on a column of silica gel (eluting solvent: benzene). The first material to emerge from the column was the desired 2,8,17-trithia[$4^{5,12}$][9]metacyclophane, which was recrystallized from ethyl acetate (85 mg, 0.27 mmol, 5.5% yield). The melting behavior was unusual: at 170–180 °C, the crystals softened and bent, but did not liquefy; at 280 °C the material began to discolor; decomposition was gradual from 300–350 °C (lit.[1] mp 176 °C). ^{1}H NMR ($CDCl_3$, 250 MHz, TMS reference): δ −1.68 [septet, 1 H, J = 6 Hz, $(RSCH_2CH_2)_3CH$], 1.07 [m, 6 H, $(RSCH_2CH_2)_3CH$], 2.36 [m, 6 H, $(RSCH_2CH_2)_3CH$], 3.66 [s, 6 H, $Ar(CH_2)_3$], 7.19 [s, 3 H, ArH_3]; MS, m/z 310 ($M^{\cdot+}$, 29), 207 (M − $C_5H_{10}SH$, 15), 159 (65), 150 (59), 118 (64), 117 (65), 115 (86), 91 (100); IR ν_{max} (cm^{-1}) 2941, 2916, 2892, 2847, 1599, 1451, 1438, 1412, 1274, 1261, 1220, 1155, 1136, 876, 722.

Convenient Synthesis of 2-Halo-2′-deoxyadenosines

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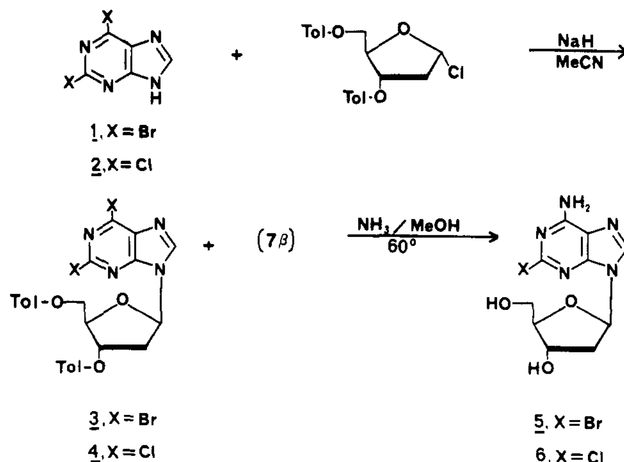
2-Halo-2′-deoxyadenosines show significant cytotoxicity against human T cells[1,2] and melanoma cells[3] in culture. The increased toxicity relative to deoxyadenosine is due to the presence of a halogen at the 2-position, a feature that prevents enzymatic deamination but allows phosphorylation in cells.[4] The phosphorylated deoxyadenosine analogues are readily incorporated into DNA, thus blocking DNA synthesis.[3] The potential use of 2-halo-2′-deoxyadenosines as anticancer agents has prompted a need for a convenient large-scale synthesis.

Current methods of synthesis of 2-bromo-2′-deoxyadenosine (2-Br-dAdo, **5**) reported by Huang et al.[5,6] involve an enzymatic glycosylation step. 2-Bromoadenine was converted to 2-Br-dAdo by the enzyme nucleoside deoxyribosyltransferase with thymidine as the sugar donor. The initial method was limited by the difficulty in the synthesis of 2-bromoadenine.[5] Consequently, an improved method was developed to give 2-bromoadenine in a multistep sequence from the naturally occurring nucleoside guanosine.[6] The ultimate enzymatic glycosylation of this base, however, requires the isolation and purification of nucleoside deoxyribosyltransferase from *Lactobacillus leichmannii*, and the scale of the reaction was limited to ca. 1 mmol.[5]

We report a convenient and large-scale synthesis of 2-Br-dAdo based on the sodium salt glycosylation method originally described by Kazimierczuk et al.[7] 2,6-Dibromopurine (**1**) was prepared in 40% yield following the



