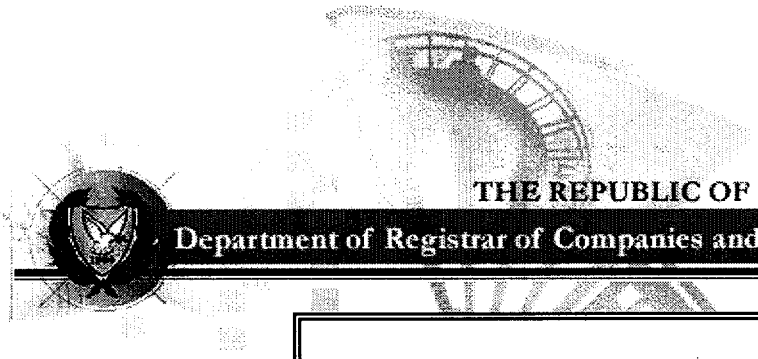

ΚΥΠΡΙΑΚΟ ΓΡΑΦΕΙΟ ΔΙΠΛΩΜΑΤΩΝ ΕΥΡΕΣΙΤΕΧΝΙΑΣ

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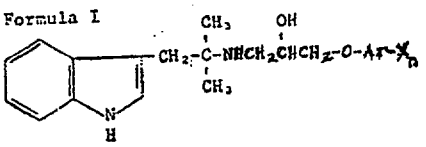
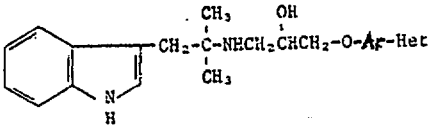
(54) Anti-hypertensive 3-indolyl-tertiary butylaminopropanols

(57) The compounds have the general Formula:

Formula I



or Formula II



wherein Ar is phenyl or naphthyl, each X is an optional substituent independently chosen from a range of cyclic and non-cyclic aromatic and non-aromatic substituents, including alkyl, alkenyl, alkynyl, alkoxy, alkenoxy, alkanyl, alkylsulphinyl, alkylthio, alkanamido, C_3 to C_6 optionally alkyl substituted cycloalkyl, optionally alkyl substituted cycloalkyl alkyl, each having up to 8 carbon atoms, phenyl, trifluoromethyl, nitro and cyanoalkyl, n indicates the number of X substituents and is from 0 to 2, and Het represents a nitrogen heterocycle, optionally containing one further hetero atom and optionally substituted with up to two ring substituents which are alkyl, N-lower alkyl carboxamido, N,N-dilower alkyl carboxamido, carbalkoxy wherein each of said foregoing groups contains up to 8 carbon atoms, oxo, or carboxamido.

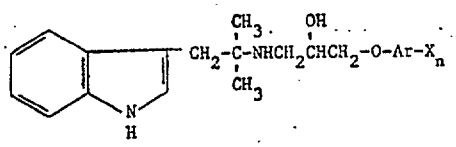
GB 2 001 633 A

SPECIFICATION

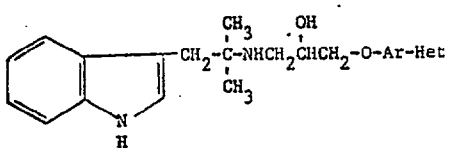
3-Indolyl-tertiary butylaminopropanols

The present invention is concerned with heterocyclic carbon compounds of the indole series having an amino substituent and with drug, bio-affecting and body-treating processes employing these compounds.

The present invention includes the compounds of Formula I and Formula II and the acid addition salts of these substances



(Formula I),



(Formula II)

In the foregoing structural formulas the symbols Ar, X, n, and Het have the following meanings.

Ar is phenyl or naphthyl,

X refers to optional Ar-attached substituents which are independently alkyl, alkenyl, alkynyl, alkoxy, alkenoxy, alkanoyl, alkenoyl, alkanoyloxy, alkenoyloxy, alkylsufonyl, alkysulfinyl, alkylthio, alkanoamido, cycloalkyl having 3 to 6 ring members and 1 to 3 optional alkyl substituents, cycloalkylalkyl having 3 to 5 ring members and 1 to 3 optional alkyl substituents wherein each of the foregoing groups has up to 8 carbon atoms, phenyl, trifluoromethyl, nitro, amino, hydroxyl, halogen, carboxamido, cyano, or cyanoalkyl having from 2 to 4 carbon atoms.

n is the integer 0, 1, or 2 signifying the number of X groups, and

Het is a nitrogen heterocycle, preferably a 5-member ring with four carbon atoms and one nitrogen atom, having 5 or 6 ring members and up to 1 additional hetero atom which is oxygen, sulfur, or nitrogen wherein said heterocycle bears from 0 to 2 ring substituents each independently being alkyl, N-lower alkyl carboxamido, N,N-dilower alkyl carboxamido, carbalkoxy wherein each of said foregoing groups contains up to 8 carbon atoms, oxo, or carboxamido.

The compounds of the present invention are unique as antihypertensive agents in that they combine adrenergic β-blocking and vasodilator activity. They also have utility as anti-anginal agents, anti-stress agents, antiarrhythmic agents, antithrombogenic agents and in the treatment of conditions where it is desirable to reduce the oxygen demand of the heart such as post-myocardial infarct management. Preferred members have a particularly desirable combination of the foregoing actions, and ancillary pharmacological effects, or a lack thereof, which particularly suits them for specific indications from among those listed. Those of Formula I wherein Ar is phenyl, n = 1, and X is located in the ortho position are preferred for antihypertensive use. The utility of the compounds of Formulas I and II can be demonstrated in various animal models including antagonism of isoproterenol in the conscious rat treated orally (adrenergic β-receptor blocking action), the spontaneous hypertensive rat (antihypertensive action), the dog hind limb preparation (vasodilator action), ouabain-induced ventricular tachycardia in the dog (antiarrhythmic action), in the coronary artery occluded dog (antiarrhythmic action), *in vitro* by measuring platelet aggregation in platelet-rich plasma photometrically following challenge with a thrombogenic agent such as adenosine diphosphate or collagen (antithrombogenic action), and in various other animal and laboratory models.

