

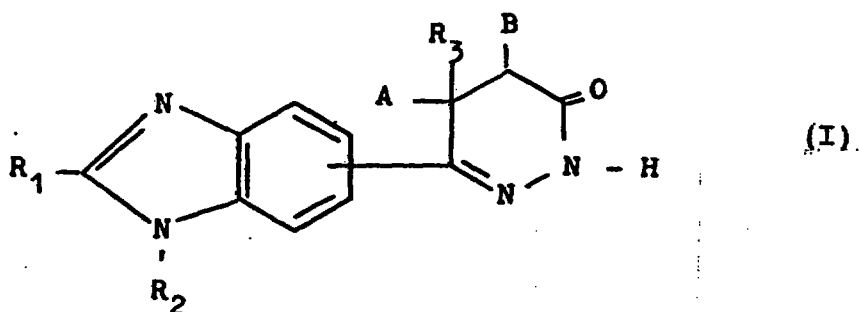
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Benzimidazoles, their preparation and
pharmaceutical compositions containing these
compounds

British Patent 1 466 547 already describes benzimidazoles substituted by a pyridazine group which is substituted in the 2 and/or 4 position by a methyl group, these benzimidazoles having a hypotensive, antithrombotic and cardiotonic activity.

It has now been found that the benzimidazoles substituted by a pyridazine ring which is substituted in the 5 position by an alkyl group have a greater potency and/or better oral resorption.

The present invention thus relates to new benzimidazoles of general formula



which are substituted in the 5 or 6 position by a pyridazine ring which is substituted in the 5 position by an alkyl group, the physiologically acceptable acid addition salts thereof with inorganic or organic acids, processes for preparing them and pharmaceutical compositions containing these compounds.

The compounds of general formula I above and the physiologically acceptable acid addition salts thereof have valuable pharmacological properties, and in particular, besides an antiviral, interferon-inducing and ulcer-inhibiting activity, a cardiovascular activity, i.e. cardiogenic, hypotensive and/or anti-thrombotic activities.

In general formula I above,

a and b each represent a hydrogen atom or together represent another bond,

R_1 represents a hydrogen atom, a trifluoromethyl group, an alkyl group with 1 to 11 carbon atoms, a cycloalkyl group with 3 to 7 carbon atoms, a hydroxy or mercapto group optionally substituted by an alkyl group with 1 to 6 carbon atoms, a phenylalkyl group with 1 to 3 carbon atoms in the alkyl part or a phenyl group which may be mono-, di- or trisubstituted by a halogen atom, an alkyl group with 1 to 4 carbon atoms an alkylsulphonyl group with 1 to 6 carbon atoms and/or a hydroxy or mercapto group optionally substituted by an alkyl group with 1 to 6 carbon atoms, whilst the substituents of the phenyl nucleus may be the same or different,

R_2 represents a hydrogen atom, an alkyl group with 1 to 6 carbon atoms, a cycloalkyl group with 3 to 6 carbon atoms or a phenylalkyl group with 1 to 3 carbon atoms in the alkyl part and

R_3 represents an alkyl group with 1 to 6 carbon atoms.

Thus, in accordance with the definitions given for the groups R_1 , R_2 and R_3 hereinbefore:

R_1 may represent, in particular, a hydrogen atom or a trifluoromethyl, methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, sec.butyl, tert.butyl, n-pentyl, 2-pentyl, tert.-pentyl, isopentyl, n-hexyl, n-undecyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, hydroxy, methoxy, ethoxy, propoxy, isopropoxy, mercapto, methylmercapto, ethylmercapto, propylmercapto, isopropylmercapto, hexylmercapto, benzyl, 1-phenylethyl, 2-phenylethyl, 1-phenylpropyl, 2-phenylpropyl, 1-phenyl-2-propyl, 3-phenylpropyl, phenyl, fluorophenyl, difluorophenyl, chlorophenyl, dichlorophenyl, bromophenyl, dibromophenyl, methylphenyl, dimethylphenyl, tert.-butylphenyl, hydroxyphenyl, dihydroxyphenyl, methoxyphenyl, dimethoxyphenyl, trimethoxyphenyl, n-hexoxyphenyl, mercaptophenyl, dimercaptophenyl, methylmercaptophenyl, dimethylmercaptophenyl, methylsulfinylphenyl, dimethylsulfinylphenyl, fluorohydroxyphenyl, fluoromethoxyphenyl, fluoromercaptophenyl, fluoromethylmercaptophenyl, chlorohydroxyphenyl,

chloromethoxyphenyl, chloromercaptophenyl, chloromethylmercaptophenyl, bromohydroxyphenyl, bromomethoxyphenyl, bromomercaptophenyl, bromomethylmercaptophenyl, hydroxymethoxyphenyl, hydroxymercaptophenyl, hydroxymethylmercaptophenyl, methoxymercaptophenyl, methoxymethylmercaptophenyl or methoxymethylsulfinylphenyl group,

R_2 may represent a hydrogen atom or a methyl, ethyl, propyl, isopropyl, butyl, pentyl, isopentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, benzyl, 1-phenylethyl, 2-phenylethyl or 3-phenylpropyl group, and

R_3 may represent a methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec.butyl or tert.butyl group.

Preferred compounds of general formula I are those wherein

A and B each represent a hydrogen atom or together represent another bond,

R_1 represents a hydrogen atom or a methyl, isopropyl, n-pentyl, 2-pentyl, n-hexyl, n-undecyl, cyclopropyl, cyclohexyl, cycloheptyl, hydroxy, ethoxy, mercapto, methylmercapto, isopropylmercapto, hexylmercapto, trifluoromethyl, 1-phenylethyl, 1-phenyl-2-propyl, phenyl, 2-fluorophenyl, 4-chlorophenyl, 4-hydroxyphenyl,

2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2,4-dimethoxyphenyl, 3,4-dimethoxyphenyl, 4-n-hexyloxyphenyl, 3,4,5-trimethoxyphenyl, 2-methoxy-4-methylmercaptophenyl, 4-methylphenyl, 4-tert.butylphenyl, 2-methoxy-4-methylsulfinylphenyl or 2-bromo-5-methoxyphenyl group,

R_2 represents a hydrogen atom or a methyl, 3-methylbutyl, cyclopropyl, cyclohexyl or benzyl group;

R_2 represents a hydrogen atom or a methyl, 3-methylbutyl, cyclopropyl, cyclohexyl or benzyl group; and

R_3 represents a methyl, ethyl or n-butyl group, and the physiologically acceptable acid addition salts thereof with inorganic or organic acids.

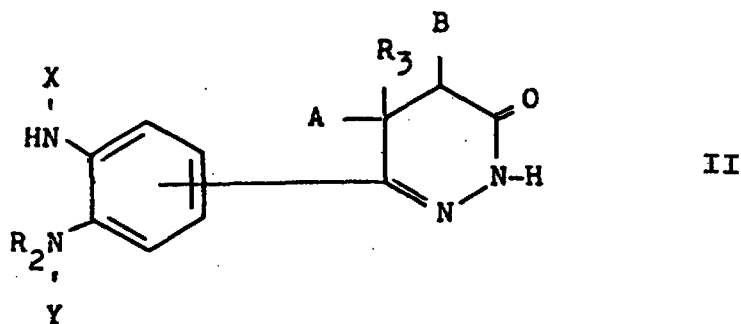
Especially preferred compounds of general formula I, however, are those wherein A and B each represent a hydrogen atom or together represent another bond, R_1 represents a hydrogen atom or a methyl, 2-pentyl, 1-phenylethyl, ethoxy, methylmercapto, 4-methylphenyl, 2-fluorophenyl, 4-methoxyphenyl, 4-hexyloxyphenyl or 2,4-dimethoxyphenyl group; R_2 represents a hydrogen atom or a methyl or benzyl group; and R_3 represents a methyl group, and the physiologically acceptable acid addition salts thereof with inorganic or organic acids.

Furthermore, the new benzimidazoles of this invention may occur in the form of their racemates or optically active enantiomers on account of their

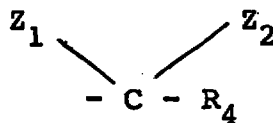
optically active carbon atoms in the 5 position of the pyridazine ring if A and B each represent a hydrogen atom.

