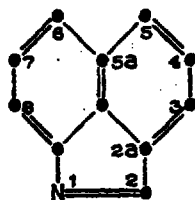


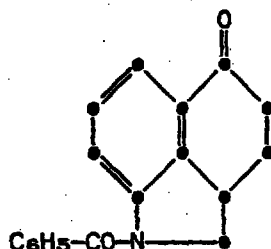
Description

This invention concerns a class of novel 6-substituted-4-dialkylaminotetrahydrobenz[c,d]indoles, which have been discovered to be central serotonin agonists, and therefore useful as anti-obesity, anti-alcoholism, senile dementia, and anti-smoking agents.

The benz[c,d]indole ring system (I) has been known since 1949.

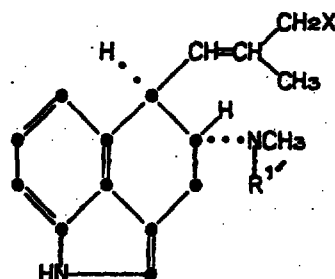


For example Uhle *et al.* *J. Am. Chem. Soc.*, 71, 1611 (1949); *ibid.* 73, 2402 (1951); Grob *et al.* *Helv. Chim. Acta.*, 33, 1796, 1955 (1950), 35, 2095 (1952), 36, 839 (1953) and Stoll *et al.* *ibid.* 33, 2254, 2257 (1950); 35, 148 (1952), prepared, among other compounds, a 5-keto-1,3,4,5-tetrahydrobenz[c,d]indole plus the corresponding 4-amino and 4-acetylamino derivatives. A useful starting material for the synthesis of these compounds was a 1-benzoyl-1,2,2a,3,4,5-hexahydro derivative, II.



formed by the Friedel-Crafts ring closure of 1-benzoyl-2(3-indoliny)propionylchloride. Kornfeld *et al.*, *J.A.C.S.*, 78, 3087 (1956) also prepared this compound and converted it, via a series of intermediates, to the 4-amino-5-keto derivative which was, in itself, a key intermediate in the first total synthesis of lysergic acid. In this synthetic procedure, a fourth ring (an N-methyl piperidine ring) was grafted onto an appropriately substituted tricyclic 1,2,2a,3,4,5-hexahydrobenz[c,d]indole. Stoll *et al.* *Helv. Chim. Acta.*, 35, 148 (1952) also prepared ($\pm$)-4-dimethylamino-1,3,4,5-tetrahydrobenz[c,d]indole. Bach and Kornfeld, United States Patent 4,110,339, prepared the corresponding 4-(di-n-propyl)amino compound. Ledelec *et al.*, United States patent 4,447,438 discloses 4-piperidyl-substituted-1H-indole having dopaminergic properties.

Certain naturally occurring alkaloids, agroclavine and elymoclavine, have been converted by Cassady *et al.*, *J. Med. Chem.*, 17, 300 (1974) to N-methyldioxychanoclavine, N-methylchanoclavine, and chanoclavine, all 4,5-disubstituted tetrahydrobenz[c,d]indoles (III).

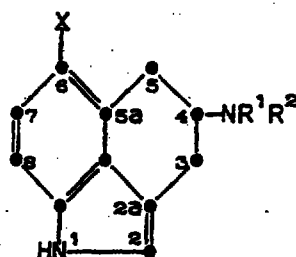


wherein X is H or OH and R' is CH₃ or H. Compounds according to III were without significant prolactin inhibiting activity, unlike the Bach-Kornfeld ($\pm$)-4-(di-n-propyl)amino-1,3,4,5-tetrahydrobenz[c,d]indole, which was found to be a selective dopamine agonist as shown by its action in inhibiting dopamine uptake in bovine striatal membrane *in vitro*. The corresponding 4-(dimethyl)amino derivative of Stoll *et al.* (*loc. cit.*) was used only as an intermediate. The 4-aminotetrahydrobenz[c,d]indoles and related derivatives are weak serotonin antagonists with one exception, the 4-acetylamino-5-oxo derivative — see Harris and Uhle, *J. Pharm. & Exper. Therap.*, 128, 358 (1960).

Some 4-amino-tetrahydrobenzindole derivatives having CNS activity are disclosed in EP-A-148440, while EP-A-29581 discloses some 4-alkylamino-1,3,4,5-tetrahydro-benz-(c,d)-indole derivatives useful as antihypertensives, prolactin inhibitors and anti-Parkinson agents.

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Surprisingly, it has now been discovered that the class of compounds shown by formula IV below are strong central serotonin agonists, useful as an anti-depressant, anti-obesity, anti-alcoholism, senile dementia or anti-smoking agent. The present compounds display minimal other activity, usually dopaminergic properties, which are undesired side-effects in the prior art compounds. This invention provides 4-amino-substituted-6-substituted-1,3,4,5-tetrahydrobenz[c,d]indoles of the formula

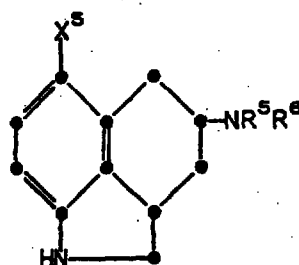


IV

wherein R¹ and R² are individually hydrogen, methyl, ethyl, n-propyl or allyl, and X is F, Cl, Br, CN, CONH₂, NH₂ or NO₂ or a pharmaceutically-acceptable salt thereof.

The compounds of formula IV are prepared by:

a) reacting a compound of the formula

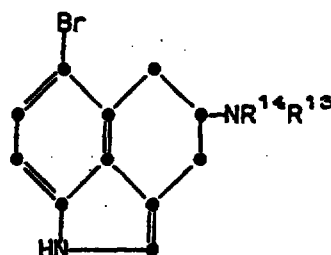


XVI f

wherein X⁵ is F, Cl, Br or NO₂

R⁵ and R⁶ are individually methyl, ethyl, n-propyl or allyl, with an oxidizing agent to provide the compounds of formula IV wherein X is F, Cl, Br, or NO₂, and R¹ and R² are individually methyl, ethyl, n-propyl or allyl; or

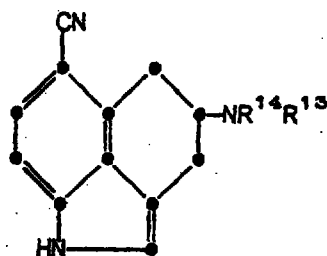
b) reacting a compound of the formula



XXXI Ia

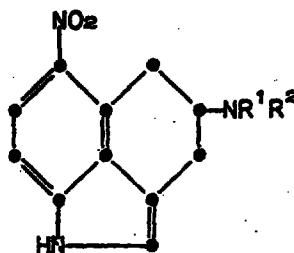
wherein R¹⁴ and R¹³ are individually ethyl, n-propyl or allyl, with cuprous cyanide or an alkali metal or alkaline earth metal cyanide and cuprous iodide in 1-methyl-2-pyrrolidone to provide the compounds of formula IV wherein X is CN and R¹ and R² are individually ethyl, n-propyl or allyl; or

c) reacting a compound of the formula



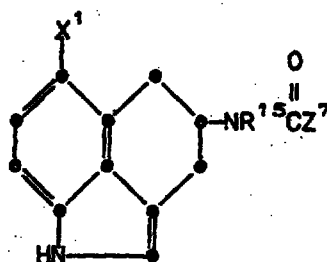
XXXIII

wherein R¹⁴ and R¹³ are defined as before, with a hydroxide base in a C₁—C₄ alkanol to provide the compounds of formula IV wherein X is CONH₂ and R¹ and R² are individually ethyl, n-propyl or allyl; or
d) reacting a compound of the formula



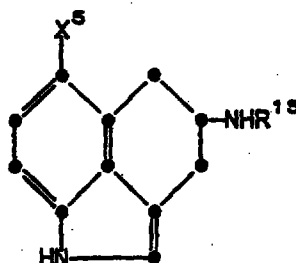
XLIII

wherein R¹ and R² are defined as before, with a reducing agent to provide the compounds of formula IV wherein X is NH²; or
e) reacting a compound of the formula



XIVb

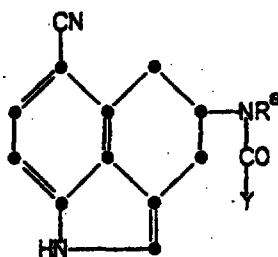
wherein X¹ is F or Cl, Z⁷ is C₁—C₃ alkyl, C₁—C₃ alkoxy, halo C₁—C₃ alkyl, or O-benzyl, and R¹⁵ is H or C₁—C₃ alkyl, with basic cleavage or when Z⁷ is O-benzyl with catalytic hydrogenation to provide the compounds of formula IV wherein X is F or Cl and R¹ is hydrogen and R² is C₁—C₃ alkyl or hydrogen; or
f) reacting a compound of the formula



XIVc

wherein X⁵ and R¹⁶ are defined as before, with an alkylating agent or by reductive amination to provide the compounds of formula IV where X is F, Cl, Br, NO₂, O(C₁—C₃ alkyl), O-acyl or O-benzyl, and R¹ and R² are individually methyl, ethyl, n-propyl, or allyl or one of R¹ and R² may be hydrogen; or

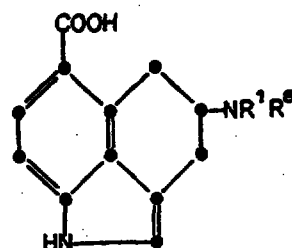
g) reacting a compound of the formula



LV

where R^8 is hydrogen, methyl, ethyl or n-propyl and Y is hydrogen, methyl, ethyl or chloromethyl, with a borane complex to provide the compounds of formula IV where X is CN and R^1 and R_2 are individually hydrogen, methyl, ethyl or n-propyl; or

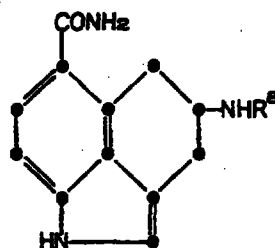
h) reacting a compound of the formula



LVa

where R^1 and R^8 are defined as before, with a peptide coupling agent and ammonia to provide the compounds of formula IV where X is CONH_2 , R^2 is H, methyl, ethyl or n-propyl and R^1 is defined as before; or

i) reacting a compound of the formula



LVb

wherein R^8 is defined as before, with an R^1 halide or by reductive amination with a hydrogen catalyst to yield the compounds of formula IV where X is CONH_2 , R^2 is H, methyl, ethyl or n-propyl and R^1 is defined as before;

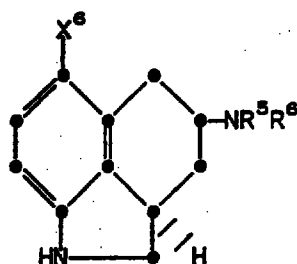
j) optionally salifying the compounds of formula IV.

Compounds of formula IV in which X is NO_2 , Br, or CN, are, in addition, useful intermediates for preparing other compounds coming within the scope of formula IV. Illustrative of some of those groups which NR^1R^2 represents are amino, methylamino, n-propylamino, ethyl-n-propylamino, diethylamino, ethylamino and n-propylamino.

The term "acyl" includes groups derived from both carboxylic and sulfonic acids; i.e., groups of the general structure R^3Z^1 wherein Z^1 is CO or SO_2 (indicating radicals derived from carboxylic or sulfonic acids) and R^3 is C_1 — C_3 alkyl, C_3 — C_8 cycloalkyl, phenyl, benzyl, naphthyl and substituted phenyl wherein said substituents can be 1 or 2 members of Cl, Br, F, methyl, ethyl, methoxy or ethoxy. Illustrative acyl moieties thus include benzoyl, p-tosyl, acetyl, propionyl, isobutyryl, mesyl, ethylsulfonyl, n-propylsulfonyl, p-chlorobenzenesulfonyl, 3,4-methylenedioxybenzoyl, anisoyl, ethoxybenzenesulfonyl, 2,4-xylylsulfonyl, 3,4-dichlorobenzenesulfonyl, cyclopropylcarbonyl, cyclobutylsulfonyl, cycloheptylcarbonyl, cyclohexylcarbonyl, cyclooctylcarbonyl, cyclopentylcarbonyl, α -naphthoyl, β -naphthoyl, α -naphthylsulfonyl, and β -naphthylsulfonyl. Since the O-acylated groups of formula IV above are chiefly useful as intermediates, or in some instances as prodrugs, it will be apparent to those skilled in the art that other acyl groups than those given above can function in an equivalent manner to protect the OH group.

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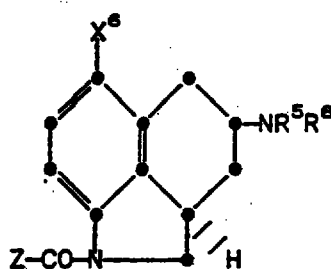
Useful intermediates for preparing the compounds of formula IV are shown by the following formulae.
A compound of the formula



LX

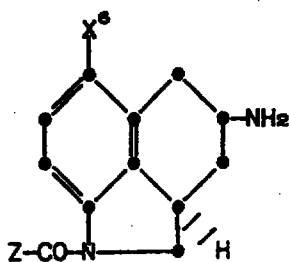
wherein

R⁵ and R⁶ are individually methyl, ethyl, n-propyl or allyl;
X⁶ is NO₂, Br, Cl, or F; or an acid addition salt thereof.
A compound of the formula



LXI

wherein X⁶, R⁵ and R⁶ are defined as before, and Z is a protecting group, or an acid addition salt thereof.
A compound of the formula



LXII

wherein X⁶ and Z are as defined as before, or an acid addition salt thereof.

Pharmaceutically-acceptable acid addition salts of the compounds of formula IV include salts derived from non-toxic inorganic acids such as: hydrochloric acid, nitric acid, phosphoric acid, sulfuric acid, hydrobromic acid, hydroiodic acid, phosphorous acid and others, as well as salts derived from non-toxic organic acids such as aliphatic mono and dicarboxylic acids, phenyl-substituted alkanolic acids, hydroxyalkanoic and hydroxyalkandioic acids, aromatic acids, aliphatic and aromatic sulfonic acids. Such pharmaceutically-acceptable salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, nitrate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, caprylate, acrylate, formate, isobutyrate, caprate, heptanoate, propionate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, mandelate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, terephthalate, benzenesulfonate, toluenesulfonate, chlorobenzenesulfonate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, β -hydroxybutyrate, glycollate, malate, naphthalene-1-sulfonate, naphthalene-2-sulfonate and mesylate.

The compounds of formula IV are central serotonin agonists, useful as anti-depressants. Thus, included within the present invention is a pharmaceutical formulation which comprises as an active ingredient a compound of formula IV, or a pharmaceutically-acceptable salt thereof, associated with one or more pharmaceutically-acceptable carriers or excipients therefor. The formulation or the active ingredient thereof can be used as a method of treating depression, obesity, alcoholism, smoking, or senile dementia in a warm-blooded animal by administering to said animal a therapeutically-effective amount of a compound of formula IV, or a pharmaceutically-acceptable salt thereof.

Compounds according to formula IV have an asymmetric center at C-4 and thus occur as a ($\pm$) or dl

racemic mixture. This invention includes both the racemates and the individual stereoisomers of the chemical compounds represented by formula IV. The individual stereoisomers can be prepared by resolving a racemate of a 2,2a-dihydro indole intermediate (XIV, XIVa, XV, XVa, XVI, XVIa from Reaction Scheme 2 below or XXX from Reaction 1). Then oxidizing the separated stereoisomer to the indole and carrying out any further reactions to obtain a desired optically active product of formula IV. The resolution procedure can employ optically-active acids such as, for example, L-(+)-R-tartaric acid, (-)-dibenzoyltartaric acid, (+)-camphoric acid, (+)-10-camphorsulfonic acid, (-)-mandelic acid, (-)-malic acid, N-acetyl-L-glutamic acid, t-BOC-D-phenylglycine, D-(-)-S-tartaric acid, L-p-toluoyltartaric acid and the like.

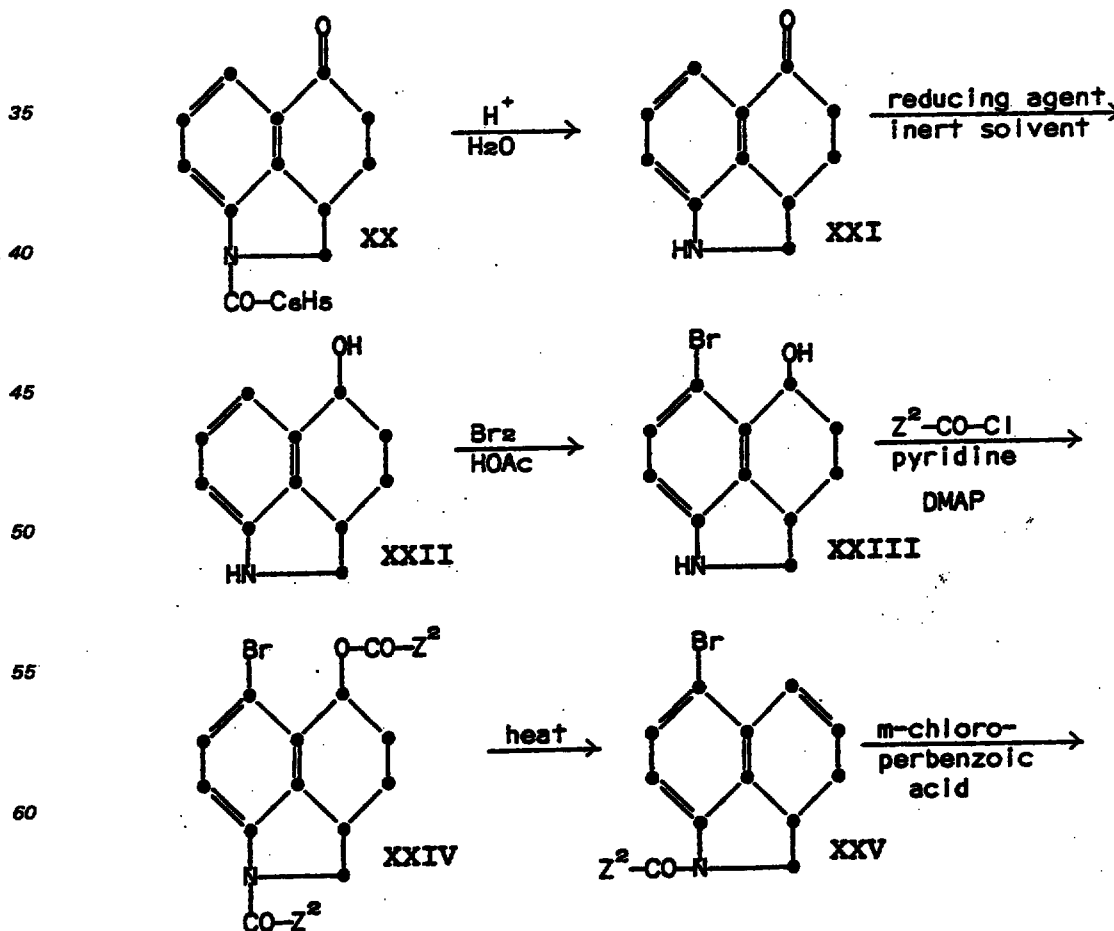
Compounds illustrative of formula IV include:

- (±)-4-diallylamino-6-chloro-1,3,4,5-tetrahydrobenz[c,d]indole sulfate
- (±)-4-methylethylamino-6-bromo-1,3,4,5-tetrahydrobenz[c,d]indole tartrate
- (±)-4-diallylamino-6-amino-1,3,4,5-tetrahydrobenz[c,d]indole succinate
- (±)-4-diethylamino-6-nitro-1,3,4,5-tetrahydrobenz[c,d]indole phosphate
- (-)-4-methyl-n-propylamino-6-aminocarbonyl-1,3,4,5-tetrahydrobenz[c,d]indole dihydrogenphosphate
- (±)-4-(di-n-propyl)amino-6-aminocarbonyl-1,3,4,5-tetrahydrobenz[c,d]indole bisulfate
- (±)-4-dimethylamino-6-aminocarbonyl-1,3,4,5-tetrahydrobenz[c,d]indole hydrobromide
- (±)-4-diethylamino-6-aminocarbonyl-1,3,4,5-tetrahydrobenz[c,d]indole tosylate
- (-)-4-diallylamino-6-aminocarbonyl-1,3,4,5-tetrahydrobenz[c,d]indole malate
- (±)-4-(di-n-propyl)amino-6-bromo-1,3,4,5-tetrahydrobenz[c,d]indole benzoate
- (-)-4-diethylamino-6-fluoro-1,3,4,5-tetrahydrobenz[c,d]indole phenylacetate
- (+)-4-dimethylamino-6-chloro-1,3,4,5-tetrahydrobenz[c,d]indole 1,4-butyndioate
- (±)-4-diallylamino-6-nitro-1,3,4,5-tetrahydrobenz[c,d]indole hydrochloride
- (±)-4-dimethylamino-6-amino-1,3,4,5-tetrahydrobenz[c,d]indole sulfate
- (+)-4-(di-n-propyl)amino-6-cyano-1,3,4,5-tetrahydrobenz[c,d]indole fumarate
- (-)-4-amino-6-bromo-1,3,4,5-tetrahydrobenz[c,d]indole propiolate

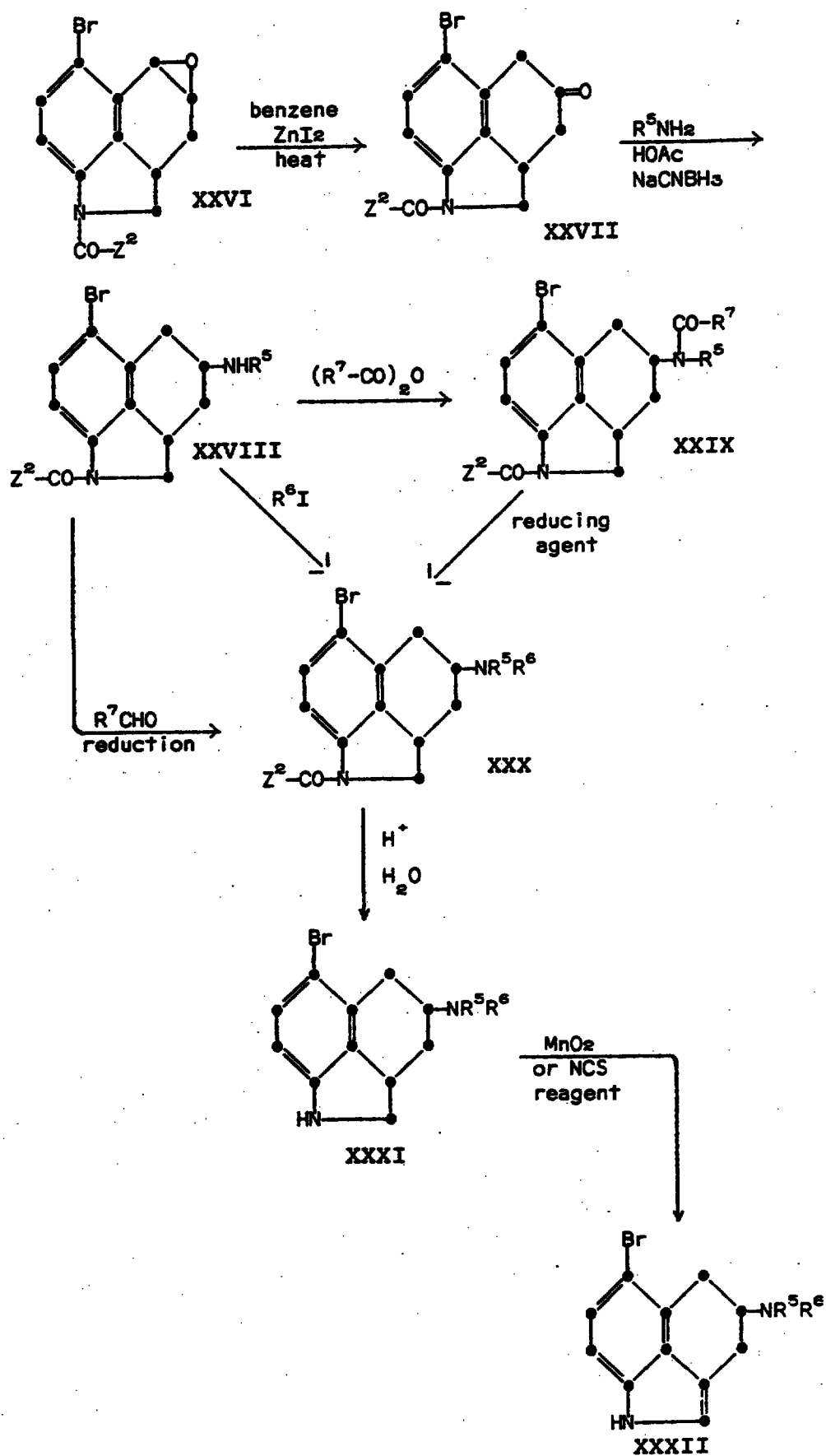
and the like.

