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INDOLO [2,3-c] QUINAZO [3,2-a] PYRIDINE DERIVATIVES

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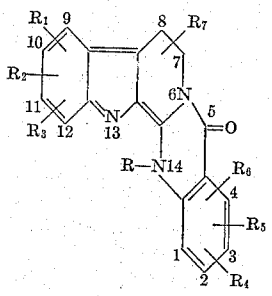
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Serial No. 616,632

6 Claims. (Cl. 167—65)

This invention relates to a medicinal composition having unusual pharmacodynamic properties and especially useful as an antihypertensive agent. This invention also relates to a novel method of producing antihypertensive activity in human beings.

The novel medicinal composition of this invention has outstanding activity as an antihypertensive agent with remarkably few side effects. Specifically, this composition lowers arterial blood pressure and slows the pulse rate. It is particularly useful in mild to moderate cases of essential hypertension and alone, or in combination with other agents, in the treatment of more severe hypertensive vascular conditions. Side effects, such as diarrhea, severe laxative action or general depression are often seen with like-acting medicinal agents. For instance the use of reserpine has been limited by the severe depression often encountered with relatively high dosage regimens. Such limiting side effects are much less pronounced with the composition of this invention.

More specifically, the medicinal composition of this invention comprises a pharmaceutical carrier and a medicament which is a member of a series of compounds represented by the following general structural formula:



wherein:

R represents alkyl having from 1 to 18 carbon atoms; aralkyl, preferably phenylalkyl, having 1 to 6 carbon atoms in the alkyl portion; or —CH_2-alkenyl, the alkenyl portion having 2 to 17 carbon atoms;

R_1 represents hydrogen, lower alkoxyl, lower alkyl, —CH_2-alkenyl, the alkenyl portion having 2 to 5 carbon atoms, halo, hydroxyl and trifluoromethyl;

R_2 and R_3, when individual radicals represent hydrogen, lower alkoxyl, lower alkyl, —CH_2-alkenyl, the alkenyl portion having 2 to 5 carbon atoms, hydroxyl, halo and trifluoromethyl and when taken together in adjacent positions, represent methylenedioxy;

R_4 represents hydrogen, lower alkoxyl, lower alkyl,

—CH_2-alkenyl, the alkenyl portion having 2 to 5 carbon atoms, hydroxyl, halo and trifluoromethyl;

R_5 and R_6, when individual radicals represent hydrogen, lower alkoxy, lower alkyl, —CH_2-alkenyl, the alkenyl portion having 2 to 5 carbon atoms, hydroxyl, halo, carbomethoxy and trifluoromethyl and when taken together in adjacent positions, represent methylenedioxy;

R_7 represents hydrogen, lower alkoxyl, lower alkyl and halo.

By the terms "lower alkyl" or "lower alkoxyl" as used herein and in the claims, branched or straight aliphatic groups having not more than 6 carbon atoms and preferably not more than 4 carbon atoms are indicated. Similarly the term "hydroxyl" is intended to include moieties hydrolyzable thereto, for example, acyloxy having 2 to 6 carbon atoms.

Preferred compounds in the composition of this invention are compounds of the above structural formula where R_1 and R_4 are members selected from the group consisting of hydrogen, lower alkoxyl and lower alkyl; R_2, R_3, R_5, R_6 and R_7 are hydrogen; and R is lower alkyl.

Where hereinafter the symbols R, R_1, R_2, R_3, R_4, R_5, R_6 and R_7 are mentioned in the description, they will indicate the substituents indicated for them above as appropriate except where otherwise specified.

Exemplary of a particularly useful compound for inclusion in the composition of this invention is 10-methoxy-14-methyl-5-oxo-5,7,8,14-tetrahydroindolo[2,3-c]quinazo-[3,2-a]pyridine.

Equivalently, non-toxic organic and inorganic acid addition salts and quaternary ammonium salts can be used. Exemplary of non-toxic acid addition salts are those formed with maleic, fumaric, benzoic, ascorbic, pamoic, succinic, bismethylenesalicylic, methylsulfonic, ethanedisulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, stearic, palmitic, itaconic, glycolic, benzenesulfonic, hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric and nitric acids. These salts are prepared by several methods but preferably by heating a suspension of the base in a large volume of methyl or ethyl alcohol with one equivalent of acid. The volume is reduced and the solution cooled to separate the crystalline salt. Often an excess of acid is used with equally satisfactory results.

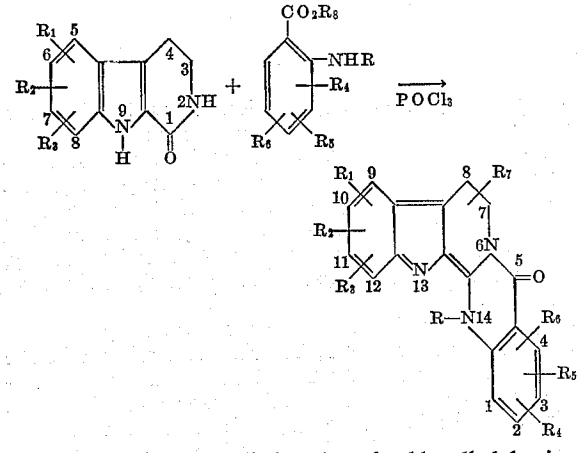
Many of the salts can be prepared by double decomposition of suitable compounds. For instance the acetates of the polycyclic bases dissolved in water will react with aqueous solutions of sodium bromide or sodium tartrate to form the slightly soluble hypotensive bromide or tartrate salts which will separate from the reaction mixture directly.

The quaternary salts are prepared by heating a suspension of the base in a suitable solvent, such as benzene or ethyl alcohol, with a reactive alkyl halide such as methyl iodide, ethyl bromide, n-hexyl bromide, benzyl chloride or another reactive ester such as methyl sulfate, ethyl sulfate or methyl p-toluene sulfonate.

The polycyclic compounds of this invention may exist as hydrates which contain variable amounts of water. The tendency to form hydrates is particularly noticeable with solutions of the free base forms of the compounds of this invention. It is intended to include in the specification and claims the hydrates as well as the non-hydrates

of the free bases and the acid addition and quaternary ammonium salts of the free bases.

These compounds, except where one or more hydroxyl groups are present, are conveniently prepared by condensing substituted 1-oxo-1,2,3,4-tetrahydropyrid[3,4-b]-indoles with substituted N-alkyl or N-aralkylanthranilic acids or esters according to the following reaction:



in which R_8 is H or alkyl and preferably alkyl having 1 to 6 carbon atoms.

The 1 - oxo - 1,2,3,4-tetrahydropyrid[3,4-b]indoles are condensed with the N-alkyl or N-aralkyl anthranilic acid or ester preferably in approximately equimolar amounts. The amounts of reactants may be varied widely, however, with appreciable yields of polycyclic compounds resulting.

The condensation is carried out by heating the reactants in the presence of phosphorus oxychloride as a condensing agent. The reaction may be carried out with widely varying amounts of condensing agent, such as with an excess of phosphorus oxychloride, which then serves as reaction medium as well, or with as little as 0.6 mole of phosphorus oxychloride in a suitable substantially inert solvent. Preferably from about 1 to 5 molar equivalents based on the 1-oxo-1,2,3,4-tetrahydropyrid[3,4-b]-indole are used in a solvent in which at least one of the reactants is partially soluble, such as an inert organic solvent, for example, benzene, toluene, xylene, chlorobenzene, chloroform, carbon tetrachloride, ethyl acetate, dioxane, dibutyl ether or cyclohexane. Alternatively, inorganic solvents which do not alter the course of the condensation may be used, for instance, phosphorus trichloride or thionyl chloride. The preferred solvents are the aromatic solvents, such as toluene, xylene or benzene. Preferably the solvent will not contain any substance that will react with the $POCl_3$, for example, a compound containing hydroxyl or amino groups, and, in any event, the amount of such substances, if present, should be insufficient to cause substantial depletion of the $POCl_3$.

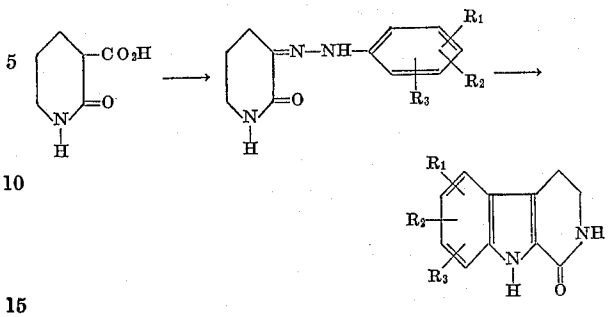
The reaction temperature is preferably maintained between about 30° C. and about 200° C. The rate of the reaction varies directly with the temperature. Advantageously temperatures of about 60–140° C. are used. It is convenient to run the reaction at the boiling point of the reaction medium; preferably, for instance, in boiling benzene, toluene or xylene.

