Studies on Biologically Active Nucleosides and Nucleotides. 3. Synthesis of 9-(3-Bromo-3-deoxy-2,5-di-*O*-acetyl-β-D-xylofuranosyl)adenine

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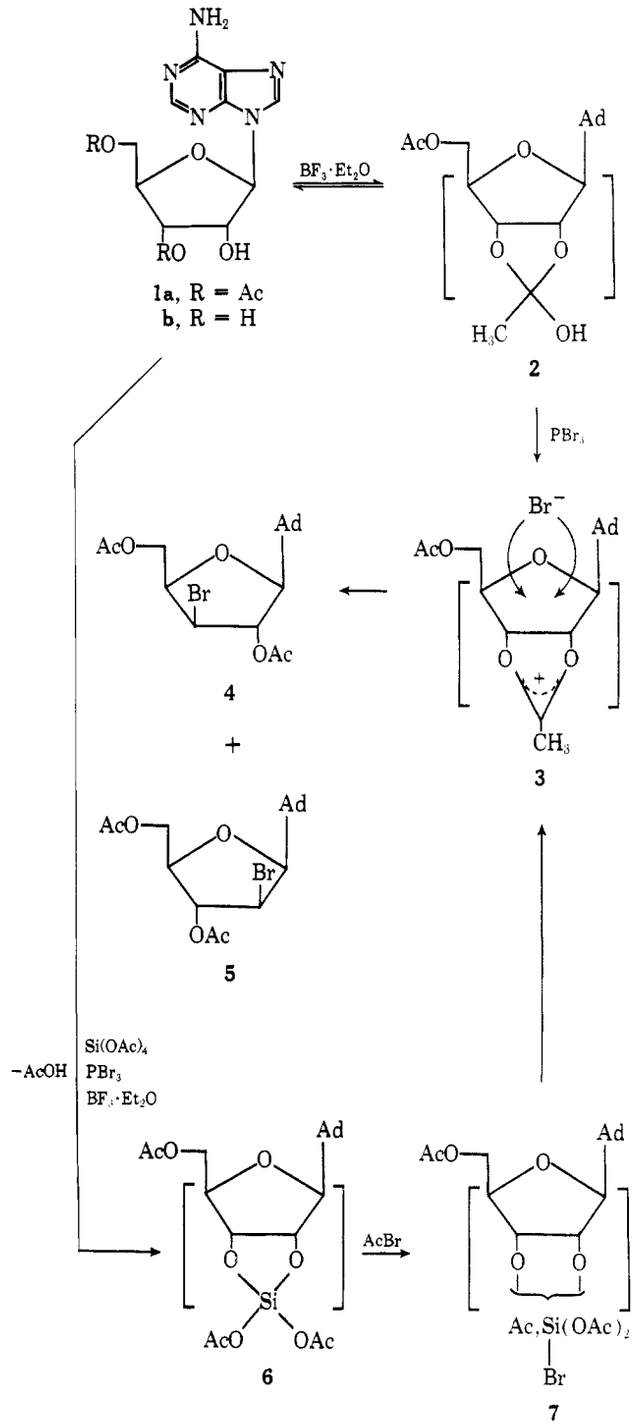
Purine nucleosides containing 3′-halo-3′-deoxyxylo functionality are versatile intermediates[1] for the preparation of trans β-hydroxy, epoxy, deoxy, and unsaturated nucleosides. For this reason considerable chemical effort has been devoted to the development of synthetic routes to the 3′-halogeno nucleosides. Two elegant syntheses of such halogen-substituted purine nucleosides have recently been reported by Robins'[1a,c] and Moffatt's groups.[1f] Robins' work involves a two-step reaction from adenosine which gives a mixture of 6-*N*-pivalamido-9-(3-chloro-3-deoxy-2,5-di-*O*-acyl-β-D-xylofuranosyl)purine and its 2′-chloroarabino isomer in approximately 60% combined yield. Moffatt has exploited the "abnormal Mattocks reaction" of α-acyloxyisobutyryl halides with adenosine which also gives the trans halo acetates with the 2′-*O*-acetyl-3′-deoxy-3′-halo-β-D-xylofuranoside isomer predominating.

