85 (47), 71 (57), 57 (100), 43 (79); ^{1}H NMR ($CDCl_3$) δ 1.5 (br m, 2, $CHMe_2$), 1.22 (br s, 6, CH_2), 0.85 (d, 12, J = 6 Hz, CH_3); IR (neat) 2950, 2880, 1460, 1380, 1360, 1170 cm^{-1}.

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Registry No. 1, 2590-12-7; 2, 27943-46-0; 2,7-dimethyloctane, 1072-16-8.

Reductive Debromination of Some Purine and Purine-Like Nucleosides

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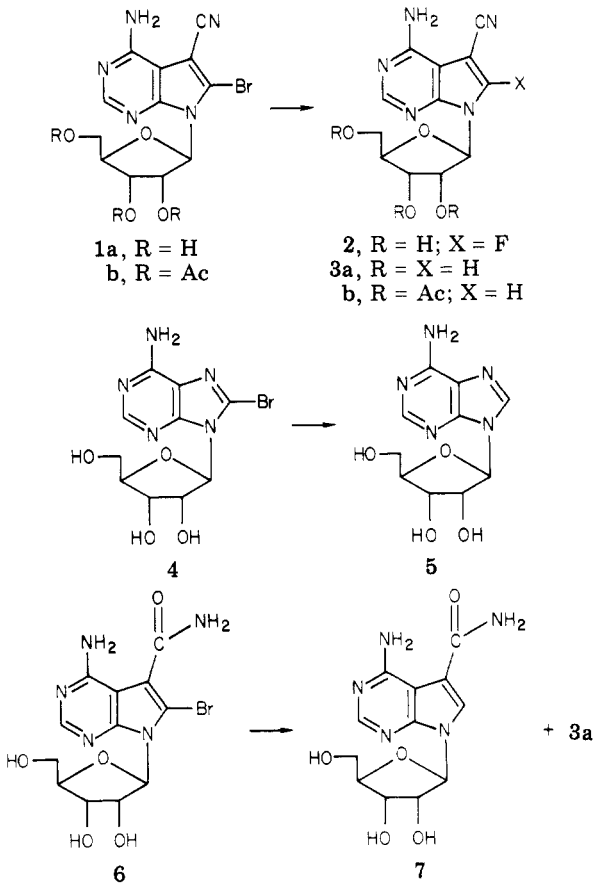
The synthetic applications of trialkylsilylating agents in the field of nucleoside and nucleotide chemistry are well-documented.[1] The three most commonly used silylating agents are hexamethyldisilazane (HMDS), trimethylsilyl chloride, and *N,O*-bis(trimethylsilyl)acetamide (BSA). It has been shown that BSA is a versatile and reactive agent for the synthesis of silylated heterocycles. These silylated heterocycles can then be condensed with a suitably blocked derivative to provide a great variety of nucleoside analogues. Due to the ubiquitous use of BSA in this area, we report a novel reaction where BSA functions as a debrominating agent in the presence of potassium fluoride and a crown ether.

In an attempt to synthesize 6-fluorotoyocamycin (**2**) from 6-bromotoyocamycin (**1**), a solution of 6-bromotoyocamycin and an excess of BSA in acetonitrile was mixed with a suspension of potassium fluoride and dicyclohexyl-18-crown-6 in acetonitrile. The reaction mixture was heated at reflux temperature in an oil bath for 48 h. After removal of the solvent, a nucleoside product was isolated by chromatography. This product (40% yield) was found to be toyocamycin (**3a**) by a comparison of the UV, ^{1}H NMR, and IR spectra and mixture melting point with an authentic sample of toyocamycin. This interesting observation prompted us to study a series of similar reactions (see Scheme I); e.g., adenosine (**5**) was isolated in 44% yield when 8-bromoadenosine (**4**) was treated with BSA, potassium fluoride, and crown ether under the same conditions. Similarly, 6-bromosangivamycin (**6**) afforded sangivamycin (**7**) in 30% yield. The isolation of toyocamycin (**3a**) in 20% yield from this same reaction would indicate that perhaps this may be a new method for the transformation of a carboxamide group into a nitrile group.

2′,3′,5′-Tri-*O*-acetyl-6-bromotoyocamycin (**1b**) was prepared and then treated under the standard conditions (9-h reflux) to provide a 60% yield of 2′,3′,5′-tri-*O*-acetyltoyocamycin (**3b**) and established that BSA is indispensible in these reactions. However, when the reaction was repeated without the addition of BSA, there was no apparent reaction even after heating for more than 48 h. We also found that the attempted reaction of 6-bromotoyocamycin (**1a**) with BSA and crown ether in the absence of potassium fluoride afforded, after heating at reflux for 72 h, only starting material. On the basis of these experiments, we have concluded that BSA and potassium fluoride are both required for the debromination reaction.

