

1

3,472,870

SULFONAMIDOTRYPTAMINES

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9 Claims

ABSTRACT OF THE DISCLOSURE

Tryptamines and N-substituted tryptamines bearing a sulfonamide substituent in the 4, 5, 6 or 7 positions of the indole ring have hypotensive, intestinal relaxant, and central nervous system depressant activity.

Tryptamine has been known for many years as a biological product involved in the intermediary metabolism of proteins, specifically of the amino acid tryptophan. One of the identified functions of tryptamine is an intermediate in formation by the animal organism of biologically active hydroxylated derivatives such as serotonin. The present invention provides a novel group of biologically active compounds having structures resembling tryptamine.

The compounds of this invention are represented by Formula I which appears below. The sulfonamide function illustrated by $R^5SO_2N-R^6$ occupies either the 4-, 5-, 6-, or 7-positions R^1 is hydrogen, benzyl, or lower alkyl having up to 4 carbon atoms R^2 is hydrogen, lower alkyl having up to 4 carbon atoms, or carboxyl.

The symbol



refers to an N-substituted heterocyclic group having up to 7 carbon atoms, an N-substituted heteropolycyclic group having up to 11 carbon atoms, or an amino group in which R^3 and R^4 may be the same or different. Morpholino, pyrrolidino, piperazino, tetrahydroquinolino, and tetrahydroquinazolino are representative of heterocyclic and heteropolycyclic groups. R^3 is hydrogen, benzyl, or lower alkyl, or lower alkenyl of up to 4 carbon atoms. R^4 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkenyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, polycycloalkyl, polycycloalkenyl, polycycloalkylalkyl, polycycloalkenylalkyl, aryl, aralkyl, aralkenyl, aryloxyalkyl, heterocyclic, heterocycloalkyl, heteropolycyclic, or heteropolycycloalkyl, each containing up to 12 carbon atoms, and having up to two substituents selected from hydroxyl, carboxyl, amino, lower alkoxy having up to 4 carbon atoms, lower alkyl having up to 4 carbon atoms, and methylenedioxy.

R^5 is alkyl, alkenyl, cycloalkyl, or cycloalkenyl each having up to 6 carbon atoms, phenyl, phenylalkyl, naphthyl, substituted phenyl, substituted phenylalkyl, or substituted naphthyl, wherein said substituent is alkoxy, alkyl, alkenyl, cycloalkyl, or cycloalkenyl having up to 6 carbon atoms, halogen, or benzyloxy. R^6 is hydrogen or lower alkyl having up to 4 carbon atoms.

Alk is an alkylene group of 2 to 6 carbon atoms with at least 2 carbon atoms separating the indole ring and the aminonitrogen substituent



Alk may be straight or branched.

2

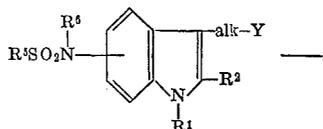
The compounds identified by Formula I possess hypotensive, central nervous system depressant, and smooth muscle depressant properties. They are relatively non-toxic, having acute toxicities for mice in the range of 250 to more than 2000 mg./kg. by the intraperitoneal and oral routes. Their pharmacologic effects are, however, elicited in doses below the toxic limit. They are preferably administered by the parenteral routes, although absorption thereof from the alimentary canal following oral or rectal administration is possible.

The process for the preparation of the compounds of Formula I involves the unitary concept of reduction or hydrolyzing a functional side chain in the 3-position of an indole containing a sulfonamido group ($R^5SO_2N-R^6$) in the 4-, 5-, 6-, or 7-positions. The functional chain in the 3-position is so constituted as to provide an aminoalkyl group,

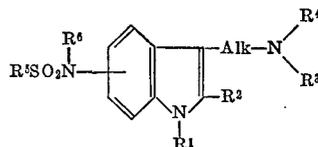


of the character shown in Formula I on reduction by chemical or catalytic means, or hydrolysis. Reducible side chains include cyanoalkyl, nitroalkenyl, oxamyl, and acylalkyl. Carboxamido alkyl side chains are contemplated for use in the hydrolytic variation. The process concept is illustrated in the following diagram.

Generalized Reaction Scheme

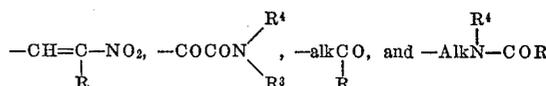


FORMULA II



FORMULA I

In Formula II, -alk-Y signifies $-CH_2CN$,



wherein R is lower alkyl and the other symbols have the meaning already assigned.

In those applications of this process employing the cyanoalkyl, nitroalkenyl, or oxamyl intermediates, chemical or catalytic reduction methods known for the transformation of nitriles, nitro compounds, and carboxamides to amines are applicable. Catalytic methods employ either noble metal or Raney nickel catalysts. Platinum oxide catalyst is quite appropriate in low pressure (15-60 p.s.i.) hydrogenations. In the case of the acylalkyl intermediates, catalytic reduction employing preferably a platinum catalyst is employed and the process is carried out in the presence of a primary amine under the conditions ordinarily used for the preparation of secondary amines by reductive alkylation. Chemical reduction methods use any of a variety of reagents known to the art for this purpose, but the hydrides such as lithium aluminum hydride and diborane are the most convenient for small scale work.

For simplicity of illustration, the description of the synthesis of specific compounds of the present invention is subdivided according to the method used for synthesis of the intermediates of Formula II. Five general methods

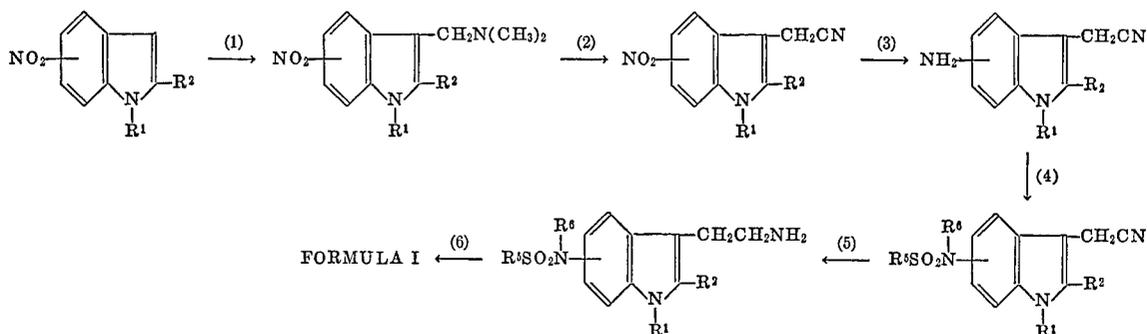
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are employed to prepare the intermediates. These methods are shown below in schematic fashion and illustrated by specific working examples which follow. They are the gramine synthesis (Reactions 1-6), the Vilsmeier aldehyde synthesis (Reactions 7-10), the oxamyl method

