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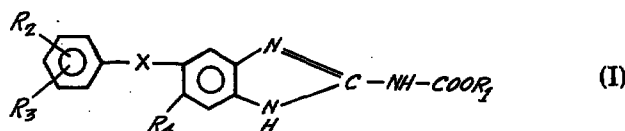
(54) ANTHELMINTICALLY ACTIVE BENZIMIDAZOLE DERIVATIVES AND PROCESSES FOR PREPARING THEM

(71) We, FARBWERKE HOECHST AKTIENGESSELLSCHAFT Vormal's Meister Lucius K. Brüning, a body corporate, organised under and according to the Laws of Germany, of, 6230 Frankfurt (Main) 80, Postfach 80 03 20, Federal Republic of Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to anthelmintically active benzimidazole derivatives, to a process for preparing them, to compositions containing them, and to a method for combating helminths using them.

2-Carbalkoxy-amino-benzimidazole derivatives carrying alkyl or acyl groups in the 5(6) position are known to the anthelmintic agents (P. Actor et al., Nature 215, 321 (1967); DOS 2.029.637).

The present invention provides anthelmintically active 2-carbalkoxy-amino-benzimidazole-5(6)-phenyl ethers of the formula (I)



in which R₁ represents an alkyl group having from 1 to 4 carbon atoms, R₂ and R₃, which may be the same or different, each represents a hydrogen atom, a hydroxyl group, an alkoxy group having from 1 to 4 carbon atoms, a halogen atom, a trifluoromethyl group, an alkyl group having from 1 to 4 carbon atoms or a carbalkoxy group having from 1 to 4 carbon atoms in the alkoxy group, R₄ represents a hydrogen or chlorine atom and X represents oxygen or sulfur.

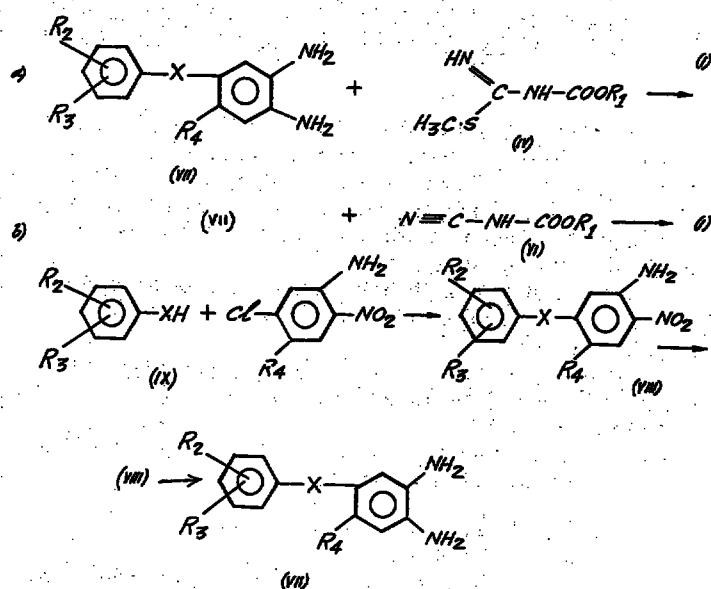
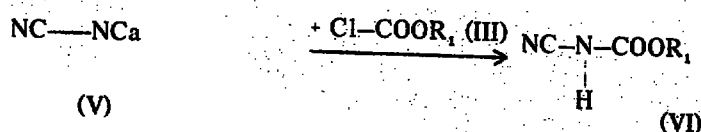
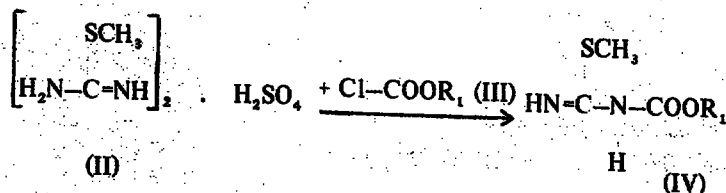
Compounds of the formula (I) in which R₁ represents methyl, R₂, R₃ and R₄ each represent hydrogen and X represents oxygen or sulfur are especially preferred.

The alkyl groups represented by R₁, R₂ and R₃ may be methyl, ethyl, propyl, isopropyl, butyl and tert. butyl groups. The alkoxy groups represented by R₂ and R₃ may be methoxy, ethoxy, propoxy, isopropoxy and butoxy groups. The halogen atoms represented by R₄ and R₃ may be fluorine, chlorine, bromine and iodine atoms. The carbalkoxy groups represented by R₂ and R₃ may be carbomethoxy, carbopropoxy and carbobutoxy groups.

