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IMPROVED SYNTHESIS OF 8-HYDROXY-2'-DEOXYADENOSINE-5'-MONOPHOSPHATE

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ABSTRACT: Sequential reaction of 2'-deoxyadenosine-5'-monophosphate with bromine, sodium benzyloxide and hydrogen (Pd/C) conveniently gave 8-hydroxy-2'-deoxyadenosine-5'-monophosphate in a 58% overall yield.

Oxidative damage to DNA, as by ionizing radiation, is considered to be important in both aging and cancer.[1] One of the major types of such damage is conversion of the purine DNA bases, adenine and guanine, to corresponding C8-hydroxy products.[2] This leads to an interest in the availability of 8-hydroxy-2'-deoxyadenosine-5'-monophosphate (8-OH-dAMP), the subject of this report.

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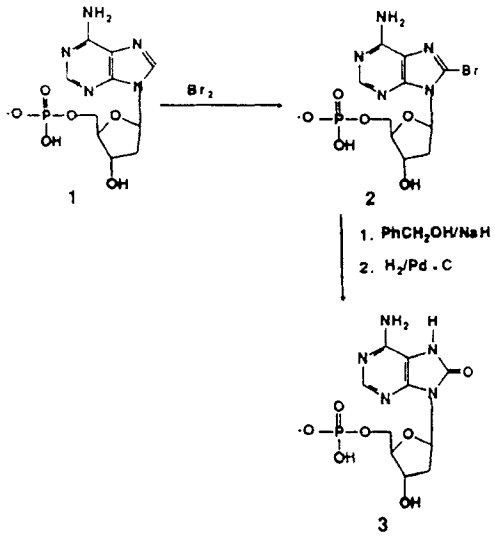
RESULTS AND DISCUSSION

8-OH-dAMP has been prepared before from 5'-dAMP.[3] The latter was first converted to 8-bromo-dAMP (purity and yield undefined), followed in turn by reaction with sodium acetate (giving 8-acetoxy-dAMP) and then tributylamine, giving 8-OH-dAMP (31% yield from the 8-bromo-dAMP). The use of inconvenient chromatograpic techniques for purification in this procedure, and the undefined or low yields, led us to develop the simpler, high-yield method reported here.

We first formed 8-bromo-dAMP in 80% yield by treating 5'-dAMP with bromine. The 8-bromo-dAMP was then treated sequentially with sodium benzyloxide and hydrogen (10% Pd/C), affording 8-OH-dAMP in 72% yield from 8-bromo-dAMP. The scheme for the synthesis is shown below. (The 8-keto tautomer is shown for **3** based on data obtained by Cho and Evans which revealed this tautomeric form for 8-hydroxyadenosine.[4])



Conveniently, both 2 and 3 are isolated by preparative reversed-phase HPLC using the same conditions.

8-Bromoadenosine has been converted to 8-hydroxyadenosine in 20% yield by sequential reaction with sodium benzyloxide and acetic acid.[4] Applying this procedure to 8-bromo-dAMP, we found, based on analytical HPLC, that some starting material remained. More strongly acidic conditions (addition of HBr) left no starting material but formed some 8-hydroxyadenine. (It is well-known that purine deoxynucleotides tend to depurinate under acidic conditions.[5]) The latter was identified by its co-elution on HPLC with an authentic sample. More successful was the reaction of the benzyloxy intermediate with hydrogen, the technique reported here.

EXPERIMENTAL

Materials

2'-Deoxyadenosine-5'-monophosphate (5'-dAMP) and benzyl alcohol were purchased from Sigma (St. Louis, MO). Sodium hydride and bromine were from Aldrich (Milwaukee, WI). An authentic sample of 8-hydroxyadenine was kindly provided by Bongsup P. Cho at the National Center for Toxicological Research, Jefferson, AR. Analytical HPLC comprised a CM4000 Multiple Solvent delivery system from Milton Roy (Bloomfield, CT) a 9060 Polychrom diode array detector (Varian, Walnut Creek, CA), and a C1-10B integrator (LDC/Milton Roy, Bloomfield, CT). Solvent A was 0.01M acetic acid (adjusted to pH 4.6 with triethylamine) and Solvent B was acetonitrile. The flow rate was 1 mL/min.

A Microsorb cartridge column, RP C_{18}, 10 cm x 4.6 mm, 5 um (Rainin Instruments, Woburn, MA), was used to follow the reaction using a 20 min gradient from 0 to 5% B. Preparative HPLC was done using the same gradient at a flow rate of 4 mL/min (Rainin 25 cm x 10 mm, RP-C_{18}, 5-um Microsorb cartridge column).

8-Bromo-2'-deoxyadenosine-5'-monophosphate.

A solution of 2'-deoxyadenosine-5'-monophosphate (123 mg, 0.35 mmol) in 5 mL of sodium acetate buffer (0.3 M, pH 5.5) was treated all at once with bromine (20 μL, 0.38 mmol) and stirred at room temperature for 5 h. Sodium bisulfite was added (until the color changed from orange to yellow, due to quenching of the bromine), followed by evaporation to dryness. Water (2 mL) was added and the product was purified by preparative HPLC to give a pale yellow solid (120 mg, 80%). ^{1}H NMR (CH_3OH-d_4), δ 2.32 (m,1H,2'-H) 3.31 (m,1H,2'-H) 3.98 (m,1H,4'-H), 4.17 (m,2H,5'-H), 4.8 (m,1H,3'-H), 6.45 (t,1H,1'-H) and 8.16 (s,1H,2-H).

8-Hydroxy-2'-deoxyadenosine-5'-monophosphate.

Sodium hydride (6 mg, 222 mmol) was added to dry (molecular sieves) benzyl alcohol (300 uL). After stirring this mixture under N_2 for 30 min, a solution of 8-bromo-2'-deoxyadenosine-5'-monophosphate (20 mg, 46.8 umol) in dry DMSO (50 ul) was added. After stirring at 55°C for 3 h (no starting material remained at this point based on HPLC), diethyl ether (1 mL) was added, and the resulting precipitate was collected, washed with ether (3 x 1 mL), air dried, and dissolved in 5 mL of methanol. Pd/C (10%, 3 mg) was added and hydrogen was applied (30 psi) with stirring at rt for 1 h.

The catalyst was removed by scintered glass filtration and washed with methanol (2 mL). Evaporation gave a crude product that was purified by preparative HPLC (retention time: 10.5 min) to give 11.8 mg (72%) of product as a white solid. ^{1}HNMR (CH_3OH-d_4): δ 2.25 (m,1H,2'-H), 3.11 (m,1H,2'-H), 3.42 (m,1H,4'-H), 4.08 (m,2H,5'-H), 4.8 (m,1H,3'-H), 6.32 (t,1H,1'-H) and 8.15 (s,1H,2-H).

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REFERENCES

(1) Beimer, L.H., *Molec. Carcinogen.*, **1990**, 3, 188; Poot, M., *Mut. Res.*, **1991**, 256, 177.

(2) Dizdaroglu, M. and Gajewski, E., *Meth. Enzymol.*, **1990**, 186B, 530.

(3) Lesiak, K.B. and Wheeler, K.T., *Rad. Res.*, **1990**, 121, 328.

(4) Cho, B.P. and Evans, F.E., *Nucleic Acids Res.*, **1991**, 19, 1041.

(5) Singer, B. and Grunberger, D., "Molecular Biology of Mutagens and Carcinogens", Plenum Press, New York, 1983.

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