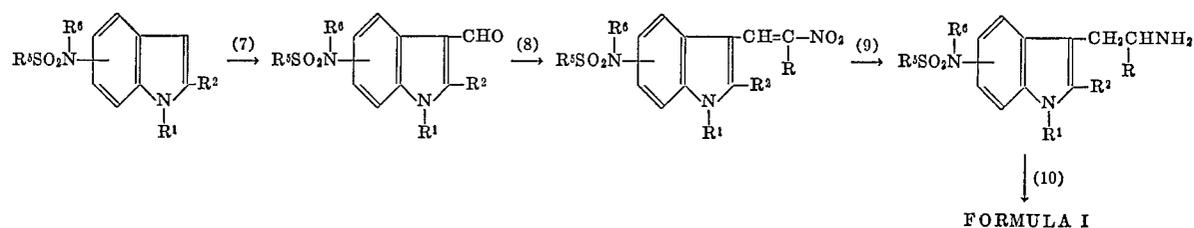
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(Reactions 11-15), reductive alkylation (Reactions 16-19), and the Fisher indole synthesis (Reactions 20-25). The first four methods involve reduction variations of the generalized scheme. The Fischer synthesis employs a hydrolytic final stage.

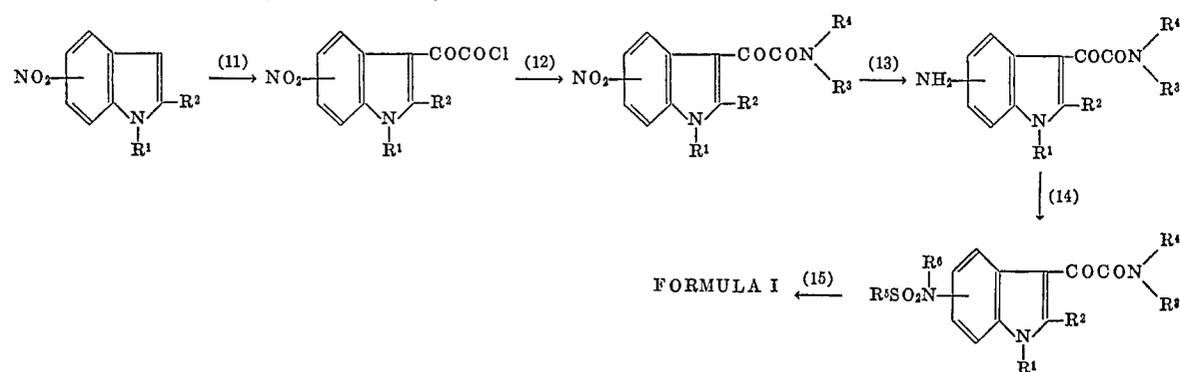
GRAMINE SYNTHESIS (Reactions 1-6)



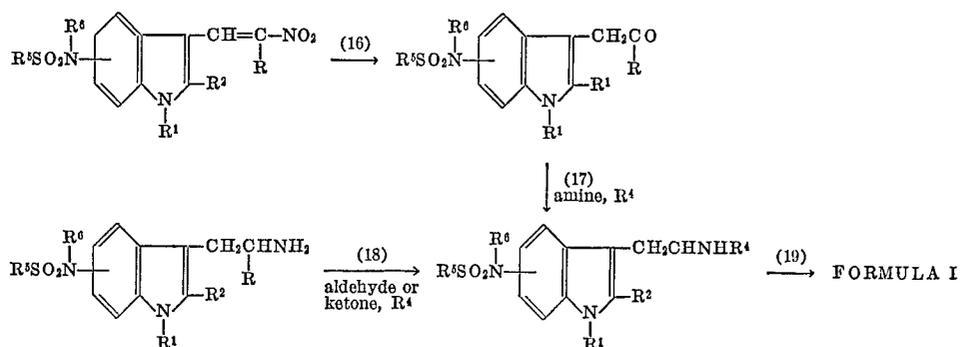
VILSMEIER ALDEHYDE SYNTHESIS (Reactions 7-10)

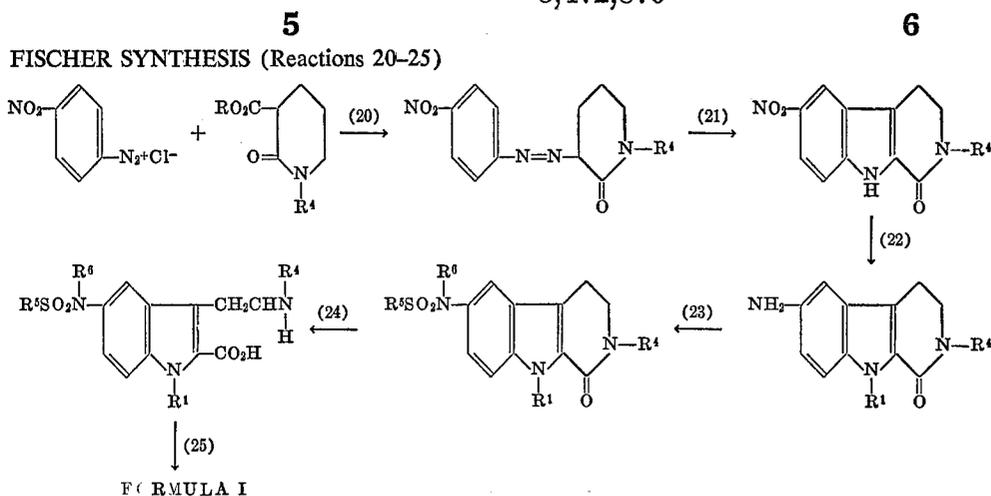


OXAMYL SYNTHESIS (Reactions 11-15)



REDUCTIVE ALKYLATION (Reactions 16-19)





In the foregoing reaction diagrams, Reactions 5, 9, 15, and 17 are representative of reduction methods conforming to the generalized reaction scheme illustrating the unitary process concept. Reaction 24 is illustrative of a hydrolytic method. Reactions 6, 10, 18, 19, and 25 are alternative supplementary steps for the conversion of primary or secondary amines of the present invention (Formula I wherein R^3 and/or R^4 are hydrogen) into secondary or tertiary amines by reductive alkylation (Reaction 18) or reaction with an appropriate R^3 or R^4 halide or other reactive ester suitable for the introduction of other R^3 and R^4 groups as defined for Formula I according to known methods for the alkylation of amines. The following examples are arranged to particularly describe the methods of the foregoing diagrams as follows.

Gramine Synthesis—Example 1-25.

Vilsmeier Aldehyde Synthesis—Example 26.

Oxamyl Synthesis—Examples 27-43.

Reductive Alkylation—Examples 44-74.

Fischer Synthesis—Examples 75-83.

