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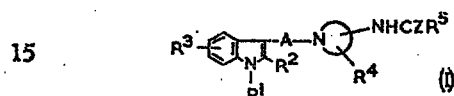


(54) INDOLES

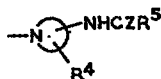
(71) We, JOHN WYETH & BROTHER LIMITED, of Huntercombe Lane South, Taplow, Maidenhead, Berkshire, a British Company, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to indole derivatives, to processes for the preparation thereof and to pharmaceutical compositions containing such derivatives.

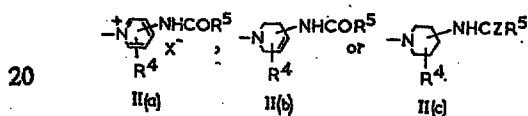
The present invention provides compounds of the general formula



in which formula



represents a ring system of the general formula



R¹ represents hydrogen, lower alkyl, lower aralkyl or aroyl, R² represents hydrogen, lower alkyl or aryl, R³ represents hydrogen,

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halogen, lower alkoxy, hydroxy or lower alkyl, R⁴ represents hydrogen, halogen or lower alkyl, R⁵ represents aryl (including heterocyclic aryl), lower alkoxy, aryloxy, lower aralkyl, lower aralkyloxy or diaryl-lower alkyl, X is an anion, A represents an alkylene or mono- or di-keto alkylene radical containing up to 4 carbon atoms, and Z is an oxo (i.e. =O) group with the proviso that Z in formula II(c) may also represent two hydrogen atoms when A is alkylene and R⁵ is aryl.

The terms "lower alkyl" and "lower alkoxy" as used herein mean the radical contains from 1 to 6, preferably 1 to 4, carbon atoms and the term "lower aralkyl" means the radical contains 7 to 10, preferably 7 to 9 carbon atoms. The "lower alkylene" group may be a branched or straight chain group, containing up to 4 carbon atoms. "A" preferably is an ethylene or acetyl group, but may, for example, be an isopropylene group.

Examples of R¹ are hydrogen, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, benzyl, benzoyl and *p*-chlorobenzoyl. Preferably R¹ is a hydrogen atom. R² can be, for example, hydrogen, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl or substituted or unsubstituted phenyl and is preferably hydrogen or methyl. R³ can be, for example, hydrogen, chlorine, methoxy, ethoxy, hydroxy, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl or isobutyl. Preferably R³ is a hydrogen atom.

Examples of R⁴ are hydrogen, chlorine, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl or isobutyl, though preferably R⁴ is a hydrogen atom.

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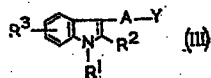
R^5 can be, for example, phenyl, substituted phenyl (e.g. phenyl substituted by halogen such as chlorine, by alkoxy, such as methoxy or ethoxy, by alkyl such as methyl or ethyl or by methylenedioxy), heterocyclic radicals (such as 3-indolyl, 2-thienyl or 2-furyl), methoxy, ethoxy, phenoxy, benzyl, benzyloxy and diphenylmethyl.

X is preferably a halide ion such as a chloride or bromide.

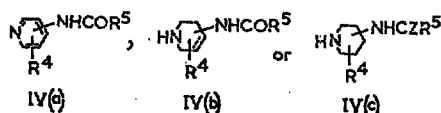
The novel compounds provided by the invention have pharmacological properties or are useful as intermediates for the preparation of compounds having pharmacological properties. The compounds generally exhibit anti-inflammatory activity and/or action on the cardiovascular system (such as hypotensive and/or anti-hypertensive activity and/or antihistamine activity) and sometimes central nervous system activity (such as sedative or anti-convulsant activities) when tested on warm blooded animals.

The compounds of general formula (I) can be prepared in a number of ways by building up the molecule from suitable starting materials in known manner.

A first general method of preparation comprises reacting a compound of the general formula



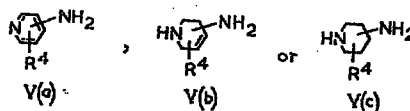
with a compound of the general formula



(where $R^1, R^2, R^3, R^4, R^5, Z$ and A have the meanings defined above and Y is a halogen atom or an equivalent radical, e.g. an organic sulphonyl radical such as a tosyl radical) and if necessary reducing.

The starting materials of general formula III are known compounds or can be made following the methods known for preparing compounds of this type, e.g. by reducing the corresponding carboxyl compounds followed by halogenation. The starting material of general formula IV(c) preferably is prepared by forming the oxime of a N-benzyl-4-piperidone, reducing to give the amine, acylating with a compound of general formula $R^5\text{COOH}$ (where R^5 has the meanings defined above) and then hydrogenolysing.

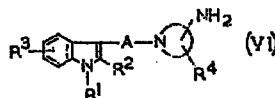
Generally, the compounds of general formula IV(a), (b) and (c) can be prepared by acylating a corresponding amino compound of the general formula



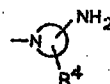
with a reactive derivative of an acid of general formula: $\text{—R}^5\text{COOH}$ (where R^4 and R^5 have the meanings defined above) and if necessary reducing the acylated product.

The products of general formula IV(a), (b) and (c) generally show pharmaceutical activity (e.g. CNS and anti-inflammatory activity).

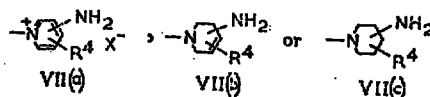
A second general method of preparation (when Z is an oxo group) comprises acylating a compound of the general formula



(in which formula

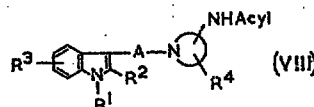


is a ring system of the general formula

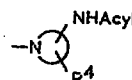


where R^1, R^2, R^3, R^4, A and X have the meanings defined above) with a reactive derivative of an acid of general formula $R^5\text{COOH}$ (where R^5 has the meanings defined above). As a reactive derivative of the acid of formula $R^5\text{COOH}$ used in a process described above, we have found it preferable usually to use a halide (for example the chloride or bromide) or an anhydride.

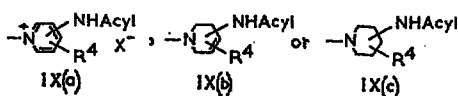
The starting materials of general formula VI generally can be prepared by hydrolysing (e.g. with a mineral acid such as hydrochloric acid) a corresponding acylamido (e.g. acetamido) compounds of the general formula



where

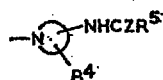


is a



ring and R^1 , R^2 , R^3 , R^4 and X have the meanings defined above and Acyl is an acyl, e.g. acetyl radical. (The compounds of general formula VIII can be prepared following the information given above but using the appropriate acylating agent). Alternatively the starting materials of general formula VI can generally be prepared by reacting a compound of general formula III with a compound of general formula V(a), (b) or (c) and if desired then effecting reduction. These starting materials of general formula VI usually exhibit central nervous system activity.

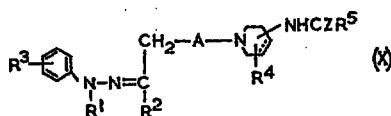
Once a pyridinium compound of general formula (I) (i.e. in which



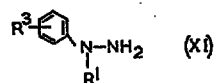
represents a ring system of general formula II(a)) has been prepared, it may be selectively reduced to one of the other compounds. For example, a pyridine ring system of general formula II(a) may be reduced with an alkali metal borohydride to a tetrahydropyridine ring system of general formula II(b). On the other hand, catalytic hydrogenation, e.g. in the presence of Raney nickel or platinum, or careful reduction with a hydride transfer agent (such as lithium aluminium hydride) causes a piperidine ring system of general formula II(c), in which Z is an oxo group, to be formed. More drastic reduction with lithium aluminium hydride, e.g. on the tetrahydropyridine ring system, also causes reduction of the double bonded oxygen group(s) to give a ring system of formula II(c) in which Z represents two hydrogen atoms.

Similarly, the starting materials of general formula VI, where the amino-substituted ring system is of formula VII(b) or VII(c), can be prepared by reducing the corresponding higher oxidation state ring systems of formula VII(a) or (b), as the case may be.

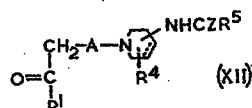
The tetrahydropyridine and piperidine compounds of general formula I can be prepared by carrying out a Fischer indole synthesis on a compound of general formula



This starting material can be prepared by condensing a phenylhydrazine of formula



with an aldehyde or ketone of general formula



in which formulae R^1 , R^2 , R^3 , R^4 , R^5 , A and Z have the meanings defined above.

