

PATENT SPECIFICATION

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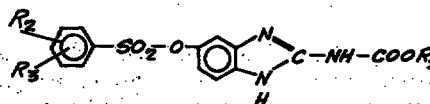
(54) ANTHELMINTICALLY ACTIVE 2-CARBALKOXYAMINO-5(6)-PHENYL SULFONYLOXY BENZIMIDAZOLES AND PROCESS FOR THEIR MANUFACTURE

(71) We, HOECHST AKTIENGESELLSCHAFT, a body corporate organised according to the laws of the Federal Republic 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 2-carbalkoxy-amino-5(6)-phenyl-sulfonyloxy benzimidazoles and to a process of their manufacture.

2-Carbalkoxy-amino-benzimidazolyl derivatives carrying alkyl, acyl, phenoxy and phenylthio groups in the 5(6)-position are known to possess anthelmintic properties (P. Actor et al., Nature 215, 321 (1967); German Offenlegungsschrift Nos. 2,029,637, 2,264,690 and 2,363,348).

The present invention provides anthelmintically active 2-carbalkoxyamino-5(6)-phenyl-sulfonyloxy benzimidazoles of the formula

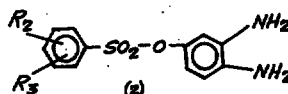


in which R₁ is an alkyl group having from 1 to 4 carbon atoms and each of R₂ and R₃ is a hydrogen atom, a hydroxy group, an alkoxy group having from 1 to 4 carbon atoms, a halogen atom, a trifluoromethyl group, an alkyl group having from 1 to 4 carbon atoms, a carbalkoxy group having from 1 to 4 carbon atoms in the alkoxy moiety, or a cyano group.

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

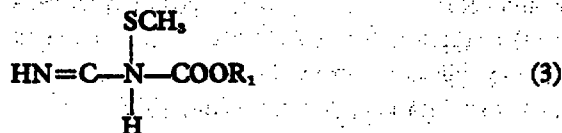
Especially preferred compounds of the formula (1) are those in which R₁ is a methyl, ethyl, propyl or butyl group, R₂ is a hydrogen or chlorine atom and R₃ is a hydrogen or chlorine atom or trifluoromethyl group.

The present invention also provides a process for the manufacture of the 2-carbalkoxyamino-5(6)-phenylsulfonyloxy benzimidazoles of the formula (1), which comprises condensing an *o*-phenylene diamine derivative of the formula



in which R₂ and R₃ have the meanings given above,

(a) with an alkyl-S-methyl-thiourea carboxylate of the formula



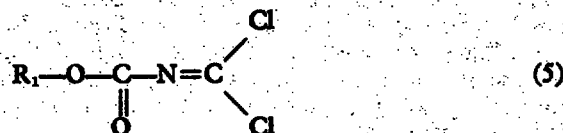
in which R_1 has the meaning given above, or

(b) with a cyanamide carboxylate of the formula



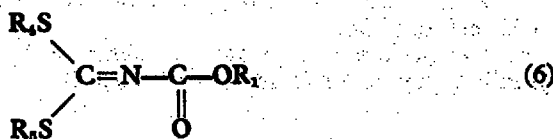
in which R_1 has the meaning given above, in both cases at a pH of from 1 to 6, preferably from 2 to 5, or

(c) with an N-dichloromethylene carbamic acid ester of the formula

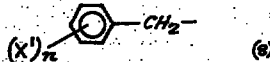


in which R_1 has the meaning given above, at a temperature of from -10° to $+40^\circ\text{C}$ in the presence of a base, or

(d) with a bis-alkyl or bis-aryl-thio-methylene-amino-formate of the formula

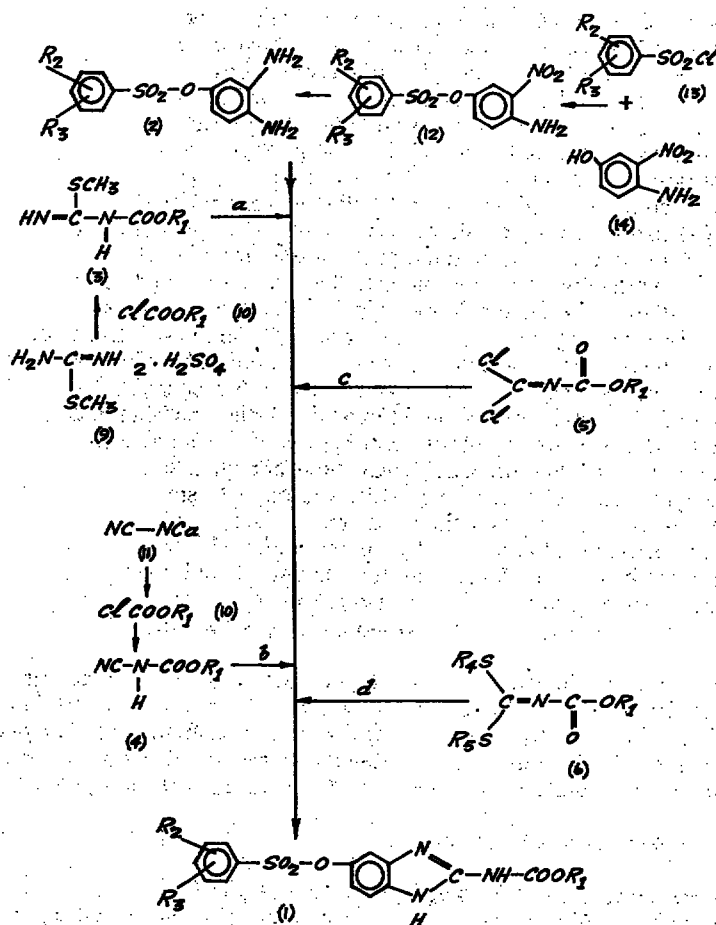


in which R_1 has the meaning given above, and each of R_4 and R_5 is an alkyl group having from 1 to 4 carbon atoms, an alkenyl group having from 3 to 5 carbon atoms, a cyclohexyl group, or an optionally substituted phenyl or benzyl group of the formula



in which each of X and X' is a halogen atom or a methyl or nitro group, or R_4 and R_5 may be linked to form a ring containing 2 or 3 methylene groups, and in which n is zero, 1 or 2.

The reactions may also be illustrated by the following reaction schemes:



According to the reaction (a), S-methyl-thiourea sulfate of the formula (9) is first mixed with a chloroformate of the formula (10), in water, and a strong base is then added dropwise, for example a 25% sodium hydroxide solution, while maintaining the temperature low, preferably at about 0°C. The alkyl-S-methyl-thiourea carboxylate of the formula (3) which is formed need not be isolated.

