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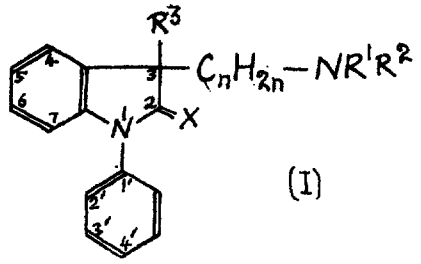
COMPLETE SPECIFICATION

N-Phenyl Indoline Derivatives

We, PFIZER LIMITED, a British Company, of Ramsgate Road, Sandwich, Kent, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The invention relates to therapeutic agents comprising N-phenyl indoline derivatives, and is particularly concerned with 3-aminoalkyl-1-phenyl indolines and 2-indolinones which we have found to be useful for their action on the central nervous system. In particular we have discovered that many of these compounds have useful anti-depressant activity, particularly when administered orally.

These compounds are those having a structural formula represented by:



(I)

where:

R^1 and R^2 each represent a hydrogen atom, a lower alkyl group, a benzyl group or together with the nitrogen atom to which they are attached form a saturated ring which, if it contains a further nitrogen atom, may be substituted at such nitrogen atom with a lower alkyl or hydroxalkyl group or a benzyl group;

R^3 represents a lower alkyl group, a phenyl group or a benzyl group;

C_nH_{2n} represents a bivalent saturated lower aliphatic hydrocarbon group in which n is at least 2 and in which the free valences are located on different carbon atoms;

X represents either an oxygen atom or two hydrogen atoms; and

any benzene ring in the structural formula or in R^1, R^2 or R^3 may be substituted with one or more halogen atoms, lower alkyl or alkoxy groups, trifluoromethyl groups, nitro groups, hydroxyl groups or sulphamoyl or N-substituted sulphamoyl groups;

and the pharmaceutically acceptable acid addition salts of such compounds.

In this specification, the term "lower," used to qualify the terms "alkyl," "hydroxyalkyl" or "aliphatic," indicates "containing

[*Price 4s. 6d.*]

not more than 8 carbon atoms in a straight or branched chain."

With the exception of the single chemical compound in which R^1, R^2 and R^3 are each methyl, C_nH_{2n} is ethylene, X is an oxygen atom and the benzene rings are unsubstituted, and its hydrochloride (which are disclosed in the Journal of Medicinal Chemistry, 1965, vol. 8, on pages 629 and 637), the compounds of formula I are novel compounds provided by the present invention.

Particular classes of novel compounds which we have found to be the most useful in accordance with this invention are those compounds of formula I having one or more of the following characteristics:

(a) at least one of R^1 and R^2 is hydrogen, and in particular R^1 is a lower alkyl group and R^2 is hydrogen;

(b) n is at least 3, and in particular C_nH_{2n} is a trimethylene or tetramethylene group;

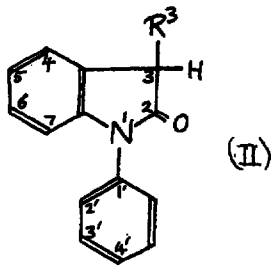
(c) R^1 is a lower alkyl group and R^2 is a benzyl group;

(d) R^3 is a methyl group.

The compounds of the invention have marked activity on the adrenergic nervous system of experimental animals, and many have properties in common with antidepressant drugs. In particular the latter antagonise the sedation induced in rats by intraperitoneally injected tetrabenazine, potentiate the response to low frequency electrical stimulation of the nictitating membrane of the cat, potentiate the effects of injected adrenaline or noradrenaline on the blood pressure of the cat, and reverse the hypothermia caused by intraventricularly injected noradrenaline, or by subcutaneously injected reserpine, in the mouse.

The compounds of formula I may be prepared by a number of methods according to the invention including the following:

(1) A 3-substituted 1-phenyl-2-indolinone of the formula:

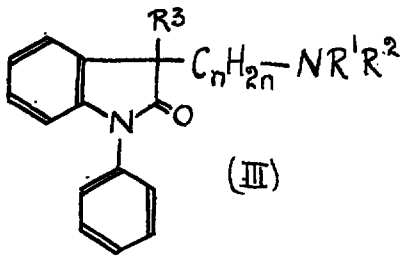


(II)

(in which any benzene ring may be substituted, as already described) may be prepared (a) when R^3 is methyl, by the method described in the Journal of Medicinal Chemistry, volume 8, pages 628 and 637 (1965), i.e. by hydrogenolysis of the corresponding 3-hydroxymethylene compound, prepared by formylation of the 3-unsubstituted 1-phenyl-2-indolinone, or (b) by condensation of a diphenylamide of an α-chloro-acid $R^3.CHCl.COOH$, in the presence of a Lewis acid catalyst (e.g. aluminium chloride). This compound is then reacted with sodamide (or sodium hydride) in a suitable solvent, e.g. toluene or dimethyl formamide, to form its sodium derivative and then with a halogenated amine of the formula

$$Hal—(C_nH_{2n})NR^1R^2$$

to yield a compound of the formula:



(III)

In this method preferably a halogenated tertiary amine is used, i.e. neither R^1 nor R^2 is hydrogen, to avoid self-condensation of the products.

When R^3 is benzyl, the compound of Formula II may also be prepared by hydrogenation of the corresponding 3-benzylidene compound, 1 - phenyl - 3 - benzylidene - 2 indolinone, which is a known compound.

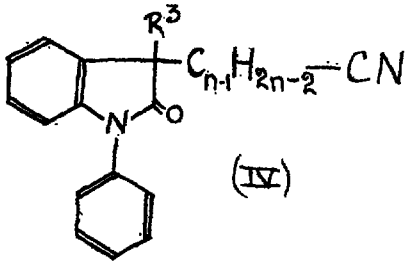
Compounds of formula II in which one or more of the benzene rings are substituted may be prepared by method (b) described above by condensing an appropriately substituted diphenylamide of an α-chloro acid, but unless the diphenylamine group is symmetrically substituted in the 4,4'-positions a mixture of isomers may be obtained, which may require separation before progressing further to compounds of formula III or other compounds hereinafter described. Thus, for example, compounds of formula II substituted in the 5- and 4'-position with halogen atoms, lower alkyl or alkoxy groups, nitro-groups or N,N-dimethyl sulphamoyl groups may be prepared from the corresponding 4,4'-disubstituted diphenylamide of an α-chloro acid.

Many of the compounds of formula II, in which R^3 is other than methyl, are themselves novel compounds.

(2) A compound of the formula II above may be reacted with a halogenated nitrile of the formula:

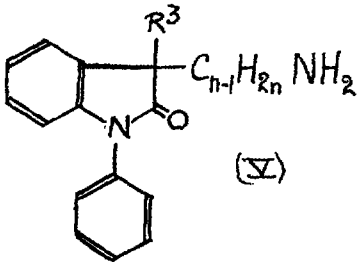
$$Hal—(C_{n-1}H_{2n-2})CN$$

to yield a compound of the formula:



(IV)

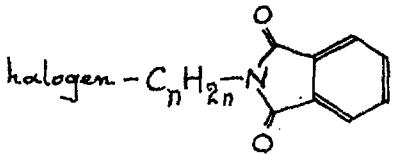
(in which any benzene group may be substituted, as already described), which is then reduced, e.g. with hydrogen and a platinum or palladium catalyst, to the corresponding primary amine of the formula:



(V)

Compounds of formula IV are themselves novel compounds.

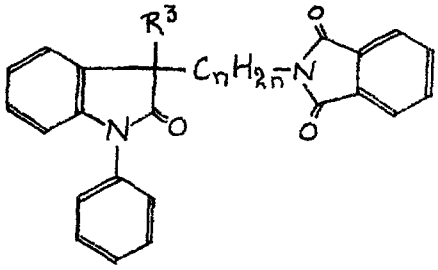
(3) A compound of the formula II may be reacted with a halogenated N-alkyl phthalimide of the formula:



or with an alkylene chloro-bromide of the formula:

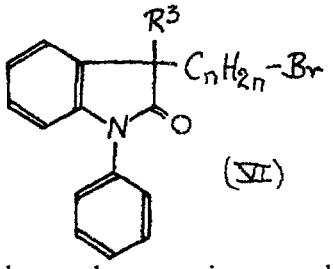
$$Br(C_nH_{2n})Cl$$

and then with potassium phthalimide, to yield a compound of the formula:



which is then hydrolysed under conditions such as to retain the indolinone structure, e.g. by hydrazine, to yield a primary amine of the formula V.

(4) A compound of formula II above may also be reacted with an alkylene chloro-bromide of the formula $Br(C_nH_{2n})Cl$ to form a compound of the formula:

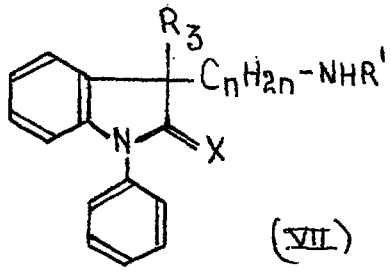


(VI)

(in which any benzene ring may be substituted, as before) which is then reacted with an amine of the formula HNR^1R^2 to yield a compound of formula II, above. As in method (1) preferably neither R^1 nor R^2 is hydrogen, i.e. a secondary amine is used.

Compounds of formula VI are themselves novel compounds.