Once a compound of general formula I, in which R^1 is hydrogen has been prepared derivatives thereof may be prepared by alkylation, aralkylation or aroylation at the 1-position. For example, an alkali metal salt (e.g. the sodium salt) can be prepared and reacted with an alkyl or aralkyl halide or with an aroylating agent.

If desired, a salt can be used instead of the basic compounds in many of the above reactions, as is well known in the art.

The reactions outlined above usually are carried out in an organic solvent which is inert under the reaction conditions, for example methanol, ethanol or dimethoxyethane. The most suitable solvent is chosen and varies depending on the particular reactants being used. If necessary heating the reactants in solution under reflux can be carried out. If necessary, reactive substituent groups can be blocked during a reaction and released later.

Since the novel tetrahydropyridine and piperidine compounds provided by the invention contain a basic nitrogen atom they can form acid addition salts with acids (e.g. hydrochloric acid) or quaternary ammonium salts, e.g. with alkyl halides (for example, methyl bromide or chloride) and the invention also provides such salts.

The invention also provides a pharmaceutical composition comprising a compound of general formula (I) or a non-toxic acid addition or quaternary ammonium salt, when formed, of a novel compound of the invention, and a pharmaceutically acceptable carrier. The carrier may be a solid or liquid and any carrier known in the art may be used. The particular dosage will depend on the compound used, chosen route of administration, and standard pharmaceutical practice. For example, the compounds may be administered orally in the form of solutions; or they may be injected parenterally in the form of sterile solutions containing other solutes. As is usual, the compounds are administered at a concentration level which will afford effective results without causing any harmful or deleterious side effects. The actual dosage used will depend on the activity of the compound used and the condition of the

patient to whom the compound is administered.

The non-limiting Examples which follow illustrate the invention. There are a number of equally correct ways of naming the compounds of general formula (I), and we have preferred to name the pyridinium compounds taking the pyridine ring as the basic unit and to name the tetrahydropyridine and piperidine compounds taking the indole moiety as the basic unit. For example, although we prefer the name 3 - [2 - (4 - [4 - chlorobenzamidol] - 1,2,5,6 - tetrahydropyrid - 1 - yl)ethyl]indole for the compound of Example 9, it could alternatively be named 1 - (2 - indol - 3 - yl)ethyl - 4 - (4 - chlorobenzamido) - 1,2,5,6 - tetrahydropyridine. Similarly, we prefer to name the corresponding piperidine compound of Example 14 as 3 - [2 - 4 - (4 - chlorobenzamido) - 1 - piperidyl]ethylindole rather than 4 - (4 - chlorobenzamido - 1 - (2 - indol - 3 - yl)ethyl - piperidine).

EXAMPLE 1

4 - Benzamido - 1 - [2 - (3 - indolyl)ethyl] - pyridinium bromide

A solution of 4-benzamidopyridine (1.98 g.) and 3 - (2 - bromoethyl)indole (2.24 g.), in absolute ethanol (15 ml.) was refluxed for 2 hours and the crystalline product (3.13 g.) was collected by filtration from the hot solution. Recrystallisation from ethanol-water gave the title compound as a hydrate, m.p. 267—269°C. (Found C, 60.26; H, 4.98; N, 9.48; Br, 18.45. $C_{22}H_{20}BrN_3O \cdot H_2O$ requires C, 60.07; H, 5.04; N, 9.45; Br, 18.15%).

The 4-benzamidopyridine was prepared by adding benzoyl chloride dropwise to an ice-cooled solution of 4-aminopyridine in pyridine. The corresponding starting materials for Examples 2 to 5 were made in a similar manner.

EXAMPLE 2

3 - Benzamido - 1 - [2 - (3 - indolyl)ethyl] - pyridinium bromide.

The procedure of Example 1 was followed by utilising 3-benzamidopyridine in place of 4-benzamidopyridine. The title compound was obtained in 77% yield as pale yellow prisms, m.p. 266—7°C. (Found C, 62.33; H, 4.92; N, 9.96; Br, 18.79. $C_{22}H_{20}BrN_3O$ requires C, 62.58; H, 4.76; N, 9.95; Br, 18.9%).

EXAMPLE 3

4 - Benzyloxycarbonylamido - 1 - [2 - (3 - indolyl)ethyl] - pyridinium bromide

3 - (2 - Bromoethyl)indole (1.12 g.) and 4 - (benzyloxycarbonylamino)pyridine (1.14 g.) were refluxed in ethanol (12.5 ml.) for 5 hours. The crystals formed on cooling were filtered off, washed with ether, dried and recrystallised from ethanol to give the title compound as pale yellow crystals in 59% yield, m.p. 176—178°C. (Found C, 60.86; H, 5.03; N, 9.52; Br, 17.82. $C_{23}H_{22}BrN_3O_2$

requires C, 61.06; H, 4.90; N, 9.29; Br, 17.66%).

EXAMPLE 4

4 - (4 - Chloro)benzamido - 1 - [2 - (3 - indolyl)ethyl]pyridinium bromide

The procedure of Example 1 was followed by using 4 - (4 - chloro)benzamido-pyridine instead of 4-benzamidopyridine. Recrystallisation from aqueous ethanol gave the title compound as yellow needles in 69% yield, m.p. 274—276°C. (Found C, 57.59; H, 4.39; N, 9.06. $C_{22}H_{19}BrClN_3O$ requires C, 57.84; H, 4.19; N, 9.20%).

EXAMPLE 5

4 - (2,2 - Diphenylacetamido) - 1 [2 - (3 - indolyl)ethyl]pyridinium bromide

The procedure of Example 1 was followed but using 4 - (2,2 - diphenylacetamido) - pyridine instead of 4-benzamidopyridine. Recrystallisation from a mixture of ethanol and ether gave the title compound as pale yellow crystals in 36% yield, m.p. 224—226°C. (Found C, 67.76; H, 5.29; N, 8.04; Br, 15.49. $C_{28}H_{26}BrN_3O$ requires C, 67.97; H, 5.12; N, 8.20; Br, 15.60%).

EXAMPLE 6

3 - [2 - (4 - Benzamido - 1,2,5,6 - tetrahydropyrid - 1 - yl)ethyl]indole

Sodium borohydride (6.0 g.) was added over 30 minutes to a stirred suspension of 4-benzamido - 1 - [2 - (3 - indolyl)ethyl] - pyridinium bromide (2.0 g.) in methanol (100 ml.). Stirring was continued 1 hour after the addition and the precipitated product filtered off, washed with cold methanol and dried to give 1.54 g. of the title compound in 97% yield, m.p. 209—211°C. after recrystallisation from methanol. (Found C, 76.42; H, 6.60; N, 12.05; $C_{22}H_{23}N_3O$ requires C, 76.49; H, 6.71; N, 12.17%).

EXAMPLE 7

3 - [2 - (3 - Benzamido - 1,2,5,6 - tetrahydropyrid - 1 - yl)ethyl]indole

3 - Benzamido - 1 - [2 - (3 - indolyl)ethyl] - pyridinium bromide was reduced with sodium borohydride, following the procedure of Example 6, to give the total compound in 86% yield as colourless crystals, m.p. 180—182°C. after recrystallisation from acetonitrile. (Found C, 76.53; H, 6.91; N, 12.01. $C_{22}H_{23}N_3O$ requires C, 76.49; H, 6.71; N, 12.17%).

EXAMPLE 8

3 - [2 - (4 - Benzyloxycarbonylamino - 1,2,5,6 - tetrahydropyrid - 1 - yl)ethyl]indole

4 - Benzyloxycarbonylamino - 1 - [2 - (3 - indolyl)ethyl]pyridinium bromide was reduced with sodium borohydride, following the procedure of Example 6, to give the title compound in 69% yield, m.p. 162—164°C. after recrystallisation from ethanol. (Found C, 73.41; H, 6.92; N, 11.21. $C_{23}H_{25}N_3O_2$ requires C, 73.57; H, 6.71; N, 11.19%).

EXAMPLE 9

3 - [2 - (4 - [4 - chlorobenzamido] - 1,2,5,6-tetrahydropyrid - 1 - yl) - ethyl]indole
 4 - (4 - Chloro)benzamido - 1 - [2 - (3-indolyl)ethyl]pyridinium bromide was reduced with sodium borohydride, following the procedure of Example 6, to give the title compound in 37% yield, m.p. 229—230°C. after recrystallisation from a mixture of ethanol and dimethylsulphoxide. (Found C, 69.47; H, 5.97; N, 10.92; Cl, 9.48. $C_{22}H_{22}ClN_3O$ requires C, 69.56; H, 5.85; N, 11.06; Cl, 9.34%).

