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PATENT SPECIFICATION

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COMPLETE SPECIFICATION

Benzimidazoles

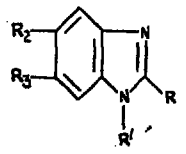
We, MERCK & CO., INC., a corporation duly organised and existing under the laws of the State of New Jersey, United States of America, of Rahway, New Jersey, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

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

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.

It has now been found that certain benzimidazoles having at the 2-position of the benzimidazole ring nucleus a heterocyclic radical containing nitrogen and sulphur possess a significant degree of anthelmintic activity and may be effectively used in the treatment and/or prevention of helminthiasis.

The new compounds of the invention have the general formula:

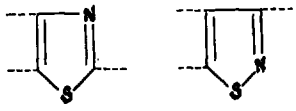


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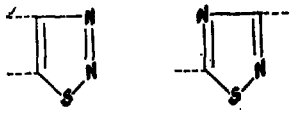
where R is a five-membered heterocyclic radical containing nitrogen and sulphur, R_1 is a hydrogen atom, a lower alkyl radical, a lower alkenyl radical or the radical $R_4C(=O)$ where R_4 is a hydrocarbon radical, preferably a lower alkyl, an aryl, or an aralkyl radical, and each of R_2 and R_3 is a hydrogen atom or a lower alkyl or lower halogenated alkyl radical. The invention also includes the acid-addition salts of these benzimidazoles. As used in the specification and claims, the term "lower", as applied to alkyl, alkenyl, and halogenated alkyl radicals, means "containing not more than five carbon atoms".

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 radical, 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:

[*Price 4s. 6d.*]



When R is a thiadiazolyl group containing two nitrogen atoms and one sulphur 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 - (2^1 - Thiazolyl) - benzimidazoles having a lower alkyl group at the 4 position of the thiazole ring and the 2 - (5^1-isothiazolyl) - benzimidazoles having a lower alkyl group at the 3 position of the isothiazole ring such as 2 - (4^1 - methyl - 2^1 - thiazolyl) - benzimidazole and 2 - (3^1-methyl - 5^1 - isothiazolyl) - benzimidazole are illustrative of this aspect of the invention.

The N—1 position of the benzimidazoles (R_1 in Formula I) may be unsubstituted or may have as substituent 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 N—1 position may also be substituted with an acyl substituent, which may be, for example, a C_{2-6} alkanoyl group, such as acetyl, propionyl butyryl and valeryl, an aroyl radical such as benzoyl, or an aralkanoyl substituent of the type illustrated by phenylacetyl.

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 are also suitable. Lower halogenated alkyl radicals, such as a trifluoromethyl substituent, may also be present at the 5 and/or 6 positions of the benzimidazole.

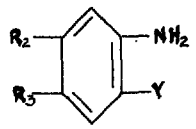
As representative of the novel substituted benzimidazole compounds falling within the scope of the invention and which may be prepared by the methods discussed below, there may be mentioned: —

2-(2^1-thiazolyl)-benzimidazole;
2-(4^1-thiazolyl)-benzimidazole;
2-(4^1-isothiazolyl)-benzimidazole;
2-[4^1-(1^1,2^1,3^1-thiadiazolyl)]-benzimidazole;
2-[5^1-(1^1,2^1,4^1-thiadiazolyl)]-benzimidazole;
2-[3^1-(1^1,2^1,5^1-thiadiazolyl)]-benzimidazole;
1-methyl-2-[3^1-(1^1,2^1,5^1-thiadiazolyl)]-benzimidazole;
1-methyl-2-(2^1-thiazolyl)-benzimidazole;
1-allyl-2-(4^1-thiazolyl)-benzimidazole;
2-(5^1-thiazolyl)-benzimidazole;
2-[4^1-(1^1,2^1,3^1-thiadiazolyl)]-5,6-dimethyl benzimidazole;
2-[4^1-(1^1,2^1,3^1-thiadiazolyl)]-5-methyl benzimidazole; and
2-(4^1-thiazolyl)-5-trifluoromethyl benzimidazole.

