

PATENTS ACT, 1949
AMENDED SPECIFICATION

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PATENT SPECIFICATION

1.187.546

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NO DRAWINGS

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Int. Cl.:—C 07 c 93/14, 121/52

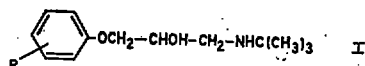
COMPLETE SPECIFICATION

Propanolamine derivatives

We, BOEHRINGER INGELHEIM G.M.B.H., a German Body Corporate, of Ingelheim am Rhein, 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 1-phenoxy-2-hydroxy-3-tertiary butylaminopropanes and processes for the preparation thereof.

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

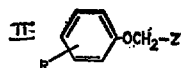


in which R represents a cyano group in the 2-position or an alkynyloxy group containing 3 to 6 carbon atoms and their physiologically acceptable acid addition salts.

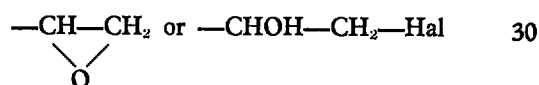
These compounds and their physiologically acceptable salts possess valuable pharmacological properties which may be of use in warm-blooded animals.

The new compounds may advantageously be prepared by the following processes in accordance with the present invention:—

a) Reaction of compounds of the general formula



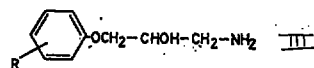
in which R is as hereinbefore defined and Z represents a



(in which Hal represents a halogen atom) group with N,N'-di-tertiary butylurea. The reaction may advantageously be carried out at a temperature between 150 and 220°C. The reactants may be either molten or dissolved in a high-boiling solvent.

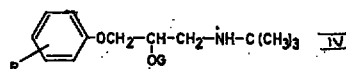
b) Reaction of compounds of the general formula II as hereinbefore defined with tertiary butylamine using known methods.

c) Introduction of the tertiary butyl group into primary amines of the general formula



in which R is as hereinbefore defined, by reaction with electrophilic tertiary butyl compounds for example, tertiary butyl halides using known methods.

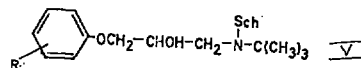
d) Cleavage of an easily removable protective group from compounds of the general formula



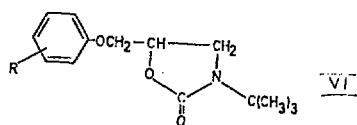
in which R is as hereinbefore defined and G represents a group readily removable by reduc-

tion or hydrolysis, for example an acyl or acetal group.

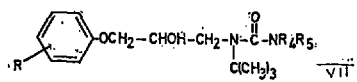
- 5 e) Removal, for example by hydrolytic or hydrogenolytic cleavage, of a readily removable protective group from an amine of the formula



- 10 in which R is as hereinbefore defined and Sch represents a group which is readily removable, for example a benzyl group or an acetyl group. f) Hydrolysis of an oxazolidinone of the formula

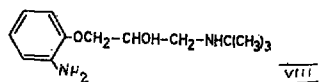


- 15 in which R is as hereinbefore defined, for example using a potassium hydroxide solution. g) Hydrolysis or pyrolysis of a substituted urea of the formula



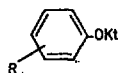
- 20 in which R is as hereinbefore defined and R₁ and R₅, which may be the same or different, each represent a hydrogen atom, an alkyl group (preferably a lower alkyl group), an aralkyl group or an aryl group (preferably a phenyl group). The hydrolysis is preferably effected by means of a strong base or a strong acid. The pyrolysis is preferably effected without the use of a catalyst.

- 25 h) For the preparation of the compound of the general formula I, in which R represents a cyano group in the 2-position, conversion of the compound of formula



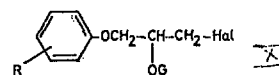
- 35 into the compound of formula I in which R represents a 2-cyano group by the Sandmeyer reaction in which the compound of the formula VIII is diazotised and heated with Cu(I)CN.

