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CERTAIN BENZIMIDAZOLES CARRYING THIAZOLYL, THIADIAZOLYL AND ISOTHIAZOLYL SUBSTITUENTS IN THE 2 POSITION

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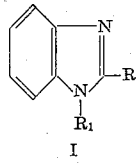
This invention relates to new compounds useful against helminthiasis. It relates generally to new derivatives of benzimidazole. More particularly, it relates to benzimidazoles having at the 2 position a heterocyclic radical containing nitrogen and sulfur. It is concerned also with methods of making such compounds.

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 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 at the 2 position of the benzimidazole ring nucleus a heterocyclic radical containing nitrogen and sulfur 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 2 position with a five-membered heterocyclic radical containing nitrogen and sulfur. A further object is provision of methods 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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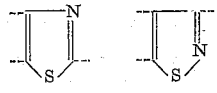
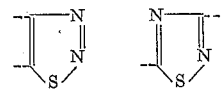
wherein R is a five-membered heterocyclic radical containing nitrogen and sulfur and R_1 is hydrogen, a lower alkyl or a lower alkenyl radical. The invention also includes within its scope acid addition salts of these benzimidazoles.

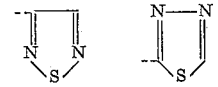
The five-membered heterocyclic radical (R in the above formula), which is attached to the benzimidazole at one of its carbon atoms, may be a thiazolyl, isothiazolyl or thiadiazolyl radical. When R is a thiazolyl or isothiazolyl moiety, the point of attachment to the benzimidazole nucleus may be at any 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.

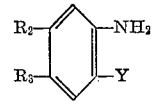
The N–1 position of the benzimidazoles (R_1 in Formula I) may be substituted with hydrogen, a lower alkyl group such as methyl, ethyl, propyl or isopropyl, or a lower alkenyl radical of the type represented by allyl and methallyl. The alkyl and alkenyl radicals preferably contain less than six carbon atoms. 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 discussed hereinbelow, there may be mentioned 2-(2'-thiazolyl)-benzimidazole, 2-(4'-thiazolyl)-benzimidazole, 2-(4'-isothiazolyl)-benzimidazole, 2-[4'-(1',2',3'-thiadiazolyl)]-benzimidazole, 2-[5'-(1',2',4'-thiadiazolyl)]-benzimidazole, 2-[3'-(1',2',5'-thiadiazolyl)]-benzimidazole, 1-methyl-2-[3'-(1',2',5'-thiadiazolyl)]-benzimidazole, 1-methyl-2-(2'-thiazolyl)-benzimidazole, 1-allyl-2-(4'-thiazolyl)-benzimidazole, 2-(5'-thiazolyl)-benzimidazole, 2-[4'-(1',2',3'-thiadiazolyl)]-5,6-dimethyl benzimidazole, 2-[4'-(1',2',3'-thiadiazolyl)]-5-methyl benzimidazole, 2-(4'-thiazolyl)-5-trifluoromethyl 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 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, and the like, 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.

The 2-thiazolyl benzimidazoles, wherein the point of

attachment to the benzimidazole moiety is either the 2 or 4 position of the thiazole ring, represent the preferred compounds of the invention. The preparation of these substances and the other 2-substituted benzimidazoles described herein comprises broadly the reaction of thiazolyl, isothiazolyl or thiadiazolyl carboxylic acid or derivative thereof, such as an ester, amide, nitrile acid halide or aldehyde, with a compound of the general formula



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wherein Y is —NO_2, —NH_2 or —NHR', R' is lower alkyl or lower alkenyl, and R_2 and R_3 are hydrogen or lower alkyl (or pseudo-alkyl).

According to one process, the 2-heterocyclic benzimidazoles 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 temperature, 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'-thiazoyl)-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 amounts 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.

