PATENT SPECIFICATION

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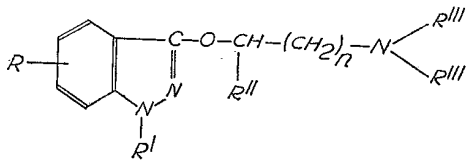
COMPLETE SPECIFICATION

1-Substituted 3-Dialkylaminoalkoxy-Indazoles, and a method for the preparation thereof

I, IGINO ANGELINI an Italian subject, Trading as AZIENDE CHIMICHE RIUNITE ANGELINI FRANCESCO, Via Amelia 70, Rome, Italy do hereby declare the invention, for which I pray that a patent may be granted to me, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to a class of 1 - substituted 3 - dialkylaminoalkoxy-indazoles having the general formula (I)



(I)

wherein: R is a hydrogen or chlorine atom;

R′ is a lower alkyl residue containing 1—4 carbon atoms, or a phenyl, benzyl, chlorobenzyl, methoxybenzyl, dimethoxybenzyl or phenylethyl residue;

R″ is a hydrogen atom or a lower alkyl group containing 1—4 carbon atoms;

each R‴ is a lower alkyl residue containing 1—4 carbon atoms, and may or may not differ from the other R‴ group;

n is 1 or 2;

and non-toxic acid-addition salts thereof.

In the compounds having the general formula (I), it is preferred that R′ represents a methyl or ethyl group, a phenyl group, a benzyl, *p* - chlorobenzyl, *p* - methoxybenzyl group, or a β - phenylethyl group; that R″ represents a methyl group; and that each R‴ represents an ethyl or a methyl group.

The compounds having the general formula (I), which can be administered in the form of their acid addition salts, such as the hyrochloride, citrate, maleate, or sulfate, are characterised by interesting analgesic and antiphlogistic properties, and a few of them also have a myorelaxing activity. 1 - benzyl - 3 - γ - dimethyl-amino - propoxy - indazole hydrochloride may be mentioned by way of example, which exhibits the following pharmacological properties:

1) an apparent analgesic activity when tested by the inflammatory pain tests (Randall and Selitto - phenyl - quinone), in which this compound appears to be 3 times as active as acetylsalicylic acid. Its activity is more moderate when tested by the hot plate test;

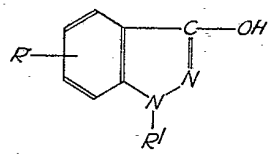
[illegible]

2) a particularly apparent antiphlogistic activity, when tested by the chronic silver nitrate test, in which the compound is three times as active as phenylbutazone;

3) an activity on polysynaptic spinal responses which is 8 times as high as that of mephenesin.

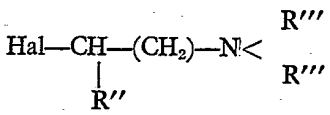
The compound is free from any central effect in that it does not inhibit conditioned responses, as is often the case with analgesic narcotics of the morphine type.

The compounds having the general formula (I) may be prepared, according to a method which is also a part of the invention, from the corresponding 3 - hydroxy-indazoles having the general formula (II)



(II)

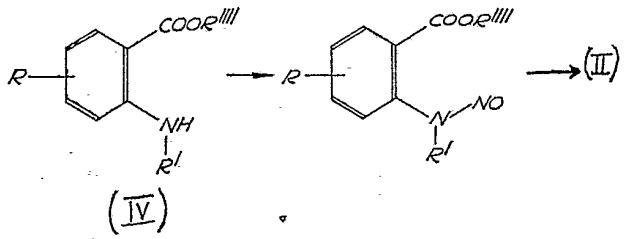
(wherein R and R′ have the above-mentioned meanings), which are converted into the corresponding alkalimetal salts, preferably into the sodium salts, and reacted with halogenoalkyl - dialkylamines having the general formula (III), in suitable inert solvents



(III)

wherein R″, R‴ and n have the above-mentioned meanings, while Hal is a halogen atom, preferably a chlorine atom.

The hydroxy-indazoles having the general formula (II) are prepared, according to the invention, from N - substituted anthranilic acids or esters having the general formula (IV); the latter compounds are nitrosated, and the obtained nitroso-derivatives are reduced with sodium hydrosulfite:



(IV)

In this reaction sequence, R and R′ have the above mentioned meanings, and R⁗ is a hydrogen atom or a lower alkyl group containing 1—4 carbon atoms, preferably a methyl group.

The following examples are given by way of illustration only, and are not limitative of the invention.

