

PATENT SPECIFICATION

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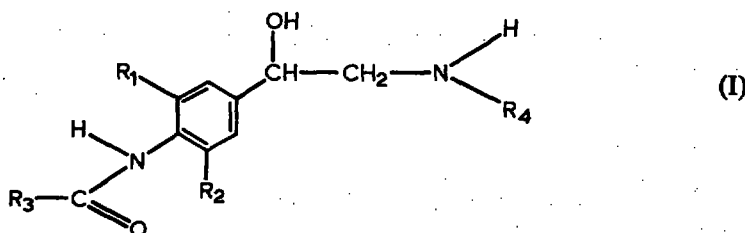


(54) 4-ACYLAMINOPHENYL-ETHANOLAMINES

(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 novel 4-acylaminophenylethanolamines, 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,



wherein

R_1 represents a hydrogen or halogen atom or a cyano group;

R_2 represents a fluorine atom, a cyano, trifluoromethyl or nitro group or an alkyl group containing from 1 to 4 carbon atoms;

R_3 represents a straight or branched chain alkoxy group containing from 1 to 5 carbon atoms, an alkenyloxy group containing from 2 to 5 carbon atoms, an aryloxy group containing from 6 to 10 carbon atoms, an aralkoxy group containing from 7 to 11 carbon atoms or an amino group, said amino group being optionally substituted by one or two substituents which are straight or branched chain alkyl groups containing from 1 to 5 carbon atoms, alkenyl groups containing from 2 to 5 carbon atoms, aryl groups containing from 6 to 10 carbon atoms or aralkyl groups containing from 7 to 11 carbon atoms; and

R_4 represents a cycloalkyl or alkyl group containing from 3 to 5 carbon atoms; and acid addition salts thereof.

The compounds according to the invention possess interesting pharmacological activity and in particular, in general, in addition to an analgesic and a uterus-spasmodic activity and an antispastic effect on the transverse muscles, the compounds according to the invention show a β_2 -mimetic and/or a β_1 -blocking activity.

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.

In the compounds according to the invention R_3 may, for example, represent a methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, sec.butoxy, isobutoxy, tert.butoxy, n-pentyloxy, isopentyloxy, tert.pentyloxy, phenoxy, naphthyloxy,

benzyloxy, phenylethyloxy, allyloxy, butenyloxy, pentenyloxy, amino, methylamino, ethylamino, n-propylamino, isopropylamino, n-butylamino, sec.butylamino, isobutylamino, tert.butylamino, n-pentylamino, dimethylamino, diethylamino, di-n-propylamino, diisopropylamino, di-n-butylamino, di-sec.butylamino, diisobutylamino, di-tert.butylamino, di-n-pentylamino, phenylamino, naphthylamino, benzylamino, phenylethylamino, methylethylamino, methylbenzylamino, methyl-n-propylamino, methyl-isopropylamino, methyl-n-butylamino, ethylpropylamino, ethyl-isopropylamino, diphenylamino, methylphenylamino, ethyl-phenylamino, isopropyl-phenylamino, allylamino, diallylamino, n-butenylamino or n-pentenylamino group.

R⁴ may, for example, represent an isopropyl, sec.butyl, isobutyl, tert.butyl, cyclopropyl, cyclobutyl or cyclopentyl group.

Preferred compounds according to the invention are those wherein R₃ represents a straight or branched chain alkoxy group containing from 1 to 5 carbon atoms, an alkenyloxy group containing from 2 to 5 carbon atoms, an aralkoxy group containing from 7 to 11 carbon atoms or, when R₁ represents a hydrogen or halogen atom and R₂ represents a fluorine atom or a trifluoromethyl or nitro group, alternatively an amino group optionally substituted by a straight or branched chain alkyl group containing from 1 to 5 carbon atoms, an alkenyl group containing from 2 to 5 carbon atoms, an aryl group containing from 6 to 10 carbon atoms or an aralkyl group containing from 7 to 11 carbon atoms. Of these compounds especially preferred are those wherein R₃ represents a straight or branched chain alkoxy group containing from 1 to 4 carbon atoms or, when R₁ represents a hydrogen or halogen atom and R₂ represents a fluorine atom or a trifluoromethyl or nitro group, alternatively an amino group optionally substituted by an alkyl group containing from 1 to 4 carbon atoms and R₄ represents an isopropyl or tert.butyl group, particularly those wherein R₃ represents an alkoxy group containing from 1 to 4 carbon atoms.

Particularly preferred compounds according to the invention are the following:

1 - (4 - ethoxycarbonylamino - 3 - chloro - 5 - fluoro - phenyl) - 2 - tert.butyl - amino - ethanol,

1 - (4 - ethoxycarbonylamino - 3 - cyano - 5 - fluoro - phenyl) - 2 - tert.butyl - amino - ethanol,

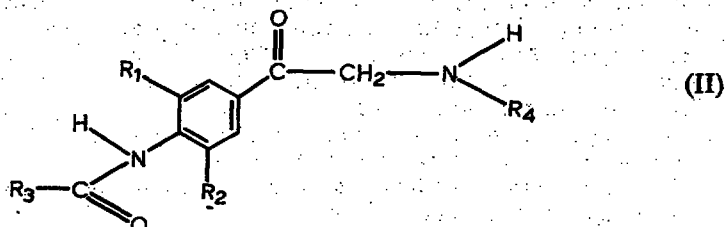
1 - (4 - ethoxycarbonylamino - 3 - cyano - phenyl) - 2 - tert.butylamino - ethanol,

1 - (4 - ethoxycarbonylamino - 3 - cyano - phenyl) - 2 - isopropylamino - ethanol,

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. Reduction of a compound of formula II,



(wherein R₁, R₂, R₃ and R₄ are as hereinbefore defined) whereby the desired compound of formula I is obtained.

