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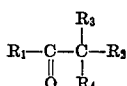
NEW PYRIDINE COMPOUNDS

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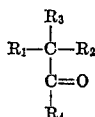
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22 Claims. (Cl. 260—296)

This invention relates to a new series of pyridine compounds. More particularly, it concerns compounds of the formulae:



and



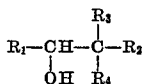
in which each of the radicals R_1 and R_2 stands for 3-pyridine or 4-pyridine radicals, and each of the radicals R_3 and R_4 for a lower hydrocarbon radical, functional ketone derivatives of such pyridine compounds, salts and quaternary ammonium compounds thereof, and mixtures of these compounds, as well as process for the preparation of these compounds.

The 3-pyridyl or 4-pyridyl radicals may be unsubstituted or may contain, for example, lower alkyl radicals, e.g. methyl or ethyl.

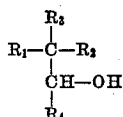
Lower hydrocarbon radicals representing R_3 and R_4 are preferably lower alkyl radicals, for example, methyl, ethyl, propyl or isopropyl.

Ketone derivatives of the pyridine compounds of this invention are preferably the oximes, as well as the semicarbazones or the thiosemicarbazones.

Intended to be included within the scope of this invention are alcohols, derived from the above ketones by reduction, and having the formulae:



and



in which R_1 , R_2 , R_3 and R_4 have the above given meaning, as well as salts and quaternary ammonium compounds thereof and mixtures of such compounds.

Salts of both, the ketones and the alcohols, as well as of the functional ketone derivatives, such as the oximes, are the therapeutically useful acid addition salts with inorganic acids, such as, hydrohalic acids, e.g. hydrochloric or hydrobromic acid; thiocyanic acid; sulfuric or phosphoric acids; or with organic acids, such as, formic, acetic, propionic, glycolic, lactic, pyruvic, oxalic, malonic, succinic, maleic, hydroxymaleic, dihydroxymaleic, fumaric, malic, tartaric, citric, ascorbic, benzoic, phenylacetic, p-aminobenzoic, p-hydroxybenzoic, anthranilic, cinnamic, mandelic, salicylic, p-aminosalicylic,

2

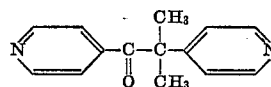
2-phenyloxybenzoic, 2-acetoxy-benzoic, methane sulfonic, ethane sulfonic, hydroxyethane sulfonic, benzene sulfonic, p-toluene sulfonic, naphthalene sulfonic or sulfanilic acid or methionine, tryptophane, lysine or arginine. Mono- or, preferably, bis-salts may be obtained.

Quaternary ammonium compounds are those with reactive esters formed by alcohols, especially lower alkanols, and strong inorganic or organic acids. Such esters are particularly lower alkyl halides, e.g. methyl iodide, methyl iodide, methyl bromide, methyl chloride, ethyl chloride, propyl chloride or isopropyl chloride; di-lower alkyl sulfates, e.g. dimethyl or diethyl sulfate; or lower alkyl aryl sulfonates, e.g. methyl toluene sulfonate. Depending on the conditions used in the procedure of formation, the mono- or the bis-quaternary ammonium compounds may be obtained.

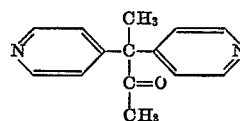
It has been found that the new pyridine compounds, functional ketone derivatives, such as the oxides, the salts and the quaternary ammonium compound thereof, as well as mixtures of such compounds, exert a suppressing effect on the activity of the adrenal cortex, and are intended to be used as medicinal agents.

Many diseases known to be directly influenced by a hyperactivity of this vital gland, such as the Cushing's Syndrome or the adrenogenital Syndrome are difficult to treat, because the adrenal cortex does not rely on an outside source for the preparation of the steroidal compounds and can therefore not be regulated by dietary measures. Until now only few compounds are known to have any slowdown effect on the activity of the adrenal cortex; none of them have proven to be satisfactory due to low activity and/or unfavorable therapeutic ratio between activity and toxicity, as well as undesirable side effects.

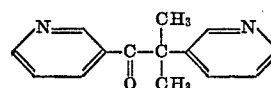
Especially valuable with respect to adrenal cortex inhibitory activity are the pyridine derivatives of the formulae:



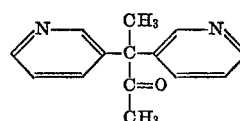
and



and of the formulae:

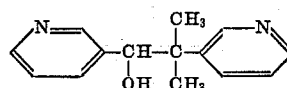


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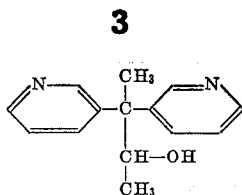


as well as the corresponding oximes and the salts, for example, the dihydrochlorides, dihydrobromide and ditartrates, thereof.

The same activity, i.e. an inhibitory effect on the adrenal cortex, is also exhibited by the alcohols derived from the ketone compounds by reduction. Representing these derivatives are the compounds of the formulae:



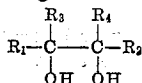
and



as well as the salts, for example, the dihydrochlorides thereof.