The invention includes compounds having the foregoing structural formulas and the acid addition salts thereof and formulations and compositions for pharmaceutical and veterinary use. For medical use, the pharmaceutically acceptable acid addition salts are preferred. The pharmaceutically acceptable acid addition salts are those salts in which anion does not contribute significantly to the toxicity or pharmacological activity of the salt, and as such, they are the pharmacological equivalents of the bases having the foregoing structural formulas. In some instances, the salts have physical properties which make them more desirable for pharmaceutical formulation purposes such as solubility, lack of hygroscopicity, compressibility with respect to tablet formation and compatibility with other ingredients with which the substances may be used for pharmaceutical purposes. Acid addition salts which do not meet the foregoing criteria for pharmaceutical acceptability, for instance as to toxicity, are sometimes useful as intermediates for isolation and purification of the present substances or for other

chemical synthetic purposes such as separation of optical isomers. Such salts are also part of the invention.

The acid addition salts are made by reaction of a base of the foregoing structural formula with the acid preferably by contact in solution. They may also be made by metathesis or treatment with an anion exchange resin whereby the anion of one salt of the substance is replaced by another anion under conditions which allows for separation of the undesired species such as by precipitation from solution or extraction into a solvent or elution from or retention on an anion exchange resin. Pharmaceutically acceptable acids for the purposes of salf formation include hydrochloric, hydrobromic, hydroiodic, citric, acetic, benzoic, phosphoric, nitric, mucic, isethionic, methanesulfonic, p-toluenesulfonic, glucosac charic, palmitic, heptanoic, oxalic, cyclamic, and others.

The compounds of the present invention shown by the foregoing structural formula contain an asymmetric carbon atom in the propanolamine side chain and occur as optically active isomers as well as racemic mixtures thereof. The present invention is intended to include each of the optically active and racemic forms. Some of the substances of the present invention contain an asymmetric carbon atom in the X or Het substituent, and diastereoisomeric pairs of racemates exist. These forms are also included.

Resolution of racemic mixtures to provide the optically active isomers of the foregoing compounds is carried out, for example, by forming a salt with an optically active acid many of which are known to those skilled in the art such as optically active tartaric, mandelic, cholic, 0,0-di-p-toluoyl tartaric, and 0,0-dibenzoyl tartaric acids, or other acids convention ally employed for this purpose. The claims, therefore, will be understood to embrace the products in the form of the several racemic mixtures as well as in the form of the optically active isomers where appropriate.

The therapeutic processes of this invention comprise systemic administration of an effective, non-toxic amount of a compound of Formula I or Formula II or a pharmaceutically acceptable acid addition salt of either to a mammal having a disease state resulting from excessive stimulation of the adrenergic β-receptors, or to a mammal requiring vasodilation, or to a mammal having hypertension. An effective amount is construed to mean a dose which exerts an adrenergic β-receptor blocking action, a vasodilator effect, or antihypertensive action in the affected animal without undue toxic side effects. By systemic administration, it is intended to include both oral and parenteral routes. Examples of parenteral administration are intravenous injection or infusion, and intraperitoneal, intramuscular or subcutaneous injection. Rectal administration by ointment or suppository may be employed. Dosage will vary according to the route of administration with from about 0.1 mcg to 100 mg/kg body weight of a compound of Formula I or Formula II or a pharmaceutically acceptable acid addition salt thereof generally providing the desired therapeutic effect. Acute toxicities measured in the mouse treated orally are within the range of about ALD_{50} 250 mg/kg to >2000 mg/kg of body weight, with non-lethal signs of drug effect such as central nervous system stimulation or depression, mydriasis, or lacrimation appearing at from $\frac{1}{2}$ to $\frac{1}{10}$ that dose.

The combination of pharmacological properties of the compound of Procedure 10, 1-[[2-(3-indolyl)-1,1-dimethylethyl]amino]-3-(2-methylphenoxy)-2-propanol hydrochloride, indicates that it is particularly desirable for antihypertensive use. It has five-fold the adrenergic β-receptor blocking potency of propranolol shown by oral administration to rats followed by challenge of the animals with isoproterenol administered intravenously. The latter is a well known adrenergic β-receptor stimulant which causes an increase in heart rate and a decrease in blood pressure. These effects of isoproterenol are antagonized by adrenergic β-receptor blocking agents, and the relative potency values given above were prepared by regression analysis of log dose-response data for the two compounds. For therapeutic use, dosage size and frequency will vary with the subject and the route of administration, with from about 0.2 mg. for intravenous administration up to about 100 mg orally being suitable for man.

The substance of Procedure 10 is distinguished from other adrenergic β-receptor blocking drugs in that it is effective in lowering the blood pressure in the spontaneously hypertensive rat. Although adrenergic β-receptor blocking agents have come into widespread use in human medicine for the treatment of hypertension, their mechanism of action is unknown and their antihypertensive activity cannot be detected by this animal test in most instances. With the present substance in the spontaneously hypertensive rat, a reduction of blood pressure of 25 mm. of Hg occurs at a dose of 100 mg/kg of body weight orally with only a minimal reduction in heart rate. This is thought to be indicative of utility in hypertensive indications where other adrenergic β-receptor blocking drugs are inoperative or less desirable.

The substance of Procedure 10 also causes a reduction in blood pressure when administered intravenously to the anesthetized dog in a dose of 3.33 mg/kg of body weight. It is further distinguished in that it does not depress heart rate or right ventricular contractile force as is the case with many prior adrenergic β-receptor blocking agents. Both a positive inotropic and a positive chronotropic effect are exhibited by the substance, and these effects are apparent even

when the animal is first treated with an adrenergic β-receptor blocking agent such as sotalol. Pulmonary artery pressure remains substantially unchanged, while aortic blood flow and total peripheral resistance are decreased, all of the foregoing in the anesthetized dog.

