



593593¹⁰

SPRUSON & FERGUSON

COMMONWEALTH OF AUSTRALIA
PATENTS ACT 1952

CONVENTION APPLICATION FOR A STANDARD PATENT

We, **ASTA Pharma Aktiengesellschaft Chemische Fabrik**
of Weismüllerstrasse 45, D-6000 Frankfurt am Main 1, Federal Republic of
Germany hereby apply for the grant of a standard patent for an invention
entitled:

"NOVEL 4-BENZYL-1-(2H)-PHTHALAZINONE DERIVATIVES"

which is described in the accompanying complete specification.

DETAILS OF BASIC APPLICATION

Number of Basic Application:-

P 35 39 873.6

Name of Convention Country in which Basic Application was filed:-

Federal Republic of Germany

Date of Basic Application:-

11 November 1985.

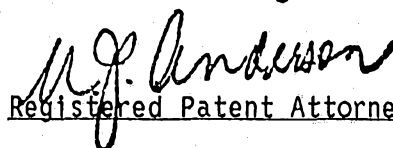
The address for service is:-

Spruson & Ferguson
Patent Attorneys
Level 33 St Martins Tower
31 Market Street
Sydney New South Wales Australia

DATED this EIGHTEENTH day of OCTOBER 1989

ASTA Pharma Aktiengesellschaft Chemische Fabrik

By:


Registered Patent Attorney.



TO: THE COMMISSIONER OF PATENTS

APPLICATION ACCEPTED AND AMENDMENTS

2609W/LPR

ALLOWED 11-12-89

SPRUSON & FERGUSON

COMMONWEALTH OF AUSTRALIA
PATENTS ACT 1952

DECLARATION IN SUPPORT OF A CONVENTION APPLICATION FOR A PATENT

In support of the Convention Application made for a patent for an invention entitled:

"NOVEL 4-BENZYL-1-(2H)-PHTHALAZINONE DERIVATIVES"

We, Dr Wolfgang Merk and Dr Günter Steinmetz, of D-6477 Limeshain 3, Bergstrasse 44; and Wildenbruchstrasse 41, D-6000 Frankfurt am Main both in the Federal Republic of Germany do solemnly and sincerely declare as follows:-

1. We are authorised by ASTA-Werke Aktiengesellschaft Chemische Fabrik, the applicant for the patent to make this declaration on its behalf.
2. The basic application as defined by Section 141 of the Act was made in Federal Republic of Germany on 11 November 1985 by ASTA-Werke Aktiengesellschaft Chemische Fabrik.
3. JURGEN ENGEL and GERHARD SCHEFFLER, of Erlenweg 3, D-8755 Alzenau and Frankenwaldstrasse 19, D-6450 Hanau 6, both in the Federal Republic of Germany [respectively], are the actual inventors of the invention and the facts upon which the applicant is entitled to make the application are as follows:

The said applicant is the assignee of the actual inventors..

4. The basic application referred to in paragraph 2 of this Declaration was the first application made in a Convention country in respect of the invention the subject of the application.

DECLARED at Hanau this

26th day of September 1989

.....
Dr Wolfgang Merk

DECLARED at Hanau this

21. day of September 1989

.....
Dr Günter Steinmetz

TO: THE COMMISSIONER OF PATENTS
AUSTRALIA

(12) PATENT ABRIDGMENT (11) Document No. AU-B-64982/86
 (19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 593593

(54) Title
 4-BENZYL-1-(2H)-PHTHALAZINONE DERIVATIVES

International Patent Classification(s)
 (51)⁴ C07D 403/04 A61K 031/50 A61K 031/55 C07D 401/04
 C07D 403/06 C07D 451/04

(21) Application No. : 64982/86 (22) Application Date : 10.11.86

(30) Priority Data

(31) Number (32) Date (33) Country
 3539873 11.11.85 DE FEDERAL REPUBLIC OF GERMANY

(43) Publication Date : 14.05.87

(44) Publication Date of Accepted Application : 15.02.90

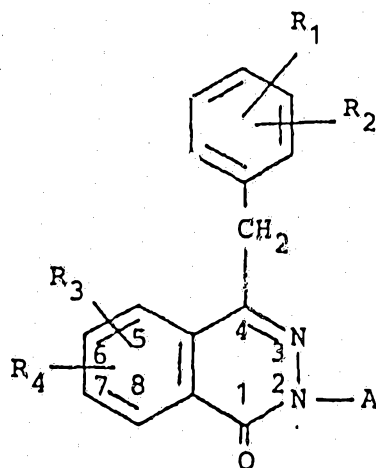
(71) Applicant(s)
 ASTA PHARMA AKTIENGESELLSCHAFT CHEMISCHE FABRIK

(72) Inventor(s)
 JURGEN ENGEL; GERHARD SCHEFFLER

(74) Attorney or Agent
 SPRUSON & FERGUSON

(57) Claim

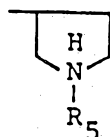
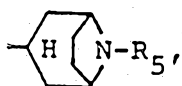
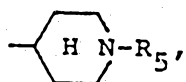
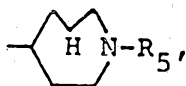
1. 4-Benzyl-1-(2H)-phthalazinone derivatives of the formula



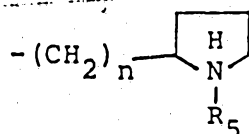
I

wherein R₁ represents fluorine, chlorine, bromine, trifluoromethyl, C₁-C₆-alkyl, hydroxy, C₁-C₆-alkoxy, C₂-C₆-alkanoyloxy, amino, C₁-C₆-alkylamino, di-C₁-C₆-alkylamino, C₂-C₆-alkanoylamino, C₂-C₆-alkanoyl-C₁-C₆-alkylamino or a nitro group, R₂ represents hydrogen or has one of the meanings given

above for R_1 , whereby R_1 and R_2 may be the same or different, R_3 and R_4 may be the same or different and represent hydrogen, halogen, C_1 - C_6 -alkyl, hydroxy, C_1 - C_6 -alkoxy, benzyloxy or C_2 - C_6 -alkanoyloxy and A represents one of the radicals



or



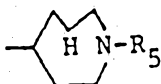
wherein $n=1$ or 2 and R_5 represents a C_1 - C_6 -alkyl group substituted by the following radicals:

- by a phenyl radical or a phenyl carbonyl radical each of which may contain one, two or three substituents, which may be the same or different, whereby the substituents are halogen atoms, trifluoromethyl, C_1 - C_6 -alkyl groups or C_1 - C_6 -alkoxy groups, or
- by a C_1 - C_6 -alkoxy radical, a mono or dihydroxy- C_1 - C_6 -alkyl radical or a hydroxy- C_1 - C_6 -alkoxy radical or
- by a mono- C_1 - C_6 -alkylamino or di- C_1 - C_6 -alkylamino radical whereby the latter may also be closed to form a 5-7 membered, nitrogen-containing ring, which may optionally contain a further oxygen atom, or

- d) by a C_3-C_8 -cycloalkyl radical or a C_3-C_8 -cycloalkylcarbonyl radical

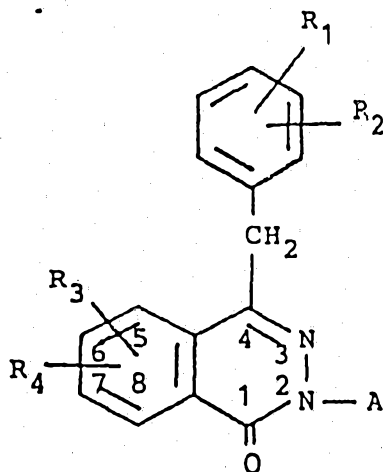
or whereby R_5 is a monounsaturated C_3-C_6 -alkyl group, a monounsaturated C_3-C_6 -alkyl group with a phenyl radical, a monounsaturated C_3-C_6 -alkylcarbonyl group or a monounsaturated C_3-C_6 -alkylcarbonyl group with a phenyl radical and physiologically acceptable acid addition salts thereof,

with the exception of the compounds wherein A represents the radical



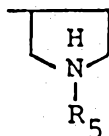
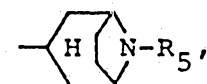
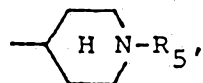
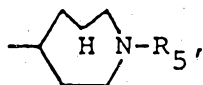
and R_5 represents allyl, benzyl, phenylethyl or methoxyethyl, R_1 represents chlorine in the 4-position and R_2 , R_3 and R_4 represent hydrogen.

A process for the preparation of 4-benzyl-1-(2H)-phthalazinone derivatives of the formula

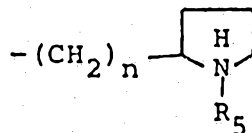


I

wherein R_1 represents fluorine, chlorine, bromine, trifluoromethyl, C_1 - C_6 -alkyl, hydroxy, C_1 - C_6 -alkoxy, C_2 - C_6 -alkanoyloxy, amino, C_1 - C_6 -alkylamino, di- C_1 - C_6 -alkylamino, C_2 - C_6 -alkanoylamino, C_2 - C_6 -alkanoyl- C_1 - C_6 -alkylamino or a nitro group, R_2 represents hydrogen or has one of the meanings given above for R_1 whereby R_1 and R_2 may be the same or different, the radicals R_3 and R_4 may be the same or different and represent hydrogen, halogen, C_1 - C_6 -alkyl, hydroxy, C_1 - C_6 -alkoxy, benzyloxy or C_2 - C_6 -alkanoyloxy and A represents one of the radicals



or



wherein $n=1$ or 2 , whereby R_5 represents a C_1 - C_6 -alkyl group substituted by the following radicals:

- a) by a phenyl radical or a phenyl carbonyl radical each of which may contain one, ^{two or} ~~to~~ three substituents, which may be the same or different, whereby the

substituents are halogen atoms, trifluoromethyl, C_1-C_6 -alkyl groups or C_1-C_6 -alkoxy groups, or

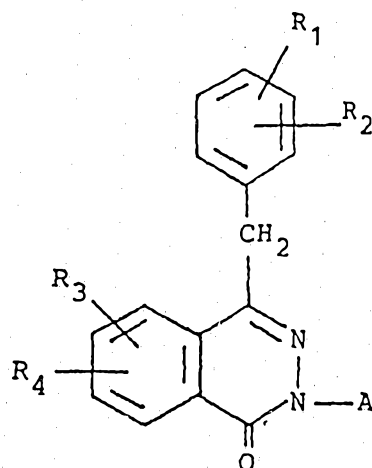
- b) by a C_1-C_6 -alkoxy radical, a mono or dihydroxy- C_1-C_6 -alkyl radical or a hydroxy- C_1-C_6 -alkoxy radical or
- c) by a mono- C_1-C_6 -alkylamino or di- C_1-C_6 -alkylamino radical whereby the latter may also be closed to form a 5-7 membered, nitrogen-containing ring, which may optionally contain a further oxygen atom, or
- d) by a C_3-C_8 -cycloalkyl radical or a C_3-C_8 -cycloalkylcarbonyl radical

or whereby R_5 is a monounsaturated C_3-C_6 -alkyl group, a monounsaturated C_3-C_6 -alkyl group with a phenyl radical, a monounsaturated C_3-C_6 -alkylcarbonyl group or a monounsaturated C_3-C_6 -alkylcarbonyl group with a phenyl radical and physiologically acceptable acid addition salts thereof, with the exception of compounds where A represents the radical



and R_5 represents allyl, benzyl, phenylethyl or methoxyethyl, R_1 represents chlorine in the 4-position and R_2 , R_3 and R_4 represent hydrogen characterized in that

- a) a compound of the formula



II

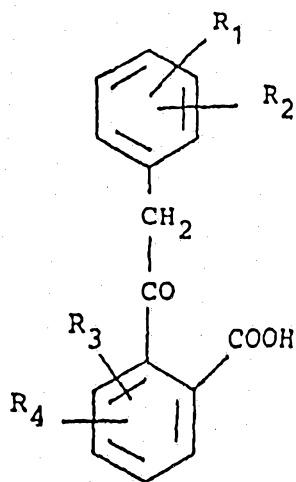
wherein R_1 , R_2 , R_3 , R_4 and A have the meanings given above and R_5 represents hydrogen, is reacted with a compound of the formula



III

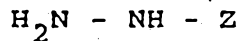
wherein R_5 has the meaning given above and X is a hydroxy group esterified with a strong inorganic or organic acid
or

b) a compound of the formula



IV

or a functional derivative thereof, wherein R_1 , R_2 , R_3 and R_4 have the meanings given above, is reacted with a hydrazine of the general formula



V

wherein Z represents hydrogen or the radical A, and A has the meaning given above, and where Z represents hydrogen, the benzylphthalazinone derivatives so obtained are subsequently reacted with a compound of the formula



VI

wherein Y represents a halogen atom or a sulfonic acid ester group and A has one of the meanings given above,

the so obtained compound is, if desired, alkylated or acylated to introduce a C_1 - C_6 -alkyl group, a benzyl group and/or a C_2 - C_6 -alkanoyl group and/or acyl groups which may be present are split off and if desired the so obtained compounds are converted into acid addition salts thereof.

