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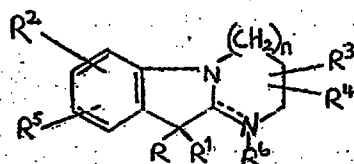
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 ROBIN MICHAEL BLACK

(54) FUSED RING INDOLE DERIVATIVES

(71) We, JOHN WYETH & BROTHER LIMITED, of Huntercombe Lane South, Taplow, Maidenhead, Berkshire, a British Company, 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 a novel series of fused ring indole derivatives, to a process for their preparation and to pharmaceutical compositions containing certain of them. The indole derivatives of this invention are derivatives of imidazo[1,2-a]indoles, pyrimido[1,2-a]indoles and diazepino[1,2-a]indoles.

The present invention provides an indole derivative of the general formula (I)



or an acid addition or quaternary ammonium salt thereof, in which n represents 0, 1 or 2, R represents a hydroxyl, lower alkoxy, aryl-lower alkoxy, tetrahydropyranyloxy or acyloxy group, R¹ represents a mono- or a bi-cyclic aryl radical or an aryl-lower alkyl, lower alkyl, lower alkenyl, lower alkynyl or amino-lower alkyl group or R and R¹ are taken together and represent an oxo group when n is 0, 1 or 2 or a ketalised oxo group when n is 1, R² and R⁵ which may be the same or different represent hydrogen, hydroxyl, lower alkyl, lower alkoxy, haloloweralkyl, halogen, amino or mono- or di-(lower)alkyl-amino or if R and R¹ together represent an oxo or ketalised oxo group, R² and/or R⁵ may also represent nitro, R³ and R⁴ which may be the same or different represent hydrogen or lower alkyl radicals or R³ represent hydrogen and R⁴ represents hydroxy, the dotted line represents an optional bond in the position indicated and R⁶, which is present only when the optional bond represented by the dotted line is absent, represents hydrogen or an aryl-lower alkyl, lower alkyl, lower alkenyl, lower alkynyl or acyl radical.

By the term "aryl" used to denote a radical or part of a radical such as aryl-lower alkyl, we mean a radical having an aromatic character. Such radicals include phenyl, naphthyl and heterocyclic radicals having an aromatic character. The term "lower" as used herein means the radical contains up to 6, preferably up to 4 carbon atoms. It is

[Price 25p]

to be understood that R^3 and R^4 may be on the same or different carbon atoms, but preferably they are both on the same carbon atom, e.g. at position 3 in the pyrimido-[1,2-a]indoles or at position 2 (or 3) in the imidazo[1,2-a]indoles. The term "amino-lower alkyl" as used in connection with the radical R^1 means unsubstituted amino-lower alkyl or mono- or di-substituted amino lower alkyl such as alkylamino-lower alkyl, dialkylamino-lower alkyl or heterocyclo-lower alkyl. When R and R^1 together represent a "ketalised oxo group" the group can be an alkylene ketal or a di-(lower alkyl)ketal group.

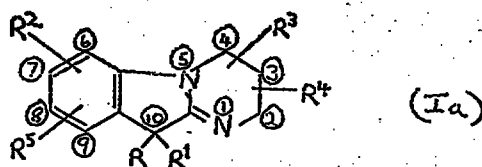
Since the compounds of the invention may possess one or more asymmetric carbon atoms, optical enantiomorphs are possible and the compounds of the invention may be the pure enantiomorphs or mixtures of such enantiomorphs, such as the racemates.

Examples of radicals R are hydroxyl, methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, benzyloxy, phenethoxy, acetoxy, propionoxy, butyryloxy, benzoyloxy, substituted benzoyloxy, phenylacetoxy, methanesulphonyloxy and *p*-toluenesulphonyloxy. Examples of mono- and bi-cyclic aryl radicals R^1 are phenyl, naphthyl, furyl, thienyl, pyridyl, indolyl, and benzothienyl, each of which may be substituted or unsubstituted. Suitable substituents are halogen (for example fluorine, chlorine or bromine), lower alkyl (for example methyl, ethyl, propyl, or butyl), lower alkoxy (for example methoxy, ethoxy, propoxy or butoxy) and halo-loweralkyl (for example trifluoromethyl). Examples of aryl-lower alkyl radicals R^1 are benzyl and phenethyl each of which may be substituted by those substituents defined above for the aryl groups R^1 . Lower alkyl radicals R^1 may be methyl, ethyl, propyl, or butyl; alkenyl radicals may be straight or branched chain radicals and may for example be allyl or dimethylallyl; alkynyl radicals may be straight or branched chain and may for example be propargyl; and aminolower alkyl radicals may for example be dimethylamino-ethyl, dimethylaminopropyl, diethylamino-propyl, diethylaminoethyl, methylaminoethyl and methylaminopropyl, morpholinopropyl and piperidinopropyl. Examples of R^1 and R^2 when taken together are oxo and ketalised oxo groups such as ethyleneketal, propyleneketal and dimethoxy. The following are examples of residues for R^2 and R^5 ; lower alkyl residues, e.g. methyl, ethyl, propyl and butyl; lower alkoxy residues, e.g. methoxy, ethoxy, propoxy and butoxy; haloloweralkyl residues may be trifluoromethyl; and halogen groups may be chlorine and bromine. Examples of lower alkyl residues R^3 and R^4 are methyl, ethyl, propyl and butyl.

Examples of aryl-lower alkyl radicals R^1 are benzyl and phenethyl each of which may be substituted by those substituents defined for the aryl groups R^1 mentioned above. Lower alkyl radicals R^1 may be straight or branched chain radicals including methyl, ethyl, propyl and butyl; alkenyl radicals may be straight or branched chain radicals and may for example be allyl or dimethyl-allyl; alkynyl radicals may be straight or branched chain and may for example be propargyl. Acyl radicals R^1 may for example be formyl, acetyl, propionyl, butyryl benzoyl, phenylacetyl or benzenesulphonyl each of which may be substituted on the aromatic ring by the substituents defined for the aryl radicals R^1 mentioned above or methanesulphonyl.

The preferred compounds are those of formula (I) in which R^2 , R^3 , R^4 and R^5 represent hydrogen atoms, R represents hydroxyl and R^1 represents a monocyclic aryl radical, particularly a phenyl, halophenyl or alkylphenyl radical and the dotted line represents a bond.

A preferred class of compounds of formula (I) are the tetrahydropyrimido[1,2-a]indoles of general formula (Ia)



or acid addition or quaternary ammonium salts thereof wherein R and R^1 have the meanings given above in connection with formula (I), R^2 and R^5 which may be the same or different represent hydrogen, hydroxyl, lower alkyl, lower alkoxy, halolower-alkyl or halogen and R^3 and R^4 which may be the same or different represent hydrogen or lower alkyl. The ring system of the pyrimido[1,2-a]indoles is numbered as shown in general formula (Ia).

Especially valuable compounds of formula (Ia) are:

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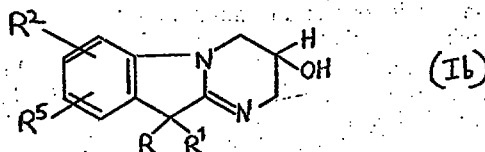
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2,3,4,10-Tetrahydro-10-phenylpyrimido[1,2-a]indol-10-ol
10-(*m*-Chlorophenyl)-2,3,4,10-tetrahydropyrimido-[1,2-a]indol-10-ol
2,3,4,10-Tetrahydro-10-(*p*-chlorophenyl)pyrimido[1,2-a]indole-10-ol
2,3,4,10-Tetrahydro-10-(2-thienyl)pyrimido[1,2-a]-indol-10-ol
10-(*m*-Fluorophenyl)-2,3,4,10-tetrahydropyrimido[1,2-a]-indol-10-ol
10-(3,4-Dichlorophenyl)-2,3,4,10-tetrahydropyrimido-[1,2-a]-indol-10-ol
10-(*m*-Chlorophenyl)-2,3,4,10-tetrahydro-3,3-dimethylpyrimido[1,2-a]indol-10-ol
2,3,4,10-Tetrahydro-10-phenyl-3,3-dimethylpyrimido-[1,2-a]-indol-10-ol
(+)-2,3,4,10-Tetrahydro-10-(*m*-chlorophenyl)pyrimido-[1,2-a]-indol-10-ol and
(-)-2,3,4,10-Tetrahydro-10-(*m*-chlorophenyl)-pyrimido-[1,2-a]-indol-10-ol.

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The invention provides tetrahydropyrimido[1,2-a]indoles other than those of general formula (Ia). For example it provides compounds of general formula (Ib).

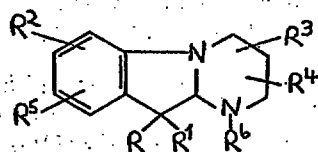


(Ib)

or acid addition or quaternary ammonium salts thereof wherein R, R¹, R² and R⁵ have the meanings given above in connection with formula (I) except that R and R¹ cannot be taken together to represent a ketalised oxo group.

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Another class of compounds within formula (I) are the hexahydropyrimido[1,2-a]indoles, for examples compounds of the general formula (Ic)



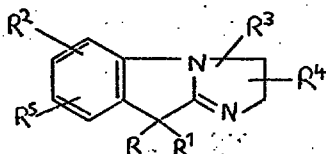
(Ic)

and acid addition and quaternary ammonium salts thereof wherein R, R¹ and R⁶ have the meanings given above in connection with formula (I) and R², R³, R⁴ and R⁵ have the meanings given above in connection with formula (Ia).

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A further class of compounds within general formula (I) are those compounds in which n is 0 or 2 i.e. the imidazo[1,2-a]indoles and the diazepino[1,2-a]indoles. A particular class of imidazo[1,2-a]indoles are those having the general formula (Id)

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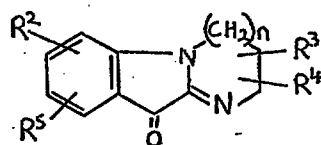


(Id)

and their acid addition and quaternary ammonium salts, wherein R and R¹ have the meaning given above in connection with formula (I) and R², R³, R⁴ and R⁵ have the meanings given above in connection with formula (Ia).

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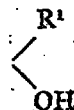
Indole derivatives of general formula (I) except those where R and R¹ are taken together and represent an oxo or ketalised oxo group, can be prepared by a process in which a ketone of general formula (II)



(II)

wherein R², R³, R⁴, R⁵ and n have the meanings given in connection with formula (I)

except that neither R^2 nor R^3 represent nitro, is reacted with an organometallic compound known in the art for the conversion of a ketone function to the group

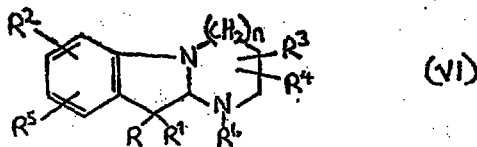


and, if desired, the resulting compound of formula (I) in which R represents a hydroxyl group and the dotted line represents a bond, is alkylated or acylated to give a corresponding compound in which R represents a lower alkoxy, aryl-lower alkoxy, tetrahydropyranyloxy or an acyloxy residue and again if desired the compound of general formula (I) in which the dotted line represents a bond is converted to an acid addition or quaternary ammonium salt thereof and if desired the compound in which the dotted line represents a bond or its quaternary ammonium salt is reduced to give a compound of formula (I) in which the bond represented by the dotted line is absent and R^6 represents an aryl-lower alkyl, lower alkyl, lower alkenyl or lower alkynyl group and if desired the resulting compound is converted to an acid addition or quaternary ammonium salt thereof and if desired in any product one group R and/or R^1 and/or R^2 and/or R^3 and/or R^4 and/or R^5 and/or R^6 , (if present), is converted into another group R and/or R^1 and/or R^2 and/or R^4 and/or R^5 and/or R^6 within the meanings defined above in connection with formula I.

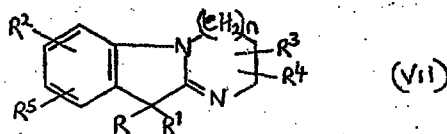
In the above process the organometallic compound is preferably chosen from (a) Grignard reagents of formula $R^1 MgY$ wherein Y is halogen and R^1 has the meanings defined above, and (b) alkali-metal compounds such as the lithium derivatives of formula $R^1 Li$ (particularly the aryl lithiums, for example phenyl lithium), and sodium and potassium acetylide. When n is 0 the organometallic compound is preferably an aryl lithium. The reaction with the organometallic compound is generally carried out in an inert organic solvent, for example ether or tetrahydrofuran, using the standard conditions known for the particular reaction concerned.

As already mentioned, if desired the compound in which R represents a hydroxyl group and the dotted line represents a bond in the position indicated may be alkylated or acylated to introduce a lower alkoxy, aryl-lower alkoxy, tetrahydropyranyloxy or acyloxy residue R. Such alkylation or acylation reactions are carried out by standard methods known in the art. For example, the hydroxy compound may be converted into its alkali-metal derivative, particularly the sodio derivative and then treated with the appropriate alkylating or acylating agent. Examples of alkylating agents are lower alkyl or aryl-lower alkyl halides such as the chlorides, bromides or iodides, while examples of acylating agents are acid halides (particularly the chlorides) or acid anhydrides of the aliphatic or aromatic carboxylic acids, as well as halides (particularly the chlorides) of some organically substituted inorganic acids such as the aliphatic or aromatic sulphonic acids.