EXAMPLE 10

3 - [2 - (4 - [2,2 - diphenylacetamido] - 1,2,5,6 - tetrahydropyrid - 1 - yl)ethyl]indole
 4 - (2,2 - Diphenylacetamido) - 1 - [2 - (3-indolyl)ethyl]pyridinium bromide was reduced with sodium borohydride, following the procedure of Example 6, to give the title compound in 83% yield, m.p. 197—198°C. after recrystallisation from ethanol. (Found C, 79.83; H, 6.61; N, 9.81. $C_{29}H_{28}N_3O$ requires C, 79.96; H, 6.71; N, 9.65%).

EXAMPLE 11

3 - [2 - (4 - Benzylaminopiperid - 1 - yl)ethyl]indole
 3 - [2 - (4 - Benzamido - 1,2,5,6 - tetrahydropyrid - 1 - yl)ethyl]indole (3.45 g.) was added over 30 minutes to a stirred suspension of lithium aluminium hydride (2.26 g.) in 1,2-dimethoxyethane (100 ml.), and the mixture was refluxed for 22 hours and then allowed to cool. The excess lithium aluminium hydride was decomposed by dropwise addition of water (6.8 mls.) with stirring. The mixture was filtered, the inorganic precipitate washed thoroughly with fresh 1,2-dimethoxyethane and the bulked organic phases evaporated to give a pale yellow oil. After standing for 3 days, the oil became semi-crystalline. Trituration with acetone caused complete crystallisation to give the title compound (650 mg), of m.p. 132—4°C. after recrystallisation from benzene/80—100° petrol. (Found C, 79.02; H, 8.06; N, 12.81. $C_{23}H_{23}N_3$ requires C, 79.24; H, 8.16; N, 12.60).

EXAMPLE 12

3 - [2 - (4 - Benzamido - 1 - piperidyl)ethyl]indole
 4 - Benzamido - 1 - [2 - (3 - indolyl)ethyl]pyridinium bromide (3.0 g.) was dissolved in 91% ethanol (300 ml.) containing triethylamine (0.08 g.) and freshly prepared W-7 Raney nickel catalyst (ca. 3 g.) was added. The mixture was hydrogenated in an autoclave at 400 p.s.i. hydrogen pressure and 50°C for 4 hours. After filtering off the catalyst the filtrate was evaporated *in vacuo* and the residue was shaken with a mixture of chloroform and 2N sodium hydroxide solution. The resulting insoluble material was filtered off

and dried to give 1.61 g. of product, m.p. 203—6°C. Recrystallisation from ethanol gave the title compound as colourless needles (1.34 g.) m.p. 208—210°C. (Found C, 75.91; H, 7.42; N, 12.27. $C_{22}H_{22}N_3O$ requires C, 76.05; H, 7.25; N, 12.10%).

EXAMPLE 13

3 - [2 - (3 - Benzamido - 1 - piperidyl)ethyl]indole
 3-Benzamido - 1 - [2 - (3 - indolyl)ethyl]pyridinium bromide was reduced following the procedure of Example 12 to give the title compound in 39% yield, m.p. 135—40°C. after recrystallisation from aqueous ethanol. (Found C, 75.99; H, 7.41; N, 11.89. $C_{22}H_{22}N_3O$ requires C, 76.05; H, 7.25; N, 12.10%).

EXAMPLE 14

3 - [2 - (4 - [4 - Chlorobenzamido] - 1 - piperidyl)ethyl]indole
 4 - (4 - Chloro)benzamido - 1 - [2 - (3-indolyl)ethyl]pyridinium bromide (2.0 g.) was suspended in 95% ethanol (300 ml.) containing triethylamine (2 ml.). Platinum oxide (200 mg.) was added and the mixture hydrogenated at 400 p.s.i. and 65°C. for 5 hours. The solution was filtered and the solvent removed *in vacuo*. The resulting residue was triturated with 2N sodium hydroxide, the gum formed was dissolved in hot ethanol, diluted with water until faintly turbid and allowed to cool when pink needles separated out, (414 mg.). These were recrystallised twice from ethanol to give the title compound, m.p. 230—232°C. (Found C, 69.00; H, 6.46; N, 10.83; Cl, 9.03. $C_{22}H_{22}ClN_3O$ requires C, 69.20; H, 6.33; N, 11.01; Cl, 9.29%).

EXAMPLE 15

3 - [2 - (4 - [4 - Methoxybenzamido] - 1 - piperidyl)ethyl]indole
 (a) A solution of 3 - [2 - (4 - amino - 1 - piperidyl)ethyl]indole, hydrate (1.305 g.) in chloroform (20 ml.) was stirred with a solution of potassium bicarbonate (750 mg.) in water (10 ml.). The mixture was cooled in an ice bath and *p*-methoxybenzoyl chloride (950 mg.) in chloroform (5 ml.) was added dropwise. The resulting precipitate was filtered off, dissolved in ethanol and made acid with ethanolic HCl to precipitate the hydrochloride. Recrystallisation from a mixture of ethanol and water gave the title compound as the hydrochloride, hydrate in 54% yield, m.p. 284—6°C. (Found C, 63.87; H, 7.06; N, 8.06; Cl, 9.83. $C_{23}H_{27}N_3O_2 \cdot HCl \cdot H_2O$ requires C, 63.95; H, 7.00; N, 8.21; Cl, 9.73%).

The starting material for this Example was made as follows: (b) A solution of 4 - acetamidopyridine (42 g.) and 3 - (2 - bromoethyl)indole (61 g.) in absolute ethanol (400 ml.) was refluxed for 16 hours. 4 - Acetamido-

1 - [2 - (3 - indolyl)ethyl]pyridinium bromide (78.3 g.) separated on cooling, m.p. of the ethanolate after crystallisation from ethanol as the ethanolate was 202—3°C.

5 4 - Acetamido - 1 - [2 - (3 - indolyl)-ethyl]pyridinium bromide (78.3 g.) was dissolved in 91% ethanol (1200 ml.) containing triethylamine (24.4 g.) and W7 Rancy nickel catalyst (ca. 30 g.) was added. Hydro-
10 genation was conducted in an autoclave at 70°C. and at an initial hydrogen pressure of 400 p.s.i. for 2 hours.

The catalyst was filtered off and the residue after evaporation of the filtrate was shaken with chloroform and 2N sodium hydroxide solution. The chloroform layer was dried and evaporated *in vacuo* to give 3 - [2 - (4 - acetamido - 1 - piperidyl)ethyl]indole as a colourless solid (44.0 g.), m.p. 167—8°C. after
15 recrystallisation from ethyl acetate.

20 3 - [2 - (4 - Acetamido - 1 - piperidyl)-ethyl]indole (43.0 g.) was dissolved in 2N hydrochloric acid (430 ml.) and refluxed for 2½ hours. The reaction mixture was cooled, filtered and basified with 10N sodium hydroxide to give 3 - [2 - (4 - amino - 1 - piperidyl)ethyl]indole as the hydrate (36.4 g.), m.p. 106—110°C. after recrystallisation from
25 acetonitrile containing 1% water. (c) Alternatively a solution of 3 - (2 - bromoethyl)-indole (2.4 g.) in acetonitrile (20 ml.) was added dropwise during one hour to a refluxing solution of 4-aminopyridine in acetonitrile (25 ml.) and refluxing continued for 3 hours. The
30 4 - amino - 1 - [2 - (3 - indolyl)ethyl]pyridinium bromide formed could be reduced with hydrogen in the presence of W7 Rancy nickel to give 3 - [2 - (4 - amino - 1 - piperidyl)-ethyl]indole.

40 In a similar manner, 3 - amino - 1 - [2 - 3 - indolyl]ethyl]pyridinium bromide, m.p. 190—192°C. and 2 - amino - 1 - [2 - (3 - indolyl)-ethyl]pyridinium bromide, m.p. 228—230°C. could be prepared from 3 - amino- or 2-
45 amino-pyridine and 3 - (2 - bromoethyl)-indole, and then reduced to give the corresponding 3 - [2 - (2- or 3 - amino - 1 - piperidyl)ethyl]indoles.