- 40 Some of the starting compounds required for the processes a) to h) are known and may be obtained by conventional processes, for example, from epoxides or halohydrins of formula II or compounds of the formula



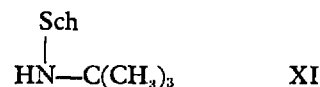
in which R is as hereinbefore defined and Kt represents a hydrogen atom or a cation, for example an alkali metal ion. The epoxides of formula II may readily be prepared from compounds of the formula IX by reaction with epichlorhydrin.

The compounds of the general formula III may be prepared from compounds of the formula II by reaction with ammonia. Compounds of the formula IV may, for example, be prepared by the reaction of the hydroxyl group of a halohydrin of formula II with a compound to form the protective group G, such as a vinyl ether or dihydropyran, and subsequent reaction of the compound of the formula

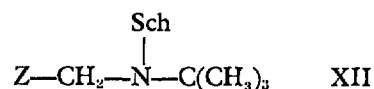


defined, thus obtained with tertiary butylamine.

Compounds of the general formula V may advantageously be prepared by the reaction of compounds of the general formula II with amines of the general formula



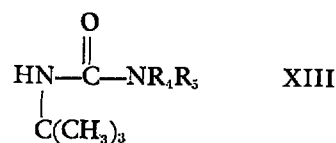
in which Sch is as hereinbefore defined, or by the reaction of a compound of the general formula IX, as hereinbefore defined, with compounds of the general formula



in which Z and Sch are as hereinbefore defined.

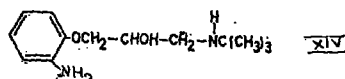
Oxazolidinones of the general formula VI may be prepared by the reaction of an epoxide of the general formula II with N-tertiary-butylurethane, prepared from chloroformic acid ethyl ester and tertiary butylamine, in the presence of LiOH.

A urea derivative of the general formula VII may be prepared, for example, according to the method described in Chem. Abstr. vol.58, p.3337c, by reacting an epoxide of the general formula II with a urea derivative of the formula



in which R₁ and R₅ are as hereinbefore defined. 1 - (2 - Aminophenoxy) - 2 - hydroxy - 3 -

tertiary - butylaminopropane of the formula VIII may be prepared by reduction of the corresponding nitro-compound of the formula



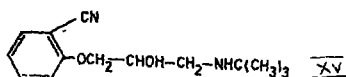
- 5 for example by means of catalytically activated hydrogen.

The compounds of the general formula I have an asymmetric carbon atom in the —CHOH grouping and may therefore occur in the form of racemates or optically active isomers. The optically active isomers may be prepared either by starting from optically active starting compounds or by resolving the racemates obtained into their optical isomers in a conventional manner. Resolution may advantageously be effected by fractional crystallisation of diastereomeric acid addition salts obtained, for example, by means of dibenzoyl- or toluyl-tartaric acid or 3-bromo-camphor-8-sulphonic acid.

The compounds of the general formula I obtained by process a) to h) may, if desired, be converted into their physiologically acceptable acid addition salts. Acids suitable for the formation of physiologically acceptable acid addition salts include, for example, hydrochloric acid, hydrobromic acid, sulphuric acid, methane-sulphonic acid, maleic acid, acetic acid, oxalic acid, lactic acid, tartaric acid and 8-chlorotheophylline.

The compounds of the general formula I and their physiologically acceptable acid addition salts have valuable pharmacological properties, particularly β -adrenolytic activity. They may, for example, be useful for the treatment or prophylaxis of diseases of coronary vessels and for the treatment of cardiac arrhythmias, in particular tachycardia, in human beings. The hypotensive properties of the compounds are also therapeutically interesting.

Substances in which the group R is in the 2-position may be particularly valuable therapeutically. 1-(2-cyanophenoxy)-2-hydroxy-3-tertiary-butylaminopropane of the formula



has proved especially effective. This compound has proved more effective and less toxic in animal tests both as regards bradycardial activity and isoproterenol-antagonistic activity [isoproterenol = 1 - (3,4 - dihydroxyphenyl)-1 - hydroxy - 2 - isopropylaminoethane] than 1 - (1 - naphthoxy) - 2 - hydroxy - 3 - isopropylaminopropane. Furthermore, the brady-

cardial activity occurs at very low doses and does not rise above a limiting value by the administration of larger doses. This indicates the absence of the undesired cardiodepressive activity normally associated with bradycardial activity. This compound possesses high anti-arrhythmic activity with strophanthin-G-intoxications and a good oral resorption.

