PATENT SPECIFICATION

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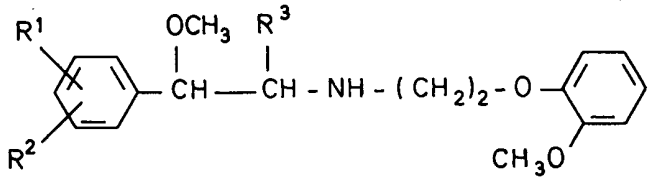
(19)

THERAPEUTICALLY ACTIVE 1-PHENYL-1-METHOXY-2-AMINOETHANE DERIVATIVES

(71) We, BEIERSDORF AKTIENGESELLSCHAFT, a joint stock company organised under the laws of the Federal Republic of Germany, of Unnastrasse 48, D—2000 Hamburg 20, Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to new therapeutically active 1 - phenyl - 1 - methoxy - 2-aminoethane derivatives, their preparation and pharmaceutical compositions containing them.

According to the invention there are provided compounds of the general formula I



(I)

in which

each of R^1 and R_2, which may be the same or different, represents a hydrogen atom, a halogen atom, a methyl group or a methoxy group, or

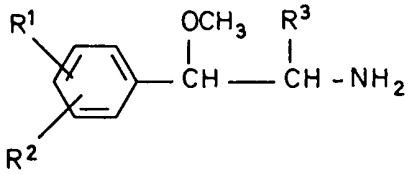
R^1 and R^2 together form a methylenedioxy group, and

R^3 represents a hydrogen atom or an alkyl group with 1 to 4 carbon atoms, and their physiologically acceptable acid addition salts.

The 1 - phenyl - 1 - methoxy - 2 - aminoethane derivatives of the general formula I and their acid addition salts have valuable pharmacological properties. In particular they have blood pressure lowering properties and generate, with subcutaneous or oral administration to rats with artificially generated hypertension or in genetically hypertensive rats, a powerful partly long term lowering of blood pressure. They are accordingly well suited as therapeutic agents, particularly for treatment of chronic high blood pressure.

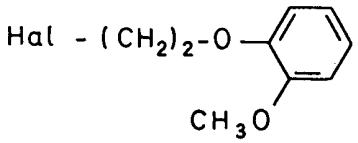
The 1 - phenyl - 1 - methoxy - 2 - aminoethane derivatives of the general formula I can be used as such, but are preferably used in the form of their well-crystallising acid addition salts, optionally together with suitable solid or liquid pharmacologically acceptable carriers and/or diluents of customary type, for the manufacture of injectable solutions as well as preferably for orally administerable pharmaceutical preparations and formulations such as dragees, pills and tablets.

The compounds of the general formula I can be prepared in a manner known per se by reaction of an amine of the general formula II



(II),

in which R^1, R^2 and R^3 have the meanings given above with a halide of the general formula III



(III)

in which Hal represents a halogen atom, preferably a bromine atom.

The reaction of a compound of the general formula II with a halide of the general formula III is preferably carried out after intimate admixture of the two substances by heating the mixture so obtained for several hours to 90 to 150°C, preferably to 110 to 130°C, wherein the molar ratio of the reactants is suitably chosen to be about 1:1 (preferably equivalent quantities). The reaction time is dependent upon the type of reactants chosen. It generally is from 2 to 5 hours.

According to a further mode of preparation of the compounds of the general formula I the reaction can also be carried out in such a fashion that the reactants are dissolved in organic solvents such as e.g. n-butanol and boiled under reflux in the presence of an acid acceptor such as for example an alkali carbonate for several hours, preferably 2 to 4 hours.

The working up and purification of the particular reaction product takes place in customary fashion and gives rise to no particular technical difficulties.

For this purpose the reaction product, if necessary after filtering off the acid acceptor and solvent, is dissolved in chloroform and shaken with a concentrated potassium carbonate solution in order to transform it into the base which is then purified in known fashion.

The corresponding well crystallising acid addition salts (hydrochlorides, oxalates and maleinates can be prepared from the purified bases in customary fashion by solution in a suitable organic solvent such as e.g. ether, acetone, isopropanol, acetonitrile or ethanol and subsequent precipitation with acids such as hydrochloric acid, oxalic acid or maleic acid, which acid addition salts can then be yet further purified if necessary by recrystallisation.