The new compounds or a mixture of such compounds may be used in the form of pharmaceutical preparations, which contain the new pyridine derivatives, the functional ketone derivatives, salts or quaternary ammonium compounds thereof or mixtures of such compounds in admixture with pharmaceutical organic or inorganic, solid or liquid carriers suitable for enteral, e.g. oral, or parenteral administration. For making up the preparations there may be employed substances which do not react with the new compounds, such as, for example, water, gelatine, lactose, starches, magnesium stearate, talc, vegetable oils, benzyl alcohols, gums, polyalkylene glycols, petroleum jelly or any other known carrier for medicaments. The pharmaceutical preparations may be in solid form, for example, as tablets, dragees or capsules, or in liquid form, for example, as solutions or emulsions. If desired, they may contain auxiliary substances, such as preserving agents, stabilizing agents, salts for varying the osmotic pressure or buffers such as sodium metaphosphate. They may also contain, in combination, other therapeutically useful substances.

Although several methods for the preparation of the new compounds may be devised from the chemical art, we prefer to prepare the new pyridine compounds of this invention by rearrangement of diols of the formula:

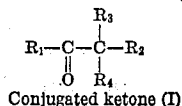


in which R_1 , R_2 , R_3 and R_4 have the above given meaning, or salts thereof, in the presence of a strong Lewis acid, and, if desired, converting the resulting ketone into the corresponding alcohol or into a functional ketone derivative thereof, and/or, converting any resulting salt into the free base, and/or converting any free base obtained into a salt or a quaternary ammonium compound thereof, and/or, if desired, separating any resulting mixture into the single compounds.

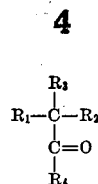
Salts of the starting materials used are especially those with inorganic acids, such as, the dihydrohalides, e.g. dihydrochlorides or dihydrobromides, or the disulfates. If the free compound is used in the rearrangement step it may be converted into a salt under the acidic conditions of the reaction.

Strong Lewis acids capable of bringing about the pinacolone rearrangement of the diols or the salts thereof, are especially strong inorganic acids, particularly sulfuric acid; other acids, such as hydrochloric or perchloric acids, give less favorable results due to the formation of byproducts. The acidic reagents are preferably used in the concentrated form; concentrated sulfuric acid is the reagent of choice. The rearrangement is preferably carried out by heating the reaction mixture from about 50° to about 200°; temperatures below 50° slow down the rate of the reaction considerably and those higher than 200° increase the formation of byproducts. Instead of carrying out the reaction at atmospheric pressure, a closed vessel may be utilized to provide increased pressure. To avoid contact with atmospheric oxygen the reaction may be performed in the presence of an inert gas, e.g. nitrogen.

Under the ordinary reaction conditions a mixture of both ketones may be obtained having the formulae:



and

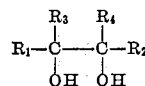


Unconjugated ketone (II)

The proportions in which the two types are formed depend on the starting material used, i.e. on the position to which the pyridine radical is attached to the diol portion, and/or on the reaction conditions. Thus, for example, the 2,3-bis-(3-pyridyl)-butane-2,3-diol and the 2,3-bis-(4-pyridyl)-butane-2,3-diol yield mixtures containing the corresponding conjugated (I) and unconjugated (II) ketones in a ratio of about 3:1, when treated with sulfuric acid. In addition to the desired pinacolone rearrangement products, the ketones, certain byproducts may be obtained, the formation of which depends again on the choice of starting material and the reagent used. For example, a byproduct, which is obtained in the rearrangement of the 2,3-bis-(4-pyridyl)-butane-2,3-diol is the 2,3-bis-(4-pyridyl)-butadiene, which may be formed by double dehydration.

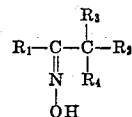
The mixture of the two ketones I and II may be separated into the two constituents by fractional crystallization, which may also be carried out after the conversion of the mixture of free bases into the mixture of the salts thereof or into the mixture of the functional ketone derivatives, e.g. the oximes, thereof. After separation into the single compounds by fractional recrystallization these may be easily reconverted into the free bases; the salts by treatment with an alkaline reagent, e.g. aqueous sodium hydroxide or aqueous ammonia, the functional ketone derivatives by acidic hydrolysis, e.g. with aqueous sulfuric acid, and, if desired, by subsequent treatment with a base. The mixtures of the free bases may also be separated by fractional distillation; however, the separation may not be complete, if the boiling points of the two constituents do not differ greatly. A further method of separation comprises absorbing the mixture on an adsorbent and eluting the constituents of the mixture. A preferred procedure is chromatography, in which the mixture is absorbed on aluminium oxide, having preferably basic properties. Aluminium oxide may be replaced by a cation exchanger, such as a sulfonated polystyrene exchanger (Dowex 50), as an adsorbent. The eluting solvents are chosen according to the relative polarity of the different constituents of the mixture.