5. A method for the control or prevention of antiallergic histaminolytic or asthma prophylactic activity in a patient requiring said control or prevention which method comprises administering to said patient an effective amount of at least one compound of Formula I according to claim 1.

593593

FORM 10

SPRUSON & FERGUSON

COMMONWEALTH OF AUSTRALIA

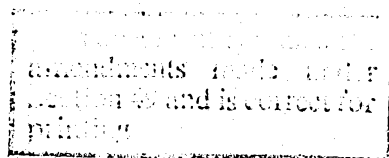
PATENTS ACT 1952

COMPLETE SPECIFICATION

(ORIGINAL)

FOR OFFICE USE:

64982/86



Class Int. Class

Complete Specification Lodged:

Accepted:

Published:

Priority:

Related Art:



Name of Applicant: ^{Pharma}ASTA-Werke Aktiengesellschaft

Address of Applicant: ~~Artur-Ladebeck-Strasse 128-152, D-4800~~
~~Bielefeld 14, Federal Republic of Germany~~

Actual Inventor(s): JÜRGEN ENGEL and GERHARD SCHEFFLER

Address for Service: Spruson & Ferguson, Patent Attorneys,
Level 33 St Martins Tower, 31 Market
Street, Sydney,
New South Wales, 2000, Australia

Complete Specification for the invention entitled:

"NOVEL 4-BENZYL-1-(2H)-PHTHALAZINONE DERIVATIVES"

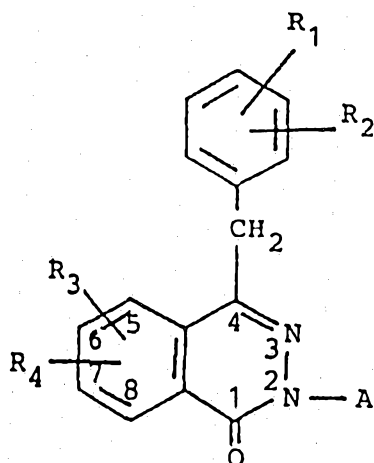
The following statement is a full description of this invention,
including the best method of performing it known to us

SBR/TGK/21T

Summary:

Novel 4-Benzyl-1-(2H)-phthalazinone derivatives

4-Benzyl-1-(2H)-phthalazinone derivatives having antiallergic activity of the formula

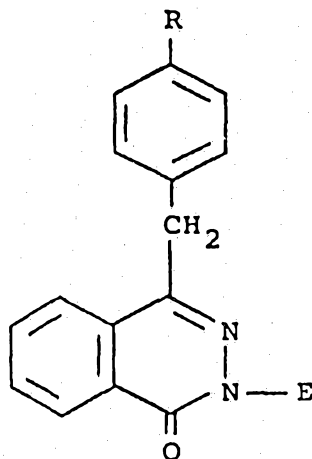


wherein R_1 represents fluorine, chlorine, bromine, trifluoromethyl, C_1 - C_6 -alkyl, hydroxy, C_1 - C_6 -alkoxy, C_2 - C_6 -alkanoyloxy, amino, C_1 - C_6 -alkylamino, di- C_1 - C_6 -alkylamino, C_2 - C_6 -alkanoylamino, C_2 - C_6 -alkanoyl- C_1 - C_6 -alkylamino or a nitro group, R_2 represents hydrogen or has one of the meanings given for R_1 , whereby R_1 and R_2 may be the same or different, the radicals R_3 and R_4 are the same or different and represent hydrogen, halogen, C_1 - C_6 -alkyl, hydroxy, C_1 - C_6 -alkoxy, ^{benzyloxy}~~benzoyloxy~~ or C_2 - C_6 -alkanoyloxy and A represents an azacycloalkanyl radical, the aza nitrogen of which contains a C_1 - C_6 -alkyl group which is substituted by various radicals, and processes for their manufacture.



Novel 4-benzyl-1-(2H)-phthalazinone derivatives

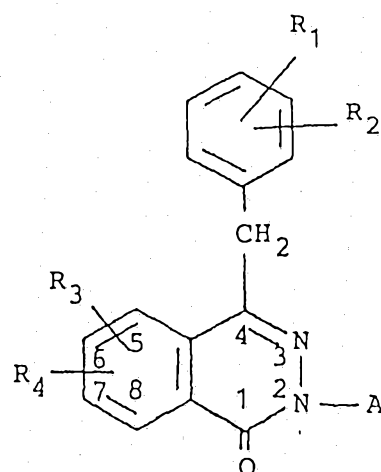
In German patent specification number 21 64 058 there are disclosed basic substituted 4-benzyl-1-(2H)-phthalazinone derivatives of the following formula



wherein R represents hydrogen or a halogen atom, a trifluoromethyl group or a lower alkyl or alkoxy group and E represents a 4-perhydroazepinyl, N-methyl-4-perhydroazepinyl, 3-quinuclidinyl, 3-tropanyl, 3-nortropanyl, N-methyl-3-pyrrolidinyl or N-methyl-2-pyrrolidinyl-methyl radical as well as physiologically acceptable acid addition salts thereof.

These compounds possess antihistamine activity.

The present invention provides
4-Benzyl-1-(2H)-phthalazinone derivatives of the
formula

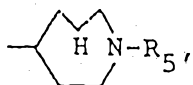


I

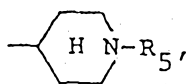
wherein R_1 represents fluorine, chlorine, bromine, trifluoromethyl, C_1 - C_6 -alkyl, hydroxy, C_1 - C_6 -alkoxy, C_2 - C_6 -alkanoyloxy, amino, C_1 - C_6 -alkylamino, di- C_1 - C_6 -alkylamino, C_2 - C_6 -alkanoylamino, C_2 - C_6 -alkanoyl- C_1 - C_6 -alkylamino or a nitro group, R_2 represents hydrogen or has one of the meanings given above for R_1 , whereby R_1 and R_2 may be the same or different, R_3 and R_4 may be the same or different and represent hydrogen, halogen, C_1 - C_6 -alkyl, hydroxy, C_1 - C_6 -alkoxy, benzyloxy or C_2 - C_6 -alkanoyloxy and



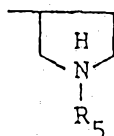
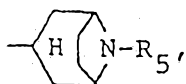
A represents one of the radicals



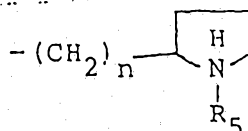
5



10



or



wherein $n=1$ or 2 and R_5 represents a C_1 - C_6 -alkyl group substituted by the following radicals:

20

a) by a phenyl radical or a phenyl carbonyl radical each of which may contain one, two or three substituents, which may be the same or different, whereby the substituents are halogen atoms, trifluoromethyl, C_1 - C_6 -alkyl groups or C_1 - C_6 -alkoxy groups, or

b) by a C_1 - C_6 -alkoxy radical, a mono or dihydroxy- C_1 - C_6 -alkyl radical or a hydroxy- C_1 - C_6 -alkoxy radical or

c) by a mono- C_1 - C_6 -alkylamino or di- C_1 - C_6 -alkylamino radical whereby the latter may also be closed to form a 5-7 membered, nitrogen-containing ring, which may optionally contain a further oxygen atom, or

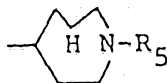
35



- d) by a C_3-C_8 -cycloalkyl radical or a C_3-C_8 -cycloalkylcarbonyl radical

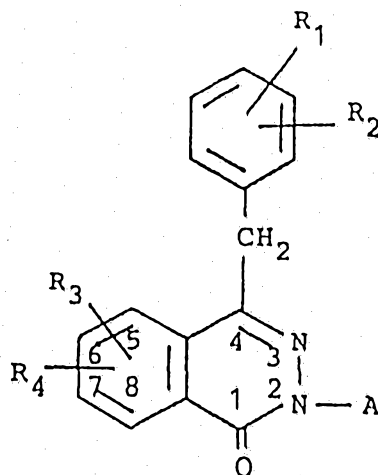
or whereby R_5 is a monounsaturated C_3-C_6 -alkyl group, a monounsaturated C_3-C_6 -alkyl group with a phenyl radical, a monounsaturated C_3-C_6 -alkylcarbonyl group or a monounsaturated C_3-C_6 -alkylcarbonyl group with a phenyl radical and physiologically acceptable acid addition salts thereof,

with the exception of the compounds wherein A represents the radical

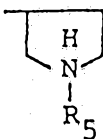
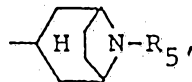
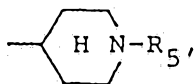
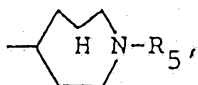


and R_5 represents allyl, benzyl, phenylethyl or methoxyethyl, R_1 represents chlorine in the 4-position and R_2 , R_3 and R_4 represent hydrogen.

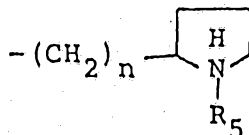
The present invention also provides a process for the preparation of 4-benzyl-1-(2H)-phthalazinone derivatives of the formula



wherein R_1 represents fluorine, chlorine, bromine, trifluoromethyl, C_1-C_6 -alkyl, hydroxy, C_1-C_6 -alkoxy, C_2-C_6 -alkanoyloxy, amino, C_1-C_6 -alkylamino, di- C_1-C_6 -alkylamino, C_2-C_6 -alkanoylamino, C_2-C_6 -alkanoyl- C_1-C_6 -alkylamino or a nitro group, R_2 represents hydrogen or has one of the meanings given above for R_1 whereby R_1 and R_2 may be the same or different, the radicals R_3 and R_4 may be the same or different and represent hydrogen, halogen, C_1-C_6 -alkyl, hydroxy, C_1-C_6 -alkoxy, benzyloxy or C_2-C_6 -alkanoyloxy and A represents one of the radicals



or



wherein $n=1$ or 2 , whereby R_5 represents a C_1-C_6 -alkyl group substituted by the following radicals:

- a) by a phenyl radical or a phenyl carbonyl radical, each may contain one, ^{two or} three substituents, which be the same or different, whereby the



substituents are halogen atoms, trifluoromethyl, C_1-C_6 -alkyl groups or C_1-C_6 -alkoxy groups, or

- 5 b) by a C_1-C_6 -alkoxy radical, a mono or dihydroxy- C_1-C_6 -alkyl radical or a hydroxy- C_1-C_6 -alkoxy radical or
- 10 c) by a mono- C_1-C_6 -alkylamino or di- C_1-C_6 -alkylamino radical whereby the latter may also be closed to form a 5-7 membered, nitrogen-containing ring, which may optionally contain a further oxygen atom, or
- 15 d) by a C_3-C_8 -cycloalkyl radical or a C_3-C_8 -cycloalkylcarbonyl radical

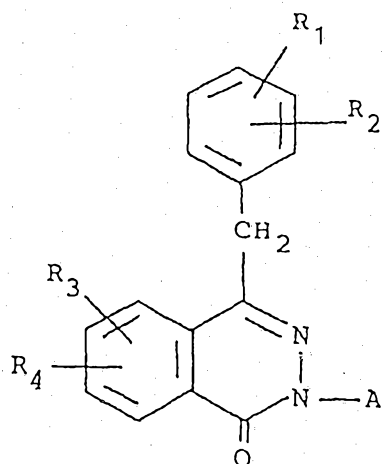
or whereby R_5 is a monounsaturated C_3-C_6 -alkyl group, a monounsaturated C_3-C_6 -alkyl group with a phenyl radical, a monounsaturated C_3-C_6 -alkylcarbonyl group or a monounsaturated C_3-C_6 -alkylcarbonyl group with a phenyl radical and physiologically acceptable acid addition salts thereof, with the exception of compounds where A represents the radical



and R_5 represents allyl, benzyl, phenylethyl or methoxyethyl, R_1 represents chlorine in the 4-position and R_2 , R_3 and R_4 represent hydrogen characterized in that

a) a compound of the formula





15

wherein R_1 , R_2 , R_3 , R_4 and A have the meanings given above and R_5 represents hydrogen, is reacted with a compound of the formula



III

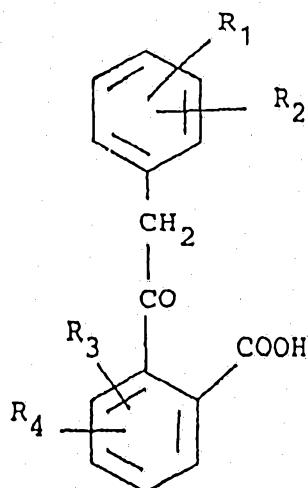
25

wherein R_5 has the meaning given above and X is a hydroxy group esterified with a strong inorganic or organic acid

or

30

b) a compound of the formula



5 or a functional derivative thereof, wherein R_1 , R_2 , R_3 and R_4 have the meanings given above, is reacted with a hydrazine of the general formula



10 wherein Z represents hydrogen or the radical A, and A has the meaning given above, and where Z represents hydrogen, the benzylphthalazinone derivatives so obtained are subsequently reacted with a compound of the formula



20 wherein Y represents a halogen atom or a sulfonic acid ester group and A has one of the meanings given above,

25 the so obtained compound is, if desired, alkylated or acylated to introduce a C_1-C_6 -alkyl group, a benzyl group and/or a C_2-C_6 -alkanoyl group and/or acyl groups which may be present are split off and if desired the so obtained compounds are converted into acid addition salts thereof.



