

1.186.723



PATENT SPECIFICATION

NO DRAWINGS

1.186.723

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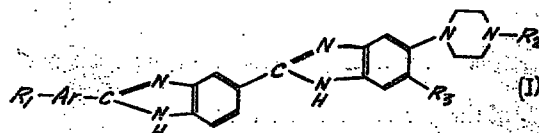
International Classification:—C 07 d 57/00, 99/04

COMPLETE SPECIFICATION

Basically Substituted Bis-Benzimidazole derivatives and process for their manufacture

We, FARBWERKE HOECHST AKTIENGESSELLSCHAFT, vormalig Meister Lucius & Brüning, a Company recognised by German Law, of 6230 Frankfurt (M)-Hoechst, Germany, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

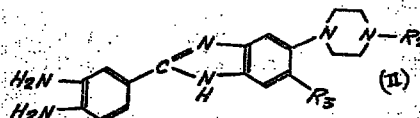
The present invention provides basically substituted bis-benzimidazole derivatives of the general formula I



in which Ar represents an arylene radical, R₁ represents one or more substituents, which may be the same or different, on the arylene ring, the substituents being selected from hydrogen atoms, halogen atoms, hydroxyl groups, lower alkyl, lower alkoxy, lower alkoxy-alkoxy mercapto, lower alkylmercapto, lower alkoxyalkylmercapto, and lower alkylene-dioxy radicals, nitro groups, phenyl radicals, and amino and lower alkylene diamino groups, which amino and lower alkylene diamino groups may be substituted by one or more lower alkyl radicals, R₂ represents a hydrogen atom, an alkyl radical which may be substituted, or a carbalkoxy, carbamido aryl or aralkyl radical, and R₃ represents a halogen atom or a lower alkyl or lower alkoxy radical, and their salts. The compounds of the present invention are distinguished by a strong anthelmintic activity.

The present invention also provides a process for preparing the compounds of formula I, wherein

a) an α -phenylenediamine derivative of the general formula II



in which R₂ and R₃ have the meanings given above, is reacted either with a carboxylic acid of the general formula III

[Price 5s. 0d.]



(III)

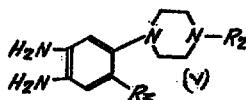
in which R_1 and Ar have the meanings given above, or with a reactive functional derivative of such an acid, or with an aldehyde of the general formula IV



(IV)

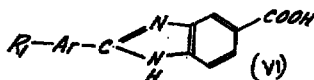
- 5 in which R_1 and Ar have the meanings given above, with the addition of an oxidizing agent if necessary, or
b) an *o*-phenylenediamine derivative of the formula V

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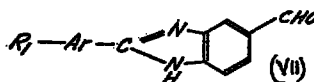


- 10 in which R_2 and R_3 have the meanings given above, is reacted either with a carboxylic acid of the general formula VI

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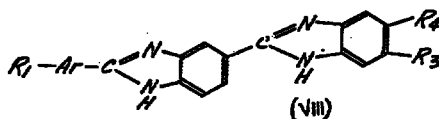


in which R_1 and Ar have the meanings given above, or a reactive functional derivative of such an acid, or with an aldehyde of the formula VII



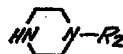
- 15 in which R_1 and Ar have the meanings given above, with the addition of an oxidizing agent if necessary, or
c) a compound of the general formula VIII

15



- 20 in which R_4 represents a halogen atom or an etherified hydroxyl group, and R_1 , Ar and R_3 have the meanings given above, is reacted with a piperazine of the formula

20



in which R_2 has the meaning given above, or

- d) a compound of the general formula I, in which R_1 represents a halogen atom or an etherified hydroxyl group, is reacted with ammonia or a primary or secondary aliphatic amine, or
25 e) a compound of the general formula I in which R_1 represents a nitro group is reduced, or
f) a compound of the general formula I, in which R_1 represents an ether group, is treated with an ether-dissociating agent, or

25

g) a compound of the general formula I, in which R_2 represents a benzyl radical, is catalytically hydrogenated to remove the benzyl group, and, if desired, a basic compound obtained is converted into a salt by reaction with a physiologically tolerable acid.

In the above and in the following description, and in the claims, the term "lower" means in all cases "containing from 1 to 4 carbon atoms in each alkyl or alkylene part of the radical or group."

Of the substituents from which R_1 may be selected, as halogen atoms there may be mentioned bromine, chlorine and fluorine atoms; as lower alkyl groups, there may be mentioned the methyl group; as lower alkoxy or lower alkoxy-alkoxy groups, there may be mentioned the following groups: isopropoxy, isobutoxy, β -methoxy-ethoxy, β -methoxy-propoxy, γ -methoxy-propoxy or β -hydroxy-ethoxy groups; as lower alkyl-mercapto or lower alkoxyalkylmercapto groups, there may be mentioned the following groups: methyl-mercapto, ethyl-mercapto, propyl-mercapto, isopropyl-mercapto, butyl-mercapto, isobutyl-mercapto, β -methoxy-ethyl-mercapto or γ -methoxy-propyl-mercapto groups; as a lower alkylene-dioxy group, there may be mentioned the ethylene-dioxy group; as lower alkyl-substituted amino groups, there may be mentioned especially dialkyl-substituted amino groups such, for example, as the following groups: diethyl-amino, dipropylamino, dibutyl-amino or mono-lower alkyl-substituted amino groups.

As substituents from which R_2 may be selected, there may be mentioned alkyl radicals containing 1 to 3 carbon atoms, such as methyl; substituted alkyl radicals, especially alkoxy-alkyl radicals such as the β -methoxy-ethyl radical or basically substituted alkyl radicals such as β -dialkylaminoethyl radicals; carbalkoxy radicals, especially carbethoxy radicals; and aralkyl radicals, especially the benzyl radical.

Of the substituents from which R_3 may be selected, as halogen atoms there may be mentioned bromine, chlorine or fluorine atoms; as lower alkyl radicals there may be mentioned the methyl radical; as lower alkoxy groups, there may be mentioned, for example, the methoxy, ethoxy, propoxy, isopropoxy, butoxy or isobutoxy radicals. As arylene radical Ar , there may be mentioned, for example, the phenylene radical or polynuclear arylene radicals such as the naphthylene radicals which, when R_1 is hydrogen, are the naphthylene-1 and naphthylene-2 radicals.

As α -phenylenediamine derivatives of the general formula II which may be used as the starting materials in method a) of the process of the present invention, there may be mentioned 2 - (3,4 - diamino - phenyl) - 5 - piperazinobenzimidazole, and furthermore 2 - (3,4 - diamino - phenyl) - 5 - (4 - piperazyl) - benzimidazoles which carry in 1-position one of the substituents listed for R_2 .

Furthermore, there may be used as the starting materials the above-mentioned 2 - (3,4 - diamino - phenyl) - 5 - piperazino - benzimidazole derivatives which are additionally substituted in the 6-position by a halogen atom, especially a bromine, chlorine or fluorine atom, or by a lower alkyl or lower alkoxy radical, for example, a methyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy or isobutoxy group.

As carboxylic acids of the general formula III which may be used as starting substances, there may be mentioned benzoic acid; substituted benzoic acids, especially those substituted in 4-position, for example, halogeno-benzoic acids, preferably bromo-, chloro- or fluoro-benzoic acid, hydroxy-benzoic acids; lower alkyl-benzoic acids, in particular 4-methyl-benzoic acid; lower alkoxy-benzoic acids and lower alkoxy-alkoxy-benzoic acids, for example, methoxy-, ethoxy-, propoxy-, isopropoxy-, butoxy-, isobutoxy-, β -methoxy-ethoxy-, β -methoxy-propoxy-, γ -methoxy-propoxy- or β -hydroxy-ethoxy-, benzoic acids; mercapto-benzoic acid, lower alkylmercapto-benzoic acids and lower alkoxyalkylmercapto-benzoic acids, for example, methyl-, ethyl-, propyl-, isopropyl-, butyl-, isobutyl-, β -methoxyethyl-, or γ -methoxy-propyl-mercaptobenzoic acids; lower alkylene-dioxy-benzoic acids such as methylene-dioxy- or ethylene-dioxy-benzoic acids; nitrobenzoic acids; phenyl-benzoic acids; amino-benzoic acids; dialkyl-substituted amino-benzoic acids such as dimethylamino-, diethylamino-, dipropylamino-, dibutylamino-benzoic acids; substituted benzoic acids which contain two or more substituents in the molecule, for example, halogeno-toluic acids, in particular 3-chloro-4-toluic acid or 4-chloro-3-toluic acid; nitroamino-benzoic acids; nitrochloro-benzoic acids; methoxy-chlorobenzoic acids; di-halogeno-benzoic acids; dihydroxy-benzoic acids or lower alkoxy-toluic acids.

