

1-PHENOXY-3-HYDROXYINDOLYL-
ALKYLAMINO-2-PROPANOLS AND PREPARATION

The present invention is concerned with heterocyclic carbon compounds of the indole series having an amino substituent,
5 and with medication utilizing these compounds.

A large body of prior art exists for many series of compounds classified as 3-(aryloxy)-2-hydroxypropylamines. Most of these series claim utility as useful agents in treatment of cardiovascular
10 diseases, particularly beta-adrenergic receptor blocking activity. Many compounds in this general class also possess a degree of vasodilating effectiveness due, in some instances, to inherent alpha-adrenergic receptor blocking activity. Various other cardiovascular drug effects, or their lack, combine to make some of these compounds
15 appear to be useful as antihypertensive agents. Most prior art, however, concerns the beta-adrenergic blocking agent property for

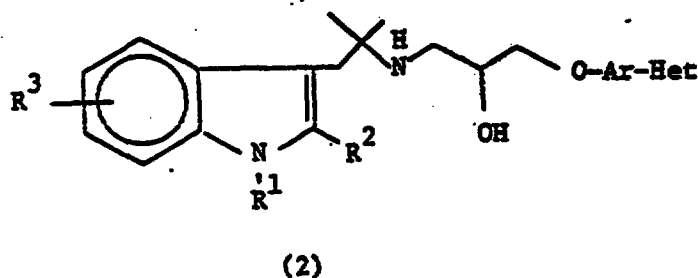
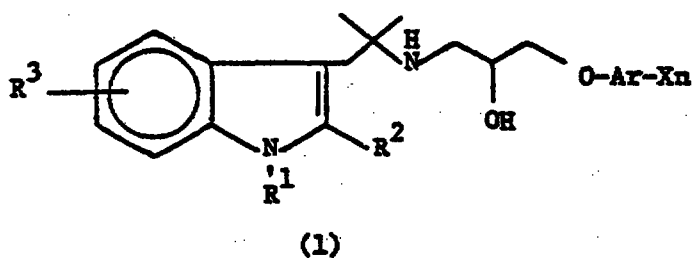
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these series of compounds. The prototype for structures of this kind is propranolol; chemically, 1-(isopropylamino)-3-(1-naphthyloxy)-2-propanol. Propranolol and some related naphthyloxy propanolamines are the subject of U.S. Patent No. 3,337,628 issued August 22, 1967.

- 5 Numerous subsequent patents have been granted covering series of compounds representing structurally modified 3-(aryloxy)-2-hydroxy-propylamines.

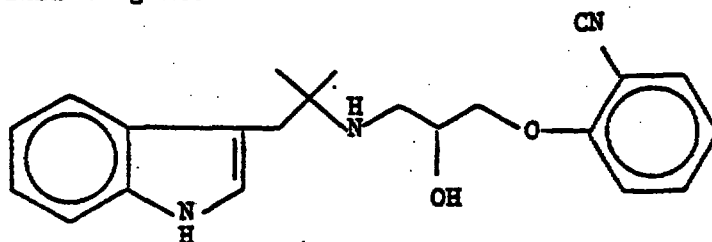
A series of indol-3-yl-tert.-butylaminopropanols (1,2) with antihypertensive properties was described in: Kreighbaum, et al.,

10. U.S. Patent No. 4,234,595 patented November 18, 1980; U.S. Patent No. 4,314,943 patented February 9, 1982; and Journal of Medicinal Chemistry, 23:3, 285-289 (1980).



In these foregoing structural formulas, the symbol R^3 can be hydrogen, halogen, lower alkyl or alkoxy but not hydroxyl.

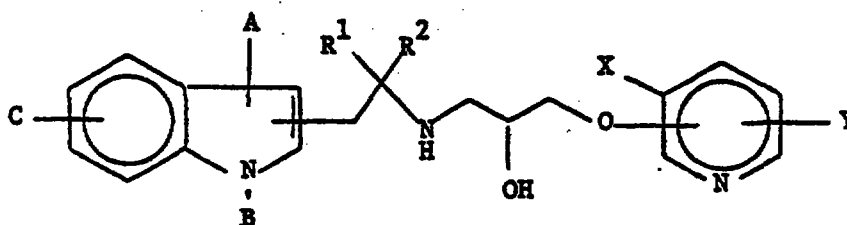
A preferred compound of the structural Formula (1) series is designated MJ 13105, also known by the United States Adopted Name as bucindolol, and is currently undergoing evaluation clinically as an antihypertensive agent.



MJ 13105

It is of interest in regard to the instant compounds that a major metabolic pathway for MJ 13105 involves 6-hydroxylation of the indole ring. This was confirmed by comparison of metabolic isolates with the synthetically available corresponding 6-hydroxyindolyl compound of the instant invention.

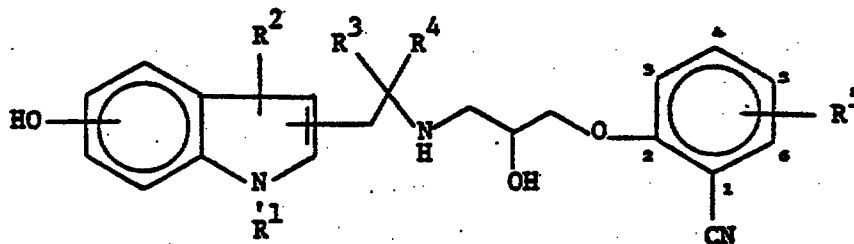
Attention is also called to applicant's pending U.S. Application Serial No. 414,748, filed September 3, 1982, which discloses a series of vasodilating agents having a range of beta-adrenergic blocking potency and possessing structural formula (3).



(3)

While in the foregoing structural formula (3), C can be hydroxyl, among other substituents, the series in general is distinguishable from the instant invention in that compounds of structure (3) are pyridinyloxypropanolamines.

- 5 The present invention includes the compounds of Formula I and the acid addition salts of these substances.



(I)

- 10 In the foregoing structural formula the symbols R¹-R⁵ have the following meanings. One of R¹ and R² is hydrogen and the other is hydrogen or C₁₋₄ alkyl, R³ and R⁴ are independently selected from hydrogen or C₁₋₄ alkyl, and R⁵ can be halogen, hydrogen, hydroxy, or C₁₋₄ alkyl. For preferred compounds R¹ is H, R² is 2-H, R³ and R⁴ are methyl, and R⁵ is hydrogen or 5-fluoro. The compounds of the present invention are useful as antihypertensive agents due in part to a combination of their adrenergic receptor-blocking and vasodilator
- 15 activities.

The invention includes compounds having the foregoing structural formula (I) and the acid addition salts thereof. In structural formula I, R^1 , R^2 , R^3 , and R^4 can be hydrogen or alkyl having 1 to 4 carbon atoms. One of R^1 and R^2 will always be hydrogen whereas R^3 and R^4 are independently selected and can both be alkyl. R^5 can be halogen, preferably fluoro or chloro; hydrogen; hydroxyl; or lower alkyl. The indolyl system is attached to the side chain at either the 2- or 3- position and the hydroxyl substituent occupies either the 4-, 5-, 6-, or 7- ring position of indole. For preferred compounds, R^1 is hydrogen; R^2 is 2-hydrogen (the indole moiety being coupled to the main side chain through its 3-position); R^3 and R^4 are methyl; and R^5 is hydrogen or 5-fluoro.