As chloroformates of the formula (10), there may be mentioned, for example,

methyl chloroformate,
ethyl chloroformate,
propyl chloroformate,
isopropyl chloroformate,
butyl chloroformate,
isobutyl chloroformate,
tert.butyl chloroformate.

The pH of the above reaction mixture is then advantageously adjusted to from 2 to 5, suitably by adding an organic acid, such as acid or lactic acid. The o-phenylene diamine derivative of the formula (2) is then added, either in the form of a free base or of an acid addition salt, for example the hydrochloride. In this latter case, it may be advantageous to add an alkali metal salt of an organic acid as a buffer.

As o-phenylene diamine derivatives of the formula (2), there are mentioned, for example,

benzene sulfonic acid-3,4-diamino-phenyl ester
4-Chloro-benzene sulfonic acid-3,4-diamino-phenyl ester
3-chloro-benzene sulfonic acid-3,4-diamino-phenyl ester
2-chloro-benzene sulfonic acid-3,4-diamino-phenyl ester
2,5-dichloro-benzene sulfonic acid-3,4-diamino-phenyl ester
3,5-dichloro-benzene sulfonic acid-3,4-diamino-phenyl ester

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	4-bromo-benzene sulfonic acid-3,4-diamino-phenyl ester	
	3-bromo-benzene sulfonic acid-3,4-diamino-phenyl ester	
	2-bromo-benzene sulfonic acid-3,4-diamino-phenyl ester	
	4-methyl-benzene sulfonic acid-3,4-diamino-phenyl ester	
5	3-methyl-benzene sulfonic acid-3,4-diamino-phenyl ester	5
	2-methyl-benzene sulfonic acid-3,4-diamino-phenyl ester	
	4-tert.butyl-benzene sulfonic acid-3,4-diamino-phenyl ester	
	2,4-dimethyl-benzene sulfonic acid-3,4-diamino-phenyl ester	
10	2-chloro-4-methyl-benzene sulfonic acid-3,4-diamino-phenyl ester	10
	2-chloro-6-methyl-benzene sulfonic acid-3,4-diamino-phenyl ester	
	3-chloro-4-methyl-benzene sulfonic acid-3,4-diamino-phenyl ester	
	3-chloro-6-methyl-benzene sulfonic acid-3,4-diamino-phenyl ester	
	3-chloro-4-carbethoxy-benzene sulfonic acid-3,4-diamino-phenyl ester	
15	4-chloro-2-methyl-benzene sulfonic acid-3,4-diamino-phenyl ester	15
	4-chloro-3-methyl-benzene sulfonic acid-3,4-diamino-phenyl ester	
	4-chloro-3,5-dimethyl-benzene sulfonic acid-3,4-diamino-phenyl ester	
	3-trifluoromethyl-benzene sulfonic acid-3,4-diamino-phenyl ester	
	4-methoxy-benzene sulfonic acid-3,4-diamino-phenyl ester	
20	3-methoxybenzene sulfonic acid-3,4-diamino-phenyl ester	20
	2-methoxy-benzene sulfonic acid-3,4-diamino-phenyl ester	
	4-propoxy-benzene sulfonic acid-3,4-diamino-phenyl ester	
	4-isopropoxy-benzene sulfonic acid-3,4-diamino-phenyl ester	
	4-butoxy-benzene sulfonic acid-3,4-diamino-phenyl ester	
	4-isobutoxy-benzene sulfonic acid-3,4-diamino-phenyl ester.	

25 The reaction components are advantageously allowed to react at a temperature of from 30 to 100°C for a period of from 30 minutes to 10 hours. Methyl mercaptan is set free as a by-product. The 2-carbalkoxyamino-5(6)-phenyl-sulfonyloxy benzimidazoles of the formula (1) are isolated in the usual manner, for example by
30 diluting the reaction mixture with water and separating the precipitated product by filtration.

In this manner, there are obtained

	2-carbomethoxyamino-5(6)-phenylsulfonyloxy-benzimidazole	
	2-carbomethoxyamino-5(6)-(4-chloro-phenylsulfonyloxy)-benzimidazole	
	2-carbomethoxyamino-5(6)-(3-chloro-phenylsulfonyloxy)-benzimidazole	
35	2-carbomethoxyamino-5(6)-(2-chloro-phenylsulfonyloxy)-benzimidazole	35
	2-carbomethoxyamino-5(6)-(2,5-dichloro-phenylsulfonyloxy)-benzimidazole	
	2-carbomethoxyamino-5(6)-(3,5-dichloro-phenylsulfonyloxy)-benzimidazole	
	2-carbomethoxyamino-5(6)-(4-bromo-phenylsulfonyloxy)-benzimidazole	
	2-carbomethoxyamino-5(6)-(3-bromo-phenylsulfonyloxy)-benzimidazole	
40	2-carbomethoxyamino-5(6)-(2-bromo-phenylsulfonyloxy)-benzimidazole	40
	2-carbomethoxyamino-5(6)-(4-methyl-phenylsulfonyloxy)-benzimidazole	
	2-carbomethoxyamino-5(6)-(3-methyl-phenylsulfonyloxy)-benzimidazole	
	2-carbomethoxyamino-5(6)-(2-methyl-phenylsulfonyloxy)-benzimidazole	
	2-carbomethoxyamino-5(6)-(4-tert.butyl-phenylsulfonyloxy)-benzimidazole	
45	2-carbomethoxyamino-5(6)-(2-chloro-4-methyl-phenylsulfonyloxy)-benzimidazole	45
	2-carbomethoxyamino-5(6)-(2-chloro-6-methyl-phenylsulfonyloxy)-benzimidazole	
	2-carbomethoxyamino-5(6)-(3-chloro-4-methyl-phenylsulfonyloxy)-benzimidazole	
	2-carbomethoxyamino-5(6)-(3-chloro-6-methyl-phenylsulfonyloxy)-benzimidazole	
50	2-carbomethoxyamino-5(6)-(3-chloro-4-carbethoxy-phenylsulfonyloxy)-benzimidazole	50
	2-carbomethoxyamino-5(6)-(4-chloro-2-methyl-phenylsulfonyloxy)-benzimidazole	
	2-carbomethoxyamino-5(6)-(4-chloro-3-methyl-phenylsulfonyloxy)-benzimidazole	
	2-carbomethoxyamino-5(6)-(4-chloro-3,5-dimethyl-phenylsulfonyloxy)-benzimidazole	
55	2-carbomethoxyamino-5(6)-(3-trifluoromethyl-phenylsulfonyloxy)-benzimidazole	55
	2-carbomethoxyamino-5(6)-(4-methoxy-phenylsulfonyloxy)-benzimidazole	
	2-carbomethoxyamino-5(6)-(3-methoxy-phenylsulfonyloxy)-benzimidazole	
	2-carbomethoxyamino-5(6)-(2-methoxy-phenylsulfonyloxy)-benzimidazole	
	2-carbomethoxyamino-5(6)-(4-propoxy-phenylsulfonyloxy)-benzimidazole	
60	2-carbomethoxyamino-5(6)-(4-isopropoxy-phenylsulfonyloxy)-benzimidazole	60
	2-carbomethoxyamino-5(6)-(4-butoxy-phenylsulfonyloxy)-benzimidazole	
	2-carbomethoxyamino-5(6)-(4-isobutoxy-phenylsulfonyloxy)-benzimidazole	
	2-carbethoxyamino-5(6)-phenylsulfonyloxy-benzimidazole	

