

1191.237



PATENT SPECIFICATION

NO DRAWINGS

1191.237

Date of Application (No. 14967/68) and filing Complete Specification: 28 March, 1968.

Application made in United States of America (No. 626,965) on 30 March, 1967.

Application made in United States of America (No. 639,315) on 18 May, 1967.

Complete Specification Published: 13 May, 1970.

Index at acceptance:—C2 C(1E5K4, 1E6K4, 1H1A1, 1H1C3, 1Q6C, 1Q7A, 1Q8A, 1Q9B, 1Q9F2, 1Q11J, 2A3, 2A7, 2R15, 3A12A4A, 3A12B3, 3A12C5, 3A13A3A4, 3A13A3B3, 3A13A3C, 3A13A3K, 3A13C1C, 3A13C9, 3A13C10B, 3A13C10F, 3A14A3D, 3A14A5, 3A14A7B, 3A14A8D, B4A1, B4H, B4M, 213, 22Y, 220, 226, 246, 25Y, 250, 251, 30Y, 305, 32Y, 321, 351, 352, 36Y, 364, 365, 650, 662, 682, 761, 762, 175—270—276, LF, LK)

International Classification:—C 07 d 57/02

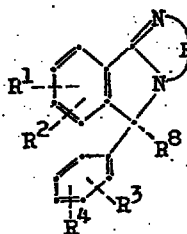
COMPLETE SPECIFICATION

1,3-Diazacycloalkeno[2,1-a]isoindole Derivatives and a process for the manufacture thereof

We, F. HOFFMANN-LA ROCHE & CO., AKTIENGESELLSCHAFT, a Swiss Company of 124—184 Grenzacherstrasse, Basle, Switzerland, 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:—

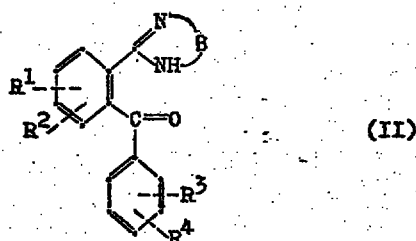
The present invention is concerned with 1,3-diazacycloalkeno[2,1-a]isoindole derivatives and a process for the manufacture thereof. The invention is also concerned with pharmaceutical preparations containing said derivatives.

The 1,3-diazacycloalkeno[2,1-a]isoindole derivatives provided by the present invention are compounds of the general formula



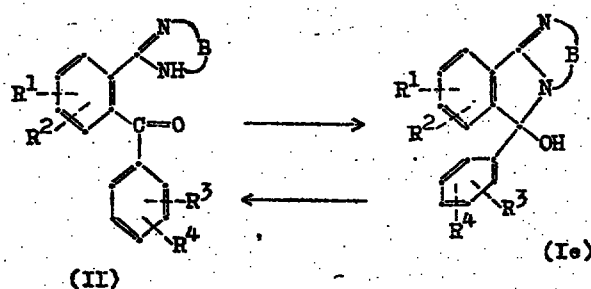
(I)
, wherein B represents an alkylene chain containing from 2 to 4 carbon atoms in which one or more of the hydrogen atoms may be replaced by lower-alkyl, R¹, R², R³ and R⁴ individually represent a halogen atom or the trifluoromethyl or hydroxy group or a lower-alkyl or lower-alkoxy group and R⁵ represents a hydroxy or lower-alkoxy group and wherein the broken lines denote that the atoms or groups attached thereby are optional, tautomers of those compounds in which R⁵ is present and represents the hydroxy group and acid addition salts of said compounds and tautomers.

The compounds of formula I in which R⁵ is present and represents the hydroxy group can undergo a prototropic shift to form compounds of the general formula



wherein B, R¹, R², R³, R⁴ and the broken lines have the significance given earlier.

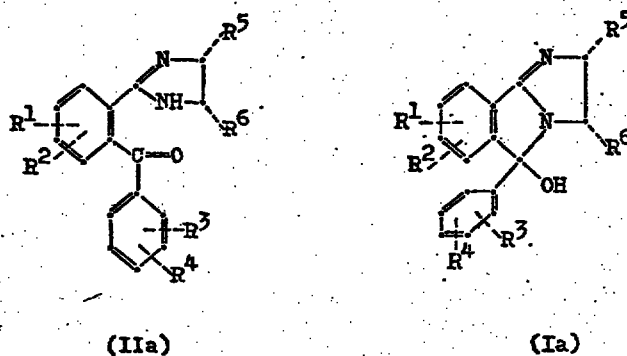
The compounds of formula II are the tautomers referred to earlier and it will be appreciated that both they as well as tautomeric mixtures with the compounds of formula I in which R⁵ is present and represents the hydroxy group also form part of this invention. Tautomeric mixtures can be represented as follows:



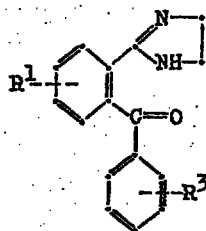
wherein B, R¹, R², R³, R⁴ and the broken lines have the significance given earlier.

It will be appreciated that the term 'lower alkyl' is used in this description and in the claims appended hereto to mean straight-chain and branched-chain hydrocarbon groups containing from 1 to 6 carbon atoms such as methyl, ethyl, propyl, isopropyl, butyl, *sec*butyl and *tert*butyl. The term 'lower alkoxy' denotes lower-alkyl ether groups in which the alkyl group has the definition given earlier. The term 'halogen' herein includes all four halogens, namely chlorine, bromine, iodine and fluorine. It will also be appreciated that the dots in the formulae given in this description and in the accompanying claims are intended to represent carbon atoms.

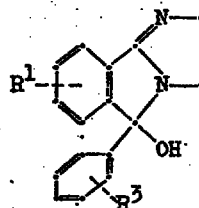
One particularly interesting class of 1,3-diazacycloalkeno[2,1-a]isoindole derivatives provided by the invention comprises those compounds of formulae I and II in which B represents an ethylene group which may carry a lower-alkyl group on one or other or both carbon atoms, that is to say, compounds of the general formulae



(wherein R¹, R², R³, R⁴ and the broken lines have the significance given earlier and R⁵ and R⁶ each represent a lower-alkyl group), and their pharmaceutically acceptable acid addition salts and tautomeric mixtures. A preferred class of 1,3-diazacycloalkeno[2,1-a]isoindole derivatives provided by the invention comprises those compounds of formulae I and II in which R² and R⁴ are absent and B represents the ethylene group, that is to say, compounds of the general formulae

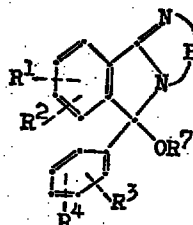


(IIb)



(IIa)

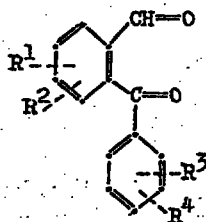
(wherein R^1 , R^3 and the broken lines have the significance given earlier), and their pharmaceutically acceptable acid addition salts and tautomeric mixtures. Especially preferred 1,3-diazacycloalkeno[2,1-a]isoindole derivatives provided by the invention are those in which R^1 (when present) represents a chlorine atom and R^3 (when present) represents a chlorine or bromine atom or the methoxy group. Also of interest are the mixed ethers of compounds of formula Ie with lower-alkanols, that is to say, compounds of the general formula



(Id)

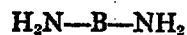
wherein B, R^1 , R^2 , R^3 , R^4 and the broken lines have the significance given earlier and R^7 represents a lower-alkyl group.

According to the process provided by the invention, the 1,3-diazacycloalkeno[2,1-a]isoindole derivatives aforesaid (that is to say, the compounds of formulae I and II and their acid addition salts) are manufactured *either* by condensing a compound of the general formula



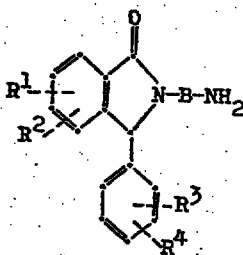
(IV)

, wherein R^1 , R^2 , R^3 , R^4 and the broken lines have the significance given earlier, with a diamine of the general formula



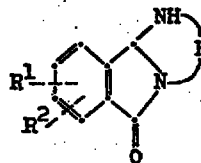
(XII)

, wherein B has the significance given earlier, or with a salt thereof, or by cyclising a compound of the general formula



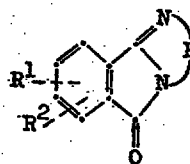
(VI)

, wherein B, R¹, R², R³, R⁴ and the broken lines have the significance given earlier, by treatment thereof with a LEWIS acid or by reacting a compound of the general formula



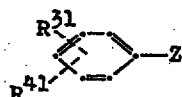
(VIII)

5 , wherein B, R¹, R² and the broken lines have the significance given earlier, or a dehydro derivative thereof of the general formula



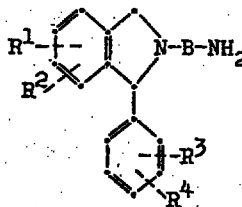
(X)

10 , wherein B, R¹, R² and the broken lines have the significance given earlier, with an organo-metallic phenyl compound of the general formula



(XI)