Thus, for example, for the preparation of the hydrochloride, the base obtained after evaporating off chloroform is taken up, depending upon its solubility, in a suitable organic solvent (ether, ethanol, isopropanol, acetone or acetonitrile) and treated with ethereal hydrochloric acid until an acid reaction is obtained. By the addition of ether or petroleum ether the crystallisation is then initiated. Correspondingly for manufacture of the oxalate an alcoholic solution of the base is acidified with 8% ethanolic oxalic acid and subsequently the crystallisation of the addition salt promoted by the addition of ether or petroleum ether.

In those cases where direct crystallisation of the salts cannot be achieved it has been shown to be effective to purify the base in a preliminary fashion via a silica gel column with chloroform, if necessary with the addition of methanol, as eluant. Then the fractions are tested by thin layer chromatography (using silica gel plates, upper phase: n-butanol/glacial acetic acid/H_2O in a ratio of 4:1:5).

Corresponding well-crystallising acid addition salts can also be obtained using sulphuric acid, phosphoric acid, toluene sulphonic acid, citric acid and malic acid.

The amines of the formula II necessary as starting materials for the preparation of the compounds according to formula I can be made according to known processes e.g. by condensation of the corresponding aromatic aldheyde with nitroalkanes, addition of sodium methylate and reduction of the nitro groups (cf. J. Med. Chemistry 12 (1969) pages 998—1001). By means of this process a mixture of the threo and erythro forms is obtained.

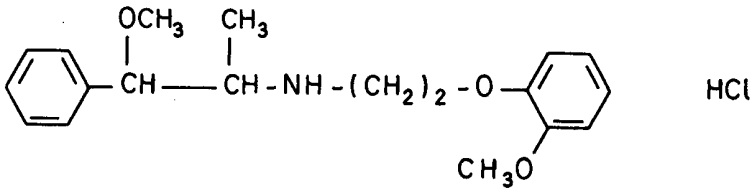
The halides of the formula III used as reactants for the amine are known com-

pounds described in the literature, which may obtained for example by the reaction of the corresponding phenols with 1,2-dibromoethane.

The invention is further described in more detail with reference to the following Examples:

EXAMPLE 1.

N - (o - Methoxyphenoxyethyl) - 1 - phenyl - 1 - methoxy - 2 - methyl - 2 - aminoethane hydrochloride

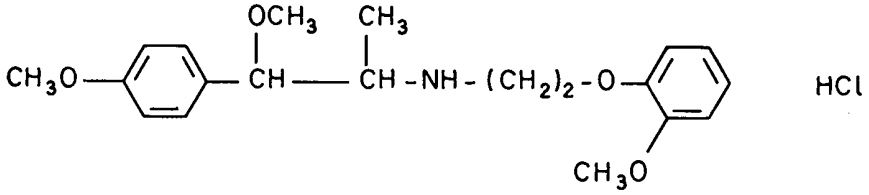


0.03 mole of 1 - phenyl - 1 - methoxy - 2 - methyl - 2 - aminoethane were mixed with 0.03 mole of o-methoxy-phenoxyethyl bromide and the mixture heated for 2½ hours to 110 to 120°C. While still warm, the resulting reaction mixture was dissolved in the molten state in 100 ml of chloroform and shaken with a concentrated aqueous potassium carbonate solution. The organic phase was then dried with solid anhydrous potassium carbonate and the solvent evaporated off. The residue (base was dissolved in acetone, acidified with 12% ethereal hydrochloric acid and treated with petroleum ether. After a few hours the hydrochloride crystallised in a still impure form which melted at about 140°C. By carrying out twice recrystallisation from butanol/ethanol with the addition of petroleum ether, the compound given above can be obtained in pure form with a melting point of 144 to 145°C.

Yield: 25%.

EXAMPLE 2.

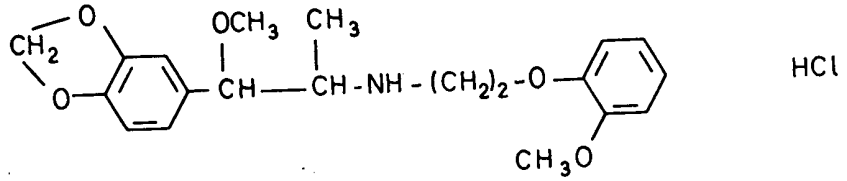
N - (o - Methoxyphenoxyethyl) - 1 - (p - methoxyphenyl) - 1 - methoxy - 2 - methyl-2 - aminoethane hydrochloride



From a mixture of equivalent quantities of 1 - (p - methoxyphenyl) - 1 - methoxy-2 - methyl - 2 - aminoethane and o - methoxyphenoxyethyl bromide there is obtained after 3 hours heating at 110 to 120°C a molten phase and this is further treated by a series of working steps analogous to those described in Example 1. The residue remaining after evaporation of the chloroform was subjected to column chromatography using silica gel. As eluant there was used chloroform with an increasing methanol content. The unitary fractions from thin layer chromatography were combined, dissolved in acetone, treated with ethereal hydrochloric acid and brought to crystallise by the addition of ether. Repeated dissolution and recrystallisation from acetone/methanol/petroleum ether mixture gave a pure product: white crystals, melting point 162 to 164°C, Yield: 20%.

