

PATENT SPECIFICATION

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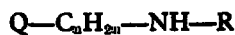
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(54) N-AMINOALKYL-HETEROCYCLES, METHODS FOR
 THEIR PREPARATION AND COMPOSITIONS CONTAINING
 THEM

(71) We, BOEHRINGER INGELHEIM GMBH, a Body Corporate orga-
 nised under the laws of the Federal Republic of Germany of Ingelheim am Rhein,
 Federal Republic of 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:—

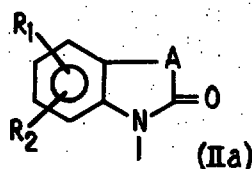
The invention relates to novel aminoalkyl heterocycles having interesting pharma-
 cological properties and being of use in the preparation of other pharmacologically
 active compounds.

According to one feature of the present invention there are provided compounds
 of general formula

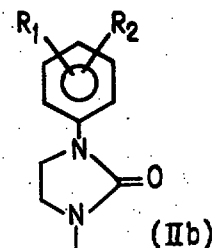


(I)

[wherein Q represents a group of the formula



or

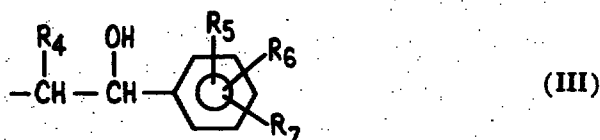


in which R₁ represents a hydrogen or halogen atom, a C₁-C₄ alkyl or alkoxy group,
 a trifluoromethyl group or an amino group and R₂, which may be the same or different
 to R₁, represents a hydrogen or halogen atom, a C₁-C₄ alkyl or alkoxy group or a tri-
 fluoromethyl group; or R₁ and R₂ together represent a methylenedioxy or ethylene-
 dioxy group; and

A represents a bivalent group of the formula $\text{—NR}_3\text{—}$ (in which R_3 represents a hydrogen atom or a C_{1-4} alkyl group), $\text{—OCH}_2\text{—}$ (in which the oxygen atom is linked to the benzene ring), —O— or $\text{—CH}_2\text{—CH}_2\text{—}$;

n represents an integer from 2 to 6; and

R represents a hydrogen atom or a benzyl group or group of the formula



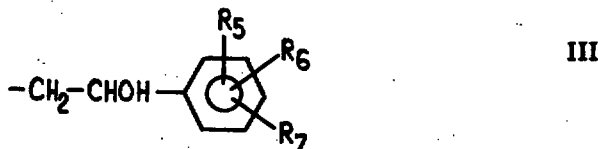
(in which R_4 represents a hydrogen atom or a methyl or ethyl group;

R_5 , R_6 and R_7 , which may be the same or different, represent hydrogen or halogen atoms or hydroxymethyl, trifluoromethyl, C_{1-4} alkyl, nitro, cyano or methylsulphonylmethyl groups, or groups of the formula $\text{—CONHR}_3'$, —CONHOH , $\text{—COOR}_3'$ or $\text{R}_3'\text{O}$ or a group of the formula $\text{—NR}_3'\text{R}$, when none of any remaining substituents R_5 , R_6 or R_7 are halogen atoms or trifluoromethyl groups, (wherein R_3' represents a hydrogen atom or a C_{1-4} alkyl group, R_3' represents a hydrogen atom or a C_{2-20} acyl, C_{1-4} alkyl or aralkyl (with 1 to 4 carbon atoms in the alkyl moiety) group, and R_3' represents a hydrogen atom or a C_{1-4} acyl, methanesulphonyl, carbamoyl, dimethylsulphamoyl or C_{2-20} alkoxycarbonyl group); R_3 represents a group of the formula —CO—NH—NH_2 and R_3 and R_3' are as hereinbefore defined; or R_3 and R_3' taken together represent a bivalent group of the formula $\text{—OCH}_2\text{O—}$, $\text{—OCH}_2\text{CH}_2\text{O—}$, —CH=CH—CH=CH— , $\text{—OCH}_2\text{—CONH—}$, $\text{—CH}_2\text{—CH}_2\text{—CO—NH—}$ or —O—CO—NH— and R_3 is as hereinbefore defined) with the proviso that when Q represents a group of formula IIb (in which one of R_1 and R_2 is hydrogen and the other is hydrogen halogen, C_{1-4} alkyl or alkoxy, or trifluoromethyl) and n represents an integer of from 2 to 4, then R is other than hydrogen or benzyl] and salts thereof.

The compounds of general formula I may exist in the form of racemates and optical isomers and it will be appreciated that all such forms of the compounds of general formula I are within the scope of the present invention.

The compounds of general formula I and the physiologically acceptable salts thereof possess interesting pharmacological properties. In particular they show a coronary-dilating action and may be useful as antihypertonic, antihypertensive, broncholytic and bloodflow enhancing agents. They also show a central nervous system effect, having an anti-depressive action.

Preferred compounds according to the invention by virtue of their especially favourable properties are compounds in which: Q represents a group of the formula IIa or IIb (wherein R_1 represents a hydrogen atom or a methoxy or amino group; and R_2 represents a hydrogen atom or a methoxy group); n represents an integer from 3 to 6; R represents a hydrogen atom or a group of the formula

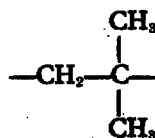


[wherein R_5 represents a hydrogen or halogen atom or a hydroxymethyl or cyano group or a group of the formula $\text{—CONHR}_3'$, $\text{R}_3'\text{O}$, or $\text{—NHR}_3'$ (wherein R_3' is as hereinbefore defined), R_6 represents a hydrogen atom or a C_{2-20} acyl, methyl or benzyl group and R_7 represents a hydrogen atom or a formyl, acetyl, methylsulfonyl, carbamoyl or dimethylsulphamoyl group), R_3 represents a hydrogen or halogen atom or a hydroxy group; and R_7 represents a hydrogen or chlorine atom or a methyl or methoxy group, with the proviso that R_3 does not represent a group of the formula $\text{—NHR}_3'$, when R_3 and/or R_7 represent halogen atoms.

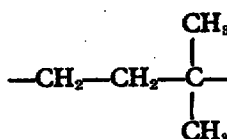
Particularly preferred compounds of general formula I by virtue of there especially favourable properties are those wherein: Q represents a group of formula IIa or IIb (in which R_1 represents a hydrogen atom or a methoxy or amino group; and R_2 represents a hydrogen atom or a methoxy group); R represents a hydrogen atom or a group of formula III in which R_1 represents a hydrogen atom or a hydroxy group and, R_2 represents a hydrogen or chlorine atom or a hydroxy, hydroxymethyl or cyano group or a group of the formula CONHR_3' or $\text{R}_3'\text{O}$ (wherein R_3' is as hereinbefore defined,

and R_4 represents a benzyl or C_1-C_4 saturated carboxylic acyl group), or R_5 and R_6 taken together represent a group of the formula $-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$, $-\text{OCH}_2\text{CONH}-$, $-\text{CH}_2-\text{CH}_2-\text{CO}-\text{NH}-$ or $-\text{O}-\text{CONH}-$; and R_7 represents a hydrogen or chlorine atom or a methyl, methoxy or hydroxy group.

In the compounds of general formula I the $-\text{C}_n\text{H}_{2n}-$ group is preferably a group of the formula $-\text{CH}_2-\text{CH}_2-$, $-\text{CH}_2-\text{CH}_2-\text{CH}_2-$, or



and above all a



group (wherein the tertiary carbon atom is linked to the nitrogen atom of the ethanolamine).

Especially preferred compounds by virtue of their particularly favourable properties are the following:—

1 - (3,4 - Methyleneedioxyphenyl) - 2 - [1,1 - dimethyl - 3 - (2 - oxo - benzimidazolidin - 1 - yl) - propylamino] - ethanol;

1 - (3,4 - Methyleneedioxyphenyl) - 2 - [1,1 - dimethyl - 3 - (3 - methyl - 2 - oxo - benzimidazolidin - 1 - yl) - propylamino] - ethanol;

1 - (3 - methylcarbamoyl - 4 - hydroxyphenyl) - 2 - [1,1 - dimethyl - 3 - (1,2,3,4 - tetrahydro - 2 - oxo - quinol - 1 - yl) - propylamino] - ethanol;

1 - (3 - methylcarbamoyl - 4 - hydroxyphenyl) - 2 - [1,1 - dimethyl - 3 - (3 - methyl - 2 - oxo - benzimidazolidin - 1 - yl) - propylamino] - ethanol;

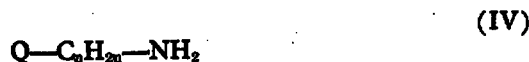
and the salts thereof.

The compounds of general formula I according to the invention and the salts thereof as well as possessing interesting pharmacological properties hereinbefore described may also be useful as intermediates in the preparation of other pharmacologically active compounds.

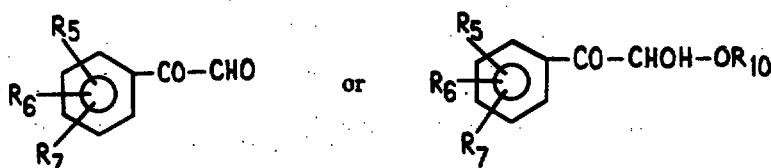
It will be appreciated that the salts of the compounds of general formula I (as hereinbefore defined) for use in medicine should be pharmacologically acceptable. Other salts, however, may be useful in the preparation of further compounds according to the invention or the pharmacologically acceptable salts thereof or, as stated above, as intermediates in the preparation of other pharmacologically active compounds.

The compounds of general formula I according to the invention may be prepared according to the following processes, which processes constitute further features of the present invention:—

1. (for the preparation of compounds of general formula I wherein R represents a group of formula III in which R_4 is hydrogen), by reacting an amine of formula



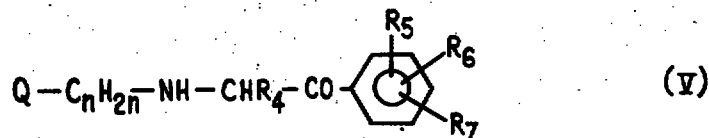
(wherein Q and n are as hereinbefore defined) with a compound of formula



(wherein R_5 , R_6 and R_7 are as hereinbefore defined and R_{10} represents a hydrogen atom or an alkyl group) under the conditions of reductive amination.

This reaction is preferably effected using a complex metal hydride as the reducing agent, and advantageously sodium borohydride. Alternatively, hydrogen in the presence of a hydrogenation catalyst, such as, for example, platinum, palladium or nickel, may be used.

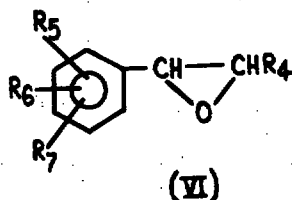
2. (for the preparation of compounds of general formula I wherein R represents a group of formula III), by reducing a compound of formula



(wherein Q, n, R₄, R₅, R₆ and R₇ are as hereinbefore defined).

The reduction is preferably effected with a complex metal hydride, and in particular, sodium borohydride, or alternatively by catalytic hydrogenation with conventional hydrogenation catalysts, such as, for example, platinum, palladium or nickel.

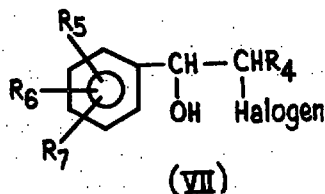
3. (for the preparation of compounds of general formula I wherein R represents a group of formula III), by reacting a compound of formula



(wherein R₄, R₅, R₆ and R₇ are as hereinbefore defined) with an amine of formula IV as hereinbefore defined.

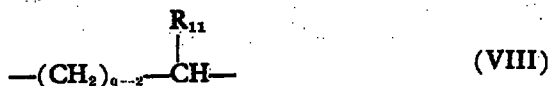
The reaction is preferably effected in the presence of an acid-binding agent, such as, for example, potassium or sodium carbonate or an excess of the amine of formula IV.

It should also be appreciated that the starting compound of formula VI may be replaced by a compound of formula

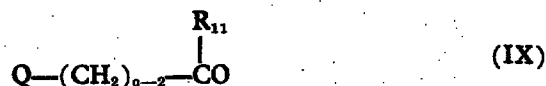


(wherein R₄, R₅, R₆ and R₇ are as hereinbefore defined) which under the reaction conditions will be converted to a compound of formula VI.

4. (for the preparation of compounds of general formula I wherein the group $-C_nH_{2n}-$ is a group of the formula



in which the group R₁₁ represents a hydrogen atom or a methyl group and q is an integer from 3 to 6), by reductive amination of a compound of formula



(wherein Q, q and R₁₁ are as hereinbefore defined) with a compound of formula



(wherein R is as hereinbefore defined). The reaction is preferably effected by using a complex metal hydride such as sodium borohydride as the reducing agent or alterna-

tively by hydrogenation in the presence of a hydrogenation catalyst such as platinum, palladium or nickel.

In this reaction process the starting compounds IX and X may be replaced by compounds of formula



(wherein Q, q, R and R_{11} are as hereinbefore defined) whereby compounds of general formula I may be produced by reaction as described above.

5. (for the preparation of compounds of general formula I, wherein R represents a group of formula (III), by the reductive removal of the $-CH_2$ -aryl group from a compound of formula



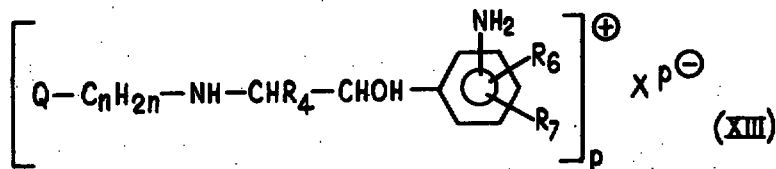
(wherein Q and n are as hereinbefore defined and R' represents a group of formula III).