It will be recognized that the length of reaction time varies with the amount of condensing agent, solubility of the reagents and the reaction temperature. In the preferred range of temperature, from fifteen minutes to five hours is usually sufficient to complete the reaction. Preferably a period of from one to three hours is used.

Many of the starting materials for this process are specifically known to the literature together with methods for their preparation. Where certain compounds desired for use as starting materials are not specifically described in the literature, they are prepared by like methods.

The 1-oxo-1,2,3,4-tetrahydropyrid[3,4-b]indoles may

be prepared conveniently by the method which is outlined below:



3-carboxypiperid-2-one is reacted with a suitably substituted benzenediazonium halide under Japp-Klingemann conditions to give a piperid-2,3-dione-3-R_1,R_2,R_3-phenylhydrazone which in turn is heated in formic acid or polyphosphoric acid solutions whereby an intramolecular rearrangement takes place to give the substituted 1-oxo-1,2,3,4-tetrahydropyrid[3,4-b]indoles. Other methods of preparing these compounds are reported in the literature. However, this method is a simple preparation which has been found to be satisfactory on a broad scale.

The ring C substituted pyrid[3,4-b]indoles are advantageously prepared, for example, by alkylating 3-dimethylaminomethylindole - 2 - carboxylate, prepared by the method of Brehm and Lindwall, J. Org. Chem., 15, 685 (1950), with 1-nitropropane under alkaline conditions in a typical gramine condensation. The resulting ethyl 3-(2-nitrobutyl)-indole-2-carboxylate is cyclized under reductive conditions with stannous chloride to give the desired starting material, 3-ethyl-1-oxo-1,2,3,4-tetrahydropyrid[3,4-b]indole.

The substituted N-alkyl or aralkyl anthranilic acid derivatives are prepared by several methods which are in the literature. Many of the substituted anthranilic acids are specifically known. Simple esterification in an excess of an alcohol with gaseous hydrogen chloride followed by N-alkylation by an alkyl halide or alkyl sulfate or by N-aralkylation by an aralkyl halide or aralkyl sulfate has proved satisfactory.

The compounds in which one or more of the substituents R_1 through R_6 are hydroxyls are prepared by first forming, by the above described method, the compound corresponding to the desired hydroxyl substituted compound but having an alkoxy radical, for example methoxy, in each position where a hydroxyl is desired. The alkoxy substituted compound is then hydrolysed to form the desired compound with hydroxyl radicals replacing the alkoxy radicals. The hydrolysing may be accomplished by refluxing with an aluminum halide, for example aluminum chloride in an inert solvent, for example, benzene or by heating under reflux with a concentrated hydrohalic acid, for example, hydrobromic acid.

Alternatively the hydroxy substituted compounds can readily be formed by first forming the corresponding acyloxy, for example, acetoxy, substituted compound and hydrolysing the acyloxy radical to a hydroxyl radical by heating under reflux in the presence of dilute hydrochloric acid. The acyloxy compound is formed by condensing a 1-oxo-1,2,3,4-tetrahydropyrid[3,4-b]indole with an N-alkyl or N-aralkylanthranilic acid or ester with either or both of the indole and the anthranilic acid or ester substituted with acyloxy radicals in the positions where hydroxyl radicals are desired. The procedure outlined above for condensing substituted 1-oxo-1,2,3,4-tetrahydropyrid[3,4-b]indoles with substituted N - alkyl or N-aralkylanthranilic acids or esters is followed here. This method is particularly advantageous where the desired compound contains both alkoxy and hydroxyl radicals since it permits the use of mild conditions to

hydrolyse the acyloxy radicals without hydrolysing the alkoxy radicals.

Reference may be made to copending application Serial No. 616,631, filed October 18, 1956, which is directed to this process. The following examples will specifically illustrate compounds useful in the composition of this invention and the method of their preparation.

EXAMPLE I

A solution of 20 g. of 3-carbethoxy-2-piperidone in 220 ml. of 5% potassium hydroxide solution is allowed to stand at room temperature for twenty-four hours. After neutralizing with glacial acetic acid and adding 46 g. of potassim acetate, the cooled solution is stirred while a previously prepared solution of the diazonium salt prepared using 14.4 g. of p-anisidine is added at 0° C.

After stirring at room temperature, the coupled diazo compound is separated by filtration and washed with isopropanol. A mixture of 9 g. of the coupled product in 80 ml. of 70% formic acid solution is heated at reflux for two hours and quenched with water. The resulting solid is recrystallized from ethanol to a pure sample of 6-methoxy-1-oxo-1,2,3,4-tetrahydropyrid[3,4-b]indole, M. P. 276–278° C.

A suspension of 1.2 g. of 6-methoxy-1-oxo-1,2,3,4-tetrahydropyrid[3,4-b]indole in 20 g. of phosphorus trichloride with 0.6 g. of phosphorus oxychloride is heated at reflux for twenty minutes. The reflux period is interrupted while 1.8 g. of methyl N-methylanthranilate is added. The reflux period is continued for two hours. The volatiles are taken off in vacuo. The residue is carefully diluted with ice water. The mixture is extracted by shaking with chloroform and ammonia water. Some unchanged pyrid[3,4-b]indole material is recovered. The chloroform extracts are concentrated, diluted with benzene, filtered and reconcentrated to separate red needles of 10-methoxy-14-methyl-5-oxo-5,7,8,14-tetrahydroindolo[2,3-c]quinazo[3,2-a]pyridine, M. P. >200° C. (decomposes gradually).

A solution of 5.0 g. of the red free base (prepared as above) in 100 ml. of dry benzene is saturated with gaseous hydrogen chloride. The yellow microcrystalline solid which separates is recrystallized from ethanol to yield pure yellow crystals of 10-methoxy-14-methyl-5-oxo-5,7,8,14-tetrahydroindolo[2,3 - c]quinazo[3,2 - a]pyridine hydrochloride, M. P. 243° C. (dec.).

A suspension of 60 g. of the red free base (prepared as above) in 2 l. of ethanol is prepared and mixed with a solution of 40 g. of tartaric acid in 1 l. of ethanol. The mixture is heated to boiling, diluted with 1 l. of hot distilled water. The clear solution is then cooled to 5° C. with stirring. After one hour at this temperature a large crop of bright yellow tartrate salt was obtained as a hydrate, M. P. 220–221° C. (dec.).

The citric, maleic, nitric, phosphorus, glycolic, ethanedisulfonic and perchloric salts of the above formed base are each prepared by dissolving equivalent amounts of the red base and the appropriate acid in minimum quantities of acetone. The salt separates almost immediately.

A solution of 3.3 g. of the red base (prepared as above) in 75 ml. of dry benzene is treated with 2.0 g. of benzyl chloride in 25 ml. of benzene. The mixture is heated under reflux for ten hours and the yellow solid separates. Filtration yields crystals of 10-methoxy-14-methyl-5-oxo-5,7,8,14-tetrahydroindolo[2,3 - c]quinazo[3,2 - a]pyridine benzyl chloride quaternary salt.

EXAMPLE II

A mixture of 5 g. of 3-carbethoxy-2-piperidone in 1.5 equivalents of 10% potassium hydroxide solution is allowed to stand at room temperature overnight. The resulting hydrolysate is then buffered with 2.6 g. of acetic acid and 11.0 g. of potassium acetate. A previously prepared solution of diazonium salt using 3.72 g. of

p-chloroaniline is added to the buffered reaction mixture at ice bath temperature.

After two hours' stirring at room temperature, the crude coupled product is separated by filtration, washed with ethanol and dried. A suspension of 4.8 g. of this chlorophenylhydrazone in 90 ml. of 70% formic acid is heated at reflux for two hours. After quenching in an excess of water, long needles of 6-chloro-1-oxo-1,2,3,4-tetrahydropyrid[3,4-b]indole are isolated by filtration and recrystallization from methanol, M. P. 225–226° C.

A suspension of 9.8 g. of finely-divided 6-chloro-1-oxo-1,2,3,4-tetrahydropyrid[3,4-b]indole in 200 ml. of xylene with 4 g. of phosphorus oxychloride is heated at reflux for fifteen minutes. A 15 g. portion of methyl N-methylanthranilate is added to the reaction mixture and the reflux period is extended for two hours with stirring. The solvent is removed in vacuo. The residue is carefully diluted with water, washed with ammonia water and extracted into chloroform. The dried organic extracts are concentrated, diluted with benzene and saturated with dry hydrogen chloride gas. Fractional crystallization of the gummy precipitate from ethanol results in 10-chloro-14-methyl - 5 - oxo - 5,7,8,14 - tetrahydroindole-[2,3-c]quinazo[3,2-a]pyridine hydrochloride, along with some starting material.

The purified hydrochloride is shaken with chloroform-ammonia water. The chloroform layer is dried, concentrated and diluted with benzene to yield orange-red needles of free base, M. P. >210° C. (decomposes gradually).