The diols of the formula:

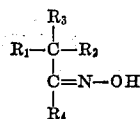


in which R_1 , R_2 , R_3 and R_4 have the above given meaning as well as the salts thereof, which are used as starting materials, are known [Allen, J. Org. Chem., vol. 15, p. 436 (1950)] or, if new may be prepared according to the methods used for the preparation of the known compounds.

The functional ketone derivatives, especially the oximes of the formulae:



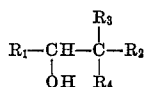
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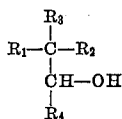
5

in which R_1 , R_2 , R_3 and R_4 have the above given meaning, as well as the semicarbazones or thiosemicarbazones, may be prepared by reacting the ketones or a mixture thereof with the ketonic reagent or a salt thereof, e.g. hydroxylamine sulfate, hydroxylamine hydrochloride, semicarbazone or thiosemicarbazone hydrochloride, in the absence or presence of a condensing agent. For example, hydroxylamine sulfate is advantageously used in the presence of an alkali metal salt of a lower alkanolic acid, e.g. sodium acetate. The reaction is preferably carried out in the presence of a diluent, such as a mixture of water and a lower alkanol, e.g. methanol or ethanol. As outlined before, the functional ketone derivatives, especially the oximes, may be reconverted into the free bases by acidic hydrolysis, e.g. treatment with aqueous sulfuric acid, and subsequent treatment with an alkaline reagent, and can therefore be used as intermediates in the preparation of the pure ketones.

The reduced compounds of the formulae:



and



in which R_1 , R_2 , R_3 and R_4 have the above-given meaning, may be prepared from the corresponding ketones by reduction. The reduction with hydrogen may be carried out in the presence of a catalyst containing a metal of the eight group of the periodic system such as palladium, e.g. palladium on charcoal; care has to be taken that the pyridine derivatives are not reduced to the corresponding piperidine compounds. The reagents of choice are the di-light metal hydrides, e.g. lithium aluminium hydride or sodium borohydride, which may be used in the presence of a solvent such as an ether solvent, e.g. diethylether or tetrahydrofuran, or a lower alkanolic solvent, e.g. methanol or ethanol; or water, depending on the type of reagent employed.

The new compounds, as well as the functional ketone derivatives, such as the oximes, may be obtained in the form of the free bases or as the salts thereof. A salt may be converted into the free base by customary procedure, for example, by reaction with an aqueous alkaline reagent, such as an alkali metal hydroxide, e.g. lithium, sodium or potassium hydroxide; an alkali metal carbonate, e.g. sodium carbonate or potassium hydrogen carbonate; or ammonia. A free base may be transformed into its therapeutically useful acid addition salts by reaction with appropriate inorganic or organic acids, such as those outlined above, for example, in the presence of a lower alkanol, e.g. methanol, ethanol, propanol or isopropanol; or an ether, e.g. diethylether, or a mixture of such solvents. Depending on the conditions used mono- or bis-salts may be obtained.

The new pyridine derivatives of this invention may be converted into the quaternary ammonium compounds by reacting the tertiary bases with an ester formed by a hydroxylated lower hydrocarbon compound and a strong inorganic or organic acid. Hydroxylated lower hydrocarbon compounds contain from 1 to 7 carbon atoms, and the esters thereof are more especially those with mineral acids, e.g. hydrochloric, hydrobromic, hydriodic, or sulfuric acid. Such esters are specifically lower alkyl halides, e.g. methyl iodide, methyl bromide, methyl chloride, ethyl bromide or propyl chloride; di-lower alkyl sulfates, e.g. dimethyl or diethyl sulfate; or lower alkyl aryl sulfonates, e.g. methyl p-toluene sulfonate. The quaternizing reactions, such as outlined above, are performed in the presence or absence of a solvent, at

6

room temperature or under cooling, at atmospheric pressure or in a closed vessel under pressure. Suitable solvents are more especially lower alkanols, e.g. methanol, ethanol, propanol, isopropanol, butanol or pentanol; or organic acid amides, e.g. formamide or dimethylformamide.

Quaternary ammonium compounds obtained may be converted into the corresponding quaternary ammonium hydroxides, for example, by reaction of resulting quaternary ammonium halides with silver oxide, or by reaction of the quaternary ammonium sulfates with barium hydroxide or by treating the quaternary ammonium salts with an anion exchanger or by electro-dialysis. From the resulting base there may be formed quaternary ammonium salts by reaction with the acids, such as the inorganic and organic acids outlined hereinbefore for the formation of acid addition salts; or with mono-lower alkyl sulfates such as methyl or ethyl sulfate. A resulting quaternary ammonium compound may also be converted directly into another quaternary ammonium salt without conversion into the quaternary ammonium hydroxide; for example, a quaternary ammonium iodide may be reacted with freshly prepared silver chloride to yield the quaternary ammonium chloride, or the quaternary ammonium iodide may be converted into the corresponding chloride by treatment with hydrochloric acid in anhydrous methanol.

The invention also comprises any modification of the general process wherein a compound obtainable as an intermediate at any stage of the process is used as starting material and the remaining step(s) of the process is(are) carried out, as well, as any new intermediates.

