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2-ARYL-1,3-DI(4-PYRIDYL)-2-PROPANOLS

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17 Claims. (Cl. 260—294.8)

ABSTRACT OF THE DISCLOSURE

Novel pharmacologically active 2 - aryl-1,3-di(4-pyridyl)-2-propanols are prepared inter alia by the reaction of a picolyl metal compound and a benzoyl halide or a benzoic acid ester.

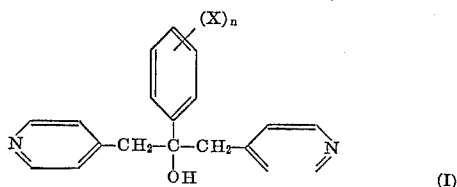
RELATED APPLICATIONS

This application is a continuation-in-part of application Ser. No. 465,764 filed June 21, 1965, which is in turn a continuation-in-part of application Ser. No. 344,198 filed Feb. 12, 1964, now abandoned, said application Ser. No. 344,198 being in turn a continuation-in-part of application Ser. No. 266,029 filed Mar. 18, 1963, now abandoned.

DETAILED DESCRIPTION

This invention relates, in general, to novel compounds and to processes for producing same. More particularly, the invention relates to pharmacologically active pyridyl compounds and to processes for their manufacture.

The compounds of this invention have the formula as follows:



in which the symbol X represents a hydrogen atom, a halogen atom, a lower alkyl group, i.e., an alkyl group having from 1 to 6 carbon atoms, a lower alkoxy group or a lower alkylmercapto group; and in which the symbol n represents the integer 1, with the proviso that where X is alkoxy, n is additionally the integer 3.

Additionally, the invention includes salts of the Formula I compounds with medicinally acceptable acids such as hydrochloric acid, sulfuric acid, nitric acid, p-toluene sulfonic acid, etc. The compounds of Formula I as well as the acid addition salts thereof relieve or diminish tremors which are brought about in animals by Tremorine, i.e., 1,4 - di-pyridolindino - 2-butyne, with a minimum of peripheral anti-cholinergic side effects. Additionally, they reduce hypothermia produced by Tremorine. Thus, the compounds are indicated for use in the study of the treatment of tremors which are characteristic of Parkinson's disease.

For example, the compounds of this invention when administered orally to animals such as mice relieve Trem-

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orine-induced tremors in single dose amounts ranging between about 7 and about 70 mg./kg. By way of illustration, the compound 2-phenyl-1,3-di(4-pyridyl)-2-propanol which has an LD_{50} of 2.8 grams/kg. orally in mice exhibits activity in the anti-Tremorine test when administered at a single oral dose of 7.1 mg./kg. The anti-Tremorine test employed in determining anti-Parkinson activity was carried out as follows:

Six mice of both sexes weighing 17 to 22 grams were employed per dose level. The test compounds were administered orally and one-half hour later 20 mg./kg. of Tremorine was administered intraperitoneally. The Tremorine-treated mice were observed for 30 minutes. Animals not exhibiting tremors within this time were considered protected. The ED_{50} is calculated by the method of Miller and Tainter (Proc. Soc. Exptl. Biol. Med., volume 57, page 261, 1944).

As a further illustration of the anti-Tremorine activity of the compounds of this invention other exemplary compounds were active in the above-described test as follows:

Compound:	ED_{50} (mg./kg.)
1,3-di(4-pyridyl)-2-(p-tolyl)-2-propanol	30
2 - (2 - fluorophenyl) - 1,3-di(4-pyridyl)-2-propanol	6.7
2 - (3 - fluorophenyl) - 1,3-di(4-pyridyl)-2-propanol	7.8
2 - (4 - chlorophenyl) - 1,3-di(4-pyridyl)-2-propanol	38
2 - (4 - fluorophenyl) - 1,3-di(4-pyridyl)-2-propanol	16.5
2 - (4 - methoxyphenyl) - 1,3 - di(4-pyridyl)-2-propanol	7.2
2 - (3 - bromophenyl) - 1,3-di(4-pyridyl) - 2-propanol	26.5
1,3 - di(4 - pyridyl) - 2-(o-tolyl)-2-propanol	70

By way of comparison the known anti-Parkinson agent α - cyclohexyl - α -phenyl-1-piperidine propanol exhibits activity in the above-described anti-Tremorine test at an oral dose of about 19 mg./kg.

The compounds of this invention have also demonstrated high potency and long duration of action in reducing hypothermia induced by Tremorine in mice. The effectiveness of the compounds of this invention against Tremorine-induced hypothermia in mice was determined by administering Tremorine intraperitoneally to mice at a level of 5 mg./kg. Rectal temperatures were taken before treatment and after treatment. Test compounds were administered orally and the Tremorine was administered 15, 45, 105, 165, 225 and 285 minutes later. The temperatures were then taken 15 minutes following administration of the Tremorine. Six mice were used for Tremorine control effects during the tests and 16 mice were used for each compound at each test interval. Activity was determined by calculation of the percent protection by drawing activity lines on graph paper using the method of "least squares." The results for illustrative compounds of this invention are given below. For comparison the activity of the known anti-Parkinson agent α -cyclohexyl- α -phenyl-1-piperidine propanol when tested by the same method is also given.

PERCENT PROTECTION AGAINST HYPOTHERMIC EFFECTS OF TREMORINE

	Dose (mg./kg. p.o.)	Percent Protection					
		0.5 hr.	1 hr.	2 hr.	3 hr.	4 hr.	5 hr.
2-(4-methylmercaptophenyl)-1,3-di(4-pyridyl)-2-propanol	30	98.0	87.6	66.9	46.2	25.5	4.8
2-(4-methoxyphenyl)-1,3-di(4-pyridyl)-2-propanol	30	100	97.1	90.2	83.2	76.3	69.3
α -cyclohexyl- α -phenyl-1-piperidine propanol	30	96.1	91.9	83.4	74.9	66.5	58

Thus, the compounds of this invention have demonstrated pharmacological effects in warm blooded animals qualitatively similar in many respects to those of α -cyclohexyl- α -phenyl-1-piperidine propanol, well-known for its therapeutic uses and properties.

Furthermore, the compounds of this invention alter the activity of the liver microsomal drug metabolizing enzymes. For example, they inhibit the following enzymatic oxidative reactions: hexobarbital to ketoexobarbital, acetanilid to p-hydroxyacetanilid, amphetamine to phenylacetone, dilantin to its p-hydroxy derivatives, etc. On prolonged administration the compounds of this invention stimulate the activity of the liver microsomal drug metabolizing enzymes. Because of their activity, these compounds provide a valuable tool for the study of the drug metabolizing enzyme systems associated with the liver microsomes and are useful in the study and treatment of diseases caused by metabolic failures of such enzyme systems, for example, in the treatment of phenylketonuria.