EXAMPLE III

A solution of 5.2 g. of 1-oxo-1,2,3,4-tetrahydropyrid [3,4-b]indole, prepared from aniline according to the coupling procedure described in Example I, in 120 ml. of toluene with 7.5 g. of phosphorus oxychloride is heated at reflux with stirring for ten minutes. After the addition of 6.5 g. of methyl 4-methoxy-N-methylanthranilate, prepared by esterifying 4-methoxy-N-methylanthranilic acid in methanol with gaseous hydrogen chloride, the reaction mixture is heated at reflux with stirring for three hours. The toluene is removed in vacuo. The residue is treated with ammonia water, then taken into chloroform with vigorous shaking. The dry chloroform extracts are concentrated, diluted with benzene-ethanol and cooled to yield a yellow crystalline hydrate. The crystalline 2-methoxy-14-methyl-5-oxo-5,7,8,14-tetrahydroindolo[2,3-c]quinazo[3,2-a]pyridine hydrate is purified by recrystallization from chloroform-ethanol, M. P. 195–196° C. (Dec.).

A mixture of 3.3 g. of the hydrate and 100 ml. of benzene is evaporated on the steam bath to remove water. A solution of 1.8 g. of isoamyl bromide in 25 ml. of benzene is added dropwise to the boiling reaction mixture. The solution is allowed to concentrate as crystals of the isoamyl bromide quaternary salt of 2-methoxy-14 - methyl - 5 - oxo - 5,7,8,14 - tetrahydroindolo[2,3 - c] quinazo [3,2-a]pyridine separate. The yellow crystals are separated by filtration and air dried.

EXAMPLE IV

A solution of 9.5 g. of 6-methyl-1-oxo-1,2,3,4-tetrahydropyrid[3,4-b]indole, prepared from the p-methylphenylhydrazone coupled product as in Example I, in 150 ml. of toluene with 4 g. of phosphorus oxychloride is heated at reflux with stirring briefly. After the addition of 15 g. of methyl N-methylanthranilate, the reaction mixture is heated at reflux for one hour. The product of the condensation is isolated as in Example II. The hydrochloride salt is recrystallized from hot water to purification. The base is then regenerated by the use of ammonia water-chloroform to yield deep red needles of 10,14 - dimethyl - 5 - oxo - 5,7,8,14 - tetrahydroindolo [2,3-c]quinazo[3,2-a]pyridine, M. P. 223–225° C. (dec.).

A solution of 4.8 g. of the acetate salt of the base,

prepared by adding ether to an acetic acid solution is dissolved in water. A solution of 1.7 g. of sodium benzoate in 20 ml. of water is added dropwise to the swirled acetate to separate the desired 10,14-dimethyl-5 - oxo - 5,7,8,14 - tetrahydroindolo[2,3 - c]quinazo[3,2-a]pyridine benzoate.

EXAMPLE V

A suspension of 2.0 g. of 6-methyl-1-oxo-1,2,3,4-tetrahydropyrid[3,4-b]indole and 1.95 g. of methyl-4-methoxy-N-methylanthranilate in 50 ml. of dry dioxane with 0.5 g. of phosphorus oxychloride is heated at reflux for three hours. The product, 10,14-dimethyl-2-methoxy-5-oxo-5,7,8,14 - tetrahydroindolo[2,3 - c]quinazo[3,2 - a]pyridine, is isolated as in Example II.

EXAMPLE VI

A suspension of 5.0 g. of 1-oxo-1,2,3,4-tetrahydropyrid[3,4-b]indole, prepared using aniline in the coupling procedure of Example I and using polyphosphoric acid as the medium for the rearrangement, in 120 ml. of dry toluene with 3 g. of freshly distilled phosphorus oxychloride is heated at reflux for fifteen minutes. After the addition of 7.5 g. of methyl N-methylanthranilate, the reflux period is extended for three hours. After distillation of the toluene under diminished pressure, the reaction product, 14-methyl-5-oxo-5,7,8,14-tetrahydroindolo [2,3-c]quinazo[3,2-a]pyridine hydrochloride, is isolated following the procedure in Example II. Purification by recrystallization from either ethanol or water gives yellow crystals, M. P. 238° C. (dec.).

The free base is recovered from the hydrochloride salt by shaking 3 g. of the salt in a mixture of ammonia water and chloroform. The dry chloroform extract is concentrated and diluted with benzene-cyclohexane to precipitate orange needles of the free base, M. P. about 198° C.

A solution of 3 g. of 14-methyl-5-oxo-5,7,8,14-tetrahydroindolo[2,3-c]quinazo[3,2-a]pyridine in 150 ml. of dry benzene is heated at reflux while 6 ml. of dry methyl iodide is added in three portions over a period of two hours. The product, 14-methyl-5-oxo-5,7,8,14-tetrahydroindolo[2,3-c]quinazo[3,2-a]pyridine methiodide, is obtained by cooling the reaction mixture, recovering the precipitate and recrystallizing the salt from 70% aqueous ethanol, M. P. 208–210° C. (dec.).

EXAMPLE VII

A suspension of 5.0 g. of finely powdered 1-oxo-1,2,3,4-tetrahydropyrid[3,4-b]indole in 50 g. of freshly distilled phosphorus trichloride with 2 g. of phosphorus oxychloride is heated at reflux briefly with stirring. After the addition of 7.5 g. of methyl N-butylanthranilate, prepared by monobutylation of anthranilic acid with n-butylbromide by the method of Gilman et al. [J. Am. Chem. Soc., 62, 977 (1940)] and subsequent esterification with methanol and dry hydrogen chloride gas, the reaction mixture is refluxed for one and one-half hours. The excess solvent is removed in vacuo. The residue is made basic with ammonia water and extracted into chloroform. The dried chloroform extract is concentrated, diluted with benzene and acidified with gaseous hydrogen chloride. The resulting dark gum is extracted with boiling water. After cooling, the filtrate is neutralized with ammonia water to give 14-butyl-5-oxo-5,7,8,14-tetrahydroindolo[2,3-c]quinazo[3,2 - a]pyridine hydrate as yellow plates from ethanol, M. P. 178–179° C.

EXAMPLE VIII

A suspension of 4 g. of 7,8-dimethyl-1-oxo-1,2,3,4-tetrahydropyrid[3,4-b]indole, M. P. 236–238° C., prepared by using 2,3-dimethylaniline hydrochloride in the coupling synthesis described in Example I, in 50 ml. of chlorobenzene with 2 g. of phosphorus oxychloride is heated at reflux for ten minutes. After the addition of 6 g. of methyl N-methylanthranilate and 25 ml. of chlorobenzene, the reaction mixture is heated at reflux for one hour. The base, 5-oxo-5,7,8,14-tetrahydro-11,12,14-trimethylindolo[2,3-c]quinazo[3,2-a]pyridine, is isolated following the procedure of Example II, as orange-red needles from benzene-chloroform, M. P. 240–243° C.

A solution of 2.2 g. of the base in 50 ml. of acetone is mixed with 1 g. of acetic acid in 25 ml. of acetone. The solution is concentrated and cooled to give crystals of 5 - oxo - 5,7,8,14 - tetrahydro-11,12,14-trimethylindolo-[2,3-c]quinazo[3,2-a]pyridine acetate.

EXAMPLE IX

A suspension of 11.4 g. of 1-oxo-8-propyl-1,2,3,4-tetrahydropyrid[3,4-b]indole, prepared by using 2-n-propylaniline as starting material in the coupling synthesis described in Example I, in 100 ml. of benzene with 4 g. of phosphorus oxychloride is heated at reflux briefly. After the addition of 9 g. of methyl N-methylanthranilate, the reaction mixture is heated at reflux for four hours. The product, 14-methyl-5-oxo-12-propyl-5,7,8,14-tetrahydroindolo[2,3-c]quinazo[3,2-a]pyridine, is isolated following the procedure in Example I.

A solution of 3.5 g. the orange base in 50 ml. of ethanol is heated to boiling and added to a solution of 1.2 g. of maleic acid in 50 ml. of ethanol. The solution is filtered hot. The filtrate is concentrated somewhat and cooled. Addition of a small amount of isooctane causes crystallization of 14 - methyl-5-oxo-12-propyl-5,7,8,14-tetrahydroindolo[2,3-c]quinazo[3,2-a]pyridine maleate.

EXAMPLE X

A suspension of 3.0 g. of 5-chloro-8-methoxy-1-oxo-1,2,3,4-tetrahydropyrid[3,4-b]indole, M. P., 214–215° C., prepared by using 5-chloro-anisidine as starting material in the coupling synthesis described in Example I, in 40 g. of phosphorus trichloride witht 2.5 g. of phosphorus oxychloride is heated at reflux with stirring for twenty minutes. After addition of 4.5 g. of methyl N-methylanthranilate, the reaction mixture is heated at reflux for two hours. The solvent is evaporated and the residue quenched in ice water. After neutralizing the aqueous mixture with dilute sodium hydroxide, the product is extracted with several portions of chloroform. The chloroform extracts are combined, dried and concentrated. Fine orange crystals of base, 9-chloro-12-methoxy-14-methyl - 5 - oxo-5,7,8,14-tetrahydroindolo[2,3,c]quinazo-[3,2-a]pyridine, crystallized from the chloroform solution, M. P. 251–252° C.