In the above reaction the reductive elimination of the $-CH_2$ -aryl group is preferably effected by catalytic hydrogenation with catalytic hydrogenation with catalysts such as platinum, palladium or nickel.

6. (for the preparation of compounds of general formula I wherein at least one of R_s to R_r represents a hydroxy group), by removing the arylmethyl group(s) from a compound of formula I wherein one or more of the hydroxy groups is arylmethylated.

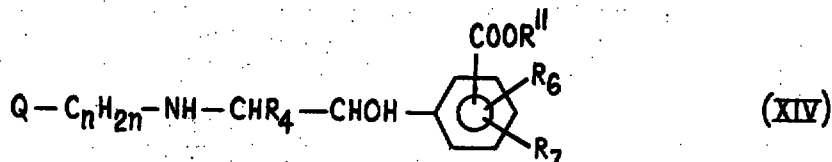
The removal of the arylmethyl group(s) may if desired be effected by catalytic hydrogenation using catalysts such as platinum, palladium, nickel, or ether-cleaving acids, such as, for example, hydrohalic acids or boron-tribromide.

7. (for the preparation of compounds of general formula I wherein R_s represents an $NH-C_1-C_4$ acyl or $NH-CO-NH_2$ group), by reacting a compound of the formula



(wherein Q, n, R_s , R_4 and R_7 are as defined above, X represents an anion and p represents the charge on the anion), with an appropriate carboxylic acid anhydride for the introduction of an acyl group or with a cyanate and acid for the introduction of a carbamoyl group, in the additional presence of at least one equimolar quantity of an acid. The additional acid is necessary for the protection of the secondary amino group by salt formation.

8. (for the preparation of compounds of general formula I wherein R_s represents a $CONHR_s'$, $CONHNH_2$ or $CONHOH$ group), by reacting an ester of the formula

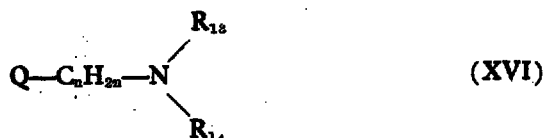


(wherein Q, n, R_s , R_4 and R_7 are as hereinbefore defined and R'' represents an alkyl or substituted alkyl group) with a compound of formula



(wherein R_{12} represents a hydrogen atom or a C_{1-4} alkyl, hydroxy or amino group).

9. (for the preparation of compounds of general formula I wherein R represents a hydrogen atom or a benzyl group), removing the protecting group(s) from a compound of formula



(wherein Q and n are as hereinbefore defined; R₁₃ represents an arylmethyl, acyl or COOR₁₅ group (in which R₁₅ represents an alkyl, aryl or alkylmethyl group) and R₁₄ represents a hydrogen atom or an arylmethyl group, e.g. a benzyl group, or R₁₃ and R₁₄ together form a dicarboxylic acid group, preferably a succinyl or phthalyl group, or a group CHR₁₅).

If in the compounds of formula XVI, R₁₃ represents an acyl or COOR₁₅ group or R₁₃ and R₁₄ together represent a dicarboxylic acid or CHR₁₅ group, the protecting groups are preferably removed hydrolytically. If R₁₃ and R₁₄ together represent a dicarboxylic acid group, for example phthalyl, the reaction may be effected by first cleaving with hydrazine followed by hydrolysis. When R₁₃ and/or R₁₄ represent arylmethyl groups, the removal of the protecting groups is advantageously effected by hydrogenolytic cleavage in the presence of hydrogenation catalysts such as platinum, palladium or nickel. Hydrogenolytic removal of the protecting groups is also possible, when in the group COOR₁₅, R₁₅ represents an arylmethyl group.

10. (for the preparation of compounds of general formula I wherein R represents a hydrogen atom), by reducing the nitro group in a compound of formula



(wherein Q and n are as hereinbefore defined) preferably by catalytic hydrogenation with conventional catalysts, for example, nickel.

Racemic mixtures produced by any of the above processes may be resolved into the optical isomers of the corresponding compounds of general formula I by conventional methods.

The basic compounds of general formula I produced by any of the above processes may, if desired, be converted into the salts thereof by conventional methods, and when produced as salts they may be converted into salts of other acids or into free bases.

Suitable acids for the preparation of acid addition salts of the compounds of general formula I (as hereinbefore defined) are, for example, hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, lactic acid, citric acid, and maleic acid.

The starting materials used in any of the above processes according to the invention may be obtained by methods known *per se*.

As stated above the compounds of general formula I show interesting pharmacological properties and in tests which we have conducted it has become evident that with compounds wherein R represents a group of formula III, the substitution in this group influences the preferred scope of action of the compound concerned.

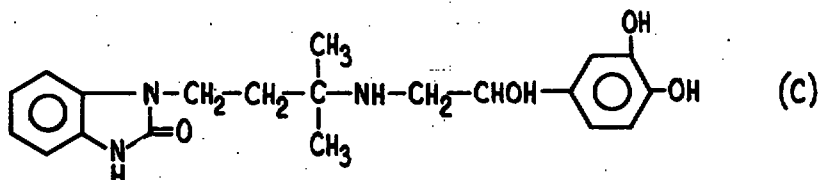
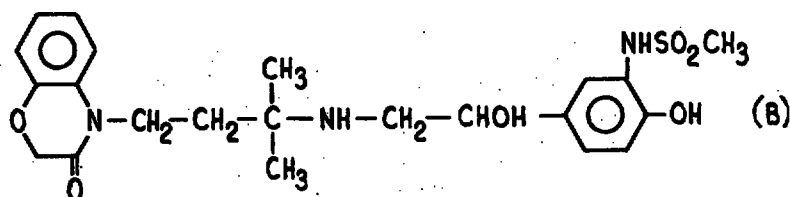
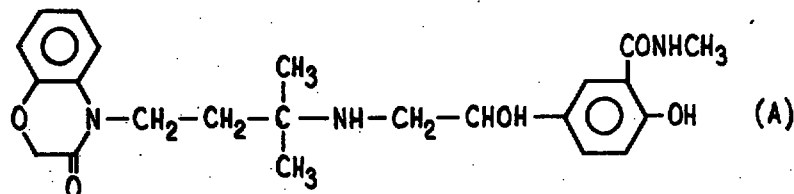
For example, when R₅, R₆ and R₇ represent lipophilic groups and/or if they give to the group III a lipophilic character (for example when R₅, R₆, R₇ represent hydrogen or halogen atoms or alkoxy, amino, alkyl or trifluoromethyl groups, or when R₇ represents a hydrogen atom and R₅ and R₆ together represent an ethylenedioxy group or, preferably a methylenedioxy group) the compounds concerned possess an advantageous anti-depressive activity.

In addition, our tests have shown that when R₅, R₆ and R₇ represent NH-acyl, amino, hydroxymethyl or OR₈ (in which R₈ represents a hydrogen atom or an acyl or aralkyl group) groups or R₅ and R₆ together represent one of the groups —OCH₂—CONH—, —CH₂—CH₂—CONH— and —O—CO—NH—, and R₇ simultaneously represents a hydroxy group, the most important activity is in general the vaso-dilating action, for example the dilation of peripheral blood-vessels, and the broncholytic action.

Furthermore, we have found that when, for example, R₅ represents a group OR₉ (wherein R₉ represents a hydrogen atom or an acyl or aralkyl group), R₆ represents a

group CONHR₃ and R₇ is preferably a hydrogen atom, the antihypertensive activity will generally be important.

The following compounds have been tested for their pharmacological activities:



Compound B has been tested to determine the peripheral dilation of vessels in the dog and has shown a half-life time 22 times longer and an action 18 times stronger than those of the commercially available product, Isoxsuprine. The bloodflow after arterial administration was measured in the left hind extremity.

In awake, genetically hypertonic rats, compound A has given results showing a decrease in the blood-pressure of 85 mmHg at a dose of 30 mg/kg i.p. With compound C the broncholytic ED₅₀ (intravenous) in the guinea pig was found to be 0.09 µg/kg, while for the commercial product Isoproterenol the corresponding ED₅₀-value is 3.0 µg/kg.

According to a further feature of the present invention there are provided pharmaceutical compositions comprising as active ingredient at least one compound of formula I (as hereinbefore defined) or a physiologically acceptable salt thereof in association with a pharmaceutical carrier or excipient.

The pharmaceutical compositions according to the invention can, for example, be in a form suitable for oral, rectal or parenteral administration. Suitable forms of administration are, for example, tablets (e.g. coated tablets), capsules, tinctures, injection solutions, suppositories or inhalation preparations.

If desired, the compositions according to the invention can be in dosage unit form. Such dosage units conveniently contain from 1 to 500 mg, and preferably 2 to 200 mg of active ingredient per dosage unit. In general, the precise quantity of active ingredient depends on the form of administration, the body weight of the person to be treated and the particular active ingredient used. It should also be appreciated that for sustained release forms of administration dosage units containing higher amounts of the active ingredient(s) may be used.

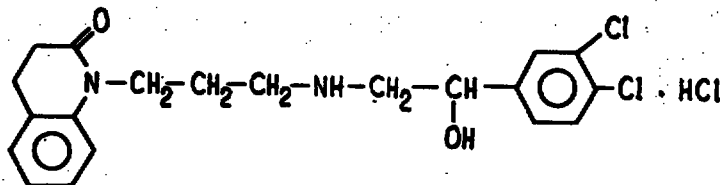
Tablets may, for example, be obtained by mixing the active ingredient with known excipients, for example with inert diluents such as calcium carbonate, magnesium stearate or talcum and/or agents for obtaining sustained release, such as carboxypoly-methylene, carboxymethyl cellulose, cellulose acetatephthalate or polyvinyl acetate. The tablets may, if desired, consist of several layers, for example to obtain sustained release or to avoid incompatibilities. Coated tablets may be obtained by coating tablet cores prepared analogously to the tablets described above, with agents commonly applied for tablet coating, for example, polyvinylpyrrolidone, shellac, gum arabic, talcum, titanium dioxide or sugar. To obtain sustained release or for avoiding incompatibilities the core may also consist of several layers. The tablet coating may also consist of several layers whereby the excipients mentioned above for tablets may be used.

Capsules comprising the active ingredient according to the invention may be pro-

duced, for example, by mixing the active ingredient with inert carriers such as lactose or sorbitol and filling gelatin capsules with the mixture.

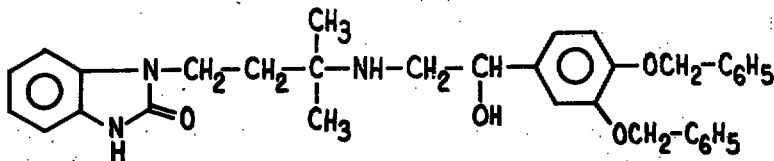
The following Examples illustrate the preparation of compounds according to the invention and pharmaceutical compositions containing them:—

Example 1.



5.36 g of 3,4-dichlorophenylglyoxal hydrate and 4.5 g of 1-(3-aminopropyl)-1,2,3,4-tetrahydroquinolin-2-one are heated to 50°C in 200 ml of ethanol for 1 hour. The reaction mixture is then mixed with 5 g of sodium borohydride with cooling to 0 to 5°C. After stirring for 2 hours at room temperature, the reaction mixture is acidified with hydrochloric acid, the ethanol distilled off and the basic compound recovered. 5.5 g of the base of the above shown salt (m.p. 95°C) are obtained, yielding on acidification with the calculated quantity of ethereal hydrochloric acid, the hydrochloride (m.p. 185°C).

Example 2.



11 g of 1-(3,4-dibenzyloxyphenyl)-1-oxo-2-hydroxy-2-ethoxyethane (m.p. 114°C) and 5.6 g of 1-(3,3-dimethyl-3-amino-propyl)-benzimidazolin-2-one are heated in 225 ml ethanol for 3 hours and then mixed at 0 to 5°C with 8 g of sodium borohydride. The solution is maintained at room temperature for 12 hours and after acidifying with hydrochloric acid, worked up. 12.7 g of the above-mentioned base (m.p. 130°C) are obtained, which is converted by the addition of maleic acid in acetonitrile to the maleate (m.p. 197°C).

The compounds of Table I are obtained analogously to the preceding Examples. In this Table and in those that follow, the yield is indicated as a % of the theoretical yield.

TABLE I

No.	Formula	Yield	m.p. Base (°C)	Salt	Salt m.p. (°C)
1		82	115		
2		66		maleate	134
3		81		maleate	217
4		78	151		
5		79		succinate	94

TABLE I (cont.)

No.	Formula	Yield	Base m.p. °C	Salt	Salt m.p. °C
6		88		p-aminobenzoate	166
7		60	93		
8		75	170	methane-sulfonate	185
9		78	amorphous		
10		74		hydrochloride	194

TABLE I (cont.)

No.	Formula	Yield	m.p. Base °C	Salt	Salt m.p. °C
11		88		hydrochloride	215
12		84		maleate	209
13		66		succinate	168
14		66		sulfate	250
15		88	135		

TABLE I (cont.)

No.	Formula	Yield	Base m.p. °C	Salt	Salt m.p. °C
16		66	126		
17		69.5	134		
18		72		hydrochloride	252
19		87		sulfate	225
20		80		p-amino benzoate	123

TABLE I (cont.)

No.	Formula	Yield	Base m.p. °C	Salt	Salt m.p. °C
21		68		sulfate	
22		82		hydrochloride	215
23		93	93		
24		82		sulfate	183
25		80	68		
26		61		maleate	137

TABLE I (cont.)

No.	Formula	Yield	Base m.p. °C	Salt	Salt m.p. °C
27		81		maleate	123
28		70		hydrochloride	193
29		78		p-aminobenzoate	118
30		73	178	maleate	161
31		62		succinate	198

TABLE I (cont.)

