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ANTHELMINTIC COMPOSITIONS AND METHOD OF USING SAME

Horace D. Brown, Plainfield, and Lewis H. Sarett, Princeton, N.J., assignors to Merck & Co., Inc., Rahway, N.J., a corporation of New Jersey

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6 Claims. (Cl. 167—53)

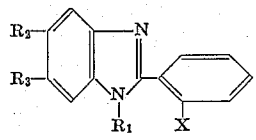
This invention relates to compounds useful against helminthiasis. It relates more particularly to new benzimidazoles. It relates further to anthelmintic compositions containing a 2-(o-halophenyl)benzimidazole as an active ingredient.

This application is a divisional of our co-pending application Serial No. 127,146, filed July 27, 1961, which latter application is a continuation-in-part of our applications Serial Nos. 39,754 and 39,761, filed June 30, 1960. Both of these latter two applications are now abandoned.

The infection known as helminthiasis involves infestation of the animal body and particularly the gastro-intestinal tract with various species of parasitic worms. It is a very widespread and serious disease, and the methods heretofore available for its treatment and prevention have not been entirely satisfactory. It is an object of this invention to provide a group of substituted benzimidazoles which are effective in controlling helminthiasis, and which lack many of the objectionable features of the known anthelmintics.

According to the present invention, it has been found that a group of benzimidazoles, having at the 2-position of the benzimidazole ring nucleus an o-halophenyl radical where the halogen has an atomic weight of between 19 and 35.5 inclusive, possess a significant degree of anthelmintic activity and may be effectively employed in the treatment and/or prevention of helminthiasis. It is one object of this invention to provide anthelmintic compositions containing such compounds. Another object is provision of a method of controlling helminthiasis with these substances. Still other objects will become apparent from the following description of the invention.

Compounds which, according to our invention, have been found to possess significant anthelmintic activity may be represented by the structural formula



(I)

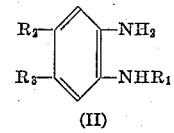
wherein R_1 can be hydrogen, lower alkyl or lower alkenyl groups, R_2 and R_3 may be either hydrogen, lower alkyl or lower alkoxy, and X is a halogen having an atomic weight of between 19 and 35.5 inclusive, i.e., fluorine or chlorine. The invention also includes within its scope acid addition salts of these benzimidazoles when R_1 is hydrogen.

The N–1 position of the benzimidazoles (R_1 in Formula I) as heretofore mentioned, may be substituted with hydrogen, a lower alkyl group such as methyl, ethyl, propyl or isopropyl, or a lower alkenyl radical of the type represented by allyl and methallyl. It is preferred that the alkyl and alkenyl radicals contain less than 6 carbon atoms. If desired, the six-membered ring of the benzimidazole nucleus may also be substituted with lower alkyl groups or lower alkoxy groups at the 5- and/or 6-positions. Where there are substituents on the six-membered ring of the benzimidazole nucleus, methyl or methoxy groups are the preferred substituents, although methyl, ethyl, propyl, methoxy, ethoxy and similar lower alkyl and lower alkoxy radicals, of course, may be employed. However, in the preferred compounds R_2 and R_3 of Formula I represent hydrogen.

As representative of the 2-substituted benzimidazole compounds which are now found to be active anthelmintic agents and which come within the scope of our invention, there may be mentioned: 2-(o-fluorophenyl)benzimidazole, 2-(o-chlorophenyl)benzimidazole, N-methyl 2-(o-fluorophenyl)benzimidazole, N-methyl 2-(o-chloropenyl)-5-methoxy benzimidazole, N-allyl 2-(o-fluorophenyl)-5-ethoxybenzimidazole, N-propyl 2-(o-fluorophenyl)benzimidazole, N-allyl 2-(o-chlorophenyl)benzimidazole, 2-(o-fluorophenyl)-5-methyl benzimidazole, 2-(o-chlorophenyl)-5-ethoxy benzimidazole, and the like.

