m-methyl, 5-m-toluoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid.

9. The isopropyl ester of the compound of Claim 8, isopropyl 5-m-toluoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate.

10. The carboxylic acid compound of Claim 2, wherein R^1 is p-methyl, 5-p-toluoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid.

11. The isopropyl ester of the compound of Claim 10, isopropyl 5-p-toluoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate.

0.05 g. of (l)-5-benzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid is substituted for the 0.1 g. of the (dl) compound of the composition of Example 44.

0.6 g. of (l)-5-benzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid is substituted for the 1.2 g. of the (dl) compound of the composition of Example 45.

EXAMPLE 46

Biodata

A. Mouse Analgesic (Anti-writhing) Assay

Protocol: The test material is administered orally by gavage in an aqueous vehicle at time 0 to 18—20 gram male Swiss-Webster mice. Twenty minutes later 0.25 ml. of a 0.02% solution of phenylquinone is injected intraperitoneally. This solution induces writhing. The animals are then observed during the next 10 minutes for writhing.

End point: The total number of mice that writhe and the average number of writhes per mouse.

Using the above protocol it is determined that 5-benzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid has approximately 430 times the analgetic acitivity of aspirin; and

(l)-5-(benzoyl)-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid has approximately 700 times the analgetic acitivity of aspirin.

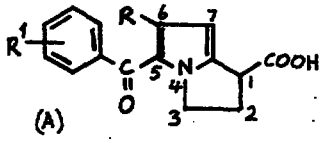
B. Mouse Acute Oral Toxicity (LD_{50})

Protocol: The test material is suspended in an aqueous carboxymethyl cellulose suspending vehicle. Concentrations are adjusted so that doses can be given in volumes of 10 ml./kg. body weight. Five groups (comprising six Swiss-Webster male mice in each group) of mice are used. A single oral dose, by stomach tube, per kilogram of body weight, of either 200 mg., 400 mg., 800 mg., or 1200 mg. of 5-(benzoyl)-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid is administered to the mice. (The fifth group is used as a control). After administration the mice are observed for a three week period.

Using the above protocol, the acute oral LD_{50} of 5-(benzoyl)-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid is approximately 200 mg./kg.

WHAT WE CLAIM IS:—

1. A compound of the general formula:



(A)

or a pharmaceutically acceptable, non-toxic ester or salt thereof, wherein R represents hydrogen or a lower alkyl group having from 1 to 4 carbon atoms and R^1 represents hydrogen, a lower alkyl group having from 1 to 4 carbon atoms, a lower alkoxy group having from 1 to 4 carbon atoms, chloro, fluoro or bromo, the R^1 substitution being at the ortho, meta or para positions of the aroyl group.

2. A compound of Claim 1, wherein R is hydrogen.

3. A compound of Claim 1, wherein R is methyl.

4. The carboxylic acid compound of Claim 2, wherein R^1 is hydrogen, 5-benzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid.

5. The isopropyl ester of the compound of Claim 4, isopropyl 5-benzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate.

6. The carboxylic acid compound of Claim 2, wherein R^1 is o-methyl, 5-o-toluoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid.

7. The isopropyl ester of the compound of Claim 6, isopropyl 5-o-toluoyl-1,2-dihydro-3H-pyrrole[1,2-a]pyrrole-1-carboxylate.

8. The carboxylic acid compound of Claim 2, wherein R^1 is m-methyl, 5-m-toluoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid.

9. The isopropyl ester of the compound of Claim 8, isopropyl 5-m-toluoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate.

10. The carboxylic acid compound of Claim 2, wherein R^1 is p-methyl, 5-p-toluoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid.

11. The isopropyl ester of the compound of Claim 10, isopropyl 5-p-toluoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate.

12. The carboxylic acid compound of Claim 2, wherein R^1 is p-methoxy, 5-p-methoxybenzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid.

13. The isopropyl ester of the compound of Claim 12, isopropyl 5-p-methoxybenzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate.

14. The carboxylic acid compound of Claim 2, wherein R^1 is o-chloro, 5-o-chlorobenzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid.

15. The isopropyl ester of the compound of Claim 14, isopropyl 5-o-chlorobenzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrole-1-carboxylate.

16. The carboxylic acid compound of Claim 2, wherein R^1 is m-chloro, 5-m-chlorobenzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid.

17. The isopropyl ester of the compound of Claim 16, isopropyl 5-m-chlorobenzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate.

18. The carboxylic acid compound of Claim 2, wherein R^1 is p-chloro, 5-p-chlorobenzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid.

19. The isopropyl ester of the compound of Claim 18, isopropyl 5-p-chlorobenzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate.

20. The carboxylic acid compound of Claim 2, wherein R^1 is p-fluoro, 5-p-fluorobenzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid.

21. The isopropyl ester of the compound of Claim 20, isopropyl 5-p-fluorobenzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate.

