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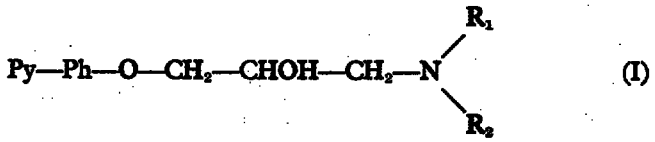
(19)



(54) NEW PYRROLYL COMPOUNDS AND PROCESSES FOR THEIR MANUFACTURE

(71) We, CIBA—GEIGY A.G., a body corporate organised according to the laws of Switzerland, of CH—4002 Basle, Switzerland, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The invention relates to new pyrrolyl compounds of the formula I



(I)

wherein Py is optionally lower alkylated 1-pyrrolyl, Ph is phenylene, R_1 is hydrogen or lower alkyl and R_2 is hydrogen, lower alkyl, aryl-lower alkyl or optionally functionally modified carboxy-lower alkyl or R_1 and R_2 together are lower alkylene, oxa-lower alkylene, thio-lower alkylene or aza-lower alkylene, and to processes for their manufacture.

In the preceding and following text, a lower alkyl radical is to be understood as a radical with up to 7 C atoms, above all with up to 4 C atoms.

Lower alkyl R_1 and R_2, and lower alkyl as a substituent of pyrrolyl Py, has up to 7 C atoms, above all up to 4 C atoms, such as straight or branched butyl, pentyl, hexyl or heptyl bonded in any desired position, but especially n-propyl, ethyl and above all methyl, isopropyl and tert-butyl and, in the case of a substituent of pyrrolyl Py, above all methyl.

Lower alkyl substituents are in particular bonded in the 2- and/or 5-position to a 1-pyrrolyl radical.

Phenylene Ph is for example meta-phenylene and especially ortho-phenylene or para-phenylene.

Aryl-lower alkyl R_2 has up to 12 C atoms, above all up to 10 C atoms, and is unbranched or, preferably, branched in the lower alkyl part, and in particular branched at the α-C atom of the lower alkyl part. The aryl part is, in particular, a phenyl radical which is optionally polysubstituted or, in particular, mono-substituted by lower alkyl, such as the lower alkyl indicated above, lower alkoxy, halogen or trifluoromethyl, but is preferably unsubstituted. Examples of aryl-lower alkyl R_2 are 1-methyl-3-phenyl-propyl and especially 1-methyl-2-phenylethyl.

Lower alkoxy has up to 7 C atoms, above all up to 4 C atoms, and is therefore preferably straight or branched butoxy, pentyloxy, hexyloxy or heptyloxy or above all iso- or n-propoxy, ethoxy or, especially, methoxy.

Halogen is, for example, bromine and especially chlorine.

Optionally functionally modified carboxy-lower alkyl R_2 preferably has up to 7 C atoms, above all up to 4 C atoms, in the lower alkyl part and is unbranched or preferably branched, in particular branched at the α-C atom. Optionally functionally modified carboxy-lower alkyl is thus preferably carboxymethyl, 2 - (2 - carboxy)-propyl, 2 - (4 - carboxy) - butyl or especially 2 - carboxyethyl or above all 2 - (3-carboxy) - propyl functionally modified at the carboxyl group. The optionally functionally modified carboxyl group is, for example, free, esterified or amidised carboxyl or nitrile.

Esterified carboxyl is, for example, carboxyl esterified with an aliphatic alcohol. Aliphatic alcohols are those in which the hydroxyl group is bonded to a C atom which is not a member of an aromatic system. Suitable aliphatic alcohols are, for example, cycloalkanols, such as those with 3—7, especially 5—7, ring members, for example cyclopropanol, cyclopentanol, cyclohexanol and cycloheptanol, cycloalkyl-lower alkanols, which contain, for example, the above cycloalkyl parts, such as cyclopentyl-methanol, cyclohexyl-methanol, 2-cyclohexyl-ethanol and cycloheptyl-methanol, phenyl-lower alkanols, such as 2-phenylethanol and benzyl alcohol, wherein phenyl radicals can also be substituted by halogen, lower alkyl and/or lower alkoxy, such as those mentioned above, and especially lower alkanols, such as n-propanol, iso-propanol, straight-chain or branched butanol, pentanol, hexanol or heptanol, and especially methanol or ethanol. Thus, esterified carboxyl is, above all, methoxycarbonyl or ethoxycarbonyl.

Amidised carboxyl is substituted or unsubstituted carbamoyl. Substituted carbamoyl has, for example, the formula —CO—NR_3—R_4, wherein R_3 is hydrogen or lower alkyl, R_4 is lower alkyl or R_3 and R_4 together are lower alkylene, oxa-lower alkylene, thia-lower alkylene or aza-lower alkylene. Lower alkyl in particular has the abovementioned meaning.

Lower alkylene R_3+R_4, and R_1+R_2, is branched or, in particular, straight-chain lower alkylene with, 2—7, above all 4—6, C atoms in the alkylene chain, and in particular represents, together with the N atom to which the lower alkylene is bonded, pyrrolidino or piperidino.

Oxa-lower alkylene R_3+R_4, and R_1+R_2, is branched or, in particular, straight-chain oxa-lower alkylene with, in particular, 4 or 5 C atoms in the oxa-alkylene chain, and in particular represents, together with the N atom to which the oxa-lower alkylene is bonded, morpholino.

Thia-lower alkylene R_3+R_4, and R_1+R_2, is branched or, in particular, straight-chain thia-lower alkylene with, in particular, 4 or 5 C atoms in the thia-alkylene chain and in particular represents, together with the N atom to which the thia-lower alkylene is bonded, thiomorpholino or 2,6-dimethylthiomorpholino.

Aza-lower alkylene R_3+R_4, and R_1+R_2, is branched or straight-chain aza-lower alkylene with, in particular, 2—6, above all 4—6, C atoms in the aza-alkylene chain, and in particular represents, together with the N atom to which the aza-lower alkylene is bonded, piperazino, N′ - methylpiperazino or N′ - (β - hydroxyethyl) - piperazino.

