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Lundt

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[54] **3-AMINOALKYLOXYINDOLES**

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Related U.S. Application Data

[63] Continuation-in-part of Ser. Nos. 39,863, May 22, 1970, abandoned, and Ser. No. 201,550, May 20, 1970, , and Ser. No. 287,311, Sept. 8, 1972.

[30] **Foreign Application Priority Data**

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[52] **U.S. Cl.**..... **260/326.15,** 260/326.11 R, 424/274

[51] **Int. Cl.**..... **C07d 27/56**

[58] **Field of Search**..... 260/326.15

[56] **References Cited**

UNITED STATES PATENTS

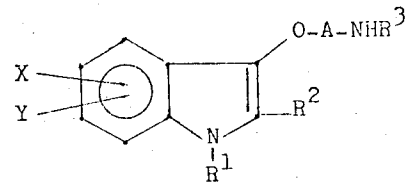
3,703,524 11/1972 Braendstroem et al..... 260/293.61

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[57] **ABSTRACT**

This invention is concerned with novel and pharmaceutically active indole derivatives having the structure:



I

and the salts thereof with physiologically acceptable acids, in which

each of X and Y is selected from the group consisting of hydrogen, hydroxy, lower alkyl having 1–3 carbon atoms and lower alkoxy having 1–3 carbon atoms,

R^1 is selected from the group consisting of hydrogen, lower alkyl having 1–4 carbon atoms and benzyl,

R^2 is selected from the group consisting of hydrogen, lower alkyl having 1–4 carbon atoms, benzyl and phenyl,

R^3 is selected from the group consisting of hydrogen, lower alkyl having 1–8 carbon atoms, cycloalkyl having 5 or 6 carbon atoms, benzyl and 2-phenylethyl, and

A is a straight or branched alkylene chain containing from 2 to 4 carbon atoms.

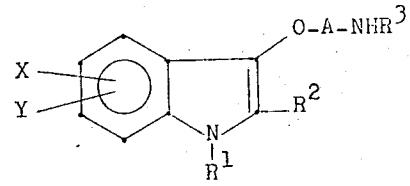
10 Claims, No Drawings

3-AMINOALKYLOXYINDOLES

This application is a continuation-in-part of copending applications Ser. No. 39,863 filed May 22, 1970 (now abandoned), Ser. No. 201,550 filed May 20, 1970 and Ser. No. 287,311 filed Sept. 8, 1972.

This invention relates to novel indole derivatives and salts thereof with physiologically acceptable acids and to processes for preparing these compounds. The invention also relates to pharmaceutical preparations comprising the said indole derivatives or their salts with physiologically acceptable acids as the active ingredients.

The present invention provides novel indole derivatives which are of the general formula:



(I)

in which:

each of X and Y is selected from the group consisting of hydrogen; hydroxy; lower alkyl having 1–3 carbon atoms and lower alkoxy having 1–3 carbon atoms,

R^1 is selected from the group consisting of hydrogen; lower alkyl having 1–4 carbon atoms and benzyl,

R^2 is selected from the group consisting of hydrogen; lower alkyl having 1–4 carbon atoms; benzyl and phenyl,

R^3 is selected from the group consisting of hydrogen; lower alkyl having 1–8 carbon atoms; cycloalkyl having 5 or 6 carbon atoms; benzyl and 2-phenylethyl, and

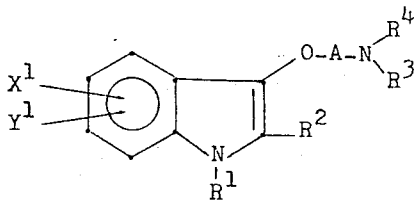
A is a straight or branched alkylene chain containing from 2 to 4 carbon atoms,

and salts of the said compounds of formula I with physiologically acceptable acids.

Examples of acids which are able to form physiologically tolerable salts with indole derivatives of the above formula are inorganic acids such as hydrochloric acid, sulfuric acid and phosphoric acid, as well as organic acids such as acetic acid, tartaric acid, citric acid, oxalic acid, fumaric acid and maleic acid.

The novel indole derivatives of the above formula (I) and their acid addition salts may according to the invention be prepared in one or more of the following manners:

a. Compounds of the general formula (I) in which X, Y, A, R^1, R^2 and R^3 are as defined in connection with formula (I) may be prepared by hydrogenolysis of the corresponding compounds of the general formula:



(II)

in which:

each of the substituents X^1 and Y^1 is selected from the group consisting of hydrogen; benzyloxy; lower alkyl having 1–3 carbon atoms and lower alkoxy having 1–3 carbon atoms, A, R^1, R_2 and R^3 are as defined above, and R^4 represents benzyl.

The particular compounds of the general formula (I)

in which R^3 represents benzyl may be prepared by partially hydrogenolysing the corresponding compounds of the general formula (II) in which R^3 and R^4 are benzyl.

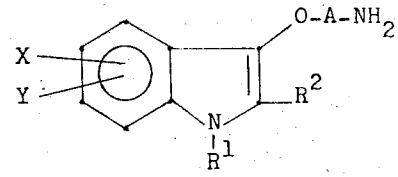
The said hydrogenolysis is performed in a solvent, such as ethanol, in the presence of a suitable catalyst, e.g., palladium on carbon, or

b. Compounds of the general formula (I) in which X, Y, A, R^1, R^2 and R^3 are as indicated in connection with formula (I), excluding, however, compounds in which R^3 represents hydrogen, may be prepared by converting under suitable hydrogenolytic conditions indole derivatives of the general formula II, in which,

X^1, Y^1, R^1, R^2 and A are as defined in connection with formula (II), and each of R^3 and R^4 is selected from the group consisting of hydrogen and benzyl, in the presence of the particular aldehyde or ketone selected as a precursor, in a reductive alkylation process, of the substitutent R^3.

The reaction is performed in a solvent such as ethanol in the presence of hydrogen and a suitable catalyst such as palladium on carbon, or

c. Compounds of the general formula (I) in which X, Y and A, R^1, R^2 and R^3 are as defined in connection with formula (I), excluding, however, compounds in which R^3 represents hydrogen, may be prepared by reacting in a suitable solvent, e.g., methanol or tetrahydrofuran, indole derivatives of the general formula:

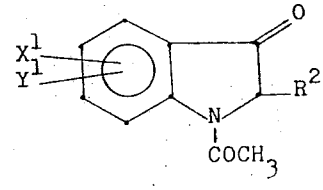


(III)

in which X, Y, R^1, R^2 and A are as defined above with the particular aldehyde or ketone selected as a precursor, in a reductive alkylation process, of the substituent R^3, followed by treatment of the reaction mixture with a suitable reductive agent, e.g., sodium borohydride, whereafter, if desired, the indole derivatives thus prepared may be converted into salts with physiologically acceptable acids. The acid addition salts are prepared by reacting the base form of the indole derivatives with no less than one equivalent of the appropriate acid in an organic solvent such as ethanol or isopropanol. Such salts may advantageously be used for the purpose of isolating and/or purifying the compounds of this invention, and may be transformed in a manner known, per se, into the corresponding salts with other physiologically acceptable acids.

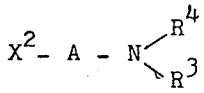
The present invention also provides processes analogous to those described and claimed in the said U.S. pat. application Ser. No. 39,863 for preparing the novel intermediary indole derivatives of the general formula (II) in which X^1, Y^1, A, R^1, R^2, R^3 and R^4 are as defined in connection with formula (II) excluding, however, compounds in which R^3 represents hydrogen.

The first step comprises condensing indoxyl derivatives of the general formula:



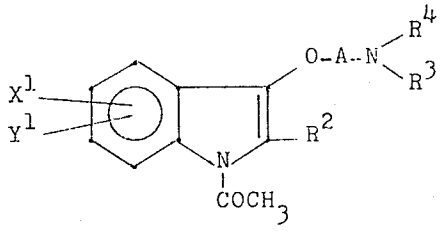
(IV)

in which X^1, Y^1 and R^2 are as defined above, with compounds of the general formula:



(V)

in which A, R^3 and R^4 are as defined above, and X^2 represents a halogen atom or a group functionally equivalent therewith, thus producing a compound of the general formula:



(VI)

in which X^1, Y^1, A, R^2, R^3 and R^4 are as defined above. The reaction is performed in a suitable solvent, such as dimethylformamide or dimethylsulfoxide in the presence of an acid-binding agent such as potassium carbonate or sodium hydride.

The intermediates of the general formula (II) in which R^1 represents hydrogen are prepared in a second step which comprises deacetylating compounds of the general formula (VI) in a suitable solvent, such as methanol or ethanol, by means of a basic agent, preferably ammonia or an alkali metal alkoxide.

For the preparation of intermediates of the general formula (II), in which R^1 is different from hydrogen, a third step is added which comprises reacting the deacetylated compounds produced in the second step above, with an alkylating agent of the general formula:

$$X^3 - R^5 \qquad \text{(VII)}$$

in which X^3 is a halogen atom and R^5 is selected from the group consisting of lower alkyl having 1–4 C-atoms and benzyl.

The reaction is performed in a suitable solvent, such as dimethylformamide or toluene, in the presence of an acid binding agent, such as sodium hydride.

The novel indole derivatives of the general formula (I) as well as their salts with physiologically acceptable acids exhibit valuable pharmacological properties and are thus of potential utility in human therapy, particularly as analgetic and antiinflammatory agents.

Thus, formula I indole derivatives have been found to exhibit, in varying degrees, anti-inflammatory activity when evaluated by various standard pharmacological tests involving both oral and parenteral administration to animals. For example, in one such test pedal inflammation was induced in rats by Carrageenin according to the method of C. A. Winther et al., (Proc. Soc. Exptl.Biol.Med., 111 (1962), p. 544), and the anti-inflammatory activity was expressed in terms of per cent inhibition of pedal inflammation. Anti-inflammatory values for a number of formula I indole derivatives administered orally are presented in Table I.

