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ACYL BENZIMIDAZOLES AND METHOD OF PREPARING 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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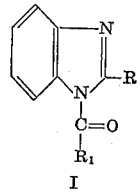
This invention relates to new compounds useful against helminthiasis. It relates generally to new 1-acyl benzimidazoles. More particularly, it relates to 1-acyl benzimidazoles having at the 2 position a heterocyclic radical containing nitrogen and sulfur. It is concerned also with methods of making such compounds from the corresponding unacylated benzimidazoles.

The infection known as helminthiasis involves infestation of the animal body, and particularly the gastrointestinal 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 1-acyl 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 benzimidazoles having an acyl radical at the 1 position of the benzimidazole ring nucleus and a heterocyclic radical containing nitrogen and sulfur at the 2 position thereof 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 the invention to provide such compounds. It is a more particular object to provide benzimidazoles substituted at the 1 position with an acyl radical and at the 2 position with a five-membered heterocyclic radical containing nitrogen and sulfur. A further object is provision of a method of synthesizing such compounds. Still other objects will become apparent from the following description of the invention.

The new compounds of our invention have the general structural formula



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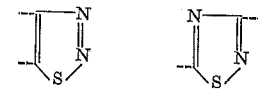
wherein R is a five-membered heterocyclic radical containing nitrogen and sulfur and R_1 is a hydrocarbonyl radical such as alkyl, aryl or aralkyl.

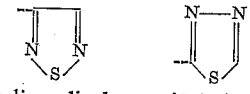
In the new compounds of this invention, the five-membered heterocyclic radical (R in the above formula), which is attached to the benzimidazole at one of its carbon atoms, may be a thiazolyl, isothiazolyl or thiadiazolyl radical. When R is a thiazolyl or isothiazolyl moiety, the point of attachment to the benzimidazole nucleus may be at any one of the three carbon atoms of the heterocyclic ring, as indicated by the broken lines in the partial structures:

When R is a thiadiazolyl group containing two nitrogen atoms and one sulfur atom in the ring, the radical may be attached to the benzimidazole at either of the two

carbon atoms in a 1,2,3-thiadiazole or a 1,2,4-thiadiazole:



With the symmetrical thiadiazoles, i.e. 1,2,5-thiadiazole or 1,3,4-thiadiazole, only one point of attachment exists:



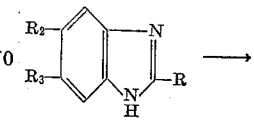
The heterocyclic radical may, if desired, be further substituted at a carbon atom with a lower hydrocarbon group such as a lower alkyl radical, the only limitation in this regard being that imposed by the availability of the substituted thiazoles, isothiazoles or thiadiazoles to be used as starting materials. 2-(2'-thiazolyl)-benzimidazoles having a lower alkyl group at the 4 position of the thiazole ring and the 2-(5'-isothiazolyl)-benzimidazoles having a lower alkyl group at the 3 position of the isothiazole ring such as 2-(4'-methyl-2'-thiazolyl)-benzimidazole and 2 - (3' - methyl - 5' - isothiazolyl) - benzimidazole are illustrative of this aspect of the invention.

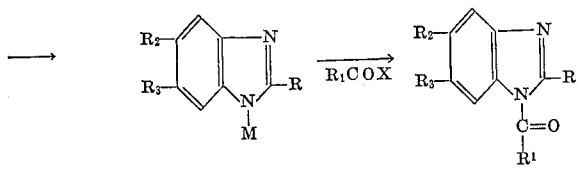
The acyl substituent at the N–1 position of the benzimidazole, which substituent is a critcal feature of the invention, may be a lower alkanoyl group ($R_1C{=}O$— where R_1 is lower alkyl) such as acetyl, propionyl, butyryl, valeryl and the like, an aroyl radical such as benzoyl or p-halobenzoyl, or an aralkanoyl substituent of the type illustrated by phenylacetyl. Thus R_1 in Formula I above may be hydrocarbonyl radicals such as methyl, ethyl, propyl, butyl, phenyl, benzyl and phenylethyl. In the preferred embodiments of the invention the N–1 substituent is a lower alkanoyl group, and the 2 substituent is a 2-thiazolyl or 4-thiazolyl radical.

If desired, the six-membered ring of the benzimidazole nucleus may also be substituted, as with lower alkyl groups at the 5 and/or 6 positions. Methyl groups are the preferred substituents although ethyl, propyl and similar lower alkyl radicals may, of course, be employed. The so-called pseudo-alkyl radicals, such as a trifluoromethyl substituent, may also be present at the 5 or 6 positions of the benzimidazole.

