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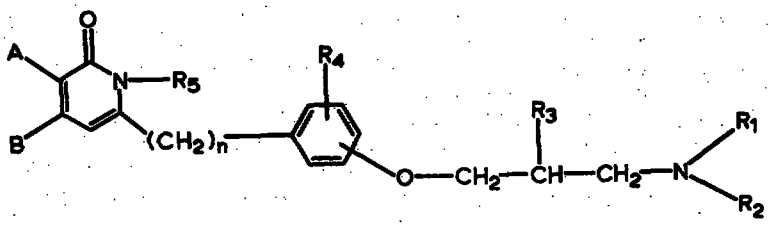


(54) ISOQUINOLINE AND NAPHTHYRIDINE SUBSTITUTED AMINOALKOXYPHENYL DERIVATIVES

(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 aminoalkoxyphenyl derivatives, 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 and B, together, with the carbon atoms to which they are attached, represent a fused phenyl ring (optionally substituted by from one to three groups which are alkoxy containing from 1 to 3 carbon atoms, amino or nitro groups) or a fused pyridyl ring;

R_1 and R_5, which may be the same or different, each represents a hydrogen atom or an alkyl containing from 1 to 3 carbon atoms group;

R_2 represents a straight or branched chain alkyl group containing from 1 to 6 carbon atoms or a group of formula —Y—Z (in which Y represents a straight chain alkylene group containing from 1 to 4 carbon atoms optionally substituted by a hydroxy group and Z represents an amino group, an alkoxycarbonyl group containing from 2 to 6 carbon atoms or a phenyl or phenoxy group, said phenyl or phenoxy group being optionally substituted by from 1 to 3 groups which are alkyl or alkoxy groups each containing from 1 to 3 carbon atoms;

R_3 represents a hydrogen atom or a hydroxy group;

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

n is 0, 1 or 2]

and acid addition salts thereof.

The compounds according to the invention possess interesting

pharmacological properties and in particular, in general an antianginous, antiarrhythmic and β-receptor-blocking effect.

It will be appreciated that, for pharmaceutical use, the salts referred to above will be physiologically compatible acid addition 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.

When the groups A, R_1, R_2, R_4 and R_5, represent or carry an alkyl group containing from 1 to 3 carbon atoms, this may be a methyl, ethyl, propyl or isopropyl group. Similarly when the groups A, R_2 and R_4 represent or carry a lower alkoxy group containing from 1 to 3 carbon atoms this may be a methoxy, ethoxy, propoxy or isopropoxy group.

When R_2 represents a group of formula —Y—Z in which Z represents a phenyl or phenoxy group optionally substituted by from 1 to 3 groups which are alkyl or alkoxy groups, Z may, for example represent a phenyl, 2-methoxyphenyl, 4-methoxyphenyl, 3,4-dimethoxyphenyl, 3,4,5-trimethoxyphenyl, phenoxy, 2-methylphenoxy, 4-methylphenoxy, 2-methoxyphenoxy or 4-methoxyphenoxy group.

A particular group of the compound according to the invention which may be mentioned are those wherein A and B, together with the carbon atoms to which they are attached, represent a phenyl, methoxyphenyl, dimethoxyphenyl or pyridyl group; R_2 represents a methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, isopropyl, isobutyl, isoamyl, tert.butyl or tert.pentyl group or a group of formula —Y—Z (in which Y represents a methylene, ethylene, hydroxyethylene, propylene, hydroxypropylene or butylene group and Z represents a phenyl, methoxyphenyl, dimethoxyphenyl, trimethoxyphenyl, methylphenyl, amino, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, pentoxycarbonyl, isopropoxycarbonyl, tert.butoxycarbonyl, tert.pentoxycarbonyl, phenoxy, methylphenoxy or methoxyphenoxy group); R_4 represents a hydrogen atom or a methoxy, ethoxy, propoxy or isopropoxy group; and R_5 represents a methyl, ethyl, propyl or isopropyl group.

Of the above group of compounds preferred compounds are those wherein R_1 represents a hydrogen atom or a methyl or ethyl group; R_2 represents an ethyl, isopropyl or tert.-butyl group or a group of formula —Y—Z (in which Y represents an ethylene, propylene, hydroxyethylene or hydroxypropylene group and Z represents a phenyl, methoxyphenyl, dimethoxyphenyl, trimethoxyphenyl, amino, methylphenyl, isopropoxycarbonyl, tert.butoxycarbonyl, phenoxy, methylphenoxy or methoxyphenoxy group; R_4 represents a hydrogen atom or a methoxy group; and R_5 represents a methyl group.

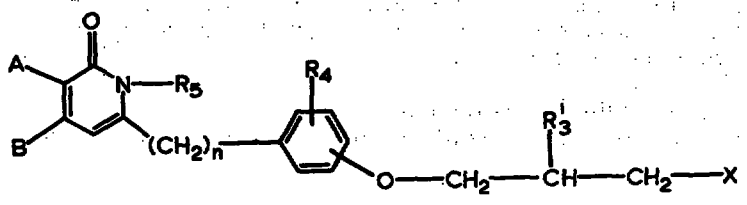
Especially preferred of such compounds are those wherein A and B, together with the carbon atoms to which they are attached, represent a phenyl, 4-methoxy-1,2-phenylene or 4,5-dimethoxy-1,2-phenylene group; R_1 represents a hydrogen atom; R_2 represents an isopropyl or tert.butyl group; and R_3 represents a hydroxy group.

Particularly preferred compounds according to the invention are the following:

2 - methyl - 3 - [4 - (2 - hydroxy - 3 - tert.butylamino - propoxy) - phenyl] - 7-methoxy - isoquinoline - 1(2H) - one,
2 - methyl - 3 - [2 - (2 - hydroxy - 3 - isopropylamino - propoxy) - phenyl] - 7-methoxy - isoquinoline - 1(2H) - one,
2 - methyl - 3 - [2 - (2 - hydroxy - 3 - isopropylamino - propoxy) - 4 - methoxy-phenyl] - 7 - methoxy - isoquinoline - 1(2H) - one
and acid addition salts thereof.

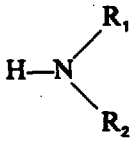
The compounds of general formula I may, for example be prepared according to the following processes, which processes constitute further features of the present invention:

A) Reaction of a compound of formula II,



(II)

(wherein A, B, R_4, R_5 and n as hereinbefore defined and either R_3' is as defined for R^3 above and X represents a group removable as an anion e.g. a halogen atom or R_3' and X together represent an epoxy group) with a compound of formula III,

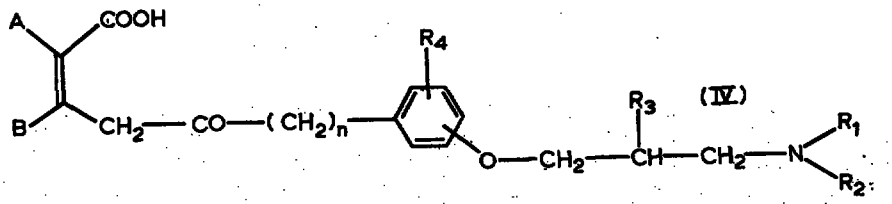


(III)

(wherein R_1 and R_2 are as hereinbefore defined).

The reaction may, if desired, be effected in the presence of a solvent, e.g. comprising isopropanol, tetrahydrofuran, dimethylformamide, dimethylsulfoxide or advantageously an excess of the compound of formula III. The reaction may also, conveniently be effected in the presence of an acid-binding agent such as e.g. an alkoxide or alkaline carbonate and optionally in a closed vessel. Reaction temperatures may, for example, be from 50 to 200°C, preferably from 80 to 160°C.

B) Reaction of a compound of formula IV,



(IV)

(wherein A, B, R_1, R_2, R_3, R_4 and n are as hereinbefore defined) or a reactive derivate thereof with a compound of formula V,

$$R_5—NH_2 \qquad (V)$$

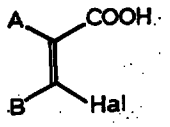
(wherein R_5 is as hereinbefore defined).