According to the invention, the new benzimidazoles, the racemates and optically active enantiomers thereof, if A and B each represent a hydrogen atom, may be prepared by the following processes:

a) cyclisation of a compound, optionally prepared in the reaction mixture, of general formula



wherein A, B, R₂ and R₃ are as hereinbefore defined, one of the groups X or Y represents a hydrogen atom and the other group X or Y or both groups X and Y represent a group of formula



wherein

Z₁ and Z₂, which may be the same or different, represent optionally substituted amino groups or hydroxy or mercapto groups optionally substituted by lower alkyl groups or

Z₁ and Z₂ together represent an oxygen or sulphur atom, an imino group optionally substituted by an alkyl

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group with 1 to 3 carbon atoms, or an alkylenedioxy or alkylenedithio group with 2 or 3 carbon atoms and

R_4 has the meanings given for R_1 hereinbefore or represents an amino group optionally substituted by an alkyl group with 1 to 3 carbon atoms, or the alkali metal salts thereof if R_4 represents a mercapto group.

The cyclisation is conveniently effected in the presence of a solvent such as, for example, ethanol, isopropanol, glacial acetic acid, chlorobenzene, toluene, xylene, glycol, glycol monomethyl ether, diethylene glycol dimethyl ether, dimethylformamide, tetralin or in an excess of an acylating agent used for the preparation of the compound of general formula II, e.g. in R_1CN , $(R_1CO)_2O$, R_1COOH , R_1CSOH or R_1CSSH or in esters, ortho esters, amides, halides or methiodides thereof. The cyclisation is preferably effected at elevated temperatures e.g. at temperatures of from 0 to 250°C, optionally in the presence of a condensating agent such as e.g. phosphorus oxychloride, thionyl chloride, sulfuryl chloride, sulfuric acid, hydrochloric acid, phosphoric acid, polyphosphoric acid, p-toluenesulfonic acid or glacial acetic acid, acetic acid anhydride. The cyclisation is also optionally effected in the presence of a base such as

e.g. potassium ethoxide or potassium tert.butoxide.

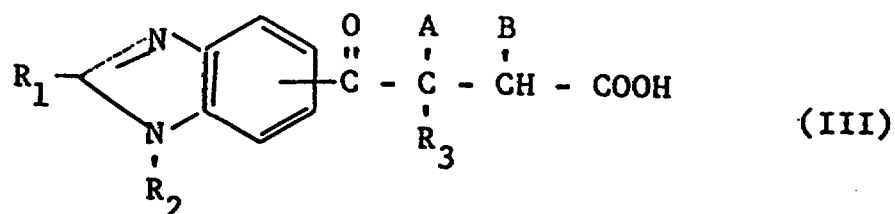
However, the cyclisation may be carried out without a solvent and/or without a condensating agent.

However, the reaction is especially advantageously carried out by reducing a corresponding 6-(acylamino-nitrophenyl)-pyridazin-3-one to the desired compound of formula II. Reduction may be effected, e.g. by means of hydrogen in the presence of a hydrogenating catalyst such as e.g.

Raney nickel, platinum or palladium/charcoal, by means of metals such as e.g. iron, tin or zinc, by means of metal salts such as e.g. iron (II) sulfate, zinc(II) chloride or chromium(II) chloride or by means of hydrazine in the presence of Raney nickel. The compound of formula II thus obtained can be cyclised in the same reaction mixture, if necessary in the presence of an acid such as e.g. hydrochloric acid, sulfuric acid, phosphoric acid, acetic acid or a carboxylic acid of formula R_1COOH , or in the presence of a condensating agent such as e.g. phosphorus oxychloride or in the presence of a base such as e.g. potassium ethoxide optionally in the presence of a solvent such as e.g. ethanol, isopropanol, glycol, dimethylformamide, dimethylsulfoxide or chlorobenzene, at temperatures of from 0 to 250°C.

For the preparation of a compound of formula I wherein R_1 represents a mercapto group, the compound of formula II is preferably prepared in situ by reaction of a corresponding 7,8-diamino compound with carbon disulfide in the presence of an alkali metal alkoxide, e.g. in the presence of potassium ethoxide, preferably in an alcoholic solvent such as e.g. ethanol. The subsequent cyclisation may then be effected by simple heating of the reaction mixture, preferably by heating up to the boiling temperature of the reaction mixture.

b) Reaction of a carboxylic acid of general formula III ,



(wherein A, B, R_1 , R_2 and R_3 are as defined above) or an ester, amide or halide thereof with hydrazine.

The reaction is conveniently carried out in the presence of a solvent such as e.g. ethanol, isopropanol, glacial acetic acid, propionic acid and/or in an excess of hydrazine or hydrazine hydrate and preferably at

elevated temperatures, e.g. at temperatures of from 0 to 150°C. The reaction may optionally, if desired, be effected in the presence of an acid as condensating agent such as e.g. sulfuric acid or p-toluenesulfonic acid. The reaction may, however, be carried out without a solvent.

A compound of formula I obtained according to process a) or b) wherein A and B each represent a hydrogen atom, may if desired be converted by dehydrogenation into a compound of formula (I) wherein A and B together represent another bond, and/or

a compound of formula I wherein R_1 represents a hydroxy or mercapto group or a phenyl group substituted by from one to three substituents selected from hydroxy and mercapto groups and/or R_2 represents a hydrogen atom, may be converted, if desired, by means of alkylation into a corresponding alkoxy, alkylmercapto and/or alkyl compound of formula I, and/or

a compound of formula I wherein R_1 represents a phenyl group substituted by at least one alkylmercapto group can be converted, if desired, by means of oxidation into a corresponding alkylsulfinylphenyl compound of formula I, and/or

a compound of formula I wherein R_1 represents an alkylmercapto group, can be converted, if desired, by means of oxidation and subsequent hydrolytic removal of the resulting alkylsulfinyl or alkylsulfonyl group into
5 a corresponding hydroxy compound of formula I.

The subsequent dehydrogenation may be carried out using a dehydrogenating agent such as e.g. bromine, phosphorus pentachloride, sodium 3-nitrobenzenesulfonate, chromium trioxide, N-bromosuccinimide,
10 hydrogen peroxide or sodium nitrite, preferably in a solvent such as e.g. glacial acetic acid, propionic acid, aqueous glacial acetic acid or nitrobenzene and preferably at temperatures of from 0 to 100°C, most preferably, at temperatures of from 50 to 80°C.

15 Alkylation may be carried out with an alkylating agent such as, for example, an alkyl halide, dialkyl sulfate, trialkyloxonium tetrafluoroborate or diazoalkane, e.g. with methyl iodide, dimethyl sulfate, diethyl sulfate, ethyl bromide or diazomethane, preferably in
20 the presence of a solvent such as e.g. methanol, ethanol, aqueous methanol, diethyl ether or dioxan and optionally in the presence of a base such as e.g. sodium bicarbonate,

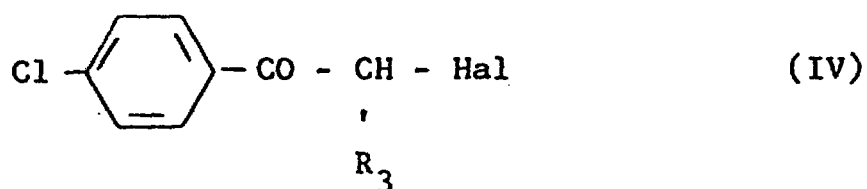
sodium carbonate, sodium hydroxide, sodium methoxide or potassium carbonate. Temperatures which are up to the boiling temperature of the solvent used are preferred.

Oxidation is preferably carried out in the presence
5 of a solvent such as glacial acetic acid or trifluoroacetic acid and preferably with about one equivalent of oxidising agent e.g. hydrogen peroxide, if an alkylsulfinylphenyl compound is to be prepared. In general temperatures of from 0 to 50°C are appropriate, preferred
10 being ambient temperatures.

Moreover, the compounds of general formula I obtained wherein A and B each represents a hydrogen atom, may be resolved into their optically active antipodes. Resolution is preferably carried out by fractional crystallisation
15 of a salt of the compound of formula I with an optically active acid such as e.g. tartaric acid, dibenzoyl-tartaric acid, malic acid, camphoric acid or camphor-sulfonic acid.

Furthermore, the compounds of general formula I can be converted, if desired, into acid addition salts by reaction with
20 inorganic or organic acids. Suitable acids include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid and
25 maleic acid.

The compounds of general formulae II and III used as starting materials can, for example, be obtained according to processes known from the art (see for example British Patent Specification 5 No. 1 466 547). Thus, a compound of general formula III can be obtained for example by reaction of a compound of formula IV ,



with malonic ester. The compound thus obtained is subsequently saponified, decarboxylated, nitrated, the chlorine atom is replaced by a corresponding amino group, acylated, the nitro group reduced and cyclised to the desired benzimidazole.