Furthermore, indole derivatives of the present invention exhibit, in varying degrees, an additional analgetic effect. Many of the formula I indole compounds exhibit both anti-inflammatory and analgetic activity and therefore may be particularly suited for the treatment of inflammatory conditions accompanied by pain.

The analgetic activity of the indole derivatives of the present invention may be demonstrated in selected pharmacological tests performed in a variety of animal species. For example, the analgetic activity was examined after subcutaneous administration to mice in the tail-clip test according to F. Haffner (Deutsche Med. Wochenschrift, 55 (1929), p. 731). The analgetic activity, in terms of ED_{50}-values, of a number of formula I indole derivatives, is presented in Table II.

An overall evaluation of the data from the various standard animal tests using these novel indole derivatives reflects a wide spectrum of anti-inflammatory activity and/or analgetic activity and indicates that the compounds of this invention may have valuable and advantageous therapeutic properties as compared to the anti-inflammatory agents and analgetic agents that are widely used at the present time.

However, for reasons of safety of administration, the preferred formula I indole derivatives are those which exhibit anti-inflammatory activity and/or analgetic activity when administered to mammals at a dosage level below that of the LD_{50}-value of that particular compound.

All of the compounds in Table I exhibit very pronounced anti-inflammatory activity at dosage levels significantly below their LD_{50}-values.

All of the compounds in Table II exhibit very pronounced analgetic activity at dosage levels significantly below their LD_{50}-values.

Table I

Compound	Anti-inflammatory effect: % inhibition 100 mg/kg orally
3-(3-aminopropoxy)indole hydrochloride	48
3-(2-isopropylaminoethoxy)indole hydrochloride	66
3-(2-n-propylaminoethoxy)indole hydrochloride	62
3-(2-aminoethoxy)-2-methylindole hydrochloride	39
3-(2-aminoethoxy)-2-phenylindole	77
3-(2-isopropylaminoethoxy)-4-methoxyindole hydrochloride	84
3-(2-isopropylaminoethoxy)-2-phenylindole hydrochloride	79
1-benzyl-3-(2-isopropylaminoethoxy)-2-phenylindole hydrochloride	67
1-benzyl-3-(2-isopropylaminoethoxy)-4-methoxyindole hydrochloride	67
1-benzyl-3-(2-isopropylaminoethoxy)indole hydrochloride	63

Table I – Continued

Compound	Anti-inflammatory effect: % inhibition 100 mg/kg orally
3-(2-aminoethoxy)-5-methylindole hydrogen oxalate	56
1-n-butyl-3-(2-isopropylaminoethoxy)indole hydrochloride	44
2-benzyl-3-(2-isopropylaminoethoxy)indole hydrochloride	31[r]
3-(2-cyclohexylaminoethoxy)-5-methoxyindole hydrochloride 52	
3-(2-ethylaminoethoxy)indole hydrochloride	53
3-(2-isopropylaminoethoxy)-5-methoxyindole hydrochloride	32

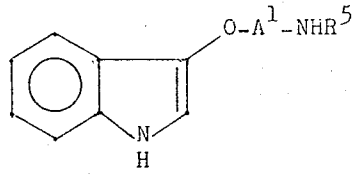
[r] 50 mg/kg orally

Table II

Compound	Analgetic effect: Haffner's test mg/kg s.c.
3-(2-aminoethoxy)indole hydrogen oxalate	9
3-(2-aminoethoxy)-5-methoxyindole	1.1
3-(2-aminoethoxy)-5-methylindole hydrogen oxalate	5
3-(2-benzylaminoethoxy)indole hydrochloride	26
3-(2-isopropylaminoethoxy)indole hydrochloride	19
3-(2-isopropylaminoethoxy)5-methoxyindole hydrochloride	8
3-(2-cyclohexylaminoethoxy)-5-methoxyindole hydrochloride	10
3-(2-aminopropoxy)indole hydrochloride	25
3-(2-(n-propylamino)ethoxy)indole hydrochloride	3.8
3-(2-isobutylaminoethoxy)indole hydrochloride	6
3-(2-(2-phenylethyl)aminoethoxy)indole hydrochloride	26
3-(2-neopenthylaminoethoxy)indole hydrogen oxalate	18
3-(2-n-hexylamino)ethoxy)indole hydrochloride	16
3-(2-ethylaminoethoxy)indole hydrochloride	1.6
3-(2-aminoethoxy)-4-methoxyindole	5
3-(2-isopropylaminoethoxy)-4-methoxyindole hydrochloride	29
1-n-butyl-3-(2-isopropylaminoethoxy)indole hydrochloride	36
2-benzyl-3-(2-isopropylaminoethoxy)indole hydrochloride	35

All formula I compounds exhibiting significant anti-inflammatory activity also possess a measurable, but varying analgetic activity, whereas some formula I compounds possess analgetic activity, only.

The group of indole derivatives within the general formula I that exhibit only analgetic effects are those having the structure



(VIII)

and the acid addition salts thereof with physiologically acceptable acids, in which R^5 is lower alkyl having 4–7 carbon atoms, benzyl and 2-phenylethyl, and A^1 is ethylene.

In addition, many of the compounds in Tables I and II exhibit high degrees of activity as to both effects.

When the compounds of the present invention are employed as therapeutic agents they may be administered alone or in combination with pharmaceutically acceptable carriers, the proportion of which is determined by the solubility and chemical nature of the compound, chosen route of administration and standard pharmaceutical practice. For example, they may be administered orally in the form of tablets or capsules containing such excipients as starch, milk sugar, certain types of clay and so forth. They may be administered sublingually in the form of troches or lozenges in which the active ingredient is mixed with sugar and corn syrups, flavoring agents and dyes; and then dehydrated sufficiently to be pressed into a solid form. They may be administered orally in the form of solutions which may contain coloring and flavoring agents, or they may be injected parenterally, that is intramuscularly, intravenously or subcutaneously. For parenteral administration, they may be used in the form of a sterile solution containing other solutes, for example, enough saline or glucose to make the solution isotonic.

The dosage of the present therapeutic agents will vary with the route of administration and the particular compound chosen. Furthermore, it will vary with the subject under treatment. In general, the compounds of this invention are most desirably administered at a concentration level that will generally afford effective results without causing any harmful or deleterious side effects and preferably at a dose level that is in the range of from 5 mg to about 2,000 mg per day, although, in individual cases, division as well as multiplication of doses may be necessary.

The preparation of the novel indole derivatives of the present invention is illustrated in detail in the following examples.

EXAMPLE I

3-(2-aminoethoxy)indole hydrogen oxalate

3-(2-dibenzylaminoethoxy)indole (35.7 g), dissolved in ethanol (400 ml of 99%) was hydrogenolyzed in the presence of palladium/carbon (10 g of 10%) at 50–60 psi and 25°C in the course of about 18 hours. The cata-

lyst was filtered off and the filtrate was concentrated in vacuum. The residue, dissolved in ethanol (30 ml) was cautiously added to a solution of oxalic acid (27 g) in ethanol (125 ml). The resulting precipitate was recrystallized from aqueous ethanol (75%), yielding 3-(2-aminoethoxy)indole hydrogen oxalate (13.6 g, 51% yield)) with mp. 134°–136°C.

Anal. calcd. for $C_{12}H_{14}O_5N_2$:

C, 54.1%; H, 5.3%; N, 10.6%.

Found:

C, 54.0%; H, 5.3%; N, 10.6%.

The intermediate, 3-(2-dibenzylaminoethoxy)indole, was prepared in the following manner:

A mixture of 1-acetylindoxyl (17.5 g), 2-dibenzylaminoethyl chloride hydrochloride (44.5 g) and potassium carbonate (62 g) in dimethylsulfoxide (DMSO, 200 ml) was left with stirring at 40°C for 12 hours. The precipitate which formed after the addition of ice-water (1 L) was filtered off and recrystallized from ethanol. Alternatively, the precipitate was extracted with ethyl acetate (2 × 600 ml) followed by concentration of the ethyl acetate extract. The residue so obtained yielded after recrystallization from ethanol 1-acetyl-3-(2-dibenzylaminoethoxy)indole (34 g, 85% yield) with mp. 105°–107°C.

1-acetyl-3-(2-dibenzylaminoethyoxy)indole (100 g) was treated for 15 min. with a refluxing solution of sodium ethoxide, prepared from sodium (29 g), in ethanol (700 ml of 99%). The reaction mixture was cooled to 10°–20°C and water (1400 ml) was slowly added. The solid material so obtained was recrystallized from a mixture of benzene (100 ml) and isooctane (200 ml), yielding 3-(2-dibenzylaminoethoxy)indole (58 g, 65% yield) with mp. 75°–76°C.

EXAMPLE 2

3-(2-aminoethoxy)-5-methoxyindole

3-(2-dibenzylaminoethoxy-5-methoxyindole (108 g) was hydrogenolyzed by a procedure analogous to that described in Example 1. The reaction mixture, freed from the catalyst, was concentrated in vacuum and the crude 3-(2-aminoethoxy)-5-methoxyindole was recrystallized from toluene (150 ml). The pure compound (40.6 g, 72% yield) had the mp. 103°–104°C.

Anal. calcd. for $C_{11}H_{14}O_2N_2$:

C, 64.1%; H, 6.8%; O, 15.5%; N, 13.6%.

Found:

C, 63.8%; H, 6.9%; O, 15.7%; N, 13.8%.

The starting material, 3-(2-dibenzylaminoethoxy)-5-methoxyindole was prepared in the following manner:

A mixture of 1-acetyl-5-methoxyindoxyl (75 g), 2-dibenzylaminoethyl chloride hydrochloride (163 g) and potassium carbonate (228 g) in DMSO (730 ml) was kept with stirring for 6 hours at 40°C. The reaction mixture was treated with icewater (4 L) and the resulting suspension was extracted with ethyl acetate (3 × 400 ml). The ethyl acetate extract was dried and concentrated in vacuum. Recrystallization of the residue from ethanol gave 1-acetyl-3-(2-dibenzylaminoethoxy)-5-methoxyindole (122 g, 78% yield) with mp. 82°–83°C. This compound was deacetylated in the manner described in Example 1. The product, 3-(2-dibenzylaminoethoxy)-5-methoxyindole, was isolated as an oil.