(5) Compounds of formula I, in which neither R^1 nor R^2 is hydrogen may be converted to compounds in which R^2 is hydrogen by a number of methods, e.g.: (a) when R^1 is an alkyl group and R^2 is a methyl group, treatment with an alkyl chloroformate converts the methyl group to an alkoxycarbonyl group which can then be removed by hydrolysis under conditions such as to retain the indoline (or indolinone) structure; or (b) when R^1 is an alkyl group and R^2 is a benzyl group, reduction with hydrogen in the presence of a palladium catalyst removes the benzyl group; each method yields a compound of the formula:



(VII)

where R^1 is an alkyl group.

(6) Compounds of formula I, in which at least one of R^1 and R^2 is hydrogen, may be converted to compounds in which R^1 and/or R^2 is alkyl or benzyl by alkylation or benzylation of the primary or secondary amino group by well-known methods, including reaction of a compound in which both R^1 and R^2 are hydrogen (i.e. a compound of formula V above) with benzaldehyde to form the corresponding benzylidenamino compound and then either (a) reducing it to the corresponding benzylamino compound (in which R^1 is hydrogen and R^2 is benzyl) or (b) treating it with a lower alkyl iodide and hydrolysing (under suitable conditions, as in method (5) (a) above) to form the corresponding monoalkylamino compound (in which R^1 is hydrogen and R^2 is alkyl).

(7) Compounds of Formula I in which X is an oxygen atom may be reduced with lithium aluminium hydride (or diborane) in ether to yield compounds of the Formula I in which X is two hydrogen atoms.

(8) Compounds of Formula I substituted in the 5-position with a halogen atom or nitro-group may also be produced by direct halogenation or nitration of the corresponding unsubstituted compound of Formula I. Alternatively the intermediate compound of formula II may first be halogenated or nitrated. In either case halogenation or nitration takes place predominantly at the 5-position.

(9) Compounds of Formula I substituted in the 5-position with a sulphamyl or N-substituted sulphamyl group may be produced by direct sulphonation of the corresponding unsubstituted compound (e.g. by means of chlorosulphonic acid) and conversion of the 5-sulphonic acid to the 5-sulphonyl chloride and then to the 5-sulphamoyl compound by well-known methods. Alternatively the intermediate compound of formula II may first be sulphonated and converted to the 5-sulphamoyl compound.

(10) Compounds of Formula I substituted in the 5-position with a hydroxy group or a lower alkoxy group may be prepared by first acetylating the corresponding unsubstituted intermediate compound of Formula II with acetyl chloride in the presence of a Lewis acid catalyst, e.g. aluminium chloride. Under these conditions acetylation takes place predominantly at the 5-position. The 5-acetyl compound is then oxidised by suitable means to the 5-acetoxy compound, which (after conversion to a compound of formula I) is then hydrolysed to the 5-hydroxy compound and converted to the 5-alkoxy compound, if required, by well-known methods.

The compounds of the invention exist in D and L optically active isomeric forms, by virtue of the asymmetric carbon atom at position 3 in the indoline nucleus, and the invention comprehends the compounds in the separated D and L forms, as well as the racemic DL-mixtues produced by the above methods.

Acids from which pharmaceutically acceptable addition salts of the compounds of the invention can be prepared are those which form non-toxic addition salts containing pharmaceutically- acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, sulphate or bisulphate, phosphate or acid phosphate, acetate, maleate, fumarate, lactate, tartrate, citrate, gluconate, saccharate and *p*-toluene sulphonate salts.

The compounds of the invention can be administered alone, but will generally be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. For example, they may be administered orally in the form of tablets containing such excipients as starch or lactose, or in capsules either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavouring or colouring agents. They may be injected parenterally, for example, intramuscularly or subcutaneously. For parenteral administration, they are best used in the form of a sterile aqueous solution which may contain other solutes, for example, enough salts or glucose to make the solution isotonic.

The invention is illustrated by the following Preparations and Examples of the preparation and characterisation of compounds of the invention and intermediates therefor, and of pharmaceutical compositions prepared therefrom. In these Preparations and Examples, all temperatures are given in °C.

A.
PREPARATION OF INTERMEDIATES.

PREPARATION A.

3-Methyl-1-Phenyl-2-Indolinone.

Diphenylamine (1,352 g.; 8 mol.) was dissolved in benzene (4 litres) and α-chloropropionyl chloride (1,270 g.; 10 mol.) was added over 70 minutes with stirring. An exothermic reaction occurred at first, the temperature rising to 56°, and diphenylamine hydrochloride separated as a solid. After the addition was complete, the mixture was heated on the steam bath for four hours, a copious stream of hydrogen chloride being evolved in the first two hours. At the end of the reaction a clear solution resulted. The benzene was evaporated, and the oily residue was poured, with stirring, into 60—80° petrol (5 litres). N.N - diphenyl - α - chloropropionamide separated as a cream-coloured, crystalline solid which was filtered off and washed with 60—80° petrol (750 ml.). The dried solid (1.9 kg; M. pt.: 90—93°) was used without further purification.

N,N - diphenyl - α - chloropropionamide (520 g.; 2 mol.) and aluminium chloride (570 g.; 4.27 mol.) were mixed together in a 5 litre beaker and gently heated with hand stirring. When the temperature reached 50° a vigorous reaction started and without further heating the temperature rose to 140°. The mixture foamed as hydrogen chloride was evolved and when the evolution ceased, it was allowed to cool to 90° and the mobile liquid poured into a mixture of ice (1 kg.) and concentrated hydrochloric acid (600 ml.). A sticky solid separated and this was extracted into chloroform. The solution was then dried over magnesium sulphate. The combined chloroform extracts from processing a total of 1.82 kg., of N,N'-diphenyl-α-chloropropionamide were concentrated to approximately one third of the original volume and then added, with stirring, to 40—60° petrol (5

litres). 3 - Methyl - 1 - phenyl - 2 - indolinone separated as a buff coloured solid which was filtered off and washed with 30—40° petrol (1 litre). A second crop was obtained by concentration of the filtrate and washings, giving a total yield of 1.44 kg. Melting point: 80—81°.

Analysis:

Calcd. for $C_{15}H_{15}NO$:	C, 80.54;	H, 5.83; N, 6.27.
Found:	C, 80.82;	H, 6.22; N, 6.34.

PREPARATION B.

3-*n*-Butyl-1-Phenyl-2-Indolinone.

Diphenylamine (440 g.; 2.6 mol.) was dissolved in benzene (1.5 litres) and α-bromohexanoyl chloride (600 g.; 2.81 mol.) was added rapidly. The reaction mixture was heated under reflux for three hours by which time evolution of HCl gas ceased. The mixture was evaporated under reduced pressure to give a pinkish oil which solidified on standing. A small sample was recrystallised from 40—60° petrol to yield N,N-diphenyl-α-bromohexanoamide as a pale yellow solid (M.pt.; 69—73°). The crude solid (880 g.; 2.55 mole) was mixed with aluminium chloride (744 g.; 5.6 mole.) in a 5 litre beaker and gently heated with hand stirring. When the temperature reached 70° a vigorous exothermic reaction ensued and the temperature rose to 120°. When the main reaction had subsided, the melt was heated to 160° and maintained for five minutes at that temperature and then cooled to 90°. The mixture was poured into ice (1 kg.) and concentrated hydrochloric acid (500 ml.). A sticky solid separated which was extracted with ether. The organic layer was successively washed with 3 N HCl, water, 10% aqueous sodium carbonate solution and water, and finally dried over anhydrous sodium carbonate. Evaporation of the ether gave 3-*n*-butyl-1-phenyl-2-indolinone as a thick oil which was distilled in vacuo. (B. pt.; 170—190° at 0.5 mm; 556 g.). The infrared and nuclear magnetic resonance spectra were consistent with the assigned structure.

PREPARATION C.

1,3-Diphenyl-2-Indolinone.

α-Chlorophenylacetyl chloride (37.8 g.; 0.2 mol.) was added to a solution of diphenylamine (33.8 g.; 0.2 mol.) in toluene (350 ml.) and the mixture heated under reflux for three hours. Evaporation of the mixture gave N,N-diphenyl - α - chlorophenylacetamide as a crystalline material (64 g.) which was used directly for the next step. A small sample was recrystallised from 40—60° petrol—benzene to give the pure product, M.pt.: 141—144°.

A mixture of N,N-diphenyl-α-chlorophenylacetamide (60 g.; 0.184 mol.) and aluminium chloride (62 g.; 0.5 mol.) was heated with hand stirring in a 2 litre beaker. At 60° a violent reaction took place and the temperature of the melt rose to 160°. When the reaction subsided, the mixture was heated to 150° for three minutes, then cooled to 90° and poured into ice (500 g.) and concentrated hydrochloric acid (100 ml.). A solid separated which was extracted with ether and the extracts were successively washed with 3 N HCl, water, 10% aqueous Na_2CO_3 and water. After drying the organic solution over Na_2SO_4 it was concentrated under reduced pressure to a small volume and treated with an equal volume of 40—60° petrol. 1,3-Diphenyl-2-indolinone deposited as a crystalline solid. Recrystallisation from 60—80° petrol gave pale yellow crystals (M. pt.: 111—113°; 42 g.).

Analysis:

Calcd. for $C_{20}H_{15}NO$:	C, 84.2;	H, 5.3; N, 4.90.
Found:	C, 84.25;	H, 5.06; N, 5.13.

PREPARATION D.