1 - (2 - Propargyloxyphenoxy) - 2 - hydroxy- - 3 - tertiary - butylaminopropane is also a preferred compound.

The present invention further provides pharmaceutical compositions containing at least one of the compounds of the invention as herein defined in association with a pharmaceutical carrier or excipient. These compositions may also include other pharmacologically active compounds for example heart-active or circulation-active sympathicomimetics or coronary dilators. The compositions may be presented in a form suitable for oral, rectal or parenteral administration. Thus, for example, compositions for oral administration may be solid or liquid and may take the form of granules, tablets, coated tablets, capsules, syrups, emulsions, suspensions or drops, such compositions comprising carriers or excipients conventionally used in the pharmaceutical art. Thus, for example, suitable tableting excipients include lactose, potato and soluble starches and magnesium stearate.

For parenteral administration, the carrier may be a sterile, parenterally acceptable liquid such as sterile water, or a parenterally acceptable oil, e.g. arachis oil, contained in ampoules. Compositions for rectal administration may take the form of suppositories, the carrier comprising a suppository base.

Advantageously, the compositions may be formulated as dosage units, each unit being adapted to supply a fixed dose of active ingredient. Tablets, coated tablets, capsules, suppositories and ampoules are examples of suitable dosage unit forms. Each dosage unit preferably contains 1 to 300 mg, (0.016—5 mg/kg) active ingredient and especially 15 to 100 mg (0.25—1.66 mg/kg) of active ingredient for oral administration and 0.1 to 25 mg (0.002—0.4 mg/kg) for parenteral administration.

The following examples illustrate the preparation of compounds according to the invention, and also pharmaceutical compositions containing such compounds as active ingredients:—

EXAMPLE 1

1 - (2 - Cyanophenoxy) - 2 - hydroxy - 3-tertiary - butylaminopropane. HCl (according to process a)

2.56 g. (0.01 mol) of 1-(cyanophenoxy)-2-hydroxy-3-bromopropane are heated for two hours at 200°C in 20 ml. of tetralin with 3.44 g (0.02 mol) N,N'-di-tertiary-butylurea. After cooling, 20 ml. of ether are added and the

organic phase is agitated with dilute HCl. After separating the aqueous phase this is made alkaline with NaOH. The separated basic constituents are taken up in ether, the ether solution is separated and dried over MgSO_4 . The ether is distilled off, the remaining residue (1.5 g) is dissolved in a little ether and filtered. Ethereal HCl is added to the filtrate, whereby the hydrochloride separates. It is removed by filtration with suction and is twice recrystallised from a little ethanol.

Yield 0.4 g; m.p. 159—163°C.

EXAMPLE 2

1 - (2 - Cyanophenoxy) - 2 - hydroxy - 3 - tertiary - butylaminopropane. HCl (according to process b)

15 g (0.085 mol) 1-(2-cyanophenoxy)-2,3-epoxypropane are dissolved in 100 ml. ethanol and 18.6 g. (0.255 mol) of tertiary-butylamine are added. After standing the mixture for one hour at ambient temperature it is heated for two hours at 60 to 70°C and subsequently the volatile constituents are distilled off *in vacuo*. The residue is digested with dilute HCl and the insoluble constituents are removed by filtration with suction. The filtrate is then made alkaline with NaOH and the separated base is dissolved in ether. After drying the ether solution over MgSO_4 the ether is distilled off and the remaining residue is dissolved in ethanol. By adding ethereal HCl the hydrochloride is separated in crystalline form. Purification is effected by recrystallisation of the product from ethanol by the addition of ether.

Yield 9.8 g; m.p. 163—165°C.