For medicinal use, the pharmaceutically acceptable acid addition salts, those salts in which the anion does not contribute significantly to toxicity or pharmacological activity of their organic cation, are preferred. The acid addition salts are obtained either by reaction of an organic base of structure I with an organic or inorganic acid, preferably by contact in solution, or by any of the standard methods detailed in the literature and available to any practitioner skilled in the art. Examples of useful organic acids are carboxylic acids such as maleic acid, acetic acid, tartaric acid, propionic acid, fumaric acid, isethionic acid, succinic acid, pantoic acid, cyclamic acid, pavalic acid, and the like; useful inorganic acid are hydrohalide acids such as HCl, HBr, HI; sulfuric acid; phosphoric acid; and the like.

It is also to be understood that the compounds of the present invention include all the optical isomer forms, that is, mixtures of enantiomers, e.g., racemic modifications as well as the individual enantiomers. These individual enantiomers are commonly designated according to the optical rotation they effect, by (+) and (-), (l) and (d), or combinations of these symbols. The symbols (L) and (D) and the symbols (S) and (R), which stand for sinister and rectus, respectively, designate an absolute spatial configuration of the enantiomer. Where no isomer designation is given for a compound, the compound is the racemic modification.

The individual optical isomers of the aryloxypropanolamine class of compounds, of which the instant compounds are members, have most generally been obtained by one of four basic methods. These are: 1) the fractional recrystallization of chiral acid salt derivatives; 2) derivatization with a chiral organic reagent, resolution and regeneration of the original compound in optically active form; 3) synthesis of the single optical isomer using chiral intermediates; and 4) column chromatography utilizing chiral stationary phases. Applications of these various methods are well known to practitioners in the art.

Biological testing of representative subject compounds of Formula I in animals demonstrates that they possess biological properties which would make them useful as antihypertensive agents. In addition to antihypertensive activity demonstrable in animal testing, the instant compounds also possess vasodilating properties along with varying degrees of adrenergic alpha- and beta-receptor blocking properties and intrinsic sympathomimetic activity. A more

5 detailed description of the specific pharmacological tests employed and the criteria used to judge the pertinent biological activity is contained in the Description of Specific Embodiments section under the subheading Biological Evaluation. Preferred representative

10 members have a particularly desirable combination of the foregoing actions, and ancillary pharmacological effects, or lack thereof, which particularly suits them for specific cardiovascular indications, e.g. use as antihypertensives. The utility of the compounds of Formula I can be demonstrated in these various animal models, as referred to above, which include antagonism of isoproterenol in the anesthetized dog treated intravenously (adrenergic beta-receptor action), the spontaneous hypertensive and DOCA salt hypertensive rat (antihypertensive action), angiotensin-maintained ganglion-blocked rat model (vasodilator action), and an anesthetized rat model (alpha-
15 adrenergic blockade), and in various other animal laboratory models (cf: Deitchman, et al., Journal Pharmacological Methods, 3, 311-321 (1980)).

As examples, two of the representative compounds of Formula I; 2-[2-hydroxy-3-[[2-(6-hydroxy-1H-indol-3-yl)-1,1-dimethylethyl]amino]propoxy]benzonitrile and 2-[2-hydroxy-3-[[2-(5-hydroxy-1H-indol-3-yl)-1,1-dimethylethyl]amino]propoxy]benzonitrile caused
20 greater than 20 mmHg mean drop in systolic blood pressure of rats in one or both of the antihypertensive tests when given at a dose level of 30 mg/kg p.o. A 3 mg/kg intravenous dose of these compounds
25 resulted in over a 20% drop in mean arterial blood pressure (taken 30 minutes after dosing) in the vasodilation test.

For use as antihypertensives, vasodilators, and/or adrenergic blocking agents, therapeutic processes of this invention comprise systemic administration, by both oral and parenteral routes, of an effective, non-toxic amount of a compound of Formula I or a

5 pharmaceutically acceptable acid addition salt thereof. An effective amount is construed to mean a dose which exerts the desired pharmacological activity, such as those stated hereinabove, without undue toxic side effects when administered to a mammal in need of such treatment. Dosage will vary, according to the subject and route of

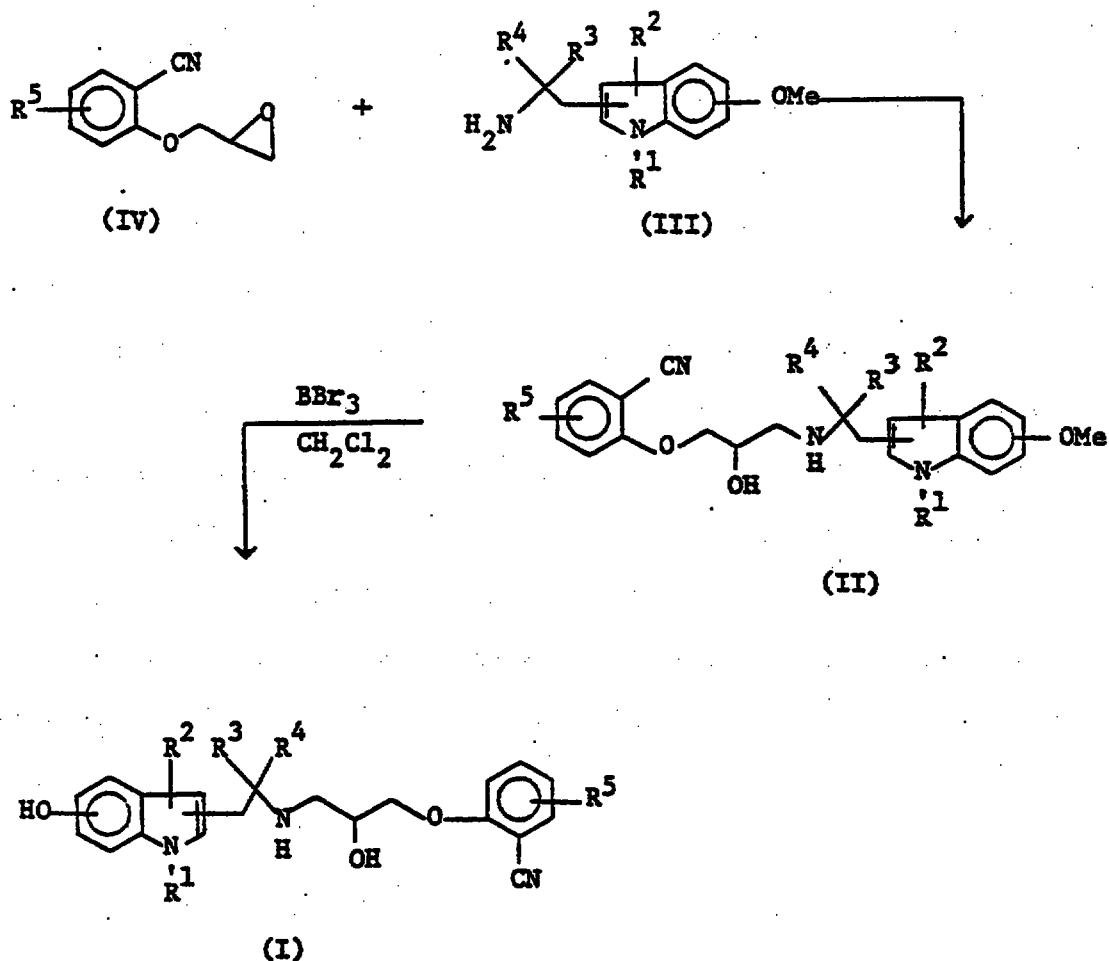
10 administration selected, with an expected range of about 0.1 mcg to 100 mg/kg body weight of a compound of Formula I or a pharmaceutically acceptable acid addition salt thereof generally providing the desired therapeutic effect. A preferred range for an effective dose would be about 0.1 to 0.5 mg/kg when given intravenously and about 0.5 to

15 5 mg/kg when given orally.

The compounds of the present invention can be prepared by a convenient general process. This process is outlined below in Scheme 1.