The 2-substituted benzimidazoles described herein are isolated as the free bases by the synthetic processes normally employed. They are readily converted to acid addition salts by the treatment with acid. Typical salts which may be formed in this manner are mineral acid salts such as the hydrohalides, e.g., hydrochloride, hydrobromide, hydroiodide, sulfates, nitrates, phosphates, aliphatic acid salts such as the acetate, trimethylacetate, t-butylacetate, or propionate, salts of polycarboxylic acids such as the citrate, oxalate, succinate and the like and salts of other insoluble organic acids such as the embonate and hydroxynaphthoate salts. Certain of these salts are much more water soluble than the free bases. This is true of the hydrohalides. Since the solubility may also be decreased by formation of an appropriate salt, it will be seen that the solubility properties of a particular compound may be generally adjusted by judicious selection of a salt. When the compounds of this invention are used in salt form as anthelmintics, it is, of course, desirable that the particular acid employed be an edible, non-toxic one.

2-(o-fluorophenyl)benzimidazole and 2-(o-chlorophenyl)benzimidazole represent the preferred compounds of the invention. The preparation of these substances and the other 2-(o-fluorophenyl)benzimidazoles of Formula I above is carried out by reacting o-fluorobenzaldehyde or o-fluorobenzoic acid or a derivative of o-fluorobenzoic acid such as o-fluorobenzamide or lower alkyl o-fluorobenzoate with a compound of the general formula



(II)

wherein R_1 may be either hydrogen, lower alkyl or lower alkenyl, and R_2 and R_3 may be either hydrogen, lower alkyl or lower alkoxy.

Alternatively, the N-alkyl and N-alkenyl 2-(o-halophenyl)benzimidazoles may be obtained by alkylation or alkenylation of a 2-(o-halophenyl)benzimidazole. If desired, the six-membered ring of the benzimidazole nucleus may also be substituted as with lower alkyl or lower alkoxy groups at the 5- and/or 6-positions. An alkali metal salt of the 2-(o-halophenyl)benzimidazole is first prepared. This may be done by intimately contacting an alkali metal hydride such as sodium hydride, lithium hydride or potassium hydride with the 2-(o-halophenyl)benzimidazole. To form the N-alkyl or N-alkenyl derivatives, the alkali metal salt of the 2-(o-fluorophenyl)benzimidazole or 2-(o-chlorophenyl)benzimidazole is reacted with an alkylating agent such as methyl chloride, ethyl bromide, allyl chloride or cinnamyl

chloride, in a suitable solvent such as benzene and/or dimethyl formamide.

The 2 - (o - fluorophenyl)benzimidazoles and 2 - (o-chlorophenyl)benzimidazoles described herein have a high degree of anthelmintic activity and are useful in the treatment and/or prevention of helminthiasis, a parasitic disease which causes widespread and often serious infection in domesticated animals such as swine, horses, cattle, sheep and goats. In treating domesticated animals, the compounds may be mixed with a non-toxic, edible carrier to form a feed supplement which is then incorporated in the animal feed in the desired concentration, or they may be administered in unit dosage forms which, in the case of large domesticated animals, take the form of boluses, or in the form of a liquid drench. Alternatively, water-soluble salts or a dispersable, wettable powder containing the anthelmintic agent may be added to the drinking water of the animals.

The preferred dosage level for treating a helminth infection will depend to a large extent on the particular 2 - (o - halophenyl)benzimidazole compound being employed, on the severity of the infection and on the particular species of animal to be treated. In general, the 2-(o-chlorophenyl) and 2-(o - fluorophenyl)benzimidazoles exhibit anthelmintic activity when administered to animals in a daily dose of about 50 to about 300 mg. per kilogram of animal body weight. It is preferred to employ in the range of 100-200 mg. per kilogram of body weight per day. The compounds may be given in a single dose or divided into a plurality of smaller doses. With the compounds of this invention highly satisfactory results in freeing the animal of helminths are achieved by administering the compounds for only a single day at the above levels. If desired, the course of treatment may be extended over a period of days in which case the optimum daily dose level may be lowered. When the compounds are to be employed primarily as prophylactic agents for the prevention of helminthic infections, the preferred daily dose level is, of course, lower than the therapeutic level and is preferably in the range of about 10-70 mg. per kilogram of body weight. The 2-(o-chlorophenyl)benzimidazoles may be incorporated in the animal feeds, and this method of administration is preferred when the compounds are to be used prophylactically, in which case they are incorporated in the feeds at concentrations such that the animal will consume daily from about 10 to about 70 mg. of 2-(o-chlorophenyl)benzimidazole per kilogram of body weight.