The compounds of the present application differ from those of the British Patent Specification No. 15 1 466 547 in having an alkyl substituent R_3 in the 5

- position of the pyridazine ring . The new benzimidazoles surprisingly show a higher activity and/or better oral resorption. The new compounds of the present application show not only a good oral resorption
- 5 but also superior pharmacological properties. Besides an antiviral, interferon-inducing and ulcer inhibiting activity they show cardiovascular activity, i.e. cardiotonic, hypotensive and/or anti-thrombotic activity.
- 10 For example the following compounds:
- A = 2-Methyl-5(6)-(5-methyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole,
- B = 2-Methyl-5(6)-(5-methyl-3-oxo-2H-6-pyridazinyl)-benzimidazole,
- 15 C = 2-Trifluoromethyl-5(6)-(5-methyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole,
- D = 5(6)-(5-Methyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole,
- E = 2-(2-Fluorophenyl)-5(6)-(5-methyl-3-oxo-4,5-dihydro-
- 20 2H-6-pyridazinyl)-benzimidazole,

- F = 2-(2,4-Dimethoxyphenyl)-5(6)-(5-methyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole,
- G = 2-Methylmercapto-5(6)-(5-methyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole,
- 5 H = 2-(4-Methoxyphenyl)-5(6)-(5-methyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole,
- I = 2-(4-Methylphenyl)-5(6)-(5-methyl-3-oxo-4,5-dihydro-2H-pyridazinyl)-benzimidazole,
- K = 2-(2-Pentyl)-5(6)-(5-methyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole hydrochloride,
- 10 L = 1-Methyl-2-(4-methoxyphenyl)-5-(5-methyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole,
- M = 1-Benzyl-2-methyl-5-(5-methyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole,
- 15 were tested in comparison with the compounds
- N = 2-Methyl-5(6)-(4-methyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole,
- O = 2-(2,4-Dimethoxyphenyl)-5(6)-(4-methyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole,
- 20 P = 2-(4-Methoxyphenyl)-5(6)-(4-methyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole and

Q = 2-(4-Methoxyphenyl)-5(6)-(2,4-dimethyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole (see British Patent Specification No. 1 466 547) with regard to their biological properties.

- 5 1. Determination of the thrombocyte aggregation according to Born and Cross (J. Physiol. 170, 397 (1964)):

The thrombocyte aggregation was measured in platelet-rich plasma of healthy human donors. The
10 decrease in optical density was measured photometrically and recorded after addition of commercial collagen of Messrs. Sigma, St. Louis, U.S.A., which contains 1 mg of collagen-fibrils per ml. The velocity of aggregation (Vmax) was determined by the angle of
15 inclination of the density curve. The point of the curve, where the most light was transmitted, served for the determination of the optical density (o.d.). To provoke maximum aggregation approx. 0.01 ml of the
20 collagen solution was added to 1 ml of platelet-rich plasma.

The following table shows the results obtained:

Table I

Compound	ED ₅₀ in $\mu\text{mol/l}$
A	0.01
B	34
C	0.1
D	0.12

2. Determination of the hypotensive and positive
inotropic activity in the cat

10 The tests were performed in cats, which were
anaesthetised with pentobarbital sodium (40 mg/kg i.p.).
The animals breathed spontaneously. The arterial blood
pressure was measured in the aorta abdominalis by a
Statham pressure transducer (P 23 Dc). The positive
15 inotropic effect was determined by measuring the pressure
in the left auricle by means of a catheter-tip manometer
(Millar PC 350 A). The contractility parameter dp/dt_{max}
was registered by means of an analog differentiating circuit.

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The substances under test were injected into the vena femoralis. Physiological sodium chloride solution or polydiol 200 was used as solvent. Each substance was tested in at least 3 cats, dose 0.1, 5 0.5 or 2.0 mg/kg i.v.. The tested substances showed an activity lasting at least 1 hour.

The following table contains the average values:

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Test Compound	Dose mg/kg i.v.	Change of blood pressure in mmHg	Increase of dp/dt in %
A	0.1	- 26/24	+ 53
B	0.5	+ 18/15	+ 25
C	0.1	- 65/35	+ 91
D	0.5	- 55/48	+ 159
E	0.5	- 8/10	+ 107
F	0.5	- 28/33	+ 89
G	0.1	- 36/40	+ 51
H	0.1	+ 3/0	+ 23
I	0.5	+ 33/15	+ 118
K	0.1	- 10/13	+ 83
L	0.1	+ 14/9	+ 17
M	0.1	- 37/33	+ 123
N	0.5	+ 5/3	+ 23 *
O	0.5	+ 15/6	+ 10 *
P	2.0	- 35/35	- 5
Q	2.0	- 40/40	- 26

* Duration of activity: 5 - 20 minutes

3. Acute toxicity:

The acute toxicity of the test compounds was determined in white mice after oral administration of a single dose (observation time: 14 days).

5 Table III

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Test compound	acute toxicity mg/kg p.o.
A	> 600 (1 out of 3 animals died)
C	> 450 (0 out of 6 animals died)
E	> 600 (0 out of 6 animals died)
H	~ 600 (3 out of 6 animals died)
I	> 600 (0 out of 6 animals died)

In view of their pharmacological properties the compounds of general formula I prepared according to the invention and the optically active enantiomers and physiologically acceptable acid addition salts thereof with inorganic or organic acids are suitable for the treatment of chronic cardiac insufficiency or angina pectoris and/or for the prophylaxis of arterial thromboembolism and arterial occlusion and for the treatment of ulcers and for combating viruses and viral diseases.

For this purpose, the new benzimidazoles, optionally together with other active substances, may be incorporated in the conventional pharmaceutical forms such as tablets, coated tablets, powders, suppositories, suspensions, ampoules or drops. The dosage unit is 5 to 200 mg, preferably 15 to 150 mg, one to four times a day.

Since the compounds of general formula I may occur in either of their tautomeric forms 1H or 3H, the place of substitution at the benzimidazole nucleus is designated 5 (6).

The Examples which follow are intended to illustrate the invention:

Example 1

2-(4-Methoxyphenyl)-5(6)-(5-methyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole hydrochloride.

5 a) Methyl 3-nitro-4-(4-methoxy-benzoylamino)-benzoyl-butyrates

A mixture of 10 g of methyl 3-(3-nitro-4-aminobenzoyl)-butyrate and 10.2 g of 4-anisic acid chloride in 100 ml of chlorobenzene was refluxed until complete reaction of the methyl 3-(3-nitro-4-aminobenzoyl)-butyrate was obtained. The resultant mixture was stirred with activated charcoal, filtered and the filtrate was mixed with cyclohexane, whereby the product was obtained as crystals. The crystals were filtered off with suction and washed with cyclohexane and petroleum ether.

Yield: 10.7 g (73 % of theory),
M.p.: 107 - 117°C.

b) 5-Methyl-6-[3-nitro-4-(4-methoxy-benzoylamino)-phenyl]-3-oxo-4,5-dihydro-2H-pyridazine

20 20 ml of 80 % hydrazine hydrate were added dropwise to 150 ml of glacial acetic acid whilst stirring and ice-cooling. After cooling the mixture obtained, 10.7 g of methyl 3-[3-nitro-4-(4-methoxy-benzoylamino)-benzoyl]-butyrate were added thereto and the resultant mixture was refluxed for 40 minutes. After cooling 25 250 ml of ice-water were added thereto. The precipitate thus formed was filtered off with suction and washed with ice-water.

Yield: 9.8 g (96 % of theory),

M.p.: 219°C

c) 5-Methyl-6-[3-amino-4-(4-methoxy-benzoylamino)-phenyl]-3-oxo-4,5-dihydro-2H-pyridazine

9.8 g of 5-methyl-6-[3-nitro-4-(4-methoxy-benzoylamino)-phenyl]-3-oxo-4,5-dihydro-2H-pyridazine were dissolved in 1000 ml of ethanol and hydrogenated for 24 hours at room temperature with a hydrogen pressure of 5 bar in the presence of 1 g of 10 % palladium charcoal. The obtained precipitate was filtered off with suction and used in the next step without removal from the catalyst. A further fraction of the product can be obtained from the mother liquors.