3-Benzyl-1-Phenyl-2-Indolinone.

3 - Benzylidene - 1 - phenyl - 2 - indolinone (17 g.) prepared as described in *Berichte*, 1914, *47*, 2120, was dissolved in hot ethyl acetate (200 ml.) and hydrogenated at 50 p.s.i. and 50° over 10% palladium on charcoal (700 mg.) until uptake ceased. The mixture was filtered and evaporated whereupon 3 - benzyl - 1 - phenyl - 2 - indolinone solidified (15.5 g.; M. pt.: 86—88°). A small portion was recrystallised from isopropanol (M.pt.: 90—94°).

Analysis:

Calcd. for $C_{21}H_{17}NO$:	C, 84.25;	H, 5.72; N, 4.68.
...Found:	C, 84,14;	H, 5.87; N, 4.47.

PREPARATION E.

5-Bromo-3-methyl-1-phenyl-2-indolinone.

To a hot solution of 3-methyl-1-phenyl-2-indolinone (11.15 g.; 0.05 mol.; prepared as in Preparation A) in 50% aqueous dioxan (150 ml.), a mixture of bromine (8 g.; 0.05 mol.) and potassium bromide (12 g.) in water (20 ml.) was added fairly rapidly. The reaction was almost instantaneous. The solvents were evaporated to give a mixture of solid and an oil. This was filtered and the solid was recrystallised from ethanol to give 5-bromo - 3 - methyl - 1 - phenyl - 2 - indolinone as colourless plates (5 g., M.pt.: 112—115°). The position of the bromination was ascertained by nuclear magnetic resonance techniques.

Analysis:

Calcd. for $C_{15}H_{12}BrNO$: C, 59.59; H, 4.01; N, 4.64; Br, 26.46.
Found: C, 59.48; H, 4.03; N, 4.68; Br, 26.74.

PREPARATION F.

3-(2-Cyanoethyl)-3-Methyl-1-Phenyl-2-Indolinone.

3 - Methyl - 1 - phenyl - 2 - indolinone (22.3 g.; 0.1 mol.; prepared as in Preparation A) was dissolved in dioxan (250 ml.) and a few drops of 40% alcoholic solution of N,N,N-trimethyl benzylammonium hydroxide were added, followed by slow addition of acrylonitrile (7.8 g., 0.15 mol.). The mixture was heated under reflux for 3—4 hours, the solvent eliminated under reduced pressure and the resultant oil, which solidified on standing, was dissolved in benzene. The solution was decolourised with charcoal and 40—60° petrol was then added hot. 3-(2-Cyanoethyl) - 3 - methyl - 1 - phenyl - 2 - indolinone separated as colourless crystals (18.5 g.; M.pt.: 111.5—112.5°).

Analysis:

Calcd. for $C_{18}H_{16}N_2O$: C, 78.23; H, 5.84; N, 10.14.
Found: C, 78.21; H, 5.90; N, 10.03.

PREPARATION G.

3-*n*-butyl-3-(2-cyanoethyl)-1-phenyl-2-indolinone.

This compound was prepared by the method of Preparation F. From 3-*n*-butyl-1-phenyl-2-indolinone (prepared as in Preparation B) and acrylonitrile.

PREPARATION H.

3-Cyanomethyl-3-Methyl-1-Phenyl-2-Indolinone.

This compound was prepared by the method of Example I (below) but using chloromethylcyanide as the alkylating agent instead of dimethylamino-propyl chloride. Recrystallised from 40—60° petrol, it had M.pt.: 112—113.5°.

Analysis:

Calcd. for $C_{17}H_{14}N_2O$: C, 77.84; H, 5.38; N, 10.68.
Found: C, 77.99; H, 5.51; N, 10.67.

PREPARATION J.

3-(3-Cyanopropyl)-3-Methyl-1-Phenyl-2-Indolinone.

This compound was prepared by the method of Example I (below) but using γ-bromobutyronitrile as the alkylating agent. B.pt.: 202° at 0.1 mm. Recrystallised from 40—60° petrol-ethanol, it had M.pt.: 109.5—110°.

Analysis:

Calcd. for $C_{19}H_{18}N_2O$: C, 78.59; H, 6.25; N, 9.65.
Found: C, 78.26; H, 6.21; N, 9.92.

PREPARATION K.

3-(2-Bromoethyl)-3-Methyl-1-Phenyl-2-Indolinone.

This compound was prepared by the method of Example I (below), but using 1,2-dibromoethane as the alkylating agent. The oily product contained some 1,2-bis(3-methyl-1-phenyl-2-indolinone-3-yl) ethane.

PREPARATION L.

3-(3-Bromopropyl)-3-Methyl-1-Phenyl-2-Indolinone.

This compound was prepared by the method of Example I (below), but using 1,3-dibromopropane as the alkylating agent. The oily product contained some 1,3-bis(3-methyl-1-phenyl-2-indolinone-3-yl) propane.

PREPARATION M.

3 - methyl - 1 - phenyl - 2 - indolinone (22.3 g.; 0.1 mol.; prepared as in Preparation A) was added to a solution of acetyl chloride (15.7 g.; 0.2 mol.) and aluminium chloride (26.6 g.; 0.2 mol.) in *sym.*-tetrachloro-ethane (250 ml.) cooled to 0°. The mixture was kept at 10° for 0.5 hr. and then heated to 90° for 1 hr., whereupon evolution of HCl took place. The mixture was poured into a mixture of ice and conc. HCl and the organic layer was separated, washed with water and evaporated to dryness after treatment with charcoal and Na_2SO_4. The residual oil was chromatographed on alumina and eluted with chloroform. The 5-acetyl-3-methyl-1-phenyl-2-indolinone was obtained from the eluates by evaporation of the solvent and then recrystallised four times from ethanol (yield: 6 g.; m.pt.: 131—132°). The position of the acetyl group was ascertained by nuclear magnetic resonance techniques.

Analysis:

Calcd. for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28.
Found: C, 77.00; H, 5.80; N, 5.51.

B. PREPARATION OF COMPOUNDS OF THE INVENTION.

EXAMPLE I.

3-(3-Dimethylaminopropyl)-3-Methyl-1-Phenyl-2-Indolinone.

3 - Methyl - 1 - phenyl - 2 - indolinone (22.3 g.: 0.1 mol. prepared as in Preparation A) in dry toluene (50 ml.) was added slowly to sodamide (4.68 g.; 0.12 mol.) in dry toluene (200 ml.). The mixture was heated under reflux for three hours by which time the evolution of NH_3 had ceased. Dimethylaminopropyl chloride (21 g., 0.173 mol., from 31 g. of the corresponding hydrochloride, was added to the cooled toluene solution. The mixture was then boiled under reflux for three hours, cooled and poured into water. The organic layer was separated from the aqueous one and the latter was extracted with ether. The combined organic fractions were washed with water, and then extracted with 4 N hydrochloric acid (4 × 40 ml.). The aqueous layer was basified with 5 N sodium hydroxide, extracted with ether and the organic layer dried over Na_2SO_4 and evaporated to give a dark oil which was distilled. The main fraction distilled at 190—200° at 1 mm., giving 3 - (3 - dimethylaminopropyl) - 3-methyl-1-phenyl-2-indolinone as an oil (22.5 g.). The hydrochloride was prepared in ethereal hydrochloride acid solution and was a colourless crystalline solid which after recrystallisations from chloroform-ethyl acetate and ethylacetate-methanol had a M. pt., of 168—170° and 1 mol. of water of crystallisation.

Analysis:

Calcd. for $C_{20}H_{27}ClN_2O_2$: C, 66.15; H, 7.50; N, 7.71.
Found: C, 66.07; H, 7.14; N, 7.41.

EXAMPLE II.

3-[2-(N-Benzyl-N-Methylamino)ethyl]-3-methyl-1-phenyl-2-indolinone.

This compound was prepared by the method of Example I, but using 2-(N-benzyl-N-methylamino)ethyl chloride as the alkylating agent instead of dimethylaminopropyl chloride. It was recrystallised from ethyl acetate as the maleate (M.pt. 165—166°).

Analysis:

Calcd. for $C_{30}H_{32}N_2O_5$: C, 71.60; H, 6.18; N, 5.76.
Found: C, 71.87; H, 5.95; N, 5.68.

EXAMPLE III.

3-[3-(N-Benzyl-N-methylamino)propyl]-3-methyl-1-phenyl-2-indolinone.

This compound was prepared by the method of Example I, but using 3-(N-benzyl-N-methylamino)propyl chloride as the alkylating agent. It was recrystallised from hot water as the hydrochloride (M.pt.: 198—205°).

Analysis:

Calcd. for $C_{26}H_{29}ClN_2O$: C, 74.18; H, 6.90; N, 6.66.
Found: C, 73,83; H, 6.93; N, 6.49.

EXAMPLE IV.

3-*n*-Butyl-3-(2-Dimethylaminoethyl)-1-Phenyl-2-Indolinone.

This compound was prepared by the method of Example I, but using 3-*n*-butyl-1-phenyl-2-indolinone (prepared as in Preparation B) as the starting material and 2-dimethylaminoethyl chloride as the alkylating agent. The free base of the product after distillation at 200—205/0.7 mm., was further purified by chromatography on a silica column. The desired material was eluted with acetone as an oil which was converted into the hydrochloride in the usual way. The crystalline hydrochloride was purified by repeated crystallisations from ethyl acetate-chloroform-ether to give pure 3-*n*-butyl-3-(2-dimethylaminoethyl) - 1 - phenyl - 2 - indolinone hydrochloride as colourless crystals (M.pt.: 157—160°).