EXAMPLE 1

3-(2'-aminoethyl)-5-methanesulfonamidoindole methanesulfonate

(a) 5-methanesulfonamidoindoleacetonitrile. — 5-aminoindole-3-acetonitrile is prepared by the reaction sequence 5-nitroindole, 5-nitrogramine, 5-nitroindole-3-acetonitrile, and thence hydrogenation of a solution of 13.7 g. (0.068 mole) of the latter in 150 ml. of ethanol at room temperature over 0.2 g. of platinum oxide catalyst at 60 p.s.i. 5-aminoindole-3-acetonitrile is obtained in 88% yield, M.P. 129-135° C. To a cooled solution of 13.2 g. (0.077 mole) of the 5-aminoindole-3-acetonitrile in 25 ml. of pyridine there is added dropwise with stirring 8.9 g. (0.077 mole) of methanesulfonyl chloride. The reaction mixture is stirred at room temperature for 3 hrs. and then warmed to 65-70° C. for 15 min. The product is recovered by pouring the reaction mixture into 500 ml. of ice water and collecting the precipitate on a filter. It is washed with water, dissolved in 10% aqueous sodium hydroxide, and reprecipitated by acidification with hydrochloric acid, yield, 10.8 g. (57%), M.P. 157-158° C. An analytical sample prepared by recrystallization from isopropanol exhibited melting point 157-159° C.

Analysis.—Calcd. for $C_{11}H_{11}N_3O_2S$: C, 53.00; H, 4.45; N, 16.86; S, 12.86. Found: C, 52.94; H, 4.68; N, 16.61; S, 12.91.

(b) Hydride reduction.—A solution of 5.0 g. (0.02 mole) of 5-methanesulfonamidoindole-3-acetonitrile in 50 ml. of dry tetrahydrofuran is added in dropwise fashion to a stirred mixture of 2.3 g. (0.06 mole) of lithium aluminum hydride in 75 ml. of dry tetrahydrofuran. The mixture is refluxed for a period of 2 hrs. and then stirred

overnight at room temperature. A solution of 4.6 ml. of water and 10 ml. of tetrahydrofuran is then added to decompose the excess lithium aluminum hydride and the reaction complex. The mixture is filtered and the filtrate concentrated by distillation at reduced pressure. The residue is dissolved in boiling ethanol, insoluble material filtered, and the filtrate concentrated at reduced pressure. The residue is further purified by trituration with isopropyl ether to yield the product weighing 5 g., M.P. 77-95° C. This material is dissolved in methanol and acidified with methanesulfonic acid to provide 2.4 g. (35%) of the methanesulfonate salt of the desired product, M.P. 229-235° C. (dec.). This material is recrystallized from hot methanol which is acidified with methanesulfonic acid, M.P. 235-237° C. (dec.).

Analysis.—Calcd. for $C_{11}H_{15}N_3O_2S \cdot CH_3SO_3H$: C, 41.25; H, 5.48; N, 12.02; S, 18.35. Found: C, 41.18; H, 5.71; N, 11.79; S, 18.06.

EXAMPLE 2

3-(2'-aminoethyl)-6-methanesulfonamidoindole hydrochloride

The method of Example 1(a) is applied to 6-nitroindole to provide 6-methanesulfonamidoindoleacetonitrile in 60% yield, M.P. 132-134° C. after recrystallization from isopropyl alcohol.

Analysis.—Calcd. for $C_{11}H_{11}N_3O_2S$: C, 53.00; H, 4.45; N, 16.86; S, 12.86. Found: C, 52.92; H, 4.68; N, 16.81; S, 13.05. This material is then reduced to 3-(2'-aminoethyl)-6-methanesulfonamidoindole as described in Example 1(b). In this instance the hydrochloride salt is prepared by treatment of the crude product with an ethanolic solution of hydrogen chloride. The product is obtained in 51% yield, which is purified for analysis by recrystallization from methanol-isopropyl ether mixture, M.P. 218-220° C.

Analysis.—Calcd. for $C_{11}H_{15}N_3O_2S \cdot HCl$: C, 45.59; H, 5.57; S, 11.06. Found: C, 45.72; H, 5.68; S, 11.30.

In this preparation the intermediate 6-nitrogramine may alternatively be prepared by nitration of gramine according to the method of Hester, J. Org. Chem. 29, 1158 (1964). 4-Nitrogramine is also obtained by this nitration method.

EXAMPLE 3

3-(2'-aminoethyl)-4-methanesulfonamidoindole hydrochloride

4-nitrogramine is prepared according to the method of Hester, loc. cit., and converted to 4-nitroindole-3-acetonitrile, which is then hydrogenated and mesylated as described in Example 1(a), yielding 4-methanesulfonamidoindoleacetonitrile in 69% yield, M.P. 210-214° C. (dec.). This material is then reduced as described in Example 1(b) to provide the desired product in 16% yield, M.P.

234–236° C. (dec.) after recrystallization from methanolisopropyl ether.

Analysis.—Calcd. for $C_{11}H_{15}N_3O_2S \cdot HCl$: C, 45.59; H, 5.57; N, 14.49; S, 10.82. Found: C, 45.85; H, 5.73; N, 14.24; S, 10.82.

EXAMPLES 4–9

The procedure of Example 1(a) is applied to the following nitroindoles to provide, after reduction of the corresponding methanesulfonamidoindole acetonitrile intermediates according to Example 1(b), the 3-(2'-aminoethyl)-substituted-indole products listed in the following table.

TABLE I.—3-(2'-AMINOETHYL) SUBSTITUTED INDOLES

Example No:	Starting Material	Product Substituents
4.....	7-nitroindole.....	7-methanesulfonamido.
5.....	2-methyl-6-nitroindole.....	6-methanesulfonamido-2-methyl.
6.....	2-methyl-5-nitroindole.....	5-methanesulfonamido-2-methyl.
7.....	2-methyl-7-nitroindole.....	7-methanesulfonamido-2-methyl.
8.....	2-(n-butyl)-5-nitroindole.....	2-(n-butyl)-5-methanesulfonamido.
9.....	2-(n-propyl)-6-nitroindole.....	6-methanesulfonamido-2-(n-propyl).

EXAMPLES 10–24

The procedure of Example 1(a) is repeated substituting various R^5 -sulfonyl halides and anhydrides for the methanesulfonyl chloride specified in that example. The resulting 5- R^5 -sulfonamidoindoleacetonitriles are then reduced by the method of Example 1(b) to the corresponding 3-(2'-aminoethyl)-5- R^5 -sulfonamidoindoles (Formula I) listed in the table.