EXAMPLE 1

a) 1 - *benzyl* - 3 - *hydroxy* - 6 - *chloro* - 1*H* - *indazole* (II R=Cl, R′=$CH_2C_6H_5$)

32 g. of methyl 4 - chloroanthranilate, 26.5 g. of benzyl chloride and 21 g. of anhydrous sodium acetate are heated to 150°C for 6 hours with stirring. The mixture is cooled and treated with water and ether. The ethereal extract is washed, dried and evaporated. 27 g. of a residue are obtained, the yield being 57%. Methyl N - benzyl - 4 - chloro - anthranilate has m.p. 79°C. 28 g. of this material are treated with 190 ml. of 1:1 HCl and 100 ml. of $CHCl_3$. A concentrated solution of 7.7g of sodium nitrite is slowly added, while cooling externally with water. The mixture is allowed to stand at room temperature for 1 hour, and the organic layer

is then removed. The latter is concentrated to dryness under reduced pressure, and the residue is added to a solution of 80 g. of NaOH in 400 ml. of water. 100 g. of sodium hydrosulfite are then added in a nitrogen stream, and with stirring. The mixture is stirred at 70°C for 2 hours, after which period a further 30 g. of the hydrosulfite are added and the reaction is completed by heating for an additional 3 hours. The reaction mass is then diluted with an equal volume of water, boiled and filtered. The filtrate is acidified with hydrochloric acid. 1 - Benzyl - 3 - hydroxy- 6 - chloro - 1H - indazole separates, and is then crystallized from alcohol. Its melting point is 229°C and the yield is 80%.

b) 1 - *Benzyl* - 3 - γ - *dimethylaminopropoxy* - 6 - *chloro* - 1*H* - *indazole*

The sodium salt of 1 - benzyl - 3 - hydroxy - 6 - chloro - 1H - indazole is first of all prepared by dissolving this compound in a solution of the equivalent amount of sodium methylate in methanol, and drying under reduced pressure. 15 g. of said salt are thoroughly powdered and suspended in 130 ml. of xylene. A solution of 7 g. of chloropropyldimethylamine in 10 ml. of xylene is then rapidly added. An additional 2 g. of the chlorinated base are added after the mixture has been heated for 2 hours, and a third 2 g. portion is finally added after one additional hour. Heating is continued for 4 more hours. The mixture is then cooled, washed with water, dried, and the solvent removed. 17 g. of a material, b.p. 197°C/0.5mm are obtained upon distillation under reduced pressure. This is found to be 1 - benzyl- 3 - γ - dimethylaminopropoxy - 6 - chloro - 1H - indazole. Its hydrochloride is prepared with an ethereal HCl solution, and is crystallized from ethyl acetate containing a few drops of ethanol. M.p. 140°C.

EXAMPLE 2

1 - *p* - *chlorobenzyl* - 3 - β - *dimethylaminoethoxy* - 1*H* - *indazole*

To a solution of 25g of NaOH and 78g of anthranilic acid in 900 ml of water, heated to 50°C, 92 g of *p* - chlorobenzyl chloride are slowly added. The reaction is completed by heating for 4 hours to 70°C. The mixture is cooled, the solid material is filtered and crystallized from ethanol. A hundred grams of N - *p* - chlorobenzyl- anthranilic acid, m.p. 146°C, are obtained. The same is dissolved in 600 ml of water with 16 g of NaOH and 24g of $NaNO_2$. To the ice-cooled solution, 1:1 HCl is added until pH=3. The reaction mixture is stirred for additional 10 minutes, then the separated nitroso derivative is filtered. The nitroso derivative is added, under stirring, to a solution of 300g of NaOH in 1600 ml of water, heated to 70°C. Four hundred grams of sodium hydrosulphite are immediately added, and the mixture is heated under stirring for an additional 2.5 hours. The next day, the solid is filtered and washed with 1:1 HCl, then thoroughly with water. After crystallization from ethanol, the 1 - *p* - chlorobenzyl - 3 - hydroxy - 1H - indazole, m.p. 178°C, is obtained, yield 70%.