Scheme I



1a, R = H
b, R = Ac

2, R = H; X = F
3a, R = X = H
b, R = Ac; X = H

4 5

6 7

It is not clear at this time what species is responsible for the observed reductions. It is interesting to note, however, that the trimethylsilyl anion has been reported[2-4] to function not only as a nucleophile in reactions with organic halides but also as a reducing agent due to its one-electron-transfer properties. Trimethylsilyl anion[5] has been prepared[2-4] through the action of alkali alkoxides on hexamethyldisilane in polar aprotic solvents. It has also been shown[6,7] that crown ethers are capable of complexing with alkali metal ions, resulting in an increased separation of charge between the alkali metal ion and its counterion. The use[6-7] of crown ethers also serves to increase the solubility of alkali metal ions in nonpolar solvents (e.g., benzene, ether, or tetrahydrofuran). It seems likely that the "naked" fluoride ion,[8] formed under our reaction conditions, may be interacting with BSA or (monotrimethylsilyl)acetamide in such a manner as to produce[9]

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trimethylsilyl anion and that this may be the species responsible for the debrominations. To the best of our knowledge, this is the first time that BSA has been reported to be a reducing agent when used in combination with fluoride ion and a crown ether.

Experimental Section

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian EM-390 spectrophotometer, using Me_2SO-d_6 as solvent and sodium 4,4-dimethyl-4-silapentane-1-sulfonate as internal standard unless otherwise stated. Thin-layer chromatography was carried out on microscope slides coated with chromatography-grade silica gel (silicAR) obtained from Mallinckrodt. Column chromatography was carried out by using J. T. Baker chromatographic-grade silica gel powder in glass columns. Concentrations were carried out in vacuo at 30–40 °C. Solvent system E is the upper layer of a mixture of ethyl acetate–*n*-propyl alcohol–water (4:1:2, v/v/v).

Standard Conditions for Debromination of Deblocked Nucleosides. To a suspension of dried (110 °C, 0.5 torr, 1 h), powdered nucleoside (0.5 mmol) in dry acetonitrile (distilled from calcium hydride) was added *N*,*O*-bis(trimethylsilyl)acetamide (0.6 mL, 2.5 mmol), using a dry syringe. A clear solution was obtained after stirring for 1 h. To this solution was added a mixture of potassium fluoride (58 mg, 1.0 mmol) and dicyclohexyl-18-crown-6 (14 mg, 0.05 mmol) in dry acetonitrile which was previously stirred for 30 min. The reaction mixture was heated at reflux temperature until starting material was no longer detected in the thin-layer chromatogram. Methanol (30 mL) was added to the reaction mixture and the solution was then stirred for 20 h at room temperature. Silica gel (1 g) was added to the solution and the solvent was removed in vacuo. The residual solid was applied to the top of a column (2 × 25 cm) containing silica gel (22 g) and the column eluted with the appropriate solvent. Progress of the chromatography was followed by TLC and fractions containing product were combined and concentrated.

Debromination of 6-Bromotoyocamycin. Treatment of 6-bromotoyocamycin[10] (**1**) under standard conditions for 45 h gave a product that was chromatographed as described above, using chloroform–methanol (13:3, v/v) as eluant. Combination of appropriate fractions yielded toyocamycin (50 mg, 34.3%), which was shown to be identical with an authentic sample of toyocamycin[11] (UV, ^{1}H NMR, R_f, IR, and mixture melting point). When the above reaction was carried out under the same conditions, but without potassium fluoride, no change in starting material was noted.

Debromination of 6-Bromosangivamycin. 6-Bromosangivamycin[12] (**6**, 194 mg) was treated as above for 72 h. Chromatography was carried out as described above, using first a mixture of chloroform–ethanol (600 mL, 8:2, v/v) and then solvent system E (300 mL). A faster running component was isolated (30 mg, 25%), which was shown to be toyocamycin by the usual criteria. A slower moving component (45 mg, 30%) was also isolated which proved to be sangivamycin.

Debromination of 8-Bromoadenosine. 8-Bromoadenosine (**4**, 173 mg) was treated as described for 96 h. Chromatography, using solvent system E, yielded 20 mg of starting material as well as a slow-moving component (40 mg, 36%, based on recovered starting material), which was shown to be adenosine by a direct comparison with an authentic sample.

