Nucleic Acid Related Compounds. 76. Synthesis of 5'(E and Z)-Chloro-4',5'-didehydro-5'-deoxyadenosines via Chlorination and Thermolysis of Adenosine 5'-Sulfoxides. Mechanism-Based Inhibition of S-Adenosyl-L-homocysteine Hydrolase

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Treatment of 2',3'-di-O-acetyl-5'-S-(4-methoxyphenyl)-5'-thioadenosine (1a), or its sulfoxides 2a(Sp) and 3a(Sb), with iodobenzenes dichloride and potassium carbonate in acetonitrile resulted in formation of the 5'-chloro-(and 5',5'-dichloro)-5'-deoxy-5'-(4-methoxyphenyl)sulfinyl)-adenosines 4a, 5a, 6a, and minor diastereomers. Deprotection of 5a gave 5'(S)-chloro-5'-deoxy-5'-(4-methoxyphenyl)sulfinyl(Sp)adenosine [5b(5'S,Sp)] whose stereochemistry and conformation were established by X-ray crystallography. The α-chlorination of sulfoxides 2a(Sp) and 3a(Sp) occurred with predominant retention of configuration at sulfur. Thermolysis of the α-chloro sulfoxides and deprotection gave the chloromethylene derivatives. The 5'(Z)-chloro-4',5'-didehydro-5'-deoxyadenosine [5b(5'S)] diastereomer was found to be a potent time-dependent inhibitor of S-adenosyl-L-homocysteine hydrolase.

Interest in the modification of nucleosides at C4', especially the introduction of a 4',5'-double bond in the carbohydrate moiety, has been stimulated by the presence of this structural feature in the nucleoside antibiotics angustmycin A (decoyinine) (A)(2a) and the 4',5'-didehydro-6-drofusfungin derivative A9145C (B). (2b) The latter is an inhibitor of methyl transferase enzymes, and this inhibition can be reversed by the addition of S-adenosylmethionine. (2b)

It was also found that synthetic 4',5'-didehydro-5'-deoxyadenosine (C) (3) was accepted as an alternative substrate by S-adenosyl-L-homocysteine hydrolase (AdoHcy hydrolase, EC 3.3.1.1) (see Figure 1). Inhibition of AdoHcy hydrolase results in higher cellular concentrations of AdoHcy which causes suppression of the methylation of biological probes; (4) especially the introduction of a 4',5'-double bond in the carbohydrate moiety of this structural feature in the nucleoside antibiotics angustmycin A (decoyinine) (A)(2a) and the 4',5'-didehydro-6-drofusfungin derivative A9145C (B). (2b)

Figure 1. Proposed mechanism for S-adenosyl-L-homocysteine hydrolase.

Transfere enzymes. (5) Therefore, the development of mechanism-based inhibitors of AdoHcy hydrolase is an attractive chemotherapeutic goal. (6)

Syntheses of unsubstituted 4',5'-unsaturated nucleosides have employed base- or silver fluoride-promoted eliminations with 5'-deoxy-5'-iodonucleosides, base-promoted eliminations with 5'-O-sulfonyle nucleosides including the synthesis of angustmycin A (A), (5) and thermal eliminations with 5'-selenoxides. (5) Nucleoside 4',5'-enol acetate (2b) and enamine (2b) derivatives were prepared from protected nucleoside 5'-aldehydes. Vinyl thioether compound D was prepared by treatment of the 5'-dithiaoacetal of a benzoylated adenosine 5'-aldehyde derivative with bromine and DBU. (10) A protected 4',5'-didehydro-5'-
deoxy-5'-iodoadenosine derivative was formed during efforts to synthesize the antibiotic nucleoside. An ethylidene (4',5'-dideoxy-5'-deoxy-5'-methyladenosine) analogue was prepared by coupling a sugar derivative with the chloromercury salt of 6-benzamido purine. Isomerization of tosylmethylene derivatives of adenosine and uridine to give the 4',5'-unsaturated allicy tosyl compound occurred under mildly basic conditions.