A solution of 3.7 g. of the orange base in 50 ml. of ethyl acetate is mixed with 1.9 g. of citric acid in 20 ml. of ethanol. The solution is concentrated by allowing to evaporate until crystals begin to form, 9-chloro-12-methoxy - 14 - methyl-5-oxo-5,7,8,14-tetrahydroindolo-[2,3-c]quinazo[3,2-a]pyridine citrate.

EXAMPLE XI

A suspension of 10.8 g. of 7-methoxy-1-oxo-1,2,3,4-tetrahydropyrid[3,4-b]indole in 100 ml. of xylene with 6 g. of phosphorus oxychloride is heated briefly at reflux with stirring. After the addition of 8.3 g. of methyl N-methylanthranilate, the reaction mixture is heated at reflux for two hours with stirring. The desired base, 11-methoxy - 14 - methyl - 5 - oxo - 5,7,8,14 - tetrahydroindolo[2,3-c]quinazo[3,2-a]pyridine, is isolated by the isolation procedure of Example II.

The base is characterized by dissolving 3.3 g. of the red base in 75 ml. of ethanol along with 1.5 g. of salicylic acid in 50 ml. of ethanol. The solution is filtered hot and concentrated to a low volume. Cooling, following addition of petroleum ether, separates a yellow salt, 11-methoxy - 14 - methyl-5-oxo-5,7,8,14-tetrahydroindolo-[2,3-a]pyridine salicylate.

EXAMPLE XII

A suspension of 6.7 g. of 6-isobutoxy-1-oxo-1,2,3,4-tetrahydropyrid[3,4-b]indole, prepared by utilizing 4-iso-

butoxyaniline in the coupling synthesis in Example I, in 450 ml. of cyclohexane with 3 g. of phosphorus oxychloride is heated at reflux with stirring briefly. After the addition of 5.8 g. of methyl N-butylanthranilate, the reflux period is extended to four hours. The volatiles are removed in vacuo. The residue is then shaken vigorously in an ice slurry which is then neutralized with ammonia water and extracted with several portions of chloroform. The dried chloroform extracts are concentrated and replaced with dry benzene. Gaseous hydrogen chloride separates the impure hydrochloride which is washed thoroughly with benzene and then converted to the orange base by shaking with sodium bicarbonate solution into benzene. The organic layer is concentrated in vacuo and the residue recrystallized from benzene to give the crystalline base, 10-isobutoxy-14-butyl-5-oxo-5,7,8,14-tetrahydroindolo[2,3-c]quinazo[3,2-a]pyridine.

The colored base is characterized by forming the maleate salt by reacting 4.2 g. of the base with 1.2 g. of maleic acid in ethanol.

EXAMPLE XIII

A 15 g. sample of 3-carbethoxy-2-piperidone is hydrolyzed overnight by standing in a dilute potassium hydroxide solution containing 1.5 base equivalents. The hydrolysate is cooled, buffered and treated with a cold diazonium salt solution prepared from 18.4 g. of p-iodoaniline. After stirring at room temperature for two hours, the coupled hydrazone is separated by filtration and dried in vacuo. This material is then heated at reflux in 500 g. of 70% formic acid for one hour. After filtration, a crystalline product separates on cooling. Purification of the 6-iodo-1-oxo-1,2,3,4-tetrahydropyrid[3,4-b]indole is accomplished by recrystallization from benzene, M. P. 229–231° C. (dec.).

A suspension of 3.0 g. of 6-iodo-1-oxo-1,2,3,4-tetrahydropyrid[3,4-b]indole in 100 ml. of toluene with 2.5 g. of phosphorus oxychloride is heated at reflux briefly, then 4.5 g. of methyl N-methylanthranilate is added and the reflux period continued for one hour. The volatiles are removed in vacuo. The residue is quenched in ice water. The aqueous mixture is then neutralized with ammonia water and extracted with chloroform which is dried and replaced with benzene. Gaseous hydrogen chloride is passed into the benzene solution to separate a yellow crystalline hydrochloride.

After recrystallization from hot water, the free base, 10 - iodo - 14 - methyl - 5 - oxo - 5,7,8,14 - tetrahydroindolo[2,3-c]quinazo[3,2-a]pyridine is regenerated from the hydrochloride salt by ammonia water, taken into benzene; orange-red needles, M. P. 224° C. (dec.).

EXAMPLE XIV

A suspension of 9.3 g. of 1-oxo-1,2,3,4-tetrahydropyrid[3,4-b]indole in 200 ml. of toluene with 6 g. of phosphorus oxychloride is heated at reflux with stirring for fifteen minutes. A 11.5 g. portion of methyl N-ethyl-4-isopropylanthranilate, prepared by esterification of 4-isopropylanthranilic acid with methanol and dry hydrogen chloride gas, then monoalkylation with ethyl iodide, is added and the reaction mixture is heated at reflux for two hours. The orange base is isolated following the procedure outlined in Example II, 14-ethyl-2-isopropyl-5-oxo - 5,7,8,14 - tetrahydroindolo[2,3 - c]quinazo[3,2 - a]-pyridine.

This base is characterized by dissolving 3.6 g. in 75 ml. of ethanol. An excess of ethanolic hydrogen bromide is added to the base solution. The solution is filtered hot and allowed to concentrate on the steam bath. Cooling separates yellow crystals of 14-ethyl-5-oxo-2-isopropyl - 5,7,8,14 - tetrahydroindolo[2,3-c] - quinazo-[3,2-a]pyridine hydrobromide.

EXAMPLE XV

A suspension of 2.7 g. of a mixture of 5(7)-bromo-1-oxo - 1,2,3,4 - tetrahydropyrid[3,4 - b]indole, prepared by using m-bromoaniline in the coupling synthesis, as described in Example XIII, in 50 ml. of toluene with 1 g. of phosphorus oxychloride is heated at reflux for ten minutes at which time 2.0 g. of methyl N-methylanthranilate is added.

After a reflux period of three hours, the yellow crystalline hydrochloride of 9(11)-bromo-14-methyl-5-oxo-5,7,8,14 - tetrahydroindolo[2,3-c]quinazo[3,2-a]pyridine is isolated following the procedure of Example XIII.

EXAMPLE XVI

A suspension of 4.1 g. of 6-fluoro-1-oxo-1,2,3,4-tetrahydropyrid[3,4-b]indole, prepared by using p-fluoroaniline, from the catalytic reduction of 1-fluoro-4-nitrobenzene, as starting material in the coupling synthesis of Example XIII, in 100 ml. of chlorobenzene with 5 g. of phosphorus oxychloride is heated at reflux briefly with stirring. After addition of 4.3 g. of methyl 4-methoxy-N-methylanthranilate, the reaction mixture is heated at reflux for four hours.

Following the isolation procedure of Example II, the base, 10-fluoro-2-methoxy-14-methyl-5-oxo-5,7,8,14-tetrahydroindolo[2,3-c]quinazo[3,2-a]pyridine, separated as red-orange crystals.

EXAMPLE XVII

A suspension of 4.8 g. of 6-n-hexoxy-1-oxo-1,2,3,4-tetrahydropyrid[3,4-b]indole, prepared from 4-hexoxyaniline by the coupling procedure described in Example I in 120 ml. of benzene with 7 g. of phosphorus oxychloride is heated at reflux with stirring for ten minutes at which time 3.5 g. of propyl N-methylanthranilate is added to the reaction mixture. The reflux period is extended to two hours. The condensation product is isolated following the procedure in Example II, to give the crystalline base 10 - hexoxy - 14 - methyl - 5 - oxo - 5,7,8,14 - tetrahydroindolo[2,3-c]quinazo[3,2-a]pyridine.

A solution of 2 g. of the base in 100 ml. of dry benzene is heated at reflux while 1 g. of n-hexyl bromide is added. The condenser is removed and the solution is allowed to concentrate on the steam bath as the crystalline hexyl bromide quaternary salt of 10-hexoxy-14-methyl - 5 - oxo - 5,7,8,14 - tetrahydroindolo - [2,3-c]-quinazo[3,2-a]pyridine separates and is isolated by filtration.

EXAMPLE XVIII

A solution of 3.4 g. of 1-oxo-1,2,3,4-tetrahydropyrid-[3,4-b]indole in 120 ml. of dry toluene with 3.5 g. of phosphorus oxychloride is heated at reflux for ten minutes. After the addition of 4.0 g. of methyl N-methyl-5-chloroanthranilate, M. P. 63–64° C., prepared by N-methylation of 5-chloroanthranilic acid with methyl sulfate followed by methanol-hydrogen chloride esterification, the reaction mixture is heated at reflux for two hours. The solution is treated as in Example II, however, the final chloroform extract is concentrated to a low volume and triturated with aqueous ethanol to separate 3-chloro-14 - methyl - 5 - oxo - 5,7,8,14 - tetrahydroindolo - [2,3-c]-quinazo[3,4-b]pyridine hydrate. Yellow plates of the hydrate are obtained by recrystallization from a large volume of aqueous ethanol, M. P. 186–188° C. (dec.).