As representative of the novel substituted benzimidazole compounds falling within the scope of our invention and which may be prepared by the methods described hereinbelow, there may be mentioned 1-acetyl-2-(2' - thiazolyl) - benzimidazole, 1 - acetyl - 2 - (4' - thiazolyl) - benzimidazole, 1 - propionyl - 2 - (4' - isothiazolyl) - benzimidazole, 1 - benzoyl - 2 - [4' - (1',2',3'-thiadiazolyl)] - benzimidazole, 1 - butyryl - 2 - [3' - (1',2',5' - thiadiazolyl)] - benzimidazole, 1 - acetyl - 2 - [3'-(1',2',5' - thiadiazolyl)] - benzimidazole, 1 - phenylacetyl - 2 - (2' - thiazolyl) - benzimidazole, 1 - propionyl-2 - (4' - thiazolyl) - benzimidazole, 1 - acetyl - 2 - [4'-(1',2',3' - thiadiazolyl)] - 5,6 - dimethyl benzimidazole, 1 - acetyl - 2 - (4' - thiazolyl) - 5 - trifluoromethyl benzimidazole, 1 - acetyl - 2 - (4' - thiazolyl) -5,6 - dimethyl benzimidazole and the like.

The 1 - lower alkanoyl - 2 - thiazolyl benzimidazoles, wherein the point of attachment of the thiazolyl radical to the benzimidazole moiety is either the 2 or 4 position of the thiazole ring, represent the preferred compounds of the invention. These substances and the other 1-acyl-2-substituted benzimidazoles described herein are prepared by acylation of an alkali metal salt of a 2-R-benzimidazole as illustrated by the flow diagram:





where R is a five-membered heterocyclic radical containing nitrogen and sulfur, R_1 is a hydrocarbonyl radical, R_2 and R_3 are hydrogen or lower alkyl (or pseudo-alkyl), M is an alkali metal and X is chlorine or bromine.

The process is carried out by first converting a 2-R-benzimidazole, where R is as above defined, to an alkali metal salt. It is preferred to form the sodium salt by reacting or intimately contacting the benzimidazole with sodium hydride in a suitable solvent medium. Satisfactory results are obtained when a slight molar excess of sodium hydride is employed, although equimolar quantities of benzimidazole and sodium hydride may be used if desired. The reaction is conveniently brought about by warming the reactants at slightly elevated temperatures, but this is not essential and room temperature is satisfactory.

The novel 1-acyl-2-R-benzimidazoles of the invention are obtained by contacting the benzimidazole alkali metal salt with an acyl halide such as acetyl chloride, acetyl bromide, propionyl chloride, butyryl chloride, valeroyl bromide, benzoyl chloride, phenylacetyl chloride and the like. Normally, the acyl halide is added directly to a solution or suspension of the benzimidazole salt in an inert solvent, and the acylation reaction allowed to proceed at temperatures of room temperature up to about 100° C. Reaction temperatures in the range of 50–75° C. are preferred. The solvent employed as the reaction medium is preferably a hydrocarbon solvent such as benzene, toluene, xylene, petroleum ether and the like either alone or mixed with other solvents miscible therewith such as dimethylformamide.

The 1-acyl benzimidazoles thus formed are recovered from the reaction mixture by techniques known in the art, such as removal of the organic solvent and crystallization of the residual solid from solvents such as ether or mixtures of ether with other solvents.

The 1-acyl-2-substituted benzimidazoles described herein have a high degree of anthelmintic activity with a low incidence of undesirable side effects. They are therefore 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, ruminants such as cattle and sheep, and in man. The compounds of this invention are normally used, in treating helminthiasis, in unit dosage forms such as tablets, capsules, powders and the like wherein the active ingredient is intimately admixed with a suitable inert carrier. In treating domesticated animals, the compounds are 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 2-heterocyclic benzimidazole may be added to the drinking water of the animals.

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

EXAMPLE 1

1-Acetyl-2-(4'-Thiazolyl)-Benzimidazole

20 g. (0.1 M) of 2-(4'-thiazolyl)-benzimidazole is dissolved in a mixture of 500 ml. of toluene and 150 ml. of dimethylformamide. Traces of water are removed by distilling 25 ml. of toluene from the mixture. 3.6 g. of sodium hydride (0.15 M) as a 50% emulsion in oil is suspended in 10 ml. of toluene and the mixture added to the benzimidazole solution at a temperature of about 60° C. The sodium hydride addition is carried out portionwise. The resulting mixture is stirred at 60° C. for one hour and at the end of this time 11.7 g. of acetyl chloride (0.15 M) is added dropwise at a temperature of 55–60° C. The mixture is refluxed gently for about 30 minutes, cooled on ice and 10 ml. of water added thereto. The resulting mixture is washed with two 50-ml. portions of 5% sodium bicarbonate solution and a small amount of solid is removed by filtration and the toluene solution concentrated to dryness in vacuo. The slightly yellow solid residue is recrystallized from ether to give 1 - acetyl - 2 - (4' - thiazolyl) - benzimidazole, M.P. 134–136° C.

