United States Patent Office 3,021,331 Patented Feb. 13, 1962

3,021,331

AZABENZOPYRIDOCOLINES

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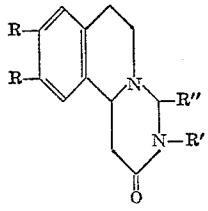
No Drawing. Filed July 20, 1959, Ser. No. 828,007
13 Claims. (Cl. 260—251)

This invention relates to new and useful hereterocyclic compounds as well as to novel methods and intermediates for their preparation. More particularly, the present invention is concerned with organic nitrogen compounds of the aforementioned type which possess a novel heterocyclic ring system as well as with their non-toxic acid addition salts. There is also included within the scope of this invention various pharmaceutical compositions which have as their essential active ingredient at least one of the herein described compounds.

The compounds which are included within the purview of this invention are selected from the azabenzopyridocoline class having the general structural formula:

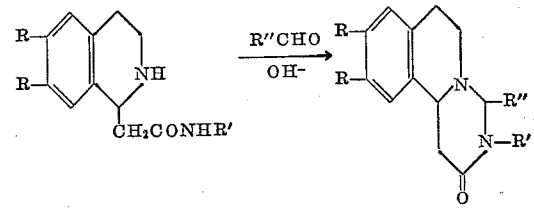


wherein R is a member of the group consisting of hydroxy, lower alkoxy and alkyl and when both R groups are taken together they form a methylenedioxy group, and R′ is a member of the group consisting of lower alkenyl, alkyl, hydroxyalkyl, acyloxyalkyl, lower alkoxyalkyl, dimethylaminoalkyl, aralkyl and aroylamino, said acyl moiety being derived from a hydrocarbon carboxylic acid having from two to eight carbon atoms, and R″ is a member of the group consisting of hydrogen, lower alkenyl, alkyl and trifluoromethyl, each alkyl moiety having from one to five carbon atoms; and the pharmaceutically acceptable acid addition and quaternary ammonium salts thereof. The system of nomenclature employed throughout this specification is that based on the Patterson system as is indicated by the hereinbefore illustrated structural formula for a 2-oxo-3-(substituted)aza-9,10-di-(lower alkoxy)-1,2,3,4,6,7-hexahydro-11b-H-benzopyridocoline [e.g. see "The Ring Index" by Patterson & Capell, New York (1940)].

In accordance with the present invention, the aforementioned azabenzopyridocoline derivatives have been found to possess interesting pharmaceutical properties which render them useful as synthetic medicinals. More particularly, these compounds have been shown to exhibit utility as tranquilizing or hypotensive agents. Of especial value in this connection are those azabenzopyridocolines which have both a 9,10-dimethoxy grouping and a 3-substituent as previously defined on the ring nitrogen atom of the secondary amino group; typical 3-substituents include such groups as allyl, n-butyl, isoamyl, γ-hydroxypropyl, β-(3,4,5-trimethoxybenzoyloxy)ethyl, γ-dimethylaminopropyl, p-chlorobenzyl and benzoylamino.

In accordance with the process for preparing the compounds of this invention, an appropriately substituted α-[1-(1,2,3,4-tetrahydroisoquinolyl)]-acetamide is treated with a compound selected from the group consisting of formaldehyde, trifluoroacetaldehyde and an aliphatic hydrocarbon carboxyaldehyde in the presence of a base as

is illustrated below by the following equation wherein R, R′ and R″ are as previously defined:



This reaction is most desirably conducted in an inert aqueous polar organic solvent medium at a temperature that is in the range of from about 20° C. to about 100° C. for a period of about 0.5 to about 5.0 hours. Preferred reaction-inert polar organic solvents in this connection include such water-miscible lower alkanols as methanol, ethanol, isopropanol, n-propanol, and the like, as well as such N,N-di(lower alkyl) substituted lower aliphatic hydrocarbon carboxamides as dimethylformamide, diethylformamide, dimethylacetamide, diethylacetamide, and the like. Formalin or 37% aqueous formadehyde, acetaldehyde, trifluoroacetaldehyde, isobutyraldehyde, acrolein, and the like, are typical examples of the reagents of choice; while the basic agent employed is preferably an alkali metal or alkaline-earth metal hydroxide in the form of a dilute aqueous solution or it is an organic tertiary amine such as triethylamine or pyridine.

The starting materials employed in the process of this invention are all easily prepared in accordance with standard organic procedures previously described in the chemical literature. For instance, the aforementioned appropriately substituted α-[1-(1,2,3,4-tetrahydroisoquinolyl)]acetamides are conveniently synthesized from their corresponding 1-carbalkoxymethyl analogs via contact with an appropriately substituted primary amine. This particular reaction can be conducted at any temperature in the range of from about 20° C. to about 150° C. for from about two to about 48 hours. An excess of the amine reagent is preferably employed inasmuch as this also serves as a suitable solvent medium in which the reaction can take place. In practice, it is most convenient to reflux a solution of the ultimate isoquinoline starting material with an excess of the amine reagent as the solvent. The 1-carboalkoxy-methyl-6,7-disubstituted-1,2,3,4-tetrahydroisoquinoline so employed is readily obtainable by any number of known procedures disclosed in the prior art and preferably by the method described by J. M. Osbond [J. Chem. Soc. (London), 1951, p. 3646 and ibid, 1953, p. 2463], which involves reacting a 2-[3,4-di(substituted)phenyl]-ethylamine with a carbalkoxyacetyl chloride, followed by a cyclization of the substituted malonamic ester so obtained and catalytic hydrogenation of the resulting cyclized product.