TABLE II.—3-(2'-AMINOETHYL)-5- R^5 -SULFONAMIDOINDOLE

Example No.:	Starting Material	R^5 -Substituent of Product
10.....	Hexanesulfonyl chloride.....	Hexyl.
11.....	Benzenesulfonyl chloride.....	Phenyl.
12.....	p-Toluenesulfonyl chloride.....	p-Tolyl.
13.....	O-Chlorobenzenesulfonyl chloride.....	o-Chlorophenyl.
14.....	m-Bromobenzenesulfonyl bromide.....	m-Bromophenyl.
15.....	p-Fluorobenzenesulfonyl chloride.....	p-Fluorophenyl.
16.....	p-Methoxybenzenesulfonyl chloride.....	p-Methoxyphenyl.
17.....	α -Naphthylenesulfonyl chloride.....	α -Naphthyl.
18.....	2-Methoxynaphthylene-7-sulfonyl chloride.....	2-methoxy-7-naphthyl.
19.....	2,5-dimethylbenzenesulfonyl chloride.....	2,5-dimethylphenyl.
20.....	2,5-dichlorobenzenesulfonyl chloride.....	2,5-dichlorophenyl.
21.....	Methanesulfonic anhydride.....	Methyl.
22.....	m-Benzoyloxybenzenesulfonyl bromide.....	m-Benzoyloxyphenyl.
23.....	p-Ethylbenzenesulfonyl chloride.....	p-Ethylphenyl.
24.....	Cyclohexanesulfonyl chloride.....	Cyclohexyl.

EXAMPLE 25

3-(2'-aminoethyl)-5-(N-methylmethanesulfonamido)-indole

5-methanesulfonamidoindole - 3 - acetonitrile, 7.8 g. (0.031 mole), is dissolved in ethanolic sodium hydroxide solution prepared by diluting 3.5 ml. of 9.15 N sodium hydroxide with 250 ml. of ethanol. A solution of 4.0 ml. (0.062 mole) of methyl iodide in 25 ml. of ethanol is then added in dropwise fashion with stirring at room temperature. The mixture is stirred at room temperature for 4 hrs. and then the solvent removed by distillation at reduced pressure. The residue is triturated with water and the solid product, 5-(N-methylmethanesulfonamido)indole-3-acetonitrile, is collected, yield, 6.5 g. (80%). This material is twice recrystallized from isopropanol to yield the purified intermediate, M.P. 144–146° C.

Analysis.—Calcd. for $C_{12}H_{13}N_3O_2S$: C, 54.73; H, 4.98; N, 15.96; S, 12.18. Found: C, 54.54; H, 5.28; N, 16.02; S, 12.39. This material is then reduced with lithium alu-

minum hydride according to the method of Example 1(b) to provide the desired product.

By substitution of diethyl sulfate, n-propyl chloride, or n-butyl bromide for methyl iodide in Example 25, corresponding 3-(2'-aminoethyl)-5-[N-(ethyl, n-propyl, or n-butyl)methanesulfonamido]indoles are obtained.

EXAMPLE 26

3-(2'-aminopropyl)-5-methanesulfonamidoindole hydrochloride

(a) 5-methanesulfonamidoindole-3-carboxaldehyde. — The Vilsmeier reagent is prepared by cooling 20 ml. of

dimethylformamide in an ice-salt bath and then adding 5.0 ml. (0.054 mole) of phosphorous oxychloride in dropwise fashion with stirring during a 15 min. period. A solution of 10.0 g. (0.048 mole) of 5-methanesulfonamidoindole in 15 ml. of dimethylformamide is then added in dropwise fashion during a period of 1 hr. Excess reagent and reaction complex is then hydrolyzed by treatment with a solution of 22 g. (0.054 mole) of sodium hydroxide in 50 ml. of water after the addition of crushed ice to the

reaction mixture. The resulting solution is heated to boiling, cooled to room temperature, acidified with concentrated hydrochloric acid, and the resulting precipitate collected on a filter and washed with water; yield, 8.4 g. (66%), M.P. 215–217° C. (dec.). A portion recrystallized from ethanol for analysis melted at 219–221° C. (dec.).

Analysis.—calcd. for $C_{10}H_{10}N_2O_3S$: C, 50.41; H, 4.23; N, 11.76; S, 13.46. Found: C, 50.69; H, 4.50; N, 11.60; S, 13.31.

(b) 5 - methanesulfonamido - 3-(2'-nitro-1'-propenyl)-indole. — 5 - methanesulfonamidoindole - 3-carboxaldehyde, 6.4 g. (0.027 mole), is mixed with 75 ml. of nitroethane containing 0.5 g. of ammonium acetate and heated at 95° for 16 hrs. The relatively insoluble carboxaldehyde gradually dissolves, affording a homogeneous reaction mixture. Subsequently the desired product commences to precipitate. At the end of the reflux period the reaction mixture is cooled and the precipitated product collected by filtration; yield, 6.2 g. (78%), M.P. 268–

270° C. (dec.), after washing with isopropanol and drying. A portion recrystallized from methanol for analysis exhibited melting point 273–275° C. (dec.).

Analysis.—Calcd. for $C_{12}H_{13}N_3O_4S$: C, 48.80; H, 4.44; N, 14.23; S, 10.86. Found: C, 48.91; H, 4.66; N, 14.05; S, 10.92.

(c) Hydride reduction.—A mixture of 10.0 g. (0.034 mole) of 5-methanesulfonamidoindole-3-(2'-nitro-1'-propenyl)-indole and 200 ml. of dry tetrahydrofuran is added in portionwise fashion to a stirred suspension of 5.4 g. (0.14 mole) of lithium aluminum hydride in 100 ml. of dry tetrahydrofuran. The mixture is refluxed for 24 hrs., cooled, and a solution of 11 ml. of water in 25 ml. of tetrahydrofuran is added thereto in dropwise fashion. The mixture is then stirred for an additional 30 min., and insoluble material collected by filtration. The product is recovered from the filter cake by extraction with three 400 ml. portions of boiling ethanol. The combined ethanolic extracts are acidified with ethanolic hydrogen chloride and then concentrated at reduced pressure. The residue remaining after evaporation of the solvent is triturated with isopropanol, collected, and dried; yield, 3.5 g. (34%), M.P. 250–255° C. (dec.). This material is recrystallized from a methanol-isopropyl ether mixture affording 3-(2'-aminopropyl)-5-methanesulfonamidoindole hydrochloride, M.P. 261–263° C. (dec.).

Analysis.—Calcd. for $C_{12}H_{17}N_3O_2S \cdot HCl$: C, 47.44; H, 5.97; N, 13.83; S, 10.55. Found: C, 47.46; H, 6.21; N, 14.13; S, 10.52.