5 The compounds according to the present invention possess
antiallergic, histaminolytic and asthma prophylactic
activity, but are, however, considerably stronger and better
than the compounds known from German patent specification
10 number 21 64 058. In addition, in contradistinction to the
known medicament AZELASTIN (the compound according to
example 5 of German patent specification number 21 64 058)
they do not have any, or at least no considerable, bitter
taste so that they can without any difficulty for example
15 also be used in the form of an aerosol. In addition, the
compounds of the present invention also possess analgesic
activity, in particular peripheral analgesic activity. This
analgesic activity is demonstrated, for example, by the
Randall-Selitto Test on rats (inflammation pain in rats).

20 The radical R_1 is preferably in the 4-position of the phenyl
ring; the radical R_2 preferably in the 3-position.

C_1 - C_6 -Alkyl groups, C_1 - C_6 -alkoxy groups or alkanoyl groups
(for example C_2 - C_6 -alkanoyloxy groups) may be straight or
25 branched chain, such radicals may, in particular, contain
from 1-4 or 2-4 carbon atoms.

30 The radicals R_3 and R_4 may be situated in the 5-, 6-, 7- and
8-positions of the 1-(2H)-phthalazinone radical, preferably
in the 6- and or 7-positions.

35 If R_5 represents a C_1 - C_6 -alkyl group which is substituted by
the given radicals, R_5 preferably contains one, two or three
carbon atoms whereby the substituent is then preferably in
the ω -position.

For example, those compounds have particularly advantageous activities in which the radicals R₁ to R₄, A and R₅ have the following meanings: R₂, R₃ and R₄ = hydrogen; R₁ = fluorine, chlorine or bromine, in particular in the 4-position, preferably fluorine in the 4-position; A = the hexahydroazepin-4-yl radical or the piperid-4-yl radical; R₅ = a C₁-C₆-alkyl group (preferably methyl, ethyl, propyl or isopropyl) which contains an unsubstituted or substituted phenyl radical or phenylcarbonyl radical in the ω-position. The substituents of this phenyl radical or phenylcarbonyl radical are, for example, a C₁-C₄-alkyl group (in particular methyl) or a halogen (for example Cl or F) or a CF₃ group in the 3-position, or three C₁-C₄-alkoxy groups (in particular methoxy groups) in the 3-, 4- and 5-positions.

If the phenyl radical or the phenylcarbonyl radical does not contain any substituent, R₁ is preferably fluorine in the 4-position, R₂, R₃ and R₄ are hydrogen, A is piperid-4-yl or preferably hexahydroazepin-4-yl and R₅ is phenylmethyl, phenylethyl, 3-phenyl-propyl or 2-phenyl-prop-1-yl or phenylcarbonylmethyl.

Process a)

5 The process can be carried out without any additional solvent or in a suitable solvent or dispersing agent. Solvents or dispersing agents which may be used include for example: aromatic hydrocarbons such as, for example, benzene, mesitylene, toluene, xylene; pyridine; lower aliphatic
10 ketones such as, for example, acetone, methylethylketone, halogenated hydrocarbons such as, for example, chloroform, 1,2-dichloroethane, tetrachloromethane, chlorobenzene, methylene chloride; ethers such as, for example, tetrahydrofuran, dioxane, diisopropyl ether; sulphoxides
15 such as, for example, dimethylsulphoxide; tertiary acid amides such as, for example, dimethylformamide, dimethylacetamide, hexamethylphosphoric acid triamide, tetramethyl urea, N-methyl pyrrolidone; lower alcohols such as, for example, methanol, ethanol, isopropanol, amyl
20 alcohol, butanol, tertiary butanol as well as mixtures thereof. The reaction may, for example, be carried out at temperatures between 20 and 200° C, preferably 40 to 160° or also 50 to 120°. Where a solvent or a dispersing agent is used, the reaction is often carried out at the reflux
25 temperature thereof. The reaction often already takes place at room temperature or at a temperature between 40 and 120° C.

30 The reaction is preferably carried out in the presence of acid binding agents such as an alkali carbonates, potash, soda, alkali acetates, alkali hydroxides or tertiary bases (triethylamine, pyridine).

35 Where X represents an esterified hydroxy group, then this may be considered to be a functional ester. A functional

ester which may be used, for example, is one with a strong organic or inorganic acid, but especially a hydrohalic acid, for example a hydrochloric, hydrobromic or hydriodic acid or a sulphonic acid such as an aryl or C₁-C₆-alkylsulphonic acid, for example a lower alkylbenzene sulphonic acid (p-toluenesulphonic acid). Solvents which may be used include, in particular, solvents such as dioxane/water, dimethylformamide/water or lower saturated aliphatic alcohols.

Novel starting materials of formula III may be prepared by methods analogous to Houben-Weyl, Methods in Organic Chemistry (Methoden der Organischen Chemie) Volume 5/3 (1962), pages 503 et seq., volume 6/2 (1963), pages 475 et seq. or volume 9 (1955), page 426.

The preparation of starting materials of formula II:

The starting material of formula II wherein R₁ represents fluorine in the 4-position, R₂ represents hydrogen and A represents a 4-piperidyl radical may for example be prepared as follows:

N-Benzoyl-N'-(N-methyl-piperidin-4-yl)-hydrazine

272 g (2 mol) of benzoic acid hydrazide are added to 1500 ml of methanol with stirring. Over 1 hour, 226 g (2 mol) of 1-methyl-4-piperidinone are then added dropwise at a temperature of 30° C. Slight cooling is necessary. The reaction mixture is stirred for half an hour at 30° C and then for a further 1 hour at 60° C. The solution is then cooled to 0° C and over a period of 2 hours 68 g (1.8 mol)

NaBH₄ is added using a spatula (strong foaming). Towards the end of the addition the mixture is warmed to room temperature. The solvent is evaporated off using a rotary evaporator and to the residue 900 g ice and 1000 ml dichloromethane are added with stirring. The organic phase is separated using a separating funnel and the aqueous phase is shaken twice with 300 ml dichloromethane in each case. The combined organic fractions are dried over MgSO₄, the dichloromethane evaporated off and the residue recrystallized in 1 litre of isopropanol with the addition of 10 g active charcoal. The reaction product is dried in a drying cupboard at 50° C in vacuo. (M.p. 149 -150° C).

4-Hydrazino-N-methylpiperidine x 2 HCl

700 ml of 37 % HCl (8.4 mol) are added to 400 ml water, 233 g (1 mol) N-benzoyl-N'-(N-methylpiperidin-4-yl)-hydrazine are then added with stirring and the reaction mixture refluxed for 2 hours. The liberated benzoic acid crystallizes out. It is cooled in an ice bath and suction filtered. The filtrate is evaporated on a rotatory evaporator. In order to remove any water present, 250 ml methanol are added and distilled off again. By stirring the oily substance in 300 ml methanol a crystalline product is obtained which is suction filtered, washed with methanol and dried under vacuum at 50° C. (M.p. 173° C).

2-(4-Fluorophenacetyl)-benzoic acid

A solution of 410 ml 29 % NaOH is heated to a temperature of 70° C using an oil bath and 250 g (1.04 mol) of 4-fluorobenzylidenephthalide added with stirring. Towards the end of the addition the oil bath temperature is raised

to 110° C. During the reaction a red oil is formed. After 3 hours the mixture is cooled, 500 ml of ice water are added and 340 ml concentrated hydrochloric acid dropwise. Pink crystals separate out. These are suction filtered and washed with chloride-free ice water. After drying at 50° C recrystallization from 900 ml toluene is carried out. (M.p. 147-150° C).

4-(4-Fluorobenzyl)-2-(N-methylpiperidin-4-yl)-1-(2H)-phthalazinone

112.3 g 85 % KOH (1.7 mol) are dissolved in 1890 ml methanol with stirring. 214 g (0.945 mol)

4-hydrazino-N-methylpiperidine x 2 HCl are added and the base liberated. The resulting KCl crystallises out. After addition of 244 g (0.945 mol)

2-(4-fluorophenacetyl)-benzoate the mixture is stirred under reflux over a period of 4 hours (in the case of other hydrazine compounds and/or phenacetylbenzoate this conversion may take somewhat longer, for example up to 20 hours). After cooling the KCl is separated off and the solution reduced on a rotary evaporator. 1000 ml ice water and 928 ml NaOH (twice molar) are added with stirring. The N-methyl compound separates out and is suction filtered, washed with ice water and dried in a drying cupboard at 50° C under vacuum. (M.p. 140-143° C).

4-(4-Fluorobenzyl)-2-(N-carbethoxy-piperidin-4-yl)-1-(2H)-phthalazinone

366.5 g (1.043 mol) 4-(4-Fluorobenzyl)-2-(N-methylpiperidin-4-yl)-1-(2H)-phthalazinone are dissolved in 1100

ml toluene which had been dried over K_2CO_3 . Any water present is azeotropically distilled off using a water separator. 390 g (3.59 mol) ethylchloroformate are added dropwise over 1 1/2 hours and the mixture stirred for 4 hours under reflux. A precipitate separates out and is suction filtered. The filtrate is evaporated on a rotary evaporator, the residue is taken up in 400 ml ether, stirred briefly and suction filtered. After washing with ether, the substance is dried in a drying cupboard. (M.p. 151-152° C).

4-(4-Fluorobenzyl)-2-(piperidin-4-yl)-1-(2H)-phthalazinone

110.2 g (0.269 mol) of the above-described N-carbethoxy-piperidine derivative are added to 181.5 g 48 % HBr (1.077 mol) with stirring. Glacial acetic acid is added dropwise to the clear solution and the mixture heated up to a temperature of 100° C on an oil bath. After 9 hours the solvent is distilled off. To the resulting viscous mass 860 ml water are added with stirring, whereupon a white substance crystallizes out. On addition of 138 ml concentrated ammonia the reaction product precipitates out as a base. The product is suction filtered, washed with water and dried in a drying cupboard at 50° C. (M.p. 157-159°).

The hydrazino starting material with the radical A wherein R_5 represents a methyl group can, for example, also be prepared as follows:

To 120 ml toluene 41.0 g (0.295 mol) tropinone (N-methyl-8-azabicyclo[3.2.1]octane-3-one) and then 22.8 g (0.31 mol) acetylhydrazine are added. The mixture is refluxed for 3 hours and the resulting water is azeotropically distilled off. The resulting product crystallizes out overnight. The remaining solvent is distilled off and the so obtained

N-acetyl-N'-[3-(N-methyl-8-azabicyclo[3.2.1]octane)]hydrazone
recrystallized from 400 ml ethyl acetate. (M.p. 155-157° C).

5 58 g (0.297 mol) of this compound, 440 ml glacial acetic
acid and 5.8 g PtO₂ (81.05 %) are then added to a shaking
autoclave and a hydrogen pressure of ca. 5.7 bar applied.
Hydrogenation is carried out at room temperature. After ca.
4 hours there is no further hydrogen uptake. The catalyst is
10 filtered off and the filtrate concentrated using a rotary
evaporator. The N-acetyl-hydrazine compound remains as an
oily residue.

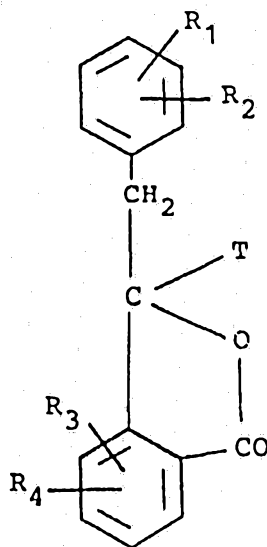
15 The 170.5 g of the oily residue so obtained are added to
1200 ml 22 % HCl. The mixture is heated under a nitrogen
atmosphere for 8 hours under reflux. The resulting solution
is evaporated on a rotary evaporator whereby a crystalline
substance remains behind. Removal of any remaining water is
effected by adding 150 ml methanol twice and then
subsequently evaporating. The residue is dried in a drying
cupboard at 50° C under vacuum. The so obtained
20 3-hydrazino-N-methyl-8-azabicyclo[3.2.1]octane x 2 HCl melts
with decomposition at 250° C.