12.9 g of 1 - chlorobenzyl - 3 - hydroxy - 1H indazole prepared above are dissolved in 250 ml. of hot toluene. 2.2g. of sodium amide are added, and the mixture is heated for 1 hour with stirring. 10 g. of freshly distilled chloroethyldi- methylamine, dissolved in 100ml of toluene, are then introduced, and heating and stirring are continued for about 4 hours. The inorganic materials are filtered off, and the mixture is extracted with 2N hydrochloric acid. The solution is then made alkaline with NaOH, extracted with ether, and dried over potassium carbonate. The solvent is removed, and the residue is distilled under reduced pressure. 14 g. of a material, b.p. 185°C/0. 1 mm., are obtained. 1 - *p* - *chlorobenzyl* - 3 - β *dimethylaminoethoxy* - 1*H* - *indazole hydrochloride* is crystallized from ethyl acetate, and has a melting point of 155°C.

EXAMPLE 3

a) 1 *methyl* - 3 - *hydroxy* - 1*H* - *indazole* (*IIR*=*H*, *R'*=CH_3)

175 g. of N - methylanthranilic acid are dissolved in 2lt. of water and 120 ml. of concentrated HCl. The mixture is cooled, and a concentrated solution of 80g. of sodium nitrite is slowly added thereto with stirring, while keeping the temperature at about 25°C. The nitroso-derivative is filtered and crystallized from a water- dioxane mixture, and is then dissolved in a solution of 500 g. of NaOH in 1500 ml. of water. The solution is saturated with nitrogen, 400 g. of sodium hydro- sulphite are added thereto, and the mixture is stirred for 6 hours at 75°C under a nitrogen blanket. It is then diluted with a little water until the solids which had separated are completely dissolved, and acidified with 750 ml. of glacial acetic

acid. The mixture is cooled, filtered and 1 - *methyl* - 3 - *hydroxy* - *indazole* is crystallized from water. The compound has a melting point of 154—6°C. The yield is 70%.

b) 1 - *methyl* - 3 - *β* - *dimethylaminoethoxy* - 1*H* - *indazole*

By the technique described in the foregoing examples, from the sodium salt of 1 - methyl - 3 - hydroxy - 1H - indazole and *β* - chloroethyldimethylamine, the 1 - methyl - 3 - *β* - dimethylaminoethoxy - 1H - indazole, b.p. 115°C/0.3 mm., is obtained. The hydrochloride melts at 161°C.

The compounds which are hereinafter listed may also be prepared by using the technique described in the preceding examples.

1 - methyl - 3 - *γ* - dimethylaminopropoxy - 1H - indazole b.p. 122°C/0.3 mm.; HCl m.p. 150°C.

1 - phenyl - 3 - *β* dimethylaminoethoxy - 1H - indazole b.p. 190° C/1 mm.; HCl m.p. 175° C.

1 - phenyl - 3 - *β* - diethylaminoethoxy - 1H - indazole b.p. 140° C/0.02 mm.; citrate m.p. 75°C.

1 - phenyl - 3 - *γ* - dimethylaminopropoxy - 1H - indazole m.p. 65° C; HCl m.p. 197°C.

1 - benzyl 3 - *β* - dimethylaminoethoxy - 1H - indazole b.p. 190° C/1 mm.; HCl m.p. 155°C

1 - benzyl - 3 - *β* - diethylaminoethoxy - 1H - indazole b.p. 170° C/0.1 mm.; citrate m.p. 104°C

1 - benzyl - 3 - *γ* - dimethylaminopropoxy - 1H - indazole b.p. 160°C/0.05 mm.; HCl m.p. 160°C
citrate m.p. 115—7°C.
maleate m.p. 113°C
sulfate m.p. 149°C

1 - *p* - chlorobenzyl - 3 - *β* - diethylaminoethoxy - 1H - indazole b.p. 170°C/0.2 m.m. HCl m.p. 124°C
citrate m.p. 93°C

1 - *p* - chlorobenzyl - 3 - *γ* - dimethylaminopropoxy - 1H - indazole b.p. 171°C/0.1 mm. HCl m.p. 120°C

1 - phenethyl - 3 - *β* - dimethylaminoethoxy - 1H - indazole b.p. 165° C/0.2 m.m. HCl m.p. 181°C

1 - benzyl - 3 - *β* - dimethylaminoethoxy - 5 - chloro - 1H - indazole b.p. 176°C/0.2 m.m. HCl m.p. 195°C

1 - *p* - methoxybenzyl - 3 - *β* - dimethylaminoethoxy - 1H - indazole b.p. 189°C/0.3 m.m. HCl m.p. 215°

1 - *p* - chlorobenzyl - 3 - *γ* - diethylaminopropoxy - 1H - indazole b.p. 205°C/0.3 m.m. HCl m.p. 96°C