EXAMPLE 16

50 3 - [2 - (4 - [3 - Methoxybenzamido] - 1 - piperidyl)ethyl]indole

A solution of 3 - [2 - (4 - amino - 1 - piperidyl)ethyl]indole hydrate (1.3 g.) in chloroform (25 ml.) was stirred with an ice cooled solution of potassium carbonate (1.38 g.) in water (10 ml.). *m*-Methoxybenzoyl chloride (950 mg.) in chloroform (10 ml.) was added dropwise, stirring was continued for 3 hours then the layers were separated. The
55 aqueous layer was re-extracted with chloroform, the combined chloroform layers were dried and evaporated *in vacuo* and the crystalline residue was recrystallised from acetonitrile to give the title compound (1.42 g.) as
60

prisms, m.p. 149—150°C. (Found C, 73.08; H, 7.33; N, 11.17. $C_{23}H_{27}N_3O_2$ requires C, 73.18; H, 7.21; N, 11.13%).

EXAMPLE 17

3 - [2 - (4 - [2 - Methoxybenzamido] - 1 - piperidyl)ethyl]indole

By following the procedure of Example 16 but utilising *o*-methoxybenzoyl chloride in place of *m*-methoxybenzoyl chloride, the title compound was obtained as pale yellow prisms in 50% yield, m.p. 152—154°C. (Found C, 73.35; H, 7.32; N, 11.22. $C_{23}H_{27}N_3O_2$ requires C, 73.18; H, 7.21; N, 11.13%).

EXAMPLE 18

3 - [2 - (4 - [3,4,5 - Trimethoxybenzamido] - 1 - piperidyl)ethyl]indole

The procedure of Example 16 was followed except that 4 - (3,4,5 - trimethoxy)benzoyl chloride was used instead of *m*-methoxybenzoyl chloride. Recrystallisation from a mixture of ethanol and water gave fine needles of the title compound as the hydrate in 79% yield, m.p. 105—108°C. (Found C, 65.74; H, 7.17; N, 9.38; $C_{25}H_{31}N_3O_4 \cdot H_2O$ requires C, 65.91; H, 7.30; N, 9.23%).

EXAMPLE 19

3 - [2 - (4 - [Indol - 3 - carboxamido] - 1 - piperidyl)ethyl]indole

The procedure of Example 16 was followed but utilising indole - 3 - carbonyl chloride instead of *m*-methoxybenzoyl chloride. The title compound was obtained as colourless microcrystals in 13% yield, m.p. 242—244°C. after recrystallisation from aqueous acetate. (Found C, 74.44; H, 6.88; N, 14.39; $C_{24}H_{26}N_4O$ requires C, 74.58; H, 6.78; N, 14.50%).

This compound was also prepared using indole - 3 - carboxylic acid and dicyclohexylcarbodiimide (i.e. indole - 3 - carboxylic acid anhydride *in situ*) as the acylating agent.

EXAMPLE 20

3 - [2 - (4 - [2,2 - Diphenylacetamido] - 1 - piperidyl)ethyl]indole

The procedure of Example 16 was followed but utilising diphenylacetyl chloride instead of *m*-methoxybenzoyl chloride. The title compound was obtained as colourless plates in 56% yield, m.p. 160—162°C., after recrystallisation from aqueous ethanol. (Found C, 79.43; H, 7.34; N, 9.71. $C_{29}H_{31}N_3O$ requires C, 79.60; H, 7.14; N, 9.60%).

EXAMPLE 21

3 - [2 - (4 - [2 - Methylbenzamido] - 1 - piperidyl)ethyl]indole

The procedure of Example 16 was followed but using *o*-toluoyl chloride as the acylating agent to give the title compound in 62% yield, m.p. 186—9°C. (Found C, 72.3; H, 7.7; N, 11.9. $C_{23}H_{27}N_3O$ requires C, 76.4; H, 7.5; N, 11.6%).

EXAMPLE 22

3 - [2 - (4 - [3 - Methylbenzamido] - 1-piperidyl)ethyl]indole

The procedure of Example 16 was followed but using *m*-toluoyl chloride as the acylating agent to give the title compound in 56% yield, m.p. 172—4°C. (Found C, 72.3; H, 7.6; N, 11.6. $C_{23}H_{27}N_3O$ requires C, 76.4; H, 7.5; N, 11.6%).

EXAMPLE 23

3 - [2 - (4 - [4 - Methylbenzamido] - 1-piperidyl)ethyl]indole

The procedure of Example 16 was followed but using *p*-toluoyl chloride as the acylating agent to give the title compound in 55% yield, m.p. 200—202°C. (Found C, 76.2; H, 7.5; N, 11.4. $C_{23}H_{27}N_3O$ requires C, 76.4; H, 7.5; N, 11.6%).

EXAMPLE 24

3 - [2 - (4 - [2 - Furylcarboxamido] - 1-piperidyl)ethyl]indole

The procedure of Example 16 was followed but using furan - 2 - carbonyl chloride as the acylating agent to give the title compound, m.p. 146—8°C. in 81% yield. (Found C, 71.0; H, 6.95; N, 12.4. $C_{20}H_{23}N_3O_2$ requires C, 71.2; H, 6.9; N, 12.45%).

EXAMPLE 25

3 - [2 - (4 - [2 - Chlorobenzamido] - 1-piperidyl)ethyl]indole

The procedure of Example 16 was followed but using *o*-chlorobenzoyl chloride as the acylating agent to give the title compound in 39% yield, m.p. 163—164°C. (Found C, 69.0; H, 6.2; N, 11.0. $C_{22}H_{24}ClN_3O$ requires C, 69.2; H, 6.3; N, 11.0%).

EXAMPLE 26

3 - [2 - (4 - [3,4 - Methyleneedioxybenzamido] - 1-piperidyl)ethyl]indole

The procedure of Example 16 was followed but using 3,4 - dioxymethylenebenzoyl chloride as the acylating agent to give the title compound in 58% yield, m.p. 189—190°C. (Found, C, 70.4; H, 6.55; N, 10.8. $C_{23}H_{26}N_3O_3$ requires C, 70.6; H, 6.4; N, 10.7%).

EXAMPLE 27

3 - [2 - (4 - [2 - Carboxybenzamido] - 1-piperidyl)ethyl]indole

3 - [2 - (4 - Amino - 1 - piperidyl)ethyl]indole (2.0 g.) in chloroform (100 ml.) was stirred at room temperature while phthalic anhydride (1.14 g.) was added in portions. After stirring for 2 hours the precipitate was collected and recrystallised from ethanol water to give the title compound as a hydrate (1.96 g.) m.p. 165—170°C. (Found C, 67.36; H, 7.06; N, 10.20. $C_{23}H_{27}N_3O_3 \cdot H_2O$ requires C, 67.46; H, 6.64; N, 10.26%).

EXAMPLE 28

3 - [2 - (4 - [3 - Trifluoromethylbenzamido] - 1-piperidyl)ethyl]indole

The procedure of Example 16 was followed, but replacing *m*-methoxybenzoyl chloride by *m*-trifluoromethylbenzoyl fluoride to give the title compound in 56% yield, m.p. 186—8°C. (Found C, 66.4; H, 6.0; N, 10.1. $C_{23}H_{24}F_3N_3O$ requires C, 66.5; H, 5.8; N, 10.8%).

EXAMPLE 29

3 - [2 - (4 - [4 - Phenylbenzamido] - 1-piperidyl)ethyl]indole

The procedure of Example 16 was followed, but replacing *m*-methoxybenzoyl chloride by *p*-phenylbenzoyl chloride to give the title compound as the monohydrate in 44% yield, m.p. 271—2°C. (Found C, 78.9; H, 6.95; N, 10.1. $C_{28}H_{30}N_3O$ requires C, 78.6; H, 6.95; N, 9.8%).

EXAMPLE 30

3 - [2 - (4 - [2 - Phenylacetamido] - 1-piperidyl)ethyl]indole

The procedure of Example 16 was followed, but replacing the *m*-methoxybenzoyl chloride by phenylacetyl chloride to give the title compound in 58% yield, m.p. 165—8°C. (Found C, 76.3; H, 7.7; N, 11.7. $C_{23}H_{27}N_3O$ requires C, 76.4; H, 7.5; N, 11.65%).