This is a continuation-in-part application of our applications Serial No. 661,620, filed May 27, 1957, now abandoned, and Serial No. 688,845, filed October 8, 1957, now abandoned.

The following examples illustrate the invention. They are not to be construed as being limitations thereon. Temperatures are given in degrees centigrade.

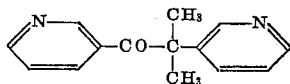
Example 1

A mixture of 3.43 g. of 2,3-bis-(3-pyridyl)-2,3-butanediol and 25 ml. of concentrated sulfuric acid is heated to 76° and kept at that temperature for 7½ hours. It is then poured on ice, neutralized with 50% aqueous solution of sodium hydroxide and the pH is adjusted to 8 with solid sodium carbonate. The aqueous solution is three times extracted with ethyl acetate, the separated organic layer dried over sodium sulfate and evaporated to dryness. The residue is distilled and 1.86 g. of a viscous, colorless oil is obtained which is purified by distillation, B.P. 140-160°/0.07 mm. The infrared spectrum shows the presence of a mixture of two compounds, one containing a conjugated, the other one an unconjugated carbonyl group, without the presence of a compound containing a hydroxyl group; thus the rearrangement has taken place.

The resulting mixture does not crystallize and is converted into the mixture of the oximes by treatment of a solution of the mixture in 20 ml. of ethanol with a solution of 1.8 g. of hydroxylamine sulfate in 3 ml. of water. 1.8 g. of sodium acetate in 5 ml. of water is added, and the mixture is refluxed for 5 hours, then extracted with ethyl acetate, and the ethyl acetate solution is washed with a saturated aqueous sodium chloride solution and dried over sodium sulfate. After evaporating the solvent, the residue is triturated with warm ether and 1.1 g. of a crystalline oxime is obtained, M.P. 168-171.

0.1 g. of the resulting oxime is dissolved in 5 ml. of 2 N aqueous sulfuric acid and the mixture is refluxed for three hours and allowed to stand overnight. After being rendered basic by adding a concentrated aqueous solution of sodium hydroxide and adjusted to a pH of 8 with sodium carbonate, the mixture is extracted three times with ethyl acetate; the organic layer is

washed with water, dried and evaporated. Upon distillation of the residue an oily product is obtained, B.P. 130–160°/0.3 mm. Infrared analysis shows the presence of a uniform compound, containing a conjugated carbonyl group. The 2-methyl-1,2-bis-(3-pyridyl)-propane-1-one of the formula:



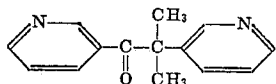
crystallizes upon standing at room temperature or by covering the oily distillate with pentane and cooling to –80° and filtering the oily crystals. It melts after recrystallization from a mixture of ether, hexane and petroleum ether at 48–50°.

The isomeric compound containing an unconjugated carbonyl group can be isolated from the filtrate resulting after the trituration of the mixture of the oximes with warm ether.

The 2,3-bis-(3-pyridyl)-2,3-butanediol used as the starting material may be prepared as follows: A solution of 1430 g. of 3-acetyl-pyridine in 7042 ml. of a 1 N aqueous solution of potassium hydroxide is placed into the cathode chamber containing a mercury cathode with a surface of 353 cm.² and is separated from the anode chamber by an Alundum membrane. As anode a platinum wire is used and the anolyte consists of a 1 N solution of aqueous potassium hydroxide which is replenished from time to time. The electrolysis is carried out at a reference potential of –2.4 volts v. a standard calomel electrode. An initial current density of 0.0403 ampere/cm.² is obtained which drops to 0.0195 ampere/cm.² at the end of the reduction, which is carried on over a period of 1682 minutes at 15–20°. The catholyte is filtered, the solid material is washed with water and dried. 430 g. of the 2,3-bis-(3-pyridyl)-butane-2,3-diol is recrystallized from water, M.P. 244–245°.

Example 2

A total amount of 300 g. of 2,3-bis-(3-pyridyl)-2,3-butanediol is added in 10 to 20 g. portions to 1000 ml. of concentrated sulfuric acid while stirring. During the addition the temperature is kept at 50–60° and is then raised to 75° at which temperature it is maintained for 7 hours and allowed to stand at room temperature for 12 hours. The sulfuric acid solution is poured on ice and the pH brought to about 8 by addition of a 50% aqueous solution of sodium hydroxide; the temperature is kept below 50°. The aqueous solution is extracted twice with ether and the ether solution is washed twice with a saturated aqueous solution of sodium chloride, then dried over sodium sulfate, and the ether evaporated to dryness under reduced pressure. 175 g. of the resulting residue (according to infrared studies, the product is a mixture containing a compound having a conjugated carbonyl group and a compound having an unconjugated carbonyl group) is dissolved in a mixture of 50 ml. of ether and 50 ml. of pentane and cooled in the refrigerator. After seeding with the crystalline 2-methyl-1,2-bis-(3-pyridyl)-propane-1-one, obtained according to the process described in Example 1, and keeping the solution in the cool over night, 72 g. of the 2-methyl-1,2-bis-(3-pyridyl)-propane-1-one of the formula:



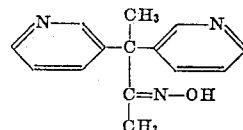
is obtained and recrystallized from a 1:1-mixture of ether and pentane.