1 - *p* - methoxybenzyl - 3 - *γ* - dimethylaminopropoxy - 1H - indazole b.p. 200°C/0.4 m.m. HCl m.p. 120°C

1 - benzyl - 3 - *γ* - dimethylaminopropoxy - 5 - chloro - 1H - indazole b.p. 187°C/0.2 m.m. HCl m.p. 160°C

1 - phenethyl - 3 - *γ* - dimethylaminopropoxy - 1H - indazole b.p. 174°C/0.2 m.m. HCl m.p. 173°C

1 - *p* - chlorobenzyl - 3 - *α* - methyl - *β* - dimethyl - aminoethoxy - 1H - indazole b.p. 180°C/0.1 m.m. HCl m.p. 178°C

1 - *p* - methoxybenzyl - 3 - *α* - methyl - *β* - dimethylaminoethoxy - 5 - chloro - 1H-indazole b.p. 198° C/0.2 m.m.; HCl m.p. 135°C

1 - p - methoxybenzyl - 3 - *γ* - dimethylaminopropoxy - 5 - chloro - 1H - indazole b.p. 220°C/0.5 m.m. HCl m.p. 117°C

1 - *p* - methoxybenzyl - 3 - *β* - dimethylaminoethoxy - 5 - chloro - 1H - indazole b.p. 207°C/0.4 m.m. HCl m.p. 130°C

1 - benzyl - 3 - *β* - dimethylaminoethoxy - 6 - chloro - 1H - indazole b.p. 180°C/0.2 m.m. HCl m.p. 199°C

1 - benzyl - 3 - *α* - methyl - *β* - dimethylaminoethoxy - 6 - chloro - 1H indazole b.p. 187° C/0.2 m.m. HCl m.p. 148°C

1 - butyl - 3 - *β* - dimethylaminoethoxy - 5 - chloro - 1H - indazole b.p. 173°C/0.3 m.m. HCl m.p. 122°C

1 - butyl - 3 - *γ* - dimethylaminopropoxy - 5 - chloro - 1H - indazole b.p. 166° C/0.2 m.m. HCl m.p. 139°C.

1 - butyl - 6 - chloro - 3 - *β* - dimethylaminoethoxy - 1H - indazole b.p. 155°C/0.5 m.m.

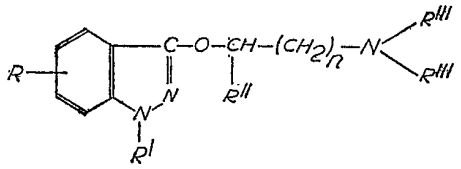
1 - benzyl - 3 - γ - dimethylaminopropoxy - 4 - chloro - 1H - indazole b.p. 188°C/0.2 m.m. HCl m.p. 160°C
1 - *p* - chlorobenzyl - 3 - β - dimethylaminoethoxy - 6 chloro - 1H - indazole b.p. 193°C/0.5 m.m. HCl m.p. 190°C
1 - *p* - chlorobenzyl - 3 - γ - dimethylaminopropoxy - 6 - chloro - 1H - indazole b.p. 197°C/0.3 m.m. HCl m.p. 173°C
1 - *m* - chlorobenzyl - 3 - γ - dimethylaminopropoxy - 1H - indazole b.p. 195°C/0.5 m.m. HCl m.p. 97°C
1 - *o* - chlorobenzyl - 3 - γ - dimethylaminopropoxy - 1H - indazole b.p. 185°C/0.2 m.m. HCl m.p. 140°C
1 - (*m,p* - dimethoxybenzyl) - 3 - γ - dimethylaminopropoxy - 1H - indazole b.p. 209°C/0.3 m.m. HCl m.p. 111°C.

The following intermediate compounds have also been obtained:

1 - *p* - methoxybenzyl - 3 - hydroxy - 1H - indazole m.p. 161°C
1 - phenethyl - 3 - hydroxy - 1H - indazole m.p. 145°C
N - nitroso - N - benzyl - anthranilic acid m.p. 120°C (dec.)
1 - benzyl - 3 - hydroxy - 5 - chloro - 1H - indazole m.p. 213°C
1 - *p* - methoxybenzyl - 3 - hydroxy - 5 - chloro - 1H - indazole m.p. 199°C
1 - *m* - chlorobenzyl - 3 - hydroxy - 1H - indazole m.p. 151°C
1 - *p* - chlorobenzyl - 3 - hydroxy - 6 chloro - 1H - indazole m.p. 236°C
1 - *o* - chlorobenzyl - 3 - hydroxy - 1H - indazole m.p. 231°C
1 - benzyl - 3 - hydroxy - 4 - chloro - 1H - indazole m.p. 223°C
1 - (*m,p* - dimethoxybenzyl) - 3 - hydroxy - 1H - indazole m.p. 166°C
1 - butyl - 3 - hydroxy - 6 - chloro - 1H - indazole m.p. 171°C
1 - butyl - 3-hydroxy - 5 - chloro - 1H - indazole m.p. 120°C.

