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PATENT SPECIFICATION (11) 1 544 880

1 544 880

(21) Application No. 36376/77 (22) Filed 31 Aug. 1977
(31) Convention Application No. 2639291
(32) Filed 1 Sept. 1976 in
(33) Federal Republic of Germany (DE)
(44) Complete Specification published 25 April 1979
(51) INT CL² C07D 237/32 A61K 31/495 C07D 239/88 405/12 491/04
(52) Index at acceptance
C2C 1494 1594 159X 1604 213 220 226 22Y 246 247 250 252 253 255 25Y 28X 29X 29Y 305 30Y 313 314 31Y 322 323 32Y 339 351 352 364 36Y 386 388 43X 620 625 634 644 650 662 672 699 761 762 765 802 80Y LK TN TR

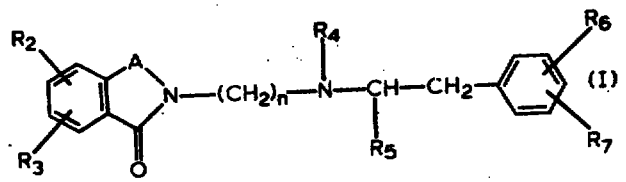
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(54) SUBSTITUTED ~~AMINOALKYL~~ AMINOALKYL PHTHALAZINONES AND QUINAZOLINONES

(71) We, DR. KARL THOMAE GESELLSCHAFT MIT BESCHRANKTER HAFTUNG, a Body Corporate organised under the laws of the Federal Republic of Germany of Biberach an der Riss, 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: —

This invention relates to new aminoalkyl phthalazinones and quinazolinones, to processes for their preparation and to pharmaceutical compositions containing them.

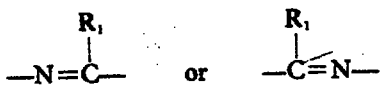
According to one feature of the present invention there are provided compounds of general formula I,



(I)

wherein

A represents a group of formula



in which R_1 represents a hydrogen atom or an alkyl group containing from 1 to 3 carbon atoms;

either R_2 and R_3, which may be the same or different, each represents an alkoxy group containing from 1 to 3 carbon atoms, or together represent a methylenedioxy or ethylenedioxy group;

R_4 represents a hydrogen atom, an alkyl group containing from 1 to 3 carbon atoms or a benzyl group;

R_5 represents a hydrogen atom or an alkyl group containing from 1 to 3 carbon atoms;

either R_6 represents a hydrogen atom or an alkoxy group containing from 1 to 3 carbon atoms and R_7 represents an alkoxy group containing from 1 to 3 carbon atoms, or R_6 and R_7 together represent a methylenedioxy or ethylenedioxy group; and

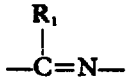
n is 2 or 3;

and acid addition salts thereof.

The compounds according to the invention possess interesting pharmacological properties and in particular, in general, a heart-frequency decreasing and a hypotensive effect.

It will be appreciated that, for pharmaceutical use, the salts referred to above will be physiologically compatible salts but other acid addition salts may find use, for example in the preparation of compounds of general formula I and their physiologically compatible acid addition salts.

Preferred compounds according to the invention are those wherein R_1 represents a hydrogen atom or a methyl or isopropyl group; either R_2 and R_3 each represents a methoxy group or together represent a methylenedioxy or ethylenedioxy group; R_4 represents a hydrogen atom or a methyl or benzyl group; R_5 represents a hydrogen atom; and either R_6 represents a hydrogen atom or a methoxy group and R_7 represents a methoxy group or R_6 and R_7 together represent a methylenedioxy or ethylenedioxy group. Of these compounds especially preferred are those wherein A represents a group of formula

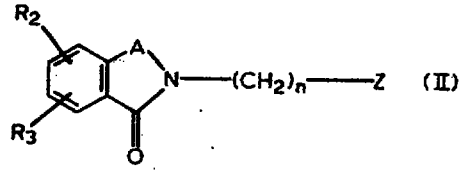


in which R_1 represents a hydrogen atom or a methyl group; either R_2 and R_3 each represents a methoxy group, one being in the 6-position and the other in the 7-position of the bicyclic ring, or together they represent a methylenedioxy or ethylenedioxy group; R_4 represents a hydrogen atom or a methyl group; and either R_6 represents a hydrogen atom or a methoxy group in the 3-position of the phenyl ring and R_7 represents a methoxy group in the 4-position of the phenyl ring, or R_6 and R_7 together represent a methylenedioxy or ethylenedioxy group.

Particularly preferred compounds according to the invention are 1 - [4 - methyl - 6,7 - dimethoxy - 1(2H) - phthalazinone - 2 - yl] - 3 - [N - methyl - N - {2 - (3,4 - dimethoxyphenyl) - ethyl} - amino] - propane and acid addition salts thereof.

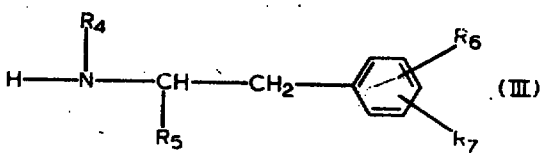
The compounds of general formula I may be prepared, for example, by the following processes, which processes constitute further features of the present invention:

a) Reaction of a compound of formula II,



(II)

(wherein A, R_2, R_3 and n are as hereinbefore defined and Z represents a leaving group e.g. a chlorine, bromine or iodine atom or an alkylsulphonyloxy or arylsulphonyloxy group) with a compound of formula III,

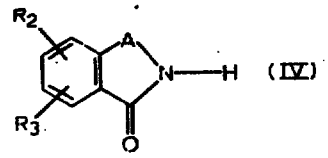


(III)

(wherein R_4, R_5, R_6 and R_7 are as hereinbefore defined).

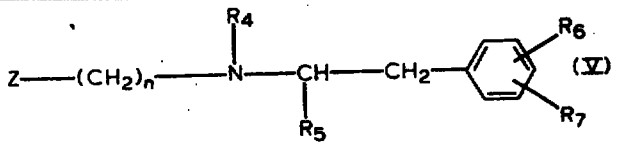
The reaction is optionally carried out in the presence of a solvent such as, for example, ether, tetrahydrofuran, methylformamide, dimethylformamide, dimethylsulphoxide, chlorobenzene or benzene. The reaction is conveniently effected at temperatures of from −50 to 250°C depending on the reactivity of the group Z. Preferably the reaction is effected at the boiling point of the reaction mixture. The presence of an acid-binding agent, such as, for example, an alcoholate, an alkali metal hydroxide, an alkali metal carbonate e.g. potassium carbonate or a tertiary organic base e.g. triethylamine or pyridine and/or of a reaction accelerator such as, for example, potassium iodide, may be of advantage.

b) Reaction of a compound of formula IV,



(IV)

(wherein A, R_2 and R_3 are as hereinbefore defined) with a compound of formula V,

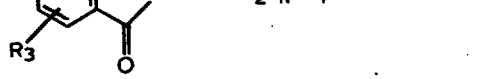


(V)

(wherein R_4, R_5, R_6, R_7 and n are as hereinbefore defined and Z represents a leaving group e.g. a chlorine, bromine or iodine atom or an alkylsulphonyloxy or arylsulphonyloxy group).