Analysis:

Calcd. for $C_{22}H_{29}ClN_2O$: C, 70.86; H, 7,84; N, 7.51; Cl, 9.51.
Found: C, 70.75; H, 7.69; N, 7.65; Cl, 9.59

EXAMPLE V.

3-*n*-Butyl-3[2-(N-Benzyl-N-Methylamino)-ethyl]-1-Phenyl-2-Indolinone.

This compound was prepared by the method of Example I but using 3-*n*-butyl-1-phenyl-2-indolinone as the starting material and 2 - (N - benzyl - N - methylamino)-ethyl chloride as the alkylating agent. It had B.pt.: 220—230°/0.2 mm. Although no solid derivative could be obtained, nor any satisfactory analysis of the free base, the infrared and nuclear magnetic resonance spectra were consistent with the assigned structure.

EXAMPLE VI (A).

3-*n*-Butyl-3-(3-Dimethylaminopropyl)-1-Phenyl-2-Indolinone.

This compound was prepared by the method of Example I, but using 3-*n*-butyl-1-phenyl-2-indolinone as the starting material. It was recrystallised from ethyl acetate chloroform as the maleate (M.pt.: 144—145°).

Analysis:

Calcd. for $C_{27}H_{34}N_2O_5$: C, 69.50; H, 7.35; N, 6.00.
Found: C, 69.49; H, 7.05; N, 6.14.

EXAMPLE VI (B).

The compound of Example VI (A) was also prepared as follows:

To 3 - (3 - aminopropyl) - 3 - *n* - butyl-1-phenyl-2-indolinone (12 g.; 0.0374 mol; prepared as in Example XX below) 90% formic acid solution (5.1 g.; 0.1 mol.) was added with cooling, followed by 37% aqueous formaldehyde solution (7.5 ml.; 0.1 mol.). The mixture was heated on the water bath (90°) for two hours, then heated under reflux for three hours and finally evaporated, basified and extracted with ether. The residual oil obtained after evaporation of the solvent was distilled at 180—190°/0.2 mm. (6.5 g.). The maleate salt from this oil was prepared in ether in the usual way. It was recrystallised from ethyl acetate—chloroform to give pure 3-*n*-butyl-3-(3-dimethylaminopropyl)-1-phenyl-2-indolinone maleate as colourless crystals (6 g., m.pt.: 144—145°).

Analysis:

Calcd. for $C_{27}H_{34}N_2O_5$: C, 69.50; H, 7.35; N, 6.00.
Found: C, 69.49; H, 7.05; N, 6.14.

EXAMPLE VII.

5-Bromo-3-(3-Dimethylaminopropyl)-3-Methyl-1-Phenyl-2-Indolinone.

This compound was prepared by the method of Example I, but using 5-bromo-3-methyl-1-phenyl-2-indolinone (prepared as in Preparation E) as the starting material. It was recrystallised from methanol/40—60° petrol as the hydrochloride (M.pt.: 263—265°).

Analysis:

Calcd. for $C_{20}H_{21}BrClN_2O$: C, 56.68; H, 5.71; N, 6.61; Br, 18.85; Cl, 8.36.
Found: C, 56.92; H, 5.74; N, 6.38; Br, 19.24; Cl, 8.99.

EXAMPLE VIII.

3-Benzyl-3-[3-(N-Benzyl-N-Methylamino)-propyl]-1-phenyl-2-Indolinone.

3 - Benzyl - 1 - phenyl - 2 - Indolinone (15 g.; 0.05 mol.; prepared as in Preparation D) was dissolved in dry dimethylformamide (60 ml.) and treated carefully with sodium hydride (1.2 g.; 0.05 mol.) at 60°. 3-(N-Benzyl-N-methylamino) propyl chloride (9.9 g.; 0.05 mol.) was added and the mixture was heated to 60° for four hours. It was allowed to cool, poured into water and ether extracted. The organic extract was washed with water, dried and evaporated to give an oil which was treated with oxalic acid in ether. The 3 - benzyl - 3 - [3 - (N - benzyl-N - methylamino) - propyl] - 1 - phenyl - 2-indolinone oxalate solidified as colourless crystals (M.pt.: 158—160°).

Analysis:

Calcd. for $C_{34}H_{34}N_2O_5$: C, 74.16; H, 6.22; N, 5.09.
Found: C, 74.03; H, 6.31; N, 5.27.

EXAMPLE IX.

3-(3-Dimethylaminopropyl)-1,3-di-phenyl-2-indolinone.

This compound was prepared by the method of Example VIII, but using 1,3-di-phenyl-2-indolinone (prepared as in Preparation C) as starting material and 3-dimethyl-amino-propyl chloride as the alkylating agent. It was recrystallised from ethyl acetate-isopropanol as the hydrochloride (M.pt.: 240.5—242°).

Analysis:

Calcd. for $C_{25}H_{27}ClN_2O$: C, 73.83; H, 6.53; N, 6.65.
Found: C, 73.77; H, 6.69; N, 6.88.

EXAMPLE X.

3-Methyl-3-[2-(4-Methyl-1-Piperazinyl)-ethyl]-1-Phenyl-2-Indolinone.

Crude 3 - (2 - bromoethyl) - 3 - methyl-1-phenyl-2-indolinone (33 g.; 0.1 mol.; prepared as in Preparation K), N-methyl-piperazine (20 g.; 0.2 mol.) and ethanol (50 ml.) were heated under reflux for five hours. The mixture was concentrated in vacuo (1 mm., 100°) and the residue was neutralised with sodium carbonate solution, extracted with ether and methylene chloride and the combined organic extracts were washed with water and evaporated to give an oil. The oil was dissolved in dry ether and treated with an excess of ethereal solution of maleic acid. The 3 - Methyl - 3 - [2 - (4 - methyl - 1-piperazinyl)ethyl] - 1 - phenyl - 2 - indolinone di-maleate separated as a white solid which recrystallised from ethanol-water (15 g.; M.pt.: 178—179°).

Analysis:

Calcd. for $C_{30}H_{33}N_3O_9$: C, 61.95; H, 6.07; N, 7.23.
Found: C, 61.82; H, 6.09; N, 6.94.

EXAMPLE XI.

3-Methyl-3-[2-(4-Hydroxyethyl-1-piperazinyl)-ethyl]-1-Phenyl-2-Indolinone.

This compound was prepared by the method of Example X, but using N-hydroxy-ethyl piperazine instead of N-methyl piperazine. It was recrystallised from isopropanol as the di-maleate (M.pt.: 148—149°).

Analysis:

Calcd. for $C_{31}H_{37}N_3O_{10}$: C, 60.87; H, 6.10; N, 6.87.
Found: C, 61.15; H, 6.49; N, 7.10.

EXAMPLE XII.

3-Methyl-3-(3-Piperidinopropyl)-1-Phenyl-2-Indolinone.

This compound was prepared by the method of Example X, but using crude 3-(3-bromopropyl) - 3 - methyl - 1 - phenyl - 2-indolinone (prepared as in Preparation L) and piperidine as starting materials. It was re-crystallised from ethanol as the oxalate (M.pt.: 219—220°).

Analysis:

Calcd. for $C_{25}H_{30}N_2O_5$: C, 68.47; H, 6.90; N, 6.39.
Found: C, 68.22; H, 6.98; N, 6.16.

EXAMPLE XIII.
3-Methyl-3-[3-(4-Methyl-1-Piperazinyl)-propyl]-1-Phenyl-2-Indolinone.
This compound was prepared as for Example XII, but using N-methyl piperazine instead of piperidine. It was recrystallised from ethanol as the di-maleate (M.pt.: 178.5—179.5°).

Analysis:
Calcd. for $C_{31}H_{37}N_3O_9$: C, 62.51; H, 6.26; N, 7.06.
Found: C, 62.69; H, 6.23; N, 6.76.

EXAMPLE XIV.
3-Methyl-3-[3-(4-Hyroxyethyl-Piperazinyl)-propyl]-1-Phenyl-2-Indolinone.
This compound was prepared as for Example XII, but using N-hydroxyethyl piperazine instead of piperidine. It was recrystallised from isopropanol as the di-maleate (M.pt.: 141.5—142°).

Analysis:
Calcd. for $C_{32}H_{39}N_3O_{10}$: C, 61.43; H, 6.28; N, 6.72.
Found: C, 61.41; H, 6.27; N, 6.69.

EXAMPLE XV (A).
3-(3-Benzylaminopropyl)-3-Methyl-1-Phenyl-2-Indolinone.
This compound was prepared as for Example X, but using benzylamine instead of piperidine. It was recrystallised from isopropanol—water as the oxalate (M.pt.: 198—199°).

Analysis:
Calcd. for $C_{27}H_{28}N_2O_5$: C, 70.42; H, 6.13; N, 6.08.
Found: C, 70.35; H, 6.35; N, 5.97.