The new compounds possess valuable pharmacological properties. Thus they show an excitation-inhibiting action, as can be demonstrated on determining the pargyline-reserpine antagonism on intraperitoneal administration to mice. The new compounds therefore are useful for the treatment of states of excitation. They block cardiac β-receptors, as is evident from the determination of the antagonism to tachycardia when administered intravenously to narcotised cats. They also block vascular β-receptors, as is manifest from the determination of vasodilatation when administered intravenously to narcotised cats, and they also block cardiac β-receptors, as is clear from the determination of tachycardia on isolated guinea pig hearts. The new compounds therefore are useful as blockers of adrenergic β-receptors in the treatment of heart and circulatory ailments, e.g. arrhythmic disturbances, angina pectoris, and hypertension.

Compounds to be singled out are compounds Ia of the formula I, wherein Py is optionally mono- or di-lower alkylated 1-pyrrolyl, Ph is phenylene, R_1 is hydrogen or lower alkyl and R_2 is hydrogen, lower alkyl, aryl-lower alkyl, carbamoyl-lower alkyl or cyano-lower alkyl or R_1 and R_2 together are lower alkylene, oxa-lower alkylene, thia-lower alkylene or aza-lower alkylene.

Compounds to be singled out particularly are compounds Ib of the formula I, wherein Py is optionally mono- or di-lower alkylated 1-pyrrolyl, Ph is ortho- or para-phenylene, R_1 is hydrogen or lower alkyl and R_2 is hydrogen, lower alkyl, phenyl-lower alkyl, carbamoyl-lower alkyl or cyano-lower alkyl or R_1 and R_2 together are lower alkylene, oxa-lower alkylene, thia-lower alkylene or aza-lower alkylene.

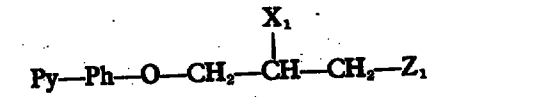
Compounds which are particularly suitable are compounds Ic of the formula I, wherein Py is 1-pyrrolyl, methyl-1-pyrrolyl or dimethyl-1-pyrrolyl, Ph is ortho- or para-phenylene, R_1 is hydrogen, methyl or ethyl and R_2 is methyl, ethyl, isopropyl, tert.-butyl, α-methyl-phenethyl, carbamoyl-lower alkyl with up to 5 C atoms or cyano-lower alkyl with up to 5 C atoms, or R_1 and R_2 together with the N atom to which they are bonded are pyrrolidino, piperidino, morpholino, thiomorpholino, piperazino, N′ - methylpiperazino or N′ - (β - hydroxyethyl) - piperazino.

Compounds to be singled out very particularly are compounds I_d of the formula I, wherein Py is 1-pyrrolyl or mono- or di-lower alkylated 1-pyrrolyl, Ph is ortho-

or para-phenylene, R_1 is hydrogen or lower alkyl and R_2 is lower alkyl or R_1 and R_2 together are lower alkylene, oxa-lower alkylene, thia-lower alkylene or aza-lower alkylene and, in particular, Py is 1-pyrrolyl or 2,5 - dimethyl - 1 - pyrrolyl, Ph is ortho- or para-phenylene, R_1 is hydrogen, R_2 is iso-propyl or tert. - butyl or R_1 and R_2 together with the N atom to which they are bonded are morpholino, and above all the compounds mentioned in the examples.

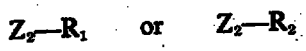
The new compounds are obtained according to methods which are in themselves known.

Thus, for example, a possible procedure is to react a compound of the formula II



(II)

with a compound of the formula III



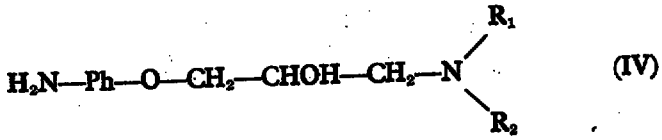
(III)

wherein Py, Ph, R_1 and R_2 have the above meanings, one of the radicals Z_1 and Z_2 is —NH—R_2 or —NH—R_1 and the other is reactively esterified hydroxyl and X_1 is hydroxyl or, if Z_2 is —NH—R_2 or —NH—R_1, Z_1 together with X_1 is epoxy. However, Z_1 must not denote NH_2.

A reactive esterified hydroxyl group is, in particular, a hydroxyl group esterified by a strong inorganic or organic acid, above all a hydrogen halide acid, such as hydrochloric acid, hydrobromic acid or hydriodic acid, or sulphuric acid, or a strong organic sulphonic acid, such as a strong aromatic sulphonic acid, for example benzenesulphonic acid, p-bromobenzenesulphonic acid or p-toluenesulphonic acid. Thus, Z_1 or Z_2 in particular represents chlorine, bromine or iodine.

This reaction is carried out in the usual manner. If a reactive ester is used as the starting material, the reaction is preferably carried out in the presence of a basic condensation agent and/or with an excess of amine. Examples of suitable basic condensation agents are alkali metal hydroxides, such as sodium hydroxide or potassium hydroxide, alkali metal carbonates, such as potassium carbonate, and alkali metal alcoholates, such as sodium methylate, potassium ethylate and potassium tertiary butylate.

A further possible procedure is to react a compound of the formula IV



(IV)

with a γ-oxo-alkanone or a tautomer or functional derivative thereof.

A γ-oxo-alkanone, a tautomer or a functional derivative can be in the monomeric or in the polymeric form. A functional derivative can be open-chain or cyclic, such as an open-chain or cyclic acetal, ketal or acylal or an open-chain or cyclic α-halogeno-ether, enol-ether or enol-ester. A γ-oxo-alkanone can also be present as a mixture with its tautomer and/or its functional derivatives. As examples of suitable γ-oxo-lower alkanones there may be mentioned: Succinaldehyde, 2-methyl-succinaldehyde, 2,3-dimethyl-succinaldehyde, levulinaldehyde, 4-oxo-hexaldehyde and 2,5-hexanedione. As examples of suitable derivatives of γ-oxo-lower alkanones there may be mentioned: Monomeric acetals of succinaldehyde, such as succinaldehyde - mono - diethylacetal, -bis-dimethylacetal, and -bis-diethylacetal, acylals such as succinaldehyde - 1,1 - diacetate (4,4 - diacetoxy - butyraldehyde), enol - ethers such as 1,4 - diphenoxy-butadiene and enol - esters such as 1,4 - diacetoxy - butadiene. Further suitable compounds are, for example, derivatives of tetra-hydrofurane, which react, for example, like the acetals or acylals of succinaldehyde or like open-chain α - halogeno-ethers. Such compounds are, for example, optionally lower alkyl-substituted 2,5 - dialkoxytetrahydrofurances and related compounds, such as 2,5 - dimethoxy-, 2,5 - diethoxy-, 2,5 - dipropoxy-, 2,5 - dibutoxy-, 2,5 - bisallyloxy-, 2,5 - bis - (2 - chloroethoxy)-, 2,5 - diphenoxy- and 2,5 - bis - (3,4 - xylyloxy) - tetrahydrofurane, 2-methyl - 2,5 - dimethoxy - tetrahydrofurane and 3 - methyl - 2,5 - dimethoxy - tetrahydrofurane, and also 2,5 - diacyloxy - tetrahydrofuranes, such as 2,5 - diacetoxy-

