United States Patent [19]

Glamkowski et al.

[11] **4,448,784**

[45] **May 15, 1984**

[54] **1-(AMINOALKYLPHENYL AND AMINOALKYLBENZYL)-INDOLES AND INDOLINES AND ANALGESIC METHOD OF USE THEREOF**

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[21] Appl. No.: **367,707**

[22] Filed: **Apr. 12, 1982**

[51] **Int. Cl.**[3] **A61K 31/405**; C07D 209/08

[52] **U.S. Cl.** **424/274**; 548/491; 548/469

[58] **Field of Search** 548/491, 469; 424/274

[56] **References Cited**

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Primary Examiner—Paul M. Coughlan, Jr.
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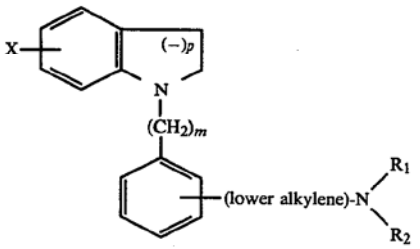
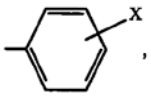
[57] **ABSTRACT**

The invention relates to 1-(aminoalkylphenyl and aminoalkylbenzyl)indoles and indolines of the formula:

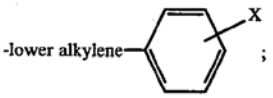


where R_1 and R_2 are the same or different and are hydrogen, lower alkyl, cycloalkyl and acyl of the formula

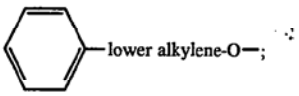
where R_3 is lower alkyl, lower alkoxy, cycloalkyl, phenyl of the formula



and Ar lower alkyl of the formula -lower alkylene



X is hydrogen, halogen, lower alkoxy, Ar lower alkoxy of the formula



m and p are independently integers of 0 and 1 and the pharmaceutically acceptable acid addition salts thereof.

31 Claims, No Drawings

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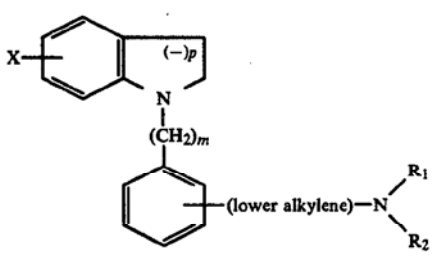
1-(AMINOALKYLPHENYL AND AMINOALKYLBENZYL)-INDOLES AND INDOLINES AND ANALGESIC METHOD OF USE THEREOF

To the best of our knowledge the compounds of the present invention have not heretofore been described or suggested.

The compounds of the present invention have the general formula

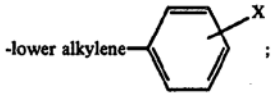


(I)

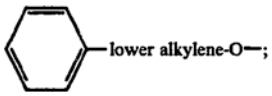
where R_1 and R_2 are the same or different and are hydrogen, lower alkyl, cycloalkyl and acyl of the formula

where R_3 is lower alkyl, lower alkoxy, cycloalkyl, phenyl of the formula

and Ar lower alkyl of the formula

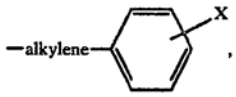


X is hydrogen, halogen, lower alkoxy, Ar lower alkoxy, of the formula

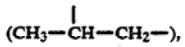


m and p are independently an integer of 0 or 1 and the pharmaceutically acceptable acid addition salts thereof.

In the above definitions the term "lower" means the group it is describing contains from 1 to 6 carbon atoms. The term "alkyl" refers to a straight or branched chain hydrocarbon containing no unsaturation, e.g. methyl, ethyl, isopropyl, 2-butyl, neopentyl, n-hexyl, etc.; the term "alkoxy" refers to a monovalent substituent which consists of an alkyl group linked through an ether oxygen having its free valence bond from the ether oxygen, e.g. methoxy, ethoxy, propoxy, butoxy, pentoxy, etc.; the term "cycloalkyl" refers to a monovalent substituent consisting of a saturated hydrocarbon group possessing at least one carbocyclic ring, of 3 to 7 carbon atoms, e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, etc., having its free valence bond from a carbon of the carbocylic ring; the term "Ar lower alkyl" refers to a monovalent substituent which consists of an aryl group, e.g., phenyl, p-nitrophenyl, o-tolyl, m-methoxy phenyl etc. linked through a lower alkylene group having its free valence bond from a carbon of the lower alkylene group, and having a formula of



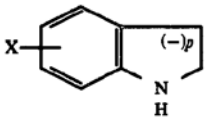
where X is as previously defined; the term "alkylene" refers to a bivalent radical of the lower branched or unbranched alkyl group it is derived from having valence bonds from two terminal carbons thereof, e.g. ethylene ($-CH_2CH_2-$), propylene ($-CH_2CH_2CH_2-$) isopropylene



etc.; and the term "halogen" refers to a member of the family consisting of fluorine, chlorine, bromine and iodine.