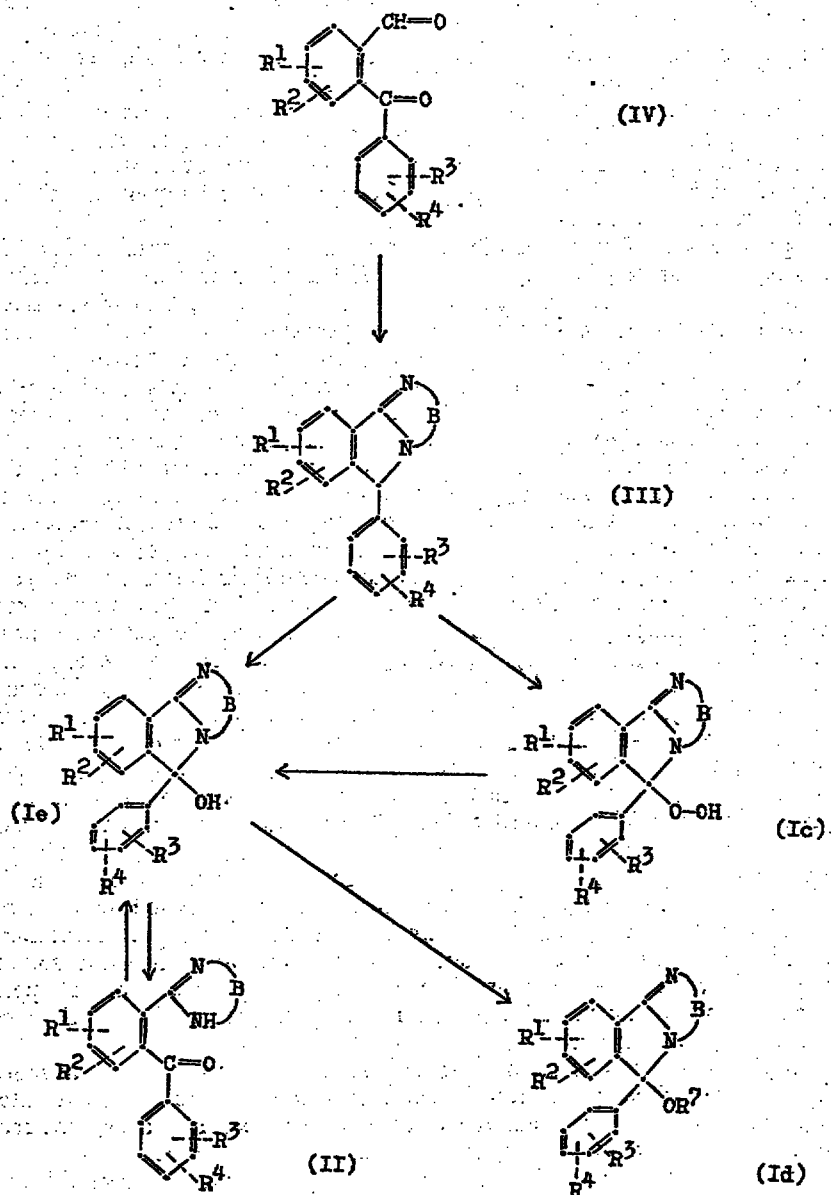
, wherein Z represents Li, Mg Br, MgI or Mg Cl, R³¹ and R⁴¹ individually represent a halogen atom or the trifluoromethyl group or a lower-alkyl or lower-alkoxy group and the broken lines have the significance given earlier, or by treating a compound of the general formula



(XIII)

20 , wherein B, R¹, R², R³, R⁴ and the broken lines have the significance given earlier, with an oxidising agent and, if desired, oxidising any product in which R⁵ is absent to a corresponding product in which R⁵ is present and represents a hydroxy group, if desired, lower-alkylating a resulting product in which R⁵ is present and represents a hydroxy group to a corresponding product in which R⁵ is present and represents a lower-alkoxy group, if desired, separating a racemic mixture obtained into its optically active antipodes and, also if desired, converting any base obtained into an acid addition salt.

25 One embodiment of the present process can be illustrated by the following formula scheme in which B, R¹, R², R³, R⁴, R⁷ and the broken lines have the significance given earlier.



With regard to the foregoing formula scheme, the starting materials of formula IV are claimed *per se* in the specification of our copending Application for Letters Patent No. 28271/69 (now Serial No. 1191238) and can be prepared as described therein.

The starting materials of formula IV are readily condensed with diamines of formula XII by mixing the components or by reacting them in the presence of an organic solvent such as benzene, toluene or an alcohol such as a lower-alkanol. The condensation is conveniently carried out at room temperature or above, preferably at a temperature between about 20°C and 150°C. Alternatively, the diamine of formula XII can be used in the form of a salt, in which case the condensation is carried out by heating the mixture of components to a melt.

The condensation products (that is to say, the compounds of formula III) can be readily oxidised; for example, by treatment with an oxidising agent such as hydrogen peroxide or by exposure to gaseous oxygen at room temperature to give the peroxides of formula Ic which are readily reduced to the corresponding end products. The oxidation is conveniently carried out in an organic solvent such as an alcohol or N,N-dimethyl-formamide at room temperature. Higher or lower temperatures (e.g. between 20°C and 100°C) can also be employed.

Since the peroxides of formula Ic readily undergo reduction, the mixture obtained upon treatment of a compound of formula III with an oxidising agent will ordinarily contain the end products of formula Ie together with the peroxides of formula Ic. Complete reduction of the peroxide can be accomplished without separating it from the mixture and, preferably, the oxidation product is submitted directly to treatment with a reducing agent. If desired, however, the peroxide of formula Ic can be separated from the mixture obtained upon treatment of a compound of formula III with an oxidising agent by any of the usual techniques (e.g. chromatographic separation or fractional crystallization).

The peroxides of formula Ic are claimed *per se* in the specification of our copending Application for Letters Patent No. 28272/69 (now Serial No. 1191239).

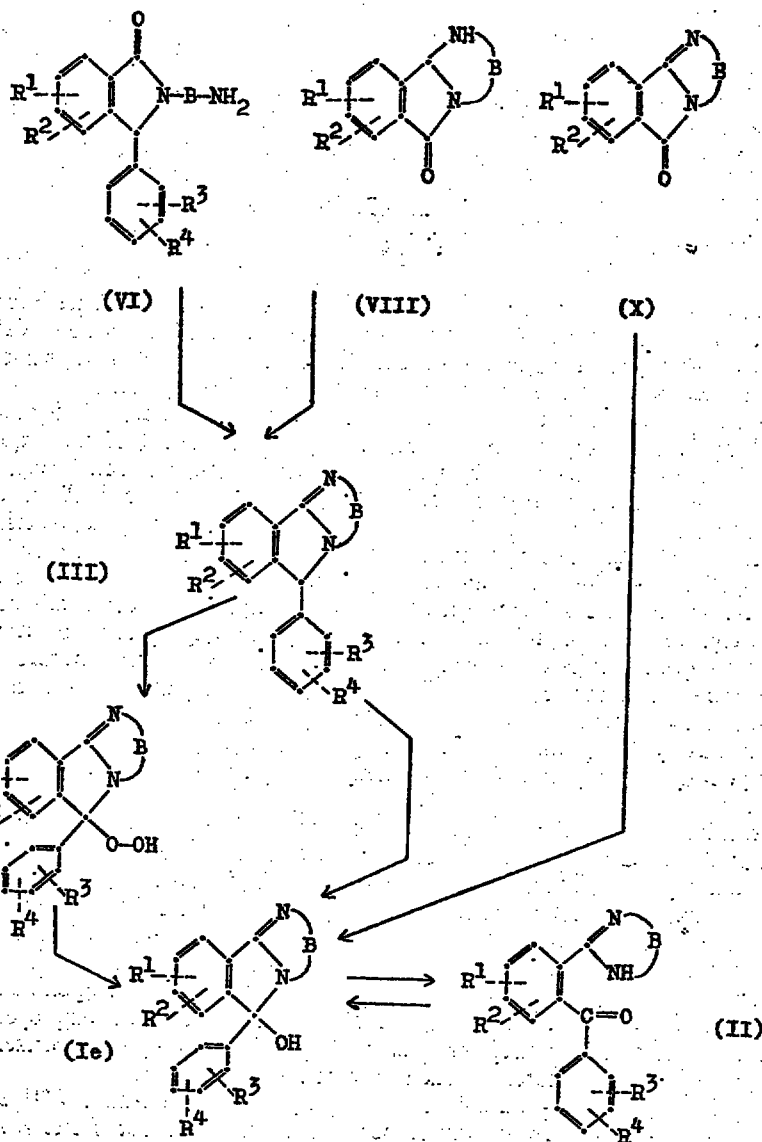
The reduction of a peroxide is conveniently carried out by means of any reducing agent conventionally used for the reduction of peroxides (such as sodium sulphite or trialkyl-phosphite), preferably in the presence of an organic solvent such as an alcohol (e.g. methanol or ethanol) or N,N-dimethyl-formamide or, when using a salt of the peroxide, the reduction can be carried out in an aqueous solvent (e.g. in an aqueous-alcoholic solvent). The reduction is suitably carried out at room temperature or above, preferably at a temperature between about 20°C and 100°C.

As mentioned earlier, the hydroxyl proton of a compound of formula Ie can undergo a prototropic shift to form the corresponding isomeric product of formula II. In solution, the product obtained upon oxidation and reduction of a compound of formula III will ordinarily be a mixture of the tautomeric forms Ie and II. The relative amounts of the isomeric forms present is dependent upon such factors as the solvent system employed, the pH of the medium and the particular product, that is to say, the meaning of B, R¹, R², R³ and R⁴ in formulae Ie and II. For example, in a solution of chloroform the product obtained upon oxidation and reduction of 5-phenyl-2,3-dihydro-5H-imidazo[2,1-a]isoindole contains a mixture of the isomers 5-hydroxy-5-phenyl-2,3-dihydro-5H-imidazo[2,1-a]isoindole and 2-(2-benzoyl-phenyl)-2-imidazoline in a ratio of about 1:1. The acid addition salts isolated in the ordinary manner from the reaction product of the oxidation and reduction of 5-phenyl-2,3-dihydro-5H-imidazo[2,1-a]isoindole are ordinarily obtained as those of compounds of formula II.

Compounds of formula Id are prepared from compounds of formula Ie by treating an acid addition salt (e.g. the hydrochloride or hydrobromide) of a compound of formula Ie with a lower-alkanol, preferably at an elevated temperature. The etherification can be suitably carried out using the lower-alkanol as the solvent or in the presence of an inert organic solvent such as ether and preferably at a temperature between about room temperature and the reflux temperature of the etherification mixture (i.e. up to about 150°C).

The novel compounds of formula Id as well as the compounds of formulae Ic and III are obtained as racemates. Racemic mixtures can be separated into the optically active antipodes if desired. It will thus be appreciated that both the racemic mixtures and optically active antipodes form part of this invention.