tetra - hydrofurane, as well as 2,5 - dihalogeno - tetrahydrofuranes, such as 2,5 - dichloro - tetrahydrofurane and 2,5 - dibromo - tetrahydrofurane, and also compounds which are simultaneously to be classified under two types, such as 2 - chloro - 5-(2 - chloroethoxy) - tetrahydrofurane and 2 - allyloxy - 5 - chloro - tetrahydrofurane.

Polymeric compounds of the abovementioned nature are obtained, for example, when polymeric aldehydes, such as polymeric succinaldehyde, are reacted with amounts of acetalising or acylating materials, or mixtures of materials, which are less than equivalent to the succinaldehyde units present.

The reaction of a compound IV with a γ-oxo-alkanone, a tautomer thereof or a functional derivative thereof, can be carried out in the usual manner, especially warm, such as at about +30° to +140° and in the presence or absence of a diluent and/or condensation agent.

Suitable media for the reaction according to the invention are, when using a free γ-oxo-alkanone, any solvent in which this compound is soluble, for example lower alkanols, such as methanol and ethanol, or lower alkanecarboxylic acids, such as acetic acid. Acetals and acylals of the γ-oxo-lower alkanones, as well as cyclic acetal-like derivatives are advantageously reacted in lower alkanecarboxylic acids, such as acetic acid, as the solvent and condensation agent, or in the presence of catalytic amounts of an acid condensation agent, such as p-toluene, sulphonic acid, in the presence or absence of an inert organic solvent or diluent, such as, for example, benzene, toluene, o- dichlorobenzene or acetonitrile. The reaction of α-halogeno-ethers is carried out, for example, in inert organic solvents, such as halogeno-lower alkanes, for example chloroform or the abovementioned solvents. The reaction temperature is preferably between room temperature and the boiling point of the solvent or diluent used, for example +25° to +140°, the lowest range in particular being relevant to the last-mentioned halogen compounds.

In resulting compounds, it is possible, within the scope of the definition of the end products, to modify, introduce or remove substituents in the usual manner, or to convert resulting compounds in the usual manner into other end products.

Thus, it is possible, in resulting compounds, to hydrolyse functionally modified carboxyl groups, as a constituent of R_2, to free carboxyl groups in the usual manner, preferably in the presence of a strong base, such as a strong organic or, above all, inorganic base, preferably a metal base, for example an alkaline earth metal or alkali metal carbonate or, above all, hydroxide, for example calcium hydroxide, sodium hydroxide or potassium hydroxide, or in the presence of a strong acid, for example a strong mineral acid, especially a hydrogen halide acid, for example hydrochloric acid or above all hydrobromic acid, or sulphuric acid. If desired, oxidising agents such as nitrous acid, can be added when hydrolysing the carbamoyl group.

The nitrile group as a constituent of R_2 can also be hydrolysed to the carbamoyl group in the usual manner, for example as described above for the hydrolysis to the free carboxyl group. Equally, it is also possible to convert the carbamoyl group into the nitrile group by dehydration in the usual manner, for example by heating and/or by the action of dehydrating agents.

Free carboxyl groups as a constituent of R_2 can be esterified in the usual manner, for example by reaction with a corresponding alcohol, preferably in the presence of an acid, such as a mineral acid, for example sulphuric acid or hydrochloric acid, or in the presence of a water-binding agent, such as dicyclohexylcarbodiimide, or by reaction with an appropriate diazo compound, for example a diazoalkane. The esterification can also be carried out by reaction of a salt, preferably an alkali metal salt, of the acid with a reactively esterified alcohol, for example a halide, such as the chloride, of the corresponding alcohol.

Free carboxyl groups can also be converted into amidised carboxyl groups in the usual manner, for example by reaction with ammonia or a primary or secondary amine and, if necessary, dehydration of the ammonium salt formed as an intermediate.

Free carboxyl groups can, for example, also be converted into acid halide or acid anhydride groups in the usual manner, for example by reaction with halides of phosphorus or sulphur, such as thionyl chloride, phosphorus pentachloride or phosphorus tribromide, or with acid halides, such as chloroformic acid esters or oxalyl chloride. The acid anhydride or acid halide groups can then be converted into esterified carboxyl groups in the usual manner by reaction with corresponding alcohols, if desired, in the presence of acid-binding agents, such as organic or inorganic bases.

Functionally modified carboxyl groups as a constituent of R_2 can furthermore be converted into esterified or amidised carboxyl groups according to customary methods. Thus, resulting acid anhydrides, acid halides, for example acid chlorides,

or ketenes can be converted into esters or amides by reaction with, respectively, an alcohol or ammonia or a primary or secondary amine, if desired in the presence of acid-binding agents, such as organic or inorganic bases. Resulting nitriles can also be converted analogously, by reaction with an alcohol into the corresponding imino-ethers which can be hydrolysed in the usual manner to the corresponding esters.

The reactions mentioned can optionally be carried out simultaneously or successively and in any desired sequence.

The reactions mentioned are carried out in the usual manner in the presence or absence of diluents, condensation agents and/or catalytic agents, at lowered, ordinary or elevated temperature, if appropriate in a closed vessel.