The acids which are used to prepare the pharmaceutically acceptable acid addition salts of the aforementioned azabenzopyridocoline bases are those which form non-toxic acid addition salts containing pharmaceutically acceptable anions, such as the hydrochloride, hydrobromide, hydriodide, nitrate, sulfate or bisulfate, phosphate or acid phosphate, acetate, lactate, citrate or acid citrate, tartrate or bitartrate, oxalate, succinate, maleate, gluconate and saccharate salts. Suitable quaternary ammonium salts of the azabenzopyridocoline derivatives of this invention include those which are obtained by reacting azabenzopyridocoline bases of the foregoing type with a pharmaceutically acceptable organic halide, such as methyl iodide, ethyl chloride, allyl chloride, benzyl bromide, and the like, or with an equally acceptable sulfuric acid lower alkyl ester or an arylsulfonic acid lower alkyl ester, such as dimethyl sulfate, diethyl sulfate, methyl benzenesulfonate, ethyl toluenesulfonate, and the like.

As previously indicated, the compounds of the present invention are readily adapted to therapeutic use as hypotensive agents in addition to being useful as sedatives and muscle-relaxants. Furthermore, the toxicity of these azabenzopyridocolines has been found to be quite low when they are administered to mice in amounts that are generally considered to be sufficient to achieve the desired effects; moreover, no harmful pharmacological side effects have been observed to occur as a result of their administration. The aforementioned biological activity of the herein described compounds is well illustrated by a series of tests previously described in the literature and hence, well-known to those skilled in the art. For instance, the percent decrease in serotonin and norepinephrine levels in the rabbit was determined in accordance with the procedure described by P. Shore et al. in the Journal of Pharmacology and Experimental Therapeutics [J. Pharm. Exp. Ther., vol. 122, p. 295 (1958)] as well as by S. Udenfriend et al. in Science [Sci., vol. 122, p. 972 (1955)].

In accordance with a method of treatment of the present invention, the herein described azabenzopyridocoline derivatives can be administered to a subject via the oral or parenteral routes. In general, these compounds are most desirably administered at a concentration level that will generally afford effective results without causing any harmful or deleterious side effects and preferably at a level that is in the range of from about 50 mg. to about 500 mg. per day, although variations will necessarily occur depending upon the weight of the subject being treated and the particular route of administration chosen. However, a dosage level that is in the range of from about 0.7 mg. to about 7.0 mg. per kg. of body weight per day is most desirably employed in order to achieve effective results. Nevertheless, it is to be appreciated that still other variations may also occur in this respect, depending upon the species of animal being treated and its individual response to said medicament, as well as on the particular type of formulation chosen and the time period and interval at which such administration is carried out. In some instances, doses below the lower limit of the aforesaid range may be more than adequate while in other cases still larger doses may be administered without causing any harmful side effects.

In connection with the use of the azabenzopyridocoline compounds of this invention for the treatment of agitated subjects, it is to be noted that they may be administered either alone or in combination with a pharmaceutically acceptable carrier by either of the routes previously indicated, and that such administration can be carried out in both single and multiple dosages. More particularly, the novel compounds of this invention can be administered in a wide variety of dosage forms, i.e., they may be combined with various pharmaceutically acceptable inert carriers in the form of tablets, capsules, lozenges, troches, hard candies, aqueous suspensions, injectable solutions, elixirs, syrups, and the like. Such carriers include solid diluents or fillers, sterile aqueous media and various nontoxic organic solvents, etc. Moreover, the oral pharmaceutical compositions may be sweetened and/or flavored by means of various agents of the type commonly employed for such a purpose. In general, the therapeutically-active compounds of this invention are present in such dosage forms at concentration levels ranging from about 0.020% to about 90% by weight of the total composition, i.e., in amounts generally considered to be sufficient for providing the desired unit dosage previously indicated.

For purposes of oral administration, tablets containing various excipients such as sodium citrate and calcium phosphate may be employed along with various disintegrants such as alginic acid and certain complex silicates, together with binding agents such as polyvinylpyrrolidone, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, citric acid and talc are often very useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in soft and hard-shelled gelatin capsules; preferred materials in this connection also include lactose or milk sugar, and high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the essential active ingredient may be combined with various sweetening and flavoring agents, coloring matter or dyes and, if so desired, emulsifying and/or suspending agents, together with such diluents as water, ethanol, propylene glycol, glycerin and various combinations thereof.

For purposes of parenteral administration, solutions of the azabenzopyridocoline bases in sesame or peanut oil or in aqueous-propylene glycol may be employed, as well as sterile aqueous solutions of the corresponding water-soluble salts previously enumerated. Such aqueous solutions should be suitably buffered if necessary, wherein the liquid diluent is first rendered isotonic with sufficient glucose or saline. All these solutions are particularly suitable for intravenous, intramuscular and intraperitoneal injection purposes. In this connection, the sterile aqueous media employed are readily obtained by standard techniques well-known to those in the art. For instance, when distilled water is ordinarily used as the liquid diluent the final preparation can be passed through a suitable bacterial filter, such as a sintered glass filter or a diatomaceous earth or unglazed porcelain filter. Preferred filters of this type include the Berkefeld, the Chamberland and the asbestos disc-metal Seitz filter, wherein the fluid is sucked through the filter candle into a sterile container with the aid of a suction pump. Needless to say, aseptic conditions must necessarily be maintained throughout all such operations connected with the preparation of these injectable solutions.