Parallel efforts by our laboratory and the Marion Merrell Dow group have resulted in syntheses of 5'-fluoro-5',S-alkyl (and aryl)-5'-thionucleosides and derived 5'-halo, 5',5'-dihalo, and other 4',5'-modified nucleoside derivatives. Several of these are antiviral and antineoplastic agents, and 4',5'-dideoxy-5'-(Z)-fluoroadenosine (F) is a potent mechanism-based inhibitor of AdoHcy hydrolase with antiretroviral, antimalarial, and antiinflammatory activity. During the course of this work, the synthesis and biological activity of 5'-halogenated-4',5'-unsaturated adenosine derivatives including "5'-(Z)-chloro-4',5'-dideoxy-5'-deoxyadenosine" were reported.

We now report alternative syntheses of 5'-chloro and 5',5'-dichloro-4',5'-dideoxy-5'-deoxyadenosine derivatives via chlorination of 3',5'-di-O-acetyl-5'-S-(4-methylthiophenyl)-5'-thioadenosine (1a), or its 2a(Sa) and 3a(Sa) sulfoxides, with iodobenzene dichloride followed by thermolysis of the α-chloro sulfoxides (Scheme I). Our stereochemical assignments were made with X-ray crystallography, NMR spectroscopy, and stannyl radical-mediated hydrodechlorination reactions.

The authentic 5'-(Z)-chloro-4',5'-dideoxy-5'-deoxyadenosine (9b) diastereomer causes potent time-dependent inactivation of AdoHcy hydrolase.

Results and Discussion

From available procedures for the synthesis of α-chloro thioethers and α-chloro sulfoxides, we examined transformations with N-chlorosuccinimide (NCS) and iodo-

benzene dichloride. The latter was reported to give cleavage products with phenyl trityl sulfide and benzyl trityl sulfide, presumably via S-chlorosulfonyl intermediates. However, Colonna and co-workers reported conversions of other thioethers and sulfoxides to α-chloro sulfoxides with PhICl2 and studied stereochemical consequences at the sulfur and α-carbon atoms.

Conversion of adenosine to 5'-S-(4-methylthiophenyl)-5'-thioadenosine (1b) followed by acetylation efficiently afforded protected sulfide 1a. Treatment of 1a (or its S-phenyl analogue) with 1 equiv of NCS or PhICl2 under various conditions gave complex reaction mixtures which contained unchanged 1a and its sulfoxide diastereomers 2a and 3a. It is noteworthy that the latter sulfoxides gave mainly deoxyadenosine starting material 1a upon treatment with thionyl chloride, since other thioethers and sulfoxides were converted to α-chloro thioethers with this reagent.

Treatment of 1a with 3 equiv of NCS or PhICl2 overnight at ambient temperature resulted in its disappearance (TLC). 1H NMR spectra of the reaction mixture confirmed the absence of 1a and its sulfoxides 2a and 3a. Addition of K2CO3 to the initial mixture of 1a and PhICl2 resulted in accelerated reaction rates and improved yields of α-chlorination products. Potassium carbonate might promote the conversion of intermediate S-chlorosulfonyl

A = adeninyl; An = (CH2)4CNH2; Series a = cyclo,C,b = R = H.

Key: (a) m-CPBA/CH2Cl2/-40 °C; (b) PhICl2 (1.05 equiv)/(CH3CN or pyridine)/-20 °C; (c) NH3/MeOH; (d) PhICl2/K2CO3/MeCN; (e) BuSH/ABN/CH2Cl2; (f) i-Pr2NEt/(diglyme or MeSO)/Δ.

(18) For review about chemistry of α-chloro sulfoxides, see: Dilworth, B. M.; McKeever, A. Tetrahedron 1986, 42, 3731 and references cited therein.
Figure 2. Computer-generated X-ray crystal structure of 5'(S)-chloro-5'-deoxy-5'-(4-methoxyphenyl)sulfinyl(S~)adenosine [6b(5'S,5'S)].

species to 5'-chloro sulfoxides by proton abstraction from C5'. Iodobenzene dichloride gave higher yields, and reactions were easier to work up than those with NCS.