EXAMPLE 31

3 - [2 - 4 - Benzamido - 1 - piperidyl)ethyl] - 2 - methylindole

(a) 3 - (2 - Bromoethyl) - 2 - methylindole (2.38 g.) in ethanol (25 ml.) was refluxed with 4-acetamidopyridine (1.36 g.) for 6½ hours. 4 - Acetamido - 1 - [2 - (2 - methylindol - 3 - yl)ethyl]pyridinium bromide, m.p. 205—207°C. (2.24 g., 60%) separated on cooling. This quaternary bromide (14.4 g.) was suspended in 95% ethanol containing triethylamine (15 ml.) and W7 Raney nickel (about 10 g.) and hydrogenated for 4 hours at 400 p.s.i. and 75°C. Filtration from catalyst, evaporation of the filtrate and trituration with 2N sodium hydroxide solution (100 ml.) gave 3 - [2 - (4 - acetamido - 1 - piperidyl)ethyl] - 2 - methylindole (10.12 g., 76%), m.p. 83—85°C.

The acetamido-compound (8.57 g.) was refluxed in 2N HCl (200 ml.) for 2½ hours. After cooling, the solution was made strongly basic, extracted into chloroform, heated with charcoal, filtered and evaporated to give 3 - [2 - (4 - amino - 1 - piperidyl)ethyl] - 2 - methylindole as a brown foam (7.02 g., 95%). (b) The brown foam (1.3 g.) in chloroform (20 ml.) was stirred with potassium carbonate (1.38 g.) in water (10 ml.) and ice-cooled while benzoyl chloride (703 mg.) in chloroform (15 ml.) was added slowly dropwise. Stirring was continued for 2 hours then the aqueous phase was separated and re-extracted with chloroform. The combined organic phases were dried, charcoaled and evaporated. The result-

ing foam solidified on trituration with ether to give 3 - [2 - (4 - benzamido - 1 - piperidyl)ethyl] - 2 - methylindole as yellow microcrystals (1.21 g., 67%). It was recrystallised from aqueous ethanol as needles, m.p. 209—211°C. (Found C, 76.26; H, 7.71; N, 11.63. $C_{23}H_{27}N_3O$ requires C, 76.42; H, 7.53; N, 11.63%).

EXAMPLE 32

10 3 - [2 - (4 - [4 - Methoxybenzamido] - 1 - piperidyl)ethyl] - 2 - methylindole

The procedure of Example 31(b) was followed, but using *p*-methoxybenzoyl chloride in place of benzoyl chloride to give the title compound as prisms of monohydrate which were recrystallised from ethanol (55% yield) m.p. 110—114°C. (Found C, 70.52; H, 7.81; N, 10.4. $C_{24}H_{29}N_3O_2 \cdot H_2O$ requires C, 70.39; H, 7.63; N, 10.26%).

EXAMPLE 33

20 3 - [2 - (4 - [4 - Chlorobenzamido] - 1 - piperidyl)ethyl] - 2 - methylindole

The procedure of Example 31(b) was followed but using *p*-chlorobenzoyl chloride in place of benzoyl chloride to provide the title compound as the hydrochloride in 34% yield, m.p. 243—245°C. after recrystallisation from ethanol ether. (Found C, 63.80; H, 6.38; Cl, 16.25. $C_{23}H_{26}ClN_3O \cdot HCl$ requires C, 63.89; H, 6.30; Cl, 6.40%).

EXAMPLE 34

3 - [2 - (4 - Benzamido - 1 - piperidyl)ethyl] - 1 - methylindole

35 (a) 3 - [2 - (4 - Amino - 1 - piperidyl)ethyl]indole (13.05 g.) was added portionwise to sodamide in liquid ammonia (from 2.5 g. sodium and *ca* 500 ml. ammonia). After stirring for 1 hour, methyl iodide (7.8 g.) in dry ether (100 ml.) was added dropwise. Stirring was continued until the ammonia had evaporated, then water (100 ml.) was added dropwise to the residue. The resulting solid was collected and recrystallised from acetonitrile containing 1% water to give 3 - [2 - (4 - amino - 1 - piperidyl)ethyl] - 1 - methylindole as the hydrate (10.16 g.) m.p. 102—4°C. (b) A mixture of this amine (2.0 g.) in chloroform (40 ml.) and potassium carbonate (2.0 g.) in water (20 ml.) was stirred vigorously and ice-cooled while benzoyl chloride (1.15 g.) in chloroform (10 ml.) was added slowly dropwise. Stirring was continued for 2 hours, then the aqueous layer was separated and re-extracted twice with chloroform. The combined chloroform layers were dried ($MgSO_4$) and evaporated to give a colourless solid (2.67 g.). Recrystallisation from aqueous ethanol provided the title compound as colourless needles (1.60 g.) m.p. 178—179°C. (Found C, 76.39; H, 7.64; N, 11.48. $C_{23}H_{27}N_3O$ requires C, 76.42; H, 7.53; N, 11.63%).

EXAMPLE 35

3 - [2 - (4 - [4 - Chlorobenzamido] - 1 - piperidyl)ethyl] - 1 - methylindole

The procedure of Example 34(b) was followed but replacing the benzoyl chloride by *p*-chlorobenzoyl chloride to give the title compound in 71% yield, m.p. 212—214°C. (Found C, 69.8; H, 6.8; N, 10.5. $C_{23}H_{26}ClN_3O$ requires C, 69.8; H, 6.6; N, 10.6%).

EXAMPLE 36

3 - [2 - (4 - [4 - Methylbenzamido] - 1 - piperidyl)ethyl] - 1 - methylindole

The procedure of Example 34(b) was followed but replacing the benzoyl chloride by *p*-toluoyl chloride to give the title compound in 71% yield, m.p. 198—199°C. (Found C, 76.6; H, 7.9; N, 11.2. $C_{24}H_{29}N_3O$ requires C, 76.8; H, 7.8; N, 11.2%).

EXAMPLE 37

3 - [2 - (4 - [4 - Methoxybenzamido] - 1 - piperidyl)ethyl] - 1 - methylindole

The procedure of Example 34(b) was followed, but replacing the benzoyl chloride by *p*-methoxybenzoyl chloride to give the title compound in 73.5% yield, m.p. 198—199°C. (Found, C, 73.6; H, 7.6; N, 10.5. $C_{24}H_{29}N_3O_2$ requires C, 73.6; H, 7.5; N, 10.4%).

EXAMPLE 38

3 - [2 - (4 - Benzamido - 1 - piperidyl)ethyl] - 1 - benzylindole

(a) 3 - [2 - (4 - Amino - 1 - piperidyl)ethyl]indole (2.61 g.) was added to sodamide in liquid ammonia prepared from sodium (500 mg.) and liquid ammonia (*ca.* 100 ml.). After $\frac{1}{2}$ hour, benzyl chloride (1.39 g.) in ether (20 ml.) was added dropwise. Stirring was continued until the ammonia evaporated. The 1-benzyl derivative formed was isolated by extraction with chloroform as a brown oil (2.95 g.).

(b) The crude derivative (2.56 g.) in chloroform (40 ml.) was stirred with potassium carbonate (2.1 g.) in water (20 ml.) and treated dropwise with benzoyl chloride (1.17 g.) in chloroform (10 ml.). The aqueous layer was re-extracted with chloroform and the combined extracts were dried and evaporated to give a brown solid (3.44 g.). Recrystallisation from aqueous ethanol gave the title compound as colourless microcrystals (1.52 g.) m.p. 152—153°C. (Found C, 79.80; H, 7.21; N, 9.76. $C_{26}H_{31}N_3O$ requires C, 79.60; H, 7.14; N, 9.60%).

EXAMPLE 39

3 - [2 - (4 - [4 - Chlorobenzamido] - 1 - piperidyl)ethyl] - 1 - benzylindole

The procedure of Example 38(b) was followed, but replacing the benzoyl chloride by *p*-chlorobenzoyl chloride to give the title compound in 57% yield, m.p. 193—4°C. (Found C, 73.7; H, 6.3; N, 8.8. $C_{26}H_{30}ClN_3O$ requires C, 73.8; H, 6.4; N, 8.9%).

EXAMPLE 40

3 - [2 - (4 - [4 - Methoxybenzamido] - 1 - piperidyl)ethyl] - 1 - benzyindole

- 5 The procedure of Example 38(b) was followed, but replacing the benzoylchloride by *p*-methoxybenzoyl chloride to give the title compound in 61% yield, m.p. 191—2°C. (Found C, 76.7; H, 7.4; N, 8.9. $C_{28}H_{33}N_3O_2$ requires C, 77.05; H, 7.1; N, 9.0%).