The means employed for administering these benzimidazoles to animals are not critical, and any of the methods now used or available for treating animals infected with or susceptible to parasitic infections are satisfactory. When these substances are employed therapeutically to treat an established infection, they are conveniently administered in a unit dosage form such as in a capsule, bolus, tablet, or as a liquid drench. It will be noted that all of these methods contemplate oral administration, since this is the most effective method of treating the worm-infested stomach or intestinal tract.

When the 2-(o-chlorophenyl) or 2-(o-fluorophenyl) benzimidazoles are to be administered in unit dosage form, capsules, boluses or drenches containing the desired amount of anthelmintic distributed in a pharmaceutically acceptable vehicle are usually employed. These are prepared by intimately and uniformly mixing the active ingredient with suitable finely divided diluents, suspending agents, fillers, disintegrating agents and/or binders such as starch, lactose, talc, magnesium stearate, vegetable gums and the like. These unit dosage formulations may be widely varied with respect to their total weight and content of anthelmintic agent, depending on factors such as the type of host animal to be treated, the dose level desired, and the severity and type of parasitic infestation. For large animals, such as sheep, swine or cattle, boluses weighing up to 15 grams

may be used, although it is preferred to employ boluses weighing from 2-10 grams and containing from 1–5 grams of the anthelmintic agent. These boluses, as well as smaller size tablets, contain binders and lubricants, and are compounded by techniques known in this art. Capsules are readily prepared by mixing the active ingredients with a diluent such as starch or lactose and filling into the capsule.

In order to treat infected animals by means of a drench, the 2-(o-halophenyl)benzimidazoles are mixed with a suspending agent such as bentonite and the solid product added to water just prior to administration. Alternatively, ready-to-use drench formulations, such as those disclosed in U.S. Patent No. 2,918,403 are sometimes utilized. The preferred drenches in accordance with this invention contain from about 5–50% by weight of 2-(o-halophenyl)benzimidazole compound.

The 2-(o-halophenyl)benzimidazoles described herein may also be administered as a component of the feed of the animals or dissolved or suspended in the drinking water. According to the invention, novel feed and feed supplement compositions are provided in which compounds of Formula I above are present as an active anthelmintic ingredient. Such compositions comprise the benzimidazoles intimately dispersed in or admixed with an inert carrier or diluent, i.e., one that is non-reactive with respect to the 2-(o-halophenyl)benzimidazole and that may be administered with safety to the animals. The carrier or diluent is preferably one that is or may be an ingredient of the animal ration.

In the feed supplement compositions the active ingredient is present in relatively large amounts. These supplements are suitable for addition to the feed either directly or after an intermediate dilution or blending step. Examples of carriers or diluents suitable for such compositions are solid orally ingestible carriers such as distillers' dried grains, corn meal, citrus meal, fermentation residues, ground oyster shells, Attapulgus clay, wheat shorts, molasses solubles, corn cob meal, edible vegetable substances, toasted dehulled soya flour, soybean mill feed, antibiotic mycelia, soya grits, crushed limestone and the like. The anthelmintic agents are intimately dispersed or admixed through the solid inert carrier by methods such as grinding, stirring, milling, or tumbling. By selecting proper diluents and by altering the ratio of carrier to active ingredient, compositions of any desired concentration may be prepared. Formulations containing from about 5% to about 50% by weight, and preferably from about 10–30% by weight, of active ingredient are particularly suitable for addition to feeds. The active compound is normally dispersed or mixed uniformly in the diluent but in some instances may be sorbed on the carrier.

Examples of typical feed supplements containing the 2-(o-halophenyl)benzimidazole dispersed in a solid carrier are:

A.

	Lbs.
2-(o-chlorophenyl)benzimidazole	20.0
Corn distillers' dried grains	80.0

B.

2-(o-fluorophenyl)benzimidazole hydrochloride	5.0
Wheat standard middlings	95.0

C.

2-(o-chlorophenyl)-5-methoxy benzimidazole	35.0
Wheat shorts	65.0

D.