EXAMPLE 3.

N - (o - Methoxyphenoxyethyl) - 1 - (3,4 - methylenedioxyphenyl) - 1 - methoxy-2 - methyl - 2 - aminoethane hydrochloride

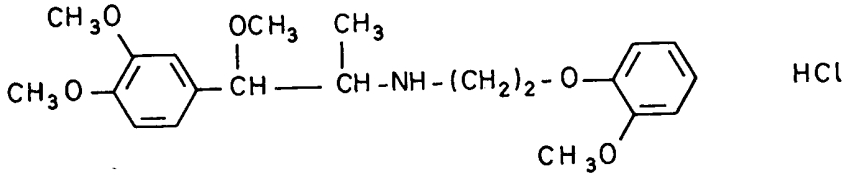


Equal molecular quantities of 1 - (3,4 - methylenedioxyphenyl) - 1 - methoxy-2 - methyl - 2 - aminoethane and o - methoxyphenoxyethyl bromide were mixed, the mixture heated for 2½ hours to 120 to 130°C and the reaction product obtained then worked up as described in Example 1. Column chromatographic separation was not necessary. The residue (base) obtained after evaporation of chloroform was taken up in acetonitrile, acidified with ethereal hydrochloric acid and brought to crystallise with addition of ether. It was then recrystallised from ethanol and ether.

Melting point of the compound given above: 178 to 180°C. Yield: 21%.

EXAMPLE 4.

N - (o - Methoxyphenoxyethyl) - 1 - (3,4 - dimethoxyphenyl) - 1 - methoxy - 2-methyl - 2 -aminoethane hydrochloride

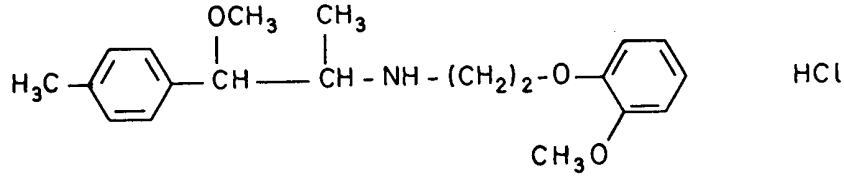


Equal quantities of 1 - (3,4 - dimethoxyphenyl) - 1 - methoxy - 2 - methyl - 2-aminoethane and o - methoxyphenoxyethyl bromide were mixed together, heated for 2½ hours to 120 to 125°C and worked up as described in Example 1. Using a silica gel column, 25 fractions were taken with chloroform as elution agent from which fractions 13 to 18 were combined and from which the hydrochloride could be brought to crystallise from isopropanol and ethereal hydrochloric acid with the addition of ether.

M.Pt: 176 to 177°C, Yield: 15%:

EXAMPLE 5.

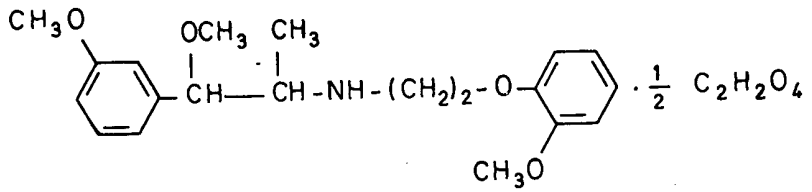
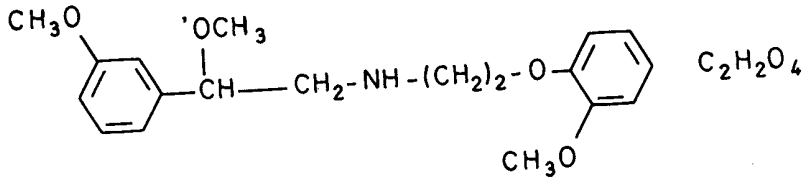
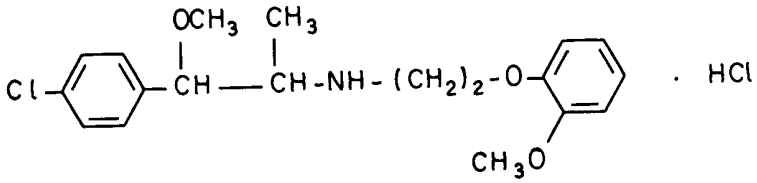
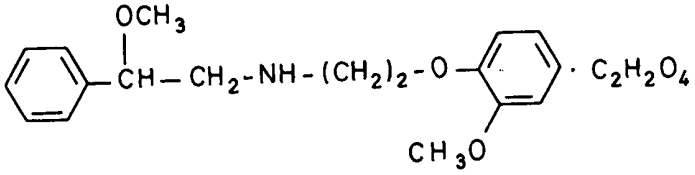
N - (o - Methoxyphenoxyethyl) - 1 - (p - methylphenyl) - 1 - methoxy - 2 - methyl-2 - aminoethane hydrochloride