Treatment of 1a with PhI(Cl (2.25 equiv) in CH2CN in the presence of K2CO3 gave the 5'-chloro sulfoxide diastereomers 5a and 6a in 68% combined yield. Partial chromatographic separation of 5a (1H NMR 5.42 (d, J5'=4.2 Hz, H5')) and 6a (δ 4.94 (d, J5'=4.2 Hz, H5')) from the other products was achieved. Diastereomer 5a(5'S,S at sulfur (S~)) was produced in ~46% yield (67% of the total α-chloro sulfoxides), 6a(5'R,S~) in ~14% yield, and other diastereomers including 6',5'-dichloro sulfoxides 4a in ~9% yield (5a/6a/other isomers ~5.2:1.5:1). Deacytation (NH4MeOH) of 5a and crystallization afforded 5b(5'/5',S~) whose configurations at sulfur and C5' were determined by X-ray crystallography (Figure 2). The configuration of 6a(5'R,S~) was deduced by chemical interconversions (see below). The attempted analogous deacytation of 6a resulted in spontaneous decomposition with release of adenine.

The computer drawing of 5b(5'/5',S~) is shown in Figure 2. The sugar ring has a pseudorotation angle of 158° indicating a 'T3 conformation.25 Both the adenine and benzene rings are planar, as expected. The dihedral angle between the least-squares planes of these rings is 15° which makes the extended or open conformation of these two aromatic ring systems essentially coplanar. In fact, the average deviation of a ring atom from the least-squares plane calculated for the nine adenine and six benzene heavy atoms is 0.30 Å and the maximum deviation of a ring atom from that plane is 0.76 Å. Interestingly, the average deviation of heavy atoms from the least-squares plane calculated for all non-hydrogen atoms in the molecule is 0.63 Å and the largest deviation of any heavy atom is 2.36 Å (O sulfoxide). Because of the scarcity of observed data, only the atoms Cl, S, and O were refined anisotropically. As a result, only one of the hydrogen atoms, H08, which could be involved in hydrogen bonds was located in difference maps. However, it appears that all hydrogen atoms bonded to oxygen and nitrogen atoms are involved in intramolecular hydrogen bonding. Criteria used for this inference are the short donor−acceptor interatomic distances and C−D−A angles near 109°. There is no evidence for intramolecular hydrogen bonding, which is consistent with the "planar" conformation of the molecule.

The glycosyl torsion angle C8−N9−C1'−O4' is −115° and the C5'−C4'−C5−S torsion angle has a value of 166° (1°). Experimental details, crystallographic parameters, and structural data are available.24

Thermolysis of 5a(5'S,S~) (150 °C, 36 h) with Hüning's base in diglyme gave the 5'(E)-chloromethylene compound 8a. More mild treatment of 6a(5'R,S~) (145 °C, 5 h) gave the less thermally-stable 5'(Z)-chloromethylene diastereomer 9a. Marked differences in the rates of syn-elimination from sulfoxides 5a and 6a allowed the preparation of 8a and 9a from mixtures of the precursor α-chloro sulfoxides. Thermolysis of 5a/6a (~3.5:1) at ~145 °C for 4–5 h resulted in formation of 8a/9a (~1:5.7). The more thermally stable, unreacted 5a was readily recovered by chromatography. Deacytation of the 8a/9a mixture, HPLC, and crystallization gave the 5'-chloromethylene products 8b(E) and 9b(Z).