2-carbopropoxyamino-5(6)-phenylsulfonyloxy-benzimidazole
 2-carbisopropoxyamino-5(6)-phenylsulfonyloxy-benzimidazole
 2-carbobutoxyamino-5(6)-phenylsulfonyloxy-benzimidazole
 2-carbisobutoxyamino-5(6)-phenylsulfonyloxy-benzimidazole
 2-carbotert.butoxyamino-5(6)-phenylsulfonyloxy-benzimidazole.

According to reaction (b), a chloroformate of the formula (10), as used for method (a), is first added to an aqueous suspension of cyanamide in the form of a salt, advantageously the calcium salt of the formula (11), while maintaining the temperature between 40 and 60°C by cooling.

After filtration of dark-coloured by-products which separate, the cyanamide carboxylate of the formula (4) is obtained in the filtrate.

The cyanamide carboxylate of the formula (4) thus obtained is combined with an *o*-phenylene diamine derivative of the formula (2), and the pH of the mixture is adjusted to between 1 to 6, preferably 2 to 4, by adding a mineral acid, for example concentrated hydrochloric acid. To complete the reaction, the reaction mixture is advantageously maintained at a temperature of from 30 to 100°C for a period of 30 minutes to 10 hours, depending on the reactivity of the *o*-phenylene diamine derivative used. After the reaction mixture has been cooled, the precipitated reaction product of the formula (1) is isolated by filtration and washing.

The *o*-phenylene diamine derivative of the formula (2) may be used either in the form of a free amine in the manner mentioned above with an alkyl-S-methyl thiourea carboxylate of the formula (3) or in the form of an acid addition salt with a suitable inorganic or organic acid, such as hydrochloric acid, sulfuric acid, acetic acid or oxalic acid.

According to the reaction (c), 1 mol of an *o*-phenylenediamine derivative of the formula (2) is suitably reacted with 1 mol of an N-dichloromethylene carbamic acid ester of the formula (5) in the presence of 2 mols of a base.

As bases, there may be mentioned alkali metal or alkaline earth metal hydroxides, carbonates and hydrogenocarbonates, or tertiary organic bases, for example sodium hydroxide, sodium bicarbonate, sodium carbonate, potassium carbonate, potassium bicarbonate, triethylamine, pyridine and methylated pyridines.

The N-dichloromethylene carbamic acid esters of the formula (5) may be prepared according to the method described in German Offenlegungsschrift No. 1,932,297 by reacting dichloromethylene carbamic acid chloride with an alcohol in the presence of an inert organic solvent such as ether, dioxan, tetrahydrofuran, benzene or toluene, at a temperature of from 0° to 40°C.

As examples of N-dichloromethylene carbamic acid esters of the formula (5), there may be mentioned N-dichloromethylene carbamic acid methyl ester, as well as the ethyl ester, isopropyl ester, propyl ester, n-butyl ester and sec.-butyl ester.

The reaction temperatures may be varied greatly, generally from -10° to +60°C, preferably from 0° to 30°C.

According to the reaction (d), 1 mol of the *o*-phenylene diamine derivative of the formula (2) is advantageously reacted with 1 mol of bis-alkyl or bis-aryl-thiomethylene-amino formate of the formula (6) in an inert solvent, such as tetrahydrofuran, dioxan, isopropyl ether or chloroform, at an elevated temperature, advantageously at the boiling temperature of the solvent used.

According to the present invention, it is also possible to prepare the bis-alkyl or bis-aryl-thiomethylene-amino-formate of the formula (6) in situ from the hydrochloride of imino-thiocarbonic acid ester by adding a chloroformate of the formula (10), as used for method (a).

In such a case, use must be made of an acid binder, for example an organic or inorganic base, such as sodium hydroxide, sodium bicarbonate or triethylamine. As reaction medium, polar and non polar solvents are suitable, for example ether, acetone, dioxan, water, dimethylformamide, benzene or cyclohexane. During this reaction, the temperature should advantageously not exceed 20°C.

The bis-alkyl and bis-aryl-thiomethylene-amino-formate may be obtained by reacting the corresponding dithio-imino-carbonic acid esters with chloroformates of the formula (10) according to the method described in U.S. Patent No. 3,562,290.

Examples of bis-alkyl or bis-aryl-thiomethylene-amino-formates are as follows:—

bis-methylthio-methylene-amino-formic acid-methyl ester,
 bis-methylthio-methylene-amino-formic acid-ethyl ester,
 bis-methylthio-methylene-amino-formic acid-propyl ester,

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bis-methylthio-methylene-amino-formic acid-isopropyl ester,
bis-methylthio-methylene-amino-formic acid-butyl ester,
bis-methylthio-methylene-amino-formic acid-sec.butyl ester,
bis-butylthio-methylene-amino-formic acid-methyl ester,
methylthio-butylthio-methylene-amino-formic acid-methyl ester,
allylthio-cyclohexylthio-methylene-amino-formic acid-methyl ester,
methylthio-phenylthio-methylene-amino-formic acid-methyl ester,
methylthio-(3,4-dichlor-benzyl-thio)methylene-amino-formic acid-methyl ester or
methylthio-(2-chloro-4-methylthio)-methylene-amino-formic acid methyl ester.