The activity of the compounds of this invention in altering the liver microsomal drug metabolizing enzymes was first established by in vitro experiments on rat liver microsomal enzyme fractions carried out as follows:

Male albino rats of the Charles River strain weighing between 150 and 250 grams were sacrificed by cervical dislocation and the livers were quickly removed and placed on cracked ice. The livers were weighed and a 1:2 (w./v.) homogenate in 0.1 molar sodium phosphate, pH 7.4, was prepared in an ice-cooled Waring blender. The liver was homogenized for a period of about thirty seconds and the resulting homogenate was centrifuged at 1,000 times gravity for a period of thirty minutes at a temperature of 0° C. in an international refrigerated centrifuge, model ER-2. The supernatant was further centrifuged at 9,000 times gravity for a period of twenty minutes, at a temperature of 0° C. in a Spinco model L ultracentrifuge. The supernatant fraction, which contained the microsomes and the soluble cellular material, was used in the study hereinafter described.

In the study a reaction mixture was prepared using 2 ml. of the enzyme fraction obtained as described in the preceding paragraph, a substrate of 0.5 ml. of sodium hexobarbital, 1.0 ml. of a solution containing 2 μ moles of triphosphopyridine nucleotide and 20 μ moles of glucose-6-phosphate disodium salt, 40 μ moles of nicotinamide hydrochloride and 20 μ moles magnesium chloride, 0.5 ml. of a compound of Formula I and the mixture was adjusted to a final volume of 5.0 ml. with 0.1 molar sodium dihydrogen phosphate buffer, pH 7.4. In the preparation of this reaction mixture, the ingredients, except the substrate, i.e., sodium hexobarbital, and the inhibitor, i.e., a compound of Formula I, were preincubated for a period of about fifteen minutes at a temperature of about 37° C. under a mixture of 95 percent oxygen-5 percent carbon dioxide. After the addition of the substrate and inhibitor, the mixture was incubated for a period of about fifteen minutes under the same conditions. The reaction was terminated by placing 3 ml. of the incubation tube containing 20 ml. of hexane (washed with 0.5 volume of 0.1 molar sodium dihydrogen phosphate buffer, pH 5.5), 1.5 grams of sodium chloride and 1.0 ml. of 0.1 molar sodium dihydrogen phosphate buffer (washed with 2 volumes of heptane), pH 5.5.

In each experiment a zero time tube and a blank tube were run. The zero time tube was prepared as follows: One ml. of a solution containing 2 μ moles of triphosphopyridine nucleotide, 20 μ moles of glucose-6-phosphate disodium salt and 20 μ moles of magnesium chloride were incubated for a period of fifteen minutes with 2 ml. of enzyme and 1.5 ml. of 0.1 molar sodium dihydrogen phosphate buffer, pH 7.4. An aliquot of 2.7 ml. of the incubation mixture and 0.3 ml. of substrate was added to a centrifuge tube containing the heptane extraction mixture described heretofore. The blank tube was prepared

in the same way as the zero time tube except that 2.0 ml. of buffer was used. The blank tube was preincubated for a period of about fifteen minutes and incubated for a period of about fifteen minutes.

The hexobarbital was extracted by vigorously shaking the reaction mixture containing the heptane, sodium chloride and buffer for a period of about forty-five minutes in an International Bottle shaker, following which it was centrifuged at 1,000 times gravity for a period of about twenty minutes at a temperature of about 20° C. The supernatant (heptane) was removed with a 10 ml. pipette, with a suction bulb attached, and it was placed in another 50 ml. ground glass stoppered centrifuge tube containing 5.0 ml. of 0.1 molar sodium dihydrogen phosphate buffer (washed with 2 volumes of heptane) of pH 5.5. The tubes were shaken by hand for a period of about fifteen seconds and then allowed to stand until the phases separated. Fifteen ml. of the resulting supernatant was placed in a 50 ml. ground glass stoppered centrifuge tube and 4 ml. of 0.8 molar sodium monohydrogen phosphate, pH 11 (adjusted with 5.0 molar sodium hydroxide), was added and the tubes were shaken for a period of about three minutes on the International Bottle shaker. After centrifuging the tubes for a period of about three minutes at 1,000 times gravity, the buffer phase was removed with a 5 ml. pipette and transferred to a silica cuvette. The absorbency of the solution at 245 $m\mu$ was read in a Beckman D.U. spectrophotometer against a blank containing the pH buffer. A standard solution of sodium hexobarbital (20 μ g./ml.) was used. The absorbance of this solution was about 0.590.

From the absorbancy data thus obtained there was calculated the extent to which the compounds of Formula I inhibited the oxidation of hexobarbital by the rat liver microsomal enzyme fraction. The results for illustrative compounds are as follows:

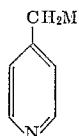
Compound	Concentration μ moles/liter	Percent Inhibition
2-phenyl-1,3-di(4-pyridyl)-2-propanol.....	100	100
	10	77
	1	0
2-(4-methoxyphenyl)-1,3-di(4-pyridyl)-2-propanol.....	10	38

A group of five mice were injected with 2-phenyl-1,3-di(4-pyridyl)-2-propanol (100 mg./kg., i.p.) for ten successive days. Five control mice were given saline each day. Twenty-four hours after the last injection the mice were given DL-phenylalanine-3- C^{14} (4 μ C/mouse, i.p.). Four hours later the mice were sacrificed and their livers were extirpated. An alcoholic liver extract was prepared and an aliquot of this material was placed on paper and chromatographed in a system which clearly separates phenylalanine from tyrosine. The amino acid spots were identified with ninhydrin, cut out and eluted from the paper with 50 percent ethanol. The radioactivity of the eluates were counted and the percent conversion of phenylalanine to tyrosine was calculated. In two separate experiments the mice treated with 2-phenyl-1,3-di(4-pyridyl)-2-propanol synthesized 2.2 and 2.8 times more tyrosine than the control.

In another set of experiments rats were injected with 2-phenyl-1,3-di(4-pyridyl)-2-propanol (100 mg./kg./day, i.p.) for four days. On the fifth day the treated and control rats were sacrificed and their livers were extirpated. A supernatant fraction was obtained by centrifuging the liver homogenate at 9000 $\times$ g. The enzyme fraction from the control and treated rats was incubated in a medium containing a TPNH generating system, oxygen and radioactive phenylalanine. After 1 hour of incubation the radioactive phenylalanine and tyrosine were isolated by paper chromatography and counted. The synthesis of tyrosine from phenylalanine was stimulated 75 percent and 58 percent, respectively, in two separate experiments. This effect has been confirmed clinically as shown by clinical results in the examples appended hereto.