Alternatively, the 2-heterocyclic benzimidazole compounds may be synthesized by reacting together o-phenylene-diamine and an aldehydo heterocyclic compound such as thiazole-4-aldehyde or 1,2,3-thiadiazole-4-aldehyde in a reaction medium comprising nitrobenzene. A 1-alkyl-2-heterocyclic benzimidazole, such as 1-methyl-2[4'-(1',2',3'-thiadiazolyl)]-benzimidazole is produced from N-methyl-o-phenylenediamine. Good results are obtained by heating the reaction mixture slowly to the reflux temperature (ca. 210° C.), and maintaining that temperature for a very short time. If desired, a solvent such as a lower alkanol may be used to promote solubility of the reactants at lower temperatures. Such solvents are allowed to distil off during the heating period. The 2-heterocyclic benzimidazoles are readily recovered. In many cases they crystallize directly on cooling the nitrobenzene solution. Alternatively, they may be crystallized by addition of ether or petroleum ether to the nitrobenzene solution.

According to a further embodiment of the invention,

2-heterocyclic benzimidazoles are prepared by condensation of a heterocyclic aldehyde with a compound of Formula II above. The reaction is preferably brought about in a suitable solvent such as a lower alkanol, e.g. methanol, ethanol, isopropanol or t-butanol. The first product formed is the Schiff base of the aldehyde and the primary amine. In normal practice this is not isolated but rather converted directly to the benzimidazole. When an o-phenylenediame or an N-substituted-o-phenylenediame is used, the ring closure of the Schiff base to the 2-heterocyclic benzimidazole is effected with a suitable oxidizing agent such as cupric acetate, lead tetracetate, mercuric acetate, air and the like.

Alternatively, in those cases where an o-nitroaniline is one of the starting materials, an ester or an acid halide derivative of the hetrocycle is employed. An intermediate anilide is formed initially. The nitro group is then reduced and benzimidazole formation effected by treatment of the intermediate anilide with a reducing system such as zinc-hydrochloric acid or zinc-acetic acid.

Where a heavy metal reagent is used to bring about benzimidazole formation from an o-phenylenediamine in the above two processes, an insoluble heavy metal salt of the 2-heterocyclic benzimidazole is formed. This material is readily converted to the free benzimidazole by removal of the heavy metal with reagents suitable for this purpose such as hydrogen sulfide, ammonium polysulfide, ammonium hydroxide and the like.

In an additional embodiment of our invention 2-heterocyclic benzimidazoles are prepared by heating a mixture of an o-phenylenediame or an N-alkyl-o-phenylenediamine and a lower alkyl heterocyclic carboxylate with an aqueous mineral acid such as aqueous sulfuric or phosphoric acid in a closed system, i.e. an autoclave or bomb. The process is conducted at temperatures of from about 120–180° C. for 3–10 hours, and the 2-heterocyclic benzimidazole recovered from the acid reaction mixture by application of the isolation and purification techniques described hereinabove.

1-substituted-2-heterocyclic benzimidazoles, where R_1 in Formula I above is alkyl or alkenyl, may further be synthesized by alkylation or alkenylation of the 2-heterocyclic benzimidazole itself. According to this method, an alkali metal salt of the benzimidazole is reacted with an ester of a strong acid and a lower alkanol or lower alkenol, such as methyl bromide, methyl iodide, allyl bromide and the like, or with an alkyl sulfate such as dimethyl sulfate.

The 2-substituted 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, ruminants such as cattle and sheep and even in man. 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 purposes of illustration and not by way of limitation:

EXAMPLE 1

2-(2'-thiazolyl)-benzimidazole

A mixture of 13.6 g. (.11 mole) of thiazole-2-carboxamide, 11.5 g. (.11 mole) 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. A second crop of product, M.P. 245° C., is obtained by concentrating the filtrate to a small volume and cooling.

EXAMPLE 2

2-(4'-thiazolyl)-benzimidazole

Three g. of thiazole-4-carboxylic acid hydrobromide (14.3 m. mole) and 2 g. of o-phenylenediamine (18.5 m. mole) 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.

EXAMPLE 3

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 one hour at 125° C. the temperature is raised to 225° C. for one 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.