As reactive derivatives there may be used the acid chlorides of the mentioned carboxylic acids, their acid anhydrides and their imino-ethers, preferably the ethyl- or β -methoxy-ethyl-imino-ethers; furthermore, the chlorides of the corresponding ortho-carboxylic acids such as benzotrichloride.

If a carboxylic acid itself is used as starting substance, this may be melted for

some time at an elevated temperature, preferably at a temperature above the melting point of the reactants, with an *o*-phenylenediamine derivative described above. The product formed thereby may be isolated as the free base by first dissolving the reaction mixture in acetic acid, filtering it if necessary and combining it with ammonia. It is also possible to heat the carboxylic acid together with the *o*-phenylenediamine derivative in a semi-concentrated mineral acid such, for example, as 20% by volume hydrochloric acid, for a prolonged period of time, to an elevated temperature, advantageously to 200°C, under pressure, and to isolate the product formed as the free base by adding ammonia to the solution which, if necessary or desired, has been filtered previously. For purification, the base may be dissolved in a lower aliphatic alcohol, for example methanol, isopropanol or butanol, and reprecipitated as a hydrate by the addition of a small amount of water.

If an acid chloride is used as starting substance, an excess amount of the acid chloride, from which an aforescribed carboxylic acid is derived, may be heated with one of the *o*-phenylenediamine derivatives, preferably to the boiling point of the acid chloride, and, after cooling, a diacyl compound is obtained. This may be converted into a product of the invention upon heating in an excess quantity of a mineral acid, preferably a hydrohalic acid such as semi-concentrated hydrochloric acid or polyphosphoric acid. The product may be isolated by evaporation of the excess acid under reduced pressure and precipitation of the base by means of a substance having an alkaline action.

If an imino-ether (which may be obtained from the corresponding acid nitrile in a known manner, for example, by the reaction with gaseous hydrogen chloride and alcohol, preferably ethanol or methyl glycol, described by Pinner in "Die Imidoäther und ihre Derivate", Berlin 1892) is used as starting substance, this ether may be reacted according to the process of the present invention with a corresponding derivative of an *o*-phenylenediamine in the presence of a solvent having an acid reaction, preferably a lower aliphatic carboxylic acid such, for example, as glacial acetic acid or propionic acid at an elevated temperature, preferably at the boiling temperature of the solvent used.

In order to isolate the product, the solvent may be evaporated under reduced pressure, suitably in the vacuum produced by a water jet pump, when the reaction is complete. The residue is dissolved in water and the base is liberated by the addition of a substance having an alkaline action, for example, ammonia or a sodium hydroxide solution.

If, instead of a carboxylic acid or one of the reactive derivatives thereof, an aldehyde of the general formula IV is used as starting substance, an aldehyde which corresponds to a benzoic acid of the formula III may be used. The aldehyde may be heated with an *o*-phenylenediamine derivative in a dilute acid, for example, dilute acetic acid, with the addition of an oxidizing agent, preferably copper acetate, for some time to an elevated temperature, advantageously to the boiling temperature of the reaction mixture. The products formed can be isolated by salting out their hydrohalides by the addition of a strong hydrohalic acid or of a concentrated solution of a halide, especially sodium chloride or potassium iodide. Alternatively, the products can be isolated by introducing hydrogen sulphide into the reaction mixture when the reaction is complete, thereby decomposing the dissolved copper salt: the precipitated copper sulphide is filtered off with suction and the filtrate is evaporated to dryness to give the desired product.

For the method b) of the process of the invention, the *o*-phenylenediamine derivatives of the general formula (V) which may be used as starting materials are 4 - (3,4 - diamino - phenyl) - piperazine and its derivatives in which the piperazine ring may be substituted in the 1-position by one of the substituents listed for R₂, and which may carry in the phenyl radical, in the *o*-position, a halogen atom, a lower alkyl or lower alkoxy group.

As carboxylic acids of the general formula VI which may be used as starting materials, there may be mentioned 2 - phenyl - benzimidazole - 6 - carboxylic acid and the derivatives thereof in which the phenyl group carries in 2-position the same substituents as those in the above-mentioned benzoic acid derivatives of the general formula III, for example 2 - (*p* - hydroxy- or alkoxy - phenyl) - benzimidazole - 6 - carboxylic acids, and further, 2 - (1- or 2 - naphthyl) - benzimidazole - 6 - carboxylic acid.

As reactive derivatives of these acids, there may be used the same compounds as those used in the case of carboxylic acids of the general formula III. The method of carrying out the reaction corresponds to the method a) of the process of the present invention.

If, instead of a carboxylic acid of the general formula VI, an aldehyde of the gen-

eral formula VII is used, there may be employed 2 - phenyl - benzimidazole - 6 - aldehyde and those of its derivatives which are substituted in a manner corresponding to that of the carboxylic acids described above of the general formula VI.

In this case, the method of carrying out the process corresponds to the method described under a) for the reaction of aldehydes of the general formula IV.

As compounds of the general formula VIII which may be used as starting substances in method c) of the process of the invention, there may be mentioned 2 - (2 - phenyl - 6 - benzimidazolyl) - 6 - chloro- or 6 - fluoro - benzimidazole, 2 - (2 - phenyl - 6 - benzimidazolyl) - 6 - alkoxy- or 6 - aryloxy - benzimidazole, especially 2 - (2 - phenyl - 6 - benzimidazolyl) - 6 - methoxy- or -6 - phenoxy - benzimidazole as well as the substitution products of the mentioned compounds in which the phenyl group is substituted by one of the substituents listed for R₁; furthermore 2 - (1- or 2 - naphthyl - 6 - benzimidazolyl) - 6 - chloro-, -fluoro-, -methoxy- or -phenoxy-benzimidazole may be used.

For the reaction with the compounds of the formula VIII there may be used, in addition to piperazine itself, its derivatives which are substituted at the N₁-atom, preferably 1-methyl-, ethyl-, propyl-, isopropyl-, butyl-, isobutyl-, benzyl-, phenyl-, β -hydroxyethyl-, β -methoxy-methyl-, β -diethyl-amino-ethyl-, or carbethoxy-ethyl-piperazine.

The reaction can be effected in the presence or in the absence of a solvent. As solvents, there are preferably used aromatic hydrocarbons, for example, benzene, toluene or xylene, or dimethylformamide or dimethyl sulphoxide; toluene is preferred.

The said reaction may be carried out at an elevated temperature, advantageously at the boiling temperature of the solvent used. It is advantageous to add an acid binding agent; as such, there may be used, for example sodium carbonate or a tertiary organic base, but it is also possible to use an excess of the amine employed.

The reaction products can be isolated by dissolving the reaction mixture in water and precipitating the products by the addition of strong hydrohalic acids or of concentrated solutions of a halide, especially sodium chloride or potassium iodide. From the aqueous solution of the precipitated hydrohalides, the free bases are separated by the addition of substances having an alkaline action, for example ammonia.

In the method d) of the process of the present invention, there may be used as starting substances 2 - (2 - phenyl - 6 - benzimidazolyl) - 6 - piperazino - benzimidazole derivatives in which the phenyl nucleus Ar is substituted by a halogen atom or by an etherified hydroxy group. The compounds are reacted with ammonia, or a primary or secondary aliphatic amine, for example dimethylamine, diethylamine or ethylamine, propylamine, in the manner described under c).