EXAMPLE 3

3-(2-aminoethoxy)-5-hydroxyindole hydrogen oxalate.

5-benzyloxy-3-(2-dibenzylaminoethoxy)indole was subjected to hydrogenolysis and worked up in the manner described in Example 1, thus affording 3-(2-aminoethoxy)-5-hydroxyindole hydrogen oxalate with mp. 165°–166°C in 50% yield.

The starting material, 5-benzyloxy-3-(2-dibenzylaminoethoxy)indole, was synthesized by aminoalkylation of 1-acetyl-5-benzyl-oxyindoxyl in a procedure analogous to that described in Example 1 and deacetylation of the product was effected as indicated in the same example. 5-benzyloxy-3-(2-dibenzylaminoethoxy)indole with mp. 87°–88°C crystallized direct from the reaction mixture without addition of water. The overall yield, based on 1-acetyl-5-benzyloxyindoxyl, was 68.5%.

EXAMPLE 4

3-(2-aminoethoxy)-5-methylindole hydrogen oxalate

In a procedure analogous to that of Example 1, but starting from 3-(2-dibenzylaminoethoxy)-5-methylindole, 3-(2-aminoethoxy)-5-methylindole hydrogen oxalate with mp. 139°–140°C was obtained in 35% yield. The crystalline salt contains water of hydration which is retained tenaciously, even after drying in vacuum.

The intermediate, 3-(2-dibenzylaminoethoxy)-5-methylindole was prepared in the following manner:

1-acetyl-5-methylindoxyl was aminoalkylated by the procedure described in Example 2, yielding 1-acetyl-3-(2-dibenzylaminoethoxy)-5-methylindole with mp. 104°–105°C in 68% yield.

1-acetyl-3-(2-dibenzylaminoethoxy))-5-methylindole (32 g), dissolved in methanol (350 ml) saturated with ammonia was heated in an autoclave to 60°C for 6 hours. The reaction mixture was cooled and concentrated in vacuum, leaving a residue which after recrystallization from a mixture of benzene (60 ml) and isooctane (250 ml) afforded 3-(2-dibenzylaminoethoxy)-5-methylindole with mp. 57°–58°C. The yield was 50%.

EXAMPLE 5

3-(3-aminopropoxy)indole hydrochloride

A solution of 3-(3-dibenzylaminopropoxy)indole hydrochloride in ethanol was subjected to hydrogenolysis in a manner similar to that of Example 1. The product, 3-(3-aminopropoxy)indole hydrochloride, with mp. 176°–178°C was obtained in 41% yield.

3-(3-dibenzylaminopropoxy)indole hydrochloride was synthesized by the following procedure:

A mixture of 1-acetylindoxyl (35 g), 3-dibenzylaminopropyl chloride hydrochloride (68.2 g) and potassium carbonate (91 g) in DMSO (400 ml) was left with stirring at 60°C for 24 hours. The reaction mixture was treated with ice-water (1.5 L) and the aqueous suspension was extracted with ethyl acetate (3 × 500 ml). The ethyl acetate extract was dried and freed of solvent. Recrystallization from ethanol yielded 1-acetyl-3-(3-dibenzylaminopropoxy)indole (34.5 g, 42% yield) with mp. 99°–100°C.

Sodium (12.8 g) was dissolved in ethanol (290 ml of 99%) and 1-acetyl-3-(3-dibenzylaminopropoxy)indole (46 g) was added. The mixture was refluxed for 30 minutes, cooled to about 25°C and subsequently treated with ice-water (1.7 L). The resulting emulsion was extracted with ethyl acetate (3 × 200 ml). Addition of a solution of hydrogen chloride in ethanol to the dried

ethyl acetate phase afforded a crystalline precipitate of 3-(3-dibenzylaminopropoxy)indole hydrochloride (42.5 g, 93.5% yield) with mp. 180°–181°C.

EXAMPLE 6

3-(2-methylaminoethoxy)indole hydrochloride

3-(2-(N-benzyl-N-methylamino)ethoxy)indole (10 g), dissolved in ethanol (150 ml of 99%) was hydrogenated in the presence of palladium/carbon (2 g of 10%) at 50–60 psi and 25°C for 10–18 hours. After removal of the catalyst, the solution was concentrated in vacuum and the residue was dissolved in isopropanol (30 ml). Addition of a solution of hydrogen chloride in isopropanol at 0°–5°C converted the base into a crystalline hydrochloride. Recrystallization from isopropanol afforded 3-(2-methylaminoethoxy)indole hydrochloride (4.7 g, 70% yield) with mp. 140°–141°C.

Anal. calcd. for $C_{11}H_{15}ON_2Cl$:

C, 58.3%; H, 6.7%; O, 7.1%; N, 12.4%; Cl, 15.6%

Found:

C, 58.0%; H, 7.0%; O, 7.3%; N, 12.4%; Cl, 15.5%;

3-(2-(N-benzyl-N-methylamino)ethoxy)indole is prepared by the method described below:

A mixture of 1-acetylindoxyl (17.5 g), 2-(N-benzyl-N-methylamino)ethyl chloride hydrochloride (33 g) and potassium carbonate (62 g) was refluxed for 48 hours in ethyl acetate (500 ml) containing water (5 ml). After chilling, the reaction mixture was filtered and the filtrate was concentrated. The residue so obtained was recrystallized from isopropanol, affording 1-acetyl-3-(2-(N-benzyl-N-methylamino)ethoxy)indole (22 g, 68% yield) with mp. 72°–74°C.

1-acetyl-3-(2-(N-benzyl-N-methylamino)ethoxy)indole was deacetylated according to the procedure described in Example 4. The product, 3-(2-(N-benzyl-N-methylamino)ethoxy)indole, was isolated as an oil.

EXAMPLE 7

3-(2-benzylaminoethoxy)indole hydrochloride

3-(2-dibenzylaminoethoxy)indole (7.1 g, 20 mmol) was dissolved in ethanol (100 ml of 99%) containing hydrogen chloride (20 mmol). Partial hydrogenolysis was performed in the presence of palladium/carbon (2 g of 10%) at 50–60 psi and 25°C in the course of 3 hours. Removal of the catalyst, concentration of the solution in vacuum and recrystallization of the resulting residue from isopropanol yielded 3-(2-benzylaminoethoxy)indole hydrochloride (2.5 g, 41% yield) with mp. 179°–180°C.

Anal. calcd. for $C_{17}H_{19}ON_2Cl$:

C, 67.4%; H, 6.3%; N, 9.3%; Cl, 11.7%

Found:

C, 67.4%; H, 6.3%; N, 9.4%; Cl, 11.8%

EXAMPLE 8

3-(2-isopropylaminoethoxy)indole hydrochloride

3-(2-dibenzylaminoethoxy)indole (7.1 g), dissolved in a mixture of ethanol (75 ml of 99%) and acetone (25 ml) was hydrogenated in the presence of palladium/-carbon (2 g of 10%) at 50–60 psi and 25°C for 18 hours. The catalyst was filtered off and the filtrate was concentrated in vacuum. The resulting residue was dissolved in isopropanol (30 ml) and converted at 0°–5°C into the crystalline 3-(2-isopropylaminoethoxy)indole hydrochloride (3.45 g) with mp. 160°–163°C. Recrystallization from ethanol (yield: 2.1 g, 45%) raised the mp. to 183°–185°C.

Anal. calcd. for $C_{13}H_{19}ON_2Cl$:

C, 61.3%; H, 7.5%; N, 11.0%; Cl, 13.9%

Found:

C, 61.3%; H, 7.8%; N, 11.0%; Cl, 13.9%

EXAMPLE 9

3-(2-cyclohexylaminoethoxy)indole hydrochloride

By the same procedure as that of Example 8, but substituting cyclohexanone for acetone, 3-(2-cyclohexylaminoethoxy)indole hydrochloride with mp. 225°–227°C was obtained in 42% yield.

EXAMPLE 10

3-(2-isopropylaminoethoxy)-5-methoxyindole hydrochloride

A mixture of 3-(2-aminoethoxy)-5-methoxyindole (5.15 g) and acetone (20 ml) in methanol (50 ml) was subjected to hydrogenation in the presence of palladium/carbon (1 g of 10%) at 50–60 psi and 25°C for 2 hours. The reaction mixture was worked up in the usual way, thus affording 3-(2-isopropylaminoethoxy)-5-methoxyindole hydrochloride (5.9 g) with mp. 190°–191°C. Recrystallization from ethanol (yield: 4.95 g, 69%) gave a compound with mp. 200°–201°C.

Anal. calcd. for $C_{14}H_{21}O_2N_2Cl$:

C, 59.0%; H, 7.4%; N, 9.8%; Cl, 12.4%

Found:

C, 59.1%; N, 7.4%; N, 10.0%; Cl, 12.4%

EXAMPLE 11

3-(2-n-butylaminoethoxy)-5-methoxyindole hydrochloride

3-(2-aminoethoxy)-5-methoxyindole (5.15g) was dissolved in dry methanol (50 ml), a solution of n-butyraldehyde (2.1 g) in dry methanol (10 ml) was added at 0°–5°C and the mixture was left at that temperature for 30 minutes. Reductive alkylation was performed in the presence of palladium/carbon (1 g of 10%) and hydrogen (50–60 psi) at 25°C for 2 hours. The reaction mixture was worked up as described in previous examples and yielded 3-(2-n-butylaminoethoxy)indole hydrochloride (3.8 g) with mp. 189°–190°C. Recrystallization from ethanol (yield: 2.9 g, 39%) raised the mp. to 193°–194°C.