There may also be mentioned: —
1-acetyl-2-(2^1-thiazolyl)benzimidazole;
1-acetyl-2-(4^1-thiazolyl)benzimidazole;
1-propionyl-2-(4^1-isothiazolyl)-benzimidazole;
1-benzoyl-2-[4^1-(1^1,2^1,3^1-thiadiazolyl)]-benzimidazole;
1-butyryl-2-[3^1-(1^1,2^1,5^1-thiadiazolyl)]-benzimidazole;
1-acetyl-2-[3^1-(1^1,2^1,5^1-thiadiazolyl)]-benzimidazole;
1-phenylacetyl-2-(2^1-thiazolyl)-benzimidazole;
1-propionyl-2-(4^1-thiazolyl)-benzimidazole;
1-acetyl-2-[4^1-(1^1,2^1,3^1-thiadiazolyl)]-5,6-dimethyl benzimidazole;
1-acetyl-2-(4^1-thiazolyl)-5-trifluoromethyl benzimidazole; and
1-acetyl-2-(4^1-thiazolyl)-5,6-dimethyl benzimidazole.

The 2-substituted benzimidazoles described herein are isolated as the free bases by the synthetic processes normally used. 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, sulphates, nitrates and phosphates, aliphatic acid salts such as the acetate, trimethylacetate, *t*-butylacetate, or propionate, salts of polycarboxylic acids such as the citrate, oxalate and succinate 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 be edible and non-toxic.

The 2-thiazolyl benzimidazoles, in which 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 involves the reaction of a 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:



II

where Y is $—NO_2$ or $—NHR^1$, R^1 is a hydrogen atom or a lower alkyl or lower alkenyl radical and each of R_2 and R_5 is a hydrogen atom or a lower alkyl or lower halogenated alkyl radical.

According to one process, the 2-heterocyclic benzimidazoles are prepared by reacting together *o*-phenylenediamine or an appropriately substituted derivative of it 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 reactants, 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, its lower alkyl ester or amide may be used. 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 to thiazole-2-carboxylic acid as starting material in the synthesis of 2-(2^1-thiazolyl)benzimidazole since the free acid tends to decompose to thiazole itself at reaction temperature. It is preferred to use 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 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.

Alternatively, the 2-heterocyclic benzimidazole compounds may be synthesized by reacting together *o*-phenylenediamine and an aldehydo heterocyclic compound such as a 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-(1^1,2^1,3^1-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 the 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*-phenylenediamine or an N-substituted-*o*-phenylenediamine 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, or air.

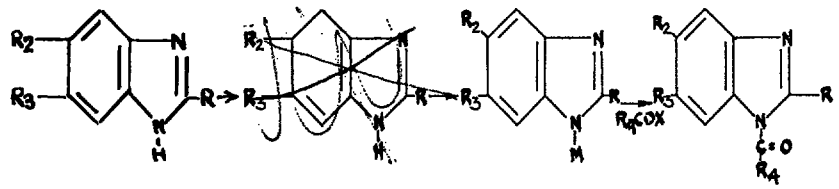
Alternatively, in those cases where an *o*-nitroaniline is one of the starting materials, an ester or an acid halide derivative of the heterocycle is used. An intermediate anilide is formed initially. The nitro group is then reduced and benzimidazole formation effected by treatment of the intermediate 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 sulphide, ammonium polysulphide and ammonium hydroxide.

In an additional embodiment of the invention, 2-heterocyclic benzimidazoles are prepared by heating a mixture of an *o*-phenylenediamine or an N-alkyl-*o*-phenylenediamine and a lower alkyl heterocyclic carboxylate with an aqueous mineral acid such as aqueous sulphuric 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 a lower alkyl or lower alkenyl ester of a strong acid, such as methyl bromide, methyl iodide and allyl bromide or with an alkyl sulphate such as dimethyl sulphate.

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 following flow diagram:



where R is a five-membered heterocyclic radical containing nitrogen and sulphur, R_4 is a hydrocarbon radical, R_2 and R_3 are hydrogen or lower alkyl or lower halogenated 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 with a slight molar excess of sodium hydride, 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 and phenylacetyl chloride. 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 and petroleum ether 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 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 nontoxic 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 dispersible, 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-(2¹-Thiazolyl)-Benzimidazole.