The o-phenylene diamine derivative of the formula (2) used as a starting material can be obtained by reduction of a corresponding amino-nitro derivative of the formula (12). The reduction may be carried out, for example by hydrogenation in the presence of Raney nickel and a solvent, such as methanol or dimethylformamide, at a temperature of from 20 to 60°C, or by a treatment with reducing agents, such as sodium dithionite.

The amino-nitro derivatives of the formula (12) can be obtained by reacting a benzene sulfonic acid chloride of the formula (13) with 3-nitro-4-amino-phenol of the formula (14), in an inert solvent in the presence of a base, such as triethylamine.

The 2-carbalkoxyamino-5(6)-phenyl-sulfonyloxy benzimidazoles of the invention are valuable chemitherapeutic agents and are suitable for combating diseases caused by parasites in both humans and other animals, such as helminths and liver flukes.

They are especially active against a great number of helminths, for example *Haemonchus*, *Trichostrongylus*, *Ostertagia*, *Strongyloides*, *Cooperia*, *Chabertia*, *Oesophagostomum*, *Hyostrongylus*, *Ankylostoma*, *Ascaris* and *Heterakis*. They are most active against gastro-intestinal Strongylides, which most especially infest ruminants. The infestation of animals by these parasites causes great economical damage, so that the compounds of the present invention are mainly used in veterinary drugs.

The present invention therefore also provides pharmaceutical compositions containing as active ingredient a compound of the formula (1) in admixture or conjunction with a pharmaceutically suitable carrier and a method for combating parasites which comprises administering to an infested non-human organism a compound of the formula (1).

The compound of the formula (1) can be administered in doses of from 0.5 to 50 mg per kg of body weight for 1 to 14 days, depending on the individual case.

For oral administration, there may be used tablets, dragees, capsules, powder, granules or pastes, which contain the active substance in conjunction with the usual excipients and adjuvants for example starch, cellulose powder, talcum, magnesium stearate, sugar, gelatin, calcium carbonate, finely divided silicic acid, carboxymethyl cellulose and similar substances.

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 an antioxidant and/or surface-active substances, such as sorbitane fatty acid esters. In addition, there can be used aqueous suspensions which are prepared using ethoxylated sorbitane fatty acid esters, optionally with the addition of thickeners, such as polyethylene glycol or carbomethyl cellulose.

The concentrations of the compounds of the present invention in the compositions are preferably in the range of from 2 to 20% by weight for veterinary drugs; 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 activity of the compounds of the present invention was determined with the aid of chemotherapeutic investigations made on lambs, each having a weight of about 30 kg, which had been infested for test purposes with larvae of *Haemonchus contortus* and *Trichostrongylus colubriformis* respectively. The test animals were kept in tiled boxes which were cleaned thoroughly every day. After the prepotence period (i.e. time between infestation and sexual maturity of the parasites, when secretion of eggs or larvae begins), the number of eggs per gram of excrement was determined by the modified McMaster method according to Wetzel (Tierärztliche Umschau, 6, 209—210 (1951)). Immediately after this, the treatment of the lambs was started (generally 4 to 8 animals, at least 2 animals, per active substance). The dosage units of the compounds of the invention were administered to the animals in the form of a suspension each in 10 ml of a 1% Tylose suspension ('Tylose' is a registered Trade Mark). On the 7th, 14th and 28th day after this treatment, the number of eggs per gram of excrement was again determined according to the above

method, and the percentage decrease, compared to the initial value prior to the treatment, was calculated.

The products of the invention have an excellent activity not only when administered *per os* but also parenterally at doses as low as 2 mg/kg of body weight. Therefore, they are far superior to comparable benzimidazole derivatives, especially to all known 2-benzimidazolyl carbamates substituted in the 5(6)-position.

The following Examples illustrate the invention.

Process (a)

EXAMPLE 1

47.7 Grams of a 25% sodium hydroxide solution were added dropwise while cooling with ice at a temperature not exceeding 10°C to a thoroughly stirred mixture of 22.2 g of S-methyl-thiourea sulfate in 35 ml of water and 10.2 ml of methylchloroformate. Stirring was continued for half an hour, and then a mixture of 17 ml of glacial acetic acid and 100 ml of water was added.

Subsequently, 15.8 g of benzene sulfonic acid 3,4-diaminophenyl ester dissolved in 100 ml of isopropanol were added, and the mixture was refluxed for 2 hours, whereupon a solid began to precipitate after a short time. The solid was suction-filtered, carefully washed with methanol and then with water. The crude product was purified by recrystallizing it twice from glacial acetic acid/methanol. The yield of pure 2-carbomethoxyamino-5(6)-phenyl-sulfonyloxy benzimidazole was 9.6 g, and this compound had a decomposition point of 242°C.

The benzene-sulfonic acid 3,4-diamino phenyl ester was prepared by hydrogenating 17.5 g of benzene sulfonic acid 3-nitro-4-amino phenyl ester in 200 ml of dimethylformamide with a special nickel catalyst (Ruhr-catalyst) at room temperature under an excess pressure of 50 atmospheres of hydrogen. The catalyst was then separated by filtration and the solvent was removed in vacuo. The residue consisted of benzene sulfonic acid 3,4-diamino phenyl ester and was used directly for ring closure without further purification.

To prepare the benzene sulfonic acid 3-nitro-4-amino-phenyl ester, 15.4 g of 3-nitro-4-amino-phenol in 100 ml of acetone were mixed with 14 ml of triethylamine, and a solution of 17.6 g of benzene sulfonic acid chloride in 30 ml of acetone was added dropwise while stirring at a temperature not exceeding an internal temperature of 20°C in an ice bath. Stirring was continued for 3 hours at room temperature, the triethylamine hydrochloride was separated by suction-filtration and the filtrate was evaporated to dryness. The product was stirred with 50 ml of methanol and suction-filtered. Washing with methanol and drying resulted in 18.2 g of benzene sulfonic acid 3-nitro-4-amino phenyl ester, m.p. 140°C.

