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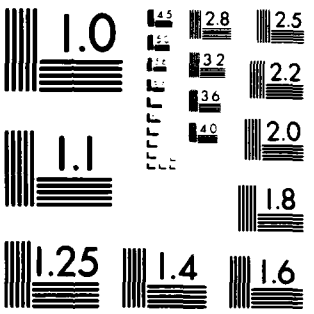

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FOREIGN TECHNOLOGY DIVISION

A METHOD FOR OBTAINING NEW CYCLICAL IMIDES OF DERIVATIVE BENZIMIDAZOLES

by

Leszek Konopski and Barbara Serafinowa

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A METHOD FOR OBTAINING NEW CYCLICAL IMIDES OF DERIVATIVE BENZIMIDAZOLES

by Leszek Konopski and Barbara Serafinowa

The subject of the invention is a method for obtaining new cyclical imides condensed from benzimidazol rings, with a biological activity, especially in relation to the central nervous system. These compounds are represented in sample 1 or 2, in which R designates the hydrogen atom, the alkyl group or the basic alkyl group, and X the oxygen atom or imine group. These new compounds were not known until now.

The method for obtaining compounds like those in sample 1 or 2, in which R and X have the significance given above depends, according to the invention, on the fact that the 2-cyanobenzimidazol is alkylated in position 1 by the action of bromoacetane, methyl acrylane, ethyl, acrylonitril, which obtains a corresponding ester or nitril 1-alkylocarboxy-2-cyanobenzimidazol in the general sample 3, in which Z is the carboethoxyl, carbomethoxyl or nitril group, and n designates the total number 1 or 2. The compound in sample 3 yields subsequently cyclization by the action of the mineral acid, especially sulphuric acid in a solution of acetic acid, obtaining the compound in sample 1 or 2, in which R designates the hydrogen atom, the alkyl group or basic alkyl group, and X the imine group. The compounds containing the imine group are separated or transferred into the compounds in samples 1 or 2, in which R designates the hydrogen atom, the alkyl group or the basic alkyl group, and X the oxygen atom, through hydrolysis by the dilute mineral acid.

The new compounds created by the invention's method shows a

biological activity. Given orally to mice in dosages of 200 mg/kg it counteracted reserpine hypothermy and prolonged the duration of amphetamine stereotypy in rats. Moreover, when given to rats in dosages of 200 mg/kg it braked in 45% the development of stomach ulcers caused by a four hour immobilization and cooling.

The compounds' toxicity is small, amounting more or less to 2 g/kg in mice given an oral dose.

Example I. 2.9 g (.02 mole) of 2-cyanobenzimidazol and 2.1 g (.02 mole) of exsiccated sodium carbonate are heated to boiling in 150 cm^3 of ethyl alcohol with 3.3 g (.02 mole) of bromoacetane for 1.5 hours. After evaporation of part of the solvent 3.05 g of raw 1-carboethoxymethylo-2-cyanobenzimidazol is obtained, whose crystallization from 50% ethanol has a melting point of 115-117°C. The yield amounts to 69%.

Example II. 2.9 g (.02 mole) of 2-cyanobenzimidazol and 1.6 g (.03 mole) of acrylonitril are heated to boiling in 15 cm^3 of pyridine containing a catalitic amount of trimethylobenzyloammonium hydroxide for 6 hours. After pouring in water raw 1-(2-cyanoetylo)-2-cyanobenzimidazol is filtered out. After crystallization from an ethanol and methanol mixture 3 g of the pure compound is obtained with a melting point of 188-190°C. The yield amounts to 74%.

Example III. 1.15 g (.005 mole) of 1-carboethoxymethylo-2-cyanobenzimidazol is dissolved in a boiling mixute of .55 cm^3 of concentrated sulphuric acid and 1.5 cm^3 of acetic acid, and then

heated to 65°C, mixing for 1.5 hours. In the course of the reaction falls out the product's residue which after its end and that of the reactive mixture's cooling is filtered, washed with water saturated with a sodium hydrocarboxide solution and again with water. .75 g of raw 2,4-diketoperhydropirazino (1,2 a) benzimidazol is obtained, which after crystallization from dioxane has a melting point of 304-305°C. Its yield amounts to 75%.

Example IV. 1.3 g (.0066 mole) of 1-(2-cyanoethylo)-2 cyanobenzimidazol is heated for 45 minutes until boiling in a mixture of 2 cm^3 of sulphuric acid and 3 cm^3 of acetic acid. After pouring on ice and neutralization with a water solution of sodium bicarbonate to a pH=4-4.2 raw 3.5 diketoperhydro-1,4-diazepino(1,2-a)benzimidazol is obtained. After crystallization from dioxane .4 g of the pure product is obtained with a melting point of 275-276°C. The yield amounts to 28%.