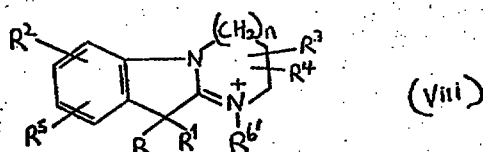
The compounds of general formula (I) in which the bond represented by the dotted line is absent having the general formula (VI)



wherein R, R^1 , R^2 , R^3 , R^4 , R^5 , R^6 and n have the meanings given above in connection with formula (I) except that R and R^1 cannot be taken together to represent an oxo group, can be prepared by reducing, for example, with a hydride transfer agent such as a complex metal hydride a compound of general formula (VII)



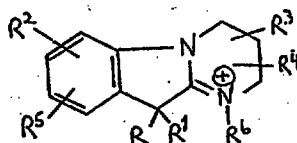
or a quaternary ammonium salt thereof in which the cation has the formula (VIII)



wherein R, R¹, R², R³, R⁴, R⁵ and n have the meanings given immediately above and R⁶ is an aryl-lower alkyl, lower alkyl, lower alkenyl or lower alkynyl radical, and if desired converting one group R and/or R¹ and/or R² and/or R⁵ and/or R⁶ into another group R and/or R¹ and/or R² and/or R⁵ and/or R⁶ within the above defined meanings of R, R¹, R², R⁵ and R⁶ or, if desired converting a free base into an acid addition or quaternary ammonium salt thereof.

For example, when it is desired to prepare a compound of general formula (Ic) in which R, R¹, R², R³, R⁴ and R⁶ have the meanings defined in connection with formula (VI) and R⁵ represents hydrogen, a compound of general formula (Ia) in which R, R¹, R², R³, R⁴ and R⁵ have the meanings defined above in connection with formula (VI) may be reduced by methods known in the art. Preferably the reduction is effected by means of a hydride transfer reagent, particularly a complex metal hydride such as sodium borohydride or lithium aluminium hydride. The reaction is conducted using the standard conditions known for the particular reducing agent concerned.

When it is desired to prepare a compound of general formula (Ic) in which R, R¹, R², R³, R⁴ and R⁵ have the meanings defined in connection with formula (VI) and R⁶ is an aryl-lower alkyl, lower alkyl, alkenyl or alkynyl radical, a quaternary compound in which the cation has the general formula

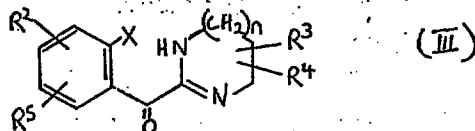


in which R, R¹, R², R³, R⁴, R⁵ and R⁶ have the meanings defined immediately above, is reduced as described above.

Once a compound of general formula (I) has been prepared in which R, R¹, R², R³, R⁴, R⁵ and R⁶ have the meanings defined in connection with formula (I), one group R and/or R¹ and/or R² and/or R³ and/or R⁴ and/or R⁵ and/or R⁶ (if present) may, if desired, be converted into another group R and/or R¹ and/or R² and/or R³ and/or R⁴, R⁵ and/or R⁶ each within the above defined meanings of R, R¹, R², R³, R⁴, R⁵ and R⁶. For example, when R² and/or R⁵ is a hydrogen atom, this may be converted into a halogen or nitro group, particularly at the 8-position of the pyrimido[1,2-a]indoles, by known methods. When the chloro compound is desired this may be obtained by treatment with N-chlorosuccinimide. Furthermore, when R² and/or R⁵ is a lower alkoxy radical (particularly a methoxy radical), this may be de-etherified by known methods to give the corresponding hydroxy radical R² and/or R⁵ or conversely a hydroxyl radical R³ and/or R⁵ may be alkylated by known methods to give a lower alkoxy radical R³ and/or R⁵. When R¹ is an alkynyl radical, this may be reduced to an alkenyl radical R¹. A dimethylaminoalkyl radical R¹ may be mono-demethylated to give the corresponding methylaminoalkyl radical. If desired a hydroxyl function R may be alkylated or acylated to form a lower alkoxy, aryl-lower alkoxy or acyloxy residue R by the methods described hereinbefore.

When R⁶ is a hydrogen atom, the compound may be alkylated or acylated by known methods to introduce a group R⁶ other than hydrogen. If necessary, any reactive group in a compound may be protected by known methods before performing any of the above reactions and then removed by known methods subsequent to the reaction.

The ketone starting materials of the general formula (II) can be prepared by cyclisation of a ketone of general formula (III)



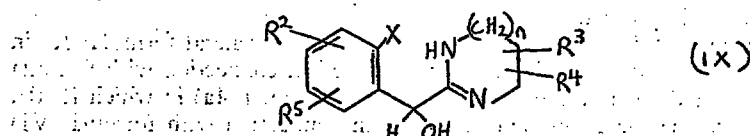
where R², R³, R⁴, R⁵ and n have the meanings given above in connection with formula

(II) and X is halo and, if desired, conversion of one group R^2 and/or R^5 into another group R^2 and/or R^5 by known methods.

The ketone of general formula (III) can be cyclised by a modified Ullmann Reaction. For example, the ketone may be treated with a metallic agent such as copper or a salt thereof, especially cupric oxide or cuprous chloride. The reaction is generally carried out in the presence of a base such as an alkaline metal carbonate (e.g. potassium carbonate), triethylamine or N-ethylmorpholine and preferably in a solvent (e.g. dimethylacetamide, pyridine, hexamethylphosphoric triamide or preferably dimethylformamide).

The group X is preferably bromo and, in the ketone of general formula (IV) R^2 and R^5 are preferably hydrogen, or electron-attracting groups such as halogen.

The ketones of general formula (III) can be prepared by oxidation of the corresponding hydroxy compounds of general formula (IX)



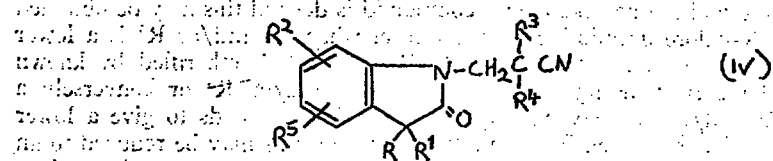
wherein R^2 , R^3 , R^4 , R^5 , n and X have the meanings given above. Preferably the oxidation is carried out with a mild oxidising agent such as manganese dioxide (for example, in solvents such as dichloromethane, chloroform, benzene, acetone or aqueous acetone) or lead tetra-acetate (for example, in pyridine). The compound of formula (IX) in which R^3 is hydrogen and R^4 is hydroxy may be selectively oxidised to the compound of general formula (III) in which R^3 and R^4 have the same meanings by the use of suitable mild oxidising agents such as precipitated manganese dioxide.

The compounds of general formula (IX) are described in the literature or may be prepared from known compounds by known methods. For example they may be prepared by the method described by Neilson et al J. Chem. Soc. (C), 1968, 1853.

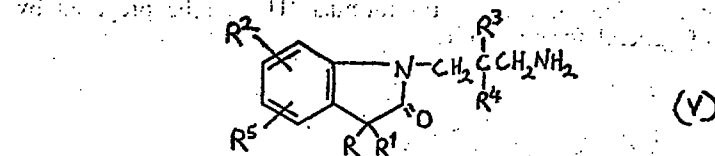
The ketone starting materials of general formula (II), in which n is 1, may be prepared by an alternative method which comprises hydrolysing the corresponding compound of general formula (I) in which R and R^1 are taken together and represent a ketalised oxo group.

The hydrolysis may be carried out by methods known *per se*, for example, by heating with acid, e.g. dilute mineral acid such as hydrochloric acid. The yields of ketone (II), which is usually isolated as its mineral acid salt by this method, is only in the region of 50%. A preferred method for the hydrolysis consists in treating the compound with concentrated sulphuric acid at room temperature. By this process the ketone (II) is usually isolated as its free base and in yields of the order of 90%.

In a method for preparing the compounds of formula I in which n is 1 and R and R^1 are taken together and represent a ketalised oxo group, a substituted isatin of general formula (IV)



wherein R and R^1 have the meanings defined immediately above and R^2 , R^3 , R^4 and R^5 are as defined in connection with formula (I) is hydrogenated. The hydrogenation is usually carried out in the presence of a nickel, palladium or platinum catalyst and at elevated temperatures and pressures. The use of temperatures in the region of 100°C usually gives rise to the tricyclic compound directly. In some instances and also when using somewhat lower temperatures, the product isolated consists of a mixture of the desired tricyclic compound and an intermediate amine of formula (V)



The amine may be dehydrated to obtain the desired tricyclic compound by subjecting the mixture to azotropic distillation with a solvent such as benzene, xylene or toluene.

and a liquid. Solid form compositions include powders, tablets and capsules. A solid carrier can be one or more substances which may also act as flavouring agents, lubricants, solubilisers, suspending agents, binders, or tablet-disintegrating agents; it can also be an encapsulating material. In powders the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets the active ingredient is mixed with a carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain from 5 to 99, preferably 10—80% of the active ingredient. Suitable solid carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low melting wax and cocoa butter. The term "composition" is intended to include the formulation of an active ingredient with encapsulating material as carrier to give a capsule in which the active ingredient (with or without other carriers) is surrounded by carrier, which is thus in association with it. Similarly cachets are included.

Sterile liquid form compositions include sterile solutions, suspensions, emulsions, syrups and elixirs. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable sterile liquid carrier, such as sterile water, sterile organic solvent or a mixture of both. Preferably a liquid carrier is one suitable for parenteral injection. Where the active ingredient is sufficiently soluble it can be dissolved in normal saline as a carrier; if it is too insoluble for this it can often be dissolved in a suitable organic solvent, for instance aqueous propylene glycol or polyethylene glycol solutions. Aqueous propylene glycol containing from 10 to 75% of the glycol by weight is generally suitable. In other instances compositions can be made by dispersing the finely-divided active ingredient in aqueous starch or sodium carboxymethyl cellulose solution, or in a suitable oil, for instance arachis oil. Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilised by intramuscular, intraperitoneal or subcutaneous injection. In many instances a compound is orally active and can be administered orally either in liquid or solid composition form.

Preferably the pharmaceutical composition is in unit dosage form. In such form, the composition is sub-divided in unit doses containing appropriate quantities of the active ingredient; the unit dosage form can be a packaged composition, the package containing specific quantities of compositions, for example packeted powders or vials or ampoules. The unit dosage form can be a capsule or tablet itself, or it can be the appropriate number of any of these in packaged form. The quantity of active ingredient in a unit dose of composition may be carried or adjusted from 5 mg. or less to 500 or more, according to the particular need and the activity of the active ingredient. The invention also includes the compounds in the absence of carrier where the compounds are in unit dosage form.

The following Examples illustrate the invention:

EXAMPLE 1

3,4'-Dihydrospiro[1,3-dioxolane-2,10'(2H,10H)pyrimido[1,2-a]indole 2'-Oxospiro[1,3-dioxolane-2,3'-indoline]-1'-propionitrile (37g.) was reduced at an initial pressure of 1200 p.s.i. and final temperature of 100°C in ethanol (200ml.) half saturated with ammonia, in the presence of Raney Nickel (6g.) for 3 hours. After cooling, the catalyst was filtered off and the solvent removed under reduced pressure to leave a viscous oil. The oil was dissolved in xylene (200ml.) and heated under reflux with stirring for 26 hours in an apparatus fitted with a water separator. The xylene was removed under reduced pressure, the dark oil dissolved in hot ethyl acetate and treated with decolourising charcoal. The product, 25.9 g. of colourless needles, had m.p. 114—115°C. (Found): 68.0; H, 5.9; N, 12.2. $C_{13}H_{14}N_2O_2$ requires C, 67.8; H, 6.1; N, 12.2%).

EXAMPLE 2

3,4-Dihydropyrimido[1,2-a]indol-10[2H]-one 3,4'-Dihydrospiro [1,3-dioxolane-2,10'(2H,10H)pyrimido(1,2-a)indole] (12.2 g.) was suspended in water (50 ml.) and concentrated hydrochloric acid (50 ml.) added with stirring. The mixture was heated at 85°C for 5 hours. The mixture was evaporated to a red oil under reduced pressure, dissolved in absolute ethanol (100 ml.) and evaporated to 50 ml. On cooling, the product, in the form of its hydrochloride, separated as crimson needles (1.9 g.), m.p. 215—225°C (decomp). (Found: C, 59.0; H, 5.0; N, 12.3. $C_{11}H_{10}N_2O$. HCl requires C, 59.3; H, 5.0; N, 12.6%).