In an analogous manner, the following compounds were prepared from correspondingly modified starting materials:

- 2) Via 4-chloro-benzenesulfonic acid-3-nitro-4-amino-phenyl ester, (m.p. 137°C) and 4-chloro-benzenesulfonic acid-3,4-diamino-phenyl ester, the 2-carbomethoxyamino-5(6)-(4-chloro)-phenylsulfonyloxy-benzimidazole, m.p. 230°C (decomp.).
- 3) Via 3-chloro-benzenesulfonic acid-3-nitro-4-amino-phenyl ester, (m.p. 154°C) and 3-chloro-benzenesulfonic acid-3,4-diamino-phenyl ester, the 2-carbomethoxyamino-5(6)-(3-chloro-phenylsulfonyloxy)-benzimidazole, m.p. 250°C, (decomp.).
- 4) Via 2-chloro-benzenesulfonic acid-3-nitro-4-amino-phenyl ester and 2-chloro-benzenesulfonic acid-3(4-diamino-phenyl ester, the 2-carbomethoxyamino-5(6)-(2-chloro-phenylsulfonyloxy)-benzimidazole.
- 5) Via 2,5-dichloro-benzenesulfonic acid-3-nitro-4-amino-phenyl ester and 2,5-dichloro-benzenesulfonic acid-3,4-diamino-phenyl ester the 2-carbomethoxyamine-5(6)-(2,5-dichloro-phenylsulfonyloxy)-benzimidazole.
- 6) Via 3,5-dichloro-benzenesulfonic acid-3-nitro-4-amino-phenyl ester, (m.p. 170°C) and 3,5-dichloro-benzenesulfonic acid-3,4-diamino-phenyl ester, the 2-carbomethoxyamino-5(6)-(3,5-dichloro-phenylsulfonyloxy)-benzimidazole, m.p. 280°C, (decomp.).

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- 7) Via 4-bromo-benzenesulfonic acid-3-nitro-4-amino-phenyl ester and 4-bromo-benzenesulfonic acid-3,4-diamino-phenyl ester, the 2-carbomethoxyamino-5(6)-(4-bromo-phenylsulfonyloxy)-benzimidazole.
- 5 8) Via 3-bromo-benzenesulfonic acid-3-nitro-4-amino-phenyl ester, (m.p. 158°C) and 3-bromo-benzenesulfonic acid-3,4-diamino-phenyl ester, the 2-carbomethoxyamino-5(6)-(3-bromo-phenylsulfonyloxy)-benzimidazole, m.p. 242°C, decomp. 5
- 10 9) Via 2-bromo-benzenesulfonic acid-3-nitro-4-amino-phenyl ester and 2-bromo-benzenesulfonic acid-3,4-diamino-phenyl ester, the 2-carbomethoxyamino-5(6)-(2-bromo-phenylsulfonyloxy)-benzimidazole. 10
- 10) Via 4-methyl-benzenesulfonic acid-3-nitro-4-amino-phenyl ester, (m.p. 149°C) and 4-methyl-benzenesulfonic acid-3,4-diamino-phenyl ester, the 2-carbomethoxyamino-5(6)-(4-methyl-phenylsulfonyloxy)-benzimidazole, m.p. 237°C, (decomp.).
- 15 11) Via 3-methyl-benzenesulfonic acid-3-nitro-4-amino-phenyl ester, (m.p. 142°C) and 3-methyl-benzenesulfonic acid-3,4-diamino-phenyl ester, the 2-carbomethoxyamino-5(6)-(3-methyl-phenylsulfonyloxy)-benzimidazole, m.p. 250°C, (decomp.). 15
- 20 12) Via 2-methyl-benzenesulfonic acid-3-nitro-4-amino-phenyl ester and 2-methyl-benzenesulfonic acid-3,4-diamino-phenyl ester, the 2-carbomethoxyamino-5(6)-(2-methyl-phenylsulfonyloxy)-benzimidazole 20
- 13) Via 4-tert.butyl-benzenesulfonic acid-3-nitro-4-amino-phenyl ester and 4-tert.butyl-benzenesulfonic acid-3,4-diamino-phenyl ester, the 2-carbomethoxyamino-5(6)-(4-tert.butyl-phenylsulfonyloxy)-benzimidazole.
- 25 14) Via 2,4-dimethyl-benzenesulfonic acid-3-nitro-4-amino-phenyl ester and 2,4-dimethyl-benzenesulfonic acid-3,4-diamino-phenyl ester, the 2-carbomethoxyamino-5(6)-(2,4-dimethyl-phenylsulfonyloxy)-benzimidazole. 25
- 30 15) Via 2-chloro-4-methyl-benzenesulfonic acid-3-nitro-4-amino-phenyl ester and 2-chloro-4-methyl-benzenesulfonic acid-3,4-diamino-phenyl ester, the 2-carbomethoxyamino-5(6)-(2-chloro-4-methyl-phenylsulfonyloxy)-benzimidazole. 30
- 35 16) Via 2-chloro-6-methyl-benzenesulfonic acid-3-nitro-4-amino-phenyl ester and 2-chloro-6-methyl-benzenesulfonic acid-3,4-diamino-phenyl ester, the 2-carbomethoxyamino-5(6)-(2-chloro-6-methyl-phenylsulfonyloxy)-benzimidazole. 35
- 17) Via 3-chloro-4-methyl-benzenesulfonic acid-3-nitro-4-amino-phenyl ester and 3-chloro-4-methyl-benzenesulfonic acid-3,4-diamino-phenyl ester, the 2-carbomethoxyamino-5(6)-(3-chloro-4-methyl-phenylsulfonyloxy)-benzimidazole.
- 40 18) Via 3-chloro-6-methyl-benzenesulfonic acid-3-nitro-3-amino-phenyl ester and 3-chloro-6-methyl-benzenesulfonic acid-3,4-diamino-phenyl ester, the 2-carbomethoxyamino-5(6)-(3-chloro-6-methyl-phenylsulfonyloxy)-benzimidazole. 40
- 45 19) Via 4-chloro-2-methyl-benzenesulfonic acid-3-nitro-4-amino-phenyl ester and 4-chloro-2-methyl-benzenesulfonic acid-3,4-diamino-phenyl ester, the 2-carbomethoxyamino-5(6)-(4-chloro-2-methyl-phenylsulfonyloxy)-benzimidazole. 45
- 50 20) Via 4-chloro-3-methyl-benzenesulfonic acid-3-nitro-4-amino-phenyl ester and 4-chloro-3-methyl-benzenesulfonic acid-3,4-diamino-phenyl ester, the 2-carbomethoxyamino-5(6)-(4-chloro-3-methyl-phenylsulfonyloxy)-benzimidazole. 50