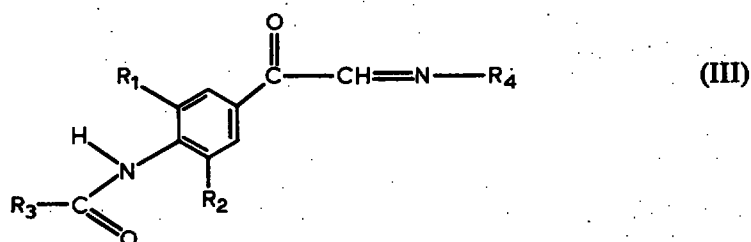
The reduction is preferably effected in the presence of a solvent such as methanol, aqueous methanol, ethanol, isopropanol, butanol, diethyl ether, tetrahydrofuran or dioxan. Reduction may, for example, be effected by means of a complex metal hydride such as, e.g. sodium borohydride or lithium-aluminium hydride in which case the reduction is preferably effected in the presence of methanol, aqueous methanol, diethyl ether or tetrahydrofuran as solvent and preferably at temperatures of from -20 to 50°C. Reduction may alternatively be effected, if desired, by means of aluminium isopropylate in the presence of a primary or secondary alcohol e.g. isopropanol. A preferred reaction temperature

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with aluminium isopropylate is the boiling point of the reaction mixture and preferably the acetone formed during the reduction is continuously removed by distillation.

Reduction may also be effected, if desired, by means of catalytically activated hydrogen, for example by means of hydrogen in the presence of platinum, palladium, Raney nickel or Raney cobalt. Preferably such a reduction is effected at a hydrogen pressure of from 1 to 5 atmospheres and preferably at ambient temperatures. According to a further embodiment reduction may be effected by means of nascent hydrogen, e.g. by means of activated metallic aluminium and water or zinc and hydrochloric acid. Preferred reaction temperatures are then from -20°C to the boiling point of the reaction mixture.

B. Reduction of a compound of formula III,



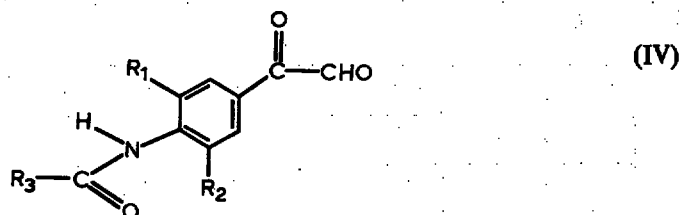
(wherein R_1 , R_2 , R_3 and R_4 are as hereinbefore defined) whereby the desired compound of formula I is obtained.

The reduction is preferably effected in a suitable solvent such as methanol, aqueous methanol, ethanol, butanol, diethyl ether, tetrahydrofuran or dioxan.

Reduction may, for example, be effected by means of a complex metal hydride such as, for example, sodium borohydride or lithium aluminium hydride, preferably in the presence of methanol, aqueous methanol, diethyl ether or tetrahydrofuran as solvent and preferably at temperatures of from -20°C to the boiling point of the reaction mixture e.g. at temperatures of from 0 to 50°C .

Reduction may alternatively be effected, if desired, by means of catalytically activated hydrogen e.g. by means of hydrogen in the presence of platinum, palladium, Raney nickel or Raney cobalt. Such a reduction is preferably effected at a hydrogen pressure of from 1 to 5 atmospheres and preferably at temperatures of from 0 to 100°C , most preferably at ambient temperatures.

The compound of formula III may itself be prepared, preferably *in situ*, by reaction of a compound of formula IV,



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



(wherein R_4 is as hereinbefore defined). Preferably the reaction is effected in the presence of a solvent such as exemplified hereinabove in relation to the reduction of the compound of formula III. According to a preferred embodiment the reaction of the compound of formula IV with the compound of formula V is carried out under the reducing conditions exemplified above in order to yield the desired compound of formula I directly.

The compounds of general formula I may, if desired, be converted into their

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physiologically compatible-acid addition salts by reaction with an appropriate acid. Suitable acids include, for example, hydrochloric, hydrobromic, sulfuric, phosphoric, lactic, citric, tartaric, maleic and fumaric acid. Preferably the compound of formula I and the acid are used in substantially equimolar quantities.

The compounds of general formulae II and IV, useful as starting materials in the above-described processes, may be prepared according to methods known from the literature. Thus, for example, a compound of formula II may be obtained by reaction of a corresponding 2-haloacetophenone with a corresponding amine. A compound of formula IV may be obtained, for example, by oxidation of a corresponding acetophenone with selenium dioxide (see Examples). The compounds of general formulae II and IV thus formed may, if desired, be used directly, without isolation, in the processes according to the invention.

As mentioned above, the compounds of general formula I and their physiologically compatible acid addition salts possess interesting pharmacological properties. Those compounds which we have tested exhibit an analgesic, uterus-spasmolytic and an antispastic effect on the transverse muscles especially a β_2 -mimetic (broncholytic) and/or β_1 -blocking effect with good oral resorption. The rapidity with which an efficient effect takes place after oral administration is particularly remarkable. Such compounds are thus suitable for tokolysis, decrease in blood-circulation by peripheral vasodilation, mobilisation of body fat and for the treatment of allergic conditions e.g. allergic asthma and allergic inflammable conditions, spastic pulmonary diseases of different origins and heart rhythm disturbances.