In the previous work[2] of this series, we have shown that the reaction of tetraacetoxysilane with pyrimidine ribonucleosides in the presence of Lewis acid led to the formation of 2,2′-anhydro-1-(3′,5′-di-*O*-acetyl-β-D-arabinofuranosyl)pyrimidines. We have also shown[3] that such conversion could be achieved by treating pyrimidine ribonucleosides with acid anhydrides or acid chlorides in the presence of boron trifluoride etherate. The reaction mechanism has been explained via the opening of a 2′,3′-*O*-acetoxonium ion intermediate by the C_2-carbonyl oxygen. In this note, we extend the above work to the synthesis of 9-(3-bromo-3-deoxy-2,5-di-*O*-acetyl-β-D-xylofuranosyl)adenine (**4**) which would also be a useful intermediate for the transformations of the 2′,3′-cis diol function of adenosine.

Our initial study was done using 3′,5′-di-*O*-acetyl adenosine (**1a**).[4] The reaction of **1a** with a large excess of lithium bromide in the presence of boron trifluoride etherate was carried out in acetonitrile at room temperature for 24 h. TLC examination showed the sluggishness of the reaction and the extensive cleavage of the glycosyl bond. Following a simple workup, **4** was isolated in 26% yield. The structure of **4** was confirmed by its NMR spectrum (see Experimental Section) and by direct comparison with an authentic sample prepared by the acetylation of 9-(2-*O*-acetyl-3-bromo-3-deoxy-β-D-xylofuranosyl)adenine.[1f] In order to improve the yield, the reaction was investigated under various conditions, and the best result (55%) was obtained when 1.1 molar equiv of phosphorus tribromide was used in lieu of lithium bromide. Examination of the crude product from this reaction by NMR spectroscopy indicated the presence of 9-(2-bromo-2-deoxy-3,5-di-*O*-acetyl-β-D-arabinofuranosyl)adenine (**5**) as a minor product. The formation of **4** and **5** strongly suggests that the reaction did not proceed via direct displacement of the hydroxyl by phosphorus tribromide but a nucleophilic attack by bromide ion on the acetoxonium ion **3** from the β face of the sugar at either $C_{3'}$ or $C_{2'}$ (Scheme I). In the case of the reaction using phosphorus tribromide, the interaction of the hydroxy group of the ortho ester **2** with phosphorus tribromide would generate bromide ion, and at the same time the equilibrium between **1a** and **2** would be shifted to the right. This mechanism is akin to that proposed for the halogenation[5] of cyclic α-ketal acids with phosphorus pentahalides.

Scheme I



We then turned our attention to the direct synthesis of **4** from adenosine (**1b**). The reaction of **1b** with 2 molar equiv of tetraacetoxysilane and 1.1 molar equiv of phosphorus tribromide in the presence of boron trifluoride etherate was carried out in acetonitrile at room temperature. Following removal of water-soluble by-products by extraction, direct crystallization of the crude product gave **4** in 47% yield. In addition, the crystalline 2′-bromo isomer **5** (3%) and 2′,3′,5′-tri-*O*-acetyladenosine[6] (2%) were isolated from the mother liquors by chromatography on silicic acid. The structural assignment of **5** rests upon NMR analysis and the fact that the treatment of **5** with sodium methoxide afforded 9-(2,3-anhydro-β-D-ribofuranosyl)adenine. A suggested mechanism for this bromination is shown in Scheme I. The 1,3-dioxa-2-silacyclopentane derivative **6** would undergo ring cleavage by

acetyl bromide generated in situ to give the 2′,(3′)-*O*-acetyl derivative **7**, which would then cyclize to **3**. The formation of silyl halides and alkyl acetates by the action of acetyl halides on alkoxysilanes has been reported.[7] Attempts to prepare **4** by treatment of **1b** with acetic anhydride and phosphorus tribromide in the presence of boron trifluoride etherate in acetonitrile were unsuccessful, and resulted in the formation of 2′,3′,5′-tri-*O*-acetyladenosine as a major product, although a small amount of **4** could be detected (NMR) in the reaction.