Throughout this application, Me stands for a methyl group and Ac stands for the acetate ion, $C_2H_3O_2^-$.

Scheme 1



R^1 - R^5 are as defined above.

This process involves the coupling of a suitable methoxylated indolalkylamine (III) with an R^5 -substituted phenoxy epoxide intermediate (IV). Synthetic methodology required to reach this point in the preparation of Formula I products is analogous to a synthetic process used to prepare bucindolol. The pertaining Kreighbaum, et al. patents U.S. 4,234,595 and U.S. 4,314,943, and

J. Med. Chem., 23:3, 285-289 (1980) article are hereby incorporated into this patent application in their entirety by reference. An additional step, however, is required as the resulting methoxylated indole analog (II) is converted to the desired (I) product by

5 cleavage of the methoxy group with boron tribromide in methylene chloride solution. Other synthetic methods resulting in conversion to hydroxylated products, e.g. such as hydrogenolysis of benzyloxy precursors, are well known to the chemical practitioner and may also be adapted for use in a modified process.

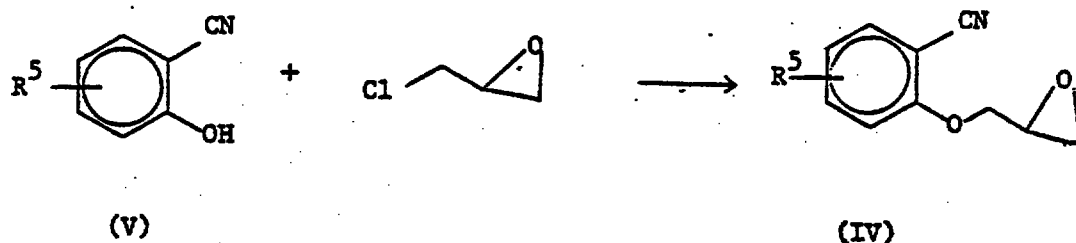
10 The coupling of the epoxy ether intermediate (IV) with the indolylalkylamine (III) to give intermediate (II) is carried out simply by heating the epoxy ether either neat or in the presence of a reaction inert organic solvent with an appropriate indolylalkylamine as shown. No catalyst or condensation agent is usually required.

15 Suitable solvents include 95% ethanol but other reaction-inert organic liquids in which the reactants are soluble may be employed. These may include but are not limited to benzene, tetrahydrofuran, dibutyl ether, butanol, hexanol, methanol, dimethoxyethane, ethylene glycol, etc. Suitable reaction temperatures are from about 60-200°C.

20 The required reaction intermediates, III and IV, may be obtained by several methods and are not limited to the following. The phenoxy epoxide intermediates (IV) can be obtained by alkylation of the appropriate R⁵-substituted cyanophenol (V) with epichlorohydrin as in Scheme 2; or in recalcitrant cases by using epibromohydrin, K₂CO₃

25 and dimethylformamide.

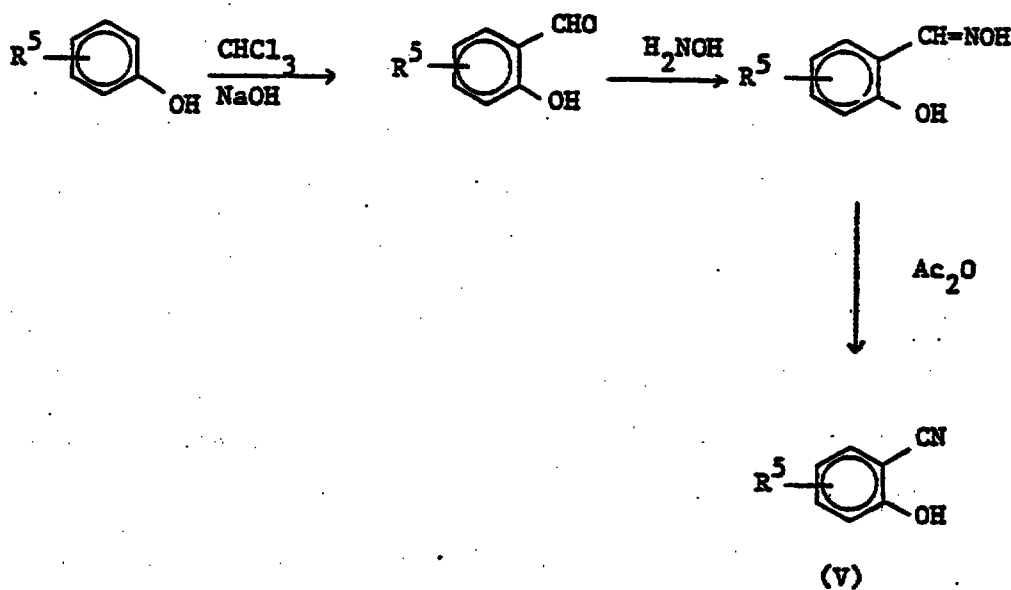
Scheme 2



While many cyanophenols (V) are commercially available, they may also be conveniently prepared from readily available phenols via the synthesis outlined as Scheme 3.

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Scheme 3



This sequence essentially involves formylation of an R^5 -substituted phenol according to Reimer-Tiemann conditions to afford the salicylaldehyde derivative which is converted via the oxime intermediate to the desired salicylonitrile (V). It should be noted that when

10 Formula I products in which R^5 is hydroxyl are desired, the IV

intermediate in which R⁵ is methoxy is to be used in Scheme 1. Cleavage by BBr₃ to the hydroxyl group is effected in the last step of the synthesis.

For the intermediate indolylalkylamines of structure III, typical synthetic procedures for their preparation are available in the Kreighbaum, et al., patents and the J. Med. Chem. article cited hereinabove and incorporated by reference into this patent application. Although these referenced procedures are applicable to the preparation of other indolylalkylamine intermediates which may be desired but are not specifically disclosed therein, representative syntheses of Formula III compounds will be given hereinbelow for further exemplification of intermediates which may be required for the present invention.

Finally, it is of interest that a 6-hydroxyindolyl compound of Formula I (2-[2-hydroxy-3-[[2-(6-hydroxy-1H-indol-3-yl)-1,1-dimethylethyl]amino]propoxy]benzonitrile) which structurally corresponds to bucindolol (R¹, R², R⁵ are hydrogen and R³, R⁴ are methyl) was used to confirm the identity of a major metabolite of bucindolol. It is known that 6-hydroxylation is perhaps more important than 5-hydroxylation in the metabolism of tryptamine derivatives (cf: Jepson, et al., Biochim. Biophys. Acta., 62, 91 (1962); Jaccarini and Jepson, Biochim. Biophys. Acta., 156, 347 (1968)). This knowledge suggested the possibility that 6-hydroxylation of bucindolol might be an important metabolic pathway. This has been confirmed by demonstration that this 6-hydroxyindolyl compound of the instant invention agrees in mass spectrum and gas chromatographic retention time with a corresponding major hydroxy metabolite of bucindolol. In this regard,

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another aspect of the instant invention comprises 2-[2-hydroxy-3-[[2-(6-hydroxy-1H-indol-3-yl)-1,1-dimethylethyl]amino]propoxy]-benzonitrile in purified pharmaceutically acceptable form.

