

PATENT SPECIFICATION

(11)

1268 000

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NO DRAWINGS

- (21) Application No. 57613/70 (22) Filed 2 May 1969
 (62) Divided out of No. 1267998
 (31) Convention Application No. 726540 (32) Filed 3 May 1968 in
 (33) United States of America (US)
 (45) Complete Specification published 22 March 1972
 (51) International Classification C 07 d 49/38
 (52) Index at acceptance



C2C 183—199—283 213 220 227 22Y 247 250 252 25Y
 305 311 313 31Y 321 32Y 332 339 611 620 621
 630 631 660 661 671 681 694 695 708 791 LP
 ML

(54) BENZIMIDAZOLES AND A PROCESS FOR THEIR PREPARATION

(71) We, ELI LILLY AND COMPANY, a Corporation organised and existing under the Laws of the State of Indiana, United States of America, of 307, East McCarty Street, City of Indianapolis, State of Indiana, 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:—

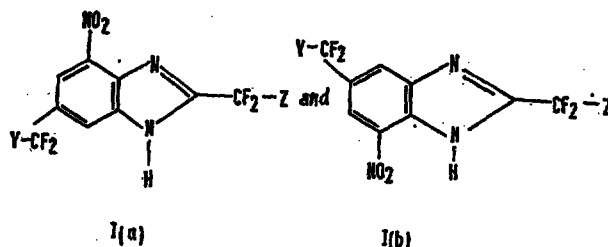
Benzimidazoles are known to be useful in combating intestinal parasites of mammals and birds. Furthermore, 2-trifluoromethylbenzimidazoles have been found to be useful as herbicides, nematocides, molluscicides, and insecticides. (British patent 1,087,561; U.S. patent 3,412,101; South African patent 65/5584; and Netherlands patent 67/13786 are exemplary.) The 2-trifluoromethyl derivatives most frequently employed as insecticides have been substituted in the benzene portion of the benzimidazole ring system with chlorine and nitro groups, with the most active compounds being 2 - trifluoromethyl - 4,5,6,7 - tetrachlorobenzimidazole, 2 - trifluoromethyl - 5,6 - dichlorobenzimidazole, and phenyl 2 - trifluoromethyl - 4 - nitro - 6 - chloro - 1 - benzimidazolecarboxylate. In general these compounds have shown their greatest activity against insects of the order Lepidoptera, such as Southern armyworm, and of the order Diptera, such as house flies and mosquitoes. For example, 2 - trifluoromethyl - 4,5 - dichlorobenzimidazole gives a complete kill of Southern armyworm larvae at 250 ppm, but is without action against milkweed bugs, oriental roaches and boll weevils at that same concentration, and in fact, its activity against house flies is excellent only at 1000 ppm. The isomeric compound, 2 - trifluoromethyl - 5,6 - dichlorobenzimidazole, has the same excellent activity against Southern armyworm larvae at 250 ppm, but no activity at the same level against milkweed bugs, house flies, oriental roach and boll weevil. In general, these chlorinated benzimidazoles do not approach, in absolute activity, the organic phosphate insecticides, nor do they have the same broad spectrum of action.

Two large classes of marketed insecticides which have been widely used and which have a reasonably broad spectrum against many orders of insects plus a low dosage range, are the organic phosphates and the chlorinated hydrocarbons. Many of the most active of the organic phosphate insecticides are extremely toxic to humans and their toxicity by intradermal absorption is of the same order of magnitude as their toxicity by inhalation. Thus, these very toxic compounds are extremely dangerous to handle, even when using a gas mask or oxygen mask. The safest of the phosphorus insecticides, Malathion, (Registered Trade Mark) is still widely used, but its spectrum is not as broad as would be desirable and many species of insects or mites have become resistant to it over the years.

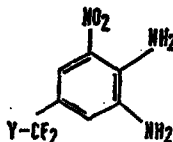
The deficiencies of the chlorinated hydrocarbons are of a different nature. Resistance is, of course, prevalent, but this problem is not as serious as might be expected because of the endless succession of new chlorinated hydrocarbons which have been produced. The chief drawback to the use of chlorinated hydrocarbons is their their persistence in soil and water for many, many years, attributed chiefly to their metabolic stability. This persistence has now begun to affect other forms of life, including birds and fish.

Thus, there is a need for compounds with both insecticide and acaricide activity, which have a broad spectrum, are safe to handle and are non-persistent.

