

1

2,995,567

## SEROTONIN ANTAGONISTS

Lewis H. Sarett, Princeton, Edward F. Rogers, Middletown, and Robert L. Clark, Woodbridge, N.J., assignors to Merck & Co., Inc., Rahway, N.J., a corporation of New Jersey  
No Drawing. Filed Sept. 4, 1957, Ser. No. 681,904  
7 Claims. (Cl. 260-319)

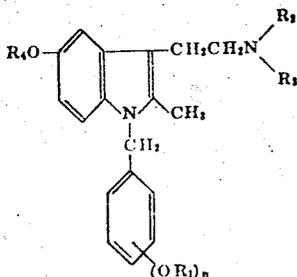
This application is a continuation-in-part of our co-pending application Serial #648,782, filed March 27, 1957, now abandoned.

This invention relates to tryptamine compounds and more particularly to tryptamine compounds having activity as serotonin antagonists.

Serotonin is widely distributed throughout the body in man and other mammals. The physiological activity of serotonin and the action of serotonin antagonists are discussed in J. Am. Med. Assn., 161, 460-461 (1956). As indicated in this article, Woolley and Shaw have suggested that the presence of serotonin is essential to normal mental processes; and mental disorders may result from serotonin deficiency. Serotonin is a vasoconstrictor, however, and excessive amounts in the blood stream appear to be responsible for various peripheral side effects, including high blood pressure. Administration of a serotonin antagonist counteracts the harmful peripheral side effects without interfering with the beneficial action of serotonin on the central nervous system.

According to the present invention new tryptamine derivatives having higher serotonin antagonist activity than previously known compounds are prepared.

The compounds of the present invention have the general formula



(I)

and the acid addition salts thereof. In this formula  $R_1$  is selected from the group consisting of hydrogen and lower alkyl radicals,  $R_2$  and  $R_3$  are selected from the group consisting of hydrogen and lower alkyl radicals,  $R_4$  is selected from the group consisting of hydrogen and lower alkyl, aralkyl, lower alkanoyl, aroyl, and aralkanoyl radicals; and  $n$  is a positive integer having the value of either 1 or 2.

The compounds according to the present invention may be divided into four groups, depending on the radical attached to the 5-position of the indole nucleus. These groups are (1) the 5-hydroxyindoles ( $R_4=H$ ), (2) the 5-acyloxyindoles ( $R_4$  is a lower alkanoyl, aroyl, or aralkanoyl radical), (3) the 5-alkoxyindoles ( $R_4$  is a lower alkyl radical), and (4) the 5-benzyloxyindoles ( $R_4$  is the benzyl radical). The 5-hydroxyindoles and the 5-acyloxyindoles generally are more active than the corresponding 5-alkoxyindoles, although the latter also display serotonin antagonist activity. The 5-benzyloxyindoles are of value as intermediates in the formation of the corresponding 5-hydroxyindoles.

Examples of compounds which may be formed according to the present invention include

2

- 1-(4-methoxybenzyl)-2-methyl-3-(2-aminoethyl)-5-hydroxyindole,
- 1-(4-hydroxybenzyl)-2-methyl-3-(2-aminoethyl)-5-hydroxyindole,
- 1-(4-methoxybenzyl)-2-methyl-3-(2-dimethylaminoethyl)-5-hydroxyindole,
- 1-(4-methoxybenzyl)-2-methyl-3-(2-aminoethyl)-5-acetoxyindole,
- 1-(4-methoxybenzyl)-2-methyl-3-(2-dimethylaminoethyl)-5-acetoxyindole,
- 1-(4-methoxybenzyl)-2-methyl-3-(2-dimethylaminoethyl)-5-isobutyroxyindole,
- 1-(4-methoxybenzyl)-2-methyl-3-(2-aminoethyl)-5-benzyloxyindole,
- 1-(4-methoxybenzyl)-2-methyl-3-(2-aminoethyl)-5-phenylacetoxyindole,
- 1-(4-methoxybenzyl)-3-(2-aminoethyl)-5-methoxyindole,
- 1-(4-ethoxybenzyl)-2-methyl-3-(2-aminoethyl)-5-methoxyindole,
- 1-(3,4-dimethoxybenzyl)-2-methyl-3-(2-aminoethyl)-5-methoxyindole,
- 1-(4-benzyloxybenzyl)-2-methyl-3-(2-aminoethyl)-5-methoxyindole,
- 1-(4-hydroxybenzyl)-2-methyl-3-(2-aminoethyl)-5-methoxyindole,
- 1-(4-methoxybenzyl)-2-methyl-3-(2-aminoethyl)-5-benzyloxyindole,
- 1-(4-methoxybenzyl)-2-methyl-3-(2-ethylaminoethyl)-5-methoxyindole,
- 1-(4-methoxybenzyl)-2-methyl-3-(2-dimethylaminoethyl)-5-methoxyindole,
- 1-(4-methoxybenzyl)-2-methyl-3-(2-dimethylaminoethyl)-5-benzyloxyindole,
- 1-(4-methoxybenzyl)-2-methyl-3-(2-isopropylaminoethyl)-5-methoxyindole,

and the acid addition salts thereof, such as the hydrochloride, sulfate, and acetate. While these compounds have been indicated as exemplary, other compounds corresponding to the above general formula are also within the scope of this invention.

