

PATENT SPECIFICATION

(11) 1428933

1428933

- (21) Application No. 28793/74 (22) Filed 28 June 1974
 (31) Convention Application No. 2334631 (32) Filed 7 July 1973 in
 (33) Germany (DT)
 (44) Complete Specification published 24 March 1976
 (51) INT CL² C07D 235/28 A61K 31/415
 (52) Index at acceptance

C2C 1416 213 220 22Y 250 252 25Y 30Y 313 31Y 338
 340 34Y 364 36Y 397 627 72Y 790 79Y RA



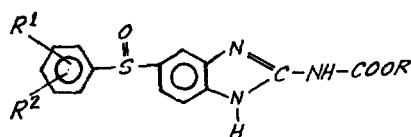
(54) 5-PHENYLSULPHINYL-2-BENZIMIDAZOLYL-CARBAMIC ACID ESTERS AND PROCESS FOR THEIR MANUFACTURE

(71) We, HOECHST AKTIENGESSELLSCHAFT, formerly known as Farbwerke Hoechst Aktiengesellschaft, vormals Meister Lucius & Brüning, 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 5 - phenylsulfinyl - 2 - benzimidazolyl - carbamic acid esters, to a process for their manufacture and to anthelmintic compositions containing them.

Benzimidazolyl carbamic acid alkyl esters carrying alkyl or acyl groups in the 5(6) position are known to possess anthelmintic properties (P. Actor et al, Nature 215, 321 (1967); DOS 2,029,637).

The present invention provides 5 - phenylsulfinyl - 2 - benzimidazolyl - carbamic acid alkyl esters of the formula

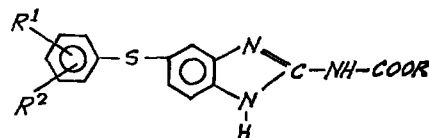


(1)

in which R is an alkyl group having from 1 to 4 carbon atoms, R¹ is a hydrogen, chlorine or bromine atom or an alkyl group having from 1 to 4 carbon atoms or a methoxy group, and R² is a hydrogen, chlorine or bromine atom or a methyl group. More particularly, the alkyl groups represented by R and R¹ may be methyl, ethyl, propyl, isopropyl, butyl, sec. - butyl, or tert. - butyl groups, preferably methyl or ethyl groups.

The present invention also provides a process for the manufacture of 5 - phenylsulfinyl - 2 - benzimidazolyl carbamic acid alkyl esters of formula (1), which comprises

oxidizing a phenylthio compound of the formula



(2)

in which R, R¹ and R² have the meanings given above, with an oxidizing agent.

As oxidizing agents, there are preferably used equivalent amounts of hydrogen peroxide in an organic acid, preferably glacial acetic acid, per-acids, for example peracetic acid, pertrifluoro - acetic acid and meta-chloroperbenzoic acid, or the salts of these acids; permanganates, hypochlorites, perchlorates, periodates and nitrogen oxides may also be used.

The reaction may advantageously be carried out by adding 30% hydrogen peroxide to a suspension of the phenylthio compound of the formula (2) in glacial acetic acid, and stirring this mixture at room temperature until a clear solution has formed. The reaction may, however, be carried out at an elevated temperature of up to about 70°C. The sulfoxide formed can be separated by adding water to the reaction solution. The separated precipitate can be isolated by filtration.

The corresponding phenylthio derivative used as starting material can be obtained by reacting 5 - phenylthio - o - phenylene diamine with S - methylthio - urea and an alkyl - chloroformate according to German Offenlegungsschrift No. 2,164,690.

The 5 - phenylsulfinyl - 2 - benzimidazolyl - carbamic acid alkyl esters of the present invention are valuable chemotherapeutic agents and are suitable for combating diseases caused by parasites in humans and animals. They are especially active against a great number of helminths, for example *Haemonchus*, *Trichostrongylus*, *Ostertagia*,

Strongyloides, *Cooperia*, *Chabertia*, *Oesophagostomum*, *Hyostrongylus*, *Ankylostoma*, *Ascaris* and *Heterakis*. Especially marked is the activity 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 also provides anthelmintically active compositions including a compound of the general formula (1) in admixture or conjunction with a carrier, suitably a pharmaceutically suitable carrier.