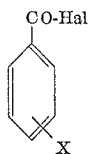
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The compounds of the present invention can be produced, in pure form and in relatively high yields, by several processes. In one of these processes a picolyl metal compound having the formula



II

in which the symbol M represents an alkali metal such as sodium, potassium or lithium and is reacted with a compound having the formula

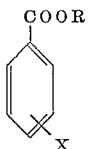


III(a)

in which the symbol X represents a hydrogen atom, a halogen atom, a lower alkyl group, i.e., an alkyl group having from 1 to 6 carbon atoms, a lower alkoxy group or a lower alkyl mercapto group; and in which Hal represents a halogen atom.

As the Formula III(a) compound, one can use, for example, benzoyl chloride, a halogen-substituted benzoyl chloride, such as 3-fluorobenzoyl chloride, 4-fluorobenzoyl chloride, 4-chlorobenzoyl chloride, etc., or a lower alkyl-substituted benzoyl chloride, such as p-toluoyl chloride, etc., an alkoxy, for example, methoxy, substituted benzoyl chloride or a lower alkyl-, for example, methyl, mercapto-substituted benzoyl chloride. Halides, other than chlorides, can be used, if desired.

In an alternate process, the picolyl metal compound of Formula II is reacted with a compound having the formula:



III(b)

in which the symbol R represents a lower alkyl group, i.e., an alkyl group having from 1 to 6 carbon atoms, such as, a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl or hexyl group or a benzyl group; and in which the symbol X has the same meaning as in Formula III(a).

As the Formula III(b) compound one can use an alkyl ester of benzoic acid, such as, methyl benzoate, ethyl benzoate, etc.; an alkyl ester of an alkyl substituted benzoic acid, such as, a methyl ester of toluic acid, an ethyl ester of toluic acid; an alkyl ester of a halogen substituted benzoic acid, such as, methyl chlorobenzoate, ethyl chlorobenzoate, methyl fluorobenzoate, ethyl fluorobenzoate, etc.; benzyl benzoate, a benzyl ester of an alkyl-substituted benzoic acid, such as, a benzyl ester of toluic acid; a benzyl ester of a halogenated benzoic acid, such as, benzyl chlorobenzoate, benzyl fluorobenzoate; an alkyl ester of a lower alkoxy, e.g. methoxy substituted benzoic acid; an alkyl ester of an alkyl-, e.g. methyl, mercapto substituted benzoic acid; a benzyl ester of a methoxy substituted benzoic acid; or a benzyl ester of a methyl mercapto benzoic acid.

In a third process for producing the compounds of this invention, a compound of Formula II is reacted with phenyl benzoate, or with a lower alkyl-substituted phenyl benzoate, a halogen-substituted phenyl benzoate, an alkoxy substituted, e.g., methoxy substituted, phenyl benzoate or an alkyl, e.g., methyl, mercapto phenyl benzoate. Thus, for example, there can be used phenyl methyl-benzoate, phenyl ethyl-benzoate, phenyl propyl-benzoate, phenyl chloro-benzoate, phenyl bromo-benzoate,

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phenyl methoxy-benzoate, phenyl methyl-mercapto-benzoate, etc., as a starting material in such process.

In still another process for producing the compounds of Formula I, a 4-picolyl magnesium bromide is reacted with phenyl benzoate or with a phenyl ester of an alkyl-substituted-, halogen-substituted-, alkoxy-substituted or alkyl mercapto-substituted benzoic acid of the type named in the preceding paragraph.

In carrying out each of the foregoing processes, there is used preferably a ratio of at least about 2.0 moles of the 4-picolyl metal compound of Formula II, or 4-picolyl magnesium bromide, for each mole of one of Formula III compounds, or phenyl benzoate or substituted phenyl benzoate, employed. A larger or smaller quantity of the 4-picolyl metal compound can be used, however, if desired.

The various processes described heretofore are carried out, in general, in a similar manner. In a first step, an organic solvent solution of the 4-picolyl metal compound, of 4-picolyl magnesium bromide, is first prepared. In general, any organic solvent in which the 4-picolyl compound is soluble, and which is inert under the reaction conditions employed, can be used in preparing this solution. Solvents which are suitable for use in the practice of this invention include, for example, benzene, diethyl ether, toluene, 4-picoline, tetrahydrofuran and the like. Mixtures of these solvents can be used, if desired.

The organic solvent solution of the 4-picolyl metal compound, which is described in the preceding paragraph, is thereafter, cooled by some appropriate means to a temperature below room temperature. In the preferred embodiment of the invention, this solution is cooled to a temperature of about 0° C. or lower. Preferably, the solution of the 4-picolyl metal compound is cooled to a temperature within the range of from about -10° C. to -60° C. thereafter, the Formula III reactant, or the unsubstituted or substituted phenyl benzoate reactant, dissolved in a suitable solvent, is added to the cooled solution of the 4-picolyl compound. In preparing the solution containing the Formula III compound, or the phenyl benzoate compound, one can use any solvent in which that compound is soluble and which is inert under the reaction conditions employed. Such solvents include, for example, ethyl ether, n-butyl ether, dioxane, tetrahydrofuran, etc., either alone or in admixture with some other organic solvent which is inert under the reaction conditions employed.

During the step of mixing the reactants, the reaction mixture should be maintained at a relatively low temperature. For best results, the reaction mixture should be maintained at a temperature below about 0° C., preferably at a temperature within the range of from about -10° C. to -60° C. After the step of mixing the reactants has been completed, the reaction mixture is stirred, while continuously cooled, until the reaction has been completed. In general the reaction can be brought to completion by stirring the reaction mixture first for a period of about one hour at a low temperature, for example, at a temperature within the range of from about -10° C. to -60° C. and, thereafter, for an additional period of about one hour at room temperature. When the reaction is complete, the reaction mixture is worked up, by appropriate and suitable means, to isolate the pyridyl compound thus produced. The crude product, in turn, can be purified by conventional means. Methods of working up the reaction mixture to isolate the reaction product therefrom, as well as methods for purifying those products, will be readily apparent to persons skilled in the art. Examples for specific procedures and techniques which are useful in accomplishing this will be found in the examples which follow hereinafter.