This invention is further illustrated by the following examples, which are not to be construed as imposing any limitations on the scope thereof. On the contrary, it is to be clearly understood that resort may be had to various other embodiments, modifications and equivalents thereof which readily suggest themselves to those skilled in the art without departing from the spirit of the present invention and/or the scope of the appended claims.

Example I

In a 250 ml. round-bottomed flask fitted with a reflux condenser and having a drying tube attached thereto, there were placed 14 g. (0.05 mole) of 1-carboethoxymethyl-6,7-dimethoxyisoquinoline. One-hundred grams (1.37 moles) of n-butylamine were then rapidly added dropwise and the resulting solution was refluxed for 24 hours under a nitrogen atmosphere. At the end of this period, the reaction solution was concentrated under reduced pressure until crystallization commenced. The residual solid material isolated in this manner was taken up in 100 ml. of benzene, the resulting solution filtered and the filtrate so obtained was subsequently concentrated in vacuo to about one-half of its original volume. Cyclohexane was then added to this solution until incipient cloud formation occurred. Upon standing, a yellow-orange solid soon deposited from the cloudy solution and this material was subsequently isolated by means of filtration. The yield of product so obtained amounted to 7.25 g. (50%), and after one recrystallization from benzene-cyclohexane there were afforded light yellow crystals of pure N-(n-butyl)-α-[1-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolyl)]acetamide, M.P. 87–88° C.

Analysis.—Calcd. for $C_{17}H_{26}O_3N_2$: C, 66.64; H, 8.55; N, 9.14. Found: C, 66.66; H, 8.55; N, 9.04.

Example II

The procedure described in Example I was followed except that 9.76 g. (0.035 mole) of 1-carboethoxymethyl-6,7-dimethoxyisoquinoline and 75 g. (1.0 mole) of iso-

butylamine were the reactants employed; in this particular case, there were obtained 5.8 g. (55%) of N-isobutyl-α-[1(6,7-dimethoxy - 1,2,3,4 - tetrahydroisoquinolyl)]acetamide, M.P. 105–108° C. In the same manner, 8.36 g. (0.03 mole) of 1-carboethoxymethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 100 g. (1.15 moles) of isoamylamine reacted to afford 6.8 g. (70%) of N-isoamyl-α-[1-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolyl)] acetamide, M.P. 74–76° C.; 6.96 g. (0.025 mole) of 1-carboethoxymethyl-6,7-dimethoxy - 1,2,3,4 - tetrahydroisoquinoline and 3.78 g. (0.62 mole) of β-hydroxyethylamine reacted to afford N-(β-hyroxyethyl)-α-[1-(6,7-dimethoxy - 1,2,3,4 - tetrahydroisoquinolyl)]-acetamide; 6.96 g. (0.025 mole) of 1-carboethoxymethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 47 g. (0.62 mole) of γ-hydroxypropylamine reacted to afford 6.8 g. (84%) of N-(γ-hydroxypropyl)-α-[1-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolyl)]acetamide, M.P. 115–119° C.; 6.96 g. (0.025 mole) of 1-carboethoxymethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 46.5 g. (0.62 mole) of β-methoxyethylamine reacted to afford N-(β-methoxyethyl)-α-[1-(6,7-dimethoxy - 1,2,3,4 - tetrahydroisoquinolyl)]acetamide; 6.96 g. (0.025 mole) of 1-carboethoxymethyl-6,7-dimethoxy - 1,2,3,4-tetrahydroisoquinoline and 55 g. (0.62 mole) of γ-methoxypropylamine reacted to afford N-(γ-methoxypropyl)-α-[1-(6,7-dimethoxy-1,2,3,4 - tetrahydroisoquinolyl)]acetamide; 6.96 g. (0.025 mole) of 1-carboethoxymethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 73 g. (0.62 mole) of γ-isopropoxypropylamine reacted to afford N-(γ-isopropoxypropyl)-α-[1-(6,7-dimethoxy - 1,2,3,4 - tetrahydroisoquinolyl)]acetamide; 6.96 g. (0.025 mole) of 1-carboethoxymethyl-6,7-dimethoxy-1,2,3,4 - tetrahydroisoquinoline and 35 g. (0.62 mole) of allylamine reacted to afford N-allyl - α-[1 - (6,7 - dimethoxy-1,2,3,4 - tetrahydroisoquinolyl)]acetamide; 6.96 g. (0.025 mole) of 1-carboethoxymethyl-6,7-dimethoxy-1,2,3,4 - tetrahydroisoquinoline and 44 g. (0.62 mole) of β-methylallylamine reacted to afford N-(β-methylallyl)-α-[1-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolyl)]acetamide; 6.96 g. (0.025 mole) of 1-carboethoxymethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 54.6 g. (0.62 mole) of β-dimethylaminoethylamine reacted to afford N-(β-dimethylaminoethyl)-α-[1-(6,7-dimethoxy-1,2,3,4 - tetrahydroisoquinolyl)]acetamide; 6.96 g. (0.025 mole) of 1-carboethoxymethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 63 g. (0.62 mole) of γ-dimethylaminopropylamine reacted to afford N-(γ-dimethylaminopropyl)-α-[1-(6,7 - dimethoxy-1,2,3,4-tetrahydroisoquinolyl)]acetamide; 6.96 g. (0.025 mole) of 1-carboethoxymethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 100 g. (0.93 mole) of benzylamine reacted to afford 7.6 g. (90%) of N-benzyl-α-[1-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolyl)]acetamide, M.P. 129.5–132.5° C.; 6.96 g. (0.025 mole) of 1-carboethoxymethyl-6,7-dimethoxy-1,2,3,4 - tetrahydroisoquinoline and 8.77 g. (0.062 mole) of p-chlorobenzylamine reacted to afford N-(p-chlorobenzyl)-α-[1-(6,7 - dimethoxy-1,2,3,4-tetrahydroisoquinolyl)]acetamide; 6.96 g. (0.025 mole) of 1-carboethoxymethyl-6,7-dimethoxy - 1,2,3,4-tetrahydroisoquinoline and 75 g. (0.62 mole) of β-phenylethylamine reacted to afford 8 g. (92%) of N-(β-phenylethyl)-α-[1-(6,7-dimethoxy - 1,2,3,4 - tetrahydroisoquinolyl)]acetamide, M.P. 114–116° C.; 6.4 g. (0.023 mole) of 1-carboethoxymethyl-6,7-dimethoxy - 1,2,3,4 - tetrahydroisoquinoline and 8.15 g. (0.06 mole) of benzohydrazide reacted to afford a 78% yield of N-(benzoylamino)-α-[1-(6,7-dimethoxy - 1,2,3,4 - tetrahydroisoquinolyl)]acetamide, M.P. 173.5–175.5° C.; 6.4 g. (0.023 mole) of 1-carboethoxymethyl-6,7 - dimethoxy - 1,2,3,4-tetrahydroisoquinoline and 15.3 g. (0.06 mole) of β-(3,4,5-trimethoxybenzoyloxy)ethylamine reacted to afford N-[β-(3,4,5-trimethoxybenzoyloxy) - ethyl]-α-[1-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolyl)]acetamide.