25 Other starting materials of formula II may be obtained in an
analogous manner. The corresponding 2-phenylacetyl-benzoic
acids contain the radicals R₁ and R₂ in the phenylacetyl
radical and R₃ and R₄ in the benzoic acid part. It is
therefore convenient first of all to prepare the
30 corresponding compound II whereby R₅ of the residue A is a
methyl group and to cleave this via the carbethoxy compound.
The basic compounds II whereby R₅ represents the methyl
group may also be produced according to processes analogous
to German DOS 21 64 058.

35

Process b)

Functional derivatives of the carboxylic acid of the general formula IV which may be used include in particular the acid halides (chloride, bromide, iodide), esters (in particular the C₁-C₆-alkanolates; (as well as) inner esters with an enolized keto group (for example p-chloro-benzylidene phthalides) and the corresponding anhydrides. Compounds of formula IV as well as the corresponding acid halides and esters with C₁-C₆-alkanolates may also be used in the form of their cyclic tautomers. These cyclic forms may be represented by the following formula:



In this formula, T represents a hydroxy group, halogen or C₁-C₆-alkoxy.

The reaction may be carried out in the presence or absence of conventional solvents and auxiliary agents at temperatures between 40 and 200° C and over a wide pH range from acid up to alkaline.

Suitable solvents which may be used include, for example, water, aromatic hydrocarbons such as, for example, benzene,

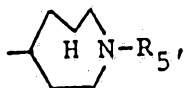
mesitylene, toluene, xylene; halogenated hydrocarbons such as, for example, chloroform, 1,2-dichloroethane, tetrachloromethane, chlorobenzene, methylene chloride; ethers such as, for example, tetrahydrofuran, dioxane, diisopropyl ether; sulfoxides such as, for example, dimethylsulphoxide; tertiary acid amides such as, for example, dimethylformamide, dimethylacetamide, hexamethylphosphoric acid amide, tetramethyl urea, N-methylpyrrolidone; lower alcohols such as, for example, methanol, ethanol, isopropanol, amyl alcohol, butanol, tertiary butanol and mixtures of the above agents as well as tertiary amines such as, for example, pyridine. Auxiliary agents which may be used include bases, acids and conventional condensation agents for these reactions.

The compounds of formula V may also be employed in the form of their N-acyl derivatives whereby these are first hydrolyzed and then without further purification or isolation immediately further employed in the same reaction medium with the compound of formula IV.

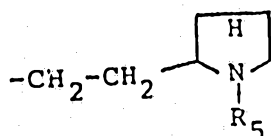
For the conversion of such benzyl-phthalazinone derivatives which are obtained when Z represents hydrogen in the formula V with a compound of the formula Y - A, the above identified solvents may also be used as well as the above identified temperature range.

Other solvents which may also, especially, be used include tertiary acid amides (for example dimethylformamide), aromatic hydrocarbons (for example toluene), lower alcohols or water, whereby the reaction is often carried out in the presence of basic substances (for instance alkali hydroxides or alkali alcoholates). The temperature used is preferably

from 50 - 200° C, and more preferably from 80 - 150° C.
 If Y represents a halogen atom in formula VI, then this may
 be chlorine, bromine or iodine. If Y in formula VI is a
 5 sulphonic acid ester group, this may, for example, be a
 C₁-C₆-alkylsulphonic acid radical (for example CH₃-SO₂-O-)
 or an arylsulphonic acid radical such as, for example, a
 C₁-C₄-alkylbenzene sulphonic acid (for example the p-toluene
 10 sulphonic acid radical). The benzyl-phthalazinone starting
 material (compound of formula I whereby in place of the
 radical A on the acid amide nitrogen atom a hydrogen atom is
 present) may, for example, also be employed in the form of
 their alkali (Na, K) salts. Such alkali salts may, for
 15 example, be obtained from the corresponding phthalazinone
 and the alkali metal in an alcoholic solution (for example
 ethanol) or using another conventional agent therefor
 between 40 - 100° C. Where the radical Z represents hydrogen
 in the starting material of formula V, a compound of formula
 VI is obtained from the subsequent reaction with the
 20 resulting 4-benzylphthalazinone whereby A is either the
 radical



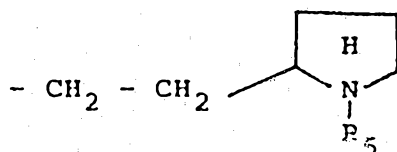
or the radical



as end product each time mixtures of compounds of the
 30 formula I wherein A is the hexahydroazapine radical

and compounds of formula I wherein A represents the 2-pyrro-
 35 lidine ethyl radical





5 (cycloammonium rearrangement). The isolation of the corresponding pure compound may, for example, be carried out in a conventional manner by fractional crystallization.

10 Preparation of starting materials of formula V:

Such starting materials may, for example, be prepared as follows:

15 Conversion of the corresponding cyclic ketones of the formula $O = A'$ with acetyl hydrazine (for example in an aromatic hydrocarbon (toluene) between $50 - 150^\circ C$) or benzoyl hydrazine (for example in an aliphatic alcohol between $20 - 100^\circ C$) to the corresponding hydrazones, followed by subsequent reduction of the same by catalytic hydrogenation (for example in glacial acetic acid in the presence of PtO_2 at a pressure of 5-6 bar) or reduction using a complex metal hydride ($NaBH_4$) in an inert reagent (lower alcohols such as methanol or dioxane) followed by subsequent hydrolytic cleaving off of the acyl group using dilute hydrochloric acid (20 - 37 %). In the case of ketones of the formula $O = A'$, A' represents the radical A, whereby via the tertiary carbon atom (by means of which A is bonded to the phthalazinone radical) in place of a hydrogen bond, there is a second bond with the keto oxygen.

A further possibility is, for example, the reaction of an acylhydrazine (for example ^{benzoyl} benzene hydrazine) with a compound of the formula VI in an inert agent (for example dimethylformamide) between 50 and $180^\circ C$ in the presence of an acid-binding agent (a tertiary amine).



5 The various R_5 radicals may, for example, be obtained before the reaction with the acylhydrazine from the cyclic ketones in which R_5 represents hydrogen by reaction with a compound of the formula R_5X ($X = Cl, Br, I$ or an alkyl or arylsulphonic acid radical) in an inert solvent, for example in the presence of a basic compound at a temperature between 20 and 200° C.

10 Starting materials of the formula IV may, for example, be prepared in known manner using the conventional Perkin synthesis from a phthalic acid anhydride containing the radicals R_3 and R_4 and the radicals R_1 and R_2 substituted by
15 phenylacetic acid.

20

25

30

35

The introduction of a C_2-C_6 -alkanoyl group by acylation is effected by the corresponding acylation of compounds of formula I wherein the radicals R_1 , R_2 , R_3 and/or R_4 represent hydroxy groups, amino groups or C_1-C_6 -alkylamino groups. The acylation is carried out by means of a C_2-C_6 -alkane carboxylic acid whereby this is preferably activated. If such an activated acid is used for the acylation, this will preferably be a compound of the formula C_2-C_6 -alkanoyl-W, wherein W represents halogen (for example chlorine or bromine), but may, for example, also be a group of the formula $-OR'$, $-SR'$ or a group of the formula $-OSO_3H$ or $-OCO-R''$ and R' represents a C_1-C_6 -alkyl radical or also a phenyl radical, which may be substituted by nitro groups, C_1-C_4 -alkoxy groups, C_1-C_4 -alkyl groups or halogen atoms (chlorine, fluorine, bromine), a cyanomethyl radical or a carboxymethyl radical and R'' represents a straight or branched chain C_1-C_5 -alkyl radical. Where W represents a halogen atom, this is preferably a chlorine, bromine or iodine atom; in the case where R' or R'' represent alkyl, alkylthio or alkoxy radicals, these are preferably of low molecular weight and contain from 1 - 4 carbon atoms. Frequently and in particular when W represents a halogen atom or the group $-OCOR''$, the presence of an acid-binding agent such as an alkali metal hydroxide, an alkali metal carbonate, an alkali metal bicarbonate, an alkali metal acetate, an alkaline earth carbonate, a tertiary amine (trialkylamines such as triethylamine, pyridine) or also alkalihydrides and the like is desirable. The acid-binding agent may also be used alone or in admixture with other conventional agents as solvents (for example pyridine). If the free acid is used, then this may be activated by the presence of condensing agents such as, for example, dicyclohexylcarbodiimide, tetraethyl pyrophosphite, 5-(3'-thiophenyl)-ethylisooxazole, sulphurous acid-bis-alkylamides (for example $SO[N(CH_3)_2]_2, N, N'$ -

carbonyldiimidazole and the like (Organic Reactions, Vol. 12, 1962, pages 205 and 239).

5 Introduction of a C_1 - C_6 -alkyl group or of the benzyl group is effected by alkylation (or benzylation) of compounds of formula I in which the radicals R_1 , R_2 , R_3 and/or R_4 represent hydroxy groups, amino groups or alkanoylamino groups.

10 This alkylation (or benzylation) may, for example, be effected by treatment of compounds of the formula C_1 - C_6 -alkyl-hal, benzyl-hal, $ArSO_2O$ - C_1 - C_6 -alkyl and $SO_2(O$ - C_1 - C_6 -alkyl) $_2$, whereby hal may represent a halogen atom (preferably chlorine, bromine or iodine) and Ar

15 represents an aromatic radical (for example a phenyl or naphthyl radical which may, for example, be substituted by one or more lower alkyl radicals). Examples of such groups are p-toluene sulphonic acid- C_1 - C_6 -alkyl esters, C_1 - C_6 -dialkyl sulphates, C_1 - C_6 -alkyl halogenides and the like. The alkylation reaction is preferably carried out in the presence of conventional acid-binding agents.

20 Acid-binding agents which may, for example, be used include those already mentioned for the acylation.

25 The acylation or the alkylation may, for example, be carried out at temperatures between -20 and $220^{\circ}C$, preferably 0 - $150^{\circ}C$, in particular 20 and $80^{\circ}C$ in inert solvents or suspension agents. Solvents or dispersing agents which may, for example, be used include: aromatic hydrocarbons such as, for example, benzene, toluene, xylene; aliphatic ketones such as, for example, acetone, methylethyl ketone; halogenated hydrocarbons such as, for example, chloroform, tetrachloromethane, chlorobenzene, methylene chloride; 30 aliphatic ethers such as, for example, butyl ether; cyclic ethers such as, for example, tetrahydrofuran, dioxane;

5 sulphoxides such as, for example, dimethylsulphoxide;
tertiary acid amides such as, for example,
dimethylformamide, N-methyl pyrrolidone, hexamethyl
phosphoric acid amide; aliphatic alcohols such as methanol,
ethanol, isopropanol, amyl alcohol, tertiary butanol,
cycloaliphatic hydrocarbons, such as cyclohexane and the
like. Aqueous mixtures of the above-mentioned solvents may
also be used. The reaction is often carried out at the
reflux temperature of the solvents or dispersing agents
used. The alkylation reaction component is often used in
excess. The alkylation may also be carried out in the
presence of tetraalkyl ammonium salts (in particular the
halides) in combination with alkali hydroxides at
temperatures between 0 - 100° C, preferably 20 - 80° C in an
aprotic solvent or also in chloroform or methylene chloride.
Aprotic solvents which may be used include in particular:
tertiary amides (dimethylformamide, N-methyl-pyrrolidone,
hexamethyl phosphoric acid triamide), dimethylsulphoxide,
acetonitrile, dimethoxyethane, acetone, tetrahydrofuran.
20 With the acylation and alkylation it is also possible to
proceed in a manner such that an alkali compound of the
compound to be treated is first prepared in that it is added
to an inert solvent such as dioxane, dimethyl formamide,
benzene or toluene with an alkali metal, alkali hydride or
alkali amide (in particular sodium or sodium compounds) or
butyl lithium at temperatures between 0 and 150° C and the
compound to be acylated or alkylated is then added.

30 In place of the above-mentioned alkylating or acylating
agents other chemically equivalent agents commonly used in
chemistry may be used. (See, for example, also L.F. and Mary
Fieser "Reagents for Organic Synthesis", John Wiley and
Sons. Inc., New York, 1967, Vol. 1, pages 1303-4 and Vol. 2,
35 page 471).

The acyl groups in compounds of formula I may be split off using solvolysis whereby the corresponding compounds of formula I are obtained containing free hydroxy groups, amino groups or C₁-C₆-alkylamino groups. This solvolytic cleaving reaction may, for example, be carried out by saponification using dilute acids or using basic materials (potash, soda, aqueous alkali solutions, NH₃) at temperatures between 10 and 150° C, in particular 20 - 100° C.