22. The carboxylic acid compound of Claim 2, wherein R^1 is o-fluoro, 5-o-fluorobenzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid.

23. The isopropyl ester of the compound of Claim 22, isopropyl 5-o-fluorobenzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate.

24. The carboxylic acid compound of Claim 3, wherein R^1 is p-fluoro, 5-p-fluorobenzoyl-1,2-dihydro-6-methyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid.

25. A sodium, potassium or calcium salt of the compounds according to Formula (A) of Claim 1.

26. The sodium salt compound of Claim 25, wherein R and R^1 are both hydrogen, sodium 5-benzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate.

27. The compound of Claim 25, wherein R is methyl and R^1 is p-fluoro, sodium 5-p-fluorobenzoyl-1,2-dihydro-6-methyl-3Hpyrrolo[1,2-a]pyrrole-1-carboxylate.

28. An (l)-acid isomer of a compound of Claim 1.

29. The compound of Claim 28, wherein R and R^1 are both hydrogen, (l)-5-benzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid.

30. The compound of Claim 28, wherein R is methyl and R^1 is p-fluoro, (l)-5-p-fluorobenzoyl-1,2-dihydro-6-methyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid.

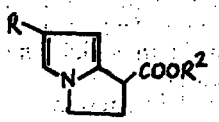
31. A sodium, potassium or calcium salt of an (l)-acid isomer of Formula (A) of Claim 1.

32. The sodium salt compound of Claim 31, wherein R and R^1 are both hydrogen, sodium (l)-5-benzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate.

33. The compound of Claim 31, wherein R is methyl and R^1 is p-fluoro, sodium (l)-5-benzoyl-1,2-dihydro-6-methyl-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate.

34. A (d)-acid isomer of a compound of Claim 1.

35. A compound of the formula



wherein R is hydrogen or a lower alkyl group having from 1 to 4 carbon atoms and R^2 is a lower alkyl group having from 1 to 4 carbon atoms.

36. A compound of Claim 35, wherein R is hydrogen and R^2 is isopropyl, isopropyl 1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylate.

37. A composition for treating inflammation, pain or pyrexia in mammals consisting essentially of a pharmaceutically acceptable non-toxic excipient and a therapeutically effective amount of a compound of Claim 1.

38. A method of treating inflammation, pain or pyrexia in non-human mammals which comprises administering to a mammal suffering therefrom a therapeutically effective amount of a compound of Claim 1.

39. A method according to Claim 38, wherein an (l)-isomer of said compound is used.

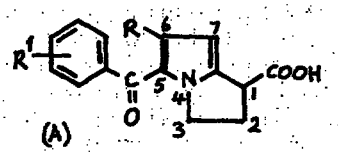
40. A composition for administration to a pregnant mammal to delay onset of

parturition consisting essentially of a pharmaceutically acceptable non-toxic excipient and a therapeutically effective amount of a compound of Claim 1.

41. A method of prolonging, or delaying the onset, of parturition in a pregnant non-human mammal, comprising administering to a pregnant non-human mammal a compound of Claim 1.

42. A method according to Claim 41, wherein an (l)-isomer of said compound is used.

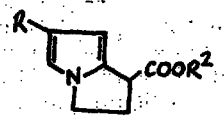
43. A process for producing a compound of the formula



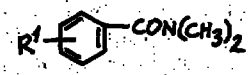
(A)

or a pharmaceutically acceptable, non-toxic ester or salt thereof, wherein R represents hydrogen or a lower alkyl group having from 1 to 4 carbon atoms and R^1 represents hydrogen, a lower alkyl group having from 1 to 4 carbon atoms, a lower alkoxy group having from 1 to 4 carbon atoms, chloro, fluoro or bromo, the R^1 substitution being at the ortho, meta or para positions of the aroyl group which comprises one or more of the following steps:

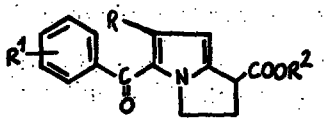
a) condensing a compound of the formula



wherein R is as defined above and R^2 is a lower alkyl group having from 1 to 4 carbon atoms, with an amide of the formula



wherein R^1 is as defined above, thereby yielding a corresponding compound of the formula



wherein R, R^1 and R^2 are as defined above;

b) hydrolyzing an alkyl ester group thereby yielding a free acid of Formula (A);

c) optionally esterifying the carboxylic acid function in a compound of Formula (A) or converting it into a pharmaceutically acceptable, non-toxic salt;

d) convering a salt of Formula (A) to the corresponding free acid.