The compounds 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 substances in conjunction with the usual excipients and adjuvants, for example starch, cellulose powder, talcum, magnesium stearate, sugar, gelatin, calcium carbonate, finely divided silicic acid, carboxy-methyl 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 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 thickeners, such as polyethylene glycol or carboxymethyl cellulose.

The concentrations of the compounds of the present invention in the compositions prepared therewith 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 following Examples illustrate the invention.

EXAMPLE 1

5 - Phenylsulfinyl - 2 - benzimidazolyl - carbamic acid methyl ester

A mixture of 75 g of 5 - phenylthio - 2 - benzimidazolyl - carbamic acid methyl ester, 750 ml of glacial acetic acid and 250 ml of 30% hydrogen peroxide was stirred at room temperature until a clear solution had formed, which took about 2 hours.

Subsequently, 1.5 l of water were added, the solution was heated to 80°C for a short time and the precipitate was suction-filtered when cool. After washing and drying, 65 g of 5 - phenylsulfinyl - 2 - benzimidazolyl - carbamic acid methyl ester were obtained, melting point: 248°C (with decomposition).

In an analogous manner, there were prepared:

2. From 5 - phenylthio - 2 - benzimidazolyl - carbamic acid ethyl ester, the 5 - phenylsulfinyl - 2 - benzimidazolyl - carbamic acid ethyl ester, m.p. 230°C (decomposition);

3. from 5 - phenylthio - 2 - benzimidazolyl - carbamic acid isopropyl ester, the 5 - phenylsulfinyl - 2 - benzimidazolyl - carbamic acid isopropyl ester, m.p. 237°C (decomposition);

4. from 5 - phenylthio - 2 - benzimidazolyl - carbamic acid butyl ester, the 5 - phenylsulfinyl - 2 - benzimidazolyl - carbamic acid butyl ester, m.p. 225°C (decomposition);

5. from 5 - (3 - methyl - phenylthio) - 2 - benzimidazolyl - carbamic acid methyl ester, the 5 - (3 - methyl - phenylsulfinyl) - 2 - benzimidazolyl - carbamic acid methyl ester, m.p. 284°C (decomposition);

6. from 5 - (4 - methyl - phenylthio) - 2 - benzimidazolyl - carbamic acid methyl ester, the 5 - (4 - methyl - phenylsulfinyl) - 2 - benzimidazolyl - carbamic acid methyl ester, m.p. 285°C (decomposition);

7. from 5 - (4 - chloro - phenylthio) - 2 - benzimidazolyl - carbamic acid methyl ester, the 5 - (4 - chloro - phenylsulfinyl) - 2 - benzimidazolyl - carbamic acid methyl ester, m.p. 287°C (decomposition);

8. from 5 - (4 - chloro - phenylthio) - 2 - benzimidazolyl - carbamic acid isopropyl ester, the 5 - (4 - chloro - phenylsulfinyl) - 2 - benzimidazolyl - carbamic acid isopropyl ester, m.p. 301°C (decomposition);

9. from 5 - (4 - methoxy - phenylthio) - 2 - benzimidazolyl - carbamic acid methyl ester, the 5 - (4 - methoxy - phenylsulfinyl) - 2 - benzimidazolyl - carbamic acid methyl ester, m.p. 275°C (decomposition);

10. from 5 - (4 - methoxy - phenylthio) - 2 - benzimidazolyl - carbamic acid isopropyl ester, the 5 - (4 - methoxy - phenylsulfinyl) - 2 - benzimidazolyl - carbamic acid isopropyl ester, m.p. 227°C (decomposition);

11. from 5 - (2,5 - dichloro - phenylthio) - 2 - benzimidazolyl - carbamic acid methyl ester, the 5 - (2,5 - dichloro - phenylsulfinyl) - 2 - benzimidazolyl - carbamic acid methyl ester, m.p. 285°C (decomposition);

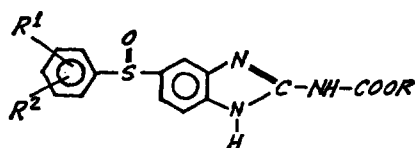
12. from 5 - (2,5 - dichloro - phenylthio) - 2 - benzimidazolyl - carbamic acid isopropyl ester, the 5 - (2,5 - dichloro - phenylsulfinyl) - 2 - benzimidazolyl - carbamic acid isopropyl ester, m.p. 265°C (decomposition);