Depending on the process conditions and starting materials, the end products are obtained in the free form or in the form of their acid addition salts which are also encompassed by the invention. Thus, for example, basic, neutral or mixed salts and possibly also hemihydrates, monohydrates, sesquihydrates or polyhydrates thereof can be obtained. The acid addition salts of the new compounds can be converted into the free compound in a manner which is in itself known, for example by means of basic agents, such as alkalis or ion exchanges. On the other hand, the resulting free bases can form salts with organic or inorganic acids. Acids used for the manufacture of acid addition salts are especially those which are suitable for forming therapeutically usable salts. As examples of such acids there may be mentioned: Hydrogen halide acids, sulphuric acid, phosphoric acids, nitric acid, perchloric acid, aliphatic, alicyclic, aromatic or heterocyclic carboxylic acids or sulphonic acids, such as formic acid, acetic acid, propionic acid, succinic acid, glycollic acid, lactic acid, malic acid, tartaric acid, citric acid, ascorbic acid, maleic acid, hydroxymaleic acid or pyruvic acid, fumaric acid, benzoic acid, anthranilic acid, p-hydroxybenzoic acid or salicylic acid, embonic acid, methanesulphonic acid, ethanesulphonic acid, cyclohexanesulphonic acid, hydroxyethanesulphonic acid and ethylenesulphonic acid, halogenobenzenesulphonic acids, toluenesulphonic acid, naphthalenesulphonic acid or sulphanilic acid, methionine, tryptophane, lysine or arginine.

Acid compounds can furthermore be in the free form or in the form of their salts with bases, such as alkali metal salts or alkaline earth metal salts, salts with ammonia or salts with amines. Suitable compounds for the manufacture of salts with bases are, for example, alkali metal, such as sodium or potassium, carbonates, bicarbonates or hydroxides, or corresponding alkaline earth metal compounds, such as calcium or magnesium compounds, or ammonia, as well as amines, such as aliphatic amines, for example lower alkylamines, such as trimethylamine or triethylamine. Aluminium salts, for example salts of two mols of acid and one mol of aluminium hydroxide, are also suitable, especially because of their slower resorption, absence of odour and the fact that they cause little gastro-intestinal disturbance.

These or other salts of the new compounds such as, for example, the picrates, can also be used to purify the resulting free bases, by converting the free compound into salts, isolating these and again liberating the compound from the salts. Because of the close relationships between the new compounds in the free form and in the form of their salts, the free compounds are, in the preceding and following text, where appropriate also to be understood to include the corresponding salts, with regard to general sense and intended use.

The invention also relates to those embodiments of the process according to which a reactant is present in the form of its salts, if relevant.

Depending on the choice of the starting materials and procedures, the new compounds can be in the form of optical antipodes or racemates, or, if they contain at least two asymmetric carbon atoms, also as racemate mixtures and/or as pure geometrical isomers or as mixtures thereof (isomer mixtures).

Resulting isomer mixtures can be separated into the two pure geometrical isomers in a known manner on the basis of the physico-chemical differences of the constituents, for example by chromatography on a suitable stationary phase, such as silica gel, or aluminium oxide, which have been pretreated with a complex-forming heavy metal compound, for example with a silver compound, or by forming a heavy metal addition compound, for example the silver nitrate complex, separating this into the addition compounds of the pure isomers, for example by fractional crystallisation and subsequently liberating the pure isomers.

Racemate mixtures can be separated into the two stereoisomeric (diastereomeric) pure racemates in a known manner on the basis of the physico-chemical differences of the constituents, for example by chromatography and/or fractional crystallisation.

Resulting racemates can be separated into the diastereomers according to known methods, for example by recrystallisation from an optically active solvent, with the

aid of micro-organisms or by reaction with an optically active acid which forms salts with the racemic compound and separation of the salts obtained in this manner, for example on the basis of their different solubilities, and the antipodes can be liberated from the diastereomers by the action of suitable agents. Particularly customary optically active acids are, for example, the D- and L- forms of tartaric acid, di-o-toluyl-tartaric acid, malic acid, mandelic acid, camphorsulphonic acid or quinic acid. Advantageously, the more active L-antipode is isolated.

Appropriately, the starting materials used for carrying out the reactions according to the invention are those which lead to the initially particularly mentioned groups of end products and especially to the end products which have been particularly described or singled out.

The starting materials are known or can, if they are new, be obtained according to methods which are in themselves known.

Compounds of the formula II can be manufactured, for example, in the usual manner, from a phenol Py—Ph—OH or a phenolate thereof, by means of epichlorohydrin or the like. Compounds of the formula IV can be manufactured, for example, in the usual manner by reaction of a phenol H_2N—Ph—OH, or a phenolate thereof with the product of the reaction of an amine of the formula HNR_1R_2 with epichlorohydrin or the like.

The new compounds can be used as medicaments, for example in the form of pharmaceutical preparations, in which they or their salts are present as a mixture with a pharmaceutical, organic or inorganic, solid or liquid excipient suitable for enteral or parenteral administration. Suitable materials for forming the excipient are those which do not react with the new compounds such as, for example, water, gelatine, lactose, starch, magnesium stearate, talc, vegetable oils, benzyl alcohols, rubber, polyalkylene glycols, white petroleum jelly, cholesterol or other known medicinal excipients. The pharmaceutical preparations can be, for example, in the form of tablets, dragées, capsules or suppositories or in a liquid form, as solutions (for example as an elixir or syrup), suspensions or emulsions. They are optionally sterilised and/or contain auxiliaries, such as preservatives, stabilisers, wetting agents or emulsifiers, salts for regulating the osmotic pressure or buffers. They can also contain yet other therapeutically valuable materials. The preparations, which can also be used in veterinary medicine, are formulated according to customary methods.

The examples which follow illustrate the invention without, however, restricting it.

Example 1

10 g (0.047 mol) of 1 - [4 - pyrrolyl - (1) - phenoxy] - 2,3 - epoxy - propane are dissolved in 100 ml of isopropanol, 4.25 ml (0.05 mol) of isopropylamine are added and the mixture is then heated to the boil for 3 hours under reflux. It is then evaporated in vacuo and the resulting crude base is crystallised from ethyl acetate. 1 - [4-Pyrrolyl - (1) - phenoxy] - 2 - hydroxy - 3 - isopropylamino - propane is obtained, of which the hydrochloride, prepared from a solution of the base in methanol and a solution of hydrogen chloride in ether, melts, at 208—210°C.