A mixture of 13.6 g. (0.11 mole) of thiazole - 2 - carboxamide, 11.5 g. (0.11 mole) of *o* - phenylenediamine and 272 g. of polyphosphoric acid is stirred and heated at 250°C. for 3 hours 30 minutes. 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 - (2¹ - 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-(4^1-Thiazolyl)-Benzimidazole.

3 g. of thiazole - 4 - carboxylic acid hydrobromide (14.3 millimole) and 2 g. of *o* - phenylenediamine (18.5 millimole) 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 toffee-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 - (4^1 - 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 ~~removed~~ traces of water. On concentration of the solution to a small volume and cooling, 2 - (4^1 - thiazolyl) - benzimidazole crystallizes, m.p. 301—302°C.

EXAMPLE 3.

2-[4^1-(1^1,2^1,3^1-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 decolorizing charcoal, filtration and removal of the solvent gives almost colourless crystals of 2 - [4^1 - (1^1,2^1,3^1 - thiadiazolyl)] - benzimidazole, m.p. 255—8°C.

EXAMPLE 4.

2-[3^1-(1^1,2^1,5^1-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 resulting 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 and, to ensure neutrality, with sodium bicarbonate solution, and dried in air. The 2 - [3^1 - (1^1,2^1,5^1 - 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.

EXAMPLE 5.

2-(4^1-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 coloured 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 - (4^1 - 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 sulphide. The precipitated copper sulphide is removed by filtration and the filtrate concentrated *in vacuo* to obtain crystalline 2 - (4^1 - 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-(4¹-Thiazolyl)-Benzimidazole.

A. To 10 g. of 2 - (4¹ - 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 sulphate, filtered and the ether removed *in vacuo* to give 1 - methyl - 2 - (4¹ - 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 - (4¹ - 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 sulphide bubbled slowly through the suspension until it is saturated with hydrogen sulphide. It is filtered and the filtrate obtained after removal of the copper sulphide 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 -(4¹ - thiazolyl) - benzimidazole precipitates.

EXAMPLE 7.

2-(4¹-Methyl-2¹-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 one 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 (2-4¹-methyl-2¹-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-(2¹-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 sulphide (with stirring). The insoluble copper sulphide is removed by filtering and the clear filtrate concentrated essentially to dryness. The 2 - (2¹ - thiazolyl) - benzimidazole thus obtained is purified by recrystallization from aqueous ethanol.

EXAMPLE 9.

2-(4¹-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 - (4¹-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 - (2^1 - 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 - (2^1 - thiazolyl) - benzimidazole monohydrochloride appear, m.p. 246°C.

B. 5 g. of 2 - (4^1 - 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 - (4^1 - thiazolyl) - benzimidazole monohydrochloride crystallizes. The product sublimes at about 265°C.

C. 50 mg. of 2 - (4^1 - thiazolyl) - benzimidazole in 5 ml. of ethanol is treated with 3 drops of 50% sulphuric acid. Dilution of the mixture with ether to turbidity and cooling yields the colorless sulphate salt of 2 - (4^1 - thiazolyl) - benzimidazole, m.p. 262—266°C.

EXAMPLE 11.

2-(5^1-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 - (5^1 - thiazolyl) - benzimidazole, m.p. 294—295°C.

EXAMPLE 12.

2-(4^1-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 - (4^1 - thiazolyl) - 5,6 - dimethyl benzimidazole is complete, the product is recovered by filtration, washed with water and treated with hydrogen sulphide as described in Example 5. After removal of the insoluble copper sulphide, the filtrate is treated with decolorizing charcoal, filtered, and the solvent removed *in vacuo* to give 2 - (4^1 - thiazolyl) - 5,6 - dimethyl benzimidazole which is purified by recrystallization from ethyl acetate.

EXAMPLE 13.

2-(4^1-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 a 1 litre of ice water and neutralized to a pH of about 6 with sodium hydroxide whereupon 2 - (4^1 - 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-(3^1-Methyl-5^1-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 - (3^1 - methyl - 5^1 - isothiazolyl)-benzimidazole.