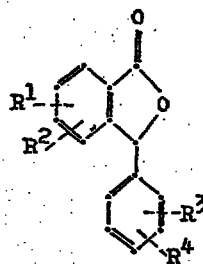
Alternatively, the compounds of formulae III, II and Ie aforesaid can be manufactured according to the following formula scheme in which B, R¹, R², R³, R⁴ and the broken lines have the significance given earlier.



According to one embodiment of the process outlined in this formula scheme, the compounds of formula III are prepared by cyclisation of a phthalimidine of formula VI. The cyclisation of a phthalimidine of formula VI is readily accomplished by treatment thereof with a LEWIS acid such as titanium tetrachloride or boron trifluoride. The oxidation and reduction of a compound of formula III to form the desired end products is accomplished by the procedures described earlier.

The treatment with a LEWIS acid is preferably carried out in the presence of an inert organic solvent (e.g. a hydrocarbon solvent such as toluene or xylene) and preferably at an elevated temperature, suitably at the reflux temperature of the solvent. A preferred temperature range for the cyclisation of the phthalimidines is a temperature between about 50°C and 200°C.

The phthalimidines of formula VI are prepared by condensing a 3-phenylphthalide of the general formula



(VII)

, wherein R^1 , R^2 , R^3 , R^4 and the broken lines have the significance given earlier, with a diamine of formula XII. The 3-phenyl-phthalides of formula VII and the diamines of formula XII are known compounds or analogues of known compounds which are readily accessible by analogy to the known compounds.

The preparation of the phthalimidine starting materials of formula VI is catalysed by salts of organic bases such as pyridine, trialkyl amines, quinoline or ethylenediamine with acids such as organic acids, mineral acids (e.g. sulphuric acid, hydrohalic acids, phosphoric acid or perchloric acid) or LEWIS acids such as zinc chloride or aluminium chloride. Preferred catalysts for the reaction are the salts of ethylenediamine and pyridine such as pyridinium hydrochloride. It is preferred to carry out the reaction using an excess of the ethylenediamine reactant as solvent. However, inert organic solvents such as alcohols (e.g. methanol or ethanol), hydrocarbons (e.g. benzene or toluene) or ethers (e.g. tetrahydrofuran or dioxane) can also be employed. The reaction is carried out at an elevated temperature, preferably at a temperature above 100°C . Especially suitable temperatures for carrying out this reaction are temperatures between about 180°C and 250°C .

Alternatively, the phthalimidine starting materials of formula VI can be prepared by catalytically hydrogenating a 9b-phenyl-1,2,3,9b-tetrahydro-5H-imidazo[2,1-a]-isoindol-5-one.

According to another embodiment of the process outlined in the foregoing formula scheme, the compounds of formula III can be manufactured from the corresponding diazacycloalkeno-isoindolones of formula VIII by reaction thereof with an appropriate organo-metallic phenyl compound of formula XI.

The reaction of a diazacycloalkeno-isoindolone of formula VIII with a phenyl-lithium compound of formula XI can conveniently be carried out in the presence of an inert solvent at about room temperature. Higher or lower temperatures, suitably those in the range of from about 10°C to 100°C can also be employed. Suitable solvents that can be used are, for example, hydrocarbons such as benzene, toluene or xylene, ethers or mixtures of such solvents.

The diazacycloalkeno-isoindolone starting materials of formula VIII are claimed *per se* in the specification of our copending Application for Letters Patent No. 28273/69 (now Serial No. 1191240) and can be prepared as described therein.

According to a further embodiment of the process outlined in the foregoing formula scheme, compounds of formula Ic can be manufactured from compounds of formula X by reaction thereof with an appropriate organo-metallic phenyl compound of formula XI. The reaction can conveniently be carried out in the presence of an inert solvent at a temperature in the range of from room temperature up to the reflux temperature of the solvent. Suitable solvents which can be used are, for example, benzene, toluene, xylene, ether, dioxane, tetrahydro-furan or mixtures of such solvents.

Examples of organo-metallic phenyl compounds of formula XI are phenyl-magnesium iodide, (3-trifluoromethyl-phenyl)-magnesium bromide, phenyl-magnesium chloride or phenyl-lithium.

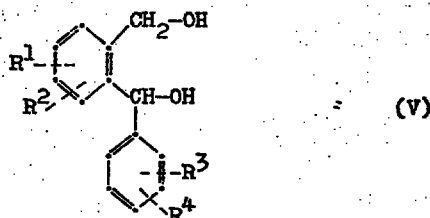
The compounds of formula X are claimed *per se* in the specification of our copending Application for Letters Patent No. 28273/69 (now Serial No. 1191240) and can be prepared as described therein.

According to another embodiment of the process of this invention, compounds of formula I in which R^3 is present and represents a hydroxy group (i.e. compounds of formula Ic) and tautomers thereof of formula II can be manufactured by treating a 1-phenyl-2-aminoalkyl-isoindoline of formula XIII with an oxidising agent (e.g. gaseous oxygen or a chemical oxidant such as chromium trioxide in acetic acid).

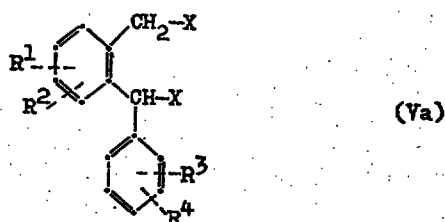
The treatment is preferably carried out in the presence of an organic solvent such as a hydrocarbon solvent (e.g. benzene or toluene), an alcanoic acid (e.g. acetic

acid or propionic acid), an ether, an alcohol or a solvent such as N,N-dimethylformamide. The treatment can suitably be accomplished at room temperature or at an elevated temperature, preferably at a temperature between about 20°C and 100°C.

The 1-phenyl-2-aminoalkyl-isoindoline starting materials of formula XIII are prepared from a diol of the general formula



, wherein R¹, R², R³, R⁴ and the broken lines have the significance given earlier, via a diester of the general formula



wherein R¹, R², R³, R⁴ and the broken lines have the significance given earlier and X stands for a halogen atom (preferably a chlorine, bromine or iodine atom) or a similar leaving group such as mesyloxy or tosyloxy. The diols of formula V are known compounds or are readily obtainable in an analogous manner to the known compounds. The diesters are obtained by the usual esterification techniques; for example, by treating the diol with one of the ordinary esterifying agents such as a halo-acid and halides such as a phosphorus halide, a thionyl halide or a tosyl halide.

The diester of formula Va is, in turn, converted into a 1-phenyl-2-aminoalkyl-isoindoline of formula XIII by condensation with a diamine of formula XII. The condensation of the diester with the diamine is conveniently carried out by adding the diester to the diamine at room temperature. Preferably, a large molar excess of diamine is used. The condensation can also be carried out at temperatures above or below room temperature, although for practical reasons it is preferred to operate at a temperature between about 0°C and 100°C. The condensation is suitably carried out in the presence of an organic solvent such as benzene, methylene chloride, ether or tetrahydro-furan or, in the case where either or both of the reactants are liquid under the conditions of the condensation, the condensation is conveniently carried out in the absence of a solvent.

Suitable salts of the compounds of formulae I and II are prepared from non-toxic organic and inorganic acids. Suitable organic acids are, for example, maleic acid, fumaric acid, ascorbic acid, tartaric acid, salicylic acid, succinic acid and citric acid. Suitable inorganic acids are, for example, the hydrohalic acids (e.g. hydrochloric acid and hydrobromic acid), sulphuric acid, sulphamic acid and phosphoric acid. The acid addition salts are readily prepared by the usual techniques for the preparation of acid addition salts.

The compounds of formulae I and II and their pharmaceutically acceptable acid addition salts are useful as psychostimulants. When administered, for example, orally to animals such as mice they produce a direct-acting stimulant effect of long duration. Among compounds of formula I and II which have been tested and found to be highly effective in tests demonstrating psychostimulant effects there can be named 2 - (2 - benzoyl - phenyl) - 2 - imidazoline, 5 - (4 - chloro - phenyl) - 5 - hydroxy - 2,3 - dihydro - 5H - imidazo[2,1 - a]isoindole, 5 - hydroxy - 5 - (4 - methoxy - phenyl) - 2,3 - dihydro - 5H - imidazo[2,1 - a]isoindole, 7 - hydroxy - 7 - phenyl - 2,3,4,5 - tetrahydro - 7H - diazepino[2,1 - a]isoindole and 5 - methoxy - 5 - phenyl - 2,3 - dihydro - 5H - imidazo[2,1 - a]isoindole.

The compounds of this invention and their pharmaceutically acceptable acid addition salts are thus useful as psychostimulants in the treatment of depressed states; for example, in cases of simple depression or in cases of chronic nervous exhaustion.

In addition to their use as psychostimulants, the compounds of formula Id and II are also useful as analgesic agents. They also show potent antiinflammatory activity, antioedema activity and muscle relaxant activity. For example, 2-(2-benzoyl-phenyl)-2-imidazoline, when submitted to standard pharmacological tests for analgesic properties, exhibits marked activity. Compounds of formulae Id and II are also useful as anorexigenic agents. Compounds of this series have also demonstrated useful cardiovascular properties. In addition to being useful as psychostimulants, the compounds of formula III are also useful as antiinflammatory and antipyretic agents.

Compounds of formula II have also been found to be active as antifungal agents. For example, they have been found to be active in vitro in *Candida albicans*, *Microsporum audouinii* and *Trichophyton mentagrophytes*. Accordingly, these compounds can be employed as antifungal agents in the treatment of pathogenic diseases caused by these organisms. They can, for example, be employed in the treatment of infectious fungal diseases such as moniliasis and dermatomycoses. For the treatment of fungal infections the compounds of formula II can be employed by applying a suitable composition. Suitable compositions are prepared by embodying a compound of formula II or a pharmaceutically acceptable salt thereof in a conventional carrier suitable for topical administration.

The novel products of this invention are mostly white crystalline odourless solids melting at temperatures of the order of 200°C. They have basic properties and can be conveniently prepared in the form of their acid addition salts. Suitable salts are prepared as described hereinabove. The salts are characteristically white crystalline odourless solids soluble in water and they have good stability under ordinary conditions.