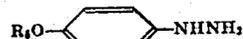
Various processes may be used to make the compounds of the present invention. Three processes which applicants have found particularly desirable will be illustrated. Each of these starts with an oxy-substituted phenylhydrazine of the general formula



(II)

or an acid addition salt thereof, where  $R_5$  is either a lower alkyl radical or the benzyl radical. The acid addition salt may be the hydrochloride, sulfate, acetate, or the like. The compound p-benzyloxyphenylhydrazine is the usual reagent for preparing indoles having a benzyloxy, hydroxy, or acyloxy substituent in the 5-position. This compound may be prepared as described by Mentzer, Beaudet, and Bory, Bull. Soc. Chim. (France), pages 421-423 (1953). The compound p-methoxyphenylhydrazine which is useful in preparing 5-methoxyindoles, may be prepared as described in Blaikie and Perkin, J. Chem. Soc. (London), volume 125, pages 296-313 (1924). Other phenylhydrazine reagents can also be made according to these procedures.

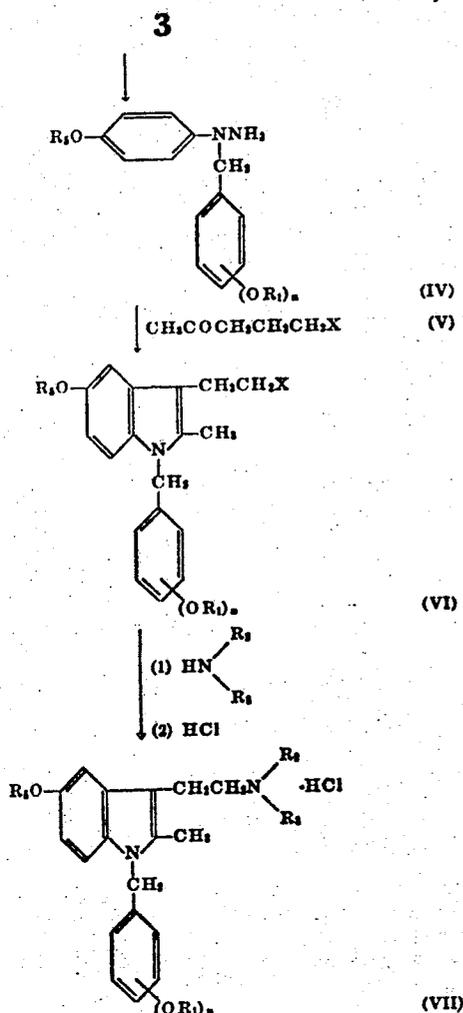
The first process, which is useful for making primary, secondary, or tertiary tryptamines, proceeds as follows:



(III)



(IV)



In the above equation  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ , and  $n$  are as defined above; and both Hal and X are either chlorine or bromine, i.e. halogen having an atomic weight in the range of 35 to 80. The halogens represented by Hal and X may be but are not necessarily identical.

The aralkyl halide reagent (III) has either one or two oxy substituents attached to the ring. The oxy substituents may be either alkoxy or aralkoxy groups. Preferred aralkyl halides are those having a single alkoxy or aralkoxy substituent attached to the para position. Examples of suitable reagents are 4-methoxybenzyl chloride, 4-benzyloxybenzyl chloride, 3,4-dimethoxybenzyl chloride, and the corresponding bromides.

The benzylation of the substituted phenylhydrazine compound, represented as the first step in the above equation, may be carried out following the procedure of Audrieth et al., *J. Org. Chem.*, volume 6, page 417 (1941), or according to the Audrieth procedure as modified by Shaw, *J. Am. Chem. Soc.*, volume 77, page 4319 (1955).

The second step in this process consists in condensing the product of the first step with a methyl gamma-halopropyl ketone (V), which may be either 5-chloropentanone-2 or 5-bromopentanone-2. The condensation is carried out in an acidic medium using a solvent such as ethanolic hydrogen chloride or glacial acetic acid. While these solvents are preferred, other acidic solvents such as ethanolic sulfuric acid and the like are also suitable. The reaction is carried out at elevated temperature such as reflux temperature. The resulting product is a haloalkyl indole (VI).

The next step of the reaction is to aminate the haloalkyl indole (VI). Ammonia, a primary amine, or a secondary amine is used for this purpose depending on

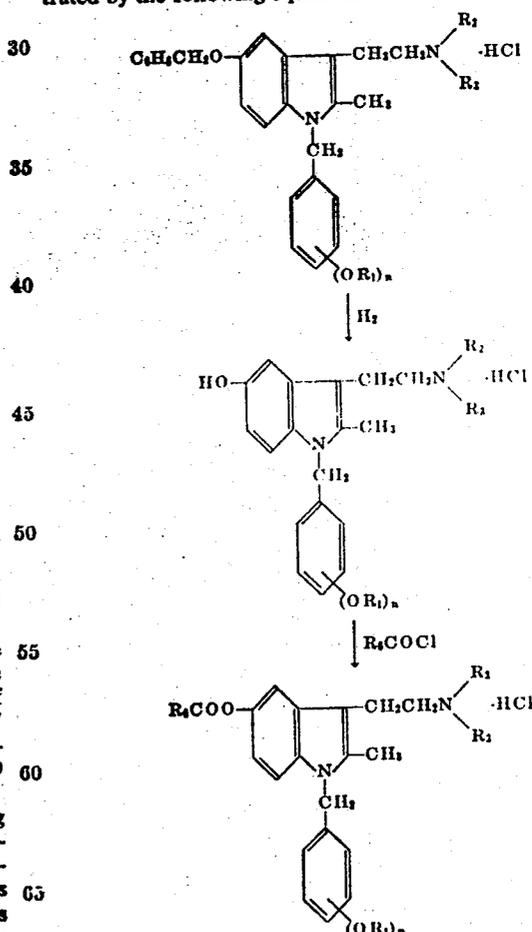
4

whether the product desired is a primary, secondary, or tertiary tryptamine. Suitable primary amines include methylamine, ethylamine, and the like. Secondary amines include dimethylamine, diethylamine, methylethyl amine, and the like. This reaction may be carried out at elevated temperature such as reflux temperature, or in a bomb, or at room temperature for an extended length of time.