The present invention also provides a process for preparing 2-carbalkoxy-amino-benzimidazole-5(6)-phenyl ethers of the formula (I), which comprises condensing at a pH of from 1 to 6, preferably from 2 to 5, an o-phenylene-diamine of the formula (VII), in which R₂, R₃, R₄ and X have the meanings given above, with either

(a) an alkyl-S-methyl-thiourea carboxylate of the formula (IV) in which R₁ has the meaning given above, or

(b) a cyanamide carboxylate of the formula (VI) in which R has the meaning given above.



For carrying out the reaction according to method (a), the S-methyl-thiourea sulfate of the formula (II) and a chloroformate of the formula (III) are first mixed in water and a strong base, for example a 25% sodium hydroxide solution, is added dropwise, while keeping the temperature low, preferably at 0° C. The alkyl-S-methyl-thiourea carboxylate of the formula (IV) need not be isolated.

The pH of the reaction mixture obtained is then preferably adjusted to a value of between 2 and 5, suitably by adding an organic acid, for example, acetic acid or lactic acid. Then, the *o*-phenylene-diamine derivative of the formula (VII) is added, either in the form of a free base or as an acid addition salt, for example, the hydrochloride. In the latter case it may be advantageous to add an alkali metal salt of an organic acid as a buffer. For the reaction it is preferred to work at a temperature of from 30° to 100° C; the duration of the reaction may be between 30 minutes and 10 hours. Methyl-mercaptan is set free as a side-product. Isolation of the 5(6)-phenoxy- or 5(6)-phenyl-mercapto-2-benzimidazole-carbamates of the formula (I) is carried out in the usual manner, for example by diluting the reaction mixture with water and filtering off the product that separates.

For carrying out the reaction according to method (b), a chloroformate of the (III) is added to an aqueous suspension of cyanamide in the form of a salt, advantageously in the form of the calcium salt (V), while maintaining the reaction temperature at from 40° to 60° C by cooling. After separation by filtration of dark side products, the cyanamide carboxylate of the formula (VI) is obtained in the filtrate. The cyanamide carboxylate (VI) so obtained is combined with an *o*-phenylene-diamine derivative (VII) and the pH of the mixture is brought to a value of between 1 and 6,

preferably 2 and 4, by addition of a mineral acid, for example, concentrated hydrochloric acid. During the reaction, the mixture is suitably kept at a temperature of from 30° to 100° C, depending on the reactivity of the *o*-phenylene-diamine derivative, for a period of from 30 minutes to 10 hours. After having allowed the reaction mixture to cool, the reaction product (I) that precipitates is isolated by filtration and washing.

The *o*-phenylene-diamine derivative (VII) used as starting material is obtained by reduction of a corresponding aminonitrodiphenyl ether or thioether of the formula (VIII) in which R₂, R₃, R, and X have the same meanings as those given in formula (I). The reduction may be effected, for example, by hydrogenation in the presence of Raney nickel and of a solvent such as methanol or dimethylformamide at temperatures in the range of from 20 to 60° C or by a treatment with reducing agents, for example with a solution of tin-2-chloride in glacial acetic acid saturated with hydrochloric acid gas; in this case, the tin double salt of the *o*-phenylenediamine (VII) is first isolated, which is then decomposed by a treatment with a concentrated sodium hydroxide solution. The diamine thus set free is then dissolved in an organic solvent which is immiscible with water.

The *o*-phenylenediamine derivative (VII) can be reacted either as free amine in the manner indicated above with an alkyl-S-methylthiourea carboxylate (IV) or with a cyanamide-carboxylate (VI), or in the form of its acid addition salt with a suitable mineral or organic acid such as hydrochloric acid, sulfuric acid, acetic acid, oxalic acid or similar acids.

The amino-nitro-diphenyl ethers or thioethers (VIII) are obtained by reaction of a phenol or thiophenol of the formula (IX), in which R₂ and R₃ and X have the same meaning as that given for formula (I), with 5-chloro-2-nitroaniline or, if they are compounds of the formula (VIII) in which R, stands for chlorine, with 4,5-dichloro-2-nitroaniline, suitably in the presence of agents having an alkaline reaction such as potassium carbonate, at temperatures between 80° C and the boiling temperature of the solvent used, within a period of time of half an hour up to 5 hours. Isolation is carried out by dilution of the reaction mixture with water and separation by filtration of the precipitate.