The reaction may, if desired, be effected in the presence of a solvent, e.g. comprising methanol, ethanol, isopropanol, dioxan, dimethylformamide or advantageously an excess of the compound of formula V. Optionally the reaction may be effected in the presence of a condensation agent such as e.g. an alkoxide and conveniently within a closed vessel. Reaction temperatures may, for example be from 50 to 200°C, preferably from 80 to 140°C.

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, e.g.hydrochloric acid, phosphoric acid, hydrobromic acid, sulfuric acid, lactic acid, citric acid, tartaric acid, oxalic acid and maleic acid.

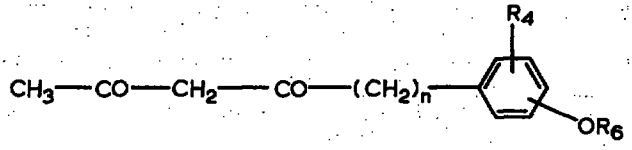
The compounds of general formulae II, III, IV and V are known from the literature or may be prepared by processes analogous to those known in the literature (see Examples).

Thus, for example, a compound of formula II may be obtained by reaction of a corresponding *o*-halo-carboxylic acid of formula VI,



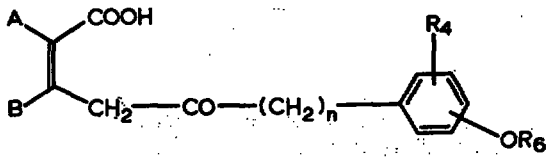
(VI)

(wherein A and B are as hereinbefore defined and Hal represents a chlorine, bromine or iodine atom) with a compound of formula VII,



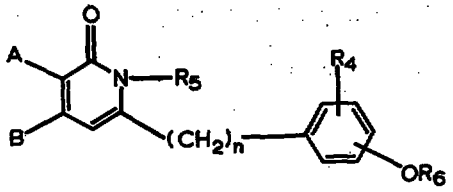
(VII)

(wherein R_4 and n are as hereinbefore defined and R_6 represents a methyl or benzyl group), conveniently in the presence of copper acetate as catalyst and in the presence of a sodium alkoxide, e.g. sodium ethoxide, and conveniently at temperatures of from 60 to 100°C. The carboxylic acid thus obtained of formula VIII,



(VIII)

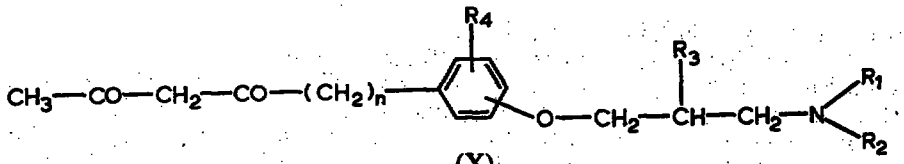
(wherein A, B, R_4, R_6 and n are as hereinbefore defined) may be reacted with an amine of formula V as hereinbefore defined, to give the corresponding cyclic ketone of formula IX,



(IX)

(wherein A, B, R_4, R_5, R_6 and n are as hereinbefore defined). The desired compound of formula II may be obtained therefrom by cleavage of the radical R_6 and reaction with a corresponding haloepihydrin or a corresponding 1-bromo-3-chloropropane in the presence of a solvent such as e.g. dimethylformamide or dimethylsulfoxide and in the presence of sodium ethoxide, conveniently at room temperature.

The starting compound of formula IV may, for example, be obtained by reaction of a corresponding phenoxy derivative of formula X,



(X)

(wherein R_1, R_2, R_3, R_4 and n are as hereinbefore defined) with a corresponding *o*-halo-carboxylic acid of formula VI as hereinbefore defined, preferably in the presence of sodium ethoxide and at temperatures of from 60 to 100°C.

As mentioned above, the compounds according to the invention possess useful pharmacological activity. Those compounds which we have tested exhibit an antianginous, antiarrhythmic and β-receptor-blocking effect. Such compounds are thus in general suitable for the treatment of certain coronary diseases and hypotension.

For example, the following compounds have been tested with respect to their biological activity:

A = 2 - Methyl - 3 - [4 - (2 - hydroxy - 3 - tert.butylamino - propoxy) - phenyl] - 7 - methoxy - isoquinoline - 1(2H) - one,

B = 2 - Methyl - 3 - [2 - (2 - hydroxy - 3 - isopropylamino - propoxy) - phenyl] - 7 - methoxy - isoquinoline - 1(2H) - one oxalate,

C = 2 - Methyl - 3 - [2 - (2 - hydroxy - 3 - isopropylamino - propoxy) - 4 - methoxy - isoquinoline - 1(2H) - one oxalate,

D = 2 - Methyl - 3 - [2 - (2 - hydroxy - 3 - tert. - butylamino - propoxy) - 4 - methoxy - phenyl] - 7 - methoxy - isoquinoline - 1(2H) - one oxalate,

E = 2 - Methyl - 3 - [4 - (2 - hydroxy - 3 - tert.butylamino - propoxy) - phenyl] - 6,7 - dimethoxy - isoquinoline - 1(2H) - one,

F = 2 - Methyl - 3 - [4 - (2 - hydroxy - 3 - isopropylamino - propoxy) - phenyl) - 6,7 - dimethoxy isoquinoline - 1(2H) - one,

G = 2 - Methyl - 3 - [3 - methoxy - 4 - (2 - hydroxy - 3 - isopropylamino - propoxy-phenyl] - 7 - methoxy - isoquinoline - 1(2H) - one and
H = 2 - Methyl - 3 - [4 - (2 - hydroxy - 3 - isopropylamino - propoxy) - phenethyl]-7 - methoxy - isoquinoline - 1(2H) - one.

1.) Effect on the blood circulation:

The examinations on blood circulation were carried out in dogs with a body weight of 19—30 kg under chloraloseurethane-"Nembutal" [Registered Trade Mark] anaesthesia (54 + 270 + 10 mg/kg i.v.). After thorax-opening with the 4th left intercostal space the animals were supplied with air by an harvard respirator.

The arterial blood-pressure was determined from the *Arteria carotis* by a Statham pressure exchanger; heart-frequency was determined electronically from the subsequency of the R-deviations on the electrocardiogram. The maximal velocity of pressure rise (dp/dt max) within the left ventricula was measured by means of a Konigsberg pressure apparatus and a Grass differential gauge.

All parameter were registered by a direct-writer. For anticoagulation the animals were injected with 10 mg/kg of polyethylenesulfonic potassium i.v. in 20% of polydiol. The test compounds were administered intravenously to groups of 4—6 dogs.

The following table shows the results:

Test Compound	Dosage mg/kg i.v.	Influence on average art. blood-pressure [mm Hg]	Duration min.	Decrease of heart-freq. [1/min]	Duration min.	Decrease of contractility dp/dt max. %	Duration min.
A	1.0	−20 ± 2	50	29 ± 15	36	50 ± 10	44
B	1.0	−24 ± 2	41	19 ± 6	50	51 ± 7	47
C	1.0	−17 ± 3	40	38 ± 2	50	53 ± 6	50
D	0.25	− 6 ± 3	24	15 ± 5	27	36 ± 13	28
E	1.0	−18 ± 11	11	25 ± 6	51	52 ± 8	51
F	1.0	− 7 ± 3	17	12 ± 6	31	33 ± 6	43
G	0.25	− 3 ± 2	20	37 ± 5	54	48 ± 6	48
H	1.0	−25 ± 15	20	34 ± 10	47	53 ± 13	47

2.) Effect on the contraction power and frequency of isolated auricles of the guinea-pig

The maximum delivered tension (isometric contraction power) and frequency were measured in spontaneously beating isolated auricles from guinea-pigs, maintained in carbogen bubbled (95% O_2 + 5% CO_2) Krebs-Henseleit solution at a temperature of 37°C and in the presence of varying concentrations of the test compounds.