The following compounds were examined with regard to their broncholytic activity:

- A = 1 - (4 - ethoxycarbonylamino - 3 - chloro - 5 - fluoro - phenyl) - 2 - tert. - butylamino - ethanol hydrochloride
 B = 1 - (4 - ethoxycarbonylamino - 3 - cyano - 5 - fluoro - phenyl - 2 - tert. butyl - amino - ethanol hydrochloride
 C = 1 - (4 - ethoxycarbonylamino - 3 - cyano - phenyl) - 2 - tert. butyl - amino - ethanol hydrochloride and
 D = 1 - (4 - ethoxycarbonylamino - 3 - cyano - phenyl) - 2 - isopropylamino - ethanol hydrochloride

The broncholytic effect of the compounds was tested according to the method of KONZETT and ROSSLER (Arch. exp. Path. Pharmac. 195, 71 (1940)) in narcotized guinea pigs. From the average percentage decrease in the bronchospasm provoked by 20 $\mu\text{g/kg}$ of acetylcholine administered intravenously obtained by administering various intravenous and intraduodenal dosages of the test compounds, an ED_{50} value was calculated using the linear regression analysis method according to LINDER (Stat. Methods, 4. Ed. pp. 148—162, Birkhauser, Basle 1964):

Test Compound	after i.v. administration		after i.d. administration
	$\text{ED}_{50} \mu\text{g/kg}$	t/2. min.	$\text{ED}_{50} \mu\text{g/kg}$
A	30.7	60	32.2
B	5.6	70	7.0
C	23.5	>50	8.7
D	64.0	>50	

Test compound B was also tested according to the method of KALLOS a. PAGEL (Acta med. scand. 91, pp. 292 (1937)) for its anti-asthmatic effect after oral administration. The guinea-pigs were sprayed with an acetylcholine aerosol flow comprising a 0.4% solution of acetylcholine in a 0.9% solution of NaCl from a pipe at 1.5 atm. A threefold increase in the period of time before onset of the asthma attack as compared with a control test was taken as giving absolute protection. From the percentage of animals showing absolute protection after the administration of various dosages, an ED_{50} was calculated according to LITCHFIELD a. WILCOXON (J. Pharmacol. exp. Ther. 96, pp. 99 (1949)):

Test Compound	after administration per os	
	ED ₅₀ µg/kg	Max. of effect in min. t/2 min.
B	14.3	15 - 30 150

The *acute toxicity* was determined in mice of both sexes with an average weight of 20 g after i.v. administration. From the percentage of animals which died within 14 day after the various dosages, the LD₅₀ was calculated according to LITCHFIELD and WILCOXON (J. Pharmacol. exp. Ther. 96, pp. 99 (1949)):

Test Compound	LD ₅₀ mg/kg i.v.
A	70.2
B	97.5
C	67.2
D	61.9

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 (including topical) administration. Preferred forms include, for example, plain tablets, coated tablets, ampoules, sprays, 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 5 to 100 µg of active ingredient and are preferably administered from 2 to 4 times per day. The oral daily dosage, which may be varied according to the compound used, the subject treated and the complaint concerned, may, thus for example, be from 10 to 400 µg per day in adults.

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

Example 1.

1 - (4 - ethoxycarbonylamino - 3 - chloro - 5 - fluoro - phenyl) - 2 - tert.butylamino - ethanol hydrochloride.

8.7 g of 4'-ethoxycarbonylamino-3'-chloro-5'-fluoroacetophenone were added in portions to a solution of 3.7 g of selenium dioxide in 30 ml of dioxan and 1 ml of water at 60°C whilst stirring. The mixture obtained was refluxed for 4 hours and, after cooling, 4.1 ml of tert.butylamine were added dropwise into the solution of 4'-ethoxycarbonylamino-3'-chloro-5'-fluoro-phenylglyoxal thus obtained whilst ice cooling. The resultant mixture was diluted with 350 ml of ethanol and filtered. 5 g of sodium borohydride were added in portions to the filtrate, containing crude 4'-ethoxy-carbonylamino-3'-chloro-5' - fluoro - phenyl - glyoxylidene - tert.butylamine with stirring and cooling with ice. After standing the mixture thus obtained overnight at room temperature, the excess sodium borohydride was destroyed with acetone. The resultant mixture was mixed with water and extracted with chloroform. The chloroform extract was washed with water, dried over sodium sulfate and, after the addition of activated charcoal then filtering, rapidly heated to

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boiling and evaporated *in vacuo*. The solid residue consisting of 1-(4-ethoxycarbonylamino-3-chloro-5-fluoro-phenyl)-2-tert.butylamino-ethanol was mixed with isopropanol and the mixture obtained was acidified with ethereal hydrochloric acid to pH 4. After addition of ether, the crystals precipitated were filtered off under suction and washed with ether.

M.p.: 192—193°C.

Analogously to Example 1 the following compounds were prepared:

(a) 1-(4-ethoxycarbonylamino-3-chloro-5-trifluoromethylphenyl)-2-tert.-butylamino-ethanol.

M.p.: 168—170°C (decomposition).

(b) 1-(4-ethoxycarbonylamino-3-bromo-5-fluoro-phenyl)-2-isopropyl-amino-ethanol hydrochloride.

M.p.: 180—182°C.

(c) 1-(4-ethoxycarbonylamino-3-bromo-5-fluoro-phenyl)-2-tert.butyl-amino-ethanol hydrochloride.