EXAMPLE XV (B).
The compound of Example XV (A) was also prepared as follows:
A mixture of 3-(3-aminopropyl)-3-methyl-1-phenyl-2-indolinone (21 g.; 0.075 mol.; prepared as in Example XVIII below), benzaldehyde (8 g.; 0.0755 mol.) and dry xylene (100 ml.) was heated under reflux with azeotropic removal of the water formed. When no more water was given off, the mixture was heated for a further hour. The xylene was removed under reduced pressure, the residue, comprising crude 3-(3-benzylidenaminopropyl) - 3 - methyl - 1 - phenyl - 2-indolinone, was dissolved in methanol (100 ml.) and this solution was added to an aqueous methanolic solution (150 ml.) of sodium borohydride (8 g.) containing 1 ml. of 2N sodium hydroxide solution. The mixture was allowed to stand over night, after which the solvents were removed under reduced pressure and the resultant oil was ether extracted. The ethereal layer was extracted with 2N hydrochloric acid, giving an aqueous solution and a gum. The ether layer was discarded and the aqueous solution containing the gum was basified and ether extracted. The organic extract was dried over anhydrous sodium sulphate and the maleate salt prepared in the usual way. The 3-(3-benzylaminopropyl) - 3 - methyl - 1 - phenyl - 2-indolinone maleate was recrystallised from isopropanol-ethyl acetate to give colourless crystals (9.4 g.; M.pt., 157—159°).

Analysis:
Calcd. for $C_{29}H_{31}N_2O_5$: C, 71.58; H, 6.22; N, 5.76.
Found: C, 71.49; H, 6.23; N, 5.62.

EXAMPLE XVI.
3-(3-Dibenzylaminopropyl)-3-Methyl-1-Phenyl-2-Indolinone.
To 3 - (3 - Benzylaminopropyl) - 3-methyl - 1 - phenyl - 2 - indolinone as free base (10 g.; 0.027 mol. prepared as in Example XV (B)) in dimethyl formamide (200 ml.), sodium hydride (50% oil-dispersed; 1.5 g.; 0.036 mol.) was added slowly at 60°. The mixture was stirred for one hour before the addition of benzyl bromide (5.2 g.; 0.03 mol.), after which the temperature (60°) and the stirring were held for a period of three hours. The reaction mixture was evaporated *in vacuo*, the residue was made alkaline and extracted into ether. The organic layer was separated, dried over $MgSO_4$ and evaporated to give an oil which was chromatographed in

a silica column. Elution of the column with benzene and benzene-chloroform gave an oil which was distilled in vacuo at 220° and 0.1 m.m. pressure Hg to yield 2 g. of 3-(3-dibenzylaminopropyl) - 3 - methyl - 1 - phenyl-2-indolinone as a colourless oil.

Analysis:

Calcd. for $C_{32}H_{32}N_2O$: C, 83.44; H, 7.00; N, 6.08.
Found: C, 84.01; H, 7.25; N, 5.49.

EXAMPLE XVII.

3-(2-Aminoethyl)-3-Methyl-1-Phenyl-2-Indolinone.

3 - Cyanomethyl - 3 - methyl - 1 - phenyl-2-indolinone (45 g.; 0.17 mol.; prepared as in Preparation H) dissolved in a mixture of glacial acetic acid (250 ml.) and conc. sulphuric acid (5 ml.) was hydrogenated at 50 p.s.i./50° over platinum oxide (0.5 g.) until the uptake of hydrogen had ceased. The catalyst was filtered and the solution was concentrated in vacuo, basified with sodium carbonate solution and ether extracted. The extracts were dried over anhydrous solid Na_2CO_3, filtered and treated with an ethereal solution of HCl gas. The 3-(2-Aminoethyl)-3-methyl - 1 - phenyl - 2 - indolinone hydrochloride precipitated and was recrystallised from ethyl acetate and isopropanol—ethyl acetate to give colourless crystals (36.2 g., M.pt.: 209—210°).

Analysis:

Calcd. for $C_{17}H_{19}ClN_2O$: C, 67.4; H, 6.32; N, 9.25.
Found: C, 67.35; H, 6.28; N, 8.92.

EXAMPLE XVIII.

3-(3-Aminopropyl)-3-Methyl-1-Phenyl-2-Indolinone.

This compound was prepared by the method of Example XVII, but using 3-(2-cyanoethyl) - 3 - methyl - 1 - phenyl - 2-indolinone (prepared as in Preparation F) as the starting material. It was recrystallised from ethyl acetate—isopropanol as the hydrochloride (M.pt.: 187—188.5°).

Analysis:

Calcd. for $C_{18}H_{21}ClN_2O$: C, 68.22; H, 6.68; N, 8.84.
Found: C, 68.40; H, 6.71; N, 8.74.

EXAMPLE XIX.

3-(4-Aminobutyl)-3-Methyl-1-Phenyl-2-Indolinone.

This compound was prepared by the method of Example XVII, but using 3-(3-cyano - propyl) - 3 - methyl - 1 - phenyl-2-indolinone (prepared as in Preparation J) as the starting material. It was recrystallised from ethyl acetate chloroform as the hydrochloride (M.pt.: 197.5—199°).

Analysis:

Calcd. for $C_{19}H_{23}ClN_2O$: C, 68.92; H, 7.0; N, 8.46.
Found: C, 68.68; H, 7.09; N, 8.33.

EXAMPLE XX.

3-(3-Aminopropyl)-3-*n*-Butyl-1-Phenyl-2-Indolinone.

This compound was prepared by the method of Example XVII, but using 3-*n*-butyl-3-(2-cyanoethyl) - 1 - phenyl - 2 - indolinone (prepared as in Preparation G) as the starting material. It was recrystallised from ethyl acetate—80—100° petrol as the maleate (M.pt.: 118—121°).

Analysis:

Calcd. for $C_{23}H_{30}N_2O_5$: C, 68.47; H, 6.90; N, 6.39.
Found: C, 68.61; H, 6.88; N, 6.26.

EXAMPLE XXI.

3-*n*-Butyl-3-(3-Methylaminopropyl)-1-Phenyl-2-Indolinone.

A mixture of 3-(3-aminopropyl)-3-*n*-butyl - 1 - phenyl - 2 - indolinone (18.2 g.; 0.0566 mol.; prepared as in Example XX) and benzaldehyde (5.9 g.; 0.0566 mol.) in dry benzene (200 ml.) were heated under reflux with azeotropic removal of the water until the calculated quantity had been collected. The reaction was evaporated to a thick oil which crystallised slowly on standing. Trituration of the semi-crystalline mass with 60—80° petrol gave a colourless solid which was recrystallised from 60—80° petrol-chloroform to yield pure 3-*n*-butyl-3-(3-benzlidenaminopropyl) - 1 - phenyl - 2 - indolinone. This compound (20 g.; 0.05 mol.) and methyl iodide (70 ml.) was heated at 100° in a pressure vessel for 4—5 hours. The reaction mixture was evaporated in vacuo and the residual oil was extracted into ether. The extract was treated with 5 N HCl, and the acidic aqueous layer was basified and ether extracted. The oil obtained on evaporation of the solvent was distilled (10.6 g., 206—210°/1 mm). The neutral fumarate was prepared in ether-isopropanol and recrystallised from isopropanol-ethyl acetate to give the 3-*n*-butyl-3 - (3 - methylaminopropyl) - 1 - phenyl - 2-indolinone hemi-fumarate as colourless crystals (10.4 g., M.pt.: 173—175°).

Analysis:

Calcd. for $C_{24}H_{30}N_2O_3$: C, 73.06; H, 7.67; N, 7.10.
Found: C, 73.28; H, 7.56; N, 7.00.

EXAMPLE XXII.

3-Methyl-3-(4-Methylaminobutyl)-1-Phenyl-2-Indolinone.

This compound was prepared by the method of Example XXI, but using 3-(4-aminobutyl) - 3 - methyl - 1 - phenyl - 2-indolinone prepared as in Example XIX as starting material. It was recrystallised from chloroform-ethyl acetate as the hydrochloride (M.pt.: 164—167°).

Analysis:

Calcd. for $C_{20}H_{25}ClN_2O$: C, 69.65; H, 7.31; N, 8.12.
Found: C, 69.12; H, 7.22; N, 9.65.

EXAMPLE XXIII.

3-(3-Dimethylaminopropyl)-3-Methyl-1-Phenyl-Indoline.

3 - (3 - Dimethylaminopropyl) - 3-methyl - 1 - phenyl - 2 - indolinone (25 g.; 0.081 mol.; prepared as in Example I) in ether (250 ml.) was added over thirty minutes to an ice-cooled suspension of lithium aluminium hydride (5 g.; 0.132 mol.) in ether (250 ml.). The reaction mixture was heated under reflux for nine hours, cooled in ice, and carefully treated with water (5 ml.) followed by 5 N NaOH (5 ml.). The mixture was filtered and the residue washed with ether. The filtrate was dried over Na_2CO_3 and evaporated. The residual oil (24.0 g.) consisting of the desired compound as free base, was dissolved in ethyl acetate and treated with an ethyl acetate solution of maleic acid which precipitated pure 3-(3-dimethylaminopropyl) - 3 - methyl - 1 - phenyl-indoline maleate as colourless crystals. (M.pt.: 124—126°).

Analysis:

Calcd. for $C_{24}H_{30}N_2O_4$: C, 70.22; H, 7.37; N, 6.82.
Found: C, 70.31; H, 7.28; N, 6.66.

EXAMPLE XXIV.

3-(2-Dimethylaminoethyl)-3-Methyl-1-Phenyl-Indoline.