EXAMPLE XIX

A suspension of 2.0 g. of 1-oxo-1,2,3,4-tetrahydropyrid-[3,4-b]indole, 2.0 g. of phosphorus oxychloride in 55 ml. of dry toluene is heated at reflux for ten minutes. After the addition of 2.5 g. of methyl 6-methylaminopiperonylate, prepared by alkylating methyl 6-aminopiperonylate, with dimethyl sulfate in benzene, the reaction mixture is heated at reflux for three hours. The solid, which separates after standing for 12 hours, is separated and shaken with ammonia water-chloroform mixture. The chloroform solution is dried, diluted with benzene and evaporated to give a red crystalline solid which is redissolved in chloroform and acidified with hydrogen

chloride gas to give the hydrochloride salt. The red base is again regenerated as before, M. P. 270–275° C. (dec.), 14 - methyl - 2,3 - methylenedioxy - 5 oxo - 5,7,8,14-tetrahydroindolo[2,3-c]quinazo[3,2-a]pyridine.

EXAMPLE XX

A suspension of 1.25 g. of 1-oxo-1,2,3,4-tetrahydropyrid[3,4-b]indole, 1.04 g. of phosphorus oxychloride, 1.5 g. of methyl 6-methylaminoveratrate, prepared by methylation of methyl 6-aminoveratrate by methyl sulfate in benzene, in 35 ml. of dry toluene is heated at reflux for about three hours. After working up the reaction mixture essentially as in Example XIX, an orange crystalline base is recovered, M. P. 210–220° C. (dec.), 2,3-dimethoxy - 14 - methyl - 5 - oxo - 5,7,8,14 - tetrahydroindolo[2,3-c]quinazo[3,2-a]pyridine.

EXAMPLE XXI

A suspension of 5.0 g. of 1-oxo-1,2,3,4-tetrahydropyrid[3,4-b]indole, 5.0 g. of phosphorus oxychloride, 12.1 g. of methyl N-octadecylanthranilate, prepared by the alkylation of methyl anthranilate with n-octadecyl bromide and potassium acetate, in 125 ml. of dry toluene is heated at reflux with stirring for 2½ hours. The filtered reaction mixture is diluted with hexane to separate a solid which is treated with ammonia water and ether. A yellow solid hydrate separates from the ethereal layer and is filtered and recrystallized from hexane. The product consists of fine yellow prisms of the hydrate of 14-octadecyl-5-oxo - 5,7,8,14 - tetrahydroindolo[3,2-a]quinazo [2,3-c]pyridine, M. P. 119° C.

EXAMPLE XXII

Ethyl 3-dimethylaminomethylindole-2-carboxylate is alkylated with 1-nitropropane in the presence of sodium hydroxide to yield ethyl 3-(2-nitrobutyl)-indole-2-carboxylate, M. P. 154–155° C. A reductive cyclization of this substituted indole by stannous chloride gives 3-ethyl-1-oxo-1,2,3,4-tetrahydropyrid[3,4-b]indole, M. P. 188–189° C.

A suspension of 0.45 g. of 3-ethyl-1-oxo-1,2,3,4-tetrahydropyrid[3,4-b]indole, 0.38 g. of methyl N-methyl anthranilate and 0.5 g. of phosphorus oxychloride in 10 ml. of dry toluene is heated at reflux for two hours. A yellow hydrochloride is obtained by following the procedure of Example XIX. After recrystallization from water, the salt is neutralized, separated and recrystallized from ethanol, pale yellow crystals of 7-ethyl-14-methyl-5-oxo-5,7,8,14-tetrahydroindolo[2,3-c]quinazo[3,2 - a]pyridine, M. P. 162–163° C. (dec.).

EXAMPLE XXIII

A suspension of 2.0 g. of 1-oxo-1,2,3,4-tetrahydropyrid[3,4-b]indole, 2 g. of phosphorus oxychloride and 2.8 g. of dimethyl N-methylaminoterephthalate, prepared by reacting dimethylaminoterephthalate with an excess of ethyl iodide at 100° C., in 75 ml. of toluene is heated at reflux for three hours. After working up the reaction mixture as in Example XIX, the base is obtained, 2-carbomethoxy-14-ethyl-5-oxo-5,7,8,14 - tetrahydroindolo [2,3-c]quinazo[3,2-a]pyridine.

EXAMPLE XXIV

A suspension of 5.0 g. of 1-oxo-1,2,3,4-tetrahydropyrid[3,4-b]indole, 5.0 g. of phosphorus oxychloride, 7.25 g. of methyl N-benzyl-anthranilate, in 110 ml. of dry toluene is heated at reflux for three and one-half hours. After working up the reaction mixture essentially as in Example XIX, orange crystals are recovered, 14-benzyl-5-oxo-5,7,8,14-tetrahydroindolo[2,3-c]quinazo-[3,2-a]pyridine.

EXAMPLE XXV

A suspension of 5.0 g. of 1-oxo-1,2,3,4-tetrahydropyrid[3,4-b]indole, 5.0 g. of phosphorus oxychloride, 10.2 g. of methyl N-(6-phenylhexyl)anthranilate, prepared by the alkylation of methyl anthranilate with 6-phenyl-n-hexyl bromide and sodium acetate, in 125 ml. of dry toluene is heated at reflux with stirring for three hours. The mixture, after working up essentially as in Example XXI, gives yellow crystals of the hydrate of 5-oxo-14-(6'-phenylhexyl - 5,7,8,14 - tetrahydroindolo[3,2-a]quinazo [2,3-c]pyridine.

EXAMPLE XXVI

A suspension of 6.0 g. of 1-oxo-1,2,3,4-tetrahydropyrid[3,4-b]indole in 150 ml. of anisone with 5.0 g. of phosphorus oxychloride is heated at reflux briefly before 5.2 g. of methyl N-methyl-3,4,5-trimethoxyanthranilate, prepared by N-methylation of methyl 3,4,5-trimethoxyanthranilate with methyl sulfate in benzene, is added. The reflux period is extended to one hour. The product is isolated following the procedure of Example XIII to give 14-methyl-5-oxo-5,7,8,14-tetrahydro-1,2,3-trimethoxyindolo[2,3-c]quinazo[3,2-a]pyridine.

EXAMPLE XXVII

A suspension of 4.6 g. of 1-oxo-1,2,3,4-tetrahydro-5,6,8-trimethylpyrid[3,4-b]indole, prepared by using 2,4,5-trimethylaniline from reduction of nitropseudocumene in the coupling procedure of Example I, in 50 ml. of toluene with 3.5 g. of methyl N-methylanthranilate and 4.0 g. of phosphorus oxychloride is heated for three hours at reflux with stirring. The desired base, 5-oxo-5,7,8,14-tetrahydro-9,10,12,14-tetramethylindolo[2,3-c]quinazo[3,2 - a]pyridine, is isolated by the procedure of Example II.

The base (500 mg.) is reacted with an excess of citric acid in ethyl acetate to form crystals of the citrate salt.

EXAMPLE XXVIII

A suspension of 6.9 g. of 6,7-methylenedioxy-1,2,3,4-tetrahydropyrid[3,4-b]indole, prepared by using 3,4-methylenedioxyaniline in the coupling synthesis of Example II, 5.0 g. of phosphorus oxychloride and 5.2 g. of methyl N-methylanthranilate in 50 ml. of toluene is heated at reflux with stirring for two hours. After working up the reaction mixture as in Example XIX, 14-methyl-10,11-methylenedioxy-5-oxo-5,7,8,14 - tetrahydroindolo[2,3-c]quinazo[3,2-a]pyridine is obtained first as the hydrochloride, and then as the red base.

EXAMPLE XXIX

A suspension of 5.1 g. of 1-oxo-1,2,3,4-tetrahydro-7-trifluoromethylpyrid[3,4-b]indole, prepared by using 3-trifluoroaniline in the coupling synthesis of Example XIII and separating the resulting 5 and 7 isomers by fractional crystallization and 4.0 g. of phosphorus oxychloride in 100 ml. of toluene is heated briefly at reflux. After the addition of 3.5 g. of methyl N-methylanthranilate, the reaction mixture is heated at reflux for two hours. The mixture is worked up as in Example XII to give the desired base, 14-methyl-5-oxo-5,7,8,14-tetrahydro-11-trifluoro-methylindolo[2,3-c]quinazo[3,2-a]pyridine.

EXAMPLE XXX

A suspension of 2.3 g. of 1-oxo-1,2,3,4-tetrahydro-5,6,8-trimethylpyrid[3,4-b]indole and 2.2 g. of methyl N-methyl-3,4,5-trimethoxyanthranilate in 75 ml. of toluene with 4.0 g. of phosphorus oxychloride is heated at reflux for five hours with stirring. The product, 14-methyl-5-oxo-5,7,8,14-tetrahydro-1,2,3-trimethoxy - 9,10,12 - trimethylindolo[2,3-c]quinazo[3,2-a]pyridine, is isolated by the procedure of Example XIII.