The compounds of the present invention can be formulated according to conventional pharmaceutical practice to provide pharmaceutical compositions of unit dosage form comprising, for example, tablets, capsules, powders, granules, emulsions, suspensions, and the like. The solid preparations contain the active ingredient in admixture with non-toxic pharmaceutical excipients such as inert diluents, for example, calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, maize, starch, or alginic acid; binding agents, for example, starch, gelatin or acacia; and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques so as to retard disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. Liquid preparations suitable for parenteral administration include solutions, suspensions, or emulsions of the compounds of Formula I. The aqueous suspensions of the pharmaceutical dosage forms of the compounds of Formula I contain the active ingredient in admixture with one or more non-toxic pharmaceutical excipients known to be suitable in the manufacture of aqueous suspensions. Suitable excipients are, for example, suspending agents such as sodium carboxymethylcellulose, methylcellulose, hydroxypropyl methylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia. Suitable disbursing or wetting agents are naturally occurring phosphatides, for example, lecithin, polyoxyethylene stearate.

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Non-aqueous suspensions may be formulated by suspending the active ingredient in vegetable oil, for example, olive oil, sesame oil, or coconut oil, or in a mineral oil, for example, liquid paraffin. The suspensions may contain a thickening agent such as beeswax, hard
5 paraffin, or cetyl alcohol. Sweetening and flavoring agents generally used in pharmaceutical compositions may also be included such as saccharin, sodium cyclamate, sugar and caramel to provide a palatable preparation. The compositions may also contain other absorbing agents, stabilizing agents, wetting agents, and buffers.

10 The compounds which constitute this invention, their methods of preparation and their biologic actions will appear more fully from consideration of the following examples, which are given for the purpose of illustration only and are not to be construed as limiting the invention in sphere or scope, and the appended claims.
15 In the following examples, used to illustrate the foregoing synthetic processes, temperatures are expressed in degrees Celsius and melting points are uncorrected. The nuclear magnetic resonances (NMR) spectral characteristics refer to chemical shifts (δ) expressed as parts per million (ppm) versus tetramethylsilane (TMS) as reference
20 standard. The relative area reported for the various shifts in the ^1H NMR spectral data corresponds to the number of hydrogen atoms of a particular functional type in the molecule. The nature of the shifts as to multiplicity is reported as broad singlet (bs), singlet (s), multiplet (m), or doublet (d). Abbreviations employed are $\text{DMSO}-d_6$
25 (deuterodimethylsulfoxide), CDCl_3 (deuteriochloroform), and are

otherwise conventional. The infrared (IR) spectral descriptions include only absorption wave numbers (cm^{-1}) having functional group identification value. The IR determinations were employed using potassium bromide (KBr) as diluent. The elemental analyses are reported as percent by weight.

Synthesis of Intermediates

A. Intermediates of Formula III: General Procedures

EXAMPLE 1

Methoxyindol-3-yl-tert.-butylamine

To 15.2 mL of a chilled 25% aqueous solution of dimethylamine the following are added sequentially with stirring and continued cooling: 16.9 mL of acetic acid, 7.2 mL of 37% formaldehyde, 27 mL of 95% ethanol. The resulting stirred solution is kept at 0° to -5° with a cooling bath while the appropriate methoxyindole (10.0 g, 0.07 mole) is added in portions. This mixture is stirred and gradually warmed to 30° over a period of one-half hour and then held at 30° with stirring for 3 hours. The reaction mixture is then chilled to 10-15° and acidified with 170 mL of 2N HCl. This acidic mixture can be decolorized (Darco[®] G-60), filtered and the filtrate made basic using 245 mL of 20% NaOH while being cooled and stirred. A resulting brown oily precipitate is ether extracted, and the extracts are water-washed, dried (MgSO_4) and concentrated to a brown oily residue (14 g). The residue is recrystallized, e.g. from isopropyl ether and hexane to yield the desired methoxygramine, usually as a tan solid.

A mixture comprised of the appropriate methoxygramine (7.7 g, 0.04 mole), 2-nitropropane (26.5 g, 0.3 mole), and NaOH (1.7 g pellets, 0.04 mole) is refluxed under a nitrogen atmosphere

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for 3-5 hours. The reaction mixture is then cooled to room temperature, acidified with 10% acetic acid and extracted with ether. The ether extracts are water-washed, dried (MgSO_4), and concentrated in vacuo to a residue. Recrystallization of the residue, e.g. from isopropyl alcohol-water gives a 3-(2-methyl-2-nitropropyl)methoxyindole.

This nitropropylindole compound and activated Raney Nickel (4.2 g) are combined in 80 mL 95% ethanol and heated to reflux. Heating is halted as a solution comprised of 85% hydrazine hydrate (7.8 g) in 8 mL of 95% ethanol is added dropwise. The reaction mixture is then heated at reflux for 2 hours, cooled to room temperature and filtered. The filtrate is concentrated to an oily residue which can be recrystallized, e.g. from ethyl acetate-isopropyl ether to give the desired methoxyindol-3-yl-t-butylamine product.

EXAMPLE 1a

6-Methoxyindol-3-yl-tert.-butylamine

A mixture of 6-methoxy gramine (0.9 g, 0.004 mole; prepared from 6-methoxyindole by the procedure of Example 1), 3.0 g (0.034 mole) of 2-nitropropane and 0.19 g (0.005 mole) of NaOH pellets was stirred at reflux in an oil bath under a nitrogen atmosphere for 2 hours, as dimethylamine escaped through the condenser. The resulting mixture was cooled to 25°, treated with a solution of 0.47 mL of glacial acetic acid in 4.1 mL of water and extracted with ether. The ether extract was washed with three portions of water, dried (MgSO_4) and evaporated to dryness. The residual brown oil crystallized upon rubbing and cooling in a small amount of isopropyl ether. The solid was isolated by filtration, washed with cold isopropyl ether and dried in air to give 0.6 g of tan solid which was

recrystallized from isopropyl alcohol-water to give 0.52 g (46%) of 3-(2-methyl-2-nitropropyl)-6-methoxyindole, m.p. 98-99°C.

A slurry of 8.0 g (0.32 mole) of the nitro compound as prepared above, 80 mL of 95% ethanol and 4.2 g of Raney Nickel

- 5 (washed with water and 95% ethanol) was heated to reflux with paddle stirring. Exterior heating was halted and a solution of 7.8 g of 85% hydrazine hydrate in 8 mL of 95% ethanol was added dropwise at a sufficient rate to maintain a gentle reflux. After the addition, the mixture was reheated at reflux for two hours and then cooled to 25°C.
- 10 Filtering and concentrating the filtrate to dryness gave a crude syrup which was chromatographed on silica gel column, eluting with CH_2Cl_2 - CH_3OH -concentrated NH_4OH (90:10:1). The tan solid thus obtained (2.9 g, m.p. 125-128°C) was recrystallized from ethyl acetate-isopropyl ether to afford 1.27 g (18%) of 6-methoxyindol-3-yl-tert.-butylamine, m.p. 125-128°.
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EXAMPLE 2

Methoxyindol-2-yl-tert.-butylamine

(R¹, R² = H, R³, R⁴ = Me)

- In this general procedure a solution comprising the
- 20 appropriate methoxyindole-2-carboxylic acid (0.06 mole) and thionyl chloride (2.0 g, 0.17 mole) in 130 mL of dry ether is stirred for 12-18 hours at room temperature under a nitrogen atmosphere. The reaction mixture is filtered and the filtrate is concentrated to an oily residue which is taken up in 150 mL of dry ether. This ether
- 25 solution is treated with 80 mL of dimethylamine in 90 mL of ether. The ethereal reaction mixture is concentrated to dryness and the

residue crystallized in isopropyl alcohol. The solid is isolated by filtration to give a 30-40% yield of the methoxyindole-2-carboxamide product.