If in one of the amino-nitro-diphenyl ethers or thioethers (VIII) R₂ or R₃ represents hydroxyl, such compounds of the formula (VIII) are used as starting substances in which R₂ or R₃ represents a methoxy group; these compounds are treated with an agent splitting of ether group, for example with hydrobromic acid.

The 2-carbalkoxy-amino-benzimidazole-5(6)-phenyl ethers of the present invention are valuable chemotherapeutic agents and are suitable for combating diseases caused by parasites in humans and animals.

They are particularly active against a great number of helminths, for example *Haemonchus*, *Trichostrongylus*, *Ostertagia*, *Strongyloides*, *Cooperia*, *Chabertia*, *Oesophagostomum*, *Hyostrongylus*, *Ankylostoma*, *Ascaris* and *Heterakis*. Particularly marked is the activity against gastro-intestinal Strongylides, which are above all infesting ruminants. The infestation of the animals by these parasites causes great economical damages, so that the compounds of the invention are mainly used in veterinary medicine.

The active substances according to the invention are administered together with suitable pharmaceutical solvents or carriers, perorally or subcutaneously, the one or the other form of administration being preferred in accordance with the prevailing circumstances.

The activity of the compounds of the invention was tested by chemotherapeutic experiments carried out on ewe-lambs having a weight of about 30 kg and which had been infested artificially with larvae of *Haemonchus contortus* or *Trichostrongylus colubriformis*. The test animals were kept in tiled stalls which were daily thoroughly cleaned. After termination of the prepatency period (time between infection and maturity of the parasites with beginning excretion of eggs or larvae), the number of eggs per gram of faeces was determined with the modified McMaster process according to Wetzel (Tierärztliche Umschau 6, 209—210 (1951)). Directly thereafter, the treatment of the sheep (in general 4 to 8 animals per active substance, at least however 2) was begun. The animals obtained perorally, in one case also subcutaneously, a suspension of 2.5 or 5 mg/kg of body weight in, each time, 10 ml of a 1% Tylose (registered Trade Mark) suspension. On the 7th, 14th and 28th day after the treatment, the number of eggs per gram of faeces was determined according to the above-indicated method and the percentage degree of decrease in comparison to the value determined before the beginning of the treatment was calculated.

The following Table indicates the activity of the new substances of the invention determined according to the above-described method in comparison to two known

compounds of similar structure; these compounds were Parbendazol (cf. P. Actor et al., *Nature* 215, 321 (1967); D. Ross, *Veterinary Record* 82, 731 (1968); D.R. Johns et al., *Australian Veterinarian Journal* 45, 460 (1969) and Mebendazol (DOS 2.029.637).

The novel active substances of the invention were designated as follows:

- 5 A = 5-phenoxy-benzimidazole-2-methyl-carbamate
 B = 5-(4-chloro-phenoxy)-benzimidazole-2-methyl-carbamate
 C = 5-(3-chloro-phenoxy)-benzimidazole-2-methyl-carbamate
 D = 5-(2-chloro-phenoxy)-benzimidazole-2-methyl-carbamate
 10 E = 5-(3-methoxy-phenoxy)-benzimidazole-2-methyl-carbamate
 F = 5-phenylmercapto-benzimidazole-2-methyl-carbamate.

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The known active substances were designated as follows:

Comp. subst. 1 = Parbendazol

Comp. subst. 2 = Mebendazol

TABLE

Active substance	Dos. cur. min. in mg/kg	Administration	Effect in %
A	2.5	peroral	100
B	5.0	peroral	94
C	2.5	peroral	100
D	5.0	peroral	96
E	2.5	peroral	100
F	2.5	peroral	100
F	2.5	subcutaneous	100
Comp. subst. 1	15.0	peroral	100
Comp. subst. 2	10.0	peroral	76 - 100

15 As the Table shows, the new carbamates of the invention are superior to known compounds of similar structure in that the Dosis curativa minima is essentially lower. 15

The Dosis tolerata maxima of the products of the invention is higher than 3200 mg/kg of body weight, upon peroral and subcutaneous administration.

20 The active substances of the formula I of the invention are administered, depending on the case, in doses ranging between 0.5 and 50 mg per kg of body weight for a period of 1 to 14 days. 20

25 For oral application, there may be used tablets, dragées, capsules, powders, granulates or pastes which contain the active substance together with the usual excipients and adjuvants such as starch, cellulose powder, talc, magnesium stearate, sugar, gelatin, calcium carbonate, finely distributed silicic acid, carboxymethyl cellulose and similar substances. 25

30 For parenteral administration, there may be used solutions, for example oily solutions, prepared using sesame oil, castor oil or synthetic triglycerides, optionally with the addition of Tocopherol as anti-oxidation agent and/or using surface-active substances such as sorbitane fatty acid ester. In addition, there may be used aqueous suspensions prepared with the use of ethoxylated sorbitane fatty acid esters, optionally with the addition of thickening agents such as polyethylene glycol or carboxymethyl cellulose. 30

The concentrations of the active substances of the invention in the preparations prepared therewith are preferably in the range of from 2 to 20% by weight; for the use as medicaments for humans, the concentrations of the active substances are preferably in the range of from 20 to 80% by weight.