As compounds of the general formula I which may be used as starting substances in the method e) of the process of the present invention, there may be mentioned derivatives of 2 - [2 - (4 - nitrophenyl) - 6 - benzimidazolyl] - benzimidazole which are substituted in the 6-position by piperazino radicals which may be substituted at the nitrogen atom.

These compounds may be hydrogenated in a solvent, preferably in an alcohol such as methanol, ethanol, methyl-glycol or dimethyl sulphoxide in the presence of finely dispersed metals of the VIII group of the Periodic System; the reaction is carried out at ordinary pressure or at an elevated pressure, preferably at 50 atmospheres gauge pressure. The products can be isolated by evaporation of the filtrates to dryness and azeotropic elimination of the water, dissolution of the residue in a solvent such as methanol and precipitation by means of a second solvent in which the products are sparingly soluble, for example acetone or methylethylketone. It is also possible to use reducing agents such as iron powder in an acid solution, ferrous hydroxide suspensions, sodium hydrosulphide, sodium hyposulphite or stannous chloride in hydrochloric acid solution.

As compounds of the general formula I which may be used as starting substances in method f) of the process of the present invention, there may be mentioned derivatives of 2 - (2 - phenyl - 6 - benzimidazolyl) - benzimidazole in which the phenyl nucleus is substituted by a lower alkoxy or a lower alkoxy-alkoxy radical, for example, a methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, β -methoxy-ethoxy, β -methoxy-propoxy, γ -methoxy-propoxy or β -hydroxy-ethoxy group, while carrying in 6-position the 4-piperazyl group, and its derivatives substituted at the N₁-atom.

This reaction may be carried out by heating an above-mentioned starting substance with an ether-dissociating agent such as a strong hydrohalic acid, preferably concentrated hydrobromic acid, or by melting it with a hydrochloride of a tertiary organic base such as pyridine or dimethyl-aniline. The product can be isolated by dissolving the

reaction mixture which, if desired or necessary, has previously been evaporated to dryness, in water and combining the solution with a substance having an alkaline action, for example, ammonia.

5 As compounds of the general formula I which are used as starting substances in the method g) of the process of the present invention, there may be mentioned 2 - (2 - phenyl - 6 - benzimidazolyl) - 6 - (1 - benzyl - 4 - piperazyl) - benzimidazole and its derivatives which are substituted by the radicals R₁ and R₂.

10 The starting substance, suitably in form of the hydrohalide, may be hydrogenated in a solvent such as an aqueous lower aliphatic alcohol, for example, methanol, in the presence of metals of the VIII group of the periodic System, for example, finely distributed platinum or palladium, at room temperature or at an elevated temperature, if desired or required with application of an excess pressure of hydrogen. Isolation of the product can be effected by evaporation of the reaction mixture, dissolution in water and addition of ammonia or also by recrystallisation of the hydrochloride from the hydrogenated solution, if necessary or desired with the addition of a substance having the same ions, for example, strong hydrohalic acids or a readily soluble hydrohalide such as sodium chloride or potassium iodide.

15 When isolated as free bases, the products of the invention separate in most cases in form of their hydrates having a smaller or higher content of water; in general, they have no characteristic sharp melting points. On the other hand, however, the products of the invention can be distinctly characterized by the typical green fluorescence of their solutions in alcohols, for example, methanol, whereas the starting substances are not fluorescent or have a deep blue fluorescence. The nitrogen analyses are advantageously carried out according to the method described by J. Unterzaucher, Chem. Ing. Technik 22, 128 (1950) or Mikrochemie 36/37, Page 706 (1951), in order to obtain exact data.

20 As acids which may be used for the formation of salts with the basic products of the invention, there may be mentioned, for example, hydrochloric acid, phosphoric acid, acetic acid, citric acid and maleic acid.

25 The products of the present invention may be used as medicaments, either as such or in the form of their physiologically tolerable salts. They have a strong anthelmintic activity which is particularly directed against filariae, whereas the known anthelmintic agent "Diethylcarbamazine" is only weakly active against the filariae *Litomosoides carinii* in rats and the compounds 2 - (2 - phenyl - 6 - benzimidazolyl) - 6 - methyl - benzimidazole and 2 - (2 - phenyl - 6 - benzimidazolyl) - benzimidazole, neither of which contains a piperazyl radical and which are known from Chem. Abstr. 48, column 4523c, have no anthelmintic action. Accordingly, the present invention also provides a pharmaceutical preparation having anthelmintic activity which comprises a compound of the invention in admixture or conjunction with a pharmaceutically suitable carrier, which preparation preferably contains from 0.5% to 50% by weight of a compound of the invention.

30 In order to test the anthelmintic action, cotton rats which had been infested with *Litomosoides carinii* were treated subcutaneously according to the method described by K. Rohde, Z. Tropenmedizin 10, 385 (1959), on five consecutive days, with different doses of the compounds to be tested. After 3 weeks, 0.05 ml of blood was taken from the tail or from the canthus, mixed with 5 ml of distilled water in a centrifuge tube and centrifuged for 2 minutes with 3000 revolutions. Then, such a quantity of liquid was removed that the remainder just filled a Zschukke counting chamber and the number of microfilariae was then determined. After one week, the rats were killed and dissected and then the test was made whether the adult worms, i.e. the macrofilariae, were still alive. This test was effected by transferring the worms to a 0.9% sodium chloride solution heated to 37°C. The live worms moved around very actively in this solution, whereas the dead worms remained motionless.

35 40 45 50 In this test, the following values of the *Dosis minima curativa* (*Dos. min. cur.*), upon subcutaneous administration, against microfilariae were found:

Known compounds											<i>Dosis minima curativa</i> in mg/kg
2-(2-Phenyl-6-benzimidazolyl)-benzimidazole											inactive
Diethylcarbamazine											30
Products of the invention											
Example:	1	2b	2c	2d	2e	2f	2g	2h	2i	2k	2l
<i>Dos. min. cur.</i>	6	1	10	2.5	1	1.5	2	4	4	10	10 mg/kg
Example:	2m	2n	2o	2q	2r	2s	3	4	5a	5b	
<i>Dos. min. cur.</i>	2	25	20	2	10	5	1.5	1	2	2	mg/kg
Example:	5c	5d	5e	5f	5g	5h	11				
<i>Dos. min. cur.</i>	4	25	4	4	5	4	10				mg/kg

In addition, the products of the present invention are also active against macrofilariae, whereas the known compounds have no such action.

Thus, for example, the *dosis curativa minima* of the compounds of the invention against macrofilariae is:

Compound of Example:	1	2f	2g	5b	
<i>Dos. min. curativa</i>	5	20	10	20	mg/kg,

under the test conditions described above.

The products of the present invention, when applied parenterally, are suitable for the therapy of human filarioses, especially those caused by *Wuchereria bancrofti*, *Loa loa* and *Brugia malayi*.

Furthermore, the products of the present invention have an extraordinarily strong bacteriostatic action against grampositive germs. The values given in the following table were determined in a series dilution test against the germs *Staphylococcus aureus* SG511, *Hemol. Streptococcus A* and *Enterococcus faecium*. In this table, the numerical values signify:

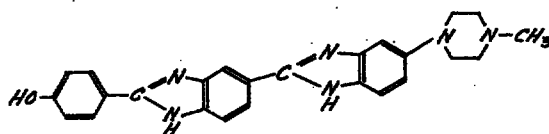
0	no inhibition up to 1000 γ /ml
1	inhibition in the range of 100 — 1000 γ /ml
2	" 10 — 100 γ /ml
3	" 1 — 10 γ /ml
4	" 0.1 — 1 γ /ml
5	" 0.01 — 0.1 γ /ml

Product of Example	Inhibition against		
	<i>Staph. aur.</i>	<i>Hemol. strept.</i>	<i>Enterococc.</i>
2a	3	4	2
2b	4	4	4
2c	3	4	3
2e	4	4	4
2l	4	4	4
2m	3	4	3
2r	3	5	2
2s	3	5	3
5c	5	3	3
5d	2	4	3
5e	3	4	2
5f	3	4	3
5g	3	4	2
5h	3	4	3

Thus the products of the present invention are suitable as medicaments against infestations with filariae; they may be administered subcutaneously or intramuscularly in form of their aqueous solutions.