Anal. calcd. for $C_{15}H_{23}O_2N_2Cl$:

C, 60.3%; H, 7.8%; N, 9.4%; Cl, 11.9%

Found:

C, 60.3%; H, 8.0%; N, 9.5%; Cl, 11.7%

EXAMPLE 12

3-(2-isopropylaminoethoxy)indole hydrochloride

In a manner similar to that described in Example 10, 3-(2-isopropylaminoethoxy)indole hydrochloride with mp. 174°–175°C was obtained in 43% yield.

EXAMPLE 13

3-(2-cyclohexylaminoethoxy)-5-methoxyindole hydrochloride

By an analogous procedure 3-(2-cyclohexylaminoethoxy)-5-methoxyindole hydrochloride with mp. 192°–193°C was obtained in 65% yield.

EXAMPLE 14

3-(2-aminopropoxy)indole hydrochloride

To a solution of sodium (11 g) in ethanol (260 ml of 99%) was added 1-acetyl-3-(2-dibenzylaminopropoxy)indole (39 g). The mixture was refluxed for 30 minutes, cooled to about 25°C and subsequently treated with ice-water (2.0 L). The resulting emulsion was extracted with ethyl acetate (3 × 330 ml) and the dried ethyl acetate extract was concentrated in vacuum. The residue, 3-(2-dibenzylaminopropoxy)indole, dissolved in ethanol (350 ml of 99%) was hydrogenated in the presence of palladium/carbon (6 g of 10%) at 50–60 psi and 25°C for 18 hours. After removal of the catalyst, the solution was concentrated in vacuum and the residue was dissolved in isopropanol (120 ml). Addition of a solution of hydrogen chloride in isopropanol at 0°–5°C converted the base into a crystalline hydrochloride. Recrystallization from isopropanol afforded 3-(2-aminopropoxy)indole hydrochloride. The overall yield of 3-(2-aminopropoxy)indole hydrochloride with mp. 95°–96°C was 60%.

Anal. calcd. for $C_{11}H_{15}ON_2Cl$:

C, 58.3%; H, 6.7%; O, 7.1%; N, 12.4%; Cl, 15.6%

Found

C, 58.0%; H, 6.9%; O, 7.2%; N, 12.4%; Cl, 15.7%

To prepare the starting material, a mixture of 1-acetylindoxyl (49 g), 1-dibenzylamino-2-chloropropane hydrochloride (130 g) and potassium carbonate (174 g) in dimethylsulfoxide (DMSO) (560 ml) was left with stirring at 40°C for 12 hours. The reaction mixture was treated with ice-water (2,500 ml) and the resulting emulsion extracted with chloroform (3 × 250 ml). The dried chloroform extract was concentrated in vacuum, leaving a residue which at room temperature was dissolved in a mixture of ethanol (4 parts) and isopropanol (1 part). From this solution, chilled to 0°–5°C, 1-acetyl-3-(2-dibenzylaminopropoxy)indole (39 g, 34%) with mp. 111°–112°C, crystallized.

EXAMPLE 15

3-(2-(1-methylbutyl)aminoethoxy)indole hydrochloride.

3-(2-dibenzylaminoethoxy)indole (7.1 g), dissolved in a mixture of ethanol (75 ml of 99%) and methyl n-propyl ketone (8.6 g) was hydrogenated in the presence of palladium/carbon (2 g of 10%) at 50–60 psi and 25°C for 18 hours. The catalyst was filtered off and the filtrate was concentrated in vacuum. The residue, dissolved in isopropanol (20 ml), was converted at 0°–5°C into the crystalline 3-(2-(1-methylbutyl)aminoethoxy) indole hydrochloride (3.5 g) with mp. 189°–192°C. Recrystallization from isopropanol (yield: 2.9 g, 51%) raised the mp. to 197°–198°C.

Anal. calcd. for $C_{15}H_{23}ON_2Cl$:

C, 63.7%; H, 8.2%; O, 5.7%; N, 9.9%; Cl, 12.5%

Found:

C, 63.6%; H, 8.3%; O, 5.8%; N, 9.9%; Cl, 12.6%

EXAMPLE 16

3-(2-n-butylaminoethoxy)indole hydrochloride.

In an analogous procedure, 3-(2-n-butylaminoethoxy)indole hydrochloride with mp. 170°–171°C was prepared in 10% yield.

EXAMPLE 17

3-(2-n-pentylaminoethoxy)indole hydrochloride.

3-(2-aminoethoxy)indole hydrogen oxalate (8 g) was dissolved in methanol (200 ml) at 60°C and a solution of sodium hydroxide (2.64 g) in methanol (50 ml) was added. The mixture was allowed to stand at 25°C for 15 minutes and the precipitated sodium oxalate was filtered off. To the filtrate was added n-valeraldehyde (2.58 g) in methanol (20 ml) at 0°–5°C in the course of 15 minutes. The reaction mixture was kept at 0°–5°C for 30 minutes and then subjected to hydrogenation in the presence of palladium/carbon (1 g of 10%) at 50–60 psi and 25°C for 2 hours. The catalyst was filtered off and the filtrate concentrated in vacuum. The resulting crystalline residue was partitioned between ethyl acetate (400 ml) and water (2 × 100 ml), and the ethyl acetate phase was dried and concentrated in vacuum. The residue was dissolved in isopropanol (160 ml), and addition of a solution of hydrogen chloride in isopropanol at 25°C, followed by cooling to 0°–5°C afforded 3-(2-n-pentylaminoethoxy) indole hydrochloride (4.9 g) with mp. 160°–161°C.

Recrystallization from ethanol (recovery: 4.1 g, 48% yield) raised the mp. to 165°–166°C.

Anal. calcd. for $C_{15}H_{23}ON_2Cl$:

C, 63.7%; H, 8.2%; O, 5.9%; N, 9.9%; Cl, 12.5%

Found:

C, 63.6%; H, 8.2%; O, 5.9%; N, 10.0%; Cl, 12.4%

In a similar manner, by substituting the appropriate aldehyde for n-valeraldehyde, the following compounds of the general formula I, in which X, Y, R^1 and R^2 are hydrogen, and A is an ethylene group, were prepared:

Example No.	R^3	Salt	Yield	Melting Point °C	Time for hydrogenation (hours)
18	$CH_3(CH_2)_3-$	HCl	40%	170–171	2
19	$(CH_3)_2CHCH_2-$	HCl	45%	189–190	2
20	$C_6H_5CH_2CH_2-$	HCl	31%	162–163	2
21	$CH_3CH_2CH_2-$	HCl	22%	198–199	2
22	$CH_3(CH_2)_6-$	HCl	30%	162–163	2

—Continued

Example No.	R^3	Salt	Yield	Melting Point °C	Time for hydrogenation (hours)
23	$(CH_3)_2CHCH_2CH_2-$	HCl	33%	181–182	2
24	$(CH_3CH_2)_2CHCH_2-$	HCl	45%	164–165	8
25	$CH_3CH_2CH_2CH(CH_3)CH_2-$	$(COOH)_2$	34%	180–181	4
26	$(CH_3)_3CCH_2-$	$(COOH)_2$	49%	177–178	6
27	$CH_3(CH_2)_5-$	HCl	45%	154–155	2
28[a]	CH_3CH_2-	HCl	38%	174–175	2

a) This compound was purified by recrystallization from isopropanol before converting it to the hydrochloride.

EXAMPLE 29

5,6-dimethoxy-3-(2-isopropylaminoethoxy)indole hydrochloride

1-acetyl-3-(2-dibenzylaminoethoxy)-5,6-dimethoxyindole was deacetylated by a procedure analogous to that of Example 1. 3-(2-dibenzylaminoethoxy)-5,6-dimethoxyindole, isolated as an oil was converted to 5,6-dimethoxy-3-(2-isopropylaminoethoxy) indole hydrochloride with mp. 197°–198°C by the method described in Example 15. Hydrogenation was complete in 7 hours and the overall yield was 15%.

The starting material, 1-acetyl-3-(2-dibenzylaminoethoxy)-5,6-dimethoxyindole, was prepared in the following manner:

6-bromoveratric acid (127 g), prepared by treated veratic acid with bromine in acetic acid, and glycine (71 g) was dissolved in water (725 ml) at 40°C and pH 10. The reaction was initiated by addition of copper powder (3.5 g). The pH was maintained at 10 by addition of a sodium hydroxide solution (6N) and the reaction temperature was kept at 40°C by cooling. After 30 minutes the reaction ceased. The reaction mixture, freed of copper powder, was added to chilled hydrochloric acid (1,000 ml of 2 N), yielding N-(carboxymethyl)-4,5-dimethoxy-anthranilic acid (114.6 g, 86%) with mp. 181°–182°C.

To a mixture of N-(carboxymethyl)-4,5-dimethoxyanthranilic acid (49 g)) in acetic anhydride (300 ml) was added tri-ethylamine (84 ml) with cooling. The solution so obtained was kept at 25°C for 1 hour and then refluxed for 30 minutes. The reaction mixture was cooled and concentrated in vacuum, leaving a residue which on treatment with ice-water (900 ml) afforded 1,3-diacetyl-5,6-dimethoxyindoxyl. This compound was dissolved in a refluxing solution of sodium sulfite (60 g) in water (1,000 ml) and ethanol (500 ml), and the solution was kept at reflux for 1½ hours. The ethanol was distilled off and from the remaining aqueous solution, chilled to 0°–5°C, crystallized 1-acetyl-5,6-dimethoxyindoxyl (26.4 g. 59% yield) with mp. 238°–242°C.

To a solution of 1-acetyl-5,6-dimethoxyindoxyl (44.7 g) and 2-dibenzylaminoethyl chloride hydrochloride (84.3 g) in DMSO (1000 ml) was cautiously added potassium carbonate (117 g). The mixture was left with stirring for 9 hours at 60°C and for another 9 hours at room temperature, followed by treatment with ice-water (5,000 ml). The resulting suspension was extracted with chlorform (2 × 1000 ml) and the chloroform extract was dried and concentrated in vacuum, leaving a residue which upon recrystallization from ethanol (275 ml) yielded 1-acetyl-3-(2-dibenzylaminoethoxy)-5,6-dimethoxyindole (45.5 g, 52.3%) with mp. 113°–115°C.