The compound of Procedure 10 possesses vasodilator activity which may account, in part, for its unique anti-hypertensive action. In the anesthetized ganglion blocked (chlorisondamine chloride) angiotension supported rat, direct acting vasodilators such as diazoxide exert a reduction in blood pressure. The substance of Procedure 10 is equivalent in potency to diazoxide in this test. The vasodilator action thereof can also be shown in the pump-perfused hind limb of the dog in doses of from 0.03 to 1.0 mg/min. of perfusion. Following oral administration to rats a decrease in urine volume and a decrease in sodium ion excretion occurs which is typical of vasodilator compounds.

The antithrombogenic action of the substance of Procedure 10 is reflected by its ability to reduce platelet aggregation *in vitro* in platelet-rich plasma following challenge with ADP or collagen. It is comparable in *in vitro* activity to suloctidil or to papaverine.

A hazard exists in the use of a preponderance of adrenergic β-receptor blocking agents in patients suffering from non-allergic bronchospasm in view of the tendency of these agents to provoke an asthmatic attack or to render the subject refractory to treatment with adrenergic β-receptor stimulants such as isoproterenol which are used in the treatment of acute attacks. The substance of Procedure 10 lacks bronchospastic liability as is demonstrated by the fact that it does not reduce pulmonary ventriculatory pressure, and evokes only moderate enhancement of the response of sensitized rats to immunologically induced broncho-constriction at a dose of 0.5 mg/kg of body weight intravenously. In contrast, propranolol at a dose of 0.5 mg/kg of body weight intravenously reduces pulmonary ventilatory pressure and precipitates an acute bronchospastic response in sensitized rats to immunologically-induced broncho-constriction.

For the preparation of pharmaceutical compositions containing the compounds of Formula I or Formula II in the form of dosage units for oral administration, the compound is mixed with a solid, pulverulent carrier such as lactose, sucrose, sorbitol, mannitol, potato starch, corn starch, amylopectin, cellulose derivatives, or gelatin, as well as with glidents such as magnesium stearate, calcium stearate, polyethylene glycol waxes or the like and pressed into tablets. The tablets may be used uncoated or coated by known techniques to delay disintegration and absorption in the gastro-intestinal tract and thereby provide a sustained action over a longer period. When coated tablets are wanted, the above prepared core may be coated with a concentrated solution of sugar, which solution may contain e.g. gum arabic, gelatin, talc, titanium dioxide or the like. Furthermore, the tablets may be coated with a lacquer dissolved in an easily volatile organic solvent or mixture of solvents and if desired, dye may be added to this coating.

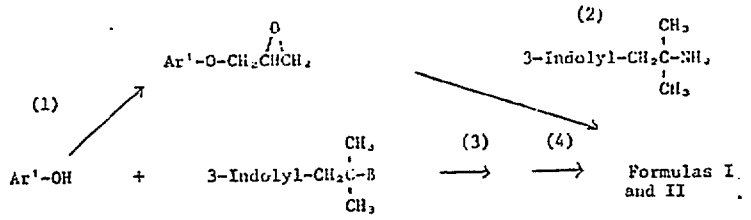
In the preparation of soft gelatin capsules consisting of gelatin and e.g. glycerine and the like, the active ingredient is mixed with a vegetable oil and encapsulated in conventional manner. Hard gelatin capsules may contain granules of the active ingredient in combination with a solid, pulverulent carrier such as lactose, saccharose, sorbitol, mannitol, starch (such as e.g. potato starch, corn starch, or amylopectin), cellulose derivatives or gelatin.

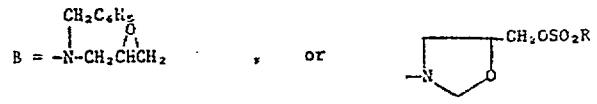
Dose units for rectal administration may be prepared in the form of suppositories containing the compound in a mixture with a neutral fat base, or in the form of a gelatin-rectal capsule with a mixture of vegetable oil or paraffin oil.

Liquid preparations suitable for oral administration are suspensions, syrups and elixirs containing from about 0.2% by weight to about 20% by weight of the active ingredient.

A suitable injectible composition comprises an aqueous solution of a water soluble pharmaceutically acceptable acid addition salt adjusted to physiologically acceptable pH.

The compounds of Formula I and Formula II can be prepared by application of known processes to the appropriate starting materials. Representative known methods for the preparation of aryloxypropanolamine compounds are disclosed in the following patents: Canadian patent No. 834,751 (Troxler) and U.S. Patent No. 3,984,436 (Jaeggi, et al). More specifically, the present invention provides a process for the preparation of the compounds of Formulas I and II according to the following reaction scheme.





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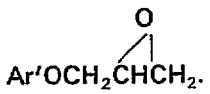
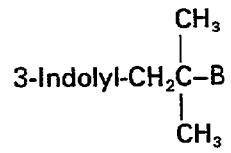
In the foregoing reaction scheme, the symbol Ar′ represents the groups ArX_n and ArHet as they are defined in Formula I and Formula II, and the symbol B is defined by Formulas III and IV in which R is a lower alkyl group of 4 or fewer carbon atoms. The preferred method is according to reactions (1) and (2) in which step (1) involves reacting the appropriately substituted phenolic compound Ar′–OH with epichlorohydrin in the presence of a catalytic quantity of an amine followed by treatment with aqueous alkali metal hydroxide, or conducting the reaction in an aqueous alkali metal hydroxide reaction medium when the amine catalyst is not required. There is produced in step (1) an Ar′ epoxypropyl ether which is caused to react in step (2) with 2-(3-indolyl)-1,1-dimethylethylamine to yield a product of Formula I or Formula II depending upon the nature of the Ar′OH starting material employed. Each of reaction steps (1) and (2) takes place facilely in ordinary laboratory or plant equipment under convenient operating conditions.