EXAMPLE 3

1 - (2 - Propargyloxyphenoxy) - 2 - hydroxy - 3 - tertiary - butylaminopropane oxalate (according to process b)

7.15 g. (0.035 mol) of 1-(2-propargyloxyphenoxy)-2,3-epoxypropane are dissolved in 70 ml of ethanol, 11g (0.15 mol) of tertiary-butylamine are added and boiling is effected for two hours under reflux. After cooling, the solvent is distilled off *in vacuo* and the oily residue is digested with dilute HCl. The aqueous phase is extracted with ether, the aqueous acidic solution is then made alkaline with NaOH. The oily base which separates is taken up in ether, the organic phase is washed with water and dried over MgSO_4 . After distilling off the ether, the residue is dissolved in absolute ether and a solution of 2g. of oxalic acid in 10 ml. of acetone is added. The precipitated oxalate is recrystallised from ethanol with addition of ether.

Yield 4.6 g; m.p. 132—134°C.

EXAMPLE 4

1 - (2 - Cyanophenoxy) - 2 - hydroxy - 3 - tertiary - butylaminopropane. HCl (according to process d)

1.66 g. (0.005 mol) of 1-(2-cyanophenoxy)-2 - tetrahydropyranyloxy - 3 - tertiary - butylaminopropane oxalate are heated in 5 ml. dilute HCl for two hours on a boiling water

bath. After cooling the mixture, it is made alkaline with NaOH and the base which separates is taken up in ether. The ethereal solution is dried over MgSO_4 and the ether is evaporated *in vacuo*. The residue is worked up in the same way as in Example 1. The melting point and mixed melting point and Rf value on thin layer chromatography of the hydrochloride are identical to those of the compound described in Examples 1 and 2.

The tetrahydropyranyl ether used as the starting material is prepared as follows:

7.8 g. (0.05 mol) of 1-(2-cyanophenoxy)-2-hydroxy-3-bromopropane are stirred with 16.8g (0.02 mol) of dihydropyran and a spatula tip of *p*-toluene-sulphonic acid. A slight exothermic reaction occurs and the temperature reaches about 35°C. The mixture is then heated for 30 minutes at 50—60°C. It is then dissolved in 100 ml. of benzene and 15 ml of tertiary-butylamine are added. After leaving the mixture for two hours at ambient temperature, it is heated under reflux for 6 hours and then evaporated *in vacuo*. The residue is dissolved in ether and agitated with water. The organic phase is dried over MgSO_4 , the ether is distilled off and the residue (11.9 g) is dissolved in a little ether. This solution is combined with an ethereal solution of oxalic acid, and the oxalate crystallises out. The product is separated and recrystallised from acetonitrile. The oxalate melts with decomposition at 102—105°C.

EXAMPLE 5

1 - (2 - Cyanophenoxy) - 2 - hydroxy - 3 - tertiary - butylaminopropane. HCl (according to process e)

2 g of 1 - (2 - cyanophenoxy) - 2 - hydroxy - 3 - (N - acetyl - N - tertiary - butylamino) - propane are mixed in 20 ml. of ethanol with a solution of 4g. KOH dissolved in 6 ml of H_2O . The mixture is then heated under reflux with stirring for two hours. The alcohol is then distilled off *in vacuo*. The residue is acidified with dilute HCl, extracted twice with ether, the aqueous phase is made alkaline with NaOH and the deposited base is extracted into ether. The ethereal solution is dried over MgSO_4 , the ether is distilled off and 650 mg. of a crude base is left as a residue which is dissolved in a little ethanol. After adding an ethereal HCl solution, colourless crystals separate, which are recrystallised from ethanol/ether: m.p. 160—163°C.

EXAMPLE 6

1 - (2 - Cyanophenoxy) - 2 - hydroxy - 3 - tertiary - butylaminopropane. HCl (according to process g)

3.5 g (0.011 mol) of $\text{N}_2\text{N}'$ -di-tertiary-butyl-N - [(2 - hydroxy - 3 - 0 - cyanophenoxy) - propyl] - urea are heated for two hours at 200°C in 10 ml tetralin with the addition of a spatula tip of LiCl. The cooled solution is then agitated with dilute HCl. After separation, the aqueous phase is made alkaline with NaOH

and the base which separates is extracted into ether. The ether solution is separated, dried over MgSO_4 and evaporated *in vacuo*. The residue is dissolved in a little ethanol, and ethereal HCl solution is added and the hydrochloride which separates is removed by filtration with suction. After dissolving and reprecipitating from ethanol, with the addition of ether, the hydrochloride melts at 157—161°C.