The resulting reaction mixture may also be separated by distillation under reduced pressure in a distillation apparatus having a small column. Approximately 95–98 percent of the product distills without decomposition at 140–142°/0.22 mm. The first half of the distillate is pure 2-methyl-1,2-bis-(3-pyridyl)-propane-1-one, the third

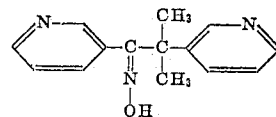
quart is a mixture of the latter compound with the 3,3-bis-(3-pyridyl)-butane-2-one, containing predominantly the former, and the last quart is an about 1:1-mixture of the two ketones. By diluting the first three quarts of the distillate with an equal amount of ether, adding pentane, until two layers are formed and seeding with crystalline 2-methyl-1,2-bis-(3-pyridyl)-propane-1-one the latter product is obtained in high yield; 134 g. of the distilled reaction mixture yields 97 g. of the crystalline 2-methyl-1,2-bis-(3-pyridyl)-propane-1-one.

To obtain a very pure sample it is redistilled under reduced pressure and crystallized, M.P. 50–51°. The product shows no melting point depression with the compound obtained according to the process of Example 1.

The mother liquor obtained from the crystallization step of the crude product with a mixture of ether and pentane contains, according to the infrared spectrum, an about 1:1-mixture of the two ketone compounds and is worked up as follows: The solvents are distilled off and 45.4 g. of the resulting residue is dissolved in ethanol. A solution of 85 g. of hydroxylamine sulfate in 100 ml. of water, then a mixture of 80 g. of sodium acetate and 20 g. of sodium carbonate in 200 ml. of water are added in succession. After refluxing for 5 hours the ethanol is removed under reduced pressure and the pH adjusted to 8 by adding an aqueous solution of potassium carbonate. The aqueous solution is extracted three times with ethyl acetate, however part of the solid material cannot be dissolved and is filtered off. The ethyl acetate solution is dried over sodium sulfate and the solvent partially evaporated. The resulting precipitate is filtered off, and ether is added to the filtrate, whereupon 16 g. of a crystalline material is formed which is filtered off, and the filtrate is evaporated to dryness. The remaining viscous oil is dissolved in ethyl acetate, ether is added and 5.5 g. of crystalline material precipitates which melts at 132–137°, and is redissolved in 70 ml. of ethyl acetate. The insoluble material is filtered off and the filtrate cooled to –8°. 4.2 of the oxime of 3,3-bis-(3-pyridyl)-butane-2-one of the formula:



precipitates, melting at 132–134°, which, according to infrared studies, is free from the corresponding oxime of 2-methyl-1,2-bis-(3-pyridyl)-propane-1-one of the formula:



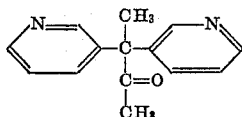
melting at 168–171°, which can be obtained according to the procedure given in Example 1. A mixture of the two samples starts to melt at 126°.

1 g. of the oxime of 3,3-bis-(3-pyridyl)-butane-2-one is refluxed for 6 hours in 20 ml. of a 2 N aqueous solution of sulfuric acid and allowed to stand at room temperature over night. The solution is made basic to pH 8 with a 10% aqueous solution of sodium hydroxide, then extracted three times with ether, which solution is then washed with a saturated aqueous solution of sodium chloride and dried over sodium carbonate. The ether is evaporated leaving 0.9 g. of a viscous oil, which does not respond to crystallization upon seeding with crystalline 2-methyl-1,2-bis-(3-pyridyl)-propane-1-one previously obtained. It is distilled, B.P. 130–135°/0.05 mm., and the distillation is stopped after one third of the original amount is collected; infrared studies of this material show a uniform compound containing an unconjugated carbonyl group.

9

The distillate is dissolved in a 1:1-mixture of water and concentrated hydrobromic acid, the water is evaporated under reduced pressure and the residue is triturated with a mixture of methanol and ether; the crystalline material is filtered off and recrystallized from the same mixture. The resulting dihydrobromide of the 3,3-bis-(3-pyridyl)-butane-2-one melts at 240–243° and gives a melting point depression with a sample of the dihydrobromide of 2-methyl-1,2-bis-(3-pyridyl)-propane-1-one to be described hereinafter.

A solution of the dihydrobromide of 3,3-bis-(3-pyridyl)-butane-2-one in water is adjusted to pH 8 with a 2 N aqueous solution of sodium hydroxide, the solution extracted with ethyl acetate which solution is dried and then evaporated. The residue is chilled to –80° in a mixture of ether and pentane, to yield the 3,3-bis-(3-pyridyl)-butane-2-one of the formula:



M.P. 47–49°. A mixture with 2-methyl-1,2-bis-(3-pyridyl)-propane-2-one previously obtained melts at room temperature.