No.	Formula	Yield	Base m.p. °C	Salt	Salt m.p. °C
32		81	139	succinate	206
33		75	141	maleate	218
34		69		maleate	168
35		83		hydrochloride	196
36		67		succinate	180

TABLE I (cont.)

No.	Formula	Yield	Base m.p. °C	Salt	Salt m.p. °C
37		84		maleate	170
38		69		hydrochloride	170
39		79		hydrochloride	116
40		70		maleate	210
41		68		hydrochloride	239

TABLE I (cont.)

No.	Formula	Yield	Base m.p. °C	Salt	Salt m.p. °C
42		50		p-aminobenzoate	152.5
43		53		p-aminobenzoate	159
44		38	163	hydrochloride	148
45		86		hydrochloride	183
46		88.5	116		

34

TABLE I (cont.)

No.	Formula	Yield	Base m.p. °C	Salt	Salt m.p. °C
47		95.4	122		
48		84.5		hydrochloride	197
49		86		hydrochloride	142
50		83		hydrochloride	176
51		77	107		

TABLE I (cont.)

No.	Formula	Yield	Base m.p. °C	Salt	Base m.p. °C
52		64	233	hydrochloride	
53		75	218	maleate	
54		70.3	196	hydrochloride	
55		70.3	181	hydrochloride	

TABLE I (cont.)

No.	Formula	Yield	Base m.p., °C	Salt	Salt m.p., °C
56		62		sulfate	259
57		89	122	hydrochloride	172
58		87	108	maleate	242
59		83	127	hydrochloride	220

TABLE I (cont.)

No.	Formula	Yield	Base m.p. °C	Salt	Salt m.p. °C
60		88	137	methanesulfonate	170
61		79	183	hydrochloride	198
62		68	116	sulfate	248
63		86		Formate	143

TABLE I (cont.)

No.	Formula	Yield	Base m.p. °C	Salt	Salt m.p. °C
64		78	112-114	hydrochloride .H ₂ O	227-228
65		71	84		
66		73		hydrochloride	197
67		79	168	maleinate	88
68		73		hydrochloride	187

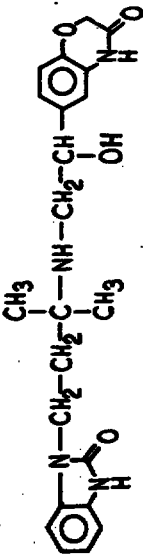
TABLE I (cont.)

No.	Formula	Yield	Base m.p. °C	Salt	Salt m.p. °C
73					
74					
75					
76					

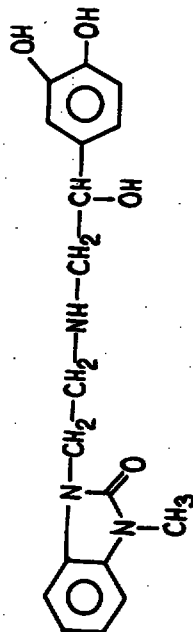
TABLE I (cont.)

No.	Formula	Yield	Base m.p. °C	Salt	Salt m.p. °C
77					
78					
79					
80					

TABLE I (cont.)

No.	Formula	Yield	Base m.p. °C	Salt	Salt m.p. °C
81					

Example 3.



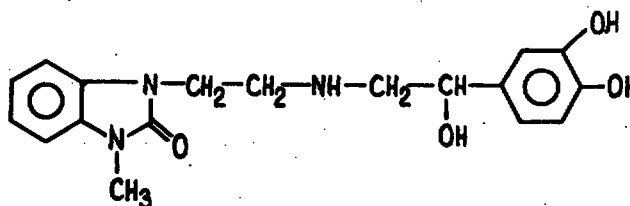
42.5 g of 3,4-dibenzoyloxyphenyl- α -bromoacetophenone and 29 g of N-methyl-N'-(2-benzylamino)ethyl-benzimidazolin-2-one are refluxed with 25 g of soda in 600 ml of acetonitrile for 2 hours. After filtering off the inorganic components, the solvent is distilled off under a reduced pressure in a rotavapor. The residue is dissolved in 900 ml of methanol and after addition of 30 ml of 12% ethereal hydrochloric acid and 15 ml of a 1% palladium chloride solution in the presence of 2 g of active charcoal, hydrogenation is effected at 60°C and 6 atmospheres pressure until 3 mol hydrogen/mol of substance is taken up. After separation of the catalyst, approx. half of the methanol is distilled off and the remaining solution mixed with 500 ml of acetonitrile. 32 g of 1-(3,4-dihydroxyphenyl)-1-oxo-2-[3-methyl-2-oxo-benzimidazolin-yl]-ethylaminoethane hydrochloride crystallizes out and after recrystallization from water, shows a melting point of 250°C. 8 g of this aminoketone are hydrogenated in 400 ml of methanol in the presence of 1 g of platinum oxide under normal conditions until 1 molar equivalent of hydrogen is taken up. The above-shown compound is isolated as the hydrochloride (m.p. 185°C) in a yield of 88%.

5

10

15

Example 4.



5 9.45 g of 1 - (3,4 - dihydroxyphenyl) - 1 - oxo - 2[3 - methyl - 2 - oxo - benzimidazolin - yl] - ethylaminoethane hydrochloride (see Example 3) in 150 ml of water, under a nitrogen atmosphere are mixed initially with 150 ml of 1 N sodium hydroxide solution and then at 20°C with 1.9 g of sodium borohydride in portions over a period of about 10 minutes. The solution is allowed to stand for some time at room temperature and is then heated to about 50°C. After cooling, hydrochloric acid is added until the solution has a pH of 4 and is then evaporated under a reduced pressure. The above-
10 shown product is isolated as the hydrochloride (m.p. 185°C) in a yield of 91% of theory.

The compounds of Table II are produced analogously to Examples 3 and 4:

TABLE II

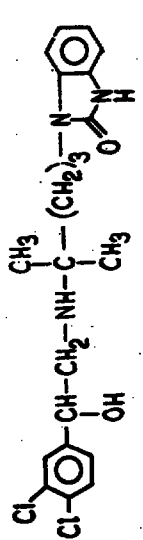
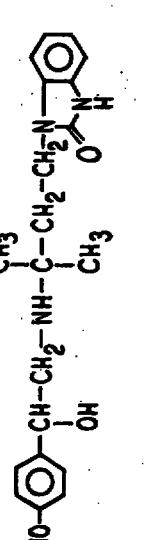
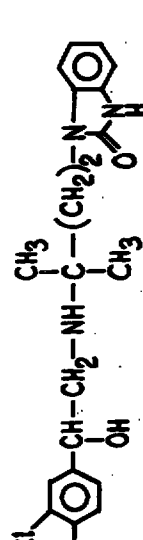
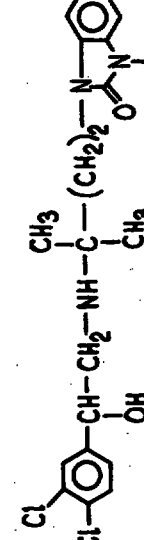
No.	Formula	Yield	Base m.p. °C	Salt	Salt m.p. °C
1		89		p-aminobenzoate	161
2		92		maleate	134
3		92		maleate	209
4		93		succinate	168

TABLE II (cont.)

No.	Formula	Yield	Base m.p. °C	Salt	Salt m.p. °C
5		90		maleate	168
6		96		maleate	210
7		93		hydrochloride	239
8		94		p-aminobenzoate	159
9		88		hydrochloride	170

46

TABLE II (cont.)

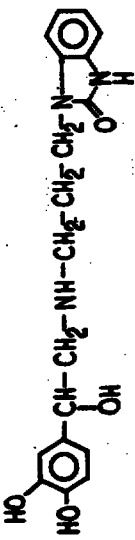
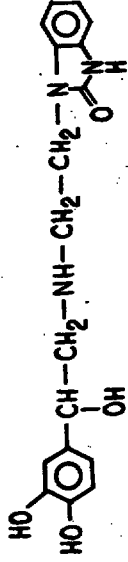
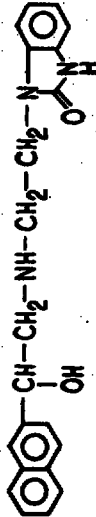
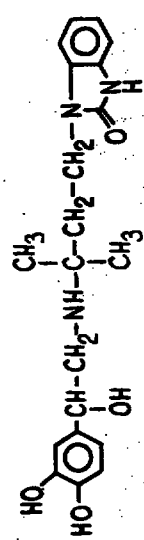
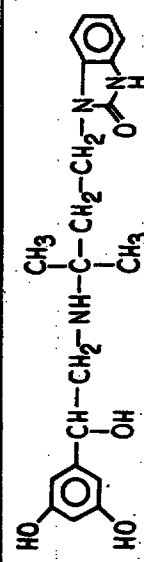
No.	Formula	Yield	Base m.p. °C	Salt	Salt m.p. °C
10		89		succinate	204
11		78		cyclamate	176
12		93	170	methane-sulfonate	185
13		90		maleate	138
14		94		maleate · H ₂ O	180

TABLE II (cont.)

No.	Formula	Yield	Base m.p. °C	Salt	Salt m.p. °C
15		85		maleate	157
16		92		maleate	180
17		90		hydrochloride . 2 H ₂ O	275
18		94		hydrochloride	265
19		93		hydrochloride	177

48

No.	Formula	Yield	base m.p. °C	Salt	Salt m.p. °C
20	 <chem>C[C@H](O)(C)CNCCc1nc2ccccc2n1</chem>	89		succinate	215
21	 <chem>C[C@H](O)(C)CNCCc1nc2ccccc2n1</chem>	92		succinate . H ₂ O	128
22	 <chem>C[C@H](O)(C)NCCc1nc2ccccc2n1</chem>	94		p-amino benzoate	166
23	 <chem>C[C@H](O)(C)NCCc1nc2ccccc2n1</chem>	91		succinate	169-171
24	 <chem>C[C@H](O)(C)NCCc1nc2ccccc2n1</chem>	90		p-amino benzoate	193

TABLE II (cont.)

No.	Formula	Yield	Base m.p. °C	Salt	Salt m.p. °C
25		84		succinate	176
26		90	212	p-aminobenzoate	234
27		92	148	p-aminobenzoate	191
28		90		hydrochloride	190
29		89		succinate	189

TABLE II (cont.)

No.	Formula	Yield	Base m.p. °C	Salt	Salt m.p. °C
30		90		Formate 1/2 CH ₃ CN	159
31		93	95	hydrochloride	185
32		94		hydrochloride	198
33		93		p-aminobenzoate	199
34		90		hydrochloride	175
35		91	206	hydrochloride	169

TABLE II (cont.)

No.	Formula	Yield	Base m.p. °C	Salt	Salt m.p. °C
36		94	200	hydrochloride	201
37		85	198	hydrochloride	157
38		92		succinate	198
39		89		acid maleate	202
40		97		acid maleate	180

TABLE II. (cont.)

No.	Formula	Yield	Base m.p. °C	Salt	Salt m.p. °C
41		92		acid maleate	168
42		89		hydrochloride	230
43		94		hydrochloride	252
44		90		succinate	173
45		91	198	hydrochloride	235

TABLE II (cont.)

No.	Formula	Yield	Base m.p. °C	Salt	Salt m.p. °C
46		84		succinate	212
47		89		succinate	218
48		94	180	hydrochloride	190
49		88		formate	214
50		92	190	hydrochloride	225

TABLE II (cont.)

No.	Formula	Yield	Base m.p. °C	Salt	Salt m.p. °C
51		87		hydrochloride	170
52		90	193	hydrochloride	196
53		96		maleate	210
54		96		hydrochloride	239
55		93		p-aminobenzoate	152,5
56		90		p-aminobenzoate	159

TABLE II (cont.)

No.	Formula	Yield	Base m.p. °C	Salt	Salt m.p. °C
57		67	163	hydrochloride	148
58		81		p-amino benzoate	190
59		79		hydrochloride	262
60		84		maleate	202
61		88		maleate	202
62		85	180	succinate	203

TABLE II (cont.)

No.	Formula	Yield	Base m.p. °C	Salt	Salt m.p. °C
63		88		p-aminobenzoate	196
64		90	180	hydrochloride	193
65		72		hydrochloride	212
66		69		hydrochloride	182
67		76		hydrochloride	221

TABLE II (cont.)

No.	Formula	Yield	Base m.p. °C	Salt	Salt m.p. °C
68		82	113	hydrochloride · H ₂ O	80-82
69		79		formate	138
70		72		methanesulfonate · H ₂ O	120
71		76		hydrochloride	252
72		81		sulfate	192

TABLE II (cont.)

