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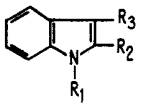
(54) INDOLE DERIVATIVES AND PROCESS FOR PREPARING THE SAME

(71) We, LABAZ, a French body corporate, of 39 Avenue Pierre 1er de Serbie, F-75008 Paris, France, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

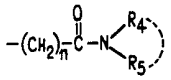
This invention relates to indole derivatives and to processes for preparing the said indole derivatives.

The indole derivatives with which the invention is concerned are represented by the general formula:



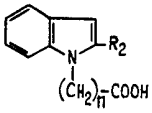
I

wherein R_1 represents a hydrogen atom or a



group, in which n is 1 or 2, R_4 and R_5, which are the same or different, each represent a hydrogen atom, a methyl, ethyl or benzyl group or represent together tetramethylene petamethylene, hexamethylene, oxydiethylene or N-methylaminodiethylene chain, R_2 represents a phenyl, isopropyl or 1-methyl-cyclopropyl group and R_3 represents a hydrogen atom, an isopropyl, methylthio or n-pentanoyl group, with the proviso that R_1 and R_3 are never identical, one of the groups R_1 and R_3 represents a hydrogen atom, and when R_1 is hydrogen, R_2 and R_3 are not both isopropyl.

The derivatives of formula I, wherein R_1 is not a hydrogen atom, may be prepared by reacting an acid derivative of the general formula:



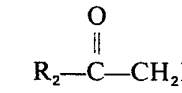
II

wherein R_2 and n have the same meanings as in formula I, with an amine of the general formula:

III

wherein R_4 and R_5 have the same meanings as in formula I.

The derivatives of formula I, wherein R_1 represents a hydrogen atom and R_3 is not a *n*-pentanoyl group, may be prepared by reacting a ketone of the general formula:

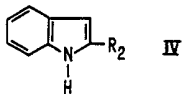


with phenylhydrazine and cyclising the phenylhydrazone so obtained by means of a dehydrating agent or by thermolysis.

The derivatives of formula I, wherein R_3 represents a *n*-pentanoyl radical, may be prepared from an appropriately substituted indole derivative by the method of Vilsmeier, which is described, for instance, by Raison in J. Chem. Soc. 3319 (1949).

The derivatives of formula I, wherein R_2 represents a phenyl group and R_3 a methylthio radical, may be prepared by reacting 2-phenyl-indole with thiourea, in the presence of ethanol and water, and then with dimethylsulphate.

The derivatives of formula II, wherein *n* is 1, may be prepared by reacting a derivative of the general formula:



IV

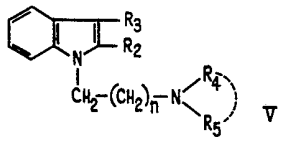
wherein R_2 has the same meanings as in formula I, with ethyl chloroacetate, and saponifying the ester so obtained.

The derivatives of formula II, wherein *n* is 2, may be prepared by reacting a compound of formula IV with acrylonitrile, in the presence of N-benzyl-trimethylammonium hydroxide in dioxan, and hydrolysing in an acid medium the compound so obtained.

The derivatives of formula IV are either known compounds or may be prepared by the above-mentioned Fischer or Bischler Indole Synthesis.

The compounds of the invention have been found to be useful as starting-products for preparing new pharmacologically active indole derivatives.

The same pharmacologically active indole derivatives, which may be prepared from the compounds of the invention, are represented by the general formula:

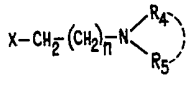


V

wherein R_2, R_3, R_4, R_5 and *n* have the same meanings as in formula I.

One method of use of the compounds of the invention consists in reducing a compound of formula I, wherein R_1 is not a hydrogen atom, by means of lithium-aluminium hydride, optionally in the presence of aluminium chloride, to give a pharmaceutically active compound of formula V.

Another method of use of the compounds of the invention consists in reacting a compound of formula I, wherein R_1 represents a hydrogen atom, with sodium hydride, then reacting the sodium derivative so obtained with a halogenated compound of the general formula:



VI

wherein X represents a halogen atom, preferably chlorine or bromine, R_4, R_5 and *n* have the same meanings as in formula I, to give a pharmacologically active copending Application No. 23942/77, Serial No. have been found to be extremely useful as antidepressive agents of the central nervous system.
copending Application No. 23942/77, have been found to be extremely useful as antidepressive agents of the central nervous system.

The compounds of the invention may also be used for preparing indole derivatives other than those of formula V.