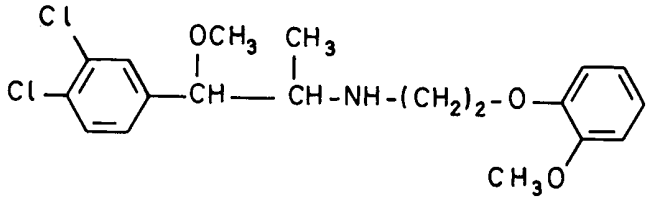
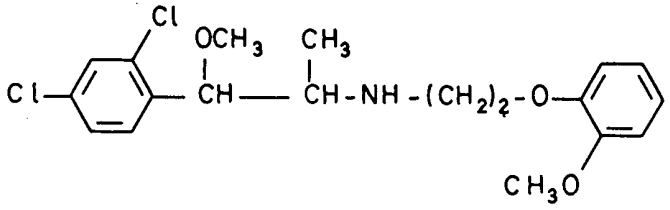
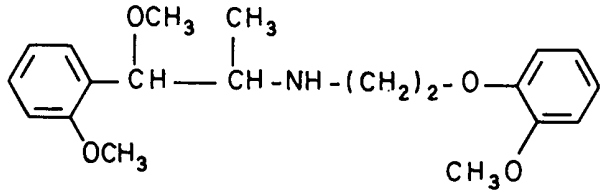
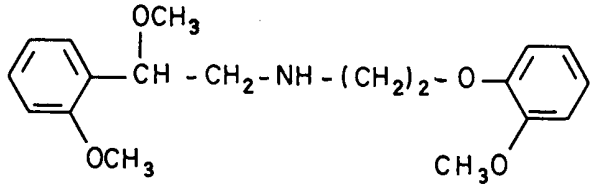


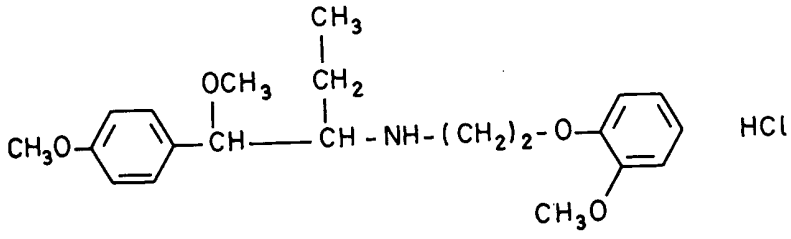
0.03 mole of 1 - (p - methylphenyl) - 1 - methoxy - 2 - methyl - 2 - amino-ethane and 0.03 mole o-methoxyphenoxyethyl bromide were dissolved in 30 ml n-butanol and after the addition of 0.06 mole of anhydrous sodium carbonate while under reflux for two hours. After cooling the mixture is filtered and the residue evaporated to dryness in vacuo. After taking up the residue in chloroform, it was washed with K_2CO_3 solution, the chloroform phase dried with solid anhydrous potassium carbonate and the solvent evaporated. Purification took place via a silica gel column with chloroform as eluant. The pure fractions were dissolved in acetone and after the addition of ethereal hydrochloric acid brought to crystallisation with ether.

M.Pt: 161 to 163°C. Yield: 25%.