Depending on the reaction conditions and the starting materials, the end products of formula I may be obtained in free form or in the form of one of their salts. The salts of the end products may be converted to their bases in a conventional manner, for example, with alkali or ion exchange agents. From the latter, salts may be prepared by treatment with organic or inorganic acids, in particular those which are suitable for the preparation of therapeutically acceptable salts.

The compounds of formula I according to the present invention contain in some cases an asymmetric carbon atom (for example the C atom of the 7-ring which is bound to the acid amide nitrogen of the phthalazinone) and are usually obtained in the form of their racemates. Such racemates may be resolved in a conventional manner, for example by fractional crystallization of the salts of racemic compounds of formula I with optically active acids or also by chromatographic racemate separation (see, for example Angewandte Chemie 92/1 (1980) page 14) into their optically active isomers. It is, however, also possible to use an optically active starting material, whereby the end product is then obtained in the corresponding optically active form. In the case of further asymmetric C-atoms, one obtains

diastereomeric mixtures. Separation can be achieved using conventional methods.

5 The present invention thus also covers racemates and diastereomeric forms as well as the corresponding optically active right and left rotating forms.

10 The compounds of the present invention are suitable for the preparation of pharmaceutical compositions and formulations. The pharmaceutical compositions or medicaments may contain as active ingredient one or more compounds of the present invention which may be in admixture with other
15 pharmacologically or pharmaceutically active substances. The preparation of medicaments can be carried out using known and conventional pharmaceutical carriers and auxiliary agents.

20

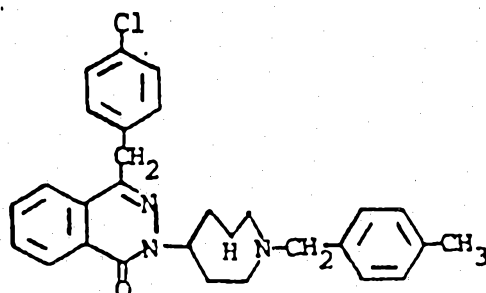
25

30

35

Example 1

4-(p-Chlorobenzyl)-2-[hexahydro-1-(p-methylbenzyl)-azepin-4-yl]-1-(2H)-phthalazinone



0.016 mol (7 g) 4-(p-Chlorobenzyl)-2-(hexahydroazepin-4-yl)-1-(2H)-phthalazinone hydrobromide are dissolved in 50 ml dioxane at 50° C. 0.048 mol (6.5 ml or 4.7 g) triethylamine are added to this solution with stirring as well as 0.016 mol (2.1 ml or 2.2 g) 4-methylbenzyl chloride. The mixture is then stirred for 5 hours at 85° C. The mixture is allowed to cool to room temperature, filtered and concentrated on a rotary evaporator. The dark oily residue is dissolved in propanolic hydrochloric acid and a viscous oily product is then precipitated by the addition of ether. The upper layer of solvent is decanted off. The oily residue is covered with ether and allowed to stand overnight in a closed flask at room temperature. The somewhat hard substance is then triturated in portions with ether, the solvent filtered off and the product dried in the air.

The product is then dissolved in warm methylethylketone, ether is added until cloudiness occurs and the salt is then allowed to crystallize out overnight. The filtered product is dried in vacuo.

Yield: 3.4 g (43 %).

M.p. 191-195° C (Hydrochloride).

The starting material may, for example, be prepared as follows:

5 60 g (0.157 mol) 4-(p-chlorobenzyl)-2-(hexahydro-1-methyl-azepin-4-yl)-1-(2H)-phthalazinone are dissolved by warming to 95° C in 600 ml dry toluene. 51.1 g (0.471 mol = 45 ml) ethyl chloroformate in 45 ml toluene are then added dropwise with stirring. The mixture is stirred for 5 hours at 95° C. After cooling to room temperature the reaction mixture is
10 suction filtered from the insoluble material and dried on a rotary evaporator. An oily residue is obtained which is triturated with a little ether and crystallizes as a white product, which melts at 103 - 105° C (yield: 53.4 g (77 %)).

15 53.4 g (0.12 mol) of the so obtained 1-carbethoxy derivative (formula I, R₅ in radical A = COOC₂H₅) and 114 ml of a 40 % solution of hydrobromic acid in glacial acetic acid are heated to 85 - 90° C under vigorous stirring for 4 hours;
20 with increasing heating the carbethoxy compound dissolves. After cooling the solution is concentrated under vacuo. From the so obtained viscous oily residue the starting material of formula I wherein R₅ represents hydrogen is obtained by recrystallization from methanol in the form of a white
25 crystalline hydrobromide.

The solvent is suction filtered, the mixture washed several times with methanol and dried in vacuo.

30 Yield.: 51 g (95 %)

M.p.: 138 - 140° C.

35 For the preparation of the free base the hydrobromide is suspended in 300 ml distilled water and made alkaline with 100 ml concentrated ammonia. After 2 hours' stirring the

mixture is suction filtered and washed with water until the washings remain neutral. The white product is dried for several days in a vacuum dessicator over P_2O_5 .

Yield: 125 g (77 % of theory)

M.p.: 123 - 125° C.

5

10

15

20

25

30

35

35

In a manner analogous to that set out in Example 1 compounds of formula I are obtained which are set out in table 1.

Unless otherwise indicated, the melting point given in column 4 is that of the corresponding hydrochloride. For Examples 2 to 8 the molecular amounts of the starting materials II and III are in each case the same. In the case of Examples 9, 10, 11 and 13 in each case 0.027 mol and in the case of Example 12, 0.015 mol of the starting material of formula II are employed. In the case of Examples 5 to 11 as well as 13 the starting material is employed in the form of the free base and in Examples 1 to 4 and 12 in the form of the hydrobromide.

The working up of the reaction product after concentration or removal of the reaction solution is carried out in Examples 6, 7, 10 and 13 in a manner analogous to that given in Example 1.

In the case of Examples 2 and 8 after concentration of the reaction mixture the so obtained residue (following crystallization) is recrystallized prior to salt formation with isopropanolic acid HCl from isopropanol, in the case of Example 3 from methanol, and of Example 5 from ethanol.

In Examples 4, 9, 11 and 12 the residue of the reaction mixture after concentration (optionally after stirring with isopropanol and ether) is first purified using kieselgel and then, after removal of the elution agent with isopropanolic hydrochloric acid to give the hydrochloride. The eluting agent is: dichloromethane/methanol/ammonia 25 % = 85/15/1.

In Example 12, after chromatographic purification the base is dissolved in acetone and the oxalate obtained by the addition of anhydrous oxalic acid dissolved in acetone. In

the case of Example 9, the residue from the chromatographic step is not converted into a salt.

5 In order to obtain the crystalline salts it is where appropriate generally necessary to effect repeated trituration with ethanol or methylethyl ketone; sometimes it is recommended to liberate the base with concentrated ammonia, to shake with ether, dry and reform the salt with
10 isopropanolic hydrochloric acid in isopropanol or methylethyl ketone and to precipitate the salt by the addition of ether (Example 13). The so obtained salt may be recrystallized once more from a suitable solvent (for example isopropanol).

15 The starting material II for Examples 2 to 4 as well as 9 to 13 is in each case 4-(p-chlorobenzyl)-2-(hexahydro-azepin-4-yl)-1-(2H)-phthalazinone. The starting material II (4-(p-fluorobenzyl)-2-(hexahydro-azepine-4-yl)-1-(2H)-phthalazinone). That for Examples 5 to 8 may, for example, be obtained as follows:

20 50 g (0.136 mol) well dried 4-(fluorobenzyl)-2-(hexahydro-1-methylazepin-4-yl)-1-(2H)-phthalazinone are dissolved in 400
25 ml toluene by warming to 80° C. Should drops of water form on the inner wall of the flask, then this residual water is distilled off by means of an azeotropic water separator.

30 Subsequently 44.5 g (0.408 mol = 38 ml) ethyl chloroformate are added dropwise and stirred for 1 1/2 hours. After cooling to room temperature the undissolved components are suction filtered off and the so obtained solution dried in vacuo. The remaining syrup which crystallizes out on its own is triturated with ether. The so obtained white crystalline
35 product is suction filtered, washed with ether and dried. Yield: 33 g (57 %)

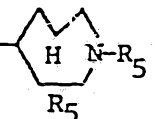
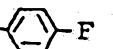
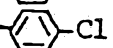
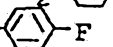
M.p. 95 - 96° C.

A mixture of 33 g (0.078 mol) of the so obtained compound and 65 ml of 40 % HBr/glacial acetic acid is slowly heated to 100° C on an oil bath and stirred for 2 hours. The reaction product is allowed to cool and reduced on a rotary evaporator. The oily residue is dissolved in 250 ml distilled water and the solution made alkaline by the addition of 40 ml concentrated ammonia. The base then precipitates out as a crystalline substance, is suction filtered and dried in a dessicator over phosphorous pentoxide.

Yield: 23 g (48 %)

M.p.: 86 - 88° C.

4-(Fluorobenzyl)-2-(hexahydro-1-methyl-azepin-4-yl)-1-(2H)-phthalazinone is obtained, for example, as follows: 230 g (0.809 mol) of N-benzoyl-N'-(1-methyl-hexahydroazepin-4-yl)-hydrazine are heated for 4 hours under reflux with 830 ml of 23% hydrochloric acid (benzoic acid precipitating). The mixture is cooled down and concentrated on a rotary evaporator, about 200 ml of toluene are added, and the mixture is again concentrated. The residue is boiled for 2 1/2 hours with 209 g of 2-(4-fluoro-phenacetyl)-benzoic acid, 149.5 g of 85% KOH and 2300 ml of methanol. The mixture is concentrated, and the residue is stirred with 3.3 litres of H₂O and 785 ml of 2-molar NaOH. The base precipitates. The mixture is then stirred, filtered with suction and the filter residue is washed with H₂O until neutral and dried at 50°C in vacuo.

Table 1							
Example No.	R ₁ R ₂ =H	A= 	M.p. (hydro- chloride) °C	Yield in %	Starting material Cl-R ₃ in mol	Triethylamine in mol	Temp. of reaction/ duration (hrs.)
2	p - Cl	-CH ₂ - 	145	68	0.016	0.048	90° C / 5
3	p - Cl	-CH ₂ - 	204 - 7	30	0.013	0.032	95° C / 4
4	p - Cl	-(CH ₂) ₂ -CO- 	140	25	0.0156	0.17	85° C / 5
5	p - F	-CH ₂ - 	197 - 199	65	0.02	0.04	85 - 90° C / 3
6	p - F	-CH ₂ -CH=CH ₂	180 - 182	64	0.02	0.04	75° C / 3
7	p - F	-CH ₂ -CH ₂ - 	212 - 215	40	0.014	0.028	95° C / 4
8	p - F	-CH ₂ - 	197 - 200	45	0.014	0.028	80° C / 3
9	p - Cl	-CO-CH=CH-C ₆ H ₅	204 - 206 Base	55	0.054	0.081	20 - 23° C / 8
10	p - Cl	-CH ₂ -CH=CH-C ₆ H ₅	224 - 226 Decomposition	69	0.054	0.081	101° C / 13
11	p - Cl	-CH ₂ - 	226 - 228 Decomposition	53	0.054	0.081	101° C / 13
12	p - Cl	-(CH ₂) ₂ -O-(CH ₂) ₂ -OH	112 - 116 Oxalate	49	0.018	0.027	101° C / 8
13	p - Cl	-(CH ₂) ₂ -N(CH ₃) ₂	248-250 (2 HCl)	44	0.054	0.054	101° C / 4

Examples 14 to 43 (Tables 2 and 3)

5 The preparation of compounds of formula I according to Examples 14 to 38 is carried out according to the following procedure:

10 10 mol dioxane, 3 mol triethylamine and 2 mol of the starting material of formula III are added to 1 mol of the starting material of formula II (free base) at room temperature. The reaction mixture is then heated for several hours at 100° C and after concentration the resulting material is poured into distilled water. The product is worked up according to Method A or B.

15 Method A: The oil, which is insoluble in water, is extracted twice with ether, the combined ethereal extracts are shaken once with water and dried over Na_2SO_4 . After evaporation the remaining oil is taken up in a mixture of isobutylmethyl ketone (or
20 ethylmethylketone) and toluene, acidified using isopropanolic hydrochloric acid and, if necessary, concentrated slightly. After seeding the warm solution with crystals obtained in a reagent glass (and/or addition of ether) a crystalline product is obtained.