The methoxyindol-2-yl carboxamide is dissolved in 100 mL of THF and this solution is added dropwise to a stirred suspension comprised of 3 g of lithium aluminum hydride in 50 mL of THF under a nitrogen atmosphere. After heating at reflux for 2 hours, the reaction mixture is cooled and decomposed with a small amount of water and dilute NaOH solution. This mixture is filtered and the filtrate is concentrated to a residual oil which is taken up in absolute ethanol and treated with a slight excess of dimethyl sulfate. The resulting alcoholic solution is stirred at room temperature for four hours and then concentrated in vacuo to dryness giving as residue a trimethylamine quaternary salt.

The crude quaternary salt product (0.01 mole) is combined with NaOH (2.0 g pellets, 0.05 mole) and 2-nitropropane (15 mL) and the mixture is heated at reflux under a nitrogen atmosphere for 1 hour. The resultant dark thick mixture is cooled, diluted with water, acidified with acetic acid to a pH of approximately 6 and then extracted with ether. These ether extracts are combined, washed with water, dried (MgSO_4) and concentrated to a dark residue which is chromatographed on a silica column and diluted with methylene chloride. Removal of the methylene chloride solvent and recrystallization of the crude material from isopropyl alcohol-water gives a methoxyindole substituted in the 2-position with a 2-methyl-2-nitropropyl moiety.

Reduction of this nitro product with Raney Nickel and hydrazine according to the procedure used in Example 1 above will yield the desired methoxyindol-2-yl-tert.-butylamine.

EXAMPLE 3

1-Methylation of Methoxyindolylalkylamines:
3-(2-Amino-2-methylpropyl)-1-methyl-methoxyindole
(R¹, R³, R⁴ = Me, R² = H)

5 In this general process 7 g (0.11 mole) of 85% KOH is ground in a mortar and quickly transferred to a nitrogen-flushed 25-mL Erlenmeyer flask. DMSO (55 mL) is added and the mixture is stirred for 5 minutes. Additions of methoxyindolyl-tert.-butylamine (0.27 mole) and iodomethane (3.78 g, 0.03 mole or any other suitable
10 alkylating agent) are each followed by 45 minutes of stirring after which the suspension is quenched in 300 mL of water. Extraction of the mixture with ethyl acetate, followed by washing of the extracts with water and brine affords a clear solution which is dried (MgSO₄) and evaporated in vacuo to an oily product. This free base may be
15 used as a intermediate without further purification. Characterization is usually made by converting the oily base to the hydrochloride salt in order to obtain a crystalline product.

EXAMPLE 4

Methoxyindol-2-ylethylamine

20 In this procedure which is essentially that of Bhat and Siddappa, J. Chem. Soc. (C), 1971, 178-81; various methoxyindol-2-carboxylate esters (commercially available or prepared by literature methods) is reduced to the corresponding 2-hydroxymethylindole derivative by reduction with lithium aluminum hydride in ether.
25 Conversion to the indol-2-carbaldehyde is accomplished by dissolving a 2-hydroxymethyl-methoxyindole (4 g) in dichloromethane (250 mL) and adding activated manganese dioxide (10 g) followed by stirring of the reaction mixture at room temperature for 20-30 hours. The reaction

is followed by TLC, monitoring the disappearance of the starting 2-hydroxymethylindole spot. If necessary, fresh quantities of manganese dioxide (2-3 g) can be added. The reaction mixture is filtered and the residual manganese dioxide washed repeatedly with a little fresh dichloromethane. The combined filtrate is evaporated to dryness to give the crude methoxyindol-2-carbaldehyde as a pale yellow solid which is then recrystallized.

The methoxyindol-2-carbaldehyde (5 g), nitromethane (8 mL), and ammonium acetate (1 g) are heated under reflux for 1/2 hour. The reaction mixture is cooled and the dark red crystals that separate are collected, washed thoroughly with water, dried and crystallized from ethanol. The nitrovinylmethoxyindole thus prepared is then reduced to the desired methoxyindol-2-ylethylamine by treatment with lithium aluminum hydride in dry ether. The reduction mixture is gently heated under reflux for 10 hours following which the excess lithium aluminum hydride is decomposed. Following filtration, the filtrate is concentrated in vacuo to give a residue which is crystallized from a suitable solvent to give the desired methoxyindol-2-ylethylamine.

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EXAMPLE 5

Methoxyindol-2-ylpropylamine

Modifying the procedure of Example 4, an appropriate methoxyindol-2-carbaldehyde (1 g) in nitroethane (0.5 mL) is treated with four drops of benzylamine; following which the mixture is heated at reflux for one hour. The cool reaction mixture on standing deposits dark red crystals which may be collected, washed with a little ether, dried, and crystallized from ethanol. These nitropropenyl indoles thus prepared are reduced with lithium aluminum

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hydride as described above in Example 4. Solid products are crystallized and the liquids are characterized as benzoyl derivatives.

EXAMPLE 6

Methoxyindol-3-ylethylamine

5 Cf: Young, J. Chem. Soc., 1958, 3493-96; This synthesis starts with methoxyindol-3-aldehydes which are either available commercially or prepared from literature methods. Using the procedure outlined in Example 4 above, an appropriate methoxyindol-3-carbaldehyde is condensed with a nitromethane using ammonium acetate
10 as a catalyst. On standing, the cooled solution gradually deposits dark red crystals which can be recrystallized from benzene or methanol to give the 3-nitrovinyl-methoxyindole which is reduced with lithium aluminum hydride, as above to yield the desired methoxyindol-3-ylethylamine.

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EXAMPLE 7

Methoxyindol-3-ylpropylamine

A selected methoxyindol-3-carbaldehyde (5 g), nitroethane (10 mL), and ammonium acetate (1 g) are heated on a steam bath with occasional shaking for 1/2 hour. On cooling, the crystals are
20 collected, washed with hot water (2 x 50 mL) and crystallized from methanol. The resulting 3-(2-nitropropenyl)-methoxyindole is reduced to the desired 3-(2-aminopropyl)-methoxyindole by treatment with lithium aluminum hydride as detailed in the above procedures.

B. Intermediates of Formula IV

EXAMPLE 8

2-[(2,3-Epoxy)propoxy]benzonitrile

A solution of 2-cyanophenol (25.0 g, 0.21 mole), epichloro-
5 hydrin (117 g, 0.26 mole), and piperidine (10 drops) was stirred and
heated at 115-120° in an oil bath for 2 hours. The reaction mixture
was then concentrated (90°/30 Torr.) to remove unreacted epichlorohydrin.
The residue was diluted with toluene and concentrated to dryness
twice to help remove the last traces of volatile material. The
10 residual oil was dissolved in 263 mL of tetrahydrofuran and this
solution was stirred at 40-50° for one hour with 263 mL of 1N NaOH.
The organic layer was separated and concentrated to give an oil which
was combined with the aqueous phase. The mixture was extracted
(CH₂Cl₂), and the extract dried (MgSO₄) and concentrated to give
15 36.6 g (100%) of oil which slowly crystallized to a waxy solid. This
intermediate product may be used without further purification in the
preparation of Formula I products.

EXAMPLE 9

2-[(2,3-Epoxy)propoxy]-5-methoxybenzonitrile

20 The requisite 5-methoxysalicylaldehyde can be obtained from
4-methoxyphenol by the Reimer-Tiemann procedure which is well
described in the literature, e.g. Cf: Kappe, et al., Arch. Pharm.,
308/5, 339 (1975). A solution comprising 0.005 mole of the starting
salicylaldehyde in 6 mL of pyridine and 6 mL of absolute ethanol is
25 treated with 0.4 g (0.02 mole) of hydroxylamine hydrochloride and
heated at reflux for 4 hours. The mixture is concentrated in vacuo
to a gray syrup which is stirred with 50 mL of H₂O and the suspension

decanted. Addition of 10 mL of H_2O to the residual glassy material followed by chilling at 5° affords, upon filtration, approximately 1.2 g of crude solid which is taken up in 25 mL of 50% ethyl ether-isopropyl ether. The ether solution is filtered, dried ($MgSO_4$),

- 5 treated with Darco G-60 and Celite, filtered and concentrated in vacuo to a waxy solid. Recrystallization from ethyl ether-Skelly B gives the corresponding benzaldehyde oxime.