literature procedure.[8] The sodium salt of **1**, obtained by the addition of sodium hydride to a solution of **1** in dry acetonitrile, was treated at room temperature with 1-chloro-2-deoxy-3,5-di-*p*-toluoyl-α-D-*erythro*-pentofuranose.[9] After it was stirred for 1 h, the reaction mixture was filtered through Celite, washed with chloroform, and evaporated to a slurry. The slurry was layered onto a short silica gel column and eluted with chloroform. The solvent was evaporated, and the residue was mixed with toluene. The resulting suspension was filtered and the solid washed with toluene to give the pure 9-β-deoxyribofuranosyl isomer **3** in 50% yield, identified by its characteristic ^{1}H NMR spectrum and by its conversion to **5** (see below). The filtrate containing residual **3** and a second isomer was purified by HPLC (silica gel column). Elution with 4% acetone in toluene gave an additional 6% yield of the 9-β isomer and 11% yield of a second product, which is thought to be the 9-α isomer.[10] Employing the same isolation procedure with 2,6-dichloropurine, the 9-β-deoxyribofuranosyl isomer **4** was isolated in pure form in 58% yield by filtration from toluene, as compared with the 59% overall yield obtained through chromatography of the reaction mixture, as described by Kazimierczuk et al.[7]

Ammonolysis of **3** effected both deblocking of the sugar and displacement of the 6-bromo group. A solution of **3** in methanol, saturated with anhydrous ammonia at 0 °C, was heated in a steel bomb at 60 °C for 32 h. After evaporation of solvent, the residue was purified on a short silica gel column by elution with 20% methanol in chloroform to give chromatographically pure **5** in 94% yield. The same procedure applied to **4** was reported to give 2-chloro-2′-deoxyadenosine (**6**) in comparable yield.[7]

The method of synthesis of 2-bromo- and 2-chloro-2′-deoxyadenosines described in this work has several advantages over current methods.[5,6] The synthesis of 2,6-dihalopurines, although proceeding in modest yields, requires inexpensive reagents, can be done on large scales, and thus provides readily available starting materials. The sodium salt glycosylation reaction applied to 6-chloropurines[7] proceeds with a strong preference for glycosylation at the 9-position relative to the 7-position and has been

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(1) Carson, D. A.; Wasson, D. B.; Kaye, J.; Ullman, B.; Martin, D. W., Jr.; Robins, R. K.; Montgomery, J. A. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 6865–6869.

(2) Carson, D. A.; Wasson, D. B.; Beutler, E. *Proc. Natl. Acad. Sci. U.S.A.* **1984**, *81*, 2232–2236.

(3) Parsons, P. G.; Bowman, E. P.; Blakley, R. L. *Biochem. Pharmacol.* **1986**, *35*, 4025–4029.

(4) Bennett, L. L., Jr.; Chang, C.-H.; Allan, P. W.; Adamson, D. J.; Rose, L. M.; Brockman, R. W.; Secrist J. A., III; Shortnacy, A.; Montgomery, J. A. *Nucleosides Nucleotides* **1985**, *4*, 107–116.

(5) Huang, M.; Hatfield, K.; Roetker, A. W.; Montgomery, J. A.; Blakley, R. L. *Biochem. Pharmacol.* 1981, *30*, 2663–2671.

(6) Huang, M.; Avery, T. L.; Blakley, R. L.; Secrist J. A., III; Montgomery, J. A. *J. Med. Chem.* **1984**, *27*, 800–802.

(7) Kazimierczuk, Z.; Cottam, H. B.; Revankar, G. R.; Robins, R. K. *J. Am. Chem. Soc.* **1984**, *106*, 6379–6382.

(8) Beaman, A. G.; Gerster, J. F.; Robins, R. K. *J. Org. Chem.* **1962**, *27*, 986–990.

(9) Hoffer, M. *Chem. Ber.* **1960**, *93*, 2777–2781.

(10) On the basis of the results of the sodium salt glycosylation of 2,6-dichloropurine,[7] the additional product was expected to be the 7-β isomer. NMR data suggests, however, that this compound is a 9-α isomer. Its ^{1}H NMR spectrum in deuteriochloroform (see the Experimental Section) resembled that of 2,6-dichloro-9-(2-deoxy-3,5-di-*O*-acetyl-α-D-ribofuranosyl)purine (Montgomery, J. A.; Hewson, K. *J. Med. Chem.* **1969**, *12*, 498–504) rather than that of the 7-β nucleoside (ref 7). The identity and mechanism of formation of this second dibromopurine nucleoside are being pursued.