The starting material can be prepared as follows:

5.0 g (31.4 mmols) of 4 - pyrrolyl - (1) - phenol, 11.6 g (9.9 ml) of epichlorohydrin and 0.1 ml of piperidine are heated for 6 hours under reflux. Instead of the piperidine, a small amount of potassium carbonate and acetonitrile can also be used. The excess epichlorohydrin is then distilled off and the residue is distilled at 160°C and 0.05 mm Hg. The resulting 1 - [4 - pyrrolyl - (1) - phenoxy] - 2,3 - epoxy-propane can be used further direct. The 4 - pyrrolyl - (1) - phenol used can, in turn, be obtained from p - aminophenol and 2,5 - dimethoxy - tetrahydrofurane in glacial acetic acid.

Example 2

40 g (0.18 mol) of 1 - (4 - amino - phenoxy) - 2 - hydroxy - 3 - isopropylamino-propane and 25 g (0.189 mol) of 2,5 - dimethoxy - tetrahydrofurane in 400 ml of glacial acetic acid are heated for 1½ hours under reflux. The acetic acid is distilled off under reduced pressure. The residue is dissolved in ethyl acetate and the solution is washed twice with sodium hydroxide solution and twice with water. The ethyl acetate phase is dried over magnesium sulphate, filtered and concentrated until crystallisation starts. 1 - [4 - Pyrrolyl - (1) - phenoxy] - 2 - hydroxy - 3 - isopropylamino-propane is obtained.

The hydrochloride is obtained from the base by reacting a solution of the base

in methanol with a solution of hydrogen chloride in ether. The hydrochloride melts at 208—210°C.

Example 3

108 g (0.482 mol) of 1 - (2 - amino - phenoxy) - 2 - hydroxy - 3 - isopropylamino - propane and 64 g (0.482 mol) of 2,5 - dimethoxy - tetrahydrofurane in 1,080 ml of glacial acetic acid are heated for 1 hour under reflux. The glacial acetic acid is distilled off under reduced pressure. The residue is partitioned between ethyl acetate and sodium hydroxide solution. The ethyl acetate phase is washed once with sodium hydroxide solution and twice with water, dried over magnesium sulphate, filtered and concentrated. The residue obtained is a dark brown oil which is taken up in ether and the ether solution is filtered. The filtrate is evaporated under reduced pressure. The residue is again dissolved in ether, the solution is filtered and the filtrate is evaporated under reduced pressure. Light yellow crystals are thus obtained, which are recrystallised from ether/petroleum ether and consist of 1 - [2 - pyrrolyl-(1) - phenoxy] - 2 - hydroxy - 3 - isopropylamino - propane, melting point 80—81°C. With hydrogen chloride in methanol, the hydrochloride is obtained, which after recrystallisation from isopropanol melts at (129°C) 130—131°C.

The starting material can be prepared as follows:

290 g (1.14 mol) of 1 - (2 - nitro - phenoxy) - 2 - hydroxy - 3 - isopropylamino-propane are dissolved in 1.5 l of ethanol.

280 ml (5.7 mols) of hydrazine hydrate are added to the solution. About 100 ml of this solution are introduced into a flask and warmed to about 70°C. Raney nickel is then added in portions. The remainder of the solution is then allowed to run in in such a way that the temperature is kept at about 70°C (reflux) by the heat of reaction. After completion of the addition, the mixture is stirred for a further hour and is filtered after it has cooled. The filtrate is concentrated until it crystallises and 1 - (2 - amino - phenoxy) - 2 - hydroxy - 3 - isopropylamino - propane of melting point 94—97°C is thus obtained.

Example 4

Tablets containing 60 mg of active substance are prepared in the usual manner, to have the following composition:

Composition

1 - [4 - Pyrrolyl - (1) - phenoxy] - 2 - hydroxy - 3-isopropylamino - propane hydrochloride	60 mg
Wheat starch	59 mg
Lactose	60 mg
Colloidal silica	10 mg
Talc	10 mg
Magnesium stearate	1 mg
	200 mg

Preparation

The 1 - [4 - pyrrolyl - (1) phenoxy] - 2 - hydroxy - 3 - isopropylamino-propane hydrochloride is mixed with a part of the wheat starch, with lactose and with colloidal silica and the mixture is forced through a sieve. A further part of the wheat starch is worked into a paste with a 5-fold amount of water on a waterbath and the powder mixture is kneaded with this paste until a slightly plastic mass has been produced.

This plastic mass is forced through a sieve of approx. 3 mm mesh width and dried, and the resulting dry granules are again forced through a sieve. The remaining wheat starch, talc and magnesium stearate are then mixed in and the mixture is pressed to give tablets weighing 200 mg and having a breaking groove. The daily dose is about ½ to 4 tablets in the case of a warm-blooded animal of about 75 kg body weight, it also being possible to administer the corresponding dose of active compound as a single tablet of appropriate composition.

Tablets containing 60 mg of 1 - [2 - pyrrolyl - (1) - phenoxy] - 2 - hydroxy-3 - isopropyl - amino - propane hydrochloride as the active compound can be prepared analogously.

Example 5

52 ml of tert.butylamine are added to a solution of 26.9 g of 1 - [o - (pyrrol - 1-yl]phenoxy - 2,3 - epoxy - propane in 250 ml of isopropanol and the mixture is heated to the boil under reflux for 1½ hours. The oil which remains after evaporating off the volatile constituents in vacuo is distilled in a high vacuum in a bulb tube

and gives 1 - tert.butylamino - 3 - [o - (pyrrol - 1 - yl) - phenoxy] - 2 - propanol as a colourless oil of boiling point 130—140°C/0.04 mm Hg. With half the equivalent amount of fumaric acid, this forms a neutral fumarate of melting point 203—204°C (from methanol).

The starting material can be prepared as follows:

a) 109 g of o-aminophenol and 132 g of 2,5 - dimethoxy - tetrahydrofurane in 700 ml of glacial acetic acid are heated to the boil for 30 minutes. After cooling, the reaction mixture is filtered and the polymeric material is thus removed. The filtrate is evaporated in vacuo, the residue is dissolved in approx. 1 litre of ethyl acetate and the solution is washed with 200 ml of water. The dark oil which remains after drying and evaporating the organic phase is distilled in a bulb tube under a high vacuum. This gives o - (pyrrol - 1 - yl) - phenol of boiling point 115—125°C/0.05 mm Hg as an oil which gradually crystallises and melts at 46—49°C.

b) 95.7 g of o - (pyrrol - 1 - yl) - phenol, 245 g of potassium carbonate and 167 g of epichlorohydrin are heated to the boil in a nitrogen atmosphere, whilst stirring. After 6 hours, the reaction mixture is cooled and filtered and the filtrate is evaporated in vacuo, ultimately at a bath temperature of 120°C. The oil which remains is dissolved in 300 ml of ether and the solution is extracted with 300 ml of 2 N sodium hydroxide solution and washed with 100 ml of water. The oil which remains after evaporating off the solvent is distilled in a high vacuum and gives 1-[o - (pyrrol - 1 - yl) - phenoxy] - 2,3 - epoxy - propane of boiling point 103—105°C/0.001 mm Hg.