As indicated heretofore, the compounds of this invention are useful, inter alia, in the study and treatment of diseases caused by metabolic failures of enzyme systems. The manner in which they are used for such purpose will be readily apparent to persons skilled in the art. In gen-

eral, the compounds can be formulated, with conventional inert adjuvants, into dosage forms suitable for oral or parenteral administration. Such dosage forms include tablets and capsules as well as solutions and suspensions. Specific examples showing the embodiment of the present compounds in particular dosage forms will be found in the examples which follow hereinafter. The frequency of administration is variable, depending upon the needs and requirements of the patient.

For a fuller understanding of the nature and objects of this invention, reference may be had to the following examples which are given merely as further illustrations of the invention and are not to be construed in a limiting sense.

Example 1

An ether-benzene solution of 1.89 liters containing 3.5 moles of phenyl lithium was added, over a 3½ hour period, to a stirring solution of 326 grams of 4-picoline (3.5 moles) in 800 ml. of tetrahydrofuran. This addition was carried out in an atmosphere of dry nitrogen. When the addition of the phenyl lithium solution to the 4-picoline solution was completed, the reaction mixture was stirred for an additional 15 minutes. The reaction mixture was then cooled to a temperature of about -20° C. There was thus produced picolyl lithium.

A mixture of 197 grams of benzoyl chloride (1.4 mole) and 100 ml. of tetrahydrofuran was added to the picolyl lithium solution, produced as described in the preceding paragraph, over a fifty-minute period. During this addition, the temperature of the reaction mixture was maintained at about -20° C. A pale green colored reaction mixture was obtained and it was stirred at a temperature of about -20° C. for a period of about sixty minutes. Thereafter, the reaction mixture was brought to about room temperature, at which temperature the mixture was stirred for a period of about sixty minutes. Subsequently, 100 ml. of water was added to the reaction mixture in a dropwise manner. The reaction mixture was then diluted with 1 liter of water, stirred vigorously and transferred to a separatory funnel. In this vessel, the reaction mixture was acidified using 800 ml. of 6 N hydrochloric acid. The acid layer was separated from the organic phase and the latter was extracted two times, using 200 ml. of 3 N hydrochloric acid each time. The acid extracts were combined, washed first three times using 500 ml. of toluene each time, and, subsequently, one time using 500 ml. of ether. Subsequently, 5 kg. of ice was added to the acid extracts which were then made alkaline using ammonium hydroxide. During this step, the acid extracts were maintained at a temperature of about 10° C.

Treatment of the acid extracts with alkali, as described in the preceding paragraph, resulted in the formation of a precipitate. This precipitate was recovered by filtration, following which it was washed five times using 1.0 liter of water each time. The precipitate was then partitioned between 400 ml. of methylene chloride and 600 ml. of water and the mixture was thoroughly shaken. The insoluble residue was removed by filtration and washed two times using 200 ml. of water each time. Thereafter, the residue was washed two times using 200 ml. of methylene chloride each time and one time using 200 ml. of ether. The product was then dried in a vacuum oven at a temperature of 50° C. (20" Hg) for a period of about 15 hours. There was obtained by this procedure, 2-phenyl-1,3-di(4-pyridyl)-2-propanol melting first at 92° to 99° C., resolidifying and melting again at 166° to 168° C.

Example 2

To a stirring solution of 0.5 mole of 4-picolyl lithium cooled to a temperature within the range of from -30° C. to -50° C., there was added 0.2 mole of p-toluoyl chloride dissolved in about 100 ml. of tetrahydrofuran. Addition of the p-toluoyl chloride to the 4-picolyl lithium was accomplished under an atmosphere of dry nitrogen in a dropwise fashion over a period of about sixty minutes.

The reaction mixture was allowed to stir overnight, following which it was diluted by the addition of 100 ml. of water. The reaction mixture was extracted three times using 150 ml. of 6 N hydrochloric acid each time. The acid extracts were collected, combined and washed three times using 150 ml. of ether each time. Thereafter, the desired product was liberated by stirring the reaction mixture with a mixture of 500 grams of ice and 300 ml. of ammonium hydroxide. During this step of the process, ice was added, as needed, to maintain the temperature at about 0° C.

The precipitate which formed in this step was recovered by filtration in the form of a brown semi-solid. The precipitate was partitioned between 300 ml. methylene chloride and 300 ml. of water. The undissolved product was recovered by filtration yielding 1,3-di(4-pyridyl)-2-(p-tolyl)-2-propanol. Upon recrystallization of the product three times from an acetone-water mixture, there was obtained the 1,3-di(4-pyridyl)-2-(p-tolyl)-2-propanol as colorless plates, melting point at 100° C. to 110° C., resolidifying and melting again at 160° C. to 161° C.

Example 3

In this example, 2-(3-fluorophenyl)-1,3-di(4-pyridyl)-2-propanol was prepared by the process described in the preceding example using 3-fluorobenzoyl chloride in place of p-toluoyl chloride.

In this procedure, after the reaction mixture had been extracted with acid and the desired product liberated, as a precipitate, by stirring the acid extracts with concentrated ammonium hydroxide, the mixture was filtered given a red semi-solid product. Vigorous stirring of this product with 300 ml. of water and 200 ml. of methylene chloride, followed by filtration and three crystallizations from an acetone-water mixture, yielded 2-(3-fluorophenyl)-1,3-di(4-pyridyl)-2-propanol, melting first at 108° to 112° C., resolidifying and melting again at 189° to 191° C.

Example 4

In this example, 2-(4-fluorophenyl)-1,3-di(4-pyridyl)-2-propanol was prepared by the process described in Example 2 using 4-fluorobenzoyl chloride in place of p-toluoyl chloride.

The precipitate, which was obtained by treating the acid extracts with concentrated ammonium hydroxide, was recovered by filtration and stirred vigorously with 40 ml. of methylene chloride and 400 ml. of water. Filtration of this mixture yielded 2-(4-fluorophenyl)-1,3-di(4-pyridyl)-2-propanol in the form of colorless crystals. Recrystallization of this product, from an acetone-water mixture, yielded the compound in the form of colorless plates, melting first at 122° to 125° C., resolidifying and melting again at 155.5° to 157° C.