EXAMPLE 15.

2-(4^1-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 - (4^1 - 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 - (4^1 - 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 - (4^1 - thiazolyl) - benzimidazole is dissolved in boiling methanol which contains a few drops of phenol - phthalein solution. 15 ml. of 1*N* sodium methoxide and 2 ml. of dimethyl sulphate are added. After a rapid reaction the solution is no longer alkaline. The same quantities of sodium methoxide and dimethyl sulphate 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 - (4^1-thiazolyl) - benzimidazole which crystallizes in petroleum ether.

EXAMPLE 17.

1-Acetyl-2-(4^1-Thiazolyl)-Benzimidazole.

20 g. (0.1 mole) of 2 - (4^1 - 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 mole) 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 mole) 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 to it. 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 - (4^1 - thiazolyl)benzimidazole, m.p. 134—136°C.

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

EXAMPLE 18.

1-Benzoyl-2-(4^1-Thiazolyl)-Benzimidazole.

20 g. of 2 - (4^1 - 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 - (4^1 - thiazolyl) - benzimidazole, m.p. 145°C.

EXAMPLE 19.

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

0.05 mole of 2 - [3 - (1^1,2^1,5^1 - 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 is 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 × 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 - (1^1,2^1,5^1 - thiadiazolyl)] - benzimidazole.

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

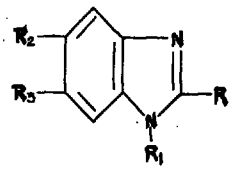
EXAMPLE 20.

1-Acetyl-2-(4^1-Isothiazolyl)-Benzimidazole.

To 10 g. of 2 - (4^1 - 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 - (4^1 - isothiazolyl) - benzimidazole is recovered in substantially pure form by the isolation method described in Example 17 above.

WHAT WE CLAIM IS:—

1. A 2-heterocyclic-substituted benzimidazole of the general formula:



where R is a five-membered heterocyclic radical containing nitrogen and sulphur, R_1 is a hydrogen atom or a C_{1-5} alkyl, a C_{2-5} alkenyl or a hydrocarbon carboxylic acyl radical, each of R_2 and R_3 is a hydrogen atom or a C_{1-5} alkyl or C_{1-5} haloalkyl radical.

2. A compound as claimed in Claim 1, in which R_1 represents an R_4—CO- radical where R_4 is an aryl, aralkyl, or C_{1-5} alkyl radical.

3. 2-(2^1-Thiazolyl)-benzimidazole.

4. 2-(4^1-Thiazolyl)-benzimidazole.

5. 2-[4^1-(1^1,2^1,3^1-Thiadiazolyl)]-benzimidazole.

6. 2-[3^1-(1^1,2^1,5^1-Thiadiazolyl)]-benzimidazole.

7. 2-(4^1-Thiazolyl)-benzimidazole hydrochloride.

8. 2-(4^1-Thiazolyl)-5,6-dimethyl benzimidazole.

9. 2-(2^1-Thiazolyl)benzimidazole hydrochloride.

10. A 2-thiazolyl benzimidazole.

11. A 2-thiadiazolyl benzimidazole.

12. A 2-isothiazolyl benzimidazole.

13. A 1 - (hydrocarbon carboxylic acyl) benzimidazole having attached to the 2 position of the benzimidazole ring a five-membered heterocyclic radical containing nitrogen and sulphur.

14. A 1-(C_{2-6} alkanoyl)-2-thiazolyl benzimidazole.

15. A 1-(C_{2-6} alkanoyl)-2-thiadiazolyl benzimidazole.

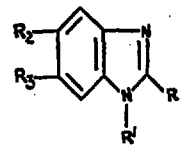
16. A 1-(C_{2-6} alkanoyl)-2-isothiazolyl benzimidazole.

17. 1-Acetyl-2-(2^1-thiazolyl)-benzimidazole.

18. 1-Acetyl-2-(4^1-thiazolyl)benzimidazole.

19. An acid-addition salt of a compound as claimed in any one of Claims 1 to 6, 8, and 10 to 18.

20. A process for the preparation of a benzimidazole of the formula:



at 50°C. for 40 minutes, cooled and 10 ml. of cold water added. The whole is washed with 5% sodium bicarbonate solution (2 × 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 - (1^1,2^1,5^1 - thiadiazolyl)] - benzimidazole.