This compound was prepared by the method of Example XXIII, but using 3-(2-dimethylaminoethyl) - 3 - methyl - 1 - phenyl-2-indolinone as starting material (prepared by the method of Example I, but using 2-dimethylaminoethyl chloride as alkylating agent). It was recrystallised from isopropanol-water as the maleate (M.pt.: 140—142°).

Analysis:

Calcd. for $C_{23}H_{28}N_2O_4$: C, 69.67; H, 7.12; N, 7.07.
Found: C, 69.37; H, 7.09; N, 6.93.

EXAMPLE XXV—XXVIII.

The following compounds were prepared by the method of Example XXIII from the corresponding 2-indolinones, prepared as in Examples II, III, IV and VI (A) or (B), respectively:

3-[2-(N-Benzyl-N-Methylamino)ethyl]-3-Methyl-1-Phenyl-Indoline.

The crude base solidified on standing (M.pt.: 72—75°) and it was recrystallised from 40—60° petrol. (M.pt.: 75—78°).

Analysis:

Calcd. for $C_{25}H_{28}N_2$: C, 84.22; H, 7.93; N, 7.86.
Found: C, 84.01; H, 7.83; N, 7.73.

3-[3-(N-Benzyl-N-Methylamino)propyl]-3-Methyl-1-Phenyl-Indoline.

The pure base distilled at 206°/0.2 mm.

Analysis:

Calcd. for $C_{26}H_{30}N_2$: C, 84.28; H, 8.16; N, 7.56.
Found: C, 84.10; H, 7.92; N, 7.37.

3-*n*-Butyl-3-(2-Dimethylaminoethyl)-1-Phenyl-Indoline.

This compound was recrystallised from isopropanol-chloroformethyl acetate as the fumarate (M.pt.: 176—179°).

Analysis:

Calcd. for $C_{26}H_{34}N_2O_4$: C, 71.20; H, 7.82; N, 6.39.
Found: C, 71.12; H, 7.59; N, 6.20.

3-*n*-Butyl-3-(3-Dimethylaminopropyl)-1-Phenyl-Indoline.

The free base distilled at 188—194°/1 mm.

Analysis:

Calcd. for $C_{23}H_{32}N_2$: C, 82.09; H, 9.59; N, 8.33.
Found: C, 82.07; H, 9.61; N, 8.43.

EXAMPLE XXIX (A).

3-Methyl-3-(3-Methylaminopropyl)-1-Phenyl-2-Indolinone.

3 - (3 - Dimethylaminopropyl) - 3 - methyl-1 - phenyl - 2 - indolinone (10 g.), prepared as in Example I, was dissolved in xylene (40 ml.) at 60° and ethyl chloroformate (10 ml.) was added. An exothermic reaction took place and the flask was cooled so as to keep the temperature below 65°. A gas was evolved and a small amount of gum precipitated. The reaction was kept at 60—70° for one hour and then a further quantity of ethyl chloroformate (10 ml.) was added and the reaction was maintained at 60—70° for a further 1—1½ hours. The temperature of the reaction mixture was then raised so as to boil off excess ethyl chloroformate. Xylene was added during this process to keep the volume of the reaction mixture constant. The distillation temperature reached 130°, and the mixture was boiled under reflux for 4 hours. After cooling, it was extracted with *N* hydrochloric acid and water and then dried over magnesium sulphate. Evaporation gave a syrup (8.3 g.) of 3-(N-ethoxycarbonyl-3-methylaminopropyl) - 3 - methyl - 1 - phenyl-2-indolinone. This was dissolved in glacial acetic acid (30 ml.) and 48% aqueous hydrobromic acid (20 ml.) and the solution boiled under reflux for 4—5 hours. The dark solution was evaporated to dryness *in vacuo* and the resulting syrup was diluted with water. This mixture was extracted with ether which removed from unchanged urethane (N-ethoxycarbonyl compound) (4.5 g.). The aqueous residue was basified with 5N caustic soda solution and then extracted with ether. The organic extract was dried over magnesium sulphate and concentrated to dryness. The resultant oil was converted to the corresponding hydrochloride in the usual way. The solid was crystallised from a mixture of chloroform and ethyl acetate when the product was

obtained as a green solid consisting of 3-methyl - 3 - (3 - methylaminopropyl) - 1-phenyl-2-indolinone hydrochloride (1.6 g.) which on drying in vacuo at 125° became a buff colour (m.pt. 168—170°).

Analysis:

Calcd. for $C_{19}H_{23}ClN_2O$: C, 68.97; H, 7.00; N, 8.46%.
Found: C, 68.72; H, 6.95; N, 8.16%.

EXAMPLE XXIX (B).

This compound was also prepared by the catalytic reduction of 3-[3-(N-benzyl-N-methylamino)propyl] - 3 - methyl - 1 - phenyl-2-indolinone hydrochloride (prepared as in Example III) using the following conditions: 10% palladium on charcoal, 360 p.s.i. and 60°. The resultant solid was recrystallised from ethyl acetate-ethanol as hydrochloride (M.pt.: 172.5—173.5°).

Analysis:

Calcd. for $C_{19}H_{23}ClN_2O$: C, 68.97; H, 7.00; N, 8.47.
Found: C, 69.36; H, 7.08; N, 8.20.

EXAMPLE XXX (A).

3-Methyl-3-(2-Methylaminoethyl)-1-Phenyl-2-Indolinone.

3 - (2 - Dimethylaminoethyl) - 3 - methyl-1-phenyl-2-indolinone (10 g.; 0.033 mol.; prepared as in Example I, but using dimethylaminoethyl chloride as alkylating agent) in dry xylene (75 ml.) was treated with ethyl chloroformate as in Example XXIX (A). The resultant syrup (8 g.) of 3-(N - ethoxycarbonyl - 3 - methylaminoethyl) - 2 - methyl - 1 - phenyl - 2 - indolinone was heated under reflux for 16—17 hours with 40% solution of hydrobromic acid in glacial acetic acid (50 ml.). The mixture was evaporated in vacuo and the resultant syrup was treated with water and ether extracted to remove unreacted urethane. The aqueous layer was basified with cold aqueous solution of Na_2CO_3 and ether extracted. The ethereal extract was dried over magnesium sulphate, filtered and treated with an ethereal solution of HCl. An oil precipitated which slowly solidified. This material was recrystallised from isopropanol-ethyl acetate to give the 3 - methyl - 3 - (2 - methylaminoethyl)-1-phenyl-2-indolinone hydrochloride as a colourless solid (6.5 g.; M.pt.: 194—196°).

Analysis:

Calcd. for $C_{18}H_{21}ClN_2O$: C, 68.24; H, 6.68; N, 8.84.
Found: C, 68.43; H, 6.73; N, 8.78.

EXAMPLE XXX (B).

This compound was also prepared by the following method: The brown syrup (8 g.) of 3 - (N - ethoxycarbonyl - 3 - methylaminoethyl) - 3 - methyl - 1 - phenyl - 2-indolinone, prepared as in Example XXX (A) was dissolved in ethanol (100 ml.) and a solution of KOH (8 g.) in water (10 ml.) was added. This mixture was boiled under reflux for 24 hours and then concentrated under reduced pressure. Water was added and the mixture was extracted with ether. Evaporation of the organic extract yielded a syrup which was dissolved in dry ether and an ethereal solution of hydrochloric acid was added. An oil was precipitated which crystallised on standing. The solid was crystallised from a mixture of isopropanol and ethyl acetate to give 3 - methyl - 3 - (2 - methylaminoethyl) - 1 - phenyl - 2 - indolinone hydrochloride (0.9 g.) as a white solid of m.p. 193—195°, which had the same elemental analysis as the product of Example XXX (A).

EXAMPLE XXX (C).

This compound was also prepared by the following procedure: 3 - [2 - (N - Benzyl-N - methylamino) - ethyl] - 3 - methyl - 1-phenyl-2-indolinone (164 g.; 0.4 mol.; prepared as in Example II) was dissolved in absolute ethanol (650 ml.) and a solution of palladium chloride (6 g.) in water (40 ml.) containing sodium chloride (4 g.) was added. The mixture was cautiously treated with a solution of sodium borohydride (6 g.) in water (40 ml.) over a period of ten minutes with stirring. Stirring was continued for a further 15 minutes and the pH then adjusted to 1 with concentrated hydrochloric acid. The mixture was hydrogenated at 50 p.s.i. and 60° for 16 hours by which time the theoretical amount of hydrogen had been absorbed. The mixture was filtered and the solvent removed under reduced pressure. The residual oil was dissolved in water (250 mls.) basified with 5 N sodium hydroxide solution and extracted with ether (4 × 200 mls.). The extracts were dried over magnesium sulphate

and treated with dry hydrogen chloride giving a gummy precipitate which, after trituration with acetone, solidified. The product was collected by filtration, washed with acetone and ether, then dried at room temperature in vacuo to give the 3-methyl-3-(3-methylaminoethyl) - 1 - phenyl - 2 - indolinone hydrochloride as a white solid (95 g.; M.pt.: 194—197°). It was recrystallised from isopropanol-ethyl acetate (M.pt.: 195—197°).

Analysis:
Calcd. for $C_{18}H_{21}ClN_2O$: C, 68.24; H, 6.68; N, 8.84.
Found: C, 68.13; H, 6.78; N, 8.71.

EXAMPLE XXXI.

3-*n*-Butyl-3-(2-Methylaminoethyl)-1-Phenyl-2-Indolinone.