The end products of the invention, preferably in the form of their acid addition salts, can be formulated into preparations suitable for administration by enteral or parenteral routes. They can be embodied in pharmaceutical unit dosage forms. Parenteral preparations will ordinarily contain less of the active ingredient than preparations intended for enteral (e.g. oral) administration. For oral administration the products of this invention can be made up in the form of tablets or capsules. Preparations suitable for oral administration may be such as to provide either immediate or sustained release of the active ingredient. In general, the preparations will be made up using pharmaceutically acceptable adjuvant materials comprising from about 60 per cent to 98 per cent of the weight of the preparations in oral dosage form.

For parenteral administration the compounds can be formulated with a liquid diluent (for example, distilled water) so as to provide a suitable parenteral dosage form. In general, the compounds of this invention are formulated with conventional inert adjuvants into dosage forms suitable for enteral or parenteral administration following conventional techniques and procedures. Suitable dosage forms include tablets and capsules as well as solutions, emulsions and suspensions. The inert adjuvants which are suitable for use in preparing the various dosage forms include inorganic or organic liquids and solids such as water, gelatin, lactose, starch, magnesium stearate, talc, vegetable oils, gums, polyalkylene glycols and petroleum jelly. In addition, the compounds can be used in combination with preservatives, stabilisers, wetting or emulsifying agents, salts for altering the osmotic pressure or buffers. If desired, the compounds can also be used in admixture with other therapeutically valuable substances.

The preferred oral dosage form (i.e. tablets or capsules) will be administered under ordinary circumstances three or four times daily. The parenteral dosage form will be administered ordinarily once or twice daily. Effective dosages for the administration of compounds of this invention will, of course, depend in all instances upon the severity and individual characteristics of each case as determined by the prescribing practitioner. It will be understood that dosage forms containing larger and smaller quantities of the active ingredient than mentioned herein can be used and that such dosage forms can be administered more or less frequently than indicated heretofore. It will also be understood that dosage forms containing inert adjuvants in quantities which are greater or less than those indicated heretofore can also be used.

The following Examples illustrate the process provided by the invention. De-

composition melting points may vary $\pm 10^\circ\text{C}$, depending on the rate of heating.

EXAMPLE 1

A solution of 21 g of *o*-benzoyl-benzaldehyde [prepared as described in the specification of our copending Application No. 28271/69 (now Serial No. 1191238)] in 250 ml of toluene and 34 ml of ethylenediamine was heated at reflux for 24 hours, during which time 11.5 ml of an aqueous phase were separated in a DEAN-STARK receiver. The resulting mixture was concentrated *in vacuo* to give an orange oil. This oil was dissolved in ethyl acetate and the solution was washed twice with water, dried and concentrated. The concentrate was dissolved in 200 ml of ethyl acetate and a solution of 5.3 ml of concentrated sulphuric acid in 100 ml of ethanol was added. A crystalline precipitate was collected and recrystallized from a mixture of methanol and ethyl acetate to give 5-phenyl-2,3-dihydro-5H-imidazo[2,1-a]isoindole sulphate as white prisms melting at $226^\circ\text{--}229^\circ\text{C}$ (with decomposition); *ultraviolet* maxima (isopropanol) at $240\text{ m}\mu$ ($\epsilon=15,000$) and $276\text{ m}\mu$ ($\epsilon=5,400$); *infrared* absorption (potassium bromide) at 1660 cm^{-1} .

Analysis calculated for $\text{C}_{16}\text{H}_{11}\text{N}_2\text{H}_2\text{SO}_4$: C 57.82%, H 4.85%, N 8.43%; found: C 57.61%, H 4.81%, N 8.73%.

The hydrochloride of 5-phenyl-2,3-dihydro-5H-imidazo[2,1-a]isoindole was obtained from the corresponding free base by treatment with 1-N aqueous hydrochloric acid. Recrystallization from a mixture of methanol and toluene gave white prisms melting at $226^\circ\text{--}228^\circ\text{C}$ (with decomposition); nuclear magnetic resonance peaks (dimethyl sulphoxide) at $\delta 3.6\text{--}4.6$ (4H, multiplet), at $\delta 6.13$ (1H, singlet) and $\delta 7.3\text{--}7.9$ (9H, multiplet).

EXAMPLE 2

A) The preparation of the starting material:

A solution of 25 g (0.1 mol) of 9b-phenyl-1,2,3,9b-tetrahydro-5H-imidazo[2,1-a]isoindolone-(5) in 150 ml of acetic acid containing 2.5 g of hydrogen chloride was shaken under one atmosphere of hydrogen at 25°C using 0.5 g of platinum oxide as catalyst. In the course of 7 hours, 3000 ml of hydrogen (theory: ca 2500 ml) were absorbed and the rate of uptake slowed down considerably. The resulting solution was poured into ice-water, basified with ammonia and extracted with methylene chloride. The organic phase was dried and concentrated. The residue crystallized with ether and after recrystallization from a mixture of methylene chloride and petroleum ether gave white prisms of 2-(2-amino-ethyl)-3-phenyl-phthalimidine melting at $90^\circ\text{--}93^\circ\text{C}$; $\gamma_{\text{CO}}^{\text{CHCl}_3} = 1685\text{ cm}^{-1}$; $\lambda_{\text{max}}^{\text{PrOH}} = 247\text{ m}\mu$ ($\epsilon=6000$), $279\text{ m}\mu$ ($\epsilon=1900$).

Analysis calculated for $\text{C}_{16}\text{H}_{11}\text{N}_2\text{O}$: C 76.16%, H 6.39%; found: C 75.81%, H 6.32%.

B) The process:

A solution of 1.2 ml of titanium tetrachloride in 30 ml of xylene was added at 25°C to a stirred solution of 2.5 g of 2-(2-amino-ethyl)-3-phenyl-phthalimidine in 150 ml of xylene. The resulting mixture was heated at reflux for 18 hours, cooled, washed with an aqueous solution of sodium carbonate and extracted with 2-N hydrochloric acid. The acidic extract was poured on ice, made alkaline with sodium hydroxide and extracted with ethyl acetate. The ethyl acetate extract was concentrated. Addition to the concentrate of a solution of sulphuric acid in a mixture of ethanol and tetrahydro-furan and further dilution with ethyl acetate gave a crystalline precipitate. Recrystallization from a mixture of methanol and ethyl acetate gave 5-phenyl-2,3-dihydro-5H-imidazo[2,1-a]isoindole sulphate as white prisms melting at $225^\circ\text{--}228^\circ\text{C}$ (with decomposition).

The base liberated from 16.6 g of 5-phenyl-2,3-dihydro-5H-imidazo[2,1-a]isoindole sulphate was dissolved in 50 ml of ethanol and to the solution were added 11 ml of a 30% (by weight) aqueous solution of hydrogen peroxide. The mixture was stirred at 25°C for 40 hours. A crop of crystals was collected and placed on a column containing 250 g of silica gel. Elution with a mixture of 1 part (by volume) of methanol and 1 part (by volume) of chloroform gave fractions from which, on concentration, there was obtained a crystalline residue. Recrystallization from a mixture of methanol and chloroform gave 5-hydroperoxy-5-phenyl-2,3-dihydro-5H-imidazo[2,1-a]isoindole as white prisms melting at $167^\circ\text{--}168^\circ\text{C}$ (with decomposition); *ultraviolet* inflections (isopropanol) at $232\text{ m}\mu$ ($\epsilon=14,000$) and $290\text{ m}\mu$ ($\epsilon=2600$), maxima at $269\text{ m}\mu$ ($\epsilon=4000$) and $275\text{ m}\mu$ ($\epsilon=4400$); *infrared* absorption (potassium bromide) at 1665 cm^{-1} .

Analysis calculated for $C_{18}H_{14}N_2O_2$: C 72.16%, H 5.30%, N 10.52%;
found: C 72.09%, H 5.39%, N 10.22%.

For characterisation purposes, the hydrochloride of 5-hydroperoxy-5-phenyl-2,3-dihydro-5H-imidazo[2,1-a]isoindole was prepared with methanolic hydrogen chloride and after recrystallization from a mixture of methanol and ether gave white platelets melting at 158—159°C (with decomposition); *ultraviolet* maxima (isopropanol) at 245 m μ (ϵ =14,800) and 278 m μ (ϵ =5200); *infrared* absorption (potassium bromide) at 1680 cm⁻¹.

A solution of 0.7 g of sodium sulphite heptahydrate in 3 ml of water was added to 0.5 g of 5-hydroperoxy-5-phenyl-2,3-dihydro-5H-imidazo[2,1-a]isoindole [claimed *per se* in the specification of our copending Application No. 28272/69 (now Serial No. 1191239) and prepared as described in Example 1 thereof] in 7 ml of N,N-dimethyl-formamide. The solution was heated to 100°C for 0.25 hour. On cooling and addition of 20 ml of water, there was obtained 2-(2-benzoyl-phenyl)-2-imidazoline.

2-(2-Benzoyl-phenyl)-2-imidazoline was also obtained from 5-hydroperoxy-5-phenyl-2,3-dihydro-5H-imidazo[2,1-a]isoindole as follows:—

A solution of 0.1 g of 5-hydroperoxy-5-phenyl-2,3-dihydro-5H-imidazo[2,1-a]isoindole and 0.33 g of triethyl phosphite in 20 ml of ethanol was kept on a steam-bath for 5 minutes, then at 25°C for 18 hours. The resulting solution was concentrated *in vacuo* and on addition of water 2-(2-benzoyl-phenyl)-2-imidazoline was obtained.

EXAMPLE 3

50 ml of 1-N aqueous sodium hydroxide solution were added to a suspension of 8.5 g of 5-phenyl-2,3-dihydro-5H-imidazo[2,1-a]isoindole sulphate in water. Extraction with methylene chloride and concentration gave an orange oil which was dissolved in a mixture of 30 ml of methylene chloride and 30 ml of ethanol. To the resulting solution were added 2.3 ml of 30% (by weight) hydrogen peroxide. After stirring at 25°C for 18 hours, a precipitate was collected which after recrystallization from methanol gave white prisms of 2-(2-benzoyl-phenyl)-2-imidazoline melting at 194°—196°C (with decomposition); *ultraviolet* inflections (isopropanol) at 225 m μ (ϵ =15,500) and 290 m μ (ϵ =2250), maxima at 269 m μ (ϵ =4100) and 276 m μ (ϵ =4250); *infrared* absorption (potassium bromide) at 1660 cm⁻¹.