- A mixture of 0.002 mole of the oxime and 1.02 g (0.01 mole) of acetic anhydride is heated at reflux for 30 minutes and then
10 cooled to 25° . Water (50 mL) was added, followed by dropwise addition of 20% NaOH to pH 10. The resulting suspension was stirred at 25° for 20 hours (to hydrolyze any acetate ester of the desired phenol derivative. The pH is adjusted to about 2 using 6N HCl and the resulting mixture is extracted with 40 mL of ethyl acetate to give an
15 organic layer which is separated, dried ($MgSO_4$) and evaporated at $65^\circ/70$ Torr. to give a tan syrup which still consists mainly of the acetate ester. Further hydrolysis of the syrup in a mixture of 7 mL of methanol, 7 mL of water and 0.1 g of NaOH pellets at 25° for 3 hours is followed by removal of the methanol at $60^\circ/70$ torr.
20 Dilution of the aqueous residue with 0.5N HCl affords a precipitate which can be recrystallized from isopropyl ether and dried to give the desired benzonitrile intermediate.

- A mixture of 0.015 mole of the 2-hydroxy-5-methoxybenzonitrile, 4.2 g (0.03 mole) of finely powdered anhydrous potassium
25 carbonate and 140 mL of DMF was stirred at 50° for 15 minutes. Epibromohydrin (2.8 g or 0.02 mole) was added in one portion and stirring was continued for 3 days. The reaction mixture was

poured into 1 liter of brine and the resulting suspension stirred for 3 hours at 0-5°. Filtering the mixture and washing the filter cake with water gave upon drying in air the crude intermediate compound which could be used without further purification.

- 5 Similarly, using other substituted 2-cyanophenols in modifications of the above procedures will provide the other intermediate compounds of Formula IV to be used in synthesis of the various Formula I compounds of this invention.

Synthesis of Products

10

EXAMPLE 10

General Procedure: 2-[2-Hydroxy-3-[(hydroxy-indolyl)alkylamino]propoxy]benzonitrile

- 15 A selected methoxyindolylalkylamine (III) is mixed with an equimolar or slight excess amount of a selected epoxy propoxy benzonitrile (IV) and the coupling is accomplished by either refluxing a solution of the reactants for approximately 18 to 24 hours or heating a neat mixture at a temperature of about 120-130° for about 1/2 to 2 hours. Ethanol and toluene are the usual solvents chosen for the reaction medium for coupling via refluxing a solution of III and IV.
- 20 In some instances, it is advantageous to follow the course of the reaction by TLC, adding additional IV epoxide until all indolylamine III has disappeared. Following reaction the mixture is concentrated to dryness and the residue is either washed and used crude in the next step or the intermediate methoxy product may be purified by
- 25 crystallization-recrystallization either as the base or a suitable acid addition salt.

A solution of the methoxyindolyl product (II) dissolved in methylene chloride and stirred under a nitrogen atmosphere at 0-10° while a several-fold excess of 1N boron tribromide in methylene chloride is added dropwise. Following addition, the reaction mixture is stirred at room temperature for about 6-8 hours. The excess boron tribromide is decomposed by chilling the reaction mixture and dropwise addition of excess water. The crude hydrobromide salt of the Formula I product may be worked up in a number of conventional ways such as recrystallization, conversion to the base and purification, conversion to the base followed by conversion to a different acid addition salt, and so forth.

The modifications necessary to adapt this procedure for the preparation of specific compounds of Formula I are well within the skill of any ordinary practitioner in the chemical arts.

EXAMPLE 11

2-[2-Hydroxy-3-[[2-(6-hydroxy-1H-indol-3-yl)-1,1-dimethylethyl]amino]propoxy]benzonitrile

A solution of 6-methoxyindol-3-yl-t-butylamine (2.6 g, 0.012 mole; prepared in Example 1a), 2-[(2,3-epoxy)propoxy]benzonitrile (2.1 g, 0.012 mole; prepared in Example 8), and 100 mL of absolute ethanol was stirred at reflux for 20 hours. Additional epoxide (0.21 g) was added and reflux was continued for 4 hours, after which the mixture was concentrated to dryness and the residue triturated in isopropyl alcohol to induce crystallization. The product was collected by filtration, washed with cold isopropyl alcohol and dried in air to give 4.0 g (85%) of the methoxy product (II), m.p. 145-146°, which was used directly in the next step.

A solution of the methoxyindole product prepared above (1.5 g, 0.004 mole) in 225 mL of methylene chloride was stirred under a nitrogen atmosphere at 5-10°C while 15.3 mL (0.015 mole) of 1M boron tribromide in methylene chloride was added dropwise. Following the addition, the ice bath was removed and the reaction mixture was stirred at 25° for 6 hours before refrigeration to 5-10° and dropwise addition of 47.5 mL of H₂O. The resulting mixture was decanted and the residual gummy solid rinsed with 2 portions of H₂O. Dissolving this crude hydrobromide salt in 50 mL of hot H₂O followed by treatment with Darco G-60, filtering, cooling (25°) and basifying (pH 8) with conc. NH₄OH gave 1.2 g of tan morphous solid which was chromatographed (silica gel 60, 230-400 mesh, EM Reagents) on a medium pressure system with chloroform-methanol-conc. NH₄OH (90:10:1). The product obtained in this manner crystallized from a small amount of 95% ethanol to afford, by gradual addition of H₂O, 1.03 g (71%) of the desired 6-hydroxy-indole product(I) as a tan solid, m.p. 90-94°.

Anal. Calcd. for C₂₂H₂₅N₃O₃·1/3H₂O: C, 68.56; H, 6.67; N, 10.90; H₂O, 1.54. Found: C, 68.69; H, 6.68; N, 10.68; H₂O, 1.80.

NMR (DMSO-d₆): 0.98 (6,s); 2.70 (4,m); 3.30 (2,bs); 3.83 (1,m); 4.11 (2,d [5.8 Hz]); 5.00 (1,bs); 6.65 (3,m); 7.20 (3,m); 7.60 (2,m); 8.71 (1,bs); 10.35 (1,bs).

IR (KBr): 760, 800, 1260, 1290, 1450, 1495, 1600, 1630, 2230, and 3300 cm⁻¹.

EXAMPLE 12

2-[2-Hydroxy-3-[[2-(5-hydroxy-1H-indol-3-yl)-
1,1-dimethylethyl]amino]propoxy]benzonitrile

A solution of 5-methoxyindol-3-yl-t-butylamine (2.7 g,
5 0.0125 mole; prepared from 5-methoxyindole utilizing the procedure
given in Example 1), 2-[(2,3-epoxy)propoxy]benzonitrile (2.2 g,
0.0125 mole), and 20 mL of acetone was refluxed for 1/2 hour. The
acetone solvent was then allowed to boil off and the oily
residue heated neat at 100° for 2 hours. Isopropyl alcohol (20 mL)
10 was added and the reaction solution refluxed for 4 hours following
which it was cooled to room temperature, diluted with 50 mL of
ether and a stirring rod was used to rub out a white powder, 4.7 g
(96%), m.p. 119-124°; TLC (9:1 CHCl₃-methanol) exhibits a single
spot, R_f 0.25. This crude methoxy product may be used directly in
15 the next step or be purified via conversion to the HCl salt. Con-
version to the HCl salt by treatment of an acetonitrile solution with
ethanolic HCl gives a crude product which is recrystallized in
butanone-95% ethanol (20:1) to off-white powder, m.p. 164-166°.