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

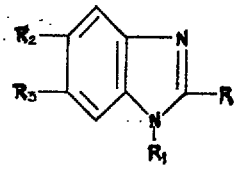
EXAMPLE 20.

1-Acetyl-2-(4^1-Isothiazolyl)-Benzimidazole.

To 10 g. of 2 - (4^1 - 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 - (4^1 - isothiazolyl) - benzimidazole is recovered in substantially pure form by the isolation method described in Example 17 above.

WHAT WE CLAIM IS:—

1. A 2-heterocyclic-substituted benzimidazole of the general formula:



where R is a five-membered heterocyclic radical containing nitrogen and sulphur, R_1 is a hydrogen atom or a C_{1-5} alkyl, a C_{2-5} alkenyl or a hydrocarbon carboxylic acyl radical, each of R_2 and R_3 is a hydrogen atom or a C_{1-5} alkyl or C_{1-5} haloalkyl radical.

2. A compound as claimed in Claim 1, in which R_1 represents an R_4—CO- radical where R_4 is an aryl, aralkyl, or C_{1-5} alkyl radical.

3. 2-(2^1-Thiazolyl)-benzimidazole.

4. 2-(4^1-Thiazolyl)-benzimidazole.

5. 2-[4^1-(1^1,2^1,3^1-Thiadiazolyl)]-benzimidazole.

6. 2-[3^1-(1^1,2^1,5^1-Thiadiazolyl)]-benzimidazole.

7. 2-(4^1-Thiazolyl)-benzimidazole hydrochloride.

8. 2-(4^1-Thiazolyl)-5,6-dimethyl benzimidazole.

9. 2-(2^1-Thiazolyl)benzimidazole hydrochloride.

10. A 2-thiazolyl benzimidazole.

11. A 2-thiadiazolyl benzimidazole.

12. A 2-isothiazolyl benzimidazole.

13. A 1 - (hydrocarbon carboxylic acyl) benzimidazole having attached to the 2 position of the benzimidazole ring a five-membered heterocyclic radical containing nitrogen and sulphur.

14. A 1-(C_{2-6} alkanoyl)-2-thiazolyl benzimidazole.

15. A 1-(C_{2-6} alkanoyl)-2-thiadiazolyl benzimidazole.

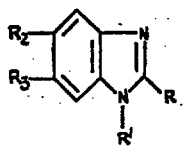
16. A 1-(C_{2-6} alkanoyl)-2-isothiazolyl benzimidazole.

17. 1-Acetyl-2-(2^1-thiazolyl)-benzimidazole.

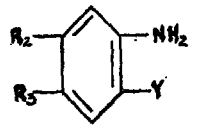
18. 1-Acetyl-2-(4^1-thiazolyl)benzimidazole.

19. An acid-addition salt of a compound as claimed in any one of Claims 1 to 6, 8, and 10 to 18.

20. A process for the preparation of a benzimidazole of the formula:



where R is a five-membered heterocyclic radical containing nitrogen and sulphur, R^1 is a hydrogen atom or a C_{1-5} alkyl or C_{2-5} alkenyl radical, and each of R_2 and R_3 is a hydrogen atom, a C_{1-5} alkyl radical or a halogenated C_{1-5} alkyl radical, which comprises reacting together a compound of the general formula RB, where B is a carboxy, carboalkoxy, carboxamido, acyl halide, cyano or aldehydo radical, and a compound of the formula:

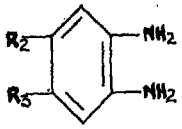


where Y is $-NO_2$ or $-NHR^1$, and when B is an aldehyde group, oxidizing the intermediate product to form the benzimidazole, and, when Y is a nitro group, reducing the intermediate product to form such a benzimidazole in which R^1 is hydrogen.

21. A process as claimed in Claim 20, in which the reactants are chosen such that R^1 in the resulting benzimidazole is a hydrogen atom, including the further step of converting the benzimidazole to its alkali metal salt and reacting the latter with an acylating agent to form an N-acyl derivative.