The product (VII) may be recovered either as the free tryptamine compound or as an acid addition salt thereof, such as the hydrochloride, sulfate, or acetate. Generally it is preferred to recover the compound in the form of an acid addition salt. The acid addition salts may be easily prepared from the corresponding tryptamine compounds by conventional acidification procedures.

All of the compounds defined by Formula VII also fall within the scope of Formula I, although the converse is not true. Compounds VII are useful as serotonin antagonists or as intermediates for conversion to serotonin antagonists, depending on the nature of the group attached to the 5-position.

The 5-alkoxyindoles conforming to Formulas I and VII are useful as serotonin antagonists. The 5-benzyloxyindoles represented by Formulas I and VII are convertible to the corresponding novel 5-hydroxyindoles and 5-acyloxyindoles, which are potent serotonin antagonists included within Formula I (but outside VII), as illustrated by the following equation:



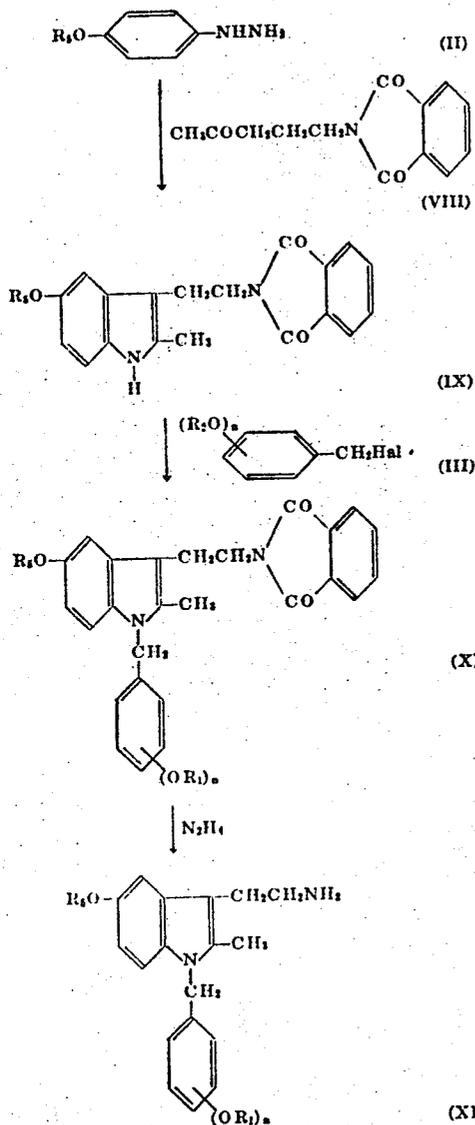
In the above equation  $R_6$  is a lower alkyl, aryl, or aralkyl radical and  $R_1$ ,  $R_2$ ,  $R_3$ , and  $n$  are as previously defined.

The hydrogenation illustrated above is carried out by conventional means such as reaction with hydrogen under superatmospheric pressure in the presence of a suitable catalyst such as palladium on charcoal.

The esterification of the 5-hydroxy radical in primary and secondary tryptamines is accomplished by saturating

5 a suitable solvent such as glacial acetic acid with hydrogen chloride, adding the 5-hydroxyindole to this solution, and then adding an acyl chloride, e.g. acetyl chloride or propionyl chloride, as the acylating agent. This procedure is necessary to prevent acylation of the tryptamine. Tertiary tryptamines can be acylated in the conventional manner using an anhydride, e.g., acetic anhydride or isobutyric anhydride.

Primary tryptamine compounds according to this invention may also be prepared according to a second general method. This method may be represented as follows:



The phenylhydrazine reagents (II) are the same as those used in the first process. Phthalimidopentanone-2 (VIII) may be prepared by condensing 5-chloropentanone-2 with potassium phthalimide or with phthalimide in the presence of potassium carbonate. The best procedure known to applicants for carrying out this condensation is as follows.

A mixture of 29.4 g. of phthalimide, 37 g. of potassium carbonate and 150 ml. of dimethylformamide is stirred and heated at 95° C. for one hour. After cooling the mixture to 60° C., 16.2 g. of 5-chloropentanone-2 is added and heating at 95° C. continued for one hour. The reaction mixture is then cooled to 15° C. and poured into 200 ml. of chloroform. A mixture of 10 ml. of 30% caustic in 400 ml. of ice cold water is then added, 75

the mixture stirred, and the chloroform layer separated. The aqueous layer is extracted with two portions of 100 ml. and 60 ml., respectively, of chloroform and the combined chloroform extracts washed with two 200-ml. portions of 0.25 N sodium hydroxide to remove phthalimide, and then with 200 ml. of water. The chloroform is then dried over magnesium sulfate and concentrated in vacuo to an oil. Crystallization is induced by cooling and trituration with water. After crystallization has started, a total of 25 ml. of water is added. After aging at 5° C. for several hours, the product 5-phthalimidopentanone-2 is filtered, washed with two 15-ml. portions of water and two 15-ml. portions of petroleum ether, and air-dried at 50° C.