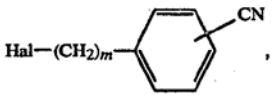
The compounds of the present invention are prepared in the following manner. The substituents X, R_1, R_2 and R_3 and the integers m and p are as defined above unless indicated otherwise.

A. A substituted indoline or indole of the formula



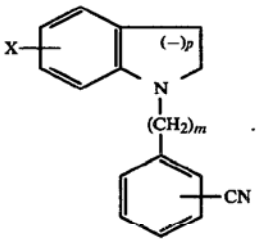
(II)

is selected. Compound (II) is reacted with a halobenzonitrile or a halo tolunitrile having the formula



(III)

where Hal is a halogen selected from F, Cl, Br and I to form an intermediate of the invention.



(IV)

Compound IV is typically obtained by reacting compounds II and III under nucleophilic substitution reac-

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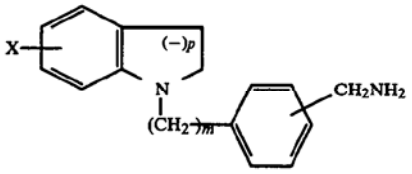
tion conditions. Typically, where p=1, compound II is reacted with compound III in the presence of a base, e.g. NaH, $(CH_3)_3$—C—OK, C_6H_5Li, and in a solvent, e.g., dimethylsulfoxide (DMSO), dimethylformamide (DMF), xylene, etc. at a temperature of 0° to 200° C. for 1 to 24 hours to form compound IV. Alternatively, where p=0, compound II is reacted with compound III in the presence of a base, e.g., K_2CO_3, $NaHCO_3$, or even an excess of the indoline II serving as base, etc, without or with an inert solvent, e.g., chloroform, methylene chloride, toluene etc. at a temperature of −10° to 100° C. for 1 to 24 hours to form compound IV.

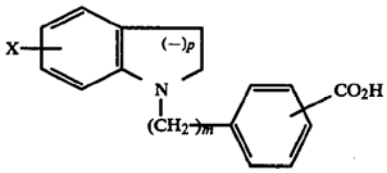
Compound IV in turn is reduced by conventional means, e.g. with a metal hydride such as $LiAlH_4$, BH_3 etc. in an inert solvent such as tetrahydrofuran (THF), diethylether, dioxan, etc. at a temperature of −10° to 100° C. for 1 to 24 hours to reduce the cyano group to form a compound of the invention

(V)



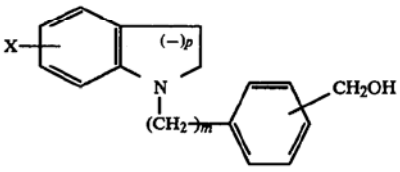
B. Compound IV is hydrolyzed in a conventional manner utilizing either an acidic or alkaline medium whereby the cyano group is hydrolyzed to a carboxyl group to give an intermediate of the invention having the formula

(VI)



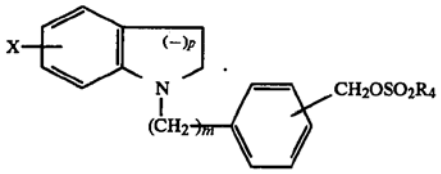
Compound VI is reduced by reaction with a metal hydride, e.g. $LiAlH_4$, BH_3, AlH_3, etc., in an inert solvent, e.g. THF, ether, dioxan, etc, typically at a temperature of −10° to 100° C. for 1 to 24 hours to form an alcohol intermediate of the invention having the formula

(VII)



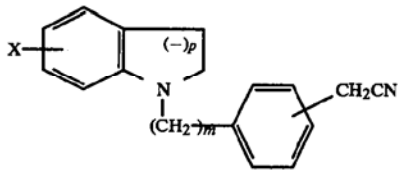
Compound VII is, in turn, reacted with a sulfonyl halide of the formula R_4SO_2—Hal (VIII) where Hal is a halogen selected from F, Cl, Br and I, and R_4 is lower alkyl. e.g. methyl, or aryl such as phenyl or tolyl, to form a sulfonate intermediate of the invention having the formula