The work presented in this note provides an alternative method for the transformation of the 2′,3′-cis diol function of purine nucleosides to the trans halo acetates.

Experimental Section

Melting points are uncorrected. NMR spectra were recorded on a Hitachi Perkin-Elmer R20A spectrometer and are reported in parts per million downfield from an internal standard of tetramethylsilane. UV spectra were measured on a Hitachi EPS-3T spectrometer. Thin-layer chromatography (TLC) was performed on Merck silica gel $60F_{254}$. Spots were detected by UV examination. Column chromatography was done using Merck silica gel 60.

Reaction of 3′,5′-Di-*O*-acetyladenosine (1a) with Lithium Bromide. Lithium bromide (5.0 g, 57 mmol) and boron trifluoride etherate (2.9 mL, 23 mmol) were added to a suspension of **1a**[4] (1.0 g, 3 mmol) in dry acetonitrile (100 mL). The resulting clear solution was kept at room temperature for 21 h. The solution was then neutralized with saturated aqueous sodium bicarbonate (20 mL) and concentrated to dryness. The residue was partitioned between chloroform (60 mL) and water (40 mL). The organic layer was washed with water (five 15-mL portions), dried ($MgSO_4$), and evaporated, leaving a solid residue. Crystallization of the residue from chloroform–hexane gave 300 mg (26%) of 9-(3-bromo-3-deoxy-2,5-di-*O*-acetyl-β-D-xylofuranosyl)adenine (**4**) with mp 165–167 °C. An analytical sample from the same solvent had mp 166–167 °C: UV λ_{max} (EtOH) 261 nm (ε 14 700); NMR (Me_2SO-d_6) δ 2.10 (s, 3, OAc), 2.17 (s, 3, OAc), 4.3–4.8 (m, 3, $C_{5'}$ H_2, $C_{4'}$ H), 4.9–5.1 (m, 1, $C_{3'}$ H), 5.9–6.1 (m, 1, $C_{2'}$ H), 6.28 (d, J = 3 Hz, 1, $C_{1'}$ H), 7.3–7.7 (br s, 2, NH_2), 8.29 (s, 1, C_2H or C_8 H), 8.41 (s, 1, C_2 H or C_8 H). Anal. Calcd for $C_{14}H_{16}N_5O_5Br$ (414.23): C, 40.59; H, 3.89; N, 16.91; Br, 19.29. Found: C, 40.45; H, 3.99; N, 16.80; Br, 19.69. This compound was identical (IR, NMR) with an authentic sample prepared by an alternate route (vide infra).

Alternative Synthesis of 4. To a suspension of 9-(2-*O*-acetyl-3-bromo-3-deoxy-β-D-xylofuranosyl)adenine[1f] (190 mg, 0.5 mmol) in pyridine (2.5 mL) was added acetic anhydride (250 mg, 2.5 mmol). The mixture was stirred at room temperature for 1.5 h and evaporated in vacuo. The residue was crystallized from chloroform–isopropyl ether to give 170 mg (80%) of **4** with mp 165–166 °C.

Reaction of 1a with Phosphorus Tribromide. Boron trifluoride etherate (2.2 mL, 17.5 mmol) and phosphorus tribromide (0.2 mL, 2.1 mmol) were added to a suspension of **1a** (700 mg, 2 mmol) in dry acetonitrile (30 mL). The resulting clear solution was kept at room temperature for 2 h and worked up as above to give a solid foam. Crystallization of the solid foam from methyl *n*-propyl ketone gave 450 mg (55%) of **4** with mp 166–167 °C. This compound was identical with the sample prepared as above.