Heating of epichlorohydrin in substantial molecular excess amount with a phenol Ar′OH containing a drop or two of piperidine as catalyst on a steam bath overnight results in the condensation shown in step (1). Some of the corresponding halohydrin intermediate is also produced and is converted without isolation to the oxirane shown by treatment of the mixture with aqueous alkali metal hydroxide. Alternatively, the Ar′OH phenol and epichlorohydrin can be caused to react in the presence of a sufficient amount of a dilute aqueous alkali metal hydroxide to neutralize the acidic Ar′OH group at room temperature with formation of the desired intermediate



Step (2) is carried out simply by heating the oxirane intermediate produced in step (1) with 2-(3-indolyl)-1,1-dimethylethylamine either neat or in the presence of a reaction inert organic solvent. No catalyst or condensation agent is required. Suitable solvents include 95% ethanol but other reaction inert organic liquids in which the reactants are soluble may be employed. These 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.

An alternate variation of the process for the preparation of compounds of Formulas I and II involves reaction of the Ar′OH starting material as defined above with a reactant of the formula



according to reaction (3) of the scheme to yield an intermediate which is transformed to the final product by hydrolysis or hydrogenolysis. The substituent B in the reactant used in step (3) is a group such as shown by III or IV which is reactive with the phenolic hydroxyl group Ar'OH to incorporate into the product an incipient propanolamine side chain.

The reactants for step (3) wherein B has Formula III are prepared by forming the N-benzyl derivative of 2-(3-indolyl)-1,1-dimethylethylamine and reacting the latter with epichlorohydrin by adaptation of the method of L. Villa et al., II. Farmaco. Sci., Ed., 24, (3) 349 (1969).

Those reactants where B has Formula IV are prepared by reductive alkylation of 2-(3-indolyl)-1,1-dimethylethylamine with glyceraldehyde according to known methods, for instance, employing 5% palladium-on-carbon catalyst in an atmosphere of hydrogen with methanol or other suitable non-reactive liquid as solvent. When using an optically active form of glyceraldehyde, an optically active end product of Formula I or Formula II is obtained. The amino propanediol resulting from the foregoing reductive alkylation reaction is then converted to the desired 2-(3-indolyl)-1,1-dimethylethyloxazolidinone reactant wherein B has Formula IV by reaction with formaldehyde employing 37% aqueous formaldehyde in refluxing benzene with continued removal of the water by distillation. Esterification with an alkanesulfonyl chloride of the formula RSO_2Cl in which R is a lower alkyl group of 1 to 4 carbon atoms introduces the necessary group which is reactive with Ar'OH.

The intermediate produced by step (3) wherein the B has Formula III is converted in step (4) to a product of Formula I or Formula II by debenzylation by known means such as catalytic hydrogenation or reaction with sodium in liquid ammonia. The intermediates produced in step (3) wherein B has formula IV are converted to the products of formulas I and II in step (4) by mild acid hydrolysis. In this instance, care must be taken to avoid decomposition of the reactant since the 3-indolyl substituent is acid sensitive. Aqueous mineral acids of from 0.1 N to 1 N concentration at temperatures of from 20–100°C. are suitable. The product is recovered as the free base from the hydrolysis mixture by neutralization thereof and collecting the precipitate.

The 2-(3-indolyl)-1,1-dimethylethylamine employed is prepared by the method of H. R. Snyder, et al., J. Am. Chem. Soc., 69, 3140 (1947) from 3-indolylmethyldimethylamine and 2-nitropropane followed by reduction of the resulting 2-(3-indolyl)-1,1-dimethylnitroethane.

In the following procedures temperatures are expressed in degrees centigrade (°). Melting points are corrected values according to the U.S.P. method where indicated (corr.). The nuclear magnetic resonance (NMR) spectral characteristics refer to chemical shift (δ) expresses as parts per million (ppm) versus tetramethylsilane (TMS) as reference standard. The relative area reported for the various shifts corresponds to the number of hydrogen atoms of the particular functional type in the molecule, and the nature of the shift as to multiplicity is reported as broad singlet (bs), singlet (s), multiplet (m), doublet (d), triplet (t), or quadruplet (q) with coupling constants (J) reported where appropriate. The format is NMR (solvent): δ (relative area, multiplicity, J value). Abbreviations employed are MeOH (methanol), DMSO-d_6 (deuterodimethylsulfoxide), i-PrOH (isopropanol), abs.EtOH (absolute ethanol), EtOAc (ethyl acetate), EtOH (95% ethanol), i-PrOH (isopropanol), i-PrOAc (isopropyl acetate), i-Pr_2O (di-isopropyl ether), d (decomposition). Other abbreviations have conventional established meanings. The infrared (IR) spectral descriptions include only absorption wave numbers (cm^{-1}) having functional group identification value. KBr was employed as diluent for all IR spectral determinations. TMS was used as internal reference for the NMR spectral determination. The elemental analyses are reported as percent by weight.

Procedure 1. 4-(Methylsulfonyl)-m-tolyloxymethyl Oxirane.—To a mixture of 3-methyl-4-methylsulfonylphenol, 8.1 g. (0.0435 mole), and 20.0 g. (0.216 mole) of epichlorohydrin, there are added two drops of piperidine to serve as condensation catalyst and the mixture is heated at 105–108° for 18 hrs. The excess epichlorohydrin is then removed by distillation using toluene as a chaser. A solution of 2.1 g. of sodium hydroxide in 50 ml. of water and 70 ml. of dimethoxyethane is then added and the mixture is stirred for 2 hrs. with occasional warming on the steam bath to convert any phenoxychlorohydrin compound to the oxirane. The solvent is then removed by distillation *in vacuo* and the residue is dissolved in a 1:1 (V/V) mixture of ether and benzene. The solution is dried over anhydrous sodium carbonate and examined by thin layer chromatography for purity of the desired oxirane using a 9:1 mixture of chloroform and a methanol for development ($R_f = 0.8$). The solvent is then removed by distillation to yield 10.7 g. of a residue constituting the desired oxirane. Measurement of the infrared absorption spectrum is employed to confirm the substantial absence of hydroxyl containing contaminants. This material is suitable for further reaction in Procedure 3 without further purification.