The reaction is optionally effected in the presence of a solvent such as, for example, acetone, dimethylformamide, dimethylsulphoxide or chlorobenzene and conveniently, depending on the reactivity of the group Z, at temperatures of from 0 to 150°C. Preferably the reaction is effected at the boiling point of the reaction mixture. The presence of an acid-binding agent, such as, for example, an alcoholate, an alkali metal hydroxide, an alkali metal carbonate e.g. potassium carbonate, an alkali metal amide or a tertiary organic base e.g. triethylamine or pyridine and/or of a reaction accelerator such as, for example, potassium iodide, may be of advantage.

c) Reaction of a compound of formula VI,

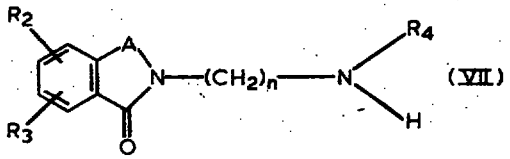


(VI)

(wherein A, R_2, R_3 and n are as hereinbefore defined) or an acetal thereof, with a compound of formula III as hereinbefore defined, in the presence of catalytically activated hydrogen.

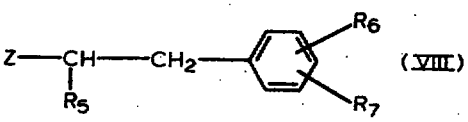
The reaction is conveniently carried out in the presence of hydrogen and palladium/charcoal. The catalytically activated hydrogen is preferably at a pressure of about 5 atmospheres. The reaction is conveniently effected in the presence of methanol, ethanol or dioxan as solvent and also conveniently at temperatures of from 0 to 100°C, preferably 20 to 80°C.

d) Reaction of a compound of formula VII,



(VII)

(wherein A, R_2, R_3, R_4 and n are as hereinbefore defined) with a compound of formula VIII,

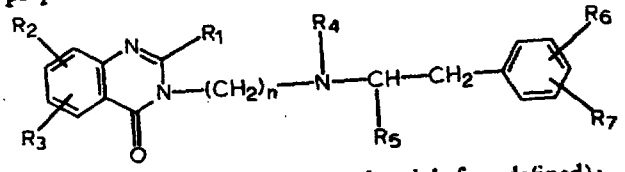


(VIII)

(wherein R_5, R_6 and R_7 are as hereinbefore defined and Z represents a leaving group e.g. a chlorine, bromine or iodine atom or an alkylsulphonyloxy or arylsulphonyloxy group).

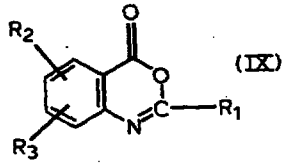
The reaction is optionally effected in the presence of a solvent such as, for example, acetone, methylene chloride, dimethylformamide, dimethylsulphoxide or chlorobenzene and conveniently, depending on the reactivity of the group Z, at temperatures of from 0 to 150°C. Preferably the reaction is effected at the boiling point of the reaction mixture. The presence of an acid-binding agent such as, for example, an alcoholate, an alkali metal hydroxide, an alkali metal carbonate e.g. potassium carbonate or a tertiary organic base e.g. triethylamine or pyridine and/or of a reaction-accelerator such as, for example, potassium iodide, may be of advantage.

e) for the preparation of compounds of general formula:



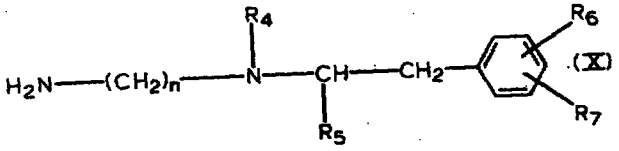
(wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7 and n are as hereinbefore defined):

Reaction of a compound of formula IX,



(IX)

(wherein R_1, R_2 and R_3 are as hereinbefore defined) with a compound of formula X,



(X)

(wherein R_4, R_5, R_6, R_7 and n are as hereinbefore defined).

The reaction is conveniently carried out in the presence of a solvent such as, for example, benzene, dioxan, an aliphatic carboxylic acid containing from 1 to 3 carbon atoms e.g. glacial acetic acid or dimethylformamide and optionally in the presence of an acidic catalyst. The reaction is conveniently effected at temperatures of from 50 to 150°C. Preferably the reaction is effected ar the boiling point of the reaction mixture.

f) for the preparation of compounds of general formula I wherein R_4 represents a hydrogen atom:

Debenzylation of a compound of formula I as hereinbefore defined wherein R_4 represents a benzyl group.

Debenzylation is preferably effected by catalytic hydrogenation, e.g. with hydrogen in the presence of palladium/charcoal. A preferred hydrogen pressure is from 1 to 7 atmospheres. The debenzylation is preferably effected in the presence of a solvent such as, for example, ethanol or ethyl acetate and preferably at temperatures of from 25 to 75°C.

g) for the preparation of compounds of general formula I wherein R_4 represents an alkyl group containing from 1 to 3 carbon atoms:

Alkylation of a compound of formula I as hereinbefore defined wherein R_4 represents an hydrogen atom.

Alkylation is preferably effected by means of an appropriate alkyl halide, e.g. an iodide or bromide, or of a dialkyl sulphate. Thus suitable agents for effecting the alkylation include, for example, methyl iodide, ethyl iodide, isopropyl bromide and dimethylsulphate. The alkylation is preferably effected in the presence of acetone, dimethylformamide or dioxan as solvent and optionally in the presence of an inorganic or tertiary organic base. Preferred temperatures for the alkylation are from 0 to 50°C. Where it is desired to prepare a compound of formula I wherein R_4 represents a methyl group, alkylation may also be effected by means of a mixture of formaldehyde and formic acid, preferably at the boiling point of the reaction mixture.

h) for the preparation of compounds of general formula I wherein R_4 represents a benzyl group:

Benzylation of a compound of formula I as hereinbefore defined wherein R_4 represents a hydrogen atom.

Benzylation may, for example, be effected by means of a benzyl halide. The benzylation is preferably effected in the presence of acetone, dimethylformamide or dioxan as solvent, preferably at temperatures of from 0 to 50°C and optionally in the presence of a base.

The compounds of general formula I may, if desired, be converted into their physiologically compatible acid addition salts by reaction with an appropriate acid. Suitable acids include, for example, hydrochloric, phosphoric, hydrobromic, sulphuric, lactic, tartaric and maleic acid.

The compounds of general formulae II to X, useful as starting materials in the processes described above, are either known from the literature or may be prepared by known processes (see Examples).

As mentioned above, the compounds according to the invention possess interesting pharmacological properties. Those compounds which we have tested exhibit both a mild hypotensive effect and especially a selective heart frequency lowering effect. The compounds of general formula I and their physiologically compatible salts are thus useful in the treatment of pectangious complaints, particularly chronic coronary insufficiency.

For example, the following compounds have been tested:

A=1 - [4 - Methyl - 6,7 - dimethoxy - 1(2H) - phthalazinone - 2 - yl] - 3 - [N - methyl - N - {2 - (3,4 - dimethoxyphenyl) - ethyl} - amino] - propane hydrochloride,

B=1 - [4 - Methyl - 6,7 - dimethoxy - 1(2H) - phthalazinone - 2 - yl] - 3 - [N - methyl - N - {2 - (4 - methoxyphenyl) - ethyl} - amino] - propane hydrochloride,

C=1 - [4 - Isopropyl - 6,7 - dimethoxy - 1(2H) - phthalazinone - 2 - yl] - 3 - [N - methyl - N - {2 - (3,4 - dimethoxyphenyl) - ethyl} - amino] - propane hydrochloride,

D=1 - [6,7 - Dimethoxy - 1(2H) - phthalazinone - 2 - yl] -3 - [N - methyl - N - {2 - (4 - methoxyphenyl) - ethyl} - amino] - propane hydrochloride and

E=1 - [4 - Methyl - 6,7 - dimethoxy - 1(2H) - phthalazinone - 2 - yl] - 2 - [N - methyl - N - {2 - (3,4 - dimethoxyphenyl) - ethyl} - amino] - ethane hydrochloride.