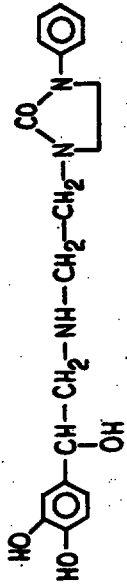
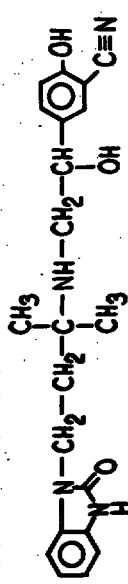
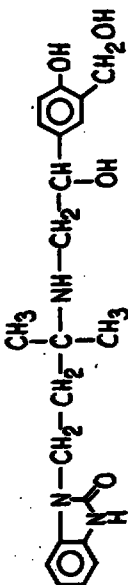
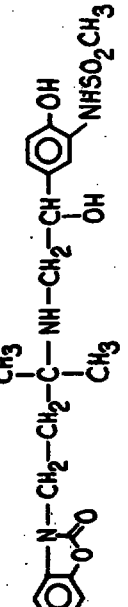
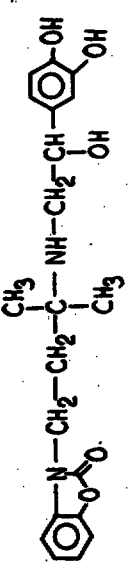
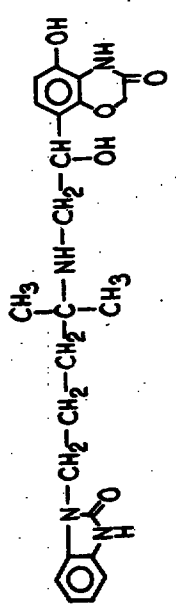
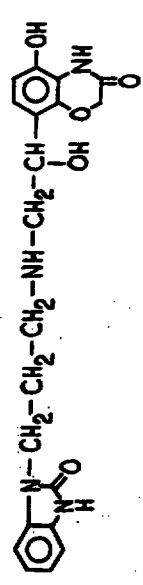
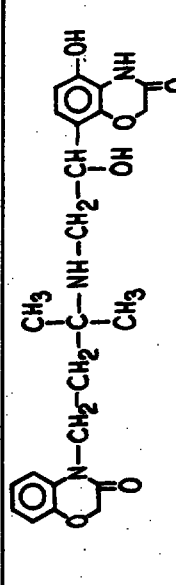
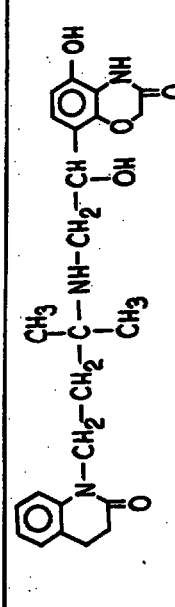
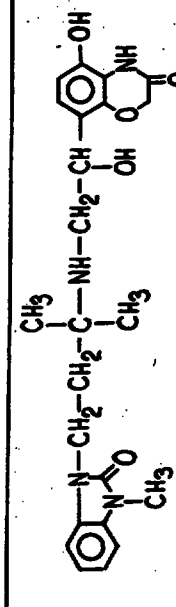
No.	Formula:	Yield	Base m.p. °C	Salt	Salt m.p. °C
73		72		hydrochloride	209
74				hydrochloride ·H ₂ O	173-176
75		83		hydrochloride	amorphous
76		78	156	hydrochloride	188
77		86		maleate	176

TABLE II (cont.)

No.	Formula	Yield	Base m.p. °C	Salt	Salt m.p. °C
78		62		hydrochloride	decomp. >230
79		57		methane- sulfonate	decomp. >230
80		67		hydrochloride	decomp. >220
81		58		sulfate	decomp. >240
82		71		hydrochloride	decomp. >230

60

TABLE II (cont.)

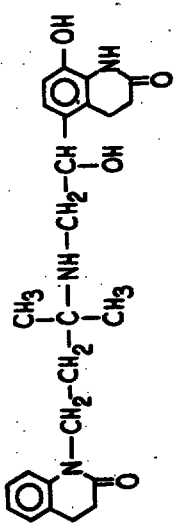
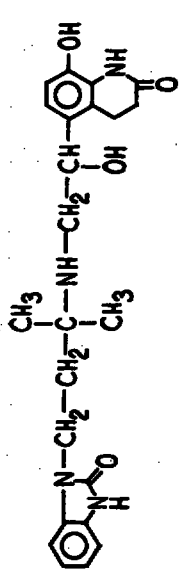
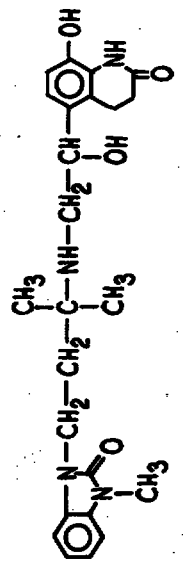
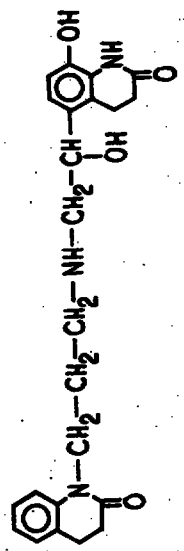
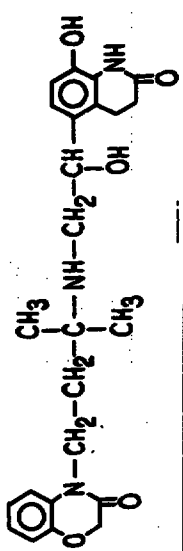
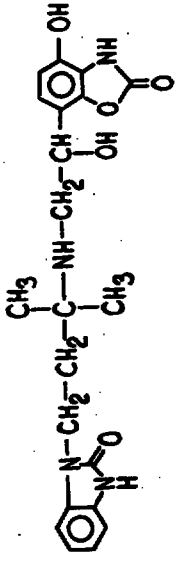
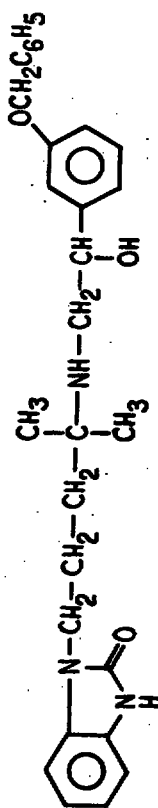
No.	Formula	Yield	Base m.p. °C	Salt	Salt m.p. °C
83		52		hydrochloride	decomp. >230
84		67		hydrochloride	decomp. >220
85		82		methane- sulfonate	decomp. >240
86				hydrochloride	decomp. >230
87		61		hydrochloride	decomp. >240

TABLE II. (cont.)

No.	Formula	Yield	Base m.p. °C	Salt	Salt m.p. °C
88		69		hydrochloride	decomp. >220

Example 5.



9.1 g of *m*-benzyloxy-*o*-bromoacetophenone in 75 ml of ethanol are mixed at -5°C with 1.2 g of sodium borohydride and stirred for half an hour. The solution is mixed with a little hydrobromic acid, the ethanol distilled off under reduced pressure and the residue taken up in ethyl acetate. The solution is shaken with sodium bicarbonate solution and water and, after drying, evaporated *in vacuo*. The residue is dissolved in 45 ml of dimethylformamide mixed with 6.57 g of 1-(4-amino-4,4-dimethylbutyl)-benzimidazolidin-2-one and 6.65 g of soda and stirred for 6 hours at 105°C. After processing, the above-mentioned product is isolated as the succinate (yield 58%). The melting point is 94°C.

The compounds of Table III are obtained analogously to Example 5.

5

10

TABLE III

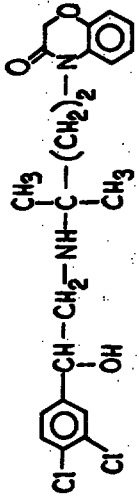
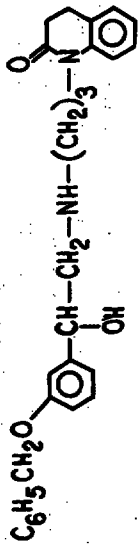
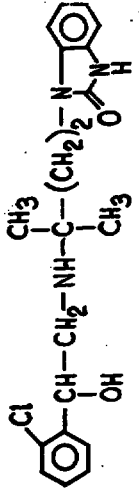
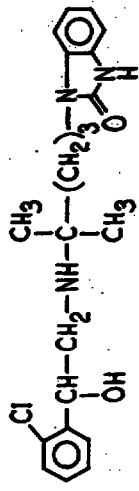
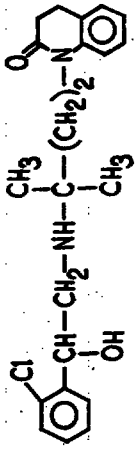
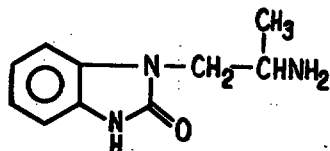
No.	Formula	Yield	Base m.p. °C	Salt	Salt m.p. °C
1		61		p-aminobenzoate	166
2		59	68		
3		62		maleate	210
4		68		hydrochloride	239
5		76		p-aminobenzoate	152.5

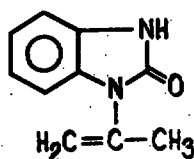
TABLE III (cont.)

No.	Formula	Yield	Base m.p. °C	Salt	Salt m.p. °C
6		73		p-aminobenzoate	159
7		64	122		
8		64		sulfate	225
9		47	170	methanesulfonate	185

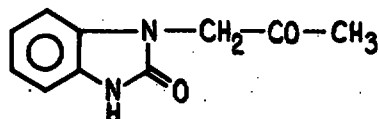
Example 6.



69.6 g of the compound

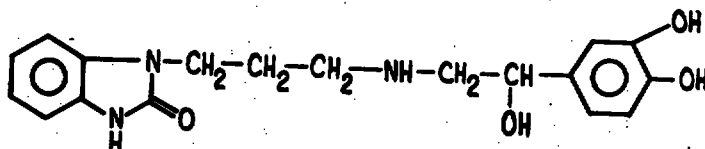


and 55.6 g of chloroacetone are reacted in the presence of potassium carbonate and potassium iodide in acetone, and after acid-catalyzed hydrolysis, 32 g of the compound



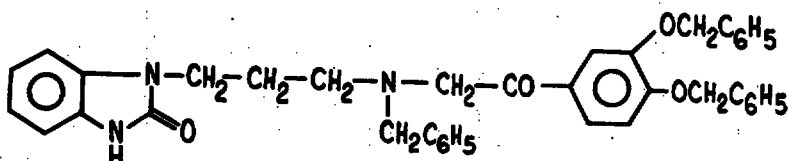
(m.p. 182°C) are obtained. 19 g of this substance in 300 ml of methanol are mixed with 25 ml of ammonia and hydrogenated with Raney-nickel as catalyst at 50 to 60°C and at a pressure of 6 atmospheres. 15.6 g of the above compound are obtained as the hydrochloride (m.p. 267—270°C).

Example 7.



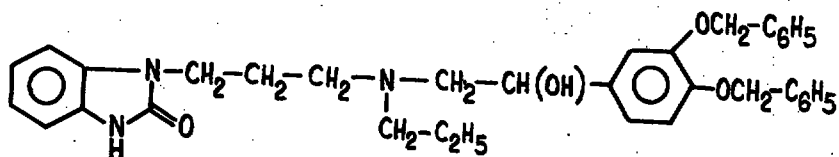
35 g of 3,4-dibenzyloxy-*m*-bromoacetophenone and 24 g of 1-(3-benzylamino-propyl)-benzimidazolinone-(2) are refluxed with 22 g of soda in 300 ml of acetonitrile for 2 hours.

The compound



is isolated as the bioxalate in a yield of 44 g (m.p. 168°C). The corresponding base (m.p. 112°C) is isolated by addition of aqueous ammonia. To 35 g of this base in 350 ml of ethanol, 29 ml of 2 N sodium hydroxide solution are added, followed by 6 g of sodium borohydride in portions over a period of 90 minutes.

The compound



is isolated as the base (m.p. 93°C).

A solution of 15 g of the base in 150 ml of methanol is hydrogenated in the presence of 3 g of palladium charcoal at 60°C and 6 atmospheres pressure until 3

equivalents of hydrogen are taken up. After removal of the catalyst, the solution is mixed with 2 g of succinic acid, and dissolved hot in 20 ml of methanol. The compound indicated above crystallizes as the succinate in a yield of 77% of theory (m.p. 204°C).

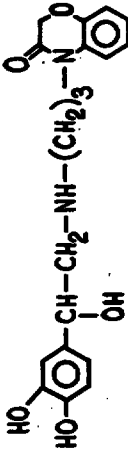
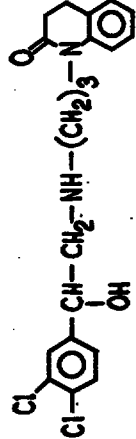
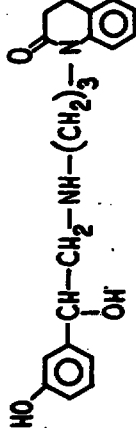
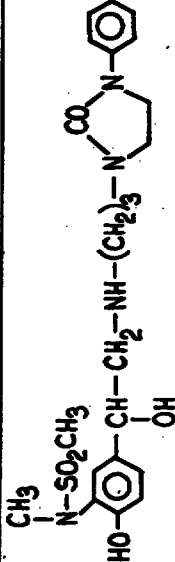
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The compounds shown in Table IV are produced analogously:

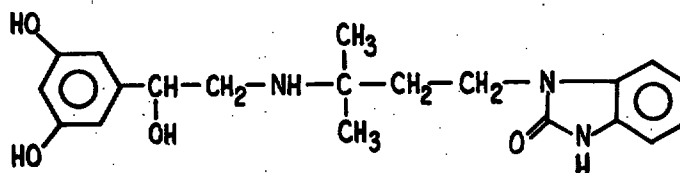
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66

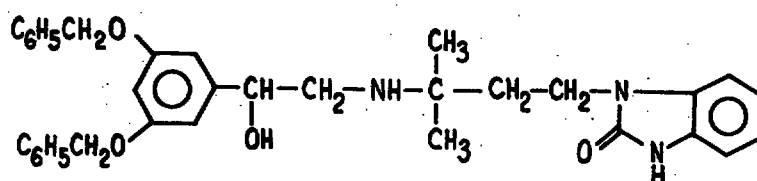
TABLE IV

No.	Formula	Yield	Base m.p. °C	Salt	Salt m.p. °C
1		81	170	methanesulfonate	185
2		77		succinate	189
3		62		hydrochloride	185
4		91		hydrochloride	198
5		82		hydrochloride	182

Example 8.