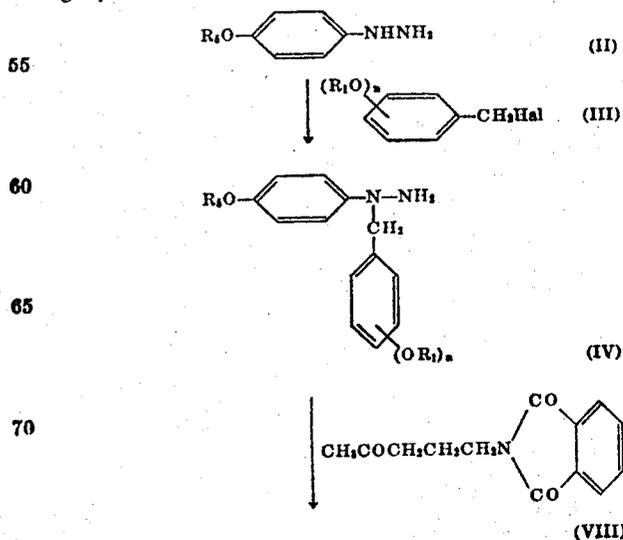
15 The phenylhydrazine reagent (II) and 5-phthalimidopentanone-2 are condensed in an acidic medium. Suitable solvents for this medium include ethanolic hydrogen chloride, glacial acetic acid, and the like. The reaction is carried out at elevated temperature, such as reflux temperature. The product (IX) is an indole having a phthalimidoalkyl side chain attached to the 3-position as indicated in the above equation. Among the indoles which may be thus formed are 2-methyl-3-(2-phthalimidoethyl)-5-methoxyindole, 2-methyl-3-(2-phthalimidoethyl)-5-benzyloxyindole, and 2-methyl-3-(2-phthalimidopropyl)-5-methoxyindole.

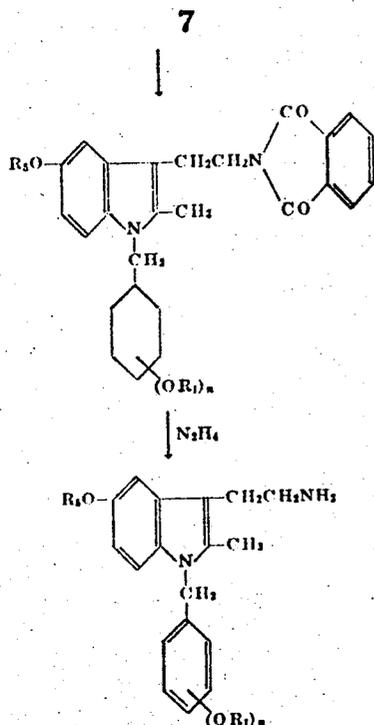
The phthalimidoethyl indole (IX) is reacted with an oxy-substituted benzyl halide (III) as indicated in the above equation. The suitable substituted benzyl halides are the same as in the first process. This reaction is carried out in an inert organic solvent such as dimethylformamide using a suitable condensing agent such as sodium hydride or sodium amide. This results in the formation of compound (X) having an oxy-substituted benzyl radical attached to the nuclear nitrogen atom.

The next step in this process is to remove the phthalimido group by reaction with hydrazine. The hydrazine is generally in the form of the monohydrate. This yields a primary tryptamine compound (XI) having serotonin antagonist activity. The primary tryptamines (XI) have the same general formula as the tryptamines (VII) described in the first method except that  $R_2$  and  $R_3$  must be hydrogen.

45 Tryptamines (XI) having a 5-benzyloxy radical may be converted to the corresponding 5-hydroxy- or 5-acyloxytryptamines as described previously.

A third general method for making compounds according to this invention is similar to the second general method except for some rearrangement in the order of steps. This method may be represented by the following equation:





All of the reagents are the same in both the second and third methods. The difference in the two methods lies in the different order in which the steps of the reaction are carried out.

The invention will now be described with reference to specific embodiments thereof.

#### EXAMPLE 1

##### (A) 2-methyl-3-(2-phthalimidoethyl)-5-methoxyindole

To a solution of 10 g. of 4-methoxyphenylhydrazine in 300 ml. of 2.3 N ethanolic hydrogen chloride were added 16.8 g. of 5-phthalimidopentanone-2. This mixture was heated under reflux with stirring for about one hour. About 100 ml. of ethanol were removed in vacuo, 50 ml. of water were added and the mixture cooled. A precipitate of 2-methyl-3-(2-phthalimidoethyl)-5-methoxyindole formed. This was removed by filtration and washed with two 25-ml. portions of water. The product was dissolved in warm acetone, using about 10 ml. of acetone per gram of product, and precipitated by the addition of about 6 ml. of water per gram. Yield about 87%; M.P. 182°-183° C.

##### (B) Preparation of 1-(4-methoxybenzyl)-2-methyl-3-(2-phthalimidoethyl)-5-methoxyindole

To a cooled, well-stirred mixture of 1 g. of a 50% emulsion of sodium hydride and 40 ml. of dry dimethylformamide was added 6.8 g. of 2-methyl-3-(2-phthalimidoethyl)-5-methoxyindole. After stirring at 20° C. for one and one-half hours, the mixture was cooled to 0° C., and 3.12 g. of 4-methoxybenzyl chloride was gradually added. After 40 minutes the solution was allowed to warm to room temperature overnight, and cooled. Gradual addition of 100 ml. of water caused crude 1-(4-methoxybenzyl)-2-methyl-3-(2-phthalimidoethyl)-5-methoxyindole to precipitate as a gum. The liquid was decanted and the gummy product was dissolved in 25 ml. of acetone. Addition of 20 ml. of water precipitated a purified product, which was recrystallized from absolute alcohol. Yield about 40%; M.P. 131°-132° C.