1H NMR spectra of these isomers had singlets for H5' at 5.90 for 8b(E) and 5.60 for 9b(Z). These shifts compare well with values reported13 for the corresponding 5'-fluoromethylene analogues (H5' peak for the Z isomer is 0.48 ppm upfield from that for the E; confirmed by us with samples prepared by thermolysis of 5'-fluoro sulfoxide derivatives whose structures were verified by X-ray crystallography and NMR14,15). Protected chloromethylene compound 8a(5'E) had a vinyl proton signal at δ 5.84 (d, J5'=4.2 Hz, H5') [9a(5'Z); δ 5.64 (d, J5'=4.2 Hz, H5')] in harmony with the usual trans cis allenic coupling constants.26 The 13C NMR signal for C5' was at δ 95.31 for 8b and 90.93 for 9b. Finally, NOE difference spectroscopy experiments showed ~5% enhancement of the vinyl proton signal at δ 5.80 for 9b upon irradiation of the signal for H5' at δ 4.75 whereas parallel experiments with 8b showed little or no enhancement at δ 5.90. Availability of only the more stable E diastereomer 8b by the Marion Merril Dow group16 and slight enhancements of its H5' signal upon irradiation at H3' in some NOE experiments apparently resulted in an erroneous tentative assignment of the 5'(Z) stereochimistry to 8b.

Since thermolyses of 5a gave 8a(5'E), and 6a gave 9a(5'Z), and thermal sulfoxide eliminations proceed with syn stereochemistry, the C5' configurations for 5a(5'S) and 6a(5'R) were indicated. The large differences in proton coupling constants for compounds 8a (J5'=3.9; 10.2 Hz) and 6a (J4'=4.2 Hz) suggested different chirality at sulfur as well. The configuration for 6a was established as S~ by stannyl radical-mediated hydrodehalogenation29 and comparison of the product 3a NMR spectra with those of 2',3'-di-O-acetyl-5'-deoxy-5'-phenylsulfinyl(S~)adenosine,14,15 [Note that the absolute configurations at sulfur in sulfoxide 2a and α-chloro sulfoxide 5a (or 3a and 6a) are the same, but the R/S configuration descriptors change owing to the change in Cahn−Ingold−Prelog priority of C5' when a chloro substituent is present. ] Thus, treatment of 5a(5'S,S~), with Bu3SnH/AIBN/CsHs/A gave 2a(S~) and 6a(5'-R,S~) gave 3a(S~) in high yields. Independent control treatments of 2a(S~) and 3a(S~) with Bu3SnH/AIBN/CsHs/A demonstrated the stable stereochemistry at sulfur under these reaction conditions.

Our chlorination results are in agreement with Colonna's

(24) X-Ray data, analyses, and experimental details are available from the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.
studies on the stereochemistry of conversions of thioethers and sulfoxides to α-halo sulfoxides.²¹b Oxidation of 1a with 3-chloroperoxybenzoic acid (m-CPBA) followed by silica column chromatography gave clean samples of sulfoxides 2a(S₅) and 3a(S₅). Treatment of 2a(S₅) with PhClO₃ (1.25 equiv) gave a mixture of 5a(5′,5′-S₅)/6a(5′,5′-S₅)/others (~15:5:3.5:1; 1H NMR) in 84% yield. Analogous treatment of 3a(S₅) gave 5a(5′,5′-S₅)/6a(5′,5′-S₅)/others (~5:5:8.5:1) in 82% yield. Thus, chlorination under these conditions gave predominant retention of configuration at sulfur. Treatment of 2a(S₅) with PhClO₃/AgNO₃/CH₃CN was found to give 5a(5′,5′-S₅)/6a(5′,5′-S₅)/others (~2:5:5:1) in 25% yield in harmony with the prior studies.²¹c

Direct treatment of 1a with 4.5 equiv of PhClO₃ gave the 5′,5′-dichloro sulfoxide diastereomers 4a [S₅,R₅ (~1:1), 67%.] plus ~15% of the 5′-chloro isomers [mainly 5a(5′,5′-S₅)].

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* Chemical shifts (δ) in MeSO-d₆ at 50.0 MHz. ¹ Proton decoupled peaks appeared as singlets. ² Assignments may be reversed. ³ Peaks also at 20.10, 20.43, 169.55, 169.64 (Ac₆). ⁴ Peaks also at 20.15, 20.32, 169.54, 169.59 (Ac₆). ⁵ Assignments were made from a spectrum of the diastereomeric mixture (Sa,Ra,Sb,Sr ~ 3:1). ⁶ Unresolved peaks were distinguished by an APT experiment.