Yield: 8.5 g (94.4 % of theory).

d) 2-(4-Methoxyphenyl)-5(6)-(5-methyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole hydrochloride

The product obtained according to the method described in (c) was refluxed in 100 ml of glacial acetic acid for 1.5 hours and the hot resultant mixture was filtered through a glass frit. 100 g of ice were added to the filtrate and the orange-yellow precipitate thus formed was filtered off and washed with dilute acetic acid. The combined filtrates were made alkaline by means of ammonia. The product thus precipitated in crystalline form, was filtered off with suction and purified on a silica gel column (eluant: methylene chloride/ethanol = 50:1 and 25:1). The hydrochloride was precipitated from methanol with ethereal hydrochloric acid.

Yield: 4.45 g (49.8 % of theory)

M.p.: 311°C (decomp.).

Example 2

2-(4-Methoxyphenyl)-5(6)-(5-methyl-3-oxo-4,5-dihydro-2H-
5 6-pyridazinyl)-benzimidazole hydrochloride

a) 2-(4-Methoxyphenyl)-5(6)-(1-oxo-2-methyl-3-methoxycarbo-
nyl-1-propyl)-benzimidazole hydrochloride

9.2 g of 5-methyl-6-[3-nitro-4-(4-methoxy-benzoylamino)-
phenyl]-3-oxo-4,5-dihydro-2H-pyridazine were hydro-
10 genated in a mixture of 300 ml of methanol and 3 ml of
glacial acetic acid for 2.5 hours at room temperature
with a hydrogen pressure of 5 bar and in the presence
of 2 g of 10 % palladium charcoal. Hydrogen chloride
gas was introduced into the resultant mixture for 2.5
15 hours under reflux. The mixture thus obtained was
mixed with ether and the product obtained was filtered
off with suction and washed with ether.

Yield: 4.5 g (50.5 % of theory),

M.p.: above 300°C.

20 b) 2-(4-Methoxyphenyl)-5(6)-(5-methyl-3-oxo-4,5-dihydro-
2H-6-pyridazinyl)-benzimidazole hydrochloride

1 ml of 80 % hydrazine hydrate was dissolved in 10 ml
of glacial acetic acid and after cooling 0.43 g of 2-
(4-methoxyphenyl)-5(6)-(1-oxo-2-methyl-3-methoxycarbon-
25 yl-1-propyl)-benzimidazole hydrochloride were added
thereto. The precipitated product was filtered off

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with suction, washed with water and purified on a silica gel column (eluant chloroform/methanol = 50:1). The hydrochloride was precipitated from ethanol with ethereal hydrochloric acid.

5 Yield: 0.3 g (70.3 % of theory),
M.p.: 314°C (decomp.).

Example 3

2-Methyl-5(6)-(5-methyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole hydrochloride

10 29 g of 5-methyl-6-(3-nitro-4-acetamino-phenyl)-3-oxo-4,5-dihydro-2H-pyridazine were hydrogenated in a mixture of 1200 ml of methanol and 100 ml of glacial acetic acid for 2.5 hours at room temperature with a hydrogen pressure of 5 bar in
15 the presence of 5 g of 10% palladium charcoal. The catalyst was subsequently filtered off and the filtrate was evaporated. The residue was dissolved in 400 ml of glacial acetic acid and the solution obtained was heated up to 100°C for 40 minutes, then poured onto 1
20 l of ice. Whilst cooling the pH of the resultant mixture was adjusted to 8 by addition of conc. ammonia. The precipitated free base was subsequently converted to the hydrochloride by dissolving it in methanol and addition of ethereal hydrochloric acid.

25 Yield: 19.7 g (70.7 % of theory),
M.p.: 308°C.

Example 4

2-Methyl-5(6)-(5-methyl-3-oxo-2H-6-pyridazinyl)-benzimidazole

30 A solution of 3 ml of bromine in 30 ml of glacial acetic acid was added dropwise to 8 g of 2-methyl-

- 5(6)-(5-methyl-3-oxo-2H-6-pyridazinyl)-benzimidazole hydrochloride, suspended in 250 ml of glacial acetic acid, whilst stirring at 70°C. After the addition was finished, the mixture obtained was kept at 70°C for 1 hour. After cooling the precipitated oily product was obtained in crystalline form by addition of 20 ml of water and heating for a short time. The crystals obtained were filtered off with suction, triturated with conc. ammonia, washed with water and recrystallized from methanol/water.
- Yield: 5.6 g (89 % of theory),
M.p.: above 300°C.

Example 5

2-(4-Methoxyphenyl)-5(6)-(5-methyl-3-oxo-2H-6-pyridazinyl)-benzimidazole

- Prepared analogously to Example 4 from 0.74 g of 2-(4-methoxyphenyl)-5(6)-(5-methyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole hydrochloride and 0.33 ml of bromine. The product was purified on a silica gel column (eluant: chloroform/methanol = 50:1).
- Yield: 0.35 g (52.6 % of theory),
M.p.: above 300°C.

Example 6

2-(2,4-Dimethoxyphenyl)-5(6)-(5-methyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole hydrochloride

- a) 2-(2,4-Dimethoxyphenyl)-5(6)-(1-oxo-2-methyl-3-ethoxycarbonyl-1-propyl)-benzimidazole hydrochloride

Prepared analogously to Example 2a from 12.2 g of 5-methyl-6-[3-nitro-4-(dimethoxy-benzoylamino)-phenyl]-3-oxo-4,5-dihydro-2H-pyridazine. The imidazole ring

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was closed with ethanolic hydrochloric acid. The product was partially purified and processed further in this form.

Yield: 4 g (31.2 % of theory).

5 b) 2-(2,4-Dimethoxyphenyl)-5(6)-(5-methyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole hydrochloride

Prepared analogously to Example 2b from the product obtained according to Example 6a.

Yield: 0.78 g (21.1 % of theory),

10 M.p.: 266°C.

Example 7

2-(4-Methylphenyl)-5(6)-(5-methyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole hydrochloride

Prepared analogously to Example 2b from 1.5 g of 2-(4-methylphenyl)-5(6)-(1-oxo-2-methyl-3-methoxycarbonyl-1-propyl)-benzimidazole hydrochloride.

Yield: 0.24 g (16.5 % of theory),

M.p.: 340°C (decomp.).

Example 8

20 2-(4-Methylphenyl)-5(6)-(5-methyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole hydrochloride

Prepared analogously to Example 1d from 21.5 g of 5-methyl-6-[2-amino-4-(4-methyl-benzoylamino)-phenyl]-3-oxo-4,5-dihydro-2H-pyridazine. (A chromatographical purification is not necessary).

Yield: 18.8 g (82.7 % of theory),

M.p.: 340°C (decomp.).

Example 9

2-Cyclopropyl-5(6)-(5-methyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole hydrochloride

Prepared analogously to Example 6 from 2.3 g of 5-methyl-6-(3-nitro-4-cyclopropylcarbonylamino-phenyl)-3-oxo-4,5-dihydro-2H-pyridazine.

Yield: 1.35 g (61.2 % of theory).

M.p.: 235 - 237 °C (decomp.).

Example 10

10 1,2-Dimethyl-5(6)-(5-methyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole

a) 5-Methyl-6-(3-amino-4-acetyl-methylamino-phenyl)-3-oxo-4,5-dihydro-2H-pyridazine

0.65 g of 5-methyl-6-(3-nitro-4-acetyl-methylamino-phenyl)-3-oxo-4,5-dihydro-2H-pyridazine were dissolved in 30 ml of ethanol and the solution obtained was mixed with 0.5 ml of 80 % hydrazine hydrate and 0.5 g of Raney nickel. The resultant mixture was heated to 30°C for 10 minutes. After filtering off the catalyst, the filtrate was mixed with glacial acetic acid and evaporated in vacuo. The residue was directly processed further.

b) 1,2-Dimethyl-5(6)-(5-methyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole

25 Prepared analogously to Example 1d from the product obtained according to Example 10a.

Yield: 0.15 g (27.4 % of theory),

M.p.: above 250°C.

Example 11

2-(2-Fluorophenyl)-5(6)-(5-methyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole hydrochloride

3.2 g of 5-methyl-6-[3-amino-4-(2-fluoro-benzoylamino)-phenyl]-3-oxo-4,5-dihydro-2H-pyridazine were suspended in 150 ml of isopropanol and hydrogen chloride gas was introduced into the mixture obtained whilst refluxing for 2 hours. After evaporation, the residue was triturated with ether whereupon the product was obtained in crystalline form.