N-methyl-2-(o-fluorophenyl) benzimidazole	50.0
Corn distillers' grains	50.0

These and similar feed supplements are prepared by uniformly mixing the appropriate 2-(o-halophenyl)benzimidazole with the carrier or carriers. Such supplements

are added to the finished animal feed in an amount adequate to give the final concentration desired for controlling or treating helminthiasis by way of the animal ration. Although the preferred level in feeds will depend on the particular compound being employed, the anthelmintic compounds of this invention are normally fed at levels of 0.10–2.0% in the feed. One advantageous method of administering the compounds of this invention to animals whose feeds are conveniently pelleted, such as sheep, is to incorporate them directly in the pellets. For instance, 2-(o-chlorophenyl)benzimidazole is readily incorporated in nutritionally adequate alfalfa pellets (during the pelleting operation) at levels of 0.5 to 5 grams per pound of pellets for therapeutic use, and at lower levels for prophylactic use, and such pellets fed to the worm-infested animals. Alternatively, the 2-(o-halophenyl)benzimidazoles may be incorporated in salt licks or salt blocks at any desired concentration (concentrations of 5–25% by weight are conveniently employed). Large animals, such as sheep, cattle and goats, then receive the anthelmintics with their salt.

The following examples are given for the purpose of illustration and not by way of limitation:

Example 1

2-(o-fluorophenyl)benzimidazole, when fed orally to mice infected with *Nematospiroides dubius,* prevented nematode larval development at dose levels of 31, 62, 125, 250 and 500 mg./kg. 2-(o-chlorophenyl)benzimidazole was effective in preventing nematode larval development at levels of 62, 250 and 500 mg./kg.

Example 2

Boluses of 2-(o-fluorophenyl)benzimidazole or 2-(o-chlorophenyl)benzimidazole suitable for oral administration to domesticated animals are prepared having the following composition:

	(A), gm.	(B), gm.
2-(o-halophenyl) benzimidazole	1.0	2.0
Dicalcium phosphate	3.0	1.0
Starch	0.535	0.702
Guar gum	0.15	0.16
Talc	0.14	0.11
Magnesium stearate	0.04	0.028

A. To prepare (A) above, the dicalcium phosphate is thoroughly mixed with the 2-(o-halophenyl)benzimidazole and the mixture reduced to a particle size finer than 60 mesh. To the mixture is added 0.330 g. of starch in the form of an aqueous starch paste and the resulting mixture granulated in the usual manner. The granules are then passed through a No. 10 mesh screen and dried at 110–130° F. for about 8 hours, and the dried material then passed through a No. 16 mesh screen. The guar gum and the balance of the starch are added and the mixture thoroughly blended. The remainder of the ingredients are then added and the whole thoroughly mixed and compressed.

B. Preparation (B) is made by thoroughly mixing the dicalcium phosphate with the 2-(o-halophenyl)benzimidazole and reducing the mixture to a particle size finer than 60 mesh. To the mixture is added 0.430 g. of starch in the form of an aqueous starch paste and the resulting mixture is then granulated in the usual manner. The granules are passed through a No. 10 mesh screen and dried at 110–130° F. for about 8 hours, and the dried material then passed through a No. 16 mesh screen. The guar gum and the balance of the starch are added and the mixture thoroughly blended. The remainder of the ingredients are then added and the whole thoroughly mixed and compressed.

Example 3

A tablet having the following composition:

	Mg.
N-methyl 2-(o-fluorophenyl)benzimidazole	125
Dicalcium phosphate	250
Starch	125
Guar gum (60 mesh)	17
Talc (60 mesh)	14
Magnesium stearate (60 mesh)	5

is prepared in the following manner.

The dicalcium phosphate, N-methyl 2-(o-fluorophenyl)benzimidazole and 50 mg. of starch are thoroughly mixed and the mixture reduced to a particle size finer than 60 mesh. 45 mg. of starch in the form of an aqueous starch paste is added to the mixture and the whole granulated in the usual manner. The granules are then passed through a No. 10 mesh screen and dried at 110–130° F. for about 8 hours. The dried material is then passed through a No. 16 mesh screen. The guar gum and the balance of the starch are added and the mixture thoroughly blended. The remainder of the ingredients are then added and the mass mixed and compressed.

Tablets containing 2-(o-chlorophenyl)benzimidazole as the active anthelmintic agent are prepared in a similar manner.

Example 4

Drenches having the following composition are prepared by standard formulating methods:

A.

2-(o-fluorophenyl)benzimidazole	gm.	2.3
Antifoam AF emulsion	gm.	0.06
Hydroxyethyl cellulose	gm.	0.3
Sodium phosphate monobasic	gm.	0.3
Benzalkonium chloride (12.8% soln.)	ml.	0.6
Water	ml. to	30.0

B.