The following Examples illustrate the invention:

EXAMPLE 1.

5-Phenoxy-benzimidazole-2-methyl-carbamate.

156 g of S-methyl-thiourea-sulfate were dissolved in 200 ml of water and then 100 ml of chloroformic acid amethyl ester and 340 g of a 25% sodium hydroxide solution were added dropwise, while stirring, at a temperature of 5 to 10° C. After having stirred for 20 minutes, the reaction mixture was combined with 600 ml of water, 100 ml of glacial acetic acid and 102 g of 3,4-diamino-diphenyl ether in 600 ml of ethanol. Stirring was continued for 90 minutes at a temperature of 85° C, during which time methyl-mercaptan was separated. After having allowed the whole to cool and to stand overnight, the 5-phenoxy-benzimidazole-2-methyl-carbamate that had formed was filtered off with suction, dissolved in 1 liter of hot glacial acetic acid and precipitated with 2 liters of methanol; the pure product which was obtained in a yield of 116 g was found to melt at 248° C (decomposition).

For preparing the 3,4-diamino-diphenyl ether used as starting material, 172.5 g of 5-chloro-2-nitro-aniline were heated for 4 hours under reflux in 500 ml of dimethyl-formamide with 94 g of phenol in the presence of 150 g of anhydrous potassium carbonate. After cooling, the reaction mixture was diluted with 1000 ml of water, the 3-amino-4-nitro-diphenyl ether that had precipitated was filtered off with suction and purified by recrystallization from isopropanol. Yield: 110 g; melting point: 142° C.

103 g of the 3-amino-4-nitro-diphenyl ether so obtained were hydrogenated in 800 ml of dimethylformamide with Raney nickel under a pressure of 100 atmospheres gauge at room temperature, the catalyst was then removed by filtration and the solution was evaporated under reduced pressure. The 3,4-diamino-diphenyl ether that had formed was obtained in the form of a syrupy mass which was dissolved in ethanol and used in the reaction as described above.

EXAMPLES 2—30.

The following compounds were prepared in analogous manner:

2. From 3-amino-4-nitro-4'-chloro-diphenyl ether (melting point 135° C) via the 3,4-diamino-4'-chloro-diphenyl ether, the 5-(4-chloro-phenoxy)-benzimidazole-2-methyl-carbamate melting at 197° C.

3. From 3-amino-4-nitro-3'-chloro-diphenyl ether (melting point 114° C) via the 3,4-diamino-3'-chloro-diphenyl ether, the 5-(3-chloro-phenoxy)-benzimidazole-2-methyl-carbamate melting at 230° C.

4. From 3-amino-4-nitro-2'-chloro-diphenyl ether (melting point 161° C) via the 3,4-diamino-2'-chloro-diphenyl ether, the 5-(2-chloro-phenoxy)-benzimidazole-2-methyl-carbamate melting at 206° C.

5. From 3-amino-4-nitro-2',5'-dichloro-diphenyl ether (melting point 140° C) via the 3,4-diamino-2',5'-dichloro-diphenyl ether, the 5-(2,5-dichloro-phenoxy)-benzimidazole-2-methyl-carbamate melting at 244° C.

6. From 3-amino-4-nitro-3',5'-dichloro-diphenyl ether (melting point 162° C) via the 3,4-diamino-3',5'-dichloro-diphenyl ether, the 5-(3,5-dichloro-phenoxy)-benzimidazole-2-methyl-carbamate melting at 226° C.

7. From 3-amino-4-nitro-4'-bromo-diphenyl ether (melting point 129° C) via the 3,4-diamino-4'-bromo-diphenyl ether, the 5-(4-bromo-phenoxy)-benzimidazole-2-methyl-carbamate melting at 248° C.

8. From 3-amino-4-nitro-3'-bromo-diphenyl ether (melting point 127° C) via the 3,4-diamino-3'-bromo-diphenyl ether, the 5-(3-bromo-phenoxy)-benzimidazole-2-methyl-carbamate melting at 232° C.