Yield: 1.35 g (40 % of theory),

M.p.: 295°C.

Example 12

2-Phenyl-5(6)-(5-methyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole hydrochloride

Prepared analogously to Example 11 from 2.0 g of 5-methyl-6-(3-amino-4-benzoylamino-phenyl)-3-oxo-4,5-dihydro-2H-pyridazine.

Yield: 0.85 g (40.5 % of theory),

M.p.: 335°C.

Example 13

2-Isopropyl-5(6)-(5-methyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole hydrochloride

Prepared analogously to Example 11 from 6.2 g of 5-methyl-6-(3-amino-4-isobutyrylamino-phenyl)-3-oxo-4,5-dihydro-2H-pyridazine.

Yield: 4.7 g (71 % of theory),

M.p.: 270 - 272°C.

Example 14

2-n-Pentyl-5(6)-5-methyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole hydrochloride

Prepared analogously to Example 11 from 1.8 g of 5-methyl-6-(3-amino-4-caproylamino-phenyl)-3-oxo-4,5-dihydro-2H-pyridazine.

Yield: 0.8 g (41.8 % of theory),

M.p.: 244°C.

Example 15

10 2-(4-Chlorophenyl)-5(6)-(5-methyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole

Prepared analogously to Example 2b from 1.45 g of 2-(4-chlorophenyl)-5(6)-(1-oxo-2-methyl-3-methoxycarbonyl-1-propyl)-benzimidazole hydrochloride.

15 Yield: 0.32 g (23 % of theory),

M.p.: sintering above 78°C.

Example 16

2-Trifluoromethyl-5(6)-(5-methyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole

20 11 g of 5-methyl-6-(3,4-diaminophenyl)-3-oxo-4,5-dihydro-2H-pyridazine were refluxed with 70 ml of trifluoroacetic acid for 2 hours. The resultant mixture was evaporated in vacuo and the residue was mixed with ice-water and made ammoniacal. After extraction with ethyl acetate, the ethyl acetate phases were evaporated and the residue was recrystallized from 50% ethanol with addition of activated charcoal. Yield: 6.4 g (50 % of theory), M.p.: 278-280°C.

Example 17

2-Trifluoromethyl-5(6)-(5-methyl-3-oxo-2H-6-pyridazinyl)-

benzimidazole

Prepared analogously to Example 4 from 6 g of 2-trifluoromethyl-5(6)-(5-methyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole.

- 5 Yield: 0.8 g (13.5 % of theory),
M.p.: above 300°C (from ethanol).

Example 18

5(6)-(5-methyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole hydrochloride

- 10 Prepared analogously to Example 16 from 2.0 g of 5-methyl-6-(3,4-diaminophenyl)-3-oxo-4,5-dihydro-2H-pyridazine and formic acid. The hydrochloride was precipitated from methanol with ethereal hydrochloric acid and recrystallized from ethanol/ether.

- 15 Yield: 0.6 g (28.9 % of theory),
M.p.: 300°C (decomp.).

Example 19

2-Mercapto-5(6)-(5-methyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole

- 20 5.2 g of potassium hydroxide were dissolved in a mixture of 50 ml of ethanol and 6.6 ml of water. 3.84 g of carbon disulfide and 11.0 g of 5-methyl-6-(3,4-diaminophenyl)-3-oxo-4,5-dihydro-2H-pyridazine were added thereto and the mixture obtained was refluxed for 3 hours. After dilution
25 with water, the resultant mixture was neutralized with glacial acetic acid. The precipitated product was filtered off with suction and washed with water.
Yield: 10.6 g of crude product (94.3 % of theory).

The product was purified on a silica gel column
(eluant: chloroform/ethanol = 9:1).

M.p.: above 300°C.

Example 20

5 2-Methylmercapto-5(6)-(5-methyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole

6.0 g of the crude product obtained according to Example 19 were dissolved in 250 ml of dimethylformamide and 3.3 g of methyl iodide and 1.4 g of sodium bicarbonate
10 were added thereto. The mixture obtained was stirred for 1 hour at room temperature then for 1 hour at 50°C. The solvent was subsequently removed in vacuo and the residue was triturated with water, then purified on a silica gel column.

15 Yield: 1.5 g (23.8 % of theory),

M.p.: 268°C (decomp.).

Example 21

2-Cyclohexyl-5(6)-(5-methyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole hydrochloride

20 Prepared analogously to Example 1c and 1d from 9.7 g of 5-methyl-6-(3-nitro-4-cyclohexylcarbonylamino-phenyl)-3-oxo-4,5-dihydro-2H-pyridazine. The hydrochloride was precipitated from acetone with ethereal hydrochloric acid and recrystallized from ethanol.

25 Yield: 2.3 g (24.7 % of theory),

M.p.: 315 -320°C

Example 22

2-(4-tert. Butylphenyl)-5(6)-(5-methyl-3-oxo-4,5-dihydro-

2H-6-pyridazinyl)-benzimidazole hydrochloride hydrate

- a) 5-Methyl-6-[3-amino-4-(4-tert. butyl-benzoylamino)-phenyl]-3-oxo-4,5-dihydro-2H-pyridazine

5 Prepared analogously to Example 1c from 12.6 g of 5-methyl-6-[3-nitro-4-(4-tert. butyl-benzoylamino)-phenyl]-3-oxo-4,5-dihydro-2H-pyridazine. After filtering off the catalyst, the product was precipitated with water.

Yield: 9.9 g (84.5 % of theory),

10 M.p.: 215 - 217°C.

- b) 2-(4-tert. Butylphenyl)-5(6)-(5-methyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole hydrochloride hydrate

15 Prepared analogously to Example 1d from the product obtained according to Example 22a.

Yield: 7.9 g (73 % of theory),

M.p.: 294 - 298°C.

Example 23

- 20 2-(2-Pentyl)-5(6)-(5-methyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole hydrochloride

- a) 5-Methyl-6-[3-amino-4-(2-methylvalerylamino)-phenyl]-3-oxo-4,5-dihydro-2H-pyridazine

Prepared analogously to Example 22a from 12.5 g of 5-methyl-6-[3-nitro-4-(2-methylvalerylamino)-phenyl]-3-oxo-4,5-dihydro-2H-pyridazine. After mixing with

water, the product was extracted with ethyl acetate.

Yield: 4.2 g (36.6 % of theory),

M.p.: 179 - 181°C.

- 5 b) 2-(2-Pentyl)-5(6)-(5-methyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole hydrochloride

Prepared analogously to Example 1d from the product obtained according to Example 23a.

Yield 1.3 g (28.4 % of theory),

M.p.: sintering from 150°C.

10 Example 24

2-(n-Hexyl)-5(6)-(5-methyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole hydrochloride

- a) 5-methyl-6-(3-amino-4-heptanoylamino-phenyl)-3-oxo-4,5-dihydro-2H-pyridazine

- 15 Prepared analogously to Example 22a from 11.75 g of 5-methyl-6-(3-nitro-4-heptanoylamino-phenyl)-3-oxo-4,5-dihydro-2H-pyridazine.

Yield: 8.0 g (78 % of theory),

M.p.: 158 - 160°C.

- 20 b) 2-(n-Hexyl)-5(6)-(5-methyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole hydrochloride

Prepared analogously to Example 1d from the product obtained according to Example 24a.

Yield: 6.2 g (73.5 % of theory),

- 25 M.p.: 225 - 227°C.

Example 25

1-Cyclohexyl-2-methyl-5(6)-(5-methyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole

- 1.3 g of 5-methyl-6-(3-amino-4-cyclohexylamino-phenyl)-
5 3-oxo-4,5-dihydro-2H-pyridazine were refluxed with 50 ml of glacial acetic acid for 6 hours. The mixture obtained was poured onto ice and neutralized with ammonia. The precipitated product was purified on a silica gel column (eluant: methylene chloride/acetone=10:0 to 9:1).
10 Yield: 0.4 g (28.5 % of theory),
M.p.: 259 - 262°C (decomp.).

Example 26

2-Hydroxy-5(6)-(5-methyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole

- 15 2g of 2-methylmercapto-5(6)-(5-methyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole were dissolved in 100 ml of glacial acetic acid. 10 ml of 30 % hydrogen peroxide were added thereto and the mixture obtained was heated to 50°C for 6 hours.
20 After 3 and after 4 hours 2 ml of hydrogen peroxide were added thereto. The resultant mixture was evaporated to a small volume in vacuo, then poured into water. The precipitate obtained was recrystallized from ethanol/cyclohexane.
25 Yield: 0.37 g (21 % of theory),
M.p.: above 300°C.