Test Compound	Dosage g/ml	Decrease of max. contraction power	Decrease of frequency
A	10^{-5}	50%	23%
	3.10^{-5}	82%	30%
C	3.10^{-6}	17%	15%
	10^{-5}	29%	29%
D	3.10^{-6}	64%	40%
E	3.10^{-5}	54%	31%
	10^{-4}	72%	46%
F	10^{-5}	30%	22%
	3.10^{-5}	43%	29%
G	10^{-5}	35%	22%
	3.10^{-5}	48%	37%

3.) Determination of the acute toxicity

The acute toxicity of the test compounds was determined in mice (observation period: 14 days) after oral and intravenous administration. The LD_{50} was established from the percentage of the animals that died after administration of various dosages during the observation period:

Test Compound	LD_{50}
A	62 mg/kg i.v.
	460 mg/kg p.p.
B	47 mg/kg i.v.
C	50 mg/kg i.v. (0 out of 5 animals died)
	500 mg/kg p.o. (0 out of 5 animals died)

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 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, suspensions, suppositories, powders 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 substance 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. The chemical structure of the new compounds was provded by IR- and NMR-spectra and by elementary analysis:

Example 1.

2 - Methyl - 3 - [4 - (2 - hydroxy - 3 - tert.butylamino - propoxy) - phenyl] - 7 - methoxy-isoquinoline - 1(2H) - one

a) 2 - Methyl - 3 - [4 - (2,3 - epoxypropoxy) - phenyl] - 7 - methoxy - isoquinoline - 1(2H) - one

1.35 g (10 mmol + 20%) of potassium tert.butoxide were added to a solution of 2.8 g (10 mmol) of 2-methyl-3-(4-hydroxyphenyl)-7-methoxy-isoquinoline-1(2H)-one in 20 ml of dimethylsulfoxide with stirring. After a short time the potassium salt was precipitated. 2.8 ml of epibromohydrin were added thereto and, after stirring at room temperature until reaction was complete, the mixture obtained was poured on ice-water. The crystalline precipitate thus formed was filtered off with suction, washed and dried.

Yield: 2.86 g (85% of theory)
M.p.: 153—155°C
$C_{19}H_{20}NO_4$ (337.37)

Calculated:	C 71.20	H 5.68	N 4.15
Found:	71.14	5.65	4.10

b) 2 - Methyl - 3 - [4 - (2 - hydroxy - 3 - tert.butylamino - propoxy) - phenyl] - 7 - methoxy - isoquinoline - 1(2H) - one

2.55 g (7.5 mmol) of the epoxide obtained according to Example 1a above were heated with 25 ml of tert.butylamine up to 120°C in a closed vessel. After 2 hours excess amine was removed *in vacuo* and the granular residue thus obtained was recrystallized from acetone.

Yield: 2.1 g (70% of theory)
M.p.: 130—131°C
$C_{24}H_{30}N_2O_4$ (410.51)

Calculated:	C 70.22	H 7.32	N 6.82
Found:	69.90	7.29	6.75

Example 2.

2 - Methyl - 3 - [4 - [2 - hydroxy - 3 - (2 - [3,4 - dimethoxyphenyl] - N - ethyl - ethylamino) - propoxyl - phenyl] - 7 - methoxy - isoquinoline - 1 (2H) - one

1.4 g (5 mmol) of 2-methyl-3-[4-(2,3-epoxypropoxy)-phenyl]-7-methoxy-isoquinoline-1(2H)-one, obtained according to Example 1a were reacted with 1.5 g of 2-(3,4-dimethoxyphenyl)-N-ethyl-ethylamine at 140°C. After reaction, the crude product obtained was filtered through a silica gel column (grain size: 0.2—0.5 mm, eluant: chloroform: methanol = 19:1). After evaporation, the product obtained was dissolved in acetone and precipitated as its oxalate by means of ethereal oxalic acid.

Yield: 76.5% of theory (as oxalate)
M.p.: 152—155°C (from methanol)
$C_{34}H_{40}N_2O_{10}$ (636.70)

Calculated:	C 64.14	H 6.33	N 4.40	
Found:	63.86	6.46	4.36	

Example 3.

2 - Methyl - 3 - [4 - [3 - (2 - [3,4 - dimethoxyphenyl] - N - methyl - ethylamino) - propoxy] - phenyl] - 7 - methoxy - isoquinoline - 1(2H) - one

a) 2 - Methyl - 3 - [4 - (3 - chloropropoxy) - phenyl] - 7 - methoxy - isoquinoline-1(2H) - one

1.35 g (10 mmol + 20%) of potassium tert.butoxide were added to a solution of 2.8 g (10 mmol) of 2-methyl-3-(4-hydroxyphenyl)-7-methoxy-isoquinoline-1(2H)-one in 20 ml of dimethylsulfoxide. After a short time the potassium salt was precipitated. 2.8 ml of 1-bromo-3-chloropropane were added to the mixture and stirring was continued at room temperature. After reaction was complete, the mixture was poured into ice-water and extracted with ethyl acetate. The combined organic extracts were dried over sodium sulfate and evaporated *in vacuo*. The colourless oil thus obtained solidified and was recrystallized from acetone/ether.

Yield: 3.2 g (89.6% of theory)
M.p.: 102—104°C
$C_{20}H_{20}ClNO_3$ (357.83)

Calculated:	C 67.13	H 5.63	N 3.91	Cl 9.90
Found:	66.97	5.61	3.96	9.65

b) 2 - Methyl - 3 - [4 - [3 - (2 - [3,4 - dimethoxyphenyl] - N - methyl - ethylamino) - propoxy] - phenyl] - 7 - methoxy - isoquinoline - 1(2H) - one

1.8 g (5 mmol) of the product obtained according to Example 3a were reacted with 1.8 g of 2-(3,4-dimethoxyphenyl)-N-methyl-ethylamine at 140°C. After reaction was complete the raw product thus obtained was filtered through a silica gel column (grain size: 0.2—0.5 mm; eluant: chloroform: methanol = 19:1). After evaporation, the product obtained was dissolved in acetone and precipitated with ethereal hydrochloric acid.

Yield: 1.45 g (52.5% of theory) as hydrochloride
M.p.: 155—160°C (from acetone)
$C_{31}H_{37}ClN_2O_5$ (553.09)

Calculated:	C 67.32	H 6.74	N 5.07	Cl 6.41
Found:	67.00	6.84	4.98	Cl 6.31

Example 4.

2 - Methyl - 3 - [4 - (2 - hydroxy - 3 - isopropylamino - propoxy) - phenyl] - 7 - methoxy-isoquinoline - 1(2H) - one

Produced analogously to Example 1 from 2-methyl-3-[4-(2,3-epoxypropoxy)-phenyl]-7-methoxy-isoquinoline-1(2H)-one and isopropylamine at a reaction temperature up to 50°C.

Yield: 63% of theory
M.p.: 140—142°C
$C_{23}H_{28}N_2O_4$ (396.48)

Calculated:	C 69.68	H 7.12	N 7.06	
Found:	69.38	7.14	7.10	

Example 5.

2 - Methyl - 3 - [4 - (2 - hydroxy - 3 - (2 - [3,4 - dimethoxyphenyl]ethylamino) - propoxy) - phenyl] - 7 - methoxy - isoquinoline - 1(2H) - one

Produced analogously to Example 2 from 2-methyl-3-[4-(2,3-epoxypropoxy)-phenyl] - 7 - methoxy - isoquinoline - 1(2H) - one and 2 - (3,4 - dimethoxyphenyl)ethylamine.

Yield: 71% of theory (as oxalate)
M.p.: 208—210°C (from acetone)
$C_{32}H_{36}N_2O_{10}$ (608.64)

Calculated:	C 63.14	H 5.96	N 4.59
Found:	62.68	5.90	4.49

Example 6.