Employing appropriate molar amounts of reactants in each case, 1-carboethoxymethyl-6,7-diethoxy-1,2,3,4-tetrahydroisoquinoline reacts with n-propylamine to afford N-(n-propyl)-α-[1-(6,7 - diethoxy-1,2,3,4 - tetrahydroisoquinolyl)]acetamide; 1-carboethoxymethyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline reacts with ethylamine to afford N-ethyl-α-[1-(6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinolyl)]acetamide; 1-carboethoxymethyl-6,7-di-n-butoxy-1,2,3,4-tetrahydroisoquinoline reacts with methylamine to afford N-methyl-α-[1-(6,7-di-n-butoxy-1,2,3,4-tetrahydroisoquinolyl)]acetamide; 1-carboethoxymethyl-6,7-di-isoamyloxy-1,2,3,4 - tetrahydroisoquinoline reacts with β-hydroxyethylamine to afford N-(β-hydroxyethyl)-α-[1-(6,7-di-isoamyloxy - 1,2,3,4 - tetrahydroisoquinolyl)]acetamide, and 1-carboethoxymethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline reacts with n-propylamine to afford N-(n-propyl)-α-[1,(6,7-dihydroxy-1,2,3,4-tetrahydroisoquinolyl)]acetamide.

Example III

In a 500 ml. three-necked, round-bottomed flask equipped with a magnetic stirring apparatus and fitted with a gas inlet tube, a gas outlet extension and a reflux condenser to which a drying tube was attached, there were placed 200 ml. of methanol and the flask and contents were cooled to 0° C. by means of an ice bath. At this point ammonia gas was introduced into the methanol until the solvent medium became completely saturated (this required about 75 minutes). To the so saturated solution there were then added 8 g. (0.0284 mole) of 1-carboethoxymethyl-6,7-dimethoxy - 1,2,3,4-tetrahydroisoquinoline. After this addition was complete, stirring was continued for a period of about four hours while the temperature of the reaction mixture was maintained at 0° C. The resulting bright clear yellow solution was then allowed to attain room temperature and stirring was continued for an additional 48 hours. Upon completion of this step, the solvent was removed by means of evaporation under reduced pressure. The solid residual material so obtained was crystallized from aqueous ethanol to afford 3.55 g. (50%) of α-[1-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolyl)]acetamide, M.P. 166–169.5° C.

Example IV

In an Erlenmeyer flask immersed in a water bath maintained at 60° C. there were placed 6.0 g. (0.02 mole) of N-(n-butyl)-α-[1-(6,7-dimethoxy - 1,2,3,4-tetrahydroisoquinolyl)]acetamide dissolved in 60 ml. of 95% ethanol. Stirring was initiated and 9 ml. of 5% aqueous sodium hydroxide were added to the ethanol solution. To the resulting well-stirred, basic solution there were then added 7.8 g. (0.06 mole) of 37% aqueous formaldehyde dissolved in 24 ml. of 95% ethanol; constant agitation was thereafter maintained for an additional two hours at this same temperature. At the end of this period, the solvent was removed by means of evaporation under reduced pressure and the solid orange-colored residue so obtained was taken up in 100 ml. of benzene. The resulting benzene solution was then extracted with two 100 ml. portions of 2 N HCl, and the combined acidic aqueous extracts were subsequently cooled to 0° C. and adjusted to a basic pH with 10% aqueous sodium hydroxide. Extraction of this basic solution was then carried out with three-200 ml. portions of benzene, and the combined benzene extracts were subsequently dried over anhydrous sodium sulfate. After removal of the drying agent by means of filtration, the resulting filtrate was concentrated in vacuo until crystallization was first observed to occur. The material so obtained was recrystallized from ethyl acetate to afford 4.5 g. (72%) of 2-oxo-3-(n-butyl)aza-9,10-dimethoxy-1,2,3,4,6,7 - hexahydro-11b-H-benzopyridocoline, M.P. 114–116° C.