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reported to give only β-anomers. The desired compound 3 was also the major product of glycosylation of the 6-bromopurine 1, although the minor component was apparently the 9-α isomer rather than the expected 7-β isomer. In addition, the facile and direct isolation of the 9-β-deoxyribofuranosyl isomers precludes lengthy chromatographic separation of glycosylation products. In the final step, the protected 2,6-dihalo nucleosides are converted nearly quantitatively to the target 2-halo-2′-deoxyadenosines. This chemical method appears to be adaptable to large-scale syntheses, as demonstrated by the 50-fold greater scale of the glycosylation of 2,6-dibromopurine as compared with the enzymatic glycosylation of 2-bromoadenine.[5]

Experimental Section

Melting points were determined on a Mel-Temp apparatus and are uncorrected. Elemental analyses were performed by the Microanalysis Laboratory, University of Massachusetts, Amherst; experimental analyses were within ±0.4% of calculated values. ^{1}H NMR spectra were obtained at 250 MHz with a Bruker WM250 instrument; chemical shifts are reported in parts per million (δ) relative to internal tetramethylsilane. UV spectra were obtained with a Gilford Response spectrophotometer.

2,6-Dibromo-9-(2-deoxy-3,5-di-*p*-toluoyl-β-D-ribofuranosyl)purine (3) and Its 9-α Isomer. A mixture of 1 (12 g, 0.043 mol) and sodium hydride (50% suspension in mineral oil, 2.27 g, 0.047 mol) in acetonitrile (225 mL) was stirred at room temperature for 1 h. 1-Chloro-2-deoxy-3,5-di-*p*-toluoyl-α-D-*erythro*-pentofuranose[9] was added in small portions during 1 h, and stirring was continued for 15 min. The mixture was filtered through Celite, and the adsorbent was washed with chloroform (250 mL). The combined filtrates were evaporated to a slurry and layered onto a short column of silica gel (ca. 300 g, 70–230 mesh). The products were eluted with chloroform (1 L), and after the solvent was evaporated, the residue was mixed with toluene. The resulting suspension was filtered and the solid washed with toluene to give 13.5 g (50%) of the 9-β isomer 3 as colorless crystals: mp 156–158 °C (from MeOH); UV (EtOH) λ_{max} 276.4 nm (ε 13 000); ^{1}H NMR (CDCl$_3$) δ 8.28 (s, 1 H, C8-H), 6.54 (pseudo t, 1 H, Cl′-H; J_{av} = 7.0 Hz), ca. 4.70 (m, 3 H, 4′, 5′, 5″-H). Anal. ($C_{26}H_{22}N_4O_5Br_2$) C, H, N, Br.

The filtrate containing residual 3 and the second product was purified by HPLC (silica gel, 50 cm × 22.5 mm). Elution with 4% acetone in toluene (550 mL) gave an additional 1.8 g (6.7%) of 3. Continued elution (400 mL) gave 3 g (11%) of a product tentatively identified as the 9-α anomer: mp 98–100 °C (from EtOH); UV (EtOH) λ_{max} 276.6 nm (ε 12 400); ^{1}H NMR (CDCl$_3$) δ 8.45 (s, 1 H, C8–H), 6.61 (pseudo q, 1 H, Cl′-H; J = 6.0, 1.3 Hz), 4.93 (m, 1 H, 4′-H), 4.64 (m, 2 H, 5′, 5″–H). Anal. ($C_{26}H_{22}N_4O_5Br_2$) C, H, N, Br.

2-Bromo-2′-deoxyadenosine (5). A solution of 3 (2.56 g, 4 mmol) in methanol (80 mL) was saturated with anhydrous ammonia at 0 °C and heated in a steel bomb at 60 °C for 32 h. The solvent was evaporated and the residue was purified on a column of silica gel (50 g, 70–230 mesh) by elution with 20% methanol in chloroform to give 1.24 g (94%) of chromatographically pure 5: mp, begins to turn brown at 193 °C and gradually darkens without melting (in agreement with the behavior of an authentic sample provided by J. A. Secrist, III); UV (EtOH) λ_{max} 265.5 nm (ε 14 900); ^{1}H NMR (Me$_2$SO-d_6) δ 8.32 (s, 1 H, C8-H), 6.27 (pseudo t, 1 H, Cl′-H, J_{av} = 7.5 Hz), all other ^{1}H NMR resonances as expected.

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Registry No. 1, 1196-41-4; 2, 5451-40-1; β-3, 110096-57-6; α-3, 110096-58-7; 4, 38925-80-3; 5, 89178-21-2; 1-chloro-2-deoxy-3,5-di-*p*-toluoyl-α-D-*erythro*-pentofuranose, 4330-21-6.