2 - Methyl - 3 - [2 - (2 - hydroxy - 3 - isopropylamino - propoxy) - phenyl] - 7 - methoxy-isoquinoline - 1(2H) - one

Produced analogously to Example 1 from 2 - methyl - 3 - [2 - (2,3 - epoxy-propoxy) - phenyl] - 7 - methoxy - isoquinoline - 1(2H) - one and isopropylamine.

Yield: 82.8% of theory (as oxalate)
M.p.: 216—218°C (from methanol)
$C_{25}H_{30}N_2O_8$ (486.50)

Calculated:	C 61.72	H 6.22	N 5.76
Found:	61.70	6.33	6.18

Example 7.

2 - Methyl - 3 - [2 - (2 - hydroxy - 3 - isopropylamino - propoxy) - 4 - methoxyphenyl]-7 - methoxy - isoquinoline - 1(2H) - one

Produced analogously to Example 1 from 2 - methyl - 3 - [2 - (2,3 - epoxy-propoxy) - 4 - methoxyphenyl] - 7 - methoxy - isoquinoline - 1(2H) - one and isopropylamine at a reaction temperature up to 200°C.

Yield: 88% of theory (as oxalate)
M.p.: 165—168°C (from methanol)
$C_{28}H_{32}N_2O_9$ (516.55)

Calculated:	C 60.45	H 6.24	N 5.42
Found:	61.28	6.16	5.38

Example 8.

2 - Methyl - 3 - [2 - (2 - hydroxy - 3 - tert.butylamino - propoxy) - 4 - methoxyphenyl]-7 - methoxy - isoquinoline - 1(2H) - one

Produced analogously to Example 1 from 2 - methyl - 3 - [2 - (2,3 - epoxy-propoxy) - 4 - methoxyphenyl] - 7 - methoxy - isoquinoline - 1(2H) - one and tert.butylamine.

Yield: 90% of theory (as oxalate)
M.p.: 115—120°C (from acetone/ether)
$C_{27}H_{34}N_2O_9$ (530.55)

Calculated:	C 61.12	H 6.46	N 5.28
Found:	60.91	6.32	5.19

Example 9.

2 - Methyl - 3 - [4 - (2 - hydroxy - 3 - tert.butylamino - propoxy) - phenyl] - 6,7 - dimethoxy - isoquinoline - 1(2H) - one

Produced analogously to Example 1 from 2 - methyl - 3 - [4 - (2,3 - epoxy-propoxy) - 6,7 - dimethoxy - isoquinoline - 1(2H) - one and tert.butylamine.

Yield: 65% of theory
M.p.: 165—166°C (from acetone/ether)
$C_{25}H_{32}N_2O_5$ (440.53)

Calculated:	C 68.15	H 7.32	N 6.36
Found:	67.70	7.23	6.41

Example 10.

2 - Methyl - 3 - [4 - (2 - hydroxy - 3 - isopropylamino - propoxy) - phenyl] - 6,7 - dimethoxy - isoquinoline - 1(2H) - one

Produced analogously to Example 1 from 2 - methyl - 3 - [4 - (2,3 - epoxy-propoxy) - phenyl] - 6,7 - dimethoxy - isoquinoline - 1(2H) - one and isopropylamine.

Yield: 81% of theory
M.p.: 206—207°C (from acetone/ether)
$C_{24}H_{30}N_2O_6$ (426.50)

Calculated:	C 67.58	H 7.09	N 6.57
Found:	67.36	7.02	6.63

Example 11.

2 - Methyl - 3 - [3 - methoxy - 4 - (2 - hydroxy - 3 - isopropylamino - propoxy) - phenyl] - 7 - methoxy - isoquinoline - 1(2H) - one

Produced analogously to Example 1 from 2 - methyl - 3 - [3 - methoxy - 4 - (2,3-epoxypropoxy) - phenyl] - 7 - methoxy - isoquinoline - 1(2H) - one and isopropylamine.

Yield: 77% of theory
M.p.: 144—146°C (from acetone)
$C_{24}H_{30}N_2O_6$ (426.507)

Calculated:	C 67.58	H 7.09	N 6.57
Found:	67.35	7.15	6.76

Example 12.

2 - Methyl - 3 - [3 - methoxy - 4 - (2 - hydroxy - 3 - (2 - [2 - methoxyphenyl] - ethylamino) - propoxy) - phenyl] - 7 - methoxy - isoquinoline - 1(2H) - one

Produced analogously to Example 2 from 2 - methyl - 3 - [3 - methoxy-4 - (2,3 - epoxypropoxy) - phenyl] - 7 - methoxy - isoquinoline - 1(2H) - one and 2 - (2 - methoxyphenyl)ethylamine.

Yield: 56% of theory (as oxalate)
M.p.: 197—199°C (from methanol)
$C_{32}H_{36}N_2O_{10}$ (608.65)

Calculated:	C 63.18	H 6.04	N 4.60
Found:	63.40	6.11	4.56

Example 13.

2 - Methyl - 3 - [4 - (2 - hydroxy - 3 - isopropylamino - propoxy) - phenethyl] - 7-methoxy - isoquinoline - 1(2H) - one

Produced analogously to Example 1 from 2 - methyl - 3 - [4 - (2,3 - epoxypropoxy) - phenethyl] - 7 - methoxy - isoquinoline - 1(2H) - one and isopropylamine.

Yield: 77% of theory
M.p.: 137—139°C (from acetone/ether)

Calculated:	C 70.75	H 7.59	N 6.60
Found:	70.40	7.48	6.61

Example 14.

2 - Methyl - 3 - [3 - methoxy - 4 - (2 - hydroxy - 3 - isopropylamino - propoxy) - phenethyl] - 7 - methoxy - isoquinoline - 1(2H) - one

Produced analogously to Example 1 from 2 - methyl - 3 - [3 - methoxy - 4-(2,3 - epoxypropoxy) - phenethyl] - 7 - methoxy - isoquinoline - 1(2H) - one and isopropylamine.

Yield: 80% of theory
M.p.: 162—164°C (from acetone/ether)
$C_{28}H_{24}N_2O_6$ (454.56)

Calculated:	C 68.70	H 7.54	N 6.16
Found:	68.60	7.54	6.03

Example 15.

2 - Methyl - 3 - [3 - methoxy - 4 - [3 - (2 - o-methoxyphenyl - ethyl - amino) - 2 - hydroxy - propoxy] - phenylethyl] - 7 - methoxy - isoquinoline - 1(2H) - one

Produced analogously to Example 2 from 2 - methyl - 3 - [3 - methoxy - 4 - (2,3-epoxypropoxy) - phenethyl] - 7 - methoxy - isoquinoline - 1(2H) - one and 2 - *o*-methoxyphenyl - ethylamine.

Yield: 74% of theory
M.p.: 117—118°C (from acetone)
$C_{32}H_{38}N_2O_6$ (546.67)

	C	H	N
Calculated:	70.30	7.01	5.13
Found:	70.20	7.03	5.04

Example 16.

2 - Methyl - 3 - [4 - (2 - hydroxy - 3 - tert.butylamino - propoxy) - phenyl] - isoquinoline - 1(2H) - one

Produced analogously to Example 1 from 2 - methyl - 3 - [4 - (2,3 - epoxypropoxy) - phenyl] - isoquinoline - 1(2H) - one and tert.butyl - amine.

Yield: 84% of theory
M.p.: 130—132°C (from acetone/ether)
$C_{23}H_{28}N_2O_3$ (380.48)

	C	H	N
Calculated:	72.61	7.42	7.36
Found:	72.80	7.48	7.22

Example 17.

2 - Methyl - 3 - [4 - [3 - (2 - [4 - methoxyphenyl] - N - methyl - ethylamino) - propoxy] - phenyl] - 7 - methoxy - isoquinoline - 1(2H) - one

Produced analogously to Example 3 from 2 - methyl - 3 - [4 - (3 - chloropropoxy) - phenyl] - 7 - methoxy - isoquinoline - 1(2H) - one and 2 - (4 - methoxyphenyl) - N - methylethylamine.