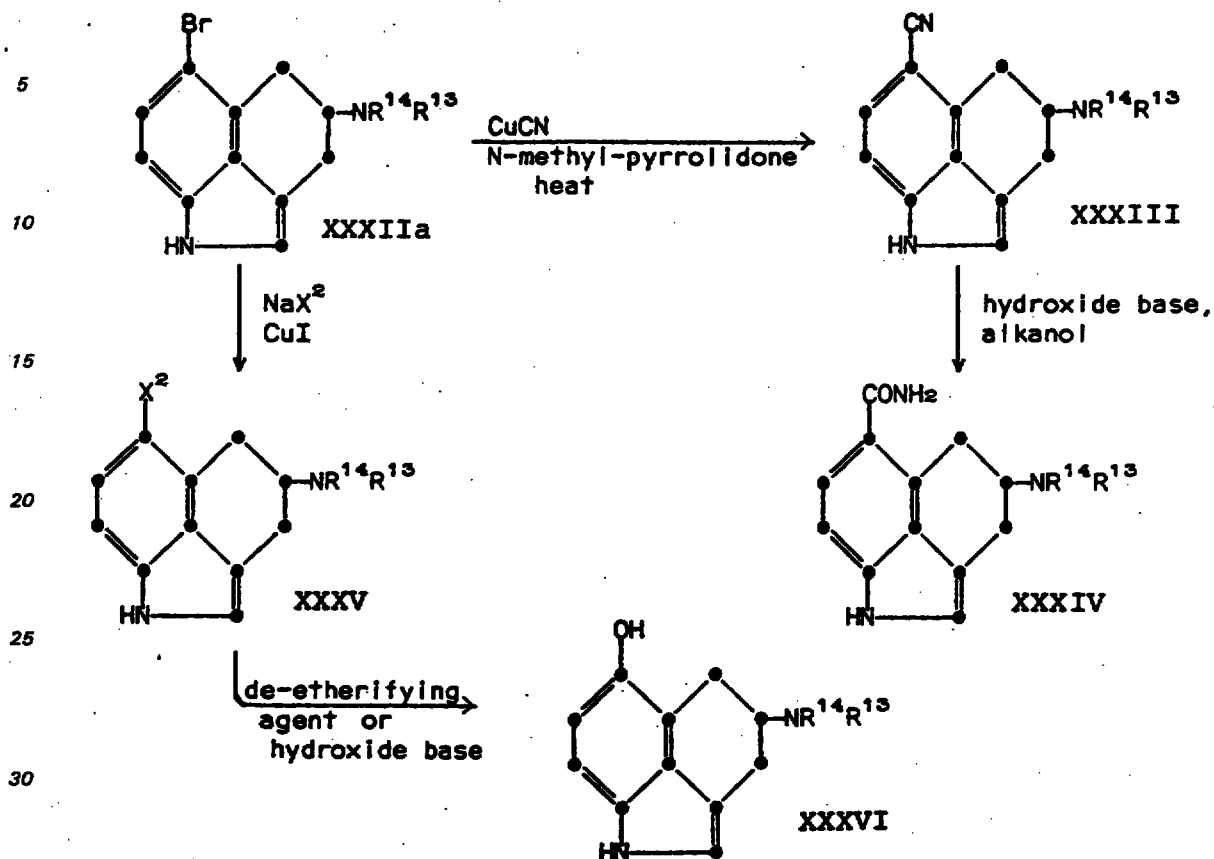
Compounds of formula IV wherein X is Cl, Br, CN or COHN₂, can be prepared according to the following reaction scheme.

Reaction Scheme 1

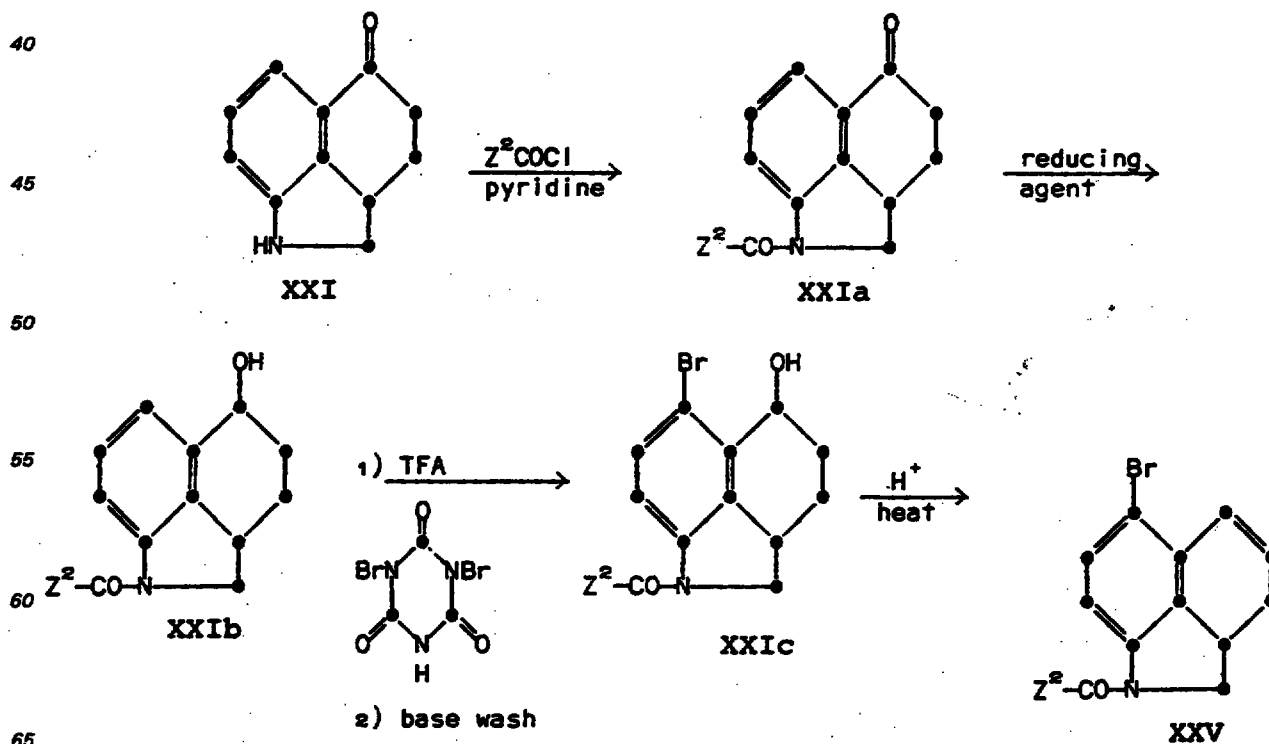


Reaction Scheme 1 cont'd.



Reaction Scheme 1 cont'd.

Also the compounds of formula XXI can be reacted by the following modification to provide the compounds of formula XXV.

Reaction Scheme 1 cont'd.

In Reaction Scheme 1,

R^5 and R^6 are individually methyl, ethyl, n-propyl or allyl;

R^7 is hydrogen, methyl or ethyl;

R^{13} and R^{14} are individually ethyl, n-propyl or allyl;

X^2 is $OCH_2C_6H_5$, $O(C_1-C_3 \text{ alkyl})$ or O-acyl;

Z^2 is $O(C_1-C_3 \text{ alkyl})$, OCH_2CCl_3 or $O(C_1-C_3 \text{ alkyl})$ substituted by halogen.

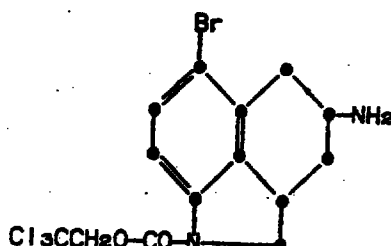
In the above reaction scheme, for example, 1-benzoyl-5-oxo 1,2,2a,3,4,5-hexahydrobenz[c,d]indole (XX) [from Kornfeld *et al.*, J.A.C.S., 78 3887 (1956) compound 4] is hydrolysed in acid to 5-oxo-1,2,2a,3,4,5-hexahydrobenz[c,d]indole (XXI) [compound 10 of Kornfeld *et al.* when R is H]. The 5-ketone is reduced to a 5-hydroxyl[(±)-5-hydroxy-1,2,2a,3,4,5-hexahydrobenz[c,d]indole (XXII)] with an alkali metal borohydride, such as $NaBH_4$, or aluminumhydride in a mutual inert solvent. Bromination in acetic acid yields the (±)-6-bromo-5-hydroxy derivative (XXIII). This compound is then reacted with 2 moles of $Z^2-CO-Cl$, e.g. ethyl chloroformate, to yield a (±)-1-ethoxycarbonyl-5-ethoxycarbonyloxy-6-bromo-1,2,2a,3,4,5-hexahydrobenz[c,d]indole (XXIV). This double acylation is conveniently carried out in pyridine solution (though other inert solvents may be used) containing DMAP as a catalyst. Heating the 5-ethoxycarbonyloxy compound results in elimination to produce 1-ethoxycarbonyl-6-bromo-1,2,2a,3-tetrahydrobenz[c,d]indole (XXV). Epoxidation of the double bond using, conveniently, m-chloroperbenzoic acid or other peracid, then rearrangement of the epoxide on heating with ZnI_2 in benzene yields the 4-oxo derivative (XXVII). Reductive amination with R^5NH_2 , e.g. n-propyl amine, and $NaCNBH_3$ yields (±)-1-ethoxycarbonyl-4-n-propylamino-6-bromo-1,2,2a,3,4,5-hexahydrobenz[c,d]indole (XXVIII). This secondary amine can then be acylated with $(R^7-CO)_2O$, e.g. propionic anhydride, and the N-propionyl group reduced with a reducing agent, such as BH_3 in THF or $NaCNBH_3$ in TFA to yield the 4-di-n-propyl compound, (±)-1-ethoxycarbonyl-4-di-n-propylamino-6-bromo-1,2,2a,3,4,5-hexahydrobenz[c,d]indole (XXX). Similarly, the secondary amine can be acylated with formic anhydride, acetic anhydride, or mixed anhydrides and then reduced to yield (XXX). Alternatively, the secondary amine (XXVIII) can be alkylated as with n-propyliodide in the presence of an organic base to yield formula XXX directly. Also, the secondary amine (XXVIII) can be reductively alkylated to yield formula XXX. Finally, hydrolysis of the Z^2-CO moiety, e.g. 1-ethoxycarbonyl amide, yields formula XXXI, oxidation of which with MnO_2 or with NCS reagent yields a 2,2a-didehydro derivative (XXXII).

Reaction of the thus-formed 6-bromo-4-di-alkyl derivative (XXXIIa) with cuprous cyanide or an alkali or alkaline earth cyanide and cuprous iodide in 1-methyl-pyrrolidone solution yields the 6-cyano-4-di-alkyl derivative (XXXIII), hydrolysis of which with a hydroxide base (KOH), NaOH in a C_1-C_4 alkanol yields (±)-4-dialkylamino-6-carboxamido-1,3,4,5-tetrahydrobenz[c,d]indole (XXXIV).

The 6-alkyloxy compounds can be prepared by reacting the 6-bromo compound (XXXIIa) with sodium methoxide, cuprous iodide and DMF to provide compounds of formula XXXV where X^2 is $O(C_1-C_3 \text{ alkyl})$ and R^{13} and R^{14} are individually ethyl, n-propyl or allyl. The 6-benzyloxy derivatives are prepared in similar fashion. The 6-acyloxy derivatives are prepared analogously with, for example, cuprous acetate or sodium acetate and cuprous iodide. The 6-hydroxy derivatives are obtained by reacting X^2 with a de-etherifying agent, for example by basic hydrolysis.

Alternatively, the 5-keto compounds of formula XXI are reacted with Z^2COCl , e.g. $EtO-COCl$, in pyridine to provide the correspondingly protected compound of formula XXIa. Subsequent reduction with, for example $NaBH_4$, yields the 5-hydroxy derivative of formula XXIb. Bromination in TFA with a base wash provides the 6-bromo derivative of formula XXIIc. Dehydration provides the compounds of formula XXV.

Preparation of the compounds of formula IV wherein X is OH is also accomplished by acylating a compound of the formula

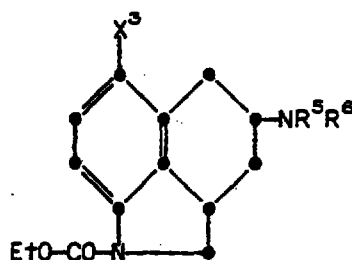


XXIb

with $C_6H_5CH_2OCOCI$ to form the corresponding 4-secondary carbamate. After removing the 1-protecting groups (by Zn and HOAc), the reaction scheme proceeds analogously as described for compounds of formula XXXIa to XXXV to XXXVI wherein the 4-position is $NCO_2CH_2C_6H_5$ and the 1-position is hydrogen. The protecting group is then removed by catalytic hydrogenation to yield the compounds of formula IV where X is OH and R^1 and R^2 are both hydrogen. Subsequent alkylation as previously described provides the compounds of formula IV where X is OH and R^1 and R^2 are individually methyl, ethyl, n-propyl or allyl, or one of R^1 and R^2 may be hydrogen.

The above reaction sequence has been illustrated with respect to the preparation of a 4-di-n-propyl

derivative. It will be apparent to those skilled in the art that substitution of methyl, ethyl or allyl amine for n-propylamine in the preparation of XXVIII would yield a 4-methyl, ethyl or allyl amino group. Likewise the thus formed secondary amine could be acylated (XXVIII) where the amine group could be methyl, ethyl, n-propyl or allyl) with formic, acetic, acrylic or propionic acid and the N-acyl group reduced to an alkyl or allyl group to form a compound of the formula



XXXa

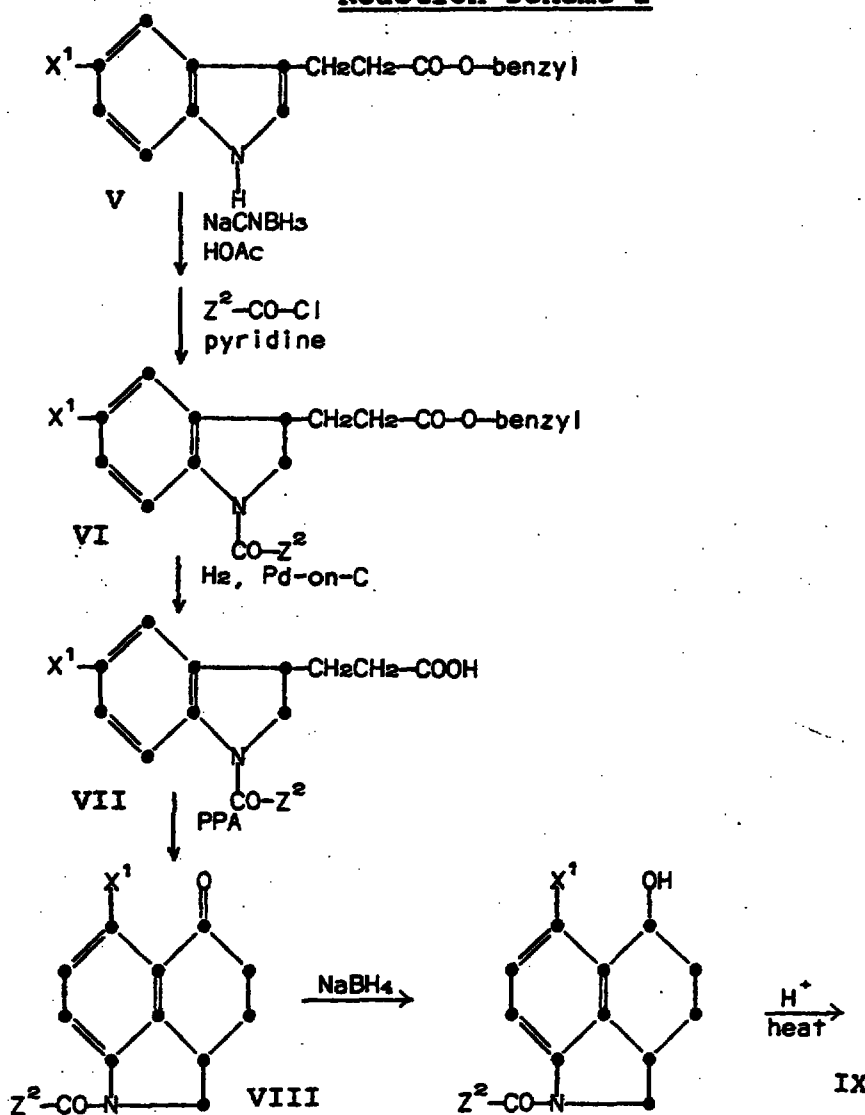
wherein X^3 is NO_2 , Cl or Br, and R^5 and R^6 are individually methyl, ethyl, n-propyl or allyl. It will be noted that the above procedure provides an easy route to unsymmetrically substituted C-4 tertiary amines.

Alternatively, the secondary amine (XXVIII) where the amine group could be methyl, ethyl, n-propyl or allyl) can be directly alkylated with CH_3I , $\text{C}_2\text{H}_5\text{I}$, n-propyl iodide or allyl bromide to yield the same tertiary amine (XXXa).

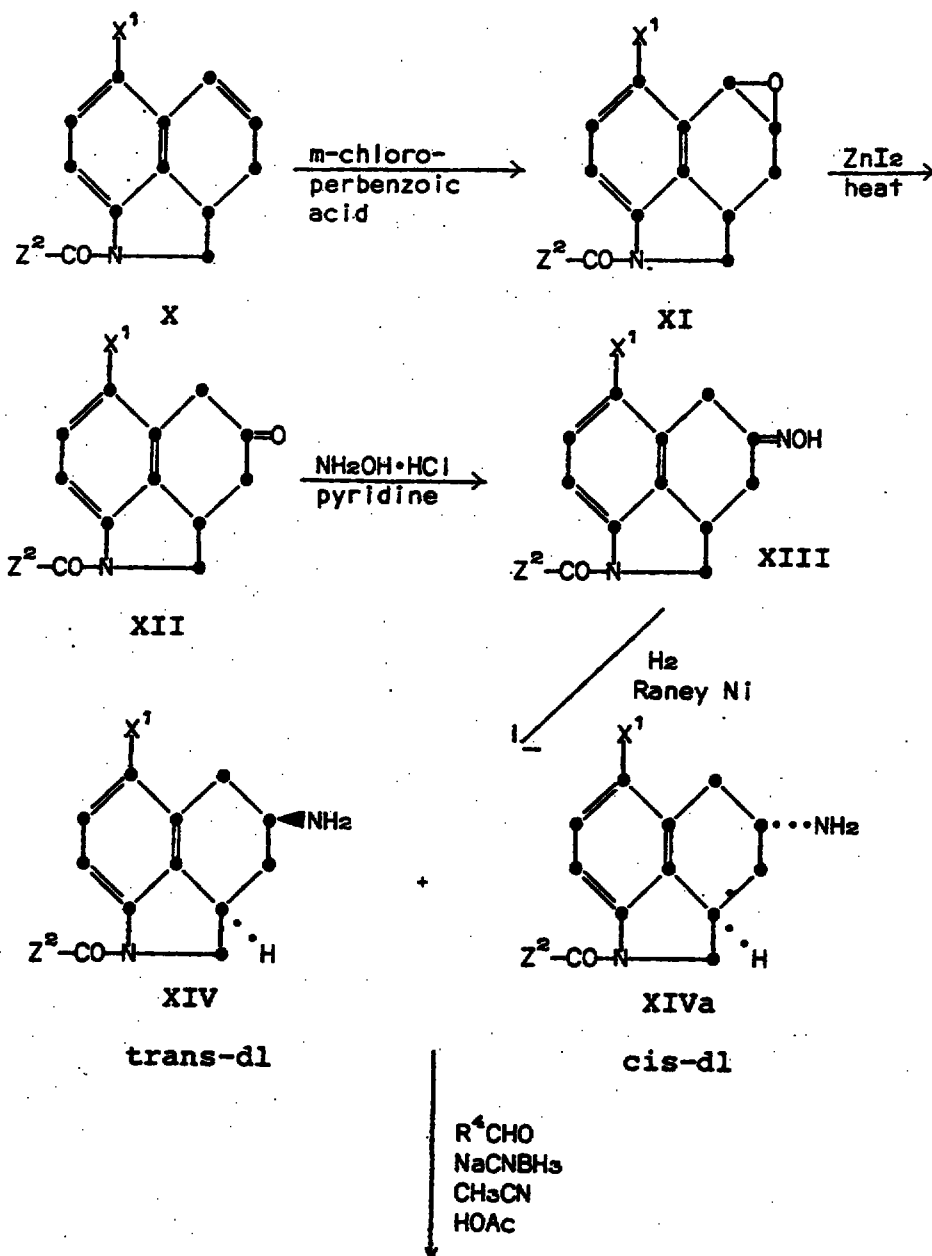
The 6-chloro derivatives can be prepared in a fashion similar to the preparation of the 6-bromo derivative but chlorine is more resistant to replacement with a cyano radical, and the chloro compound is thus not as useful as an intermediate.

Compounds of formula IV wherein X is F or Cl, can be prepared according to the following reaction scheme.

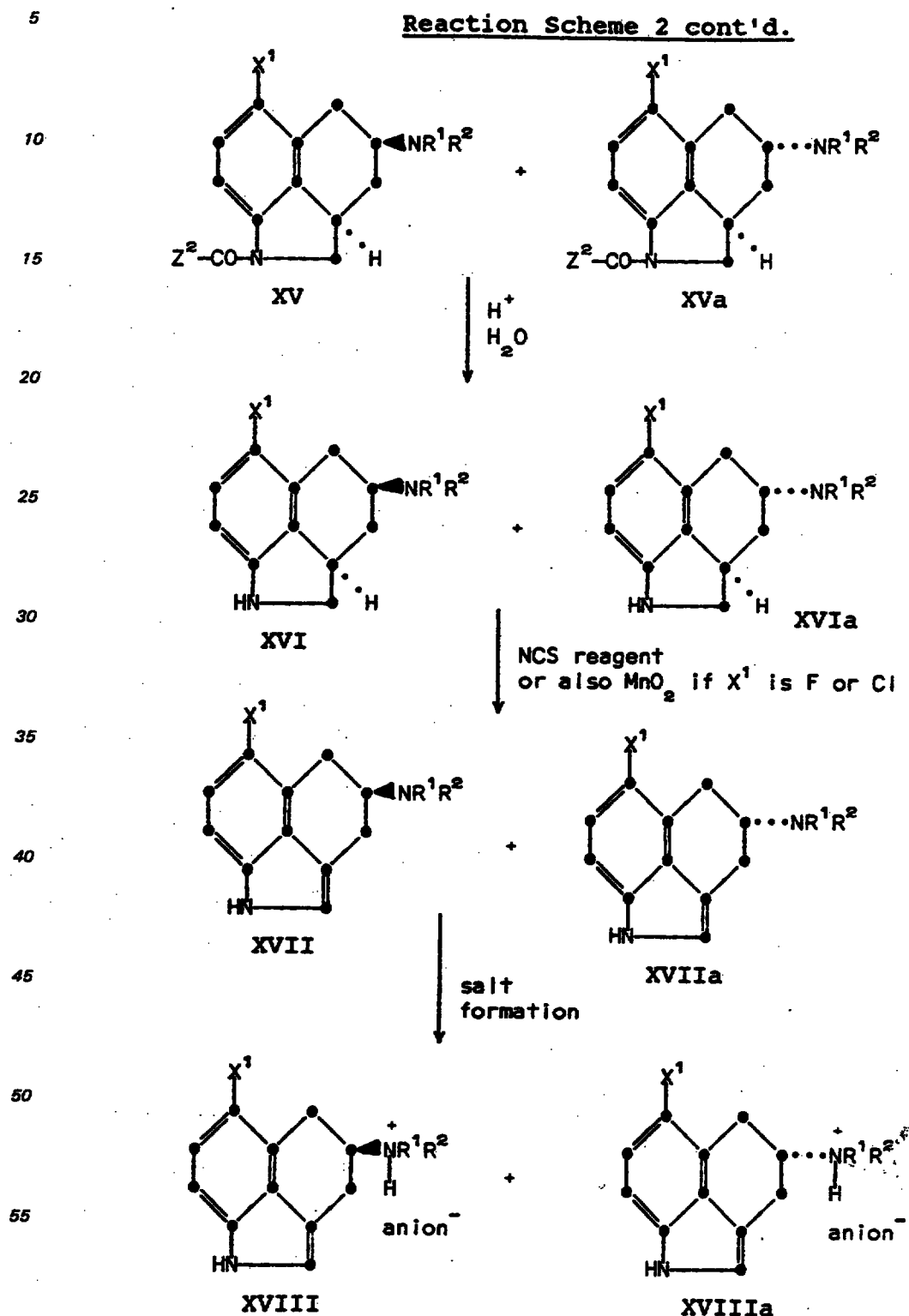
Reaction Scheme 2



Reaction Scheme 2 cont'd.