This compound was prepared by the method of Example XXX (C), but using 3-*n*-butyl - 3 - [2 - (N - benzyl - N - methylamino) - ethyl] - 1 - phenyl - 2 - indolinone (prepared as in Example V) as starting material. It was recrystallised from ethyl acetate-chloroform as the maleate (M.pt.: 154—157°).

Analysis:
Calcd. for $C_{25}H_{30}N_2O_5$: C, 68.47; H, 6.90; N, 6.39.
Found: C, 68.47; H, 6.81; N, 6.11.

EXAMPLE XXXII.

3-Benzyl-3-(3-Methylaminopropyl)-1-Phenyl-2-Indolinone.

This compound was prepared by the method of Example XXIX (B), but using 3-benzyl - 3 - [3 - (N - benzyl - N - methylamino)propyl] - 1 - phenyl - 2 - indolinone (prepared as in Example VIII) as starting material. It was recrystallised from ethanol as the oxalate (M.pt.: 162—165°).

Analysis:
Calcd. for $C_{27}H_{28}N_2O_5$: C, 70.42; H, 6.13; N, 6.08.
Found: C, 70.57; H, 6.13; N, 5.98.

EXAMPLE XXXIII (A).

3-Methyl-3-(3-Methylaminopropyl)-Phenyl-Indoline.

The free base of 3 - (3 - dimethylaminopropyl) - 3 - methyl - 1 - phenylindoline (11.8 g.), prepared as in Example XXIV, in dry xylene (50 ml.), was treated with ethyl chloroformate as in Example XXIX (A).

The resulting crude 3-(N-ethoxycarbonyl-3 - methylaminopropyl) - 3 - methyl - 1-phenyl-indoline (10.5 g.) was dissolved in *n*-butanol (125 ml.) and this solution was added to potassium hydroxide (10 g.) and water (5 ml.). The mixture was boiled under reflux for 24 hours, evaporated under reduced pressure and then diluted with water. The resultant oil was extracted into ether and the organic extract shaken with 2N hydrochloric acid. The acidic phase was basified with 5N caustic soda solution and the precipitated oil was extracted into ether. Evaporation of the ether layer gave an oil consisting of 3 - methyl - 3 - (3 - methylaminopropyl)-1-phenyl indoline as the free base.

The oil was dissolved in warm ethyl acetate and an excess of a maleic acid solution in ethyl acetate was added. On cooling, the product (5.1 g.) was precipitated as a buff solid, m.pt. 128—130°, consisting of the maleate of the base.

Analysis:
Calcd. for $C_{23}H_{28}N_2O_4$: C, 69.67; H, 7.12; N, 7.07%.
Found: C, 69.89; H, 7.05; N, 6.80%.

EXAMPLE XXXIII (B).

This compound was also prepared by the following method: 3 - Methyl - 3 - (3-methylaminopropyl) - 1 - phenyl - 2 - indolinone (40 g.; 0.136 mol.; prepared as in Example XXIX (B)) in tetrahydrofuran (400 ml.) was placed in a flask fitted with an inlet from a diborane generator. The diborane generator was charged with sodium borohydride (95 g.; 2.5 mol.) and dimethyl digol (600 ml.). After a preliminary purge of the apparatus for fifteen minutes with nitrogen, the cautious addition of boron trifluoride diethyl etherate (440 ml., 3.5 mol.) to the generator was commenced with strong ice-cooling. The generation of diborane took three

hours and at the end of this period the apparatus was purged with nitrogen for thirty minutes and the tetrahydrofuran solution in the reaction vessel was heated under reflux for one hour. The solution was then cooled in ice and cautiously treated with 5 N HCl (100 ml.). The solvents were removed in vacuo leaving a thick, colourless oil which was dissolved in hot water (300 ml.), cooled to room temperature, basified with 5 N NaOH (200 ml.) and extracted with ether (3 × 200 ml.). The extracts gave on evaporation an oil consisting of the desired compound as free base, from which the maleate salt was prepared in the usual way (M.pt.: 129—131°; 47 g.). Recrystallisation of this material from ethyl-acetate gave pure 3-methyl-3-(3-methylaminopropyl) - 1 - phenyl - indoline maleate as colourless crystals. (M.pt. 130—131°).

Analysis:

Calcd. for $C_{23}H_{28}N_2O_4$: C, 69.68; H, 7.13; N, 7.07.
Found: C, 69.62; H, 6.84; N, 7.22.

EXAMPLE XXXIII (C).

The *p*-toluene sulphonate salt of this compound was prepared as follows: the free base (prepared as in Example XXXIII (B); (100 g.) was dissolved in acetone (600 ml.) and *p*-toluene sulphonic acid monohydrate (68.7 g.) also dissolved in acetone (600 ml.), was added with agitation at 20°—30° C. The solid product, which started to crystallise within a few minutes, was allowed to granulate by standing at room temperature for 1 hour, followed by a further 16 hours at 0°—5° C, and then separated from the liquors by filtration, washed with acetone (120 ml.) and sucked dry for 30 minutes. It was then dried at 35° C for 16 hours *in vacuo* to yield 145 g. of the desired salt (M.pt. 122—122.5°).

Analysis:

Calcd. for $C_{26}H_{32}O_3N_2S$: C, 68.97; H, 7.13; N, 6.19; S, 7.09.
Found: C, 69.25; H, 6.82; N, 6.12; S, 7.02.

EXAMPLE XXXIV.

3-*n*-Butyl-3-(2-Methylaminoethyl)-1-Phenyl-Indoline.

This compound was prepared by the method of Example XXXIII (A), but using the free base of 3 - *n* - butyl - 3 - (2 - dimethylaminoethyl) - 1 - phenyl - indoline prepared as in Example XXVII as starting material. The free base of the desired compound distilled at 185—200°/1.5 mm. The maleate salt was recrystallised from ethyl acetate-chloroform (M.pt.: 153—156°).

Analysis:

Calcd. for $C_{25}H_{32}N_2O_4$: C, 70.72; H, 7.60; N, 6.60.
Found: C, 70.70; H, 7.63; N, 6.79.

EXAMPLE XXXV.

3-*n*-Butyl-3-(3-Methylaminopropyl)-1-phenyl-indoline.

This compound was prepared by the method of Example XXXIII (A), but using 3 - *n* - butyl - 3 - (3 - dimethylaminopropyl)-1-phenyl-indoline (prepared as in Example XXVIII) as starting material. The free base of the desired compound distilled at 210°—220°/1.5 mm.

Analysis:

Calcd. for $C_{22}H_{30}N_2$: C, 81.93; H, 9.38; N, 8.69.
Found: C, 81.77; H, 9.37; N, 8.79.

EXAMPLE XXXVI.

5-Chloro-3-Methyl-3-(3-Methylaminopropyl)-1-Phenyl-2-Indolinone.

Sulphuryl chloride (4.1 g.; 0.03 mol.) in glacial acetic acid (10 ml.) was added to a cooled solution of 3-methyl-3-(3-methylaminopropyl) - 1 - phenyl - 2 - indolinone hydrochloride (10 g., 0.03 mol.; prepared as in Example XXIX (B)) in glacial acetic acid (100 ml.) the temperature being kept below 20°. The mixture was stirred at room temperature for two hours, evaporated, basified and extracted into ether. The dried ethereal solution was treated with HCl gas and the precipitated oil solidified on trituration with dry ether. The solid was recrystallised from isopropanol—60—80° petrol to give the 5-chloro - 3 - methyl - 3 - (3 - methylamino-

propyl) - 1 - phenyl - 2 - indolinone hydrochloride as colourless crystals (6.3 g.; M.pt.: 196—199°). The position of the chlorine atom was ascertained by nuclear magnetic resonance techniques.

Analysis:
Calcd. for $C_{19}H_{22}Cl_2N_2O$: C, 62.46; H, 6.07; N, 7.67; Cl, 19.42.
Found: C, 62.32; H, 5.91; N, 7.49; Cl, 19.27.

EXAMPLE XXXVII.

5-Bromo-3-Methyl-3-(3-Methylamino-propyl)-1-Phenyl-2-Indolinone.

To a cooled solution of 3-methyl-3-(3-methylaminopropyl) - 1 - phenyl - 2 - indolinone hydrochloride (33 g.; 0.01 mol.; prepared as in Example XXIX (B)) in glacial acetic acid (30 ml.) a solution of bromine (1.60 g.) in glacial acetic acid (5 ml.) was added, with stirring. The mixture was allowed to stand at room temperature for thirty minutes, after which it was evaporated, basified and extracted with ether. When the dry ethereal extract was treated with dry HCl gas, an oil precipitated which solidified on trituration with ether. The solid was recrystallised from isopropanol-ethyl acetate to give the 5-bromo-3-methyl-3-(3 - methylaminopropyl) - 1 - phenyl - 2-indolinone hydrochloride as colourless crystals. (2.9 g.: M.pt.: 189—191°).

Analysis:
Calcd. for $C_{19}H_{22}BrClN_2O$: C, 55.69; H, 5.41; N, 6.83.
Found: C, 55.56; H, 5.49; N, 6.65.

C.

PHARMACEUTICAL FORMULATIONS.

The following Examples are typical of many formulations of compounds of formula I. The actual weights of active compound, excipients and other ingredients are capable of wide variation, according to the required dosage and tablet or capsule size.

EXAMPLE XXXVIII.