9. From 3-amino-4-nitro-2'-bromo-diphenyl ether (melting point 152° C) via the 3,4-diamino-2'-bromo-diphenyl ether, the 5-(2-bromo-phenoxy)-benzimidazole-2-methyl-carbamate melting at 211° C.

10. From 3-amino-4-nitro-4'-methyl-diphenyl ether (melting point 128° C) via the 3,4-diamino-4'-methyl-diphenyl ether, the 5-(4-methyl-phenoxy)-benzimidazole-2-methyl-carbamate melting at 251° C.

11. From 3-amino-4-nitro-3'-methyl-diphenyl ether (melting point 110° C) via the 3,4-diamino-3'-methyl-diphenyl ether, the 5-(3-methyl-phenoxy)-benzimidazole-2-methyl-carbamate melting at 228° C.

12. From 3-amino-4-nitro-2'-methyl-diphenyl ether (melting point 137° C) via the 3,4-diamino-2'-methyl-diphenyl ether, the 5-(2-methyl-phenoxy)-benzimidazole-2-methyl-carbamate melting at 216° C.
13. From 3-amino-4-nitro-4'-tert.butyl-diphenyl ether (melting point 94° C) via the 3,4-diamino-4'-tert.butyl-diphenyl ether, the 5-(4-tert.butyl-phenoxy)-benzimidazole-2-methyl-carbamate melting at 250° C.
14. From 3-amino-4-nitro-2',4'-dimethyl-diphenyl ether (melting point 116° C) via the 3,4-diamino-2',4'-dimethyl-diphenyl ether, the 5-(2,4-dimethyl-phenoxy)-benzimidazole-2-methyl-carbamate melting at 239° C.
15. From 3-amino-4-nitro-2'-chloro-4'-methyl-diphenyl ether (melting point 145° C) via the 3,4-diamino-2'-chloro-4'-methyl-diphenyl ether the 5-(2-chloro-4-methyl-phenoxy)-benzimidazole-2-methyl-carbamate melting at 209° C.
16. From 3-amino-4-nitro-2'-chloro-6'-methyl-diphenyl ether (melting point 164° C) via the 3,4-diamino-2'-chloro-6'-methyl-diphenyl ether, the 5-(2-chloro-6-methyl-phenoxy)-benzimidazole-2-methyl-carbamate melting at 300° C.
17. From 3-amino-4-nitro-3'-chloro-4'-methyl-diphenyl ether (melting point 139° C) via the 3,4-diamino-3'-chloro-4'-methyl-diphenyl ether, the 5-(3-chloro-4-methyl-phenoxy)-benzimidazole-2-methyl-carbamate melting at 236° C.
18. From 3-amino-4-nitro-3'-chloro-6'-methyl-diphenyl ether (melting point 141° C) via the 3,4-diamino-3'-chloro-6'-methyl-diphenyl ether, the 5-(3-chloro-6-methyl-phenoxy)-benzimidazole-2-methyl-carbamate melting at 218° C.
19. From 3-amino-4-nitro-3'-chloro-4'-carboethoxy-diphenyl ether melting point 134° C) via the 3,4-diamino-3'-chloro-4'-carboethoxy-diphenyl ether, the 5-(3-chloro-4-carboethoxy-phenoxy)-benzimidazole-2-methyl-carbamate melting at 194° C.
20. From 3-amino-4-nitro-4'-chloro-2'-methyl-diphenyl ether (melting point 142° C), via the 3,4-diamino-4'-chloro-2'-methyl-diphenyl ether, the 5-(4-chloro-2-methyl-phenoxy)-benzimidazole-2-methyl-carbamate melting at 230° C.
21. From 3-amino-4-nitro-4'-chloro-3'-methyl-diphenyl ether (melting point 135° C) via the 3,4-diamino-4'-chloro-3'-methyl-diphenyl ether, the 5-(4-chloro-3-methyl-phenoxy)-benzimidazole-2-methyl-carbamate melting at 253° C.
22. From 3-amino-4-nitro-4'-chloro-3',5'-dimethyl-diphenyl ether (melting point 158° C) via the 3,4-diamino-4'-chloro-3',5'-dimethyl-diphenyl ether, the 5-(4-chloro-3,5-dimethyl-phenoxy)-benzimidazole-2-methyl-carbamate melting at 239° C.
23. From 3-amino-4-nitro-3',5'-bis-trifluoromethyl-diphenyl ether (melting point 129° C) via the 3,4-diamino-3',5'-bis-trifluoromethyl-diphenyl ether, the 5-(3,5-bis-trifluoromethyl-phenoxy)-benzimidazole-2-methyl-carbamate melting at 238° C.
24. From 3-amino-4-nitro-4'-methoxy-diphenyl ether (melting point 169° C) via the 3,4-diamino-4'-methoxy-diphenyl ether, the 5-(4-methoxy-phenoxy)-benzimidazole-2-methyl-carbamate melting at 246° C.
25. From 3-amino-4-nitro-3'-methoxy-diphenyl ether (melting point 128° C) via the 3,4-diamino-3'-methoxy-diphenyl ether, the 5-(3-methoxy-phenoxy)-benzimidazole-2-methyl-carbamate melting at 203° C.
26. From 3-amino-4-nitro-2'-methoxy-diphenyl ether (melting point 130° C) via the 3,4-diamino-2'-methoxy-diphenyl ether, the 5-(2-methoxy-phenoxy)-benzimidazole-2-methyl-carbamate melting at 212° C.
27. From 3-amino-4-nitro-4'-propoxy-diphenyl ether (oily) via the 3,4-diamino-4'-propoxy-diphenyl ether, the 5-(4-propoxy-phenoxy)-benzimidazole-2-methyl-carbamate melting at 218° C.
28. From 3-amino-4-nitro-4'-isopropoxy-diphenyl ether (oily) via the 3,4-diamino-4'-isopropoxy-diphenyl ether, the 5-(4-isopropoxy-phenoxy)-benzimidazole-2-methyl-carbamate melting at 208° C.
29. From 3-amino-4-nitro-4'-butoxy-diphenyl ether (oily) via the 3,4-diamino-4'-butoxy-diphenyl ether, the 5-(4-butoxy-phenoxy)-benzimidazole-2-methyl-carbamate melting at 210° C.
30. From 3-amino-4-nitro-4'-iso-butoxy-diphenyl ether (oily) via the 3,4-diamino-4'-iso-butoxy-diphenyl ether, the 5-(4-iso-butoxy-phenoxy)-benzimidazole-2-methyl-carbamate melting at 198° C.