The effect of the test compounds on the heart frequency of groups of 2—5 cats and dogs of both sex was examined. The average weight of the cats was 2.5—3.5 kg and that of the dogs 18—28 kg. The animals were anaesthetized with "Nembutal" [registered Trade Mark] (30 mg/kg i.p.) and cholralose-urethan (40 mg/ml chloralose+200 mg/ml urethan as required). The test compound under examination was injected in a suitable solvent into the *Vena saphena* or the duodenum.

The heart frequency was recorded before and after administration of the test compound by means of the electrocardiogram (precordial lead) on a Grass-polygraph.

The following tables show the values recorded:

STUDIES IN CATS:

Test Compound	Dosage mg/kg	Decrease in heart frequency 1/minute	Duration of activity in minutes
A	0.5 i.v.	– 16	> 50
A	1.0 i.v.	– 23	> 70
A	2.0 i.v.	– 37	> 70
A	2.0 i.d.	– 25	> 74
A	4.0 i.d.	– 34	> 60
A	10.0 i.d.	– 41	>> 50
D	0.5 i.v.	– 6	10
D	1.0 i.v.	– 13	25
D	2.0 i.v.	– 14	25
E	1.0 i.v.	– 10	9
E	2.0 i.v.	– 13	10

STUDIES IN DOGS:

Test Compound	Dosage mg/kg	Decrease in heart frequency l/minute	Duration of activity in minutes
A	0.25 i.v.	– 10	17
A	0.5 i.v.	– 12	15
A	1.0 i.v.	– 16	24
B	0.25 i.v.	– 6	24
B	1.0 i.v.	– 23	46
C	1.0 i.v.	– 10	17
C	2.0 i.v.	– 29	10

The test compounds were all very well tolerated and showed no toxic side-effects at the dosages administered. The LD_{50} e.g. for test compound A was found in the mouse to be 63 mg/kg i.v. over a control period of 14 days.

According to a yet 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 compatible acid addition salt thereof in association with a pharmaceutical carrier or excipient.

For pharmaceutical administration the compounds of general formula I and their physiologically compatible salts may be incorporated into the conventional pharmaceutical preparations in either solid or liquid form, optionally in combination with other active ingredients. The compositions may, for example, be presented in a form suitable for oral, rectal or parenteral administration. Preferred forms include, for example, tablets, coated tablets, powders, suspensions, suppositories and solutions e.g. for injection.

The active ingredient may be incorporated in excipients customarily employed in pharmaceutical compositions such as, for example, talc, gum arabic, lactose, starch, magnesium stearate, cocoa butter, aqueous or non-aqueous vehicles, fatty substances of animal or vegetable origin, paraffin derivatives, glycols, various wetting, dispersing or emulsifying agents and/or preservatives.

Advantageously the compositions may be formulated as dosage units, each unit being adapted to supply a fixed dose of active ingredient. Suitable dosage units for adults contain from 50 to 250 mg of active ingredient.

The following non-limiting examples serve to illustrate the present invention.

Example 1

1-[4-Methyl-6,7-dimethoxy-1(2H)-phthalazinone-2-yl]-2-[N-methyl-N-{2-(3,4-dimethoxyphenyl)-ethyl}-amino]-ethane hydrochloride

a) 1-(4-Methyl-6,7-dimethoxy-1(2H)-phthalazinone-2-yl)-2-bromo-ethane

1.2 g of sodium hydride (50% dispersion in oil) were added to a solution of 5.0 g (22.7 mmol) of 4 - methyl - 6,7 - dimethoxy - 1(2H) - phthalazinone in 50 ml of dimethylformamide. After heating up to 80°C over 20 minutes, the sodium salt of 4 - methyl - 6,7 - dimethoxy - 1(2H) - phthalazinone thus obtained was alkylated by adding 30 ml of 1,2-dibromoethane at 80°C. After 2 hours, the sodium bromide thus precipitated was filtered under suction and the filtrate was evaporated to dryness under vacuum. The residue was dissolved in chloroform and the chloroform phase was extracted with water, dried over sodium sulphate and evaporated.

Yield: 5.2 g (70% of the theory).

R_f value (chloroform/methanol=9/1): 0.8.

b) 1-[4-Methyl-6,7-dimethoxy-1(2H)-phthalazinone-2-yl]-2-[N-methyl-N-{2-(3,4-dimethoxyphenyl)-ethyl}-aminoethane hydrochloride

To a solution of 2.5 g (7.6 mmol) of 1 - [4 - methyl - 6,7 - dimethoxy - 1(2H) - phthalazinone - 2 - yl] - 2 - bromo - ethane in 50 ml of chlorobenzene were added 1.5 g (7.6 mmol) of 3,4-dimethoxyphenylethyl-N-methylamine and 3.0 g of sodium carbonate and the resultant mixture was refluxed for 20 hours. After cooling the solid residue thus formed was filtered off and the filtrate was evaporated. The residue obtained was chromatographed on silica gel (chloroform/methanol=100/1), the major fractions were evaporated and the desired compound was precipitated as its hydrochloride.

Yield: 1.8 g (49% of the theory).

M.p.: 204—205°C.

Example 2

1-[4-Methyl-6,7-dimethoxy-1(2H)-phthalazinone-2-yl]-3-[N-methyl-{N-2-(3,4-dimethoxyphenyl)-ethyl}-amino]-propane hydrochloride

a) 1-[4-Methyl-6,7-dimethoxy-1(2H)-phthalazinone-2-yl]-3-chloro-propane

Produced analogously to Example 1a by reaction of 4-methyl-6,7-dimethoxy-1(2H)-phthalazinone with 1-bromo-3-chloro-propane in dimethylformamide.

R_f value (chloroform/methanol=9/1): 0.9.

b) 1-[4-Methyl-6,7-dimethoxy-1(2H)-phthalazinone-2-yl]-3-[N-methyl-N-{2-(3,4-dimethoxyphenyl)-ethyl}-amino]-propane hydrochloride

Produced analogously to Example 1b by reaction of 1 - [4 - methyl - 6,7 - dimethoxy - 1(2H) - phthalazinone - 2 - yl] - 3 - chloro - propane with 3,4 - dimethoxyphenylethyl - N - methylamine in chlorobenzene.

M.p.: 110—115°C.

R_f value (chloroform/methanol=9/1): 0.45.

Example 3

1-[4-Isopropyl-6,7-dimethoxy-1(2H)-phthalazinone-2-yl]-3-[N-methyl-N-{2-(3,4-dimethoxyphenyl)-ethyl}-amino]-propane hydrochloride

a) 1-[4-Isopropyl-6,7-dimethoxy-1(2H)-phthalazinone-2-yl]-3-chloro-propane

Produced analogously to Example 1a by reaction of 4 - isopropyl - 6,7 - dimethoxy - 1(2H) - phthalazinone with 1 - bromo - 3 - chloro - propane in dimethylformamide.

R_f value (chloroform/methanol=50/1): 0.5.

b) 1-[4-Isopropyl-6,7-dimethoxy-1(2H)-phthalazinone-2-yl]-3-[N-methyl-N-{2-(3,4-dimethoxyphenyl)-ethyl}-amino]-propane hydrochloride

Produced analogously to Example 1b by reaction of 1 - [4 - isopropyl - 6,7 - dimethoxy - 1(2H) - phthalazinone - 2 - yl] - 3 - chloro - propane with 3,4 - dimethoxyphenylethyl - N - methylamine in chlorobenzene.