EXAMPLE XXXI

A suspension of 1.9 g. of 1-oxo-1,2,3,4-tetrahydropyrid-[3,4-b]indole, 3.0 g. of phosphorus oxychloride and 3.2 g. of methyl 6-bromo-N-methyl-4-trifluoromethylanthranilate, prepared by standard reactions from 3-nitrotrifluoromethylbenzene in 50 ml. of toluene is heated at reflux with stirring for two hours. The desired base, 4-bromo-14 - methyl-5-oxo-5,7,8,14-tetrahydro-2-trifluoromethylin-

dolo[2,3-c]quinazo[3,2-a]pyridine, is isolated in small yield by the procedure of Example XIII.

EXAMPLE XXXII

A suspension of 1.9 g. of 1-oxo-1,2,3,4-tetrahydropyrid-[3,4-b]indole, 2.5 g. of phosphorus oxychloride, 2.5 g. of methyl 5-isoamoxy-N-methylanthranilate, prepared by standard procedures from methyl 2-hydroxy-6-nitrobenzoate in 75 ml. of benzene is heated at reflux for three hours. After proceeding with the isolation steps of Example I the desired base, 3-isoamoxy-14-methyl-5-oxo-5,7,8,14-tetrahydroindolo[2,3-c]quinazo[3,2-a]pyridine, is recovered as the hydrate.

EXAMPLE XXXIII

A suspension of 1.9 g. of 1-oxo-1,2,3,4-tetrahydropyrid-[3,4-b]indole, 2.0 g. of phosphorus oxychloride and 2.0 g. of methyl N-allylanthranilate, prepared by alkylation of methylanthranilate with allyl chloride, in 75 ml. of dry toluene is heated at reflux with stirring for three hours. Following the isolation procedure of Example XXI, the desired base, 14-allyl-5-oxo-5,7,8,14-tetrahydroindolo-[3,2-a]quinazo[2,3-c]pyridine, is recovered.

EXAMPLE XXXIV

A suspension of 5.0 g. of 1-oxo-1,2,3,4-tetrahydropyrid[3,4-b]indole, 5.0 g. of phosphorus oxychloride, 12.1 g. of methyl N-oleylanthranilate, prepared by the alkylation of methylanthranilate with oleyl bromide in the presence of potassium acetate, in 125 ml. of toluene is heated at reflux with stirring for four hours. The product is isolated as in Example XXI; 14-oleyl-5-oxo-5,7,8,14-tetrahydroindolo[3,2-a]quinazo[2,3-c]pyridine hydrate.

EXAMPLE XXXV

A suspension of 4.5 g. of 6-allyl-1-oxo-1,2,3,4-tetrahydro[3,4-b]indole, prepared by using p-allylaniline in the coupling procedure of Example I, 5.0 g. of phosphorus oxychloride and 3.5 g. of methyl N-methylanthranilate in 100 ml. of dry toluene is heated at reflux for two hours. After carrying the reaction through as in Example I, the base, 10-allyl-14-methyl-5-oxo-5,7,8,14-tetrahydroindolo-[2,3-c]quinazo[3,2-a]pyridine, is recovered.

EXAMPLE XXXVI

A suspension of 5.0 g. of 1-oxo-1,2,3,4-tetrahydropyrid-[3,4-b]indole, 5.0 g. of phosphorus oxychloride, 9.5 g. of methyl N-(2-phenethyl)-anthranilate, prepared by the alkylation of methylanthranilate with phenethyl bromide and sodium acetate, in 150 ml. of toluene is heated at reflux with stirring for two hours. The mixture, after working up as in Example XVIII, yields crystals of 5-oxo-14-(2'-phenethyl)-5,7,8,14-tetrahydroindolo[3,2-a]-quinazo[2,3-c]pyridine hydrate, M. P. 180° C.

EXAMPLE XXXVII

A solution of 5.0 g. of 10-methoxy-14-methyl-5-oxo-5,7,8,14-tetrahydroindolo[2,3-c]quinazo[3,2-a]pyridine (prepared as in Example I) in 100 ml. of 48% hydrobromic acid is heated at reflux for eight hours. After cooling and diluting the reaction mixture with an equal volume of water, a fine yellow solid separates. Recrystallization from aqueous ethanol gives yellow needles of 10-hydroxy-14-methyl-5-oxo-5,7,8,14-tetrahydroindolo-[2,3-c]quinazo[3,2-a]pyridine hydrobromide, M. P. 266–267° C. (dec.). This material dissolves completely in dilute sodium hydroxide solution to give a magenta colored solution whose color rapidly fades to a pale yellow.

EXAMPLE XXXVIII

A solution of 0.5 g. of 2-methoxy-14-methyl-5-oxo-5,7,8,14-tetrahydroindolo[2,3-c]quinazo[3,2-a]pyridine hydrate (prepared as in Example III) in 14 ml. of 48% hydrobromic acid is heated at reflux for four hours. After working up the reaction mixture as in Example XXXVI, yellow prisms of 2-hydroxy-14-methyl-5-oxo-5,7,8,14-tetrahydroindolo[2,3-c]quinazo[3,2-a]pyridine hydrobromide are obtained from 80% aqueous ethanol, M. P. 346° C. (dec.).

EXAMPLE XXXIX

A suspension of 4.0 g. of 10-hydroxy-14-methyl-5-oxo-5,7,8,14-tetrahydroindolo[2,3-c]quinazo[3,2-a]pyridine hydrobromide (prepared as in Example XXXVII) in 75 ml. of acetic anhydride is heated at reflux for three hours. The reaction mixture is concentrated in vacuo and the washed residue is purified by several recrystallizations from ethanol to give the desired product, 10-acetoxy-14-methyl-5-oxo-5,7,8,14-tetrahydroindolo[2,3-c]quinazo-[3,2-a]pyridine hydrobromide.

A small amount of the salt is triturated with concentrated ammonia to give a small return of the base of the 10-hydroxy starting material.

The pharmaceutical carrier may be a solid or a liquid. Exemplary solid carriers are cornstarch, lactose, talc, magnesium stearate and starch. Where a solid carrier is employed, the composition of this invention may be in the form of a tablet or a hard gelatin capsule for oral use.

Where a liquid carrier is desired, the medicament may be in a suitable oily menstruum such as, for example, peanut or soybean oil and the admixture placed, if desired, in a soft gelatin capsule. Water alone or in admixture with other agents such as carboxymethylcellulose, polyoxyethylene monostearate, acacia, tragacanth or methylcellulose is a satisfactory liquid carrier for oral use. For parenteral use the following carriers are exemplary: saline water, aqueous propylene glycol or peanut oil.

In any of the pharmaceutical forms of this invention the foregoing is illustrative of the dosage units possible and it is recognized that variations within the skill of the art are feasible and often of advantage. For instance the addition of flavor, preservatives, colors, etc., is often desirable to attain pharmaceutically elegant preparations.

The composition of this invention will preferably contain from about 1 mg. to about 150 mg. and advantageously from about 10 mg. to about 75 mg. of the medicament compound, preferably as the base. The carrier will preferably be present in an amount of from about 5 mg. to about 18 g. and advantageously in an amount of from about 25 mg. to about 5 g. Where a solid carrier is employed, it will preferably be present in an amount of from about 5 mg. to about 750 mg. and advantageously in an amount of from about 25 mg. to about 500 mg.

The following examples are illustrative:

Example A1

Composition:	Gm./capsule
10-methoxy-14-methyl-5-oxo-5,7,8,14-tetrahydroindolo[2,3-c]quinazo[3,2-a]pyridine	0.010
Lactose	0.290

Procedure.—The ingredients are mixed and pulverized sufficiently to pass through 100 mesh sieve and then incorporated into size #2 hard gelatin capsules.

Example A2

Composition:	Gm./capsule
10-hydroxy-14-methyl-5-oxo-5,7,8,14-tetrahydroindolo-[2,3-c]quinazo[3,2-a] pyridine hydrobromide	0.010
Lactose	0.290

Procedure.—The ingredients are mixed and pulverized sufficiently to pass through 100 mesh sieve and then incorporated into size #2 hard gelatin capsules.

Example A3

Composition:	Gm./capsule
10-chloro-14-methyl-5-oxo - 5,7,8,14 - tetrahydroindolo-[2,3-c] quinazo [3,2-a] pyridine	0.050
Lactose	0.250

Procedure.—The ingredients are mixed and pulverized sufficiently to pass through 100 mesh sieve and then incorporated into size #2 hard gelatin capsules.

Example A4

Composition:	Gm./capsule
Isoamyl bromide quaternary salt of 2-methoxy-14-methyl-5-oxo-5,7,8,14 - tetrahydroindolo[2,3-c]quinazo[3,2-a]pyridine	0.100
Starch	0.150

Procedure.—The ingredients are mixed and pulverized sufficiently to pass through 100 mesh sieve and then incorporated into hard gelatin capsules.