Reaction Scheme 2 cont'd.



According to Reaction Scheme 2, where X^1 is methoxy, R^4 is ethyl and R^1 and R^2 are n-propyl for the sake of convenience only, a benzyl 3-(5-methoxy-3-indolyl)propionate or the like ester (V) is reduced with sodium cyanoborohydride to the corresponding 2,3-dihydro compound. With the saturation of the 2,3 double bond, the 1-amino group becomes sufficiently basic to enable it to be protected with a standard amine protecting group such as an acyl group; i.e., ZOCi as a benzoyl derivative or ethoxy carbonyl. This protective group is formed by reacting the 2,3-dihydro compound with an acyl halide or anhydride; for example, benzoyl chloride in the presence of pyridine, to yield VI. The free acid (VII) is then prepared from the benzoyl ester (VI) by hydrogenation over a noble metal catalyst in an inert solvent. The noble metal catalyst of choice is palladium-on-carbon. The free acid thus produced — 3-(5-methoxy-1-benzoyl-2,3-dihydro-3-indolyl)propionic acid — is cyclized with a dehydrating agent, preferably polyphosphoric acid (PPA). This reagent is a particularly convenient cyclizing agent since it can also serve as a solvent for the cyclization reaction. Alternatively, the acid chloride can be prepared and cyclized in the presence of a Lewis acid, preferably $AlCl_3$ — see Kornfeld *et al.*, *J.A.C.S.*, 78, 3087 (1956) — to yield the desired benz[c,d]indole. The cyclized product (VIII) is 1-benzoyl-5-oxo-6-methoxy-1,2,2a,3,4,5-hexahydrobenz[c,d]indole. Reduction of the oxo group with sodium borohydride in a C_1 — C_4 alcohol such as ethanol yields the corresponding 5-oxy derivative (IX). This 5-oxy derivative can be dehydrated by heating in the presence of an acidic catalyst (p-toluenesulfonic acid for example) in an inert solvent to yield 1-benzoyl-6-methoxy-1,2,2a,3-tetrahydrobenz[c,d]indole (X). Preferably, however, an acid ion exchange resin is used as the acid catalyst. The 4,5 double bond is then epoxidized with a reagent such as m-chloroperbenzoic acid in an inert solvent to yield a 4,5-epoxy derivative (XI). Rearrangement of the epoxide by heating in the presence of zinc iodide yields an isomeric ketone, (isomeric with VIII), 1-benzoyl-4-oxo-6-methoxy-1,2,2a,3,4,5-hexahydrobenz[c,d]indole (XII).

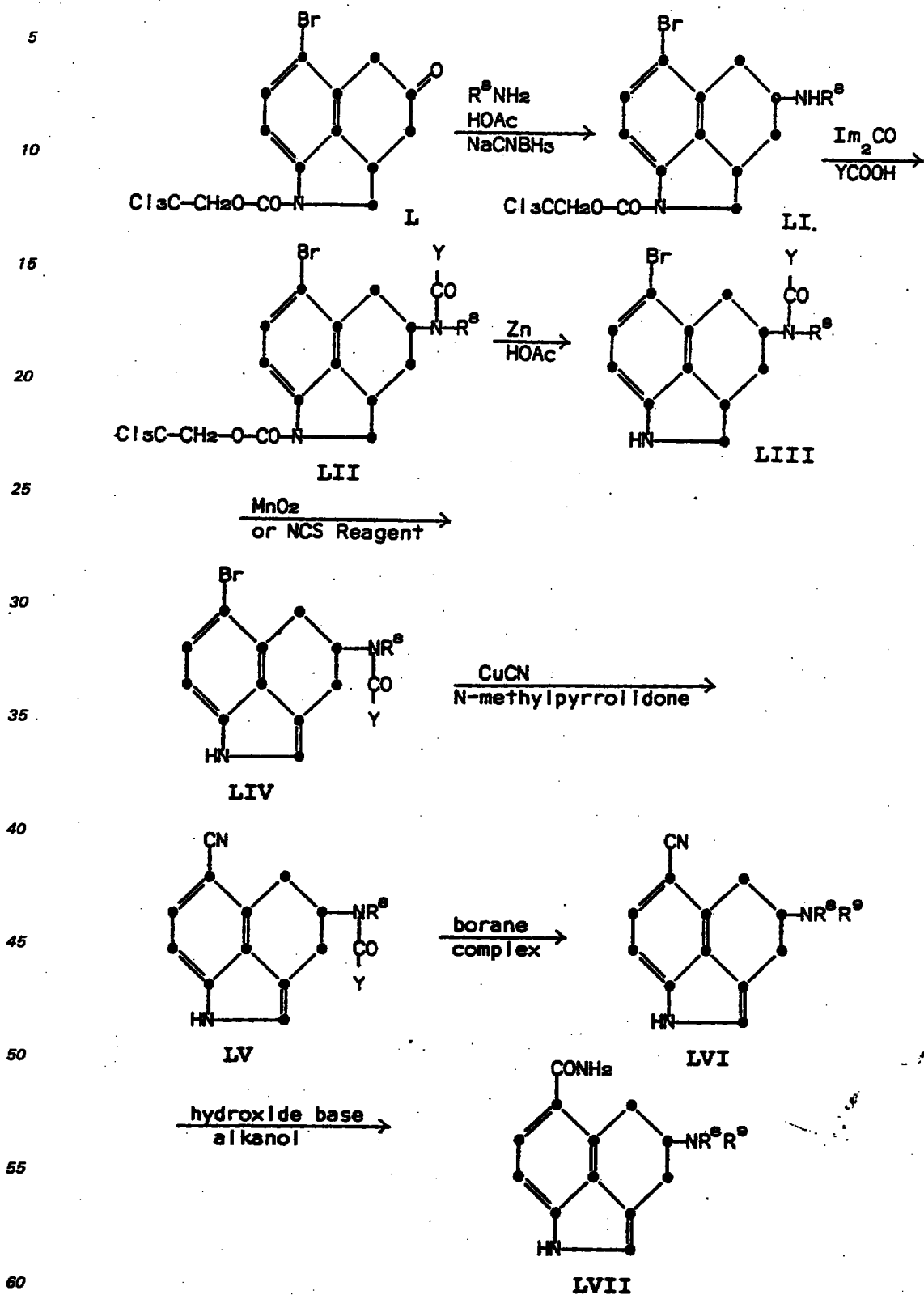
Next, the hydroxylamine derivative of this isomeric ketone (XIII) is formed and the resulting oxime reduced with Raney nickel to yield a mixture of amino derivatives, trans-dl and cis-dl-1-benzoyl-4-amino-6-methoxy-1,2,2a,3,4,5-hexahydrobenz[c,d]indole (XIV and XIVa). When R^1 and R^2 are both H in the final product, no further alkylation reaction of (XIV) is required. When R^1 and R^2 are other than H, alkylation of the primary amine group by standard procedures, for example reductive alkylation with an aldehyde, R^4CHO , and sodium cyanoborohydride in acetonitrile, to which an equivalent of glacial acetic acid has been added, yields the symmetrical di-alkylamine; (XV and XVa). Treatment of the mixture of these cis-dl and trans-dl tertiary amines with aqueous acid yields a mixture comprising trans-dl-4-dialkylamino-6-methoxy-1,2,2a,3,4,5-hexahydrobenz[c,d]indole and the corresponding cis-dl compound. Oxidation of this mixture with, for example, NCS reagent, yields ($\pm$)-4-dialkylamino-6-methoxy-1,3,4,5-tetrahydrobenz[c,d]indole (XVII and XVIIa represent the two enantiomers). The racemic mixture can readily be converted to the salt form (XVIII and XVIIIa) by standard procedures.

The preferred procedure for preparing the final products of formula IV wherein X is F or Cl and R^1 and R^2 are both hydrogen consists of a modification of Reaction Scheme 2. A compound of formula XIV or XIVa is protected at the 4-amino group by acylation (e.g. CCl_3CHCO moiety) to provide a secondary amine, followed by oxidation (as before described) to provide the indole ring. The Z^2-CO group (e.g. benzyl) is then cleaved to form the corresponding 1-unsubstituted compound. The 4-acyl protecting group is then removed by acid cleavage, e.g. zinc in acetic acid, to provide the 4-amino final product. Obviously, the 4-amino product can then be alkylated by conventional methods to obtain the other products of formula IV where R^1 and R^2 individually are methyl, ethyl, n-propyl or allyl or one of R^1 and R^2 may be hydrogen.

While the above procedure has been illustrated with reference to the preparation of a 6-methoxy derivative, the procedure is equally applicable to the preparation of other 6-(C_1 — C_3 alkyl)oxy compounds or of 6-halo compound; i.e., 6-chloro, or 6-fluoro.

When R^1 and R^2 are other than n-propyl, a different synthetic route is preferably employed which prepares the compounds of formula IV where X is Cl, Br, CN, $CONH_2$ or NH_2 , and R^1 and R^2 individually are hydrogen, methyl, ethyl, or n-propyl. This alternate route also prepares compounds of formula IV where both R^1 and R^2 are n-propyl. This alternate route is shown in the following reaction scheme.

Reaction Scheme 3



In Reaction Scheme 3, R^8 is hydrogen methyl, ethyl or n-propyl; R^9 is methyl, ethyl or n-propyl; Y is hydrogen, methyl, ethyl, or chloromethyl (this latter group is hydrolyzed from LV—LVI); Im_2CO is bis-imidazole carbonyl.

Compound LIV when R⁸ is hydrogen is selectively hydrolyzed to remove the COY moiety (e.g. basic hydrolysis such as MeOH KOH). The product has the C—4 group a primary amine. The primary amine is then reductively alkylated with an aldehyde R¹⁰CHO where R¹⁰ is H, methyl, ethyl or vinyl to yield compounds of formula IV where R¹ and R² are individually methyl, ethyl or n-propyl and X is Cl, Br or CN.

The CN groups (LVI) can then be hydrated with base, i.e. KOH in C₁—C₄ alkanol to yield the carboxamide (LVII).

Reducing agents useful in converting LV to LVI are borane complex reagents such as BH₃—(CH₃)₂S, BH₃—pyridine, BH₃—N(CH₃)₂, BH₃—THF, or B₂H₆ in an inert solvent, such as THF.

In Reaction Scheme 3, the step from formula L to LI utilizes similar chemistry to that in Reaction Scheme I (XXVII to XXVIII), except that in Reaction Scheme 3 acetic acid and NH₃ can be used to produce a 4-moiety of NH₂. The 4-amino group is converted to the benzyloxycarbonyl derivative by conventional methods. The Cl₃C—CH₂—O—CO moiety is used as a 1-position protecting group since it is readily removed by reductive cleavage with Zn and acetic acid, which reaction does not affect the C—4 carbamate function present (LII).

The C—4 amine function (LI) is acylated with a formic, acetic or propionic acid using Im₂CO, bisimidazolcarbonyl, to aid the acylation. Other condensing agents which can be employed include N,N'-disubstituted carbodiimide, and bis-imidazolyl sulfone.

The reductive cleavage of the N—1 protecting group (LII) does not affect the C—4 amide. Other N—1 protecting groups which are subject to reductive cleavage can also be used.

The oxidation step (LIII to LIV) is the same as Reaction Scheme I (XXXI to XXXII).

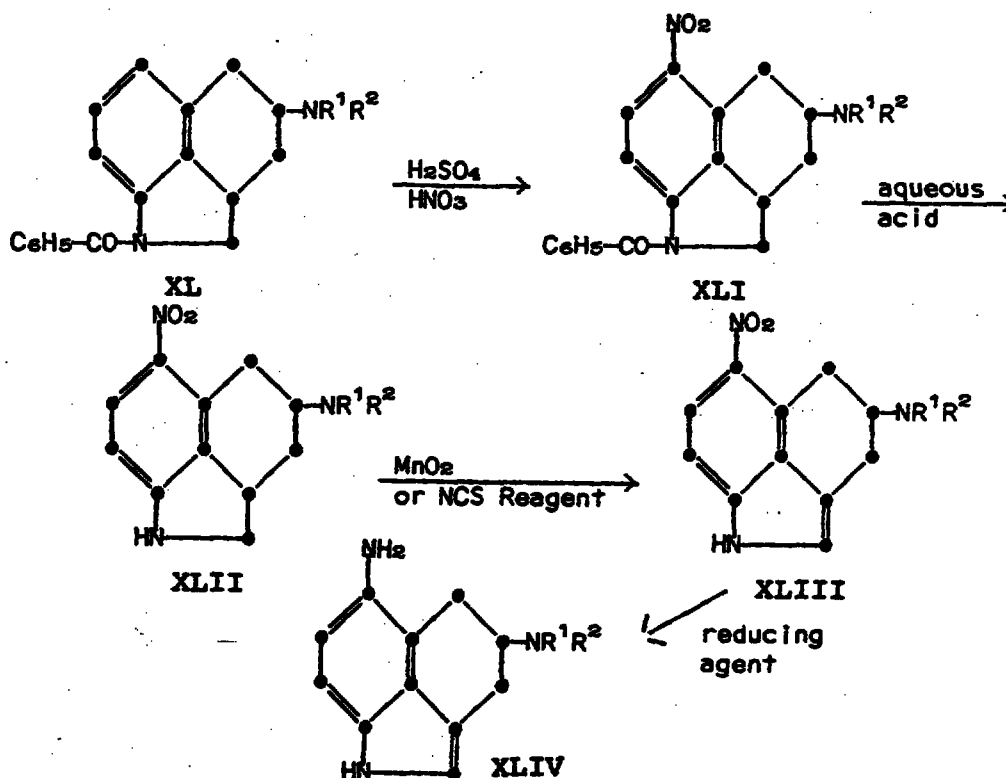
Alternatively, the 6—CN derivative (LV) is hydrolyzed to the 4—NHR⁸-6-carboxylic acid derivative, then alkylated with R¹ halide to yield the 4-R¹R⁸-6-carboxylic acid derivative. The 6-carboxylic acid moiety is coupled with NH₃ and a peptide coupling agent (e.g. Im₂CO, DCC and others) to provide the compounds of formula IV where X is CONH₂ and R¹ and R² are individually methyl, ethyl, n-propyl or allyl, provided that only one of R¹ or R² is allyl.

Similarly, the 6-CN-4-(NR⁸COY) derivative (LV) is reduced to provide the 6-CN-4-(NR⁸R¹) derivative, which then has the 6-CN hydrolyzed to 6-COOH. The reaction then proceeds as described in the previous paragraph to yield the same 6-CONH₂ product of formula IV.

Compounds according to IV above have a single asymmetric center at C-4 and occur commonly as a racemate. However, compounds according to VIII through XVI and XVIa have an additional asymmetric center at C-2a, which center is removed by the oxidative procedures. Thus, compounds IX, XIV, XIVa, XV, XVa, XVI and XVIa each have two asymmetric centers (at C-2a and C-4) and exist as two racemic pairs conveniently designated as the trans-dl and the cis-dl racemates.

Compounds of formula IV wherein X is NO₂ or NH₂ can be prepared according to the following reaction scheme.

Reaction Scheme 4



In Reaction Scheme 4, R¹ and R² are defined as before.

In Reaction Scheme 4, for example, a 1-benzoyl-4-dialkylamino-1,2,2a,3,4,5-hexahydrobenz[c,d]indole can be nitrated to yield, after removal of the benzoyl protecting group an oxidation of the indoline to a indole, compounds according to IV in which X is NO₂. This 6-nitro derivative is a particularly useful intermediate in that the nitro group can be reduced to a 6-amino function and thus produces compounds according to IV above in which X is NH₂.

The 6-nitro compound can be prepared analogously by nitrating the 5-hydroxy derivative (XXII). However, the 4-oxo compound (XXI or 6-unsubstituted-XXVII) can also be nitrated at C—6 if desired.

This invention is further illustrated by the following specific examples of the preparation of starting materials, intermediates, and final products. In the examples and application some terms are defined as follows:

	HOAC	= acetic acid
	brine	= an aqueous, saturated NaCl solution
15	DCC	= dicyclohexylcarbodiimide
	DMAP	= 4-(N,N-dimethylamino)pyridine
	DMF	= dimethylformamide
	DMSO	= dimethylsulfoxide
	EtOH	= ethanol
20	EtOAc	= ethyl acetate
	ether	= diethyl ether
	HPLC	= high performance liquid chromatography
	Im ₂ CO	= bis-imidazole carbonyl = 1,1'-carbonyl-diimidazole
	MeOH	= methanol
25	NCS	= N-chlorosuccinimide
	NCS reagent	= NCS, dimethylsulfide and triethylamine
	PPA	= polyphosphoric acid
	TFA	= trifluoroacetic acid
	THF	= tetrahydrofuran
30	TLC	= thin-layer chromatography.

Ratios are by volume when the substance is a liquid and by weight when the substance is a solid. Temperatures are in °C.

Example A

Preparation of (±)-4-Di-n-propylamino-6-bromo-1,2,2a,3,4,5-hexahydrobenz[c,d]indole

A mixture containing 5.0 g of 5-oxo-1,2,2a,3,4,5-hexahydrobenz[c,d]indole in 100 ml of ethanol was treated with 1.63 g of sodium borohydride in portions. The resulting mixture was stirred for about four hours after which time the bulk of the ethanol was removed in vacuo. The resulting residue was taken up in water, and the aqueous mixture acidified with 3M hydrochloric acid. The aqueous solution was filtered, and the filtrate treated with dilute aqueous sodium hydroxide. (±)-5-Hydroxy-1,2,2a,3,4,5-benz[c,d]indole formed in the above reaction was insoluble in the basic medium and precipitated. The precipitate was collected, washed with water and then dried. Four and seventy-two hundredths grams of (±)-5-Hydroxy-1,2,2a,3,4,5-hexahydro-benz[c,d]indole (93% yield) were obtained. The material was one spot by TLC; m.p. = 205°C.

Analysis Calculated: C, 75.83; H, 6.94; N, 8.04

Found: C, 75.75; H, 7.16; N, 7.89

A solution of 35 g of (±)-5-hydroxy-1,2,2a,3,4,5-hexahydrobenz[c,d]indole in 900 ml of cold glacial acetic acid was treated with 22 g of bromine dissolved in 100 ml of glacial acetic acid. After the bromine color had been discharged, the acetic acid was removed *in vacuo*. The residue, comprising a mixture of (±)-5-hydroxy-1,2,2a,3,4,5-hexahydrobenz[c,d]indole and the corresponding 6,8-dibromo derivative was diluted with water and the aqueous mixture made basic with 5M aqueous sodium hydroxide. The hexahydrobenz[c,d]indoles, being insoluble in base, precipitated, and the precipitate was collected. Recrystallization of the precipitate from methanol yielded about 3 g of the dibromo derivative plus about 12.5 g of the monobromo derivative and a considerable quantity of a crystal fraction which was a 1:1 mixture of starting material and monobromo derivative. (±)-5-Hydroxy-6-bromo-1,2,2a,3,4,5-hexahydrobenz[c,d]indole thus formed melted at about 172°C with decomposition. Twenty-four and one tenth grams (47% yield) of the 6-bromo derivative were obtained by recrystallization of various fractions. The product as obtained still contained a small amount of the dibromo impurity.

A reaction mixture was prepared by dissolving 27.43 g of (±)-5-Hydroxy-6-bromo-1,2,2a,3,4,5-hexahydrobenz[c,d]indole in 100 ml of pyridine and then adding in dropwise fashion 25 ml of ethyl chloroformate over a 20 minute period. About 0.5 g of 4-(N,N-dimethylamino)pyridine (DMAP) were added, and the resulting reaction mixture stirred at room temperature for about four hours. The reaction mixture was then quenched by pouring into 1 liter of an ice-water mixture. An oil which separated crystallized almost immediately. The crystals were collected and washed thoroughly with water. The dried ester amide

was a faintly pink solid melting above 215°C with decomposition; yield = 40.48 g (94%). Analysis indicated that some 6,8-dibromo compound continued as a contaminate.

Forty and one tenth grams of ($\pm$)-1-ethoxycarbonyl-5-ethoxycarbonyloxy-6-bromo-1,2,2a,3,4,5-hexahydrobenz[c,d]indole were pyrolyzed in four different ten gram runs at 215–220°C under a nitrogen atmosphere. Each run required 25–30 minutes of heating. The four dark oil residues were combined, and the combined residues taken up in toluene. The toluene solution was chromatographed over silica. One and four tenths grams of starting material were recovered from fractions containing it but the main product — 1-ethoxycarbonyl-6-bromo-1,2,2a,3-tetrahydrobenz[c,d]indole — was recrystallized from a hexane/toluene solvent mixture containing predominantly hexane to yield 19.36 g including a second crop, from hexane alone. Yield = 65% corrected for recovered starting material. The compound melted at 122–123°C.

Analysis Calculated: C, 54.56; H, 4.58; N, 4.55; Br, 25.93

Found: C, 54.59; H, 4.61; N, 4.41; Br, 25.84

The unsaturated product from the above step was epoxidized as follows:

A solution of 7.5 g of 1-ethoxycarbonyl-6-bromo-1,2,2a,3-tetrahydrobenz[c,d]indole in 250 ml of chloroform was cooled to about 0°C with an ice/salt mixture. Six grams of 85% of *m*-chloroperbenzoic acid were added. The reaction mixture was stirred at about 0°C for one hour and was then kept at refrigerator temperature overnight. The reaction mixture was washed successively with 1N aqueous sodium hydroxide, saturated aqueous sodium bisulfite, again with 1N aqueous sodium hydroxide and finally with brine. The organic solution was dried, and the solvent removed *in vacuo*. The resulting solid residue was recrystallized from a toluene/hexane solvent mixture. The first crop material obtained weighed 7.33 g and melted at 126–8°C; total yield (2 crops) = 98%.

Analysis Calculated: C, 51.87; H, 4.35; N, 4.32; Br, 24.65

Found: C, 51.83; H, 4.33; N, 4.16; Br, 24.31

A solution of 7.5 g of 1-ethoxycarbonyl-4,5-epoxy-6-bromo-1,2,2a,3,4,5-hexahydrobenz[c,d]indole obtained as above in 50 ml of benzene was added slowly to a refluxing solution of 1 g of zinc iodide in 450 ml of benzene which had been dried by distilling off 50 ml of the benzene-water azeotrope. Reflux under a nitrogen atmosphere was continued for one hour after the addition had been completed. The reaction mixture was cooled. The supernate was decanted, and the decanted solution washed with water and then with brine. The solution was dried and the solvent removed therefrom *in vacuo*. The residue, comprising 1-ethoxycarbonyl-4-oxo-6-bromo-1,2,2a,3,4,5-hexahydrobenz[c,d]indole formed in the above reaction, was crystallized from a toluene/hexane solvent mixture. Five and thirty-six hundredths grams (71% yield) of crystalline product melting at 186–8°C were obtained.