EXAMPLE 7

(-) - 1 - (2 - Cyanophenoxy) - 2 - hydroxy - 3 - tertiarybutylaminopropane. HCl (preparation by racemate separation)

24.8 g (0.1 mol) of 1-(2-cyanophenoxy)-2-hydroxy - 3 - tertiary - butylaminopropane (racemic) are dissolved in 100 ml. absolute methanol and combined with a solution of 38.6 g (0.1 mol) of (-)-di-*p*-toluyl-tartaric acid in 150 ml. abs. methanol. After standing for several hours at ambient temperature the solution is filtered and left to stand for three days at 20°C. The slowly crystallising di-*p*-toluyl-tartrate is then removed by filtration with suction and recrystallised again in the same way. 18.2g of (-) - 1 - (2 - cyanophenoxy) - 2 - hydroxy - 3 - tertiary - butylaminopropane - di - *p* - toluyl - tartrate with a m.p. of 135—137°C (decomposition) is obtained.

$[\alpha]_D^{20} = -90.5^\circ$ (in methanol).

6 g. of this tartrate are agitated in 100 ml. of ether and 50 ml. of N NaOH. The organic phase is separated and dried over MgSO_4 . After filtration ethereal HCl is added, and crystallisation occurs. 2.4 g of hydrochloride (m.p. 161—164°C) are obtained:

$[\alpha]_D^{20} = +14.7^\circ$ (in methanol).

From the mother liquor (methanolic) of said di-*p*-toluyl-tartrate, after evaporating the methanol *in vacuo*, it is possible to obtain the dextrorotatory isomer and by treatment with NaOH the base may be obtained. It may be separated with the aid of ethereal HCl from a solution in ether as hydrochloride.

EXAMPLE 8

Depot dragees

Core

1-(2-Cyanophenoxy)2-hydroxy-3-tertiary butylaminopropane.HCl	40.0 mg.
Carboxymethyl cellulose (CMC)	300.0 mg.
Stearic acid	20.0 mg.
Cellulose acetate phthalate (CAP)	40.0 mg.
	400.0 mg.

The active substance is mixed intensively with the CMC and the stearic acid and the mixture is granulated in the conventional manner, using a solution of CAP in 200 ml of a mixture of ethanol/ethyl acetate. The granulate is then pressed into 380 mg cores which may be coated in the conventional manner with a sugary 5% solution of polyvinyl pyrrolidone in water. Each dragee contains 25 mg. of active substance.

EXAMPLE 9

Injection solution

The solution is prepared from the following constituents:

1-(2-propargyloxyphenoxy)-2-hydroxy-3-tertiary-butylamino-propane.HCl	2.5 parts
Sodium salt of EDTA (ethylene-diamine tetraacetic acid)	0.2 part
Distilled water	ad 100.0 parts

The active substance and the EDTA salt are dissolved in sufficient water and made up with water to the desired volume. The solution is filtered free of suspended particles into 1 cc. ampoules under aseptic conditions. Finally the ampoules are sterilised and sealed. Each ampoule contains 25 mg. of active substance.

EXAMPLE 10

Gelatine capsules

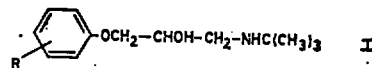
(-) - 1 - (2 - cyanophenoxy) - 2 - hydroxy - 3 - tertiary butylamino - propane.HCl	25.0 mg.
Maize starch	175.0 mg.
	200.0 mg.

The ingredients used to fill the capsule are intensively mixed and 200 mg portions of the mixture are filled into gelatine capsules of suitable size. Each capsule contains 25 mg of the optically active substance.

We are the Proprietors of British Patents Nos. 1,194,548 and 1,201,460. We make no claim herein to pharmaceutical compositions which contain a compound of formula I as herein defined or a physiologically acceptable acid addition salt thereof and also a coronary dilator as defined in claim 1 of Patent No. 1,194,548 or a compound of component (a) as specified in claim 1 of Patent No. 1,201,460. Subject to the foregoing disclaimer,

WHAT WE CLAIM IS:—

1. Compounds of the general formula



in which R represents a cyano group in the 2-position or an alkynyloxy group containing 3 to 6 carbon atoms and their physiologically acceptable acid addition salts.

