SYNTHESIS OF FUNGITOXIC DERIVATIVES OF BENZIMIDAZOLE WITH A RADIOACTIVE LABEL

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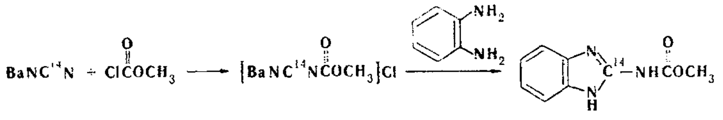
Methyl-1-butylcarbamoyl-2-benzimidazolylcarbamate with a radioactive label in the imidazole ring or methoxy group was obtained by successive reaction of barium C^{14}-cyanamide with methyl C^{14}-chloroformate, o-phenylenediamine, and butyl isocyanate.

Fungicides effective in the fight against diseases of agricultural plants were recently found among benzimidazole derivatives [1-3]. Methyl-1-butylcarbamoyl-2-benzimidazolylcarbamate is the most promising of these fungicides [4].

We synthesized this fungicide with radioactive labels in order to study the localization and pathways of metabolic transformation of it in plants and fungi.

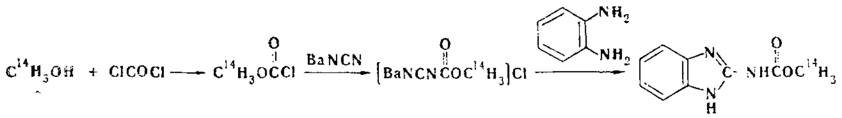
The synthesis was accomplished in two principal steps – preparation of the intermediate benzimidazolylcarbamate with a radioactive label in the 2 position (I) or in the methoxy group (II) and subsequent conversion of it to the final product.

The radioactive label was introduced into the imidazole ring by means of radioactive barium cyanamide via the following scheme:



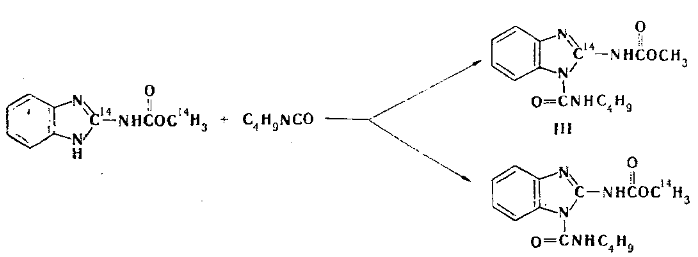
I

In order to introduce a label into the methoxy group (II), we used radioactive methanol as the intermediate in accordance with the scheme presented below:



II

The final products were obtained by condensation of I and II with excess butyl isocyanate.



III

IV

All-Union Scientific-Research Institute of Phytopathology, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1547-1548, November, 1974. Original article submitted January 29, 1974.

The mass spectra of I and II contain peaks of radioactive molecular ions with m/e 193, which constitute 20 and 5%, respectively, of the nonradioactive molecular ions with m/e 191.

The UV spectra of III and IV are identical to the spectra of nonradioactive samples [5] and have absorption maxima at 244, 288, and 297 nm.

Compounds III and IV proved to be less stable than their nonradioactive analogs on storage and underwent 30-40% decomposition after one month to give I and II.

EXPERIMENTAL

The starting C^{14}-methanol and barium C^{14}-cyanamide were obtained from the All-Union "Isotop" Association and were used without additional purification.

The activity was measured with an SL-20 liquid scintillation counter (France).

The mass spectra were recorded with an LKB-9000 spectrometer, and the UV spectra were recorded with a Perkin–Elmer 402 spectrophotometer.

The radiochemical purity was determined by thin-layer chromatography (TLC) on a Silufol UV-254 plate with elution by butanol–chloroform (1 : 1).

Methyl-2-C^{14}-benzimidazolyl-2-ylcarbamate (I). A 0.047-g (0.5 mmole) sample of methyl chloroformate was added with stirring at 0.5° to a suspension of 0.089 g (0.5 mmole) of barium C^{14}-cyanamide with a specific activity of 56.1 mCi/g in 1.5 ml of water. Stirring was continued at 30-40° for 1 h, after which the mixture was cooled to 0°, and the resulting precipitate was removed by filtration. The filtrate was added dropwise to heated (to 90-100°) o-phenylenediamine [0.054 g (0.5 mmole)] while maintaining the pH at 4-5 by the addition of hydrochloric acid. The mixture was stirred under the same conditions for 30 min, and the precipitate was separated by filtration of the hot mixture and washed successfully on the filter with 1 ml of hot water and 1 ml of acetone. The yield of product with mp 290-300° (dec.) was 64.0%. Its specific activity was 53.4 mCi/g. One radioactive spot with R_f 0.49, which is equivalent to the R_f value of a spot from a nonradioactive sample developed in UV light, was observed during chromatography.

C^{14}-Methyl-2-benzimidazolylcarbamate (II). A 0.5-ml (0.012 mmole) sample of C^{14}-methanol with a specific activity of 12.7 mCi/g was added at 0-5° to 3.57 g (0.036 mmole) of phosgene containing one drop (15-20 mg) of methyl chloroformate, and the mixture was maintained under the same conditions for 1 h and at room temperature for 3 h with simultaneous removal of the excess phosgene. The C^{14}-methyl chloroformate obtained [0.052 g (0.55 mmole)] was subjected to reaction under the conditions of the preceding example with 0.097 (0.55 mmole) of barium cyanamide and 0.059 g (0.55 mmole) of o-phenylenediamine. The yield of product with R_f 0.49 was 14.6%. Its radiochemical purity was 100%. The specific activity was 6.6 mCi/g.

Methyl-1-butylcarbamoyl-2-C^{14}-benzimidazolyl-2-ylcarbamate (III). A mixture of 0.23 g (0.12 mmole) of I and 0.023 g (0.24 mmole) of butyl isocyanate in 1 ml of dry dioxane was heated with stirring at 40-60° until the precipitate had dissolved. The dioxane was then removed by vacuum distillation, and the residue was washed with three 2-ml portions of hexane and dissolved in benzene. The benzene solution was chromatographed with a column filled with silica gel [benzene–acetone (9 : 1)]. The fractions containing III (R_f 0.87) were evaporated. The yield was up to 60%, and the specific activity was 35 mCi/g.

C^{14}-Methyl-1-butylcarbamoyl-2-benzimidazolylcarbamate (IV). This compound was obtained in 68% yield under the conditions of the preceding example from 0.153 g (0.8 mmole) of II and 0.158 g (1.6 mmole) of butyl isocyanate. The specific activity was 4.27 mCi/g.

LITERATURE CITED

1. D. J. W. Burde, Proceedings of the Fifth Conference on Insecticides and Fungicides (1969), p. 675.
2. French Patent No. 2048150 (1971); Ref. Zh. Khim., 7N599P (1972).
3. H. L. Klopping, US Patent No. 3541213 (1970); Ref. Zh. Khim., 17N690P (1971).
4. S. S. Kukalenko and É. A. Dvoichenkova, Khimiya v Sel'sk. Khoz., 11, 836 (1970).
5. Y. Soeda, S. Koska, and T. Noguchi, Agr. Biol. Chem., 36, 819 (1972).