The hydrochloride of this base was prepared by dissolving the above described compound in absolute ether and passing hydrogen chloride gas into the resulting solution until saturation was effected. The crystalline acid

addition salt so obtained was subsequently recrystallized from ethanol-diethyl-ether.

Example V

The procedure described in Example IV was followed except that 2.23 g. (0.008 mole) of N-isobutyl-α-[1-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolyl)]-acetamide dissolved in 15 ml. of 95% ethanol were reacted 2.0 g. (0.095 mole) of 37% aqueous formaldehyde in 10 ml. of 95% ethanol in the presence of 3.5 ml. of 5% aqueous sodium hydroxide; in this manner, there were obtained 1.25 g. (49%) of 2-oxo-3-(isobutyl)aza-9,10-dimethoxy-1,2,3,4,6,7 - hexahydro - 11b - H - benzopyridocoline, M.P. 107–108° C. after one recrystallization from diethyl ether. When 9 g. (0.03 mole) of N-(β-hydroxyethyl)-α-[1-(6,7 - dimethoxy - 1,2,3,4 - tetrahydroisoquinolyl)]-acetamide in 50 ml. of 95% ethanol were reacted with 7.3 g. (0.09 mole) of 37% aqueous formaldehyde in 25 ml. of 95% ethanol in the presence of 14 ml. of 5% aqueous sodium hydroxide, there were obtained 4.5 g. (59%) of 2-oxo-3-(β-hydroxyethyl)aza-9,10-dimethoxy-1,2,3,4,6,7 - hexahydro - 11b - H - benzopyridocoline, M.P. 146–147° C. after one recrystallization from isopropyl ketone. Similarly, 3.3 g. (0.0091 mole) of N-(p - chlorobenzyl) - α - [1 - (6,7 - dimethoxy - 1,2,3,4-tetrahydroisoquinolyl)]acetamide in 50 ml. of 95% ethanol and 200 ml. of chloroform were reacted with 2.85 g. (0.035 mole) of 37% aqueous formaldehyde in 10 ml. of 95% ethanol to afford 2-oxo-3-(p-chlorobenzyl)aza-9,10 - dimethoxy - 1,2,3,4,6,7 - hexahydro - 11b - H-benzopyridocoline, M.P. 143–145° C. after one recrystallization from chloroform.

In the same manner and employing appropriate molar amounts of reactants in each case, N-isoamyl-α-[1-(6,7-dimethoxy - 1,2,3,4 - tetrahydroisoquinolyl)] - acetamide and 37% aqueous formaldehyde reacted to afford 2-oxo-3-isoamylaza - 9,10 - dimethoxy - 1,2,3,4,6,7 - hexahydro-11b - H - benzopyridocoline; similarly, N - (γ - hydroxypropyl) - α - [1 - (6,7 - dimethoxy - 1,2,3,4 - tetrahydroisoquinolyl)]acetamide was converted to 2-oxo-3-(γ-hydroxypropyl)aza - 9,10 - dimethoxy - 1,2,3,4,6,7 - hexahydro - 11b - H - benzopyridocoline; N - (β - methoxyethyl) - α - [1 - (6,7 - dimethoxy - 1,2,3,4 - tetrahydroisoquinolyl)]acetamide was converted to 2-oxo-3-(β-methoxyethyl) - 9,10 - dimethoxy - 1,2,3,4,6,7 - hexahydro - 11b - H - benzopyridocoline; N - (γ - methoxypropyl) - α - [1 - (6,7 - dimethoxy - 1,2,3,4 - tetrahydroisoquinolyl)]acetamide was converted to 2-oxo-3-(γ-methoxypropyl)aza - 9,10 - dimethoxy - 1,2,3,4,6,7 - hexahydro - 11b - H - benzopyridocoline; N - (γ - isopropoxypropyl) - α - [1 - (6,7 - dimethoxy - 1,2,3,4 - tetrahydroisoquinolyl)]acetamide was converted to 2-oxo-3-(γ-isopropoxypropyl)aza - 9, 10 - dimethoxy - 1,2,3,4,6,7-hexahydro - 11b - H - benzopyridocoline; N - allyl - α-[1 - (6,7 - dimethoxy - 1,2,3,4 - tetrahydroisoquinolyl)]-acetamide was converted to 2-oxo-3-allylaza-9,10-dimethoxy - 1,2,3,4,6,7 - hexahydro - 11b - H - benzopyridocoline; N - (β - methylallyl) - α - [1 - 6,7 - dimethoxy-1,2,3,4 - tetrahydroisoquinolyl)]acetamide was converted to 2 - oxo - 3 - (β - methylallyl) - 9, 10 - dimethoxy-1,2,3,4,6,7 - hexahydro - 11b - H - benzopyridocoline; N - (β - dimethylaminoethyl) - α - [1 - 6,7 - dimethoxy-1,2,3,4 - tetrahydroisoquinolyl)]acetamide was converted to 2 - oxo - 3 - (β - dimethylaminoethyl) - aza - 9,10-dimethoxy - 1,2,3,4,6,7 - hexahydro - 11b - H - benzopyridocoline; N - (γ - dimethylaminopropyl) - α-[1-(6,7-dimethoxy - 1,2,3,4 - tetrahydroisoquinolyl)]acetamide was converted to 2 - oxo - 3 - (γ - dimethylaminopropyl) - 9,10 - dimethoxy - 1,2,3,4,6,7 - hexahydro-11b - H - benzopyridocoline; N - benzyl - α - [1 - (6,7-dimethoxy - 1,2,3,4 - tetrahydroisoquinolyl)]acetamide was converted to 2 - oxo - 3 - benzylaza - 9,10 - dimethoxy - 1,2,3,4,6,7 - hexahydro - 11b - H - benzopyridocoline; N - (β - phenylethyl) - α - [1 - (6,7 - dimethoxy-1,2,3,4 - tetrahydroisoquinolyl)]acetamide was converted to 2 - oxo - 3 - (β - phenylethyl)aza - 9,10 - dimethoxy-1,2,3,4,6,7 - hexahydro - 11b - H - benzopyridocoline; N - (benzoylamino) - α - [1 - (6,7 - dimethoxy - 1,2,3,4-tetrahydroisoquinolyl)]acetamide was converted to 2-oxo - 3 - (benzoylamino)aza - 9,10 - dimethoxy - 1,2,3,4,6,7 - hexahydro - 11b - H - benzopyridocoline; and N-[β - (3,4,5 - trimethoxybenzoyloxy)ethyl] - α - [1 - (6,7-dimethoxy - 1,2,3,4 - tetrahydroisoquinolyl)]acetamide was converted to 2 - oxo - 3 - [β - (3,4,5 - trimethoxybenzoyloxy)ethyl]aza - 9,10 - dimethoxy - 1,2,3,4,6,7-hexahydro-11b-H-benzopyridocoline.