Analysis calculated for $C_{18}H_{14}N_2O$: C 76.78%, H 5.64%, N 11.19%;
found: C 76.42%, H 5.79%, N 11.13%.

The 2-(2-benzoyl-phenyl)-2-imidazoline obtained in this manner can form the isomeric 5-hydroxy-5-phenyl-2,3-dihydro-5H-imidazo[2,1-a]isoindole.

The hydrochloride was prepared by adding a solution of hydrogen chloride in methanol to a suspension of 2-(2-benzoyl-phenyl)-2-imidazoline in methanol. Ether was added and the crystalline precipitate was collected. Recrystallization from a mixture of methanol and ether gave white prisms melting at 173°—176°C (with decomposition); *ultraviolet* maximum (isopropanol) at 252 m μ (ϵ =13,600); *infrared* absorption (potassium bromide) at 1665 cm⁻¹.

Analysis calculated for $C_{18}H_{14}N_2O.HCl$: Cl 12.36%;
found: Cl 12.22%.

The hydrobromide was prepared by adding an aqueous solution of hydrobromic acid to a suspension of 2-(2-benzoyl-phenyl)-2-imidazoline in ethanol. Addition of ether gave a precipitate which after recrystallization from a mixture of ethanol and ether gave white platelets melting at 193°—194°C (with decomposition).

Analysis calculated for $C_{18}H_{14}N_2O.HBr$: Br 24.13%;
found: Br 24.15%.

EXAMPLE 4

The 1,2,3,9b-tetrahydro-5H-imidazo[2,1-a]isoindolone-(5) hydrochloride obtained as described in Example 1 of the specification of our copending Application No. 28273/69 (now Serial No. 1191240) was treated with aqueous potassium carbonate solution. Extraction with methylene chloride gave an oil, 0.9 g of which were dissolved in a mixture of 25 ml of benzene and 10 ml of ether. To the solution were added 5.5 ml of a 2-N solution of phenyl-lithium in a mixture of benzene and ether (7:3). After stirring at 25°C for 1 hour, the solution was poured into ice-water and extracted with ethyl acetate. This solution was concentrated and the residue was exposed to air for 48 hours. On addition of methylene chloride, crystals were obtained which were dissolved in methanol. Addition of ethereal hydrochloric acid gave white prisms which after recrystallization from a mixture of methanol and ether gave

2,3-
imide
elects
) at
imide)

ided
med
erial
(N-
oling
line.
y-5-

(a)-
eam-
rated
red.

on of
rater.
was
o the
After
ation
ag at
mμ
mμ

a the

de in
Ether
om a
(with
frated

romic
on of
l and

tained
n No.
bonate
solved
added
(7:3).
r and
le was
tained
white
gave

5

10

15

20

25

30

35

40

45

50

55

60

crystals of 2-(2-benzoyl-phenyl)-2-imidazoline hydrochloride melting at 173°—175°C (with decomposition).

EXAMPLE 5

A) The preparation of the starting material:

A solution of 127 g (0.59 mol) of 2-hydroxymethyl-benzhydrol was dissolved in 900 ml of benzene, 80 g of anhydrous magnesium sulphate were added and the mixture was cooled in an ice-bath. Hydrogen bromide was bubbled into the stirred solution until saturation, which took ca 0.5 hours; during this time the temperature of the solution was kept at 15°—18°C. The ice-bath was subsequently removed and the temperature was allowed to rise to 35°C in the course of 1 hour. The mixture was then heated for a further hour at 40°—45°C on a steam-bath. During the whole time hydrogen bromide was passed into the solution to keep it saturated. The mixture was subsequently filtered and the filtrate was concentrated *in vacuo* to give a red oil which was dissolved in 200 ml of benzene and added in the course of 0.25 hour to 342 g (5.7 mol) of ethylenediamine; during the addition the mixture was stirred and cooled to maintain a temperature of ca 40°C. The mixture was then stirred at 25°C for 70 minutes. The two layers which were obtained were separated. The benzene layer was washed with water and concentrated *in vacuo*. The residual oil was dissolved in 250 ml of ether. The ethereal solution was extracted twice with 300 ml of cold 1-N hydrochloric acid. The acidic aqueous phase was made alkaline with aqueous sodium hydroxide and extracted with 350 ml of ether. The ethereal solution thus obtained was washed with 250 ml of water, dried and concentrated. The residue was an amber oil which crystallized on scratching to give 2-(2-amino-ethyl)-1-phenyl-isoindoline which melted up to ca 45°C.

In a manner analogous to the foregoing there were also prepared 2-(3-amino-propyl)-1-phenyl-isoindoline, 2-(2-amino-ethyl)-6-chloro-1-phenyl-isoindoline, 2-(2-amino-ethyl)-1-(4-methoxy-phenyl)-isoindoline, 2-(4-amino-butyl)-1-phenyl-isoindoline, 2-(2-amino-2-methyl-propyl)-1-phenyl-isoindoline, 2-(2-amino-propyl)-1-phenyl-isoindoline and 2-(2-amino-ethyl)-1-(4-hydroxy-phenyl)-isoindoline.

B) The process:

A solution of 3.3 g of chromium trioxide and 5.9 g of 2-(2-amino-ethyl)-1-phenyl-isoindoline in 250 ml of acetic acid was stirred at 55°—60°C for 18 hours. The solution was then cooled, poured on ice and made alkaline. Extraction with methylene chloride and removal of the solvent gave a brown oil which partly crystallized. Recrystallization from a mixture of chloroform and ethyl acetate gave 2-(2-benzoyl-phenyl)-2-imidazoline as white prisms melting at 194°—196°C (with decomposition).

EXAMPLE 6

To a solution of 0.85 g of 2,3-dihydro-5H-imidazo[2,1-a]isoindolone-(5) [prepared as described in the specification of our copending Application No. 28273/69 (now Serial No. 1191240)] in 15 ml of benzene cooled to 5°—10°C were added 12 ml of a 2-N solution of phenyl-lithium in a mixture of 7 parts of benzene and 3 parts of ether. The resulting mixture was stirred at 20°C for 1 hour and subsequently poured into ice-water. Extraction with methylene chloride gave a crystalline crop which after recrystallization from a mixture of methanol and methylene chloride gave 5-phenyl-5-hydroxy-2,3-dihydro-5H-imidazo[2,1-a]isoindole [or 2-(2-benzoyl-phenyl)-2-imidazoline] as white prisms having a melting point of 194°—196°C (with decomposition).

EXAMPLE 7

A solution of 5 g of 2-(2-benzoyl-phenyl)-2-imidazoline hydrochloride in 50 ml of methanol was heated at reflux for 18 hours and subsequently concentrated *in vacuo*. The concentrate was dissolved in 20 ml of methanol and 60 ml of ether were added; the crystals which precipitated were identified as starting material. The mother liquor was concentrated and the residue thus obtained was recrystallized from a mixture of methanol, methylene chloride and ether to give 5-methoxy-5-phenyl-2,3-dihydro-5H-imidazo[2,1-a]isoindole hydrochloride as white prisms melting at 139°—141°C (with decomposition); *ultraviolet* maxima (isopropanol) at 244 mμ ($\epsilon=14,400$), and 278 mμ ($\epsilon=5100$); *infrared* absorption (potassium bromide) at 1670 cm^{-1} .

Analysis calculated for $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}\cdot\text{HCl}$: C 67.83%, H 5.70%, OCH_3 10.32%; found: C 67.84%, H 5.61%, OCH_3 10.44%.

The corresponding base was obtained as a colourless oil by liberating it from the foregoing hydrochloride with alkali; *ultraviolet* inflections (in 0.1-N potassium hydroxide) at 230 mμ ($\epsilon=14,600$) and 290 mμ ($\epsilon=2700$), maxima at 269 mμ

5

10

15

20

25

30

35

40

45

50

55

60

5

10

15

20

25

30

35

40

45

50

55

60

($\epsilon=4200$) and $275\text{ m}\mu$ ($\epsilon=4600$); *infrared* absorption (smear) at 1660 cm^{-1} ; nuclear magnetic resonance peaks (deuteriochloroform) at $\delta=3.12$ (3H, singlet, OCH_3), $\gamma=2.6-3.5$ (2H, multiplet, $\text{N}-\text{CH}_2$), $\delta=4.2-4.5$ (2H, multiplet, $=\text{N}-\text{CH}_2$), $\delta=7.1-8.0$ (9H, multiplet, aromatic CH).

5

EXAMPLE 8

1 g of 2-(4-chloro-benzoyl)-benzaldehyde [prepared as described in the specification of our copending Application No. 28271/69 (now Serial No. 1191238)] was added in small portions to 1 ml of ethylenediamine; an exothermic reaction took place and after 5 minutes the resulting mixture was poured into ice-water. A yellow solid precipitate was collected and dissolved in methylene chloride. Ether and petroleum ether were added and the solution was shaken in air at 25°C . A crystalline precipitate was obtained which, after recrystallization from a mixture of methylene chloride and methanol, gave white needles of 2-[2-(4-chloro-benzoyl)-phenyl]-2-imidazoline melting at $178-180^\circ\text{C}$ (with decomposition); *ultraviolet* maxima (isopropanol) ($\epsilon=21,250$), $268\text{ m}\mu$ ($\epsilon=4300$) and $275\text{ m}\mu$ ($\epsilon=4320$), inflection at $290\text{ m}\mu$ ($\epsilon=2200$); *infrared* absorption (potassium bromide) at 166 cm^{-1} .

15

Analysis calculated for $\text{C}_{16}\text{H}_{13}\text{ClN}_2\text{O}$: C 67.49%, H 4.60

found: C 67.38%, H 4.56%.

20

2-[2-(4-Chloro-benzoyl)-phenyl]-2-imidazoline obtained in the foregoing manner can form the isomeric 5-(4-chloro-phenyl)-5-hydroxy-2,3-dihydro-5H-imidazo[2,1-a]-isoindole.