M.p.: 179—180°C.

Example 4

1-[4-Methyl-6,7-dimethoxy-1(2H)-phthalazinone-2-yl]-3-[N-methyl-N-{2-(4-methoxyphenyl)-ethyl}-amino]-propane hydrochloride

Produced analogously to Example 2b by reaction of 1 - [4 - methyl - 6,7 - dimethoxy - 1(2H) - phthalazinone - 2 - yl] - 3 - chloro - propane with 4 - methoxyphenylethyl - N - methylamine in chlorobenzene.

M.p.: 210—212°C.

Example 5

1-[6,7-Dimethoxy-1(2H)-phthalazinone-2-yl]-3-[N-methyl-N-{2-(3,4-dimethoxyphenyl)-ethyl}-amino]-propane hydrochloride

a) 1-[6,7-Dimethoxy-1(2H)-phthalazinone-2-yl]-3-chloropropane

Produced analogously to Example 1a by reaction of 6,7 - dimethoxy - 1(2H) - phthalazinone with 1 - bromo - 3 - chloropropane in dimethylformamide.

R_f value (chloroform/methanol=9/1): 0.9.

b) 1-[6,7-Dimethoxy-1(2H)-phthalazinone-2-yl]-3-[N-methyl-N-{2-(3,4-dimethoxyphenyl)-ethyl}-amino]-propane hydrochloride

Produced analogously to Example 1b by reaction of 1 - [6,7 - dimethoxy - 1(2H) - phthalazinone - 2 - yl] - 3 - chloro - propane with 3,4 - dimethoxyphenylethyl - N - methylamine in chlorobenzene. m.p.: 200°C.

Example 6

1-[4-Methyl-6,7-dimethoxy-1(2H)-phthalazinone-2-yl]-3-[N-{2-(3,4-dimethoxyphenyl)-ethyl}-amino]-propane

a) 1-[4-Methyl-6,7-dimethoxy-1(2H)-phthalazinone-2-yl]-3-[N-benzyl-N-{2-(3,4-dimethoxyphenyl)-ethyl}-amino]-propane

Produced analogously to Example 1b by reaction of 1 - [4 - methyl - 6,7 - dimethoxy - 1(2H) - phthalazinone - 2 - yl] - 3 - chloropropane with 3,4 - dimethoxyphenylethyl - N - benzylamine in chlorobenzene.

R_f value (chloroform/methanol=9/1): 0.9.

b) 1-[4-Methyl-6,7-dimethoxy-1(2H)-phthalazinone-2-yl]-3-[N-{2-(3,4-dimethoxyphenyl)-ethyl}-amino]-propane

Into a solution of 2.6 g (4.4 mmol) of 1 - [4 - methyl - 6,7 - dimethoxy - 1(2H) - phthalazinone - 2 - yl] - 3 - [N - benzyl - N - {2 - (3,4 - dimethoxyphenyl) - ethyl} - amino] - propane in 100 ml of ethanol, to which 0.3 g of palladium/charcoal (10%) had been added, was introduced hydrogen at a temperature of 50°C and at 5 atmospheres. After the absorption of hydrogen had finished, the catalyst was filtered off and the filtrate was evaporated under vacuum. The free base was obtained as a yellow oil.

Yield: 1.8 g (82% of theory).

R_f value (chloroform/methanol=9/1): 0.4.

Example 7

1-[4-Methyl-6,7-ethylenedioxy-1(2H)-phthalazinone-2-yl]-3-[N-methyl-N-{2-(3,4-dimethoxyphenyl)-ethyl}-amino]-propane hydrochloride

a) 1-[4-Methyl-6,7-ethylenedioxy-1(2H)-phthalazinone-2-yl]-3-chloro-propane

Produced analogously to Example 1a by reaction of 4 - methyl - 6,7 - ethylenedioxy - 1(2H) - phthalazinone with 1 - bromo - 3 - chloro - propane in dimethylformamide.

R_f value (chloroform/methanol=19/1): 0.9.

b) 1-[4-Methyl-6,7-ethylenedioxy-1(2H)-phthalazinone-2-yl]-3-[N-methyl-N-{2-(3,4-dimethoxyphenyl)-ethyl}-amino]-propane

Produced analogously to Example 1b by reaction of 1 - [4 - methyl - 6,7 - ethylenedioxy - 1(2H) - phthalazinone - 2 - yl] - 3 - chloro - propane with 3,4 - dimethoxyphenylethyl - N - methylamine in chlorobenzene.

Yellow oil.

R_f value (chloroform/methanol=9/1): 0.7.

Example 8

1-[4-Methyl-6,7-dimethoxy-1(2H)-phthalazinone-2-yl]-3-[N-methyl-N-{2-(3,4-methylenedioxyphenyl)-ethyl}-amino]-propane

Produced analogously to Example 2b by reaction of 1 - [4 - methyl - 6,7 - dimethoxy - 1(2H) - phthalazinone - 2 - yl] - 3 - chloro - propane with 3,4-methylenedioxyphenylethyl - N - methylamine in chlorobenzene.

Yellow oil.

R_f value (chloroform/methanol=9/1): 0.45.

Example 9

1-[4-Methyl-6,7-dimethoxy-1(2H)-phthalazinone-2-yl]-3-[N-methyl-N-{2-(3,4-dimethoxyphenyl)-ethyl}-amino]-propane hydrochloride

5.0 g (11.3 mmol) of the compound obtained according to Example 6b were heated in a mixture of 1.38 g (30 mmol) of formic acid and 1.5 g (20 mmol) of formalin over a period of 1 hour at 100°C. After cooling the resultant solution was made alkaline by the addition of 2N sodium hydroxide and then extracted with chloroform. The chloroform phase was washed with water, dried and evaporated under vacuum. The residue obtained was chromatographed on silica gel (chloroform/methanol=100/1) and the major fractions were evaporated. The hydrochloride was precipitated from ethereal hydrochloric acid.

M.p.: 110—115°C.

Example 10

1-[4-Methyl-6,7-dimethoxy-1(2H)-phthalazinone-2-yl]-3-[N-{2-(3,4-dimethoxyphenyl)-ethyl}-amino]-propane hydrochloride

Into a solution of 3.0 g (11.3 mmol) of 4 - methyl - 3 - (6,7 - dimethoxy - 1(2H) - phthalazinone - 2 - yl) - propionaldehyde and 2.0 g (11.3 mmol) of 3,4 -

dimethoxyphenylethylamine in 100 ml of ethanol to which 0.3 g of palladium/charcoal (10%) had been added, was introduced hydrogen at a temperature of 50°C and at 5 atmospheres over a 4 hour period. After the absorption of hydrogen had finished, the catalyst was filtered off. The filtrate was evaporated under vacuum, yielding a viscous yellow oil.

Yield: 3.7 g (67% of theory).

R_f value (chloroform/methanol=9/1): 0.4.

Example 11

1-[6,7-Dimethoxy-4(3H)-quinazolinone-3-yl]-2-[N-methyl-N-{2-(3,4-dimethoxyphenyl)-ethyl}-amino]-ethane hydrochloride

a) 1-(6,7-Dimethoxy-4(3H)-quinazolinone-3-yl)-2-bromoethane

Produced analogously to Example 1a by reaction of 6,7 - dimethoxy - 4(3H) - quinazolinone with 1,2 - dibromo - ethane in dimethylformamide. Viscous oil.