Example 27

2-(2-Methoxy-4-methylmercapto-phenyl)-5(6)-(5-methyl-
3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole

2.5 g of 5-methyl-6-[3-amino-4-(2-methoxy-4-methyl-
5 mercaptobenzoylamino)-phenyl]-3-oxo-4,5-dihydro-2H-
pyridazine were refluxed in 100 ml of glacial acetic
acid for 2.5 hours. The mixture obtained was filtered
hot and, after cooling, the filtrate was added whilst
stirring to a mixture of ice and conc. ammonia. After
10 drying, the precipitated product was recrystallized
from methylene chloride.

Yield: 1.1 g (57.7 % of theory),

M.p.: 155 - 165°C (decomp.).

Example 28

15 1-Cyclopropyl-2-methyl-5(6)-(5-methyl-3-oxo-4,5-dihydro-
2H-6-pyridazinyl)-benzimidazole

a) 5-Methyl-6-(3-amino-4-cyclopropylamino-phenyl)-3-oxo-
4,5-dihydro-2H-pyridazine

5.8 g of 5-methyl-6-(3-nitro-4-cyclopropylamino-phenyl)-
20 3-oxo-4,5-dihydro-2H-pyridazine were hydrogenated in a
mixture consisting of 100 ml of ethanol and of 20 ml of
glacial acetic acid in the presence of 0.5 g of 10 %
palladium charcoal at a hydrogen pressure of 5 bar. 120
ml of glacial acetic acid were added to the resultant
25 mixture. The catalyst was then filtered off and the
filtrate was evaporated in vacuo. The residue was
reacted in the next step without further purification.

b) 1-Cyclopropyl-2-methyl-5(6)-(5-methyl-3-oxo-4,5-

dihydro-2H-6-pyridazinyl)-benzimidazole

Prepared analogously to Example 25 from the product obtained according to Example 28a and 30 ml of glacial acetic acid (duration of heating: 3 hours, column chromatographical purification not necessary).
Yield: 4.6 g (81.5% of theory),
M.p.: 246 - 250°C.

Example 29

2-Hexylmercapto-5(6)-(5-methyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole

Prepared analogously to Example 20 from 2.6 g of 2-mercapto-5(6)-(5-methyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole and 1.7 g of 1-bromohexane (reaction temperature: 80°C, reaction time: 7 hours).
Yield: 1.0 g (29 % of theory),
M.p.: 172°C (decomp. from isopropanol/petroleum ether).

Example 30

1-Methyl-2-(4-methoxyphenyl)-5-(5-methyl-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole

A mixture of 6.4 g of 5-methyl-6-[3-nitro-4-(N-methyl-4-methoxy-benzoylamino)-phenyl]-4,5-dihydro-2H-pyridazine-3-one and 0.6 of 10 % palladium charcoal in 100 ml of ethanol was treated for 2.5 hours at room temperature with hydrogen at 5 bar. The catalyst was then filtered off with suction and the filtrate evaporated in vacuo. The residue was purified by chromatography on silica gel (eluant: methylene chloride/ethanol 19:1 to 9:1). The fractions containing the product were combined and

evaporated. The product was obtained in crystalline form by trituration with ether.

Yield: 0.15 g (3 % of theory)

M.p.: 248. - 249°C.

5 Example 31

1-Benzyl-2-methyl-5-(5-methyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole

a) 5-Methyl-6-(3-amino-4-benzylamino-phenyl)-4,5-dihydro-2H-pyridazine-3-one

10 A mixture of 6.75 g of 5-methyl-6-(3-nitro-4-benzylaminophenyl)-4,5-dihydro-2H-pyridazine-3-one and 0.7 g of 10 % palladium charcoal in a mixture of 100 ml of ethanol and 20 ml of glacial acetic acid was treated for 3.5 hours at room temperature with
15 hydrogen at 5 bar. The catalyst was then filtered off and the filtrate was evaporated. The residue was used in the next step without further purification.

b) 1-Benzyl-2-methyl-5-(5-methyl-3-oxo-4,5-dihydro-2H 6-pyridazinyl)-benzimidazole

20 The product obtained according to Example 31a was taken up in 100 ml of glacial acetic acid and refluxed for 2.5 hours. The mixture obtained was mixed with ice and made ammoniacal. The precipitated product was purified by chromatography on silica gel
25 (eluant: at first pure methylene chloride, then increasing amounts of acetone up to a mixture ratio methylene chloride/acetone = 10:3). After evaporation, the product was obtained in crystalline form by

trituration with ether.

Yield: 2.2 g (33 % of theory)

M.p.: 279°C.

Example 32

5 1-Cyclohexyl-2-methyl-6-(5-methyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole

Prepared analogously to Example 31 from 1.3 g of 5-methyl-6-(3-amino-4-cyclohexylamino-phenyl)-4,5-dihydro-2H-pyridazine-3-one. After separation of the 1-cyclohexyl-
10 2-methyl-5-(5-methyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole by chromatography on silica gel (eluant: methylene chloride/acetone = 10:0 to 9:1) the product was obtained in pure form.

Yield: 0.1 g (7 % of theory)

15 M.p.: 237°C (decomp.).

Example 33

2-Isopropylmercapto-5(6)-(5-methyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole

3.4 g of 2-mercapto-5(6)-(5-methyl-3-oxo-4,5-dihydro-2H-
20 6-pyridazinyl)-benzimidazole were dissolved in 50 ml of dimethylformamide and 1.62 g of isopropyl bromide and 1.1 g of sodium bicarbonate were added thereto. The mixture obtained was stirred for 20 hours on a steam bath then the solvent was evaporated in vacuo. The residue
25 was purified by chromatography on silica gel (eluant: chloroform/ethanol 9:1).

Yield: 0.45 g (11 % of theory)

M.p.: 120 - 121°C.

Example 34

2-(2-Methoxy-4-methylsulfinyl-phenyl)-5(6)-(5-methyl-
3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole

- 0.9 g of 2-(2-methoxy-4-methylmercapto-phenyl)-5(6)-
5 (5-methyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-
benzimidazole were dissolved in 50 ml of glacial acetic
acid and a solution of 0.24 g of 30 % hydrogen peroxide
in 10 ml of glacial acetic acid was added thereto.
After standing for 22 hours at room temperature, the
10 resultant mixture was poured onto ice and made ammoniacal.
The precipitate obtained was purified by chromatography
on silica gel (eluant: methylene chloride/ethanol 19:1).
After evaporation, the residue was crystallized by
trituration with a mixture of acetone and ether.
15 Yield: 0.5 g (53 % of theory)
M.p.: 173 - 180°C.

Example 35

2-(1-Phenyl-2-propyl)-5(6)-(5-methyl-3-oxo-4,5-dihydro-2H
6-pyridazinyl)-benzimidazole hydrochloride

- 20 5.1 g of 5-methyl-6-[3-amino-4-(3-phenyl-isobutyrylamino)-
phenyl]-4,5-dihydro-2H-pyridazine-3-one were refluxed in
100 ml of glacial acetic acid for 1.5 hours. The glacial
acetic acid was then distilled off and the residue was
taken up in a mixture of ethanol and acetone. The hydro-
25 chloride was precipitated by addition of ethereal
hydrochloric acid and obtained in crystalline form by
trituration with a mixture of ether and ethanol.
Yield: 2.4 g (45% of theory)

M.P.: 235 - 239°C.

Example 36

2-Cycloheptyl-5(6)-(5-methyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole hydrochloride

- 5 Prepared analogously to Example 35 from 5.5 g of 5-methyl-6-(3-amino-4-cycloheptylcarbonylamino-phenyl)-4,5-dihydro-2H-pyridazine-3-one.

Yield: 4.2 g (73 % of theory)

M.p.: 255 - 259°C.

10 Example 37

2-(4-Hydroxyphenyl)-5(6)-(5-methyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole hydrochloride

- Prepared analogously to Example 35 from 6.3 g of 5-methyl-6-[3-amino-4-(4-hydroxy-benzoylamino)-phenyl]-4,5-dihydro-2H-pyridazine-3-one.

Yield: 4.4 g (66 % of theory)

M.p.: 350 - 354°C.