*Analysis.*—Calculated for  $C_{28}H_{26}O_4N_2$ : C, 73.98%; H, 5.77%; N, 6.16%. Found: C, 74.13%; H, 5.72%; N, 6.32%.

8

##### (C) 1-(4-methoxybenzyl)-2-methyl-3-(2-aminoethyl)-5-methoxyindole hydrochloride

A 4-gram portion of 1-(4-methoxybenzyl)-2-methyl-3-(2-phthalimidoethyl)-5-methoxyindole was dissolved in 100 ml. of absolute alcohol and the solution heated. To the hot solution 1.5 ml. of 95% hydrazine hydrate was added with stirring. The solution was refluxed, becoming red and gradually turning yellow. Refluxing was continued for one and one-half hours and a precipitate began to form after about one-half hour. The refluxed mixture was cooled and 25 ml. of water and 5 ml. of acetic acid were added. A precipitate of phthalhydrazine was removed by filtration. The alcohol was removed in vacuo from the filtrate. This resulted in formation of an additional quantity of phthalhydrazide, which was filtered off. The filtrate was made basic and extracted several times with ether. The ether solutions were combined and alcoholic hydrogen chloride was added until the solution was acidic. The solution was cooled overnight and 1-(4-methoxybenzyl)-2-methyl-3-(2-aminoethyl)-5-methoxyindole hydrochloride was removed by filtration. This material was recrystallized from absolute alcohol. Yield 85%; M.P. 194°-197° C.

*Analysis.*—Calculated for  $C_{20}H_{24}N_2O_2 \cdot HCl$ : C, 66.56%; H, 6.98%. Found: C, 67.02%; H, 6.75%.

#### EXAMPLE 2

##### (A) 1-(3,4-dimethoxybenzyl)-2-methyl-3-(2-phthalimidoethyl)-5-methoxyindole

The compound 2-methyl-3-(2-phthalimidoethyl)-5-methoxyindole, made as described in Example 1, step A, was reacted with 3.7 g. of 3,4-dimethoxybenzyl chloride according to the procedure of Example 1, step B. Upon addition of water a red solid which was crude 1-(3,4-dimethoxybenzyl)-2-methyl-3-(2-phthalimidoethyl)-5-methoxyindole separated. This product was suitable as use as a reagent in the next step of the synthesis without further purification.

##### (B) 1-(3,4-dimethoxybenzyl)-2-methyl-3-(2-aminoethyl)-5-methoxyindole hydrochloride

The procedure of Example 1, step C, was followed except that 1-(3,4-dimethoxybenzyl)-2-methyl-3-(2-phthalimidoethyl)-5-methoxyindole was the reagent. The product was 1-(3,4-dimethoxybenzyl)-2-methyl-3-(2-aminoethyl)-5-methoxyindole hydrochloride. The pure product was crystallized from absolute ethanol; M.P. 186°-187° C.

*Analysis.*—Calculated for  $C_{21}H_{27}N_2O_3Cl$ : C, 64.51%; H, 6.96%. Found: C, 63.86%; H, 7.08%.

#### EXAMPLE 3

##### (A) 1-(4-methoxyphenyl)-1-(4-methoxybenzyl)hydrazine hydrochloride

To a mixture of 13.5 g. of 41% sodium hydride emulsion and 100 ml. of dry dimethylformamide was added a solution of 27.6 g. of 4-methoxyphenylhydrazine in 60 ml. of dry dimethylformamide. The solution was stirred for one and one-half hours and then cooled to 0° C., and 35 g. of 4-methoxybenzyl chloride were added slowly. The mixture was then stirred at room temperature for 15 hours. The gradual addition of 400 ml. of water caused 1-(4-methoxybenzyl)-1-(4-methoxyphenyl)hydrazine to separate as an oil. This was separated and the aqueous layer was extracted with three 50-ml. portions of chloroform. The combined chloroform extracts were washed and dried. The chloroform was evaporated in vacuo at a temperature under 40° C. The residue was dissolved in 30 ml. of absolute alcohol. To this solution 30 ml. of 3 N hydrogen chloride in absolute alcohol were added. This caused precipitation of 1-(4-methoxybenzyl)-1-(4-methoxyphenyl)hydrazine hydrochloride. The product was recrystallized from an ethanol-ether mixture. Yield 65%; M.P. 160°-163° C.

*Analysis.* — Calculated for  $C_{15}H_{18}N_2O_2 \cdot HCl$ : C, 61.11%; H, 6.50%; N, 9.51%. Found: C, 61.27%; H, 6.76%; N, 9.41%.

(B) 1-(4-methoxybenzyl)-2-methyl-3-(2-chloroethyl)-5-methoxyindole

A mixture of 5.0 g. of 1-(4-methoxybenzyl)-1-(4-methoxyphenyl)hydrazine hydrochloride, 30 ml. of glacial acetic acid and 2.4 ml. of 5-chloropentanone-2 was heated on a steam bath. The temperature rose to above 95° C. and then the reaction mixture cooled to about 85° C. The mixture was then heated for an additional 20 minutes on the steam bath, the solution was removed, and 10 ml. of water was added. The crude solid which separated was recrystallized from 30 ml. of absolute alcohol to give 1-(4-methoxybenzyl)-2-methyl-3-(2-chloroethyl)-5-methoxyindole. Yield 3.8 g.; M.P. 99°–103° C.