The method of Example 26 (a) is equally applicable to other methanesulfonamidoindoles to provide the corresponding aldehydes. For example, 6-methanesulfonamidoindole-3-carboxaldehyde and 7-methanesulfonamidoindole-3-carboxaldehyde and 5-(N-methylmethanesulfonamido)indole-3-carboxaldehyde may be prepared in similar fashion. These aldehydes may be condensed with nitroethane as exemplified in Example 26 (b) to provide the corresponding 3-(2'-aminopropyl)methanesulfonamidoindoles. In some instances the reduction can be better accomplished by catalytic means, such as with platinum oxide catalyst, than it can by lithium aluminum hydride reduction as is illustrated in Example 26 (c). If a trial run according to the lithium aluminum hydride method yields the starting material unreacted, that method is probably inapplicable. The recovered nitropropenyl starting material is then reduced catalytically to afford the desired product. A variety of methanesulfonamidoindoles which may be employed according to this method are described in copending application of W. A. Gould and A. A. Larsen, Ser. No. 492,836, filed October 4, 1965. Nitromethane, 1-nitropropane, and 1-nitrobutane may be substituted in the process of Example 26 (b) to afford 3-indolynitrovinyl, -nitrobutenyl, and -nitropentenyl intermediates convertible into the corresponding 3-indolylaminoalkyl compounds by reduction.

EXAMPLE 27

N-benzyl-N-methyl-5-methanesulfonamidoindole-3-oxalylamide

(a) N-benzyl-N-methyl-5-nitroindole-3-oxalylamide. — 5-nitroindole, 15.0 g. (0.0925 mole), is dissolved in 450 ml. of anhydrous ether and treated at 0° C. with 25.0 g. (0.20 mole) of oxalyl chloride dissolved in 50 ml. of ether. Treatment is in dropwise fashion during a period of 1 hr. and is followed by an 18 hr. period at room temperature to allow completion of the reaction. The yellow precipitate, which is 5-nitroindole-3-oxalyl chloride, is then collected by filtration, mixed with 250 ml. of tetrahydrofuran, and treated in dropwise fashion with 45.0 g. (0.37 mole) of benzylmethylamine dissolved in 50 ml. of tetrahydrofuran. The mixture is stirred overnight; by-product benzylmethylamine hydrochloride is separated by filtration. The filtrate is concentrated to dryness, and the residue washed first with ether and then with water before

recrystallizing from ethanol; yield, 10.5 g. (34%), M.P. 215–216° C.

Analysis.—Calcd. for $C_{18}H_{15}N_3O_4$: C, 64.09; H, 4.48; N, 12.46. Found: C, 64.32; H, 4.73; N, 12.34.

(b) N-benzyl-N-methyl-5-aminoindole-3-oxalylamide.—The oxalylamide derivative described in (a) preceding, 3.6 g. (0.0106 mole), is dissolved in 150 ml. of ethanol and hydrogenated over 0.2 g. of platinum oxide catalyst until 0.0318 mole of hydrogen has been absorbed by the reaction. The catalyst is removed by filtration, and the filtrate concentrated to a yellow oil which is employed in the next step without purification.

(c) N-benzyl-N-methyl-5-methanesulfonamidoindole-3-oxalylamide.—The aminoindole prepared in (b) preceding as a yellow oil, 0.0106 mole, is treated in 25 ml. of pyridine with 1.2 g. (0.0106 mole) of methanesulfonyl chloride with stirring. The mixture is stirred at room temperature for 2 hrs. and then warmed to 60–70° C. It is then poured into ice water. This product separates as an oil. The aqueous layer is decanted, and the oil is dissolved in 10% aqueous sodium hydroxide. The solution is filtered and acidified with concentrated hydrochloric acid. The product is again obtained as an oil, which is converted to a powder by boiling with benzene. The powder is crystallized from hot ethanol; yield, 0.9 g., M.P. 170–172° C.

Analysis.—Calcd. for $C_{19}H_{19}N_3O_4S$: C, 59.21; H, 4.97; N, 10.90; S, 8.32. Found: C, 59.14; H, 5.24; N, 10.79; S, 8.47.

The product of Example 27(c) is then reduced to provide 3-[2-(N-benzyl-N-methylamino)ethyl]-5-methanesulfonamidoindole by means of a reducing agent such as sodium, propanol, a metal hydride, or catalytically at from 1 to 4 atmospheres pressure employing 5% palladium-on-barium sulfate catalyst under acid conditions. Under the latter conditions the N-benzyl group is lost by hydrogenolysis to provide 3-(2-methylaminoethyl)-5-methanesulfonamidoindole.

This method is convenient for the preparation of the compounds of Formula I having a variety of R^3 and R^4 substituents, simply by substituting various amines for benzylmethylamine in the procedure of Example 27(a). It is especially suited for the N-substituted heterocyclic and heteropolycyclic types, and for those groups subject to hydrogenation or hydrogenolysis. By use of this method and substituting the amines listed in Table III, various 3-[2-(R^3, R^4 -amino)ethyl]-5-methanesulfonamidoindoles are obtained.

TABLE III.—3-(2- R^3, R^4 -AMINOETHYL)-5-METHANESULFONAMIDOINDOLES

[Examples 28–43]

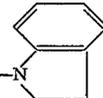
Example No.	Amine	Substituent of Product
28	Diethylamine	$-N(C_2H_5)_2$
29	Indoline	
30	N-methylpiperazine	$-N(CH_2)_5N-CH_3$
31	N-benzylpiperazine	$-N(CH_2)_5NH$
32	Pyrrolidine	$-N(CH_2)_4$
33	Piperidine	$-N(CH_2)_6$
34	Hexamethyleimine	$-N(CH_2)_6$

TABLE III.—Continued

Example No.	Amine	Substituent of Product
35	Thiamorpholine	
36	Morpholine	
37	Styrylamine	$\text{--NHCH=CHC}_6\text{H}_5$
38	Nortropane	
39	Perhydroisoquinoline	
40	Cyclohex-3-enylamine	
41	Benzylamine	$\text{--NHCH}_2\text{--}$
42	N-acetylenediamine	$\text{--NHCH}_2\text{CH}_2\text{NHC}_6\text{H}_5$
43	β -Naphthylamine	

is collected on a filter and the filtrate concentrated to afford a second crop of material affording a total yield of 63% of the desired product, which on recrystallization from ethanol-isopropanol mixture exhibits melting point 140–141° C.

Analysis.—Calcd. for $\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}_3\text{S}$: C, 54.12; H, 5.29; N, 10.52. Found: C, 53.81; H, 5.68; N, 10.36.

(b) Reductive alkylation.—A mixture of 3.5 g. (0.013 mole) of 5-methanesulfonamidindole-3-acetone, 3.1 g. (0.026 mole) of phenethylamine, 0.8 g. (0.013 mole) of acetic acid, and 0.2 g. of platinum oxide in 150 ml. of ethanol is hydrogenated at 60 p.s.i. until 0.013 mole of hydrogen have been absorbed. The catalyst is filtered, the filtrate acidified with concentrated hydrochloric acid, and concentrated at reduced pressure. The residue, after removal of the solvent, is triturated with isopropanol, affording 3.6 g. (68%) of 5-methanesulfonamido-3-[2-(phenethylamino)propyl]-indole hydrochloride, which is recrystallized from isopropanol (charcoal treatment), M.P. 188–190° C.