WHAT I CLAIM IS:—

1) As new compounds, 1 - substituted 3 - dialkylamino - alkoxy - indazoles of the general formula (I)



(I)

wherein: R is a hydrogen or chlorine atom;
R′ is a lower alkyl residue containing 1—4 carbon atoms, or a phenyl, benzyl, chlorobenzyl, methoxybenzyl, dimethoxybenzyl or phenylethyl residue;
R″ is a hydrogen atom or a lower alkyl residue containing 1—4 carbon atoms;
each R‴ is a lower alkyl residue containing 1—4 carbon atoms and may or may not differ from the other R‴ group;
n is a 1 or 2; and non-toxic acid addition salts thereof.

2) As a new compound according to Claim 1, 1 - *p* - chlorobenzyl - 3 - β-dimethylaminoethoxy - 1H - indazole, or a non-toxic acid addition salt thereof.

3) As a new compound according to Claim 1, 1 - benzyl - 3 - γ - dimethylaminopropoxy - 6 - chloro - 1H - indazole, or a non-toxic acid addition salt thereof.

4) As a new compound according to Claim 1, 1 - methyl - 3 - β - dimethylaminoethoxy - 1H - indazole or a non-toxic acid-addition salt thereof.

5) As a new compound according to Claim 1, 1 - methyl - 3 - γ - dimethylaminopropoxy - 1H - indazole or a non-toxic acid-addition salt thereof.

6) As a new compound according to Claim 1, 1 - phenyl - 3 - β - dimethylaminoethoxy - 1H - indazole or a non-toxic acid-addition salt thereof.

7) As a new compound according to Claim 1, 1 - phenyl - 3 - β - diethylaminoethoxy - 1H - indazole or a non-toxic acid-addition salt thereof.

8) As a new compound according to Claim 1, 1 - phenyl - 3 - γ - dimethylaminopropoxy - 1H - indazole, or a non toxic acid-addition salt thereof.

9) As a new compound according to Claim 1, 1 - benzyl - 3 - β - dimethylaminoethoxy - 1H - indazole or a non-toxic acid-addition salt thereof.

10) As a new compound according to Claim 1, 1 - benzyl - 3 - β - diethylaminoethoxy - 1H - indazole or a non-toxic acid-addition salt thereof.

11) As a new compound according to Claim 1, 1 - benzyl - 3 - γ - dimethylaminopropoxy - 1H - indazole, or a non-toxic acid addition salt thereof.

12) As a new compound according to Claim 1, 1 - *p* - chlorobenzyl - 3 - β-diethylaminoethoxy - 1H - indazole, or a non-toxic acid-addition salt thereof.

13) As a new compound according to Claim 1, 1 - *p* - chlorobenzyl - 3 - γ-dimethylaminopropoxy - 1H - indazole, or a non-toxic acid-addition salt thereof.

14) As a new compound according to Claim 1, 1 - phenethyl - 3 - β - dimethylaminoethoxy - 1H - indazole, or a non-toxic acid addition salt thereof.

15) As a new compound according to Claim 1, 1 - benzyl - 3 - β - dimethylaminoethoxy - 5 - chloro - 1H - indazole, or a non-toxic acid-addition salt thereof.

16) As a new compound according to Claim 1, 1 - *p* - methoxybenzyl - 3 - β-dimethylaminoethoxy - 1H - indazole, or a non-toxic acid-addition salt thereof.

17) As a new compound according to Claim 1, 1 - *p* - chlorobenzyl - 3 - γ-diethylaminopropoxy - 1H - indazole, or a non-toxic acid-addition salt thereof.

18) As a new compound according to Claim 1, 1 - *p* - methoxybenzyl - 3 - γ-dimethylaminopropoxy - 1H - indazole, or a non-toxic acid-addition salt thereof.

19) As a new compound according to Claim 1, 1 - benzyl - 3 - γ - dimethylaminopropoxy - 5 - chloro - 1H - indazole, or a non-toxic acid-addition salt thereof.