M.p.: 197—198°C (decomposition).

(d) 1-(4-ethoxycarbonylamino-3-fluoro-phenyl)-2-tert.butylamino-ethanol hydrochloride.

M.p.: 235—236°C.

(e) 1-(4-ethoxycarbonylamino-3-cyano-5-fluoro-phenyl)-2-tert.butyl-amino-ethanol hydrochloride.

M.p.: 198—200°C (decomposition).

(f) 1-(4-ethoxycarbonylamino-3-nitro-phenyl)-2-tert.butylamino-ethanol hydrochloride.

M.p.: 189—190°C (decomposition).

(g) 1-(4-ethoxycarbonylamino-3-fluoro-5-iodo-phenyl)-2-cyclopropyl-amino-ethanol.

M.p.: 127—130°C.

(h) 1-[3-fluoro-5-iodo-4-(3-methylureido)-phenyl]-2-tert.butylamino-ethanol hydrochloride.

M.p.: sintering from 115°C (amorphous substance).

Mass-spectrum ($C_{14}H_{17}N_3O_2FI$)

Molpeak of the base: Found: 409. Calcul. 409.25.

(i) 1-[3-fluoro-5-iodo-4-(3-methylureido)-phenyl]-2-cyclopropylamino-ethanol hydrochloride.

M.p.: 167—170°C.

(j) 1-(3-cyano-5-fluoro-4-isobutyloxycarbonylamino-phenyl)-2-tert.-butylamino-ethanol hydrochloride.

(The excess sodium borohydride was destroyed with dilute hydrochloric acid).

M.p.: 189—191°C.

(k) 1-(4-benzyloxycarbonylamino-3-fluoro-5-iodo-phenyl)-2-cyclopropyl-amino-ethanol.

(The excess sodium borohydride was destroyed with dilute hydrochloric acid).

M.p.: 135—137°C.

(l) 1-(4-allyloxycarbonylamino-3-fluoro-5-iodo-phenyl)-2-cyclopropyl-amino-ethanol.

(The excess sodium borohydride was destroyed with dilute hydrochloric acid).

M.p.: 122—123°C.

(m) 1-(3-fluoro-4-isobutyloxycarbonylamino-5-iodo-phenyl)-2-cyclo-propyl-amino-ethanol.

(The excess sodium borohydride was destroyed with dilute hydrochloric acid).

M.p.: 126—128°C.

(n) 1-(4-ethoxycarbonylamino-3-cyano-phenyl)-2-isopropyl-amino-ethanol.

M.p.: 112—115°C.

(o) 1-(4-ethoxycarbonylamino-3-cyano-phenyl)-2-tert. butyl-amino-ethanol.

M.p.: 78—82°C.

Example 2.

1 - (4 - ethoxycarbonylamino - 5 - bromo - 3 - methyl - phenyl) - 2 - tert.butylamino - ethanol.

6.5 g of bromine were added dropwise into a boiling solution of 12 g of 4'-ethoxycarbonylamino-5'-bromo-3'-methyl-acetophenone in 200 ml of chloroform, whereupon hydrobromic acid was rapidly formed. The solution obtained, containing 4'-ethoxycarbonylamino-5'-2-dibromo-3'-methylacetophenone, was mixed with 14.6 g of tert.butylamine. After refluxing for 30 minutes the resultant solution, containing 4'-ethoxycarbonylamino-5'-bromo-3'-methyl-2-tert.butylamino-acetophenone, was evaporated *in vacuo*. The residue was dissolved in 50 ml of methanol and 20 ml of water. Reduction was effected by addition thereto of a solution of 3.8 g of sodium borohydride in 20 ml of water with simultaneous adjustment of the pH to between 6 and 8 by addition of dilute hydrochloric acid. After reduction was complete, the methanol was distilled off *in vacuo*. The residue obtained was mixed with water and the resultant solution was made alkaline by addition of liquid ammonia and extracted with chloroform. The organic phase was separated, dried and evaporated *in vacuo*. The evaporation residue was purified over a silica gel column (eluant: chloroform/methanol 2:1). After evaporation, the residue was dissolved in ethanol and the solution obtained was mixed with ethereal hydrochloric acid to yield 1-(4-ethoxycarbonylamino-5-bromo-3-methyl-phenyl)-2-tert.butylamino-ethanol hydrochloride.

M.p.: 212—214°C (decomposition).

Analogously to Example 2 the following compounds were prepared:

(a) 1 - (4 - ethoxycarbonylamino - 3 - chloro - 5 - trifluoromethyl - phenyl) - 2 - tert.butylamino - ethanol

M.p.: 168—170°C (decomposition).

(b) 1 - (4 - ethoxycarbonylamino - 3 - bromo - 5 - fluoro - phenyl) - 2 - isopropyl - amino - ethanol hydrochloride.

M.p.: 180—182°C.

(c) 1 - (4 - ethoxycarbonylamino - 3 - bromo - 5 - fluoro - phenyl) - 2 - tert.butyl - amino - ethanol hydrochloride.

M.p.: 197—198°C (decomposition).

(d) 1 - (4 - ethoxycarbonylamino - 3 - fluoro - phenyl) - 2 - tert.butylamino - ethanol hydrochloride.

M.p.: 235—236°C.

(e) 1 - (4 - ethoxycarbonylamino - 3 - cyano - 5 - fluoro - phenyl) - 2 - tert.butyl - amino - ethanol hydrochloride.

M.p.: 198—200°C (decomposition).