Analysis.—Calcd. for $\text{C}_{20}\text{H}_{25}\text{N}_3\text{O}_2\text{S}\cdot\text{HCl}$: C, 58.88; H, 6.41; N, 10.30; S, 7.86. Found: C, 58.98; H, 6.43; N, 10.02; S, 7.88.

EXAMPLES 45–73

The following amines are substituted for phenethylamine on a chemically equivalent basis in the procedure of Example 44(b). The products named in the table are obtained in analogous fashion by reductive alkylation according to that method.

TABLE IV.—5-METHANESULFONAMIDO-3-(2-R⁴-AMINOPROPYL)-INDOLES BY REDUCTIVE ALKYLATION

Example No.:	Amine	R ⁴ -Substituent of Product
45	1-(4-methoxyphenyl)-2-propylamine	1-(4-methoxyphenyl)-2-propyl.
46	1-(3,4-dimethoxyphenyl)-2-propylamine	1-(3,4-dimethoxyphenyl)-2-propyl.
47	Isopropylamine	Isopropyl.
48	1-methyl-3-phenylpropylamine	1-methyl-3-phenylpropyl.
49	1-(3,4-methylenedioxyphenyl)-2-propylamine	1-(3,4-methylenedioxyphenyl)-2-propyl.
50	2-(4-tolyl)ethylamine	2-(4-tolyl)ethyl.
51	1-phenoxy-2-propylamine	1-phenoxy-2-propyl.
52	2-aminoindane	2-indanyl.
53	2-aminobicyclo-[2,2,1]-octane	Bicyclo-[2,2,1]octane-2-yl.
54	2-aminomethylbicyclo-[2,2,1]octane	2-bicyclo-[2,2,1]octylmethyl.
55	Cyclohexylamine	Cyclohexyl.
56	α -Aminoisobutyric acid	1-(1-carboxy-2-methyl)propyl.
57	2-phenylcyclopropylamine	2-phenylcyclopropyl.
58	Cyclopentylmethylamine	Cyclopentylmethyl.
59	Cyclopropylamine	Cyclopropyl.
60	1,3-dimethylbutylamine	1,3-dimethylbutyl.
61	1,4-dimethylpentylamine	1,4-dimethylpentyl.
62	2,2-diphenylethylamine	2,2-diphenylethyl.
63	3-methoxypropylamine	3-methoxypropyl.
64	Aniline	Phenyl.
65	1-naphthylamine	1-naphthyl.
66	2-aminopyridine	2-pyridyl.
67	Cyclohexylmethylamine	Cyclohexylmethyl.
68	1-aminoadamantane	1-adamantanyl.
69	2-amino-2-methyl-1-propanol	1-hydroxy-2-methyl-2-propyl.
70	3-aminoazabicyclo-[2,2,2]octane	Azabicyclo[2,2,2]oct-3-yl.
71	1-(2-aminoethyl)pyrrole	1-(2-aminoethyl)pyrrolidyl.
72	1-naphthylmethylamine	1-naphthylmethyl.
73	2-dimethylaminoethylamine	2-dimethylaminoethyl.

EXAMPLE 44

5-methanesulfonamido-3-[2-(phenethylamino)propyl]indole hydrochloride

(a) 5-methanesulfonamidindole-3-acetone.—A mixture of 10.0 g. (0.034 mole) of 5-methanesulfonamido-3-(2'-nitro-1-propenyl)indole, 20 g. of powdered iron, 1.0 g. of ferric chloride, and 200 ml. of water is heated to reflux and treated in dropwise fashion with 13.0 ml. of concentrated hydrochloric acid. The mixture is then refluxed for 5 hrs., filtered, and the filtrate cooled to allow crystallization of precipitated material to occur. The precipitate

EXAMPLE 74

5-methanesulfonamido-3-(2-isopropylaminoethyl)indole

3-(2-aminoethyl)-5-methanesulfonamidindole, 5.0 g. (0.0198 mole), is dissolved in 100 ml. of absolute ethanol and 3.5 g. (0.06 mole) of acetone is added thereto. The solution is then subjected to catalytic hydrogenation at room temperature and a pressure of 2 atmospheres employing platinum oxide catalyst. The calculated quantity of hydrogen (0.0198 mole) is absorbed in the course of 1 to 2 hrs., and the product is isolated by separation of the

catalyst and concentration of the ethanolic solution in vacuo.

EXAMPLE 75

3-(2-aminoethyl)-5-methanesulfonamidoindole-2-carboxylic acid hydrochloride

(a) 2,3-dioxopiperidine 3-p-nitrophenylhydrazone.—3-carbethoxy-2-piperidone, 25.0 g. (0.147 mole), is kept overnight with an aqueous solution of 8.8 g. of potassium hydroxide in 450 ml. of water. A solution of p-nitrobenzenediazonium chloride is then prepared by dissolving 22.4 g. of 4-nitroaniline in 450 ml. of hot water containing 37.5 g. of hydrogen chloride, with 12.5 g. of sodium nitrite dissolved in 75 ml. of water. This solution is then clarified by filtration and added to the piperidone solution, while maintaining the temperature at 5–10° C. The mixture is stirred for 4 hr. at this temperature, at which time evolution of carbon dioxide has ceased. The precipitated product is collected by filtration, washed with water, and dried; yield, 28.1 g. (77%), M.P. 230–235° C.

(b) 6-nitro-1,2,3,4-tetrahydro-9H-pyrido[3,4b]indol-1-one.—A mixture of 60 g. of polyphosphoric acid and 10.0 g. (0.04 mole) of 2,3-dioxopiperidine 3-p-nitrophenyl hydrazone is heated at 110° C. until gas evolution ceases. The mixture is then mixed with 500 ml. of ice water and the solid precipitate collected on a filter. It is recrystallized from 9:1 acetic acid-water, and then washed with isopropanol; yield, 6.4 g., fails to melt at 300° C.

(c) 6-amino-1,2,3,4-tetrahydro-9H-pyrido[3,4b]indol-1-one.—The product of (b) preceding, 6.0 g. (0.026 mole), is hydrogenated over 0.5 g. of platinum oxide catalyst employing 200 ml. of absolute ethanol as reaction medium. Hydrogenation is carried out at 60 p.s.i. for a period sufficient to permit the consumption of 0.078 mole of hydrogen. The reaction mixture is then heated to boiling and diluted with sufficient ethanol to dissolve the precipitated organic material. The catalyst is then removed by filtration and the filtrate allowed to cool, resulting in crystallization of the product; weight, 2.5 g., M.P. 279–281° C. (dec.). The filtrate is concentrated to provide additional crops of material for a total yield of 6.3 g. (84%).