A solution of 7 g of the compound of formula



5

in 200 ml of methanol is hydrogenated in the presence of 1 g of palladium charcoal under normal conditions until 2 equivalents of hydrogen are taken up. The compound indicated above is obtained in a yield of 94% of theory as its maleate (m.p. 180°C with 1 mol of crystal water).

5

The compounds shown in Table V are produced analogously:

TABLE V

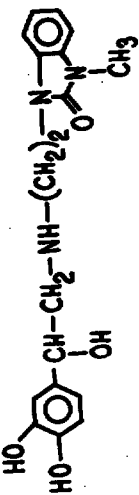
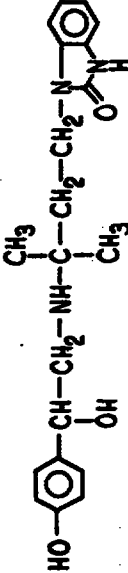
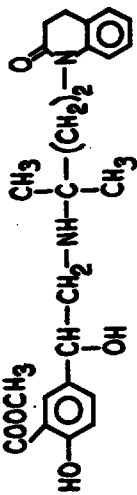
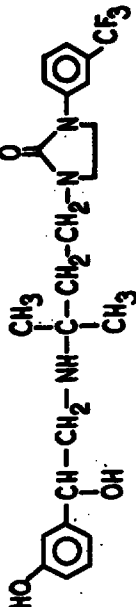
No.	Formula	Yield	Base m.p. °C	Salt	Salt m.p. °C
1		91		hydrochloride	185
2		92		cyclamate	176
3		89		maleate	134
4		90		succinate	204
5		90		hydrochloride	170
6		85		hydrochloride	158

TABLE V (cont.)

No.	Formula	Yield	Base. m.p. °C	Salt	Salt m.p. °C
7		86		maleate	168
8		91		hydrochloride	265
9		90		hydrochloride × 2 H ₂ O	275
10		85		maleate	180
11		91		maleate	157
12		94		maleate	138

TABLE V (cont.)

No.	Formula	Yield	Base m.p. °C	Salt	Salt m.p. °C
13		83		succinate	176
14		93		p-aminobenzoate	193
15		92		succinate	171
16		93		succinate × H ₂ O	128
17		92		succinate	215

TABLE V (cont.)

No.	Formula	Yield	Base m.p. °C	Salt	Salt m.p. °C
18		90		hydrochloride	177
19		84		formate	214
20		90	190	hydrochloride	225
21		82		hydrochloride	170
22		93	193	hydrochloride	196
23		9		hydrochloride	175

TABLE V (cont.)

No.	Formula	Yield	Base m.p. °C	Salt	Salt m.p. °C
24		94	206	hydrochloride	169
25		91	200	hydrochloride	201
26		86	198	hydrochloride	157
27		84		acid maleate	202
28		92		acid maleate	180

TABLE V (cont.)

No.	Formula	Yield	Base m.p. °C	Salt	Salt m.p. °C
29		92	212	p-aminobenzoate	234
30		93	148	p-aminobenzoate	191
31		92		hydrochloride	190
32		86		succinate	189
33		84		formate × 1/2 CH ₃ CN	159

72

TABLE V (cont.)

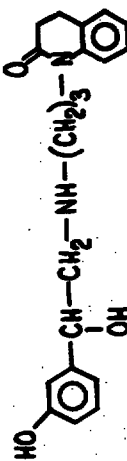
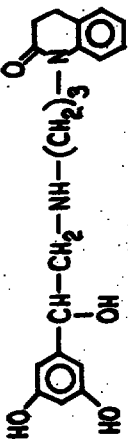
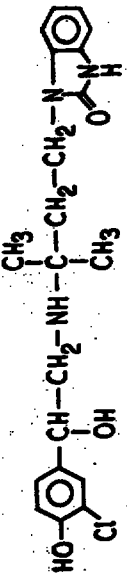
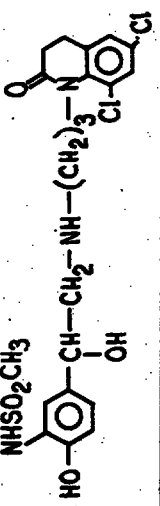
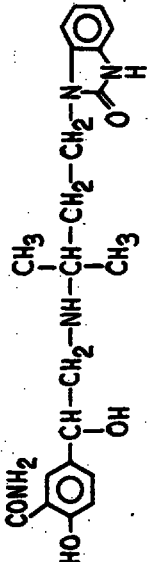
No.	Formula	Yield	Base m.p. °C	Salt	Salt m.p. °C
34		89		hydrochloride	198
35		90		p-aminobenzoate	199
36		81		acid maleate	168
37		81		hydrochloride	230
38		84		hydrochloride	252

TABLE V (cont.)

No.	Formula	Yield	Base m.p. °C	Salt	Salt m.p. °C
39		90		succinate	173
40		93	198	hydrochloride	235
41		85		succinate	212
42		82		succinate	218
43		84	180	hydrochloride	190

TABLE V (cont.)

No.	Formula	Yield	Base m.p. °C	Salt	Salt m.p. °C
44		81		p-aminobenzoate	190
45		82	180	succinate	203
46		89		p-aminobenzoate	196
47		92	180	hydrochloride	193
48		82		hydrochloride	212

TABLE V (cont.)

No.	Formula	Yield	Base m.p. °C	Salt	Salt m.p. °C
49		79		hydrochloride	182
50		79		hydrochloride	221
51		80	113	hydrochloride × H ₂ O	80 - 82
52		75		formate	138
53		82		methanesulfonate × H ₂ O	120

TABLE V (cont.)

No.	Formula	Yield	Base m.p., °C	Salt	Salt m.p., °C
54		86		sulfate	192
55		88	173	hydrochloride	203
56		73.6	175	hydrochloride	216
57		63		hydrochloride	181
58		74	169	dihydrochloride	206

TABLE V (cont.)

No.	Formula	Yield	Base m.p. °C	Salt	Salt m.p. °C
59		72			
60		69		hydrochloride	amorphous
61		87	156	hydrochloride	188
62		75		maleate	176

64

1,571,231

64

TABLE V (cont.)

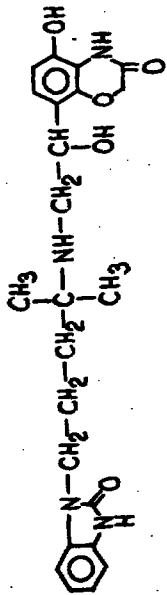
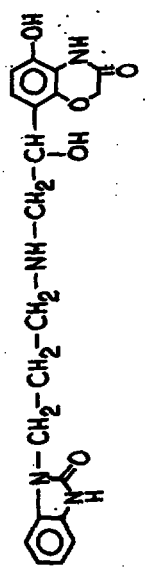
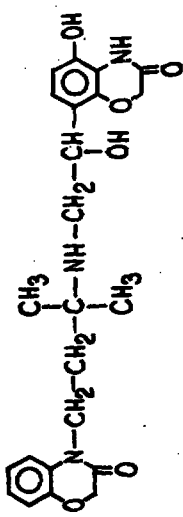
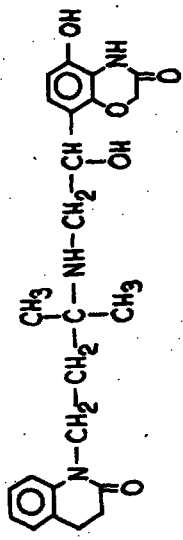
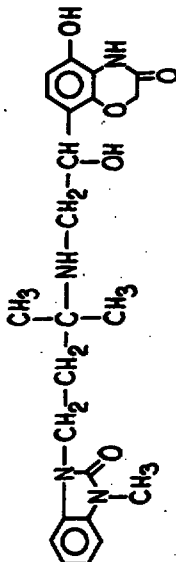
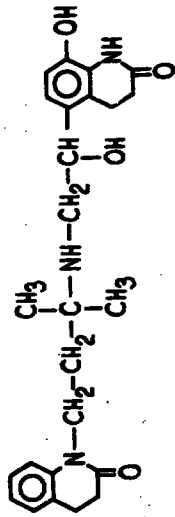
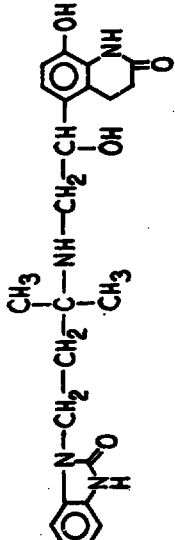
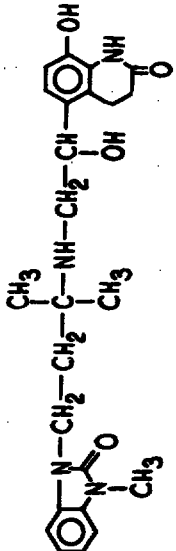
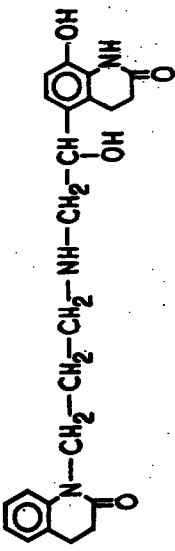
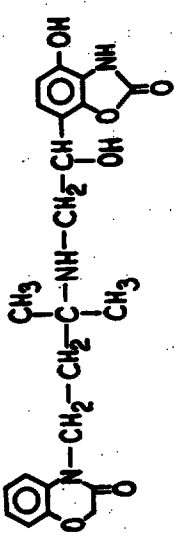
No.	Formula	Yield	Base m.p. °C	Salt	Salt m.p. °C
63		74		hydrochloride	decomp. >230
64		92		methanesulfonate	decomp. >230
65		88		hydrochloride	decomp. >220
66		87		sulfate	decomp. >240

TABLE V (cont.)

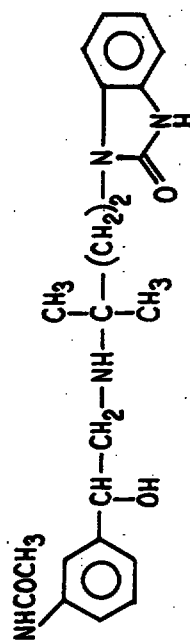
No.	Formula	Yield	Base m.p. °C	Salt	Salt m.p. °C
67		78		hydrochloride	decomp. >230
68		80		hydrochloride	decomp. >230
69		78		hydrochloride	decomp. >220
70		72		methanesulfonate	decomp. >240

49

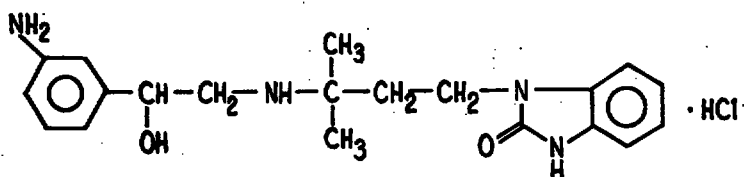
TABLE V (cont.)

No.	Formula	Yield	Base m.p., °C	Salt	Salt m.p., °C
71		81		hydrochloride	decomp. >230
72		69			

Example 9.

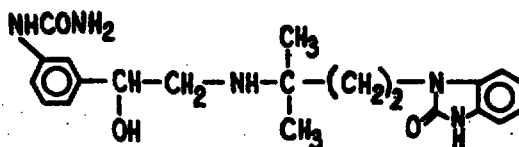


A mixture of 3.9 g of



and 2 g of acetic anhydride in 40 ml of dimethylformamide is heated over a boiling waterbath for 1 hour. After having distilling off the solvent *in vacuo*, the base is liberated with ammonia, taken up in ethyl acetate and dried. The ethyl acetate is distilled off and the base mixed in acetonitrile with the calculated quantity of maleic acid. The above compound is obtained as the maleate in a yield of 3.5 g. After recrystallization from methanol a melting point 202°C is obtained.

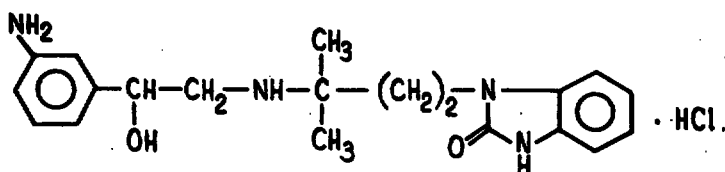
Example 10.



10

A solution of 6.1 g of

10

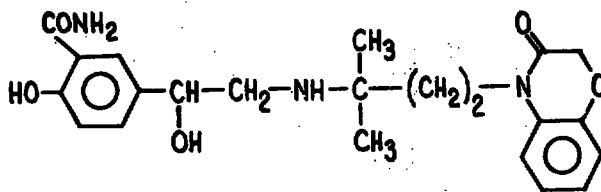


15

in a mixture of 20 ml of water and 7.5 ml of glacial acetic acid is mixed with a solution of 1.41 g of potassium cyanate in 7.5 ml of water at 35°C. After standing overnight, the base is liberated with ammonia, separated by shaking three times with isobutanol and converted into the maleate in ethanol. 6 g of the above compound are obtained as the maleate, having a melting point of 202°C after recrystallization from water.

15

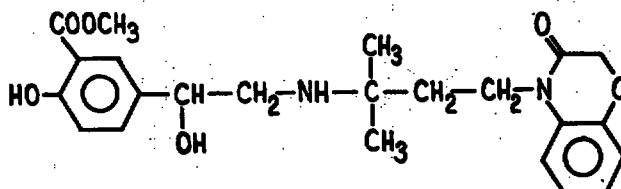
Example 11.



20

A mixture of 5 g of

20



25

in 100 ml of methanol and 100 ml of conc. ammonia solution is gently heated until dissolved. After being allowed to stand, 4.3 g of the above base are obtained (m.p. 198°C), which may be converted in ethanol into the corresponding hydrochloride (m.p. 235°C).