(f) 1 - (4 - ethoxycarbonylamino - 3 - nitro - phenyl) - 2 - tert.butyl - amino - ethanol hydrochloride.

M.p.: 189—190°C (decomposition).

(g) 1 - (4 - ethoxycarbonylamino - 3 - fluoro - 5 - iodo - phenyl) - 2 - cyclopropyl - amino - ethanol.

M.p.: 127—130°C.

(h) 1 - [3 - fluoro - 5 - iodo - 4 - (3 - methylureido) - phenyl] - 2 - tert.butylamino - ethanol hydrochloride.

M.p.: sintering from 115°C (amorphous substance)

Mass-spectrum ($C_{14}H_{17}N_3O_2FI$)

Molpeak of the base: Found: 409. Calcul.: 409.25.

(i) 1 - [3 - fluoro - 5 - iodo - 4 - (3 - methylureido) - phenyl] - 2 - cyclopropylamino - ethanol hydrochloride.

M.p.: 167—170°C.

(j) 1 - (3 - cyano - 5 - fluoro - 4 - isobutyloxycarbonylamino - phenyl) - 2 - tert. - butylamino - ethanol hydrochloride.

M.p.: 189—191°C.

(k) 1 - (4 - benzyloxycarbonylamino - 3 - fluoro - 5 - iodo - phenyl) - 2 - cyclo - propylamino - ethanol.

M.p.: 135—137°C.

(l) 1 - (3 - fluoro - 4 - isobutyloxycarbonylamino - 5 - iodo - phenyl) - 2 - cyclo - propylamino - ethanol.

M.p.: 126—128°C.

(m) 1 - (4 - ethoxycarbonylamino - 3 - cyano - phenyl) - 2 - isopropyl - amino - ethanol.

M.p.: 112—115°C.

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(n) 1 - (4 - ethoxycarbonylamino - 3 - cyano - phenyl) - 2 - tert.butyl - amino - ethanol.

M.p.: 78—82°C.

(o) 1 - [3 - cyano - 4 - (3 - tert.butylureido) - phenyl] - 2 - tert.butyl - amino - ethanol.

M.p.: 105—110°C (decomposition).

Mass-spectrum ($C_{18}H_{22}N_4O_2$)

Molpeak of the base: Found: 332. Calcul.: 332.45.

The 4'-(3-tert.butylureido)-2-bromo-3'-cyano-acetophenone used as a starting material was prepared by reaction of 4'-phenoxy-carbonylamino-2-bromo-3'-cyano-acetophenone with tert.butylamine at room temperature.

Example A.

Tablets containing 10 γ of 1-(4-ethoxycarbonylamino-3-cyano-5-fluoro-phenyl)-2-tert.butylamino-ethanol hydrochloride.

Composition:

1 tablet contains:	
active ingredient	0.01 mg
lactose	82.49 mg
potato starch	33.00 mg
polyvinylpyrrolidone	4.00 mg
magnesium stearate	0.50 mg
	<u>120.00 mg</u>

Method of preparation.

The active ingredient and polyvinylpyrrolidone were dissolved in ethanol. A mixture of the lactose and potato starch was homogeneously moistened with the active ingredient solution and granulated through a screen of 1.5 mm mesh size. The granulate was dried at 50°C and passed through a screen of 1.0 mm mesh size. The granulate thus obtained was mixed with the magnesium stearate and compressed to form the tablets.

Weight of tablet: 120 mg

Punch: 7 mm, arcuate

Example B.

Coated tablets containing 5 γ of 1-(4-ethoxycarbonylamino-3-cyano-5-fluoro-phenyl)-2-tert.butylamino-ethanol hydrochloride.

Composition:

1 coated tablet core contains:	
active ingredient	0.005 mg
lactose	82.495 mg
potato starch	33.000 mg
polyvinylpyrrolidone	4.000 mg
magnesium stearate	0.500 mg
	<u>120.000 mg</u>

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Method of preparation:

The tablet cores were prepared analogously to Example A.

Weight of core: 120 mg

Punch: 7 mm, arcuate

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The cores were covered according to known processes with a coating consisting essentially of sugar and talcum. The finished coated tablets were then polished with bees wax.

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Weight of coated tablets; 200.0 mg

Example C.

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Gelatine capsules containing 10% of 1-(4-ethoxycarbonylamino-3-cyano-5-fluorophenyl)-2-tert.butylamino-ethanol hydrochloride.

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Composition:

1 capsule contains:
active ingredient 0.010 mg

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lactose 59.990 mg

15

corn starch 60.000 mg

120.000

Method of preparation:

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The active ingredient was intimately mixed with the lactose and corn starch and filled into gelatine capsules of suitable size.

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Capsule weight: 120.0 mg

Example D.

Ampoules containing 10% of 1-(4-ethoxycarbonylamino-3-cyano-5-fluorophenyl)-2-tert.butylamino-ethanol hydrochloride.

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Composition:

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1 ampoule contains:
active ingredient 0.01 mg

citric acid 2.5 mg

sodium hydrogen phosphate 7.5 mg

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sodium chloride 4.6 mg

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ampoule water ad. 2.0 ml

Method of preparation:

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The active ingredient, buffer substances and sodium chloride were dissolved in ampoule water and the solution obtained was subsequently filtered sterile.

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Filling: in brown ampoules of 2 ml capacity in an inert atmosphere (N₂)

Sterilisation: 20 minutes at 120°C.

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Example E.
Suppositories containing 10 γ of 1-(4-ethoxycarbonylamino-3-cyano-5-fluoro-phenyl)-2-tert.butylamino-ethanol hydrochloride.