**Experimental Section**

Uncorrected melting points were determined on a microstage block. ¹H (200-MHz) and ¹³C (50-MHz) NMR spectra were determined with Me₂SO-d₆ solutions unless otherwise noted. NOE experiments were performed at 500 MHz. UV spectra were determined with MeOH solutions. Iodo benzene dichloride was prepared as described.²⁷ TLC was performed on Merck Kieselgel 60 F₂₅₄ sheets with: S₅, MeOH/EtOAc (2:25), and S₅, MeOH/CHCl₃ (1:9). "Chromatography" was performed on silica columns. Reagent-grade chemicals were used, and solvents were redistilled. CH₂CN was dried by reflux over and distillation from CaH₂. Preparative and analytical HPLC were performed on C₁₈ reversed-phase columns.

²³,³-Di-O-acetyl-5′-S-[(4-methoxyphenyl)-5′-thiadenosine (1a). A stirred suspension of 5′-S-[(4-methoxyphenyl)-5′-thiadenosine (1b, 3.89 g, 10 mmol) in Ac₂O (2.86 mL, 30.8 g, 275 mmol) was cooled in an ice bath, and pyridine (17 mL) was added. Stirring was continued at ~0 °C for 7 h or until TLC (Si₅) indicated complete reaction. MeOH (50 mL) was added, stirred was continued for 30 min, and the solution was evaporated. The residue was partitioned (2% AcOH/H₂O/CHCl₃), and the organic phase was washed (H₂O, NaHCO₃/H₂O, brine, and H₂O, dried (Na₂SO₄), and evaporated to give 1a (4.64 g, 98% ) as a white solid foam (TLC homogeneous) used directly in subsequent reactions: ¹H NMR (CDCl₃) δ 2.02, 2.12 (m, 1, H4), 5.9 Hz, 2, H5(5')), 5.78 (s, 3, OCH₃), 4.33 (dd, Jₗ₋₁₋₂ = 3.7 Hz, 1, H4'), 5.61 (dd, Jₗ₋₁₋₂ = 5.3 Hz, 1, H3(5')), 7.63 (dd, Jₗ₋₁₋₂ = 6.1 Hz, 1, H2(5')), 6.11 (d, 1, H1(5')), 6.78 (d, Jₗ₋₁₋₂ = 8.5 Hz, 2, Ar), 7.34 (d, 2, Ar), 7.90 (s, 1, H2(5')), 8.32 (s, 1, H8); MS m/z 473.1377 (3, [M⁺]C₉H₁₀N₃O₃S = 473.1369).

²³,³-Di-O-acetyl-5′-S-[(4-methoxyphenyl)sulfonyl]adenosine [2a(S₅) and 3a(S₅)]. A solution of m-CPBA (414 mg as 85% reagent, 2.04 mmol) in CH₂Cl₂ (25 mL) was added dropwise to a cold (~50 °C) stirred solution of 1a (946 mg, 2 mmol) in CH₂Cl₂ (25 mL). TLC indicated complete reaction as soon as the addition was finished. The solution was poured into ice-cold saturated NaHCO₃ (35 mL), and the mixture was extracted with CHCl₃ (2 × 35 mL). The combined organic phase was washed with brine and then H₂O, dried (MgSO₄), and evaporated to give 2a(S₅) and 3a(S₅) (~1:1.9; 286 mg, 29%), and 2a(S₅) (333 mg, 34%). 2a(S₅): ¹H NMR (CDCl₃) δ 2.05, 2.12 (m, 1, 5′-S₅), 5.9 (s, 3, Ac₆'), 3.10 (dd, Jₗ₋₁₋₂ = 13.1 Hz, 1, H5'), 3.55 (dd, Jₗ₋₁₋₂ = 10.9 Hz, 1, H5'), 3.83 (s, 3, OCH₃), 4.75 (dd, Jₗ₋₁₋₂ = 4.9 Hz, 1, H4'), 5.63 (br s, 2, NH₃), 7.57 (dd, Jₗ₋₁₋₂ = 5.4 Hz, 1, H1, 6.11 (d, 1, H1(5')), 6.11 (d, 1, H1(5')), 6.78 (d, Jₗ₋₁₋₂ = 8.5 Hz, 2, Ar), 7.34 (d, 2, Ar), 7.90 (s, 1, H2(5')), 8.32 (s, 1, H8); MS m/z 473.1377 (3, [M⁺]C₉H₁₀N₃O₃S = 473.1369).