The following Examples illustrate the invention.

EXAMPLE 1



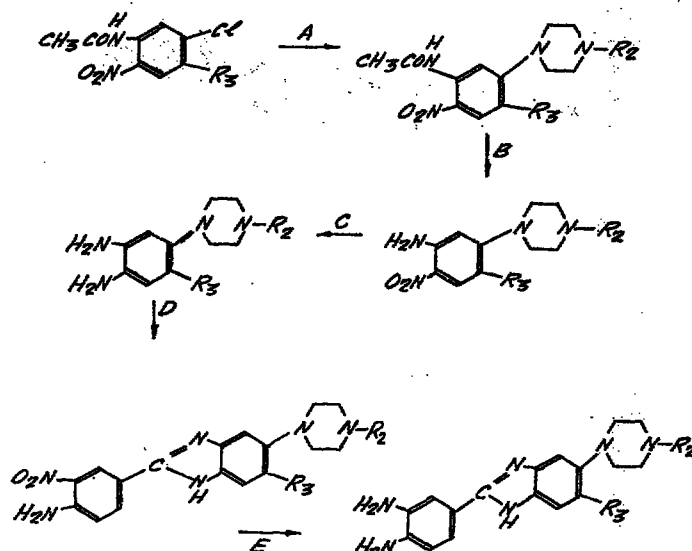
a) 205 Grams of 2 - (3,4 - diamino - phenyl) - 6 - (1 - methyl - 4 - piperazyl) - benzimidazole in 1 l of glacial acetic acid were heated for 2 hours on a steam bath, under an atmosphere of nitrogen, with 160 g of ethyl - 4 - hydroxybenzimidatehydrochloride. The glacial acetic acid was then evaporated under reduced pressure, the residue was dissolved in 350 ml of water and the solution was combined with a mixture of 1 l of isopropanol and 100 ml of concentrated ammonia. The whole was stirred for one hour on a steam bath, and then cooled. The precipitate was filtered off with suction, washed with isopropanol and then with water and dried on a steam bath. For purification, the crude 2 - [2 - (4 - hydroxy - phenyl) - 6 - benzimidazolyl] - 6 - (1 - methyl - 4 - piperazyl) - benzimidazole was dissolved in 3.2 l of boiling methanol, the hot solution was combined with 600 ml of water and treated with charcoal. The filtrate was combined, while still hot, with 1.2 litres of water and allowed to cool. The mixture was allowed to stand for several hours and the magma-like precipitate was filtered off with suction, washed with isopropanol and then with absolute ether, and dried on a steam bath. Yield: 110 g. The product melts at 235°C upwards with decomposition. %Nitrogen for 2 H₂O: Calculated: 18.3, Found: 18.2.

In order to obtain the hydrochloride, the base was dissolved in methanol, the solution was combined with an alcoholic solution of hydrogen chloride and the hydrochloride

was precipitated by means of acetone. It was filtered off with suction, washed with acetone and dried on a steam bath. Yield: 127 g, decomposition point: 280°C.

In order to obtain the phosphate, 42.4 g of the free base were dissolved in a mixture of 400 ml of water and 40 ml of glacial acetic acid on a steam bath and, while stirring, 12 g of a 85% phosphoric acid and then 500 ml of methanol were added. After the mixture had been boiled for a short time, a yellow precipitate separated; the whole was stirred for 1 hour with heating, allowed to cool and filtered off with suction. After washing three times with water, the product was dried on a steam bath. Yield: 31 g. Decomposition point: 315°C.

b) The preparation of the 2 - (3,4 - diamino - phenyl) - 6 - (4 - piperazyl) - benzimidazoles required as starting substances, was effected according to the following reaction scheme:



$R_2 = \text{CH}_3$; $R_3 = \text{H}$:

A 50 g of 5 - chloro - 2 - nitro - acetanilide were heated for 4 hours under reflux with 30 g of 1 - methyl - piperazine and 33 g of anhydrous potassium carbonate in 50 ml of dimethylformamide. The mixture was combined with 300 ml of water and the precipitate was filtered off with suction. For purification, the product was dissolved in dilute hydrochloric acid, the solution was clarified with charcoal, and the 5 - (1 - methyl - 4 - piperazyl) - 2 - nitro - acetanilide was precipitated again by the addition of a sodium hydroxide solution. Yield: 54 g. Melting point: 135°C.

B By boiling the entire product from A for one hour in a mixture of 100 ml of water and 50 ml of concentrated hydrochloric acid, evaporating to dryness, dissolving the residue in water and precipitating the product by means of a sodium hydroxide solution, 44 g of 5 - (1 - methyl - 4 - piperazyl) - 2 - nitro - aniline melting at 155°C were obtained.

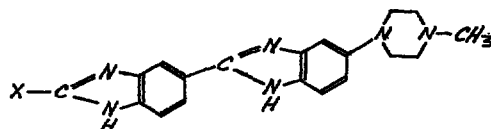
C 40 g of the product from B were hydrogenated with Raney nickel in 120 ml of methanol, separated from the catalyst by filtration and the solvent was separated by evaporation. The crude 5 - (1 - methyl - 4 - piperazyl) - 1,2 - diamino - benzene thus obtained was used as the starting material for stage D.

D 51 g of ethyl - 3 - nitro - 4 - amino - benzimidate hydrochloride in 300 ml of glacial acetic acid were stirred for 2 hours on a steam bath with the crude product obtained in stage C. The glacial acetic acid was distilled off, the residue was dissolved in 500 ml of water, filtered hot and the 2 - (3 - nitro - 4 - amino - phenyl) - 6 - (1 - methyl - 4 - piperazyl) - benzimidazole was precipitated by means of ammonia. After purification by dissolution in a mixture of 250 ml of methanol and 30 ml of glacial acetic acid, filtration and reprecipitation with ammonia, there were obtained, after filtration with suction, washing with acetone and drying, 55 g of pure product melting at 183—185°C.

- 5 *E* 30 g of the nitro compound from D were hydrogenated at 90°C with Raney nickel in 150 ml of 1-normal acetic acid. After separation of the catalyst by filtration, the 2 - (3,4 - diamino - phenyl) - 6 - (1 - methyl - 4 - piperazyl) - benzimidazole was precipitated by means of ammonia and the crude product was purified by dissolution in 500 ml of 1-normal acetic acid with the addition of 25 g of charcoal. After precipitation by means of ammonia, there were obtained 18 g of pure compound melting at 268°C.

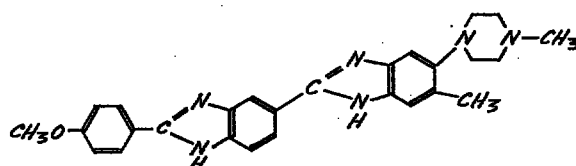
EXAMPLE 2

- 10 From equivalent amounts of 2 - (3,4 - diamino - phenyl) - 6 - (1 - methyl - 4 - piperazyl) - benzimidazole and corresponding ethyl benzimidate hydrochlorides, the following compounds were prepared in a manner analogous to that described in Example 1 a:



	Substituent of the ethyl benzimidate hydrochloride	X in product	Melting point in °C	% Nitrogen	
				Calc.:	Found:
a	2-hydroxy-	2-hydroxy-phenyl-	from 200 up	19.0 (1 H ₂ O)	19.2
b	4-methoxy-	4-methoxy-phenyl-	255	18.1 (1 $\frac{1}{2}$ H ₂ O)	18.5
c	3-methoxy-	3-methoxy-phenyl-	220	18.8 ($\frac{1}{2}$ H ₂ O)	18.9
d	4-propoxy-	4-propoxy-phenyl-	286	17.3 (1 H ₂ O)	17.5
e	4-ethoxy-	4-ethoxy-phenyl-	268	17.5 (1 $\frac{1}{2}$ H ₂ O)	17.3
f	4-butoxy-	4-butoxy-phenyl-	270	16.4 ($\frac{1}{2}$ H ₂ O, $\frac{1}{2}$ C ₂ H ₅ OH)	16.4
g	3,4-methylene- dioxy-	3,4-methylene- dioxy-phenyl-	from 200 up	17.2 (2 H ₂ O)	17.0
h	—	2-phenyl-	190	18.5 (1 $\frac{1}{2}$ H ₂ O, 1/3 C ₂ H ₅ OH)	18.4
i	4-methyl-	4-methyl-phenyl-	from 200 up	18.2 (1 H ₂ O, $\frac{1}{2}$ C ₂ H ₅ OH)	18.1
k	3-methyl-	3-methyl-phenyl-	236	19.1 (1 H ₂ O)	19.1
l	4-chloro-	4-chloro-phenyl-	from 200 up	17.9 (1 $\frac{1}{2}$ H ₂ O)	18.1
m	4-dimethylamino-	4-dimethylamino- phenyl-	210	20.1 (2 H ₂ O)	20.0
n	3-chloro-4-methyl	3-chloro-4-methyl- phenyl-	from 200 up	17.7 (1 H ₂ O)	17.9
o	4-chloro-3-methyl-	4-chloro-3-methyl- phenyl-	256	18.4	18.5
p	3-nitro-4-amino	3-nitro-4-amino- phenyl-	240	22.2 (2 H ₂ O)	21.9
q	4-phenyl-	4-diphenyl-	310	16.7 (1 H ₂ O)	16.4
r	3,4-benzo	2-naphthyl-	245	18.0 ($\frac{1}{2}$ H ₂ O)	17.9
s	3-nitro-4-(2- diethyl-amino- ethylamino)-	3-nitro-4-(2-diethyl- aminoethylamino)- phenyl-	294	21.9 ($\frac{1}{2}$ H ₂ O)	22.0
t	4-nitro-	4-nitro-phenyl-	210	19.3 (3 H ₂ O)	19.0

EXAMPLE 3



2-[2-(4-Methoxy-phenyl)-6-benzimidazolyl]-5-methyl-6-(1-methyl-4-piperazyl)-benzimidazole

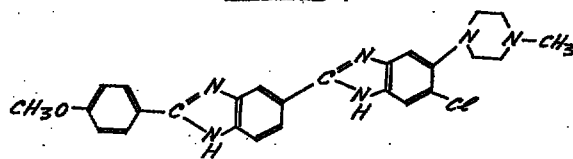
11.3 g of 2 - (3,4 - diamino - phenyl) - 5 - methyl - 6 - (1 - methyl - 4 - piperazyl) - benzimidazole were heated for 2 hours on a steam bath in 80 ml of glacial acetic acid with 8 g of ethyl - 4 - methoxy - benzimidate hydrochloride and worked up as described in Example 1 a. For purification, the crude product was dissolved in 100 ml of isopropanol while heating, filtered off while hot and the filtrate was combined with 10 ml of water. After cooling, the hydrate of 2 - [2 - (4 - methoxy - phenyl) - 6 - benzimidazolyl] - 5 - methyl - 6 - (1 - methyl - 4 - piperazyl) - benzimidazole that had separated was filtered off with suction, washed with isopropanol and ether and dried on a steam bath. Yield: 10.3 g. Melting point: from 196°C upwards (with sintering). Nitrogen: Calc.: 17.5 (1 $\frac{1}{2}$ H₂O). Found: 17.4.

For conversion of the free base into the hydrochloride, the method described in Example 1 a was used.

In order to prepare the 2 - (3,4 - diamino - phenyl) - 5 - methyl - 6 - (1 - methyl - 4 - piperazyl) - benzimidazole required as the starting substance, 50 g of 6 - chloro - 3 - nitro - 4 - acetamino - toluene in 50 ml of dimethylformamide were stirred for 2 hours under reflux with 30 g of 1 - methyl - piperazine and 30 g of potassium carbonate and the 4 - methyl - 5 - (1 - methyl - 4 - piperazyl) - 2 - nitroacetanilide was isolated according to the method described in Example 1 b, stage A. Yield: 44 g. Melting point 166°C.

The hydrolysis to obtain 4 - methyl - 5 - (1 - methyl - 4 - piperazyl) - 2 - nitro - aniline (melting point: 208°C), the hydrogenation to obtain the 4 - methyl - 5 - (1 - methyl - 4 - piperazyl) - 1,2 - diaminobenzene and the reaction with ethyl - 3 - nitro - 4 - amino benzimidate hydrochloride to obtain 2 - (3 - nitro - 4 - amino - phenyl) - 5 - methyl - 6 - (1 - methyl - 4 - piperazyl) - benzimidazole (melting point 280°C) and the hydrogenation of this product to obtain 2 - (3,4 - diamino - phenyl) - 5 - methyl - 6 - (1 - methyl - 4 - piperazyl) - benzimidazole melting at 155°C, were carried out in a manner analogous to that described in Example 1 b (B-E).

EXAMPLE 4



2-[2-(4-methoxy-phenyl)-6-benzimidazolyl]-5-chloro-6-(1-methyl-4-piperazyl)-benzimidazole

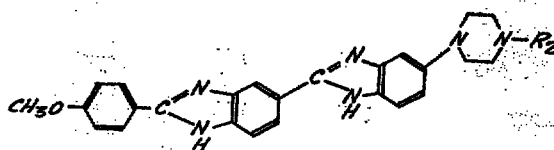
12 g of 2 - (3,4 - diamino - phenyl) - 5 - chloro - 6 - (1 - methyl - 4 - piperazyl) - benzimidazole in 100 ml of glacial acetic acid were heated for 2 hours on a steam bath with 8 g of ethyl - 4 - methoxy - benzimidate hydrochloride and the product was worked up as described in Example 1 a. For purification, the crude product was dissolved in 100 ml of hot isopropanol, filtered while still hot and combined with 15 ml of water. After cooling, the hydrate of 2 - [2 - (4 - methoxy - phenyl) - 6 - benzimidazolyl] - 5 - chloro - 6 - (1 - methyl - 4 - piperazyl) - benzimidazole that had separated was filtered off with suction, washed with isopropanol and ether and dried on the steam bath. Yield: 12 g. Melting point: 207°C (with sintering). For conversion into the hydrochloride, the method described in Example 1 a was used. % Nitrogen: Calc.: 16.5 (4 H₂O). Found: 16.5.

In order to prepare the 2 - (3,4 - diamino - phenyl) - 5 - chloro - 6 - (1 - methyl - 4 - piperazyl) - benzimidazole required as the starting substance, 60 g of 4,5 - dichloro - 2nitro - acetanilide were boiled for half an hour under reflux in 50 ml of dimethylformamide with 35 g of 1 - methyl - piperazine and 35 g of potassium carbonate, and

the 4 - chloro - 5 - (1 - methyl - 4 - piperazyl) - 2 - nitro - acetanilide was isolated in a yield of 58 g (melting point 150°C) according to the method described in Example 1 b (A). The further reactions to produce, in turn, the 4 - chloro - 5 - (1 - methyl - 4 - piperazyl) - 2 - nitro - aniline (melting point 202°C), 4 - chloro - 5 - (1 - methyl - 4 - piperazyl) - 1,2 - diamino - benzene and 2 - (3 - nitro - 4 - amino - phenyl) - 5 - chloro - 6 - (1 - methyl - 4 - piperazyl) - benzimidazole (melting point 298°C) to 2 - (3,4 - diamino - phenyl) - 5 - chloro - 6 - (1 - methyl - 4 - piperazyl) - benzimidazole (melting point 258°C) were carried out under the conditions described in Example 1 b (B to E).