Similarly, N - (n - propyl) - α - [1 - (6,7 - diethoxy-1,2,3,4 - tetrahydroisoquinolyl)]acetamide was converted to 2 - oxo - 3 - (n - propyl)aza - 9,10 - diethoxy-1,2,3,4,6,7 - hexahydro - 11b - H - benzopyridocoline; N-ethyl - α - [1 - (6,7 - methylenedioxy - 1,2,3,4 - tetrahydroisoquinolyl)]acetamide was converted to 2 - oxo-3 - ethylaza - 9,10 - methylenedioxy - 1,2,3,4,6,7 - hexahydro - 11b - H - benzopyridocoline; N - methyl - α - [1-(6,7 - di - n - butoxy - 1,2,3,4 - tetrahydroisoquinolyl)]-acetamide was converted to 2 - oxo - 3 - methylaza-9,10 - di(n - butoxy) - 1,2,3,4,6,7 - hexahydro - 11b - H-benzopyridocoline; N - (β - hydroxyethyl)aza - α - [1-(6,7 - di - isoamyloxy - 1,2,3,4 - tetrahydroisoquinolyl)]-acetamide was converted to 2 - oxo - 3 - (β - hydroxyethyl)aza - 9,10 - di(isoamyloxy) - 1,2,3,4,6,7 - hexahydro - 11b - H - benzopyridocoline; N - (n - propyl)-α-[1-(6,7 - dihydroxy - 1,2,3,4 - tetrahydroisoquinolyl)]-acetamide was converted to 2 - oxo - 3 - (n - propyl)aza-9,10 - dihydroxy - 1,2,3,4,6,7 - hexahydro - 11b - H-benzopyridocoline; and α - [1 - (6,7 - dimethoxy - 1,2,3,4 - tetrahydroisoquinolyl)]acetamide was converted to 2 - oxo - 3 - aza - 9,10 - dimethoxy - 1,2,3,4,6,7 - hexahydro-11b-H-benzopyridocoline.

Example VI

The procedure described in Example V is followed except that other aldehydes are individually employed in lieu of formaldehyde. Thus, when 6.0 g. (0.02 mole) of N - (n - butyl) - α - [1 - (6,7 - dimethoxy - 1,2,3,4-tetrahydroisoquinolyl)]-acetamide and 2.64 g. (0.06 mole) of acetaldehyde are reacted in accordance with this same procedure, the product obtained is 2-oxo-3-(n - butyl)aza - 4 - methyl - 9,10 - dimethoxy - 1,2,3,4,6,7 - hexahydro - 11b - H - benzopyridocoline. In the same manner and employing appropriate molar amounts of reactants in each case, N - (isobutyl) - α - [1 - (6,7-dimethoxy - 1,2,3,4 - tetrahydroisoquinolyl)]acetamide and trifluoroacetaldehyde react to afford 2-oxo-3-isobutyl-aza - 4 - trifluoromethyl - 9,10 - dimethoxy - 1,2,3,4,6,7 - hexahydro - 11b - H - benzopyridocoline; N - (γ-hydroxypropyl) - α - [1 - (6,7 - dimethoxy - 1,2,3,4-tetrahydroisoquinolyl)]acetamide and n - valeraldehyde react to afford 2 - oxo - 3 - (γ - hydroxypropyl)aza - 4-(n - butyl) - 9,10 - dimethoxy - 1,2,3,4,6,7 - hexahydro-11b - H - benzopyridocoline; N - [β - (3,4,5 - trimethoxybenzoyloxy)ethyl] - α - [1 - (6,7 - dimethoxy - 1,2,3,4 - tetrahydroisoquinolyl)]acetamide and acrolein react to afford 2 - oxo - 3 - [β - (3,4,5 - trimethoxybenzoyloxy)ethyl] - 4 - allyl - 9,10 - dimethoxy - 1,2,3,4,6,7-hexahydro - 11b - H - benzopyridocoline; N - (n - butyl)-α - [1 - 6, 7 - dimethoxy - 1,2,3,4 - tetrahydroisoquinolyl)]acetamide and crotonaldehyde react to afford 2-oxo-3 - (n - butyl)aza - 4 - propenyl - 9,10 - dimethoxy - 1,2,3,4,6,7 - hexahydro - 11b - H - benzopyridocoline; and N - (isobutyl) - α - [1 - (6,7 - dimethoxy - 1,2,3,4-tetrahydroisoquinolyl)]acetamide and α,β - dimethylacrolein react to afford 2 - oxo - 3 - isobutyl - aza - 4-(α - methylpropenyl) - 9,10 - dimethoxy - 1,2,3,4,6,7-hexahydro-11b-H-benzopyridocoline.