Tablets were compounded of the following ingredients:

Product of Example XXIX (as hydrochloride)	10.0	*mg/tablet*
Di-calcium phosphate	120.0	
Maize starch	20.0	
Magnesium stearate (lubricant)	1.8	
Sodium lauryl sulphate (lubricant)	0.2	
	152.0	

These ingredients were blended, compressed, granulated and then re-compressed into tablets.

EXAMPLE XXXIX.

Capsules were prepared from the following ingredients:

Product of Example XXIX (as hydrochloride)	10.0	*mg/capsule*
Maize starch	127.0	
Microcrystalline cellulose	127.0	
Magnesium stearate	5.4	
Sodium lauryl sulphate	0.6	
	270.0	

These ingredients were blended and filled into hard gelatine capsules of appropriate size.

EXAMPLES XL AND XLI.

Tablets and capsules were prepared from the product of Example XXXIII (C) (as *p*-toluene sulphonate) using ingredients in the same proportions as in Examples XXXVIII and XXXIX, respectively.

The dosage in which the compounds of formula I should be administered will depend on the individual patient, the route of administration and the clinical result which is desired, but in general the dosage will be in the range from 5 to 150 mg. per day when administered orally. For the most potent compounds of the invention, including the products of Examples XXIX and XXXIII, the preferred range is from 10 to 30 milligrams administered orally in 2 or more equal doses per day, e.g. in tablets or capsules containing 5 or 10 mg. of the compound.

WHAT WE CLAIM IS:—

1. Compounds of the formula I herein and their pharmaceutically acceptable acid addition salts, with the proviso that, when R^1, R^2 and R^3 are each methyl, X is an oxygen atom and the benzene rings are unsubstituted, then C_nH_{2n} is other than ethylene.

2. Compounds of the formula I herein, in which at least one of R^1 and R^2 is hydrogen, and their pharmaceutically acceptable acid addition salts.

3. A compound as claimed in claim 2, in which R^1 is a lower alkyl group (as herein defined) and R^2 is hydrogen.

propyl) - 1 - phenyl - 2 - indolinone hydrochloride as colourless crystals (6.3 g.; M.pt.: 196—199°). The position of the chlorine atom was ascertained by nuclear magnetic resonance techniques.

Analysis:
Calcd. for $C_{19}H_{22}Cl_2N_2O$: C, 62.46; H, 6.07; N, 7.67; Cl, 19.42.
Found: C, 62.32; H, 5.91; N, 7.49; Cl, 19.27.

EXAMPLE XXXVII.

5-Bromo-3-Methyl-3-(3-Methylamino-propyl)-1-Phenyl-2-Indolinone.

To a cooled solution of 3-methyl-3-(3-methylaminopropyl) - 1 - phenyl - 2 - indolinone hydrochloride (33 g.; 0.01 mol.; prepared as in Example XXIX (B)) in glacial acetic acid (30 ml.) a solution of bromine (1.60 g.) in glacial acetic acid (5 ml.) was added, with stirring. The mixture was allowed to stand at room temperature for thirty minutes, after which it was evaporated, basified and extracted with ether. When the dry ethereal extract was treated with dry HCl gas, an oil precipitated which solidified on trituration with ether. The solid was recrystallised from isopropanol-ethyl acetate to give the 5-bromo-3-methyl-3-(3 - methylaminopropyl) - 1 - phenyl - 2-indolinone hydrochloride as colourless crystals. (2.9 g.: M.pt.: 189—191°).

Analysis:
Calcd. for $C_{19}H_{22}BrClN_2O$: C, 55.69; H, 5.41; N, 6.83.
Found: C, 55.56; H, 5.49; N, 6.65.

C.

PHARMACEUTICAL FORMULATIONS.

The following Examples are typical of many formulations of compounds of formula I. The actual weights of active compound, excipients and other ingredients are capable of wide variation, according to the required dosage and tablet or capsule size.

EXAMPLE XXXVIII.

Tablets were compounded of the following ingredients:

Product of Example XXIX (as hydrochloride)	10.0	*mg/tablet*
Di-calcium phosphate	120.0	
Maize starch	20.0	
Magnesium stearate (lubricant)	1.8	
Sodium lauryl sulphate (lubricant)	0.2	
	152.0	

These ingredients were blended, compressed, granulated and then re-compressed into tablets.

EXAMPLE XXXIX.

Capsules were prepared from the following ingredients:

Product of Example XXIX (as hydrochloride)	10.0	*mg/capsule*
Maize starch	127.0	
Microcrystalline cellulose	127.0	
Magnesium stearate	5.4	
Sodium lauryl sulphate	0.6	
	270.0	

These ingredients were blended and filled into hard gelatine capsules of appropriate size.

EXAMPLES XL AND XLI.

Tablets and capsules were prepared from the product of Example XXXIII (C) (as *p*-toluene sulphonate) using ingredients in the same proportions as in Examples XXXVIII and XXXIX, respectively.

The dosage in which the compounds of formula I should be administered will depend on the individual patient, the route of administration and the clinical result which is desired, but in general the dosage will be in the range from 5 to 150 mg. per day when administered orally. For the most potent compounds of the invention, including the products of Examples XXIX and XXXIII, the preferred range is from 10 to 30 milligrams administered orally in 2 or more equal doses per day, e.g. in tablets or capsules containing 5 or 10 mg. of the compound.

WHAT WE CLAIM IS:—

1. Compounds of the formula I herein and their pharmaceutically acceptable acid addition salts, with the proviso that, when R^1, R^2 and R^3 are each methyl, X is an oxygen atom and the benzene rings are unsubstituted, then C_nH_{2n} is other than ethylene.

2. Compounds of the formula I herein, in which at least one of R^1 and R^2 is hydrogen, and their pharmaceutically acceptable acid addition salts.

3. A compound as claimed in claim 2, in which R^1 is a lower alkyl group (as herein defined) and R^2 is hydrogen.

* C L M S *

4. Compounds of the formula I herein, in which R^1 is a lower alkyl group (as herein defined) and R^2 is a benzyl group, and their pharmaceutically acceptable acid addition salts.

5. A compound as claimed in claim 3 or claim 4, in which R^1 is a methyl group.

6. A compound as claimed in any of claims 2 to 5, in which n is at least 3.

7. A compound as claimed in claim 6, in which C_nH_{2n} is a trimethylene group.

8. A compound as claimed in any of claims 2 to 7, in which R^3 is a methyl group.

9. 3 - Methyl - 3 - (2 - methylaminoethyl) - 1 - phenyl - 2 - indolinone and its hydrochloride salt.

10. 3 - Methyl - 3 - (3 - methylaminopropyl) - 1 - phenyl - 2 - indolinone and its hydrochloride salt.

11. 3 - Methyl - 3 - (3 - methylaminopropyl) - 1 - phenyl - indoline and its maleate salt.

12. 3 - Methyl - 3 - (3- methylaminopropyl) - 1 - phenyl - indoline *p* - toluene sulphonate.

13. 3 - Methyl - 3 - (4 - methylaminobutyl) - 1 - phenyl - 2 - indolinone and its hydrochloride salt.

14. 3 - Methyl - 3 - (3 - dimethylaminopropyl) - 1 - phenyl - 2 - indolinone and its hydrochloride salt.

15. 3 - Methyl - 3 - (3 - dimethylaminopropyl) - 1 - phenyl - indoline and its maleate salt.

16. 3 - Methyl - 3 - (3 - [N - benzyl - N-methyl]amino - propyl) - 1 - phenyl - 2-indolinone and its hydrochloride salt.

17. A composition comprising a compound of the formula I herein or a pharmaceutically acceptable acid addition salt thereof, and a pharmaceutical carrier.

18. A composition comprising a compound as claimed in any of claims 2 to 16, and a pharmaceutical carrier.

19. A method of preparing a compound of the formula I herein in which neither R^1 nor R^2 is hydrogen, which comprises reacting the sodium derivative of a compound of the formula II herein with a halogenated tertiary amine of the formula $Hal—(C_nH_{2n})—NR^1R^2$, in which neither R^1 nor R^2 is hydrogen.

20. A method of preparing a compound of the formula I herein in which neither R^1 nor R^2 is hydrogen, which comprises reacting a compound of the formula II herein with an alkylene chloro-bromide of the formula $Br—(C_nH_{2n})—Cl$ and reacting the bromo-alkyl derivative so formed with a secondary amine of the formula R^1R^2NH, in which neither R^1 nor R^2 is hydrogen.

21. A method of preparing a compound of formula I herein in which R^1 is an alkyl group and R^2 is hydrogen, which comprises reducing a compound of formula I in which R^1 is an alkyl group and R^2 is benzyl with hydrogen in the presence of a palladium catalyst, whereby the benzyl group is removed.

22. A method of preparing a compound of the formula I herein in which R^1 and R^2 are both hydrogen, which comprises reacting a compound of the formula II herein with a halogenated nitrile of the formula

$$Hal—(C_{n-1}H_{2n-2})—CN,$$

in which $(C_{n-1}H_{2n-2})$ represents a bivalent saturated lower aliphatic hydrocarbon group in which n is at least 2, and reducing the cyano group to an amino-methyl group.

23. A compound as claimed in claim 1, substantially as described in any one of Examples I to XXXVII herein.

24. A pharmaceutical composition substantially as herein described and in particular with reference to any one of Examples XXXVIII to XLI herein.

25. A method of preparing a compound of formula I substantially as herein described and in particular with reference to any one of Examples I to XXXVII herein.

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