Example 5

In this example, a solution of 35.0 grams (0.2 mole) of p-chlorobenzoyl chloride in 25 ml. of anhydrous tetrahydrofuran was added, slowly, over a period of about twenty minutes to a stirring 0.5 molar solution of 4-picolyl lithium. During this addition, the reaction mixture was maintained at a temperature of about -20° C. When this addition was completed, the reaction mixture was stirred at a temperature of about -20° C. for a period of about thirty minutes, following which it was stirred at room temperature for an additional sixty-minute period. Thereafter, 800 ml. of water was added to the reaction mixture, following which the mixture was made acid using 3 N hydrochloric acid. The layers, which were thus formed, were separated and the organic phase was extracted two times, using 200 ml. of 3 N hydrochloric acid each time. The acid layers were combined, washed three times using 300 ml. of ether each time, made alkaline with 10 N sodium hydroxide solution and diluted to a volume of 4.0 liters using ice water. On standing, a precipitate formed. After standing for a period of

about 18 hours, the precipitate was recovered by filtration, washed with 500 ml. of water and subsequently partitioned between 200 ml. of water and 50 ml. of methylene dichloride. The suspension, thus formed, was stirred for about 30 minutes and then filtered. The precipitate was recrystallized from aqueous acetone to yield 2-(4-chlorophenyl) - 1,3 - di(4-pyridyl)-2-propanol as pale yellow prisms, melting first at 87° to 102° C., resolidifying and melting again at 181° to 183° C.

Example 6

In this example, 24 grams (0.11 mole) of m-bromobenzoyl chloride in 125 ml. of anhydrous tetrahydrofuran was added, in dropwise fashion over a period of about 75 minutes, to a stirring 0.5 molar solution of 4-picolyllithium. The reaction mixture was maintained at a temperature of about -40° C. during such addition and for a period of sixty minutes after the addition had been completed. Thereafter, the reaction mixture was stirred at room temperature for a period of about 60 minutes. Subsequently, 800 ml. of water was added to the reaction mixture following which the mixture was made acid using 3 N hydrochloric acid. The layers, thus formed, were separated and the organic phase was extracted twice using 200 ml. of 3 N hydrochloric acid each time. The acid layers were combined, washed three times using 500 ml. of ether each time, made alkaline with 10 N sodium hydroxide solution, cooled and re-extracted three times using 200 ml. of methylene chloride each time. The methylene chloride layers were combined, washed three times using 200 ml. of water each time and concentrated to an oil. The oil was triturated three times using 250 ml. of water each time, the layers being separated after each washing. The residual oil was then crystallized by the addition of a small amount of acetone. After two recrystallizations from benzene, there was obtained 2-(3-bromophenyl)-1,3-di(4-pyridyl)-2-propanol in the form of colorless prisms melting at 154° to 157° C.

3.0 grams of the 2-(3-bromophenyl)-1,3-di(4-pyridyl)-2-propanol, which was produced as described in the preceding paragraph, was added to 100 ml. of methylene chloride and this solution was saturated with hydrogen chloride gas. The solution was concentrated to an oil and crystallized by the addition of a small amount of ethanol. Recrystallization from an ethanol-ether mixture yielded the dihydrochloride salt of 2-(3-bromophenyl)-1,3-di(4-pyridyl)-2-propanol in the form of white prisms melting at 211° to 212° C.

Example 7

In this example, there was added to a stirring solution of 0.5 mole of 4-picolyllithium, under dry nitrogen, and cooled to a temperature of -30° to -50° C., 34.12 grams (0.2 mole) of p-methoxy benzoyl chloride dissolved in 50 ml. of tetrahydrofuran. Addition of the methoxy benzoyl chloride solution was accomplished, in a dropwise fashion, over a period of about one hour. Thereafter, the reaction mixture was stirred at room temperature for a period of about 17 hours, following which the reaction mixture was diluted with 50 ml. of water. The reaction mixture was extracted three times using 150 ml. portions of 6 N hydrochloric acid each time. The acid extracts were combined, washed three times using 150 ml. of ether each time and poured, with stirring, into 300 ml. of concentrated ammonium hydroxide and 500 grams of ice. By this procedure there was obtained 2-(4-methoxyphenyl)-1,3-di(4-pyridyl)-2-propanol in the form of a colorless precipitate. This compound was separated from the solution by filtration, washed with 500 ml. of water, and recrystallized from an acetone and water mixture. The compound melted first at 80° C. to 100° C., resolidified and melted again at 130° to 133° C. Three subsequent recrystallizations from an acetone-water mixture yielded pure 2-(4-methoxyphenyl)-1,3-di(4-pyridyl)-2-propanol having a melting point at 131° to 133° C.

Example 8

In this example, a solution of 116.4 grams (1.25 mole) of 4-picoline in 290 ml. of tetrahydrofuran was first prepared. To this solution, there was added, over a period of about 3½ hours at a temperature of about 30° C., 2.28 moles of phenyl lithium in a benzene-ether solution. The mixture was stirred for a period of about 15 minutes, following which it was cooled to a temperature of -20° C. To this cooled mixture, there was added 116 grams of 3,4,5-trimethoxy benzoyl chloride dissolved in 260 ml. of tetrahydrofuran. This addition was accomplished over a period of about 40 minutes, during which time the mixture was retained at a temperature of approximately -20° C. Stirring was continued an additional sixty minutes after the addition was complete. Subsequently, 330 ml. of water were added to the reaction mixture, in dropwise fashion, the temperature of the mixture being maintained at 30° C. The reaction mixture was then acidified and the aqueous phase was drawn off. The organic layer was extracted three times using 200 ml. portions of cold 10% hydrochloric acid each time. The combined acid extracts were back washed with 300 ml. of ether and made alkaline by the addition of concentrated ammonium hydroxide. During this step, the temperature of the reaction mixture was maintained below about 12° C. The precipitate which formed during the neutralization step was removed by filtration and partitioned between 600 ml. of methylene chloride and 600 ml. of water. The insoluble product was obtained by filtration and it was washed first with 200 ml. of cold water and subsequently two additional times using 200 ml. portions of methylene chloride each time. The product, thus obtained, namely, 1,3 - di(4 - pyridyl) - 2 - (3,4,5-trimethoxyphenyl)-2-propanol, melted at a temperature of 151° to 154° C. On recrystallization from ethanol, the compound melted at a temperature of 168° to 170° C.

Example 9

In this example, 0.2 mole of p-methyl mercapto benzoyl chloride, dissolved in 150 ml. of tetrahydrofuran, was added dropwise, over a period of about sixty minutes at a temperature within the range of from about -30° to -50° C. under dry nitrogen, to a solution containing 0.5 mole of 4-picolyllithium. The reaction mixture was allowed to stir overnight, following which the reaction mixture was diluted with 100 ml. of water. The reaction mixture was thereafter extracted three times using 150 ml. of 6 N hydrochloric acid each time. The acid extracts were combined and washed three times using 150 ml. of ether each time. Subsequently, the reaction mixture was treated with 500 grams of ice and 300 ml. of concentrated ammonium hydroxide, at a temperature of about 0° C., to yield, as a precipitate, 2-(4-methylmercaptophenyl)-1,3-di(4-pyridyl)-2-propanol. The reaction mixture was subsequently extracted with methylene chloride, following which the organic phase was dried over sodium sulfate and reduced, in vacuo, to a gummy residue. The residue was, thereafter, washed with ether and continuously extracted for a period of 48 hours using hexane. There was thus obtained as an insoluble product, 2-(4-methylmercaptophenyl)-1,3-di(4-pyridyl)-2-propanol. This product, after recrystallization three times from acetone, was obtained in the form of light yellow plates melting at 164.5° to 167° C.