(IX)



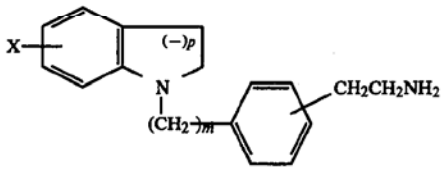
where R_4 is lower alkyl, e.g. methyl, or phenyl. Typically compound VII is reacted with compound VIII in an inert solvent, e.g. dichloromethane, ether, etc. at a temperature of 0° to 100° C. for 1 to 24 hours to form compound IX. Compound IX is then reacted with an inorganic cyanide, e.g. NaCN, KCN, in a conventional manner in the presence of a solvent, typically an aprotic polar solvent such as methanol, ethanol, dimethyl formamide (DMF), N-methyl-2-pyrrolidone or dimethyl sulfoxide (DMSO), to form an intermediate of the invention having the formula

(X)



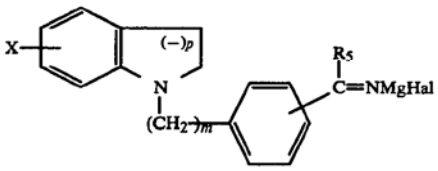
The cyano group of compound X is reduced in the manner previously described to form a compound of the invention having the formula

(XI)



C. Compound IV is reacted in a conventional manner with a Grignard reagent of the formula R_5 MgHal, (XII) where Hal is a halogen selected from Cl, Br and I and R_5 is an alkyl group of 1 to 5 carbon atoms, or phenyl to form an intermediate of the invention having the formula

(XIII)



Typically, compound IV is reacted with the Grignard reagent (XII) in an inert solvent, e.g. tetrahydrofuran (THF), ether, dioxan etc., at a temperature of 0° to 100° C. for 1 to 24 hours to form compound XIII. Compound XIII is then reduced by reduction with metal halide, e.g. $LiAlH_4$, as previously described for the reduction of the cyano group, to form a compound of the invention having the formula

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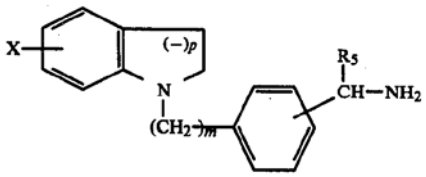
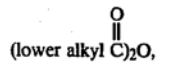


(XIV)

D. The N-alkyl or N-acyl derivatives of compounds V, XI and XIV are prepared in a conventional manner, as for example by reaction with a lower alkyl halide or a cycloalkyl halide or an acylhalide of the formula

where Hal is a halogen selected from F, Cl, Br and I and R_3 is as previously defined, whereby a mono- or bi-substituted compound of the invention, Compound I, is obtained where at least R_1 or R_2 is lower alkyl, cycloalkyl or acyl of the formula

Alternatively, compounds V, XI and XIV can be reacted in a conventional manner with an alkylchloroformate followed by reduction of the resultant compound, as with $LiAlH_4$, $NaBH_4$, to form compound I of the invention where at least R_1 or R_2 is methyl. In another alternative embodiment, compounds V, XI and XIV can be reacted in a conventional manner with an acid anhydride,



to form compound I of the invention where at least R_1 or R_2 is lower alkyl.

E. Where p is 1 in compound IV, it is typically reduced to compound IV where p is 0 by reaction with sodium cyanoborohydride. Typically this reaction is carried out in a solvent of THF, acetonitrile, or acetic acid at a temperature of 0° to 100° C. for 1 to 24 hours.

The compounds of the invention are useful as analgesic agents due to their ability to alleviate pain in mammals. The activity of the compound is demonstrated in the 2-phenyl-1,4-benzoquinone-induced writhing test in mice, a standard assay for analgesia [Proc. Soc. Exptl. Biol. Med., 95, 729 (1975)]. The analgesic activity of some of the compounds expressed in terms of percent inhibition of writhing is given in Table I.