22. A process as claimed in Claim 20, in which the reactants are chosen such that R^1 in the resulting benzimidazole is a hydrogen atom, including the further step of converting the benzimidazole to its alkali metal salt and reacting the latter with an ester of a strong acid and a C_{1-5} alkanol or a C_{2-5} alkenol.

23. A process for preparing a compound as claimed in Claim 1 in which R_1 is a hydrogen atom, which comprises reacting an orthophenylenediamine compound of the formula:



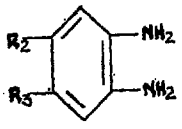
where R_2 and R_3 are as defined in Claim 1 with a compound of formula:

R.COOH, $R.CO.NH_2$ or $R.COO(C_{1-5}$ alkyl)

where R is as defined in Claim 1.

24. A process as claimed in Claim 23, carried out at 175—275°C. for 2 to 6 hours.

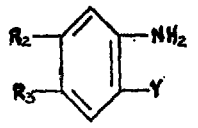
25. A process for preparing a compound as claimed in Claim 1 in which R_1 is a hydrogen atom, which comprises reacting an orthophenylenediamine compound of the formula:



where R_2 and R_3 are as defined in Claim 1 with a compound of formula:
R.CHO in a reaction medium comprising nitrobenzene.

26. A process as claimed in Claim 24, carried out by heating the reaction mixture slowly to reflux temperature and maintaining that temperature for a very short time.

27. The process that comprises condensing a compound of formula:



where Y, R_2 and R_3 are as defined in Claim 20, with a compound of formula R.CHO, where R is as defined in Claim 1, to produce a Schiff base of the aldehyde and the $-NH_2$ group, oxidizing the latter to close the ring, and, when a heavy metal oxidizing

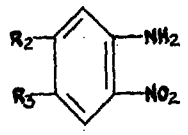
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agent is used, adding a reagent to precipitate an insoluble salt or other compound of the heavy metal.

28. A process as claimed in Claim 27, in which cupric acetate, lead tetracetate or mercuric acetate is used as oxidizing agent and hydrogen sulphide, ammonium polysulphide or ammonium hydroxide is used to precipitate the copper, lead or mercury.

29. A process as claimed in Claim 27, in which air is used as oxidizing agent.

30. The process that comprises reacting a compound of general formula:



in which R_2 and R_5 are as defined in Claim 1, with an ester or acid halide of a heterocyclic carboxylic acid of formula R.COOH, where R is as defined in Claim 1, to produce an anilide with the $-NH_2$ group, and heating the latter with a reducing system to convert the nitro group to a primary amino group and simultaneously effect ring-closure to produce a compound as claimed in Claim 1 in which R_1 is hydrogen.

31. A process as claimed in Claim 30, in which the reducing system comprises zinc and hydrochloric or acetic acid and the zinc is precipitated from the resulting product by ammonium polysulphide or ammonium hydroxide.

32. A process as claimed in Claim 20, in which B in the compound RB represents a carbo(C_{1-5} alkoxy)radical, and the reaction is carried out in the presence of an aqueous mineral acid in a closed system at 120—180°C. for 3 to 10 hours.

33. A process for preparing a compound as claimed in Claim 1 in which R_1 represents C_{1-5} alkyl or C_{2-5} alkenyl, which comprises reacting an alkali metal salt of the corresponding 1-unsubstituted compound with a C_{1-5} alkyl or C_{2-5} alkenyl ester of a strong acid or with a C_{1-5} alkyl sulphate.

34. A process for preparing a compound as claimed in Claim 1, substantially as hereinbefore described with reference to any one of the foregoing Examples.

35. A compound as claimed in Claim 1, when prepared by a process as claimed in any one of Claims 20 to 34 or an obvious chemical equivalent of such a process.

36. A composition suitable for administration to domestic animals, comprising a compound as claimed in any one of Claims 1 to 19 and 35 mixed with or dispersed in a non-toxic carrier or diluent.

37. A composition as claimed in Claim 36, in the form of an animal feed supplement, a dispersible wettable powder, a bolus or a liquid drench.

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P.S.

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