Example 10

In this example, a solution of 39.6 grams (0.2 mole) of phenyl benzoate in 100 ml. of anhydrous tetrahydrofuran was slowly added to 0.5 molar solution of 4-picolyllithium. During this addition, temperature of the reaction mixture rose to a temperature of about 40° C. The reaction mixture was stirred for a period of about one hour, following which it was treated with 800 ml. of water. The aqueous phase was made acidic by the addition of 350 ml. of 3 N hydrochloric acid. Subsequently,

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the mixture was shaken and the layers comprising the two-phase system were separated. The organic phase was extracted two times using 200 ml. of 3 N hydrochloric acid each time. The acid layers were then combined, washed three times using 500 ml. of ether each time, made alkaline with 10 N sodium hydroxide solution and diluted to a volume of about 4 liters with ice water. The mixture was allowed to stand at room temperature for a period of about 18 hours, during which time a precipitate formed. The precipitate was recovered by filtration and washed with 500 ml. of water. The product was purified by partitioning between 200 ml. of water and 50 ml. of methylene chloride. Filtration and subsequent recrystallization of the product from aqueous acetone yielded 2-phenyl-1,3-di(4-pyridyl)-2-propanol melting at 164° to 166° C.

Example 11

In this example, included herein to demonstrate an alternate procedure for making 2-phenyl-1,3-di(4-pyridyl)-2-propanol, 4-picolyl magnesium bromide starting material was prepared by the dropwise addition of 64.9 grams (0.7 mole) of 4-picoline to a refluxing solution of ethyl magnesium bromide in 350 ml. of tetrahydrofuran. The ethyl magnesium bromide which was used, was prepared from 17 grams (0.7 mole) of magnesium and 76.3 grams (0.7 mole) of ethyl bromide.

The 4-picolyl magnesium bromide solution, produced as described in the preceding paragraph, was cooled to a temperature of about -6° C. Thereafter, a solution of 63.7 grams (0.3 mole) of benzyl benzoate in 60 ml. of tetrahydrofuran was added, with the temperature of the reaction mixture, during such addition, being maintained within the range of about -4° C. to -6° C. When the addition of the benzyl benzoate solution was completed, the reaction mixture was allowed to reach room temperature, following which it was stirred at such temperature for a period of about 18 hours. The Grignard complex was decomposed by the addition of 375 ml. of 2 N hydrochloric acid and the tetrahydrofuran was removed under reduced pressure. The solution was thereafter made strongly acidic using hydrochloric acid. Thereafter, the acid solution was extracted four times, using 200 ml. of ether each time. The aqueous phase was then made alkaline using sodium hydroxide solution. The alkaline aqueous phase was filtered and the filtrate was extracted four times using 200 ml. of methylene chloride each time. The organic layers were then combined, washed two times using 50 ml. of water each time and finally dried over anhydrous sodium sulfate. The solution was filtered and subsequently evaporated to yield 2-phenyl-1,3-di(4-pyridyl)-2-propanol, which compound, after recrystallization from aqueous alcohol, melted at 164° to 166° C.

Example 12

In this example, 20 grams of 2-phenyl-1,3-di(4-pyridyl)-2-propanol, produced as described in Example 1, was dissolved in 3000 cc. of ethyl acetate and saturated with dry hydrogen chloride. The resulting precipitate was filtered and the filter cake dried, in vacuo, at 60° C. over concentrated sulfuric acid. The crude cake was then digested for thirty minutes with 1000 cc. of refluxing ethyl acetate. Upon filtering and drying in vacuo at 60° C., there was obtained 2-phenyl-1,3-di(4-pyridyl)-2-propanol dihydrochloride, melting at 227° to 229° C., with decomposition.

Example 13

In this example, 0.2 mole of m-toluic acid chloride dissolved in 150 ml. of tetrahydrofuran was added in a dropwise fashion over a period of about sixty minutes to a stirred solution of 0.5 mole of 4-picolyl lithium. This addition was carried out under an atmosphere of dry nitrogen, with the 4-picolyl lithium solution being maintained at a temperature of from about -30° C. to -50° C. on a bath of dry ice-acetone. After about three hours, the reaction mixture was treated with 100 ml. of water, fol-

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lowing which it was extracted three times using 150 ml. portions of 6 N hydrochloric acid each time. The acid extract was then washed three times, using 150 ml. portions of ether each time. Thereafter, the product was liberated by stirring into a mixture of 500 grams of ice and 300 ml. of concentrated ammonium hydroxide. Ice was added to the mixture to maintain the temperature thereof at about 0° C.

The mixture, thus obtained, was filtered to obtain a solid, orange-colored product. This product was washed with a mixture of 200 ml. of methylene chloride and 400 ml. of water. The solid product, thus obtained, upon recrystallization from an acetone, yielded 1,3-di(4-pyridyl)-2-(o-tolyl)-2-propanol melting at 154° C. to 156° C. as white prisms.

Example 14

In this example, 0.2 mole of m-toluic acid chloride dissolved in 150 ml. of tetrahydrofuran was added, in a dropwise fashion over a period of about sixty minutes, to a stirred solution of 0.5 mole of 4-picolyl lithium. This addition was carried out under an atmosphere of dry nitrogen, with the 4-picolyl lithium solution being cooled to a temperature of -30° C. to -50° C. in a bath of dry ice-acetone. After about three hours, the reaction mixture was treated with 100 ml. of water, following which it was extracted three times, using 150 ml. portions of 6 N hydrochloric acid each time. Thereafter, the acid extracts were combined and washed three times using 150 ml. portions of ether each time. The product was then liberated by stirring the reaction mixture into a mixture of 500 grams of ice and 300 ml. of concentrated ammonium hydroxide. Ice was added, as needed, to maintain the temperature at about 0° C.

The basic mixture, thus obtained, was filtered and the solid, which remained after filtration, was washed with water. The product was then washed with 200 ml. of methylene chloride and 400 ml. of water. Upon filtration, there was obtained 1,3-di(4-pyridyl)-2-m-tolyl-2-propanol, melting point at 146° C. to 149° C. Recrystallization of this product from an acetone yielded 1,3-di(4-pyridyl)-2-(m-tolyl)-2-propanol in the form of colorless prisms, melting at 150° C. to 151° C.