25

The compounds given in Table VI are obtained analogously:—

TABLE VI

No.	Formula	Yield	Base m.p. °C	Salt	Salt m.p. °C
1		83	172	hydrochloride	204
2		86	113	hydrochloride × H ₂ O	80-82
3		84	180	hydrochloride	190
4		84		hydrochloride	221

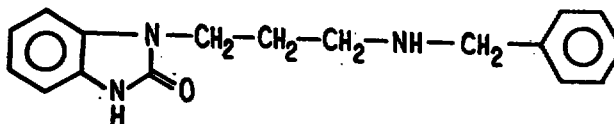
TABLE VI (cont.)

No.	Formula	Yield	Base m.p. °C	Salt	Salt m.p. °C
5		91	190	hydrochloride	225
6		86		hydrochloride	195
7		83.5		hydrochloride	147
8		77		hydrochloride	178 (decomp.)

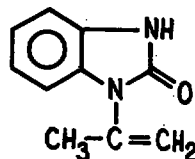
TABLE VI (cont.)

No.	Formula	Yield	Base m.p. °C	Salt	Salt m.p. °C
9		95		hydrochloride	208 (decomp.)
10		90	145	hydrochloride	215 (decomp.)
11		88		hydrochloride	197 (decomp.)
12		63	157	hydrochloride	137

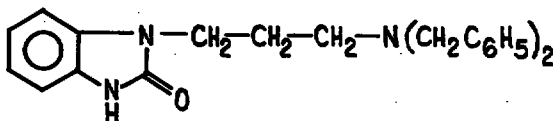
Example 12.



To a solution of 0.42 mol of sodium in 200 ml of absolute ethanol are added 69.6 g of



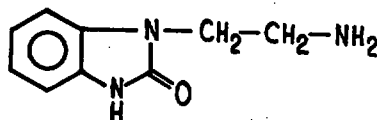
and subsequently 0.44 mol of 3-(dibenzylamino)-propylchloride in 300 ml of absolute ethanol. The reaction mixture is refluxed for 6 hours and after separating the sodium chloride produced it is mixed with stirring and cooling with 45 ml of conc. sulphuric acid. After 3 hours 700 ml of water are added, the alcohol is distilled off and after addition of ammonia the compound



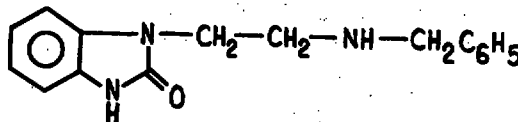
is isolated (m.p. 146°C from acetonitrile).

60 g of this compound are hydrogenated in a mixture of 400 ml of methanol and 200 ml of water in the presence of 16 ml of conc. hydrochloric acid and palladium charcoal at 60°C and 6 atm. pressure until 1 equivalent of hydrogen is taken up. The above compound is isolated with a yield of 88% of theory. (m.p. 60°C).

Example 13.

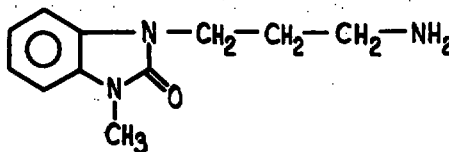


A solution of 53.4 g of

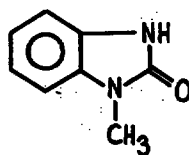


in 420 ml of methanol and 80 ml of water is hydrogenated in the presence of 20 ml of conc. hydrochloric acid and palladium charcoal at 60°C and 6 atm. pressure until 1 equivalent of hydrogen has been taken up. The above compound is isolated as the hydrochloride with a yield of 91% of theory. (m.p. 315°C).

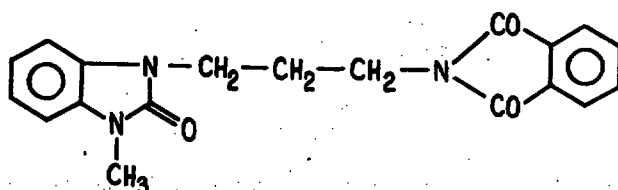
Example 14.



To a solution of 31.1 g of

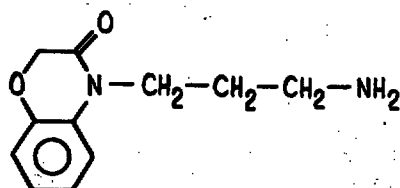


in 150 ml of hexamethyl-phosphorus-triamide are added, under a nitrogen atmosphere, 10.1 g of sodium hydride and 45 g of N-(3-chloropropyl)-phthalimide and stirred for 5 hours at 100°C. The crude product compound

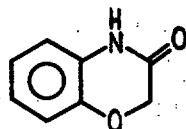


is refluxed in 1 l of ethanol with 13 g of 85% hydrazinehydrate for 90 minutes, mixed with 21 ml of conc. hydrochloric acid and 100 ml of water and reheated for 20 minutes. The precipitated phthalic acid hydrazide is removed by suction filtration and the above compound is isolated as the hydrochloride (m.p. 195°C from ethanol).

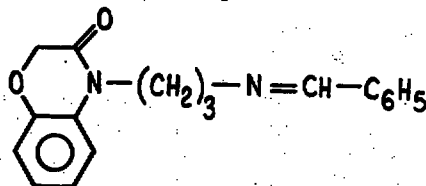
Example 15.



To a solution of 9.2 g of



in 40 ml of absolute hexamethyl-phosphorus-triamide are added, under a nitrogen atmosphere, 3.3 g of sodium hydride (55%) and, after the calculated quantity of hydrogen has been released, a solution of 3-benzalaminopropylchloride (b.p.₁₂ 140°C) in 13 ml of hexymethyl-phosphorus-triamide is added. After stirring for 5 hours at 100°C the solution is poured onto ice, the compound



isolated by shaking with ether and hydrolyzed without purification with 2 N hydrochloric acid. The above compound is isolated as the hydrochloride (m.p. 152—155°C) in a yield of 67% of theory.

The compounds of Table VII are produced analogously to Examples 12 to 15.

TABLE VII

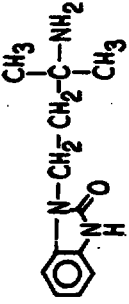
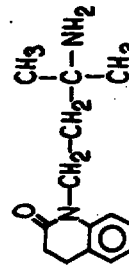
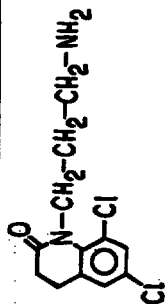
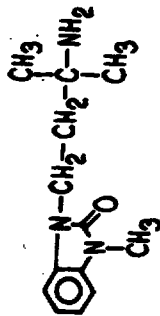
No.	Formula	Yield	Base m.p. °C	Salt	Salt m.p. °C
1		84.5	175	hydrochloride × H ₂ O	280
2		54		hydrochloride	150
3		62		maleate	157
4		55		hydrochloride	214-216
5		90		hydrochloride	277-79

TABLE VII (cont.)

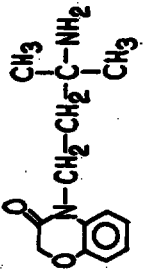
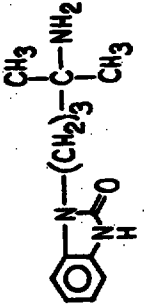
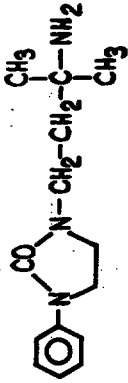
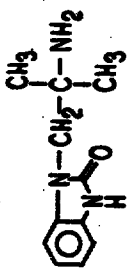
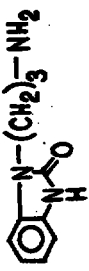
No.	Formula	Yield	Base m.p. °C	Salt	Salt m.p. °C
6		68		hydrochloride	237-239
7		75		hydrochloride	266-268
8		74	76	hydrochloride × H ₂ O	140.5
9		92	135	hydrochloride	306
10		89		hydrochloride	253

TABLE VII (cont.)

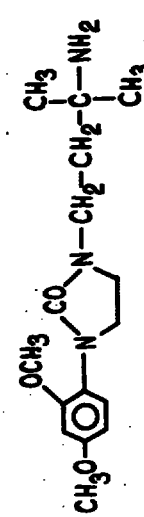
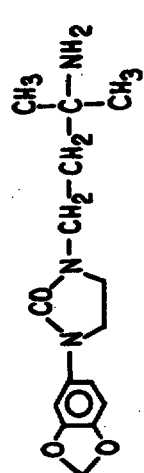
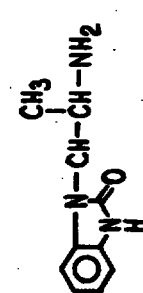
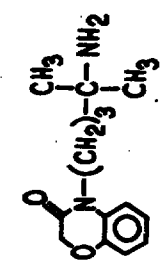
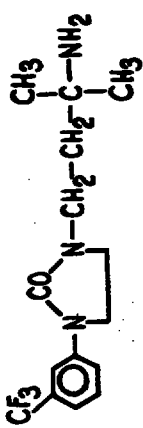
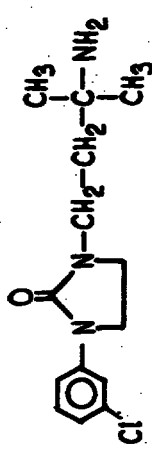
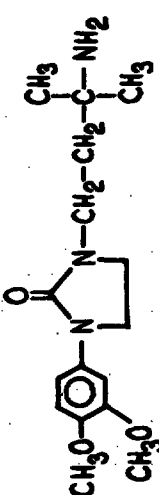
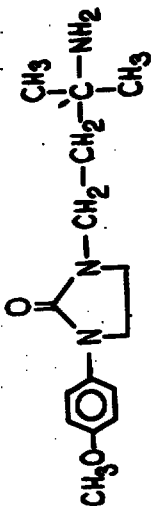
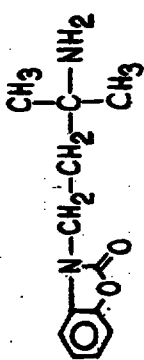
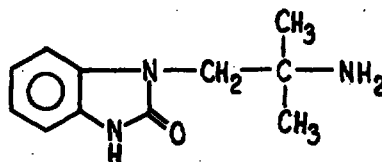
No.	Formula	Yield	Base m.p. °C	Salt	Salt m.p. °C
11		65		p-aminobenzoate	245
12		70		p-aminobenzoate	225
13		82		p-aminobenzoate	233
14		80		hydrochloride	267-70
15		62		maleate	179

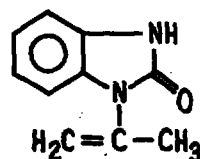
TABLE VII (cont.)

No.	Formula	Yield	Base m.p. °C	Salt	Salt m.p. °C
16		87	81		
17		72.3		hydrochloride	185
18		61		hydrochloride	225
19		60		hydrochloride	202
20		89		hydrochloride	225

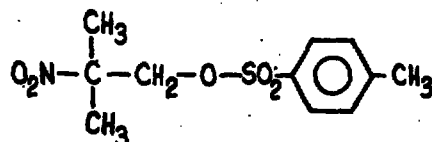
Example 16.



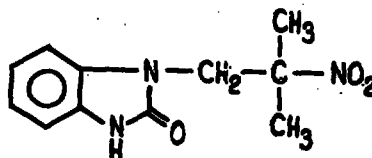
A solution of 174 g of



5 in 700 ml of absolute hexamethyl-phosphorus-triamide is mixed with 48 g a 55% suspension of sodium hydride and after the evolution of hydrogen has finished — 341 g of



10 (m.p. 76°C) dissolved in 450 ml of hexamethyl-phosphorus-triamide is added. The solution is stirred for 5 hours at 100°C, poured onto ice, shaken with ether and after evaporation of the solvent from the ether phase, the residue is dissolved in 3 l of ethanol and 300 ml of 5 N sulfuric acid added. The following day the compound



15 is isolated, with a 61% yield (m.p. 198°C). 58.75 g of this compound are dissolved in 1700 ml of methanol and after addition of Raney-nickel, hydrogenated at 6 atm. and 40 to 60°C. The compound indicated above is isolated in a yield of 92% of theory (m.p. 135°C). The hydrochloride has a melting point of 306°C.

Example I.

Tablets

20	Composition:					
	Active ingredient acc. to invention	2	parts	by	weight	20
	stearic acid	6	"	"	"	
	glucose	592	"	"	"	

25 The components are processed in the conventional way to produce tablets of 600 mg in weight. If desired, the content of active ingredient can be increased or decreased and the quantity of glucose decreased or increased correspondingly.

Example II.

Suppositories

30	Composition:					
	Active ingredient acc. to invention	100	parts	by	weight	30
	lactose, in powder form	45	"	"	"	
	cocoa-butter	1555	"	"	"	

The components are processed in the conventional way to form suppositories of 1.7 g in weight.

Example III.

Capsules

Composition:

Active ingredient acc. to invention	10 parts by weight
lactose	490 " " "
corn starch	400 " " "

1000 mg portions of the finely powdered mixture are filled into hard gelatine capsules.

Example IV.

Tablets

Composition:

1-(3,4-methylenedioxyphenyl)-2-[1,1-dimethyl-3-(2-oxo-benzimidazolidin-1-yl)-propylamino]-ethanol-maleate	2 parts by weight
stearic acid	6 " " "
glucose	592 " " "

The components are processed to produce tablets of 600 mg weight in the conventional way, the tablets being mainly for use as antidepressants.

Example V.

Suppositories

Composition:

1-(3-methylcarbamoyl-4-hydroxyphenyl)-2-[1,1-dimethyl-3-(3-methyl-2-oxo-benzimidazolidine-1-yl)-propylamino]-ethanol hydrochloride	10 parts by weight
lactose, pulverized	90 " " "
cocoa butter	1600 " " "

The components are formed into suppositories of 1.7 g weight in the conventional way and may be used for decreasing the blood pressure.