Procedure 2. 2-Chlorophenoxymethyl Oxirane.—A solution of 12.9 g. of 2-chlorophenol (0.1 mole) in 125 ml. of water containing 6.5 g. (0.162 mole) of sodium hydroxide, and 18.5 g. (0.2 mole) of epichlorohydrin are stirred together at 25° for 20 hrs. The mixture is then

extracted twice with 70 ml. portions of methylene chloride. The extract is dried over anhydrous sodium carbonate and the solvent removed by distillation *in vacuo*. The residue constitutes the desired oxirane and is suitable for further transformation as is described in Procedure 4.

Procedure 3. 1-[[2-(2-Indolyl)-1,1-dimethylethyl]amino]-3-[4-(methylsulfonyl)-m-tolyloxy]-2-propanol.—The oxirane of Procedure 1, 10.7 g., was dissolved in 150 ml. of toluene, 8.2 g. (0.044 mole) of 2-(3-indolyl)-1,1-dimethylethylamine was added and the mixture was refluxed for 18 hrs. The toluene was removed by distillation *in vacuo* and a portion of the residue was converted to the acetate salt, m.p. 142–147°C. The structure was confirmed by examination of the infrared absorption and nuclear magnetic resonance spectra. The remainder of the sample was converted to the hydrochloride salt by treatment of an acetonitrile solution thereof with 8 *N* ethanolic HCl. After recrystallization from CH_3CN/MeOH 12.5 g. of product was obtained, m.p. 174.0–177.0° (corr.).

Anal. Found: C, 59.40; H, 6.90; N, 5.87.

NMR (DMSO-d_6): 1.29 (6, s); 2.52 (3, s); 3.12 (3, s); 3.16 (4, m); 4.18 (3, m); 5.95 (1, bs); 7.10 (8, m); 9.00 (2, bs); and 11.12 (1, bs).

IR: 740, 765., 1120, 1290, 1450, 1590, and 3270.

Procedure 4. 1-(2-Chlorophenoxy)-3-[[2-(3-indolyl)-1,1-dimethlethyl]amino]-2-propanol.—A portion of the oxirane produced in Procedure 2, 7 g. (0.033 mole), was refluxed in solution with 6.3 g. (0.033 mole) of 2-(3-indolyl)-1,1-dimethylethylamine in 70 ml. of ethanol. After 24 hrs. the solvent was removed by distillation *in vacuo* and the viscous liquid residue was dissolved in 200 ml. of ether, acidified with 8 *N* ethanolic HCl and the solvents again removed by distillation. Crystallization was induced by adding acetonitrile and rubbing with a glass rod. Recystallized from acetonitrile and di-isopropyl ether to yield 4.8 g. of product, m.p. 150.5–153.5°C. (corr.).

Anal. Found: C, 61.54; H, 6.41; N, 6.94. NMR (DMSO-d_6): 1.28 (6, s); 3.22 (4, m); 4.25 (3, m); 5.96 (1, bs); 7.23 (9, m); 8.84 (2, bs); and 11.12 (1, bs).

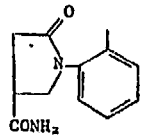
IR: 745, 1250, 1455, 1480, 1590, and 2780.

By adaptation of the foregoing procedures, the products listed in the following table were prepared.

PRODUCTS OF FORMULAS I AND II PROCEDURES 5–14

Procedure No.	ArX_n or ArHet	m.p.° (corr.)	Recryst. Solvent	Elemental Analysis	NMR(DMSO-d_6)	Ir
5	1-naphthyl	232.0–233.0 hydrochloride	MeOH/CH_3CH	C, 70.47 H, 7.07 N, 6.47	1.28 (6, s) 3.24 (4, m) 4.28 (3, m) 6.01 (1,d), 4.4 Hz 7.39 (12, m) 8.90 (2, bs) 11.00 (1, bs)	750, 775, 800 1110, 1270, 1400, 1460, 1580, 2780,
6	3-methylphenyl	165.0–167.0 hydrochloride	MeOH/*i*-PrOH	C, 67.76 H, 7.62 N, 7.05	1.30 (6, s) 2.28 (3, s) 3.18 (4, m) 4.13 (3, m) 5.93 (1, bs) 7.10 (9, m) 8.72 (1, bs) 9.12 (1, bs) 11.00 (1, bs)	745, 770, 1160, 1260, 1450, 1490, 1580, 1600, 2780
7	3-chlorophenyl	197.0–198–0 hydrochloride	MeOH/abs.EtOH	C, 61.34 H, 6.36 N, 6.75 Ch, 17.14	1.30 (6, s) 3.20 (4, m) 4.17 (3, m) 6.03 (1, d, 5.0 Hz) 7.20 (9, m) 8.86 (1, bs) 9.30 (1, bs)	750, 770, 1110, 1230, 1275, 1475, 1580, 1590, 2800, 3340
8	2-ethoxyphenyl	173.0–175.0 hydrochloride	MeOH/*i*-PrOH	C, 65.86 H, 7.51 N, 6.63	1.30 (6, s) 1.32 (3, t, 7.0 Hz) 3.29 (4, m) 4.11 (5, m) 5.99 (1, bs) 7.22 (9, m) 8.90 (1, bs) 9.31 (1, bs)	740, 755, 1130, 1215, 1260, 1510, 1580, 1590, 2800,
9	2-acetylphenyl	161.0–163.0 hydrochloride	CH_3CN	C, 65.73 C, 65.59 H, 7.10 H, 6.94 N, 7.05 N, 7.03	1.30 (6, s) 2.65 (3, s) 3.20 (4, m) 4.30 (3, m) 6.04 (1, bs) 7.41 (9, m) 8.86 (1, bs)	745, 755, 1240, 1450, 1485, 1590, 1665, 2780

