SYNTHESIS OF 2-(DIMETHYLAMINO-^{3}H)-6-[BIS(1-AZIRIDINYL)PHOSPHINYLAMINO]-7-METHYLPURINE (FOPURINE-^{3}H)

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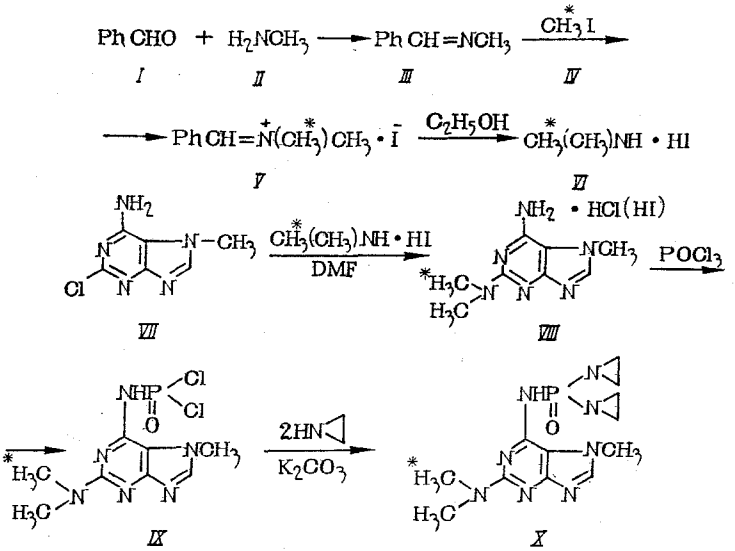
We have previously reported the synthesis of ^{32}P-labeled fopurine and the preliminary results of a study of the products of its biotransformation in experimental animals [1].

For further studies of the metabolism of this compound we have synthesized fopurine, 2-(dimethylamino)-6-[bis(1-aziridinyl)phosphinylamino]-7-methylpurine, with a ^{3}H radiolabel in the dimethylamino group. The labeled starting compound for the synthesis was dimethylamine- H (VI), which in turn was prepared from methyl-^{3}H iodide (IV).

The reaction of (IV) with benzylidenemethylamine (III), prepared by condensation of benzaldehyde (I) with methylamine (II) in aqueous solution, gave the quaternary salt (V). Refluxing of (V) with 90% ethyl alcohol gave dimethylamine-^{3}H hydroiodide (VI) in 43.8% radiochemical yield.

We then reacted 2-chloro-6-amino-7-methylpurine (VII) with (VI) in dimethylformamide (DMF) to get a mixture of 2-(dimethylamino-^{3}H)-6-amino-7-methylpurine hydrochloride and hydroiodide (VIII). Phosphorylation of (VIII) with phosphorus oxychloride gave [2-(dimethylamino-^{3}H)-7-methyl-6-purinyl]phosphoramidic dichloride (IX), which we converted by reaction with ethylenimine in aqueous alkaline solution to 2-(dimethylamino-^{3}H)-6-[bis(1-aziridinyl)-phosphinylamino]-7-methylpurine (X) (fopurine-^{3}H) in 21% radiochemical yield.



EXPERIMENTAL CHEMICAL PART

Dimethylamine-^{3}H Hydroiodide (VI). A 20% solution of (II) (25 g) was added to (I) (10.6 g) over a period of 20 min. The mixture was kept at 15-18°C for 12-14 h, whereupon the solution was saturated with sodium chloride and the product was extracted with ether. The dried ethereal solution was distilled and the fraction with bp 183-185°C was collected. The yield of (III) was 8.3 g (70%). A flask fitted with a reflux condenser was charged with (III) (1.134 g) and (IV) (1.37 g; specific activity 1.5 μCi/mg). The mixture was refluxed on a water bath for 3 h. To the resulting viscous dark red oil (V), which solidified on cooling,

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was added 90% ethyl alcohol (10 ml). The mixture was heated on a water bath for 1.5 h and then carefully evaporated on a porcelain dish. The residue, which solidified on cooling, was dissolved in ethyl alcohol (minimum quantity) and precipitated with ether. The operation was repeated twice to give (VI) (0.75 g, 45.4%) with specific activity 8.4 μCi/mg. The radiochemical yield was 43.8%, mp 153-155°C.

2-(Dimethylamino-^{3}H)-6-[bis(1-aziridinyl)phosphinylamino]-7-methylpurine (X) (Fopurine-^{3}H). A mixture of (VII) (98%; 0.38 g) in DMF (2.5 ml) and (VI) (0.36 g) was refluxed for 2.5 h and kept at 15-18°C for 12-14 h. The resulting precipitate was filtered off, washed on the filter with DMF (1 ml), and dried at 130-140°C. It was crystallized from ethyl alcohol (1:10) to give (VIII) (0.306 g) as a mixture of the hydrochloride and hydroiodide salts. Freshly distilled phosphorus oxychloride (6 ml) was then added to (VIII) (0.3 g). The suspension was refluxed for 13 h, whereupon the excess phosphorus oxychloride was distilled off under vacuum (40-50 mm Hg), bath temperature 60-80°C. The residue was carefully mixed with toluene (4 liter) and the residual phosphorus oxychloride was distilled off with toluene. This operation with toluene was repeated twice. Chloroform (12 ml) was added to the reaction mixture. The suspension was cooled to −5 to −7°C and a freshly prepared solution of potassium carbonate (0.4 g) and ethylenimine (0.21 g) in water (2 ml) was immediately added, with vigorous stirring and cooling. The temperature in the mixture rose to 10-15°C during this process. Cooling was discontinued and the reaction mixture was stirred for 30-40 min; the temperature in the mixture gradually rose to 18-20°C. Stirring was continued at this temperature for another 30 min or so, with checking lest the pH of the aqueous layer should fall below 8.0. The chloroform layer was separated, dried over anhydrous sodium sulfate for 1 h, and filtered. The filtrate was refluxed for 20-30 min with activated charcoal, filtered, and evaporated to dryness under vacuum. The residue was crystallized from alcohol (1:5), filtered, washed with alcohol, and dried at 50-60°C to give (X) (0.15 g, 22.4%) with specific activity 4.5 μCi/mg. The radiochemical yield was 21%, mp 249-250°C (decomposition).

Determination of the Radiochemical Purity of Fopurine-^{3}H

A weighed quantity of (X) was dissolved in chloroform and chromatographed on Silufol plates in the solvent systems chloroform–ethyl acetate–methanol (2:2:1) and propanol–ammonia (7:3) against an authentic specimen. The chromatographic plates were divided into strips of width 5 mm, which were scraped into bottles of scintillation fluid and scanned with an Ansitron liquid scintillation counter. Measurement gave one peak in all cases (R_f 0.2 and 0.5, respectively), containing not less than 95% of the radioactivity and with the same R_f as the authentic specimen (visualized with iodide vapor).

LITERATURE CITED

1. Yu. I. Savin, A. S. Singin, L. A. Nikolaeva, et al., Khim.-Farm. Zh., No. 12, 23-26 (1977).