Example VI.

Capsules

Composition:

1-(3-methylcarbamoyl-4-hydroxyphenyl)-2-[1,1-dimethyl-3-(1,2,3,4-tetrahydro-2-oxo-quinol-1-yl)-propylamino]-ethanol hydrochloride	200 parts by weight
lactose	440 " " "
corn starch	360 " " "

1000 mg portions of the finely powdered mixture are filled into hard gelatin capsules (for use as a blood pressure decreasing agent).

Example VII.

Tablets

Composition:

1-(3-methanesulfonamido-4-hydroxyphenyl)-2-[1,1-dimethyl-3-[3-(3,4-dimethoxyphenyl)-2-oxoimidazolidin-1-yl]-propylamino]-ethanol hydrochloride	10 parts by weight
stearic acid	6 " " "
glucose	584 " " "

The components are processed to form tablets of 600 mg weight and may be used, for example, as broncholytics.

WHAT WE CLAIM IS:—

1. Compounds of general formula



(I)

(91)

78

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Example III.

Capsules

Composition:

5	Active ingredient acc. to invention	10 parts by weight	5
	lactose	490 " " "	
	corn starch	400 " " "	

1000 mg portions of the finely powdered mixture are filled into hard gelatine capsules.

Example IV.

10 Tablets

Composition:

15	1-(3,4-methylenedioxyphenyl)-2-[1,1-dimethyl-3-(2-oxo-benzimidazolidin-1-yl)-propylamino]-ethanol-maleate	2 parts by weight	15
	stearic acid	6 " " "	
	glucose	592 " " "	

The components are processed to produce tablets of 600 mg weight in the conventional way, the tablets being mainly for use as antidepressants.

Example V.

20 Suppositories

Composition:

25	1-(3-methylcarbamoyl-4-hydroxyphenyl)-2-[1,1-dimethyl-3-(3-methyl-2-oxo-benzimidazolidine-1-yl)-propylamino]-ethanol hydrochloride	10 parts by weight	25
	lactose, pulverized	90 " " "	
	cocoa butter	1600 " " "	

The components are formed into suppositories of 1.7 g weight in the conventional way and may be used for decreasing the blood pressure.

Example VI.

30 Capsules

Composition:

35	1-(3-methylcarbamoyl-4-hydroxyphenyl)-2-[1,1-dimethyl-3-(1,2,3,4-tetrahydro-2-oxo-quinol-1-yl)-propylamino]-ethanol hydrochloride	200 parts by weight	35
	lactose	440 " " "	
	corn starch	360 " " "	

1000 mg portions of the finely powdered mixture are filled into hard gelatin capsules (for use as a blood pressure decreasing agent).

Example VII.

45 Tablets

Composition:

45	1-(3-methanesulfonamido-4-hydroxyphenyl)-2-[1,1-dimethyl-3-[3-(3,4-dimethoxyphenyl)-2-oxoimidazolidin-1-yl]-propylamino]-ethanol hydrochloride	10 parts by weight	45
	stearic acid	6 " " "	
	glucose	584 " " "	

50 The components are processed to form tablets of 600 mg weight and may be used, for example, as broncholytics.

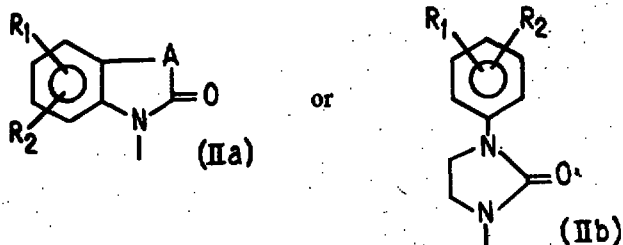
WHAT WE CLAIM IS:—

1. Compounds of general formula



(I)

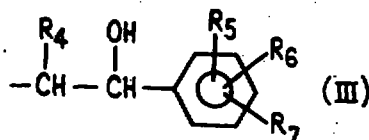
[wherein Q represents a group of the formula



in which R_1 represents a hydrogen or halogen atom, a C_1-C_4 alkyl or alkoxy group, a trifluoromethyl group or an amino group and R_2 , which may be the same or different to R_1 , represents a hydrogen or halogen atom, a C_1-C_4 alkyl or alkoxy group or a trifluoromethyl group; or R_1 and R_2 together represent a methylenedioxy or ethylenedioxy group; and A represents a bivalent group of the formula $-NR_3-$ (in which R_3 represents a hydrogen atom or a C_1-C_4 alkyl group) $-OCH_2-$ (in which the oxygen atom is linked to the benzene ring), $-O-$ or $-CH_2-CH_2-$;

n represents an integer from 2 to 6; and

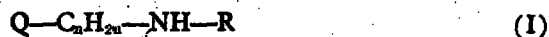
R represents a hydrogen atom or a benzyl group or a group of the formula



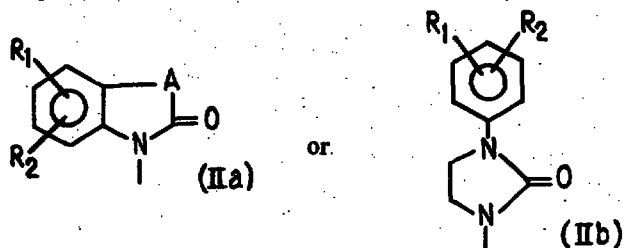
(in which R_4 represents a hydrogen atom or a methyl or ethyl group;

R_5 , R_6 and R_7 , which may be the same or different, represent hydrogen or halogen atoms or hydroxymethyl, trifluoromethyl, C_1-C_4 alkyl, nitro, cyano or methylsulphonylmethyl groups, or groups of the formula $-CONHR_8'$, $-CONHOH$, $-COOR_8'$ or $R_8'O$ or a group of formula $NR_8'R_9$, when none of any remaining substituents R_5 , R_6 or R_7 are halogen atoms or trifluoromethyl groups, (wherein R_8' represents a hydrogen atom or a C_1-C_4 alkyl group, R_8 represents a hydrogen atom or a C_2-C_{20} acyl, C_1-C_4 alkyl or aralkyl (with 1 to 4 carbon atoms in the alkyl moiety) group, and R_9 represents a hydrogen atom or a C_1-C_4 acyl, methanesulphonyl, carbamoyl, dimethylsulphamoyl or C_2-C_3 alkoxy carbonyl group); R_8 represents a group of the formula $-CO-NH-NH_2$ and R_5 and R_6 are as hereinbefore defined; or R_5 and R_6 taken together represent a bivalent group of the formula $-OCH_2O-$, $-OCH_2CH_2O-$, $-CH=CH-CH=CH-$, $-OCH_2-CONH-$, $-CH_2-CH_2-CO-NH-$ or $-O-CO-NH-$; and R_7 is as hereinbefore defined) with the proviso that when Q represents a group of formula IIb (in which one of R_1 and R_2 is hydrogen and the other is hydrogen, halogen, C_1-C_4 alkyl or alkoxy, or trifluoromethyl) and n represents an integer of from 2 to 4, then R is other than hydrogen or benzyl] and salts thereof.

2. Compounds of general formula



[wherein Q represents a group of the formula



in which R_1 and R_2 , which may be the same or different, represent hydrogen or halogen atoms, C_1-C_4 alkyl or alkoxy groups or trifluoromethyl groups; or R_1 and R_2 together represent a methylenedioxy or ethylenedioxy group;



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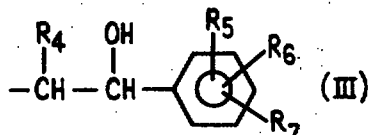
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A represents a bivalent group of the formula $\text{—NR}_3\text{—}$ (in which R_3 represents a hydrogen atom or a C_{1-4} alkyl group), $\text{—OCH}_2\text{—}$, (in which the oxygen atom is linked to the benzene ring) or $\text{—CH}_2\text{—CH}_2\text{—}$;

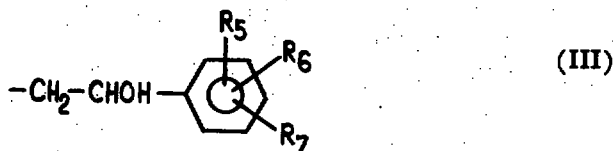
n represents an integer from 2 to 6; and

R represents a hydrogen atom or a benzyl group or a group of the formula



(in which R_4 represents a hydrogen atom or a methyl or ethyl group; R_5 , R_6 and R_7 , which may be the same or different, represent hydrogen or halogen atoms or hydroxymethyl, trifluoromethyl, C_{1-4} alkyl, nitro, cyano or methylsulphonylmethyl groups, or groups of the formula $\text{—CONHR}_3'$, —CONHOH— , $\text{—COOR}_3'$ or $\text{R}_3'\text{O}$ or a group of formula $\text{NR}_3'\text{R}_4$, when any remaining substituents R_5 , R_6 or R_7 are halogen atoms or trifluoromethyl groups, (wherein R_3' represents a hydrogen atom or C_{1-4} alkyl group; R_5 represents a hydrogen atom or a C_{2-20} acyl, C_{1-4} alkyl or aralkyl (with 1 to 4 carbon atoms in the alkyl moiety) group; and R_6 represents a hydrogen atom or a C_{1-4} acyl, methanesulphonyl, carbamoyl, dimethylsulphamoyl or C_{2-5} alkoxy carbonyl group); or R_5 and R_6 taken together represent a bivalent group of the formula $\text{—OCH}_2\text{O—}$, $\text{—OCH}_2\text{CH}_2\text{O—}$, —CH=CH—CH=CH— , $\text{—OCH}_2\text{—CONH—}$, $\text{—CH}_2\text{—CH}_2\text{—CO—NH—}$ or —O—CO—NH— and R_7 is as hereinbefore defined) with the proviso that when Q represents a group of formula IIb (in which one of R_1 and R_2 is hydrogen and the other is hydrogen, halogen, C_{1-4} alkyl or alkoxy, or trifluoromethyl) and n represents an integer of from 2 to 4, then R is other than hydrogen or benzyl] and salts thereof.

3. Compounds as claimed in claim 1 wherein Q represents a group of the formula IIa or IIb (as defined in claim 1 in which R_1 represents a hydrogen atom or a methoxy or amino group; and R_2 represents a hydrogen atom or a methoxy group); n represents an integer from 3 to 6; R represents a hydrogen atom or a group of the formula



in which R_5 represents a hydrogen or halogen atom or a hydroxymethyl or cyano group or a group of the formula $\text{—CONHR}_3'$, $\text{R}_3'\text{O}$ or —NHR_3 (wherein R_3' is as defined in claim 1; R_5 represents a hydrogen atom or a C_{2-20} acyl, methyl or benzyl group; and R_6 represents a hydrogen atom or a formyl, acetyl, methanesulphonyl, carbamoyl or dimethylsulphamoyl group); R_6 represents a hydrogen or halogen atom or a hydroxy group; and R_7 represents a hydrogen or chlorine atom or a methyl or methoxy group with the proviso that if R_6 and/or R_7 represent halogen atoms then R_5 is other than the group —NHR_3 .

4. Compounds as claimed in claim 1 wherein Q represents a group of the formula IIa or IIb (as defined in claim 1 in which R_1 represents a hydrogen atom or a methoxy or amino group; and R_2 represents a hydrogen atom or a methoxy group); and R represents a hydrogen atom or a group of formula III as defined in claim 1 [in which R_5 represents a hydrogen atom or a hydroxy group and R_6 represents a hydrogen or chlorine atom or a hydroxy, hydroxymethyl or cyano group or a group of the formula $\text{—CONHR}_3'$ or $\text{R}_3'\text{O}$ (wherein R_3' is as defined in claim 1 and R_5 represents a benzyl or C_{1-4} saturated carboxylic acyl group); or R_5 and R_6 taken together represent a group of the formula —CH=CH—CH=CH— , $\text{—OCH}_2\text{CONH—}$, $\text{—CH}_2\text{—CH}_2\text{—CO—NH—}$ or —O—CONH— and R_7 represents a hydrogen or chlorine atom or a methyl, methoxy or hydroxy group].

5. 1 - (3,4 - Methyleneedioxyphenyl) - 2 - [1,1 - dimethyl - 3 - (2 - oxo - benzimidazolidin - 1 - yl) - propylamino] - ethanol and salts thereof.

6. 1 - (3,4 - Methyleneedioxyphenyl) - 2 - [1,1 - dimethyl - 3 - (3 - methyl - 2 - oxo - benzimidazolidin - 1 - yl) - propylamino] - ethanol and salts thereof.

7. 1 - (3 - Methylcarbamoyl - 4 - hydroxyphenyl) - 2 - [1,1 - dimethyl - 3 - (1,2,3,4 - tetrahydro - 2 - oxo - quinol - 1 - yl) - propylamino] - ethanol and salts thereof.



8. 1 - (3 - Methylcarbamoyl - 4 - hydroxyphenyl) - 2 - [1,1 - dimethyl - 3 - (3-methyl - 2 - oxo - benzimidazolidin - 1 - yl) - propylamino] - ethanol and salts thereof.

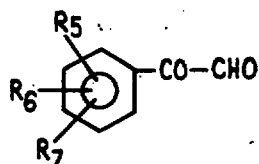
9. 1 - (3 - Methanesulfonamido - 4 - hydroxyphenyl) - 2 - {1,1 - dimethyl - 3 - [3 - (3,4 - dimethoxyphenyl) - 2 - oxo - imidazolidin - 1 - yl] - propylamino} - ethanol and salts thereof.

10. Compounds of general formula I as defined in claim 1 and salts thereof as herein specifically disclosed with the exception of those compounds claimed in claims 5 to 9.