PRODUCTS OF FORMULAS I AND II PROCEDURES 5–14 *(continued)*

Procedure No.	ArX_n or ArHet	m.p.° (corr.)	Recryst. Solvent	Elemental Analysis	NMR(DMSO-d_6)	Ir
10*	2-methylphenyl	173.0–174.5 hydrochloride	MeOH/EtOAc	C, 68.09 H, 7.77 N, 7.16	1.30 (6, s) 2.20 (3, s) 3.28 (4, m) 4.25 (3, m) 6.02 (1, d, 4.2 Hz) 7.22 (9, m) 9.15 (2, bs) 11.30 (1, bs)	750, 1170, 1250, 1460, 1500, 2800, 3300
11	2-(1H-pyrrol-1-yl]-phenyl	124,0–126.0 base	EtOAc/i-PrOAc	C, 74.40 H, 7.32 N, 10.38	1.10 (6, s) 2.33 (1, bs) 2.80 (4, m) 3.96 (3, m) 5.92 (1, bs) 6.33 (2, m) 7.19 (11, m) 8.10 (1, bs)	740, 1100, 1230, 1450, 1510, 1590, 3160, 3400
12	(4-methylsulfonyl)-phenyl	217.0–220.0 hydrochloride	MeOH/abs.EtOH	C, 58.32 H, 6.62 N, 6.90	1.30 (6, s) 3.16 (3, s) 3.35 (4, m) 4.26 (3, m) 6.07 (1, bs) 7.0–8.0(9, m) 8.85 (1, bs) 9.25 (1, bs)	760, 780, 1155, 1300, 1510, 1600, 2800
13		224.5–227.5 hydrochloride hemihydrate	abs.EtOH/ EtOAc	C, 61.41 C, 61.24 H, 6.90 H, 6.59 N, 10.81 N, 10.72 Ch, 7.34	1.30 (6, s) 2.55 (2, m) 3.25 4.25 (10, m) 6.05 (1, bs) 7.25 (11, m) 8.90 (1, bs) 9.31 (1, bs)	760, 1430, 1510, 1600, 1680, 3400
14	(2-methylsulfonyl)-phenyl	175.0–179 0 hydrochloride hemihydrate	MeOH/i-Pr_2O	C, 57.23 C, 57.37 H, 6.91 H, 6.61 N, 5.90 N, 5.94	1.39 (6, s) 3.60 (3, s) 3.62 (4, m) 4.42 (3, m) 6.22 (1, m) 7.42 (9, m) 9.00 (1, bs) 9.51 (1, bs)	750, 1130, 1150, 1300, 1450, 1485, 1590, 1625

*Procedure 10 involved reaction of the 2-(3-indolyl)-1,1-dimethylethylamine and the oxirane intermediate at 140° for ½ hr. with no solvent or diluent.

Procedure 15. Tablets.—The following ingredients are blended in the proportion by weight indicated according to conventional pharmaceutical techniques to provide a tablet base.

Ingredient	Amount
Lactose	79
Corn starch	10
Talcum	6
Tragancanth	4
Magnesium stearate	1

This tablet base is blended with sufficient 1-[[2-(3-indolyl)-1,1-dimethylethyl]amino]-3-(2-methylphenoxy)-2-propanol hydrochloride (Procedure 10) to provide tablets containing 10, 20, 40, 80, 160 and 320 mg. of active ingredient, and compressed in a conventional tablet press.

Procedure 16. Dry Filled Capsules. The following ingredients are blended in a conventional manner in the proportion by weight indicated.

Ingredient	Amount
Lactose, U.S.P.	50
Starch	5
Magnesium stearate	2

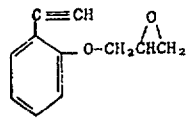
Sufficient 1-[[2-(3-indolyl)-1,1-dimethylethyl]amino]-3-(2-methylphenoxy)-2-propanol hydrochloride (Procedure 10) is added to the blend to provide capsules containing 10, 20, 40, 80, 160 and 320 mg. of active ingredient which is filled into hard gelatin capsules of a suitable size.

Procedure 17. Solution.—A solution of 1-[[2-(3-indolyl)-1,1-dimethylethyl]amino]-3-(2-methyl phenoxy)-2-propanol hydrochloride (Procedure 10) is prepared from the following ingredients.

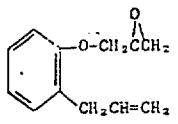
Ingredient	Amount
Active ingredient	20 g.
Sucrose, U.S.P.	400 g.
Sorbitol, U.S.P.	100 g.
Bentonite	20 g.
Flavors, q.s.	
Water, q.s. to make 1 liter	

Each milliliter of the solution contains approximately 20 mg. of the active ingredient.

By application of the methods of Procedures 1 or 2 to the appropriate phenol, or by other conventional methods, the following oxiranes are prepared and then converted to products of Formula I or II by reaction with 2-(3-indolyl)-1,1-dimethylethylamine according to Procedures 3 or 4.



Proc. 18



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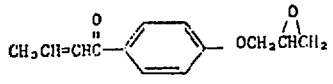

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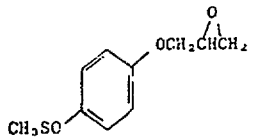

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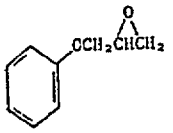

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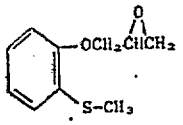

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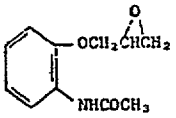

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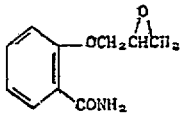

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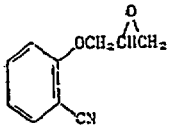

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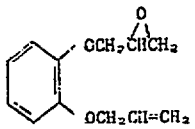

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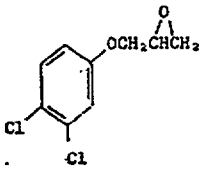

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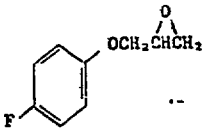

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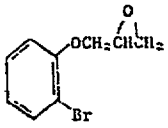

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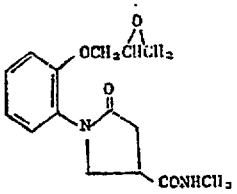

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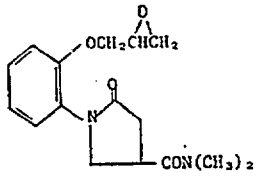

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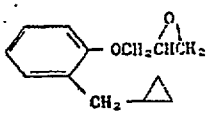

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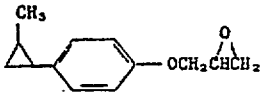