Example 6

50 ml of isopropylamine are added to a solution of 26.9 g of 1 - [o - (pyrrol-1 - yl) - phenoxy] - 2,3 - epoxy - propane in 250 ml of isopropanol and the mixture is heated to the boil under reflux for 1½ hours. The oil which remains after evaporating off the volatile constituents in vacuo is distilled in a bulb tube under a high vacuum and gives 1 - iso - propylamino - 3 [o - (pyrrol - 1 - yl) - phenoxy] - 2-propanol as a colourless oil of boiling point 125—135°C/0.04 mm Hg. The distillate which crystallises can be recrystallised from ether,petroleum ether and gives crystals of melting point 80—81°C and is in every respect identical with the product obtained in Example 3.

Example 7

A solution of 15 g of 1 - [o - (pyrrol - 1 - yl) - phenoxy] - 2,3 - epoxy-propane and 7 g of morpholine in 150 ml of isopropanol is heated for 2 hours to the boil under reflux. After evaporation in vacuo, an oil remains, which crystallises and after recrystallisation from butanone gives 1 - morpholino - 3 - [o - (pyrrol - 1 - yl)-phenoxy] - 2 - propanol of melting point 81—82°C. It forms a neutral fumarate of melting point 136—137°C (from butanone).

Example 8

30 g of 1 - [o - (2,5 - dimethyl - pyrrol - 1 - yl) - phenoxy] - 2,3 - epoxy-propane, dissolved in 200 ml of isopropanol, are mixed with 60 ml of isopropylamine and the mixture is heated to the boil under reflux for 2 hours. The oil which remains after evaporation is recrystallised from petroleum ether with addition of active charcoal and gives 1 - [o - (2,5 - dimethyl - pyrrol - 1 - yl) - phenoxy] - 3 - isopropylamino - 2 - propanol of melting point 73—75°C. Its neutral fumarate melts at 186—188°C (from acetone).

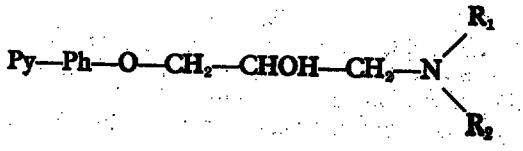
The starting materials required can be prepared analogously to Example 5:

a) o - Aminophenol and 2,5 - hexanedione give o - (2,5 - dimethyl - pyrrol - 1-yl) - phenol of melting point 95—99°C.

b) o - (2,5 - Dimethyl - pyrrol - 1 - yl) - phenol and epichlorohydrin give 1-[o - (2,5 - dimethyl - pyrrol - 1 - yl) - phenoxy] - 2,3 - epoxy - propane of boiling point 120—122°C/0.08 mm Hg.

WHAT WE CLAIM IS:—

1. Pyrrolyl compounds of the formula I



(I)

and gives 1 - tert.butylamino - 3 - [o - (pyrrol - 1 - yl) - phenoxy] - 2 - propanol as a colourless oil of boiling point 130—140°C/0.04 mm Hg. With half the equivalent amount of fumaric acid, this forms a neutral fumarate of melting point 203—204°C (from methanol).

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b) 95.7 g of o - (pyrrol - 1 - yl) - phenol, 245 g of potassium carbonate and 167 g of epichlorohydrin are heated to the boil in a nitrogen atmosphere, whilst stirring. After 6 hours, the reaction mixture is cooled and filtered and the filtrate is evaporated in vacuo, ultimately at a bath temperature of 120°C. The oil which remains is dissolved in 300 ml of ether and the solution is extracted with 300 ml of 2 N sodium hydroxide solution and washed with 100 ml of water. The oil which remains after evaporating off the solvent is distilled in a high vacuum and gives 1-[o - (pyrrol - 1 - yl) - phenoxy] - 2,3 - epoxy - propane of boiling point 103—105°C/0.001 mm Hg.

Example 6

50 ml of isopropylamine are added to a solution of 26.9 g of 1 - [o - (pyrrol-1 - yl) - phenoxy] - 2,3 - epoxy - propane in 250 ml of isopropanol and the mixture is heated to the boil under reflux for 1½ hours. The oil which remains after evaporating off the volatile constituents in vacuo is distilled in a bulb tube under a high vacuum and gives 1 - iso - propylamino - 3[o - (pyrrol - 1 - yl) - phenoxy] - 2-propanol as a colourless oil of boiling point 125—135°C/0.04 mm Hg. The distillate which crystallises can be recrystallised from ether$_3$petroleum ether and gives crystals of melting point 80—81°C and is in every respect identical with the product obtained in Example 3.

Example 7

A solution of 15 g of 1 - [o - (pyrrol - 1 - yl) - phenoxy] - 2,3 - epoxy-propane and 7 g of morpholine in 150 ml of isopropanol is heated for 2 hours to the boil under reflux. After evaporation in vacuo, an oil remains, which crystallises and after recrystallisation from butanone gives 1 - morpholino - 3 - [o - (pyrrol - 1 - yl)-phenoxy] - 2 - propanol of melting point 81—82°C. It forms a neutral fumarate of melting point 136—137°C (from butanone).

Example 8

30 g of 1 - [o - (2,5 - dimethyl - pyrrol - 1 - yl) - phenoxy] - 2,3 - epoxy-propane, dissolved in 200 ml of isopropanol, are mixed with 60 ml of isopropylamine and the mixture is heated to the boil under reflux for 2 hours. The oil which remains after evaporation is recrystallised from petroleum ether with addition of active charcoal and gives 1 - [o - (2,5 - dimethyl - pyrrol - 1 - yl) - phenoxy] - 3 - isopropylamino - 2 - propanol of melting point 73—75°C. Its neutral fumarate melts at 186—188°C (from acetone).