When this process is repeated employing 0.1 M of 2-(2' - thiazolyl) - benzimidazole or 2 - [4' - (1',2',3' - thiadiazolyl)]-benzimidazole as the starting material, there is obtained respectively 1 - acetyl - 2 - (2' - thiazolyl)-benzimidazole and 1 - acetyl - 2 - [4' - (1',2',3' - thiadiazolyl)]-benzimidazole.

EXAMPLE 2

1-Benzoyl-2-(4'-Thiazolyl)-Benzimidazole

20 g. of 2-(4'-thiazolyl)-benzimidazole in a mixture of 400 ml. of benzene and 175 ml. of dimethylformamide is treated at 60° C. with 3.6 g. of sodium hydride. The sodium hydride is added as a 50% emulsion in oil mixed with 10 ml. of benzene. The addition is carried out slowly and the mixture heated with stirring at 60° C. for 45 minutes after completion of the sodium hydride addition. At the end of this time, 14 g. of benzoyl chloride is added slowly at a temperature of 60° C. and the resulting mixture heated for 40 minutes at that temperature and with stirring. The reaction mixture is then cooled to about 10° C., 15 ml. of water added and the entire mixture washed with 5% sodium bicarbonate solution. The organic solvent solution is filtered to remove any solid material and the benzene layer concentrated to dryness in vacuo. The residue is crystallized from ethyl ether to give substantially pure 1-benzoyl-2-(4'-thiazolyl)-benzimidazole, M.P. 145° C.

EXAMPLE 3

1-Propionyl-2-[3-(1',2',5'-Thiadiazolyl)]-Benzimidazole

0.05 M of 2-[3-(1',2',5'-thiadiazolyl)]-benzimidazole in 400 ml. of benzene is treated with 1.8 g. of sodium hydride (52% emulsion in oil) in 5 ml. of benzene. The mixture is stirred at 40° C. for 90 minutes. 4.6 g. of propionyl chloride are then added slowly with stirring of the reaction mixture. The mixture is then stirred at 50° C. for 40 minutes, cooled and 10 ml. of cold water added. The whole is washed with 5% sodium bicarbonate solution (2 x 50 ml.), filtered, and the benzene layer concentrated to dryness. The residual solid is crystallized from the minimum volume of ether to give substantially pure 1-propionyl-2-[3-(1',2',5'-thiadiazolyl)]-benzimidazole.

1-phenylacetyl-2-(4'-thiazolyl)-5-methyl benzimidazole and 1-phenylacetyl-2-(4'-methyl-2'-thiazolyl) - benzimidazole are prepared in like fashion by reacting phenylacetyl bromide with 2-(4'-thiazolyl)-5-methyl benzimidazole and 2-(4'-methyl-2'-thiazolyl)-benzimidazole respectively.

EXAMPLE 4

1-Acetyl-2-(4'-Isothiazolyl)-Benzimidazole

To 10 g. of 2-(4'-isothiazolyl)-benzimidazole in 200 ml. of benzene and 70 ml. of dimethylformamide is added slowly with stirring 1.9 g. of sodium hydride (50% emulsion in oil) in 5 ml. of benzene. The mixture is stirred at 50° C. for 1 hour, and then 4 g. of acetyl chloride added slowly. The resulting mixture is refluxed gently for 30 minutes, then cooled and 10 ml. of water added to the cold reaction mixture. 1-acetyl-2-(4'-isothiazolyl)-benzimid-

azole is recovered in substantially pure form by the isolation method described in Example 1 above.