2′,3′,5′-Tri-*O*-acetyl-6-bromotoyocamycin (1b). Acetic anhydride (0.7 mL, 7.54 mmol) was added to a suspension of 6-bromotoyocamycin (**1a**, 370 mg, 1.03 mmol) in pyridine (15 mL). The mixture was stirred at room temperature for 4 h (clear solution occurred in 10 min). The solvent was removed in vacuo and the residual solid was coevaporated in succession with ethanol (2 × 15 mL), water (2 × 15 mL), and finally toluene (2 × 15 mL). The solid was crystallized from methanol to afford 2′,3′,5′-tri-*O*-acetyl-6-bromotoyocamycin (**1b**) in a quantitative yield: mp 200 °C; ^{1}H NMR ($CDCl_3$) δ 2.00, 2.06, and 2.11 (3 s, 9, 3 CH_3CO), 5.77 (br s, 2, NH_2), 6.16 (m, 2, H_1', H_2'), 8.26 (s, 1, H_2).

Anal. Calcd for $C_{18}H_{18}N_5O_7Br$: C, 43,52; H, 3.65; N, 14.17. Found: C, 43.85, H, 3.48; N, 13.73.

Debromination of 2′,3′,5′-Tri-*O*-acetyl-6-bromotoyocamycin (1b). 2′,3′,5′-Tri-*O*-acetyl-6-bromotoyocamycin (**1b**, 496 mg, 1.0 mmol) was dissolved in dry acetonitrile (20 mL). BSA (1.0 mL, 4.0 mmol) was added to the solution while stirring at 25 °C. To this solution was added a mixture of potassium fluoride (106 mg, 2.0 mmol) and dicyclohexyl-18-crown-6 (28 mg, 0.1 mmol) in dry acetonitrile which had already been stirred vigorously for 30 min. The reaction mixture was then heated at reflux for 9 h. The resulting dark-brownish solution was evaporated in vacuo to dryness. The residual syrup was dissolved in chloroform (7 mL) and applied to the top of a column (3 × 30 cm) of silica gel (30 g). The column was eluted with chloroform–ethyl acetate (4:1, v/v). Fractions containing the product were combined and concentrated to yield 250 mg (60%) of 2′,3′,5′-tri-*O*-acetyltoyocamycin (**3b**), mp 158 °C. The UV spectrum of this product was identical with that of toyocamycin: ^{1}H NMR (Me_2SO-d_6) δ 2.03, 2.05, 2.13 (3 s, 9, 3 CH_3CO), 6.30 (d, 1, H_1'), 6.94 (br s, 2, NH_2), 8.23 (s, 1, H_5 or H_2), 8.42 (s, 1, H_2 or H_5). Further treatment of **3b** (150 mg, 0.36 mmol) with methanolic ammonia (15 mL, saturated at 0 °C) at 5 °C for 2 h afforded 80 mg (76.4%) of toyocamycin (**3a**) which was shown to be identical with an authentic sample by a comparison of the UV, ^{1}H NMR, TLC, and melting point.

When BSA was left out of the above reaction, no change in starting material was observed.

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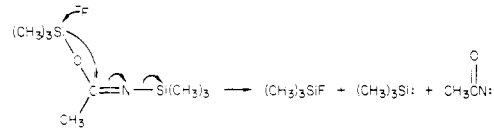
Registry No. **1a**, 20201-55-2; **1b**, 74112-93-9; **3a**, 606-58-6; **3b**, 74098-09-2; **4**, 2946-39-6; **5**, 5682-25-7; **6**, 20201-56-3; **7**, 18417-89-5.

(9) One could imagine fluoride ion attacking BSA to produce trimethylsilyl anion in the following manner:



This mechanism predicts the formation of acetyl nitrene which could rearrange to give methyl isocyanate or react with solvent. It is interesting to speculate that the reaction of BSA with other bases (e.g., alkoxides) might be a useful means of producing the trimethylsilyl anion.

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Orientation in Dehydrohalogenation of 2-Halobutanes Promoted by 2,6-Di-*tert*-butylpiperidide Base

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Positional orientation in base-promoted 1,2-eliminations from 2-substituted alkanes is strongly influenced by base association.[1] For example, in *t*-BuOK-promoted eliminations from 2-bromobutane, the relative proportion of 1-butene increases from 30% in dimethyl sulfoxide (Me_2SO)

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