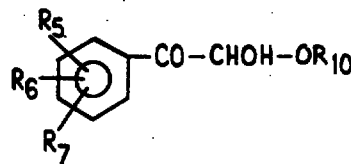
11. A process for the preparation of compounds of general formula I as defined in claim 1 (wherein R represents a group of formula III in which R₁ is hydrogen) which comprises reacting a compound of formula



(wherein Q and n are as defined in claim 1) with a compound of formula



or



(wherein R₅, R₆ and R₇ are as defined in claim 1, and R₁₀ represents a hydrogen atom or an alkyl group) under the conditions of reductive amination.

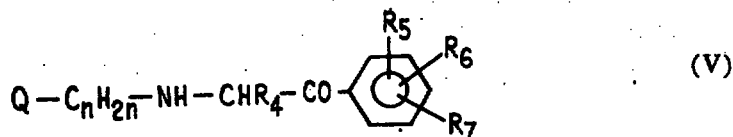
12. A process as claimed in claim 1 wherein the reaction is effected in the presence of a complex metal hydride.

13. A process as claimed in claim 12 wherein the complex metal hydride comprises sodium borohydride.

14. A process as claimed in claim 11 wherein the reaction is effected in the presence of hydrogen and a hydrogenation catalyst.

15. A process as claimed in claim 14 wherein the hydrogenation catalyst comprises platinum, palladium or nickel.

16. A process for the preparation of compounds of general formula I as defined in claim 1 (wherein R represents a group of formula III) which comprises reducing a compound of formula



(wherein Q, n, R₄, R₅, R₆ and R₇ are as defined in claim 1).

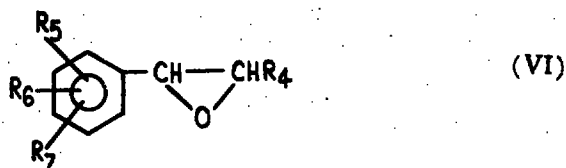
17. A process as claimed in claim 16 wherein the reduction is effected in the presence of a complex metal hydride.

18. A process as claimed in claim 17 wherein the complex metal hydride comprises sodium borohydride.

19. A process as claimed in claim 16 wherein the reduction is effected by catalytic hydrogenation.

20. A process as claimed in claim 19 wherein the hydrogenation catalyst comprises platinum, palladium or nickel.

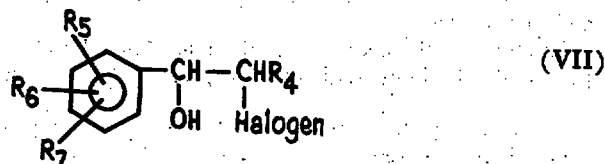
21. A process for the preparation of compounds of general formula I as defined in claim 1 (wherein R represents a group of formula III) which comprises reacting a compound of formula





(wherein R_4 to R_7 are as defined in claim 1) with an amine of formula IV (as defined in claim 11).

22. A process for the preparation of compounds of general formula I as defined in claim 1 (wherein R represents a group of formula III) which comprises reacting a compound of formula



(wherein R_4 to R_7 are as defined in claim 1) with an amine of formula IV as defined in claim 11.

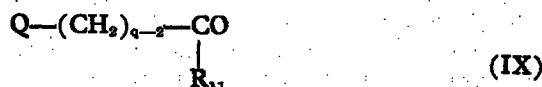
23. A process as claimed in either of claims 21 and 22 wherein the reaction is effected in the presence of an acid-binding agent.

24. A process as claimed in claim 23 wherein the acid-binding agent comprises potassium or sodium carbonate or an excess of the amine of formula IV.

25. A process for the preparation of compounds of general formula I as defined in claim 1 (wherein the group $-\text{C}_n\text{H}_{2n}-$ is a group of the formula



in which q is an integer from 3 to 6 and R_{11} represents a hydrogen atom or a methyl group) which comprises reductively aminating a compound of formula



(wherein Q is as defined in claim 1, and R_{11} and q are as hereinbefore defined) with a compound of formula



(wherein R is as defined in claim 1).

26. A process for the preparation of compounds of general formula I as defined in claim 1 (wherein the group $-\text{C}_n\text{H}_{2n}-$ is a group of the formula VIII as defined in claim 25) which comprises reducing a compound of formula



(wherein Q and R are as defined in claim 1, and R_{11} and q are as defined in claim 25).

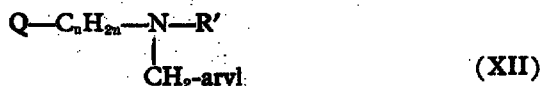
27. A process as claimed in either of claims 25 and 26 wherein the reaction is effected in the presence of a complex metal hydride.

28. A process as claimed in claim 27 wherein the complex metal hydride comprises sodium borohydride.

29. A process as claimed in either of claims 25 and 26 wherein the reaction is effected in the presence of hydrogen and a hydrogenation catalyst.

30. A process as claimed in claim 29 wherein the hydrogenation catalyst comprises platinum, palladium or nickel.

31. A process for the preparation of compounds of general formula I as defined in claim 1 (wherein R represents a group of formula III) which comprises reductively removing the $-\text{CH}_2\text{-aryl}$ group from a compound of formula





(wherein Q and n are as defined in claim 1 and R' represents a group of formula III as defined in claim 1).

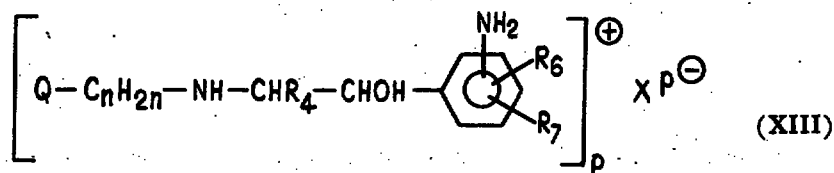
32. A process as claimed in claim 31 wherein the reduction is effected by catalytic hydrogenation.

33. A process for the preparation of compounds of formula I as defined in claim 1 (wherein R represents a group of formula III in which at least one of R₅ to R₇ represents a hydroxy group) which comprises removing the arylmethyl group(s) from a compound of formula I as defined in claim 1 wherein one or more of the hydroxy groups present is/are arylmethylated.

34. A process as claimed in claim 33 wherein the removal of the arylmethyl group(s) is effected by catalytic hydrogenation.

35. A process as claimed in claim 33 wherein the removal of the arylmethyl group(s) is effected in the presence of an ether-cleaving acid.

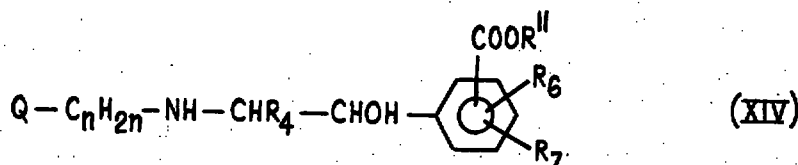
36. A process for the preparation of compounds of general formula I as defined in claim 1 (wherein R represents a group of formula III in which R₅ represents an NH—C₁—C₄ acyl group) which comprises reacting a compound of formula



(wherein Q, n, R₄, R₆ and R₇ are as defined in claim 1, X represents an anion and p represents the charge on the anion) with an appropriate carboxylic acid anhydride, in the presence of at least an equimolar quantity of an acid.

37. A process for the preparation of compounds of general formula I as defined in claim 1 (wherein R represents a group of formula III in which R₅ represents an NH—CO—NH₂ group) which comprises reacting a compound of formula XIII as defined in claim 36 with a cyanate and an acid, in the presence of at least an equimolar quantity of an acid.

38. A process for the preparation of compounds of general formula I as defined in claim 1 (wherein R represents a group of formula III in which R₅ represents a CONHR₃, CONHNH₂ or CONHOH group) which comprises reacting an ester of the formula

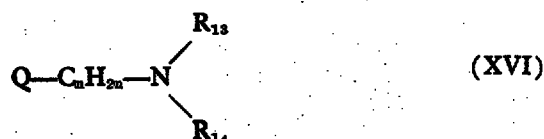


(wherein Q, n, R₄, R₆ and R₇ are as defined in claim 1 and R'' represents an alkyl or substituted alkyl group) with a compound of formula



(wherein R₁₂ represents a hydrogen atom or a C₁₋₄ alkyl, hydroxy or amino group).

39. A process for the preparation of compounds of general formula I as defined in claim 1 (wherein R represents a hydrogen atom or a benzyl group) which comprises removing the protecting group(s) from a compound of formula



[wherein Q and n are as defined in claim 1; R₁₃ represents an arylmethyl, acyl or COOR₁₅ group (in which R₁₅ represents an alkyl, aryl or arylmethyl group) and R₁₄ represents a hydrogen atom or an arylmethyl group; or R₁₃ and R₁₄ together form a



dicarboxylic acid group or a group of the formula CHR_{15} (in which R_{15} is as above defined)].

40. A process as claimed in claim 39 wherein the reaction is effected using a compound of formula XVI in which R_{13} represents an acyl group or a group of the formula COOR_{15} , or R_{13} and R_{14} together represent a dicarboxylic acid or CHR_{15} group, and the protecting groups are removed hydrolytically.

41. A process as claimed in claim 39 wherein the reaction is effected using a compound of formula XVI in which R_{13} and R_{14} together represent a dicarboxylic acid group and the reaction is effected by cleaving with hydrazine followed by hydrolysis.

42. A process as claimed in claim 39 wherein the reaction is effected using a compound of formula XVI in which R_{13} represents an arylmethyl group or a group of the formula COOR_{15} (in which R_{15} represents an arylmethyl group) and R_{14} represents an arylmethyl group, and the removal of the protecting groups is effected by catalytic hydrogenation.

43. A process for the preparation of compounds of general formula I as defined in claim 1 (wherein R represents a hydrogen atom) which comprises reducing the nitro group in a compound of formula



(wherein Q and n are as defined in claim 1).

44. A process as claimed in claim 43 wherein the reduction is effected by catalytic hydrogenation.

45. A process for the preparation of optically active isomers of the compounds of general formula I as defined in claim 1 which comprises resolving a racemic mixture of a compound of formula I prepared by a process as claimed in any of claims 11 to 14.

46. A process as claimed in any of claims 11 to 45 wherein the compound of formula I as defined in claim 1 produced is converted to a salt thereof.

47. A process as claimed in any of claims 11 to 15 for the preparation of compounds as defined in claim 2 wherein the compound of formula IV is one in which Q is as defined in claim 2.

48. A process as claimed in any of claims 16 to 20 for the preparation of compounds as defined in claim 2 wherein the compound of formula V is one in which Q is as defined in claim 2.

49. A process as claimed in any of claims 21 to 24 for the preparation of compounds as defined in claim 2 wherein the compound of formula IV is one in which Q is as defined in claim 2.

50. A process as claimed in any of claims 25 and 27 to 30 for the preparation of compounds as defined in claim 2 wherein the compound of formula IX is one in which Q is as defined in claim 2.

51. A process as claimed in claim 26 for the preparation of compounds as defined in claim 2 wherein the compound of formula XI is one in which Q is as defined in claim 2.

52. A process as claimed in either of claims 31 and 32 for the preparation of compounds as defined in claim 2 wherein the compound of formula XII is one in which Q is as defined in claim 2.

53. A process as claimed in any of claims 33 to 35 for the preparation of compounds as defined in claim 2 wherein the starting compound of formula I is one in which Q is as defined in claim 2.

54. A process as claimed in either of claims 36 and 37 for the preparation of compounds as defined in claim 2 wherein the compound of formula XIII is one in which Q is as defined in claim 2.

55. A process as claimed in claim 38 for the preparation of compounds as defined in claim 2 wherein the compound of formula XIV is one in which Q is as defined in claim 2.

56. A process as claimed in any of claims 39 to 42 for the preparation of compounds as defined in claim 2 wherein the compound of formula XVI is one in which Q is as defined in claim 2.

57. A process as claimed in either of claims 43 and 44 for the preparation of compounds as defined in claim 2 wherein the compound of formula XVII is one in which Q is as defined in claim 2.

58. A process for the preparation of optically active isomers of the compounds of general formula I as defined in claim 2 which comprises resolving a racemic mixture



of a compound of formula I prepared by a process as claimed in any of claims 47 to 57.

59. A process as claimed in any of claims 47 to 58 wherein the compound of formula I as defined in claim 2 produced is converted to a salt thereof.

60. A process for the preparation of compounds of general formula I as defined in claim 1 and salts thereof substantially as herein described.

61. A process for the preparation of compounds of general formula I as defined in claim 1 and salts thereof substantially as herein described in any of Examples 1 to 16.

62. Compounds as claimed in claim 1 whenever prepared by a process as claimed in any of claims 11 to 46, 60 and 61.

63. Compounds as claimed in claim 2 whenever prepared by a process as claimed in any of claims 47 to 59.

64. Pharmaceutical compositions comprising as active ingredient at least one compound of formula I as defined in claim 1 or a physiologically acceptable salt thereof in association with a pharmaceutical carrier or excipient.

65. Compositions as claimed in claim 64 in a form suitable for oral, rectal or parenteral administration.

66. Compositions as claimed in either of claims 64 and 65 in the form of tablets, capsules, tinctures, injection solutions, suppositories, or inhalation preparations.

67. Compositions as claimed in any of claims 64 to 66 in dosage unit form.

68. Compositions as claimed in claim 67 wherein each dosage unit contains 1 to 500 mg of the said active ingredient.

69. Compositions as claimed in claim 68 wherein each dosage unit contains 2 to 200 mg of the said active ingredient.

70. Pharmaceutical compositions comprising as active ingredient at least one compound as defined in claim 2 in association with a pharmaceutical carrier or excipient.

71. Pharmaceutical compositions as claimed in claim 64 substantially as herein described.

72. Pharmaceutical compositions as claimed in claim 64 substantially as herein described in any of Examples I to VII.

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