EXAMPLE 30

3(2-n-butylaminoethoxy)indole hydrochloride

1-acetyl-3-(2-(N-benzyl-N-n-butylamino)ethoxy)indole (21.2 g) was treated for 15 minutes with a refluxing solution of sodium (6.9 g) in ethanol (325 ml of 99%). The reaction mixture was chilled and added to ice-water (1,500 ml). The resulting suspension was extracted with ethyl acetate (3 × 500 ml) and the extract was dried and concentrated in vacuum. The residue, containing 3-(2-(N-benzyl-N-n-butylaminoethoxy)indole was dissolved in ethanol (300 ml of 99%), treated with charcoal (5 g) and subjected to hydrogenolysis in the presence of palladium/carbon (2 g of 10%) for 2 hours at 25°C and 50–60 psi. The catalyst was filtered off and the filtrate concentrated in vacuum. To the residue, dissolved in isopropanol (175 ml) was added hydrogen chloride in isopropanol at 35°C. After chilling to 0°–5°C, 3-(2-n-butylaminoethoxy)indole hydrochloride (12.4 g, 20% overall yield) with mp. 170°–171°C was obtained.

The intermediate, 1-acetyl-3-(2-(N-benzyl-N-n-butylamino-ethoxy)indole (mp. 44°–45°C) was pre-

pared in 36% yield by a procedure analogous to that described in Example 2.

EXAMPLE 31

3-(2-isopropylaminoethoxy)indole hydrochloride

A procedure analogous to that of the previous example was used for the preparation of 3-(2-isopropylaminoethoxy)-indole hydrochloride with mp. 188°–189°C. The overall yield was 71%. The starting material, 1-acetyl-3-(2-(N-benzyl-N-isopropylamino)ethoxy)indole, was synthesized in the following manner:

1-acetylindoxyl (40.3 g), 2-(N-benzyl-N-isopropylamino)-ethyl chloride hydrochloride (63.0 g) and potassium carbonate (95.3 g) was mixed with DMSO (350 ml). The reaction mixture was kept with stirring at 40°C for 18 hours and slowly added to ice-water (1.4 L), thus affording the crystalline 1-acetyl-3-(2-(N-benzyl-N-isopropylamino)ethoxy)indole (64.7 g) with mp. 59°–72°C. Recrystallization from isopropanol (yield: 49.6 g, 62 %) raised the mp. to 83°–85°C.

EXAMPLE 32

3-(2-isopropylaminopropoxy)indole hydrochloride

In a manner analogous to that described in Example 17, 3-(2-isopropylaminopropoxy)indole hydrochloride with mp. 225°–226°C was prepared in 47% yield.

EXAMPLE 33

3-(2-aminoethoxy)-2-methylindole hydrochloride

1-acetyl-3-(2-dibenzylaminoethoxy)-2-methylindole(10.6 g) was treated with a refluxing solution of sodium ethoxide, prepared from metallic sodium (2.9 g), in ethanol (150 ml of 99%). After cooling to room temperature and addition of ice-water (750 ml) the reaction mixture was extracted with ethyl acetate (2 × 250 ml); extract was dried and concentrated in vacuum.

The residue, consisting of 3-(2-dibenzylaminoethoxy)-2-methylindole, was dissolved in ethanol (100 ml of 99%) and subjected to hydrogenolysis in the presence of palladium/carbon (2 g of 10% at 25°C and 50–60 psi for 24 hours. The product, freed of catalyst and solvent, was dissolved in isopropanol (40 ml). Addition at 0°–5°C of a solution of hydrogen chloride in isopropanol, followed by ether (200 ml) afforded the crystalline 3-(2-aminoethoxy)-2-methylindole hydrochloride (3.5 g) with mp. 170°–175°C. Recrystallization from isopropanol gave the pure compound (2 g, 35% yield) with mp. 183°–184°C.

Anal. calcd. for $C_{11}H_{15}ON_2Cl$:

C, 58,3%; H, 6.7%; N, 12.4%; Cl, 15.6%

Found:

C, 58.2%; H, 6.9%; N, 12.2%; Cl, 15.6%

The intermediate, 1-acetyl-3-(2-dibenzylaminoethoxy)-2-methylindole was prepared in the following manner:

A mixture of 1-acetyl-2-methylindoxyl (37.6 g), 2-(dibenzylamino)ethyl chloride hydrochloride (88.2 g) and finely ground potassium carbonate (124.4 g) in DMSO (400 ml) was kept with stirring at 45°C for 24 hours. The reaction mixture was added to ice-water (2 L) and extracted with ethyl acetate (3 × 500 ml). The extract was dried and concentrated in vacuum. When a solution of the residue in isopropanol (150 ml) was chilled slowly to 0°–5°C, a crystalline precipitate of 1-acetyl-3-(2-dibenzylaminoethoxy)-2-methylindole (24 g, 29% yield) with mp. 78°–80°C was obtained. Recrystallization from isopropanol raised the mp. to 82°–83°C.

EXAMPLE 34

3-(2-isobutylaminoethoxy)-2-methylindole hydrochloride

To a solution in methanol (125 ml) of crude 3-(2-aminoethoxy)-2-methylindole, prepared from 1-acetyl-3-(2-dibenzylaminoethoxy)-2-methylindole (12.3 g) as described in Example 33, was added a solution of isobutyraldehyde (2.16 g) in methanol (20 ml) and the mixture was kept at 0°–5°C for 30 minutes. Palladium/-carbon (1 g of 10%) was added and the reaction mixture was hydrogenated at 25°C and 50–60 psi for 2 hours. Filtration from the catalyst, followed by evaporation in vacuum of the solvent left a residue which was dissolved in isopropanol (80 ml). Addition at 0°–5°C of a solution of hydrogen chloride in isopropanol gave the crystalline 3-(2-isobutylaminoethoxy)-2-methylindole hydrochloride (4.1 g) with mp. 150°–165°C. The pure compound with mp. 168°–169°C (3.5 g, 40% yield) was obtained by recrystallization from isopropanol.

Anal. calcd. for $C_{17}H_{24}ON_2Cl$:

C, 63.7%; H, 8.2%; N, 9.9%; Cl, 12.5%

Found:

C, 63.0%; H, 8.2%; N, 9.8%; Cl, 13.0%

EXAMPLE 35

3-(2-aminoethoxy)-2-phenylindole

3-(2-dibenzylaminoethoxy)-2-phenylindole (10 g), dissolved in a mixture of ethanol (200 ml) and toluene (200 ml) was subjected to hydrogenolysis in the presence of palladium/carbon (3 g of 10%) at 25°C and 50–60 psi for 18 hours.

Filtration from the catalyst, followed by evaporation in vacuum of the solvent left a residue of 3-(2-aminoethoxy)-2-phenylindole which was purified by recrystallization from toluene. The recrystallized product (2.8 g, 48% yield) had mp. 114°–115°C.

Anal. calcd. for $C_{16}H_{16}ON_2$:

C, 76.2%; H, 6.4%; N, 11.1%

C, 75.8% H, 6.7%; N, 10.9%

The intermediate, 3-(2-dibenzylaminoethoxy)-2-phenylindole, was prepared in the following manner:

A mixture of 1-acetyl-2-phenylindoxyl (50 g), 2-dibenzylaminoethyl chloride hydrochloride (88.5 g) and finely ground potassium carbonate (124.4 g) in DMSO (400 ml) was left with vigorous stirring at 60°C for 5 hours. The reaction mixture was added to ice-water (2L) and extracted with ethyl acetate (3 × 500 ml). The extract was dried and concentrated in vacuum. The residue so obtained, consisting of 1-acetyl-3-(2-dibenzylaminoethoxy)-2-phenylindole, was treated for 15 minutes with a refluxing solution of sodium ethoxide, prepared from metallic sodium (23 g), in ethanol (1 L of 99%).

When the reaction mixture was left at 0°–5°C the crystalline 3-(2-dibenzylaminoethoxy)-2-phenylindole (57 g, 71% yield) with mp. 147°–149°C was obtained.

EXAMPLE 36

3-(2-isobutylaminoethoxy)-2-phenylindole hydrochloride

To a solution of crude 3-(2-aminoethoxy)-2-phenylindole, prepared from 3-(2-dibenzylaminoethoxy)-2-phenylindole (10 g) as described in Example 35, in anhydrous methanol (150 ml) was added in the course of 15 minutes at 0°–5°C a

solution of isobutyraldehyde (1.66 g) in methanol (20 ml) and the mixture was kept at 0°–5°C for 30 minutes. The reaction mixture was then hydrogenated for 2 hours at room temperature and 50–60 psi in the presence of palladium/carbon (1 g of 10%). Filtration from the catalyst, followed by evaporation in vacuum of the solvent left a residue which was dissolved in isopropanol (140 ml). Addition at 0°–5°C of a solution of hydrogen chloride in isopropanol yielded 3-(2-isobutylaminoethoxy)-2-phenylindole hydrochloride (3.7 g) with mp. 233°–235°C. Recrystallization from ethanol (yield: 3.1 g, 44%) raised the mp. to 236°–238°C.

Anal. calcd. for $C_{20}H_{25}ON_2Cl$:
C, 69.6%; H, 7.3%; N, 8.1%; Cl, 10.3%
Found:
C, 69.2% H, 7.5%; N, 8.1%; Cl, 10.6%

EXAMPLE 37

3-(2-aminoethoxy)-6-methoxyindole

3-(2-dibenzylaminoethoxy)-6-methoxyindole (15 g), dissolved in ethanol (350 ml of 99%), was subjected to hydrogenolysis in the presence of palladium/carbon (5g of 10%) at 25°C and 50–60 psi for 7 hours.