Yield: 75% of theory (as hydrochloride)
M.p.: 229—230°C (from acetone/ether)
$C_{30}H_{35}ClN_2O_4$ (523.07)

	C	H	N	Cl
Calculated:	68.88	6.75	5.36	6.78
Found	68.60	6.70	5.36	6.82

Example 18.

2 - Methyl - 3 - [4 - [3 - (2 - [3,4,5 - trimethoxyphenyl] - N - methyl - ethylamino) - propoxy] - phenyl] - 7 - methoxy - isoquinoline - 1(2H) - one

Produced analogously to Example 3 from 2 - methyl - 3 - [4 - 3 - chloropropoxy)-phenyl] - 7 - methoxy - isoquinoline - 1(2H) - one and 2 - (3,4,5 - trimethoxyphenyl)-N - methyl - ethylamine.

Yield: 53% of theory (as oxalate)
M.p.: 224—225°C (from methanol)
$C_{34}H_{40}N_2O_{10}$ (636.68)

	C	H	N
Calculated:	64.13	6.33	4.40
Found:	63.71	6.19	4.55

Example 19.

2 - Methyl - 3 - [4 - [3 - (2 - hydroxy - 3 - o - cresyl - propylamino) - propoxy] - phenyl] - 7 - methoxy - isoquinoline - 1(2H) - one

Produced analogously to Example 3 from 2 - methyl - 3 - [4 - (3 - chloropropoxy) - phenyl] - 7 - methoxy - isoquinoline - 1(2H) - one and 2 - hydroxy - 3-*o* - cresyl - propylamine.

Yield: 70% of theory (as oxalate)
M.p.: 178—182°C (from methanol)
$C_{32}H_{36}N_2O_9$ (592.65)

Calculated:	C 64.85	H 6.12	N 4.73
Found:	64.50	6.21	4.66

Example 20.

2 - Methyl - 3 - [4 - [3 - (2 - hydroxy - 3 - p - cresyl - propylamino) - propoxy] - phenyl] - 7 - methoxy - isoquinoline - 1(2H) - one

Produced analogously to Example 3 from 2 - methyl - 3 - [4 - (3 - chloropropoxy) - phenyl] - 7 - methoxy - isoquinoline - 1(2H) - one and 2 - hydroxy - 3 - *p*-cresyl - propylamine.

Yield: 64% of theory (as oxalate)
M.p.: 195—197°C (from methanol)
$C_{32}H_{36}N_2O_9$ (592.65)

Calculated:	C 64.85	H 6.12	N 4.73
Found:	64.70	6.13	4.83

Example 21.

2 - Methyl - 3 - [4 - [3 - (2 - hydroxy - 3 - o - methoxyphenoxy - propylamino) - propoxy] - phenyl] - 7 - methoxy - isoquinoline - 1(2H) - one

Produced analogously to Example 3 from 2 - methyl - 3 - [4 - (3 - chloropropoxy) - phenyl] - 7 - methoxy - isoquinoline - 1(2H) - one and 2 - hydroxy - 3 - *o* - methoxyphenoxy - propylamine.

Yield: 77% of theory (as oxalate)
M.p.: 156—158°C (from methanol)
$C_{32}H_{36}N_2O_{10}$ (608.65)

Calculated:	C 63.14	H 5.96	N 4.60
Found:	62.78	5.74	4.59

Example 22.

2 - Methyl - 3 - [4 - [3 - (2 - hydroxy - 3 - p - methoxyphenoxy - propyl - amino) - propoxy] - phenyl] - 7 - methoxy - isoquinoline - 1(2H) - one

Produced analogously to Example 3 from 2 - methyl - 3 - [4 - (3 - chloropropoxy) - phenyl] - 7 - methoxy - isoquinoline - 1(2H) - one and 2 - hydroxy - 3 - *p*-methoxyphenoxy - propylamine.

Yield: 77% of theory (as oxalate)
M.p.: 172—175°C (from methanol)
$C_{32}H_{36}N_2O_{10}$ (608.65)

Calculated:	C 63.14	H 5.96	N 4.60
Found:	62.92	5.91	4.46

Example 23.

2 - Methyl - 3 - [4 - [3 - (2 - o - methoxyphenyl - ethylamino) - propoxy] - phenyl] - 7 - methoxy - isoquinoline - 1(2H) - one

Produced analogously to Example 3 from 2 - methyl - 3 - [4 - (3 - chloropropoxy) - phenyl] - 7 - methoxy - isoquinoline - 1(2H) - one and 2 - *o* - methoxyphenyl - ethyl - amine.

Yield: 67% of theory (as oxalate)
M.p.: 216—218°C (from methanol)
$C_{31}H_{34}N_2O_8$ (562.60)

Calculated:	C 66.18	H 6.09	N 4.98
Found:	66.10	6.18	4.85

Example 24.

2 - Methyl - 3 - [4 - [3 - (3 - aminopropylamino) - propoxy] - phenyl] - 7 - methoxy-isoquinoline - 1(2H) - one

Produced analogously to Example 3 from 2 - methyl - 3 - [4 - (3 - chloropropoxy) - phenyl] - 7 - methoxy - isoquinoline - 1(2H) - one and 1,3 - diaminopropane.

Yield: 50.8% of theory (as dioxalate)
M.p.: 220—225°C (from methanol)
$C_{27}H_{33}N_3O_{11}$ (575.56)

	C	H	N
Calculated:	58.50	5.95	6.45
Found:	58.33	5.87	6.30

Example 25.

2 - Methyl - 3 - [4 - [3 - (2 - hydroxy - 3 - phenoxy - propylamino) - propoxy] - phenyl] - 7 - methoxy - isoquinoline - 1(2H) - one

Produced analogously to Example 3 from 2 - methyl - 3 - [4 - (3 - chloropropoxy) - phenyl] - 7 - methoxy - isoquinoline - 1(2H) - one and 2 - hydroxy - 3-phenoxy - propylamine.

Yield: 73% of theory (as oxalate)
M.p.: 170—175°C (from methanol)
$C_{31}H_{34}N_2O_8$ (578.60)

	C	H	N
Calculated:	64.35	5.92	4.84
Found:	63.70	5.96	4.89

Example 26.

2 - Methyl - 3 - [4 - [3 - (2 - hydroxy - 2 - phenyl - ethylamino) - propoxy] - phenyl] - 7 - methoxy - isoquinoline - 1(2H) - one

Produced analogously to Example 3 from 2 - methyl - 3 - [4 - (3 - chloropropoxy) - phenyl] - 7 - methoxy - isoquinoline - 1(2H) - one and 2 - hydroxy-2 - phenyl - ethyl - amine.

Yield: 74% of theory (as oxalate)
M.p.: 215—220°C (from methanol)
$C_{30}H_{32}N_2O_8$ (458.55)

	C	H	N
Calculated:	65.68	5.88	5.11
Found:	65.83	5.88	5.26

Example 27.

2 - Methyl - 3 - [4 - [3 - (2 - amino - ethylamino) - propoxy] - phenyl] - 7 - methoxy-isoquinoline - 1(2H) - one

Produced analogously to Example 3 from 2 - methyl - 3 - [4 - (3 - chloropropoxy) - phenyl] - 7 - methoxy - isoquinoline - 1(2H) - one and 1,2 - diamino - ethane.

Yield: 73% of theory (as dioxalate)
M.p.: 235—240°C (from methanol)
$C_{28}H_{31}N_3O_{11}$ (561.56)

	C	H	N
Calculated:	55.61	5.56	7.46
Found:	55.87	5.64	7.38

Example 28.

2 - Methyl - 3 - [4 - [3 - (2 - isopropyloxycarbonylethylamino) - propoxy] - phenyl] - 7 - methoxy - isoquinoline - 1(2H) - one

Produced analogously to Example 3 from 2 - methyl - 3 - [4 - (3 - chloropropoxy) - phenyl] - 7 - methoxy - isoquinoline - 1(2H) - one and isopropyl β-amino-propionate.