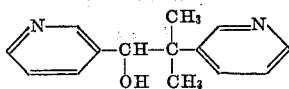
The 1:1-mixture of the two ketones one of which contains a conjugated carbonyl group, the other an unconjugated carbonyl group, obtained after the crystallization of the reaction mixture from ether and pentane, may also be separated into the two constituents as follows: 5.7 g. of said mixture in 10 ml. of benzene is placed on a column containing 250 g. of aluminium oxide (basic, activity III) which has been washed with hexane. The 1:1-mixture fraction of hexane and benzene and the benzene fraction contain a total of 1.64 g. of crystalline 2-methyl-1,2-bis-(3-pyridyl)-propane-1-one, the ether fraction 2.10 g. of the oily 3,3-bis-(3-pyridyl)-butane-2-one.

Example 3

2 g. of 2-methyl-1,2-bis-(3-pyridyl)-propane-1-one is dissolved in 20 ml. of water and 10 ml. of concentrated hydrobromic acid. The water is evaporated and the residue triturated with a mixture of ethanol and ether; the resulting dihydrobromide of 2-methyl-1,2-bis-(3-pyridyl)-propane-1-one is recrystallized from a mixture of methanol and ether; M.P. 277–278°.

Example 4

A solution of 6.42 g. of 2-methyl-1,2-bis-(3-pyridyl)-propane-1-one in 25 ml. of ether is slowly added to a boiling suspension of 1.08 g. of lithium aluminium hydride in 50 ml. of ether, and the mixture is refluxed for 8 hours. The excess of lithium aluminium hydride is carefully destroyed with water and a 6 N aqueous solution of hydrogen chloride is added to dissolve the precipitate. The aqueous solution is adjusted to pH 8 with a 2 N aqueous solution of sodium hydroxide and then twice extracted with ethyl acetate; the latter solution is washed with a saturated aqueous solution of sodium chloride and dried over magnesium sulfate. The organic solvent is evaporated and 6.0 g. of the remaining viscous oil is distilled, B.P. 130–150°/0.05 mm. Upon standing, the oil crystallizes and is recrystallized from a mixture of ethyl acetate and pentane to yield the 2-methyl-1,2-bis-(3-pyridyl)-propane-1-ol of the formula:



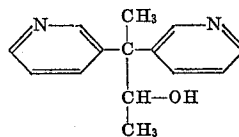
M.P. 104–105°.

Example 5

By treating 6.1 g. of 3,3-bis-(3-pyridyl)-butane-2-one with 2.0 g. of lithium aluminium hydride as described in

10

Example 4, 5.7 g. of crystalline material is obtained from the ethyl acetate extraction which after crystallization from a mixture of ethanol, ether and pentane, and distillation yields the 3,3-bis-(3-pyridyl)-butane-2-ol of the formula:

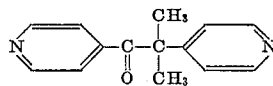


B.P. 140°/0.1 mm., which melts at 165–166°.

Example 6

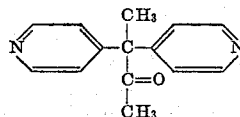
A solution of 5 g. of 2,3-bis-(4-pyridyl)-butane-2,3-diol in 30 ml. of concentrated sulfuric acid is allowed to stand at 60–66° for 14 hours and at room temperature for an additional 8 hours and is then poured on ice. The aqueous mixture is rendered basic to pH 8 with a 50% aqueous solution of sodium hydroxide and extracted three times with ethyl acetate. The organic solution is washed with a saturated aqueous solution of sodium chloride and dried over sodium sulfate and then concentrated to about 10 ml. under reduced pressure. Some unreacted starting material which precipitates is filtered off and the filtrate evaporated to dryness. After trituration with ether the crystalline material is collected and recrystallized from a mixture of ethanol, ether and pentane to yield the 2,3-bis-(4-pyridyl)-butadiene, M.P. 133–135°.

The filtrate obtained after trituration with ether is evaporated to dryness and the oily residue distilled to yield 1.05 g. of an oil. Infrared studies show that a mixture of an unconjugated and a conjugated ketone is obtained, which is redistilled, B.P. 122–126°/0.1 mm. 0.650 of the distillate is crystallized from a mixture of ethanol, ether and pentane and a solid material is obtained, which is recrystallized from a mixture of ether and pentane. Infrared studies show a uniform material containing a conjugated carbonyl group; the 2-methyl-1,2-bis-(4-pyridyl)-propane-1-one of the formula:



is obtained in colorless needles, M.P. 75–76°.

The mother's liquor obtained from the crystallization of the distillate is evaporated to dryness and the crystalline residue is chromatographed on an aluminium oxide column (neutral, activity III). An additional amount of 2-methyl-1,2-bis-(4-pyridyl)-propane-1-one is eluated with a mixture of benzene and hexane and with benzene; the 3,3-bis-(4-pyridyl)-butane-2-one of the formula:



is eluated with ether and is recrystallized from a mixture of ether and pentane, M.P. 73–74°.