EXAMPLE 3

3,4-Dihydropyrimido[1,2-a]indol-10[2H]-one
Finely powdered 3,4'-dihydrospiro[1,3-dioxolane-2,10'(2H,10H)pyrimido(1,2-a)-

A solid lubricants, also be which is in edient is ions and contain riers are starch, melting mulation in which r, which nulsions, pharma-olvent or njection. al saline organic Aqueous illy suit-divided m, or in hich are or sub-adminis- orm, the ie active ntaining mpoules. ropriate n a unit r more, vention in unit uced at 200ml.) s. After pressure r reflux : xylene ate and les, had 2, 67.8; 12.2 g.)) added evapor- al.) and chloride, 2, 59.0; (1,2-a)-	8 5 10 15 20 25 30 35 40 45 50 55 60	5 10 15 20 25 30 35 40 45 50 55 60	indole] (10g.) was added portionwise to stirred concentrated sulphuric acid (50ml.) which was maintained at 25°C by icebath cooling. On completion of the addition the mixture was stirred at room temperature overnight, poured onto ice and neutralised with concentrated aqueous ammonia solution, keeping the temperature below 30°C. The mixture was extracted with chloroform and dried over anhydrous magnesium sulphate. After evaporation, the product was crystallised from benzene/light petroleum (b.p. 60—80°C.) affording 7.3 g. of stout crimson needles, m.p. 121—122°C. (Found: C, 71.0; H, 5.4; N, 14.7. $C_{11}H_{10}N_2O$ requires C, 70.95; H, 5.4; N, 15.05%). EXAMPLE 4 2,3,4,10-Tetrahydro-10-phenylpyrimido[1,2-a]indol-10-ol Finely powdered 3,4-dihydropyrimido[1,2-a]indol-10[2H]-one hydrochloride (3.82 g.) was added portionwise to phenyl magnesium bromide [from magnesium (12.9 g.) and bromobenzene (8.2 g.)] in ether (100 ml.). On completion, the reaction mixture was heated under reflux overnight, cooled and poured onto a mixture of ice and ammonium chloride (10 g.). The yellow solid which was deposited was filtered off and washed with water and ether affording 3.67 g. of off white powder, m.p. 246—7°C. (decomp). The base could be recrystallised from ethanol as colourless rhombs, m.p. 247—8°C. (Found: C, 77.6; H, 6.2; N, 10.5. $C_{17}H_{16}N_2O$ requires C, 77.3; H, 6.1; N, 10.6%). The hydrochloride of the base could be obtained by dissolving in hot absolute ethanol and adding a solution of hydrogen chloride gas in dry ether. The product, colourless needles, had m.p. 264—70°C (decomp). (Found: C, 68.2; H, 5.7; N, 9.2. $C_{17}H_{16}N_2O \cdot HCl$ requires C, 67.85; H, 5.7; N, 9.3%). EXAMPLE 5 2,3,4,10-Tetrahydro-10-phenylpyrimido[1,2-a]indol-10-ol Phenyl lithium (0.05 mole.) in ether was added dropwise to a stirred suspension of the pyrimido[1,2-a]indol-10[2H]-one hydrochloride of Example 2 (2.2 g.) in dry ether (1L) under a stream of nitrogen. The colourless solution formed was left at room temperature overnight and decomposed by the addition of water (35 ml.) and 2N hydrochloric acid (15 ml.). The solid formed was filtered off, washed with water and dried affording the title compound (1.57 g.) m.p. 220—225°C. Recrystallisation from ethanol raised the m.p. to 246—7°C. EXAMPLE 6 2,3,4,10-Tetrahydro-10-phenylpyrimido[1,2-a]indol-10-ol 3,4-Dihydropyrimido[1,2-a]indol-10-one (5.58 g.) in dry tetrahydrofuran was added dropwise with stirring to phenyl magnesium bromide (0.05 mole.) in dry ether (200 ml.). The reaction mixture was heated under reflux with stirring for 3 hours. The reaction mixture was decomposed by pouring onto a mixture of ice and ammonium chloride affording 6.38 g. pink powder, m.p. 230—5°C (decomp.). Recrystallisation from ethanol raised the m.p. to 246—8°C (decomp). EXAMPLE 7 2,3,4,10-Tetrahydro-10-(p-chlorophenyl)-pyrimido[1,2-a]indol-10-ol Finely powdered 3,4-dihydropyrimido[1,2-a]indol-10[2H]-one hydrochloride (6.5 g. 0.03 mole.) was reacted with p-chlorophenyl magnesium bromide (0.2 mole.) in dry ether (700 ml.) as described in Example 4. Work up with ice and ammonium chloride afforded the base m.p. 185—191°C (decomp). (Found: C, 68.4; H, 5.3; N, 9.4. $C_{17}H_{15}N_2ClO$ requires C, 68.1; H, 5.1; N, 9.4%). A total of 2.6 g. of hydrochloride was obtained by dissolving in ethanol and heating with a solution of hydrogen chloride in dry ether, m.p. 275—279°C (decomp). (Found: C, 60.3; H, 5.3; N, 7.6; Cl, 9.9. $C_{17}H_{15}N_2ClO \cdot HCl \cdot \frac{1}{2} C_2H_5OH$ requires C, 60.4; H, 5.35; N, 7.8; Cl, 10.1%). EXAMPLE 8 2,3,4,10-Tetrahydro-10-(o-tolyl)pyrimido[1,2-a]indole-10-ol 3,4-Dihydropyrimido[1,2-a]indol-10[2H]-one hydrochloride (6.66 g.; 0.03 mole.) was reacted with o-tolyl magnesiumbromide (0.1 mole.) in ether (1L) as described in Example 4. Work up afforded the base (4.1 g.), m.p. 205—207°C (decomp.). (Found: C, 77.5; H, 6.7; N, 9.9. $C_{18}H_{18}N_2O$ requires C, 77.7; H, 6.5; N, 10.1%). Treatment of the base in isopropanol with dry hydrogen chloride in ether afforded the hydrochloride as colourless fine needles (4.4 g.), m.p. 300—302°C (decomp). (Found: C, 68.7; H, 6.25; N, 8.8. $C_{18}H_{18}N_2O \cdot HCl$ requires C, 68.7; H, 6.1; N, 8.9%).
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EXAMPLE 9

2,3,4,10-Tetrahydro-10-(*p*-tolyl)pyrimido[1,2-*a*]indol-10-ol

Following the method of Example 4, 6.6 g. of 3,4-dihydropyrimido[1,2-*a*]indole-10[2H]-one hydrochloride and *p*-tolyl magnesium bromide (0.15 ml.) in dry ether (1500 ml.) afforded the title compound hydrochloride (1.28 g.) as colourless needles, m.p. 265—267°C (decomp). (Found: C, 68.9; H, 6.3; N, 8.9; $C_{18}H_{18}N_2O$. HCl requires C, 68.7; H, 6.1; N, 8.9).

EXAMPLE 10

2,3,4,10-Tetrahydro-10-methylpyrimido[1,2-*a*]indol-10-ol

Following the method of Example 6, 3,4-dihydropyrimido[1,2-*a*]indole-10-[2H]-one (3.72 g.) was reacted with methylmagnesium iodide (0.06 mole.) in ether (500 ml.). After heating under reflux for 4 hours and leaving overnight the reaction mixture was poured onto ice and ammonium chloride, the ether layer separated and aqueous layer extracted with chloroform. The chloroform extracts were dried over anhydrous magnesium sulphate and evaporated to a solid which was recrystallised from isopropanol affording 2.1 g. of fawn rhombs, m.p. 189—191°C. (Found: C, 71.6; H, 7.1; N, 13.9. $C_{12}H_{14}N_2O$ requires C, 71.3; H, 7.0; N, 13.85%). When this solid was dissolved in isopropanol and treated with anhydrous hydrogen chloride in ether, 2.0 g. of hydrochloride were obtained, m.p. 210—212°C (decomp.). (Found: C, 60.8; H, 6.3; N, 11.7. $C_{12}H_{14}N_2O$. HCl requires C, 60.4; H, 6.3; N, 11.7%).

EXAMPLE 11

10-Benzyl-2,3,4,10-tetrahydropyrimido[1,2-*a*]indol-10-ol

Following the method of Example 6, the 3,4-dihydropyrimido[1,2-*a*]indole-10-[2H]-one (3.72 g.) was added dropwise to a stirred solution of benzylmagnesium chloride (0.04 mole.) in dry ether (300 ml.). The reaction was heated under reflux for 4 hours and left overnight and decomposed by pouring onto ice and ammonium chloride yielding the required base (4.3 g.), m.p. 225—30°C (decomp.). Treatment of an isopropanol solution with hydrogen chloride in dry ether afforded the hydrochloride as colourless fine needles, m.p. 241—243°C (decomp.). (Found: C, 68.9; H, 6.2; N, 9.1. $C_{18}H_{18}N_2O$. HCl requires C, 68.7; H, 6.1; N, 8.9%).

EXAMPLE 12

10-(*m*-Chlorophenyl)-2,3,4,10-tetrahydropyrimido[1,2-*a*]indol-10-ol

Following the method of Example 6, the 3,4-dihydropyrimido[1,2-*a*]indole-10-[2H]-one (3.72 g.) was reacted with *m*-chlorophenylmagnesiumbromide (0.04 mole.) in dry ether (500 ml.). The reaction mixture was heated under reflux 6 hours then left overnight. The mixture was poured onto ice and ammonium chloride and the product was filtered off yielding 4.1 g. of a white powder, m.p. 193—5°C (decomp.). After converting to the hydrochloride, 4.79 g. of fine needles, m.p. 275—80°C (decomp.) were obtained. (Found: C, 61.0; H, 4.9; N, 8.3. $C_{17}H_{14}N_2O$. HCl requires C, 60.9; H, 4.7; N, 8.4%).

EXAMPLE 13

8'-Chloro-3',4'-dihydrospiro[1,3-dioxolane-2,10'(2H,10H)pyrimido(1,2-*a*)indole]

3',4' - Dihydrospiro[1,3 - dioxolane - 2,10'(2H,10H)pyrimido(1,2-*a*)indole] (2.3 g.) was heated under reflux with stirring in carbon tetrachloride (50 ml.) with *N*-chlorosuccinimide (1.43 g.) for 16 hours. After cooling, the carbon tetrachloride was washed with 2*N*-sodium bicarbonate solution. The organic layer was then washed with 2*N* hydrochloric acid. The acid extracts were basified with concentrated aqueous ammonia solution and the white solid extracted into ether. After drying with anhydrous magnesium sulphate, the solvent was removed to leave an oil which was crystallised from light petroleum (b.p. 100—120°C) containing a few drops of benzene. The product (0.73 g.) as colourless needles had m.p. 112—114°C. (Found: C, 58.95; H, 5.0; N, 10.3. $C_{13}H_{13}ClN_2O_2$ requires C, 59.0; H, 4.95; N, 10.6%).

EXAMPLE 14

3',4'-Dihydrospiro[1,3-dioxolane-3'3'-dimethyl-2,10'(2H,10H)pyrimido-(1,2-*a*)indole]

(a) Isatin (7.35 g.), ethyleneglycol (11.2ml.) and toluene-*p*-sulphonic acid (2 g.) in benzene (300 ml.) was heated under reflux in an apparatus fitted with a water separator for 5 hours, when water (2.1 ml.) was collected in the water separator and the reaction mixture had become colourless. The reaction mixture was cooled, washed with sodium bicarbonate solution and water. After drying over magnesium sulphate the

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benzene was removed under reduced pressure and the residue crystallised from methanol affording 9.9 g. of 2'-oxospiro[1,3-dioxolane-2,3'-indoline] as faintly pink needles, m.p. 131—132°C. (Found: C, 62.72; H, 4.8; N, 7.2. $C_{10}H_8N_2O_3$ requires C, 62.8; H, 4.8; N, 7.2%).

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(b) t-Butylcyanide (42.0 g.) was heated at 60°C with stirring in a mixture of bromine (26 ml.) and carbon tetrachloride (1L) for 7 days, irradiating at the same time with a medium pressure ultra-violet lamp. The carbon tetrachloride was removed under reduced pressure and the residual oil dissolved in dichloromethane and washed with sodium bicarbonate then water. After drying over anhydrous magnesium sulphate the solvent was removed and the product distilled affording 26 g. of 3-bromo-2,2-dimethylpropionitrile as a colourless oil, b.p. 77—82°C at 12 mm. (Found: C, 36.1; H, 4.8; N, 7.5. C_6H_8BrN requires C, 37.1; H, 5.0; N, 8.65%).

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(c) 2'-Oxopiro[1,3-dioxolane-2,3'-indoline], (3.8 g.) was added portionwise to a stirred suspension of sodium amide (0.84 g.) in dry hexamethylphosphoric triamide (30 ml.) under a stream of nitrogen. The reaction mixture was heated to 40°C for 2 hours, cooled to 10°C and 3-bromo-2,2-dimethylpropionitrile (3.24 g.) added in one portion. The reaction mixture was stirred at room temperature for 2 days. The reaction mixture was poured into water and extracted with benzene. The benzene extracts were washed with dilute hydrochloric acid, dried over anhydrous magnesium sulphate and evaporated to a dark oil. Crystallisation from absolute ethanol afforded 3.05 g. of 2'-oxopira[1,3-dioxolane-2,3'-indoline]-1-[2,2-dimethylpropionitrile] as colourless rhombs m.p. 112—113°C. (Found: C, 66.5; H, 6.2; N, 10.3. $C_{18}H_{16}N_2O_3$ requires C, 66.2; H, 5.9; N, 10.3%).