R_f value (chloroform/methanol=9/1): 0.85.

b) 1-[6,7-Dimethoxy-4(3H)-quinazolinone-3-yl]-2-[N-methyl-N-{2-(3,4-dimethoxyphenyl)-ethyl}-amino]-ethane hydrochloride

Produced analogously to Example 1b by reaction of 1 - (6,7 - dimethoxy - 4(3H) - quinazolinone - 3 - yl) - 2 - bromo - ethane with 3,4 - dimethoxyphenylethyl - N - methylamine in chlorobenzene.

M.p.: 205—208°C.

Example 12

1-[6,7-Dimethoxy-4(3H)-quinazolinone-3-yl]-3-[N-methyl-N-{2-(3,4-dimethoxyphenyl)-ethyl}-amino]-propane hydrochloride

a) 1-(6,7-Dimethoxy-4(3H)-quinazolinone-3-yl)-3-chloro-propane

Produced analogously to Example 1a by reaction of 6,7 - dimethoxy - 4(3H) - quinazolinone with 1 - bromo - 3 - chloro - propane in dimethylformamide.

R_f value (chloroform/methanol=19/1): 0.75.

b) 1-[6,7-Dimethoxy-4(3H)-quinazolinone-3-yl]-3-[N-methyl-N-{2-(3,4-dimethoxyphenyl)-ethyl}-amino]-propane hydrochloride

Produced analogously to Example 1b by reaction of 1 - (6,7 - dimethoxy - 4(3H) - quinazolinone - 3 - yl) - 3 - chloro - propane with 3,4 - dimethoxyphenyl-ethyl - N - methylamine in chlorobenzene.

R_f value (chloroform/methanol=9/1): 0.4.

Example 13

1-[6,7-Dimethoxy-4(3H)-quinazolinone-3-yl]-3-[N-{2-(3,4-dimethoxyphenyl)-ethyl}-amino]-propane hydrochloride

a) 1-[6,7-Dimethoxy-4(3H)-quinazolinone-3-yl]-3-[N-benzyl-{2-(3,4-dimethoxyphenyl)-ethyl}-amino]-propane

Produced analogously to Example 1a by reaction of 1 - (6,7 - dimethoxy - 4(3H) - quinazolinone - 3 - yl) - 3 - chloro - propane with 3,4 - dimethoxyphenyl-ethyl - N - benzylamine in chlorobenzene.

R_f value (chloroform/methanol=9/1): 0.75.

b) 1-[6,7-Dimethoxy-4(3H)-quinazolinone-3-yl]-3-[N-{2-(3,4-dimethoxyphenyl)-ethyl}-amino]-propane hydrochloride

Produced analogously to Example 6b by debenzylation of 1 - (6,7 - dimethoxy - 4(3H) - quinazolinone - 3 - yl) - 3 - [N - benzyl - {2 - (3,4 - dimethoxyphenyl) - ethyl} - amino] - propane in the presence of palladium/charcoal (10%) with hydrogen.

R_f value (chloroform/methanol=9/1): 0.45.

M.p.: 192—194°C.

Example 14

1-[2-Methyl-6,7-dimethoxy-4(3H)-quinazolinone-3-yl]-3-[N-methyl-N-{2-(3,4-dimethoxyphenyl)-ethyl}-amino]-propane hydrochloride

A solution of 3.0 g (13.5 mmol) of 1 - [N - methyl - N - {2 - (3,4 - dimethoxyphenyl) - ethyl} - amino] - 3 - amino - propane and 3.3 g (13.0 mmol) of 2 - methyl - 6,7 - dimethoxy - 4H - 3,1 - benzoxazine - 4 - one in 50 ml of glacial acetic acid was refluxed for 4 hours. The mixture thus obtained was evaporated under vacuum and the residue was digested in 2N sodium hydroxide. The resultant mixture was extracted with chloroform. The chloroform phase was washed with a saturated sodium carbonate solution and with water, dried over sodium sulphate and evaporated. The crude product was purified by means of chromatography (chloroform/methanol=

30/1) on silica gel. By addition of ethereal hydrochloric acid to a solution of the product, the hydrochloride was precipitated and recrystallised from acetone/methanol.

Yield: 3.9 g (61% of theory).

M.p.: 215—217°C.

Example 15

1-[2-Methyl-6,7-dimethoxy-4(3H)-quinazolinone-3-yl]-3-[N-{2-(3,4-dimethoxyphenyl)-ethyl}-amino]-propane hydrochloride

Produced analogously to Example 14 by reaction of 2 - methyl - 6,7 - dimethoxy - 4H - 3,1 - benzoxazine - 4 - one with 1 - [N - {2 - (3,4 - dimethoxyphenyl) - ethyl} - amino] - 3 - amino - propane in glacial acetic acid.

M.p.: 243—245°C.

Example 16

1-[2-Methyl-6,7-dimethoxy-4-(3H)-quinazolinone-3-yl]-2-[N-methyl-N-{2-(3,4-dimethoxyphenyl)-ethyl}-amino]-ethane hydrochloride

a) 1-(2-Methyl-6,7-dimethoxy-4(3H)-quinazolinone-3-yl)-2-methylamino-ethane

Produced analogously to Example 14 from N - methylethylenediamine and 2 - methyl - 6,7 - dimethoxy - 4H - 3,1 - benzoxazine - 4 - one in glacial acetic acid.

Viscous oil.

Yield: 53% of theory.

b) 1-[2-Methyl-6,7-dimethoxy-4(3H)-quinazolinone-3-yl]-2-[N-methyl-N-{2-(3,4-dimethoxyphenyl)-ethyl}-amino]ethane hydrochloride

2.0 g (7.2 mmol) of 1 - (2 - methyl - 6,7 - dimethoxy - 4(3H) - quinazolinone - 3 - yl) - 2 - methylamino - ethane, 1.4 g (7.0 mmol) of 3,4 - dimethoxyphenylethyl chloride, 3.0 g of potassium carbonate and a small quantity of potassium iodide were refluxed together in chlorobenzene for 48 hours. After cooling the solution obtained was filtered and the filtrate was evaporated to dryness under vacuum. The crude product was purified by chromatography on silica gel (chloroform/methanol=50/1). The major fractions were evaporated and the residue was dissolved in acetone. The hydrochloride was precipitated by the addition of ethereal hydrochloric acid.

Yield: 1.1 g (30% of theory).

M.p.: 237—239°C.

Example 17

1-[4-Methyl-6,7-dimethoxy-1(2H)-phthalazinone-2-yl]-3-[N-methyl-N-{2-(3,4-dimethoxyphenyl)-ethyl}-amino]-propane hydrochloride

0.5 g of sodium hydride were added to a solution of 3.0 g (13.0 mmol) of 4 - methyl - 6,7 - dimethoxy - 1(2H) - phthalazinone in 100 ml dimethylformamide. After heating up the resultant mixture to 80°C for 30 minutes, a solution of 8.5 g (35.2 mmol) of 1 - [N - methyl - N - {2 - (3,4 - dimethoxyphenyl) - ethyl} - amino] - 3 - bromo - propane in 100 ml of dimethylformamide was added thereto dropwise. After then heating up to 140°C for 8 hours, the mixture thus obtained was cooled, diluted with water and extracted several times with chloroform.

The organic phase was dried over sodium sulphate and evaporated to dryness under vacuum. The residue obtained was chromatographed (chloroform/methanol=100/1) on silica gel. The major fraction was evaporated and the residue was dissolved in acetone. The base was precipitated as its hydrochloride.

Yield: 0.6 g (10% of theory).

M.p.: 110—115°C.