Filtration from the catalyst, followed by evaporation in vacuum of the solvent left a crystalline residue (7g) containing 3-(2-aminoethoxy)-6-methoxyindole. A fraction (2 g) of this residue, recrystallized from isopropanol, yielded the pure compound (0.6 g, 26%) with mp. 129°–132°C. The remainder (5 g) was used in the following Example 38.

Anal. calcd. for $C_{11}H_{14}O_2N_2$:
C, 64.1%; H, 6.7%; N, 13.6%
Found:
64.0%; H, 6.9%; N, 13.5%

The starting material, 3-(2-dibenzylaminoethoxy)-6-methoxyindole, was prepared in the following manner:

A mixture of 1-acetyl-6-methoxyindoxyl (28.7 g), 2-dibenzylaminoethyl chloride hydrochloride (62.0 g) and finely ground potassium carbonate (87.0 g) in DMSO (275 ml) was stirred vigorously at 40°C for 18 hours. The reaction mixture was added to ice-water (1,250 ml) and extracted with ethyl acetate (4 × 300 ml). The extract was dried and the solvent was evaporated in vacuum, leaving a residue which was recrystallized from a mixture of ethanol (150 ml) and ethyl acetate (50 ml). The compound 1-acetyl-3-(2-dibenzylaminoethoxy)-6-methoxyindole with mp. 96°–97°C (21 g, 35% yield) so obtained was dissolved in ethanol (275 ml of 99%) containing sodium ethoxide prepared in situ from metallic sodium (5.5 g). Refluxing the solution for 15 minutes followed by chilling to 0°–5°C yielded the crystalline 3-(2-dibenzylaminoethyl)-6-methoxyindole (16.5 g, 87%) with mp. 83°–84°C.

EXAMPLE 38

3-(2-isobutylaminoethoxy)-6-methoxyindole hydrogen oxalate

The crude 3-(2-aminoethoxy)-6-methoxyindole (5 g), prepared in Example 37 above, was subjected to a reductive alkylation with isobutyraldehyde in a manner analogous to that described in Example 36, followed by filtration and evaporation of the solvent. A chilled solution of the residue in ethanol (90 ml of 99%) was added at 0°–5°C in the course of 20 minutes to a solution of oxalic acid (6.3 g) in ethanol (50 ml) and the mixture was left for 30 minutes at the same temperature. The crystalline 3-(2-isobutylaminoethoxy)-6-methoxyindole hydrogen oxalate was isolated and recrystallized from aqueous ethanol (75%). The pure compound (2.7 g, 32%) has mp. 160°–161°C.

Anal. calcd. for $C_{17}H_{24}O_6N_2$:
C, 57.9%; H, 6.9%; N, 10.0%
Found:
C, 56.9%; H, 6.7%; N, 7.8%

EXAMPLE 39

3-(2-aminoethoxy)-4-methoxyindole

3-(2-dibenzylaminoethoxy)-4-methoxyindole (17 g), dissolved in ethanol (550 ml of 99%) was hydrogenolysed in the presence of palladium/carbon (5 g of 10%) at 25°C and 50–60 psi in the course of 26 hours. Filtration from the catalyst, followed by evaporation in vacuum of the solvent left a residue (9.2 g). One half of this residue was recrystallized from isopropanol, yielding 3-(2-aminoethoxy)-4-methoxyindole (275g, 55% yield) with mp. 146°–150°C. The other half of the residue was used in the following Example 40.

Anal. calcd. for $C_{11}H_{14}N_2O_2$:
C, 64.1%; H, 6.9%; N, 13.6%
Found:
C, 64.3%; H, 7.0%; N, 13.5%

The intermediate, 3-(2-dibenzylaminoethoxy)-4-methoxyindole, was prepared in the following manner:

To a solution of 6-methoxyanthranilic acid (46.5 g) and sodium hydroxide (23.6 g) in water (100 ml) was added a solution of chloracetic acid (26.5 g) and sodium carbonate (18 g) in water (50 ml). After heating to 50°C for 6 hours, a solution of chloracetic acid (13.2 g), sodium hydroxide (6 g) and sodium carbonate (8.5 g) in water (25 ml) was added and heating was continued. The same addition was repeated after 12 hours, the reaction mixture was left at 50°C for further 10 hours, cooled and added slowly and with vigorous stirring to hydrochloric acid (275 ml of 4 N). N-carboxymethyl-6-methoxyanthranilic acid (36.1 g, 57%) with mp. 185°–186°C was isolated.

Triethylamine (52.5 ml) was added at room temperature to a solution of N-carboxymethyl-6-methoxyanthranilic acid (31.5 g) in acetic anhydride (190 ml). The reaction mixture was kept at 25°C for 1 hour and then heated to reflux temperature for an additional period of 30 minutes, followed by evaporation of the solvent. After treatment of the residue with ice-water (750 ml), the crystalline 1,3-diacetyl-4-methoxyindoxyl (31.1 g) with mp. 145°–148°C was obtained.

A solution of 1,3-diacetyl-4-methoxyindoxyl (31.1 g) in ethanol (800 ml of 96%) was added to a solution of sodium sulfite (44 g) in water (800 ml) at 50°C and the reaction mixture was kept at that temperature for 2 hours. Ethanol was stripped off and, after cooling, 1-acetyl-4-methoxyindoxyl with mp. 145°–146°C (18.5 g, 65% yield) was obtained from the remaining aqueous solution.

A mixture of 1-acetyl-4-methoxyindoxyl (13.1 g), 2-dibenzyl aminoethyl chloride hydrochloride (26.6 g) and potassium carbonate (33.2 g) in DMSO (125 ml) was stirred vigorously at 40°C for 18 hours. Ice-water (800 ml) was added and the mixture was extracted with ethyl acetate (3 × 200 ml). The reaction product was worked up in the usual manner and recrystallized from isopropanol, yielding 1-acetyl-3-(2-

dibenzylaminoethoxy)-4-methoxyindole (15 g, 58% yield) with mp. 125°–126°C.

The compound (20 g) was deacetylated in a refluxing solution of sodium ethoxide in ethanol (99%) in a manner analogous to that described in the previous examples. When the reaction mixture was cooled to room temperature and added slowly to ice-water (600 ml), 3-(2-dibenzylaminoethoxy)-4-methoxyindole crystallized. Recrystallization from isopropanol afforded the pure compound (17.1 g, 94%) with mp. 94°–95°C.

EXAMPLE 40

3-(2-isobutylaminoethoxy)-4-methoxyindole hydrogen oxalate

To a solution in methanol (100 ml) of the crude 3-(2-aminoethoxy)-4-methoxyindole (4.6 g), prepared in Example 39 above, was added isobutyraldehyde (3.2 g) and a molecular sieve (10 g of type 3A) and the reaction mixture was left at 25°C with stirring for 2 hours.

Sodium borohydride (1.7 g) was added portionwise in the course of 10 minutes and after additional 1 hour at 25°C the molecular sieve was filtered off, and the solvent evaporated in vacuum. The residue was partitioned between water (2 × 150 ml) and ethyl acetate (200 ml), the ethyl acetate phase was dried and concentrated in vacuum.

A solution of the residue in ethanol (25 ml of 99%) was added at 25°C to a solution of oxalic acid (6.0 g) in ethanol (50 ml of 99%). Chilling of the suspension to 0°–5°C yielded the crystalline 3-(2-isobutylaminoethoxy)-4-methoxyindole hydrogen oxalate (3.9 g). Recrystallization from aqueous ethanol (80%) yielded the pure compound (2.9 g, 51% yield) with mp. 151°–152°C.

Anal. calcd. for $C_{17}H_{24}N_2O_6$, H_2O:

C, 55.1%; H, 7.1%; N, 7.6%

Found:

C, 55.4%; H, 7.2%; N, 7.8%

EXAMPLE 41

3-(2-isopropylaminoethoxy)-4-methoxyindole hydrochloride

In a manner analogous to that described in Example 8, 3-(2-isopropylaminoethoxy)-4-methoxyindole hydrochloride with mp. 216°–218°C was obtained in 47% yield.

EXAMPLE 42

3-(2-ethylaminoethoxy)-4-methoxyindole hydrochloride

A procedure analogous to that of Example 30 was used for preparing 3-(2-ethylaminoethoxy)-4-methoxyindole hydrochloride with mp. 158°–160°C. The overall yield was 59%.

The starting material, 1-acetyl-3-(2-(N-benzyl-N-ethylamino)-ethoxy)-4-methoxyindole with mp. 73°–74°C in 34.5% yield was synthezised in the manner described in the same example.

EXAMPLE 43

3-(2-ethylaminoethoxy)-2-phenylindole hydrochloride

Starting from 1-acetyl-2-phenylindole, 3-(2-ethylaminoethoxy)-2-phenylindole hydrochloride with mp. 257°–259°C was prepared using procedures analogous to those described in example 31. In this example debenzylation was complete after 24 hours and the catalyst had to be exchanged after 8 hours. The overall yeild was 35%.

EXAMPLE 44

3-(2-isopropylaminoethoxy)-2-phenylindole hydrochloride

3-(2-dibenzylaminoethoxy)-2-phenylindole was converted to 3-(2-isopropylaminoethoxy)-2-phenylindole hydrochloride with mp. 207°–208°C by the method described in Example 8. The reaction was performed in toluene instead of ethanol. The yield was 45%.

EXAMPLE 45

3-(2-aminoethoxy)-2-benzylindole

2-benzyl-3-(2-dibenzylaminoethoxy)indole (4.66 g), dissolved in a mixture of toluene (50 ml) and ethanol (50 ml) was hydrogenolyzed in the presence of palladium/carbon (3 g of 10%) at 50–60 psi and 25°C in the course of about 60 hours. The catalyst was filtered off and the filtrate concentrated in vacuum. The residue was recrystallized from a 1:1 mixture of isooctane and ethyl acetate, affording 3-(2-aminoethoxy)-2-benzylindole (0.80 g, 29% yield) with mp. 113°–114°C.