TABLE I

Compound	Dose (subcutaneous) mg/kg of body Weight	Inhibition Of writhing %
3-(1-indolinyl)benzene-methanamine hydrochloride	4.2	50
2-(1-indolinyl)benzene-methanamine hydrochloride	14.1	50
4-(1-indolinyl)benzene-methanamine hydrochloride	25.0	50
3-[5-chloro-1-indolinyl]benzene-methanamine hydrochloride	4.7	50

TABLE I-continued

Compound	Dose (subcutaneous) mg/kg of body Weight	Inhibition Of writhing %
3-(1-indolyl)benzenemethanamine hydrochloride	19.1	50
3-(5-chloro-1-indolinylmethyl)-benzenemethanamine fumarate	20.2	50
N—cyclopropylcarbonyl-3-(1-indolinyl)-benzenemethanamine	10.0	59.0
N—cyclopropylmethyl-3-(1-indolinyl)benzenemethanamine hydrochloride	10.0	49.0
N,N—dimethyl-3-(1-indolinyl) benzenemethanamine hydrochloride	25.0	50.0
3-(1-indolinyl)-2-benzene ethanamine.½ fumarate	10.0	57.0
3-(1-indolinyl)-α-methylbenzene-methanamine hydrochloride	10.0	40.0
propoxyphene	3.9	50

The analgesic relief of pain is achieved when the compounds of the invention are administered to a subject requiring such treatment at an effective oral, parenteral or intravenous dose of from 1.0 to 25 mg/kg of body weight per day. A preferred effective dose within this range is from about 1 to 10 mg/kg of body weight per day. A particularly preferred effective amount is about 5 mg/kg of body weight per day. It is to be understood, however, that for any particular subject, specific dosage regimens should be adjusted according to the individual need. It is further to be understood that the dosages set forth herein are examples only and that they do not, to any extent, limit the scope of practice of the invention.

Effective amount of the compounds of the present invention may be administered to a subject by one of various methods, for example, orally as in capsules or tablets, parenterally in the form of sterile solutions or suspensions, and in some cases intravenously in the form of sterile solutions. The compounds of the invention, while effective themselves, may be formulated and administered in the form of their pharmaceutically acceptable acid addition salts for purposes of stability, convenience of crystallization, increased solubility and the like.

Preferred pharmaceutically acceptable acid addition salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, nitric, phosphoric, perchloric acids and the like as well as organic acids such as tartaric, citric, acetic, succinic, maleic, fumaric acids and the like.

The compounds of the present invention may be administered orally, for example, with an inert diluent or with an edible carrier. They may be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the compounds may be incorporated with excipients and used in the form of tablets, troches, capsules, elixirs, suspensions, syrups, wafers, chewing gums and the like. These preparations should contain at least 4% of the 1-(aminoalkylphenyl) or 1-(aminoalkyl benzyl)-indoles or indolines of the invention, the active ingredient, but may be varied depending upon the particular form and may conveniently be between 4% to about 70% of the weight of the unit. The amount of the compound present in such compositions is such that a suitable dosage will be obtained. Preferred compositions and preparations according to the present invention are prepared so

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that an oral dosage unit form contains between 5.0–300 milligrams of the 1-(aminoalkylphenyl and aminoalkylbenzyl)indoles and indolines of the invention.

The tablets, pills, capsules, troches and the like may also contain the following adjuvants: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, corn starch and the like; a lubricant such as magnesium stearate or Sterotex; a glidant such as colloidal silicon dioxide; and a sweetening agent such as sucrose or saccharin may be added or a flavoring agent such as peppermint, methyl salicylate or orange flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as a fatty oil. Other dosage unit forms may contain other various materials which modify the physical form of the dosage unit, for example, as coatings. Thus, tablets or pills may be coated with sugar, shellac, or other enteric coating agents. A syrup may contain, in addition to the present compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors. Materials used in preparing these various compositions should be pharmaceutically pure and non-toxic in the amounts used.

For the purpose of parenteral therapeutic administration, the compounds of the present invention may be incorporated into a solution or suspension. These preparations should contain at least 0.1% of the 1-(aminoalkylphenyl and aminoalkylbenzyl) indoles and indolines of the invention, but may be varied to be between 0.1 and about 50% of the weight thereof. The amount of the inventive compound present in such compositions is such that a suitable dosage will be obtained. Preferred compositions and preparations according to the present invention are prepared so that a parenteral dosage unit contains between 5.0 to 100 milligrams of the 1-(aminoalkylphenyl and aminoalkylbenzyl) indoles and indolines of the invention.

The solutions or suspensions may also include the following adjuvants: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl paraben; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylene diaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parenteral preparation can be enclosed in ampules, disposable syringes or multiple dose vials made of glass or plastic.

The following examples are for illustrative purposes and are not to be construed as limiting the invention disclosed herein. All temperatures are given in degrees centigrade.