The following Examples illustrate the preparation and use of the compounds of the invention:

EXAMPLE 1

2-Phenyl-3-methylthio-indole

In a two-litre flask were mixed 120.5 g (0.6 mol) of 2-phenyl indole, 95 g (1.25 mol) of thiourea, one litre of pure ethanol, and 200 ml of water and 157.7 g (0.62 mol) of iodine were added by small fractions, the reaction medium being heated to 50°C by means of a water-bath.

The mixture was allowed to cool to room temperature and 100 g of sodium hydroxide were added in 30 minutes, after which a further 50 g of sodium hydroxide was added.

After the dissolution of the sodium hydroxide, 80 g of dimethylsulphate were added at room temperature.

The reaction medium was refluxed for 30 minutes, was cooled and water was added until the final product precipitated. This final product was filtered off and washed with water several times. The precipitate was recrystallized from a mixture of hexane and benzene to give 2-phenyl-3-methylthio-indole.

Yield:87%

Melting Point:103°C.

EXAMPLE 2

2-Phenyl-3-pentanoyl-indole

Into a 500-ml flask cooled to 5°C by means of a ice-bath were introduced 38.7 g (0.3 mol) of N,N-dimethylvaleramide, obtained by reacting dimethylamine with pentanoyl chloride, and 33.5 g (0.22 mol) of freshly distilled phosphorus oxychloride were added drop-by-drop over a period of about 20 minutes. At the end of the operation of addition, the flask was removed from the ice-bath and 38.7 g (0.2 mol) of 2-phenyl-indole were added.

The mixture was stirred at 40°C for 30 minutes, then at 87°C in a boiling water-bath for one hour.

The reaction medium was cooled to 30°C and a solution of 80 g of sodium hydroxide in 120 ml of water was added drop-by-drop and the mixture was heated by means of a boiling water-bath for about 90 minutes, until the release of dimethylamine ceased. The reaction medium was poured into a two-litre beaker containing a solution of 100 ml of 37% hydrochloric acid in one litre of water.

After 30 minutes of stirring, the crude product was filtered off, washed and dried. After two recrystallizations from ethanol, 2-phenyl-3-pentanoyl-indole was obtained.

Yield:65%

Melting Point:139°C.

EXAMPLE 3

2-Phenyl-3-isopropyl-indole

Isobutyl phenyl ketone phenylhydrazone was cyclised by heating to 135°C for 10 minutes, in the presence of 3.5 parts by weight of polyphosphoric acid, containing 4 parts of phosphoric anhydride and 5 parts of 85% phosphoric acid.

The product so obtained was poured into water and the precipitate which formed was filtered off and dried. 2-Phenyl-3-isopropyl-indole was obtained after recrystallization from heptane.

Yield:70%

Melting Point:115°C.

EXAMPLE 4

3-(2'-Phenyl-1'-indolyl)-N-methylpropionamide

a) Preparation of 1-(2'-cyano-ethyl)-2-phenyl-indole

To 72 g (0.37 mol) of 2-phenyl-indole in 200 ml of dioxan were added 6 ml of N-benzyl-trimethylammonium hydroxide and 26 ml (0.6 mol) of acrylonitrile. The mixture was heated to 60°C for 15 hours by means of a thermostated water-bath and the reaction medium was then cooled in a freezer until crystallization of the final product.

After filtration and three recrystallizations from ethanol, 1-(2'-cyano-ethyl)-2-phenyl-indole was obtained.

Yield:80%

Melting Point:90°C.

b) Preparation of 3-(2'-phenyl-1'-indolyl)-propionic acid

1-(2'-Cyano-ethyl)-2-phenyl-indole was refluxed in the presence of 36% hydrochloric acid and almost all the acid precipitated from the hot medium.

After filtration and purification by transforming the acid into its sodium salt, the substance was recrystallized from ethanol and 3-(2'-phenyl1'-indolyl)-propionic acid was obtained.

Yield:85%

Melting Point:129°C.

c) Preparation of 3-(2'-phenyl-1'-indolyl)-N-methylpropionamide

While stirring, 14 ml of triethylamine were added to 26.5 g (0.1 mol) of 3-(2'-phenyl-1'-indolyl) propionic acid in 50 ml of anhydrous tetrahydrofuran. The temperature was maintained between −5°C and −10°C by means of a mixture of dry ice and acetone and 10 ml of ethyl chloroformate in a small quantity of tetrahydrofuran was poured into the solution, care being taken that the temperature did not exceed 0°C.

The reaction medium was allowed to stand at −5°C for 30 minutes and methylamine, previously cooled to −10°C, was added.