2. Compounds as claimed in claim 1 in which R represents a 2-alkynyloxy group.

3. 1 - (2 - Cyanophenoxy) - 2 - hydroxy - 3 - tertiarybutylaminopropane and its physiologically acceptable acid addition salts.

4. 1 - (2 - Propargyloxyphenoxy) - 2 - hydroxy - 3 - tertiarybutylamino propane and its physiologically acceptable acid addition salts.

5. Compounds as claimed in any of the preceding claims in which the said physiologically



* C L M S *

and the base which separates is extracted into ether. The ether solution is separated, dried over MgSO_4 and evaporated *in vacuo*. The residue is dissolved in a little ethanol, and ethereal HCl solution is added and the hydrochloride which separates is removed by filtration with suction. After dissolving and reprecipitating from ethanol, with the addition of ether, the hydrochloride melts at 157—161°C.

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Sodium salt of EDTA (ethylenediamine tetraacetic acid)	0.2 part
Distilled water	ad 100.0 parts

The active substance and the EDTA salt are dissolved in sufficient water and made up with water to the desired volume. The solution is filtered free of suspended particles into 1 cc. ampoules under aseptic conditions. Finally the ampoules are sterilised and sealed. Each ampoule contains 25 mg. of active substance.

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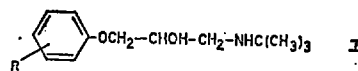
(-) - 1 - (2 - cyanophenoxy) - 2 -	
hydroxy - 3 - tertiary butylamino -	
propane.HCl	25.0 mg.
Maize starch	175.0 mg.
	200.0 mg.

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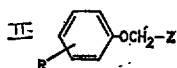
4. 1 - (2 - Propargyloxyphenoxy) - 2 - hydroxy - 3 - tertiarybutylamino propane and its physiologically acceptable acid addition salts.

5. Compounds as claimed in any of the preceding claims in which the said physiologically

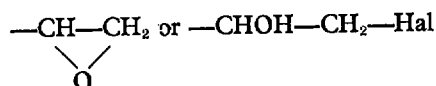
acceptable acid addition salts are addition salts with hydrochloric acid, hydrobromic acid, sulphuric acid, oxalic acid, lactic acid, tartaric acid or 8-chlorotheophylline.

- 5 6. Compounds as claimed in claim 1 as herein specifically described, being other than as claimed in claim 3 or claim 4.

- 10 7. A process for the preparation of compounds of the formula I, as defined in claim 1, in which a compound of the formula



in which R is as defined in claim 1 and Z represents a



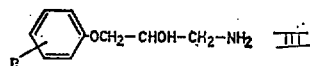
- 15 (in which Hal represents a halogen atom) group is reacted with N,N'-di-tertiary butyl urea whereby a compound of the formula I is obtained.

- 20 8. A process as claimed in claim 7, in which the reaction is effected at a temperature between 150 and 220°C.

9. A process as claimed in claim 7 or claim 8 in which the reaction is effected in the presence of a high-boiling solvent.

- 25 10. A process for the preparation of compounds of the formula I, as defined in claim 1, in which a compound of the formula II, as defined in claim 7, is reacted with tertiary-butylamine whereby a compound of the formula I is obtained.

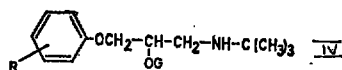
- 30 11. A process for the preparation of compounds of the formula I, as defined in claim 1, in which a compound of the formula



- 35 in which R is as defined in claim 1, is reacted with an electrophilic tertiary-butyl compound whereby a compound of formula I is obtained.

- 40 12. A process as claimed in claim 11 in which the said electrophilic tertiary-butyl compound is a tertiary-butyl halide.

13. A process for the preparation of compounds of the formula I, as defined in claim 1, in which a compound of the formula

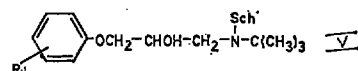


- 45 in which R is as defined in claim 1 and G represents a group readily removable by reduction or hydrolysis is reduced or hydrolysed

whereby a compound of formula I is obtained.