Anal. calcd. for $C_{17}H_{18}N_2O$:

C, 76.7%; H, 6.8%; N, 10.5%

Found:

C, 76.3%; H, 6.6%; N, 10.4%

The starting material, 2-benzyl-3-(2-dibenzylaminoethoxy) indole, was prepared in the following manner:

o-chlorobenzoic acid (156.6 g) and phenylalanine (289 g) were heated to reflux in water (1.5 L) at pH 9. Cuprous oxide (4 g) was added, and the pH was maintained at pH 9 by addition of a sodium hydroxide solution (6 N) while the reaction mixture was kept under reflux for 8 hours. After 3 hours a further portion of cuprous oxide (4 g) was added. The reaction mixture, freed of insoluble salts, was added to chilled hydrochloric acid (800 ml of 6 N), yielding N-(1-carboxy-2-phenylethyl)anthranilic acid (204 g, 72%) with mp. 130°–140°C.

To a mixture of N-(1-carboxy-2-phenylethyl)anthranilic acid (173 g) and acetic anhydride (900 ml) was added triethylamine (180 ml) with cooling. The solution so obtained was kept at 25°C for 2 hours and refluxed for 30 minutes. The reaction mixture was cooled and concentrated in vacuum, leaving a residue which on treatment with ice-water (3 L) afforded 2-benzyl-1,3-diacetylindoxyl. A solution of this compound in ethanol (1.8 L) was added to a refluxing solution of sodium sulfite (184 g) in water (2.8 L), and reflux was continued for a further 1½ hours. From the reaction mixture, cooled to 20°C, 1-acetyl-2-benzylindoxyl (71 g, 45% yield) with mp. 115°–117°C crystallized.

To a mixture of 1-acetyl-2-benzylindoxyl (71 g), 2-(dibenzylamino)ethyl chloride hydrochloride (118 g) in DMSO (670 ml) was cautiously added potassium carbonate (147 g). The reaction mixture was left with stirring for 18 hours at 50°C, and then treated with ice-water (3.5 L). The resulting emulsion was extracted with ethyl acetate (3 × 750 ml), and the ethyl acetate extract was dried and concentrated in vacuum, leaving 1-acetyl-2-benzyl-3-(2-dibenzylaminoethoxy)indole as an oil. This compound was treated for 30 minutes with a refluxing solution of sodium ethoxide, prepared from sodium (18.5 g) in ethanol (1.4 L, 99%). The reaction

mixture was cooled to 10°–20°C and added to water (6.5 L). The resulting emulsion was extracted with ethyl acetate (3 × 1 L) and the ethyl acetate was dried and concentrated in vacuum, leaving a residue, which after recrystallization from a mixture of isooctane (1.8 L) and benzene (0.6 L) yielded 2-benzyl-3-(2-dibenzylaminoethoxy)indole (43 g) with mp. 96°–98°C. The over-all yield was 36%.

EXAMPLE 46

2-benzyl-3-(2-isopropylaminoethoxy)indole hydrochloride

2-benzyl-3-(2-dibenzylaminoethoxy)indole (18.6 g), dissolved in toluene (150 ml), ethanol (150 ml) and acetone (50 ml) was subjected to hydrogenation in the presence of palladium/carbon (6 g of 10%) at 50–60 psi and 25°C for 60 hours. The catalyst was filtered off, and the filtrate concentrated in vacuum. The resulting residue was dissolved in isopropanol and converted at 0°–5°C into the crystalline 2-benzyl-3-(2-isopropylaminoethoxy)indole hydrochloride (9.9 g) with mp. 204°–205°C. Recrystallization from ethanol raised the mp. to 211°C. The yield was 5.8g(40%).

Anal. calcd. for $C_{20}H_{25}Cl\ N_2O$:

C, 69.6%; H, 7.3%; Cl, 10.3%; N, 8.1%

Found:

C, 69.6%; H, 7.3%; Cl, 10.5%; N, 8.1%

EXAMPLE 47

1-benzyl-3-(2-isopropylaminoethoxy)indole hydrochloride

1-acetyl-3-(2-(N-benzyl-N-isopropylamino)ethoxy)indole (59.5 g) was deacetylated by the procedure described in Example 30.

The crude 3-(2-(N-benzyl-N-isopropylamino)ethoxy)indole was dissolved in dimethylformamide, DMF, (500 ml) and the solution was concentrated in vacuum. The residue dissolved in DMF (500 ml) was added in the course of 15 minutes at 25°C to a stirred suspension of sodium hydride (8.6 g of a 50% suspension in mineral oil) in DMF (250 ml). The reaction mixture was left with stirring at 25°C for 2 hours and benzyl chloride (22.8 g) dissolved in DMF (30 ml) was added in the course of 15 minutes. The reaction mixture was kept at 25°C for another hour and then poured into ice-water (5 L). The resulting emulsion was extracted with ethyl acetate (3 × 750 ml) and the ethyl acetate extract was concentrated in vacuum. The residue containing 1-benzyl-3-(2-(N-benzyl-N-isopropylamino)ethoxy)indole was dissolved in ethanol (400 ml of 99%), treated with charcoal (7 g) and then subjected to hydrogenolysis in the presence of palladium/carbon (10 g of 10%) at 50–60 psi and 25°C for 10 hours. The catalyst was filtered off and to the filtrate, concentrated in vacuum to about 200 ml, was added a solution of hydrogen chloride at 60°C. After chilling to 0°–5°C, 1-benzyl-3-(2-isopropylaminoethoxy)indole hydrochloride (36 g, 61% over-all yield) with mp. 199°–200°C was obtained.

Anal. calcd. for $C_{20}H_{25}Cl\ N_2O$:

C, 69.6%; H, 7.3%; Cl, 10.3%; N, 8.1%

Found:

C, 69.8%; H, 7.2%; Cl, 10.4%; N, 8.3%

EXAMPLE 48

1-benzyl-3-(2-isopropylaminoethoxy)-2-phenylindole hydrochloride

3-(2-(N-benzyl-N-isopropylamino)ethoxy-2-phenylindole (28.3 g) was converted to 1-benzyl-3-(2-(N-benzyl-N-isopropylamino)ethoxy)-2-phenylindole by a procedure analogous to that of the previous example. The latter compound, recrystallized from ethanol, was dissolved in toluene (120 ml) and ethanol (240 ml) and hydrogenolyzed in the presence of palladium/carbon (4 g of 10%) at 25°C and 50–60 psi for 5 hours. The catalyst was filtered off and the filtrate concentrated in vacuum. To the residue, dissolved in isopropanol, was added a solution of hydrogen chloride in isopropanol at 0°–5°C, and 1-benzyl-3-(2-isopropylaminoethoxy)-2-phenylindole hydrochloride (26.8 g) with mp. 188°–189°C was obtained. Recrystallization from ethanol raised the mp. to 193°C. The over-all yield was 22.7 g (73%).

Anal. calcd. for $C_{26}H_{29}Cl\ N_2O$:

C, 74.2%; H, 7.0%; Cl, 8.4%; N, 6.7%

Found:

C, 74.0%; H, 7.0 %; Cl, 8.4%; N, 6.7%

The starting material, 3-(2-(N-benzyl-N-isopropylamino) ethoxy)-2-phenylindole with mp. 112°–114°C, was prepared in the manner described in Example 31. The yield was 79% starting from 1-acetyl-2-phenylindole.

EXAMPLE 49

3-(2-isopropylaminoethoxy)-4-methoxyindole hydrochloride

In a manner similar to that described in Example 30, 3-(2-isopropylaminoethoxy)-4-methoxyindole hydrochloride with mp. 218°C was prepared in 69% yield.

The starting material, 1-acetyl-3-(2-(N-benzyl-N-isopropylamino)ethoxy)-4-methoxyindole, was prepared in the following manner:

To a mixture of 1-acetyl-4-methoxyindoxyl (15.3 g) and 2-(N-benzyl-N-isopropylamino)ethyl chloride hydrochloride (27.9g) in DMSO (150 ml) was cautiously added potassium carbonate (41.5 g). The reaction mixture was left with stirring for 18 hours at 50°C and then poured into ice-water (600 ml). The resulting emulsion was extracted with ethyl acetate (3 × 200 ml), and the extract was dried and concentrated in vacuum. The residue so obtained yielded, after trituration with isopropanol, 1-acetyl-3-(2-(N-benzyl-N-isopropylamino)ethoxy)-4-methoxyindole (24 g, 74%) with mp. 104°–105°C.

EXAMPLE 50

1-benzyl-3-(2-isopropylaminoethoxy)-4-methoxyindole hydrochloride

1-acetyl-3-(2-(N-benzyl-N-isopropylamino)ethoxy)-4-methoxyindole (20.0 g) was converted to 1-benzyl-3-(2-(N-benzyl-N-isopropylamino)ethoxy-4-methoxyindole by procedure analogous to those described in Example 47. The latter compound, isolated as an oil, was dissolved in a mixture of toluene (100 ml) and ethanol (200 ml), treated with charcoal (4 g) and then subjected to hydrogenolysis in the presence of palladium/carbon (3 g of 10%) at 50–60 psi and 25°C for 18 hours. The catalyst was filtered off, and the filtrate concentrated in vacuum. To the residue, dissolved in isopropanol, was added a solution of hydrogen chloride in isopropanol at 20°–30°C. After chilling to 0°–5°C, 1-benzyl-3-(2-isopropylaminoethoxy)-4-methoxyindole hydrochloride (15.4 g) with mp. 181°–183°C was obtained. The over-all yield was 80%.