Example V. 1.15 g (.005 mole) of 1 carboethoxymethylo-2-cyanobenzimidazol is dissolved in a mixture of 2 cm^3 ethanol and 5 cm^3 of a concentrated water solution of ammonia and is left for 14 days at room temperature. .6 g of raw 2-keto-4-iminoerhydropirazyno(1,2a)banzimidazol is obtained. After crystallization from dioxane the pure compound is obtained with a melting point of 294-296°C. The yield amounts to 60%.

Example VI. 8.6 g (.038 mole) of 1-carboethoxymethyl-2-cyanobenzimidazol, 20 cm^3 of 40% water solution of methyloamine, 10 cm^3 of ethanol are emptied into a clear solution and left at a temperature of 30°C for 6 days. 1.05 g of raw 2-keto-e-methylo-4-iminoperhydropirazyno(1,2-a)benzimidazol are obtained, which

after crystallization from dioxane has a melting point of 234-236°C. The yield amounts to 11%.

The drained material after the reaction reaches a volume of 10 cm^3 and is added to 15 cm^3 of 15% sulphuric acid. The mixture is heated to boiling for 1 hour and after cooling 4.7 g of raw 2,4-diketo-3-methyloperhydropirrazyno(1,2-a)benzimidazol is filtered. This has a melting point of 297-298°C after crystallization from dioxane. The yield amounts to 50%.

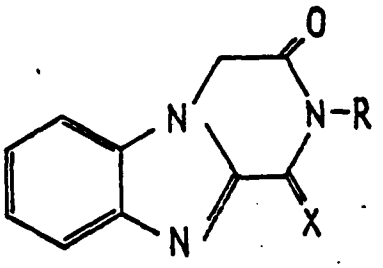
The Patent's Specifications

1. The method for creating new cyclical imides of derived benzimidazol with general samples 1 or 2, in which R designates the hydrogen atom, and X the oxygen atom, is characterized by the fact that 2-cyanobenzimidazol is alkylated in position 1 by bromoacetane, arylane, methyl, ethyl or acrylonitril, and we obtain a corresponding ester or nitril with general sample 3, in which Z designates the carboethoxyl, carbomethoxyl or nitril group, and n designates the entire number 1 or 2. Next, this is subjected to cyclization by the action of the mineral acid, the best being sulphuric acid in a solution of acetic acid.

2. The method for creating new cyclical imides of derived benzimidazoles with general samples 1 or 2, in which R designates the hydrogen atom, the alkyl group or the basic alkyl group, and X the imide group, is characterized by the fact that 2-cyanobenzimidazol is alkylated in position 1 by the action of bromoacetane, methyl acrylane, ethyl or acrylonitril, and the corresponding ester or nitril with general sample 3 is obtained,

in which Z designates the carboetholxyl, carbomethoxyl or nitril group and n the total number 1 or 2. This is next subjected to cyclization by the action of ammonia or first order amine.

3. The method for creating new cyclical imides of derived benzimidazoles with general samples 1 or 2, in which R designates the hydrogen atom, the alkyl group or the basic alkyl group, and X the imide group, is characterized by the fact that 2-cyanobenzimidazol is alkylated in position 1 by the action of bromoacetane, methyl acrylane, ethyl or acrylonitril, and the corresponding ester or nitril with general sample 3 is obtained, in which Z designates the carboetholxyl, carbomethoxyl or nitril group and n the total number 1 or 2. This is next subjected to cyclization by the action of ammonia or first order amine for the compound with samples 1 or 2, in which R designates the hydrogen atom, the alkyl group or the basic alkyl group, and X designates the imine group and is subjected to hydrolysis, useful against the action of the mineral acid's dilution.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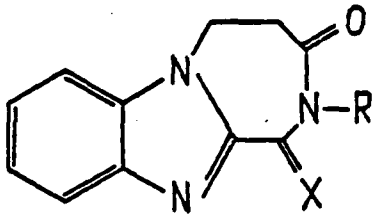
X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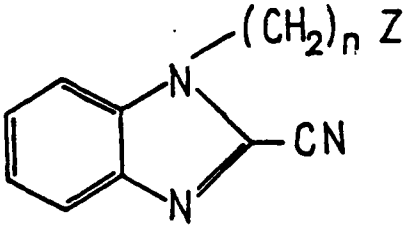
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