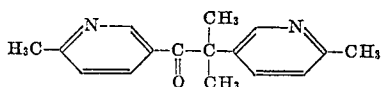
The 2,3-bis-(4-pyridyl)-butane-2,3-diol used as the starting material in the above reaction may be prepared according to the procedure given in Example 1, i.e. by electrolytically reducing 4-acetyl-pyridine, using as a catholyte a solution of 100 g. of the 4-acetyl-pyridine in 460 ml. of a 1 N aqueous solution of potassium hydroxide; the resulting 2,3-bis-(4-pyridyl)-butane-2,3-diol (99 g.) is recrystallized from a mixture of ethyl acetate and methanol, M.P. 219–220°.

Example 7

A solution of 3 g. of 2,3-bis-(6-methyl-3-pyridyl)-butane-2,3-diol in 10 ml. of concentrated sulfuric acid is kept at 105° for 3 hours and at 60–70° for an additional 18 hours, then poured on ice, and made basic to

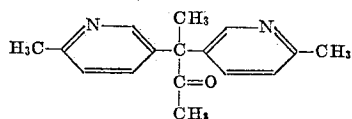
11

pH 8 with a 50% aqueous solution of sodium hydroxide. The basic solution is extracted three times with ethyl acetate, which solution is washed and dried, then evaporated to dryness. Infrared studies of the resulting viscous oil, which crystallizes spontaneously and melts over a range of 62–85°, show the presence of a compound having a conjugated and a compound having an unconjugated carbonyl group. 1.35 g. of the product is recrystallized three times from a mixture of benzene and pentane to yield the 2-methyl-1,2-bis-(6-methyl-3-pyridyl)-propane-1-one of the formula:



M.P. 95.5–96.5°. Infrared studies show this product free from any compound containing an unconjugated carbonyl group.

The mother liquor obtained from the recrystallization contains according to infrared studies a compound showing an unconjugated carbonyl group. The residue (0.72 g.) is chromatographed on 35 g. of aluminium oxide (basic, activity III). 0.26 g. of 2-methyl-1,2-bis-(6-methyl-3-pyridyl)-propane-1-one is eluted with a mixture of benzene and hexane; 0.22 g. of the 3,3-bis-(6-methyl-3-pyridyl)-butane-2-one of the formula:



is eluted with a mixture of benzene and ether and is recrystallized from a mixture of benzene and pentane, M.P. 87–88°.

The 2,3-bis-(6-methyl-3-pyridyl)-butane-2,3-diol used as the starting material may be prepared according to the procedure given in Example 1 by electrolytic reduction using as catholyte a solution of 6.8 g. of the 3-acetyl-6-methyl-pyridine in 25 ml. of a 20% aqueous solution of potassium hydroxide and 25 ml. of ethanol; 4.3 g. of the desired diol is obtained after recrystallization from a mixture of ethanol and ethyl acetate, M.P. 219°.

Example 8

A mixture of 2 g. 3,4-bis-(3-pyridyl)-hexane-3,4-diol in 10 ml. of concentrated sulfuric acid is kept at room temperature for 20 hours and then poured on ice. The pH of the solution is raised to 10 by adding aqueous sodium hydroxide, the solution is then extracted twice with ether, which extract is washed with a saturated aqueous solution of sodium chloride, dried over sodium sulfate and evaporated to dryness. 0.5 g. of an oil is distilled, B.P. 140–160°/0.05 mm. to yield a yellow viscous oil, which, according to infrared studies contains a mixture of 2-ethyl-1,2-bis-(3-pyridyl)-butane-1-one and 4,4-bis-(3-pyridyl)-hexane-3-one.

The starting material used in this reaction may be prepared according to the procedure described in Example 1, by electrolytic reduction using as a catholyte the solution of 6 g. of 3-propionyl-pyridine in 7.5 ml. of ethanol and 22.5 ml. of 1.5 N aqueous potassium hydroxide; the 3,4-bis-(3-pyridyl)-hexane-3,4-diol melts at 188–189°.

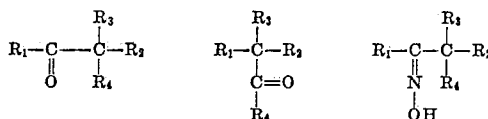
Example 9

A mixture of 2 g. of 2-methyl-1,2-bis-(3-pyridyl)-propane-1-one and 6 ml. of methyl iodide in 60 ml. of 95 percent ethanol is refluxed for 4 hours and the reaction mixture concentrated to about 10 ml. 2.6 g. of the dimethiodide of 2-methyl-1,2-bis-(3-pyridyl)-propane-1-one precipitates and is recrystallized from ethanol, M.P. 225–229°.

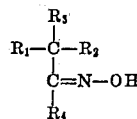
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What is claimed is:

1. A member of the group consisting of compounds of the formulae:



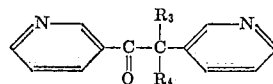
10 and



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in which each of the radicals R_1 and R_2 stands for a member of the group consisting of 3-pyridyl and 4-pyridyl, and each of the radicals R_3 and R_4 stands for lower alkyl, and the therapeutically acceptable acid addition salts thereof.

2. Compounds of the formula:



25

in which each of the radicals R_3 and R_4 stands for lower alkyl.

3. 2-methyl-1,2-bis-(3-pyridyl)-propane-1-one.