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- 21) Via 4-chloro-3,5-dimethyl-benzenesulfonic acid-3-nitro-4-amino-phenyl ester and 4-chloro-3,5-dimethyl-benzenesulfonic acid-3,4-diamino-phenyl ester, the 2-carbomethoxyamino-5(6)-(4-chloro-3,5-dimethyl-phenyl-sulfonyloxy)-benzimidazole.
- 5 22) Via 3-trifluoromethyl-benzenesulfonic acid-3-nitro-4-amino-phenyl ester, (m.p. 131°C) and 3-trifluoromethyl-benzenesulfonic acid-3,4-diamino-phenyl ester, the 2-carbomethoxyamino-5(6)-(3-trifluoromethyl-phenylsulfonyloxy)-benzimidazole, m.p. 215°C (decomp). 5
- 10 23) Via 4-methoxy-benzenesulfonic acid-3-nitro-4-amino-phenyl ester and 4-methoxy-benzenesulfonic acid-3,4-diamino-phenyl ester, the 2-carbomethoxyamino-5(6)-(4-methoxy-phenylsulfonyloxy)-benzimidazole. 10
- 15 24) Via 3-methoxy-benzenesulfonic acid-3-nitro-4-amino-phenyl ester and 3-methoxy-benzenesulfonic acid-3,4-diamino-phenyl ester, the 2-carbomethoxyamino-5(6)-(3-methoxy-phenylsulfonyloxy)-benzimidazole. 15
- 25 25) Via 2-methoxy-benzenesulfonic acid-3-nitro-4-amino-phenyl ester and 2-methoxy-benzenesulfonic acid-3,4-diamino-phenyl ester, and 2-carbomethoxyamino-5(6)-(2-methoxy-phenylsulfonyloxy)-benzimidazole.
- 20 26) Via 4-propoxy-benzenesulfonic acid-3-nitro-4-amino-phenyl ester and 4-propoxy-benzenesulfonic acid-3,4-diamino-phenyl ester, the 2-carbomethoxyamino-5(6)-(4-propoxy-phenylsulfonyloxy)-benzimidazole. 20
- 27) Via 4-isopropoxy-benzenesulfonic acid-3-nitro-4-amino-phenyl ester and 4-isopropoxy-benzenesulfonic acid-3,4-diamino-phenyl ester, the 2-carbomethoxyamino-5(6)-(4-isopropoxy-phenylsulfonyloxy)-benzimidazole.
- 25 28) Via 4-butoxy-benzenesulfonic acid-3-nitro-4-amino-phenyl ester and 4-butoxy-benzenesulfonic acid-3,4-diamino-phenyl ester, the 2-carbomethoxyamino-5(6)-(4-butoxy-phenylsulfonyloxy)-benzimidazole. 25
- 30 29) Via 4-isobutoxy-benzenesulfonic acid-3-nitro-4-amino-phenyl ester and 4-isobutoxy-benzenesulfonic acid-3,4-diamino-phenyl ester, the 2-carbomethoxyamino-5(6)-(4-isobutoxy-phenylsulfonyloxy)-benzimidazole. 30
- 30) Via 3-cyano-benzenesulfonic acid-3-nitro-4-amino-phenyl ester and 3-cyano-benzenesulfonic acid-3,4-diamino-phenyl ester, the 2-carbomethoxyamino-5(6)-(3-cyano-phenylsulfonyloxy)-benzimidazole.
- 35 31) Via benzenesulfonic acid-3-nitro-4-amino-phenyl ester and benzenesulfonic acid-3,4-diamino-phenyl ester, the 2-carbomethoxyamino-5(6)-phenylsulfonyloxy-benzimidazole. 35
- 32) Via benzenesulfonic acid-3-nitro-4-amino-phenyl ester and benzenesulfonic acid-3,4-diamino-phenyl ester, the 2-carbopropoxyamino-5(6)-phenylsulfonyloxy-benzimidazole.
- 40 33) Via benzenesulfonic acid-3-nitro-4-amino-phenyl ester and benzenesulfonic acid-3,4-diamino-phenyl ester, the 2-carboisopropoxyamino-5(6)-phenylsulfonyloxy-benzimidazole. 40
- 34) Via benzenesulfonic acid-3-nitro-4-amino-phenyl ester and benzenesulfonic acid-3,4-diamino-phenyl ester, the 2-carbobutoxyamino-5(6)-phenylsulfonyloxy-benzimidazole. 45
- 35) Via benzenesulfonic acid-3-nitro-4-amino-phenyl ester and benzenesulfonic acid-3,4-diamino-phenyl ester, the 2-carboisobutoxyamino-5(6)-phenylsulfonyloxy-benzimidazole.
- 50 36) Via benzenesulfonic acid-3-nitro-4-amino-phenyl ester and benzenesulfonic acid-3,4-diamino-phenyl ester, the 2-carbotert.butoxyamino-5(6)-phenylsulfonyloxy-benzimidazole. 50

37) Via 3,4-dichloro-benzenesulfonic acid-3-nitro-4-amino-phenyl ester, m.p. 149°C and 3,4-dichloro-benzenesulfonic acid-3,4-diamino-phenyl ester the 2-carbomethoxyamino-5(6)-(3,4-dichloro-phenylsulfonyloxy)-benzimidazole, m.p. 255° (decomposition).

38) Via 3-trifluoromethyl-benzenesulfonic acid-3-nitro-4-amino-phenyl ester, m.p. 131°C and 3-trifluoromethyl-benzenesulfonic acid-3,4-diamino-phenyl ester the 2-carbomethoxyamino-5(6)-(3-trifluoromethyl-phenylsulfonyloxy)-benzimidazole, m.p. 227°C (decomposition).

39) Via 3-trifluoromethyl-benzenesulfonic acid-3-nitro-4-amino ester, m.p. 131°C and 3-trifluoromethyl-benzenesulfonic acid-3,4-diamino-phenyl ester the 2-carbisopropoxyamino-5(6)-(3-trifluoromethyl-phenylsulfonyloxy)-benzimidazole, m.p. 205°C (decomposition).

40) Via 3-trifluoromethyl-benzenesulfonic acid-3-nitro-4-amino-phenyl ester, m.p. 131°C and 3-trifluoromethyl-benzenesulfonic acid-3,4-diamino-phenyl ester the 2-carbisobutoxyamino-5(6)-(3-trifluoromethyl-phenylsulfonyloxy)-benzimidazole, m.p. 243°C (decomposition).

Process (b)

EXAMPLE 41

To a solution of 42 g of cyanamide in 210 ml of water, 90 g of chloroformic acid methyl ester and 218 g of a 33% sodium hydroxide solution were added. The mixture was then stirred for 1.5 hours at 30–35°C, then a solution of 213 g of benzenesulfonic acid 3,4-diamino phenyl ester in 1 l of isopropanol was added, and the temperature was raised to 80°C. After addition of 200 ml of glacial acetic acid, the reaction mixture was maintained at 90°C for another 3 to 4 hours. It was then allowed to cool and stored overnight in a refrigerator. The precipitated 2-carbomethoxyamino-5(6)-phenylsulfonyloxy-benzimidazole was suction-filtered and washed with isopropanol and water. The crude product was purified by recrystallization from glacial acetic acid/methanol. Yield: 80 g, decomposition point: 242°C.