Example VII

2-oxo-3-[β-(3,4,5-trimethoxybenzoyloxy)ethyl] - 9,10-dimethoxy-1,2,3,4,6,7-hexahydro - 11b-H-benzopyridocoline was prepared by treating the corresponding non-

acylated azabenzopyridocoline in chloroform with 3,4,5-trimethoxybenzoyl chloride at room temperature for about 15 minutes; this product proved to be identical with that described in Example V as attested to by melting point and mixed point determinations.

In the same manner, treatment of each of the other hydroxyalkylazabenzopyridocolines described in the previous examples with 3,4,5-trimethoxybenzoyl chloride affords the corresponding 3,4,5-trimethoxybenzoyl esters. Moreover, other hydrocarbon carboxylic acid esters of hydroxyalkylazabenzopyridocoline derivatives have also been prepared by this same procedure by employing the appropriate acyl chloride in each case; such other esters which have been specifically obtained in this manner include the acetate, propionate, valerate, caproate, benzoate, p-chlorobenzoate, phenylacetate, 2-thenoate and 2-furoate. For instance, 2-oxo-3-(β-hydroxyethyl)aza-9,10-dimethoxy - 1,2,3,4,6,7 - hexahydro-11b-H-benzopyridocoline and acetyl chloride react to afford the corresponding acetate, while 2-oxo-3-(γ-hydroxypropyl)aza-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11b - H - benzopyridocoline and benzoyl chloride react to afford the corresponding benzoate.

Example VIII

The non-toxic acid addition salts of each of the azabenzopyridocoline derivatives described in the previous examples are prepared by either one of two general methods. In the case of the hydrohalide salts, such as the hydrochloride, hydrobromide and hydriodide, this is accomplished by first dissolving the azabenzopyridocoline base compound in absolute ether followed by introduction of the appropriate hydrogen halide gas into the solution until the saturation is effected, whereupon the desired salt precipitates from the solution; the crystalline product so obtained is then recrystallized from acetone to yield the pure hydrohalide salt. In the case of the corresponding nitrate, sulfate or bisulfate, phosphate or acid phosphate, acetate, lactate, citrate or acid citrate, tartrate or bitartrate, oxalate, succinate, maleate, gluconate and saccharate salts, the respective acid and the appropriate azabenzopyridocoline derivative are both dissolved in ethanol and the two solutions are then mixed, followed by the addition of diethyl ether to the resulting reaction mixture in order to effect precipitation of the desired salt from solution.

Example IX

2-oxo-3-(n-butyl)aza - 9,10 - dimethoxy - 1,2,3,4,6,7-hexahydro-11b-H-benzopyridocoline is reacted with an equimolar amount of methyl chloride in an isopropanol solvent medium by allowing said reaction solution to stand at room temperature for 18 hours, and then raising the temperature to 90–100° C. for 30 minutes. The crystals which separate can be recrystallized from isopropanol-methyl ethyl ketone to afford the methyl chloride quaternary ammonium salt of 2-oxo-3-(n-butyl)aza-9,10-dimethoxy - 1,2,3,4,6,7 - hexahydro - 11b-H-benzopyridocoline.

This same azabenzopyridocoline base also reacts with methyl iodide in anhydrous diethyl ether to offer the corresponding quaternary ammonium iodide. Reaction of the above base with ethyl bromide in methyl ethyl ketone at 50–60° C. for 18 hours and then at 100° C. for 2 hours yields the corresponding ethyl quaternary ammonium chloride.

In the same manner, each of the other azabenzopyridocoline base compounds described in the previous examples are reacted with each of the aforementioned methyl halides, as well as with allyl chloride and benzyl bromide to afford the corresponding quaternary ammonium halides.

Similarly, reaction of each of these azabenzopyridocoline bases with such reagents as dimethyl sulfate, diethylsulfate, methyl benzenesulfonate and ethyl p-toluenesulfonate yields the corresponding quaternary ammonium sulfates.

Example X

A dry solid pharmaceutical composition was prepared by blending the following materials in the proportions by weight specified:

2-oxo-3-(n-butyl)aza - 9,10 - dimethoxy - 1,2,3,4,6,7-hexahydro-11b-H-benzopyridocoline	10
Sodium citrate	50
Alginic acid	20
Polyvinylpyrrolidone	15
Magnesium stearate	5

After the dried composition was thoroughly blended, tablets were punched from the resulting mixture, each tablet being of such size that it contained 50 mg. of the active ingredient.