Analysis Calculated: C, 51.87; H, 4.35; N, 4.32; Br, 24.65

Found: C, 51.75; H, 4.29; N, 4.50; Br, 24.80

A reaction mixture was prepared from 14 g of 1-ethoxycarbonyl-4-oxo-6-bromo-1,2,2a,3,4,5-hexahydrobenz[c,d]indole, 28.3 g of *n*-propylamine, 4.9 ml of glacial acetic acid and 300 ml of acetonitrile. The reaction mixture was stirred under a nitrogen atmosphere for about one hour. $3\text{Å} \times 10^{-4}\mu\text{m}$ molecular sieves were added to absorb water. Next, 5.6 g of sodium cyanoborohydride were added followed by 14 ml of glacial acetic acid. This new reaction mixture was stirred for an additional two hours at which time 7 ml of glacial acetic acid were added. The reaction mixture was stirred for another two hours, and another 7 ml of glacial acetic acid added. Finally, the supernate was decanted from the molecular sieves, and the bulk of the volatile constituents were removed *in vacuo*. The residual solution was poured into cold 2N aqueous sodium hydroxide. The alkaline mixture was extracted with methylene dichloride. The methylene dichloride extract was washed with 0.5N aqueous sodium hydroxide and then with brine. The solvent was removed *in vacuo*. The resulting residue was dissolved in 1N aqueous hydrochloric acid to which methanol had been added. This acidic solution was washed with ether, and the ether wash discarded. The acidic solution was then made basic with 5N aqueous hydroxide, and the now insoluble ($\pm$)-1-ethoxycarbonyl-4-*n*-propylamino-6-bromo-1,2,2a,3,4,5-hexahydrobenz[c,d]indole formed in the above reaction separated and was extracted into methylene dichloride. The methylene dichloride extract was separated, and the solvent removed therefrom to yield 16.7 g of an orange oil which was used in the next step without further purification.

The above crude product was dissolved in 50 ml of acetonitrile, 3 ml of *n*-propyl iodide and 2 ml of diisopropylethylamine. This solution was allowed to remain in the dark for about three weeks. At this point in time, the solvent was removed under reduced pressure, and the residual mixture partitioned between ether and 0.5N aqueous sodium hydroxide. The organic layer was separated, and the aqueous alkaline layer extracted several times more with ether. The ether extracts were combined and the combined extracts washed with brine and then dried. The ether was removed *in vacuo* to yield a residue. Xylene was added to the residue and removed by evaporation to remove any remaining diisopropylethylamine. The unpurified residue slowly crystallized. The crystals were dissolved in 20 ml of methylene dichloride and 1 ml of acetic anhydride was added thereto. After about an hour, the volatile constituents were removed *in vacuo* and the resulting residue dissolved in methylene dichloride. The methylene dichloride solution was stirred with aqueous saturated sodium carbonate to remove any excess acetic anhydride. The methylene dichloride layer was separated, and the methylene dichloride removed by evaporation. The residue was dissolved in a mixture of dilute hydrochloric acid and methanol. The resulting cloudy solution was washed with ether and the ether was discarded. The acidic layer was then made basic with 5N aqueous sodium

hydroxide and the now insoluble base which separated was extracted into methylene dichloride. Evaporation of the solvent gave a moist crystalline residue. The residue was treated with hexane, and the hexane solution separated from hexane-insoluble brown oil by decantation. The hexane was evaporated *in vacuo*, and the residue chromatographed over 25 g of silica gel using ethyl acetate as the eluant. Fractions containing the desired material were combined and the solvent removed therefrom *in vacuo*. The white, crystalline residue was transferred to a filter paper using cold isooctane. A total yield of 2.39 g of ($\pm$)-1-ethoxycarbonyl-4-di-n-propylamino-6-bromo-1,2,2a,3,4,5-hexahydrobenz[c,d]indole was obtained in two crops. m.p. = 90–94°C.

Analysis Calculated: C, 58.68; H, 7.14; N, 6.84; Br, 19.52

Found: C, 58.98; H, 6.88; N, 6.59; Br, 18.74

Alternatively, a solution of 15.7 g of the crude secondary amine ($\pm$)-1-ethoxycarbonyl-4-n-propylamino-6-bromo-1,2,2a,3,4,5-hexahydrobenz[c,d]indole in 80 ml of pyridine was cooled to about 0°C. Sixteen ml of propionic anhydride were added slowly. Then solution was allowed to remain at ambient temperature overnight. The bulk of the pyridine solvent was removed under vacuum, and the residual solution was stirred with an excess of aqueous sodium carbonate for several hours to remove any unreacted propionic anhydride and any by-product propionic acid. The aqueous mixture was extracted with methylene dichloride, and the methylene dichloride extract separated and washed with 0.5 M aqueous sodium hydroxide, 1N hydrochloric acid and brine. The organic solution was dried and the solvent removed therefrom *in vacuo* leaving a viscous oil. The oil was dissolved in 50 ml of THF and this solution added over about a 15 minute period to 85 ml of 1M diborane in THF kept at about 0°C. After the addition had been completed, the cooling bath was removed, and the reaction mixture heated to reflux temperature for about 1.5 hours. The reaction mixture was then cooled to about 0°C and 50 ml of methanol were added cautiously. The resulting reaction was stirred overnight at room temperature. The methanol was removed *in vacuo*. Additional methanol was added and again removed by evaporation. The resulting residue began to solidify. The semisolid residue was partitioned between diethyl ether and 1M hydrochloric acid containing added methanol. The solid which precipitated as a result of these operations was collected by filtration. The filtrate was made basic by the addition of aqueous sodium hydroxide and the alkaline mixture extracted with methylene dichloride. The above ether layer, the methylene dichloride extract and the separated solid were combined and the solvent evaporated. The residue was heated with wet DMSO, and this solution was then diluted with water plus sufficient 1M aqueous sodium hydroxide to maintain basic conditions. The alkaline mixture was extracted with ether. The ether extract was in turn extracted with 1M hydrochloric acid containing some methanol. The acidic extract was again made basic, and the resulting alkaline mixture extracted with methylene dichloride. The methylene dichloride extracts were combined. Upon evaporation of the solvent, fifteen and fifty-nine hundredths grams of crude salmon colored compound were obtained. The solid was dissolved in ethyl acetate and chromatographed over silica gel. Fractions containing the desired material were combined and the solvent removed therefrom *in vacuo*. Recrystallization of the resulting solid from isooctane gave ($\pm$)-1-ethoxycarbonyl-4-di-n-propylamino-6-bromo-1,2,2a,3,4,5-hexahydrobenz[c,d]indole melting 87–9°C; yield = 14.8 g. (94%).

A solution of 1 g of the above tertiary amine in 10 ml of 6N hydrochloric acid was heated to reflux temperature under nitrogen overnight. TLC indicated that only a trace of starting material remained and that the chief product was ($\pm$)-4-di-n-propylamino-6-bromo-1,2,2a,3,4,5-hexahydrobenz[c,d]indole. The acidic solution was poured into dilute aqueous sodium hydroxide, and the resulting alkaline layer extracted with methylene dichloride. The methylene dichloride extract was separated and the separated extract washed with brine and then dried. Evaporation of the solvent yielded a viscous oil which crystallized upon cooling. Recrystallization of the precipitate from isooctane gave 0.683 g (83% yield) of ($\pm$)-4-di-n-propylamino-6-bromo-1,2,2a,3,4,5-hexahydrobenz[c,d]indole melting at about 62–3°C.

Analysis Calculated: C, 60.53; H, 7.47; N, 8.31; Br, 23.69

Found: C, 60.71; H, 7.57; N, 8.30; Br, 23.78

A run on a larger scale (14.8 g of starting material) gave an 88% yield of the desired hydrolysis product.

Example B

Preparation of ($\pm$)-4-Di-n-propylamino-6-nitro-1,2,2a,3,4,5-hexahydrobenz[c,d]indole

One-half gram of ($\pm$)-1-benzoyl-4-di-n-propylamino-1,2,2a,3,4,5-hexahydrobenz[c,d]indole from United States Patent 4,110,339, column 3, line 49, in 5 ml of 18M sulfuric acid was prepared in the cold and the resulting solution kept at ice bath temperature. Seven hundredths ml of 90% nitric acid were added thereto in dropwise fashion via a pipette. The solution was stirred in the cold for about one hour and then poured over ice. The acidic mixture was neutralized by the careful addition of solid sodium carbonate. ($\pm$)-1-Benzoyl-4-di-n-propylamino-6-nitro-1,2,2a,3,4,5-hexahydrobenz[c,d]indole formed in the above reaction, being insoluble in the alkaline layer, separated and was extracted into methylene dichloride. The methylene dichloride layer was separated, washed with water and then dried. The solvent was removed *in vacuo*, and the crude residue chromatographed over Florisil®, using toluene containing increasing amounts (2–5%) of ethyl acetate as the eluant. Fractions shown by TLC to contain the desired material were combined and the solvent evaporated therefrom to yield a viscous red oil weighing 0.35 g (61% yield). The red oil was used without further purification since the nmr was in agreement with the proposed structure.

The above material was dissolved in 7 ml of 6N hydrochloric acid, and the resulting solution heated to reflux temperature under a nitrogen atmosphere for about two hours. At this point, TLC indicated no more starting material remained. The reaction was quenched with cold 5N aqueous sodium hydroxide. The free base was extracted with methylene dichloride. The methylene dichloride extract was washed with brine and then dried. TLC indicated only one mobile spot. The solvent was removed, and the residue chromatographed over Florisil® using ethyl acetate as the eluant. Fractions containing the desired product were collected, the solvent removed therefrom and the residue recrystallized from isooctane. (±)-4-Di-n-propylamino-6-nitro-1,2,2a,3,4,5-hexahydrobenz[c,d]indole thus prepared melted at 97–100°C; weight = 0.194 g. (69% yield).

Analysis Calculated: C, 67.30; H, 8.31; N, 13.85
Found: C, 67.47; H, 8.21; N, 13.71

Example I

Preparation of (±)-4-Di-n-propylamino-6-bromo-1,2,2a,3,4,5-hexahydrobenz[c,d]indole

A mixture containing 5.0 g of 5-oxo-1,2,2a,3,4,5-hexahydrobenz[c,d]indole in 100 ml of ethanol was treated with 1.63 g of sodium borohydride in portions. The resulting mixture was stirred for about four hours after which time the bulk of the ethanol was removed *in vacuo*. The resulting residue was taken up in water, and the aqueous mixture acidified with 3M hydrochloric acid. The aqueous solution was filtered, and the filtrate treated with dilute aqueous sodium hydroxide. (±)-5-Hydroxy-1,2,2a,3,4,5-benz[c,d]indole formed in the above reaction was insoluble in the basic medium and precipitated. The precipitate was collected, washed with water and then dried. Four and seventy-two hundredths grams of (±)-5-hydroxy-1,2,2a,3,4,5-hexahydrobenz[c,d]indole (93% yield) were obtained. The material was one spot by TLC; m.p. = 205°C.

Analysis Calculated: C, 75.83; H, 6.94; N, 8.04
Found: C, 75.75; H, 7.16; N, 7.89

A solution of 35 g of (±)-5-hydroxy-1,2,2a,3,4,5-hexahydrobenz[c,d]indole in 900 ml of cold glacial acetic acid was treated with 22 g of bromine dissolved in 100 ml of glacial acetic acid. After the bromine color had been discharged, the acetic acid was removed *in vacuo*. The residue, comprising a mixture of (±)-5-hydroxy-6-bromo-1,2,2a,3,4,5-hexahydrobenz[c,d]indole and the corresponding 6,8-dibromo derivative was diluted with water and the aqueous mixture made basic with 5M aqueous sodium hydroxide. The hexahydrobenz[c,d]indoles, being insoluble in base, precipitated, and the precipitate was collected. Recrystallization of the precipitate from methanol yielded about 3 g of the dibromo derivative plus about 12.5 g of the monobromo derivative and a considerable quantity of a crystal fraction which was a 1:1 mixture of starting material and monobromo derivative. (±)-5-Hydroxy-6-bromo-1,2,2a,3,4,5-hexahydrobenz[c,d]indole thus formed melted at about 172°C with decomposition. Twenty-four and one tenth grams (47% yield) of the 6-bromo derivative were obtained by recrystallization of various fractions. The product as obtained still contained a small amount of the dibromo impurity.

A reaction mixture was prepared by dissolving 27.43 g of (±)-5-Hydroxy-6-bromo-1,2,2a,3,4,5-hexahydrobenz[c,d]indole in 100 ml of pyridine and then adding in dropwise fashion 25 ml of ethyl chloroformate over a 20 minute period. About 0.5 g of dimethylaminopyridine were added, and the resulting reaction mixture stirred at room temperature for about four hours. The reaction mixture was then quenched by pouring into 1 liter of an ice-water mixture. An oil which separated crystallized almost immediately. The crystals were collected and washed thoroughly with water. The dried ester amide was a faintly pink solid melting above 215°C with decomposition; yield = 40.48 g (94%). Analysis indicated that some 6,8-dibromo compound continued as a contaminate.

Forty and one tenth grams of (±)-1-ethoxycarbonyl-5-ethoxycarbonyloxy-6-bromo-1,2,2a,3,4,5-hexahydrobenz[c,d]indole were pyrolyzed in four different ten gram runs at 215–220°C. under nitrogen atmosphere. Each run required 25–30 minutes of heating. The four dark oily residues were combined, and the combined residues taken up in toluene. The toluene solution was chromatographed over silica. One and four tenths grams of starting material were recovered from fractions containing it but the main product — 1-ethoxycarbonyl-6-bromo-1,2,2a,3,4,5-hexahydrobenz[c,d]indole — was recrystallized from a hexane/toluene solvent mixture containing predominantly hexane to yield 19.36 g including a second crop, from hexane alone. Yield = 65% corrected for recovered starting material. The compound melted at 122–123°C.

Analysis Calculated: C, 54.56; H, 4.58; N, 4.55; Br, 25.93
Found: C, 54.59; H, 4.61; N, 4.41; Br, 25.84

The unsaturated product from the above step was epoxidized as follows:

A solution of 7.5 g of 1-ethoxycarbonyl-6-bromo-1,2,2a,3-tetrahydrobenz[c,d]indole in 250 ml of chloroform was cooled to about 0°C with an ice/salt mixture. Six grams of 85% of m-chloroperbenzoic acid were added. The reaction mixture was stirred at about 0°C for one hour and was then kept overnight at about 4°C. The reaction mixture was washed successively with 1N aqueous sodium hydroxide, saturated aqueous sodium bisulfite, again with 1N aqueous sodium hydroxide and finally with brine. The organic solution was dried, and the solvent removed *in vacuo*. The resulting solid residue was recrystallized from a

toluene/hexane solvent mixture. The first crop material obtained weighed 7.33 g and melted at 126–8°C; total yield (2 crops) = 98%.

Analysis Calculated: C, 51.87; H, 4.35; N, 4.32; Br, 24.65

Found: C, 51.83; H, 11.33; N, 4.16; Br, 24.31

A solution of 7.5 g of 1-ethoxycarbonyl-4,5-epoxy-6-bromo-1,2,2a,3,4,5-hexahydrobenz[c,d]indole obtained as above in 50 ml of benzene was added slowly to a refluxing solution of 1 g of zinc iodide in 450 ml of benzene which had been dried by distilling off 50 ml of the benzene-water azeotrope. Reflux under a nitrogen atmosphere was continued for one hour after the addition had been completed. The reaction mixture was cooled. The supernate was decanted, and the decanted solution washed with water and then with brine. The solution was dried and the solvent removed therefrom *in vacuo*. The residue, comprising 1-ethoxycarbonyl-4-oxo-6-bromo-1,2,2a,3,4,5-hexahydrobenz[c,d]indole formed in the above reaction, was crystallized from a toluene/hexane solvent mixture. Five and thirty-six hundredths grams (71% yield) of crystalline product melting at 186–8°C were obtained.

Analysis Calculated: C, 51.87; H, 4.35; N, 4.32; Br, 24.65

Found: C, 51.75; H, 4.29; N, 4.50; Br, 24.80

A reaction mixture was prepared from 14 g of 1-ethoxycarbonyl-4-oxo-6-bromo-1,2,2a,3,4,5-hexahydrobenz[c,d]indole, 28.3 g of n-propylamine, 4.9 ml of glacial acetic acid and 300 ml of acetonitrile. The reaction mixture was stirred under a nitrogen atmosphere for about one hour. $3\text{Å } 3 \times 10^{-4}\mu\text{m}$ molecular sieve was added to absorb water. Next, 5.6 g of sodium cyanoborohydride were added followed by 14 ml of glacial acetic acid. This new reaction mixture was stirred for an additional two hours at which time 7 ml of glacial acetic acid were added. The reaction mixture was stirred for another two hours, and the process repeated again. Finally the supernate was decanted from the molecular sieve, and the volatile constituents were removed *in vacuo*. A residual solution (mainly acetic acid) was poured into cold 2N aqueous sodium hydroxide. The alkaline mixture was extracted with methylene dichloride. The methylene dichloride extract was washed with 0.5N aqueous sodium hydroxide and then with brine. The solvent was removed *in vacuo*. The resulting residue was dissolved in 1N aqueous hydrochloric acid to which methanol had been added. This acidic solution was washed with ether, and the ether wash discarded. The acidic solution was then made basic with 5N aqueous sodium hydroxide, and the now insoluble ($\pm$)-1-ethoxycarbonyl-4-n-propylamino-6-bromo-1,2,2a,3,4,5-hexahydrobenz[c,d]indole formed in the above reaction separated and was extracted into methylene dichloride. The methylene dichloride extract was separated, and the solvent removed therefrom to yield 16.7 g of an orange oil which was used in the next step without further purification.

The above crude product was dissolved in 50 ml of acetonitrile, 3 ml of n-propyl iodide and 2 ml of diisopropylethylamine. This solution was allowed to remain in the dark for about three weeks. At this point in time, the solvent was removed under reduced pressure, and the residual mixture partitioned between ether and 0.5N aqueous sodium hydroxide. The organic layer was separated, and the aqueous alkaline layer extracted several times more with ether. The ether extracts were combined and the combined extracts washed with brine and then dried. The ether was removed *in vacuo* to yield a residue. Xylene was added to the residue and removed by evaporation to remove any remaining diisopropylethylamine. The unpurified residue slowly crystallized. The crystals were dissolved in 20 ml of methylene dichloride and 1 ml of acetic anhydride was added thereto. After about an hour, the volatile constituents were removed *in vacuo* and the resulting residue dissolved in methylene dichloride. The methylene dichloride solution was stirred with aqueous saturated sodium bicarbonate to remove any excess acetic anhydride. The methylene dichloride layer was separated, and the methylene dichloride removed by evaporation. The residue was dissolved in a mixture of dilute hydrochloric acid and methanol. The resulting cloudy solution was washed with ether and the ether was discarded. The acidic layer was then made basic with 5N aqueous sodium hydroxide and the now insoluble base which separated was extracted into methylene dichloride; TLC (1:9 MeOH EtOAc). Evaporation of the solvent gave a moist crystalline residue. The residue was treated with hexane, and the hexane solution separated from hexane-insoluble brown oil by decantation. TLC indicated a single spot. The hexane was evaporated *in vacuo*, and the residue chromatographed over 25 g of silica gel using ethyl acetate as the eluant. Fractions containing the desired material were combined and the solvent removed therefrom *in vacuo*. The white, crystalline residue was transferred to a filter paper using cold isooctane. A total yield of 2.39 g of ($\pm$)-1-ethoxycarbonyl-4-di-n-propylamino-6-bromo-1,2,2a,3,4,5-hexahydrobenz[c,d]indole was obtained. m.p. = 90–94°C.

Analysis Calculated: C, 58.68; H, 7.14; N, 6.84; Br, 19.52

Found: C, 58.98; H, 6.88; N, 6.59; Br, 18.74

Alternatively, a solution of 15.7 g of the crude amine product, ($\pm$)-1-ethoxycarbonyl-4-n-propylamino-6-bromo-1,2,2a,3,4,5-hexahydrobenz[c,d]indole in 80 ml of pyridine was cooled to about 0°C. Sixteen ml of propionic anhydride were added slowly. The solution was allowed to remain at ambient temperature overnight. The bulk of the pyridine solvent was removed under vacuum, and the residual solution was stirred with an excess of aqueous sodium carbonate for several hours to remove any unreacted propionic anhydride and any by-product propionic acid. The aqueous mixture was extracted with methylene dichloride, and the methylene dichloride extract separated and washed with 0.5 M aqueous sodium hydroxide, 1N hydrochloric acid and brine. The organic solution was dried and the solvent removed therefrom *in vacuo* leaving a viscous oil. The oil was dissolved in 50 ml of THF and this solution added over

about a 15 minute period to 85 ml of 1M diborane in THF kept at about 0°C. After the addition had been completed, the cooling bath was removed, and the reaction mixture heated to reflux temperature for about 1.5 hours. The reaction mixture was then cooled to about 0°C and 50 ml of methanol were added cautiously.

The resulting reaction was stirred overnight at room temperature. The methanol was removed in vacuo. Additional methanol was added and again removed by evaporation. The resulting residue began to solidify. The semisolid residue was partitioned between diethyl ether and 1M hydrochloric acid containing added methanol. The solid which precipitated as a result of these operations was collected by filtration. The filtrate was made basic by the addition of aqueous sodium hydroxide and the alkaline mixture extracted with methylene dichloride. The above ether layer, the methylene dichloride extract and the separated solid were combined and the solvent evaporated. The residue was heated with wet DMSO, and this solution was then diluted with water plus sufficient 1M aqueous sodium hydroxide to maintain basic additions. The alkaline mixture was extracted with ether. The ether extract was in turn extracted with 1M hydrochloric acid containing some methanol. The acidic extract was again made basic, and the resulting alkaline mixture extracted with methylene dichloride. The methylene dichloride extracts were combined. TLC indicated that the chief product in this solution was ($\pm$)-1-ethoxycarbonyl-4-di-n-propylamino-6-bromo-1,2,2a,3,4,5-hexahydrobenz[c,d]indole formed in the above reactions. Fifteen and fifty-nine hundredths grams of crude salmon colored compound were obtained. The solid was dissolved in ethyl acetate and chromatographed over silica gel. Fractions containing the desired material were combined and the solvent removed therefrom *in vacuo*. Recrystallization of the resulting solid from isooctane gave ($\pm$)-1-ethoxycarbonyl-4-di-n-propylamino-6-bromo-1,2,2a,3,4,5-hexahydrobenz[c,d]indole melting 87–9°C; yield = 14.8 g. (94%).

A solution of 1 g of the above tertiary amine in 10 ml of 6N hydrochloric acid was heated to reflux temperature under nitrogen overnight. TLC indicated that only a trace of starting material remained and that the chief product was ($\pm$)-4-di-n-propylamino-6-bromo-1,2,2a,3,4,5-hexahydrobenz[c,d]indole formed in the above hydrolysis. The acidic solution was poured into dilute aqueous sodium hydroxide, and the resulting alkaline layer extracted with methylene dichloride. The methylene dichloride extract was separated and the separated extract washed with brine and then dried. Evaporation of the solvent yielded a viscous oil which crystallized upon cooling. Recrystallization of the precipitate from isooctane gave 0.683 g (83% yield) of ($\pm$)-4-di-n-propylamino-6-bromo-1,2,2a,3,4,5-hexahydrobenz[c,d]indole melting at about 62–3°C.

Analysis Calculated: C, 60.53; H, 7.47; N, 8.31; Br, 23.69
Found: C, 60.71; H, 7.57; N, 8.30; Br, 23.78

A run on a larger scale (14.8 g of starting material) gave an 88% yield of the desired hydrolysis product.