*Analysis.*—Calculated for  $C_{20}H_{22}NO_2Cl$ : C, 69.85%; H, 6.45%. Found: C, 70.65%; H, 6.97%.

(C) 1-(4-methoxybenzyl)-2-methyl-3-(2-ethylaminoethyl)-5-methoxyindole hydrochloride

A mixture of 5 g. of 1-(4-methoxybenzyl)-2-methyl-3-(2-chloroethyl)-5-methoxyindole and 50 ml. of anhydrous ethylamine was heated in a bomb at 100° C. for 24 hours. The excess ethylamine was removed and the residue dissolved in ether, washed, dried, and dry hydrogen chloride added. A precipitate of 1-(4-methoxybenzyl)-2-methyl-3-(2-ethylaminoethyl)-5-methoxyindole hydrochloride was recovered. The product was recrystallized from alcohol-ether. Yield 4.9 g.; M.P. 179°–181° C.

*Analysis.*—Calculated for  $C_{22}H_{28}N_2O_2 \cdot HCl$ : C, 67.94%; H, 7.51%; N, 7.20%. Found: C, 67.88%; H, 7.48%; N, 7.51%.

EXAMPLE 4

(A) 1-(4-methoxybenzyl)-2-methyl-3-(2-isopropylaminoethyl)-5-methoxyindole hydrochloride

A solution of 4 g. of 1-(4-methoxybenzyl)-2-methyl-3-(2-chloroethyl)-5-methoxyindole prepared as described in Example 3, in 50 ml. of isopropylamine, was heated in a bomb at 100° for 24 hours. Some isopropylamine hydrochloride was removed by filtration. The filtrate was evaporated. Sodium hydroxide was added to the residue which was then extracted with ether. The ether layer was washed, and dried and dry hydrogen chloride added. The product 1-(4-methoxybenzyl)-2-methyl-3-(2-isopropylaminoethyl)-5-methoxyindole hydrochloride separated. It was crystallized from ethyl acetate by the addition of ether, M.P. 147°–149°.

*Analysis.*—Calculated for  $C_{23}H_{30}N_2O_2 \cdot HCl$ : C, 68.55%; H, 7.74%; N, 6.95%. Found: C, 68.79%; H, 7.89%; N, 6.80%.

EXAMPLE 5

1-(4-methoxybenzyl)-2-methyl-3-(2-dimethylaminoethyl)-5-methoxyindole hydrochloride.

A mixture of 5 g. of 1-(4-methoxybenzyl)-2-methyl-3-(2-chloroethyl)-5-methoxyindole, 200 ml. of absolute ethanol and 100 ml. of 25% dimethylamine was stirred at room temperature for 6 days. The solution was made basic with sodium hydroxide and evaporated to dryness, and the residue dissolved in ether. The ether was washed with water and dried. Hydrogen chloride added to precipitate 1-(4-methoxybenzyl)-2-methyl-3-(2-dimethylaminoethyl)-5-methoxyindole hydrochloride as a gum which soon solidified. The product was crystallized from alcohol-ether; M.P. 181°–182°.

*Analysis.*—Calculated for  $C_{22}H_{28}N_2O_2 \cdot HCl$ : C, 67.94%; H, 7.51%; N, 7.20%. Found: C, 67.70%; H, 7.26%; N, 7.28%.

(A) 1-(4-methoxybenzyl)-1-(4-benzylphenyl)hydrazine hydrochloride

To a well-stirred suspension of 11.2 g. of 50% sodium hydride emulsion in 100 ml. of dry dimethylformamide were slowly added 39 g. of 4-benzylphenoxyphenylhydrazine in 100 ml. of dimethylformamide. After stirring for 45 minutes the mixture was cooled and 36 g. of 4-methoxybenzyl chloride slowly added. The temperature was gradually allowed to warm up to room temperature and the mixture stirred 12 hours. Over a period of about one hour, 420 ml. of water were added, and a solid was precipitated. This was dissolved in about 1.5 liter of ether, washed with water, dried, and alcoholic hydrogen chloride was added. A dark oil separated which solidified almost immediately. It was crystallized from about 350 ml. of methanol by the addition of 1.5 liters of ether. Yield 29 g. A small amount of the product was recrystallized; M.P. 182°–183° C.

*Analysis.*—Calculated for  $C_{21}H_{22}N_2O_2 \cdot HCl$ : C, 68.01%; H, 6.25%. Found: C, 67.71%; H, 6.09%.

(B) 1-(4-methoxybenzyl)-2-methyl-3-(2-phthalimidoethyl)-5-benzoyloxyindole

A mixture of 3.4 g. of 1-(4-methoxybenzyl)-1-(4-benzoyloxyphenyl)hydrazine hydrochloride, 2.3 g. of 5-phthalimidopentanone-2, and 25 ml. of glacial acetic acid was heated on a steam bath to a maximum temperature of 100° C. for 20 minutes. After cooling 25 ml. of water was added slowly. A gum separated. Methanol was added and the mixture warmed, causing the gum to be converted to a solid precipitate of 1-(4-methoxybenzyl)-2-methyl-3-(2-phthalimidoethyl)-5-benzoyloxyindole. Yield 4.7 g.; M.P. 125°–126° C. A dimorphic form of this material melts at 173°–175° C.

*Analysis.*—Calculated for  $C_{34}H_{30}N_2O_4$ : C, 76.95%; H, 5.70%. Found: C, 77.18%; H, 5.47%.