The 2-heterocyclic benzimidazoles employed as starting material in making the compounds of this invention are prepared by reacting together o-phenylenediamine and a heterocyclic carboxylic acid (or derivative thereof) in polyphosphoric acid. The process is carried out at elevated temperatures, and preferably at temperatures of about 150–300° C. The optimum reaction time and temperature will, of course, depend to some extent on the particular reactants being employed, but in general good yields of the desired compounds are obtained by conducting the process at temperatures of about 175° to about 275° C. for from 2 to 6 hours. When the heterocyclic reactant is one that tends to decompose at elevated temperatures, e.g. 4-carboalkoxy-1,2,3-thiadiazole, it is helpful to preheat the reaction mixture at about 100–150° C. for a short period of time, and then to complete the reaction at the higher temperatures referred to above. The heterocyclic carboxylic acid itself may be used as one of the starting compounds or, alternatively, a lower alkyl ester or the amide of such acid may be employed. In cases where the free acid tends to decarboxylate at elevated temperatures, an amide or ester is used as the reactant for best results. For example, thiazole-2-carboxamide is preferred over thiazole-2-carboxylic acid as starting material in the synthesis of 2-(2'-thiazolyl)-benzimidazole since the free acid tends to decompose to thiazole itself at reaction temperature. It is preferred to employ substantially equimolar amounts of the heterocyclic compound and the diamine, and from about 5–20 parts by weight of polyphosphoric acid per part of heterocycle, although it will be appreciated by those skilled in this art that the relative amount of reactants is not a critical feature of the invention. The desired 2-substituted benzimidazoles are recovered by cooling the reaction mixture and diluting it with water. Where the benzimidazoles do not crystallize readily under these conditions, they are precipitated by neutralizing the quenched mixture with a base such as ammonium hydroxide, an alkali metal hydroxide or an alkali metal carbonate. This synthesis of these new benzimidazoles, and the 2-substituted benzimidazoles produced thereby, are claimed in our copending application Serial No. 2,856, filed January 18, 1960, now Patent No. 3,017,415.

Examples illustrating the preparation of the 2-R-benzimidazoles, where R is a five-membered heterocyclic radical containing nitrogen and sulfur, follow:

(*a*) *2-(2'-thiazolyl)-benzimidazole.*—A mixture of 13.6 g. (.11 M) of thiazole-2-carboxamide, 11.5 g. (.11 M) of o-phenylenediamine and 272 g. of polyphosphoric acid is stirred and heated at 250° C. for 3½ hours. The reaction mixture is then cooled and poured into excess ice water with stirring. The resulting red solution is filtered to remove a small amount of black insoluble material and then treated with decolorizing charcoal. The charcoal is removed by filtration, and the filtrate treated with 50% sodium hydroxide solution until just pink to phenolphthalein paper. The resulting precipitate is filtered off and washed with water. It is then dissolved in a minimum amount of boiling ethanol, treated with decolorizing charcoal, and the charcoal removed by filtration. Water is added to the boiling filtrate until its total volume is about 250 ml. 2-(2'-thiazolyl)-benzimidazole crystallizes out immediately. The product is filtered, washed with cold 30% ethanol, and air dried, M.P. 245–246° C.

(*b*) *2-(4'-thiazolyl)-benzimidazole.*—Three g. of thiazole-4-carboxylic acid hydrobromide (14.3 MM) and 2 g. of o-phenylenediamine (18.5 MM) are mixed and added to 60 g. of polyphosphoric acid. The mixture is heated slowly with stirring to 240° C. and maintained at this temperature for 3 hours. The hot solution is then poured onto about 200 g. of ice. A taffy-like mass separates which dissolves on stirring. The mixture is filtered and the filtrate neutralized with 30% sodium hydroxide. At a pH of about 6, 2-(4'-thiazolyl)-benzimidazole precipitates. It is filtered, washed with water, and dried in air, M.P. 296–298° C.

This product is extracted with boiling ethanol. Some benzene is added to the extract and the solution boiled to remove traces of water. On concentration of the solution to a small volume and cooling, 2-(4'-thiazolyl)-benzimidazole crystallizes, M.P. 301–302° C.

(*c*) *2-[4'-(1',2',3'-thiadiazolyl)] - benzimidazole.*—6.0 g. of 4-carbethoxy-1,2,3-thiadiazole and 8.0 g. of o-phenylenediamine are added to 120 g. of polyphosphoric acid preheated to about 80° C. in a nitrogen atmosphere. After stirring for 1 hour at 125° C., the temperature is raised to 225° C. for 1 hour. The brown solution is cooled to about 100° C. and poured (with stirring) in a thin stream into 200 cc. of cold water. A dark green amorphous solid is filtered off and the filtrate neutralized to pH ca. 7 with sodium hydroxide solution. The crystalline solid which precipitates is filtered, washed with water and dried. Extraction of this solid with several 200 ml. portions of acetone, treatment of the solution with Darco, filtration and removal of the solvent gives almost colorless crystals of 2-[4'-(1',2',3'-thiadiazolyl)] - benzimidazole, M.P. 255–8° C.