Example J

Preparation of N-formyl ($\pm$)-4-methylamino-6-cyano-1,3,4,5-tetrahydrobenz[c,d]indole

A solution of 16.8 g of ($\pm$)-5-oxo-1,2,2a,3,4,5-hexahydrobenz[c,d]indole in 100 ml of pyridine was stirred at ice bath temperature while 16 ml of 2,2,2-trichloroethylchloroformate was added slowly over a 10 minutes period. The reaction mixture was allowed to warm to room temperature under an N₂ atmosphere at which temperature it was stirred for an additional 3 hours. A majority of the pyridine was removed *in vacuo*. The resulting residue was partitioned between toluene and water. The toluene layer was separated and the aqueous layer extracted twice more with equal volumes of toluene. The toluene extracts were combined and the combined extracts washed several times with 1N hydrochloric acid (until the separated aqueous layer was acid to litmus). The combined toluene extracts were evaporated *in vacuo*. The resulting residue was recrystallized from toluene/hexane (1:1) to give 31.62 g (93% yield) of ($\pm$)-(2,2,2-trichloroethoxycarbonyl)-5-oxo-1,2,2a,3,4,5-hexahydrobenz[c,d]indole melting at about 130–132°C.

Following the procedure of Example A, 31.0 g of ($\pm$)-1-(2,2,2-trichloroethoxycarbonyl)-5-oxo-1,2,2a,3,4,5-hexahydrobenz[c,d]indole were reduced with NaBH₄ in ethanol to yield ($\pm$)-1-(2,2,2-trichloroethoxycarbonyl)-5-hydroxy-1,2,2a,3,4,5-hexahydrobenz[c,d]indole; yield = 30.1 (97%); m.p. = 119–121°C (from ethanol).

A solution was prepared by dissolving 23.41 g of ($\pm$)-1-(2,2,2-trichloroethoxycarbonyl)-5-hydroxy-1,2,2a,3,4,5-hexahydrobenz[c,d]indole in 190 ml of chilled (0°C) trifluoroacetic acid (TFA). When solution was complete, 9.58 g of bromocyanuric acid were added in small amounts (1.25 hr. addition time). The reaction mixture was stirred for 2 hours at about 0°C. TLC in 100% methylene chloride indicated that no starting material remained. The reaction mixture was chilled and then made basic (to litmus) by the addition of an excess of 5N aqueous sodium hydroxide. The alkaline mixture was extracted with 200 ml portions of CH₂Cl₂. The combined CH₂Cl₂ extracts were washed with dilute aqueous sodium hydroxide. Two grams of tetrabutylammonium hydrogen sulfate were added to the dilute sodium hydroxide and the CH₂Cl₂ layer shaken with the NaOH solution until TLC indicated that all bi-product 5-trifluoroacetate had been hydrolyzed back to the 5-hydroxy derivative. The CH₂Cl₂ was removed *in vacuo* and the residue chromatographed over silica gel using CH₂Cl₂ as the eluant. Fractions containing the desired 6-bromo derivative were combined and the solvent removed. Recrystallization of the residue from diethylether provided ($\pm$)-1-(2,2,2-trichloroethoxycarbonyl)-5-hydroxy-6-bromo-1,2,2a,3,4,5-benz[c,d]indole and melted at about 123–125°C; yield (2 crops) = 18.74 g (65%).

Analysis Calculated: C, 39.15; H, 3.05; N, 3.26; Br, 18.60

Found: C, 39.34; H, 3.85; N, 3.44; Br, 18.38

Mass spectrum: M+ = 429

A reaction mixture was prepared by placing 18.74 g of the above 6-bromo derivative, 475 ml of toluene, 8 g of Amberlyst® 15, an ion exchange resin known to catalyze dehydration, in a 1 l round-bottom flask equipped with magnetic stirrer, Dean-Stark trap, reflux condensor and drying tube. The reaction mixture was heated to reflux. After one hour, TLC revealed no remaining starting material. The solution was decanted from the Amberlyst® beads, and then decolorized with carbon. The decolorizing solution was filtered through hyflo supercel. The filtrate was evaporated to dryness *in vacuo*. CH₂Cl₂ was added and the solvent again removed *in vacuo*. The residue was crystallized from hexane. Yellowish crystals of (±)-1-(2,2,2-trichloroethoxycarbonyl)-6-bromo-1,2,2a,3-tetrahydrobenz[c,d]indole thus prepared melted at about 95—99°C. Recrystallization from ether gave crystals melting at 98—101°C (96% yield).

Following the procedure of Example A, the above $\Delta^{4,5}$ compound was epoxidized with m-chloroperbenzoic acid in CHCl₃ to yield (±)-1-(2,2,2-trichloroethoxycarbonyl)-4,5-epoxy-6-bromo-1,2,2a,3,4,5-hexahydrobenz[c,d]indole. 11.8 g of epoxide was removed based on 17.64 g of starting olefin. The epoxide was rearranged to the corresponding 4-oxo derivative by the procedure of Example A (zinc iodide in benzene), 7.29 g (from 11.8 g of starting olefin) of (±)-1-(2,2,2-trichloroethoxycarbonyl)-4-oxo-6-bromo-1,2,2a,3,4,5-hexahydrobenz[c,d]indole were obtained (62% yield).

A cold solution of 4.4 g of methylamine in 100 ml of acetonitrile was prepared. 1.9 ml of acetic acid were added followed by 1.5 g of sodium cyanoborohydride followed by about 5 g of (±)-1-(2,2,2-trichloroethoxycarbonyl)-4-oxo-6-bromo-1,2,2a,3,4,5-hexahydrobenz[c,d]indole. The reaction mixture was continuously stirred and every two hours additional acetic acid was added in the following amounts — 6.2 ml, 1.3 ml and 1 ml, respectively. The reaction mixture was poured into ice-cold 2N aqueous NaOH. The alkaline mixture was extracted with CH₂Cl₂. The organic layer was separated and the solvent removed therefrom *in vacuo*. The residue was partitioned between 1N hydrochloric acid and ether. The ether layer was discarded. The acidic aqueous layer was made basic with NaOH and the now alkaline layer extracted with CH₂Cl₂. The organic extract was washed with brine and dried. 6.2 g of (±)-1-(2,2,2-trichloroethoxycarbonyl)-4-methylamino-6-bromo-1,2,2a,3,4,5-hexahydrobenz[c,d]indole, formed in the above reaction were obtained as a viscous oil. The oil was dissolved in 2.5 ml of THF and this solution added to a solution of 5 g of bis-imidazole carbonyl and 1.5 g of 98% formic acid in 100 ml of THF which had been stirred for 1 hour at room temperature under a nitrogen atmosphere. The reaction mixture was stirred for 3 hours at room temperature, at which time the solvent was removed *in vacuo*. The residue was partitioned between ether and saturated aqueous sodium bicarbonate. After standing overnight, a small amount of CH₂Cl₂ was added to dissolve residual solid. The alkaline aqueous phase was separated and the separated phase extracted with ether/CH₂Cl₂. The combined organic phases were washed with 1N hydrochloric acid and then with brine. The combined phases were dried and the solvent removed *in vacuo*. 7.48 g of N-formyl (±)-1-(2,2,2-trichloroethoxycarbonyl)-4-methylamino-6-bromo-1,2,2a,3,4,5-hexahydrobenz[c,d]indole formed in the above acylation were obtained as a glass. The glassy residue was dissolved in 220 ml of glacial acetic acid and 25 ml of water. 2.34 g of zinc dust were added and the mixture stirred under N₂ for 2 hours at room temperature. The suspension was filtered to remove unreacted zinc dust. The bulk of the acetic acid was then removed *in vacuo*. The oily residue was taken up in CH₂Cl₂ and saturated aqueous sodium bicarbonate added with care. A colorless zinc salt separated. The mixture was filtered through hyflo supercel. The organic layer was separated and the alkaline aqueous layer extracted with CH₂Cl₂. The combined CH₂Cl₂ extracts were washed with brine and then dried. Evaporation of the volatile constituents gave a glassy residue. The residue was dissolved in ethyl acetate. Crystals appeared. The bulk of the ethyl acetate was removed by decantation and toluene added. The mixture was chilled. Crystalline N-formyl (±)-4-methylamino-6-bromo-1,2,2a,3,4,5-hexahydrobenz[c,d]indole thus prepared was collected by filtration; weight = 2.15 g; m.p. = 177—179°C.

Analysis Calculated: C, 52.90; H, 5.12; N, 9.49; Br, 27.07

Found: C, 52.65; H, 5.31; N, 9.23; Br, 27.20

Evaporation of the filtrate to dryness yielded an oil which was purified by chromatography over silica gel using ethyl acetate as the eluant, yield 1.22 g of the oil as the epimer of the above crystalline product;

Analysis Calculated: C, 52.90; H, 5.12; N, 9.49; Br, 27.07

Found: C, 53.14; H, 5.25; N, 9.21; Br, 27.02

Total yield of both epimers = 78%.

Two grams of the crystalline epimer were dissolved in 100 ml of CH₂Cl₂. Eight grams of activated MnO₂ were added and the resulting suspension sonicated at 50—55 KHz under N₂ for 3 hours. The reaction mixture was filtered and the solvent evaporated to dryness *in vacuo*, leaving as residue 1.63 g of N-formyl (±)-4-methylamino-6-bromo-1,3,4,5-tetrahydrobenz[c,d]indole. The oily epimer, 1.15 g, was similarly oxidized to yield 1.02 g of N-formyl (±)-4-methylamino-6-bromo-1,3,4,5-tetrahydrobenz[c,d]indole. The two N-formyl products were combined, dissolved in hot ethyl acetate containing 5% methanol, and chromatographed over 50 g of silica gel using ethyl acetate as eluant. The product from the column was recrystallized affording 2.17 g (69%) of N-formyl (±)-4-methylamino-6-bromo-1,3,4,5-tetrahydrobenz[c,d]indole. m.p. 204—205°C.

Analysis Calculated: C, 53.26; H, 4.47; N, 9.56; Br, 27.26

Found: C, 53.00; H, 4.67; N, 9.28; Br, 27.06

A mixture of 0.70 g of cuprous cyanide, 1.00 g of N-formyl (±)-4-methylamino-6-bromo-1,3,4,5-tetrahydrobenz[c,d]indole, and 10 ml of N-methyl-2-pyrrolidone was heated at 200°C under N₂ for 4 hours.

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After cooling, the mixture was poured into water and CH_2Cl_2 . The mixture was filtered, the aqueous phase was washed with CH_2Cl_2 . The organic phase and CH_2Cl_2 washings were combined, washed with 1N HCl, then with NaCl solution, and dried over Na_2SO_4 . The solvent was removed *in vacuo* and the residue was chromatographed over silica gel using ethyl acetate as eluant. The fractions containing the desired product were combined and evaporated to yield 0.39 (48%) of N-formyl ($\pm$)-4-methylamino-6-cyano-1,3,4,5-tetrahydrobenz[c,d]indole. m.p. 205–207°C.

Analysis Calculated: C, 70.28; H, 5.48; N, 17.56;

Found: C, 70.56; H, 5.51; N, 17.30.

Example 1

Preparation of ($\pm$)-4-Di-n-propylamino-6-bromo-1,3,4,5-tetrahydrobenz[c,d]indole

A suspension of 0.44 g of N-chlorosuccinimide in 16 ml of toluene was chilled to about 0°C. Three tenths ml of dimethylsulfide were added. After 15 minutes, the reaction mixture was cooled in a dry ice-acetone bath to about -60°C. Six tenths grams of ($\pm$)-4-di-n-propylamino-6-bromo-1,2,2a,3,4,5-tetrahydrobenz[c,d]indole (prepared in Example A) and 2 ml of toluene were added over a 15 minute period. The reaction mixture was stirred at about -60°C for about two hours at which point 0.8 ml of triethylamine were added. The cooling bath was removed and stirring continued for about 2½ hours at ambient temperature. The reaction mixture was then poured into cold 1N aqueous sodium hydroxide and the now alkaline mixture extracted several times with toluene. The toluene extracts were combined, and the combined extracts washed with brine and then dried. The solvent was removed and the resulting residue chromatographed over 15 g of Florosil® using a 1:9 ethyl acetate/toluene solvent mixture as the eluant. Fractions containing the desired product were combined and rechromatographed over silica using the same eluant. Fractions containing the desired product were again combined and the solvent evaporated therefrom to leave a slightly greenish oil. This oil was dissolved in about 20 ml of pentane and filtered to remove a colorless precipitate. The pentane was then removed by evaporation *in vacuo*. A yellow green oil weighing 0.303 g. (51% yield) was obtained comprising ($\pm$)-4-di-n-propylamino-6-bromo-1,3,4,5-tetrahydrobenz[c,d]indole formed in the above oxidation. The product crystallized upon standing; m.p. = 72–73°C.

Analysis Calculated: C, 60.90; H, 6.91; N, 8.36; Br, 23.83

Found: C, 60.77; H, 6.87; N, 8.28; Br, 23.61

Example 2

Preparation of ($\pm$)-4-Di-n-propylamino-6-bromo-1,3,4,5-tetrahydrobenz[c,d]indole

A solution of 1 g of ($\pm$)-4-di-n-propylamino-6-bromo-1,2,2a,3,4,5-hexahydrobenz[c,d]indole (prepared in Example A) and 50 ml of hexane was prepared. Four grams of activated manganese dioxide were added and the resulting suspension sonicated 50–55 KHz under a nitrogen atmosphere for about one hour. TLC at this point indicated almost no starting material remaining. The reaction mixture was suction filtered, and the precipitate of manganese dioxide obtained was thoroughly washed with fresh hexane. The hexane was removed from the filtrate and the resulting residue chromatographed as before. Fractions containing the desired indole were combined and the solvent removed by evaporation. Recrystallization of the resulting residue from isooctane yielded 0.62 g (62% yield) of ($\pm$)-4-di-n-propylamino-6-bromo-1,3,4,5-tetrahydrobenz[c,d]indole melting at 73–74°C.

Example 3

Preparation of ($\pm$)-4-Di-n-propylamino-6-cyano-1,3,4,5-tetrahydrobenz[c,d]indole

A solution was prepared by dissolving 0.7 g of cuprous cyanide in 10 ml of N-methyl-2-pyrrolidone (previously purged with nitrogen). One gram of ($\pm$)-4-di-n-propylamino-6-bromo-1,3,4,5-tetrahydrobenz[c,d]indole was added to the cuprous cyanide solution. The solution was heated under a nitrogen atmosphere at 200°C for one hour. The reaction mixture was then cooled and the cooled mixture partitioned between ethyl acetate and dilute aqueous ammonium hydroxide. The alkaline layer was extracted several times with ethyl acetate. The ethyl acetate layers were combined and the combined layers washed successively with dilute aqueous ammonium hydroxide, dilute aqueous ethylenediamine and brine. The ethyl acetate layer was then dried and the solvent removed therefrom. The residual oil was dissolved in ether, and the ether solution washed twice with brine. The ether layer was separated and the ether removed therefrom *in vacuo*. The residue was next dissolved in ether, and the ether diluted with several volumes of petroleum ether. The supernate was decanted and the dark residual oil treated with a mixture of ether and petroleum ether again. The combined supernates were evaporated yielding a viscous orange oil as a residue. Chromatography of this residue over silica gel using 1:10 ethyl acetate/toluene as the eluant yielded fractions containing the desired ($\pm$)-4-di-n-propylamino-6-cyano-1,3,4,5-tetrahydrobenz[c,d]indole formed in the above reaction. Recrystallization of the solids thus obtained from a toluene/hexane solvent mixture yielded crystalline material melting at 132–133°C; yield = 44%.

Analysis Calculated: C, 76.83; H, 8.24; N, 14.83

Found: C, 76.56; H, 8.09; N, 14.86

Example 4

Preparation of ($\pm$)-4-Di-n-propylamino-6-carbamoyl-1,3,4,5-tetrahydrobenz[c,d]indole

About 1.5 g of powdered potassium hydroxide were suspended in 10 ml of distilled t-butanol and 0.3 ml of DMSO. Three tenths grams of ($\pm$)-4-di-n-propylamino-6-cyano-1,3,4,5-tetrahydrobenz[c,d]indole were added. The mixture was heated to reflux temperature under a nitrogen atmosphere for about 72 hours. At this point, TLC indicated only partial reaction. Reflux was continued for another 24 hours. The reaction mixture was then quenched by the addition of cold water and the aqueous mixture extracted with methylene dichloride. The organic layer was separated and the separated layer washed with brine and then dried. Evaporation of the solvent yielded a residue which was chromatographed over Florisil® using ethyl acetate containing increasing amounts of methanol, up to 10%. The starting material was eluted with 5% methanol/95% ethyl acetate, and the desired product, ($\pm$)-4-di-n-propylamino-6-carbamoyl-1,3,4,5-tetrahydrobenz[c,d]indole, was eluted with the 10% methanol/90% ethyl acetate. Fourteen hundredths grams of product were obtained and about 0.17 g of starting material. The recovered starting material was treated as above with powdered KOH in t-butanol and DMSO. The second hydration mixture was heated to reflux temperature for about four days. The reaction mixture was quenched as before, but TLC indicated that hydration reaction was still not complete. However, the 6-carbamoyl derivative obtained from the second run was about 0.5 g. Again, the recovered starting material was treated as before and refluxed with base for about one week and an additional quantity of the 6-carbamoyl derivative obtained. All the fractions containing ($\pm$)-4-di-n-propylamino-6-carbamoyl-1,3,4,5-tetrahydrobenz[c,d]indole were combined and the combined fractions chromatographed over Florisil using ethyl acetate followed by 1:1 methanol/ethyl acetate as the eluant. The starting material was eluted with the ethyl acetate. The ($\pm$)-4-Di-n-propylamino-6-carbamoyl-1,3,4,5-tetrahydrobenz[c,d]indole, thus isolated, melted at 163–5°C after successive recrystallizations from toluene/hexane and toluene. One hundred seventy-three thousands grams of the compound was obtained (54% yield).

Analysis Calculated: C, 72.21; H, 8.42; N, 14.03
Found: C, 72.23; H, 8.27; N, 13.57

Example 5

Preparation of ($\pm$)-4-Di-n-propylamino-6-nitro-1,3,4,5-hexahydrobenz[c,d]indole

A solution was prepared by dissolving 0.15 g of ($\pm$)-4-di-n-propylamino-6-nitro-1,2,2a,3,4,5-hexahydrobenz[c,d]indole (prepared in Example B) in 10 ml of methylene dichloride. Six tenths grams of manganese dioxide were added and the mixture sonicated at 50–55 KHz under a nitrogen atmosphere for about ten hours. The mixture was filtered through supercel and the supercel washed with fresh methylene dichloride. The solvent was removed from the filtrate, and the resulting residue was chromatographed over silica gel using toluene containing increasing amounts (5–10%) of ethyl acetate. Fractions containing ($\pm$)-4-di-n-propylamino-6-nitro-1,3,4,5-tetrahydrobenz[c,d]indole were combined to yield 0.102 g of that product. Recrystallization from a toluene/hexane solvent mixture gave 0.087 g (58% yield) of compound melting at 130–2°C.

Analysis Calculated: C, 67.75; H, 7.69; N, 13.94
Found: C, 67.74; H, 7.74; N, 13.81

Example 9

Preparation of ($\pm$)-4-Dimethylamino-6-cyano-1,3,4,5-tetrahydrobenz[c,d]indole

A mixture of 0.42 g of N-formyl ($\pm$)-4-methylamino-6-cyano-1,3,4,5-tetrahydrobenz[c,d]indole (prepared in Example J) and 12 ml of THF was treated with 1.9 ml of 2M borane-methyl sulfide complex in THF. After stirring the mixture for 2 hours at room temperature, the reaction was quenched with 1 ml of methanol, the solvents removed *in vacuo*, and the residue taken up in 2 ml of DMSO. To the solution was added a few drops of saturated NaHCO₃ solution. The mixture was heated on a steam bath for 10 minutes, water added, and the product extracted with CH₂Cl₂. The extracts were washed with NaCl solution, dried over Na₂SO₄, and the solvents removed *in vacuo*. The crystalline residue was chromatographed over Florisil® using ethyl acetate as eluant. The fractions containing product were evaporated, and the residue recrystallized from ethyl acetate/toluene to yield 0.24 g (60%) of ($\pm$)-4-dimethylamino-6-cyano-1,3,4,5-tetrahydrobenz[c,d]indole. m.p. 196–198°C.

Mass spectroscopy = 225 (parent peak)

Example 10

Preparation of ($\pm$)-4-Dimethylamino-6-carbamoyl-1,3,4,5-tetrahydrobenz[c,d]indole

To a suspension of 1.25 g of powdered KOH in dry t-butanol was added 0.25 g of 18-crown-6-ether followed by 0.20 g of ($\pm$)-4-dimethylamino-6-cyano-1,3,4,5-tetrahydrobenz[c,d]indole. The mixture was refluxed for 48 hours under N₂, then 0.3 ml of DMSO was added. The mixture was refluxed for another 72 hours. The mixture was then treated with 0.25 ml of water then refluxed another 24 hours. The reaction was quenched with water and the product extracted with CH₂Cl₂. The extract was washed with brine, then dried over Na₂SO₄. The solvent was removed, and the residue was chromatographed over Florisil using 5% methanol/95% ethyl acetate followed by 10% methanol/90% ethyl acetate. (The former solvent gave starting material and the latter solvent gave the product). The ($\pm$)-4-dimethylamino-6-carbamoyl-1,3,4,5-

tetrahydrobenz[c,d]indole thus isolated weighed 2 mg (1%); $R_f = 0.10$ (solvent system $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}/\text{concentrated NH}_4\text{OH}$, 45:5:1).

In the above procedure (Examples J and 9), use of ammonia in place of methylamine in the reaction with $(\pm)$ -1-(2,2,2-trichloroethoxycarbonyl)-4-oxo-6-bromo-1,2,2a,3,4,5-hexahydrobenz[c,d]indole yields $(\pm)$ -1-(2,2,2-trichloroethoxycarbonyl)-4-amino-6-bromo-1,2,2a,3,4,5-hexahydrobenz[c,d]indole. This primary amine can then be acylated with, for example, formic acid and bis-imidazolecarbonyl to yield an amide, which group is carried through the reductive (Zn and acetic acid) removal of the 1-(2,2,2-trichloroethoxycarbonyl) group to yield an indoline, oxidation with MnO_2 to yield an indole, replacement of the 6-bromo formation with cyanide to yield a 6-cyano group and finally hydrolysis (3N hydrochloric acid/THF) to yield $(\pm)$ -4-amino-6-cyano-1,3,4,5-tetrahydrobenz[c,d]indole. The primary amine group can then be reductively alkylated with an aldehyde (formaldehyde, acetaldehyde, propionaldehyde) and, for example, sodium cyanoborohydride or other suitable borohydride reducing agent, to yield the dialkylamine function. The cyano group can then be hydrated to the carboxamide to yield a $(\pm)$ -4-($\text{C}_1\text{—C}_3$ alkyl) amino-4-aminocarbonyl-1,3,4,5-tetrahydrobenz[c,d]indole.

The central serotonergic action of drugs according to IV above was demonstrated in two ways. The first method was to show inhibition of tritiated serotonin uptake according to the following protocol. (Weak inhibition of tritiated spiperone uptake was also determined.) Several $(\pm)$ -4-di-n-propylamino-6-substituted-1,3,4,5-tetrahydroindoles plus the corresponding drug from Bach-Kornfeld United States Patent 4,110,339 lacking a C-6 substituent were tested.