(C) 1-(4-methoxybenzyl)-2-methyl-3-(2-aminoethyl)-5-benzoyloxyindole hydrochloride

To a hot stirred solution of 4 g. of 1-(4-methoxybenzyl)-2-methyl-3-(2-phthalimidoethyl)-5-benzoyloxyindole in 150 ml. of methanol was added 3 ml. of hydrazine hydrate. The solution was heated under reflux for three hours. The solvents were removed in vacuo until considerable precipitate had separated. After adding 20 ml. of water and 10 ml. of acetic acid, the remaining precipitate was removed by filtration. The filtrate was evaporated in vacuo until an oily precipitate began to separate. At this time ether and sodium hydroxide were added and the basic solution and precipitate extracted with ether several times. The combined ether extract was washed, dried and alcoholic hydrogen chloride added to precipitate a gelatinous precipitate of 1-(4-methoxybenzyl)-2-methyl-3-(2-aminoethyl)-5-benzoyloxyindole hydrochloride. This was crystallized from 10 ml. of methanol by the addition of 30 ml. of ether. Yield 1.5 g.; M.P. 196°–198° C. Further recrystallization raised the melting point to 203°–205° C.

*Analysis.*—Calculated for  $C_{26}H_{28}N_2O_2 \cdot HCl$ : C, 71.45%; H, 6.69%. Found: C, 71.40%; H, 6.68%.

(D) 1-(4-methoxybenzyl)-2-methyl-3-(2-aminoethyl)-5-hydroxyindole hydrochloride

A solution 4.3 g. of 1-(4-methoxybenzyl)-2-methyl-3-(2-aminoethyl)-5-benzoyloxyindole hydrochloride in 150 ml. of ethanol was treated with hydrogen in the presence of a catalyst consisting of 2 g. of 5% palladium on charcoal. This resulted in the formation of 1-(4-methoxybenzyl)-2-methyl-3-(2-aminoethyl)-5-hydroxyindole hydrochloride. Yield 75%; M.P. 253°–254° C.

11

*Analysis.*—Calculated for  $C_{19}H_{22}N_2O_2 \cdot HCl$ : C, 65.80%; H, 6.68%. Found: C, 65.85%; H, 6.47%.

(E) 1-(4-methoxybenzyl)-2-methyl-3-(2-aminoethyl)-5-acetoxyindole hydrochloride

A solution of 4 ml. of glacial acetic acid was saturated with hydrogen chloride. The 0.5 g. of 1-(4-methoxybenzyl)-2-methyl-3-(2-aminoethyl)-5-hydroxyindole hydrochloride was added. It did not go into solution. To the suspension was added 3 ml. of acetyl chloride. The mixture was shaken for 5 minutes, and a solution resulted. The solution was allowed to stand another 5 minutes, and ether was added to precipitate 1-(4-methoxybenzyl)-2-methyl-3-(2-aminoethyl)-5-acetoxyindole hydrochloride. It was crystallized from glacial acetic acid by the addition of ethyl acetate; M.P. 234°–235° C. 50% yield.

*Analysis.*—Calculated for  $C_{21}H_{24}N_2O_3 \cdot HCl$ : C, 64.85%; H, 6.48%. Found: C, 65.23%; H, 6.44%.

## EXAMPLE 7

1-(4-hydroxybenzyl)-2-methyl-3-(2-aminoethyl)-5-hydroxyindole hydrochloride

A mixture of 1 g. of 1-(4-methoxybenzyl)-2-methyl-3-(2-aminoethyl)-5-methoxyindole hydrochloride made as described in Example 1-C, and 7.0 g. of pyridine hydrochloride was heated to 200° C. for 5 minutes. The dark solution was cooled, diluted with water and neutralized with sodium bicarbonate. An oil separated and was dissolved in sodium hydroxide. This solution was made acidic with carbon dioxide and the solution filtered. Ammonium hydroxide was added to the filtrate and a solid separated, M.P. about 155° C. This was 1-(4-hydroxybenzyl)-2-methyl-3-(2-aminoethyl)-5-hydroxyindole.

## EXAMPLE 8

(A) 1-(4-methoxybenzyl)-2-methyl-3-(2-chloroethyl)-5-benzyloxyindole

A mixture of 6 g. of 1-(4-methoxybenzyl)-1-(4-benzyloxyphenyl)hydrazine hydrochloride, prepared as described in Example 3, 30 ml. of glacial acetic acid, and 2.8 ml. of 5-chloropentanone-2 was heated on a steam bath. The internal temperature rose to 102° to 104° C. After 30 minutes the mixture was cooled and 10 ml. of water added. A black oil separated and crystallized on standing for about 16 hours. The product 1-(4-methoxybenzyl)-2-methyl-3-(2-chloroethyl)-5-benzyloxyindole was recrystallized from 15 ml. of absolute alcohol. Yield 6.7 g.; M.P. 65° to 67° C.

*Analysis.*—Calculated for  $C_{26}H_{26}NO_2Cl \cdot HCl$ : C, 74.35%; H, 6.24%. Found: C, 74.56%; H, 6.15%.