EXAMPLE 5

From 12 g of ethyl - 4 - methoxy benzimidate hydrochloride and 16.8 g of 2 - (3,4 - diamino - phenyl) - 6 - (1 - ethyl - 4 - piperazyl) - benzimidazole or equivalent amounts of 2 - (3,4 - diamino - phenyl) - 6 - 1 - substituted - 4 - piperazyl - benzimidazoles, the following compounds were prepared according to the method described in Example 1 a:



	R ₂ in product	Melting point °C	% Nitrogen	
			Calc.:	Found:
a	ethyl	188	17.9 (. 1 H ₂ O)	18.0
b	isopropyl	214	16.1 (.2 H ₂ O, 1/2 C ₃ H ₇ OH)	16.0
c	butyl	260	16.7 (.1 1/2 H ₂ O)	16.9
d	benzyl	169	16.1 (1/2 H ₂ O)	16.5
e	H	267	14.1 (3 1/2 H ₂ O)	14.2
f	β-hydroxyethyl	190	17.0 (1 1/2 H ₂ O)	16.6
g	carbethoxy	285	17.0	17.1
h	β-diethylaminoethylamino	166	17.8 (1 1/2 H ₂ O)	17.8
i	phenyl	300	16.8	16.7

For preparing the 2 - (3,4 - diamino - phenyl) - 6 - (1 - substituted - 4 - piperazyl) - benzimidazoles (II) required as starting materials equivalent amounts of 5 - chloro - 2 - nitro - acetanilide were reacted with 1-substituted piperazine derivative according to the reaction sequence (A → B → C → D → E) described in Example 1 b.

Melting point (in °C) of the intermediate products obtained according to the method described in Example 1 b

	R ₂	A	B	C	D	E
a	ethyl	102	125	—	188	170
b	isopropyl	87	127	131	199	284
c	butyl	89	110	—	170	267
d	benzyl	136	162	—	170	206
e	H					
f	β-hydroxyethyl	157	160	—	120	200
g	carbethoxy	155	180	—	120	231
h	β-diethylamino-ethylamino	82	82	—	115	236
i	phenyl	184	206	202	256	281

EXAMPLE 6

5 g of 2 - (3,4 - diamino - phenyl) - 6 - (1 - methyl - 4 - piperazyl) - benzimidazole in 50 ml of benzoyl chloride were heated on a wire net. When 120° was reached, the temperature spontaneously rose to 150°C. The whole was allowed to react for half an hour under reflux. After cooling, the yellow magma was diluted with acetone and filtered off with suction. The residue was suspended in 100 ml of hot isopropanol and ammonia was added until the solution showed an alkaline reaction. A clear solution formed intermediately. The thick precipitate which was then separated constituted a dibenzoyl compound of 2 - (2 - phenyl - 6 - benzimidazolyl) - 6 - (1 - methyl - 4 - piperazyl) - benzimidazole and was filtered off with suction and washed with water and with isopropanol. Yield: 7.2 g. Melting point: 247°C.

The dibenzoyl product was heated for 12 hours to 200°C in a quantity of 20% hydrochloric acid ten times greater than the quantity of the dibenzoyl product in a tube which had been closed by melting. The hydrochloric acid was then evaporated under reduced pressure and the base was precipitated by the addition of ammonia. Yield: 4 g. By reprecipitation and recrystallization from a mixture of isopropanol and water, 2 - (2 - phenyl - 6 - benzimidazolyl) - 6 - (1 - methyl - 4 - piperazyl) - benzimidazole was obtained in pure form which was identical with the product obtained according to Example 2 h.

EXAMPLE 7

8 g of 2 - (3,4 - diamino - phenyl) - 6 - (1 - methyl - 4 - piperazyl) - benzimidazole (described in Example 1 b (E)) were fused with 6 g of benzoic acid and this molten mass was kept at 200°C for 2 hours. After cooling, it was dissolved in acetic acid and the 2 - (2 - phenyl - 6 - benzimidazolyl) - 6 - (1 - methyl - 4 - piperazyl) - benzimidazole that had formed was precipitated by means of ammonia. The product was purified by dissolution in 100 ml of isopropanol and precipitation with 50 ml of water; it was identical with the product obtained according to Example 2 h.

EXAMPLE 8

8.1 g of 2 - (3,4 - diamino - phenyl) - 6 - (1 - methyl - 4 - piperazyl) - benzimidazole (described in Example 1 b (E)) were heated at 200°C for 12 hours in a tube closed by melting with 4 g of benzoic acid and 75 ml of 20% by volume hydrochloric acid. The reaction mixture was then combined with 500 ml of water, undissolved matter was filtered off, and the base was precipitated by means of ammonia. By reprecipitation in dilute acetic acid by means of ammonia and recrystallization from a mixture of isopropanol and water, there was obtained pure 2 - (2 - phenyl - 6 - benzimidazolyl) - 6 - (1 - methyl - 4 - piperazyl) - benzimidazole which was identical with the product obtained according to Example 2 h.

EXAMPLE 9

5.5 g of benzaldehyde were added, while heating and stirring, to a mixture of 16.3 g of 2 - (3,4 - diamino - phenyl) - 6 - (1 - methyl - 4 - piperazyl) - benzimidazole (described in Example 1 b (E)) and 20 g of cupric acetate in 250 ml of 2N-acetic acid. The whole was stirred for 1 hour on the steam bath and combined with 250 ml of concentrated hydrochloric acid and filtered off with suction after cooling. For purification, the product was mixed, while stirring, with 100 ml of hydrochloric acid having a strength of 20% and then with acetone. Finally, it was recrystallized from a mixture of isopropanol and water; after drying, 5 g of 2 - (2 - phenyl - 6 - benzimidazolyl) - 6 - (1 - methyl - 4 - piperazyl) - benzimidazole were obtained. The compound was identical with the product described in Example 2 h.

EXAMPLE 10

5.6 g of 4 - (1 - methyl - 4 - piperazyl) - 1,2 - diamino - benzene (described in Example 1 b (C)) were heated for 1 hour with 10 g of 2 - phenyl - 6 - benzimidazole - imino - methyl - glycol ether hydrochloride in 100 ml of glacial acetic acid, the glacial acetic acid was distilled off under reduced pressure, and the product was dissolved in water and precipitated by means of ammonia. The dried crude product was recrystallized twice from 200 ml of hot isopropanol and 30 ml of water. Yield: 6.5 g of pure 2 - (2 - phenyl - 6 - benzimidazolyl) - 6 - (1 - methyl - 4 - piperazyl) - benzimidazole, which was identical with the product described in Example 2 h.

The 2 - phenyl - 6 - benzimidazole - iminomethyl - glycol ether hydrochloride required as the starting substance was obtained by heating 30 g of 3,4 - diamino - benzonitrile in 250 ml of glacial acetic acid for 1 hour under reflux with 45 g of ethyl benzimidate hydrochloride. The glacial acetic acid was distilled off under reduced pressure, the residue was dissolved in methanol, rendered alkaline by means of ammonia and finally diluted with water. For purification, the product was recrystallized from a mixture of methanol and water: 33 g of pure 2 - phenyl - 6 - benzimidazole - nitrile melting at 196°C were obtained. The conversion into the corresponding imino-ether hydrochloride was effected by saturating, without external cooling, a solution of the nitrile in 15 times its quantity of methyl-glycol with gaseous hydrogen chloride, allowing the whole to stand for several days and separating by filtration with suction the imino-ether hydrochloride formed. After washing with absolute ether and drying over potassium hydroxide, 37 g of product which could be further used without purification were obtained.

EXAMPLE 11

28 g of 2 - [2 - (4 - nitro - phenyl) - 6 - benzimidazolyl] - 6 - (1 - methyl - 4 - piperazyl) - benzimidazole (prepared according to the method described in Example 2 t) were hydrogenated in 400 ml of methanol in the presence of Raney nickel as the catalyst. The filtrate was evaporated to dryness and the water that had formed during the reaction was removed by repeated evaporations with ethanol. The pasty residue was dissolved in 100 ml of methanol, filtered and combined with 700 ml of acetone, whereupon the 2 - [2 - (4 - amino - phenyl) - 6 - benzimidazolyl] - 6 - (1 - methyl - 4 - piperazyl) - benzimidazole separated as a hydrate containing 1 1/2 mol of water of crystallisation. Yield: 18 g.

By recrystallisation from butanol, an addition product with 1 mol of butanol was obtained. This addition product was found to melt at 230°C. Nitrogen: Calc.: 18.7. Found: 18.7.