(d) 6-methanesulfonamido-1,2,3,4-tetrahydro-9H-pyrido[3,4b]indol-1-one.—6-amino-1,2,3,4-tetrahydro-9H-pyrido[3,4b]indol-1-one, 6.5 g. (0.0325 mole), is dissolved in 50 ml. of pyridine and treated in dropwise fashion with 3.8 g. (0.0325 mole) of methanesulfonyl chloride. The mixture is stirred at room temperature for 4 hrs., heated to 65–70° C. for 15 min., and then poured into 500 ml. of ice water. The product is collected on a filter and purified by dissolving in aqueous 2 N sodium hydroxide and reprecipitating by acidifying with concentrated hydrochloric acid. The product is collected, washed with water, and dried, yield, 7.7 g. (85%), M.P. 279–281° C. (dec.). This material is recrystallized from acetic acid-water, M.P. 282–283° C. (dec.).

Analysis.—Calcd. for $C_{12}H_{13}N_3O_3S$: C, 51.60; H, 4.69; N, 15.04; S, 11.48. Found: C, 51.68; H, 4.85; N, 15.01; S, 11.29.

(e) Hydrolysis.—The product of (d) preceding, 2.8 g. (0.01 mole), is refluxed overnight with a solution of 10 g. of potassium hydroxide in 40 ml. of water and 60 ml. of ethanol. The mixture is cooled, filtered, and the filtrate diluted with 300 ml. of water. Acidification with concentrated hydrochloric acid results in precipitation of 3-(2-aminoethyl)-5-methanesulfonamidoindole-2-carboxylic acid hydrochloride; yield, 2.7 g. (78%), M.P. 282–283° C. (dec.). This material is recrystallized from methanol-isopropyl ether, M.P. 271.5–272° C. (dec.).

Analysis.—Calcd. for $C_{12}H_{15}N_3O_4S \cdot HCl$: C, 43.18; H, 4.83; N, 12.59; S, 9.60. Found: C, 43.27; H, 4.92; N, 12.60; S, 9.52.

EXAMPLE 76

3-(2-aminoethyl)-5-methanesulfonamido-1-methylindole-2-carboxylic acid hydrochloride

(a) 6-nitro-9-methyl-1,2,3,4-tetrahydro-9H-

pyrido[3,4d]indole-1-one.—6-nitro-1,2,3,4-tetrahydro-9H-pyrido[3,4b]indol-1-one, 2.0 g. (0.0087 mole, Example 75(b)), is dissolved in 40 ml. of acetone containing 6 ml. of 20% aqueous potassium hydroxide, heated to reflux, and 3.2 ml. of dimethylsulfate added. The product appears as a yellow precipitate which is collected after diluting the reaction mixture with water. It is washed with water and then with cold alcohol; yield, 2.3 g., M.P. 287–288° C. (dec.).

(b) 6-amino-9-methyl-1,2,3,4-tetrahydro-9H-pyrido[3,4b]indol-1-one.—The product of (a) preceding, 13.3 g. (0.054 mole), is hydrogenated over 0.5 g. of platinum oxide at 60 p.s.i. employing 250 ml. of absolute ethanol as reaction medium. After absorption of 0.162 mole of hydrogen, the catalyst is filtered and the residue concentrated by distillation of the solvent. The residue is triturated with isopropanol and filtered; yield, 9.6 g. (82%), M.P. 158–161° C.

(c) 6-methanesulfonylamido-9-methyl-1,2,3,4-tetrahydro-9H-pyrido[3,4b]indol-1-one.—The product of (b) preceding, 3.8 g. (0.0175 mole), is dissolved in 35 ml. of pyridine and treated in dropwise fashion with 2.1 g. (0.0175 mole) of methanesulfonyl chloride. The mixture is stirred for 4 hrs. at room temperature and then warmed for 10 min. at 60–70° C. The product is recovered by pouring the mixture into 500 ml. of ice water and filtering. It is a light purple-colored solid which is dissolved in dilute aqueous sodium hydroxide solution, filtered, and acidified with dilute hydrochloric acid. The precipitate is collected and washed with water; yield, 4.0 g. (79%), M.P. 265–268° C. (dec.), as obtained and after recrystallization from acetic acid-water.

Analysis.—Calcd. for $C_{13}H_{15}N_3O_3S$: C, 53.23; H, 5.15; N, 14.33; S, 10.93. Found: C, 53.47; H, 5.32; N, 14.19; S, 11.00.

(d) Hydrolysis.—The product of (c) preceding, 2.9 g. (0.01 mole), is refluxed overnight with a solution of 10 g. of potassium hydroxide in 40 ml. of water and 60 ml. of ethanol. The mixture is then cooled, filtered, and diluted to 300 ml. of water. The filtrate is acidified with concentrated hydrochloric acid, the 3-(2-aminoethyl)-5-methanesulfonamido-1-methylindole-2-carboxylic acid hydrochloride, which precipitates, is collected on a filter, washed with hydrochloric acid, and dried; yield, 3.1 g. (89%), M.P. 253–255° C. (dec.). This material is recrystallized from methanol-isopropyl ether, M.P. 243.5° C. (dec.) $\pm 3^\circ$.

Analysis.—Calcd. for $C_{13}H_{17}N_3O_4S$: C, 44.89; H, 5.21; N, 12.0; S, 9.22. Found: C, 45.03; H, 5.38; N, 11.96; S, 9.34.

EXAMPLE 77

3-(2-aminoethyl)-5-(N-methylmethanesulfonamido)indole-2-carboxylic acid

(a) 6-(N-methylmethanesulfonamido)-1,2,3,4-tetrahydro-9H-pyrido[3,4b]indol-1-one.—6-methanesulfonamido-1,2,3,4-tetrahydro-9H-pyrido[3,4b]indol-1-one, 8.4 g. (0.03 mole, Example 75(d)) is dissolved in 200 ml. of ethanol containing 0.031 mole of sodium hydroxide. A solution of 4.0 ml. of methyl iodide in 25 ml. of ethanol is then carefully added thereto. The mixture is stirred at room temperature for 20 hrs., filtered, the filter cake washed with ethanol, and dried; yield, 7.4 g., M.P. 265–273° C. This material is triturated with a small volume of aqueous 2 N sodium hydroxide, filtered, and dried; weight, 3.2 g., M.P. 217–220° C. Approximately 3.7 g. of unreacted starting material is recovered by acidification of the sodium hydroxide filtrate. The product is recrystallized from acetonitrile to provide the purified material, M.P. 226.5–228° C.

Analysis.—Calcd. for $C_{13}H_{15}N_3O_3S$: C, 53.23; H, 5.15; N, 14.33; S, 10.93. Found: C, 53.49; H, 5.38; N, 14.55; S, 10.93.