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(d) The product of Example 14(c) (2.7 g.) was reduced in ethanolic ammonia in the presence of Raney Nickel as described for Example 1. After work up, the product was heated under reflux with toluene for 24 hours. Removal of the toluene and recrystallisation from benzene afforded 1.23 g. of the title compound as colourless rhombs, m.p. 109—110°C. (Found: C, 70.0; H, 7.2; N, 11.1. $C_{18}H_{18}N_2O$ requires C, 69.7; H, 7.0; N, 10.85%).

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EXAMPLE 15

8-Chloro-2,3,4,10-tetrahydropyrimido[1,2-a]indol-10[2H]-one
8' - Chloro - 3',4' - dihydro - spiro[1,3 - dioxolane - 2,10'(2H,10H)pyrimido - (1,2-a)indole] (8.0 g.) was finely powdered and added to concentrated sulphuric acid (50 ml.) as described in Example 3. Following the method of that example, work up and recrystallisation from benzene afforded red plates (5.8 g.) m.p. 163—165°C (decomp.). (Found: C, 60.2; H, 3.9; N, 12.8. $C_{11}H_8ClN_2O$ requires C, 59.9; H, 4.1; N, 12.7%).

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EXAMPLE 16

8-Chloro-2,3,4,10-tetrahydro-10-phenylpyrimido[1,2-a]indol-10-ol
Following the method of Example 6, 8-Chloro-2,3,4,10-tetrahydropyrimido[1,2-a]indol-10-one in tetrahydrofuran (60 ml.) was added to a solution of phenylmagnesium bromide (0.026 mole.) in ether (50 ml.). Mixture was heated under reflux with stirring for 5 hours and after leaving overnight poured onto a mixture of ice and ammonium chloride. The solid formed was filtered off, and washed with water and ether to give 2.74 g. of a fawn powder, m.p. 240—250°C (decomp.). (Found: C, 67.6; H, 5.3; N, 8.9. $C_{17}H_{15}ClN_2O$ requires C, 68.9; H, 5.6; N, 9.4%).

The powder was suspended in hot absolute ethanol and treated with a solution of dry hydrogen chloride gas in dry ether to give 1.89 g. of fine needles, m.p. 279—282°C (decomp.). (Found: C, 61.25; H, 4.8; N, 8.5. $C_{17}H_{15}ClN_2O.HCl$ requires C, 60.9; H, 4.8; N, 8.1%).

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EXAMPLE 17

8-Chloro-2,3,4,10-tetrahydro-10-(m-chlorophenyl)pyrimido[1,2-a]indol-10-ol
Following the method of Example 6, 8-Chloro-2,3,4,10-tetrahydropyrimido[1,2-a]indol-10-one (2.8 g.) in dry tetrahydrofuran (60 ml.) was added to m-chlorophenylmagnesium bromide (0.03 mole.) in ether (60 ml.). Reaction mixture heated under reflux for 4 hours. After leaving overnight, the reaction mixture was poured onto ice and ammonium chloride. Organic layer separated and aqueous layer extracted with methylene dichloride. Organic layer extracted with 2N-hydrochloric acid, acid layer basified, extracted into methylene dichloride; after drying over magnesium sulphate, solvent removed and residue dissolved in absolute ethanol and treated with a solution of hydrogen chloride in dry ether. Pale pink rhombs (1.61 g.), m.p. 279°C (decomp.) were obtained. (Found: C, 54.8; H, 4.15; N, 7.3. $C_{17}H_{14}Cl_2N_2O.HCl$ requires C, 55.2; H, 4.1; N, 7.6%).

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EXAMPLE 18

10-(*m*-Anisyl)-2,3,4,10-tetrahydropyrimido[1,2-*a*]indol-10-ol

Following the method of Example 6, 2,3,4,10-tetrahydropyrimido[1,2-*a*]indole-10-one (3.72 g.) in dry tetrahydrofuran (50 ml.) was added to *m*-anisylmagnesiumbromide (0.04 mole.) in ether (50 ml.). Heated under reflux with stirring for 5 hours, left overnight then poured onto ice and ammonium chloride. After acid base extraction, 2.16 g. base obtained, m.p. 255°C (decomp.). The solid was converted to its hydrochloride by solution in ethanol and addition of hydrogen chloride in dry ether to give 2.2 g. colourless rhombs, m.p. 260—262°C (decomp.). (Found: C, 65.5; H, 6.0; N, 8.5. $C_{18}H_{18}N_2O_2$. HCl requires C, 65.3; H, 5.8; N, 8.5%).

EXAMPLE 19

2,3,4,10-Tetrahydro-10-(*m*-tolyl)pyrimido[1,2-*a*]indol-10-ol

Following the method of Example 6, 2,3,4,10-tetrahydropyrimido[1,2-*a*]indol-10-one in tetrahydrofuran (50 ml.) was added to *m*-tolylmagnesium bromide (0.05 mole.) in ether (200 ml.). On completion of the addition the mixture was heated under reflux for 3 hours. After leaving overnight, the reaction mixture was poured onto a mixture of ice and ammonium chloride. The organic layer was separated and the aqueous layer extracted with chloroform. After drying, the chloroform was removed to leave a red oil. Trituration with ether afforded a white solid. The solid was recrystallised from benzene-ether to give pale yellow rhombs (1.36 g.), m.p. 179—80°C. (Found: C, 77.4; H, 6.7; N, 9.8. $C_{18}H_{18}N_2O$ requires C, 77.7; H, 6.5; N, 10.1%).

EXAMPLE 20

2,3,4,10-Tetrahydro-10-(2-thienyl)pyrimido[1,2-*a*]indol-10-ol

2,3,4,10-Tetrahydropyrimido[1,2-*a*]indol-10-one (3.72 g.) in dry tetrahydrofuran (150 ml.) was added to 2-thienyl magnesium bromide (0.05 mole.) as described in Example 19. On completion of the addition the reaction was stirred under reflux for 4 hours. The reaction mixture was poured onto ice and ammonium chloride and filtered to afford 4.38 g. of a grey powder. The powder was suspended in absolute ethanol, and treated with a solution of hydrogen chloride in dry ether, the mixture was boiled and then treated with charcoal and filtered. On dilution with ether the title compound was obtained as colourless needles (3.68 g.), m.p. 226—228°C (decomp.). (Found: C, 58.6; H, 5.0; N, 9.9. $C_{15}H_{14}N_2OS$. HCl requires C, 58.7; H, 4.9; N, 9.1%).

EXAMPLE 21

10-(*m*-Fluorophenyl)-2,3,4,10-tetrahydropyrimido[1,2-*a*]indol-0-ol

3,4-Dihydropyrimido[1,2-*a*]indol-10[2H]-one (3.72g) in dry tetrahydrofuran (100 ml.) was added dropwise to a stirred solution of *m*-fluorophenyl magnesium bromide (0.05 mole) in dry ether. The reaction mixture was stirred under reflux for 4 hours, cooled and decomposed by pouring onto a mixture of ice and ammonium chloride. The organic layer was separated and the aqueous layer extracted with chloroform. Combined organic extracts were washed with water and dried over anhydrous magnesium sulphate. After removal of the solvent, the residue was triturated with ether affording 3.3g. of fawn solid. The solid was suspended in boiling absolute ethanol, a solution of hydrogen chloride gas in dry ether added and the resulting solution treated with charcoal and filtered. On cooling the filtrate the title compound as its hydrochloride crystallised as needles (3.3g.), m.p. 280—90°C (decomp.). (Found: C, 64.0; H, 5.1; N, 8.9. $C_{17}H_{15}FN_2O.HCl$ requires C, 64.05; H, 5.1; N, 8.9%).

EXAMPLE 22

10-(1-Naphthyl)-2,3,4,10-tetrahydropyrimido[1,2-*a*]indol-10-ol

Following the method of the previous example 3,4-dihydropyrimido[1,2-*a*]indol-10(2H)-one (2.86g.) in dry tetrahydrofuran (100 ml.) was added to 1-naphthylmagnesium bromide (0.05 mole). After work up and removal of the solvent the base was obtained as an oil which was converted to the hydrochloride in the usual way. The product (3.8g.) had m.p. 270—274°C (decomp.). (Found: C, 71.0; H, 5.5; N, 7.7. $C_{21}H_{18}N_2.HCl.1/4H_2O$ requires C, 71.25; H, 5.5; N, 7.9%).

EXAMPLE 23

10-(*o*-Chlorophenyl)-2,3,4,10-tetrahydropyrimido[1,2-*a*]indol-10-ol

Following the method of Example 21, 3,4-dihydropyrimido[1,2-*a*]indol-10[2H]-one (2.8g.) was added to a solution of *o*-chlorophenylmagnesium bromide (0.05 mole.) in dry tetrahydrofuran (100 ml.). After pouring the reaction mixture onto ice and ammonium chloride solution the solid formed was filtered and washed with water and

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ether. The hydrochloride was obtained in the usual way as colourless rhombs (3.47g.) m.p. 287—90°C (decomp.). Found: C, 60.1; H, 5.8; N, 7.7. $\text{C}_{17}\text{H}_{15}\text{ClN}_2\text{O} \cdot \text{HCl} \cdot \frac{1}{2} \text{C}_2\text{H}_5\text{OH}$ requires C, 60.35; H, 5.9; N, 7.7%.

EXAMPLE 24

5 2,3,4,10-Tetrahydro-10-(*m*-trifluoromethylphenyl)pyrimido[1,2-*a*]indol-10-ol 5

Following the method of Example 21, 3,4-dihydropyrimido[1,2-*a*]indol-10[2H]-one (2.7g.) was added to a solution of *m*-trifluoromethylphenylmagnesium bromide (0.05 mole). After pouring onto ice and ammonium chloride solution, the precipitated base was removed and the organic layer worked up and evaporated to give a further quantity of base. The base was converted to the hydrochloride in the usual way yielding 3.95g. of the title compound as the hydrochloride, m.p. 291—2°C (decomp.). (Found: C, 58.6; H, 4.3; N, 7.5. $\text{C}_{18}\text{H}_{15}\text{F}_3\text{N}_2\text{O} \cdot \text{HCl}$ requires C, 58.6; H, 4.4; N, 7.6%).

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EXAMPLE 25

15 10-(3,4-Dichlorophenyl)-2,3,4,10-tetrahydropyrimido[1,2-*a*]indol-10-ol 15

Following Example 21, 3,4-dihydropyrimido[1,2-*a*]indol-10[2H]-one (2.7g.) was reacted with 3,4-dichlorophenylmagnesium bromide (0.05 mole). After work up, the organic layer was separated and the aqueous layer extracted with chloroform. The combined organic extracts were treated with 2N hydrochloric acid and the precipitated hydrochloride filtered and dried. Recrystallisation from methanol/ether afforded 3.4g. of colourless needles, m.p. 287—90°C (decomp.). (Found: C, 54.9; H, 4.1; N, 7.5. $\text{C}_{17}\text{H}_{14}\text{Cl}_2\text{N}_2\text{O} \cdot \text{HCl}$ requires C, 55.2; H, 4.1; N, 7.6%).

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EXAMPLE 26

25 10-(*p*-Fluorophenyl)-2,3,4,10-tetrahydropyrimido[1,2-*a*]indol-10-ol 25

Following the method of Example 21, 3,4-dihydropyrimido[1,2-*a*]indol-10[2H]-one (2.5g.) was reacted with *p*-fluorophenylmagnesium chloride (0.05 mole). The hydrochloride was formed in the usual way, yielding 2.4g. of cream coloured needles, m.p. 270—272°C. (Found: C, 63.9; H, 4.9; N, 8.6. $\text{C}_{17}\text{H}_{16}\text{FN}_2\text{O} \cdot \text{HCl}$ requires C, 64.0; H, 5.1; N, 8.8%).

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EXAMPLE 27

30 2,3,4,10-Tetrahydro-10-(*o*-trifluoromethylphenyl)pyrimido[1,2-*a*]indol-10-ol 30

Following the method of Example 21, 3,4-dihydropyrimido[1,2-*a*]indol-10[2H]-one (2.79g.) was reacted with *o*-trifluoromethylphenylmagnesium bromide (0.05 mole). The hydrochloride was obtained as fine needles (3.72 g.), m.p. 255—7°C (decomp.). (Found: C, 58.4; H, 4.9; N, 7.3. $\text{C}_{18}\text{H}_{15}\text{F}_3\text{N}_2\text{O} \cdot \text{HCl} \cdot \frac{1}{2} \text{C}_2\text{H}_5\text{OH}$ requires C, 58.2; H, 4.9; N, 7.15%).

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EXAMPLE 28

40 10-(2,3-Dichlorophenyl)-2,3,4,10-tetrahydropyrimido[1,2-*a*]indol-10-ol 40

Following the method of Example 21, 3,4-dihydropyrimido[1,2-*a*]indol-10[2H]-one (1.86g.) was reacted with 2,3-dichlorophenylmagnesium bromide (0.025 mole). After work up, the base was obtained as an oil which afforded 1.93g. of the hydrochloride, m.p. 292—4°C (decomp.). (Found: C, 52.7; H, 4.1; N, 7.3. $\text{C}_{17}\text{H}_{14}\text{Cl}_2\text{N}_2\text{O} \cdot \text{HCl} \cdot \text{H}_2\text{O}$ requires C, 52.7; H, 4.4; N, 7.2%).