20) As a new compound according to Claim 1, 1 - phenethyl - 3 - γ - dimethylaminopropoxy - 1H - indazole, or a non-toxic acid-addition salt thereof.

21) As a new compound according to Claim 1, 1 - *p* - chlorobenzyl - 3 - α-methyl - β - dimethylamino - ethoxy - 1H - indazole, or a non-toxic acid-addition salt thereof.

22) As a new compound according to Claim 1, 1 - *p* - methoxybenzyl - 3-α - methyl - β - dimethylaminoethoxy - 5 - chloro - 1H - indazole, or a non-toxic acid-addition salt thereof.

23) As a new compound according to Claim 1, 1 - *p* - methoxybenzyl - 3 - γ-dimethylaminopropoxy - 5 - chloro - 1H - indazole, or a non-toxic acid-addition salt thereof.

24) As a new compound according to Claim 1, 1 - *p* - methoxybenzyl - 3 - β-dimethylaminoethoxy - 5 - chloro - 1H - indazole, or a non-toxic acid-addition salt thereof.

25) As a new compound according to Claim 1, 1 - benzyl - 3 - β - dimethylaminoethoxy - 6 - chloro - 1H - indazole, or a non-toxic acid-addition salt thereof.

26) As a new compound according to Claim 1, 1 - benzyl - 3 - α - methyl-β - dimethylaminoethoxy - 6 - chloro - 1H - indazole, or a non-toxic acid-addition salt thereof.

27) As a new compound according to Claim 1, 1 - butyl - 3 - β - dimethylaminoethoxy - 5 - chloro - 1H - indazole, or a non-toxic acid-addition salt thereof.

28) As a new compound according to Claim 1, 1 - butyl - 3 - γ - dimethylaminopropoxy - 5 - chloro - 1H - indazole, or a non-toxic acid-addition salt thereof.

29) As a new compound according to Claim 1, 1 - butyl - 6 - chloro - 3 - β-dimethylaminoethoxy - 1H - indazole, or a non - toxic acid - addition salt thereof.

30) As a new compound according to Claim 1, 1 - benzyl - 3 - γ - dimethylaminopropoxy - 4 - chloro - 1H - indazole, or a non-toxic acid-addition salt thereof.

31) As a new compound according to Claim 1, 1 - *p* - chlorobenzyl - 3 - β-dimethylaminoethoxy - 6 - chloro - 1H - indazole, or a non-toxic acid-addition salt thereof.

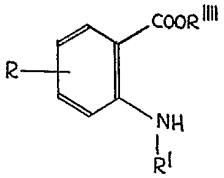
32) As a new compound according to Claim 1, 1 - *p* - chlorobenzyl - 3 - γ-dimethylaminopropoxy - 6 - chloro - 1H - indazole, or a non-toxic acid-addition salt thereof.

33) As a new compound according to Claim 1, 1 - *m* - chlorobenzyl - 3 - γ-dimethylaminopropoxy - 1H - indazole, or a non-toxic acid-addition salt thereof.

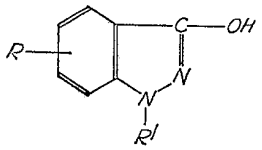
34) As a new compound according to Claim 1, 1 - *o* - chlorobenzyl 3 - γ-dimethylaminopropoxy - 1H - indazole, or a non-toxic acid-addition salt thereof.

35) As a new compound according to Claim 1, 1 - (*m,p* - dimethoxybenzyl)-3 - γ - dimethylaminopropoxy - 1H - indazole, or a non-toxic acid-addition salt thereof.

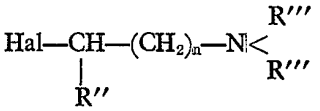
36) A method of preparing the compounds according to Claim 1, characterized in that an anthranilic acid or ester having the general formula



wherein R and R′ are as defined in claim 1 and R′′′′ is a hydrogen atom or a lower alkyl group containing 1—4 carbon atoms, preferably a methyl group, is nitrosated; the obtained N - nitroso derivative is reduced with sodium hydrosulfite, and the 3 - hydroxy - indazole which is prepared in this way, having the general formula



wherein R and R′ are as defined in claim 1, is reacted in the form of an alkali metal derivative with a halogenoalkyl - dialkylamine having the general formula



wherein R′′, R′′′, and n are as defined in claim 1, and Hal is a halogen atom, preferably a chlorine atom and the so obtained 1 - substituted - 3 - dialkylamino-alkoxy - indazole is optionally converted into a non-toxic acid addition salt.

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