Example 15

In this example, 0.2 mole of p-isopropylbenzoic acid chloride dissolved in 150 ml. of tetrahydrofuran was added in a dropwise fashion over a period of about sixty minutes to a stirred solution of 0.5 mole of 4-picolyl lithium. This addition was carried out under an atmosphere of dry nitrogen with the 4-picolyl lithium solution being cooled to a temperature of from about -30° C. to -50° C. on a bath of dry ice-acetone. After about three hours, the reaction mixture was treated with 100 ml. of water, following which it was extracted three times, using 150 ml. portions of 6 N hydrochloric acid each time. The acid extract was then washed three times, using 150 ml. portions of ether each time. Thereafter, the product was liberated by stirring into a mixture of 500 grams of ice and 300 ml. of concentrated ammonium hydroxide. Ice was added to the mixture, as needed, to maintain the temperature thereof at about 0° C.

The mixture, thus obtained, was filtered to yield a colorless crystalline product. Recrystallization of this product from an acetone yielded 1,3-di(4-pyridyl)-2-(4-isopropylphenyl)-2-propanol, as colorless prisms, melting point at 148° C. to 156° C. Upon recrystallization from acetone, there was obtained 1,3-di(4-pyridyl)-2-(4-isopropylphenyl)-2-propanol melting at 163° C. to 166° C.

Example 16

In this example, 0.2 mole of 2-fluorobenzoyl chloride dissolved in 150 ml. of tetrahydrofuran was added, in a dropwise fashion over a period of about sixty minutes, to a stirring solution of 0.5 mole of 4-picolyl lithium. This addition was carried out under an atmosphere of

dry nitrogen, with the 4-picoyl lithium solution being cooled to a temperature within the range of from about -30°C . to -50°C . in a bath of dry ice-acetone. The reaction mixture was allowed to stir overnight, following which it was hydrolyzed by the addition of 100 ml. of water. Thereafter, the reaction mixture was extracted three times, using 150 ml. portions of 6 N hydrochloric acid each time. The acid extracts were combined and washed three times, using 150 ml. portions of ether each time. The product was liberated by stirring the washed acid extracts into a mixture of 500 grams of ice and 300 ml. of ammonium hydroxide. The mixture was filtered to obtain a gum-like, orange solid. Vigorous stirring of this product with 400 ml. of water and 100 ml. of methylene chloride, followed by filtration yielded 2-(2-fluorophenyl)-1,3-di(4-pyridyl)-2-propanol melting at 157°C . to 160°C . This compound, after recrystallization three times from an acetone-water mixture, was obtained in the form of colorless needles melting at 159°C . to 161°C .

Example 17

This example is included herein to demonstrate the preparation of dosage forms of a compound representative of the compounds of this invention.

(a) Capsule Formulation: 10 mg. of 2-phenyl-1,3-di(4-pyridyl)-2-propanol were mixed with 165 mg. of lactose, U.S.P. and 30 mg. of corn starch, U.S.P. The mixture was then blended by passing through a Fitzpatrick Comminuting Machine with a No. 1A screen with knives forward. The blended powder was, thereafter, returned to the mixer and 5 mg. of talc was added thereto and blended therewith. The product was subsequently filled into hard shell gelatin capsules.

(b) Tablet Formulation: 5.10 mg. of 2-phenyl-1,3-di(4-pyridyl)-2-propanol were mixed with 84.40 mg. of lactose, U.S.P., 10.0 mg. of corn starch and 0.50 mg. of magnesium stearate. The mixture was blended by passing through a Fitzpatrick Comminuting Machine, filled with a No. 1A screen with knives forward. The powder was then slugged on a tablet compressing machine, following which the slugs were comminuted using a No. 16 screen. The mixture was compressed at a tablet weight of 100 mg. using tablet punches having a diameter of approximately $\frac{1}{4}$ inch.

(c) Parenteral Formulation: 25 mg. of 2-phenyl-1,3-di(4-pyridyl)-2-propanol was slurried in a small amount of water. To the slurry there was added slowly 1 N hydrochloric acid to pH 3.0. The solution was filtered and allowed to stand for twenty-four hours. Thereafter, the filtrate was filtered through a 02 Selas candle. The filtrate was then filled into ampuls, under an atmosphere of nitrogen, which were then sealed. The ampuls were sterilized for twenty minutes at a temperature of 250°F .

Example 18

The activity of an exemplary compound of this invention has also been converted clinically as follows:

Nine adult patients were selected from an average population. The patients were kept on 6 weeks of constant nitrogen intake prior to the study. Each patient was given a loading dose of L-phenylalanine (0.1 gram/kg.) prior to treatment with 2-phenyl-1,3-di(4-pyridyl)-2-propanol and this was repeated at the end of 4 weeks in one patient and 35-40 days in the others. The dosage of 2-phenyl-1,3-di(4-pyridyl)-2-propanol for all patients was 100 mg. per day, orally, for 4-6 weeks. Results are as follows:

Part 1 (single patient study).—There was a significant lowering of the blood phenylalanine levels after 4 weeks of treatment with 2-phenyl-1,3-di(4-pyridyl)-2-propanol. The decrease ranged from 17.5% at 0 hour to 36.0-41.5% at 1-4 hours (Table 1A). Even more impressive was the rise in tyrosine levels following treatment with 2-phenyl-1,3-di(4-pyridyl)-2-propanol, in the range of 300-350% (Table 1B). These results would indicate that an increased conversion of phenylalanine to tyrosine had

taken place, rather than decreased absorption or increased elimination.

Part 2.—Eight other patients were treated as described above. All showed decreases in blood phenylalanine levels ranging between 30 and 40%. Six of these patients, treated with 2-phenyl-1,3-di(4-pyridyl)-2-propanol, 35-40 days, have had detailed chemical data submitted (Table 2). These 6 patients showed decreases of phenylalanine in their bloods, but individual variations were seen and are represented in Table 2. The means values for these 6 patients are shown in Table 3 and show a mean decrease in phenylalanine blood levels of around 40%.

All patients had blood counts at the beginning and end of their trials. No decrease in white blood cells were seen. In 4 cases transaminase determinations showed normal values at the end of trials. There was no clinical evidence of jaundice, and in those patients who were able to communicate, no subjective complaints were reported.