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EXAMPLE 29

45 3,4-Dihydro-3,3-dimethylpyrimido[1,2-*a*]indol-10[2H]-one 45

3',4' - Dihydrospiro[1,3 - dioxolane - 3',3' - dimethyl - 2,10'(2H,10H)pyrimido-[1,2-*a*]indole (8.5g.) was added portion-wise to concentrated sulphuric acid (100 ml.) keeping the temperature below 30°C, and controlling the rate of addition so that all the ketal had dissolved before the next portion was added. After leaving stirring at room temperature overnight, the mixture was poured onto ice and neutralised with concentrated aqueous ammonia keeping the temperature below 30°C. The red oil was extracted into methylene dichloride, dried over anhydrous magnesium sulphate, evaporated to a red foam which afforded 5.98g. of scarlet rhombs, m.p. 125—126°C from benzene-light petroleum (b.p. 40—60°C). (Found: C, 73.3; H, 6.7; N, 13.0. $\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}$ requires C, 72.9; H, 6.6; N, 13.1%).

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EXAMPLE 30

10-(*m*-Chlorophenyl)-2,3,4,10-tetrahydro-3,3-dimethylpyrimido[1,2-*a*]indol-10-ol

Following the method of Example 21, 3,4-dihydropyrimido-3,3-dimethyl[1,2-*a*]indol-10[2H]-one (2.4g.) was added to a solution of *m*-chlorophenyl magnesium bromide (0.05 mole). After work up, the base was filtered off and converted to the hydro-

chloride in the usual way giving 2.0g. of the title compound hydrochloride m.p. 271—273°C (decomp.). (Found: C, 62.8; H, 5.5; N, 7.6. $C_{19}H_{19}ClN_2O.HCl$ requires C, 62.8; H, 5.55; N, 7.7%).

EXAMPLE 31

5 2,3,4,10-Tetrahydro-10-phenyl-3,3-dimethylpyrimido[1,2-a]indol-10-ol
Following the method of Example 21, 3,4-dihydro-3,3-dimethylpyrimido[1,2-a]-indol-10[2H]-one (3g.), was reacted with phenyl magnesium bromide (0.05 mole). After work up, 2.4g. of the hydrochloride was obtained m.p. 260—261°C (decomp.). (Found: C, 69.0; H, 6.75; N, 8.3. $C_{19}H_{20}N_2O.HCl$ requires C, 69.4; H, 6.4; N, 8.5%).

EXAMPLE 32

10 3,4-Dihydro-8-methoxypyrimido[1,2-a]indol-10(2H)-one

a) 5-Methoxy-2,3-dioxindoline-1-propionitrile
5-Methoxyisatin (20.28g.) and 40% aqueous solution of benzyl trimethylammonium hydroxide (5ml.) was heated to reflux in absolute ethanol (500ml.) and acrylonitrile (19ml.) added dropwise. The mixture was heated under reflux for 30 minutes, cooled and the purple crystals filtered off to afford 17.39g. of the title compound. The product was recrystallised from aqueous dimethylformamide for characterisation, m.p. 182—185°C. (Found: C, 62.5; H, 4.5; N, 12.2. $C_{12}H_{10}N_2O_3$ requires C, 62.5; H, 4.4; N, 12.2%).

20 b) 2'-Oxospiro[1,3-dioxolane-2,3'-[5-methoxyindoline]]-1'-propionitrile
Ethane-1,2-diol (12ml.), 5-methoxy-2,3-dioxindoline-1-propionitrile (16.4g.), benzene (500ml.) and toluene-*p*-sulphonic acid (0.5g.) were heated together under reflux in an apparatus fitted with a water separator. After 12 hours, the theoretical quantity of water had separated. The mixture was washed with water then sodium bicarbonate solution and the organic phase dried over anhydrous magnesium sulphate. After removal of the solvent and recrystallisation from propan-2-ol 13.6g. of the product was obtained, m.p. 110—111°C. (Found: C, 61.5; H, 5.2; N, 10.3. $C_{14}H_{14}N_2O_4$ requires C, 61.2; H, 5.1; 10.2%).

30 c) 3',4'-Dihydrospiro[1,3-dioxolane-2,10'(2H,10H)-8'-methoxypyrimido
[1,2-a]indole]
The product of part (b) (13g.) was reduced at an initial pressure of 1100 p.s.i. of hydrogen and a temperature of 40°C in absolute ethanol (400 ml.) half saturated with ammonia in the presence of W7 Raney Nickel (2.0g.) for a period of 4 hours. The reaction mixture was cooled, the catalyst filtered off and the ethanol removed under reduced pressure. The product was dissolved in toluene and heated under reflux with phosphorus oxychloride (10 drops) for 12 hours. The insoluble material was filtered off and the toluene removed under reduced pressure to leave an oil which spontaneously crystallised. The oil was converted to the hydrochloride and recrystallised from propan-2-ol affording 5.65g. of product which decomposed at 300—360°C. (Found: C, 56.53; H, 5.7; N, 9.15. $C_{14}H_{16}N_2O_3.HCl$ requires C, 56.65; H, 5.8; N, 9.4%).

40 d) The product of part (c) (4.6g.) was added with stirring to concentrated sulphuric acid (50ml.) keeping the temperature below 20°C. The mixture was stirred for 30 minutes then poured into ice. After neutralisation with ammonia, the purple product was extracted into chloroform, dried over magnesium sulphate and, after removal of the solvent, recrystallised from benzene affording 2.7g. of purple rhombs, m.p. 150—151°C. (Found: C, 66.9; H, 5.7; N, 12.7. $C_{12}H_{12}N_2O_2$ requires C, 66.7; H, 5.6; N, 13.0%).

EXAMPLE 33

50 10-(*m*-Chlorophenyl)-2,3,4,10-tetrahydro-8-methoxy-pyrimido[1,2-a]indol-10-ol
Following the method of example 21, 3,4-dihydro-8-methoxypyrimido[1,2-a]indol-10(2H)-one, (1.45g.), was reacted with *m*-chlorophenylmagnesium bromide (0.025 mole). Work up afforded 1.36g. of the hydrochloride, m.p. 282—283°C. (decomp.). (Found: C, 59.2; H, 5.1; N, 7.6. $C_{18}H_{17}ClN_2O_2.HCl$ requires C, 59.1; H, 5.0; N, 7.6%).

EXAMPLE 34

55 2,3,4,10-Tetrahydro-8-methoxy-10-phenylpyrimido[1,2-a]indol-10-ol
Following the method of Example 21, 3,4-dihydro-8-methoxypyrimido[1,2-a]indol-10(2H)-one (1.45g.) was reacted with phenylmagnesium bromide (0.025 mole.).

p. 271—
requires

ol
o[1,2-a]-
35 mole).
decomp.).
N, 8.5%).

lammon-
rylonitrile
es, cooled
e product
p. 182—
; H, 4.4;

(16.4g.),
der reflux
quantity of
carbonate
r removal
obtained,
C, 61.2;

0 p.s.i. of
ated with
ours. The
ved under
flux with
filtered off
ntaneously
n propan-
C, 56.53;

rated sul-
stirred for
le product
removal of
p. 150—
; H, 5.6;

-10-ol
2-a]indol-
ie (0.025
decomp.).
; H, 5.0;

l
do[1,2-a]
35 mole.).

Work up afforded 1.29g. of the hydrochloride, m.p. 285—8°C. (decomp.). (Found: C, 64.1; H, 5.8; N, 8.4. $C_{18}H_{18}N_2O_2 \cdot HCl$ requires C, 65.25; H, 5.8; N, 8.45%).

EXAMPLE 35

2,3,4,10-Tetrahydro-8-nitropyrimido[1,2-a]indol-10(2H)-one

Finely powdered 3',4'-dihydrospiro[1,3-dioxolane-2,10'(2H,10H)-pyrimido (1,2-a) indole (6.92g.) was added to concentrated sulphuric acid (30ml.). On completion of the addition, the mixture was stirred at room temperature for 2 hours, cooled to $-10^{\circ}C$ and fuming nitric acid (2ml.) added dropwise. The reaction was allowed to warm to room temperature then stirred for 30 minutes. The mixture was poured onto ice and neutralised with concentrated aqueous ammonia below $30^{\circ}C$. The precipitate was filtered off and extracted with hot benzene. The yellow residue weighed 5.95g. and decomposed without melting between $300-360^{\circ}C$. (Found: C, 57.2; H, 4.05; N, 18.3. $C_{11}H_8N_3O_3$ requires C, 57.1; H, 3.9; N, 18.2%).

EXAMPLE 36

10-(o-Fluorophenyl)-2,3,4,10-tetrahydropyrimido[1,2-a]indol-10-ol

3,4-Dihydropyrimido[1,2-a]indol-10(2H)-one (1.86 g.) in dry tetrahydrofuran (80ml.) was added to a solution of o-fluorophenyllithium (0.02 mole.) in ether (50ml.) at $-60^{\circ}C$. On completion of the addition the colourless reaction mixture was stirred at $-60^{\circ}C$ for 2 hours then poured onto ice and ammonium chloride solution. When the mixture had warmed to room temperature, the base was filtered off. The hydrochloride was formed in the usual way yielding 2.8g., m.p. $269-70^{\circ}C$ (decomp.). (Found: C, 63.6; H, 5.0; N, 8.6. $C_{17}H_{15}FN_2O \cdot HCl$ requires C, 64.05; H, 5.1; N, 8.6%).

EXAMPLE 37

2,3,4,10-Tetrahydro-10-(2,6-dimethylphenyl)pyrimido[1,2-a]indol-10-ol

3,4-Dihydropyrimido[1,2-a]indol-10(2H)-one (1.86g.) in tetrahydrofuran was added to 2,6-dimethylphenyl magnesium bromide (0.02 mole), prepared by the "entrainment" method. The reaction mixture was worked up as described in Example 21 and the hydrochloride obtained as colourless needles (1.35g.) m.p. $274-6^{\circ}C$ (decomp.). (Found: C, 69.5; H, 6.55; N, 8.4. $C_{19}H_{20}N_2O \cdot HCl$ requires C, 69.0; H, 6.4; N, 8.5%).

EXAMPLE 38

10-Ethynyl-2,3,4,10-tetrahydropyrimido[1,2-a]indole-10-ol

3,4-Dihydropyrimido[1,2-a]indol-10(2H)-one (7.4g.) in tetrahydrofuran was reacted with ethynylmagnesium bromide (0.15 mole.) as described in Example 21. After work up, 5.8g. of the base was obtained, m.p. $224-6^{\circ}C$ (decomp.). The hydrochloride had m.p. $210-215^{\circ}C$ (decomp.). (Found: C, 62.5; H, 5.4; N, 11.0. $C_{13}H_{12}N_2O \cdot HCl$ requires C, 62.8; H, 5.3; N, 11.3%).

EXAMPLE 39

2,3,4,10-Tetrahydro-10-(m-chlorophenyl)pyrimido[1,2-a]indol-10-ol acetate

2,3,4,10 - Tetrahydro - 10 - (m - chlorophenyl)pyrimido[1,2-a]indol - 10 - ol ((3g.) was dissolved in acetic anhydride (100 ml.) and left at room temperature for 48 hours. The acetic anhydride was removed under reduced pressure and the residue re-evaporated with toluene (50 ml.). The residue was dissolved in the minimum quantity of ethanol and treated with a solution of hydrogen chloride in dry ether. The product hydrochloride was obtained as colourless rhombs (3.24g.), m.p. $213-216^{\circ}C$ (decomp.). (Found: C, 60.4; H, 4.8; N, 7.3. $C_{19}H_{17}N_2O_2 \cdot HCl$ requires C, 60.5; H, 4.8; N, 7.4%).

EXAMPLE 40

(+)-2,3,4,10-Tetrahydro-10-(m-chlorophenyl)pyrimido[1,2-a]indol-10-ol

2,3,4,10 - Tetrahydro - 10 - (m - chlorophenyl)pyrimido[1,2-a]indol - 10 - ol (6.6g.) was dissolved in hot absolute ethanol and L(+)(natural) tartaric acid (3.3g.) added. The mixture was heated until solution was complete. Crystallisation afforded a total of 2.23g. of the L(+)-tartarate salt. Recrystallisation 3 times and evaporation of the mother liquors afforded a total of 2.1g. $[\alpha]_D^{25} + 70.9^{\circ}$ (c 1 in methanol), m.p. $118^{\circ}C$ (decomp.). (Found: C, 55.7; H, 5.0; N, 6.2. $C_{17}H_{15}ClN_2O \cdot (CHOH \cdot COOH)_2$ requires C, 56.2; H, 4.7; N, 6.2%).