Anal. Calcd. for C₂₃H₂₇N₃O₃·HCl: C, 64.25; H, 6.56;
20 N, 9.77. Found: C, 64.14; H, 6.54; N, 9.68.

Using the procedure given above in Example 11 for boron
tribromide cleavage of the methoxy group, but employing the 5-methoxy-
indole intermediate product (II) prepared above, the desired
5-hydroxy indole product (I) in the form of its hydrobromide salt may
25 be obtained. The pure hydrobromide salt is a beige powder, m.p.
219-221°.

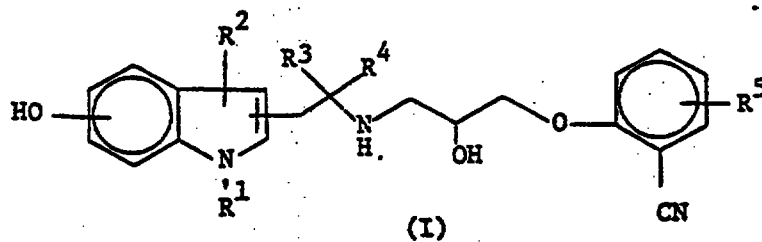
Anal. Calcd. for C₂₂H₂₅N₃O₃·HBr: C, 57.40; H, 5.70;
N, 9.13. Found: C, 56.90; H, 5.67; N, 9.45.

NMR (DMSO- d_6): 1.32 (6,s); 3.08 (2,m); 3.36 (2,m); 4.30 (3,m); 5.90 (1,bs); 7.10 (6,m); 7.71 (2,m); 8.55 (3,bs); 10.95 (1,bs).

IR (KBr): 750, 800, 1265, 1290, 1455, 1495, 1580, 1600, 2230, and 3300 cm^{-1} .

- 5 Starting with appropriate methoxyindolalkylamines (III) and epoxypropoxybenzonitriles (IV), additional examples of Formula I products may be synthesized using substantially the same procedures as outlined hereinabove with only slight modifications which would be well within the skill of a practitioner in the chemical arts. Some
- 10 additional products of Formula I which may be synthesized by these means are shown in Table 1.

Table 1



Example	-OH	R ¹	R ²	R ³	R ⁴	R ⁵
13	4-	H	2-H	Me	Me	H
14	7-	H	2-H	Me	Me	H
5 15	4-	Me	2-H	Me	Me	H
16	5-	Me	2-H	Me	Me	5-F
17	6-	Me	2-H	Me	Me	5-OH
18	7-	Me	2-H	Me	Me	H
19	4-	Me	3-H	H	Me	H
10 20	5-	Me	3-H	H	Me	5-F
21	6-	Me	3-H	H	Me	H
22	7-	Me	3-H	H	H	4-Me
23	4-	H	2-Me	H	Me	H
24	5-	H	2-Me	H	H	H
15 25	6-	H	2-Me	Me	Me	H
26	7-	H	2-Me	Me	Me	H
27	4-	H	3-Me	H	H	5-OH
28	5-	H	3-Me	H	Me	5-F
29	6-	H	3-Me	H	Me	H
20 30	7-	H	3-Me	H	H	5-Br
31	4-	H	2-H	H	Me	5-Me
32	5-	H	2-H	H	Me	4-Cl
33	6-	H	2-H	H	Me	H
34	7-	H	2-H	H	Me	4-OH

Biological Evaluation

These biological tests were used to gauge the antihypertensive profile of selected compounds of Formula I.

EXAMPLE 35

5 The efficacy of antihypertensive agents other than adrenergic beta-receptor blocking agents is commonly estimated in the spontaneously hypertensive rat. Blood pressure values are determined for test animals prior to and 2 and 4 hours after oral doses of 30-100 mg/kg of test compounds. Heart rate is determined with each pressure
10 measurement as well. A fall in blood pressure at 2 or 4 hours after the single dose in the range of 15-20 mmHg is considered "questionable". "Active" and "inactive" designations are decreases greater and less than that range, respectively.

EXAMPLE 36

15 Another test useful in determining efficacy of antihypertensive agents utilizes DOCA-salt hypertensive rats. These hypertensive rats are prepared as follows: male rats of the Sprague-Dawley strain weighing approximately 90 g are individually caged with free access to food and water for a 5-day pretreatment period, after
20 which, the drinking water is replaced with 1% saline solution. During a 3-week treatment period, the rats are given a total of 10 subcutaneous injections containing 10 mg of DOCA (deoxycorticosterone acetate) in 0.2 mL suspending vehicle (0.25% Tween* 80 and 0.125% CMC in normal saline solution). After the final injection, the 1% saline
25 is replaced by distilled water and the animals are available for use one week later.

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The test is made by selecting non-fasted animals with elevated systolic blood pressures (>160 mmHg). Blood pressure values are determined for these test animals prior to and four hours after oral doses of 30-100 mg/kg of test compounds. During the test period the animals are housed in metabolism cages without feed or water and urine is collected for 4 hours. Heart rate and body weight are both determined with each pressure measurement as well. A fall in blood pressure 4 hours after dosing which lies in the range of 15-20 mmHg is considered "questionable". "Active" and "inactive" designations are decreases greater and less than that range.

EXAMPLE 37

The angiotensin II-supported ganglion-blocked rat model is utilized as a screening test for estimation of the direct vasodilator component of activity. Percentage changes in blood pressure in anesthetized rats 30 minutes after intravenous dosing are determined. The intravenous dosing is done with test compounds at 3 mg/kg. Borderline activity is defined as approximately a 10% decrease in blood pressure measured 30 minutes after dosing. "Active" and "inactive" designations are increases greater and less than that.

EXAMPLE 38

Diastolic blood pressure and heart rate responses to a fixed challenge dose of isoproterenol are obtained before and 15 minutes after graded doses of test compound administered intravenously over a 3 minute interval to anesthetized dogs. A branch of a femoral artery and vein are cannulated to record blood pressure and to administer the drugs which are dissolved in saline. The vagi were sectioned bilaterally in the mid-cervical region of the neck and the

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dogs are ventilated mechanically (Harvard respiratory) with room air at a rate of 20/minute and a stroke volume of 20 mL/kg. Heart rate is monitored with a cardiometer triggered by the pressure pulse. All measurements are recorded on a Beckman R-612 recorder. The drug effect is expressed in terms of a cumulative dose (microgram/kg) causing 50% inhibition of isoproterenol response.

EXAMPLE 39

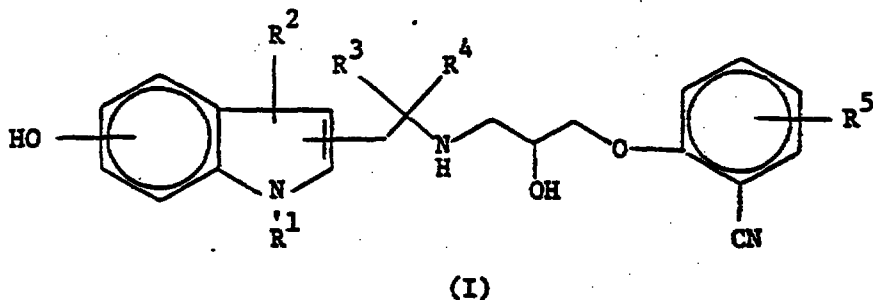
Rats (male Wistar) are anesthetized with a combination of urethane and chloralase intraperitoneally. Following induction of anesthesia, chlorisondamine is injected into the peritoneal cavity to produce ganglion blockage. A femoral artery was cannulated to monitor blood pressure and heart rate and two femoral veins were cannulated to administer compounds. The trachea was intubated and rats were allowed to breath spontaneously. Animals were challenged before and 15 minutes after intravenous administration of test compound with graded doses of phenylephrine and the changes in blood pressure recorded. Data were plotted to obtain dose-response curves and the dose of phenylephrine required to elicit a 50 mmHg (ED_{50}) increase in blood pressure was interpolated from the curves. Dose shifts are calculated by dividing the ED_{50} after drug by the ED_{50} before drug.