Example A5

Composition:	Gm./capsule
10,14-dimethyl-5 - oxo- 5,7,8,14 - tetrahydroindolo[2,3-c]quinazo-[3,2,-a] pyridine	0.050
Calcium carbonate	0.150

Procedure.—The ingredients are mixed and pulverized sufficiently to pass through 100 mesh sieve and then incorporated into hard gelatin capsules.

Example A6

Composition:	Gm./capsule
10,14-dimethyl-2-methoxy-5-oxo-5,7,8,14-tet - rahydroindolo-[2,3-c]quinazo [3,2-a] pyridine	0.001
Mannitol	0.299

Procedure.—The ingredients are mixed and pulverized sufficiently to pass through 100 mesh sieve and then incorporated into hard gelatin capsules.

Example A7

0.025 gram of 14 - methyl - 5 - oxo - 5,7,8,14 - tetrahydroindolo[2,3-c]quinazo[3,2-a]pyridine hydrochloride is mixed with soybean oil to produce a flowable mass. The thus produced composition is then encapsulated in a soft gelatin capsule.

Example A8

0.015 gram of 14 - butyl - 5 - oxo - 5,7,8,14 - tetrahydroindolo[2,3-c]quinazo[3,2-a]pyridine hydrate is mixed with soybean oil to produce a flowable mass. The thus produced composition is then encapsulated in a soft gelatin capsule.

Example A9

0.030 gram of 5-oxo-5,7,8,14-tetrahydro-11,12,14-trimethylindolo[2,3-c]quinazo[3,2-a]pyridine acetate are encapsulated in a soft gelatin capsule following the procedure of Example A8.

Example A10

0.030 gram of 14-methyl-5-oxo-12-propyl-5,7,8,14-tetrahydroindolo[2,3-c]quinazo[3,2-a]pyridine are encapsulated in a soft gelatin capsule following the procedure of Example A8.

Example A11

0.050 gram of 9-chloro-12-methoxy-14-methyl-5-oxo-5,7,8,14 - tetrahydroindolo[2,3-c]-quinazo[3,2-a]pyridine are mixed with peanut oil to produce a flowable mass which is then encapsulated in a soft gelatin capsule.

Example A12

0.050 gram of 11-methoxy-14-methyl-5-oxo-5,7,8,14-tetrahydroindolo[2,3-c]quinazo[3,2-a]pyridine are mixed with peanut oil to produce a flowable mass which is then encapsulated in a soft gelatin capsule.

Example A13

0.025 gram of 10-isobutoxy-14-butyl-5-oxo-5,7,8,11-tetrahydroindolo[2,3-c]quinazo[3,2-a]pyridine are mixed with peanut oil to produce a flowable mass which is then encapsulated in a soft gelatin capsule.

Example A14

Composition:	Gm./tablet
10 - iodo - 14 - methyl - 5 - oxo - 5,7,8,14-tetrahydroindolo - [2,3 - c]quinazo[3,2 - a] pyridine	0.050
Lactose	0.250

Procedure.—The above ingredients were thoroughly mixed, granulated using a 10% gelatin solution and compressed into tablets using an admixture of 7% starch and 1% magnesium stearate based on tablet weight.

Example A15

Composition:	Gm./tablet
14 - ethyl - 2 - isopropyl - 5 - oxo - 5,7,8,11-tetrahydroindolo - [2,3 - c]quinazo[3,2 - a] pyridine	0.025
Lactose	0.175
Starch	0.045

Procedure.—The above ingredients were thoroughly mixed, granulated using a 10% gelatin solution and compressed into tablets using talc as a lubricant.

Example A16

Composition:	Gm./tablet
5(7) - bromo - 14 - methyl - 1 - oxo - 5,7,8,11-tetrahydroindolo - [2,3 - c]quinazo[3,2 - a] pyridine	0.075
Lactose	0.125
Starch	0.045

Procedure.—The above ingredients were thoroughly mixed, granulated using a 10% gelatin solution and compressed into tablets using talc-stearic acid as a lubricant.

Example A17

Composition:	Gm./tablet
10 - fluoro - 2 - methoxy - 14 - methyl - 1-oxo - 5,7,8,11 - tetrahydroindolo - [2,3 - c] quinazo[3,2-a]pyridine	0.025
Lactose	0.275

Procedure.—The above ingredients were thoroughly mixed, granulated using a 50% sucrose solution and compressed into tablets using an admixture of 7% starch and 1% magnesium stearate based on tablet weight.

Example A18

Composition:	Gm./tablet
10 - hexoxy - 14 - methyl - 5 - oxo - 5,7,8,14-tetrahydroindolo[2,3 - c]quinazo - [3,2 - a] pyridine	0.100
Lactose	0.100
Starch	0.045

Procedure.—The above ingredients were thoroughly mixed, granulated using a 10% gelatin solution and compressed into tablets using talc as a lubricant.

Example A19

Composition:	Gm./tablet
10 - acetoxy - 14 - methyl - 5 - oxo - 5,7,8,14-tetrahydroindolo - [2,3 - c]quinazo[3,2 - a] pyridine hydrobromide	0.010
Lactose	0.090

Procedure.—The above ingredients were thoroughly mixed, granulated using a 10% gelatin solution and compressed into tablets using an admixture of 1% magnesium stearate based on tablet weight.

Example A20

Composition:

	Gm./tablet
3 - chloro - 14 - methyl - 1 - oxo - 5,7,8,14-tetrahydroindolo - [2,3 - c]quinazo[3,4 - b] pyridine hydrate	0.050
Lactose	0.150
Starch	0.045

Procedure.—The above ingredients were thoroughly mixed, granulated using a 50% sucrose solution and compressed into tablets using talc as a lubricant.

Example A21

Composition:

	Percent w./v.
10 - methoxy - 14 - methyl - 5 - oxo - 5,7,8, 14 - tetrahydroindolo[2,3 - c]quinazo [3,2-a]pyridine tartrate	0.153
Dextrose, anhydrous	4.90
Water for injection q. s.	100.00

The above ingredients are mixed to make a solution and filtered. The filtrate is autoclaved at 120° C. at 18 pounds pressure for 25 minutes. The thus treated composition is suitable for injection.

Example A22

Composition:

	Gm./5 cc.
10 - methoxy - 14 - methyl - 5 - oxo - 5,7,8,14-tetrahydroindolo - [2,3 - c]quinazo[3,2 - a] pyridine	0.010
Sucrose	2.500
Methyl cellulose 400	0.050
Purified water in an amount to bring the total volume to 5 cc.	

The 10 - methoxy - 14 - methyl - 5 - oxo - 5,7,8,14-tetrahydroindolo[2,3-c]quinazo[3,2-a]pyridine is reduced to a fine powder so that all will pass a 325 mesh sieve. The remaining ingredients are mixed to make the vehicle. The 10 - methoxy - 14 - methyl - 5 - oxo - 5,7,8,14-tetrahydroindolo - [2,3 - c]quinazo[3,2 - a]pyridine is incorporated in the thus formed vehicle and homogenized.

Example A23

Composition:

	Gm./capsule
14 - methyl - 2,3 - methylenedioxy - 5 - oxo-5,7,8,14 - tetrahydroindolo - [2,3 - c]quinazo[3,2-a]pyridine	0.010
Lactose	0.290

Procedure.—The ingredients are mixed and pulverized sufficiently to pass through 100 mesh sieve and then incorporated into size #2 hard gelatin capsules.

Example A24

Composition:

	Gm./capsule
2,3 - dimethoxy - 14 - methyl - 5 - oxo - 5,7,8, 14 - tetrahydroindolo[2,3 - c] - quinazo [3,2-a]pyridine	0.010
Lactose	0.290

Procedure.—The ingredients are mixed and pulverized sufficiently to pass through 100 mesh sieve and then incorporated into size #2 hard gelatin capsules.

Example A25

Composition:

	Gm./capsule
14 - octadecyl - 5 - oxo - 5,7,8,14 - tetrahydroindolo[3,2 - a]quinazo - [2,3 - c] pyridine	0.050
Lactose	0.250

Procedure.—The ingredients are mixed and pulverized sufficiently to pass through 100 mesh sieve and then incorporated into size #2 hard gelatin capsules.

Example A26

Composition:

	Gm./capsule
7 - ethyl - 14 - methyl - 5 - oxo - 5,7,8,14-tetrahydroindolo[2,3 - c]quinazo - [3,2 - a] pyridine	0.100
Starch	0.150

Procedure.—The ingredients are mixed and pulverized sufficiently to pass through 100 mesh sieve and then incorporated into hard gelatin capsules.

Example A27

Composition:

	Gm./capsule
2 - carbomethoxy - 14 - ethyl - 5 - oxo-5,7,8,14 - tetrahydroindolo - [2,3 - c]quinazo[3,2-a]pyridine	0.050
Calcium carbonate	0.150

Procedure.—The ingredients are mixed and pulverized sufficiently to pass through 100 mesh sieve and then incorporated into hard gelatin capsules.