EXAMPLE 4

2-[3'-(1',2',5'-thiadiazolyl)]-benzimidazole

12.8 g. (0.081 mole) of 3-carbethoxy-1,2,5-thiadiazole, 11 g. (0.1 mole) 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°). Recrystalization from ethyl acetate raises the M.P. to 272–274° C.

EXAMPLE 5

2-(4'thiazolyl)-5-methyl benzimidazole

30.4 g. of 4-methyl-2-nitroaniline in 400 ml. of ethanol is treated with hydrogen at a pressure of about 40 lbs. per square inch in the presence of 4 g. of 5% paladium on charcoal catalyst. A pressure drop of 23 lbs. per square inch takes place. The solution is filtered and 22.6 g. of 4-thiazole aldehyde is added to the colored filtrate containing the methylated o-phenylenediamine. The reaction mixture is stirred at room temperature for one hour during which time the Schiff base forms.

40 g. of cupric acetate monohydrate in 400 ml. of water is added to the above solution in small portions. The reaction mixture is heated under slight reflux with stirring to complete the precipitation of the copper salt of 2-(4'-thiazolyl)-5-methyl benzimidazole. The mixture is then cooled, filtered and the green solid washed with water. The solid salt is then suspended in about 500 ml. of ethanol and the mixture saturated with a slow stream of hydrogen sulfide. The precipitated copper sulfide is removed by filtration and the filtrate concentrated in vacuo to obtain crystalline 2-(4'-thiazolyl)-5-methyl benzimidazole.

The hydrobromide salt of this product is prepared by dissolving the product in hot alcoholic hydrogen bromide, treating the hot solution with activated charcoal, removing the charcoal by filtration, and adding about 3 volumes of ether to the alcoholic solution. The hydrobromide salt crystallizes on cooling.

EXAMPLE 6

1-methyl-2-(4'-thiazolyl)-benzimidazole

A. To 10 g. of 2-(4'-thiazolyl)-benzimidazole in 100 ml. of dry dimethylformamide is added 2.3 g. of a 52% sodium hydride emulsion in mineral oil. The mixture is stirred at room temperature for about 20 minutes and then warmed carefully to about 50° C. for 10 minutes. It is cooled to room temperature and 7.1 g. of methyl iodide in 10 ml. of dimethylformamide is added slowly to the cooled solution. The reaction mixture is then heated to about 80° C. for 20 minutes, cooled, diluted with 200 ml. of water and extracted with three 100-ml. portions of ether. The ether extracts are combined, washed with water, dried over sodium sulfate, filtered and the ether removed in vacuo to give 1-methyl-2-(4'-thiazolyl)-benzimidazole which may be purified by crystallization from ethyl acetate.

When the above process is carried out employing allyl bromide in place of methyl bromide, 1-allyl-2(4'-thiazolyl)-benzimidazole is obtained.

B. The above product is also produced by adding 5 g. of N-methyl-o-phenylenediamine dihydrochloride in 75 ml. of 50% alcohol to a solution of 10 g. of cupric acetate and 6 g. of thiazole-4-aldehyde in 300 ml. of water. The addition is carried out at about 0° C. and the reaction mixture is then heated in a hot water bath for about 30 minutes.

The resulting brown solid is recovered by filtration and washed with cold water and ethanol. It is then suspended in dilute hydrochloric acid and a stream of hydrogen sulfide bubbled slowly through the suspension until it is saturated with hydrogen sulfide. It is filtered and the filtrate obtained after removal of the copper sulfide is concentrated to dryness and the residue dissolved in a small volume of water. The solution is neutralized with potassium carbonate solution and extracted with chloroform. The chloroform extract is concentrated to dryness and the resulting residue extracted with petroleum ether. On concentration of the petroleum ether extracts, to a small volume, 1-methyl-2-(4'-thiazolyl) - benzimidazole precipitates.

EXAMPLE 7

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 Example 1.

The hydrochloride salt is obtained by treatment of the base with ethanolic hydrogen chloride by the method described in Example 10.