The mixture was stirred for several hours and, while stirring, 600 ml of a cold 5% aqueous solution of sodium hydroxide were poured into the reaction medium.

The oil which formed was extracted with ether, which was then eliminated under reduced pressure.

After recrystallization of the amide from isopropanol, 3-(2'-phenyl-1'-indolyl)-N-methylpropionamide was obtained.

Yield:75%

Melting Point:126°C.

EXAMPLE 5

(2-phenyl-1-indolyl)-acetamide

a) Preparation of (2-phenyl-1-indolyl) acetic acid

While stirring and under nitrogen atmosphere, a solution of 20 g (0.105 mol) of 2-phenyl-indole in 50 ml of dimethylformamide was added to a suspension of 5.5 g (0.115 mol) of NaH in 100 ml of dimethylformamide, the release of hydrogen being controlled. 16 g (0.13 mol) of ethyl chloroacetate were added and the reaction medium was heated to 70°C for 3 hours by means of a water-bath.

The mixture was poured into water containing a little acetic acid and was extracted with ether.

The ethereal phase was then washed several times with water and dried over magnesium sulphate. The (2-phenyl-1-indolyl) ethyl acetate so obtained was saponified with a 20% alcoholic solution of potassium hydroxide.

The ethanol was evaporated off and the residue was dissolved in water. The 2-phenyl-indole which did not react was extracted with ether.

The aqueous phase was purified by boiling in the presence of active carbon and was acidified with hydrochloric acid. The white precipitate which formed was recrystallized from ethanol.

b) Preparation of (2-phenyl-1-indolyl)-acetamide

The same method as in Example 4c was used but starting from (2-phenyl-1-indolyl) acetic acid, adding liquid ammonia instead of methylamine and first cooling the reaction medium to −20°C. After recrystallization from isopropanol, (2-phenyl-1-indolyl)-acetamide was obtained.

Yield:95%

Melting Point:190°C.

By the same method, but using the appropriate starting-products, the following compounds were prepared:

Compounds	Melting Point °C	Yield %
(2-Phenyl-1-indolyl)-N-methyl-acetamide	190 (isopropanol)	35
N-[(2-Phenyl-1-indolyl)acetyl]-morpholine	235 (toluene)	60
N-[(2-Phenyl-1-indolyl)acetyl)]-N-methyl-piperazine	175 (cyclohexane/ethanol)	45

Compounds	Melting Point °C	Yield %
(2-Phenyl-1-indolyl)-N,N-dimethyl-acetamide	161 (cyclohexane)	70
(2-Phenyl-1-indolyl)-N,N-diethyl-acetamide	128 (cyclohexane)	72
N-[(2-Phenyl-1-indolyl)acetyl] pyrrolidine	184 (benzene)	37
N-[(2-phenyl-1-indolyl)acetyl]	147 (ethylacetate)	65

EXAMPLE 6

1-(3'-N-methylamino-propyl)-2-phenyl-indole

While stirring and at room temperature a solution of 5.56 g (0.02 mole) of 3-(2'-phenyl-1'-indolyl)-N-methylpropionamide), prepared as in Example 4, in a minimum of tetrahydrofuran, was poured into a mixture of 2.66 g (0.02 mol) of aluminium chloride, 3.05 g (0.08 mol) of Li Al H_4 and 100 ml of tetrahydrofuran.

After the end of the operation of addition, the mixture was refluxed for 5 hours and was allowed to cool. The reaction medium was slowly hydrolysed under nitrogen atmosphere with cracked ice.

The gel which formed was vigorously stirred in the presence of ether, was filtered off and washed several times with ether. The ethereal phases were collected and evaporated off (not to dryness). The product was taken up in ether, washed with water and dried over magnesium sulphate.

Melting Point of the hydrochloride:187°C.

By the above-described method, but using the appropriate starting-products, the following compounds were prepared:

Compounds	Melting Point °C
1-(2'Methylamino-ethyl)-2-phenyl-indole hydrochloride	197 (isopropanol)
1-(2'-Mopholino-ethyl)-2-phenyl-indole	80 (hexane)
1-(2'-Diethylamino-ethyl)-2-phenyl-indole acid oxalate	180 (ethanol)
1-(2'-N-Methylpiperazinyl-ethyl)2-phenyl-indole dihydrochloride	180 (isopropanol)
1-(2'-Aminoethyl)-2-phenyl-indole hydrochloride	222 (isopropanol)
1-(2'-Hexamethyleneimino-ethyl)2-phenyl-indole fumarate	212 (ethanol)
1-(3'-Amino-propyl)-2-phenyl-indole hydrochloride hexamethyleneimino	acid 222 (isopropanol)