44. The process of Claim 43 in which the condensation is effected in the presence of phosphorous oxychloride.

45. The process of Claim 43, wherein the amide used in step a) is N,N-dimethyl-benzamide.

46. The process of Claim 43, wherein the amide used in step a) is N,N-dimethyl-o-toluamide.

47. The process of Claim 43, wherein the amide used in step a) is N,N-dimethyl m-toluamide.

48. The process of Claim 43, wherein the amide used in step a) is N,N-dimethyl p-toluamide.

49. The process of Claim 43, wherein the amide used in step a) is N,N-dimethyl p-methoxy-benzamide.

50. The process of Claim 43, wherein the amide used in step a) is N,N-dimethyl o-chloro-benzamide.

51. The process of Claim 43, wherein the amide used in step a) is N,N-dimethyl m-chloro-benzamide.

52. the process of Claim 43, wherein the amide used in step a) is N,N-dimethyl p-chloro-benzamide.

53. The process of Claim 43, wherein the amide used in step a) is N,N-dimethyl p-fluoro-benzamide.

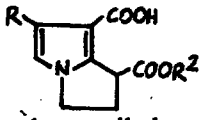
54. The process for preparing a compound of Claim 1 which comprises, optionally with one or more of the steps of Claim 43, racemizing a (d)-acid isomer or a salt thereof to the corresponding compound of Formula (A).

55. A process which comprises, optionally with one or more of the steps of Claim 43, separating a free acid of Formula (A) of Claim 1 into its corresponding (l)- and (d)-acid isomers.

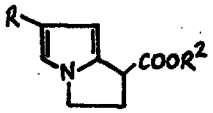
56. A process of Claim 43, wherein step (c) is carried out on a (d)- or (l)-acid isomer of a compound of Formula (A).

57. A process of Claim 43, wherein in step (d) an individual isomer of a salt of Formula (A) is converted to the corresponding free acid.

58. The process which comprises decarboxylating a compound of the formula



wherein R represents hydrogen or a lower alkyl group having 1 to 4 carbon atoms and R^2 is a lower alkyl group of 1 to 4 carbon atoms; to produce the compounds of the formula



wherein R and R^2 are as defined above.

59. The dicyclohexylamine salt of the compound of Claim 6, dicyclohexylamine salt of 5-o-toluoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid.

60. The dicyclohexylamine salt of the compound of Claim 14, dicyclohexylamine salt of 5-o-chlorobenzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid.

61. 5-p-ethoxybenzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid.

62. A (dl)-compound according to Claim 1 as exemplified herein.

63. A compound according to Claim 28 as exemplified herein.

64. A compound according to Claim 34 as exemplified herein.

65. A compound according to Claim 35 as exemplified herein.

66. A process for producing a (dl)-compound of Claim 1, substantially as described herein.

67. A processs for producing an individual (d)- or (l)-isomer of a compound of Claim 1, substantially as described herein.

68. A compound according to Claim 1, whenever prepared by a process according to any one of Claims 43 to 53 and 66.

69. A compound of Claim 1 whenever prepared by a process according to Claim 54.

70. A (d)- or (l)-isomer of a compound of Claim 1 whenever prepared by a process according to Claim 55, 56, 57 or 67.

71. A pharmaceutical composition comprising a compound according to any one of Claims 2 to 27, 59 to 62 and 68, with a suitable excipient.

72. A pharmaceutical composition comprising an (l)-isomeric compound of any one of Claims 28 to 33, 63, 69 and 70 with a suitable excipient.

73. A pharmaceutical composition substantially as exemplified herein, comprising a (dl) compound as defined in Claim 1.

74. A pharmaceutical composition substantially as exemplified herein, comprising the (l)-isomer of a compound as defined in Claim 1.

MEWBURN, ELLIS & CO.,
Chartered Patent Agents,
70/72 Chancery Lane,
London, WC2A 1AD,
Agents for the Applicants.

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* C L M S *

ERRATA

SPECIFICATION No. 1,554,075

Page 2, *in the reaction sequence insert* ↓ from formula (III) to formula (IV)
Page 5, *flow diagram after* (A')-(d)-acid isomer *complete the arrow leading to Formula (A') insert* ⊱
Page 5, *flow diagram at side of forked arrow insert* Separate using HPLC
Page 5, line 35, *for* pyrines *read* purines
Page 6, line 52, *for* adidtion *read* addition
Page 9, line 39, *for* Vi *read* VI
Page 10, line 15, *for* yrrole *read* pyrrole
Page 17, line 27, *after* 250 ml. *delete* of
Page 18, line 23, *for* chlorobenzyl *read* chlorobenzoyl
Page 20, line 7, *for* substituted *read* substituting
Page 20, line 16, *for* obtained *read* obtaining
Page 20, line 45, *for* hydro *read* dihydro
Page 20, line 49, *for* capsules *read* capsule
Page 21, line 9, *for* sheel *read* shell
Page 23, line 51, *for* pyrrol *read* pyrrolo
Page 24, line 48, *for* pyrrole *read* pyrrolo
Page 26, line 28, *for* convering *read* converting

THE PATENT OFFICE
4th February, 1980