25

The corresponding hydrochloride was prepared by adding a solution of hydrogen chloride in ether to a suspension of 5-(4-chloro-phenyl)-5-hydroxy-2,3-dihydro-5H-imidazo[2,1-a]isoindole. After stirring for 0.5 hour, a crystalline crop was collected and recrystallized from a mixture of chloroform and ether to give white prisms melting at $168-171^\circ\text{C}$ (with decomposition); *ultraviolet* inflection (isopropanol) at $220\text{ m}\mu$ ($\epsilon=22,000$), maxima at $252\text{ m}\mu$ ($\epsilon=12,900$) and $266\text{ m}\mu$ ($\epsilon=13,000$); *infrared* absorption (potassium bromide) at 1670 cm^{-1} .

30

Analysis calculated for $\text{C}_{16}\text{H}_{13}\text{ClN}_2\text{O}\cdot\text{HCl}$: Cl 22.08%;

found: Cl 22.18%.

EXAMPLE 9

2 g of 2-(4-methoxy-benzoyl)-benzaldehyde [prepared as described in the specification of our copending Application No. 28271/69 (now Serial No. 1191238)] were added in small portions to 4 ml of ethylenediamine. The resulting solution was stirred for 10 minutes, poured into ice-water and extracted with methylene chloride. The methylene chloride solution was concentrated and the residue was dissolved in ethanol. A stream of air was passed through the ethanolic solution for 18 hours. A crystalline precipitate was collected and, after recrystallization from a mixture of chloroform and ether, gave white prisms of 2-[2-(4-methoxy-benzoyl)-phenyl]-2-imidazoline melting at $171-174^\circ\text{C}$ (with decomposition); *ultraviolet* maxima (isopropanol) at $227\text{ m}\mu$ ($\epsilon=20,200$), $277\text{ m}\mu$ ($\epsilon=8800$) and $282\text{ m}\mu$ ($\epsilon=8750$), inflection at $292\text{ m}\mu$ ($\epsilon=7200$); *infrared* absorption (potassium bromide) at 1660 cm^{-1} .

40

Analysis calculated for $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_2$: C 72.84%, H 5.75%, N 9.99%;

found: C 73.07%, H 5.71%, N 9.83%.

45

2-[2-(4-Methoxy-benzoyl)-phenyl]-2-imidazoline obtained in the foregoing manner can form the isomeric 5-hydroxy-5-(4-methoxy-phenyl)-2,3-dihydro-5H-imidazo[2,1-a]isoindole.

50

EXAMPLE 10

0.9 g of 2-benzoyl-4-chloro-benzaldehyde [prepared as described in the specification of our copending Application No. 28271/9 (now Serial No. 1191238)] were added in small portions to 2 ml of ethylenediamine. The resulting solution was stirred for 10 minutes and poured into ice-water. The solid yellow precipitate was collected and dissolved in ether. The ethereal solution was shaken in air for 0.75 hour. The white precipitate obtained was recrystallized from a mixture of methylene chloride and methanol to yield 2-(4-chloro-2-benzoyl-phenyl)-2-imidazoline melting at $200-202^\circ\text{C}$ (with decomposition); *ultraviolet* maxima (isopropanol) at $242\text{ m}\mu$ ($\epsilon=17,500$), $278\text{ m}\mu$ ($\epsilon=3800$) and $286\text{ m}\mu$ ($\epsilon=3300$), inflections at $270\text{ m}\mu$ ($\epsilon=3450$) and $295\text{ m}\mu$ ($\epsilon=2400$); *infrared* absorption (potassium bromide) at 1665 cm^{-1} .

60

Analysis calculated for $\text{C}_{16}\text{H}_{13}\text{ClN}_2\text{O}$: C 67.49%, H 4.60%;

found: C 67.42%, H 4.90%.

2-(4-Chloro-2-benzoyl-phenyl)-2-imidazoline obtained in the foregoing manner can form the isomeric 7-chloro-5-hydroxy-5-phenyl-2,3-dihydro-5H-imidazo[2,1-]isoindole.

EXAMPLE 11

A solution of 6 g of 2-(4-bromo-benzoyl)-benzaldehyde [prepared as described in the specification of our copending Application No. 28271/69 (now Serial No. 1191238)] and 6.6 ml of ethylenediamine in 50 ml of toluene was heated at reflux for 18 hours; during this time 0.5 ml of an aqueous phase separated in a DEAN-STARK receiver. The mixture was concentrated *in vacuo* and the residual orange oil was dissolved in a mixture containing 15 ml of ethanol, 15 ml of methylene chloride and 1.5 ml of a 30% (by weight) aqueous solution of hydrogen peroxide. After stirring at 25°C for 18 hours, a white precipitate was collected and recrystallized from methanol to give white needles of 2-[2-(4-bromo-benzoyl)-phenyl]-2-imidazoline melting at 187°—189°C (with decomposition); *ultraviolet* maxima (isopropanol) at 227 mμ ($\epsilon=22,800$), 259 mμ ($\epsilon=4700$) and 275 mμ ($\epsilon=4800$), infection at 292 mμ ($\epsilon=2300$); *infrared* absorption (potassium bromide) at 1660 cm⁻¹.

Analysis calculated for $C_{16}H_{13}BrN_2O$: C 58.37%, H 3.98%;
found: C 58.27%, H 3.75%.

2-[2-(4-Bromo-benzoyl)-phenyl]-2-imidazoline obtained in the foregoing manner can form the isomeric 5-(4-bromo-phenyl)-5-hydroxy-2,3-dihydro-5H-imidazo[2,1]-isindole.

The corresponding hydrochloride was prepared by adding ethereal hydrogen chloride to a solution of 5-(4-bromo-phenyl)-5-hydroxy-2,3-dihydro-5H-imidazo[2,1-a]isoindole in a mixture of methylene chloride and methanol. The precipitate was recrystallized from a mixture of ethanol and ether to give white prisms melting at 155°—158°C (with decomposition); *ultraviolet* inflection (isopropanol) at 223 m μ (ϵ =20,000), maxima at 251 m μ (ϵ =12,200) and 271 m μ (ϵ =13,300); *infrared* absorption (potassium bromide) at 1660 cm⁻¹.

Analysis calculated for $C_{16}H_{13}BrN_2O \cdot HCl$: Cl 9.70%
found: Cl 9.82%.

EXAMPLE 12

A solution of 10.5 g of 2-benzoyl-benzaldehyde and 22 ml of propylenediamine in 125 ml of toluene was heated at reflux for 18 hours; during this time, 4.5 ml of an aqueous phase separated in a DEAN-STARK receiver. The solution was concentrated *in vacuo*. The residue crystallized and was collected on a filter, washed with ethyl acetate and dissolved in a mixture of methylene chloride and ethanol. To the resulting solution was added a solution of sulphuric acid in a mixture of tetrahydrofuran and ethanol. On addition of ethyl acetate there was obtained a solid which after recrystallization from a mixture of ethanol and petroleum ether, gave white prisms of 6-phenyl-2,3,4,6-tetrahydro-pyrimido[2,1-a]isoindole sulphate melting at 170°—172°C (with decomposition); *ultraviolet* maximum (isopropanol) at 238 μ ($\epsilon=18,200$), inflections at 246 μ ($\epsilon=16,000$), 265 μ ($\epsilon=5600$), 276 μ ($\epsilon=3400$) and 285 μ ($\epsilon=2100$); *infrared* absorption (potassium bromide) at 1675 cm^{-1} .

Analysis calculated for $C_{17}H_{16}N_2 \cdot H_2SO_4$: C 58.94%, H 5.24%;
found: C 58.62%, H 5.49%.

EXAMPLE 13

A solution of 10.5 g of 2-benzoyl-benzaldehyde and 28.5 ml of 1,4-diaminobutane in 100 ml of toluene was heated at reflux for 18 hours; during this time, 2.5 ml of an aqueous phase separated in a DEAN-STARK receiver. The solution was exposed to air for 60 hours, concentrated and diluted with 300 ml of carbon tetrachloride. The crystalline precipitate which was obtained was suspended in 40 ml of ethanol. To the suspension was added a solution of 1.9 g of oxalic acid in 40 ml of methanol and the mixture was concentrated and diluted with ether. The precipitate was collected and recrystallized from a mixture of methanol and ether to give the oxalic acid salt as white prisms melting at *ca* 200°C (with decomposition). This salt was suspended in a mixture of aqueous sodium carbonate solution and methylene chloride. The methylene chloride solution was concentrated and the residue was recrystallized from a mixture of chloroform and ether to give 7-hydroxy-7-phenyl-2,3,4,5-tetrahydro-7H-diazepino[2,1-a]isoindole as white needles melting at 216°—220°C (with decomposition); *ultraviolet* maxima (isopropanol) at 258 $m\mu$ ($\epsilon=5000$), 265 $m\mu$ ($\epsilon=5100$) and 273 $m\mu$ ($\epsilon=4800$), inflections at 230 $m\mu$

($\epsilon=15,000$) and 290 $m\mu$ ($\epsilon=2400$); infrared absorption (potassium bromide) at 1650 cm^{-1} .

Analysis calculated for $C_{18}H_{18}N_2O$: C 77.67%, H 6.52%, O 5.75%;
found: C 77.64%, H 6.75%, O 5.64%.