14. A process as claimed in claim 13, in which G represents a acyl group or an acetal group.

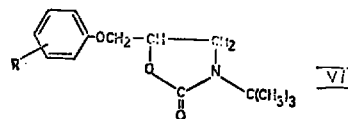
15. A process for the preparation of compounds of the formula I, as defined in claim 1, in which a compound of the formula



in which R is as defined in claim 1 and Sch represents a readily removable group, is reacted to remove the group Sch whereby a compound of the formula I is obtained.

16. A process as claimed in claim 15 in which Sch represents a benzyl group or an acetyl group.

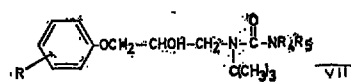
17. A process for the preparation of compounds of the formula I, as defined in claim 1, in which a compound of the formula



in which R is as defined in claim 1, is hydrolysed whereby a compound of the formula I is obtained.

18. A process as claimed in claim 17 in which the hydrolysis is effected using a potassium hydroxide solution.

19. A process for the preparation of compounds of the formula I, as defined in claim 1, in which a compound of the formula



in which R is as defined in claim 1 and R₄ and R₅ which may be the same or different each represent a hydrogen atom, an alkyl group, an aralkyl group or an aryl group, is subjected to hydrolysis or pyrolysis whereby a compound of the formula I is obtained.

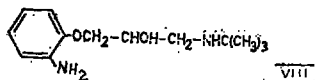
20. A process as claimed in claim 19 in which R₄ and R₅ each represent a lower alkyl group, or a phenyl group.

21. A process as claimed in claim 19 or claim 20 in which the hydrolysis is effected by means of a strong base or a strong acid.

22. A process as claimed in claim 19 or claim 20 in which the pyrolysis is effected in the absence of a catalyst.

23. A process for the preparation of a compound of the formula I as defined in claim 1 in which R represents a cyano group in the 2-position, in which a compound of the formula





is diazotised and heated with Cu(I)CN whereby the compound of formula I is obtained.

24. A process as claimed in any of claims 7 to 23 in which the compound of formula I obtained is converted into a physiologically acceptable acid addition salt.

25. A process as claimed in any of claims 7 to 24 in which the compound of formula I or acid addition salt thereof is obtained as a racemic mixture which is subsequently resolved into its optically active isomers.

26. A process for the preparation of compounds as claimed in claim 1 in the form of optically active isomers in which a compound of formula I in the form of a racemic mixture is resolved into its optically active isomers.

27. A process as claimed in claim 25 or claim 26 in which resolution is effected by fractional crystallisation of diastereomeric acid addition salts.

28. A process as claimed in any of claims 7 to 27 substantially as herein described.

29. A process for the preparation of compounds as claimed in claim 1, substantially as herein described in any of Examples 1 to 7.

30. Compounds as claimed in claim 1, when prepared by a process as claimed in any of claims 7 to 29.

31. Pharmaceutical compositions comprising a compound of the general formula I, as defined in claim 1, or a physiologically acceptable

acid addition salt thereof together with a pharmaceutical carrier or excipient.

32. Compositions as claimed in claim 31 in the form of tablets, coated tablets, solutions or emulsions.

33. Compositions as claimed in claim 31 or claim 32 in the form of dosage units.

34. Compositions as claimed in claim 33 in which each dosage unit contains 1 to 300 mg. of a compound as claimed in any of claims 1 to 6 and 30.

35. Compositions as claimed in claim 34 for oral administration in which each dosage unit contains from 15 to 100 mg. of a compound as claimed in any of claims 1 to 6 and 30.

36. Compositions as claimed in claim 33 for parenteral administration in which each dosage unit contains from 0.1 to 25 mg. of a compound as claimed in any of claims 1 to 6 and 30.

37. Compositions as claimed in any of claims 31 to 36 containing a further pharmacologically active substance.

38. Compositions as claimed in claim 37 in which the said further pharmacologically active substance is a heart or circulation-active sympathicomimetic or a coronary dilator.

39. Pharmaceutical compositions as claimed in claim 31 substantially as herein described.

40. Pharmaceutical compositions substantially as herein described in any of Examples 8 to 10.

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