Composition:

5	1 suppository contains:		5
	active ingredient	0.01 mg	
	suppository mass (e.g. "Witepsol" [registered Trade Mark] W 45)	1 699.99 mg	
		<u>1 700.00 mg</u>	

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Method of preparation:

The finely pulverized active ingredient was stirred into the molten suppository mass, cooled to 40°C, with the aid of an immersion homogenizer. At 37°C the mass was poured into slightly precooled moulds.

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Weight of suppository: 1.7 g

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Example F.
Syrup containing 1 γ /ml of 1-(4-ethoxycarbonylamino-3-cyano-5-fluoro-phenyl)-2-tert.butylamino-ethanol hydrochloride.

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Composition:

20	100 ml of syrup contain:		20
	active ingredient	0.0001 g	
	benzoic acid	0.1 g	
	tartaric acid	1.0 g	
	sugar	50.0 g	
	orange aroma	1.0 g	
25	food colouring	0.05 g	25
	distilled water ad.	100.0 ml	

Method of preparation:

About 60 g of distilled water were heated up to 80°C and the benzoic acid, tartaric acid, active ingredient, food colouring and sugar were dissolved successively therein. After cooling to room temperature, the aroma was added and the resultant solution was made up to the desired volume, then filtered.

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Example G.

Coated tablets containing 25% of 1-(4-ethoxycarbonylamino-3-cyano-5-fluorophenyl)-2-tert.butylamino-ethanol hydrochloride.

Composition:

5	1 coated tablet contains:		5
	active ingredient	0.025 mg	
	lactose	82.475 mg	
	potato starch	33.000 mg	
	polyvinylpyrrolidone	4.000 mg	
10	magnesium stearate	0.500 mg	10
		<u>120.000 mg</u>	

Method of preparation:

Analogously to Example A.

Example H.

15 Ampoules containing 20% of 1-(4-ethoxycarbonylamino-3-cyano-5-fluorophenyl)-2-tert.butylamino-ethanol hydrochloride. 15

Composition:

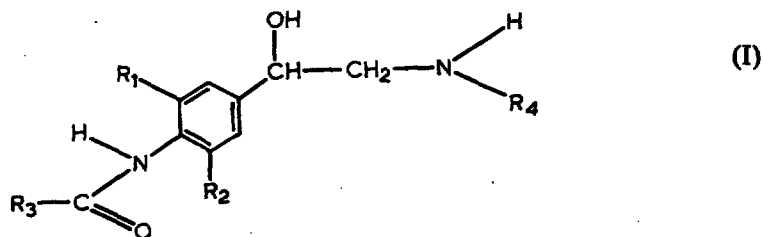
	1 ampoule contains:		
	active ingredient	0.02 mg	
20	citric acid	2.5 mg	20
	sodium hydrogen phosphate	7.5 mg	
	sodium chloride	4.6 mg	
	ampoule water ad.	2.0 ml	

Process of preparation:

Analogously to Example D.

WHAT WE CLAIM IS:—

1. Compounds of general formula I,



wherein

- 30 R_1 represents a hydrogen or halogen atom or a cyano group; 30
- R_2 represents a fluorine atom, a cyano, trifluoromethyl or nitro group or an alkyl group containing from 1 to 4 carbon atoms;
- 35 R_3 represents a straight or branched chain alkoxy group containing from 1 to 5 carbon atoms, an alkenyloxy group containing from 2 to 5 carbon atoms, an aryloxy group containing from 6 to 10 carbon atoms, an aralkoxy group containing from 7 to 11 carbon atoms or an amino group, said amino group being optionally 35



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Example G.

Coated tablets containing 25% of 1-(4-ethoxycarbonylamino-3-cyano-5-fluorophenyl)-2-tert.butylamino-ethanol hydrochloride.

Composition:

5	1 coated tablet contains:		5
	active ingredient	0.025 mg	
	lactose	82.475 mg	
	potato starch	33.000 mg	
	polyvinylpyrrolidone	4.000 mg	
10	magnesium stearate	0.500 mg	10
		<u>120.000 mg</u>	

Method of preparation:

Analogously to Example A.

Example H.

15 Ampoules containing 20% of 1-(4-ethoxycarbonylamino-3-cyano-5-fluorophenyl)-2-tert.butylamino-ethanol hydrochloride. 15

Composition:

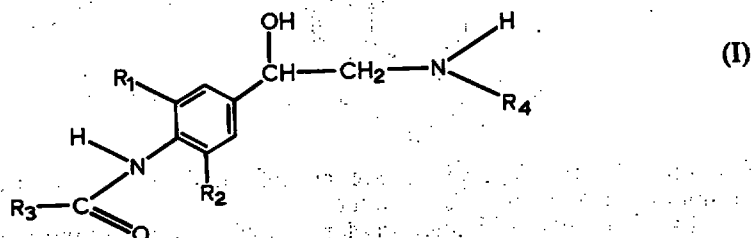
	1 ampoule contains:		
	active ingredient	0.02 mg	
20	citric acid	2.5 mg	20
	sodium hydrogen phosphate	7.5 mg	
	sodium chloride	4.6 mg	
	ampoule water ad.	2.0 ml	

Process of preparation:

25 Analogously to Example D. 25

WHAT WE CLAIM IS:—

1. Compounds of general formula I,



wherein

- 30 R_1 represents a hydrogen or halogen atom or a cyano group; 30
- R_2 represents a fluorine atom, a cyano, trifluoromethyl or nitro group or an alkyl group containing from 1 to 4 carbon atoms;
- 35 R_3 represents a straight or branched chain alkoxy group containing from 1 to 5 carbon atoms, an alkenyloxy group containing from 2 to 5 carbon atoms, an aryloxy group containing from 6 to 10 carbon atoms, an aralkoxy group containing from 7 to 11 carbon atoms or an amino group, said amino group being optionally 35

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substituted by one or two substituents which are straight or branched chain alkyl groups containing from 1 to 5 carbon atoms, alkenyl groups containing from 2 to 5 carbon atoms, aryl groups containing from 6 to 10 carbon atoms or aralkyl groups containing from 7 to 11 carbon atoms; and

5 R_4 represents a cycloalkyl or alkyl group containing from 3 to 5 carbon atoms; and acid addition salts thereof. 5

2. Compounds as claimed in claim 1 wherein R_3 represents a straight or branched chain alkoxy group containing from 1 to 5 carbon atoms, an alkenyloxy group containing from 2 to 5 carbon atoms, an aralkoxy group containing from 7 to 11 carbon atoms, or, when R_1 represents a hydrogen or halogen atom and R_2 represents a fluorine atom or a trifluoromethyl or nitro group, alternatively an amino group optionally substituted by a straight or branched chain alkyl group containing from 1 to 5 carbon atoms, an alkenyl group containing from 2 to 5 carbon atoms, an aryl group containing from 6 to 10 carbon atoms or an aralkyl group containing from 7 to 11 carbon atoms. 10 15

3. Compounds as claimed in claim 2 wherein R_3 represents a straight or branched chain alkoxy group containing from 1 to 4 carbon atoms or, when R_1 represents a hydrogen or halogen atom and R_2 represents a fluorine atom or a trifluoromethyl or nitro group, alternatively an amino group optionally substituted by an alkyl group containing from 1 to 4 carbon atoms and R_4 represents an isopropyl or tert.butyl group. 20

4. Compounds as claimed in claim 3 wherein R_3 represents an alkoxy group containing from 1 to 4 carbon atoms.

5. 1 - (4 - Ethoxycarbonylamino - 3 - chloro - 5 - fluoro - phenyl) - 2 - tert. - butylamino - ethanol and acid addition salts thereof. 25

6. 1 - (4 - Ethoxycarbonylamino - 3 - cyano - 5 - fluoro - phenyl) - 2 - tert. - butylamino - ethanol and acid addition salts thereof.

7. 1 - (4 - Ethoxycarbonylamino - 3 - cyano - phenyl) - 2 - tert.butylamino - ethanol and acid addition salts thereof. 30

8. 1 - (4 - Ethoxycarbonylamino - 3 - cyano - phenyl) - 2 - isopropylamino - ethanol and acid addition salts thereof. 30

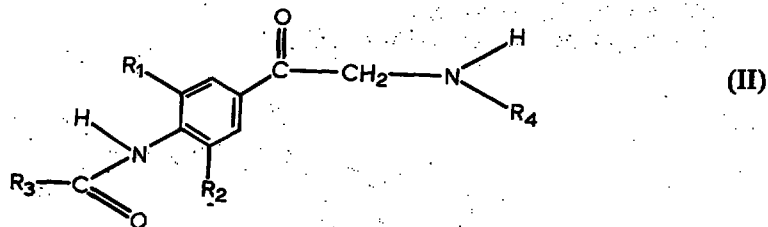
9. Compounds as claimed in any of the preceding claims in the form of physiologically compatible acid addition salts.

10. Compounds of general formula I as defined in claim 1 wherein R_3 represents an alkoxy group containing from 1 to 4 carbon atoms. 35

11. Compounds as claimed in claim 1, other than those claimed in any of claims 5 to 8, as herein specifically disclosed in any one of Examples 1, 1a to 1o, 2 and 2a to 2o.

12. Compounds as claimed in claim 10, other than those claimed in any of claims 5 to 8, as herein specifically disclosed in any one of Examples 1, 1a to 1f, 2, 2m, and 2n. 40

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



45 (wherein R_1 , R_2 , R_3 and R_4 are as defined in claim 1) whereby the desired compound of formula I is obtained. 45

14. A process as claimed in claim 13 wherein the reduction is effected in the presence of methanol, aqueous methanol, ethanol, isopropanol, butanol, diethyl ether, tetrahydrofuran or dioxan as solvent.

15. A process as claimed in claim 13 or claim 14 wherein reduction is effected by means of a complex metal hydride. 50

16. A process as claimed in claim 15 wherein the complex metal hydroxide is sodium borohydride or lithium aluminium hydride.

17. A process as claimed in claim 15 or claim 16 wherein the reduction is effected in the presence of methanol, aqueous methanol, diethyl ether or tetrahydrofuran as solvent. 55



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18. A process as claimed in any of claims 15 to 17 wherein the reduction is effected at temperatures of from -20 to $+50^{\circ}\text{C}$.

19. A process as claimed in claim 13 or claim 14 wherein reduction is effected by means of aluminium isopropylate in the presence of a primary or secondary alcohol.

20. A process as claimed in claim 19 wherein the alcohol is isopropanol.

21. A process as claimed in claim 19 or claim 20 wherein the reduction is effected at the boiling point of the reaction mixture.

22. A process as claimed in any of claims 19 to 21 wherein the acetone formed is continuously removed by distillation.

23. A process as claimed in claim 13 or claim 14 wherein reduction is effected by means of catalytically activated hydrogen.

24. A process as claimed in claim 23 wherein reduction is effected by means of hydrogen in the presence of platinum, palladium, Raney nickel or Raney cobalt.