Example A

Tablets containing 100 mg of 1-[4-methyl-6,7-dimethoxy-1(2H)-phthalazinone-2-yl]-3-[N-methyl-N-{2-(3,4-dimethoxyphenyl)-ethyl}-amino]-propane hydrochloride

Composition:

Active ingredient	100.0 mg
lactose	50.0 mg
polyvinylpyrrolidone	5.0 mg
carboxymethylcellulose	19.0 mg
magnesium stearate	1.0 mg
	175.0 mg

Method of preparation:

The active ingredient and lactose were homogeneously moistened together with an aqueous solution of the polyvinylpyrrolidone and the mixture obtained was passed through a screen. After drying, the granulate thus formed was mixed with the

remaining ingredients and the resultant mixture was pressed into tablets in the conventional manner.

Example B

Coated tablets containing 50 mg of 1-[4-methyl-6,7-dimethoxy-1(2H)-phthalazinone-2-yl]-3-[N-methyl-N-{2-(3,4-dimethoxyphenyl)-ethyl}-amino]-propane hydrochloride

1 coated tablet core contains:

Active ingredient	50.0 mg
dried corn starch	20.0 mg
soluble starch	2.0 mg
carboxymethylcellulose	7.0 mg
magnesium stearate	1.0 mg
	80.0 mg

Method of preparation:

The mixture was processed to coated tablet cores as described in Example A. The cores were then coated with sugar and gum arabic according to conventional methods.

Example C

Suppositories containing 150 mg of 1-[4-methyl-6,7-dimethoxy-1(2H)-phthalazinone-2-yl]-3-[N-methyl-N-{2-(3,4-dimethoxyphenyl)-ethyl}-amino]-propane hydrochloride

Composition:

Active ingredient	150.0 mg
suppository mass	1 550.0 mg
	1 700.0 mg

Method of preparation:

The active ingredient was stirred into the molten suppository mass to form a suspension. The liquid mixture was then poured into cooled suppository moulds.

Example D

Suspension containing 50 mg/ml of 1-[4-methyl-6,7-dimethoxy-1(2H)-phthalazinone-2-yl]-3-[N-methyl-N-{2-(3,4-dimethoxyphenyl)-ethyl}-amino]-propane hydrochloride

100 ml of suspension contain:

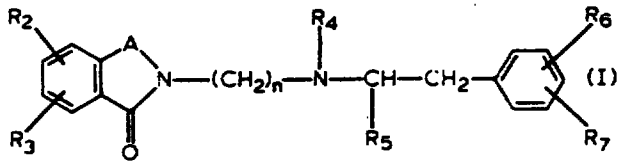
Active ingredient		5.0 g
carboxymethylcelluose		0.1 g
methyl *p*-hydroxybenzoate		0.05 g
propyl *p*-hydroxybenzoate		0.01 g
sugar		10.0 g
glycerine		5.0 g
70% sorbitol solution		20.0 g
flavouring		0.3 g
distilled water	ad	100.0 ml

Method of preparation:

The benzoic acid esters as well as the glycerine and carboxymethylcellulose were dissolved, whilst stirring, in the water heated up to 70°C. The solution thus obtained was cooled to room temperature and the active ingredient was added whilst stirring and homogeneously dispersed. After adding and dissolving the sugar, the sorbitol solution and the flavouring the suspension was placed under vacuum for deaeration whilst stirring.

WHAT WE CLAIM IS:—

1. Compounds of general formula I,



remaining ingredients and the resultant mixture was pressed into tablets in the conventional manner.

Example B

Coated tablets containing 50 mg of 1-[4-methyl-6,7-dimethoxy-1(2H)-phthalazinone-2-yl]-3-[N-methyl-N-{2-(3,4-dimethoxyphenyl)-ethyl}-amino]-propane hydrochloride

1 coated tablet core contains:

Active ingredient	50.0 mg
dried corn starch	20.0 mg
soluble starch	2.0 mg
carboxymethylcellulose	7.0 mg
magnesium stearate	1.0 mg
	80.0 mg

Method of preparation:

The mixture was processed to coated tablet cores as described in Example A. The cores were then coated with sugar and gum arabic according to conventional methods.

Example C

Suppositories containing 150 mg of 1-[4-methyl-6,7-dimethoxy-1(2H)-phthalazinone-2-yl]-3-[N-methyl-N-{2-(3,4-dimethoxyphenyl)-ethyl}-amino]-propane hydrochloride

Composition:

Active ingredient	150.0 mg
suppository mass	1 550.0 mg
	1 700.0 mg

Method of preparation:

The active ingredient was stirred into the molten suppository mass to form a suspension. The liquid mixture was then poured into cooled suppository moulds.

Example D

Suspension containing 50 mg/ml of 1-[4-methyl-6,7-dimethoxy-1(2H)-phthalazinone-2-yl]-3-[N-methyl-N-{2-(3,4-dimethoxyphenyl)-ethyl}-amino]-propane hydrochloride

100 ml of suspension contain:

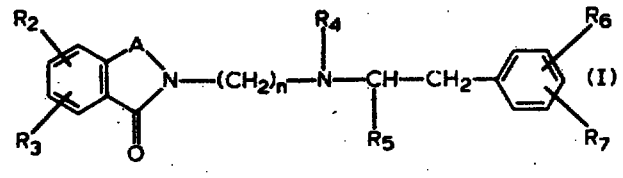
Active ingredient		5.0 g
carboxymethylcelluose		0.1 g
methyl *p*-hydroxybenzoate		0.05 g
propyl *p*-hydroxybenzoate		0.01 g
sugar		10.0 g
glycerine		5.0 g
70% sorbitol solution		20.0 g
flavouring		0.3 g
distilled water	ad	100.0 ml

Method of preparation:

The benzoic acid esters as well as the glycerine and carboxymethylcellulose were dissolved, whilst stirring, in the water heated up to 70°C. The solution thus obtained was cooled to room temperature and the active ingredient was added whilst stirring and homogeneously dispersed. After adding and dissolving the sugar, the sorbitol solution and the flavouring the suspension was placed under vacuum for deaeration whilst stirring.

WHAT WE CLAIM IS:—

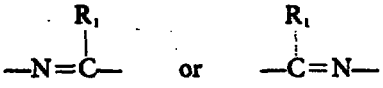
1. Compounds of general formula I,



* C L M S *

wherein

A represents a group of formula



in which R_1 represents a hydrogen atom or an alkyl group containing from 1 to 3 carbon atoms;

either R_2 and R_3, which may be the same or different, each represents an alkoxy group containing from 1 to 3 carbon atoms, or together represent a methylenedioxy or ethylenedioxy group;

R_4 represents a hydrogen atom, an alkyl group containing from 1 to 3 carbon atoms or a benzyl group;

R_5 represents a hydrogen atom or an alkyl group containing from 1 to 3 carbon atoms;

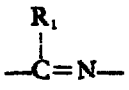
either R_6 represents an hydrogen atom or an alkoxy group containing from 1 to 3 carbon atoms and R_7 represents an alkoxy group containing from 1 to 3 carbon atoms, or R_6 and R_7 together represent a methylenedioxy or ethylenedioxy group; and

n is 2 or 3;

and acid addition salts thereof.

2. Compounds as claimed in claim 1 wherein R_1 represents a hydrogen atom or a methyl or isopropyl group; either R_2 and R_3 each represents a methoxy group or together represent a methylenedioxy or ethylenedioxy group; R_4 represents a hydrogen atom or a methyl or benzyl group; R_5 represents a hydrogen atom; and either R_6 represents a hydrogen atom or a methoxy group and R_7 represents a methoxy group or R_6 and R_7 together represent a methylenedioxy or ethylenedioxy group.