Reaction of Adenosine (1b) with Tetraacetoxysilane and Phosphorus Tribromide. Phosphorus tribromide (2.0 mL, 20.6 mmol) was added to a solution of tetraacetoxysilane[2] (9.9 g, 37.5 mmol) in dry acetonitrile (200 mL). The solution was kept at room temperature for 3 h. To this solution, **1b** (5 g, 18.7 mmol) and boron trifluoride etherate (42 mL, 0.326 mol) were added and the mixture was stirred at room temperature for 18 h. The resulting clear solution was poured into saturated aqueous sodium bicarbonate (500 mL), and the acetonitrile was largely removed in vacuo. The aqueous residue was extracted with chloroform (three 100-mL portions), and the organic phase was dried ($MgSO_4$). Evaporation of the solvent left a syrup which was crystallized from ethanol (30 mL). The crystals were collected, washed with ether, and dried thoroughly in vacuo at 80–90 °C to give 3.7 g (47%) of **4** with mp 165–167 °C, identical (IR, NMR) with that above. The mother liquors from the crystallization were evaporated, and the residue was chromatographed on a column of silicic acid (2.5 × 40 cm). The required fraction was eluted with chloroform–methanol (95:5). The eluate was evaporated and the residue (1.8 g) was crystallized from methyl *n*-propyl ketone to give 270 mg (3%) of 9-(2-bromo-2-deoxy-3,5-di-*O*-acetyl-β-D-arabinofuranosyl)adenine (**5**) with mp 138–140 °C: UV λ_{max} (MeOH) 260 nm (15 500); NMR (Me_2SO-d_6) δ 2.07 (s, 3, OAc), 2.17 (s, 3, OAc), 4.1–4.7 (m, 3, $C_{4'}$ H, $C_{5'}$ H_2), 5.0–5.3 (m, 1, $C_{2'}$ H), 5.8–6.1 (m, 1, $C_{3'}$ H), 6.49 (d, J = 6 Hz, 1, $C_{1'}$ H), 7.2–7.6 (br s, 2, NH_2), 8.20 (s, 1, C_2 H or C_8 H), 8.30 (s, 1, C_2 H or C_8 H). Anal. Calcd for $C_{14}H_{16}N_5O_5Br$ (414.23): C, 40.59; H, 3.89; N, 16.91; Br, 19.20. Found: C, 40.72; H, 4.08; N, 16.56; Br, 19.52. The mother liquors from the crystallization of **5** were evaporated and the residue was crystallized from ethanol, giving 120 mg (2%) of 2′,3′,5′-tri-*O*-acetyladenosine with mp 167–168 °C. This compound was identical with the sample prepared by an alternate route.[6]

Conversion of 5 to 9-(2,3-Anhydro-β-D-ribofuranosyl)adenine. To a suspension of **5** (500 mg, 1.2 mmol) in methanol (25 mL) was added 1 M methanolic sodium methoxide (3.6 mL). The resulting solution was stirred and heated at 50–55 °C for 20 min. After cooling, the mixture was neutralized with acetic acid and evaporated in vacuo. The crystalline residue was washed with water, then methanol, and dried, giving 220 mg (73%) of 9-(2,3-anhydro-β-D-ribofuranosyl)-adenine with mp ~180 °C dec. This material was identical (IR, NMR) with an authentic sample prepared by a different route.[1f]

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Registry No.—**a**, 6554-24-1; **b**, 58-61-7; **4**, 62805-48-5; **5**, 62805-49-6; 9-(2-*O*-acetyl-3-bromo-3-deoxy-β-D-xylofuranosyl)adenine, 42867-78-7; 2,3′,5′-tri-*O*-acetyladenosine, 7387-57-7; 9-(2,3-anhydro-β-D-ribofuranosyl)adenine, 2627-64-7.

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Bridgehead Free Radicals. The Tri-*n*-butyltin Hydride Reduction of Bridgehead Halides

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Some years ago, we reported on the stability of bridgehead free radicals as measured by the rates of unimolecular decomposition of *tert*-butyl peresters, and suggested that the results (included in Table I) were in accord with a preferred planar geometry for carbon-free radicals.[1] We ourselves, and Ruchardt (among others),[2] expressed some concern that the transition state for perester decomposition (1) might have

1

some charge separation, which would cause the rates to reflect carbonium ion, rather than radical, stabilities. This concern was reinforced by our measurement of a ρ^* of −1.6 for decomposition of some substituted adamantyl peresters.[3]

Consequently, we sought a reaction free of such complications, and settled upon the tri-*n*-butyltin hydride reduction of halides (eq 1).[4] This reduction is known to be a radical chain