Yield: 53% of theory (as oxalate)
M.p.: 174—175°C (from acetone)
$C_{28}H_{34}N_2O_8$ (542.58)

Calculated:	C 61.08	H 6.32	N 5.16
Found:	61.70	6.53	5.23

Example 29.

2 - Methyl - 3 - [4 - [3 - (2 - isobutyloxycarbonylethylamino) - propoxy] - phenyl]- 7 - methoxy - isoquinoline - 1(2H) - one

Produced analogously to Example 3 from 2 - methyl - 3 - [4 - (3 - chloropropoxy) - phenyl] - 7 - methoxy - isoquinoline - 1(2H) - one and isobutyl β - aminopropionate.

Yield: 22% of theory (as oxalate)
M.p.: 190—195°C (from acetone)
$C_{29}H_{36}N_2O_9$ (556.62)

Calculated:	C 62.57	H 6.52	N 5.03
Found:	62.90	6.66	5.03

Example 30.

6 - Methyl - 7 - [4 - [2 - hydroxy - 3 - (2 - [3,4 - dimethoxyphenyl] - N - methyl-ethyl - amino) - propoxy] - phenyl] - 1,6 - naphthyridine - 5(6H) - one

Produce analogously to Example 2 from 6 - methyl - 7 - [4 - (2,3 - epoxypropoxy) - phenyl] - 1,6 - naphthyridine - 5(6H) - one and 2 - (3,4 - dimethoxyphenyl) - N - methyl - ethylamine.

Yield: 70% of theory (as oxalate)
M.p.: 85—95°C
$C_{31}H_{35}N_3O_9$ (593.6)

Calculated:	C 62.72	H 5.94	N 7.08
Found:	62.22	5.95	6.98

Example 31.

6 - Methyl - 7 - [4 - (2 - hydroxy - 3 - isopropylamino - propoxy) - phenyl] - 1,6-naphthyridine - 5(6) - one

Produced analogously to Example 1 from 6 - methyl - 7 - [4 - (2,3 - epoxypropoxy) - phenyl] - 1,6 - naphthyridine - 5(6) - one and isopropylamine.

Yield: 92% of theory.
M.p.; 135—139°C
$C_{21}H_{25}N_3O_2$ (367.46)

Calculated:	C 68.64	H 6.86	N 11.44
Found:	67.03	6.69	11.39

Example 32.

6 - Methyl - 7 - [4 - [2 - hydroxy - 3 - (2 - [3,4 - dimethoxyphenyl] - ethyl-amino) - propoxy] - phenyl] - 1,6 - naphthyridine - 5(6H) - one

Produced analogously to Example 2 from 6-methyl-7-[4-(2,3-epoxypropoxy)-phenyl] - 1,6 - naphthyridine - 5(6H) - one and 2 - (3,4 - dimethoxyphenyl)-ethylamine.

Yield: 64% of theory (as oxalate)
M.p.: 82—95°C
$C_{30}H_{33}N_3O_9$ (579.60)

Calculated:	C 62.17	H 5.74	N 7.25
Found:	61.56	5.80	6.32

Example 33.

6 - Methyl - 7 - [4 - [2 - hydroxy - 3 - (2 - [4 - methoxyphenyl] - N - methyl-ethyl - amino) - propoxy] - phenyl] - 1,6 - naphthyridine - (6H) - one

Produced analogously to Example 2 from 6 - methyl - 7 - [4 - 2,3 - epoxypropoxy) - phenyl] - 1,6 - naphthyridine - 5(6H) - one and 2 - (4 - methoxyphenyl) - N - methyl - ethylamine.

Yield: 61% of theory (as oxalate)
M.p.: 66—73°C
$C_{30}H_{33}N_3O_8$ (563.60)

	C	H	N
Calculated:	63.93	5.90	7.45
Found:	63.94	5.75	7.14

Example 34.

6 - Methyl - 7 - [4 - [2 - hydroxy - 3 - (2 - [3,4,5 - trimethoxyphenyl] - N - methyl-ethylamino) - propoxy] - phenyl] - 1,6 - naphthyridine - H) - one

Produced analogously to Example 2 from 6 - methyl - 7 - [4 - (2,3 - epoxy-propoxy) - phenyl] - 1,6 - naphthyridine - 5(6H) - one and 2 - (3,4,5 - trimethoxy-phenyl) - N - methyl - ethylamine.

Yield: 35.5% of theory (as oxalate)
M.p.: 87—95°C
$C_{32}H_{37}N_3O_{10}$ (623.7)

	C	H	N
Calculated:	61.63	5.98	6.74
Found:	61.38	5.84	6.77

Example 35.

6 - Methyl - 7 - [4 - (2 - hydroxy - 3 - tert.butylamino - propoxy) - phenyl] - 1,6 - naphthyridine - 5(6H) - one

Produced analogously to Example 1 from 6 - methyl - 7 - [4 - 2,3 - epoxy-propoxy) - phenyl] - 1,6 - naphthyridine - 5(6H) - one and tert.butyl-amine.

Yield: 41% of theory (as oxalate)
M.p.: 248—250°C
$C_{24}H_{29}N_3O_7$ (471.5)

	C	H	N
Calculated:	61.14	6.20	8.91
Found:	60.70	6.42	8.89

Example 36.

6 - Methyl - 7 - [4 - (2 - hydroxy - 3 - diethylamino - propoxy) - phenyl] - 1,6 - naphthyridine - 5(6H) - one

Produced analogously to Example 1 from 6 - methyl - 7 - [4 - (2,3 - epoxy-propoxy) - phenyl] - 1,6 - naphthyridine - 5(6H) - one and diethylamine.

Yield: 70% of theory (as oxalate)
M.p.: 143—145°C
$C_{24}H_{29}N_3O_7$ (471.4)

	C	H	N
Calculated:	61.14	6.20	8.91
Found:	61.22	6.25	9.01

Example 37.

6 - Methyl - 7 - [4 - [3 - (2 - [3,4 - dimethoxyphenyl] - N - methyl - ethyl - amino)-propoxy] - phenyl] - 1,6 - naphthyridine - 5(6H) - one

Produced analogously to Example 3 from 6 - methyl - 7 - [4 - (3 - chloro-propoxy) - phenyl] - 1,6 - naphthyridine - 5(6H) - one and 2 - (3,4 - dimethoxy-phenyl) - N - methyl - ethylamine.

Yield: 45% of theory (as oxalate)
M.p.: 167—170°C
$C_{31}H_{35}N_3O_8$ (577.6)

	C	H	N
Calculated:	64.46	6.11	7.27
Found:	64.45	6.16	7.05

Example 38.

6 - Methyl - 7 - [4 - [3 - (2 - [4 - methoxyphenyl] - N - methyl - ethylamino) - propoxyl-phenyl] - 1,6 - naphthyridine - 5(6H) - one

Produced analogously to Example 3 from 6 - methyl - 7 - [4 - (3 - chloropropoxy) - phenyl] - 1,6 - naphthyridine - 5(6H) - one and 2 - (4 - methoxyphenyl)-N - methyl - ethylamine.

Yield: 45% of theory (as oxalate)
M.p.: 188—190°C
$C_{30}H_{33}N_3O_7$ (547.6)

Calculated:	C 65.80	H 6.07	N 7.67	
Found:	66.72	5.85	7.74	

Example 39.

2 - Methyl - 3 - [4 - [3 - (2 - [4 - methoxyphenyl] - N - methyl - ethylamino) - propoxy] - phenyl] - 7 - methoxy - isoquinoline - 1(2H) - one

2.5 g (5 mmol) of 2 - [4 - [3 - (2 - [4 - methoxyphenyl]ethyl - N - methylamino) - propoxy] - acetophenyl] - 5 - methoxy - benzoic acid were added to 25 ml of methylamine in a closed vessel. After 3 hours at 50°C the excess methylamine was distilled off and the crude product thus obtained was filtered through a silica gel column (grain size: 0.2—0.5 mm, eluant: chloroform: methanol = 19:1). After evaporation, the residue obtained was dissolved in acetone and the product was precipitated as the hydrochloride by addition of ethereal hydrochloric acid.