EXAMPLE 41

3 - [2 - (4 - Benzamido - 1 - piperidyl) - 1 - oxoethyl]indole

- 10 (a) A solution of bromoethyl - 3 - indolyl ketone (2.38 g.) and 4-aminopyridine (0.94 g.) in ethanol (50 ml.) was refluxed for 5 hours.
15 4 - Amino - 1 - [2 - (3 - indolyl) - 2 - oxoethyl]pyridinium bromide (2.62 g., 79%) m.p. 312—315°C. crystallised on cooling. This quaternary salt (2.48 g.) was finely ground and suspended in 95% ethanol (300 ml.) containing triethylamine (3 ml.) and W7 Raney nickel (ca. 2 g.) and hydrogenated at 800 p.s.i. and 80°C. for 5 hours. The catalyst was filtered off and the filtrate was evaporated. The residue in water was made strongly basic and extracted three times with chloroform. After drying and evaporating the extracts, the residual solid was triturated with a little chloroform and filtered off. Recrystallisation from ethanol-ether gave 3 - [2 - (4 - amino - 1 - piperidyl) - 1 - oxoethyl]indole as needles (32%) m.p. 203—5°C.

- 20 (b) The amine (2.58 g.) was finely ground and suspended in chloroform (100 ml.). A solution of potassium carbonate (2.76 g.) in water (20 ml.) was added and the mixture was stirred and ice-cooled while benzoyl chloride (1.41 g.) in chloroform (20 ml.) was added dropwise. The solid formed was filtered off, washed and dried to give the title compound as colourless microcrystals (3.28 g., 91%) m.p. 204—6°C. (Found C, 72.94; H, 6.47; N, 11.48. $C_{22}H_{23}N_3O_2$ requires C, 73.10; H, 6.41; N, 11.63%).

EXAMPLE 42

3 - [2 - (4 - [4 - Chlorobenzamido] - 1 - piperidyl) - 1 - oxoethyl]indole

- 45 The procedure of Example 41(b) was followed, but replacing the benzoyl chloride by *p*-chlorobenzoyl chloride to give the title compound in 83% yield, m.p. 231—233°C. (Found C, 66.7; H, 5.7; N, 10.6. $C_{22}H_{22}ClN_3O_2$ requires C, 66.7; H, 5.6; N, 10.6%).

EXAMPLE 43

55 3 - [2 - (4 - [4 - Methoxybenzamido] - 1 - piperidyl) - 1 - oxoethyl]indole

- 60 The procedure of Example 41(b) was followed, but replacing the benzoyl chloride by *p*-methoxybenzoyl chloride to give the title compound in 74% yield, m.p. 227—9°C. (Found C, 70.4; H, 6.4; N, 10.9. $C_{23}H_{25}N_3O_3$ requires C, 70.6; H, 6.4; N, 10.7%).

EXAMPLE 44

3 - [2 - (4 - Benzamido - 1 - piperidyl)ethyl] - 5 - methoxy - 2 - methylindole

(a) 5 - Methoxy - 2 - methylindole - 3 - acetic acid (50 g.) in tetrahydrofuran (400 ml.) was added dropwise to a stirred suspension of lithium aluminium hydride (50 g.) in tetrahydrofuran (800 ml.). The mixture was heated under reflux for 1 hour, then water (150 ml.) was added dropwise and the inorganic material was filtered off and washed well by suspending in ether. Evaporation of the combined filtrate and washing provided 3 - (2 - hydroxy) ethyl - 5 - methoxy - 2 - methylindole as a crystalline solid (45.3 g., 96.7%), m.p. 98—101°C.

(b) The foregoing alcohol (45.3 g.) was added as quickly as possible to boiling 48% hydrobromic acid (450 ml.). One minute later the solution was poured onto ice (1 Kg.) and extracted with ether. The extracts were washed twice with saturated sodium bicarbonate solution, dried over potassium carbonate and evaporated to provide 3 - (2 - bromo)ethyl - 5 - methoxy - 2 - methylindole as an oil (56.3 g.). This oil was dissolved in acetonitrile (225 ml.) and a solution of 4-acetamidopyridine (28.4 g.) in acetonitrile (120 ml., warmed to effect dissolution) was added. After three hours at room temperature the crystalline product was collected (in three crops) to give 4 - acetamido - 1 - [2 - (5 - methoxy - 2 - methylindol - 3 - yl)ethyl] - pyridinium bromide (58.7 g., 81.7%), m.p. 258—9°C. after recrystallisation from ethanol.

(c) The pyridinium bromide (13.64 g.) was dissolved in methanol (600 ml.) and sodium borohydride (27 g.) was added portionwise with stirring and ice-cooling. Stirring was continued for 2 hours while the mixture warmed to room temperature, then the methanol was distilled out *in vacuo* and water was added to the residue. Extraction with chloroform and evaporation of the dried extracts gave a brown foam which was dissolved in acetonitrile. Ether was added and the resulting precipitate was filtered off and discarded. This was repeated twice, then the final filtrate was evaporated and the residue crystallised from acetonitrile to give 3 - [2 - (4 - acetamido - 1,2,5,6 - tetrahydropyrid - 1 - yl)ethyl] - 5 - methoxy - 2 - methylindole as colourless needles (6.27 g., 57%), m.p. 176—178°C.

(d) The foregoing tetrahydropyridine (4.66 g.) in 50% aqueous acetic acid (50 ml.) was hydrogenated for 18 hours at 50 p.s.i. and 50°C. in the presence of platinum oxide (500 mg.). After filtering off the catalyst and evaporating the filtrate *in vacuo* the residue was dissolved in water and basified with potassium carbonate. Extraction with chloroform and evaporation of the dried extracts gave a foam which was chromatographed on Woelm basic alumina, the eluant being chloro-

form. The product was obtained from two 50 ml. fractions and recrystallised from ethyl acetate to give 3 - [2 - (4 - acetamido - 1 - piperidyl)ethyl] - 5 - methoxy - 2 - methylindole as colourless prisms (3.27 g., 70%), m.p. 193—195°C.

(e) This acetamido compound (2.124 g.) was then hydrolysed following the procedure of Example 15(b) to give 3 - [2 - (4 - amino - 1 - piperidyl)ethyl] - 5 - methoxy - 2 - methylindole as an oil which crystallised on standing (2.26 g.). This amine was dissolved in chloroform (40 ml.) and benzoylated following the procedure of Example 16 to give the title compound as colourless prisms from ethyl acetate (1.49 g.), m.p. 180—181°C. (Found C, 73.24; H, 7.50; N, 11.10. $C_{24}H_{20}N_2O_2$ requires C, 73.62; H, 7.47; N, 10.73%).

EXAMPLE 45

3 - [3 - (4 - Benzamido - 1 - piperidyl)propyl]indole

A mixture of the tosylate of 3 - (3 - hydroxypropyl)indole (1.73 g.), 4-benzamidopiperidine (1.02 g.), and finely ground potassium carbonate (1.38 g.), in isopropanol (25 ml.) was stirred and refluxed for 24 hours. The hot mixture was filtered and the filtrate allowed to cool whereupon the title compound crystallised out to give 1.38 g. (100%), m.p. 174—8°C. A sample recrystallised from aqueous ethanol melted at 179—180°C. (Found: C, 76.4; H, 7.7; N, 11.6. $C_{23}H_{27}N_3O$ requires C, 76.4; H, 7.5; N, 11.6%).

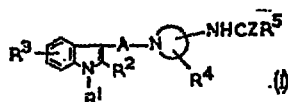
EXAMPLE 46

4 - Benzamido - 1 - (indole - 3 - oxalyl) - piperidine

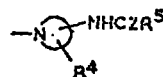
A mixture of 4 - benzamidopiperidine (1.00 g.) (obtained by N-benzylating 4-piperidone, forming the oxime, reducing to give the amine, benzoylating and then hydrogenolysing off the protecting group) in ethyl acetate (75 ml.) and potassium carbonate (1.38 g.) in water (20 ml.) was stirred and ice cooled while indole-3-oxalyl chloride (1.04 g.) in ethyl acetate (70 ml.) was added dropwise during 15 min. Stirring was continued 15 min. then the layers were separated and the ethyl acetate layer was dried over $MgSO_4$. On standing overnight, the title compound crystallised as colourless microneedles (770 mg.) m.p. 266—268°C. (Found: C, 70.1; H, 5.8; N, 11.2. $C_{22}H_{21}N_3O_2$ requires C, 70.4; H, 5.6; N, 11.2%).