The benzenesulfonic acid 3,4-diamino phenyl ester was obtained as in Example 1 via the benzenesulfonic acid 3-nitro-4-amino phenyl ester which is likewise disclosed in Example 1.

In an analogous manner, the following compounds were prepared using the correspondingly modified starting compounds:

42) Via 3-trifluoromethyl-benzenesulfonic acid-3-nitro-4-amino-phenyl ester, m.p. 131°C and 3-trifluoromethyl-benzenesulfonic acid-3,4-diamino-phenyl ester the 2-carbomethoxyamino-5(6)-(3-trifluoromethyl-phenylsulfonyloxy)-benzimidazole, m.p. 215°C (decomposition).

43) Via 3-trifluoromethyl-benzenesulfonic acid-3-nitro-4-amino-phenyl ester, m.p. 131°C and 3-trifluoromethyl-benzenesulfonic acid-3,4-diamino-phenyl ester the 2-carbisopropoxyamino-5(6)-(3-trifluoromethyl-phenylsulfonyloxy)-benzimidazole, m.p. 205°C (decomposition).

44) Via 3-trifluoromethyl-benzenesulfonic acid-3-nitro-4-amino-phenyl ester, m.p. 131°C and 3-trifluoromethyl-benzenesulfonic acid-3,4-diamino-phenyl ester the 2-carbisobutoxyamino-5(6)-(3-trifluoromethyl-phenylsulfonyloxy)-benzimidazole, m.p. 243°C (decomposition).

Process (c)

EXAMPLE 45

26.4 Grams of benzenesulfonic acid 3,4-diamino phenyl ester, 20.2 g of triethylamine and 300 ml of chloroform were mixed, and a solution of 15.6 g of N-dichloromethylene carbamic acid methyl ester in 50 ml of chloroform was slowly added while stirring to this mixture at a temperature of at most 20°C. The reaction mixture was

stirred for another hour, the precipitate was suction-filtered and washed with chloroform.

For purification, the crude product was recrystallized in glacial acetic acid/methanol, and after suction-filtration it was washed and dried. The yield of 2-carbomethoxyamino-5(6)-phenylsulfonyloxy benzimidazole was 5 g, decomposition point: 242°C.

The benzenesulfonic acid 3,4-diamino-phenyl ester was obtained as in Example 1 from the benzenesulfonic acid 3-nitro-4-amino-phenyl ester which is also disclosed in Example 1.

In an analogous manner, the following compounds were prepared using the correspondingly modified starting materials:

46) Via 3-trifluoromethyl-benzenesulfonic acid-3-nitro-4-amino-phenyl ester, m.p. 131°C

and 3-trifluoromethyl-benzenesulfonic acid-3,4-diamino-phenyl ester
the 2-carbomethoxyamino-5(6)-(3-trifluoromethyl-phenylsulfonyloxy)-
benzimidazole, m.p. 215°C (decomposition).

47) Via 3-trifluoromethyl-benzenesulfonic acid-3-nitro-4-amino-phenyl ester, m.p. 131°C

and 3-trifluoromethyl-benzenesulfonic acid-3,4-diamino-phenyl ester
the 2-carbisopropoxyamino-5(6)-(3-trifluoromethyl-phenylsulfonyloxy)-
benzimidazole, m.p. 205°C (decomposition).

48) Via 3-trifluoromethyl-benzenesulfonic acid-3-nitro-4-amino-phenyl ester, m.p. 131°C

and 3-trifluoromethyl-benzenesulfonic acid-3,4-diamino-phenyl ester
the 2-carbisobutoxyamino-5(6)-(3-trifluoromethyl-phenylsulfonyloxy)-
benzimidazole, m.p. 243°C (decomposition).

Process (d)

EXAMPLE 49

17.9 Grams of bis-methylthio-methylene aminoformic acid methyl ester were added to 26.4 g of benzenesulfonic acid 3,4-diamino-phenyl ester in 200 ml of tetrahydrofuran, and the mixture was refluxed for 4 hours. It was then allowed to cool and the precipitated 2-carbomethoxyamino-5(6)-phenylsulfonyloxy-benzimidazole was suction-filtered and purified by recrystallization from glacial acetic acid/methanol. Yield: 12 g, decomposition point: 242°C.

The reaction product was identical with the product obtained according to Example 1.

The benzenesulfonic acid 3,4-diamino phenyl ester was obtained as in Example 1 from the benzenesulfonic acid 3-nitro-4-amino-phenyl ester which is likewise disclosed in Example 1.

EXAMPLE 50

To a cooled solution of 19.7 g of imino-dithiocarbonic acid methyl ester hydrochloride and 12.5 g of chloroformic acid methyl ester in 50 ml of water, a 10% sodium hydroxide solution was added dropwise while taking care that the temperature did not exceed 10°C. As soon as the pH-value had adjusted to 7.5, 26.4 g of benzenesulfonic acid 3,4-diamino phenyl ester in 50 ml of glacial acetic acid were added, and the mixture was refluxed for 2 hours while stirring. It was then allowed to cool, and the 2-carbomethoxyamino-5(6)-phenyl-sulfonyloxy-benzimidazole formed was suction-filtered. It was identical in its properties with the reaction product disclosed in Example 49.

In an analogous manner, the following compounds were prepared using correspondingly modified starting materials:

51) Via 3-trifluoromethyl-benzenesulfonic acid-3-nitro-4-amino-phenyl ester, m.p. 131°C

and 3-trifluoromethyl-benzenesulfonic acid-3,4-diamino-phenyl ester
the 2-carbomethoxyamino-5(6)-(3-trifluoromethyl-phenylsulfonyloxy)-
benzimidazole, m.p. 215°C (decomposition).

52) Via 3-trifluoromethyl-benzenesulfonic acid-3-nitro-4-amino-phenyl ester, m.p. 131°C

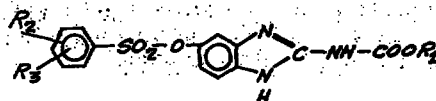
and 3-trifluoromethyl-benzenesulfonic acid-3,4-diamino-phenyl ester
the 2-carbisopropoxyamino-5(6)-(3-trifluoromethyl-phenyl-sulfonyloxy)-
benzimidazole, m.p. 205°C (decomposition).