Yield: 1.4 g (25.6% of theory) (as hydrochloride)
M.p.: 226—228°C (from acetone/ether)
$C_{30}H_{35}ClN_2O_4$ (523.07)

Calculated:	C 68.88	H 6.75	N 5.36	Cl 6.78
Found:	68.43	6.82	5.39	6.73

Example 40.

2 - Methyl - 3 - [4 - [3 - (2 - [3,4 - dimethoxyphenyl] - N - methyl - ethyl - amino)-propoxy] - phenyl] - 7 - methoxy - isoquinoline - 1(2H) - one

Produced analogously to Example 40 from 2 - [4 - [3 - (2 - [3,4 - dimethoxyphenyl] - ethyl - N - methyl - amino) - propoxy] - aceto - phenyl] - 5 - methoxybenzoic acid and methylamine at a reaction temperature up to 200°C.

Yield: 31.6% of theory (as hydrochloride)
M.p.: 157—159°C (from acetone)
$C_{31}H_{37}ClN_2O_6$ (553.09)

Calculated:	C 67.32	H 6.74	N 5.07	Cl 6.41
Found:	67.14	6.71	5.12	6.37

Example A.

Tablets containing 100 mg of 2 - methyl - 3 - [4 - (2 - hydroxy - 3 - tert.butylamino - propoxy) - phenyl] - 7 - methoxy - isoquinoline - 1(2H) - one.

Composition:

Active ingredient	100.0 mg
lactose	50.0 mg
polyvinylpyrrolidone	5.0 mg
carboxymethylcellulose	19.0 mg
magnesium stearate	1.0 mg
	1750 mg

Method of preparation:

The active ingredient and lactose were homogeneously moistened with an aqueous solution of the polyvinyl-pyrrolidone and passed through a screen. After

drying the granulate was mixed with the remaining ingredients and the mixture obtained was pressed into tablets in the usual manner.

Example B.

Suppositories containing 150 mg of 2 - methyl - 3 - [4 - (2 - isopropylamino - propoxy) - phenyl] - 6,7 - dimethoxy - isoquinoline - 1(2H) - one

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 and suspended therein. The liquid mixture thus formed was poured into cooled suppository moulds.

Example C.

Coated tablets containing 50 mg of 2 - methyl - 3 - [4 - (2 - hydroxy - 3 - tert.-butylamino - propoxy) - phenyl] - 7 - methoxy - isoquinoline - 1(2H) - one

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 ingredients were processed to coated tablets cores as described in Example A. The cores were then coated with sugar and gum arabic.

Example D.

Suspension containing 50 mg/ml of 2 - methyl - 3 - [4 - (2 - hydroxy - 3 - isopropylamino - propoxy) - phenyl] - 6,7 - dimethoxy - isoquinoline - 1(2H)-one

100 mg of suspension contain:

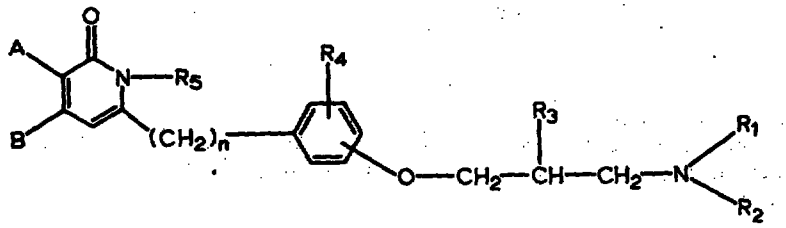
Active ingredient	5.0 g
carboxymethylcellulose	0.1 g
methyl *p*-hydroxybenzoate	0.05 g
propyl *p*-hydroxybenzoate	0.01 g
sugar	10.0 g
glycerine	5.0 g
70% sorbitol solution	20.0 g
flavouring	0.3 g
distilled water ad.	100.0 g

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 obtained was cooled to room temperature and the active ingredient was added with stirring and homogeneously dispersed. After adding and dissolving the sugar, the sorbitol solution and the flavouring, the resultant suspension was evacuated for deaeration under stirring.

WHAT WE CLAIM IS:—

1. Compounds of general formula I,



(I)

[wherein

A and B, together with the carbon atoms to which they are attached, represent a fused phenyl ring (optionally substituted by from one to three groups which are alkoxy, containing from 1 to 3 carbon atoms, amino or nitro groups) or a fused pyridyl ring;

R_1 and R_5, which may be the same or different, each represents a hydrogen atom or an alkyl group containing from 1 to 3 carbon atoms;

R_2 represents a straight or branched chain alkyl group containing from 1 to 6 carbon atoms or a group of formula —Y—Z (in which Y represents a straight chain alkylene group containing from 1 to 4 carbon atoms optionally substituted by a hydroxy group and Z represents an amino group, an alkoxycarbonyl group containing from 2 to 6 carbon atoms or a phenyl or phenoxy group, said phenyl or phenoxy group being optionally substituted by from 1 to 3 groups which are alkyl or alkoxy groups each containing from 1 to 3 carbon atoms;

R_3 represents a hydrogen atom or a hydroxy group;

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

n is 0, 1 or 2]

and acid addition salts thereof.

2. Compounds as claimed in claim 1 wherein A and B, together with the carbon atoms to which they are are attached represent a phenyl, methoxyphenyl, dimethoxyphenyl or pyridyl group; R_2 represents a methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, isopropyl, isobutyl, isoamyl, tert.butyl or tert.pentyl group or a group of formula —Y—Z (in which Y represents a methylene, ethylene, hydroxyethylene, propylene, hydroxypropylene or butylene group and Z represents a phenyl, methoxyphenyl, dimethoxyphenyl, trimethoxyphenyl, methylphenyl, amino, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, pentoxycarbonyl, isopropoxycarbonyl, tert.butoxycarbonyl, tert.pentoxycarbonyl, phenoxy, methylphenoxy or methoxyphenoxy group); R_4 represents a hydrogen atom or a methoxy, ethoxy, propoxy or isopropoxy group; and R_5 represents a methyl, ethyl, propyl or isopropyl group.

3. Compounds as claimed in claim 2 wherein R_1 represents a hydrogen atom or a methyl or ethyl group; R_2 represents an ethyl, isopropyl or tert.butyl group or a group of formula —Y—Z (in which Y represents an ethylene propylene, hydroxyethylene or hydroxypropylene group and Z represents a phenyl, methoxyphenyl, dimethoxyphenyl, trimethoxyphenyl, amino, methylphenyl, isopropoxycarbonyl, tert.butoxycarbonyl, phenoxy, methylphenoxy or methyoxyphenoxy group; R_4 represents a hydrogen atom or a methoxy group; and R_5 represents a methyl group.

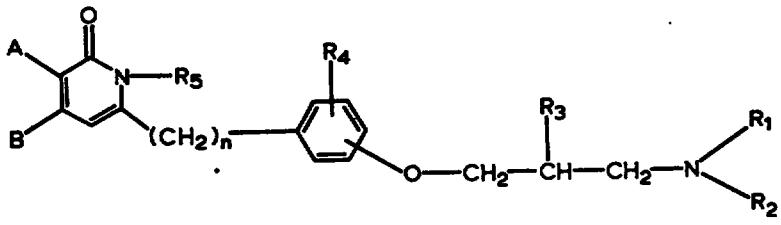
4. Compounds as claimed in claim 3 wherein A and B, together with the carbon atoms to which they are attached represent a phenyl, 4-methoxy-1,2-phenylene or 4,5-dimethoxy-1,2-phenylene group; R_1 represents a hydrogen atom; R_2 represents an isopropyl or tert.butyl group; and R_3 represents a hydroxy group.

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 obtained was cooled to room temperature and the active ingredient was added with stirring and homogeneously dispersed. After adding and dissolving the sugar, the sorbitol solution and the flavouring, the resultant suspension was evacuated for deaeration under stirring.