EXAMPLE 14

45.4 g of the orange oil containing 2-(2-chloro-benzoyl)-benzaldehyde [obtained as described in the specification of our copending Application No. 28271/69 (now Serial No. 1191238)], 52.5 g (0.875 mol) of ethylenediamine and 400 ml of benzene were heated at reflux for 5 hours in a round bottomed flask equipped with a DEAN-STARK trap and a condenser; ca 6 ml of aqueous phase separated in the trap. The resulting mixture was cooled, washed three times with saturated brine and dried over anhydrous sodium sulphate. Air was then bubbled through the benzene solution for 15 hours but only a small amount of solid separated. The benzene was removed *in vacuo* and the residue was dissolved in 150 ml of ethanol and 40 ml (0.350 mol) of 30% hydrogen peroxide. After stirring for 3 hours, the ethanol was removed *in vacuo* and 300 ml of benzene were added to the residue. The aqueous phase was separated and the benzene solution was dried over anhydrous sodium sulphate and evaporated *in vacuo* to leave a pale yellow oil. 150 ml of ether were added and a crystalline solid separated. The mixture was filtered to give a pale yellow solid of melting point 164°—167°C (with decomposition). The ether filtrate was stirred at room temperature, exposed to air, for two days. The precipitated solid was filtered off to give an additional pale yellow solid. Thin layer chromatography of the combined solids showed the presence of one major component (Rf 0.41) and a minor component (Rf 0.67). The major component was 2-[2-(2-chloro-benzoyl)-phenyl]-2-imidazoline and the minor component was 5-hydroperoxy-5-(2-chloro-phenyl)-2,3-dihydro-5H-imidazo[2,1-a]isoindole. [5-hydroperoxy-5-(2-chloro-phenyl)-2,3-dihydro-5H-imidazo[2,1-a]isoindole is claimed *per se* in the specification of our copending Application No. 28272/69 (now Serial No. 1191239). The process step described in this paragraph is also described in Example 2 of the specification of said copending Application.]

To a suspension of the pale yellow solid obtained according to the preceding paragraph in 60 ml of refluxing methanol there was added over a period of 5 minutes a solution of 4.28 g (0.017 mol) of sodium sulphite heptahydrate in 30 ml of water. After heating at reflux for a further 0.25 hour, the mixture was cooled and filtered. The filtered solid was washed three times with 20 ml of water and dried. Recrystallization from methanol/chloroform gave 2-[2-(2-chloro-benzoyl)-phenyl]-2-imidazoline as colourless prisms of melting point 180°—181°C (with decomposition).

Analysis calculated for $C_{16}H_{13}ClN_2O$: C 67.49%, H 4.60%, N 9.84%;
found: C 67.15%, H 4.56%, N 9.66%;

2-[2-(2-Chloro-benzoyl)-phenyl]-2-imidazoline obtained in the foregoing manner can form the isomeric 5-hydroxy-5-(2-chloro-phenyl)-2,3-dihydro-5H-imidazo[2,1-a]isoindole.

200 ml of ether were added to a hot solution of 6.0 g (21.2 mmol) of 2-[2-(2-chloro-benzoyl)-phenyl]-2-imidazoline in 25 ml of 6-N methanolic hydrogen chloride and 35 ml of methanol and the resulting mixture was cooled. Filtration gave 2-[2-(2-chloro-benzoyl)-phenyl]-2-imidazoline hydrochloride of melting point 178°—180°C (with decomposition). Dilution of the mother liquors with 200 ml of ether followed by cooling and filtering afforded an additional quantity of hydrochloride. Recrystallization from methanol/ether gave colourless prisms of melting point 178°—180°C (with decomposition).

Analysis calculated for $C_{16}H_{14}Cl_2N_2O$: Cl 22.08%;
found: Cl 22.00%.

EXAMPLE 15

A solution of 23 g of 1-bromo-3-trifluoromethyl-benzene in 50 ml of ether was slowly added to 2.4 g of magnesium turnings stirred in 20 ml of ether. The resulting mixture was heated at gentle reflux for 1 hour, then cooled in an ice-bath. A solution of 3.5 g of 2,3-dihydro-5H-imidazo[2,1-a]isoindolone-(5) [prepared, for example, as described in the specification of our copending Application No. 28273/69 (now Serial No. 1191240)] in 50 of benzene was slowly added thereto. The resulting brown solution was kept at 25°C for 17 hours, then poured into an aqueous solution of ammonium chloride. The organic phase was removed and on dilution with ether gave a crystalline material which was recrystallized from a mixture of methanol and

ethyl acetate to yield 5-(3-trifluoromethyl-phenyl)-5-hydroxy-2,3-dihydro-5H-imidazo-[2,1-a]isoindole [or 2-[2-(3-trifluoromethyl-benzoyl)-phenyl]-2-imidazoline] as tan plates having a melting point of 199°—202°C (with decomposition); *ultraviolet* maximum (isopropanol) at 275 m μ (ϵ =4,000), inflections at 228 m μ (ϵ =13,500), 265 m μ (ϵ =3,800) and 290 m μ (ϵ =2,250); *infrared* absorption (potassium bromide) at 1660 cm⁻¹, sharp, strong.

Analysis calculated for C₁₇H₁₃F₃N₂O: C 64.15%, H 4.11%, N 8.80%;
found: C 63.65%, H 4.35%, N 8.93%.

The following Examples illustrate the manner in which pharmaceutical preparations containing the novel derivatives provided by the invention may be obtained:

EXAMPLE A

Tablets each containing 10.0 mg of 2-(2-benzoyl-phenyl)-imidazoline, 113.5 mg of lactose, 70.5 mg of corn starch, 8.0 mg of pregelatinized corn starch and 3.0 mg of calcium stearate and each having a total weight of 205.0 mg were prepared by mixing the 2-(2-benzoyl-phenyl)-2-imidazoline with the lactose, corn starch and pregelatinized corn starch in a mixer of suitable size, passing the resulting mix through a comminuting machine, returning it to the mixer and moistening it with water so as to form a thick paste, passing the moist mass through a screen, drying the resulting moist granules at 40°C and compressing the dried granules at a tablet weight of 205.0 mg using standard concave punches having a diameter of 8 mm.

EXAMPLE B

Suppositories each containing 0.025 g of 2-(2-benzoyl-phenyl)-2-imidazoline, 1.230 g of hydrogenated coconut oil and 0.045 g of carnauba wax and each having a total weight of 1.3 g were prepared by melting the hydrogenated coconut oil and the carnauba wax.

In a glass-lined container of suitable size (stainless steel may also be used), mixing well, cooling the mixture to 45°C, adding 2-(2-benzoyl-phenyl)-2-imidazoline which had been reduced to a fine powder with no lumps, stirring until complete and uniform dispersion had been obtained, and pouring the resulting mixture into suppository moulds to yield suppositories having an individual weight of 1.3 g; the suppositories were cooled and removed from the moulds, then were individually wrapped in wax paper for packaging (foil may also be used).

EXAMPLE C

Capsules each containing 25 mg of 2-(2-benzoyl-phenyl)-2-imidazoline, 158 mg of lactose, 37 mg of corn starch and 5 mg of talc and each having a total net weight of 225 mg were prepared by mixing the 2-(2-benzoyl-phenyl)-2-imidazoline with the lactose and corn starch in a suitable mixer, further blending the resulting mixture by passing it through a comminuting machine, returning the resulting blended powder to the mixer, adding the talc, blending thoroughly and filling the mixture thus obtained into hard-shell gelatin capsules on a capsulating machine.

EXAMPLE D

A parenteral formulation, each ml of which contained 2.5 mg of 2-(2-benzoyl-phenyl)-2-imidazoline, tartaric acid *q.s.* to pH 3.0, 4.5 mg of anhydrous phenol and water for injection *q.s.* to 1.0 ml, was prepared by slurring the 2-(2-benzoyl-phenyl)-2-imidazoline in part of the water for injection, solubilising the 2-(2-benzoyl-phenyl)-2-imidazoline by slowly adding the tartaric acid to a pH of approximately 3.0, adding the anhydrous phenol, filtering the resulting solution, allowing it to stand for 24 hours, then filtering it through a porous candle and filling it into ampoules of the desired size and sealing the ampoules under an atmosphere of nitrogen; all ampoules were inspected and those containing excessive amounts of fibres were rejected.

EXAMPLE E

A parenteral formulation was prepared in duplex ampoules, one containing the dry active substance and the other containing a special diluent.

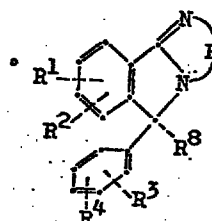
The dry fill ampoule was prepared by filling 25 mg of a parenteral grade of fibre-free 2-(2-benzoyl-phenyl)-2-imidazoline into a 5 ml ampoule; the ampoules were sealed and sterilized at 125°C for 2 hours.

Immediately before use the powder was solubilized with 2 ml of a special diluent from a second ampoule. The special diluent, each ml of which contained 16 mg of

5 tartaric acid and water for injection *q.s.* to 1.0 ml was prepared by dissolving the tartaric acid in part of the water for injection in a suitable container under an atmosphere of nitrogen, making the solution up to volume, filtering it through a porous candle filter and filling it into 2 ml flint ampoules (the filling should be carried out under an atmosphere of nitrogen); the ampoules were sealed, sterilized at 100°C for 0.5 hour and subsequently inspected, those which leaked or contained fibres being discarded.

WHAT WE CLAIM IS:—

1) Compounds of the general formula



15 , wherein B represents an alkylene chain containing from 2 to 4 carbon atoms in which one or more of the hydrogen atoms may be replaced by lower-alkyl, R¹, R², R³ and R⁴ individually represent a halogen atom or the trifluoromethyl or hydroxy group or a lower-alkyl or lower-alkoxy group and R⁸ represents a hydroxy or lower-alkoxy group and the broken lines denote that the atoms or groups attached thereby are optional, tautomers of those compounds in which R⁸ is present and represents the hydroxy group and acid addition salts of said compounds and tautomers.

2) Compounds of the formula written in claim 1, and acid addition salts thereof.

3) Compounds of the formula written in claim 1, wherein R⁸ is present and represents the hydroxy group.

4) Compounds as set forth in claim 2 or claim 3, wherein R² and R⁴ are absent.

5) Compounds as set forth in claim 2, claim 3 or claim 4, wherein B represents the ethylene group.

6) Compounds as set forth in any one of claims 2 to 5 inclusive, wherein R¹ (when present) represents a chlorine atom and R³ (when present) represents a chlorine or bromine atom or the methoxy group.

7) 5-Hydroxy-5-phenyl-2,3-dihydro-5H-imidazo[2,1-a]isoindole and acid addition salts thereof.

8) 5-Hydroxy-5-(4-chloro-phenyl)-2,3-dihydro-5H-imidazo[2,1-a]isoindole and acid addition salts thereof.