Example 38

- 20 2-(4-n-Hexyloxyphenyl)-5(6)-(5-methyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole hydrochloride

Prepared analogously to Example 35 from 5.7 g of 5-methyl-6-[3-amino-4-(4-n-hexyloxy-benzoyl-amino)-phenyl]-4,5-dihydro-2H-pyridazine-3-one.

Yield: 3.55 g (60 % of theory)

- 25 M.p.: 278 - 282°C.

Example 39

2-(3,4,5-Trimethoxyphenyl)-5(6)-(5-methyl-3-oxo-4,5-di-

hydro-2H-pyridazinyl)-benzimidazole

Prepared analogously to Example 35 from 14.9 g of 5-methyl-6-[3-amino-4-(3,4,5-trimethoxy-benzoylamino)-phenyl]-4,5-dihydro-2H-pyridazine-3-one. The residue
5 remaining after evaporation of the glacial acetic acid was extracted with boiling ethanol. After evaporating off the ethanol and stirring the residue with ether, the product was obtained in crystalline form.

Yield: 9.2 g (65 % of theory)

10 M.p.: 295 - 300°C.

Example 40

1-(3-Methylbutyl)-2-methyl-5-(5-methyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole

a) 5-Methyl-6-[3-amino-4-(N-acetyl-3-methylbutylamino)-phenyl]-4,5-dihydro-2H-pyridazine-3-one
15

6 g of 5-methyl-6-[3-nitro-4-(N-acetyl-3-methylbutylamino)-phenyl]-4,5-dihydro-2H-pyridazine-3-one were dissolved in 150 ml of ethanol and 4 g of Raney nickel and 3 ml of 98 % hydrazine hydrate were added thereto.

20 The solution obtained was stirred for 30 minutes at room temperature then the catalyst was filtered off and the filtrate was evaporated. The residue was used in the next step without further purification.

b) 1-(3-Methylbutyl)-2-methyl-5-(5-methyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole
25

Prepared analogously to Example 35 from the product

obtained according to Example 40a. The product was purified by chromatography on silica gel (eluant: methylene chloride/ethanol = 9:1).

Yield: 2.2 g (43 % of theory)

5 M.p.: 247°C.

Example 41

1-Benzyl-2-trifluoromethyl-5-(5-methyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole

Prepared analogously to Example 31 from 5.2 g of 5-methyl-
10 6-(3-nitro-4-benzylamino-phenyl)-4,5-dihydro-2H-pyridazine-3-one.

Yield: 1.4 g (23 % of theory)

M.p.: 210 - 212°C.

Example 42

15 2-Methyl-5(6)-(5-ethyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole

Prepared analogously to Example 31 from 1.2 g of 5-ethyl-6-(3-nitro-4-amino-phenyl)-4,5-dihydro-2H-pyridazine-3-one.

Yield: 0.5 g (41 % of theory)

20 M.p.: 291 - 295°C.

Example 43

2-(4-Methoxyphenyl)-5(6)-(5-ethyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole hydrochloride

Prepared analogously to Example 35 from 3.6 g of 5-ethyl-
25 6-[3-amino-4-(4-methoxy-benzoylamino)-phenyl]-4,5-dihydro-2H-pyridazine-3-one.

Yield: 3.6 g (91 % of theory)

M.p.: 178 - 198°C.

Example 44

2-(3-Methoxyphenyl)-5(6)-(5-methyl-3-oxo-4,5-dihydro-2H
6-pyridazinyl)-benzimidazole

Prepared analogously to Example 35 from 2.2 g of 5-
5 methyl-6-[3-amino-4-(3-methoxy-benzoylamino)-phenyl]-4,
5-dihydro-2H-pyridazine-3-one and by purification by
means of chromatography on silic gel (eluant: methylene
chloride/ethanol = 19:1).

Yield: 0.72 g (34 % of theory)

10 M.p.: 295 - 298°C

Example 45

2-(2-Bromo-5-methoxy-phenyl)-5(6)-(5-methyl-3-oxo-4,5-
dihydro-2H-6-pyridazinyl)-benzimidazole

Prepared analogously to Example 44 from 2.8 g of 5-methyl-
15 6-[3-amino-4-(2-bromo-5-methoxy-benzoylamino)-phenyl]-
4,5-dihydro-2H-pyridazine-3-one.

Yield: 0.75 g (28 % of theory)

M.p.: sintering above 70°C.

Example 46

20 2-Undecyl-5(6)-(5-methyl-3-oxo-4,5-dihydro-2H-6-
pyridazinyl)-benzimidazole

a) 5-Methyl-6-(3-amino-4-undecylcarbonylamino-phenyl)-4,
5-dihydro-2H-pyridazine-3-one

10 g of 5-methyl-6-(3-nitro-4-undecylcarbonylamino-
25 phenyl)-4,5-dihydro-2H-pyridazine-3-one were dissolved
in 100 ml of dimethylformamide and the solution
obtained was treated in the presence of 1 g of 10%
palladium charcoal with hydrogen for 1.2 hours at a

pressure of 5 bar. After filtering off the catalyst, the resultant mixture was poured onto ice and extracted with methylene chloride. The organic phase was evaporated and the oily residue was used in the next stage without further purification.

b) 2-Undecyl-5(6)-(5-methyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole

The product obtained according to Example 46a was dissolved in 100 ml of glacial acetic acid and the solution obtained was refluxed for 1 hour, then evaporated to half volume, poured onto ice and made ammoniacal. The precipitated product was recrystallized from ethyl acetate. A further fraction was obtained by chromatographical purification of the mother liquors (silica gel, eluant: methylene chloride/ethanol = 19:1).

Yield: 7.7 g (87 % of theory)

M.p.: 165 - 169°C (decomp.).

Example 47

2-Methyl-5(6)-(5-n-butyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole

Prepared analogously to Example 31 from 4 g of 5-n-butyl-6-(3-nitro-4-amino-phenyl)-4,5-dihydro-2H-pyridazine-3-one.

Yield: 1.7 g (43 % of theory)

M.p.: 184 - 186°C (decomp.).

Example 48

2-(4-Methoxyphenyl)-5(6)-(5-n-butyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole hydrochloride

Prepared analogously to Example 44 from 4.2 g of 5-n-butyl-

6-[3-amino-4-(4-methoxy-benzoylamino)-phenyl]-4,5-dihydro-2H-pyridazine-3-one. The hydrochloride was precipitated from ethyl acetate with ethereal hydrochloric acid.

Yield: 3.2 g (73 % of theory)

5 M.p.: 160 - 190°C.

Example 49

2-(1-Phenyl-1-ethyl)-5(6)-(5-methyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole hydrochloride

Prepared analogously to Example 35 from 3 g of 5-methyl-6-
10 [3-amino-4-(2-phenyl-propionylamino)-phenyl]-4,5-dihydro-2H-pyridazine-3-one.

Yield: 1.6 g (51 % of theory)

M.p.: sintering from 85°C.

Example 50

15 2-Ethoxy-5(6)-(5-methyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole hydrochloride

10.9 g of 5-methyl-6-(3,4-diaminophenyl)-4,5-dihydro-2H-pyridazine-3-one were suspended in 12.5 g of tetraethyl orthocarbonate and 10 ml of dimethylsulfoxide were added
20 thereto. The mixture obtained was refluxed for 1.5 hours, then the solvent was distilled off and the oily residue was crystallized by trituration with ether/chloroform. The hydrochloride was precipitated from acetone/ethanol 1:1 with ethereal hydrochloric acid and
25 recrystallized from ethanol/isopropanol.

Yield: 7.6 g (49 % of theory)

M.p.: above 300°C.

Example 51

2-(4-Methoxyphenyl)-5(6)-(5-methyl-3-oxo-4,5-dihydro-2H-
6-pyridazinyl)-benzimidazole hydrochloride

0.34 g of sodium methylate were added to a suspension of
5 1.1 g of 2-(4-hydroxyphenyl)-5-(5-methyl-3-oxo-4,5-
dihydro-2H-6-pyridazinyl)-benzimidazole hydrochloride in
50 ml of methanol. After a clear solution was formed
2.52 g of dimethylsulfate and a further 0.34 g of
sodium methylate were added thereto in portions. The
10 reaction time was 6 hours at room temperature. The
resultant mixture was poured onto ice, neutralised and
the precipitate obtained was purified on a silica gel
column (eluant: methylene chloride/ethanol 50:1 to
25:1). The hydrochloride was precipitated from
15 methanol with ethereal hydrochloric acid.