Anal. calcd. for $C_{21}H_{27}Cl\ N_2O_2$:
C, 67.3%; H, 7.3%; Cl, 9.5%; N, 7.5%
Found:
C, 66.9%; H, 7.3%; Cl, 9.7%; N, 7.4%

EXAMPLE 51

1-benzyl-3-(2-isopropylaminoethoxy)-2-methylindole hydrochloride

A mixture of 1-acetyl-2-methylindoxyl (25.5 g), 2-(N-benzyl-N-isopropylamino)ethyl chloride hydrochloride (50.5 g) and potassium carbonate (74.5 g) in DMSO (250 ml) was kept with stirring at 50°C for 10 hours. The reaction mixture was worked up as described in Example 45, affording 1-acetyl-3-(2-(N-benzyl-N-isopropylamino)ethoxy)-2-methylindole, which was converted to 1-benzyl-3-(2-(N-benzyl-N-isopropylamino)ethoxy)-2-methylindole by procedure analogous to those described in Example 47. The latter compound, isolated as an oil, was dissolved in ethanol (250 ml of 99%), treated with charcoal (5 g) and hydrogenolyzed in the presence of palladium/carbon (5 g of 10%) at 50–60 psi and 25°C for 24 hours. The catalyst was replaced by a fresh portion (3 g) and hydrogenolysis was continued for an addition period of 6 hours. The reaction mixture was worked up as described in the previous example and yielded, after recrystallization from isopropanol, 1-benzyl-3 -(2-isopropylaminoethoxy)-2-methylindole hydrochloride (9.6 g, 40% over-all yield) with mp. 169°–170°C.
Anal. calcd. for $C_{21}H_{27}Cl\ N_2O$:
C, 70.3%; H, 7.6%; Cl, 9.9%; N, 7.8%
Found:
C, 70.2%; H, 7.5%; Cl, 10.1%;N, 7.7%

EXAMPLE 52

1-η-butyl-3-(2-isopropylaminoethoxy)indole hydrochloride

3-(2-(N-benzyl-N-isopropylamino)ethoxy)indole (20 g) was alkylated with η-butyl bromide by the procedure described in Example 47. The product, 3-(2-(N-benzyl-N-isopropylamino)ethoxy)-1-η-butylindole, isolated as an oil, was dissolved in a mixture of toluene (100 ml) and ethanol (100 ml of 99%), treated with charcoal (3 g) and hydrogenolyzed in the presence of palladium/carbon (3 g of 10%) at 50–60 psi and 25°C for 13 hours. The catalyst was filtered off and the filtrate concentrated in vacuum. The residue was dissolved in isopropanol, and to the solution was added a solution of hydrogen chloride in isopropanol at 20°–30°C. After chilling to 0°–5°C, 1-η-butyl-3-(2-isopropylaminoethoxy)indole hydrochloride (11.9 g) with mp. 143°–144°C was obtained. Recrystallization from isopropanol afforded 10.3 g of the compound with mp. 143°–144°C. The over-all yield was 50%.
Anal. calcd. for $C_{17}H_{27}Cl\ N_2O$:
C, 65.7%; H, 8.8%; Cl, 11.4%; N, 9.0%
Found:
C, 65.8%; H, 8.5%; Cl, 11.5%; N, 9.0%

EXAMPLE 53

1-benzyl-3-(2-isopropylaminoethoxy)-5-methoxyindole hydrochloride

1-acetyl-3-(2-(N-benzyl-N-isopropylamino)ethoxy)-5-methoxyindole (50.5 g) was converted to 1-benzyl-3-(2-(N-benzyl-N-isopropylamino)ethoxy)-5-methoxyindole as described in Example 47. The latter compound was subjected to hydrogenolysis for 3 hours by the procedure described in the previous example, yielding 1-benzyl-3-(2-isopropylaminoethoxy)-5-methoxyindole hydrochloride (33.4 g, over-all yield 75%) with mp. 144°–145°C.
Anal. calcd. for $C_{21}H_{27}Cl\ N_2O$:
C, 67.3%; H, 7.3%; Cl, 9.5%; N, 7.5%
Found:
C, 67.6 %; H, 7.3%; Cl, 9.6%; N, 7.5%

The starting material, 1-acetyl-3-(2-(N-benzyl-N-isopropylamino)ethoxy)-5-methoxyindole with mp. 108°–110°C was prepared in 80% yield in a manner analogous to that described in Example 49. The reaction time was 10 hours.

EXAMPLE 54

3-(2-aminoethoxy)-5-methoxy-1-methylindole hydrochloride

3-(2-dibenzylaminoethoxy)-5-methoxy-1-methylindole hydrochloride (10 g) was treated with a solution of sodium hydroxide (50 ml of 1 N) and the resulting emulsion was extracted with chloroform (2 × 50 ml). The chloroform extract was dried and concentrated in vacuum. The residue dissolved in ethanol (200 ml of 99%) was hydrogenolized in the presence of palladium/carbon (3 g of 10%) at 50–60 psi and 25°C for 10–18 hours. The reaction mixture worked up as described in Example 52, yielded 3-(2-aminoethoxy)-5-methoxy-1-methylindole hydrochloride (3.5 g, 59%) with mp. 157°–158°C.
Anal. calcd. for $C_{12}H_{17}Cl\ N_2O_2$:
C, 56.2%; H, 6.7%; Cl, 13.8%; N, 10.9%; O, 12.5%
Found:
C, 56.1%; H, 6.7%; Cl, 13.7%; N, 10.8%; O, 12.7%
3-(2-dibenzylaminoethoxy)-5-methoxy-1-methylindole hydrochloride with mp. 177°–178°C was prepared as described in Example 47. The yield was 65%.

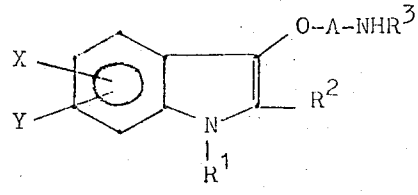
EXAMPLE 55

3-(2-aminoethoxy)-1-benzylindole hydrochloride

3-(2-aminoethoxy)-1-benzylindole hydrochloride with mp. 166°–167°C and 1-benzyl-3-(2-dibenzylaminoethoxy)indole hydrochloride with mp. 156°–157°C was prepared by procedures analogous to those of the previous example in 15% and 89%, respectively.

We claim:

1. An indole compound having the structure:



I

and the salts thereof with physiologically acceptable acids, in which

each of X and Y is selected from the group consisting of hydrogen, hydroxy, lower alkyl having 1–3 carbon atoms and lower alkoxy having 1–3 carbon atoms,

R^1 is selected from the group consisting of hydrogen, lower alkyl having 1–4 carbon atoms and benzyl,

R^2 is selected from the group consisting of hydrogen, lower alkyl having 1–4 carbon atoms, benzyl and phenyl,

R^3 is selected from the group consisting of hydrogen, lower alkyl having 1–8 carbon atoms, cycloalkyl having 5 or 6 carbon atoms, benzyl and 2-phenylethyl, and

A is a straight or branched alkylene chain containing from 2 to 4 carbon atoms.

2. The hydrochloride of a compound according to claim **1.**

3. The oxalate of a derivative according to claim **1.**

4. A compound according to claim **1,** namely, 3-(2-isopropylaminoethoxy)-indole-hydrochloride.

5. A compound according to claim **1,** namely, 3-(2-isopropylaminoethoxy)-4-methoxy-indole-hydrochloride.

6. A compound according to claim **1,** namely, 1-benzyl-3-(2-isopropylaminoethoxy)-indole-hydrochloride.

7. A compound according to claim **1,** namely, 1-benzyl-3-(2-isopropylaminoethoxy)-indole-hydrochloride.

8. A compound according to claim **1,** namely, 1-benzyl-3-(2-isopropylaminoethoxy)-2-phenyl-indole hydrochloride.

9. A compound according to claim **1,** namely, 1-benzyl-3-(2-isopropylaminoethoxy)-4-methoxy-indolehydrochloride.

10. A compound according to claim **1,** namely, 1-benzyl-3-(2-isopropylaminoethoxy)-5-methoxy-indolehydrochloride.

* * * * *

UNITED STATES PATENT OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 3,860,609

DATED : January 14, 1975

INVENTOR(S) : Behrend Friedrich Lundt

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

On the caption page, at [75], "Lyngby" should read --Søborg--
On the caption page, at [63], "May 20, 1970" should read --November 23, 1971--
On the caption page at [30], "May 27, 1970" should read --May 27, 1969--

In the specification:
Column 1, lines 5-6, "May 20, 1970" should read --November 23, 1971--
Column 1, line 64, "R_2" should read --R^2--
Column 4, line 30, "ED_{50}" should read --LD_{50}--
Column 4, lines 50-51, "propounced" should read --pronounced--
Column 4, Table I, third line from bottom of page, "1 hydrochloride" should read --hydrochloride--
Column 5, Table I, fourth line from end of Table, "hydrochloride 52" should read --hydrochloride--. The number "52" should appear in the "Anti-inflammatory...." column.
Column 5, Table II, sixth line of table, "-isopropylaminoethoxy)5-" should read -- -isopropylaminoethoxy)-5- --
Column 7, Example 2, second line, "-5-" should read --)-5 --
Column 8, Example 4, line 32, "))-5" should read --)-5 --
Column 12, Example 17, line 41, "0, 5.9%" should read --0, 5.7%--
Column 13, Example 29, line 45, "treated" should read --treating--
Column 13, Example 29, line 46, "veratic" should read --veratric--
Column 15, Example 33, line 42, "10%" should read --10%)--
Column 15, Example 33, line 52, "58,3%" should read --58.3%--
Column 16, Example 35, lines 41-42, "C, 75.8% H," should read --Found: C, 75.8%; H, --
Column 17, Example 37, line 54, "dibenzylaminoethyl" should read --dibenzylaminoethoxy--
Column 18, Example 39, line 21, "146-150" should read --147-150--
Column 24, line 47, "We claim" should read --I claim--
Column 25, Claim 3, "derivative" should read --compound--

Signed and Sealed this

fourteenth **Day of** *October 1975*

[SEAL]

Attest:

RUTH C. MASON
Attesting Officer

C. MARSHALL DANN
Commissioner of Patents and Trademarks