EXAMPLE 7

1-(3'-Dimethylamino-propyl)-2-phenyl-3-isopropyl-indole

Under nitrogen atmosphere and while stirring, a solution of 23.5 g (0.1 mol) of 2-phenyl-3-isopropyl-indole, prepared as in Example 3, in 25 ml of dry dimethylformamide was mixed with a suspension of 2.9 g (0.12 mol) of NaH in 50 ml of dry dimethylformamide, the temperature of the mixture being maintained between 10 and 15°C. The duration of the operation of addition was determined by the intensity of the hydrogen release and was about 15 minutes.

The reaction medium was allowed to cool to room temperature and 14 g (0.1 mol) of 1-chloro-3-dimethylamino-propane were added. The mixture was allowed to react for 10 hours at room temperature, or for 4 hours at 50°C.

After the end of the reaction, the mixture was poured into an iced solution of hydrochloric acid and was washed with ether in order to eliminate the non-alkylated 2-phenyl-3-isopropyl-indole

The base was regenerated from its hydrochloride, by means of a 20% solution

of sodium hydroxide, and was extracted with ether. The ethereal solution was washed with water, dried over magnesium sulphate and the solvent was evaporated off.

After recrystallization from a mixture of water and dimethylformamide, 1-(3'-dimethylamino-propyl)-2-phenyl-3-isopropyl-indole was obtained.

Yield:72%.

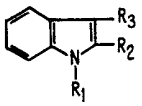
Melting Point:166°C.

By the same method but using the appropriate starting-products, the following compounds were prepared:

Compounds	Melting Point °C
1-(3'Dimethylaminopropyl)-2-(1'-methyl-cyclopropyl)-indole acid fumarate	191 (methanol)
1-(3'-Dimethylamino-propyl)-2-phenyl-3-pentanoyl-indole hydrochloride	190 (isopropanol)
1-(3'-Dimethylamino-propyl)-2-phenyl-3-methylthio-indole hydrochloride	90
1-(3'-Piperidino-propyl)-2-phenyl-indole hydrochloride	240 (isopropanol)

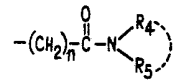
WHAT WE CLAIM IS:—

1. Indole derivatives represented by the general formula:



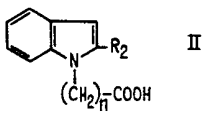
I

wherein R_1 represents a hydrogen atom or a



group, in which n is 1 or 2, R_4 and R_5, which are the same or different, each represent a hydrogen atom, a methyl, ethyl or benzyl group or represent together a tetramethylene, pentamethylene, hexamethylene, oxydiethylene or N-methyl-aminodiethylene chain, R_2 represents a phenyl, isopropyl or 1-methylcyclopropyl group and R_3 represents a hydrogen atom, an isopropyl, methylthio or n-pentanoyl group, with the proviso that R_1 and R_3 are never identical, one of the groups R_1 and R_3 represents a hydrogen atom, and when R_1 is hydrogen, R_2 and R_3 are not both isopropyl.

2. A process for preparing an indole derivative as claimed in Claim 1, where R_1 is not a hydrogen atom, which comprises reacting an acid derivative of the general formula:



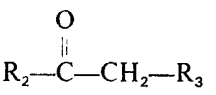
II

wherein R_2 and n have the same meanings as in Claim 1, with an amine of the general formula:

III

wherein R_4 and R_5 have the same meanings as in Claim 1.

3. Process for preparing an indole derivative as claimed in Claim 1, where R_1 is a hydrogen atom, R_2 has the same meaning as in Claim 1 and R_3 represents an isopropyl or methylthio group, which comprises reacting a ketone of the general formula:

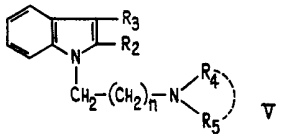


IV

with phenylhydrazine and cyclising the phenylhydrazone derivative so obtained by means of a dehydrating agent or by thermolysis.

4. An indole derivative in accordance with Claim 1, as described in any one of the foregoing Examples 1 to 5.

5. Process for preparing a compound of the general formula:



V

wherein R_2. R_3, R_4, R_5 and n have the same meanings as in Claim 1, which comprises reducing with lithium aluminium hydride, optionally in the presence of aluminium chloride, an indole derivative as claimed in Claim 1, where R_1 is not a hydrogen atom, to give the required compound.

6. Process according to Claim 5, substantially as described in the foregoing Example 6.

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