EXAMPLE 1

2-(1-Indolinyl)benzonitrile

A stirred mixture of 61.63 g (0.509 mole) 2-fluorobenzonitrile and 125.6 ml (1.12 mole) indoline under nitrogen was heated at 170°–180° C. for 22.5 hours. The resulting suspension was transferred to a separatory funnel with the aid of 400 ml of CH_2Cl_2 and this solution was washed twice with water (400 ml), four times with 4 N HCl (450 ml), water (450 ml), brine (400 ml), dried (Na_2SO_4), and concentrated to give 78.6 g (71.5%) of a liquid. The crystals which formed on standing were filtered, washed with ether and dried at 42° C. under vacuum, thus affording 4.33 g (3.9% overall) of 2-(indolinyl)benzonitrile M.P. 94.0°–96.5° C.

ANALYSIS: Calculated for $C_{15}H_{12}N_2$: 81.79%C, 5.49%H, 12.72%N, Found: 81.60%C, 5.54%H, 12.65%N.

2-(1-Indolinyl) benzenemethanamine hydrochloride

A solution of 17.18 g (0.078 mole) of 2(1-indolinyl)-benzonitrile of Example 1a in 150 ml dry tetrahydrofuran (THF) was added dropwise to a rapidly stirred ice cold solution of BH_3 in THF (236 ml of 1 M solution; 0.236 mole) under nitrogen. At the end of the addition the resultant solution was permitted to warm to room temperature and stir for 3 hours and then heated at reflux for 50 minutes. The product was then cooled to 0° C., treated dropwise with 6 N HCl (100 ml), and permitted to stand overnight (about 16 hours) at room temperature. The reaction mixture was cooled to 0° C. and made basic using solid NaOH. The resulting aqueous layer was extracted with ether (200 ml) and the combined organic portions were washed twice with brine (200 ml portions), dried over K_2CO_3, and concentrated to afford 21.1 g of crude free base. The free amine was dissolved in dry ether (300 ml), cooled to 0° C., and treated with gaseous HCl. The resulting salt was filtered, washed with dry ether (300 ml), and dried under vacuum at 40° C. thus affording 19.25 g (94.4%) of crude salt, m.p. 226°–228° C. Recrystallization of 15.59 g of the crude salt from methanol-ether afforded 10.49 g (67.3% recovery) of 2-(1-indolinyl) benzenemethanamine hydrochloride, m.p. 231°–232° C.

ANALYSIS: Calculated for $C_{15}H_{16}N_2.HCl$: 69.09%C, 6.57%H, 10.74%N, Found: 68.85%C, 6.57%H, 10.64%N.

EXAMPLE 2

4-(1-Indolinyl)benzonitrile

4.94 g (0.206 mole) 99% NaH was added in one portion to a solution of 21.6 ml (0.188 mole) indoline in 85 ml sieve dried dimethylsulfoxide (DMSO) at room temperature. The resulting slurry was permitted to stir at room temperature for 2 hours and then cooled in an ice bath. A solution of 25 g (0.206 moles) 2-fluorobenzonitrile in 35 ml DMSO was added dropwise. At the end of the addition, the ice bath was removed and the mixture was permitted to stir at room temperature overnight (about 16 hours). The product was poured onto 300 ml of ice and extracted with $CHCl_3$ (300 ml). The organic phase was thrice washed with water (500 ml portions), brine (500 ml), dried (Na_2SO_4) and concentrated to give 39.9 g (96.4%) of crude material. Two recrystallizations from isopropyl ether afforded 4-(1-indolinyl)benzonitrile, m.p. 88.5°–89.5° C.

ANALYSIS: Calculated for $C_{15}H_{12}N_2$: 81.79%C, 5.49%H, 12.72%N, Found: 81.60%C, 5.52%H, 12.72%N.

b. 4-(1-Indolinyl)benzenemethanamine hydrochloride

A solution of 12.06 g (54.8 mmole) of 4-(1-indolinyl)-benzonitrile of Example 2a in 62 ml tetrahydrofuran (THF) was added dropwise to a rapidly stirred ice cold solution of BH_3 in THF (181 ml of 0.93 M solution, 3.07 equiv. 168.4 mmole) under nitrogen. After heating at reflux for 1.5 hours, the solution was permitted to cool to room temperature and stand overnight. The ice cold reaction mixture was then treated dropwise with 6 M aq. HCl (100 ml), heated at reflux for 40 minutes, cooled

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