N-benzoyl 2-(o-chlorophenyl)benzimidazole	gm.	4.0
Antifoam AF emulsion	gm.	0.06
Hydroxyethyl cellulose	gm.	0.3
Sodium phosphate monobasic	gm.	0.3
Benzalkonium chloride (12.8% soln.)	ml.	0.6
Water	ml. to	30.0

C. Drenches may also be prepared in bulk for subdivision prior to use. The following vehicles are suitable:

1.

Benzalkonium chloride (12.8% soln.)	ml.	40
Antifoam AF emulsion	gm.	4
Hydroxyethyl cellulose	gm.	20
Distilled water	ml. to	2000

2.

Benzalkonium chloride (12.8% soln.)	ml.	0.5
Antifoam AF emulsion	gm.	4
Hydroxyethyl cellulose	gm.	20
Distilled water	ml. to	2000

The compounds of Formula I above are added to the vehicles in concentration in the range of 15–40 gm./100 ml.

The benzalkonium chloride used in the drench vehicles is a mixture of C_8–C_{18} dimethylbenzylammonium chlorides.

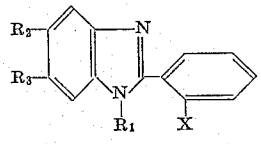
Any departure from the above description which conforms to the present invention is intended to be included within the scope of the claims.

What is claimed is:

1. An anthelmintic composition comprising an animal feed having distributed therein as an active anthelmintic agent 2-(o-halophenyl)benzimidazole in a concentration sufficient to provide a daily intake of from about 5 mg. to about 70 mg. of said benzimidazole per kilogram of

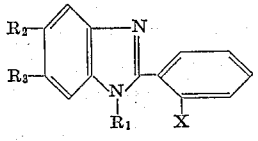
animal body weight, the halo radical of said benzimidazole having an atomic weight of between 19 and 35.5 inclusive.

2. The method of controlling helminth infections in animals that comprises orally administering to a host animal infected with helminths a chemotherapeutic dose of a member of the class consisting of a compound having the formula



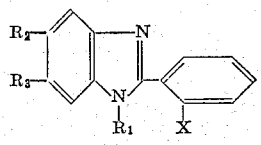
and acid addition salts thereof wherein R_1 is selected from the group consisting of hydrogen, lower alkyl and lower alkenyl, R_2 and R_3 are selected from the group consisting of hydrogen, lower alkyl and lower alkoxy, and X is a halogen having an atomic weight of between 19 and 35.5 inclusive.

3. An anthelmintic composition comprising an animal feed having distributed therein as an active anthelmintic agent from about 0.1–2.0% by weight of a member of the class consisting of a compound having the formula



and acid addition salts thereof wherein R_1 is selected from the group consisting of hydrogen, lower alkyl and lower alkenyl, R_2 and R_3 are selected from the group consisting of hydrogen, lower alkyl and lower alkoxy, and X is a halogen having an atomic weight of between 19 and 35.5 inclusive.

4. An anthelmintic composition that comprises a liquid drench vehicle containing a suspending agent and as an active anthelmintic agent a member of the class consisting of a compound having the formula



and acid addition salts thereof, wherein R_1 is selected from the group consisting of hydrogen, lower alkyl and lower alkenyl, R_2 and R_3 are selected from the group consisting of hydrogen, lower alkyl and lower alkoxy, and X is a halogen having an atomic weight of between 19 and 35.5 inclusive, the concentration of said compound being adequate to supply in a single dose from about 50–300 milligrams of said compound per kilogram of animal body weight.

5. An anthelmintic composition that comprises a liquid drench vehicle containing a suspending agent and as an active anthelmintic agent 2-(o-halophenyl)benzimidazole wherein the halo has an atomic weight of between 19 and 35.5, inclusive, and wherein the concentration of said benzimidazole is adequate to supply in a single dose from about 50–300 milligrams of 2-(o-halophenyl)benzimidazole per kilogram of animal body weight.

6. An anthelmintic composition that comprises a liquid drench vehicle containing a suspending agent and as an active anthelmintic agent 2-(o-fluorophenyl)benzimidazole, the concentration of said 2-(o-fluorophenyl)benzimidazole being adequate to supply in a single dose from about 50–300 milligrams of 2-(o-fluorophenyl)benzimidazole per kilogram of animal body weight.

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JULIAN S. LEVITT, *Primary Examiner.*

FRANK CACCIAPAGLIA, JR., LEWIS GOTTS, *Examiners.*