EXAMPLE 12

49 g of 2 - [2 - (4 - methoxy - phenyl) - 6 - benzimidazolyl] - 6 - (1 - benzyl - 4 - piperazyl) - benzimidazole - trihydrochloride were dissolved in a mixture of 500 ml of water and 500 ml of methanol and hydrogenated in the presence of palladium at 80°C and under ordinary pressure. The filtrate was evaporated, the residue was combined with acetone and the precipitate was filtered off with suction.

For purification, the crude product was introduced into 800 ml of hot methanol, the solution was filtered and allowed to stand in the heat. After a short time, pure 2 - [2 - (4 - methoxy - phenyl) - 6 - benzimidazolyl] - 6 - (4 - piperazyl) - benzimidazole - trihydrochloride precipitated in the form of a hydrate containing 3.5 mols of water of crystallisation. After filtration with suction, washing with ether and drying on a steam bath, 25 g of product melting at 267°C were obtained. % Nitrogen: Calculated: 14.1%. Found: 14.1%.

The 2 - [2 - (4 - methoxy - phenyl) - 6 - benzimidazolyl] - 6 - (1 - benzyl - 4 - piperazyl) - benzimidazole - trihydrochloride used as the starting substance was prepared in the manner described in Example 1 a from the free base described in Example 5 d.

EXAMPLE 13

5 g of 2 - [2 - (4 - methoxy - phenyl) - 6 - benzimidazolyl] - 6 - (1 - methyl - 4 - piperazyl) - benzimidazole were heated for 1 hour under reflux in 50 ml of concentrated hydrobromic acid. A clear solution formed intermediately and after some time, a dense precipitate separated. The reaction mixture was diluted, after cooling, with 100 ml of water, combined while hot with ammonia until it showed a weakly alkaline reaction and was allowed to cool. The precipitate was filtered off with suction and washed with water.

After drying on a steam bath, the crude product was dissolved for purification in 50 ml of hot isopropanol, filtered and combined with 15 ml of water. After the solution had been allowed to stand for some time, the hydrate of 2 - [2 - (4 - hydroxy - phenyl) - 6 - benzimidazolyl] - 6 - (1 - methyl - 4 - piperazyl) - benzimidazole separated; it was filtered off with suction, washed and dried. According to its melting point and fluorescence, the product was identical with the product described in Example 1a.

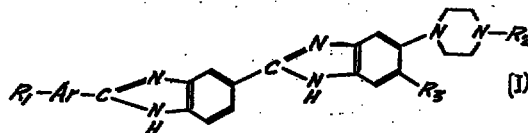
EXAMPLE 14

24 g of 2 - (3,4 - diamino - phenyl) - 6 - (1 - methyl - 4 - piperazyl) - benzimidazole (described in Example 1 b (E)) were heated on a steam bath for 3 hours, while stirring, in 150 ml of methyl-glycol with 15 g of benzotrichloride. The solvent was then distilled off, the residue was dissolved in 200 ml of water and combined, at room temperature, with 200 ml of 2-normal nitric acid. On the next day, the product was filtered off with suction and washed with dilute nitric acid and with acetone. In order to isolate the free base, the nitrate was suspended in 500 ml of water and ammonia was added until the solution showed an alkaline reaction. The free base was filtered off with suction and dissolved, for purification, in 250 ml of methanol with the addition of charcoal and the filtrate was combined, while still hot, with 100 ml of water.

The 2 - (2 - phenyl - 6 - benzimidazolyl) - 6 - (1 - methyl - 4 - piperazyl) - benzimidazole obtained in this manner in a pure form was found to be identical, according to its melting point and its fluorescence, with the product obtained according to Example 2 h.

WHAT WE CLAIM IS:—

1. A basically substituted bis-benzimidazole derivative of the general formula I



in which Ar represents an arylene radical, R₁ represents one or more substituents, which may be the same or different, on the arylene ring, the substituents being selected from hydrogen atoms, halogen atoms, hydroxyl groups, lower alkyl, lower alkoxy, lower alkoxy-alkoxy, mercapto, lower alkylmercapto, lower alkoxyalkylmercapto, and lower alkylene-dioxy radicals, nitro groups, phenyl radicals, and amino and lower alkylene diamino groups, which amino and lower alkylene diamino groups may be substituted by one or more lower alkyl radicals, R₂ represents a hydrogen atom, an alkyl radical which may be substituted, a carbalkoxy, carbamido, aryl or aralkyl radical, and R₃ represents a halogen atom or a lower alkyl or lower alkoxy radical.

2. A physiologically tolerable salt of a compound as claimed in claim 1.

3. A compound as claimed in claim 2, in which Ar represents a benzene nucleus.

4. A compound as claimed in claim 2, in which R₂ represents an alkyl radical containing 1 to 3 carbon atoms.

5. A compound as claimed in claim 2, in which R₂ represents a methyl radical.

6. A compound as claimed in claim 2, in which R₃ represents a hydrogen atom.

7. A compound as claimed in claim 2, in which R₁ represents the 4-methoxy group.

8. A physiologically tolerable acid addition salt of a compound as claimed in any one of claims 4 to 8.

9. 2 - [2 - (4 - hydroxy - phenyl) - 6 - benzimidazolyl] - 6 - (1 - methyl - 4 - piperazyl) - benzimidazole.

10. 2 - [2 - (4 - methoxy - phenyl) - 6 - benzimidazolyl] - 6 - (1 - methyl - 4 - piperazyl) - benzimidazole.

11. 2 - [2 - (3,4 - methylenedioxy - phenyl) - 6 - benzimidazolyl] - 6 - (1 - methyl - 4 - piperazyl) - benzimidazole.

EXAMPLE 13

5 g of 2 - [2 - (4 - methoxy - phenyl) - 6 - benzimidazolyl] - 6 - (1 - methyl - 4 - piperazyl) - benzimidazole were heated for 1 hour under reflux in 50 ml of concentrated hydrobromic acid. A clear solution formed intermediately and after some time, a dense precipitate separated. The reaction mixture was diluted, after cooling, with 100 ml of water, combined while hot with ammonia until it showed a weakly alkaline reaction and was allowed to cool. The precipitate was filtered off with suction and washed with water.

After drying on a steam bath, the crude product was dissolved for purification in 50 ml of hot isopropanol, filtered and combined with 15 ml of water. After the solution had been allowed to stand for some time, the hydrate of 2 - [2 - (4 - hydroxy - phenyl) - 6 - benzimidazolyl] - 6 - (1 - methyl - 4 - piperazyl) - benzimidazole separated; it was filtered off with suction, washed and dried. According to its melting point and fluorescence, the product was identical with the product described in Example 1a.

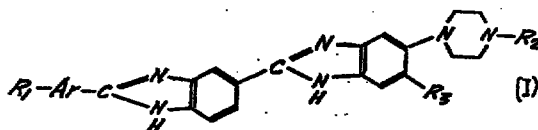
EXAMPLE 14

24 g of 2 - (3,4 - diamino - phenyl) - 6 - (1 - methyl - 4 - piperazyl) - benzimidazole (described in Example 1 b (E)) were heated on a steam bath for 3 hours, while stirring, in 150 ml of methyl-glycol with 15 g of benzotrichloride. The solvent was then distilled off, the residue was dissolved in 200 ml of water and combined, at room temperature, with 200 ml of 2-normal nitric acid. On the next day, the product was filtered off with suction and washed with dilute nitric acid and with acetone. In order to isolate the free base, the nitrate was suspended in 500 ml of water and ammonia was added until the solution showed an alkaline reaction. The free base was filtered off with suction and dissolved, for purification, in 250 ml of methanol with the addition of charcoal and the filtrate was combined, while still hot, with 100 ml of water.

The 2 - (2 - phenyl - 6 - benzimidazolyl) - 6 - (1 - methyl - 4 - piperazyl) - benzimidazole obtained in this manner in a pure form was found to be identical, according to its melting point and its fluorescence, with the product obtained according to Example 2 h.