Brain tissue was obtained from 150–200 g male Wistar rats. The cerebral cortex was dissected out and then homogenized and centrifuged according to the method described by Nelson and co-workers, *Mol. Pharmacol.*, 14, 983–995 (1978), using preincubation in buffer without added monoamine oxidase inhibitor in order to eliminate endogenous serotonin. For receptor binding, each sample contained 300–400 μg of membrane protein and 10 μM pargyline in addition to the ^3H -ligand in 1 ml of 0.05 M Tris buffer, pH = 7.4. The assay of serotonin binding was done following the method of Bennett and Snyder, *Mol. Pharmacol.*, 12, 373–389 (1976), and that for tritiated spiperone according to Peroutka and Snyder, *Mol. Pharmacol.*, 16, 687–699 (1979). The samples were incubated for 15 minutes at 37° and were then filtered through GF/C glass fiber filter pads using a Brandel M-24 cell harvester modified for receptor binding. After two 5 ml rinses, the filter discs were put into scintillation vials and counted in 10 ml of Amersham PCS scintillation fluid. Nonspecific binding of ^3H -serotonin (^3H -5HT) was determined in the presence of 10^{-5}M serotonin and of ^3H -spiperone in the presence of 10^{-6}M LSD. Specific binding was calculated as the difference between total binding with no added nonradioactive compound and the nonspecific binding. IC_{50} values were determined where the IC_{50} is the amount of substance causing 50 percent inhibition of the specific binding using 10–12 concentrations in the range of 10^{-9} to 10^{-4}M . The concentrations of ^3H -ligands were: serotonin (Amersham, 11-Ci/mmol), 2–3 nM; LSD (Amersham, 1.8 Ci/mmol), 1.8–2.6 nM; spiperone (Amersham, 20 Ci/mmol), 0.6–0.7 nM.

The results obtained are set forth in Table 1.

TABLE 1

Receptor Binding

Name of Compound	^3H -Ligand- IC_{50}^*	
	^3H -5HT	^3H -SPIP
$(\pm)$ -4-di-n-propylamino-6-aminocarbonyl-1,3,4,5-tetrahydrobenz[c,d]indole	60	4980
$(\pm)$ -4-di-n-propylamino-6-cyano-1,3,5,6-tetrahydrobenz[c,d]indole	90	390
$(\pm)$ -4-di-n-propylamino-6-nitro-1,3,5,6-tetrahydrobenz[c,d]indole	100	400
$(\pm)$ -4-dimethylamino-1,3,4,5-tetrahydrobenz[c,d]indole	120	730

*Values are in nanomoles of inhibitor.

Secondly, as a measure of central serotonin agonist activity, the decrease of serotonin metabolites in brain was measured. Also the measure of dopamine agonist activity was indicated by changes in dopamine metabolites.

The following protocol was employed. 150–200 g Wistar rats were given 0.3 mg/kg subcutaneously of $(\pm)$ -4-di-n-propylamino-6-substituted-1,3,4,5-tetrahydrobenz[c,d]indole. Then, 60 minutes later each rat was decapitated and the hypothalamus and striatum were dissected out and extracted. The amounts of homovanillic acid (HVA) and 3,4-dihydroxyphenylacetic acid (DOPAC) in the striatum and of 5-hydroxyindoleacetic acid (5HIAA) in the hypothalamus were measured by high-performance liquid

chromatography, using electrochemical detection. Serum corticosteroids were also measured. Table 2 gives the results of this experiment. In the table, columns 1 and 2 give the substitution pattern in the compounds of formula IV, columns 3—5, the 5HT or dopamine metabolite concentrations, and column 6, the serum corticosteroids.

TABLE 2

X	R ¹ and R ²	5HIAA In Hypothalamus NMoles/G	Dopamine In Striatum, DOPAC	Metabolites NMoles/G HVA	Serum Corticosterone MCG/100 ML
CN	di-nPr	2.34 ± .07	4.25 ± .25*	2.27 ± .16*	47 ± 4*
NO ₂	dinPr	2.29 ± .03*	3.74 ± .11	2.02 ± .20*	49 ± 2*
CONH ₂	di-nPr	1.58 ± .03*	6.23 ± .56	4.12 ± .27	49 ± 2*
(control)		2.59 ± .11	5.58 ± .38	4.24 ± .27	7 ± 1

Compounds were injected at 0.3 mg/kg s.c. 1 hour before rats were killed.

*statistically significant

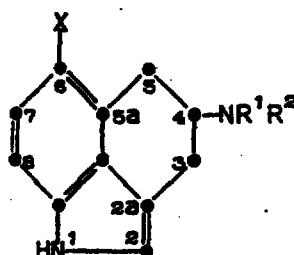
Four of the five compounds tested appear to have some dopamine agonist activity. However, the fifth compound appears to have no significant dopamine agonist activity. All but the cyano compound showed significant serotonin agonist activity at the same dose level.

Drugs which have central serotonin agonist activity are useful as antidepressants. The compounds of formula IV which have such central serotonergic activity to a marked degree with minimal agonist or antagonist actions toward NE or dopamine should be particularly useful in that their use would not be accompanied by side effects common to presently marketed antidepressants, particularly the antimuscarinic effect. Several of the marketed antidepressants are also monamine oxidase inhibitors, a nonspecific amine oxidase linked with metabolic degradation of both catecholamines and serotonin, which activity is also lacking in the drugs of formula IV.

The novel drugs of formula IV can be administered parenterally as an isotonic solution of a pharmaceutically acceptable salt. Preferably, however, the drugs are administered orally. For such route of administration, the drug is mixed with one or more pharmaceutical excipients and loaded into empty telescoping gelatin capsules or compressed into tablets, each tablet or capsule to contain a unit antidepressant dosage of the drug.

Claims for the Contracting States: BE CH DE FR GB IT LI LU NL SE

1. A compound of the formula



wherein

R¹ and R² are individually hydrogen, methyl, ethyl, n-propyl or allyl;
X is F, Cl, Br, CN, CONH₂, NH₂ or NO₂; or
a pharmaceutically-acceptable salt thereof.

2. A compound of claim 2 wherein X is Br, CN, CONH₂, or NO₂.

3. Any one of the following compounds of Claim 1 or a pharmaceutically-acceptable salt thereof:

- (±)-4-Di-n-propylamino-6-bromo-1,3,4,5-tetrahydrobenz[c,d]indole
- (±)-4-Di-n-propylamino-6-cyano-1,3,4,5-tetrahydrobenz[c,d]indole
- (±)-4-Di-n-propylamino-6-carbamoyl-1,3,4,5-tetrahydrobenz[c,d]indole
- (±)-4-Di-n-propylamino-6-nitro-1,3,4,5-tetrahydrobenz[c,d]indole
- (±)-4-Dimethylamino-6-cyano-1,3,4,5-tetrahydrobenz[c,d]indole
- (±)-4-Dimethylamino-6-carbamoyl-1,3,4,5-tetrahydrobenz[c,d]indole.



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chromatography, using electrochemical detection. Serum corticosteroids were also measured. Table 2 gives the results of this experiment. In the table, columns 1 and 2 give the substitution pattern in the compounds of formula IV, columns 3—5, the 5HT or dopamine metabolite concentrations, and column 6, the serum corticosteroids.

TABLE 2

	X	R ¹ and R ²	5HIAA In Hypothalamus NMoles/G	Dopamine In Striatum, DOPAC	Metabolites NMoles/G HVA	Serum Corticosterone MCG/100 ML
	CN	di-nPr	2.34 ± .07	4.25 ± .25*	2.27 ± .16*	47 ± 4*
	NO ₂	dinPr	2.29 ± .03*	3.74 ± .11	2.02 ± .20*	49 ± 2*
	CONH ₂	di-nPr	1.58 ± .03*	6.23 ± .56	4.12 ± .27	49 ± 2*
	(control)		2.59 ± .11	5.58 ± .38	4.24 ± .27	7 ± 1

Compounds were injected at 0.3 mg/kg s.c. 1 hour before rats were killed.

*statistically significant

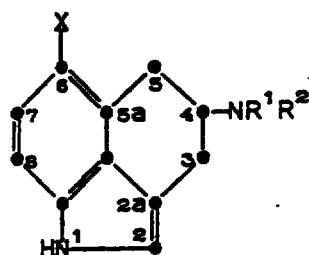
Four of the five compounds tested appear to have some dopamine agonist activity. However, the fifth compound appears to have no significant dopamine agonist activity. All but the cyano compound showed significant serotonin agonist activity at the same dose level.

Drugs which have central serotonin agonist activity are useful as antidepressants. The compounds of formula IV which have such central serotonergic activity to a marked degree with minimal agonist or antagonist actions toward NE or dopamine should be particularly useful in that their use would not be accompanied by side effects common to presently marketed antidepressants, particularly the antimuscarinic effect. Several of the marketed antidepressants are also monoamine oxidase inhibitors, a nonspecific amine oxidase linked with metabolic degradation of both catecholamines and serotonin, which activity is also lacking in the drugs of formula IV.

The novel drugs of formula IV can be administered parenterally as an isotonic solution of a pharmaceutically acceptable salt. Preferably, however, the drugs are administered orally. For such route of administration, the drug is mixed with one or more pharmaceutical excipients and loaded into empty telescoping gelatin capsules or compressed into tablets, each tablet or capsule to contain a unit antidepressant dosage of the drug.

Claims for the Contracting States: BE CH DE FR GB IT LI LU NL SE

1. A compound of the formula



wherein

R¹ and R² are individually hydrogen, methyl, ethyl, n-propyl or allyl;

X is F, Cl, Br, CN, CONH₂, NH₂ or NO₂; or

a pharmaceutically-acceptable salt thereof.

2. A compound of claim 2 wherein X is Br, CN, CONH₂, or NO₂.

3. Any one of the following compounds of Claim 1 or a pharmaceutically-acceptable salt thereof:

(±)-4-Di-n-propylamino-6-bromo-1,3,4,5-tetrahydrobenz[c,d]indole

(±)-4-Di-n-propylamino-6-cyano-1,3,4,5-tetrahydrobenz[c,d]indole

(±)-4-Di-n-propylamino-6-carbamoyl-1,3,4,5-tetrahydrobenz[c,d]indole

(±)-4-Di-n-propylamino-6-nitro-1,3,4,5-tetrahydrobenz[c,d]indole

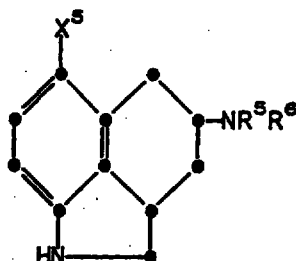
(±)-4-Dimethylamino-6-cyano-1,3,4,5-tetrahydrobenz[c,d]indole

(±)-4-Dimethylamino-6-carbamoyl-1,3,4,5-tetrahydrobenz[c,d]indole.

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4. A process for preparing a compound of formula IV, or a pharmaceutically-acceptable salt thereof, as claimed in any one of claims 1 to 3, which comprises:

a) reacting a compound of the formula

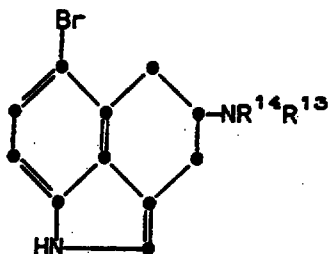


XVI f

wherein

X⁵ is F, Cl, Br or NO₂; R⁵ and R⁶ are individually methyl, ethyl, n-propyl or allyl, with an oxidizing agent to provide the compounds of formula IV wherein X is F, Cl, Br, or NO₂, and R¹ and R² are individually methyl, ethyl, n-propyl or allyl; or

b) reacting a compound of the formula

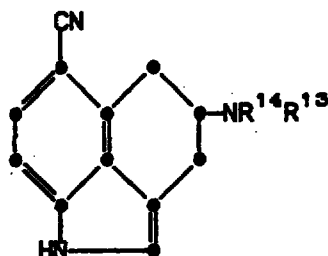


XXXII a

wherein R¹⁴ and R¹³ are individually ethyl, n-propyl or allyl, with cuprous cyanide or an alkali or alkaline earth cyanide and cuprous iodide of 1-methyl-2-pyrrolidone to provide the compounds of formula IV

wherein X is CN and R¹ and R² are individually ethyl, n-propyl or allyl; or

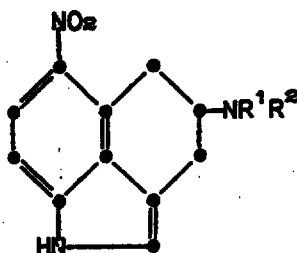
c) reacting a compound of the formula



XXXIII

wherein R¹⁴ and R¹³ are defined as before, with a hydroxide base in a C₁-C₄ alkanol to provide the compounds of formula IV wherein X is CONH₂ and R¹ and R² are individually ethyl, n-propyl or allyl; or

d) reacting a compound of the formula



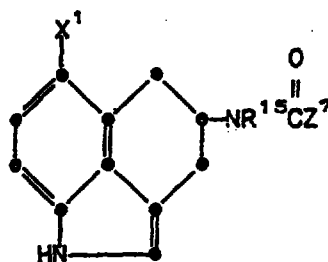
XLIII

wherein R¹ and R² are defined as before, with a reducing agent to provide the compounds of formula IV

wherein X is NH₂; or



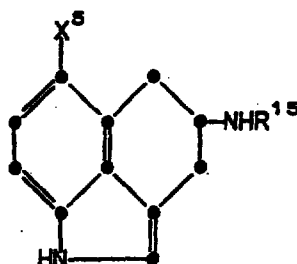
e) reacting a compound of the formula



XIVb

wherein X¹ is F or Cl, Z⁷ is C₁—C₃ alkyl, C₁—C₃ alkoxy, halo C₁—C₃ alkyl, or O-benzyl, and R¹⁵ is H or C₁—C₃ alkyl, with basic cleavage or when Z⁷ is O-benzyl with catalytic hydrogenation to provide the compounds of formula IV wherein X is F or Cl and R¹ is hydrogen and R² is C₁—C₃ alkyl or hydrogen; or

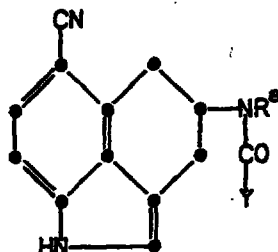
f) reacting the compound of the formula



XIVc

wherein X⁵ and R¹⁵ are defined as before, with an alkylating agent or by reductive amination to provide the compounds of formula IV where X is F, Cl, Br or NO₂, and R¹ and R² are individually methyl, ethyl, n-propyl, or allyl or one of R¹ and R² may be hydrogen; or

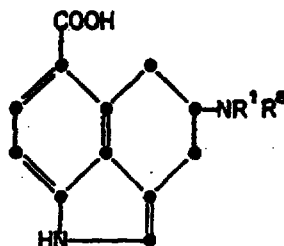
g) reacting a compound of the formula



LV

where R⁸ is hydrogen, methyl, ethyl or n-propyl and Y is hydrogen, methyl, ethyl or chloromethyl, with a borane complex to provide the compounds of formula IV where X is CN and R¹ and R² are individually hydrogen, methyl, ethyl or n-propyl; or

h) reacting a compound of the formula



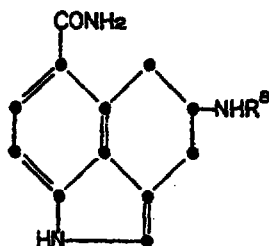
LVa

where R¹ and R⁸ are defined as before, with a peptide coupling agent and ammonia to provide the compounds of formula IV where X is CONH₂, R² is H, methyl, ethyl or n-propyl and R¹ is defined as before;

or

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i) reacting a compound of the formula



LVb

wherein R^8 is defined as before, with an R^1 halide or by reductive amination with a hydrogen catalyst to yield the compounds of formula IV where X is $CONH_2$, R^2 is H, methyl, ethyl or n-propyl and R^1 is defined as before;

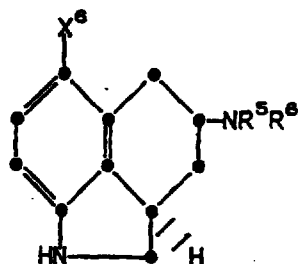
j) optionally salifying the compounds of formula IV.

5. A pharmaceutical formulation which comprises as an active ingredient a compound of formula IV, or a pharmaceutically-acceptable salt thereof, as claimed in any one of claims 1 to 3, associated with one or more pharmaceutically-acceptable carriers or excipients therefor.

6. A pharmaceutical formulation of claim 5 adapted for oral administration.

7. A compound of formula IV, or a pharmaceutically-acceptable salt thereof, as claimed in any one of claims 1 to 3, for use as a central serotonin agonist in the chemotherapy of warm-blooded animals.

8. A compound of the formula

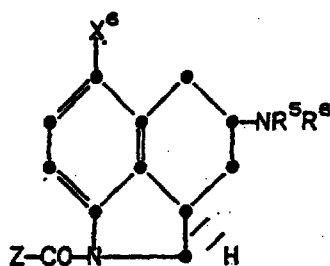


LX

wherein

R^5 and R^6 are individually methyl, ethyl, n-propyl or allyl;
 X^6 is NO_2 , Br, Cl, or F; or an acid addition salt thereof.

9. A compound of the formula

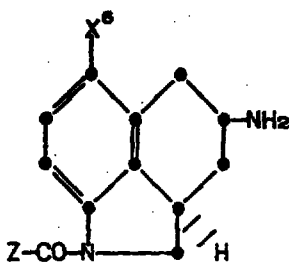


LXI

wherein

R^5 and R^6 are individually methyl, ethyl, n-propyl or allyl;
 X^6 is NO_2 , Br, Cl, or F; and
Z is a protecting group; or an acid addition salt thereof.

10. A compound of the formula



LXII

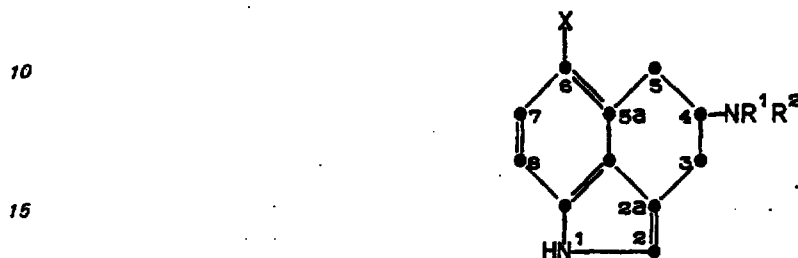
wherein



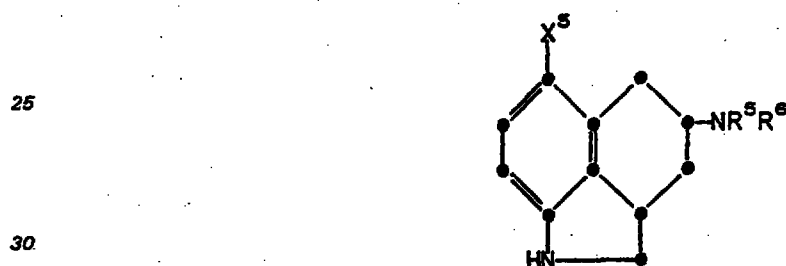
X⁵ is NO₂, Br, Cl, or F; and
Z is a protecting group; or an acid addition salt thereof.

5 Claims for the Contracting State: AT

1. A process for preparing a compound of the formula

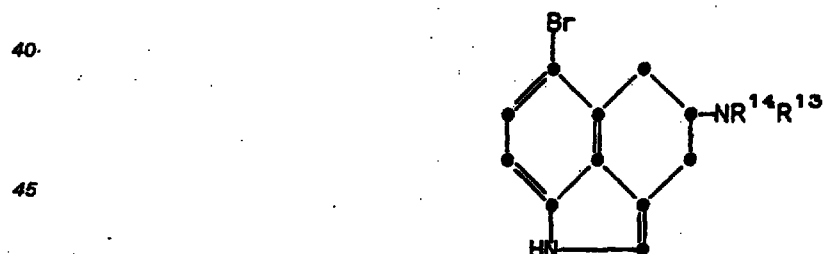


20 wherein R¹ and R² are individually hydrogen, methyl, ethyl, n-propyl or allyl, and X is F, Cl, Br, CN, CONH₂, NH₂ or NO₂; or a pharmaceutically-acceptable salt thereof; which is characterized by:
a) reacting a compound of the formula

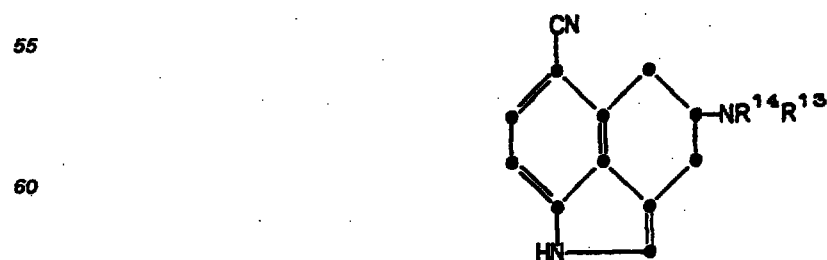


wherein

35 X⁵ is F, Cl, Br or NO₂;
R⁵ and R⁶ are individually methyl, ethyl, n-propyl or allyl, with an oxidizing agent to provide the compounds of formula IV wherein X is F, Cl, Br or NO₂, and
R¹ and R² are individually methyl, ethyl, n-propyl or allyl; or
b) reacting a compound of the formula



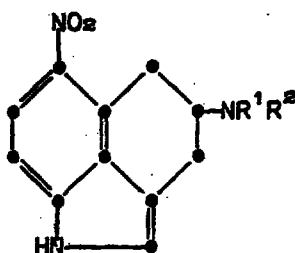
50 wherein R¹⁴ and R¹³ are individually ethyl, n-propyl or allyl, with cuprous cyanide or an alkali or alkaline earth cyanide and cuprous iodide in 1-methyl-2-pyrrolidone to provide the compounds of formula IV wherein X is CN and R¹ and R² are individually ethyl, n-propyl or allyl; or
c) reacting a compound of the formula



65 wherein R¹⁴ and R¹³ are defined as before, with a hydroxide base in a C₁—C₄ alkanol to provide the

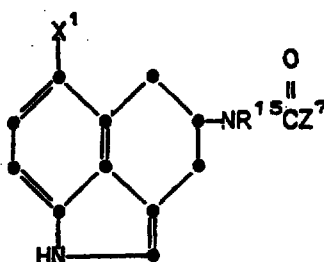
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compounds of formula IV wherein X is CONH₂ and R¹ and R² are individually ethyl, n-propyl or allyl; or
d) reacting a compound of the formula



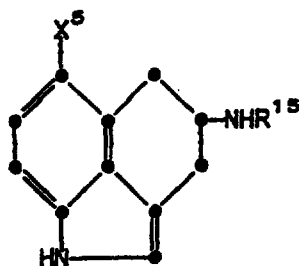
XLIII

wherein R¹ and R² are defined as before, with a reducing agent to provide the compounds of formula IV wherein X is NH₂; or
e) reacting a compound of the formula



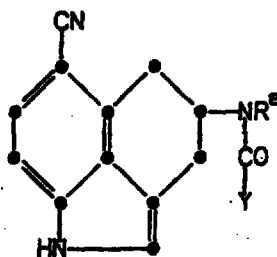
XIVb

wherein X¹ is F or Cl, Z⁷ is C₁—C₃ alkyl, C₁—C₃ alkoxy, halo C₁—C₃ alkyl, or O-benzyl, and R¹⁵ is H or C₁—C₃ alkyl, with basic cleavage or when Z⁷ is O-benzyl with catalytic hydrogenation to provide the compounds of formula IV wherein X is F or Cl and R¹ is hydrogen and R² is C₁—C₃ alkyl or hydrogen; or
f) reacting a compound of the formula



XIVc

wherein X⁵ and R¹⁵ are defined as before, with an alkylating agent or by reductive amination to provide the compounds of formula IV where X is F, Cl, Br or NO₂, and R¹ and R² are individually methyl, ethyl, n-propyl, or allyl or one of R¹ and R² may be hydrogen; or
g) reacting a compound of the formula

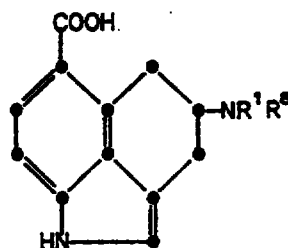


LV

where R⁶ is hydrogen, methyl, ethyl or n-propyl and Y is hydrogen, methyl, ethyl or chloromethyl, with a borane complex to provide the compounds of formula IV where X is CN and R¹ and R² are individually
hydrogen, methyl, ethyl or n-propyl; or



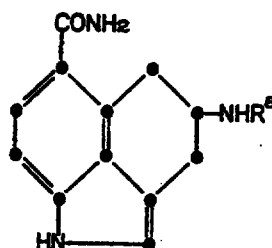
h) reacting a compound of the formula



LVa

where R^1 and R^2 are defined as before, with a peptide coupling agent and ammonia to provide the compounds of formula IV where X is CONH_2 , R^2 is H, methyl, ethyl or n-propyl and R^1 is defined as before; or

i) reacting a compound of the formula



LVb

wherein R^2 is defined as before, with an R^1 halide or by reductive amination with a hydrogen catalyst to yield the compounds of formula IV where X is CONH_2 , R^2 is H, methyl, ethyl or n-propyl and R^1 is defined as before;

j) optionally salifying the compounds of formula IV.