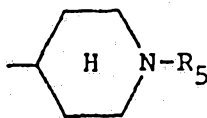
25 Method B: The oil, which is insoluble in water, is extracted three times with methylene chloride and the combined organic phases are shaken twice with
30 water. The resulting organic phase is dried over Na_2SO_4 and concentrated using a rotary evaporator, the residue is taken up in 50 - 70 ml acetone and triturated with 20 g kieselgel (which serves to adsorb the starting material). After stirring for
35 10 minutes the kieselgel is removed by suction filtration and the filtrate concentrated. The

residue after evaporation is taken up in methyl ketone/toluene, acidified with isopropanolic HCl and the solution is concentrated until cloudiness persists. Crystallization may, if necessary, be encouraged by the addition of ether. The resulting crude product is suction filtered, washed with acetone and refluxed with CH_2Cl_2 /methyl ketone. After being allowed to stand for several hours, the pure product is obtained by suction filtration, washed with a large amount of acetone and diethyl ether and the resulting crystals are dried under a vacuum at 50°C .

In the case of Examples 14 to 24, a starting material of Formula II is employed wherein R_1 represents a chlorine atom in the p-position, for Examples 25 - 43 a starting material of Formula II is employed wherein R_1 represents a fluorine atom in the p-position. In Table 2, A always represents the radical



in Table 3, A always represents the radical



The starting materials of Formula III for Examples 14 to 43 are chlorides of the formula Cl-R_5 , wherein R_5 has the meanings given in column 2 of Table 2 or Table 3.

The letter D alongside the melting point temperature means that the relevant substance melts with decomposition.

The products of the process according to the Examples 16, 19, 22, 24, 31 and 33 of Table 2 as well as Example 37 of Table 3 each contain one molecule of water of crystallization.

The preparation of compounds of Formula I according to Examples 39 - 43 is carried out (see Table 3) according to the following working procedure (the reaction temperature and the solvents are here set out in the last column of Table 3):

0.05 mol of the starting material of Formula II (free base) are added to the solvent and dissolved with stirring at a temperature of from 40 - 50° C. This is followed by the addition of the proton-accepting agent (K_2CO_3 or triethylamine) and the dropwise addition of starting material III ($Cl-R_5$). The reaction mixture is refluxed for several hours or stirred at a given temperature. After cooling to room temperature the precipitated salts are suction filtered and the filtrate is concentrated on a rotary evaporator. The residue is worked up and the resulting product is purified by recrystallization or column chromatography. In most cases there is a subsequent salt formation in order to improve solubility. In order to obtain the hydrochloride the base is suspended in ethylmethyl ketone or isopropanol, isopropanolic hydrochloric acid is added until an acidic reaction is obtained and stirred with diethyl ether until the first slight cloudiness appears. The corresponding oxalate is obtained by dissolving the substance in acetone and adding anhydrous oxalic acid which is also dissolved in acetone.

In Examples 39, 40, 41 and 43 dioxane is used as the solvent and triethylamine as the basic compound (in the case of

Example 43 0.15 mol triethylamine, in other cases 0.1 mol).
In the case of Example 42 dimethylacetamide is used as the
solvent and 0.1 mol K_2CO_3 is used as the basic compound. The
amount of starting material of Formula III R_5-Cl is 0.06 mol
in Examples 39 - 41 and 0.1 mol in both Examples 42 and 43.

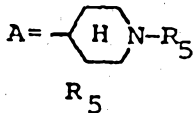
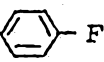
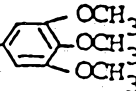
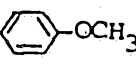
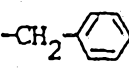
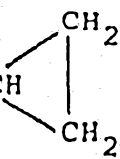
Working up: In Examples 39 - 41 the residue after
distillation of the reaction mixture is recrystallized from
ethanol (50 - 250 ml) with the addition of active charcoal
(in the case of Example 41 kieselgel addition) and
subsequently the hydrochloride is formed. In the case of
Examples 42 and 43 the oily residue is stirred in each case
with 50 ml diethylether which results in crystallization. In
the case of Example 43 a subsequent chromatography through a
kieselgel column (eluent: dichloromethane/methanol/ammonia
25 % = 85/15/1).

In Examples 14 - 43 R_2 is always hydrogen.

Table 2

Example No.	$A = \begin{array}{c} \diagup \quad \diagdown \\ \quad \\ \text{H} \quad \text{N}-R_5 \end{array}$ R_5	M.p. °C (hydrochloride)	Yield in %	Reaction time (hrs)	Working up method
14	$-\text{CH}_2-\text{CH}_2-\text{C}_6\text{H}_4-\text{Cl}$	218-223	20	10	B
15	$-\text{CH}_2-\text{CH}_2-\text{C}_6\text{H}_3(\text{Cl})_2$	210-214	34	8	A
16	$-\text{CH}_2-\text{CH}_2-\text{C}_6\text{H}_4-\text{F}$	180-186	37	12	B
17	$-\text{CH}_2-\text{CH}_2-\text{C}_6\text{H}_4-\text{CH}_3$	225-231	49	12	B
18	$-\text{CH}_2-\text{CH}_2-\text{C}_6\text{H}_4-\text{OCH}_3$	205-208	36	16	B
19	$-(\text{CH}_2)_3-\text{C}_6\text{H}_5$	192-195	77	5	B
20	$-(\text{CH}_2)_3-\text{C}_6\text{H}_4-\text{CH}_3$	207-212 D	80	1	A
21	$-(\text{CH}_2)_3-\text{C}_6\text{H}_4-\text{OCH}_3$	228-234 D	33	5	A
22	$-(\text{CH}_2)_3-\text{C}_6\text{H}_4-\text{F}$	204-207	90	2	B
23	$-(\text{CH}_2)_3-\text{C}_6\text{H}_3(\text{F})_2$	189-194	33	6	A
24	$-(\text{CH}_2)_3-\text{C}_6\text{H}_3(\text{OCH}_3)_2$	123-135 D	20	6	B
25	$-\text{CH}_2-\text{CH}_2-\text{C}_6\text{H}_4-\text{F}$	194-197	30	10	B
26	$-\text{CH}_2-\text{CH}_2-\text{C}_6\text{H}_4-\text{Cl}$	215-219 D	33	10	A
27	$-\text{CH}_2-\text{CH}_2-\text{C}_6\text{H}_3(\text{Cl})_2$	215-218 D	34	3	A
28	$-\text{CH}_2-\text{CH}_2-\text{C}_6\text{H}_4-\text{CH}_3$	241-244 D	30	8	A
29	$-\text{CH}_2-\text{CH}_2-\text{C}_6\text{H}_4-\text{OCH}_3$	182-186 D	23	10	A
30	$-\text{CH}_2-\text{CH}_2-\text{C}_6\text{H}_2(\text{OCH}_3)_3$	181-186 D	46	16	B
31	$-(\text{CH}_2)_3-\text{C}_6\text{H}_4-\text{OCH}_3$	185-191 D	50	4	B
32	$-(\text{CH}_2)_3-\text{C}_6\text{H}_4-\text{F}$	207-211	29	4	B
33	$-(\text{CH}_2)_3-\text{C}_6\text{H}_3(\text{F})_2$	190-193	15	4	B
34	$-(\text{CH}_2)_3-\text{C}_6\text{H}_2(\text{F})_3$	189-191	69	6	B

Table 3

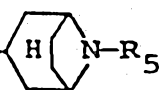
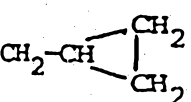
Example No.	A = 	M.p. °C (hydrochloride)	Yield in %	Reaction time (hrs)	Working up method
35	$-(CH_2)_3-$ 	209-211	90	5	A
36	$-(CH_2)_3-$ 	191-195	62	2	B
37	$-(CH_2)_3-$ 	172-176	64	13	B
38	$-(CH_2)_2-$ 	191-195D	63		B
					Volume of solvent/ Reaction temperature (see p.36)
39	$-CH_2-$ 	219-221	53	3	120/85- 90°C
40	$-CH_2-CH=CH_2$	157-158	57	3	120/70°C
41	$-(CH_2)_2-$ 	246-248	59	8	120/101°C
42	$-(CH_2)_2-OCH_3$	180-183	46	6	115/120°C
43	$-CH_2-$ 	195-197	15	16	70/101°C

Examples 44 - 48

The preparation of compounds of Formula I (R_1 = fluorine in the 4-position; R_2 = hydrogen; A see Table 4) according to Examples 44 - 48 is carried out according to the following working procedure:

0.011 mol of the starting material of Formula II (free base) are taken up in 50 ml dioxane (30 ml dioxane in the case of Example 48; 25 ml dioxane in the case of Example 49) and dissolved with stirring at a temperature of 40 - 50 ° C. 0.033 mol triethylamine (in the case of Example 49 0.013 mol) are added in each case followed by the dropwise addition of the starting material of Formula III ($Cl-R_2$). The reaction mixture is refluxed for several hours or stirred at a given temperature. After cooling to room temperature the precipitated salts are dried on a suction filter and the filtrate concentrated on a rotary evaporator. The residue is worked up and the resulting product purified by recrystallization (Examples 44, 45, 47 and 48) or column chromatography (Example 46). Elution agent: dichloromethane/methanol/ammonia 25 % = 85/15/1. In most cases salt formation is effected to improve solubility. In order to obtain the hydrochloride the base is suspended in ethylmethyl ketone or isopropanol, treated with an isopropanolic HCl until an acidic reaction is obtained and diethylether is added until the first slight cloudiness occurs.

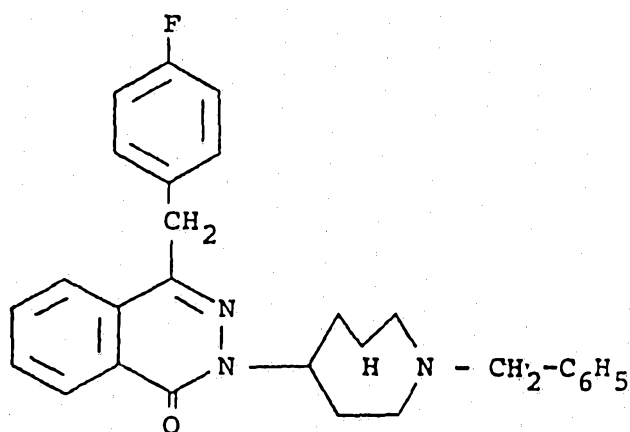
Table 4

Example No.	A =  R ₅	M.p. (hydrochloride) ° C	Yield in %	Starting material III Cl-R ₂ in Mol	Temp. of reaction/ duration (hrs.)
44	CH ₂ -CH=CH ₂	135-140 sinters at 130°C	73	0.033	101°C/8
45	CH ₂ - 	156-157 (Base)	45	0.047	101°C/24
46		152-160	26	0.054	101°C/32
47	-(CH ₂)-CO- 	143-146	56	0.033	101°C/6
48	-(CH ₂) ₂ - 	245-247	30	0.033	101°C/10
49	-CH ₂ -  R ₁ =p-Cl	230-232	53	0.0065	90°C/6

Examples for Process b):

Example 50:

5 4-(4-Fluoro-benzyl)-2-(hexahydro-1-benzylazepin-4-yl)-1-(2H)-phthalazinone



34 g (0.088 mol) 1-benzoyl-2-(hexahydro-1-benzylazepin-4-yl)-hydrazine x HCl are refluxed together with 90 ml 23 % HCl for 4 hours under stirring. After cooling the reaction mixture is rotated in a vacuum to effect drying. The remaining residue is admixed with 22.7 g (0.088 mol) of 2-(p-fluorophenacetyl)-benzoic acid and 14 g (0.25 mol) potassium hydroxide dissolved in 250 ml methanol and the solution subsequently stirred for 2 hours at room temperature. Finally the solvent is distilled off in vacuo and the residue is treated with 500 ml H₂O and 85 ml 2N NaOH. The reaction product precipitates out with stirring in the form of its base as a crystalline precipitate which is filtered off and thoroughly washed with H₂O. The product is

dried in a dessicator over phosphorous pentoxide and
recrystallized from isopropanol.

Yield: 26 g

M.p. 197 - 199° C.

5

10

15

20

25

30

35

The starting materials may, for example, be obtained as follows:

5 1-Benzoyl-2-(hexahydro-1-benzylazepin-4-yl)-hydrazine x HCl

A mixture of 68.3 g (0.27 mol) N-benzylazepine-one-(4)-hydrochloride, 38 g (0.28 mol) benzoylhydrazine and 250 ml methanol are stirred for 1.5 hours at 30° C until solution takes place. After cooling to 4° C, 15.3 g (0.27 mol) potassium hydroxide dissolved in 150 ml methanol are added dropwise with stirring whilst maintaining the above temperature (ice cooling). After addition has taken place 15.8 g (0.42 mol) sodium borohydride are added in small portions over a period of 1 hour with maintenance of the temperature of the reaction medium at 14 - 18° C (exothermic reaction; strong foaming due to H₂ production) and the reaction mixture is subsequently stirred at room temperature for a further 2 hours. Subsequently 120 ml isopropanolic hydrochloric acid are added to bring the pH of the reaction mixture to 5 and stirring is carried out for 2 hours under ice water cooling. After filtering off the inorganic salts, the filtrate is concentrated in vacuo. The remaining oil is treated with 250 ml acid/methanol = 10:1. The hydrochloride precipitates out as a crystalline product on stirring. The precipitate is suction filtered and dried. Yield: 27 g (35 %) M.p. 176 - 180° C.