EXAMPLE 8

2-(2'-thiazolyl)-benzimidazole

To 11 g. of o-phenylenediamine in 100 ml. of ethanol is added with stirring 11.3 g. of thiazole-2-aldehyde in 100 ml. of ethanol. This mixture is stirred for about 1 hour at room temperature after which time 20 g. of cupric acetate monohydrate in 200 ml. of water is added dropwise with rapid stirring. After this addition is completed, the reaction mixture is heated at gentle reflux for about 30 minutes. It is then cooled and the copper salt recovered by filtration and washed with water. It is then suspended in 250 ml. of 95% ethanol and saturated with hydrogen sulfide (with stirring). The insoluble copper sulfide is removed by filtering and the clear filtrate concentrated essentially to dryness. The 2-(2'-thiazolyl)-benzimidazole thus obtained is purified by recrystallization from aqueous ethanol.

EXAMPLE 9

2-(4'-thiazolyl)-benzimidazole

22.6 g. of thiazole-4-aldehyde in 25 ml. of methanol is added to a suspension of 22 g. of o-phenylenediamine in 75 ml. of nitrobenzene. The resulting mixture is stirred at room temperature for a few minutes and then heated slowly to 210° C. for one minute. During the heating period, the methanol is removed by distillation. The reaction mixture is then cooled with stirring to about 10° C. whereupon the 2-(4'-thiazolyl)-benzimidazole crystallizes. It is filtered off and washed with ether. Any nitrobenzene remaining with the product is removed by recrystallization of the benzimidazole from alcohol.

EXAMPLE 10

A. 5 g. of 2-(2'-thiazolyl)-benzimidazole is added with stirring to 100 ml. of ethanol saturated with dry hydrogen chloride. An additional 125 ml. of ethanol is added to give a dark brown solution. The solution is treated with 5 g. of activated charcoal and the charcoal removed by filtration. The clear filtrate is diluted with three times its volume of ethyl ether and the resulting mixture chilled. After a short time, crystals of 2-(2'-thiazolyl)-benzimidazole monohydrochloride appear, M.P. 246° C.

B. 5 g. of 2-(4'-thiazolyl)-benzimidazole is added at room temperature to 100 ml. of absolute ethanol saturated with dry hydrogen chloride. An additional 150 ml. of ethanol is added and the mixture warmed to give a clear solution. This warm solution is treated with 3 g. of activated charcoal and the charcoal removed by filtration. The resulting solution is diluted with dry ethyl ether to a volume of one liter. On cooling and chilling in an ice bath, 2-(4'-thiazolyl)-benzimidazole monohydrochloride crystallizes. The product sublimes at about 265° C.

C. 50 mg. of 2-(4'-thiazolyl)-benzimidazole in 5 ml. of ethanol is treated with 3 drops of 50% sulfuric acid. Dilution of the mixture with ether to turbidity and cooling yields the colorless sulfate salt of 2-(4'-thiazolyl)-benzimidazole, M.P. 262–266° C.

EXAMPLE 11

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 Example 1 above. The crude product obtained is recrystallized from ethyl acetate to give substantially pure 2-(5'-thiazolyl)-benzimidazole, M.P. 294–295° C.

EXAMPLE 12

2(4'-thiazolyl)-5,6-dimethyl benzimidazole

8 g. of 4-thiazolyl aldehyde in 100 ml. of ethanol is added at room temperature to 10 g. of 4,5-dimethyl-o-phenylenediamine in 200 ml. of ethanol. The mixture is stirred for one hour at room temperature and a solution of 16 g. of cupric acetate in 400 ml. of water is added in small portions. When formation of the insoluble copper salt of 2-(4'-thiazolyl)-5,6-dimethyl benzimidazole is complete, the product is recovered by filtration, washed with water and treated with hydrogen sulfide as described in Example 5. After removal of the insoluble copper sulfide, the filtrate is treated with decolorizing charcoal, filtered, and the solvent removed in vacuo to give 2-(4'-thiazolyl)-5,6-dimethyl benzimidazole which is purified by recrystallization from ethyl acetate.