(*d*) *2-[3'-(1'-,2',5' - thiadiazolyl)] - benzimidazole.*—12.8 g. (0.081 M) of 3-carbethoxy-1,2,5-thiadiazole, 11 g. (0.1 M) of o-phenylenediamine and 50 g. of polyphosphoric acid are mixed and heated with stirring at 175° C. in a nitrogen atmosphere for 3 hours. At this time, the dark solution is cooled to about 100° C. and then slowly poured with stirring into about 500 ml. of cold water. The tacky threads slowly change to a brown solid. The suspension is neutralized to pH ca. 7 to precipitate the remainder of the product. The solid is washed with water, sodium bicarbonate solution to insure neutrality and dried in air. The 2-[3'-(1',2',5'-thiadiazolyl)]-benzimidazole is then recrystallized from ethyl acetate solution with a decolorizing charcoal treatment, M.P. 268–70° C. (sublimation >240°). Recrystallization from ethyl acetate raises the M.P. to 272–274° C.

(*e*) *2-(4'-methyl-2'-thiazolyl)-benzimidazole.*—17 g. of 2-carbethoxy-4-methyl thiazole is added with stirring to 11 g. of o-phenylenediamine in 125 g. of polyphosphoric acid. The resulting viscous mixture is heated slowly with stirring to about 125° C. and stirred at this temperature for 1 hour. The volatile material is allowed to escape through an air-cooled condenser. The temperature is then raised to 175° C. for 3 hours. At the end of this time, the reaction mixture is cooled and poured into excess ice water. The 2-(4'-methyl-2'-thiazolyl)-benzimidazole is recovered according to the isolation procedure described in part (*a*) above.

(*f*) *2-(5'-thiazolyl)-benzimidazole.*—13.2 g. of thiazole-5-carboxamide, 11.5 g. of o-phenylenediamine and 272 g. of polyphosphoric acid are reacted according to the procedure of part (*a*) above. The crude product is obtained is recrystallized from ethyl acetate to give substantially pure 2-(5'-thiazolyl)-benzimidazole, M.P. 294–195° C.

(*g*) *2-(4'-isothiazolyl)-benzimidazole.*—15 g. of 4-carbethoxy isothiazole is added at room temperature to 11 g. of o-phenylenediamine in 150 g. of polyphosphoric acid. The mixture is stirred and the temperature raised to 125° C. for 2 hours. It is then heated at 175° C. for an additional 2 hours. The mixture is then poured into 1 liter of ice water and neutralized to a pH of about 6 with sodium hydroxide whereupon 2-(4'-isothiazolyl)-benzimidazole precipitates. The product is filtered off and extracted with hot acetone. The acetone extracts are treated with decolorizing charcoal and the filtrate obtained after removal of the charcoal is concentrated to dryness in vacuo to give the desired product, M.P. 319–320° C.

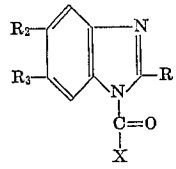
(*h*) *2-(3'-methyl-5'-isothiazolyl)-benzimidazole.*—32 g. of 3-methyl-5-carbomethoxy isothiazole are reacted with

22 g. of o-phenylenediamine in 175 g. of polyphosphoric acid according to the procedure set forth in part (*g*). There is obtained in this fashion 2-(3'-methyl-5'-isothiazolyl)-benzimidazole.

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. A benzimidazole having the formula



wherein R is a five-membered heterocyclic radical selected from the class consisting of thiazolyl, thiadiazolyl and isothiazolyl rings wherein one carbon atom of said ring is attached to the benzimidazole ring, and the remaining carbon atoms of said ring are substituted with a member of the class consisting of hydrogen and lower alkyl, X is a member of the class consisting of lower alkyl, phenyl, p-halophenyl and phenyl loweralkyl, and R_2 and R_3 are selected from the class consisting of hydrogen, lower alkyl and trifluoromethyl.

2. 1-phenylacetyl-2-thiazolyl benzimidazole.
3. 1-lower alkanoyl-2-thiazolyl benzimidazole.
4. 1-lower alkanoyl-2-thiadiazolyl benzimidazole.
5. 1-lower alkanoyl-2-isothiazolyl benzimidazole.
6. 1-acetyl-2-(2'-thiazolyl)-benzimidazole.
7. 1-acetyl-2-(4'-thiazolyl)-benzimidazole.
8. 1-benzoyl - 2-[4'-(1',2',3' - thiadiazoyl)]-benzimidazole.
9. 1-benzoyl-2-(4'-thiazolyl)-benzimidazole.

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