Functionalization of Aromatic and Heterocyclic Systems. Regioselective Introduction of 2-Oxoalkyl Chain or Cyano Functions via Organoiron Complexes

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Selective functionalization of aromatic and heterocyclic systems is an important problem in synthetic organic chemistry. Numerous methods have recently been described for selective alkylation of nitroarenes;[1–5] however, while each of the methods is illustrated by interesting synthetic applications, none of them is general.

Our earlier studies reported the ready formation of cyclohexadienyl adducts in reactions of arenes or heterocycles bearing an electron-withdrawing function and complexed with an iron (Cp) moiety, with ketone enolate, or cyano anions[6] (Scheme I).

Such adducts have synthetic potential, since removal of the iron (Cp) moiety in demetalation–rearomatization reactions would lead to functionalized arenes or heterocycles. We confirmed this conclusion with the isolation of a new compound, 2,5-dichlorophenylpropanone, from the demetalation of the precursor cyclohexadienyl complex[6a,b] using a procedure employing buffered CAN as an oxidant.[7]

Careful investigation of that reaction involving GC and GC–MS examination of liberated arenes or heterocycles proved that demetalation could be followed by rearomatization by the abstraction of either endo hydride or exo cyano/oxoalkyl function. Thus, in the case of complex 1, besides **1a** (50%) a significant amount (20%) of *p*-dichlorobenzene was found, and other demetalations gave the following results: **5** gave 72% of **5a** and 20% of benzophenone; **8** gave 64% of **8a** and 22% of anthraquinone; **10** gave 30% of **10a** as well as 34% of xanthone.

In the present study we obtained functionalized arenes and heterocycles **1a**–**11a** (Scheme II) using a superior procedure for the oxidative demetalation. Buffered CAN has been replaced by DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone), which has been widely used in studies of arene systems[2–5] and occasionally with metal complexes.[8]

(1) (a) Makosza, M. In *Current Trends in Organic Synthesis*; Nozaki, H., Ed.; Pergamon: Oxford, 1983. (b) Makosza, M.; Winiarski, J. *J. Org. Chem.* 1984, *49*, 1494. (c) Makosza, M.; Kinowski, A.; Danikiewicz, W.; Mudryk, B. *Liebigs Ann. Chem.* 1986, 69.

(2) (a) Kienzle, F. *Helv. Chim. Acta* 1978, *61*, 449. (b) Bartoli, G.; Medici, A.; Rosini, G.; Tavernari, D. *Synthesis* 1978, 436. (c) Bartoli, G.; Bosco, M.; Melandri, A.; Boicelli, A. C. *J. Org. Chem.* 1979, *44*, 2087. (d) Bartoli, G. *Acc. Chem. Res.* 1984, *17*, 109. (e) Bartoli, G.; Bosco, M.; Dalpozzo, R. *Tetrahedron Lett.* 1985, *26*, 115.

(3) Bartoli, G.; Bosco, M.; Dalpozzo, R.; Todesco, P. E. *J. Org. Chem.* 1986, *51*, 3694.

(4) RajanBabu, T. V.; Reddy, G. S.; Fukunaga, T. *J. Am. Chem. Soc.* 1985, *107*, 5473.

(5) Bartoli, G.; Dalpozzo, R.; Grossi, L.; Todesco, P. E. *Tetrahedron* 1986, *42*, 2563.

(6) (a) Sutherland, R. G.; Chowdhury, R. L.; Piórko, A.; Lee, C. C. *J. Chem. Soc., Chem. Commun.* 1985, 1296. (b) Sutherland, R. G.; Chowdhury, R. L.; Piórko, A.; Lee, C. C. *Can. J. Chem.* 1986, *64*, 2031. (c) Sutherland, R. G.; Chowdhury, R. L.; Piórko, A.; Lee, C. C. *J. Organomet. Chem.* 1987, *319*, 379. (d) Lee, C. C.; Chowdhury, R. L.; Piórko, A.; Sutherland, R. G. *J. Organomet. Chem.* 1986, *310*, 391. (e) Sutherland, R. G.; Chowdhury, R. L.; Piórko, A.; Lee, C. C., in preparation.

(7) Pearson, A. J.; Bruhn, P. R.; Richards, I. C. *Isr. J. Chem.* 1984, *24*, 93.

(8) Semmelhack, M. F.; Hall, H. T., Jr.; Farina, R.; Yoshifuji, M.; Clark, G.; Bargar, T.; Hirotsu, K.; Clardy, J. *J. Am. Chem. Soc.* 1979, *101*, 3535.

0022-3263/87/1952-4618$01.50/0 © 1987 American Chemical Society