The invention provides a process for preparing a benzimidazole compound of the formulae:



wherein Y is F or H; when Y is H, Z is F, H, Cl, $-\text{CF}_3$ or $-\text{CF}_2-\text{CF}_3$; when Y is F, Z is H, Cl, $-\text{CF}_3$ or $-\text{CF}_2-\text{CF}_3$; which comprises heating an *o*-phenylenediamine of the formula



wherein Y is as defined above, with an acid of the formula $\text{Z}-\text{CF}_2-\text{C}(=\text{O})-\text{OH}$ where-

in Z is as defined above.

The invention also provides a process wherein the reaction described above is carried out in the presence of dilute hydrochloric acid.

The insecticidal compositions containing the compounds of this invention and their use as insecticides and acaricides are described and claimed in our copending Application No. 22589/69 (Serial No. 1267998).

The following Example describes a process which is analogous to one which may be used to prepare the *o*-phenylenediamine starting material for the process of the present invention.

A solution of 40.5 g. of 2,6 - dinitro - 4 - trifluoromethyl - 1 - chlorobenzene in 300 ml. of benzene was mixed with 250 ml. of 14 N ammonium hydroxide. The reaction mixture was stirred at room temperature for about 1.5 hours, at which point in time another 100 ml. of 14 N ammonium hydroxide were added and the stirring was continued for an additional 2 hours. The organic layer was separated, was washed with water and was dried. Removal of the solvents *in vacuo* yielded 2,6 - dinitro - 4 - trifluoromethylaniline, which melted at about 142—144°C. after recrystallization from a hexane-benzene solvent mixture.

Twenty-four grams of 2,6 - dinitro - 4 - trifluoromethylaniline were dissolved in 300 ml. of ethanol. The solution was heated to about 35°C. and 110 ml. of a 20 percent ammonium polysulfide solution containing 5 percent free sulfur was added. The temperature of the reaction mixture rose spontaneously to about 60°C., at which temperature it was maintained by heating for about 10 minutes. The reaction mixture was cooled to about 40°C. and poured into water. The resulting mixture was filtered. Excess benzene was added to the filtrate which was then evaporated to dryness *in vacuo* using the water-benzene azeotrope. Recrystallization of the resulting solid yielded purified 3 - nitro - 5 - trifluoromethyl - *o* - phenylenediamine melting at about 121—123°C.

The following Example describes a process analogous to one which may be used to prepare compounds of the present invention.

A reaction mixture containing 3 g. of 3 - nitro - 5 - trifluoromethyl - *o* - phenylenediamine, 10 ml. of trifluoroacetic acid and 25 ml. of water was refluxed for about 4 hours. The reaction product containing 2,6 - bis(trifluoromethyl) - 4 - nitro - benzimidazole was poured into water and stirred until it solidified. The benzimidazole was dissolved in base at pH=11 and the solution filtered. The pH was then lowered

to about 7, at which point 2,6 - bis(trifluoromethyl) - 4 - nitrobenzimidazole began to crystallize. The compound was separated by filtration, the filter cake washed with water and then dried. Recrystallization from a benzene-hexane solvent mixture yielded 2,6 - bis(trifluoromethyl) - 4 - nitrobenzimidazole, melting at about 95—97°C.

Analysis, Calc.: C, 36.13; N, 14.05; H, 1.01
Found: C, 36.24; N, 13.87; H, 1.32.

Compounds in which the substituent on the 2-position of the benzimidazole ring is other than trifluoromethyl are prepared by the method of Smith and Stienle, J. Am. Chem. Soc. 75, 1292 (1953), which method in this instance involves the heating of an appropriately substituted *o*-phenylene diamine with trifluoroacetic acid, pentafluoropropionic acid, difluoroacetic acid, heptafluorobutyric acid, or chlorodifluoroacetic acid, optionally in the presence of dilute HCl. 2 - Chlorodifluoromethyl - 4 - nitro - 6 - trifluoromethylbenzimidazole prepared in this way melts at about 97—98°C. after recrystallization from hexane.

Analysis, Calc.: C, 34.25; H, 0.96; N, 13.31
Found: C, 34.50; H, 1.01; N, 13.35.