The following compounds numbers 6 to 14 were synthesised analogously to Example 4:

Example No.		M. Pt. °C	Prepared from
6		144–145°	Solution of the base in acetonitrile plus ethanolic oxalic acid; recrystallisation from isopropanol/ether
7		186–187°	Solution of the base in ethanol + ethanolic oxalic acid + ether; recrystallisation from methanol
8		142–143°	Solution of the base in acetone + ethereal hydrochloric acid + petroleum ether; recrystallisation from acetone/ethanol and petroleum ether
9		185–187°	Solution of the base in acetone + ethanolic oxalic acid and petroleum ether

Example No.		M. Pt. °C	Prepared from
10	 HCl	164–166°	Solution of the base in acetonitrile + ethereal HCl and ether
11	 HCl	180–182°	Solution of the base in acetonitrile/ethanol (4 : 1) + ethanolic HCl and ether
12	 HCl	184–185°	Solution of the base in acetonitrile + ethereal HCl and ether
13	 $C_2H_2O_4$	183–184°	Solution of the base in ethanol + ethanolic oxalic acid and ether

Example No.		M. Pt. °C	Prepared from
14	 HCl	142–144°	Solution of the base in toluene + ethanolic HCl + ether; recrystallisation from acetonitrile/ether

To show the superior blood pressure reducing properties of 1 - phenyl - 1-methoxy - 2 - aminoethane derivatives obtained according to the Examples, guanethidine (=2 - (octahydro - 1' - azocinyl) ethyl - guanidine sulphate), a commercial preparation of good effectiveness and with the same direction of action, was used as comparison compound. The test compounds were administered via a stomach tube (per orally) to awaken hypertensive rats (according to Goldblatt). The systolic blood pressure was plethysmographically measured at the root of the tail of the rats directly before administration as well as 4 and 24 hours after administration.

In the following Table, there is given in each case the individual compounds tested (compounds according to Examples 2, 3 and 4 and guanethidine as a comparison compound), the number of animals tested and the reduction of the systolic blood pressure in percentage of the initial value 4 and 24 hours after a single administration of the dose indicated.

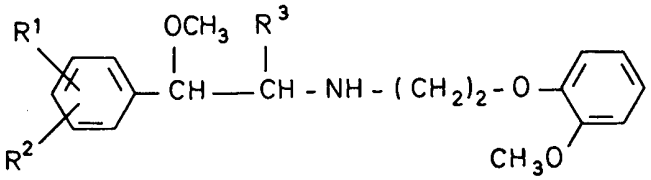
TABLE

Compound according to	Number of animals	Dose mg/kg p.o.	Percentage reduction of systolic blood pressure after	
			4 hours	24 hours
Example 2	9	10	– 21	– 5
3	8	3	– 21	– 2
4	8	10	– 24	– 3
Guanethidine	10	20	– 10	– 5

In the Table the superiority of the new compounds according to the invention relative to the comparison compound with respect to blood pressure reduction action is shown.

WHAT WE CLAIM IS:—

1. A compound of the general formula I



in which

each of R^1 and R^2, which may be the same or different, represents a hydrogen atom, a halogen atom, a methyl group or a methoxy group, or

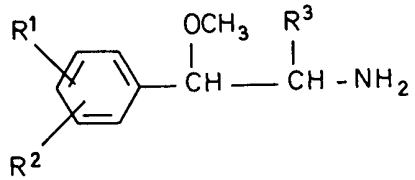
R^1 and R^2 together form a methylenedioxy group, and

R^3 represents a hydrogen atom or an alkyl group with 1 to 4 carbon atoms, or

a physiologically acceptable acid addition salt thereof.

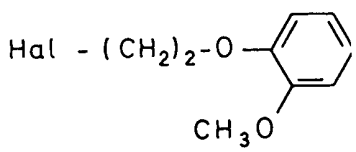
2. A compound according to claim 1 specifically identified herein.

3. A process for the preparation of a compound as claimed in claim 1, which process comprises reacting an amine of the general formula II



(II)

(in which R^1, R^2 and R^3 are as defined in claim 1) with a halide of the general formula III



(III)

(in which Hal represents a halogen atom), and, if desired, converting a free base so obtained into a physiologically acceptable acid addition salt.

4. A process according to claim 3 wherein, in the compound of the formula III, Hal represents a bromine atom.

5. A process for the preparation of a compound as claimed in claim 1 substantially as described in or with reference to any one of the foregoing Examples.

6. A compound according to claim 1 prepared by the process in any one of claims 3 to 5.

7. A pharmaceutical composition comprising a compound of the general formula I as defined in claim 1 or a physiologically acceptable acid addition salt thereof and a pharmacologically acceptable carrier and/or diluent.

8. A composition according to claim 7 which comprises a compound as claimed in claim 2.

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