2-(p-Fluoro-phenacetyl)-benzoic acid

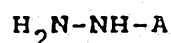
35 250 g (1.04 mol) p-Fluoro-benzylidene phthalide are added to 410 ml (3.9 mol) 29 % sodium hydroxide using an oil bath

temperature of 70°C with stirring. Towards the end of the addition the oil bath temperature is raised to 110°C. A red coloured oil is thereby obtained. On cooling, this oil precipitates as a crystalline product. This substance is dissolved in 500 ml distilled water (red-coloured solution) and the solution is acidified under stirring by the dropwise addition of 340 ml concentrated hydrochloric acid. The precipitate is suction filtered, washed several times with distilled water and dried in a vacuum. Finally, the product is recrystallized from toluene.

Yield 220.8 g (82 %)

M.p. 146 - 150°C.

In an analogous manner to the above example compounds of Formula I may be obtained (for example the compounds given in Tables 1 to 4) from in each case 0.088 mol of phenacetylbenzoic acid substituted by the radicals R_1 , R_2 , R_3 and R_4 (for example 2-(p-chloro-phenacetyl)-benzoic acid or 2-(p-fluorophenacetyl)-benzoic acid) and 0.088 mol of a hydrazine of the formula

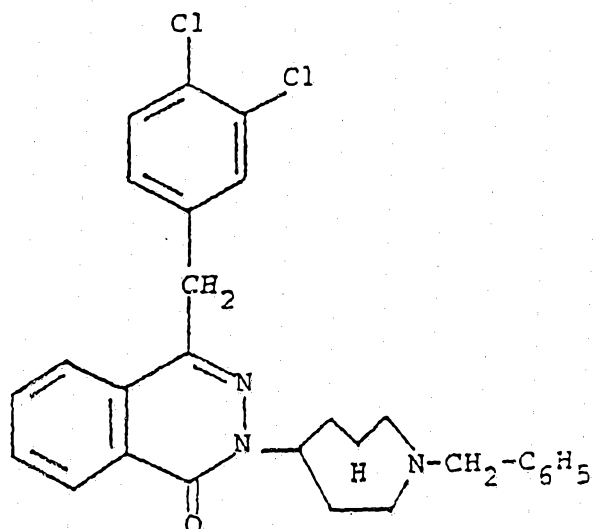


The hydrazine may in this case be employed in the form of its acyl derivative (benzoyl or acetyl derivative) in which case, before the actual reaction the acyl group is split off giving the free hydrazine.

The hydrochlorides may, for example, be obtained by treatment of the corresponding base with isopropanol/HCl, followed by precipitation with ether and recrystallization from ethyl methyl ketone ether.

Example 51

4-(3,4-Dichlorobenzyl)-2-(hexahydro-1-benzyl-azepin-4-yl)-1-(2H)-phthalazinone



A solution of 3.28 g (8.15 mmol) of 4-(3,4-dichlorobenzyl)-2-(hexahydro-1H-azepin-4-yl)-1-(2H)-phthalazinone, 3.4 ml (29.5 mmol) of benzyl chloride and 9 ml (64.6 mmol) of triethylamine in 20 ml of dioxane is heated for 12 hours at 200°C.

10 The mixture is then concentrated, and the residue is treated with water and extracted by shaking with dichloromethane. The organic phase is dried with MgSO_4 , filtered and concentrated. The remaining oil crystallizes overnight. The crystals are suspended in ether and triturated. After filtering off with suction and washing of the substance with ether, the solution is evaporated on a rotary evaporator.

This gives a colorless crystalline substance of M.p. 117-118°C. Yield 0.55 g (14%).

Example 52

4-(3,4-Dichlorobenzyl)-2-(hexahydro-1-phenethyl-azepin-4-yl)-1-(2H)-phthalazinone

3.36 g (8.35 mmol) of 4-(3,4-dichlorobenzyl)-2-(hexahydro-1H-azepin-4-yl)-1-(2H)-phthalazinone, 4 ml (29.3 mmol) of phenethyl bromide and 4.5 ml (32.20 mmol) of triethylamine are dissolved in 20 ml of dioxane.

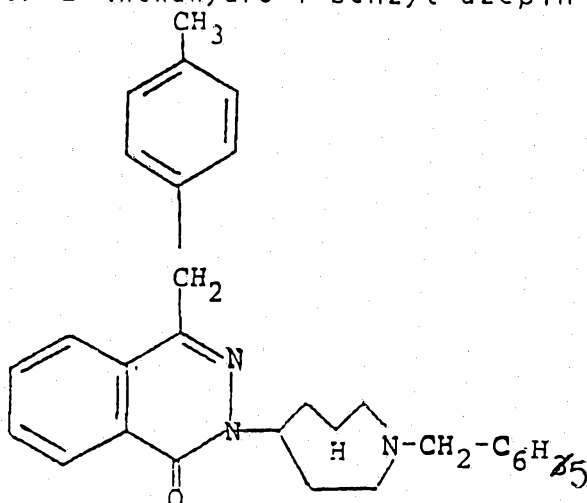
The reaction mixture is heated for 12 hours at 100°C with stirring.

- 10 The mixture is evaporated on a rotary evaporator, the residue is treated with water, eluted with dichloromethane, dried with MgSO_4 , filtered and concentrated, and the resulting oil is chromatographed over a silica gel column. The base obtained from the corresponding eluates is converted into the oxalate.

Yield 0.39 g (about 8%), M.p. 161 - 162°C.

Example 53

4-(4-Methylbenzyl)-2-(hexahydro-1-benzyl-azepin-4-yl)-1-(2H)-phthalazinone



3.02 g (8.69 mmol) of 4-(4-methylbenzyl)-2-(hexahydro-1H-azepin-4-yl)-1-(2H)-phthalazinone, 3 ml (26.00 mmol) of benzyl chloride and 3.6 ml (25.8 mmol) of triethylamine are dissolved in 20 ml of dioxane.

The reaction mixture is heated for 10 hours at 100°C with stirring. It is then concentrated, and the residue is treated with water and extracted by shaking with dichloromethane. The solution is dried with MgSO₄, filtered and concentrated. The oily residue is chromatographed over a silica gel column.

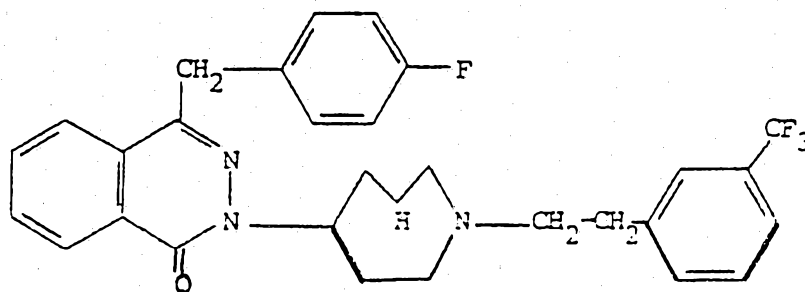
After concentrating the eluate, a crystalline product is obtained which is suspended in ether, triturated and filtered off with suction.

Yield: 1 g (26.3%), M.p. 128 - 129°C.



54
Example 55

4-(4-Fluoro-benzyl)-2-(1-[2-(3-trifluoromethyl-phenyl)-ethyl]-hexahydroazepin-4-yl)-1-(2H)-phthalazinone



10.5 g (0.03 mol) of 4-(4-fluoro-benzyl)-2-(hexahydro-azepin-4-yl)-1-(2H)-phthalazinone, 9.1 g of triethylamine and 5 drops of dimethylformamide are added to 80 ml of dioxane, 10 g (0.04 mol) of 2-(3-trifluoromethyl-phenyl)-ethyl bromide are added dropwise at room temperature to this mixture and the whole is heated for 6 hours under reflux. After cooling, the mixture is filtered with suction. The solution is concentrated on a rotary evaporator, the residue is dissolved in 150 ml of CHCl_3 and the solution is extracted with twice 50 ml of H_2O . The CHCl_3 phase is dried over MgSO_4 , filtered and concentrated. The residue is triturated with ether, left to stand overnight, filtered off with suction, rinsed with ether and dried in vacuo at 40°C . The hydrochloride is prepared in isopropanol with ethereal hydrochloric acid and recrystallized from 40 times the quantity of acetone. The hydrochloride melts at $184 - 187^\circ\text{C}$ (yield 6.1 g).



Examples for the preparation of pharmaceutical preparations

5

⁵⁵
Example 56

Tablets, 5 mg active ingredient

50 g of the active ingredient according to Example 5, 450 g lactose, 150 g maize starch and 10 g highly purified amorphous silicon dioxide are passed through a sieve (mesh size 0.8 mm), mixed and granulated with 200 g of a 5 % aqueous gelatine solution in a vortex mixer. The dry granulate, 242 g microcrystalline cellulose, 80 g maize starch and 8 g magnesium stearate are passed through a sieve (0.8 mm mesh size), mixed homogenously and made up by pressing into a tablet in a conventional manner having a weight of 100 mg and a diameter of 6 mm.
1 tablet contains 5 mg active ingredient.

20

⁵⁶
Example 57

Capsules, 5 mg active ingredient

50 g active ingredient according to Example 7, 50 g maize starch, 1070 g calciumbiphosphate-dihydrate and 10 g highly purified, amorphous silicon dioxide are passed through a sieve (0.8 mm mesh size), homogenized and granulated in a vortex mixer with 200 g of 10 % aqueous gelatine solution. 200 g Maize starch and the dry granulate are passed through a sieve (0.8 mm mesh size), homogenized and dosed in a conventional manner into 140 mg hard gelatine capsules size 3.
1 capsule contains 5 mg active ingredient.

30

⁵⁷
Example 58

Water-in-oil cream, 1 % active ingredient

10 g micronized active ingredient according to Example 5 are added to a melt (70° C) from 250 mg white Vaseline, 20 g of

35



an emulsifier made up of fatty acid monoesters of glycerine or of other multivalent alcohols (Lunacera alba), 5 g cetyl alcohol and 30 g of a non-ionic emulsifier (Cremophor^R water-in-oil-7) with the aid of a high-speed dispersing apparatus. 10 g phenoxyethanol, 20 g glycerine and 655 g water are added to this melt at 70° C by means of a high-speed emulsifying apparatus and the emulsion is cooled to 30° C with stirring.

1 g cream contains 10 mg active ingredient.

58
Example 59

Oil-in-water cream, 1 % active ingredient

10 g micronized active ingredient according to Example 7 are suspended in 100 g low-viscosity paraffin and made up into a melt (70° C) made up of 60 g polyoxyethanol polyol fatty acid ester, 20 g of a mixture of cetyl alcohol and stearyl alcohol (1:1), 40 g stearic acid and 55 g of a solubilizing agent made up of a mixture of triglycerides of saturated plant fatty acids C₈, C₁₀ and C₁₂ (Miglyol^R 812). The aqueous phase is made up of 10 g phenoxyethanol, 30 g glycerine, 655 g water and 20 g 1N-sodium hydroxide. The two phases are mixed at 60° C with the aid of a high-speed dispersing apparatus emulsified and stirred until cold.

1 g cream contains 10 mg active ingredient.



Examples of Use and Dosage of Compounds of the Invention

5 The compounds of the present invention display good asthma prophylactic and antiallergic activity in allergic (ovalbumin) asthma in wake guinea pigs. For example, using the above set out test methods at a dose of 0.5 mg/kg body weight in guinea pig brings about a 50 % protection against allergically-induced asthmatic attacks.

10 The lowest dosage found to be active in the above mentioned animal tests is, for example, 0.1 mg/kg by the oral route. As a general dosage range giving rise to activity (animal tests as above) one may, for example, use 0.01 - 3 mg/kg by the oral route and especially 0.1 - 1 mg/kg.

15
20 The general activity of the compounds according to the present invention is comparable to the activity of the known compound disodium chromoglycinic acid, but the following special differences exist: good peroral activity; leucotriene C₄ antagonism.

25 Indications for the compounds of the present invention which may be considered include: prophylactic treatment of bronchial asthma.

30 Contraindications: none.

The pharmaceutical preparations contain in general between 0.1 to 30 preferably 0.5 to 10 and more preferably 1 to 5 mg of the inventive active components.