(b) Hydrolysis.—The product of (a) preceding is hydrolyzed with alcoholic potassium hydroxide as described

in Example 75(e) to provide the desired product in the fashion described there.

EXAMPLES 78-83

The following R⁵-sulfonyl halides are substituted for methanesulfonyl chloride in the procedure of Example 75(d). The resulting product is then hydrolyzed according to procedure 75(e) to give various 3-(2-aminoethyl)-5-R⁵-sulfonamidoindole-2-carboxylic acids. Table V contains a listing of various sulfonyl halides that may be employed, and identifies the product resulting from this procedure.

TABLE V.—3-(2-AMINOETHYL)-5-R⁵-SULFONAMIDOINDOLE-2-CARBOXYLIC ACIDS

Example No:	Sulfonyl halide	R ⁵ -Substituent of Product
78.....	Vinylsulfonyl chloride.....	CH ₂ =CH—
79.....	Prop-2-enylsulfonyl chloride.....	CH ₂ =CHCH ₂ —
80.....	Styrylsulfonyl chloride.....	C ₆ H ₅ CH=CH—
81.....	Cyclohex-3-enylsulfonyl chloride.....	
82.....	2,5-methylenecyclohex-3-enylsulfonyl chloride.....	
83.....	Benzylsulfonyl chloride.....	C ₆ H ₅ CH ₂ —

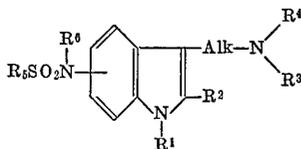
The compounds of Formula I are amphoteric substances, forming salts with both acids and bases. These salts are also considered part of the present invention and it is intended to include not only the pharmaceutically acceptable salts which have the physiological uses referred to above, but also other salts, since they have utility as intermediates in preparation of pharmaceutically preferred forms of the present products, including the free base. For example, acid addition salts with optically active acids such as D-camphorsulfonic acid, L- or D-tartaric acid are useful for resolution of enantiomeric pairs of the present compounds and are considered part of this invention.

Examples of pharmaceutically acceptable acid addition salts include the hydrochloride, hydrobromide, acetate, propionate, phosphate, nitrate, succinate, gluconate, mucate, sulfate, methanesulfonate, ethanesulfonate, p-toluenesulfonate etc. salts. Pharmaceutically acceptable metal salts include the sodium, potassium, lithium, magnesium, calcium, barium, zinc, and aluminum salts. The sulfoamide free bases of Formula I are also pharmaceutically acceptable forms.

The present salts may be prepared in conventional fashion by treatment of one of the present compounds with an acid or base. For the preparation of salts with monobasic acids and monoacidic bases, use of equimolar quantities of the two reactants is convenient. In the formation of salts of polyacidic bases and polybasic acids, it is convenient to reduce the molecular proportion of the acid or base so that but one chemical equivalent thereof is employed.

What is claimed is:

1. A compound of the group (a) having the formula



wherein the group



is located in the 4-, 5-, 6-, or 7-positions of the indole ring and

Alk is an alkylene group of 2 to 6 carbon atoms with at least two carbon atoms separating the ring and the nitrogen atom,

R¹ is hydrogen, benzyl, or lower alkyl having up to 4 carbon atoms,

R² is hydrogen, carboxyl, or lower alkyl having up to 4 carbon atoms,

R³ is hydrogen, benzyl, lower alkyl, or lower alkenyl having up to 4 carbon atoms,

R⁴ is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl and phenylalkyl, each containing up to 12 carbon atoms,

R⁵ is alkyl or alkenyl, each having up to 10 carbon atoms, and

R⁶ is hydrogen or lower alkyl having up to 4 carbon atoms, and (b) the pharmaceutically acceptable acid addition and metal salts of (a).

2. The compound of claim 1 in which Alk is ethylene, R¹, R², R³, R⁴ and R⁶ are hydrogen atoms, and R⁵ is the methyl group.

3. 3-(2-aminoethyl)-4-methanesulfonamidoindole.

4. 3-(2-aminoethyl)-5-methanesulfonamidoindole.

5. 3-(2-aminoethyl)-6-methanesulfonamidoindole.

6. The compound of claim 1 wherein Alk is propylene, R¹, R², R³, R⁴ and R⁶ are hydrogen, and R⁵ is methyl.

7. 3-(2-aminopropyl)-5-methanesulfonamidoindole.

8. The compound of claim 1 wherein R¹, R², R³ and R⁶ are hydrogen, R⁵ is methyl, R⁴ is phenethyl, and Alk is propylene.

9. 5-methanesulfonamido-3-[2-(phenethylamino)-propyl]indole.

References Cited

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ALEX MAZEL, Primary Examiner

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U.S. Cl. X.R.

260-243, 247.1, 268, 288, 294.8, 296, 297, 319.1, 326.13, 326.14, 326.15, 326.16, 999

UNITED STATES PATENT OFFICE
CERTIFICATE OF CORRECTION

Patent No. 3,472,870 Dated October 14, 1969

Inventor(s) AUBREY A. LARSEN and WILLIAM A. GOULD (deceased)
BARBARA E. GOULD - widow & legal rep. of the estate of WM. A. GOULD

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

1. 2, line 29, "Genealized" should be -- Generalized --;
line 48, after "COR" insert a comma -- , --.

2. 3 bottom of page, REDUCTIVE ALKYLATION "R¹" should
4 be -- R² --.

3. 3 bottom of page, REDUCTIVE ALKYLATION "CH₂CHNHR⁴"
4 should be -- CH₂CHNHR⁴ --.
R

4. 5, line 37, "Example" should be -- Examples --.

5. 7, Table II, Example 13, "O-chlorobenzenesulfonyl"
should be -- o-chlorobenzenesulfonyl --.

6. 8, line 33, "hydroyzed" should be -- hydrolyzed --.

7. 10, line 8, "nad" should be -- and --;
line 75, Example 34, " " should be --



8. 11 Example 53, "cotane" should be -- octane --.
9. 12

10. 13, line 23, "hydrozone" should be -- hydrazone --.

11. 14, line 19, "methanesulfonylamido" should be --
methanesulfonamido --; line 72, "53,49" should be --
53.49 --.

12. 15, Table V, Example 82, "enysulfonyl" should be --
enylsulfonyl --.

Continued

3,472,870

(2)

Col. 15, line 65 (claim 1), in the formula " R_5SO_2N " should be
-- R^5SO_2N --.

Col. 16, line 45 (claim 3), "methanesulfonamidonindole" should
be -- methanesulfonamidoindole --.

SIGNED AND
SEALED
MAY 26 1970

~~(SEAL)~~

Attest:

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Attesting Officer

WILLIAM E. SCHUYLER, J.
Commissioner of Patent