WHAT WE CLAIM IS:—

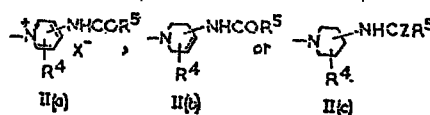
1. Compounds of the general formula



in which formula



represents a ring system of the general formula



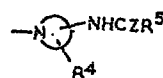
R^1 represents hydrogen, lower alkyl, lower aralkyl or aroyl, R^2 represents hydrogen, lower alkyl or aryl, R^3 represents hydrogen, halogen, lower alkoxy, hydroxy or lower alkyl, R^4 represents hydrogen, halogen or lower alkyl, R^5 represents aryl (including heteroaryl), lower alkoxy, aryloxy, lower aralkyl, lower aralkyloxy or diaryl-lower alkyl, X is an anion, A represents an alkylene or mono- or di-ketol alkylene radical containing up to 4 carbon atoms, Z is an oxo group with the proviso that Z in the formula II(c) may also represent two hydrogen atoms when A is alkylene and R^5 is aryl, the terms "lower alkyl" and "lower alkoxy" mean the radical contains 1 to 6 carbon atoms and the term "lower aralkyl" means the radical contains 7 to 10 carbon atoms.

2. The non-toxic acid addition and quaternary ammonium salts of the tetrahydropyridine and piperidine compounds claimed in Claim 1.

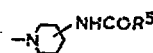
3. Compounds as claimed in Claim 1, wherein A is an alkylene radical containing up to 4 carbon atoms.

4. Compounds as claimed in Claim 3 wherein A is an ethylene radical.

5. Compounds as claimed in Claim 3 or Claim 4, wherein



represents a ring system of the general formula



where R^5 has the meanings defined in Claim 1.

6. Compounds as claimed in Claim 5, wherein R^5 is a phenyl, halophenyl, methoxyphenyl or methylphenyl radical.

7. Compounds as claimed in Claim 1, wherein A is a $-COOH_2-$ radical.



form. The product was obtained from two 50 ml. fractions and recrystallised from ethyl acetate to give 3 - [2 - (4 - acetamido - 1 - piperidyl)ethyl] - 5 - methoxy - 2 - methylindole as colourless prisms (3.27 g., 70%), m.p. 193—195°C.

(c) This acetamido compound (2.124 g.) was then hydrolysed following the procedure of Example 15(b) to give 3 - [2 - (4 - amino - 1 - piperidyl)ethyl] - 5 - methoxy - 2 - methylindole as an oil which crystallised on standing (2.26 g.). This amine was dissolved in chloroform (40 ml.) and benzoylated following the procedure of Example 16 to give the title compound as colourless prisms from ethyl acetate (1.49 g.), m.p. 180—181°C. (Found: C, 73.24; H, 7.50; N, 11.10. $C_{24}H_{29}N_3O_2$ requires C, 73.62; H, 7.47; N, 10.73%).

EXAMPLE 45

3 - [3 - (4 - Benzamido - 1 - piperidyl)propyl]indole

A mixture of the tosylate of 3 - (3 - hydroxypropyl)indole (1.73 g.), 4-benzamidopiperidine (1.02 g.), and finely ground potassium carbonate (1.38 g.), in isopropanol (25 ml.) was stirred and refluxed for 24 hours. The hot mixture was filtered and the filtrate allowed to cool whereupon the title compound crystallised out to give 1.38 g. (100%), m.p. 174—8°C. A sample recrystallised from aqueous ethanol melted at 179—180°C. (Found: C, 76.4; H, 7.7; N, 11.6. $C_{23}H_{27}N_3O$ requires C, 76.4; H, 7.5; N, 11.6%).

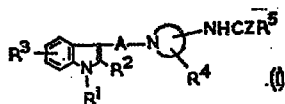
EXAMPLE 46

4 - Benzamido - 1 - (indole - 3 - oxalyl) - piperidine

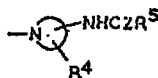
A mixture of 4 - benzamidopiperidine (1.00 g.) (obtained by N-benzylating 4-piperidone, forming the oxime, reducing to give the amine, benzoylating and then hydrogenolysing off the protecting group) in ethyl acetate (75 ml.) and potassium carbonate (1.38 g.) in water (20 ml.) was stirred and ice cooled while indole-3-oxalyl chloride (1.04 g.) in ethyl acetate (70 ml.) was added dropwise during 15 min. Stirring was continued 15 min. then the layers were separated and the ethyl acetate layer was dried over $MgSO_4$. On standing overnight, the title compound crystallised as colourless microneedles (770 mg.) m.p. 266—268°C. (Found: C, 70.1; H, 5.8; N, 11.2. $C_{22}H_{21}N_3O_3$ requires C, 70.4; H, 5.6; N, 11.2%).

WHAT WE CLAIM IS:—

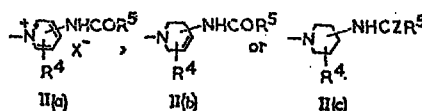
1. Compounds of the general formula



in which formula



represents a ring system of the general formula



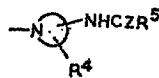
R^1 represents hydrogen, lower alkyl, lower aralkyl or aryl, R^2 represents hydrogen, lower alkyl or aryl, R^3 represents hydrogen, halogen, lower alkoxy, hydroxy or lower alkyl, R^4 represents hydrogen, halogen or lower alkyl, R^5 represents aryl (including heteroaryl), lower alkoxy, aryloxy, lower aralkyl, lower aralkyloxy or diaryl-lower alkyl, X is an anion, A represents an alkylene or mono- or di-ketol alkylene radical containing up to 4 carbon atoms, Z is an oxo group with the proviso that Z in the formula II(c) may also represent two hydrogen atoms when A is alkylene and R^5 is aryl, the terms "lower alkyl" and "lower alkoxy" mean the radical contains 1 to 6 carbon atoms and the term "lower aralkyl" means the radical contains 7 to 10 carbon atoms.

2. The non-toxic acid addition and quaternary ammonium salts of the tetrahydropyridine and piperidine compounds claimed in Claim 1.

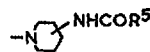
3. Compounds as claimed in Claim 1, wherein A is an alkylene radical containing up to 4 carbon atoms.

4. Compounds as claimed in Claim 3 wherein A is an ethylene radical.

5. Compounds as claimed in Claim 3 or Claim 4, wherein



represents a ring system of the general formula



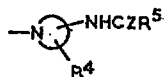
where R^5 has the meanings defined in Claim 1.

6. Compounds as claimed in Claim 5, wherein R^5 is a phenyl, halophenyl, methoxyphenyl or methylphenyl radical.

7. Compounds as claimed in Claim 1, wherein A is a $-COOH_2$ -radical.



8. Compounds as claimed in Claim 7, wherein



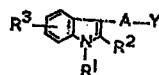
5 represents a ring system of the general formula



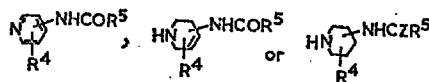
where R⁵ has the meanings defined in Claim 1.

9. Compounds as claimed in Claim 8, wherein R⁵ is a phenyl, halophenyl, methoxyphenyl or methylphenyl radical.
10. 4 - Benzamido - 1 - [2 - (3 - indolyl)ethyl]pyridinium bromide.
11. 3 - Benzamido - 1 - [2 - (3 - indolyl)ethyl]pyridinium bromide.
12. 4 - Benzyloxycarbonylamino - 1 - [2 - (3 - indolyl)ethyl]pyridinium bromide.
13. 4 - (4 - Chlorobenzamido - 1 - [2 - (3 - indolyl)ethyl]pyridinium bromide.
14. 4 - (2,2 - Diphenylacetamido) - 1 - [2 - (3 - indolyl)ethyl]pyridinium bromide.
15. 3 - [2 - (4 - Benzamido - 1,2,5,6-tetrahydropyrid - 1 - yl)ethyl]indole.
16. 3 - [2 - (3 - Benzamido - 1,2,5,6-tetrahydropyrid - 1 - yl)ethyl]indole.
17. 3 - [2 - (4 - Benzyloxycarbonylamino - 1,2,5,6 - tetrahydropyrid - 1 - yl)ethyl]indole.
18. 3 - [2 - (4 - Chlorobenzamido) - 1,2,5,6 - tetrahydropyrid - 1 - yl)ethyl]indole.
19. 3 - [2 - (4 - [2,2 - Diphenylacetamido] - 1,2,5,6 - tetrahydropyrid - 1 - yl)ethyl]indole.
20. 3 - [2 - (4 - Benzylaminopiperid - 1 - yl)ethyl]indole.
21. 3 - [2 - (4 - Benzamido - 1 - piperidyl)ethyl]indole.
22. 3 - [2 - (3 - Benzamido - 1 - piperidyl)ethyl]indole.
23. 3 - [2 - (4 - [4 - Chlorobenzamido] - 1 - piperidyl)ethyl]indole.
24. 3 - [2 - (4 - [4 - Methoxybenzamido] - 1 - piperidyl)ethyl]indole.
25. 3 - [2 - (4 - [3 - Methoxybenzamido] - 1 - piperidyl)ethyl]indole.
26. 3 - [2 - (4 - [2 - Methoxybenzamido] - 1 - piperidyl)ethyl]indole.
27. 3 - [2 - (4 - [3,4,5 - Trimethoxybenzamido] - 1 - piperidyl)ethyl]indole.
28. 3 - [2 - (4 - [Indol - 3 - carboxamido] - 1 - piperidyl)ethyl]indole.
29. 3 - [2 - (4 - (2,2 - Diphenylacetamido) - 1 - piperidyl)ethyl]indole.
30. 3 - [2 - (4 - [2 - Methylbenzamido] - 1 - piperidyl)ethyl]indole.
31. 3 - [2 - (4 - [3 - Methylbenzamido] - 1 - piperidyl)ethyl]indole.