Example XI

A dry solid pharmaceutical composition was prepared by combining the following materials in the proportions by weight specified:

2-oxo-3-(isobutyl)aza - 9,10 - dimethoxy - 1,2,3,4,6,7-hexahydro-11b-H-benzopyridocoline	10
Polyethylene glycol (average molecular weight, 4000)	30
Lactose	40
Calcium carbonate	20

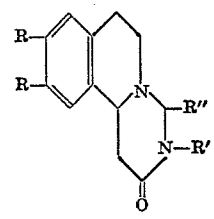
The dried solid mixture so prepared was thoroughly agitated so as to obtain a powdered product that was completely uniform. Soft elastic and hard shelled gelatin capsules containing this pharmaceutical composition were then prepared, employing a sufficient quantity of material so as to furnish 250 mg. of the active ingredient in each capsule.

Example XII

An aqueous propylene glycol solution containing 2-oxo-3-(γ-hydroxypropyl)aza - 9,10 - dimethoxy-1,2,3,4,6,7-hexahydro-11b - H-benzopyridocoline hydrochloride was prepared by dissolving the latter compound in propylene glycol-water (1:3 by weight) with the aid of gentle heating. The amount of compound employed was such that the resulting solution contained 5 mg. of the active ingredient per ml. After cooling to room temperature, it was sterilized by means of filtration through a Seitz filter. The sterile aqueous propylene glycol solution so obtained was suitable for intramuscular administration to animals.

What is claimed is:

1. A compound selected from the class of azabenzopyridocolines having the structural formula:



wherein R is a member of the group consisting of hydroxy, lower alkoxy and lower alkyl and when both R groups are taken together they form a methylenedioxy group; R' is a member of the group consisting of lower alkenyl, lower alkyl, hydroxy lower alkyl, lower alkoxy lower alkyl, dimethylamino lower alkyl, phenyl lower alkyl, benzoylamino, and acyloxy lower alkyl, the acyl moiety being the acyl moiety of a hydrocarbon carboxylic acid having from two to eight carbon atoms; and R'' is

a member of the group consisting of hydrogen, lower alkenyl, lower alkyl and trifluoromethyl, each lower alkyl moiety in the R, R' and R'' group having from one to five carbon atoms; the pharmaceutically acceptable acid addition salts and quaternary ammonium salts thereof, said quaternary ammonium salts being selected from the group consisting of pharmaceutically acceptable organic halide salts, pharmaceutically acceptable sulfuric acid lower alkyl ester salts and pharmaceutically acceptable aryl sulfonic acid lower alkyl ester salts.

2. A 2-oxo-3-lower alkenylaza-9,10-di(lower alkoxy)-1,2,3,4,6,7-hexahydro-11b-H-benzopyridocoline.

3. 2 - oxo - 3-allylaza-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11b-H-benzopyridocoline.

4. 2 - oxo - 3-(β-methylallyl)aza-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11b-H-benzopyridocoline.

5. A 2-oxo-3-lower alkylaza-9,10-di(lower alkoxy)-1,2,3,4,6,7-hexahydro-11b-H-benzopyridocoline.

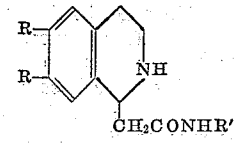
6. 2 - oxo - 3-(isobutyl)aza-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11b-H-benzopyridocoline.

7. A 2-oxo-3-dimethylamino lower alkylaza - 9,10-di(lower alkoxy)-1,2,3,4,6,7-hexahydro - 11b - H - benzopyridocoline.

8. A 2-oxo-3-phenyl lower alkylaza-9,10-di(lower alkoxy) - 1,2,3,4,6,7 - hexahydro - 11b-H-benzopyridocoline, said alkyl radical having 1 to 2 carbon atoms.

9. 2 - oxo - 3-(β-phenylethyl)aza-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11b-H-benzopyridocoline.

10. The process which comprises reacting a substituted α[1-(1,2,3,4-tetrahydroisoquinolyl)]acetamide having the formula:



wherein R is a member of the group consisting of hydroxy, lower alkoxy and lower alkyl and when both R groups are taken together they form a methylenedioxy group, and R' is a member of the group consisting of lower alkenyl, lower alkyl, hydroxy lower alkyl, lower alkoxy lower alkyl, dimethylamino lower alkyl, phenyl lower alkyl, benzoylamino and acyloxy lower alkyl, the acyl moiety being the acyl moiety of a hydrocarbon carboxylic acid having from two to eight carbon atoms, in a reaction-inert aqueous polar organic solvent with a compound selected from the group consisting of formaldehyde, trifluoroacetaldehyde and an aliphatic hydrocarbon carboxaldehyde having from one to five carbon atoms in the presence of a basic agent at a temperature that is in the range of from about 20° C. to about 100° C. for about 0.5 to about 5.0 hours.

11. 2 - oxo - 3-(benzoylamino)aza-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11b-H-benzopyridocoline.

12. A 2-oxo-3-(lower alkoxy lower alkyl)aza-9,10-di(lower alkoxy)-1,2,3,4,6,7-hexahydro-11b-H-benzopyridocoline wherein the alkyl moiety has from one to five carbon atoms.

13. 2 - oxo - 3-(γ-methoxypropyl)aza-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11b-H-benzopyridocoline.

No references cited