EXAMPLE 41

(—)-2,3,4,10-Tetrahydro-10-(*m*-chlorophenyl)pyrimido[1,2-*a*]indol-10-ol

The mother liquors from example 40 containing the (—) isomer, were evaporated to dryness and converted to the base (3.84g.). The base was dissolved in hot ethanol and treated with D(—) (unnatural) tartaric acid. After working up as in Example 40, 2.0g of the laevo base as the D(—) tartarate salt was obtained. $[\alpha]_D^{24} -71.4^\circ$ (c 1 in methanol.), m.p. 118°C (decomp.).

EXAMPLE 42

2,3,4,10-Tetrahydro-10-(2-pyridyl)pyrimido[1,2-*a*]indol-10-ol

3,4-Dihydropyrimido[1,2-*a*]indol-10-(2H)-one (4.0g.) in dry tetrahydrofuran (10ml) was added to a solution of 2-pyridyl lithium (0.04 mole) at -40°C . The reaction mixture was allowed to warm up to room temperature over 2 hr. then decomposed by adding to ice and ammonium chloride. The organic layer was separated and the aqueous layer extracted with chloroform. After drying over anhydrous magnesium sulphate the solvent was removed and the base obtained as 2.73g of a fawn powder. The hydrochloride was formed in the usual way, affording 3.0g. m.p. 268–70°C. (Found: C, 56.0; H, 5.2; N, 12.4. $\text{C}_{16}\text{H}_{18}\text{N}_2\text{O} \cdot 2\text{HCl} \cdot 1/4\text{H}_2\text{O}$ requires C, 56.1; H, 5.0; N, 12.3%).

EXAMPLE 43

10-(*m*-Chlorophenyl)-2,3,4,10-tetrahydro-10-hydroxy-1-methylpyrimido-[1,2-*a*]indolinium iodide

10-(*m*-Chlorophenyl)-2,3,4,10-tetrahydropyrimido[1,2-*a*]indol-10-ol (2.94g.) was dissolved in hot 2-propanol (50ml.) and methyl iodide (2ml.) added. Heated under reflux for 30 minutes. On cooling the indolinium iodide separated, 4.03g. decomposed without melting at 250–254°C. (Found: C, 49.3; H, 4.3; N, 6.6. $\text{C}_{18}\text{H}_{18}\text{ClIN}_2\text{O}$ requires C, 49.1; H, 4.1; N, 6.35%).

EXAMPLE 44

10-(*m*-Chlorophenyl)-1,2,3,4,10,10a-hexahydro-1-methylpyrimido[1,2-*a*]indol-10-ol

The quaternary salt prepared in the above example (2.5g.) was added portionwise to a stirred suspension of lithium aluminium hydride (1.8g.) in dry tetrahydrofuran (100ml.). The reaction mixture was stirred under reflux for 5 hours, cooled and decomposed by the addition of water (5ml.). The precipitated organic material was filtered, the filtrate dried over anhydrous magnesium sulphate and evaporated to an oil which was crystallised from benzene light petroleum (b.p. 60–80°C) affording 941mg. m.p. 135–137°C. (Found: C, 68.2; H, 6.8; N, 7.8. $\text{C}_{18}\text{H}_{19}\text{ClN}_2\text{O}$ requires C, 68.7; H, 6.1; N, 7.8%).

EXAMPLE 45

1,2,3,4,10,10a-Hexahydro-10-phenylpyrimido[1,2-*a*]indol-10-ol

1,2,3,4-Tetrahydro-10-phenylpyrimido[1,2-*a*]indol-10-ol (1.9g.) was added as a slurry in dry tetrahydrofuran to a suspension of lithium aluminium hydride (0.6g.) in dry tetrahydrofuran (20ml.). The reaction mixture was stirred under reflux for 3 hours, cooled and decomposed with water. After separation of the organic material and removal of solvent a yellow oil was obtained which solidified on trituration with ether giving 1.0g., m.p. 147°C. (Found: C, 76.25; H, 7.0; N, 10.4. $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}$ requires C, 76.7; H, 6.8; N, 10.5%).

The fumarate was obtained from 2-propanol, m.p. 157°C. (Found: C, 70.3; H, 6.2; N, 8.4. $[\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}]_2 \cdot \text{C}_4\text{H}_4\text{O}_4$ requires C, 70.35; H, 6.2; N, 8.6%).

EXAMPLE 46

1,2,3,4,10,10a-Hexahydrospiro[1,3-dioxolane-2,10'-[3,3-dimethyl]-pyrimido[1,2-*a*]indol]

2'-Oxospiro[1,3-dioxolane-2,3'-indoline]-1'-[2,2-dimethylpropionitrile] (17.5g.) was reduced at an initial pressure of 1500 p.s.i. and 100°C for 5 hours in ethanol (200ml) half saturated with ammonia in the presence of Raney nickel W.7. (8g.). The catalyst was removed and the ethanol removed under reduced pressure. The residual oil was crystallised from benzene, affording 12.09g., m.p. 93–96°C. (Found: C, 69.7; H, 7.7; N, 10.8. $\text{C}_{15}\text{H}_{20}\text{N}_2\text{O}_2$ requires C, 69.2; H, 7.7; N, 10.8%).

EXAMPLE 47

3,4-Dihydropyrimido[1,2-*a*]indol-10[2H]-one

A *o*-Bromophenyl (1,4,5,6-tetrahydro-2-pyrimidyl)ketone
(a) A solution of α -*o*-bromophenyl-(1,4,5,6-tetrahydro-2-pyrimidyl)methanol (20 g.)

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of ethanol
ample 40,
4° (c 1 in

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hydrofuran
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composed
d and the
magnesium
n powder.
3—70°C.
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- 10 - ol
l.) added.
ed, 4.03g.
; N, 6.6.

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ol-10-ol
ortionwise
hydrofuran
id decom-
s filtered,
which was
mg. m.p.
7; H, 6.1;

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lded as a
(0.6g.) in
3 hours,
erial and
with ether
requires

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C, 70.3;
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ylpropio-
or 5 hours
ckel W.7.
pressure.
3—96°C.
10.8%).

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ol (20 g.)

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in dichloromethane (1000 ml.) was stirred with precipitated manganese dioxide (150 g.) at room temperature for 48 hours. After filtration, the manganese dioxide was stirred with fresh dichloromethane (400 ml.) for a further hour, filtered, and the combined filtrates dried over magnesium sulphate. Removal of the solvent under reduced pressure and crystallisation of the residue from petroleum (b.p. 60—80°) yielded the product (12.1 g.) as colourless needles, m.p. 100—101°. [Found: C, 49.45; H, 4.15; N, 10.45%. $C_{11}H_{11}BrN_2O$ requires C, 49.45; H, 4.15; N, 10.5%].

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(b) A solution of α -*o*-bromophenyl-(1,4,5,6-tetrahydro-2-pyrimidyl)methanol (2.69 g., 0.01 mole) and lead tetraacetate (5.3 g., 0.012 mole) in dry pyridine (40 ml.) was stirred at room temperature for 60 hours. After removal of the pyridine under reduced pressure the residue was diluted with water and extracted with chloroform. The combined extracts were washed with water, dried ($MgSO_4$) and the solvent removed to give a brown residue. Crystallisation from petroleum (b.p. 60—80°), after treatment with charcoal, yielded the product.

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B 3,4-Dihydropyrimido[1,2-a]indol-10[2H]-one

A mixture of *o*-bromophenyl-(1,4,5,6-tetrahydro-2-pyrimidyl)ketone (0.67 g., 0.0025 mole), potassium carbonate (0.345 g., 0.0025 mole) and cupric oxide (0.025 g.) in dry dimethylformamide (5 ml.) was stirred under nitrogen at 90° for 2 hours. The mixture was diluted with benzene (100 ml.), filtered the filtrate washed with water (4×50 ml.) and dried ($MgSO_4$). Removal of the solvent and crystallisation of the residue from benzene cyclohexane, after treatment with charcoal, yielded the product (0.088 g.) as orange needles, m.p. 118—121°.

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EXAMPLE 48

2,3-Dihydro-2,2 (or 3,3)-dimethylimidazo[1,2-a]-indol[9H]-9-one

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(a) A solution of ethyl *o*-bromomandelimidate hydrochloride (29.4 g., 0.1 mole) and 1,2-diamino-2-methyl propane (8.8 g., 0.1 mole) in absolute ethanol (150 ml.) was heated under reflux for 5 hours. Removed of the solvent and crystallisation of the residue from isopropanol/ether yielded a crude hydrochloride (23.4 g.). An aqueous solution of the crude hydrochloride was basified (NaOH) with simultaneous scratching of the flask to yield α -(*o*-bromophenyl)-4,4(or 5,5)-dimethyl-2-imidazolinemethanol as the crystalline free base (16.2 g., m.p. 128—130°). Alternatively the free base may be extracted into chloroform, the extracts dried ($MgSO_4$), and the residue after removal of the solvent triturated with petroleum (60—80°).

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An analytical sample of the hydrochloride was prepared by acidifying a solution of the free base in isopropanol with ethereal HCl, m.p. 213—217°; [Found: C, 45.35; H, 5.05; N, 8.6%; $C_{12}H_{13}BrN_2O.HCl$ requires C, 45.1; H, 5.05; N, 8.75%].

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(b) A solution of α -(*o*-bromophenyl)-4,4 (or 5,5)-dimethyl-2-imidazolinemethanol (15.8 g.) in dichloromethane (750 ml.) was stirred with precipitated manganese dioxide (150 g.) at room temperature for 40 hours. The manganese dioxide was filtered and stirred with a further portion of dichloromethane (400 ml.) for 1 hour. After filtering the combined filtrates were dried ($MgSO_4$), the solvent removed and the residue recrystallised from petroleum b.p. 60—80° to yield *o*-bromophenyl-4,4 (or 5,5)-dimethyl-2-imidazolinyl ketone (11.01 g., m.p. 107—108°). [Found: C, 51.25; H, 4.85; N, 10.05%; $C_{12}H_{13}BrN_2O$ requires C, 51.25; H, 4.65; N, 9.95%].

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(c) A solution of *o*-bromophenyl-4,4 (or 5,5)-dimethyl-2-imidazolinyl ketone (0.7 g., 0.0025 mole) in dry dimethylformamide (5 ml.) was stirred with anhydrous potassium carbonate (0.345 g., 0.0025 mole) and cupric oxide (0.030 g.) under dry nitrogen at 125°C for 1½ hours. The reaction mixture was diluted with benzene (100 ml.), filtered, the filtrate washed with water (4×50 ml.) and dried ($MgSO_4$). Removal of the solvent under reduced pressure and crystallisation of the residue from cyclohexane yielded the title compound as deep crimson needles (0.244 g.), m.p. 136—138°. [Found: C, 71.7; H, 6.1; N, 13.9%; $C_{12}H_{12}N_2O$ requires C, 72.0; H, 6.05; N, 14.0%]. The hydrochloride crystallised as orange prisms from ethanol/etheral HCl dec. >ca. 230°. [Found: C, 56.8; H, 6.2; N, 10.95% $C_{12}H_{12}N_2O.HCl$ requires C, 56.6; H, 5.95; N, 11.0%].

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EXAMPLE 49

2,3-Dihydro-2,2 (or 3,3)-dimethylimidazo[1,2-a]indol[9H]-9-one

A solution of *o*-chlorophenyl-4,4 (or 5,5)-dimethyl-2-imidazolinyl ketone (0.59 g., 0.0025 mole; prepared in a manner analogous to that described in Example 48 steps (a) and (b) for the corresponding *o*-bromophenyl compound) in dry dimethylformamide (5 ml.) was stirred with anhydrous potassium carbonate (0.345 g., 0.0025 mole and cuprous chloride (0.030g.) under dry nitrogen at 125° for 3 hours. The reaction was

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worked up as described in Example 48 step (c) to yield the product (0.255 g., m.p. 136—138°).

EXAMPLE 50

9-(*m*-chlorophenyl)-2,3-dihydro-2,2 (or 3,3)-dimethylimidazo [1,2-*a*]indol-9[H]-9-ol

To a stirred solution of *m*-chlorophenyllithium [prepared from *m*-bromochlorobenzene (9.6 g., 0.05 mole) and a 1.67 M solution of *n*-butyllithium in pentane (27 ml., 0.045 mole)] in dry ether (25 ml.) under nitrogen at 0°C was added 2,3-dihydro-2,2 (or 3,3)-dimethylimidazo[1,2-*a*]indol-9[H]-9-one (3.0 g., 0.015 mole) in dry tetrahydrofuran (50 ml.) over five minutes. The dark green solution was stirred for 30 minutes at 0°C., poured onto ice/ammonium chloride solution and extracted with chloroform. The combined extracts were washed with water, dried (MgSO₄), the solvent removed and the residue triturated with petroleum (b.p. 60—80°) to yield the white crystalline product (4.01 g.).

The crude base (3.5 g.) was dissolved in a small volume of ethanol, acidified with ethereal HCl, diluted with a large volume of ether and the hydrochloride allowed to crystallise (Yield 3.72 g., dec. >ca. 205°). [Found: C, 61.9; H, 5.3; N, 8.0%; C₁₈H₁₇ClN₂O.HCl requires C, 61.9; H, 5.2; N, 8.0%].