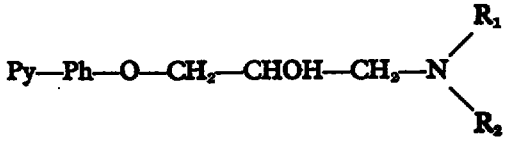
The starting materials required can be prepared analogously to Example 5:

a) o - Aminophenol and 2,5 - hexanedione give o - (2,5 - dimethyl - pyrrol - 1-yl) - phenol of melting point 95—99°C.

b) o - (2,5 - Dimethyl - pyrrol - 1 - yl) - phenol and epichlorohydrin give 1-[o - (2,5 - dimethyl - pyrrol - 1 - yl) - phenoxy] - 2,3 - epoxy - propane of boiling point 120—122°C/0.08 mm Hg.

WHAT WE CLAIM IS:—

1. Pyrrolyl compounds of the formula I



(I)

wherein Py is optionally lower-alkylated 1 - pyrrolyl, Ph is phenylene, R_1 is hydrogen or lower alkyl and R_2 is hydrogen, lower alkyl, aryl-lower alkyl or optionally functionally modified carboxy-lower alkyl or R_1 and R_2 together are lower alkylene, oxa-lower alkylene, thia-lower alkylene or aza-lower alkylene, their antipodes and salts.

2. Compounds Ia of the formula I, wherein Py is optionally mono- or di-lower alkylated 1 - pyrrolyl, Ph is phenylene, R_1 is hydrogen or lower alkyl and R_2 is hydrogen, lower alkyl, aryl-lower alkyl, carbamoyl-lower alkyl or cyano-lower alkyl or R_1 and R_2 together are lower alkylene, oxa-lower alkylene, thia-lower alkylene or aza-lower alkylene.

3. Compounds Ib of the formula I, wherein Py is optionally mono- or di-lower alkylated 1 - pyrrolyl, Ph is ortho- or para-phenylene, R_1 is hydrogen or lower alkyl, and R_2 is hydrogen, lower alkyl, phenyl-lower alkyl, carbamoyl-lower alkyl or cyano-lower alkyl or R_1 and R_2 together are lower alkylene, oxa-lower alkylene, thia-lower alkylene or aza-lower alkylene.

4. Compounds Ic of the formula I, wherein Py is 1 - pyrrolyl, methyl - 1-pyrrolyl or dimethyl - 1 - pyrrolyl, Ph is ortho- or para-phenylene, R_1 is hydrogen, methyl or ethyl and R_2 is methyl, ethyl, isopropyl, tert.-butyl α-methyl-phenethyl, carbamoyl-lower alkyl with up to 5 C atoms or cyano-lower alkyl with up to 5 C atoms or R_1 and R_2 together with the N atom to which they are bonded are pyrrolidino, piperidino, morpholino, thiomorpholino, piperazino, N' - methylpiperazino or N' - (β - hydroxyethyl) - piperazino.

5. Compounds Id of the formula I, wherein Py is 1 - pyrrolyl or mono- or di-lower alkylated 1 - pyrrolyl, Ph is ortho-or para-phenylene, R_1 is hydrogen or lower alkyl and R_2 is lower alkyl or R_1 and R_2 together are lower alkylene, oxa-lower alkylene, thia-lower alkylene or aza-lower alkylene and in particular Py is 1 - pyrrolyl or 2,5 - dimethyl - 1 - pyrrolyl, Ph is ortho- or para-phenylene, R_1 is hydrogen, R_2 is iso-propyl or tert.-butyl or R_1 and R_2 together with the N atom to which they are bonded are morpholino.

6. The compounds of the general formula I as mentioned in Examples 1 to 3.

7. The compounds of the general formula I as mentioned in Examples 5 to 8.

8. The compounds mentioned in one of Claims 1—4 and 6 in the form of their dextro-rotatory optical antipodes.

9. The compounds mentioned in one of Claims 1—4 and 6 in the form of their laevo-rotatory optical antipodes.

10. One of the compounds mentioned in one of Claims 1—4, 6 and 8—9, in the free form.

11. One of the compounds mentioned in one of Claims 1—4, 6 and 8—9, in the form of its salts.

12. One of the compounds mentioned in one of Claims 1—4, 6 and 8—9, in the form of its therapeutically usable salts.

13. Pharmaceutical preparations containing one of the compounds mentioned in one of Claims 1—4, 6, 8, 9, 10 and 12 together with a therapeutically usable excipient.

14. The compounds mentioned in Claims 5 and 7, in the form of their dextro-rotatory optical antipodes.

15. The compounds mentioned in Claims 5 and 7, in the form of their laevo-rotatory optical antipodes.

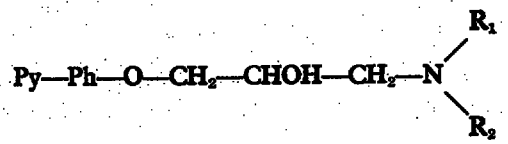
16. One of the compounds mentioned in one of Claims 5, 7, 14 and 15, in the free form.

17. One of the compounds mentioned in one of Claims 5, 7, 14 and 15, in the form of its salts.

18. One of the compounds mentioned in one of Claims 5, 7, 14 and 15, in the form of its therapeutically usable salts.

19. Pharmaceutical preparations containing one of the compounds mentioned in one of Claims 5, 7, 14, 15, 16 and 18 together with a therapeutically usable excipient.

20. Process for the manufacture of new pyrrolyl compounds of the formula I

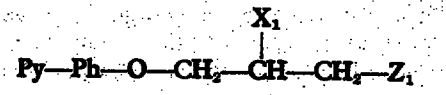


(I)

wherein Py is optionally lower-alkylated 1 - pyrrolyl, Ph is phenylene, R_1 is hydrogen

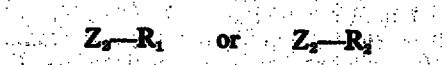
or lower alkyl and R_2 is hydrogen, lower alkyl, aryl-lower alkyl or optionally functionally modified carboxy-lower alkyl or R_1 and R_2 together are lower alkylene, oxa-lower alkylene, thia-lower alkylene or aza-lower alkylene, characterised in that

a) a compound of the formula II



(II)

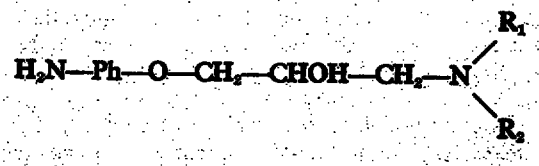
is reacted with a compound of the formula III



(III)

wherein Py, Ph, R_1 and R_2 have the above meanings, one of the radicals Z_1 and Z_2 is —NH—R_2 or —NH—R_1 and the other is reactively esterified hydroxyl and X_1 is hydroxyl or, if Z_2 is —NH—R_2 or —NH—R_1, Z_1 together with X_1 is epoxy, or

b) a compound of the formula X



(IV)

is reacted with a γ-oxo-alkanone, or a tautomer or functional derivative thereof, and if desired, resulting compounds are converted, within the scope of the end products, into one another, and/or resulting racemates are separated into the antipodes and/or resulting free compounds are converted into salts or resulting salts into free compounds or other salts.