3. Compounds as claimed in claim 2 wherein A represents a group of formula



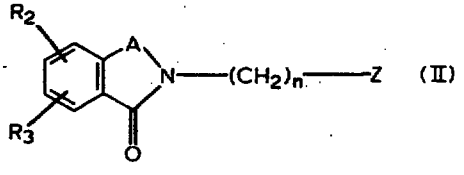
in which R_1 represents a hydrogen atom or a methyl group; either R_2 and R_3 each represents a methoxy group, one being in the 6-position and the other in the 7-position of the bicyclic ring, or together they represent a methylenedioxy or ethylenedioxy group; R_4 represents a hydrogen atom or a methyl group; and either R_6 represents a hydrogen atom or a methoxy group in the 3-position of the phenyl ring and R_7 represents a methoxy group in the 4-position of the phenyl ring, or R_6 and R_7 together represent a methylenedioxy or ethylenedioxy group.

4. 1 - [4 - Methyl - 6,7 - dimethoxy - 1(2H) - phthalazinone - 2 - yl] - 3 - [N - methyl - N - {2 - (3,4 - dimethoxyphenyl) - ethyl} - amino] - propane and acid addition salts thereof.

5. Compounds as claimed in any of the preceding claims in the form of physiologically compatible acid additions salts.

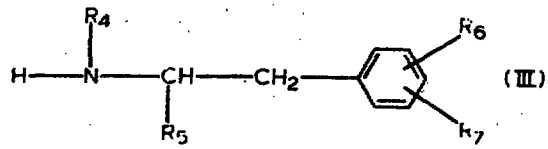
6. Compounds as claimed in claim 1, other than those claimed in claim 4, as herein specifically disclosed in any of Examples 1, 3 to 8 and 10 to 16.

7. A process for the preparation of compounds of general formula I as defined in claim 1 which comprises reacting a compound of formula II,



(II)

(wherein A, R_2, R_3 and n are as defined in claim 1 and Z represents a leaving group) with a compound of formula III,



(III)

(wherein R_4, R_5, R_6 and R_7 are as defined in claim 1).

* C L M S *

8. A process as claimed in claim 7 wherein, in the compound of formula II, Z represents a chlorine, bromine or iodine atom or an alkylsulphonyloxy or arylsulphonyloxy group.

9. A process as claimed in claim 7 or claim 8 wherein the reaction is effected in the presence of a solvent.

10. A process as claimed in claim 9 wherein the solvent comprises ether, tetrahydrofuran, methylformamide, dimethylformamide, dimethylsulphoxide, chlorobenzene or benzene.

11. A process as claimed in any of claims 7 to 10 wherein the reaction is effected at temperatures of from −50 to 250°C.

12. A process as claimed in any of claims 7 to 10 wherein the reaction is effected at the boiling point of the reaction mixture.

13. A process as claimed in any of claims 7 to 12 wherein the reaction is effected in the presence of an acid-binding agent.

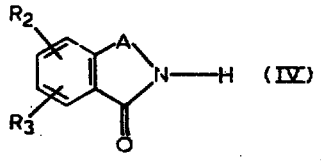
14. A process as claimed in claim 13 wherein the acid-binding agent comprises an alcoholate, an alkali metal hydroxide, an alkali metal carbonate or a tertiary organic base.

15. A process as claimed in claim 14 wherein the acid-binding agent comprises potassium carbonate, triethylamine or pyridine.

16. A process as claimed in any of claims 7 to 15 wherein the reaction is effected in the presence of a reaction accelerator.

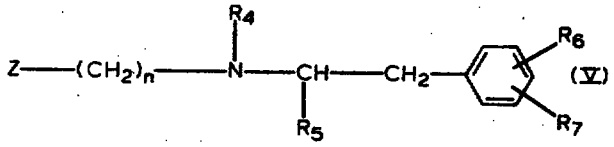
17. A process as claimed in claim 16 wherein the reaction accelerator comprises potassium iodide.

18. A process for the preparation of compounds of general formula I as defined in claim 1 which comprises reacting a compound of formula IV,



(IV)

(wherein A, R_2 and R_3 are as defined in claim 1) with a compound of formula V,



(V)

(wherein R_4, R_5, R_6, R_7 and n are as defined in claim 1 and Z represents a leaving group).

19. A process as claimed in claim 18 wherein, in the compound of formula V, Z is as defined in claim 8.

20. A process as claimed in claim 18 or claim 19 wherein the reaction is effected in the presence of a solvent.

21. A process as claimed in claim 20 wherein the solvent comprises acetone, dimethylformamide, dimethylsulphoxide or chlorobenzene.

22. A process as claimed in any of claims 18 to 21 wherein the reaction is effected at temperatures of from 0 to 150°C.

23. A process as claimed in any of claims 18 to 21 wherein the reaction is effected at the boiling point of the reaction mixture.

24. A process as claimed in any of claims 18 to 23 wherein the reaction is effected in the presence of an acid-binding agent.

25. A process as claimed in claim 24 wherein the acid-binding agent comprises an alcoholate, an alkali metal hydroxide, an alkali metal carbonate, an alkali metal amide or a tertiary organic base.

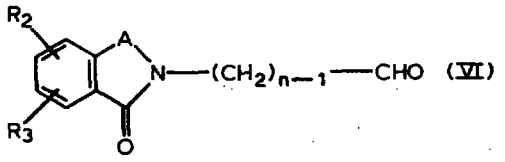
26. A process as claimed in claim 25 wherein the acid-binding agent comprises potassium carbonate, triethylamine or pyridine.

27. A process as claimed in any of claims 18 to 26 wherein the reaction is effected in the presence of a reaction accelerator.

28. A process as claimed in claim 27 wherein the reaction accelerator comprises potassium iodide.

* C L M S *

29. A process for the preparation of compounds of general formula I as defined in claim 1 which comprises reacting a compound of formula VI,



(VI)

(wherein A, R_2, R_3 and n are as defined in claim 1) or an acetal thereof, with a compound of formula III as defined in claim 7 in the presence of catalytically activated hydrogen.

30. A process as claimed in claim 29 wherein the reaction is effected in the presence of hydrogen and palladium/charcoal.

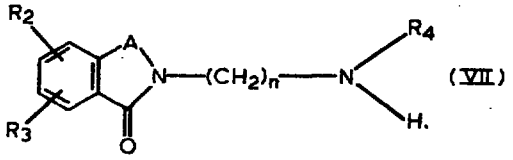
31. A process as claimed in claim 29 or claim 30 wherein the reaction is effected with a hydrogen pressure of about 5 atmospheres.

32. A process as claimed in any of claims 29 to 31 wherein the reaction is effected in the presence of methanol, ethanol or dioxan as solvent.

33. A process as claimed in any of claims 29 to 32 wherein the reaction is effected at temperatures of from 0 to 100°C.

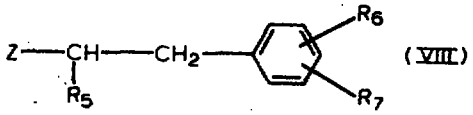
34. A process as claimed in claim 33 wherein the reaction is effected at temperatures of from 20 to 80°C.

35. A process for the preparation of compounds of general formula I as defined in claim 1 which comprises reacting a compound of formula VII,



(VII)

(wherein A, R_2, R_3, R_4 and n are as defined in claim 1) with a compound of formula VIII,



(VIII)

(wherein R_5, R_6 and R_7 are as defined in claim 1 and Z represents a leaving group).