9 - (*p*-Chlorophenyl) - 2,3 - dihydro - 2,2 (or 3,3) - dimethylimidazo - [1,2-*a*]indol-9[H]-9-ol, m.p., dec. >ca. 215° and 2,3-dihydro-2,2 (or 3,3)-dimethyl-9-phenylimidazo[1,2-*a*]indol-9[H]-9-ol, m.p. dec. >ca. 240°, were prepared in an analogous manner by reaction of *p*-chlorophenyllithium or phenyllithium with 2,3-dihydro-2,2 (or 3,3)-dimethylimidazo[1,2-*a*]indol-9[H]-9-one.

EXAMPLE 51

2,3-Dihydroimidazo[1,2-*a*]indol-9[H]-9-one

(a) A solution of α -(*o*-bromophenyl)-2-imidazolinemethanol (16.0 g.) in acetone (160 ml.) was stirred with precipitated manganese dioxide (100 g.) [previously deactivated by stirring with water] for 2 hours. After filtering and washing the manganese dioxide with acetone, the solution was evaporated to a small volume under reduced pressure, diluted with water and extracted with chloroform. The combined extracts were dried (MgSO₄), the solvent removed and the residue allowed to crystallise from a small volume of ether to yield crude *o*-bromophenyl 2-imidazolinyl ketone (11.5 g.). A sample recrystallised from benzene-petroleum (b.p. 60—80°) had m.p. 149—151°. [Found: C, 47.9; H, 3.7; N, 11.1%; C₁₀H₈N₂BrO requires C, 47.5; H, 3.6; N, 11.1%].

(b) A solution of *o*-bromophenyl 2-imidazolinyl ketone (0.63 g., 0.0025 mole) in dry DMF (5 ml.) was stirred with potassium carbonate (0.35 g., 0.0025 mole) and cupric oxide (0.030 g.) under dry nitrogen at 140°C. for ½ hour. The mixture was diluted with benzene (100 ml., filtered and the filtrate washed with water (4 × 50 ml.). Removal of the solvent and crystallisation of the residue from cyclohexane gave the product as red needles (0.131 g), dec. >ca. 100°C [Found: C, 70.2; H, 4.7; N, 16.45%; C₁₀H₈NO₂ requires C, 69.8; H, 4.7; N, 16.3%].

EXAMPLE 52

Capsules

a) 10-(*m*-Chlorophenyl)-2,3,4,10-tetrahydropyrimido[1,2-*a*]indol-10-ol 20 mg.
Lactose 108 mg.
Talc 2 mg.

Batches of the active ingredient and lactose are sieved through a 40 mesh (British Standard) screen and mixed together. Water is added until the mix acquires a suitable consistency for granulation and the wet mass is passed through a 16 mesh (British Standard) screen. The talc is sifted through a 40 mesh (British Standard) screen, added to dried granules and mixed. Hard gelatine capsules are then filled with the mixture.

b) 10-(*m*-Chlorophenyl)-2,3,4,10-tetrahydropyrimido[1,2-*a*]indol-0-ol 10 mg.
Lactose 117 mg.
Manoxol O.T. (dioctyl sodium sulphonate; "Manoxol" is a Registered Trade Mark) 1 mg.
Talc 2 mg.

Capsules containing the above were made by the procedure given in (a) above

5 g., m.p.

5

omochloro-
ne (27 ml.,
hydro-2,2
dry tetra-
ed for 30
acted with
SO₄), the
o yield the

10

dified with
allowed to
N, 8.0%;

15

- [1,2-a]
-9-phenyl-
analogous
hydro-2,2

20

25

in acetone
ly deactiv-
manganese
er reduced
ed extracts
lise from a
(11.5 g.).
49—151°.
H, 3.6];

30

5 mole) in
mole) and
ixture was
x 50 ml.).
e gave the
; H, 4.7;

35

45

sh (British
a suitable
sh (British
d) screen,
l with the

50

10 mg.
117 mg.

55

1 mg.
2 mg.

(a) above

except that the Manoxol O.T. was dissolved in a 50:50 mixture of industrial methylated spirits and water and used in the granulation stage instead of water.

EXAMPLE 53

Tablets

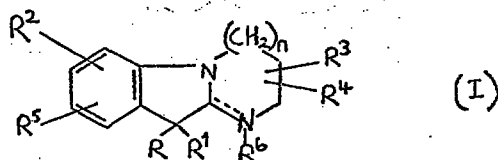
5	10-(<i>m</i> -Chlorophenyl)-2,3,4,10-tetrahydropyrimido[1,2- <i>a</i>]indol-0-ol	20 mg.	5
	Lactose	100 mg.	
	Avicel (microcrystalline cellulose; "Avicel" is a Registered Trade Mark)	30 mg.	
	Dried maize starch	40 mg.	
	Magnesium stearate	5 mg.	

10 Tablets of the above composition were made by milling the active ingredient to 40 mesh (British Standard), sieving through a 40 mesh (British Standard) sieve, mixing the milled material with the other components and compressing to form tablets.

10

WHAT WE CLAIM IS:—

1. An indole derivative of the general formula (I)

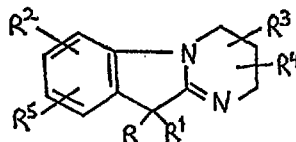


15

or an acid addition or quaternary ammonium salt thereof, in which *n* represents 0, 1 or 2, *R* represents a hydroxyl, lower alkoxy, aryl-lower alkoxy, tetrahydropyranyloxy or acyloxy group, *R*¹ represents a mono- or a bi-cyclic aryl radical or an aryl-lower alkyl, lower alkyl, lower alkenyl, lower alkynyl or amino-lower alkyl group or *R* and *R*¹ are taken together and represent an oxo group when *n* is 0, 1 or 2 or a ketalised oxo group when *n* is 1, *R*² and *R*⁵ which may be the same or different represent hydrogen, hydroxyl, lower alkyl, lower alkoxy, halolower-alkyl, halogen, amino or mono- or di-(lower)alkyl-amino or if *R* and *R*¹ together represent an oxo or ketalised oxo group *R*² and/or *R*⁵ may also represent nitro, *R*³ and *R*⁴ which may be the same or different represent hydrogen or lower alkyl radicals or *R*³ represents hydrogen and *R*⁴ represents hydroxy, the dotted line represents an optional bond in the position indicated and *R*⁶, which is present only when the optional bond represented by the dotted line is absent, represents hydrogen or an aryl-lower alkyl, lower alkyl, lower alkenyl, lower alkynyl, or acyl radical.

2. An indole derivative as claimed in Claim 1 wherein *R* represents a hydroxyl, lower alkoxy, aryl(lower)alkoxy, tetrahydropyranyloxy or acyloxy group and *R*¹ represents a mono- or bi-cyclic aryl radical or an aryl-lower alkyl, lower alkyl, lower alkenyl, lower alkynyl or amino-lower alkyl group.

3. An indole as claimed in Claim 1 having the general formula



35

or an acid addition or quaternary ammonium salt thereof, wherein *R* and *R*¹ are as defined in Claim 1, *R*² and *R*⁵ which may be the same or different represent hydrogen, hydroxyl, lower alkyl, lower alkoxy, haloloweralkyl or halogen and *R*³ and *R*⁴ which may be the same or different represent hydrogen or lower alkyl.

4. An indole as claimed in Claim 3 wherein *R* represents a hydroxyl, lower alkoxy, aryl-lower alkoxy, tetrahydropyranyloxy or acyloxy group and *R*¹ represents a mono- or a bi-cyclic aryl radical or an aryl-lower alkyl, lower alkyl, lower alkenyl, lower alkynyl or amino-lower alkyl group.

5. An indole as claimed in Claim 4 wherein *R*², *R*³, *R*⁴ and *R*⁵ each represent hydrogen atoms.

45

except that the Manoxol O.T. was dissolved in a 50:50 mixture of industrial methylated spirits and water and used in the granulation stage instead of water.

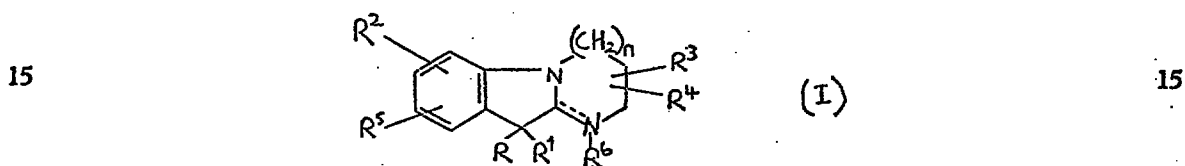
EXAMPLE 53

Tablets

- | | | | |
|---|--|---------|---|
| 5 | 10-(<i>m</i> -Chlorophenyl)-2,3,4,10-tetrahydropyrimido[1,2- <i>a</i>]indol-0-ol | 20 mg. | 5 |
| | Lactose | 100 mg. | |
| | Avicel (microcrystalline cellulose; "Avicel" is a Registered Trade Mark) | 30 mg. | |
| | Dried maize starch | 40 mg. | |
| | Magnesium stearate | 5 mg. | |
- 10 Tablets of the above composition were made by milling the active ingredient to 40 mesh (British Standard), sieving through a 40 mesh (British Standard) sieve, mixing the milled material with the other components and compressing to form tablets. 10

WHAT WE CLAIM IS:—

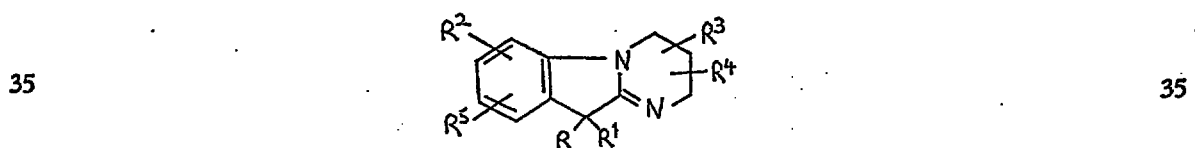
1. An indole derivative of the general formula (I)



or an acid addition or quaternary ammonium salt thereof, in which *n* represents 0, 1 or 2, *R* represents a hydroxyl, lower alkoxy, aryl-lower alkoxy, tetrahydropyranyloxy or acyloxy group, *R*¹ represents a mono- or a bi-cyclic aryl radical or an aryl-lower alkyl, lower alkyl, lower alkenyl, lower alkynyl or amino-lower alkyl group or *R* and *R*¹ are taken together and represent an oxo group when *n* is 0, 1 or 2 or a ketalised oxo group when *n* is 1, *R*² and *R*⁵ which may be the same or different represent hydrogen, hydroxyl, lower alkyl, lower alkoxy, halolower-alkyl, halogen, amino or mono- or di-(lower)alkyl-amino or if *R* and *R*¹ together represent an oxo or ketalised oxo group *R*² and/or *R*⁵ may also represent nitro, *R*³ and *R*⁴ which may be the same or different represent hydrogen or lower alkyl radicals or *R*³ represents hydrogen and *R*⁴ represents hydroxy, the dotted line represents an optional bond in the position indicated and *R*⁶, which is present only when the optional bond represented by the dotted line is absent; represents hydrogen or an aryl-lower alkyl, lower alkyl, lower alkenyl, lower alkynyl, or acyl radical. 20

2. An indole derivative as claimed in Claim 1 wherein *R* represents a hydroxyl, lower alkoxy, aryl(lower)alkoxy, tetrahydropyranyloxy or acyloxy group and *R*¹ represents a mono- or bi-cyclic aryl radical or an aryl-lower alkyl, lower alkyl, lower alkenyl, lower alkynyl or amino-lower alkyl group. 25

3. An indole as claimed in Claim 1 having the general formula



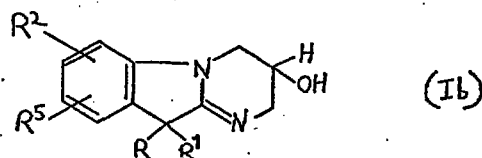
or an acid addition or quaternary ammonium salt thereof, wherein *R* and *R*¹ are as defined in Claim 1, *R*² and *R*⁵ which may be the same or different represent hydrogen, hydroxyl, lower alkyl, lower alkoxy, haloloweralkyl or halogen and *R*³ and *R*⁴ which may be the same or different represent hydrogen or lower alkyl. 40

4. An indole as claimed in Claim 3 wherein *R* represents a hydroxyl, lower alkoxy, aryl-lower alkoxy, tetrahydropyranyloxy or acyloxy group and *R*¹ represents a mono- or a bi-cyclic aryl radical or an aryl-lower alkyl, lower alkyl, lower alkenyl, lower alkynyl or amino-lower alkyl group. 45

5. An indole as claimed in Claim 4 wherein *R*², *R*⁵, *R*⁴ and *R*⁵ each represent hydrogen atoms. 45

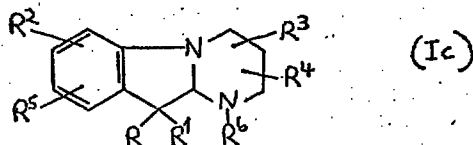


6. An indole as claimed in Claim 4 or 5 wherein R^1 represents a phenyl, halo-phenyl or alkylphenyl radical.
7. 2,3,4,10-Tetrahydro-10-phenylpyrimido[1,2-a]indol-10-ol.
8. 10-(*m*-Chlorophenyl)-2,3,4,10-tetrahydropyrimido[1,2-a]indol-10-ol.
9. 2,3,4,10-Tetrahydro-10-(*p*-chlorophenyl)pyrimido[1,2-a]indol-10-ol.
10. 2,3,4,10-Tetrahydro-10-(2-thienyl)pyrimido[1,2-a]indol-10-ol.
11. 10-(*m*-Fluorophenyl)-2,3,4,10-tetrahydropyrimido[1,2-a]indol-10-ol.
12. 10-(3,4-Dichlorophenyl)-2,3,4,10-tetrahydropyrimido[1,2-a]indol-10-ol.
13. 10-(*m*-Chlorophenyl)-2,3,4,10-tetrahydro-3,3-dimethylpyrimido[1,2-a]indol-10-ol.
14. 2,3,4,10-Tetrahydro-10-phenyl-3,3-dimethylpyrimido[1,2-a]indol-10-ol.
15. (+)-2,3,4,10-Tetrahydro-10-(*m*-chlorophenyl)pyrimido[1,2-a]indol-10-ol.
16. (-)-2,3,4,10-Tetrahydro-10-(*m*-chlorophenyl)pyrimido[1,2-a]indol-10-ol.
17. An acid addition salt of a compound claimed in any one of Claims 7 to 10.
18. An acid addition salt of a compound claimed in any one of Claims 11 to 16.
19. An indole as claimed in Claim 1 having the general formula (Ib)



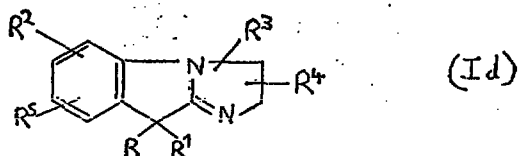
or an acid addition or quaternary ammonium salt thereof, wherein R^2 and R^5 are as defined in Claim 1 and R and R^1 are as defined in Claim 1 except that they cannot be taken together to represent a ketalised oxo group.