Example A28

Composition:

	Gm./capsule
14 - benzyl-5-oxo - 5,7,8,14 - tetrahydroindolo [2,3-c]quinazo[3,2-a]-pyridine	0.001
Mannitol	0.299

Procedure.—The ingredients are mixed and pulverized sufficiently to pass through 100 mesh sieve and then incorporated into hard gelatin capsules.

Example A29

Composition:

	Gm./tablet
5 - oxo-14 - (6'-phenylhexyl) - 5,7,8,14-tetrahydroindolo[3,2 - a]quinazo - [2,3 - c]pyridine	0.050
Lactose	0.250

Procedure.—The above ingredients were thoroughly mixed, granulated using a 10% gelatin solution and compressed into tablets using an admixture of 7% starch and 1% magnesium stearate based on tablet weight.

Example A30

Composition:

	Gm./tablet
14-methyl - 5 - oxo - 5,7,8,14-tetrahydro-1,2,3-trimethoxyindolo[2,3 - c]quinazo[3,2 - a] pyridine	0.025
Lactose	0.175
Starch	0.045

Procedure.—The above ingredients were thoroughly mixed, granulated using a 10% gelatin solution and compressed into tablets using talc as a lubricant.

Example A31

Composition:

	Gm./tablet
5-oxo - 5,7,8,14 - tetrahydro - 9,10,12,14-tetramethylindolo[2,3 - c] - quinazo[3,2-a]pyridine	0.075
Lactose	0.125
Starch	0.045

Procedure.—The above ingredients were thoroughly mixed, granulated using a 10% gelatin solution and compressed into tablets using talc-stearic acid as a lubricant.

Example A32

Composition:

	Gm./tablet
14 - methyl - 10,11 - methylenedioxy - 5 - oxo-5,7,8,14 - tetrahydroindolo - [2,3 - c]quinazo[3,2-a]pyridine	0.025
Lactose	0.275

Procedure.—The above ingredients were thoroughly mixed, granulated using a 50% sucrose solution and compressed into tablets using an admixture of 7% starch and 1% magnesium stearate based on tablet weight.

Example A33

Composition:

	Gm./tablet
14 - methyl - 5 - oxo - 5,7,8,14 - tetrahydro-11-trifluoromethylindolo[2,3 - c] - quinazo [3,2-a]pyridine	0.100
Lactose	0.100
Starch	0.045

Procedure.—The above ingredients were thoroughly

mixed, granulated using a 10% gelatin solution and compressed into tablets using talc as a lubricant.

Example A34

Composition:	Gm./tablet
14 - methyl - 5 - oxo - 5,7,8,14 - tetrahydro-1,2,3-trimethoxy - 9,10,12 - trimethylindolo [2,3-c]quinazo[3,2-a]pyridine	0.010
Lactose	0.090

Procedure.—The above ingredients were thoroughly mixed, granulated using a 10% gelatin solution and compressed into tablets using an admixture of 1% magnesium stearate based on tablet weight.

Example A35

Composition:	Gm./tablet
4 - bromo - 14 - methyl - 5 - oxo - 5,7,8,14-tetrahydro - 2 - trifluoromethylindolo[2,3-c] quinazo[3,2-a]pyridine	0.050
Lactose	0.150
Starch	0.045

Procedure.—The above ingredients were thoroughly mixed, granulated using a 50% sucrose solution and compressed into tablets using talc as a lubricant.

Example A36

Composition:	Gm./capsule
3 - isoamoxy - 14 - methyl - 5 - oxo - 5,7,8,14-tetrahydroindolo[2,3 - c] quinazo[3,2 - a] pyridine	0.010
Lactose	0.290

Procedure.—The ingredients are mixed and pulverized sufficiently to pass through 100 mesh sieve and then incorporated into size #2 hard gelatin capsules.

Example A37

Composition:	Gm./capsule
14 - allyl - 5 - oxo - 5,7,8,14 - tetrahydroindolo [3,2-a]quinazo-[2,3-c]pyridine	0.010
Lactose	0.290

Procedure.—The ingredients are mixed and pulverized sufficiently to pass through 100 mesh sieve and then incorporated into size #2 hard gelatin capsules.

Example A38

Composition:	Gm./capsule
14-oleyl - 5 - oxo - 5,7,8,14 - tetrahydroindolo [3,2-a]quinazo[2,3-c]pyridine hydrate	0.010
Lactose	0.290

Procedure.—The ingredients are mixed and pulverized sufficiently to pass through 100 mesh sieve and then incorporated into size #2 hard gelatin capsules.

Example A39

Composition:	Gm./capsule
10 - allyl-14-methyl-5-oxo-5,7,8,14-tetrahydro-indolo[2,3-c]quinabo[3,2-a]pyridine	0.050
Lactose	0.250

Procedure.—The ingredients are mixed and pulverized sufficiently to pass through 100 mesh sieve and then incorporated into size #2 hard gelatin capsules.

Example A40

Composition:	Gm./capsule
5 - oxo-14-(2'-phenethyl)-5,7,8,14-tetrahydro-indolo [3,2 - a]quinazo[2,3 - c]pyridine hydrate	0.100
Starch	0.150

Procedure.—The ingredients are mixed and pulverized sufficiently to pass through 100 mesh sieve and then incorporated into hard gelatin capsules.

Example A41

Composition:	Gm./capsule
10 - hydroxy-14-methyl-5-oxo-5,7,8,14 - tetrahydroindolo[2,3 - c]quinazo[3,2-a]pyridine hydrobromide	0.050
Calcium carbonate	0.150

Procedure.—The ingredients are mixed and pulverized sufficiently to pass through 100 mesh sieve and then incorporated into hard gelatin capsules.

Example A42

Composition:	Gm./capsule
2 - hydroxy-14-methyl-5-oxo-5,7,8,14-tetrahydroindolo[2,3-c]quinazo[3,2-a]pyridine hydrobromide	0.001
Mannitol	0.299

Procedure.—The ingredients are mixed and pulverized sufficiently to pass through 100 mesh sieve and then incorporated into hard gelatin capsules.

Example A43

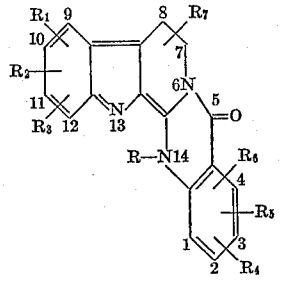
Composition:	Gm./tablet
10 - acetoxy - 14 - methyl-5-oxo-5,7,8,14-tetrahydroindolo[2,3 - c]quinazo[3,2-a]pyridine hydrobromide	0.050
Lactose	0.250

Procedure.—The above ingredients were thoroughly mixed, granulated using a 10% gelatin solution and compressed into tablets using an admixture of 7% starch and 1% magnesium stearate based on tablet weight.

The method in accordance with this invention comprises administering internally the above described medicinal composition to a human being to produce antihypertensive activity. Oral administration is preferred.

What is claimed is:

1. An antihypertensive medicinal composition comprising a pharmaceutical carrier and a compound of the class consisting of a free base and its acid addition, methyl iodide, ethyl bromide, n-hexyl bromide, benzyl chloride, methyl sulfate, ethyl sulfate and methyl p-toluene sulfonate, salts, the free base having the formula:



in which R is a member selected from the group consisting of alkyl having from 1 to 18 carbon atoms, phenylalkyl, having 1 to 6 carbon atoms in the alkyl portion and —CH_2-alkenyl, the alkenyl portion having 2 to 17 carbon atoms; R_1 is a member selected from the group consisting of hydrogen, lower alkoxyl, lower alkyl, —CH_2-alkenyl, the alkenyl portion having 2 to 5 carbon atoms, halo, hydroxyl and trifluoromethyl; R_2 and R_3 are members selected from the group consisting of hydrogen, lower alkoxyl, lower alkyl, —CH_2-alkenyl, the alkenyl portion having 2 to 5 carbon atoms, hydroxyl, halo and trifluoromethyl; R_4 is a member selected from the group consisting of hydrogen, lower alkoxyl, lower alkyl, —CH_2-alkenyl, the alkenyl portion having 2 to 5 carbon atoms, hydroxyl, halo and trifluoromethyl; R_5 and R_6 are members selected from the group consisting of hydrogen, lower alkoxyl, lower alkyl, —CH_2-alkenyl, the alkenyl portion having 2 to 5 carbon atoms, hydroxyl, halo, carbomethoxy and trifluoromethyl; R_7 is a member selected from the group consisting of hydrogen, lower alkoxyl, lower alkyl and halo.

2. The composition of claim 1 characterized in that R_1 and R_4 are members selected from the group consisting of hydrogen, lower alkoxy and lower alkyl; R_2, R_3, R_5, R_6 and R_7 are hydrogen and R is lower alkyl.

3. The composition of claim 1 characterized in that the carrier is a solid.

4. The composition of claim 1 characterized in that the carried is a liquid.

5. The composition of claim 1 characterized in that the composition is in the form of a tablet.

6. The composition of claim 1 characterized in that the composition is in the form of a capsule.

References Cited in the file of this patent

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