EXAMPLE 31.

5-Phenoxy-benzimidazole-2-methyl-carbamate.

15.6 g of S-methyl-thiourea sulfate were dissolved in 20 ml of water and 10 ml of chloroformic acid methyl ester and 34 g of 25% sodium hydroxide solution were added dropwise, while stirring, at a temperature in the range of from 5 to 15° C. Stirring was continued for 20 minutes and the reaction mixture was combined with

20 ml of glacial acetic acid, 100 ml of water, 23.6 g of 3,4-diamino-diphenyl ether hydrochloride and 8.5 g of sodium acetate and the mixture was then stirred for 1 hour at a temperature of 85° C, during which time methyl mercaptan separated. The isolation and purification of the 5-phenoxy-benzimidazole-2-methyl-carbamate also obtained in Example 1 was effected as described in Example 1.

The hydrochloride of the 3,4-diamino-diphenyl ether used as starting material was obtained from the filtrate, from which the Raney nickel had been removed, as described in Example 1, paragraph 3, by evaporation, dissolution in methanol and acidification with alcoholic hydrochloric acid. The reaction mixture was concentrated, combined with isopropanol and the hydrochloride of 3,4-diamino-diphenyl ether that had separated was filtered off with suction. After recrystallization from water, the hydrochloride was found to have a decomposition point of 200° C.

EXAMPLE 32.

5-Phenoxy-benzimidazole-2-butylcarbamate.

The process was carried in a manner analogous to that described in Example 31, but using 13.7 g of chloroformic acid butyl ester instead of the chloroformic acid methyl ester. The yield of 5-phenoxy-benzimidazole-2-butyl-carbamate was 7.5 g; melting point 188° C.

EXAMPLE 33.

5-Phenoxy-6-chloro-benzimidazole-2-methyl-carbamate.

42.7 g of S-methyl-thiourea sulfate in 65 ml of water were combined, while stirring, at 5—15° C, with 24.6 g of chloroformic acid methyl ester and then with 92 g of 25% sodium hydroxide solution. Stirring was continued for 20 minutes and the mixture was then combined with 120 ml of water, 32 ml of glacial acetic acid, 36 g of 3,4-diamino-6-chloro-diphenyl ether and 120 ml of alcohol. The whole was heated for 90 minutes to 85° C, during which time methyl-mercaptan separated. After cooling, the crude product was filtered off with suction, dissolved in 1.5 liter of glacial acetic acid and combined with 2 liters of methanol. Upon cooling, 30 g of 5-phenoxy-6-chloro-benzimidazole-2-methyl-carbamate melting at 270° C were obtained.