21. Process according to Claim 20a), characterised in that a reactive esterified hydroxy group is a hydroxyl group with a hydrogen halide acid, sulphuric acid or a sulphonic acid.

22. Process according to one of Claims 20 and 21, characterised in that a reactive esterified hydroxyl group is chlorine, bromine or iodine.

23. Process according to Claim 20b), characterised in that the reaction is effected at elevated temperature.

24. Process according to one of Claims 20—23, characterised in that a reactant is present in the form of its salts, if relevant.

25. Process according to Claim 20, characterised in that in resulting compounds of the formula I, wherein R_2 contains a modified carboxyl group, this modified carboxyl group is converted into the free carboxyl group by hydrolysis.

26. Process according to Claim 20, characterised in that in resulting compounds of the formula I, wherein R_2 contains a nitrile group, this nitrile group is converted into the carboxyl group or into the carbamoyl group.

27. Process according to Claim 20, characterised in that in resulting compounds of the formula I, wherein R_2 contains a carbamoyl group, this carbamoyl group is converted into the nitrile group.

28. Process according to Claim 20, characterised in that in resulting compounds of the formula I, wherein R_2 contains a free carboxyl group, this carboxyl group is esterified.

29. Process according to Claim 20, characterised in that in resulting compounds of the formula I, wherein R_2 contains a free carboxyl group, this carboxyl group is converted into an amidised carboxyl group or into an acid halide group.

30. Process according to Claim 20, characterised in that in resulting compounds of the formula I, wherein R_2 contains a functionally modified carboxyl group, this functionally modified carboxyl group is converted into an esterified or amidised carboxyl group.

31. Process according to one of Claims 20—30, characterised in that compounds Ia of the formula I are manufactured, wherein Py is optionally mono- or di-lower alkylated 1 - pyrrolyl, Ph is phenylene, R_1 is hydrogen or lower alkyl and R_2 is hydrogen, lower alkyl, aryl-lower alkyl, carbamoyl-lower-alkyl or cyano-lower alkyl or R_1 and R_2 together are lower alkylene, oxa-lower alkylene, thia-lower alkylene or aza-lower alkylene.

32. Process according to one of Claims 20—30, characterised in that compounds Ib of the formula I are manufactured, wherein Py is optionally mono- or di-lower

alkylated 1 - pyrrolyl, Ph is ortho- or para-phenylene, R_1 is hydrogen or lower alkyl, R_2 is hydrogen, lower alkyl, phenyl-lower alkyl, carbamoyl-lower alkyl or cyano-lower alkyl or R_1 and R_2 together are lower alkylene, oxa-lower alkylene, thia-lower alkylene or aza-lower alkylene.

33. Process according to one of Claims 20—30, characterised in that compounds Ic of the formula I are manufactured, wherein Py is 1 - pyrrolyl, methyl - 1 - pyrrolyl or dimethyl - 1 - pyrrolyl, Ph is ortho- or para-phenylene, R_1 is hydrogen, methyl or ethyl and R_2 is methyl, ethyl, isopropyl, tert.-butyl, α-methyl-phenethyl, carbamoyl-lower alkyl with up to 5 C atoms or cyano-lower alkyl with up to 5 C atoms or R_1 and R_2 together with the N atom to which they are bonded are pyrrolidino, piperidino, morpholino, thiomorpholino, piperazino, N′ - methylpiperazino or N′ - (β-hydroxyethyl) - piperazino.

34. Process according to one of Claims 20—30, characterised in that compounds Id of the formula I are manufactured, wherein Py is 1 - pyrrolyl or mono- or di-lower alkylated 1 - pyrrolyl, Ph is ortho- or para-phenylene, R_1 is hydrogen or lower alkyl and R_2 is lower alkyl or R_1 and R_2 together are lower alkylene, oxa-lower alkylene, thia-lower alkylene or aza-lower alkylene and in particular Py is 1 - pyrrolyl or 2,5 - dimethyl - 1 - pyrrolyl, Ph is ortho- or para-phenylene, R_1 is hydrogen, R_2 is iso-propyl or tert.-butyl or R_1 and R_2 together with the N atom to which they are bonded are morpholino.

35. Process according to one of Claims 20—30, characterised in that the compounds mentioned in Examples 1 to 3 are manufactured.

36. Process according to one of Claims 20—30, characterised in that the compounds mentioned in Examples 5 to 8 are manufactured.

37. Process according to one of Claims 20—33 and 35, characterised in that the new compounds are manufactured in their dextrorotatory form.

38. Process according to one of Claims 20—33 and 35, characterised in that the new compounds are manufactured in their laevorotatory form.

39. Process according to one of Claims 20—33, 35, 37 and 38, characterised in that the new compounds are manufactured in the free form.

40. Process according to one of Claims 20—33, 35, 37 and 38, characterised in that the new compounds are manufactured in the form of their salts.

41. Process according to one of Claims 20—33, 35, 37 and 38, characterised in that the new compounds are manufactured in the form of their therapeutically usable salts.

42. Process according to Claim 34 and 36, characterised in that the new compounds are manufactured in their dextrorotatory form.

43. Process according to Claim 34 and 36, characterised in that new compounds are manufactured in their laevorotatory form.

44. Process according to Claim 34, 36, 42 and 43, characterised in that the new compounds are manufactured in the free form.

45. Process according to one of Claims 34, 36, 42 and 43, characterised in that the new compounds are manufactured in the form of their salts.

46. Process according to one of Claims 34, 36, 42 and 43, characterised in that the new compounds are manufactured in the form of their therapeutically usable salts.

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