25. A process as claimed in claim 23 or claim 24 wherein the reduction is effected at a hydrogen pressure of from 1 to 5 atmospheres.

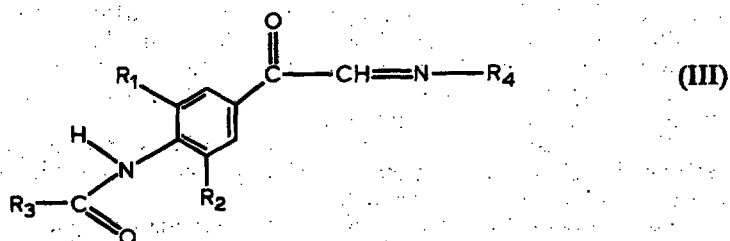
26. A process as claimed in any of claims 23 to 25 wherein the reduction is effected at ambient temperatures.

27. A process as claimed in claim 13 or claim 14 wherein reduction is effected by means of nascent hydrogen.

28. A process as claimed in claim 27 wherein reduction is effected by means of activated metallic aluminium and water or zinc and hydrochloric acid.

29. A process as claimed in claim 27 or claim 28 wherein the reduction is effected at temperatures of from -20°C to the boiling point of the reaction mixture.

30. A process for the preparation of compounds of general formula I as defined in claim 1 which comprises reducing a compound of formula III,



(wherein R_1 , R_2 , R_3 and R_4 are as defined in claim 1) whereby the desired compound of formula I is obtained.

31. A process as claimed in claim 30 wherein the reduction is effected in the presence of methanol, aqueous methanol, ethanol, butanol, diethyl ether, tetrahydrofuran or dioxan as solvent.

32. A process as claimed in claim 30 or claim 31 wherein reduction is effected by means of a complex metal hydride.

33. A process as claimed in claim 32 wherein the complex metal hydride is sodium borohydride or lithium aluminium hydride.

34. A process as claimed in claim 32 or claim 33 wherein the reduction is effected in the presence of methanol, aqueous methanol, diethyl ether or tetrahydrofuran as solvent.

35. A process as claimed in any of claims 32 to 34 wherein the reduction is effected at temperatures of from -20°C to the boiling point of the reaction mixture.

36. A process as claimed in any of claims 32 to 34 wherein the reduction is effected at temperatures of from 0 to 50°C .

37. A process as claimed in claim 30 or claim 31 wherein reduction is effected by means of catalytically activated hydrogen.

38. A process as claimed in claim 37 wherein reduction is effected by means of hydrogen in the presence of platinum, palladium, Raney nickel or Raney cobalt.

39. A process as claimed in claim 37 or claim 38 wherein the reduction is effected at a hydrogen pressure of from 1 to 5 atmospheres.

40. A process as claimed in any of claims 37 to 39 wherein the reduction is effected at temperatures of from 0 to 100°C .

41. A process as claimed in claim 40 wherein the reduction is effected at ambient temperatures.

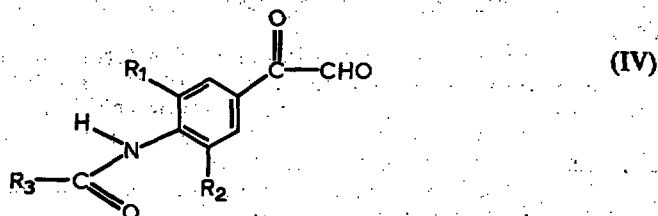


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42. A process as claimed in any of claims 37 to 41 wherein the compound of formula III is prepared by reaction of a compound of formula IV,



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



(wherein R_4 is as defined in claim 1).

43. A process as claimed in claim 42 wherein the compound of formula III is prepared *in situ*.

44. 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.

45. A process as claimed in claim 44 wherein the acid is hydrochloric, hydrobromic, sulfuric, phosphoric, lactic, citric, tartaric, maleic or fumaric acid.

46. A process as claimed in claim 44 or claim 45 wherein the compound of formula I and the acid are reacted in substantially equimolar quantities.

47. A process as claimed in any of claims 13 to 46 for the preparation of compounds as claimed in claim 10

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

49. A process for the preparation of compounds of general formula I as defined in claim 1 or their physiologically compatible acid addition salts substantially as herein described in any one of Examples 1, 1a to 1o, 2 and 2a to 2o.

50. A process for the preparation of compounds as defined in claim 10 substantially as herein described in any one of Examples 1, 1a to 1f, 2, 2m and 2n.

51. 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 of claims 13 to 46, 48 and 49.

52. Compounds as claimed in claim 10 whenever prepared by a process as claimed in claim 47 or claim 50.

53. 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.

54. Compositions as claimed in claim 53 in a form suitable for oral, rectal or parenteral administration.

55. Compositions as claimed in claim 53 or claim 54 in the form of plain tablets, coated tablets, ampoules, sprays, suppositories and solutions.

56. Compositions as claimed in any of claims 53 to 55 in the form of dosage units.

57. Compositions as claimed in claim 56 wherein each dosage unit contains from 5 to 100 μ g of active ingredient.

58. Compositions as claimed in any of claims 53 to 57 wherein the active ingredient comprises a compound as claimed in any of claims 5 to 8.

59. Compositions as claimed in claim 53 wherein the active ingredient comprises a compound as claimed in claim 10.

60. Pharmaceutical compositions as claimed in claim 53 substantially as herein described.

61. Pharmaceutical compositions substantially as herein described in any one of Examples A to H.



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