TABLE 1A

SINGLE PATIENT-PHENYLALANINE LOADING-PRE AND POST TREATMENT 2-PHENYL-1,3-DI-(4-PYRIDYL)-2-PROPANOL (100 MG. DAILY FOR 4 WEEKS)

[Blood Phenylalanine (mg. percent)]

	Pre-Treatment	Post Treatment	Percent Change
Hours:			
0	46.1	38.1	-17.5
1	91.8	53.3	-41.5
2	95.3	57.7	-39.5
3	76.1	51.1	-34.0
4	69.7	44.4	-36.0

TABLE 1B

BLOOD TYROSINE CONVERSION 2-PHENYL-1,3-DI-(4-PYRIDYL)-2-PROPANOL (100 MG. DAILY FOR 4 WEEKS)

	Pre-Treatment	Post Treatment	Percent Change
Hours:			
0	0.9	2.8	+300
1	1.3	3.9	+300
2	1.0	3.5	+350
3	0.9	3.4	+340
4	0.9	3.2	+350

TABLE 2

Patient No. 1—Blood phenylalanine, mg. percent
[40 days of drug]

0 hours	17.8	0 hours	15.1
1 hour	32.9	1 hour	24.2
2 hours	37.9	2 hours	23.1
3 hours	34.2	3 hours	23.0
4 hours	31.7	4 hours	25.0

Patient No. 2—Blood phenylalanine mg. percent
[40 days of drug]

0 hours	20.3	0 hours	9.3
1 hour	32.9	1 hour	14.2
2 hours	38.3	2 hours	21.9
3 hours	38.3	3 hours	21.9
4 hours	34.6	4 hours	21.9

Patient No. 3—Blood phenylalanine mg. percent
[35 days of drug]

0 hours	22.5	0 hours	12.3
1 hour	28.3	1 hour	21.3
2 hours	30.0	2 hours	20.5
3 hours	35.9	3 hours	22.0
4 hours	34.1	4 hours	23.6

Patient No. 4—Blood phenylalanine mg. percent
[35 days of drug]

0 hours	24.1	0 hours	13.7
1 hour	34.1	1 hour	21.3
2 hours	34.1	2 hours	21.3
3 hours	36.6	3 hours	20.5
4 hours	35.9	4 hours	25.9

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Patient No. 5—Blood phenylalanine mg. percent
[35 days of drug]

0 hours	-----	46.1	0 hours	-----	38.1
1 hour	-----	91.8	1 hour	-----	53.3
2 hours	-----	95.3	2 hours	-----	57.7
3 hours	-----	69.7	3 hours	-----	51.1
4 hours	-----	76.7	4 hours	-----	44.4

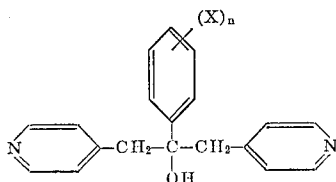
Patient No. 6—Blood phenylalanine mg. percent
[40 days of drug]

0 hours	-----	28.9	0 hours	-----	10.0
1 hour	-----	33.7	1 hour	-----	12.1
2 hours	-----	32.6	2 hours	-----	14.6
3 hours	-----	46.7	3 hours	-----	15.1
4 hours	-----	53.7	4 hours	-----	19.5

The study indicates that 4-6 weeks of treatment with 2-phenyl-1,3-di-(4-pyridyl)-2-propanol at 100 mg. daily tends to lower phenylalanine blood levels in chronic adult PKU patients.

We claim:

1. A compound selected from the group consisting of a member having the formula



in which X represents a member selected from the group consisting of hydrogen, halogen, lower alkyl, lower alkoxy and lower alkylmercapto; and in which *n* represents the integer 1, with the proviso that where X is alkoxy, *n* is additionally the integer 3 and salts thereof with medicinally acceptable acids.

2. The compound according to claim 1 wherein X is hydrogen, i.e., the compound 2-phenyl-1,3-di(4-pyridyl)-2-propanol.

3. The compound according to claim 1 wherein X is methyl and is in para-position, i.e., the compound 1,3-di(4-pyridyl)-2-(p-tolyl)-2-propanol.

4. A compound according to claim 1 wherein X is halo, i.e., a 2-(halophenyl)-1,3-di(4-pyridyl)-2-propanol.

5. The compound according to claim 1 wherein X is fluoro and is in meta-position, i.e., the compound 2-(3-fluorophenyl)-1,3-di(4-pyridyl)-2-propanol.

6. The compound according to claim 1 wherein X is

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fluoro and is in para-position, i.e., the compound 2-(4-fluorophenyl)-1,3-di(4-pyridyl)-2-propanol.

7. The compound according to claim 1 wherein X is chloro and is in para-position, i.e., the compound 2-(4-chlorophenyl)-1,3-di(4-pyridyl)-2-propanol.

8. The compound according to claim 1 wherein X is bromo and is in meta-position, i.e., the compound 2-(3-bromophenyl)-1,3-di(4-pyridyl)-2-propanol.

9. The compound according to claim 1 wherein *n* is 1 and X is methoxy and is in para-position, i.e., the compound 2-(4-methoxyphenyl)-1,3-di(4-pyridyl)-2-propanol.

10. The compound according to claim 1 wherein *n* is 3 and X is methoxy and is in para and meta-positions, i.e., the compound 1,3-di(4-pyridyl)-2-(3,4,5-trimethoxyphenyl)-2-propanol.

11. The compound according to claim 1 wherein X is methylmercapto and is in para-position, i.e., the compound 2-(4-methylmercaptophenyl)-1,3-di(4-pyridyl)-2-propanol.

12. A salt of a compound according to claim 1 wherein X is hydrogen, i.e., a salt of 2-phenyl-1,3-di(4-pyridyl)-2-propanol with a medicinally acceptable acid.

13. The dihydrochloride according to claim 12, i.e., 2-phenyl-1,3-di(4-pyridyl)-2-propanol dihydrochloride.

14. The compound according to claim 1 wherein X is methyl and is in ortho-position, i.e., the compound 1,3-di(4-pyridyl)-2-(o-tolyl)-2-propanol.

15. The compound according to claim 1 wherein X is methyl and is in meta-position, i.e., the compound 1,3-di(4-pyridyl)-2-(m-tolyl)-2-propanol.

16. The compound according to claim 1 wherein X is isopropyl and is in para-position, i.e., the compound 1,3-di(4-pyridyl)-2-(4-isopropylphenyl)-2-propanol.

17. The compound according to claim 1 wherein X is fluoro and is in ortho-position, i.e., the compound 2-(2-fluorophenyl)-1,3-di(4-pyridyl)-2-propanol.

References Cited

FOREIGN PATENTS

6,508,725 1/1966 Netherlands.

OTHER REFERENCES

Chemical Abstracts, vol. 64, par. 15, 855-15, 856, May 1966.

HENRY R. JILES, *Primary Examiner*.

A. L. ROTMAN, *Assistant Examiner*.