36. A process as claimed in claim 35 wherein, in the compound of formula VIII, Z is as defined in claim 8.

37. A process as claimed in claim 35 or claim 36 wherein the reaction is effected in the presence of a solvent.

38. A process as claimed in claim 37 wherein the solvent comprises acetone, methylene chloride, dimethylformamide, dimethylsulphoxide or chlorobenzene.

39. A process as claimed in any of claims 35 to 38 wherein the reaction is effected at temperatures of from 0 to 150°C.

40. A process as claimed in any of claims 35 to 38 wherein the reaction is effected at the boiling point of the reaction mixture.

41. A process as claimed in any of claims 35 to 40 wherein the reaction is effected in the presence of an acid-binding agent.

42. A process as claimed in claim 41 wherein the acid-binding agent comprises an alcoholate, an alkali metal hydroxide, an alkali metal carbonate or a tertiary organic base.

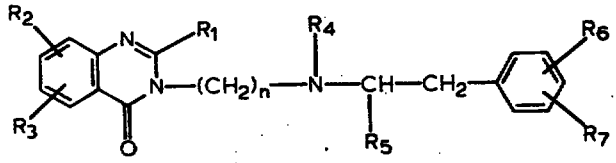
43. A process as claimed in claim 42 wherein the acid-binding agent comprises potassium carbonate, triethylamine or pyridine.

44. A process as claimed in any of claims 35 to 43 wherein the reaction is effected in the presence of a reaction-accelerator.

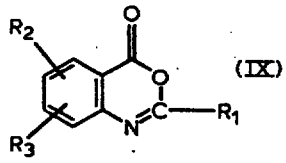
45. A process as claimed in claim 44 wherein the reaction accelerator comprises potassium iodide.

46. A process for the preparation of compounds of general formula:

* C L M S *

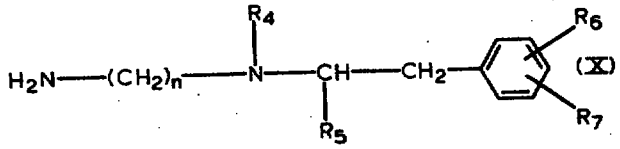


(wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7 and n are as defined in claim 1) which comprises reacting a compound of formula IX,



(IX)

(wherein R_1, R_2 and R_3 are as defined in claim 1) with a compound of formula X,



(X)

(wherein R_4, R_5, R_6, R_7 and n are as defined in claim 1).

47. A process as claimed in claim 46 wherein the reaction is effected in the presence of a solvent.

48. A process as claimed in claim 47 wherein the solvent comprises benzene, dioxan, an aliphatic carboxylic acid containing from 1 to 3 carbon atoms or dimethylformamide.

49. A process as claimed in claim 48 wherein the solvent comprises acetic acid.

50. A process as claimed in any of claims 46 to 49 wherein the reaction is effected in the presence of an acidic catalyst.

51. A process as claimed in any of claims 46 to 50 wherein the reaction is effected at temperatures of from 50 to 150°C.

52. A process as claimed in any of claims 46 to 50 wherein the reaction is effected at the boiling point of the reaction mixture.

53. A process for the preparation of compounds of general formula I as defined in claim 1 wherein R_4 represents a hydrogen atom which comprises debenzylating a compound of formula I as defined in claim 1 wherein R_4 represents a benzyl group.

54. A process as claimed in claim 53 wherein debenzylation is effected by catalytic hydrogenation.

55. A process as claimed in claim 54 wherein debenzylation is effected with hydrogen in the presence of palladium/charcoal.

56. A process as claimed in claim 54 or claim 55 wherein the hydrogen is at a pressure of from 1 to 7 atmospheres.

57. A process as claimed in any of claims 53 to 56 wherein the debenzylation is effected in the presence of a solvent.

58. A process as claimed in claim 57 wherein the solvent comprises ethanol or ethyl acetate.

59. A process as claimed in any of claims 53 to 58 wherein the debenzylation is effected at temperatures of from 25 to 75°C.

60. A process for the preparation of compounds of general formula I as defined in claim 1 wherein R_4 represents an alkyl group containing from 1 to 3 carbon atoms which comprises alkylating a compound of formula I as defined in claim 1 wherein R_4 represents a hydrogen atom.

61. A process as claimed in claim 60 wherein alkylation is effected by means of an appropriate alkyl halide or dialkyl sulphate.

62. A process as claimed in claim 61 wherein alkylation is effected by means of an appropriate alkyl iodide or bromide.

63. A process as claimed in any of claims 60 to 62 wherein the alkylation is effected in the presence of acetone, dimethylformamide or dioxan as solvent.

* C L M S *

64. A process as claimed in any of claims 60 to 63 wherein the alkylation is effected in the presence of a base.

65. A process as claimed in any of claims 60 to 64 wherein the alkylation is effected at temperatures of from 0 to 50°C.

66. A process as claimed in claim 60 for the preparation of compounds of general formula I wherein R_4 represents a methyl group wherein alkylation is effected by means of a mixture of formaldehyde and formic acid.

67. A process as claimed in claim 66 wherein the alkylation is effected at the boiling point of the reaction mixture.

68. A process for the preparation of compounds of general formula I as defined in claim 1 wherein R_4 represents a benzyl group which comprises benzylating a compound of formula I as defined in claim 1 wherein R_4 represents a hydrogen atom.

69. A process as claimed in claim 68 wherein benzylation is effected by means of a benzyl halide.

70. A process as claimed in claim 68 or claim 69 wherein the benzylation is effected in the presence of acetone, dimethylformamide or dioxan as solvent.

71. A process as claimed in any of claims 68 to 70 wherein the benzylation is effected in the presence of a base.

72. A process as claimed in any of claims 68 to 71 wherein the benzylation is effected at temperatures of from 0 to 50°C.

73. A process for the preparation of physiologically compatible acid addition salts of compounds of general formula I as defined in claim 1 which comprises reacting a compound of formula I as defined in claim 1 with an appropriate acid.

74. A process as claimed in claim 68 wherein the acid comprises hydrochloric, phosphoric, hydrobromic, sulphuric, lactic, tartaric or maleic acid.

75. A process for the preparation of compounds of general formula I as defined in claim 1 and their physiologically compatible acid addition salts substantially as herein described.

76. A process for the preparation of compounds of general formula I as defined in claim 1 and their physiologically compatible acid addition salts substantially as herein described in any of Examples 1 to 17.

77. Compounds of general formula I and their physiologically compatible salts whenever prepared by a process as claimed in any of claims 7 to 76.

78. Compounds of general formula I and their physiologically compatible salts whenever prepared by a process as claimed in any of claims 7 to 67, 73, 74 and 76.

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

80. Compositions as claimed in claim 79 in a form suitable for oral, rectal or parenteral administration.

81. Compositions as claimed in claim 79 or claim 80 in the form of tablets, coated tablets, powders, suspensions, suppositories and solutions.

82. Compositions as claimed in any of claims 79 to 81 in the form of dosage units.

83. Compositions as claimed in claim 82 wherein each dosage unit contains from 50 to 250 mg of active ingredient.

84. Compositions as claimed in any of claims 79 to 83 wherein the active ingredient comprises a compound as claimed in claim 4.

85. Pharmaceutical compositions as claimed in claim 79 substantially as herein described.

86. Pharmaceutical compositions substantially as herein described in any of Examples A to D.

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Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1979
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.

* C L M S *

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ERRATUM

SPECIFICATION No. 1,544,880

Page 1, Heading (54), *for* AMINOAKYL *read* AMINOALKYL

THE PATENT OFFICE
23rd August, 1982