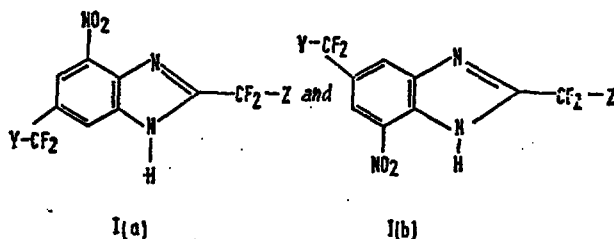
Compounds in which the substituent in the 6(5) position of the benzene ring of the benzimidazole is difluoromethyl are prepared from 2,6 - dinitro - 4 - difluoromethylbenzene according to the above procedure. This latter compound is prepared by the reaction of SF₄ and 3,5 - dinitro - 4 - hydroxybenzaldehyde to yield 2,6 - dinitro - 4 - difluoromethylphenol which is converted to the corresponding chloride by conventional means. 2 - Trifluoromethyl - 4 - nitro - 6 - difluoromethylbenzimidazole was prepared from the corresponding diamine by a process analogous to that described above for preparing 2,6 - bis(trifluoromethyl) - 4 - nitrobenzimidazole and melted at about 132—134°C. after recrystallization from benzene.

Analysis, Calc.: C, 38.44; H, 1.43; N, 14.93
Found: C, 38.30; H, 1.40; N, 14.82

Most of the compounds coming within the scope of Formulae I(a) and I(b) above are phytotoxic at application rates considerably higher than those at which the compounds are insecticidally active, and many are effective herbicides for a wide variety of plants at application rates of 8 pounds per acre or higher. However, the extreme effectiveness of the insecticides represented by Formula I(a) and I(b) provides a sufficient margin of safety to enable their use, either in the soil in the presence of growing or seedling crops, or by a one-time application to the foliage, as agricultural insecticides.

WHAT WE CLAIM IS:—

1. A process for preparing a benzimidazole compound of the formulae:



wherein Y is F or H; when Y is H, Z is F, H, Cl, —CF₃ or —CF₂—CF₃; and when Y is F, Z is H, Cl, —CF₃ or —CF₂—CF₃; which comprises heating an *o*-phenylene diamine of the formula

to about 7, at which point 2,6 - bis(trifluoromethyl) - 4 - nitrobenzimidazole began to crystallize. The compound was separated by filtration, the filter cake washed with water and then dried. Recrystallization from a benzene-hexane solvent mixture yielded 2,6 - bis(trifluoromethyl) - 4 - nitrobenzimidazole, melting at about 95—97°C.

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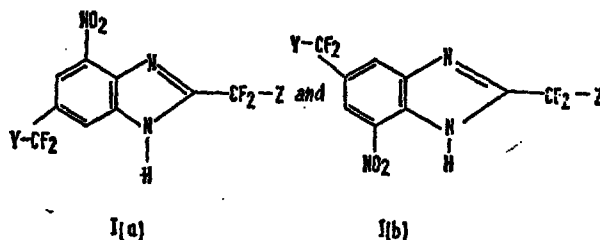
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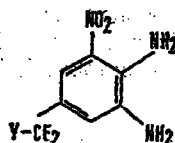
WHAT WE CLAIM IS:—

1. A process for preparing a benzimidazole compound of the formulae:



wherein Y is F or H; when Y is H, Z is F, H, Cl, —CF₃ or —CF₂—CF₃; and when Y is F, Z is H, Cl, —CF₃ or —CF₂—CF₃; which comprises heating an *o*-phenylene diamine of the formula

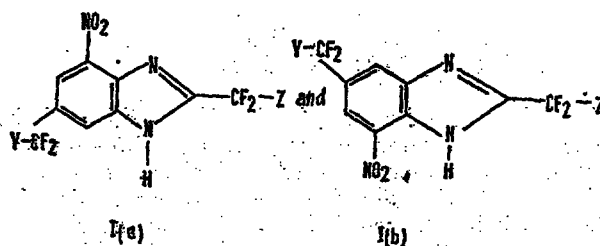




wherein Y is as defined above, with an acid of the formula $Z-CF_2-C(=O)OH$ where-
in Z is as defined above.

2. The process of claim 1, wherein the reaction is carried out in the presence of dilute hydrochloric acid.

3. A process for preparing a benzimidazole compound of the formula



wherein Y is F or H; when Y is H, Z is F, H, Cl, $-CF_3$ or $-CF_2CF_3$; and when Y is F, Z is H, Cl, $-CF_3$ or $-CF_2CF_3$; substantially as hereinbefore described.

4. 2 - Chlorodifluoromethyl - 4 - nitro - 6 - trifluoromethylbenzimidazole.
5. 2 - Trifluoromethyl - 4 - nitro - 6 - difluoromethylbenzimidazole.

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Chartered Patent Agents,
Agents for the Applicant(s).

Reference has been directed in pursuance of Section 9, subsection (1) of the Patents Act, 1949, to patents Nos. 1,159,789 and 1,087,561.

Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1972.
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.