2. The process of claim 1(a) for preparing ($\pm$)-4-di-n-propylamino-6-bromo-1,3,4,5-tetrahydrobenz[c,d]indole which is characterized by reacting ($\pm$)-4-di-n-propylamino-6-bromo-1,2,2a,3,4,5-hexahydrobenz[c,d]indole with N-chlorosuccinimide, dimethylsulfide and triethylamine.

3. The process of claim 1(a) for preparing ($\pm$)-4-di-n-propylamino-6-bromo-1,3,4,5[c,d]indole which is characterized by reacting ($\pm$)-4-di-n-propylamino-6-bromo-1,2,2a,3,4,5-hexahydrobenz[c,d]indole with manganese dioxide.

4. The process of claim 1(b) for preparing ($\pm$)-4-di-n-propylamino-6-cyano-1,3,4,5-tetrahydrobenz[c,d]indole which is characterized by reacting ($\pm$)-4-di-n-propylamino-6-bromo-1,3,4,5-tetrahydrobenz[c,d]indole with cuprous cyanide.

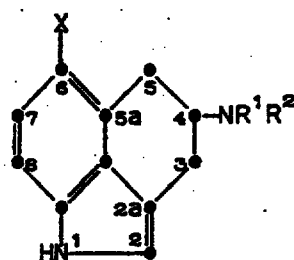
5. The process of claim 1(c) for preparing ($\pm$)-4-di-n-propylamino-6-carbamoyl-1,3,4,5-tetrahydrobenz[c,d]indole which is characterized by reacting ($\pm$)-4-di-n-propylamino-6-cyano-1,3,4,5-tetrahydrobenz[c,d]indole with potassium hydroxide in t-butanol.

6. The process of claim 1(a) for preparing ($\pm$)-4-di-n-propylamino-6-nitro-1,3,4,5-tetrahydrobenz[c,d]indole which is characterized by reacting ($\pm$)-4-di-n-propylamino-6-nitro-1,2,2a,3,4,5-hexahydrobenz[c,d]indole with manganese dioxide.

7. The process of claim 1(c) for preparing ($\pm$)-4-dimethylamino-6-carbamoyl-1,3,4,5-tetrahydrobenz[c,d]indole which is characterized by reacting ($\pm$)-4-dimethylamino-6-cyano-1,3,4,5-tetrahydrobenz[c,d]indole with potassium hydroxide in t-butanol.

8. The process of claim 1(g) for preparing ($\pm$)-4-dimethylamino-6-cyano-1,3,4,5-tetrahydrobenz[c,d]indole which is characterized by reacting N-formyl ($\pm$)-4-dimethylamino-6-cyano-1,3,4,5-tetrahydrobenz[c,d]indole with $\text{BH}_3\text{-(CH}_3)_2\text{S}$ in THF.

1. Verbindung der Formel (IV)



IV

worin R¹ und R² jeweils unabhängig Wasserstoff, Methyl, Ethyl, n-Propyl oder Allyl sind, und X für F, Cl, Br, CN, CONH₂, NH₂ oder NO₂ steht, oder ein pharmazeutisch annehmbares Salz hiervon.

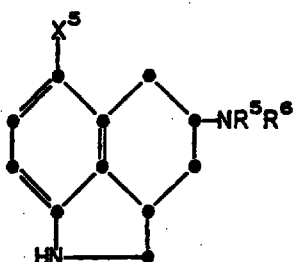
2. Verbindung nach Anspruch 1, dadurch gekennzeichnet, daß X für Br, CN, CONH₂ oder NO₂ steht.

3. Irgendeine der folgenden Verbindungen nach Anspruch 1 oder ein pharmazeutische annehmbares Salz hiervon, nämlich:

- (±)-4-Di-n-propylamino-6-brom-1,3,4,5-tetrahydrobenz[c,d]indol,
- (±)-4-Di-n-propylamino-6-cyano-1,3,4,5-tetrahydrobenz[c,d]indol,
- (±)-4-Di-n-propylamino-6-carbamoyl-1,3,4,5-tetrahydrobenz[c,d]indol,
- (±)-4-Di-n-propylamino-6-nitro-1,3,4,5-tetrahydrobenz[c,d]indol,
- (±)-4-Dimethylamino-6-cyano-1,3,4,5-tetrahydrobenz[c,d]indol oder
- (±)-4-Dimethylamino-6-carbamoyl-1,3,4,5-tetrahydrobenz[c,d]indol.

4. Verfahren zur Herstellung einer Verbindung der Formel (IV) oder eines pharmazeutisch annehmbaren Salzes hiervon nach einem der Ansprüche 1 bis 3, dadurch gekennzeichnet, daß

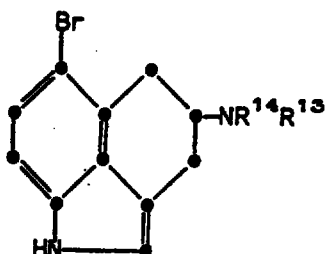
(a) eine Verbindung der Formel (XVI f)



XVI f

worin X⁵ für F, Cl, Br oder NO₂ steht und R⁵ sowie R⁶ jeweils unabhängig Methyl, Ethyl, n-Propyl oder Allyl sind, mit einem Oxidationsmittel zu Verbindungen der Formel (IV), worin X für F, Cl, Br oder NO₂ steht und R¹ sowie R² unabhängig Methyl, Ethyl, n-Propyl oder Allyl sind, oxidiert wird, oder

(b) eine Verbindung der Formel (XXXII a)

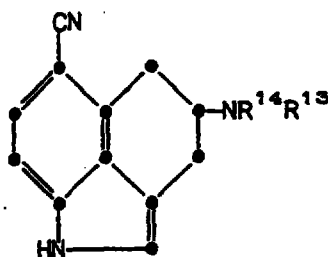


XXXII a

worin R¹⁴ und R¹³ unabhängig Ethyl, n-Propyl oder Allyl bedeuten, mit Kupfer (I) cyanid oder einem Alkalimetallcyanid oder Erdalkalimetallcyanid und Kupfer(I)iodid in 1-Methyl-2-pyrrolidon zu Verbindungen der Formel (IV), worin X für CN steht und R¹ sowie R² jeweils unabhängig Ethyl, n-Propyl oder allyl bedeuten, umgesetzt wird, oder

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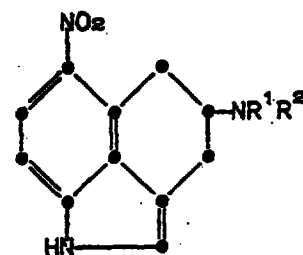
(c) eine Verbindung der Formel (XXXIII)



XXXIII

15 worin R¹⁴ und R¹³ wie oben definiert sind, einer Hydroxidbase in einem C₁—C₄-Alkanol zu Verbindungen der Formel (IV), worin X für CONH₂ steht und R¹ sowie R² unabhängig Ethyl, n-Propyl oder allyl bedeuten, umgesetzt wird, oder

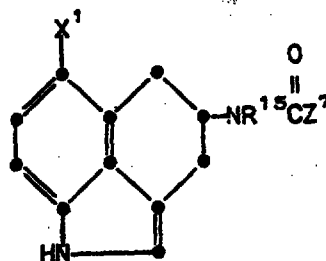
(d) eine Verbindung der Formel (XLI)



XLI

30 worin R¹ und R² wie oben definiert sind, mit einem Reduktionsmittel zu Verbindungen der Formel (IV), worin X für NH₂ steht, umgesetzt wird, oder

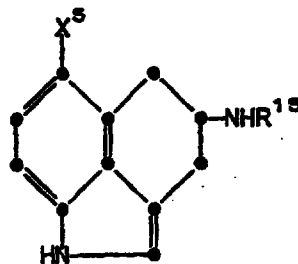
(e) eine Verbindung der Formel (XIVb)



XIVb

45 worin R¹ für F oder Cl steht, Z⁷ C₁—C₃-Alkyl, C₁—C₃-Alkoxy, Halogen-C₁—C₃-Alkyl oder O-Benzyl bedeutet und R¹⁵ für H oder C₁—C₃-Alkyl steht, durch eine basische Spaltung oder, falls Z⁷ für O-Benzyl steht, durch katalytische Hydrierung zu Verbindungen der Formel (IV), worin X für F oder Cl steht, R¹ Wasserstoff ist und R² C₁—C₃-Alkyl oder Wasserstoff bedeutet, umgesetzt wird, oder

(f) eine Verbindung der Formel (XIVc)

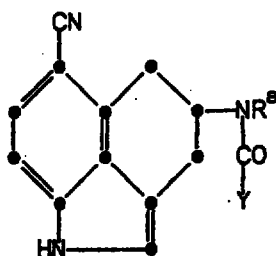


XIVc

65 worin X⁵ und R¹⁵ wie oben definiert sind, mit einem Alkylierungsmittel oder durch reduktive Aminierung zu Verbindungen der Formel (IV), worin X für F, Cl, Br oder NO₂ steht und R¹ sowie R² unabhängig Methyl,

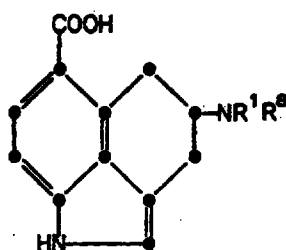
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Ethyl, N-Propyl oder Allyl bedeuten oder einer der Substituenten R^1 und R^2 auch Wasserstoff sein kann, umgesetzt wird, oder
(g) eine Verbindung der Formel (LV)



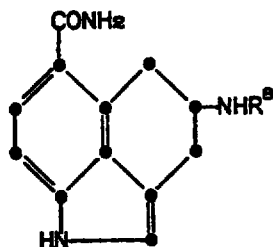
LV

worin R^8 Wasserstoff, Methyl, Ethyl oder n-Propyl bedeutet und Y Wasserstoff, Methyl, Ethyl oder Chlormethyl ist, mit einem Borankomplex zu Verbindungen der Formel (IV), worin X für CN steht und R^1 sowie R^2 unabhängig Wasserstoff, Methyl, Ethyl oder n-Propyl bedeuten, umgesetzt wird, oder
(h) eine Verbindung der Formel (LVa)



LVa

worin R^1 und R^8 wie oben definiert sind, mit einem Peptidkupplungsmittel und mit Ammoniak zu Verbindungen der Formel (IV), worin X für CONH_2 steht, R^2 Wasserstoff, Methyl, Ethyl oder n-Propyl bedeutet und R^1 wie oben definiert ist, umgesetzt wird, oder
(i) eine Verbindung der Formel (LVb)



LVb

worin R^8 wie oben definiert ist, mit einem R^1 -Halogenid oder durch reduktive Aminierung mit einem Wasserstoffkatalysator zu Verbindungen der Formel (IV), worin X für CONH_2 steht, R^2 Wasserstoff, Methyl, Ethyl oder n-Propyl bedeutet und R^1 wie oben definiert ist, umgesetzt wird, und
(j) die erhaltenen Verbindungen der Formel (IV) gegebenenfalls in Salze überführt werden.

5. Pharmazeutische Formulierung, dadurch gekennzeichnet, daß sie eine Verbindung der Formel (IV) oder ein pharmazeutisch annehmbares Salz hiervon nach einem der Ansprüche 1 bis 3 als Wirkstoff in Verbindung mit einem oder mehreren pharmazeutisch annehmbaren Trägern oder Hilfsstoffen hierfür enthält.

6. Pharmazeutische Formulierung nach Anspruch 5 in einer zur oralen Verabreichung geeigneten Form.

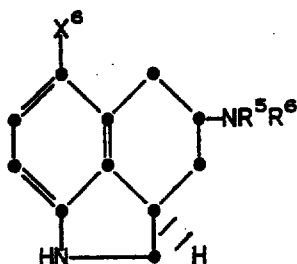
7. Verbindung der Formel (IV) oder ein pharmazeutisch annehmbares Salz hiervon nach einem der

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Ansprüche 1 bis 3 zur Verwendung als zentraler Serotoninagonist bei der chemotherapeutischen Behandlung warmblütiger Tiere.

8. Verbindung der Formel (LX)

5



LX

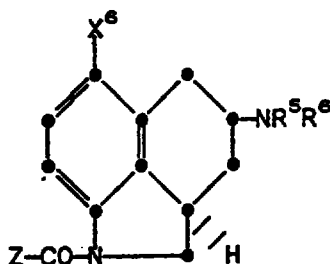
10

worin R⁵ und R⁶ jeweils unabhängig Methyl, Ethyl, n-Propyl oder Allyl bedeuten und X⁶ für NO₂, Br, Cl oder F steht, oder ein Säureadditionssalz hiervon.

15

9. Verbindung der Formel (LXI)

20



LXI

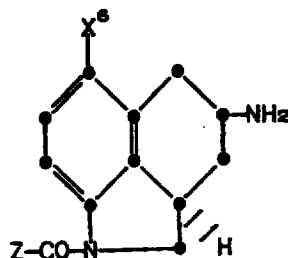
25

worin R⁵ und R⁶ jeweils unabhängig Methyl, Ethyl, n-Propyl oder Allyl sind, X⁶ für NO₂, Br, Cl oder F steht, und Z eine Schutzgruppe ist, oder ein Säureadditionssalz hiervon.

30

10. Verbindung der Formel (LXII)

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LXII

40

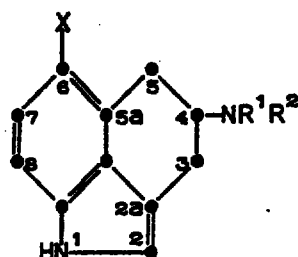
worin X⁶ für NO₂, Br, Cl oder F steht und Z eine Schutzgruppe ist, oder ein Säureadditionssalz hiervon.

45

50 Patentansprüche für den Vertragsstaat: AT

1. Verfahren zur Herstellung einer Verbindung der Formel (IV)

55



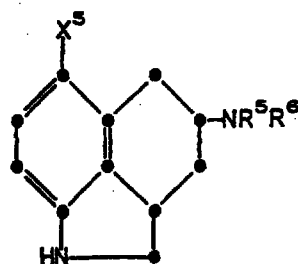
IV

60

65 worin R¹ und R² jeweils unabhängig Wasserstoff, Methyl, Ethyl, n-Propyl oder Allyl sind, und

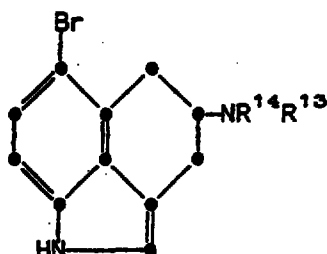


X für F, Cl, Br, CN, CONH₂, NH₂ oder NO₂ steht,
oder eines pharmazeutisch annehmbaren Salzes hiervon, dadurch gekennzeichnet, daß
(a) eine Verbindung der Formel (XVIf)



XVIf

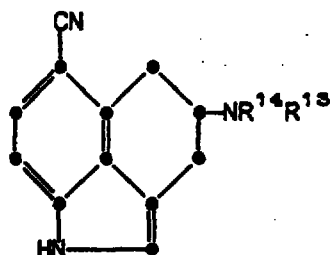
worin X⁵ für F, Cl, Br oder NO₂ steht und R⁵ sowie R⁶ jeweils unabhängig Methyl, Ethyl, n-Propyl oder Allyl sind, mit einem Oxidationsmittel zu Verbindungen der Formel (IV), worin X für F, Cl, Br oder NO₂ steht und R¹ sowie R² unabhängig Methyl, Ethyl, n-Propyl oder Allyl sind, oxidiert wird, oder
(b) eine Verbindung der Formel (XXXIIa)



XXXIIa

worin R¹⁴ und R¹³ unabhängig Ethyl, n-Propyl oder Allyl bedeuten, mit Kupfer (I) cyanid oder einem Alkalimetallcyanid oder Erdalkalimetallcyanid und Kupfer(I)iodid in 1-Methyl-2-pyrrolidon zu Verbindungen der Formel (IV), worin X für CN steht und R¹ sowie R² jeweils unabhängig Ethyl, n-Propyl oder allyl bedeuten, umgesetzt wird, oder

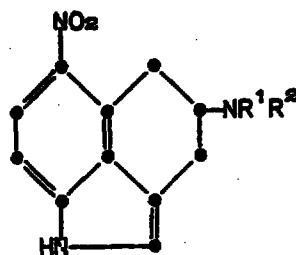
(c) eine Verbindung der Formel (XXXIII)



XXXIII

worin R¹⁴ und R¹³ wie oben definiert sind, einer Hydroxidbase in einem C₁-C₄-Alkanol zu Verbindungen der Formel (IV), worin X für CONH₂ steht und R¹ sowie R² unabhängig Ethyl, n-Propyl oder allyl bedeuten, umgesetzt wird, oder

(d) eine Verbindung der Formel (XLIIf)

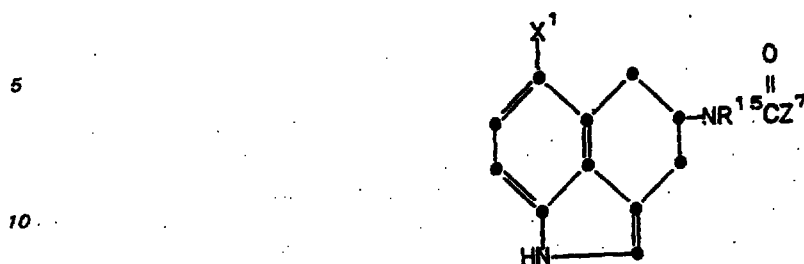


XLIIf

worin R¹ und R² wie oben definiert sind, mit einem Reduktionsmittel zu Verbindungen der Formel (IV), worin X für NH₂ steht, umgesetzt wird, oder

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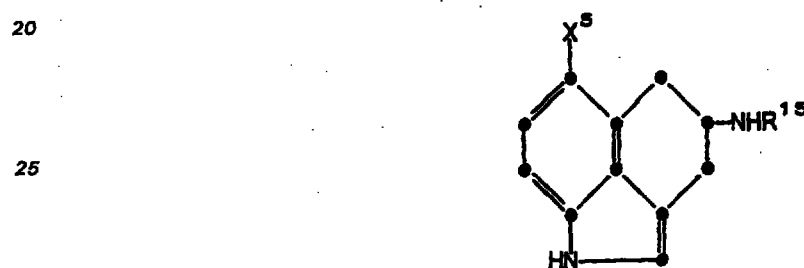
(e) eine Verbindung der Formel (XIVb)



XIVb

15 worin R¹ für F oder Cl steht, Z⁷ C₁—C₃-Alkyl, C₁—C₃-Alkoxy, Halogen-C₁—C₃-Alkyl oder O-Benzyl bedeutet und R¹⁵ für H oder C₁—C₃-Alkyl steht, durch eine basische Spaltung oder, falls Z⁷ für O-Benzyl steht, durch katalytische Hydrierung zu Verbindungen der Formel (IV), worin X für F oder Cl steht, R¹ Wasserstoff ist und R² C₁—C₃-Alkyl oder Wasserstoff bedeutet, ungesetzt wird, oder

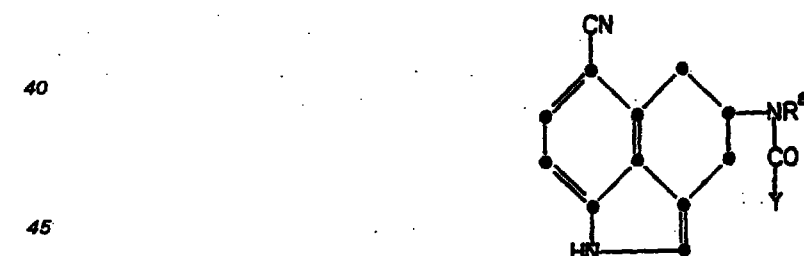
(f) eine Verbindung der Formel (XIVc)



XIVc

30 worin X⁵ und R¹⁵ wie oben definiert sind, mit einem Alkylierungsmittel oder durch reduktive Aminierung zu Verbindungen der Formel (IV), worin X für F, Cl, Br oder NO₂ steht und R¹ sowie R² unabhängig Methyl, Ethyl, N-Propyl oder Allyl bedeuten oder einer der Substituenten R¹ und R² auch Wasserstoff sein kann, umgesetzt wird, oder

35 (g) eine Verbindung der Formel (LV)



LV

50 worin R⁸ Wasserstoff, Methyl, Ethyl oder n-Propyl bedeutet und Y Wasserstoff, Methyl, Ethyl oder Chlormethyl ist, mit einem Borankomplex zu Verbindungen der Formel (IV), worin X für CN steht und R¹ sowie R² unabhängig Wasserstoff, Methyl, Ethyl oder n-Propyl bedeuten, umgesetzt wird, oder

(h) eine Verbindung der Formel (LVa)

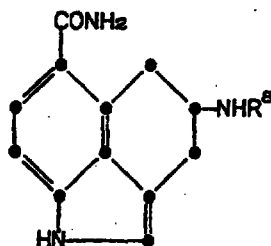


LVa

65 worin R¹ und R⁸ wie oben definiert sind, mit einem Peptidkupplungsmittel und mit Ammoniak zu.



Verbindungen der Formel (IV), worin X für CONH₂ steht, R² Wasserstoff, Methyl, Ethyl oder n-Propyl bedeutet und R¹ wie oben definiert ist, umgesetzt wird, oder
(ii) eine Verbindung der Formel (LVb)



LVb

worin R⁸ wie oben definiert ist, mit einem R¹-Halogenid oder durch reduktive Aminierung mit einem Wasserstoffkatalysator zu Verbindungen der Formel (IV), worin X für CONH₂ steht, R² Wasserstoff, Methyl, Ethyl oder n-Propyl bedeutet und R¹ wie oben definiert ist, umgesetzt wird, und

(j) die erhaltenen Verbindungen der Formel (IV) gegebenenfalls in Salze überführt werden.

2. Verfahren nach Anspruch 1 (a) zur Herstellung von (±)-4-Di-n-propylamino-6-brom-1,3,4,5-tetrahydrobenz[c,d]indol, dadurch gekennzeichnet, daß (±)-4-Di-n-propylamino-6-brom-1,2,2a,3,4,5-hexahydrobenz[c,d]indol mit -Chlorsuccinimid, Dimethylsulfid und Triethylamin umgesetzt wird.

3. Verfahren nach Anspruch 1 (a) zur Herstellung von (±)-4-Di-n-propylamino-6-brom-1,3,4,5-tetrahydrobenz[c,d]indol, dadurch gekennzeichnet, daß (±)-4-Di-n-propylamino-6-brom-1,2,2a,3,4,5-hexahydrobenz[c,d]indol mit Mangandioxid umgesetzt wird.

4. Verfahren nach Anspruch 1 (b) zur Herstellung von (±)-4-Di-n-propylamino-6-cyano-1,3,4,5-tetrahydrobenz[c,d]indol, dadurch gekennzeichnet, daß (±)-4-Di-n-propylamino-6-brom-1,3,4,5-tetrahydrobenz[c,d]indol mit Kupfer(I)-cyanid umgesetzt wird.

5. Verfahren nach Anspruch 1 (c) zur Herstellung von (±)-4-Di-n-propylamino-6-carbamoyl-1,3,4,5-tetrahydrobenz[c,d]indol, dadurch gekennzeichnet, daß (±)-4-Di-n-propylamino-6-cyano-1,3,4,5-tetrahydrobenz[c,d]indol mit Kaliumhydroxid in t-Butanol umgesetzt wird.