53) Via 3-trifluoromethyl-benzenesulfonic acid-3-nitro-4-amino-phenyl ester, m.p. 131°C

and 3-trifluoromethyl-benzenesulfonic acid-3,4-diamino-phenyl ester
the 2-carbisobutoxyamino-5(6)-(3-trifluoromethyl-phenylsulfonyloxy)-
benzimidazole, m.p. 243°C (decomposition).

WHAT WE CLAIM IS:—

1. A 2-carbalkoxyamino-5(6)-phenylsulfonyloxy benzimidazole of the formula

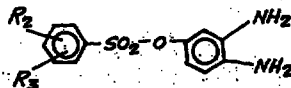


in which R₁ is an alkyl group having from 1 to 4 carbon atoms, and each of R₂ and R₃ is a hydrogen atom, a hydroxy group, an alkoxy group having from 1 to 4 carbon atoms, a halogen atom, a trifluoromethyl group, an alkyl group having from 1 to 4 carbon atoms, a carbalkoxy group having 1 to 4 carbon atoms in the alkoxy moiety, or a cyano group.

2. A compound as claimed in claim 1, in which R₁ is an alkyl group having from 1 to 4 carbon atoms, R₂ is a hydrogen atom and R₃ is a trifluoromethyl group.

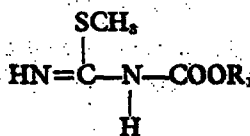
3. A compound as claimed in claim 1, in which R₁ is a methyl group, R₂ is a hydrogen atom and R₃ is a trifluoromethyl group.

4. A process for the manufacture of a compound as claimed in claim 1, which comprises condensing an *o*-phenylene diamine derivative of the formula



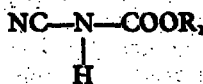
in which R₂ and R₃ have the meanings specified in claim 1,

(a) with an alkyl-S-methyl-thiourea carboxylate of the formula



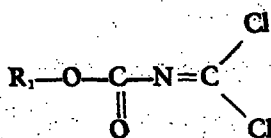
in which R₁ has the meaning specified in claim 1, or

(b) with a cyanamide carboxylate of the formula



in which R₁ has the meaning specified in claim 1, in both cases at a pH of from 1 to 6, or

(c) with an N-dichloromethylene carbamic acid ester of the formula



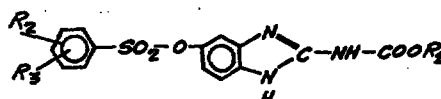
in which R₁ has the meaning specified in claim 1, or

52) Via 3-trifluoromethyl-benzenesulfonic acid-3-nitro-4-amino-phenyl ester, m.p. 131°C
and 3-trifluoromethyl-benzenesulfonic acid-3,4-diamino-phenyl ester
the 2-carbisopropoxyamino-5(6)-(3-trifluoromethyl-phenyl-sulfonyloxy)-
benzimidazole, m.p. 205°C (decomposition).

53) Via 3-trifluoromethyl-benzenesulfonic acid-3-nitro-4-amino-phenyl ester, m.p. 131°C
and 3-trifluoromethyl-benzenesulfonic acid-3,4-diamino-phenyl ester
the 2-carbisobutoxyamino-5(6)-(3-trifluoromethyl-phenylsulfonyloxy)-
benzimidazole, m.p. 243°C (decomposition).

WHAT WE CLAIM IS:—

1. A 2-carbalkoxyamino-5(6)-phenylsulfonyloxy benzimidazole of the formula

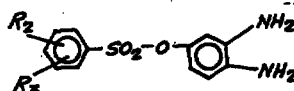


in which R₁ is an alkyl group having from 1 to 4 carbon atoms, and each of R₂ and R₃ is a hydrogen atom, a hydroxy group, an alkoxy group having from 1 to 4 carbon atoms, a halogen atom, a trifluoromethyl group, an alkyl group having from 1 to 4 carbon atoms, a carbalkoxy group having 1 to 4 carbon atoms in the alkoxy moiety, or a cyano group.

2. A compound as claimed in claim 1, in which R₁ is an alkyl group having from 1 to 4 carbon atoms, R₂ is a hydrogen atom and R₃ is a trifluoromethyl group.

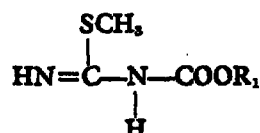
3. A compound as claimed in claim 1, in which R₁ is a methyl group, R₂ is a hydrogen atom and R₃ is a trifluoromethyl group.

4. A process for the manufacture of a compound as claimed in claim 1, which comprises condensing an *o*-phenylene diamine derivative of the formula



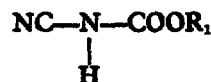
in which R₂ and R₃ have the meanings specified in claim 1,

(a) with an alkyl-S-methyl-thiourea carboxylate of the formula



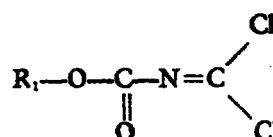
in which R₁ has the meaning specified in claim 1, or

(b) with a cyanamide carboxylate of the formula



in which R₁ has the meaning specified in claim 1, in both cases at a pH of from 1 to 6, or

(c) with an N-dichloromethylene carbamic acid ester of the formula

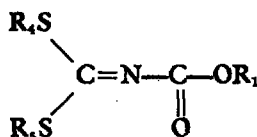


in which R₁ has the meaning specified in claim 1, or



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(d) with a bis-alkyl or bis-aryl-thiomethylene-amino-formate of the formula



5 in which R_1 has the meaning specified in claim 1, and each of R_4 and R_5 is an alkyl group having from 1 to 4 carbon atoms, an alkenyl group having from 3 to 5 carbon atoms, a cyclohexyl group or an optionally substituted phenyl or benzyl group of the formula



10 in which each of X and X' is a halogen atom or a methyl or nitro group, or R_4 and R_5 may be linked to form a ring containing 2 or 3 methylene groups, and in which n is zero, 1 or 2.

5. A process as claimed in claim 4 carried out substantially as described in any one of the Examples herein.

6. A compound as claimed in claim 1 whenever prepared by a process as claimed in claim 4 or claim 5.

15 7. A pharmaceutical composition containing as active ingredient a compound as claimed in claim 1 in admixture or conjunction with a pharmaceutically suitable carrier.

8. A method for combating parasites which comprises administering to an infested non-human organism a compound as claimed in claim 1.

ABEL & IMRAY,
Chartered Patent Agents,
Northumberland House,
303—306 High Holborn,
London WC1V 7LH.

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