WHAT WE CLAIM IS:—

1. A basically substituted bis-benzimidazole derivative of the general formula I



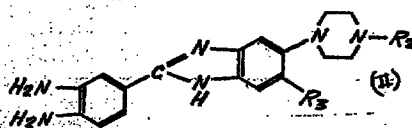
in which Ar represents an arylene radical, R₁ represents one or more substituents, which may be the same or different, on the arylene ring, the substituents being selected from hydrogen atoms, halogen atoms, hydroxyl groups, lower alkyl, lower alkoxy, lower alkoxy-alkoxy, mercapto, lower alkylmercapto, lower alkoxyalkylmercapto, and lower alkylene-dioxy radicals, nitro groups, phenyl radicals, and amino and lower alkylene diamino groups, which amino and lower alkylene diamino groups may be substituted by one or more lower alkyl radicals, R₂ represents a hydrogen atom, an alkyl radical which may be substituted, a carbalkoxy, carbamido, aryl or aralkyl radical, and R₃ represents a halogen atom or a lower alkyl or lower alkoxy radical.

2. A physiologically tolerable salt of a compound as claimed in claim 1.
3. A compound as claimed in claim 2, in which Ar represents a benzene nucleus.
4. A compound as claimed in claim 2, in which R₂ represents an alkyl radical containing 1 to 3 carbon atoms.
5. A compound as claimed in claim 2, in which R₂ represents a methyl radical.
6. A compound as claimed in claim 2, in which R₃ represents a hydrogen atom.
7. A compound as claimed in claim 2, in which R₁ represents the 4-methoxy group.
8. A physiologically tolerable acid addition salt of a compound as claimed in any one of claims 4 to 8.
9. 2 - [2 - (4 - hydroxy - phenyl) - 6 - benzimidazolyl] - 6 - (1 - methyl - 4 - piperazyl) - benzimidazole.
10. 2 - [2 - (4 - methoxy - phenyl) - 6 - benzimidazolyl] - 6 - (1 - methyl - 4 - piperazyl) - benzimidazole.
11. 2 - [2 - (3,4 - methylenedioxy - phenyl) - 6 - benzimidazolyl] - 6 - (1 - methyl - 4 - piperazyl) - benzimidazole.

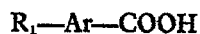


12. 2 - [2 - (4 - ethoxy - phenyl) - 6 - benzimidazolyl] - 6 - (1 - methyl - 4 - piperazyl) - benzimidazole.
13. 2 - [2 - (4 - butoxy - phenyl) - 6 - benzimidazolyl] - 6 - (1 - methyl - 4 - piperazyl) - benzimidazole.
14. 2 - [2 - (4 - dimethylamino - phenyl) - 6 - benzimidazolyl] - 6 - (1 - methyl - 4 - piperazyl) - benzimidazole.
15. 2 - [2 - (4 - diphenyl) - 6 - benzimidazolyl] - 6 - (1 - methyl - 4 - piperazyl) - benzimidazole.
16. 2 - [2 - (4 - methoxy - phenyl) - 6 - benzimidazolyl] - 5 - methyl - 6 - (1 - methyl - 4 - piperazyl) - benzimidazole.
17. 2 - [2 - (4 - methoxy - phenyl) - 6 - benzimidazolyl] - 5 - chlor - 6 - (1 - methyl - 4 - piperazyl) - benzimidazole.
18. 2 - [2 - (4 - methoxy - phenyl) - 6 - benzimidazolyl] - 6 - (1 - ethyl - 4 - piperazyl) - benzimidazole.
19. 2 - [2 - (4 - methoxy - phenyl) - 6 - benzimidazolyl] - 6 - (1 - isopropyl - 4 - piperazyl) - benzimidazole.
20. 2 - [2 - (4 - propoxy - phenyl) - 6 - benzimidazolyl] - 6 - (1 - methyl - 4 - piperazyl) - benzimidazole.
21. 2 - (2 - phenyl - 6 - benzimidazolyl) - 6 - (1 - methyl - 4 - piperazyl) - benzimidazole.
22. 2 - [2 - (4 - tolyl) - 6 - benzimidazolyl] - 6 - (1 - methyl - 4 - piperazyl) - benzimidazole.
23. 2 - [2 - (3 - nitro - 4 - <2 - diethyl - amino - ethyl - amino> - phenyl) - 6 - benzimidazolyl] - 6 - (1 - methyl - 4 - piperazyl) - benzimidazole.
24. 2 - [2 - (4 - methoxy - phenyl) - 6 - benzimidazolyl] - 6 - (1 - butyl - 4 - piperazyl) - benzimidazole.
25. 2 - [2 - (4 - methoxy - phenyl) - 6 - benzimidazolyl] - 6 - (4 - piperazyl) - benzimidazole.
26. 2 - [2 - (4 - methoxy - phenyl) - 6 - benzimidazolyl] - 6 - (1 - β - hydroxy - ethyl - 4 - piperazyl) - benzimidazole.
27. 2 - [2 - (4 - methoxy - phenyl) - 6 - benzimidazolyl] - 6 - (1 - carbethoxy - 4 - piperazyl) - benzimidazole.
28. 2 - [2 - (4 - methoxy - phenyl) - 6 - benzimidazolyl] - 6 - (1 - β - diethyl - aminoethylamino - 4 - piperazyl) - benzimidazole.
29. A compound as claimed in claim 1 and described in any one of the Examples herein, other than the compounds claimed in claims 9 to 28.
30. A pharmaceutical preparation comprising a compound as claimed in any one of claims 1 to 29, in admixture or conjunction with a pharmaceutically suitable carrier.
31. A preparation as claimed in claim 30 which contains from 0.5% to 50% by weight of a compound as claimed in any one of claims 1 to 29.
32. A process for the manufacture of a compound as claimed in claim 1 or claim 2 wherein

a) an *o*-phenylenediamine derivative of the general formula II

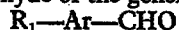


- in which R_2 and R_3 have the meanings given above, is reacted either with a carboxylic acid of the general formula III



(III)

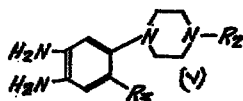
- in which R_1 and Ar have the meanings given above, or with a reactive functional derivative of such an acid, or with an aldehyde of the general formula



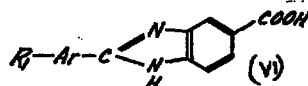
(IV)

- in which R_1 and Ar have the meanings given above, with the addition of an oxidizing agent, if necessary, or

b) an *o*-phenylenediamine derivative of the formula V



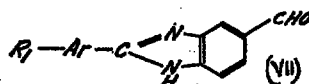
in which R_2 and R_3 have the meanings given above, is reacted either with a carboxylic acid of the general formula VI



5

in which R_1 and Ar have the meanings given above, or with a reactive functional derivative of such an acid, or with an aldehyde of the formula VII

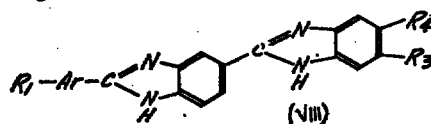
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in which R_1 and Ar have the meanings given above, with the addition of an oxidizing agent, if necessary, or

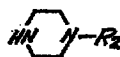
c) a compound of the general formula VIII

10



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in which R_4 represents a halogen atom or an etherified hydroxyl group, and R_1 , Ar and R_5 have the meanings given above, is reacted with a piperazine of the formula



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in which R_2 has the meaning given above, or

d) a compound of the general formula I, in which R_1 represents a halogen atom or an etherified hydroxyl group, is reacted with ammonia or a primary or secondary aliphatic amine, or

15

e) a compound of the general formula I, in which R_1 represents a nitro group, is reduced, or

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f) a compound of the general formula I, in which R_1 represents an ether group, is treated with an ether-dissociating agent, or

20

g) a compound of the general formula I, in which R_2 represents a benzyl radical, is catalytically hydrogenated, and, if desired, a basic compound obtained is converted into a salt by reaction with a physiologically tolerable acid.

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33. A process as claimed in claim 32 conducted substantially as described in any one of the Examples.

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