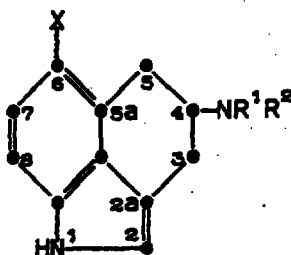
6. Verfahren nach Anspruch 1 (a) zur Herstellung von (±)-4-Di-n-propylamino-6-nitro-1,3,4,5-tetrahydrobenz[c,d]indol, dadurch gekennzeichnet, daß (±)-4-Di-n-propylamino-6-nitro-1,2,2a,3,4,5-hexahydrobenz[c,d]indol mit Mangandioxid umgesetzt wird.

7. Verfahren nach Anspruch 1 (c) zur Herstellung von (±)-4-Dimethylamino-6-carbamoyl-1,3,4,5-tetrahydrobenz[c,d]indol, dadurch gekennzeichnet, daß (±)-4-Dimethylamino-6-cyano-1,3,4,5-tetrahydrobenz[c,d]indol mit Kaliumhydroxid in t-Butanol umgesetzt wird.

8. Verfahren nach Anspruch 1 (g) zur Herstellung von (±)-4-Dimethylamino-6-cyano-1,3,4,5-tetrahydrobenz[c,d]indol, dadurch gekennzeichnet, daß N-Formyl-(±)-4-methylamino-6-cyano-1,3,4,5-tetrahydrobenz[c,d]indol mit BH₃-(CH₃)₂S in THF umgesetzt wird.

Revendications pour les Etats contractants: BE CH DE FR GB IT LI LU NL SE

1. Composé de formule:



IV

dans laquelle

R¹ et R² représentent chacun individuellement un atome d'hydrogène, un groupe méthyle, un groupe éthyle, un groupe n-propyle ou un groupe allyle;

X représente F, Cl, Br, CN, CONH₂, NH₂ ou NO₂; ou
un sel pharmaceutiquement acceptable de ce composé.

2. Composé selon la revendication 1, dans lequel X représente BR, CN, CONH₂ ou NO₂.

3. L'un ou l'autre des composés ciaprès de la revendication 1 ou un de leurs sels pharmaceutiquement acceptables:

le (±)-4-di-n-propylamino-6-bromo-1,3,4,5-tétrahydrobenz[c,d]indole,

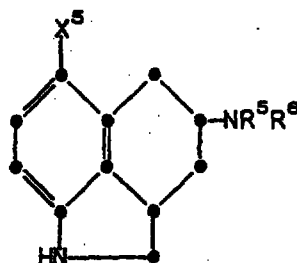
le (±)-4-di-n-propylamino-6-cyano-1,3,4,5-tétrahydrobenz[c,d]indole,

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le (±)-4-di-n-propylamino-6-carbamoyl-1,3,4,5-tétrahydrobenz[c,d]indole,
le (±)-4-di-n-propylamino-6-nitro-1,3,4,5-tétrahydrobenz[c,d]indole,
le (±)-4-diméthylamino-6-cyano-1,3,4,5-tétrahydrobenz[c,d]indole,
le (±)-4-diméthylamino-6-carbamoyl-1,3,4,5-tétrahydrobenz[c,d]indole.

4. Procédé de préparation d'un composé de formule IV, ou d'un de ses sels pharmaceutiquement acceptables selon l'une quelconque des revendications 1 à 3, caractérisé e ce qu'il comprend les étapes qui consistent à:

a) faire réagir un composé de formule:



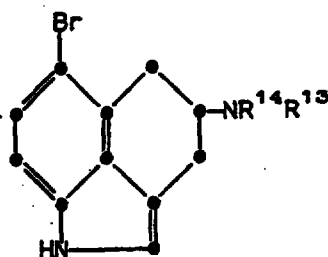
XVI f

dans laquelle

X⁵ représente F, Cl, Br ou NO₂;

R³ et R⁴ représentent chacun individuellement un groupe méthyle, un groupe éthyle, un groupe n-propyle ou un groupe allyle, avec un agent oxydant pour obtenir les composés de formule IV dans laquelle X représente F, Cl, Br ou NO₂, tandis que R¹ et R² représentent chacun individuellement un groupe méthyle, un groupe éthyle, un groupe n-propyle ou un groupe allyle; ou

b) faire réagir un composé de formule:

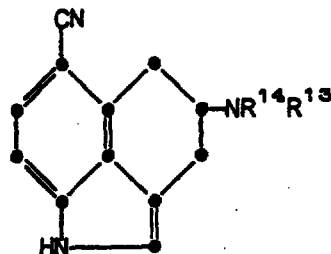


XXXII a

dans laquelle

R¹⁴ et R¹³ représentent chacun individuellement un groupe éthyle, un groupe n-propyle ou un groupe allyle, avec du cyanure cuivreux ou un cyanure d'un métal alcalin ou d'un métal alcalinoterreux et de l'iodure cuivreux dans de la 1-méthyl-2-pyrrolidone pour obtenir les composés de formule IV dans laquelle X représente CN, tandis que R¹ et R² représentent chacun individuellement un groupe éthyle, un groupe n-propyle ou un groupe allyl; ou

c) faire réagir un composé de formule:



XXXIII

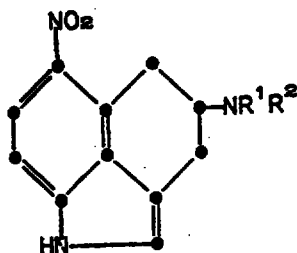
dans laquelle

R¹⁴ et R¹³ ont les significations définies précédemment, avec une base hydroxyde dans un alcool en

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C₁—C₄ pour obtenir les composés de formule IV dans laquelle X représente CONH₂, tandis que R¹ et R² représentent chacun individuellement un groupe éthyle, un groupe n-propyle ou un groupe allyle; ou
d) faire réagir un composé de formule:

5



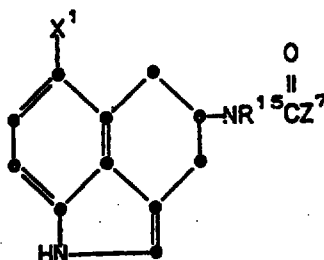
XLI II

10

15

dans laquelle
R¹ et R² ont les significations définies précédemment, avec un agent réducteur pour obtenir les composés de formule IV dans laquelle X représente NH₂; ou
e) faire réagir un composé de formule:

20



XIVb

25

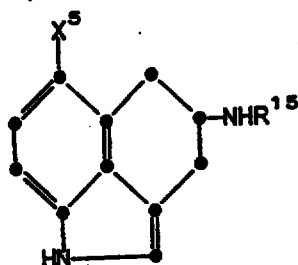
30

dans laquelle
X¹ représente F ou Cl, Z⁷ représente un groupe alkyle en C₁—C₃, un groupe alcoxy en C₁—C₃, un groupe halo-alkyle en C₁—C₃ ou un groupe O-benzyle et R¹⁵ représente H ou un groupe alkyle en C₁—C₃, avec clivage basique ou lorsque Z⁷ représente un groupe O-benzyle, avec hydrogénation catalytique pour obtenir les composés de formule IV dans laquelle X représente F ou Cl et R¹ représente un atome d'hydrogène, tandis que R² représente un groupe alkyle en C₁—C₃ ou un atome d'hydrogène; ou

35

f) faire réagir un composé de formule:

40



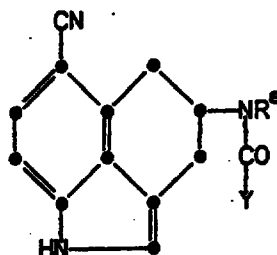
XIVc

45

50

dans laquelle
X⁵ et R¹⁵ ont les significations définies précédemment, avec un agent d'alkylation ou par amination réductrice pour obtenir les composés de formule IV dans laquelle X représente F, Cl, Br ou NO₂, tandis que R¹ et R² représentent chacun individuellement un groupe méthyle, un groupe éthyle, un groupe n-propyle ou un groupe allyle ou encore und es radicaux R¹ et R² peut être un atome d'hydrogène; ou
g) faire réagir un composé de formule:

55



LV

60

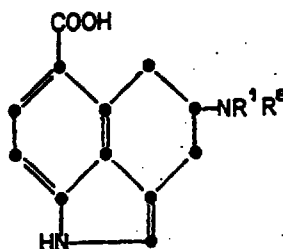
65

dans laquelle
R⁶ représente un atome d'hydrogène, un groupe méthyle, un groupe éthyle ou un groupe n-propyle, et



Y représente un atome d'hydrogène, un groupe méthyle, un groupe éthyle ou un groupe chlorométhyle, avec un complexe de borane pour obtenir les composés de formule IV dans laquelle X représente CN, tandis que R¹ et R² représentent chacun individuellement un atome d'hydrogène, un groupe méthyle, un groupe éthyle ou un groupe n-propyle; ou

h) faire réagir un composé de formule:

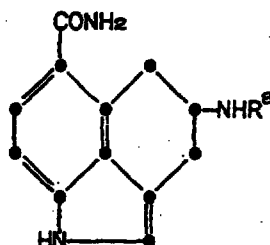


LVa

dans laquelle

R¹ et R² ont les significations définies précédemment, avec un agent de couplage de peptide et de l'ammoniac pour obtenir les composés de formule IV dans laquelle X représente CONH₂, R² représente H, un groupe méthyle, un groupe éthyle ou un groupe n-propyle et R¹ a la signification définie précédemment; ou

i) faire réagir un composé de formule:



LVb

dans laquelle

R³ a la signification définie précédemment, avec un halogénure R¹ ou par amination réductrice avec un catalyseur d'hydrogène pour obtenir les composés de formule IV dans laquelle X représente CONH₂, R² représente H, un groupe méthyle, un groupe éthyle ou un groupe n-propyle, et R¹ a la signification définie précédemment;

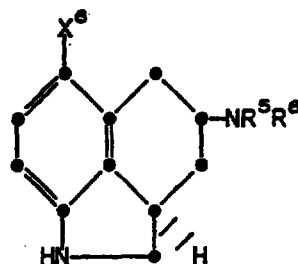
j) facultativement salifier les composés de formule IV.

5. Formulation pharmaceutique comprenant, comme ingrédient actif, un composé de formule IV, ou un de ses sels pharmaceutiquement acceptables selon l'une quelconque des revendications 1 à 3, en association avec un ou plusieurs excipients ou supports pharmaceutiquement acceptables pour ce composé ou ce sel.

6. Formulation pharmaceutique selon la revendication 5, adaptée pour une administration par voie orale.

7. Composé de formule IV ou un de ses sels pharmaceutiquement acceptables selon l'un quelconque des revendications 1 à 3, en vue de l'utiliser comme agoniste central de sérotonine dans la chimiothérapie des animaux à sang chaud.

8. Composé de formule:



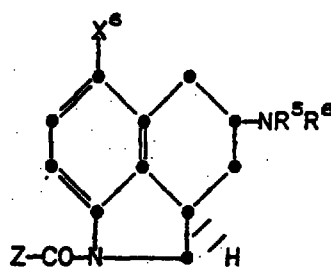
LX

dans laquelle

R⁵ et R⁶ représentent chacun individuellement un groupe méthyle, un groupe éthyle, un groupe n-propyle ou un groupe allyle;

X⁶ représente NO₂, Br, Cl ou F; ou un de ses sels d'addition d'acide.

9. Composé de formule:



LXI

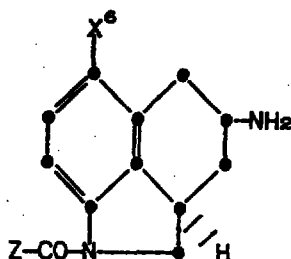
dans laquelle

R⁵ et R⁶ représentent chacun individuellement un groupe méthyle, un groupe éthyle, un groupe n-propyle ou un groupe allyle;

X⁶ représente NO₂, Br, Cl ou F; et

Z représente un groupe protecteur;
ou un sel d'addition d'acide de ce composé.

10. Composé de formule:



LXII

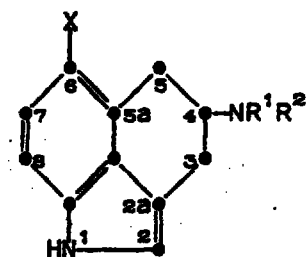
dans laquelle

X⁶ représente NO₂, Br, Cl ou F; et

Z représente un groupe protecteur;
ou un de ses sels d'addition d'acide.

Revendications pour l'Etat contractant: AT

1. Procédé de préparation d'un composé de formule:



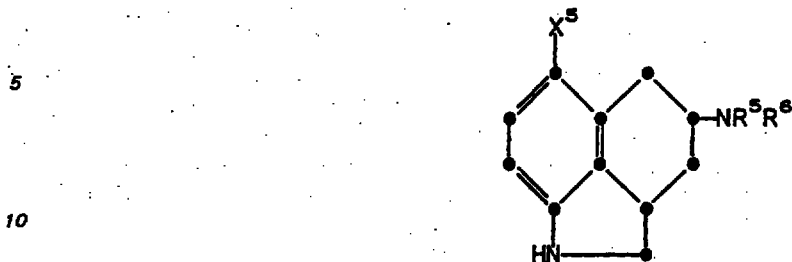
IV

dans laquelle

R¹ et R² représentent chacun individuellement un atome d'hydrogène, un groupe méthyle, un groupe éthyle, un groupe n-propyle ou un groupe allyle, tandis que X représente F, Cl, Br, CN, CONH₂, NH₂ ou NO₂; ou d'un de ses sels pharmaceutiquement acceptables, caractérisé en ce qu'il comprend les étapes qui consistent à:

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a) faire réagir un composé de formule:



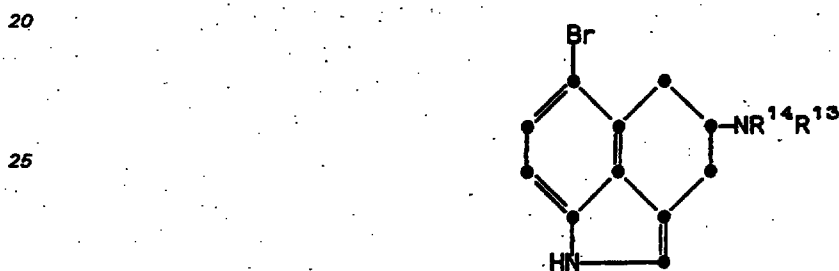
XVI f

dans laquelle

X⁵ représente F, Cl, Br ou NO₂;

R³ et R⁴ représentent chacun individuellement un groupe méthyle, un groupe éthyle, un groupe n-propyle ou un groupe allyle, avec un agent oxydant pour obtenir les composés de formule IV dans laquelle X représente F, Cl, Br ou NO₂, tandis que R¹ et R² représentent chacun individuellement un groupe méthyle, un groupe éthyle, un groupe n-propyle ou un groupe allyle; ou

b) faire réagir un composé de formule:

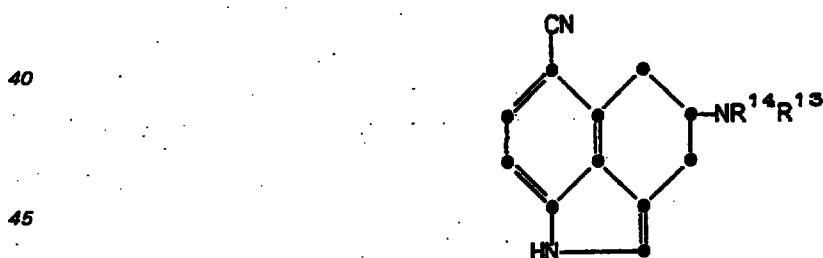


XXXII a

dans laquelle

R¹⁴ et R¹³ représentent chacun individuellement un groupe éthyle, un groupe n-propyle ou un groupe allyle, avec du cyanure cuivreux ou un cyanure d'un métal alcalin ou d'un métal alcalino-terreux et de l'iodure cuivreux dans de la 1-méthyl-2-pyrrolidone pour obtenir les composés de formule IV dans laquelle X représente CN, tandis que R¹ et R² représentent chacun individuellement un groupe éthyle, un groupe n-propyle ou un groupe allyl; ou

c) faire réagir un composé de formule:

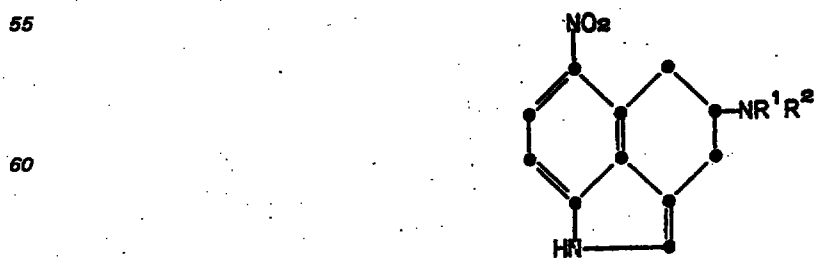


XXXIII

dans laquelle

R¹⁴ et R¹³ ont les significations définies précédemment, avec une base hydroxyde dans un alcool en C₁-C₄ pour obtenir les composés de formule IV dans laquelle X représente CONH₂, tandis que R¹ et R² représentent chacun individuellement un groupe éthyle, un groupe n-propyle ou un groupe allyle; ou

d) faire réagir un composé de formule:



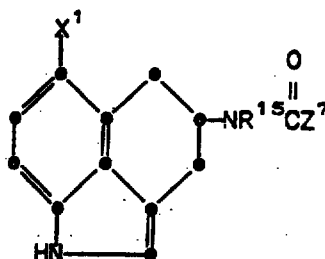
XLIII

65 dans laquelle



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R¹ et R² ont les significations définies précédemment, avec un agent réducteur pour obtenir les composés de formule IV dans laquelle X représente NH₂; ou
e) faire réagir un composé de formule:

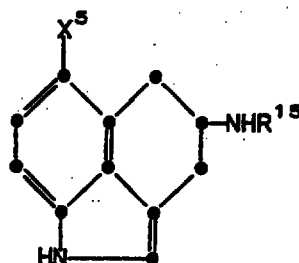


XIVb

15 dans laquelle

X¹ représente F ou Cl, Z⁷ représente un groupe alkyle en C₁-C₃, un groupe alcoxy en C₁-C₃, un groupe halo-alkyle en C₁-C₃ ou un groupe O-benzyle, tandis que R¹⁵ représente H ou un groupe alkyle en C₁-C₃, avec clivage basique ou lorsque Z⁷ représente un groupe O-benzyle, avec hydrogénation catalytique pour obtenir les composés de formule IV dans laquelle X représente F ou Cl, tandis que R¹ représente un atome d'hydrogène et R² représente un groupe alkyle en C₁-C₃ ou un atome d'hydrogène; ou

f) faire réagir un composé de formule:

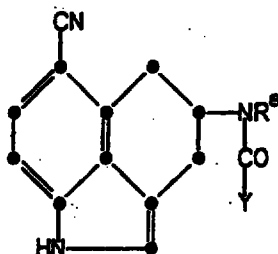


XIVc

30 dans laquelle

X⁵ et R¹⁵ ont les significations définies précédemment, avec un agent d'alkylation ou par amination réductrice pour obtenir les composés de formule IV dans laquelle X représente F, Cl, Br ou NO₂, tandis que R¹ et R² représentent chacun individuellement un groupe méthyle, un groupe éthyle, un groupe n-propyle ou un groupe allyle ou encore und es radicaux R¹ et R² peut être un atome d'hydrogène; ou

g) faire réagir un composé de formule:

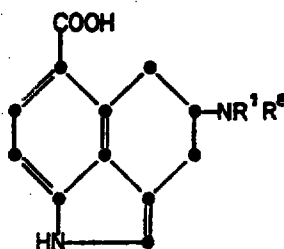


LV

45 dans laquelle

R⁸ représente un atome d'hydrogène, un groupe méthyle, un groupe éthyle ou un groupe n-propyle, et Y représente un atome d'hydrogène, un groupe méthyle, un groupe éthyle ou un groupe chlorométhyle, avec un complexe de borane pour obtenir les composés de formule IV dans laquelle X représente CN, tandis que R¹ et R² représentent chacun individuellement un atome d'hydrogène, un groupe méthyle, un groupe éthyle ou un groupe n-propyle; ou

h) faire réagir un composé de formule:



LVa

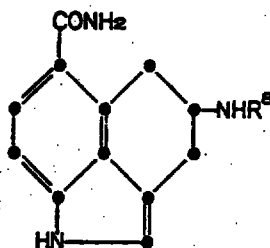
60 dans laquelle

R¹ et R⁸ ont les significations définies précédemment, avec un agent de couplage de peptide et de



l'ammoniac pour obtenir les composés de formule IV dans laquelle X représente CONH_2 , R^2 représente H, un groupe méthyle, un groupe éthyle ou un groupe n-propyle et R^1 a la signification définie précédemment; ou

i) faire réagir un composé de formule:



LVb

dans laquelle

R^8 a la signification définie précédemment, avec un halogénure R^1 ou par amination réductrice avec un catalyseur d'hydrogène pour obtenir les composés de formule IV dans laquelle X représente CONH_2 , R^2 représente H, un groupe méthyle, un groupe éthyle ou un groupe n-propyle, et R^1 a la signification définie précédemment;

j) facultativement salifier les composés de formule IV.

2. Procédé selon la revendication 1(a) en vue de préparer le ($\pm$)-4-di-n-propylamino-6-bromo-1,3,4,5-tétrahydrobenz[c,d]indole, caractérisé en ce qu'on fait réagir le ($\pm$)-4-di-n-propylamino-6-bromo-1,2,2a,3,4,5-hexahydrobenz[c,d]indole avec le N-chlorosuccinimide, le sulfure de diméthyle et la triéthylamine.

3. Procédé selon la revendication 1(a) en vue de préparer le ($\pm$)-4-di-n-propylamino-6-bromo-1,3,4,5-tétrahydrobenz[c,d]indole, caractérisé en ce qu'on fait réagir le ($\pm$)-4-di-n-propylamino-6-bromo-1,2,2a,3,4,5-hexahydrobenz[c,d]indole avec du dioxyde de manganèse.

4. Procédé selon la revendication 1(b) en vue de préparer le ($\pm$)-4-di-n-propylamino-6-cyano-1,3,4,5-tétrahydrobenz[c,d]indole, caractérisé en ce qu'on fait réagir le ($\pm$)-4-di-n-propylamino-6-bromo-1,3,4,5-tétrahydrobenz[c,d]indole avec du cyanure cuivreux.

5. Procédé selon la revendication 1(c) en vue de préparer le ($\pm$)-4-di-n-propylamino-6-carbamoyl-1,3,4,5-tétrahydrobenz[c,d]indole, caractérisé en ce qu'on fait réagir le ($\pm$)-4-di-n-propylamino-6-cyano-1,3,4,5-tétrahydrobenz[c,d]indole avec de l'hydroxyde de potassium dans du t-butanol.

6. Procédé selon la revendication 1(a) en vue de préparer le ($\pm$)-4-di-n-propylamino-6-nitro-1,3,4,5-tétrahydrobenz[c,d]indole, caractérisé en ce qu'on fait réagir le ($\pm$)-4-di-n-propylamino-6-nitro-1,2,2a,3,4,5-hexahydrobenz[c,d]indole avec du dioxyde de manganèse.

7. Procédé selon la revendication 1(c) en vue de préparer le ($\pm$)-4-diméthylamino-6-carbamoyl-1,3,4,5-tétrahydrobenz[c,d]indole, caractérisé en ce qu'on fait réagir le ($\pm$)-4-diméthylamino-6-cyano-1,3,4,5-tétrahydrobenz[c,d]indole avec de l'hydroxyde de potassium dans du t-butanol.

8. Procédé selon la revendication 1(g) en vue de préparer le ($\pm$)-4-diméthylamino-6-cyano-1,3,4,5-tétrahydrobenz[c,d]indole, caractérisé en ce qu'on fait réagir le N-formyl-($\pm$)-4-méthylamino-6-cyano-1,3,4,5-tétrahydrobenz[c,d]indole avec $\text{BH}_3-(\text{CH}_3)_2\text{S}$ dans du tétrahydrofurane.