For preparing the 3,4-diamino-6-chloro-diphenyl ether, 20.7 g of 4,5-dichloro-2-nitroaniline in 150 ml of dimethylformamide were boiled under reflux for 6 hours with 9.4 g of phenol in the presence of 14 g of anhydrous potassium carbonate. After having allowed the whole to cool, 150 ml of water were added, stirring was continued for 3 hours and the crude product was filtered off with suction. After recrystallization from a mixture of glacial acetic acid and methanol, 3-amino-4-nitro-6-chloro-diphenyl ether melting at 131° C was obtained.

41.5 g of the 3-amino-4-nitro-6-chloro-diphenyl-ether so obtained were hydrogenated in 300 ml of dimethylformamide with Raney nickel at normal pressure and 40° C. The filtrate obtained after removal of the catalyst was concentrated under reduced pressure. The remaining brown highly viscous mass, constituting the 3,4-diamine-6-chloro-diphenyl ether, was used for the reaction according to paragraph 1 without any purification.

EXAMPLES 34—36.

In a manner analogous to that described in Example 33, the following products were prepared:

34. From 3-amino-4-nitro-6-chloro-4'-diphenyl ether (melting point 210° C) via the 3,4-diamino-6-chloro-4'-chlorodiphenyl ether, the 5-(4-chlorophenoxy)-6-chloro-benzimidazole-2-methyl-carbamate melting at 305° C.

35. From 3-amino-4-nitro-6-chloro-3'-chloro-diphenyl-ether (melting point 126° C) via the 3,4-diamino-6-chloro-3'-chloro-diphenyl ether, the 5-(3-chlorophenoxy)-6-chloro-benzimidazole-2-methyl-carbamate melting at 263 C.

36. From 3-amino-4-nitro-6-chloro-2'-chloro-diphenyl ether (melting point 167° C) via the 3,4-diamino-6-chloro-2'-chloro-diphenyl ether, the 5-(2-chlorophenoxy)-6-chloro-benzimidazole-2-methyl-carbamate melting at 238° C.

EXAMPLE 37

5-(4-Hydroxy-phenoxy)-benzimidazole-2-methyl-carbamate.

66 g of S-methyl-thiourea sulfate in 170 ml of water were combined, at 5 to 15° C, while stirring, with 31 ml of chloroformic acid methyl ester and then with 140 g of 25% sodium hydroxide solution. After having stirred for 20 minutes, the mixture was

combined with 275 ml of water, 48 ml of glacial acetic acid, 52.7 g of 3,4-diamino-4'-hydroxy-diphenyl ether and 275 ml of ethanol. The whole was heated for 2 hours under reflux, the crude product was filtered off with suction when cooled; after recrystallization, 33 g of 5-(4-hydroxyphenoxy)-benzimidazole-2-methyl-carbamate melting at 238° C were obtained.

For preparing the 3,4-diamino-4'-hydroxy-diphenyl ether used as starting material, 117 g of 4-hydroxy-anisole in 400 ml of dimethylformamide were reacted with 163 g of 5-chloro-2-nitro-aniline in the presence of 132 g of anhydrous potassium carbonate for 4 hours under reflux. After having allowed the reaction mixture to cool, it was diluted with 400 ml of water, the crude product was filtered off with suction; after recrystallization from methyl glycol, 151 g of 3-amino-4-nitro-4'-methoxy-diphenyl ether melting at 169° C were obtained.

100 g of the 3-amino-4-nitro-4'-methoxy-diphenyl ether so obtained were heated for 4 hours to the boiling temperature with 1 liter of 48% hydrobromic acid. A clear solution was formed in which a precipitate separated after a short period of time. After cooling it was filtered off with suction and recrystallized from a mixture of 250 ml of ethanol and 130 ml of water, whereby 60 g of the 3-amino-4-nitro-4'-hydroxy-diphenyl ether melting at 196° C were obtained.

60 g of the nitro-compound so obtained were hydrogenated in 400 ml of dimethylformamide with Raney nickel at a hydrogen pressure of 50 atmospheres gauge and room temperature. The catalyst was removed by filtration with suction and the filtrate was concentrated under reduced pressure. The crude 3,4-diamino-4'-hydroxy-diphenyl ether was then further reacted without any purification.

EXAMPLES 38 and 39.

In a manner analogous to that described in Example 37, the following products were prepared:

38. From 3-amino-4-nitro-3'-methoxy-diphenyl ether (melting point 128° C) via the 3-amino-4-nitro-3'-hydroxy-diphenyl ether (oily) and 3,4-diamino-3'-hydroxy-diphenyl ether, the 5-(3-hydroxy-phenoxy)-benzimidazole-2-methylcarbamate melting at 197° C.