32. 3 - [2 - (4 - [4 - Methylbenzamido] - 1 - piperidyl)ethyl]indole.
33. 3 - [2 - (4 - [2 - Furylcarboxamido] - 1 - piperidyl)ethyl]indole.
34. 3 - [2 - (4 - [2 - Chlorobenzamido] - 1 - piperidyl)ethyl]indole.
35. 3 - [2 - (4 - [3,4 - Methyleneedioxybenzamido] - 1 - piperidyl)ethyl]indole.
36. 3 - [2 - (4 - [2 - Carboxybenzamido] - 1 - piperidyl)ethyl]indole.
37. 3 - [2 - (4 - [2 - Trifluoromethylbenzamido] - 1 - piperidyl)ethyl]indole.
38. 3 - [2 - (4 - [4 - Phenylbenzamido] - 1 - piperidyl)ethyl]indole.
39. 3 - [2 - (4 - [2 - Phenylacetamido] - 1 - piperidyl)ethyl]indole.
40. 3 - [2 - (4 - Benzamido - 1 - piperidyl)ethyl] - 2 - methylindole.
41. 3 - [2 - (4 - [4 - Methoxybenzamido] - 1 - piperidyl)ethyl] - 2 - methylindole.
42. 3 - [2 - (4 - [4 - Chlorobenzamido] - 1 - piperidyl)ethyl] - 2 - methylindole.
43. 3 - [2 - (4 - Benzamido - 1 - piperidyl)ethyl] - 1 - methylindole.
44. 3 - [2 - (4 - [4 - Chlorobenzamido] - 1 - piperidyl)ethyl] - 1 - methylindole.
45. 3 - [2 - (4 - [4 - Methoxybenzamido] - 1 - piperidyl)ethyl] - 1 - methylindole.
46. 3 - [2 - (4 - [4 - Methoxybenzamido] - 1 - piperidyl)ethyl] - 1 - methylindole.
47. 3 - [2 - (4 - Benzamido - 1 - piperidyl)ethyl] - 1 - benzylindole.
48. 3 - [2 - (4 - [4 - Chlorobenzamido] - 1 - piperidyl)ethyl] - 1 - benzylindole.
49. 3 - [2 - (4 - [4 - Methoxybenzamido] - 1 - piperidyl)ethyl] - 1 - benzylindole.
50. 3 - [2 - (4 - Benzamido - 1 - piperidyl)ethyl] - 1 - oxoethylindole.
51. 3 - [2 - (4 - [4 - Chlorobenzamido] - 1 - piperidyl)ethyl] - 1 - oxoethylindole.
52. 3 - [2 - (4 - [4 - Methoxybenzamido] - 1 - piperidyl)ethyl] - 1 - oxoethylindole.
53. 3 - [2 - (4 - Benzamido - 1 - piperidyl)ethyl] - 5 - methoxy - 2 - methylindole.
54. 3 - [3 - (4 - Benzamido - 1 - piperidyl)propyl]indole.
55. 4 - Benzamido - 1 - (indole - 3-oxalyl)piperidine.
56. A process for the preparation of a compound as claimed in Claim 1, which comprises reacting a compound of the formula



with a compound of the general formula

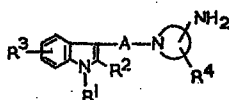


where R¹, R², R³, R⁴, R⁵, A and Z have the

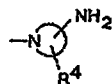


meanings defined in Claim 1 and Y is a halogen atom or equivalent radical.

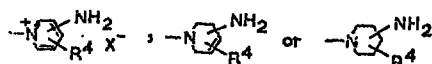
57. A process for the preparation of compounds as claimed in Claim 1, which comprises acylating a compound of the general formula



with a reactive derivative of an acid of general formula $R^5\text{COOH}$ where



represents a ring system of the general formula

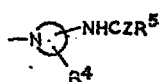


and R^1 , R^2 , R^3 , R^4 , R^5 and A have the meanings defined in Claim 1, whereby a compound in which Z is =O is obtained.

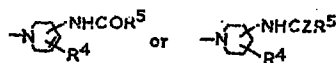
58. A process as claimed in Claim 57, wherein the product obtained is then reduced.

59. A process as claimed in Claim 57, or 58, wherein the acylating agent is a halide.

60. A process for the preparation of the compounds claimed in Claim 1, in which

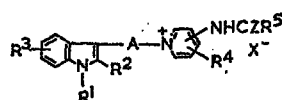


represents a ring system of the general formula



(in which Z, R^4 and R^5 have the meanings defined in Claim 1), which comprises selectively reducing a corresponding compound having a more highly unsaturated ring system.

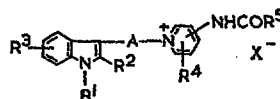
61. A process as claimed in Claim 58, wherein a compound of the general formula



(where R^1 , R^2 , R^3 , R^4 , R^5 , X^- and A have the meanings defined in Claim 1) is hydrogenated in the presence of a hydrogenation catalyst.

62. A process as claimed in Claim 61 wherein the hydrogenation catalyst is platinum or Raney nickel.

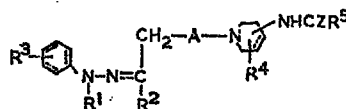
63. A process as claimed in Claim 60 wherein a compound of the general formula



(where R^1 , R^2 , R^3 , R^4 , R^5 , X^- and A have the meanings defined in Claim 1) is reduced with an alkali metal borohydride.

64. A process as claimed in Claim 63, wherein the product obtained is then further reduced with a hydride transfer agent.

65. A process for preparing tetrahydropyridine and piperidine compounds as claimed in Claim 1, which comprises carrying out a Fischer indole synthesis on a compound of the general formula



(where R^1 , R^2 , R^3 , R^4 , R^5 , A and Z have the meanings defined in Claim 1 and the broken line indicates that a double bond optionally is present in the 3,4-position of the ring.)

66. A process as claimed in any of Claims 56 to 65 wherein the compound obtained contains a hydrogen atom in the 1-position and this compound is then lower alkylated, lower aralkylated or aroylated.

67. A process as claimed in any of Claims 56 to 66, wherein A is an alkylene group containing up to 4 carbon atoms.

68. A process as claimed in Claim 67, wherein A is an ethylene group.

69. A process as claimed in any of Claims 56 to 66, wherein A is an oxoethylene group.

70. A process as claimed in any of Claims 67 or 68, wherein R^5 is a phenyl, halophenyl, methoxyphenyl or methylphenyl group.

71. A process as claimed in Claim 69, wherein R^5 is a phenyl, halophenyl, methylphenyl or methoxyphenyl group.

72. A process as claimed in any of Claims 54 to 68, substantially as described with reference to any of Examples 1 to 26 or 31.

73. A process as claimed in any of Claims 56 to 71, substantially as described with reference to any of Examples 27 to 30 or 32 to 44.

74. Indoles when prepared by the process claimed in any of Claims 54 to 66, 69, 71 or 73.

75. Indoles when prepared by the process claimed in any of Claims 67, 68, 70 or 72.

76. A pharmaceutical composition comprising a compound as claimed in any of



* C L H S *

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Claims 1 to 55, 74 or 75, and a pharmaceutically acceptable carrier.

- 5 77. A pharmaceutical composition as claimed in Claim 76, wherein the compound is one in which A is an ethylene group.

78. A pharmaceutical composition as claimed in Claim 77, wherein the compound is one in which R⁵ is a phenyl, halophenyl, methoxyphenyl or methylphenyl group.

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