1
Administration may, for example, take place in the form of
tablets, capsules, pills, dragees, suppositories, ointments,
5 gels, creams, powders, dusting powders, aerosols or in
liquid form. Liquid formulations which may, for example, be
used include oily or alcoholic or aqueous solutions as well
as suspensions and emulsions. Preferred forms of
administration are tablets which contain between 0.5 and 10
10 mg or solutions which contain from 0.01 - 5 % active
substance.

Individual doses of the active components of the present
invention may, for example, be the following:
15

- 20
a) for oral medicaments between 0.5 - 10 mg,
preferably 1 - 3 mg;
- 25
b) for parenteral medicaments (for example intravenous or
intramuscular) between 0.05 - 3 mg,
preferably 0.1 - 1 mg;
- 30
c) for medicaments for inhalation (solutions or aerosols)
between 0.1 - 2 mg,
preferably 0.5 - 1 mg;
- 35
d) for medicaments for rectal or vaginal application
between 0.1 - 10 mg,
preferably 0.5 - 5 mg;



- e) for medicaments for local application on the skin and mucous membrane (for example in the form of solutions, lotions, emulsions, ointments, etc.) between 1 - 10 mg, preferably 0.5 - 5 mg.

- The dosage forms are in each case calculated with reference to the free base.

It is, for example, possible to use a 3 times daily dose of 1 to 3 tablets containing from 0.5 - 5 mg active ingredient or, for example, by intravenous injection 1 to 3 times daily an ampoule containing from 1 to 5 ml with 1 to 5 mg of substance. For oral administration the minimum daily dosage is, for example, 0.5 mg; the maximum daily dose on oral administration should not exceed 50 mg.

For the treatment of dogs and cats the oral single dose is, in general, between 0.03 and 5 mg/kg body weight; the parenteral dosage is generally between about 0.01 and 3 mg/kg body weight.

For the treatment of horses and bovines the oral individual dosage is generally between about 0.03 and 5 mg/kg; the parenteral individual dose is between about 0.01 and 3 mg/kg body weight.

The acute toxicity of the compounds according to the present invention in mice (expressed by the LD 50 mg/kg; method



1 according to Miller and Tainter: Proc. Soc. Exper. Biol. a.
Med. 57 (1944) 261) may, for example, lie on oral
administration between 500 and 1000 mg/kg.

5 The medicaments may be used in human medicine, veterinary
medicine as well as in agriculture alone or in admixture
with other pharmacologically active substances.

10

15

20

25

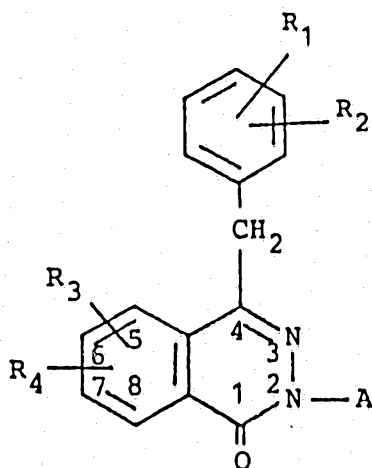
30

35



10 The claims defining the invention are as follows:

1. 4-Benzyl-1-(2H)-phthalazinone derivatives of the formula

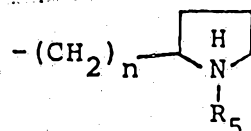
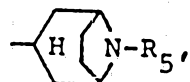
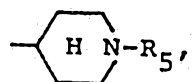
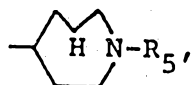


I

wherein R_1 represents fluorine, chlorine, bromine, trifluoromethyl, C_1 - C_6 -alkyl, hydroxy, C_1 - C_6 -alkoxy, C_2 - C_6 -alkanoyloxy, amino, C_1 - C_6 -alkylamino, di- C_1 - C_6 -alkylamino, C_2 - C_6 -alkanoylamino, C_2 - C_6 -alkanoyl- C_1 - C_6 -alkylamino or a nitro group, R_2 represents hydrogen or has one of the meanings given above for R_1 , whereby R_1 and R_2 may be the same or different, R_3 and R_4 may be the same or different and represent hydrogen, halogen, C_1 - C_6 -alkyl, hydroxy, C_1 - C_6 -alkoxy, benzyloxy or C_2 - C_6 -alkanoyloxy and



A represents one of the radicals



or

wherein $n=1$ or 2 and R_5 represents a $\text{C}_1\text{--C}_6$ -alkyl group substituted by the following radicals:

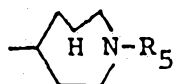
- a) by a phenyl radical or a phenyl carbonyl radical each of which may contain one, two or three substituents, which may be the same or different, whereby the substituents are halogen atoms, trifluoromethyl, $\text{C}_1\text{--C}_6$ -alkyl groups or $\text{C}_1\text{--C}_6$ -alkoxy groups, or
- b) by a $\text{C}_1\text{--C}_6$ -alkoxy radical, a mono or dihydroxy- $\text{C}_1\text{--C}_6$ -alkyl radical or a hydroxy- $\text{C}_1\text{--C}_6$ -alkoxy radical or
- c) by a mono- $\text{C}_1\text{--C}_6$ -alkylamino or di- $\text{C}_1\text{--C}_6$ -alkylamino radical whereby the latter may also be closed to form a 5-7 membered, nitrogen-containing ring, which may optionally contain a further oxygen atom, or



- d) by a C_3-C_8 -cycloalkyl radical or a C_3-C_8 -cycloalkylcarbonyl radical

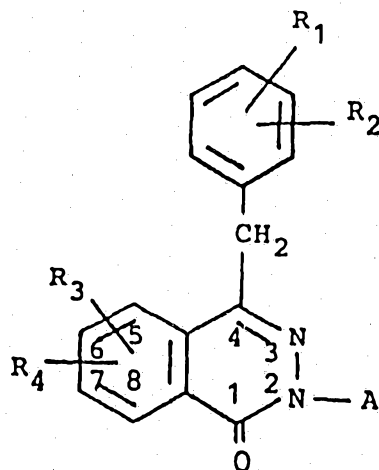
or whereby R_5 is a monounsaturated C_3-C_6 -alkyl group, a monounsaturated C_3-C_6 -alkyl group with a phenyl radical, a monounsaturated C_3-C_6 -alkylcarbonyl group or a monounsaturated C_3-C_6 -alkylcarbonyl group with a phenyl radical and physiologically acceptable acid addition salts thereof,

with the exception of the compounds wherein A represents the radical



and R_5 represents allyl, benzyl, phenylethyl or methoxyethyl, R_1 represents chlorine in the 4-position and R_2 , R_3 and R_4 represent hydrogen.

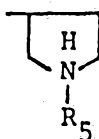
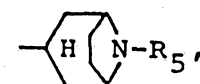
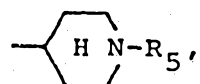
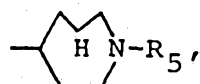
2. A process for the preparation of 4-benzyl-1-(2H)-phthalazinone derivatives of the formula



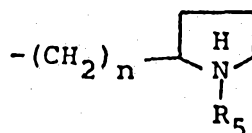
I



wherein R_1 represents fluorine, chlorine, bromine, trifluoromethyl, C_1-C_6 -alkyl, hydroxy, C_1-C_6 -alkoxy, C_2-C_6 -alkanoyloxy, amino, C_1-C_6 -alkylamino, di- C_1-C_6 -alkylamino, C_2-C_6 -alkanoylamino, C_2-C_6 -alkanoyl- C_1-C_6 -alkylamino or a nitro group, R_2 represents hydrogen or has one of the meanings given above for R_1 whereby R_1 and R_2 may be the same or different, the radicals R_3 and R_4 may be the same or different and represent hydrogen, halogen, C_1-C_6 -alkyl, hydroxy, C_1-C_6 -alkoxy, benzyloxy or C_2-C_6 -alkanoyloxy and A represents one of the radicals



or



wherein $n=1$ or 2 , whereby R_5 represents a C_1-C_6 -alkyl group substituted by the following radicals:

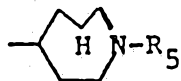
- a) by a phenyl radical or a phenyl carbonyl radical each of which may contain one, ^{two or} three substituents, which may be the same or different, whereby the



substituents are halogen atoms, trifluoromethyl, C_1-C_6 -alkyl groups or C_1-C_6 -alkoxy groups, or

- b) by a C_1-C_6 -alkoxy radical, a mono or dihydroxy- C_1-C_6 -alkyl radical or a hydroxy- C_1-C_6 -alkoxy radical or
- c) by a mono- C_1-C_6 -alkylamino or di- C_1-C_6 -alkylamino radical whereby the latter may also be closed to form a 5-7 membered, nitrogen-containing ring, which may optionally contain a further oxygen atom, or
- d) by a C_3-C_8 -cycloalkyl radical or a C_3-C_8 -cycloalkylcarbonyl radical

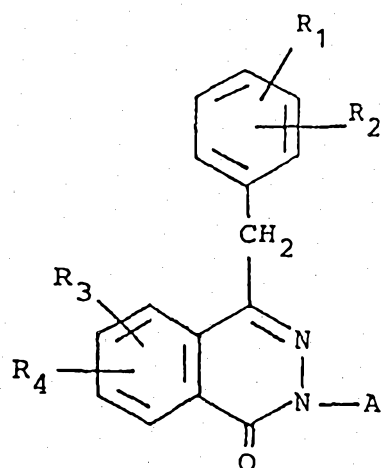
or whereby R_5 is a monounsaturated C_3-C_6 -alkyl group, a monounsaturated C_3-C_6 -alkyl group with a phenyl radical, a monounsaturated C_3-C_6 -alkylcarbonyl group or a monounsaturated C_3-C_6 -alkylcarbonyl group with a phenyl radical and physiologically acceptable acid addition salts thereof, with the exception of compounds where A represents the radical



and R_5 represents allyl, benzyl, phenylethyl or methoxyethyl, R_1 represents chlorine in the 4-position and R_2 , R_3 and R_4 represent hydrogen characterized in that

- a) a compound of the formula





II

wherein R_1 , R_2 , R_3 , R_4 and A have the meanings given above and R_5 represents hydrogen, is reacted with a compound of the formula

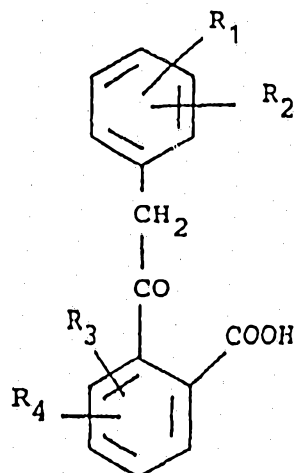


III

wherein R_5 has the meaning given above and X is a hydroxy group esterified with a strong inorganic or organic acid

or

b) a compound of the formula



IV



or a functional derivative thereof, wherein
 R_1 , R_2 , R_3 and R_4 have the meanings given
 above, is reacted with a hydrazine of the
 general formula



wherein Z represents hydrogen or the
 radical A, and A has the meaning given
 above, and where Z represents hydrogen, the
 benzylphthalazinone derivatives so obtained
 are subsequently reacted with a compound of
 the formula



wherein Y represents a halogen atom or a
 sulfonic acid ester group and A has one of
 the meanings given above,

the so obtained compound is, if desired, alkylated
 or acylated to introduce a C_1 - C_6 -alkyl group, a
 benzyl group and/or a C_2 - C_6 -alkanoyl group and/or
 acyl groups which may be present are split off and
 if desired the so obtained compounds are converted
 into acid addition salts thereof.



3. Medicaments containing a compound of the general formula I as defined in claim 1 in association with conventional carriers and/or diluents for auxiliary agents.

4. A process for the preparation of a medicament characterized in that a compound of the general formula I as defined in claim 1 is brought into a therapeutically acceptable form together with conventional pharmaceutical carriers and/or diluents or other auxiliary agents to give pharmaceutical formulations or to yield a therapeutically acceptable formulation.

5. A method for the control or prevention of antiallergic histaminolytic or asthma prophylactic activity in a patient requiring said control or prevention which method comprises administering to said patient an effective amount of at least one compound of Formula I according to claim 1.

6. 4-Benzyl-1-(2H)-phthalazinone derivatives as herein described with reference to any one of Examples 1 to 55.

7. A process for preparing 4-Benzyl-1-(2H)-phthalazinone derivatives said process being substantially as herein described with reference to any one of Examples 1 to 54.

8. A pharmaceutical composition substantially as herein described with reference to any one of Examples 55 to 58.

DATED this TWENTY-NINTH day of MAY 1989

^{Pharma}
Asta-Werke Aktiengesellschaft

Patent Attorneys for the Applicant
SPRUSON & FERGUSON



TMR/109M