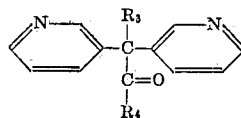
30

4. The oxime of 2-methyl-1,2-bis-(3-pyridyl)-propane-1-one.

5. 2-ethyl-1,2-bis-(3-pyridyl)-butane-1-one.

6. The dimethiodide of 2-methyl-1,2-bis-(3-pyridyl)-propane-1-one.

7. Compounds of the formula:



35

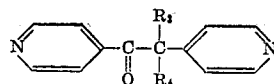
in which each of radicals R_3 and R_4 stands for lower alkyl.

8. 3,3-bis-(3-pyridyl)-butane-2-one.

9. The oxime of 3,3-bis-(3-pyridyl)-butane-2-one.

10. 4,4-bis-(3-pyridyl)-hexane-3-one.

11. Compounds of the formula:

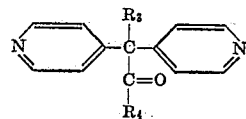


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in which each of the radicals R_3 and R_4 stands for lower alkyl.

12. 2-methyl-1,2-bis-(4-pyridyl)-propane-1-one.

13. Compounds of the formula:

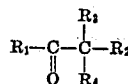


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in which each of the radicals R_3 and R_4 stands for lower alkyl.

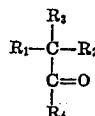
14. 3,3-bis-(4-pyridyl)-butane-2-one.

15. In the process for the preparation of a member of the group consisting of compounds of the formulae:



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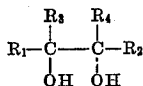
and



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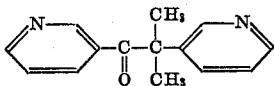
in which each of the radicals R_1 and R_2 stands for a member of the group consisting of 3-pyridyl and 4-pyridyl, and each of the radicals R_3 and R_4 stands for lower alkyl, and therapeutically acceptable acid addition salts thereof, the step which comprises treating a member of the group consisting of compounds of the formula:



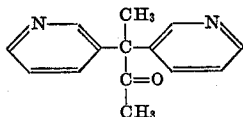
in which R_1 , R_2 , R_3 and R_4 have the above-given meaning, and the acid addition salts thereof, with a strong inorganic acid.

16. Process according to claim 15, wherein concentrated sulfuric acid is used.

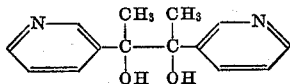
17. In the process for the preparation of a mixture of the compounds of the formulae:



and



the step which comprises treating the diol of the formula:



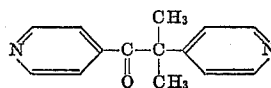
with concentrated sulfuric acid.

18. Process for the preparation of 2-methyl-1,2-bis-(3-pyridyl)-propane-1-one which comprises treating 2,3-bis-(3-pyridyl)-butane-2,3-diol with concentrated sulfuric acid and separating the 2-methyl-1,2-bis-(3-pyridyl)-propane-1-one from the resulting mixture by fractional crystallization.

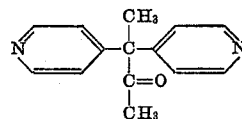
19. Process for the preparation of 2-methyl-1,2-bis-(3-pyridyl)-propane-1-one which comprises treating 2,3-bis-(3-pyridyl)-butane-2,3-diol with concentrated sulfuric acid and separating the 2-methyl-1,2-bis-(3-pyridyl)-propane-1-one from the resulting mixture by fractional distillation.

14

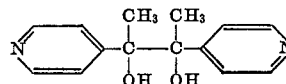
20. In the process for the preparation of a mixture of the compounds of the formulae:



and



the step which comprises treating the diol of the formula:



with concentrated sulfuric acid.

21. Process for the preparation of 2-methyl-1,2-bis-(4-pyridyl)-propane-1-one which comprises treating 2,3-bis-(4-pyridyl)-butane-2,3-diol with the concentrated sulfuric acid and separating the 2-methyl-1,2-bis-(4-pyridyl)-propane-1-one from the resulting mixture by fractional crystallization.

22. Process for the preparation of 2-methyl-1,2-bis-(4-pyridyl)-propane-1-one which comprises treating 2,3-bis-(4-pyridyl)-butane-2,3-diol with the concentrated sulfuric acid and separating the 2-methyl-1,2-bis-(4-pyridyl)-propane-1-one from the resulting mixture by fractional distillation.

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UNITED STATES PATENT OFFICE
CERTIFICATE OF CORRECTION

Patent No. 2,966,493

December 27, 1960

Milton Joel Allen et al.

It is hereby certified that error appears in the above numbered patent requiring correction and that the said Letters Patent should read as corrected below.

Column 2, line 9, after "e.g." strike out "methyl iodide," line 18, for "oxides" read -- oximes --; column 4, line 41, for "absorbing" read -- adsorbing --; line 44, for "absorbed" read -- adsorbed --.

Signed and sealed this 31st day of October 1961.

(SEAL)

Attest:

ERNEST W. SWIDER

Attesting Officer

DAVID L. LADD

Commissioner of Patents

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