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CLAIMS

1. A compound having the formula



(I)

and the acid addition salts thereof wherein

one of

R^1 and R^2 is hydrogen and the other is hydrogen or C_{1-4} alkyl;

5 R^3 and R^4 are independently selected from hydrogen or C_{1-4} alkyl;

R^5 is halogen, hydrogen, hydroxy, or C_{1-4} alkyl;

the phenoxypropanolaminoalkyl side chain is attached to the indole ring at either the 2- or 3-position; and the hydroxyl substituent group

10 occupies either the 4-, 5-, 6-, or 7- ring position of indole.

2. A compound of claim 1 wherein the indolyl ring is attached at its 3- position to the phenoxypropanolaminoalkyl side chain.

3. A compound of claim 1 or 2 wherein R^1 and R^2 are hydrogen.

4. A compound of claim 1 or 2 wherein R^3 and R^4 are methyl.

5. A compound of claim 1, 2 or 4 wherein R^5 is hydrogen or 5-fluoro.

6. A compound of claim 3 wherein R^3 and R^4 are methyl.

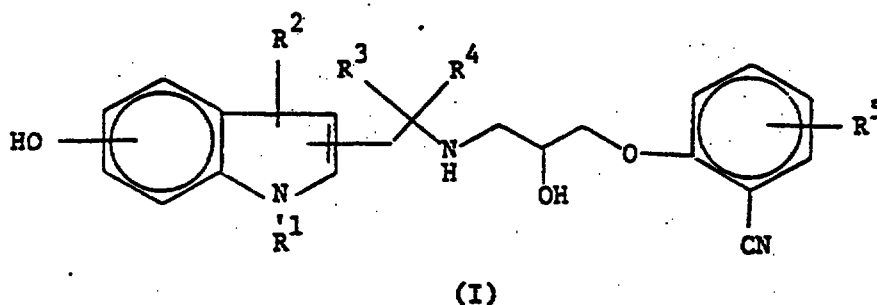


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7. A compound of claim 6 wherein R⁵ is hydrogen or 5-fluoro.
8. A compound of any of claims 1-7 wherein the HO substituent occupies the 6- ring position of indole.
9. A compound of claim 1 which is 2-[2-hydroxy-3-[[2-(6-hydroxy-1H-indol-3-yl)-1,1-dimethylethyl]amino]propoxy]benzonitrile.
10. A compound of claim 1 which is 2-[2-hydroxy-3-[[2-(5-hydroxy-1H-indol-3-yl)-1,1-dimethylethyl]amino]propoxy]benzonitrile.
11. Medication comprising a non-toxic antihypertensive effective dose of a compound claimed in claim 1, for use in a method of treating a mammal for hypertension.
12. Medication as claimed in claim 11 wherein the said compound is 2-[2-hydroxy-3-[[2-(6-hydroxy-1H-indol-3-yl)-1,1-dimethylethyl]amino]propoxy]benzonitrile.
13. A pharmaceutical composition in unit dosage form suitable for systemic administration to a mammalian host comprising a pharmaceutically acceptable carrier and an amount of a Formula I compound as claimed in claim 1 to provide an effective antihypertensive but non-toxic dose of from 0.1 mcg to 100 mg of said compound of Formula I per kg body weight of said host.
14. A pharmaceutical composition of claim 13, wherein the Formula I compound is 2-[2-hydroxy-3-[[2-(6-hydroxy-1H-indol-3-yl)-1,1-dimethylethyl]amino]propoxy]benzonitrile.
15. A pharmaceutical composition of claim 13, wherein the Formula I compound is 2-[2-hydroxy-3-[[2-(5-hydroxy-1H-indol-3-yl)-1,1-dimethylethyl]amino]propoxy]benzonitrile.



16. A process for preparing a compound having the formula



and the acid addition salts thereof wherein

one of

R^1 and R^2 is hydrogen and the other is hydrogen or C_{1-4} alkyl;

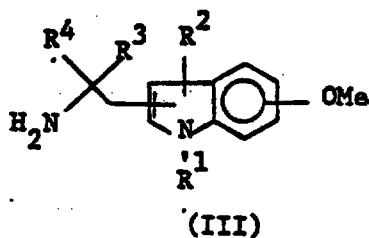
R^3 and R^4 are independently selected from hydrogen or C_{1-4} alkyl;

R^5 is halogen, hydrogen, hydroxy, or C_{1-4} alkyl;

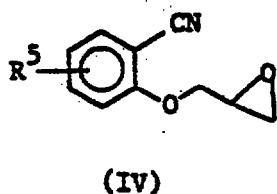
the phenoxypropanolaminoalkyl side chain is attached to the indole ring at either the 2- or 3-position; and the hydroxyl substituent group occupies either the 4-, 5-, 6-, or 7- ring position of indole,

said process comprising:

a) coupling a methoxylated indolalkylamine III



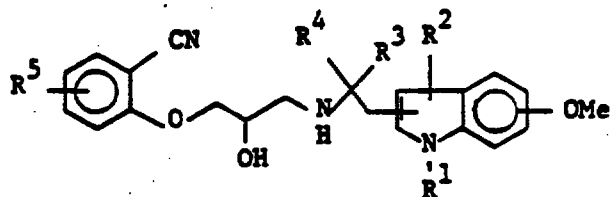
wherein R^1 , R^2 , R^3 , and R^4 are as defined hereinbefore, with an (R^5 -substituted phenoxy epoxide) IV



wherein R^1 , R^2 , R^3 , and R^4 are as defined hereinbefore, by heating III and IV together either neat or in the presence of a reaction inert organic solvent, so as to produce an intermediate II



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(II)

wherein R^1 , R^2 , R^3 , R^4 , and R^5 are as defined hereinbefore; then

b) reacting intermediate II under suitable conditions so as to cleave the methoxy group to a hydroxyl group and so as thus to form the compound of formula I; and then

c) optionally, if a pharmaceutically acceptable acid addition salt of formula I is desired, then converting the product in step (b) to said salt by standard techniques.

17. A process according to claim 16, wherein step (b) comprises reacting intermediate II with boron tribromide in methylene chloride solution under reaction conditions so as to form the compound of formula I.

18. Medication comprising a non-toxic vasodilating effective dose of a compound of claim 1, for use in a method of treating a mammal having need of vasodilating treatment.

19. Medication comprising a non-toxic adrenergic-blocking effective dose of a compound of claim 1, for use in a method of treating a mammal having need of adrenergic-blocking treatment.

20. A pharmaceutical composition according to claim 13, 14, or 15, wherein said dose of said formula I compound is to be administered intravenously to said mammal and provides 0.1 to 0.5 mg of said formula I compound per kg body weight of said mammal.

21. A pharmaceutical composition according to claim 13, 14, or 15, wherein said dose of said formula I compound is to be administered orally to said mammal and provides 0.5 to 5.0 mg of said formula I compound per kg body weight of said mammal.



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22. A process as claimed in claim 16, substantially as described in respect of any of the foregoing Examples 10 to 34.

5

23. A compound of the formula "(I)" (or acid addition salt thereof) prepared by a process as claimed in claim 16, 17 or 22.

24. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of the formula "(I)" (or acid addition salt thereof) as claimed in claim 23.

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