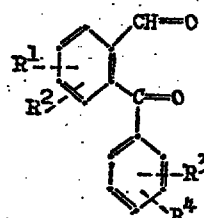
9) 5-Hydroxy-5-(4-methoxy-phenyl)-2,3-dihydro-5H-imidazo[2,1-a]isoindole and acid addition salts thereof.

10) 5-Methoxy-5-phenyl-2,3-dihydro-5H-imidazo[2,1-a]isoindole and acid addition salts thereof.

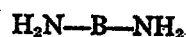
11) Tautomers of compounds set forth in any one of claims 3 to 9 inclusive and acid addition salts thereof.

12) A pharmaceutical preparation comprising a compound as set forth in claim 1, a tautomer of such a compound in which R⁸ is present and represents the hydroxy group or a pharmaceutically acceptable acid addition salt of either in association with a compatible pharmaceutical carrier.

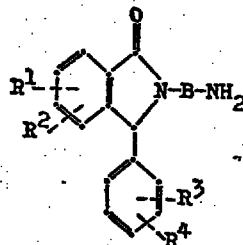
13) A process for the manufacture of the 1,3-diazacycloalkeno[2,1-a]isoindole derivatives claimed in claim 1, which process comprises *either* condensing a compound of the general formula



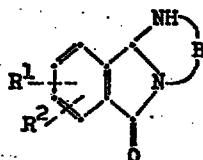
, wherein R^1 , R^2 , R^3 , R^4 and the broken lines have the significance given in claim 1, with a diamine of the general formula



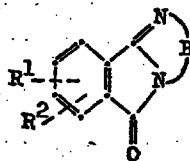
, wherein B has the significance given in claim 1, or with a salt thereof, or cyclising a compound of the general formula



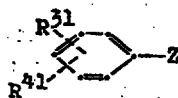
, wherein B, R^1 , R^2 , R^3 , R^4 and the broken lines have the significance given in claim 1, by treatment thereof with a LEWIS acid or reacting a compound of the general formula



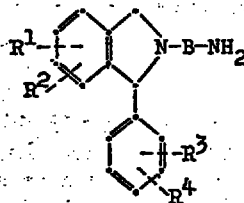
, wherein B, R^1 , R^2 and the broken lines have the significance given in claim 1, or a dehydro derivative thereof of the general formula



, wherein B, R^1 , R^2 and the broken lines have the significance given in claim 1, with an organo-metallic phenyl compound of the general formula



, wherein Z represents Li, MgBr, MgI or MgCl, R^{31} and R^{41} individually represent a halogen atom or the trifluoromethyl group or a lower-alkyl or lower-alkoxy group and the broken lines have the significance given in claim 1, or treating a compound of the general formula



, wherein B, R^1 , R^2 , R^3 , R^4 and the broken lines have the significance given in claim 1, with an oxidising agent and, if desired, oxidising any product in which R^5 is

absent to a corresponding product in which R^8 is present and represents a hydroxy group, if desired, lower-alkylating a resulting product in which R^8 is present and represents a hydroxy group to a corresponding product in which R^8 is present and represents a lower-alkoxy group, if desired, separating a racemic mixture obtained into its optically active antipodes and, also if desired, converting any base obtained into an acid addition salt.

14) A process as set forth in claim 13, wherein *either* a compound of the formula first written in that claim is condensed with a diamine of the formula second written in that claim *or* a compound of the formula third written in that claim is cyclised by treatment with a LEWIS acid *or* a compound of the formula seventh written in that claim is treated with an oxidising agent *and*, if desired, any product in which R^8 is absent is oxidised to a corresponding product in which R^8 is present and represents a hydroxy group, if desired, a resulting product in which R^8 is present and represents a hydroxy group is lower-alkylated to a corresponding product in which R^8 is present and represents a lower-alkoxy group *and*, also if desired, converting any base obtained into an acid addition salt.

15) A process as set forth in claim 13, wherein a compound of the formula fourth written in that claim is reacted with an organo-metallic phenyl compound of the formula sixth written in that claim and, if desired, a racemic mixture obtained is separated into its optically active antipodes and, also is desired, a product obtained is converted into an acid addition salt.

16) A process as set forth in claim 13 or claim 14, wherein a compound of the formula third written in claim 13 is treated with titanium tetrachloride or boron trifluoride.

17) A process as set forth in claim 13 or claim 14, wherein a compound of the formula seventh written in claim 13 is treated with chromium trioxide or gaseous oxygen.

18) A process as set forth in claim 13 or claim 14, wherein the oxidation of a compound of the formula written in claim 1 in which R^8 is absent to the corresponding compound in which R^8 is present and represents a hydroxy group includes the treatment of the intermediately formed hydroperoxy-substituted compound with a reducing agent.

19) A process as set forth in any one of claims 13, 14 and 18, wherein the oxidation of a compound of the formula written in claim 1 in which R^8 is absent is carried out with hydrogen peroxide or gaseous oxygen.

20) A process as set forth in claim 18, wherein the reducing agent is sodium sulphite or triethyl phosphite.

21) A process as set forth in claim 13 or claim 14, wherein the lower alkylation of the compound of the formula written in claim 1 in which R^8 is present and represents the hydroxy group is carried out with the aid of a lower-alkanol.

22) A process as set forth in any one of claims 13 to 21 inclusive, wherein R^2 and R^4 or R^{41} as the case may be are absent.

23) A process as set forth in any one of claims 13 to 22 inclusive, wherein B represents the ethylene group.

24) A process as set forth in any one of claim 13 to 23 inclusive, wherein R^1 (when present) represents a chlorine atom and R^3 and R^{31} (when present) represent a chlorine or bromine atom or the methoxy group.

25) A process as set forth in any one of claims 13, 14, 16 and 18 to 24 inclusive, wherein α -benzoyl-benzaldehyde is treated with ethylenediamine or a 2-(2-amino-alkyl)-3-phenyl-phthalimidine is cyclised by treatment with a LEWIS acid, the resulting compound is oxidised and if desired, the oxidation product is converted into an acid addition salt.

26) A process as set forth in any one of claims 13, 15, 16 and 18 to 24 inclusive, wherein 1,2,3,9b-tetrahydro-5H-imidazo[2,1-a]isoindol-5-one is treated with an organo-metallic phenyl compound in which R^{31} and R^{32} are absent, the resulting compound is oxidised and, if desired, the oxidation product is converted into an acid addition salt.

27) A process as set forth in any one of claims 13, 14, 17 and 21 to 24 inclusive, wherein 2-(2-amino-ethyl)-1-phenyl-isoindoline is treated with an oxidising agent and, if desired, the resulting compound is converted into an acid addition salt.

28) A process as set forth in any one of claims 13, 14, 16 and 18 to 24 inclusive, wherein 2-(4-chloro-benzoyl)-benzaldehyde is treated with ethylenediamine or 2-(2-amino-ethyl)-3-(4-chloro-phenyl)-phthalimidine is cyclised by treatment with a LEWIS

hydroxy
and
and
ained
ained 5

formula
ritten
clised
ritten 10
which
id re-
resent
ct in
con- 15

formula
pound
tained
tained 20

of the
boron 25

of the
aseous 25

n of a
spond-
les the
with a 30

in the
absent 35

sodium 40

ylation
nt and 40

rein R² 45

n B re- 45

rein R¹
present 50

clusive,
-amino-
id, the
nverted 55

clusive,
ith an
resulting
into an 60

clusive,
ent and,
60

clusive,
or 2-(2-
LEWIS

acid, the resulting compound is oxidised and, if desired, the oxidation product is converted into an acid addition salt.

29) A process as set forth in any one of claims 13, 15, 16 and 18 to 24 inclusive, wherein 1,2,3,9b-tetrahydro-5H-imidazo[2,1-a]isoindol-5-one is treated with a 4-chloro-phenyl organo-metallic compound, the resulting compound is oxidised and, if desired, the oxidation product is converted into an acid addition salt.

30) A process as set forth in any one of claims 13 and 22 to 24 inclusive, wherein 5-phenyl-2,3-dihydro-5H-imidazo[2,1-a]isoindol-5-one is treated with an organo-metallic phenyl compound in which R³¹ and R⁴¹ are absent and, if desired, the resulting compound is converted into an acid addition salt.

31) A process as set forth in any one of claims 13, 14, 17 and 21 to 24 inclusive, wherein 2-(2-amino-ethyl)-1-(4-chloro-phenyl)-isoindoline is treated with an oxidising agent and, if desired, the resulting compound is converted into an acid addition salt.

32) A process as set forth in any one of claims 13, 14, 16 and 18 to 24 inclusive, wherein 2-(4-methoxy-phenyl)-benzaldehyde is treated with ethylenediamine or 2-(2-amino-ethyl)-3-(4-methoxy-phenyl)-phthalimidine is cyclised by treatment with a LEWIS acid, the resulting compound is oxidised and, if desired, the oxidation product is converted into an acid addition salt.

33) A process as set forth in any one of claims 13, 15, 16 and 18 to 24 inclusive, wherein 1,2,3,9b-tetrahydro-5H-imidazo[2,1-a]isoindol-5-one is treated with a 4-methoxy-phenyl organo-metallic compound, the resulting compound is oxidised and, if desired, the oxidation product is converted into an acid addition salt.

34) A process as set forth in any one of claims 13, 15, 17 and 21 to 24 inclusive, wherein 2-(2-amino-ethyl)-1-(4-methoxy-phenyl)-isoindoline is treated with an oxidising agent and, if desired, the resulting compound is converted into an acid addition salt.

35) A process as set forth in any one of claims 25 to 28 inclusive, wherein the product obtained is methylated and, if desired, the resulting compound is converted into an acid addition salt.

36) A process for the manufacture of the 1,3-diazacycloalkeno[2,1-a]isoindole derivatives set forth in claim 1, substantially as described with reference to the Examples.

37) 1,3-Diazacycloalkeno[2,1-a]isoindole derivatives as set forth in claim 1, when manufactured by the process claimed in any one of claims 13 to 36 inclusive.

W. D. WHITAKER,
Patent Agent.

For: F. Hoffman-La Roche & Co.,
Aktiengesellschaft.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1970.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from
which copies may be obtained.