EXAMPLE 13

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.

EXAMPLE 14

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 Example 13. There is obtained in this fashion 2-(3'-methyl-5'-isothiazolyl)-benzimidazole.

EXAMPLE 15

2-(4'-thiazolyl)-benzimidazole

13 g. of 4-thiazolyl acid chloride and 13 g. of o-nitroaniline are stirred together in 35 ml. of pyridine at room temperature for about 12 hours. At the end of this time, the mixture is quenched in ice water and the solid nitroanilide recovered by filtration and washed with dilute sodium carbonate solution. The solid is suspended in 150 ml. of glacial acetic acid, and 80 ml. of 6-N-hydrochloric acid added to the suspension. 60 g. of zinc dust is added in small portions to the acetic mixture. After the zinc addition is complete, and the reaction is essentially finished (by visual observation), the reaction mixture is filtered and the filtrate neutralized with concentrated ammonium hydroxide to precipitate 2-(4'-thiazolyl)-benzimidazole. The product is purified by recrystallization from ethyl acetate. The acid chloride employed as starting material is obtained by treating 4-carboxy thiazole with thionyl chloride by known methods.

2-(4'-thiazolyl)-5-trifluoromethyl benzimidazole is prepared by the method set forth in the preceding paragraph employing 20.5 g. of 3-nitro-4-aminobenzotrifluoride as starting material in place of o-nitroaniline.

EXAMPLE 16

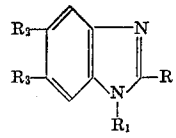
3 g. of 2-(4'-thiazolyl)-benzimidazole is dissolved in boiling methanol which contains a few drops of phenolphthalein solution. 15 ml. of 1 N sodium methoxide and 2 ml. of dimethyl sulfate are added. After a rapid reaction the solution is no longer alkaline. The same quantities of sodium methoxide and dimethyl sulfate are added

again followed by 25 ml. of sodium methoxide solution. The final solution is concentrated to dryness and the residue extracted with benzene. The extracts are treated with activated charcoal and concentrated to a residue of 1-methyl-2-(4'-thiazolyl)-benzimidazole which crystallizes in petroleum ether.

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. 2-(2'-thiazolyl)-benzimidazole.
2. 2-(4'-thiazolyl)-benzimidazole.
3. 2-[4'-(1',2',3'-thiadiazolyl)]-benzimidazole.
4. 2-[3'-(1',2',5'-thiadiazolyl)]-benzimidazole.
5. 2-(4'-thiazolyl)-benzimidazole hydrochloride.
6. 2(4'-thiazolyl)-5,6-dimethyl benzimidazole.
7. 2-(2'-thiazolyl)-benzimidazole hydrochloride.
8. 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 groups, R_1 is selected from the group consisting of hydrogen, lower alkyl and lower alkenyl, and R_2 and R_3 are selected from the class consisting of hydrogen, lower alkyl and trifluoromethyl groups and acid non-toxic addition salts thereof.

9. 2-thiazolyl benzimidazole.
10. 2-thiadiazolyl benzimidazole.
11. 2-isothiazolyl benzimidazole.
12. A non-toxic acid addition salt of 2-thiazolyl benzimidazole.

References Cited in the file of this patent

UNITED STATES PATENTS

2,985,661 Hein et al. ---------- May 23, 1961

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Elderfield: "Heterocyclic Compounds," vol. 5, pp. 205, 274–9 (1957).

UNITED STATES PATENT OFFICE

CERTIFICATE OF CORRECTION

Patent No. 3,017,415 January 16, 1962

Lewis H. Sarett et al.

It is hereby certified that error appears in the above numbered patent requiring correction and that the said Letters Patent should read as corrected below.

Column 3, line 7, after "nitrile" insert a comma; column 10, line 9, for "acid non-toxic" read -- non-toxic acid --.

Signed and sealed this 10th day of August 1965.

(SEAL)
Attest:

ERNEST W. SWIDER
Attesting Officer

EDWARD J. BRENNER
Commissioner of Patents