20. An indole as claimed in Claim 1 having the general formula (Ic)



or an acid addition or quaternary ammonium salt thereof, wherein R , R^1 and R^6 are as defined in Claim 1 and R^2 , R^3 , R^4 and R^5 are as defined in Claim 3.

21. An indole as claimed in Claim 20 wherein R represents a hydroxyl radical.
22. An indole as claimed in Claim 20 or 21 wherein R^1 represents a monocyclic aryl radical.
23. An indole as claimed in any one of claims 19 to 21 wherein R^6 represents hydrogen or lower alkyl.
24. An indole as claimed in Claim 1 wherein n is 0 or 2.
25. An indole as claimed in Claim 24 having the general formula (Id)



or an acid addition or quaternary ammonium salt thereof wherein R and R^1 are as defined in Claim 1 and R^2 , R^3 , R^4 and R^5 are as defined in Claim 3.

26. An optically active enantiomorph of an indole claimed in any one of Claims 1, 2, 19, 24 or 25.
27. An optically active enantiomorph of an indole claimed in any one of claims 4 to 10 and 17.
28. An optically active enantiomorph of an indole claimed in any one of claims 11 to 16, 18 and 20 to 23.
29. A process for preparing an indole derivative of general formula (I) as claimed



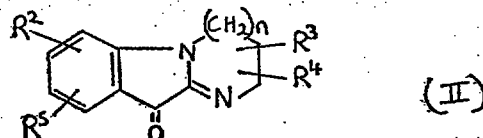
* C L M S *

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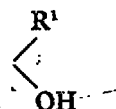
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in Claim 1 except that R and R¹ cannot be taken together to represent an oxo or ketalised oxo group in which process a ketone of general formula (II)

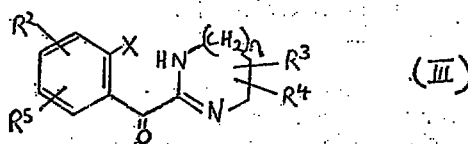


wherein R², R³, R⁴, R⁵ and n have the meanings given in Claim 1 except that neither R² nor N³ represents nitro is reacted with an organometallic compound known in the art for the conversion of a ketone function to the group



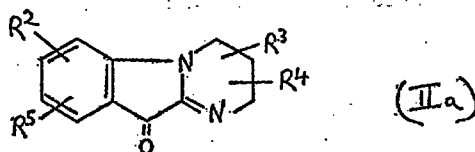
and, if desired, the resulting compound of formula (I) in which R represents a hydroxyl group and the dotted line represents a bond is alkylated or acylated to give a corresponding compound in which R represents a lower alkoxy, aryl-lower alkoxy, tetrahydropyranyloxy or an acyloxy residue and again if desired the compound of general formula (II) in which the dotted line represents a bond is converted to an acid addition or quaternary ammonium salt thereof and if desired the compound in which the dotted line represents a bond or its quaternary ammonium salt is reduced to give a compound of formula (I) in which bond represented by the dotted line is absent and R⁶ represents an aryl-lower alkyl, lower alkyl, lower alkenyl or lower alkynyl group and if desired the resulting compound is converted to an acid addition or quaternary ammonium salt thereof and if desired in any product one group R and/or R¹ and/or R² and/or R³ and/or R⁴ and/or R⁵ and/or R⁶, (if present), is converted into another group R and/or R¹ and/or R² and/or R³ and/or R⁴ and/or R⁵ and/or R⁶ within the meanings defined in Claim 1.

30. A process as claimed in Claim 29 wherein the ketone of general formula (II) is prepared by cyclisation of a ketone of general formula (III)

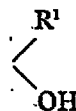


wherein R², R³, R⁴, R⁵ and n are as defined in Claim 29 and X is halo and, if desired, conversion of one group R² and/or R⁵ into another group R² and/or R⁵ by known methods.

31. A process for preparing an indole as claimed in Claim 4 which comprises reacting a ketone of general formula (IIa)



wherein R², R³, R⁴ and R⁵ are as defined in Claim 2 with an organometallic compound known in the art for the conversion of a ketone function to the group



and if desired alkylating or acylating the resulting compound in which R represents a

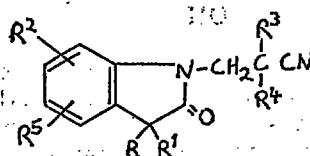


hydroxyl group to give a corresponding compound in which R represents a lower alkoxy, aryl-lower alkoxy, tetrahydropyranyloxy or an acyloxy residue and again if desired converting one group R and/or R¹ and/or R² and/or R³ in a product into another group R and/or R¹ and/or R² and/or R³ within the meanings defined in Claim 2 and, if desired, converting a free base into an acid addition or quaternary ammonium salt thereof.

32. A process as claimed in Claim 31 wherein the organometallic compound is a Grignard reagent of formula R'MgY where Y is a halogen, an aryl lithium or sodium or potassium acetylide.

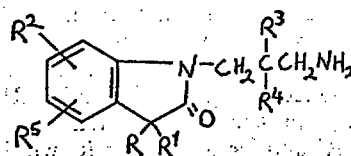
33. A process for preparing an indole of general formula (IIa) as defined in Claim 31 which comprises hydrolysing a compound of general formula (Ia) given in Claim 3 wherein R², R³, R⁴ and R⁵ are as defined in Claim 3 and R and R¹ are taken together and represent a ketalised oxo group.

34. A process for preparing a compound of general formula Ia as defined in Claim 33 which comprises hydrogenating a substituted isatin of general formula



(IV)

or dehydrating an amine of general formula (V)



(V)

wherein in formulae (IV) and (V) R, R¹, R², R³, R⁴ and R⁵ have the meanings given in Claim 33.

35. A process as claimed in Claim 34 wherein the hydrogenation is carried out in presence of a nickel, palladium or platinum catalyst at elevated temperatures and pressures.

36. A process as claimed in Claim 34 wherein the amine of general formula (V) is dehydrated by subjecting it to azeotropic distillation.

37. A process as claimed in Claim 29 wherein n is 0 or 2.

38. A process as claimed in Claim 37 wherein the organometallic compound is an aryl lithium.

39. A process for preparing a ketone of general formula (II) as defined in Claim 29 which comprises cyclising a ketone of general formula (III) as defined in Claim 30.

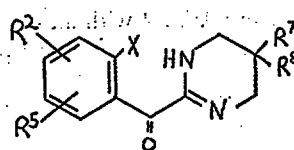
40. A process as claimed in Claim 39 wherein the ketone of formula (III) is cyclised by a modified Ullmann reaction by treatment with a metallic agent.

41. A process as claimed in Claim 40 wherein the metallic agent is copper or a salt thereof.

42. A process as claimed in any one of claims 39 to 41 wherein the cyclisation is effected in presence of a base.

43. A process as claimed in any one of Claims 39 to 42 wherein n is 0 or 1.

44. A process as claimed in any one of Claims 39 to 42 wherein the compound cyclised has the formula (IIIa)



(IIIa)

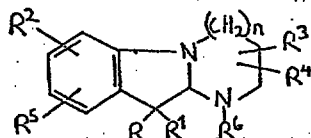
wherein R² and R⁵ have the meanings given in Claim 2, R⁷ and R⁸ which may be the same or different represent hydrogen or lower alkyl radicals or R⁷ represents hydrogen and R⁸ represents a hydroxy group and X represents halo.



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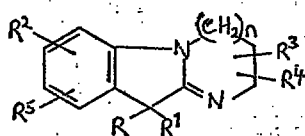
23

45. A process for preparing an indole of general formula



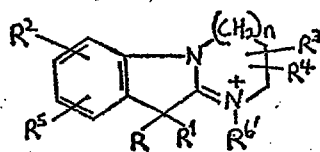
(VI)

wherein R^2 , R^3 , R^4 , R^5 , R^6 and n have the meanings given in Claim 1 and R and R^1 have the meanings given in Claim 1 except that they cannot be taken together to represent an oxo group, which comprises reducing a compound of general formula (VII)



(VII)

or a quaternary ammonium salt thereof in which the cation has the formula (VIII)

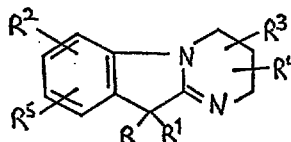


(VIII)

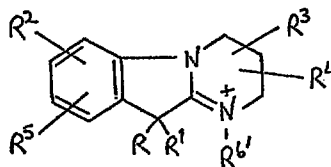
wherein R , R^1 , R^2 , R^3 , R^4 , R^5 and n have the meanings given above and $R^{6'}$ is an aryl-lower alkyl, lower alkyl, lower alkenyl, or lower alkynyl radical and, if desired, converting one group R and/or R^1 and/or R^2 and/or R^5 and/or R^6 into another group R and/or R^1 and/or R^2 and/or R^5 and/or R^6 within the above defined meanings of R , R^1 , R^2 , R^5 , R^6 or, if desired, converting a free base into an acid addition or quaternary ammonium salt thereof.

46. A process as claimed in Claim 45 wherein the reduction is carried out with a hydride transfer agent.

47. A process as claimed in Claim 45 or 46 wherein the compound reduced has the general formula



or a quaternary ammonium salt thereof in which the cation has the formula



wherein R^2 , R^3 , R^4 and R^5 are as defined in Claim 2, $R^{6'}$ is as defined in Claim 45.

48. A process for preparing an indole as claimed in Claim 1 substantially as hereinbefore described with reference to any one of Examples 1 to 20.



49. A process for preparing an indole as claimed in Claim 1 substantially as hereinbefore described with reference to any one of Examples 21 to 46.

50. A process for preparing an indole as claimed in Claim 1 substantially as hereinbefore described with reference to Example 47.

5 51. A process for preparing an indole as claimed in Claim 1 substantially as hereinbefore described with reference to any one of Examples 48 to 51. 5

52. An indole derivative whenever prepared by the process claimed in any one of Claims 29, 30, 37 to 43, 45, 46 or 51.

10 53. An indole derivative whenever prepared by the process claimed in any one of Claims 31 to 36 and 48. 10

54. An indole derivative whenever prepared by the process claimed in Claim 44 or 50.

55. An indole derivative whenever prepared by the process claimed in Claim 47 or 49.

15 56. An indole derivative as claimed in Claim 1 substantially as hereinbefore described with reference to any one of Examples 1 to 20. 15

57. An indole derivative as claimed in Claim 1 substantially as hereinbefore described with reference to any one of Examples 21 to 46.

20 58. An indole derivative as claimed in Claim 1 substantially as hereinbefore described with reference to Example 47. 20

59. An indole derivative as claimed in Claim 1 substantially as hereinbefore described with reference to any one of Examples 48 to 51.

60. A pharmaceutical preparation comprising an indole derivative as claimed in Claim 2, in association with a pharmaceutically acceptable carrier.

25 61. A pharmaceutical preparation comprising an indole derivative as claimed in any one of Claims 4 to 10, 17 and 27 in association with a pharmaceutically acceptable carrier. 25

62. A pharmaceutical preparation comprising an indole derivative as claimed in any one of Claims 11 to 16, 18, 21 and 22 in association with a pharmaceutically acceptable carrier.

30 63. A pharmaceutical preparation substantially as hereinbefore described with particular reference to Example 52 or 53. 30

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