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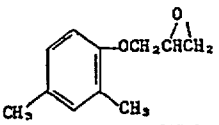

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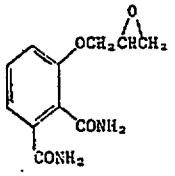

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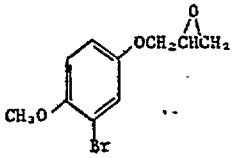

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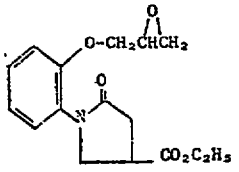

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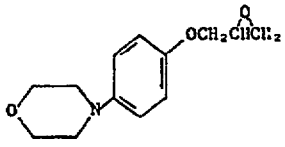

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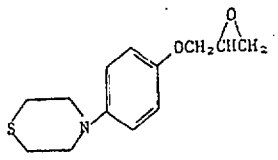

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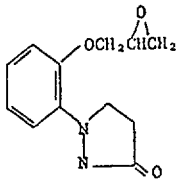

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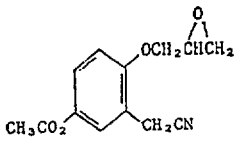

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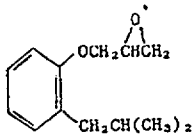

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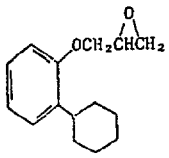

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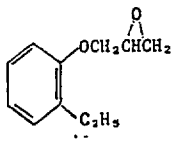

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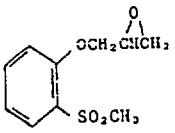

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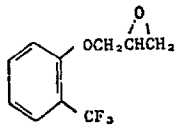

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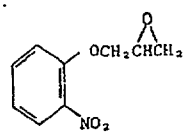

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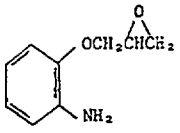

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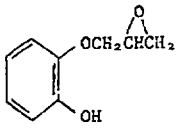

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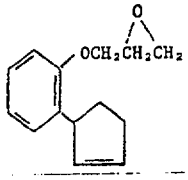

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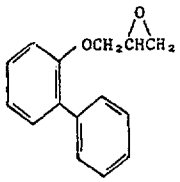

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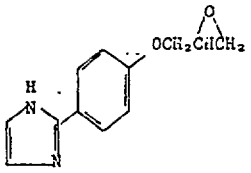


Proc. 53

Physical properties were determined as follows:

Procedure 19.—1-[[2-(3-indolyl)-1,1-dimethylethyl]amino]-3-[2-(2-propenyl)phenoxy]-2-propanol hydrochloride, m.p. 163.0–168.6° (corr.), recrystallized from MeOH/I-Pr_2O.

Anal. Found: C, 69.22; H, 7.56; N, 6.70.

NMr (DMSO-d_6): 1.30 (6, s); 3.32 (6, m); 4.20 (3, m); 5.03 (2, m); 6.00 (2, m); 7.25 (9, m); 8.90 (1, bs); 9.60 (1, bs); and 11.40 (1, bs).

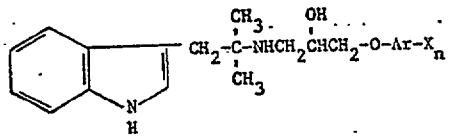
IR: 752, 1120, 1245, 1455, 1490, 1590, 1600, 2790, 2980, and 3350.

Procedure 43. 1-[[2-(3-Indolyl)-1,1-dimethylethyl]amino]-3-[2-(2-methyl-1-propyl)phenoxy]-2-propanol hydrochloride, m.p. 163.0–166.0° (corr.), recrystallized from MeOH/CH_3CN.
Anal. Found: C, 69.34; H, 8.19; N, 6.49.
NMR (DMSO-d_6): 0.81 (3, t, 7.0 Hz); 1.17 (3, d, 7.0 Hz); 1.32 (6, s); 1.39 (2, m); 3.28 (5, m); 4.22 (3, m); 6.04 (1, bs); 7.22 (9, m); 9.00 (1, bs); 9.60 (1, bs); 11.20 (1, bs).
IR: 750, 1100, 1240, 1450, 1490, 1582, 1600, 2780, 2960, and 3320.

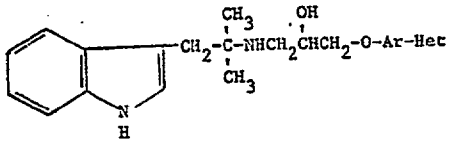
Procedure 45.—3-(2-Ethylphenoxy)-1-[[2-(3-indolyl)-1,1-dimethylethyl]amino]-2-propanol hydrochloride, m.p. 170.0–171.5° (Corr.) recrystallized from EtOH.
Anal. Found: C, 68.36; H, 7.95; N, 6.85.
NMR (DMSO-d_6): 0.81 (3, t, 7.0 Hz); 1.17 (3, d, 7.0 Hz); 1.32 (6, s); 1.39 (2, m); 3.28 (5, m); 4.22 (3, m); 6.04 (1, bs); 7.22 (9, m); 9.00 (1, bs); 9.60 (1, bs); 11.20 (1, bs).
IR: 750, 1100, 1240, 1450, 1490, 1582, 1600, 2780, 2960, and 3320.

CLAIMS

1. A compound of the general formula:–



(Formula I), or



(Formula II)

or an acid addition salt thereof, wherein
Ar is phenyl or naphthyl,
X refers to an optional Ar-attached substituent each which is independently alkyl, alkenyl, alkynyl, alkoxy, alkenoxy, alkanoyl, alkenoyl, alkanoyloxy, alkenoyloxy, alkylsulfonyl, alkylsulfinyl, alkylthio, alkanoamido, cycloalkyl having 3 to 6 ring members and 1 to 3 optional alkyl substituents, cycloalkyl-alkyl having 3 to 6 ring members and 1 to 3 optional alkyl substituents, wherein each of the foregoing groups has up to 8 carbon atoms, phenyl, trifluoromethyl, nitro, amino, hydroxyl, halogen, carboxamido, cyano or cyanoalkyl having from 2 to 4 carbon atoms,
n is 0, 1, or 2 signifying the number of X groups, and
Het is a nitrogen heterocycle having 5 or 6 ring members and optionally 1 additional hetero atom which is oxygen, sulfur, or nitrogen wherein said heterocycle bears from 0 to 2 ring substituents which are each independently alkyl, N-lower alkyl carboxamido, N,N-dilower alkyl carboxamido, carboxalkoxy wherein each of said foregoing groups contains up to 8 carbon atoms, oxo, or carboxamido.