(B) 1-(4-methoxybenzyl)-2-methyl-3-(2-dimethylaminoethyl)-5-benzyloxyindole hydrochloride

A mixture of 6.7 g. of 1-(4-methoxybenzyl)-2-methyl-3-(2-chloroethyl)-5-benzyloxyindole and 50 ml. of dimethylamine was heated in a bomb at 100° C. for 12 hours. The dimethylamine was removed and the residue extracted with ether. The ether extract was dried and alcoholic hydrogen chloride added. A precipitate of 1-(4-methoxybenzyl)-2-methyl-3-(2-dimethylaminoethyl)-5-benzyloxyindole hydrochloride was formed. This precipitate was recrystallized from 15 ml. of absolute alcohol by the addition of ether. Yield 4.5 g.; M.P. 133° to 136° C.

*Analysis.*—Calculated for  $C_{28}H_{32}N_2O_2 \cdot HCl$ . C, 72.31%; H, 7.15%. Found: C, 72.10%; H, 7.00%.

(C) 1-(4-methoxybenzyl)-2-methyl-3-(2-dimethylaminoethyl)-5-hydroxyindole hydrochloride

A solution of 4.6 g. of 1-(4-methoxybenzyl)-2-methyl-3-(2-dimethylaminoethyl)-5-benzyloxyindole hydrochloride in 25 ml. of methanol was hydrogenated at 40 p.s.i.g.

12

in the presence of 1 g. of 5% palladium on charcoal as a catalyst. The catalyst was removed, and the reaction mixture concentrated. The product 1-(4-methoxybenzyl)-2-methyl-3-(2-dimethylaminoethyl)-5-hydroxyindole hydrochloride crystallized upon concentration. Yield 1.5 g.; M.P. 258° to 259° C.

*Analysis.*—Calculated for  $C_{21}H_{26}N_2O_2 \cdot HCl$ . C, 67.12%; H, 7.24%. Found: C, 67.36%; H, 7.20%.

(D) 1-(4-methoxybenzyl)-2-methyl-3-(5-dimethylaminoethyl)-5-acetoxyindole hydrochloride

A mixture of 600 mg. of 1-(4-methoxybenzyl)-2-methyl-3-(2-dimethylaminoethyl)-5-hydroxyindole hydrochloride and 12 ml. of acetic anhydride was heated under reflux for 20 minutes. The resulting cloudy solution was filtered, using a diatomaceous filter aid, then 100 ml. of petroleum ether was added to the filtrate. The product 1-(4-methoxybenzyl)-2-methyl-3-(2-dimethylaminoethyl)-5-acetoxyindole hydrochloride crystallized from solution. Yield 430 mg.; M.P. 177° to 178° C.

*Analysis.*—Calculated for  $C_{23}H_{28}N_2O_3 \cdot HCl$ : C, 66.26%; H, 7.01%. Found: C, 66.21%; H, 6.90%.

## EXAMPLE 9

1-(4-methoxybenzyl)-2-methyl-3-(2-dimethylaminoethyl)-5-isobutyroxyindole hydrochloride

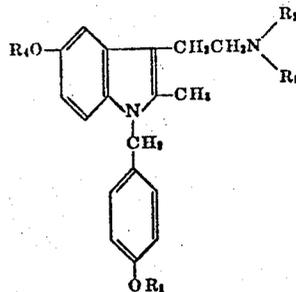
A mixture of 800 mg. of 1-(4-methoxybenzyl)-2-methyl-3-(2-dimethylaminoethyl)-5-hydroxyindole hydrochloride prepared as described in Example 8-C, and 10 ml. of isobutyric anhydride was heated under reflux for 15 minutes. The reaction mixture was filtered, using a diatomaceous filter aid. Ether was added to the filtrate to precipitate the product 1-(4-methoxybenzyl)-2-methyl-3-(2-dimethylaminoethyl)-5-isobutyroxyindole hydrochloride. Yield 800 mg.; M.P. 130° to 132° C.

*Analysis.*—Calculated for  $C_{25}H_{32}N_2O_3 \cdot HCl$ : C, 67.33%; H, 7.68%. Found: C, 67.31%; H, 7.45%.

While the present invention has been described in detail with reference to specific embodiments thereof, it is understood that variations may be made without departing from the spirit of this invention. Accordingly the scope of this invention is to be measured by the scope of the appended claims.

What is claimed is:

1. A compound selected from the group consisting of 60 compounds of the formula



where  $R_1$  is selected from the group consisting of hydrogen and methyl,  $R_2$  and  $R_3$  are selected from the group consisting of hydrogen and lower alkyl, and  $R_4$  is selected from the group consisting of hydrogen, and lower alkyl, benzyl, and lower alkanoyl, and the non-toxic acid addition salts thereof.

2. 1-(4-methoxybenzyl)-2-methyl-3-(2-aminoethyl)-5-hydroxyindole.

3. 1-(4-methoxybenzyl)-2-methyl-3-(2-aminoethyl)-5-acetoxyindole.

4. 1-(4-methoxybenzyl)-2-methyl-3-(2-dimethylaminoethyl)-5-acetoxyindole.

## 13

5. A non-toxic acid addition salt of 1-(4-methoxybenzyl)-2-methyl-3-(2-aminoethyl)-5-hydroxyindole.
6. A non-toxic acid addition salt of 1-(4-methoxybenzyl)-2-methyl-3-(2-aminoethyl)-5-acetoxyindole.
7. A non-toxic acid addition salt of 1-(4-methoxybenzyl)-2-methyl-3-(2-dimethylaminoethyl)-5-acetoxyindole.

## 14

References Cited in the file of this patent

## UNITED STATES PATENTS

2,825,734 Spector \_\_\_\_\_ Mar. 4, 1958

## OTHER REFERENCES

Wilkins: New Eng. Journ. of Med., vol. 255, #3, page 117 (1956).