WHAT WE CLAIM IS:—

1. Compounds of general formula I,



(I)

[wherein

A and B, together with the carbon atoms to which they are attached, represent a fused phenyl ring (optionally substituted by from one to three groups which are alkoxy, containing from 1 to 3 carbon atoms, amino or nitro groups) or a fused pyridyl ring;

R_1 and R_5, which may be the same or different, each represents a hydrogen atom or an alkyl group containing from 1 to 3 carbon atoms;

R_2 represents a straight or branched chain alkyl group containing from 1 to 6 carbon atoms or a group of formula —Y—Z (in which Y represents a straight chain alkylene group containing from 1 to 4 carbon atoms optionally substituted by a hydroxy group and Z represents an amino group, an alkoxycarbonyl group containing from 2 to 6 carbon atoms or a phenyl or phenoxy group, said phenyl or phenoxy group being optionally substituted by from 1 to 3 groups which are alkyl or alkoxy groups each containing from 1 to 3 carbon atoms;

R_3 represents a hydrogen atom or a hydroxy group;

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

n is 0, 1 or 2]

and acid addition salts thereof.

2. Compounds as claimed in claim 1 wherein A and B, together with the carbon atoms to which they are are attached represent a phenyl, methoxyphenyl, dimethoxyphenyl or pyridyl group; R_2 represents a methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, isopropyl, isobutyl, isoamyl, tert.butyl or tert.pentyl group or a group of formula —Y—Z (in which Y represents a methylene, ethylene, hydroxyethylene, propylene, hydroxypropylene or butylene group and Z represents a phenyl, methoxyphenyl, dimethoxyphenyl, trimethoxyphenyl, methylphenyl, amino, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, pentoxycarbonyl, isopropoxycarbonyl, tert.butoxycarbonyl, tert.pentoxycarbonyl, phenoxy, methylphenoxy or methoxyphenoxy group); R_4 represents a hydrogen atom or a methoxy, ethoxy, propoxy or isopropoxy group; and R_5 represents a methyl, ethyl, propyl or isopropyl group.

3. Compounds as claimed in claim 2 wherein R_1 represents a hydrogen atom or a methyl or ethyl group; R_2 represents an ethyl, isopropyl or tert.butyl group or a group of formula —Y—Z (in which Y represents an ethylene propylene, hydroxyethylene or hydroxypropylene group and Z represents a phenyl, methoxyphenyl, dimethoxyphenyl, trimethoxyphenyl, amino, methylphenyl, isopropoxycarbonyl, tert.butoxycarbonyl, phenoxy, methylphenoxy or methyoxyphenoxy group; R_4 represents a hydrogen atom or a methoxy group; and R_5 represents a methyl group.

4. Compounds as claimed in claim 3 wherein A and B, together with the carbon atoms to which they are attached represent a phenyl, 4-methoxy-1,2-phenylene or 4,5-dimethoxy-1,2-phenylene group; R_1 represents a hydrogen atom; R_2 represents an isopropyl or tert.butyl group; and R_3 represents a hydroxy group.

5. 2-Methyl-3-[4-(2-hydroxy-3-tert.butylamino-propoxy)-phenyl]-7-methoxy-isoquinoline-1(2H)-one and acid addition salts thereof.

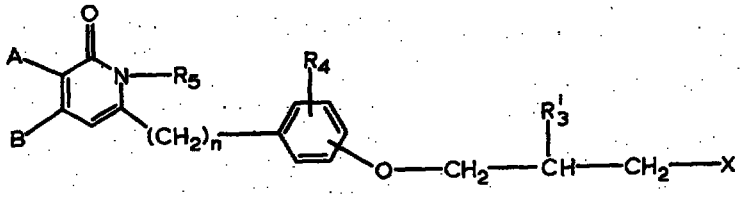
6. 2-Methyl-3-[2-(2-hydroxy-3-isopropylamino-propoxy)-phenyl]-7-methoxy-isoquinoline-1(2H)-one and acid addition salts thereof.

7. 2-Methyl-3-[2-(2-hydroxy-3-isopropylamino-propoxy)-4-methoxyphenyl]-7-methoxy-isoquinoline-1(2H)-one and acid addition salts thereof.

8. Compounds as claimed in any preceding claim in the form of physiologically compatible acid addition salts.

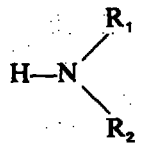
9. Compounds as claimed in claim 1, other than those claimed in any one of claims 5 to 7 as herein specifically disclosed in any one of Examples 1 to 40.

10. 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, B, R_4, R_5 and n are as defined in claim 1 and either R_3' is as defined for R^3 in claim 1 and X represents a group removable as an anion or R_3' and X together represent an epoxy group) with a compound of formula III,



(III)

(wherein R_1 and R_2 are as defined in claim 1).

11. A process as claimed in claim 10 wherein, in the compound of formula II, X represents a halogen atom.

12. A process as claimed in claim 10 or claim 11 wherein the reaction is effected in the presence of a solvent.

13. A process as claimed in claim 12 wherein the solvent comprises isopropanol, tetrahydrofuran, dimethylformamide, dimethylsulphoxide or an excess of the compound of formula III.

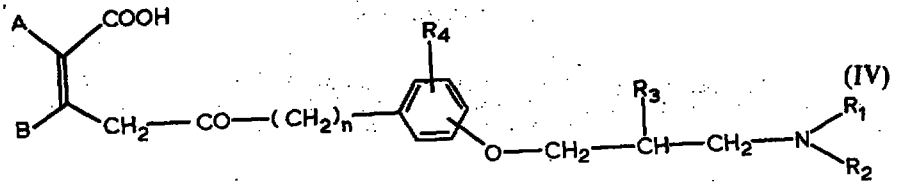
14. A process as claimed in any one of claims 10 to 13 wherein the reaction is effected in the presence of an acid-binding agent.

15. A process as claimed in claim 14 wherein the acid-binding agent comprises an alkoxide or alkaline carbonate.

16. A process as claimed in any one of claims 10 to 15 wherein the reaction is effected at temperatures of from 50 to 200°C.

17. A process as claimed in claim 16 wherein the reaction is effected at temperatures of from 80 to 160°C.

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, B, R_1, R_2, R_3, R_4 and n are as defined in claim 1) or a reactive derivative thereof with a compound of formula V,

$$R_5—NH_2 \qquad (V)$$

(wherein R_5 is as defined in claim 1).

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

20. A process as claimed in claim 19 wherein the solvent comprises methanol, ethanol, isopropanol, dioxan, dimethylformamide or an excess of the compound of formula V.

21. A process as claimed in any one of claims 18 to 20 wherein the reaction is effected in the presence of a condensation agent.

22. A process as claimed in claim 21 wherein the condensation agent comprises an alkoxide.

23. A process as claimed in any one of claims 18 to 22 wherein the reaction is effected at temperatures of from 50 to 200°C.

24. A process as claimed in claim 23 wherein the reaction is effected at temperatures of from 80 to 140°C.

25. A process as claimed in any of claims 10 to 24 wherein the reaction is effected in a closed vessel.

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

27. A process as claimed in claim 26 wherein the acid is hydrochloric, phosphoric, hydrobromic, sulfuric, lactic, citric, tartaric, oxalic or maleic acid.

28. 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.

29. 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 one of Examples 1 to 40.

30. Compounds of general formula I as defined in claim 1 and their physiologically compatible acid addition salts whenever prepared by a process as claimed in any one of claims 10 to 29.

31. 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.

32. Compositions as claimed in claim 31 in a form suitable for oral, rectal or parenteral administration.

33. Compositions as claimed in claim 31 or claim 32 in the form of tablets, coated tablets, suspensions, suppositories, solutions and powders.

34. Compositions as claimed in any one of claims 31 to 33 in the form of dosage units.

35. Compositions as claimed in claim 34 wherein each dosage unit contains from 50 to 250 mg of active ingredient.

36. Compositions as claimed in any one of claims 31 to 35 wherein the active ingredient comprises a compound as claimed in any one of claims 5 to 7.

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

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

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