SYNTHESIS OF CARBON-, PHOSPHORUS-, AND SULFUR-LABELED ETHYLENEIMIDES OF PHOSPHORIC AND THIOPHOSPHORIC ACIDS

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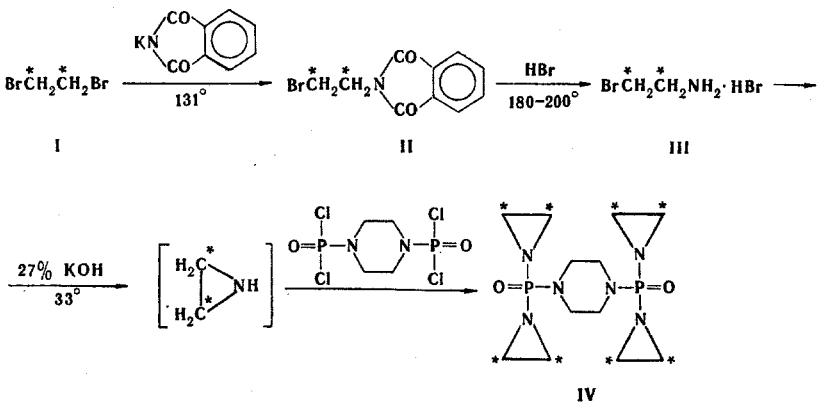
A method is proposed for the preparation of ^{14}C-1,2-ethyleneimine from ^{14}C-1,2-dibromoethane. ^{14}C-Dipine (^{14}C-1,4-piperazinediylbis[bis(1-aziridinyl)phosphine oxide]) (labeled ethylene rings), ^{32}P-thiodipine, and ^{35}S-thiodipine were synthesized.

In order to study the mechanism of the action and pathways of biotransformation of antitumorigenic preparations of a number of ethyleneimides of phosphoric and thiophosphoric acids, we undertook the synthesis of ^{14}C-dipine (1,4-piperazinediylbis[bis(1-aziridinyl)phosphine oxide]), ^{32}P-thiodipine, and ^{35}S-thiodipine.

In contrast to the known methods for the synthesis of compounds containing a ^{14}C-labeled ethyleneimine group, in which the authors used ^{14}C-1,2-ethanolamine [1, 2] or K^{14}CN [3] as the starting radioactive compound, we worked out the conditions for the preparation of ^{14}C-1,2-ethyleneimine from ^{14}C-1,2-dibromoethane (I). We synthesized ^{14}C-dipine via the following scheme:



I II III IV

The reaction of I with potassium phthalimide gave N-(2-bromo-^{14}C-1,2-ethyl)phthalimide (II) and, as a side product, N,N'-(^{14}C-1,2-ethylene)diphthalimide, the separation of which was achieved by utilizing their different solubilities in boiling carbon disulfide. Refluxing phthalimide derivative II with concentrated HBr gave 2-bromo-^{14}C-1,2-ethylamine (III), which was converted to ^{14}C-1,2-ethyleneimine by the action of alkali. The labeled ethyleneimine, without isolation in the individual state, was subjected to reaction with 1,4-piperazinediylbis[bis-(chloro)phosphine oxide] [4] to give ^{14}C-dipine (IV). Our use of an aqueous alkaline solution of ^{14}C-1,2-ethyleneimine without preparative isolation enabled us to considerably simplify the operation with the labeled compound and to raise the yield of final product IV. The yield of ^{14}C-dipine based on the starting ^{14}C-1,2-dibromoethane was 25-30% (50-60% based on the use of excess I).

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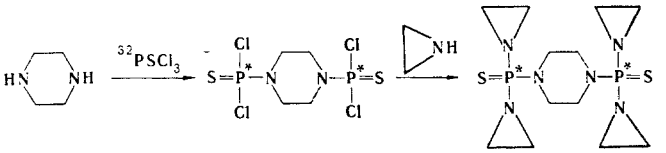
In order to obtain ^{32}P-thiodipine and ^{35}S-thiodipine we used the known method for the preparation of the unlabeled preparation [5] with allowance for the peculiarities involved in work with radioactive isotopes.

The synthesis of ^{32}P-thiodipine was realized by phosphorylation of anhydrous piperazine (V) with phosphorus thiotrichloride containing the ^{32}P isotope. The resulting ^{32}P-labeled acid (VI) gave ^{32}P-thiodipine (VII) on reaction with ethyleneimine.



V VI VII

The reaction of VI with ethyleneimine was carried out both in an anhydrous medium and in an aqueous alkaline solution of ethyleneimine. The yield of ^{32}P-thiodipine in the first case was 60-70%, as compared with 50-60% in the second case. In the subsequent syntheses the reaction was carried out with anhydrous ethyleneimine.

The synthesis of ^{35}S-thiodipine was carried out via the scheme used to prepare ^{35}P-thiodipine, but ^{35}S-labeled phosphorus thiotrichloride was used as the phosphorylating agent.

Particular attention in the present research was directed to the purification and identification of the synthesized labeled compounds by means of thin-layer chromatography (TLC). In order to determine the radiochemical impurities that are not detectable by the usual chromatographic methods we used radiochromatography and autoradiography.

EXPERIMENTAL METHOD

Chromatography was carried out on Silufol UV-254 plates with methanol—water (1:1) (system No. 1) and dioxane—methylene chloride (10:9) (system No. 2). The chromatograms were developed in iodine vapors. The level of radioactivity along the chromatographic plates was scanned with an FH-452 radiochromatograph.

N-(2-Bromo-^{14}C-1,2-ethyl)phthalimide (II). This compound, with mp 82-83° (from aqueous alcohol) (mp 79-80° [6]), was obtained in 50% yield from 8.1 g (43.2 mmole) of ^{14}C-1,2-dibromoethane (I) (specific activity 8.5 μCi/g) and 4.0 g (21.6 mmole) of potassium phthalimide by the method in [6].

2-Bromo-^{14}C-1,2-ethylamine Hydrobromide (III). This compound with mp 157-160° (mp 155-160° [7]), was obtained in 91% yield by refluxing II with 8-10 ml of concentrated HBr (sp. gr. 1.49) by the method in [7].

^{14}C-1,2-Ethyleneimine. A 2.05-g (0.01 mole) sample of hydrobromide III was cyclized in 13 ml of 27% KOH solution at 33° for 45-50 min. The resulting aqueous alkaline solution of ^{14}C-1,2-ethyleneimine, without isolation and purification, was used immediately for the preparation of ^{14}C-dipine.

^{14}C-Dipine (IV). This compound, with mp 187-189° [from benzene (1:10)] (mp 187-189° [8]), R_f 0.4 (system No. 1), and a specific activity of 2.0 μCi/g, was obtained in 60% yield by the method in [8]. Its radiochemical purity was no less than 99%.

^{32}P-Thiodipine (VII). This compound, with mp 201-203° [from dimethylformamide (1:7)] (mp 201-203° [5]), R_f 0.8 (system No. 2), and specific activity 5.0 μCi/g, was obtained in 63% yield (based on $^{32}PSCl_3$) from $^{32}PSCl_3$ with a specific activity of 8.75 μCi/ml.

^{35}S-Thiodipine. This compound, with mp 201-203°, R_f 0.8, and a specific activity of 13.0 μCi/g, was also obtained in 64% yield by the method in [5] from $^{35}PSCl_3$ with a specific activity of 25.0 μCi/ml.

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