2. A compound as claimed in claim 1 having Formula I wherein Ar is phenyl, X is in the ortho-position, and n is 1.

3. A compound as claimed in claim 1 having Formula I wherein Ar is phenyl, X is alkyl, and n is 1.

4. A compound as claimed in claim 3 wherein X is methyl.

5. 1-[[2-(3-Indolyl)-1,1-dimethylethyl]amino]-3-(2-methylphenoxy)-2-propanol.

6. 1-[[2-(3-Indolyl)-1,1-dimethylethyl]amino]-3-(2-methylphenoxy)-2-propanol hydrochloride.

7. A compound as claimed in claim 1 having Formula I, wherein Ar is phenyl, X is cyano, and n is 1.

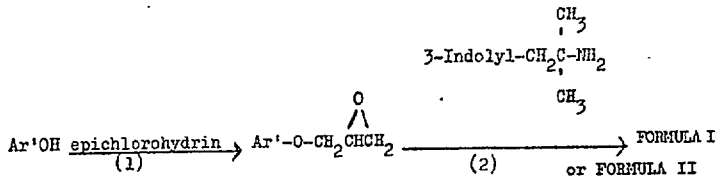
8. A compound as claimed in claim 1 and identified as the product of any one of Procedures 1 to 9 or 11 to 14, or 18 to 53 by name, partial formula or by reactants used.

9. A pharmaceutically acceptable acid addition salt of a compound as claimed in claim 1 of Formula I or Formula II.

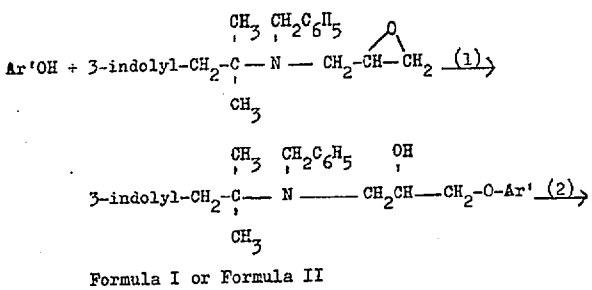
10. A compound as claimed in claim 1 and substantially as hereinbefore described in any one of Procedures 1 to 14 or 18 to 53.

11. A process for preparing a compound as claimed in claim 1, which process comprises carrying out any one of reaction schemes 1 to 3 below,

SCHEME 1:-

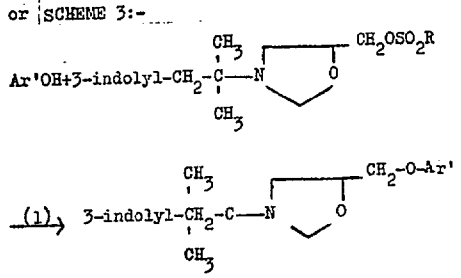


SCHEME 2:-



Formula I or Formula II

or SCHEME 3:-



Formula I or Formula II,

wherein Ar' is the group Ar-X_n or Ar-Het as defined in claim 1, and wherein step (1) of scheme 1 is carried out by reacting Ar'OH with epichlorohydrin in the presence of a catalytic quantity of an amine followed by treatment with aqueous alkali metal hydroxide, or with epichlorohydrin in an aqueous alkali metal hydroxide reaction medium, the product of step (1) being reacted in step (2) with 2-(3-indolyl)-1,1-dimethylethylamine; step (2) of scheme 2 is carried out by reductive debenzylation; and step 2 of scheme (3) is carried out by mild acid hydrolysis.

12. A process for preparing a compound as claimed in claim 1 substantially as hereinbefore described in any one of procedures 1 to 14 or 18 to 53.

13. A compound as claimed in claim 1 when produced by a process as claimed in claim 11 or claim 12.

14. A method of inhibiting β-adrenergic activity in a mammal having a disease state resulting from excessive activation of the β-adrenergic receptors which comprises administering to said mammal a non-toxic effective adrenergic β-receptor inhibiting dose of a compound as claimed in any one of claims 1 to 10 or claim 13.

15. A method of exerting a vasodilator effect in a mammal which comprises administering to a mammal in need of vasodilatation a non-toxic vasodilator effective dose of a compound as claimed in any one of claims 1 to 10 or claim 13.

16. A method of alleviating hypertension which comprises administering to a mammal having hypertension a non-toxic antihypertensive effective dose of a compound claimed in any one of claims 1 to 10 or claim 13.

17. A pharmaceutical or veterinary formulation of a compound as claimed in any one of claims 1 to 10 or claim 13.

18. A pharmaceutical or veterinary composition comprising a compound as claimed in any one of claims 1 to 10 or claim 13 and a pharmaceutically acceptable or veterinarily acceptable carrier or diluent.

19. A formulation or composition as claimed in claim 17 or claim 18 in unit dosage form.

20. A formulation or composition as claimed in claim 19 in the form of a tablet, capsule or suppository.

21. An injectable solution or a suspension, syrup or elixir for oral administration containing a compound as claimed in any one of claims 1 to 10 or claim 13.

22. A pharmaceutical or verterinary formulation substantially as hereinbefore described in any one of procedures 15 to 17.

23. A compound as claimed in any one of claims 1 to 10 or claim 13, a formulation as claimed in claim 17 or a composition as claimed in claim 18 for use in the treatment of hypertension, stress, arrythmia, and/or for producing vasodilation, adrenergic β-blocking and/or reduced heart oxygen demand.

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