13. from 5 - (2 - methyl - 5 - tert. - butyl - phenylthio) - 2 - benzimidazolyl - carbamic acid methyl ester, the 5 - (2 - methyl - 5 - tert. - butyl - phenylsulfinyl) - 2 - benzimidazolyl - carbamic acid methyl ester, m.p. 236°C (decomposition);

14. from 5 - (2 - methyl - 5 - tert. - butyl - phenylthio) - 2 - benzimidazolyl - carbamic acid isopropyl ester, the 5 - (2 - methyl - 5 - tert. - butyl - phenylsulfinyl) - 2 - benzimidazolyl - carbamic acid isopropyl ester, m.p. 241°C (decomposition) and
15. from 5 - (4 - tert. - butyl - phenylthio) - 2 - benzimidazolyl - carbamic acid methyl ester, the 5 - (4 - tert. - butyl - phenylsulfinyl) - 2 - benzimidazolyl - carbamic acid methyl ester, m.p. 240°C (decomposition).

WHAT WE CLAIM IS:—

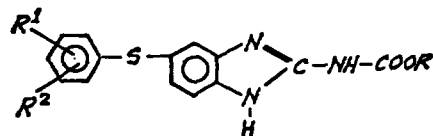
1. A 5 - phenylsulfinyl - 2 - benzimidazolyl - carbamic acid alkyl ester of the formula



- in which R is an alkyl group having from 1 to 4 carbon atoms, R¹ is a hydrogen, chlorine or bromine atom or an alkyl group having from 1 to 4 carbon atoms or a methoxy group, and R² is a hydrogen, chlorine or bromine atom or a methyl group.

2. A process for the manufacture of a 5 - phenylsulfinyl - 2 - benzimidazolyl - carbamic

acid alkyl ester according to claim 1 which comprises oxidizing a phenylthio derivative of the formula



in which R, R¹ and R² have the meanings specified in claim 1, with an oxidizing agent.

3. A process according to claim 2 carried out substantially as described in any one of Examples 1 to 15 herein.

4. A compound according to claim 1 whenever manufactured by a process according to claim 2 or claim 3.

5. An anthelmintically active composition including as active ingredient a compound according to claim 1 in admixture or conjunction with a carrier.

6. A method for combating helminth infestation in an animal other than a human, which comprises administering to the animal a compound according to claim 1 or a composition according to claim 5.

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

acid alkyl ester according to claim 1 which comprises oxidizing a phenylthio derivative of the formula

*c1ccc(cc1)S*2C=NC(=N2)C(=O)O*

in which R, R¹ and R² have the meanings 30
specified in claim 1, with an oxidizing agent.

3. A process according to claim 2 carried out substantially as described in any one of Examples 1 to 15 herein.

4. A compound according to claim 1 when-
ever manufactured by a process according to
claim 2 or claim 3.

c1ccc(cc1)S(=O)(=O)c2ccc3c(c2)n[nH]3C(=O)NCC(=O)O

5. An anthelmintically active composition including as active ingredient a compound according to claim 1 in admixture or conjunction with a carrier.

in which R is an alkyl group having from 1 to 4 carbon atoms, R' is a hydrogen, chlorine or bromine atom or an alkyl group having from 1 to 4 carbon atoms or a methoxy group, and R² is a hydrogen, chlorine or bromine atom or a methyl group.

6. A method for combating helminth infestation in an animal other than a human, which comprises administering to the animal a compound according to claim 1 or a composition according to claim 5. 45

25 2. A process for the manufacture of a 5 - phenylsulfinyl - 2 - benzimidazolyl - carbamic

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

Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1976.
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from
which copies may be obtained.



PATENTS ACT 1949

SPECIFICATION NO 1428933

Amendment is made in accordance with the Decision of the Principal Examiner acting for the Comptroller-General, dated the 8th day of February 1977 under Section 14 in the following manner:-

Reference has been directed in pursuance of Section 8 of the Patents Act 1949 to Patent No 1455728.

THE PATENT OFFICE
26 August 1977

Bas 41057/8