39. From 3-amino-4-nitro-2'-methoxy-diphenyl ether (melting point 130° C) via the 3-amino-4-nitro-2'-hydroxy-diphenyl ether (melting point 134° C) and 3,4-diamino-2'-hydroxy-diphenyl ether, the 5-(2-hydroxy-phenoxy)-benzimidazole-2-methyl-carbamate melting at 223° C.

EXAMPLE 40.

5-Phenylmercapto-benzimidazole-2-methyl-carbamate.

20.9 g of S-methyl-thiourea were reacted as described in Example 1 in 27 ml of water with 13.5 ml of chloroformic acid methyl ester, 45.7 ml of 25% sodium hydroxide solution, 27 ml of glacial acetic acid, 100 ml of water and 29 g of 3,4-diamino-diphenyl-thioether. After recrystallization from a mixture of glacial acetic acid and methanol, 14 g of 4-phenylmercapto-benzimidazole-2-methyl-carbamate melting at 233° C were obtained.

For preparing the 3,4-diamino-diphenyl-thioether used as starting material, 22 g of thiophenol were heated for 6 hours under reflux in 100 ml of dimethylformamide with 5-chloro-2-nitro-aniline in the presence of 30 g of anhydrous potassium carbonate. The whole was allowed to cool, 100 ml of water were added and the crude product was filtered off with suction. After recrystallization from isopropanol, 38 g of 3-amino-4-nitro-diphenyl-thioether melting at 112° C were obtained.

38 g of the 3-amino-4-nitro-diphenyl-thioether so obtained were added to a solution prepared by dissolving 180 g of crystal-water containing stannous chloride in 200 ml of glacial acetic acid and saturation with gaseous hydrochloric acid at room temperature. A precipitate separated after a short time. The solvent was then removed by distillation under reduced pressure and the residue was combined with ice and an excess of concentrated sodium hydroxide solution. The oil that had separated was taken up in ether. After evaporation of the ether, the 3,4-diamino-diphenyl-thioether remained behind in the form of an oil which was used in the reaction without any purification.

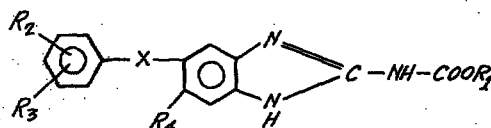


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WHAT WE CLAIM IS:—

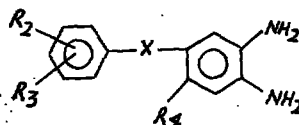
1 A 2-carbalkoxy-amino-benzimidazole-5(6)-phenyl ether of the formula



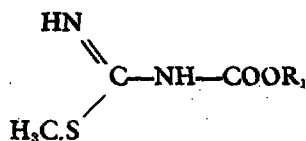
in which R₁ represents an alkyl group having from 1 to 4 atoms, R₂ and R₃, which may be the same or different, each represents a hydrogen atom, a hydroxyl group, an alkoxy group having from 1 to 4 carbon atoms, a halogen atom, a trifluoromethyl group, an alkyl group having from 1 to 4 carbon atoms or a carbalkoxy group having from 1 to 4 carbon atoms in the alkoxy group, R₄ represents a hydrogen or chlorine atom and X represents oxygen or sulfur.

2. A compound according to claim 1 and specifically mentioned herein.

3. A process for preparing a 2-carbalkoxy-amino-benzimidazole-5(6)-phenyl ether according to claim 1, which comprises condensing at a pH of from 1 to 6 an *o*-phenyl-diamine derivative of the formula



in which R₂, R₃, R₄ and X have the meanings specified in claim 1, with either
(a) an alkyl-S-methyl-thiourea-carboxylate of the formula



in which R₁ has the meaning specified in claim 1, or
(b) a cyanamide-carboxylate of the formula



in which R₁ has the meaning specified in claim 1.

4. A process according to claim 3, carried out substantially as described in any one of Examples 1 to 40 herein.

5. A compound according to claim 1 prepared by a process according to claim 3 or claim 4.

6. A pharmaceutical or veterinary composition comprising, as active ingredient, a 2-carbalkoxy-amino-benzimidazole-5(6)-phenyl ether according to claim 1 in admixture or conjunction with a pharmaceutically suitable carrier.

7. A method for combating helminths which comprises administering to an infested organism other than a human being an effective amount of a 2-carbalkoxy-amino-benzimidazole-5(6)-phenyl ether according to claim 1.

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