Yield: 0.59 g (52 % of theory)

M.p.: 311°C (decomp.).

Example 52

2-(4-Methoxyphenyl)-5(6)-(5-methyl-3-oxo-4,5-dihydro-2H-
20 6-pyridazinyl)-benzimidazole hydrochloride

a) 5-Methyl-6-[3-amino-4-(4-methoxy-benzoylamino)-
phenyl]-4,5-dihydro-2H-pyridazine-3-one

203 g of 5-methyl-6-[3-nitro-4-(4-methoxy-benzoyl-
amino)-phenyl]-4,5-dihydro-2H-pyridazine-3-one were
25 dissolved in 1.7 l of dimethylformamide and the
solution obtained was treated with hydrogen in the
presence of 20 g of 10% palladium charcoal for 2 hours
at a pressure of 5 bar. After filtering off the

catalyst, the filtrate was poured onto 7.5 l of ice-water and the precipitated product was dried at 120°C.

Yield: 182 g (97 % of theory)

M.p.: 253°C.

5 b) 2-(4-Methoxyphenyl)-5(6)-(5-methyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole hydrochloride

180 g of 5-methyl-6-[3-amino-4-(4-methoxy-benzoyl-amino)-phenyl]-4,5-dihydro-2H-pyridazine-3-one were suspended in 1.5 l of glacial acetic acid and the suspension obtained was refluxed for 30 minutes. After distilling off 350 ml of the solvent at a reduced pressure, the remaining mixture was treated with activated charcoal at 70°C and filtered. After cooling to 20°C, the filtrate was added dropwise to a mixture of 2 l of ice-water and 1.5 l of conc. ammonia whilst stirring. By addition of more ice the temperature was kept below 20°C. The precipitated product was washed with water and dried at 80°C. By dissolving in isopropanol, mixing with conc. hydrochloric acid and diluting with 2 l of acetone, the base was converted to the hydrochloride. The free base still contained in the mother liquors was treated correspondingly.

Yield: 176 g (93 % of theory)

M.p.: 300 - 306°C (decomp.).

25 Example 53

2-(4-Methoxyphenyl)-5(6)-(5-methyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole hydrochloride

0.22 g of 5-methyl-6-(3,4-diaminophenyl)-4,5-dihydro-2H-pyridazine-3-one and 0.2 g of 4-methoxy-benzamidine

hydrochloride were triturated together and heated to 160°C for 40 minutes. The resultant mixture was purified by chromatography on silica gel (eluant: methylene chloride/ethanol 50:1 to 25:1) and the
5 hydrochloride was precipitated from methanol with ethereal hydrochloric acid.

Yield: 0.04 g (10 % of theory)

M.p.: 303 - 307°C (decomp.).

Example 54

10 2-(4-Methoxyphenyl)-5(6)-(5-methyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole hydrochloride

A mixture of 0.22 g of 5-methyl-6-(3,4-diaminophenyl)-4,5-dihydro-2H-pyridazine-3-one, 0.15 g of 4-methoxybenzonitrile and 0.17 g of p-toluenesulfonic acid was
15 heated for 30 minutes to 160°C, then further processed analogously to Example 32.

Yield: 0.06 g (16 % of theory)

M.p.: 304 - 309°C (decomp.).

Example 55

20 2-(4-Methoxyphenyl)-5(6)-(5-methyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole hydrochloride

Prepared analogously to Example 54 with 0.22 g of potassium tert. butylate instead of p-toluenesulfonic acid.

Yield: 0.03 g (8 % of theory)

25 M.p.: 305 - 306°C (decomp.).

Example 56

2-(4-Methoxyphenyl)-5(6)-(5-methyl-3-oxo-4,5-dihydro-2H-
6-pyridazinyl)-benzimidazole hydrochloride

A mixture of 0.22 g of 5-methyl-6-(3,4-diaminophenyl)-
5 4,5-dihydro-2H-pyridazine-3-one and 0.42 g of S-methyl-
4-methoxy-thiobenzoic acid morpholide iodide was heated
in 3 ml of ethylene glycol for 10 minutes to 140°C.
After cooling, the resultant mixture was poured onto ice-
water and the product obtained was taken up in ether and
10 purified analogously to Example 53.

Yield: 0.13 g (35 % of theory)

M.p.: 309 - 311°C (decomp.).

Example 57

2-(4-Methoxyphenyl)-5(6)-(5-methyl-3-oxo-4,5-dihydro-2H-
15 6-pyridazinyl)-benzimidazole hydrochloride

A mixture of 0.22 g of 5-methyl-6-(3,4-diaminophenyl)-
4,5-dihydro-2H-pyridazine-3-one and 0.29 g of phenyl 4-
methoxy-benzoate was heated for 30 minutes to 150°C.
The resultant mixture was further processed analogously
20 to Example 53.

Yield: 0.23 g (62 % of theory)

M.p.: 108 - 111°C (decomp.).

Example A

Tablets containing 100 mg of 2-(4-methoxyphenyl)-5(6)-
(5-methyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole hydrochloride

5 Composition:

1 tablet contains:

Active ingredient	100.0 mg
Lactose	50.0 mg
Polyvinylpyrrolidone	5.0 mg
10 Carboxymethylcellulose	19.0 mg
Magnesium stearate	1.0 mg
	175.0 mg

The active ingredient and the lactose were homogeneously
moistened with an aqueous solution of the polyvinylpyrro-
15 lidone and granulated.

Moist screening: 1.5 mm

Drying: in a circulation air drier at 50°C

Dry screening: 1 mm

The granulate and the remaining auxiliary products were
20 mixed and pressed into tablets.

Weight of tablet: 175 mg

Punch: 8 mm diameter

Example B

Coated tablets containing 50 mg of 2-(4-methoxyphenyl)-
25 5(6)-(5-methyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimidazole hydrochloride

1 coated tablet core contains:

Active ingredient	50.0 mg
Corn starch dried	20.0 mg

Soluble starch	2.0 mg
Carboxymethylcellulose	7.0 mg
Magnesium stearate	1.0 mg
	80.0 mg

5 The active ingredient and the starch were homogeneously moistened with an aqueous solution of the soluble starch and granulated.

Moist screening: 1.0 mm
Dry screening: 1.0 mm

10 Drying: in a circulation air drier at 50°C
The granulate and the remaining auxiliary products were mixed and pressed into cores.

Weight of core: 80 mg
Punch: 6 mm

15 Radius of curvature: 5 mm

The finished cores were covered with a sugar coating in conventional manner.

Weight of coated tablet: 120 mg

Example C

20 Suppositories containing 75 mg of 2-(4-methoxyphenyl)-
5(6)-(5-methyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benz-
imidazole hydrochloride

1 suppository contains:

Active ingredient 75.0 mg

Suppository mass

(e.g. Witepsol H 19 and

5	Witepsol W 45)	1 625.0 mg
		1 700.0 mg

Method of preparation:

The suppository mass was melted. At 38°C the pulverized active ingredient was homogeneously dispersed in the melt.

10 The suppository mass was cooled to 35°C and poured into pre-cooled moulds.

Weight of suppository : 1.7 g

Example D

Ampoules containing 50 mg of 2-(4-methoxyphenyl)-5(6)-
15 (5-methyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benzimi-
dazole hydrochloride

1 ampoule contains:

Active ingredient 50.0 mg

Sorbitol 250.0 mg

20 Water dist. ad 5.0 mg

Method of preparation:

The active ingredient and sorbitol were dissolved in distilled water and the mixture obtained was made up to the given volume and filtered sterile.

25 Filling: into 5 ml ampoules

Sterilization: 20 minutes at 120°C

Example E

Drops solution containing 25 mg/ml of 2-(4-methoxyphenyl)-
5(6)-(5-methyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)-benz-
imidazole hydrochloride

5	Active ingredient	5.0	g
	methyl p-hydroxybenzoate	0.035	g
	propyl p-hydroxybenzoate	0.015	g
	Aniseed oil	0.05	g
	Menthol	0.06	g
10	Saccharin sodium	1.0	g
	Glycerine	10.0	g
	Distilled water	ad	100.0 ml

Method of preparation:

- 15 The methyl and propyl p-hydroxybenzoates were dissolved
in ethanol and the aniseed oil and menthol were added
thereto. Subsequently, the active ingredient, glycerine
and saccharin sodium were dissolved in water and the
solution obtained was added to the first solution
20 obtained above. The combined solutions were filtered
sterile.