Inhibition of S-Adenosyl-L-homocysteine Hydrolase


H3O'), 6.05 (d, J = 1.8 Hz, H1'), 6.17 (d, J = 2.5 Hz, H2'), 7.51 (d, J = 4.2 Hz, H3'), 7.4 (s, 1, H4'), 7.45 (d, J = 2.5 Hz, H5'), 5.29 (br s, 2, NHz'), 5.32 (br s, 2, NHz').

Treated of 1a (150 mg, 0.32 mmol) in CH3CN (15 mL) with PhICl (93 mg, 0.34 mmol) at -20 °C for 10 min gave Sa(S'R)/Sa(S~) (1:1:2; 117 mg, 75%) and recovered 1a (15 mg, 10%) after an additional run of 1a (100 mg, 0.2 mmol) in pyridine (10 mL) with PhICl (61 mg, 0.22 mmol) gave Sa(3S',3S)/Sa(3S,R) (1:1.2:1; 65 mg, 63%) and recovered 1a (8 mg, 8%).

5'-Deoxy-5'-(4-methoxyphenyl)sulfinyl(S'R)adenosine [2b(Sa)]. A solution of 2a(Sa) (96 mg, 0.2 mmol) in MeOH (5 mL) was stirred with NH3/MeOH (10 mL) at ambient temperature for 2 h. Evaporation of volatiles and crystallization of the residual white solid from MeOH gave 2b(Sa) (71 mg, 86%): mp 264-265 °C dec; UV max 250 nm (e, 15,000), 252 nm (19, M = 252 nm); 'H NMR σ 3.08 (dd, J = 13.4 Hz, J = 2.8 Hz, H2'), 3.56 (dd, J = 3.5 Hz, J = 1.0 Hz, H4'), 4.23 (d, J = 4.9 Hz, H3'), 4.32 (d, J = 4.9 Hz, H5'), 0.061 mmol) with PhICl (21 mg, 0.077 mmol), K2CO3 (18 mg, 0.13 mmol) in MeOH (5 mL), and stirring was continued at -0 °C (ice bath) for 45 min. Other diastereomers (-15.5:5:1; 132 mg, 84%). (c) Treatment of 2a(Sa) (147 mg, 0.3 mmol) with PhICl (103 mg, 0.375 mmol) and K2CO3 (42 mg, 0.3 mmol) in CH3CN (6 mL) at ambient temperature for 7 h gave Sa(S'R)/Sa(S~)/other diastereomers (-5.5:6:1; 123 mg, 84%). (d) Treatment of 2a(Sa) (30 mg, 0.061 mmol) with PhICl (21 mg, 0.077 mmol), K2CO3 (16 mg, 0.12 mmol), and AgNO3 (5 mg, 0.035 mmol) in CH3CN (4 mL) at ambient temperature for 4 h gave Sa(S'R)/Sa(S~)/other diastereomers (-2.5:5:5.1; 8 mg, 25%).

2'-Di-O-acetyl-5'-chloro-5'-deoxy-5'-(4-methoxyphenyl)sulfinyl(S'R)adenosine [6a(S'R)]. Method A (from Sulfoxide). General Procedure for Chlorination. (a) Treatment of 7a(S'R) (172 mg, 0.52 mmol) with PhICl (172 mg, 0.825 mmol) gave 7b(S'R) (212 mg, 100%) at ambient temperature for 24 h gave Sa(3S',3S)/Sa(3S,R) (5a >> 5a) (-6.7:1, 675 mg 57%) after workup and purification described for Sa(5'S,5S). The dichloro sulfoxides 4a migrated slightly faster (TLC) than 5a(SS,SS) which allowed partial separation of 4a: 1H NMR (CDCl3) δ 1.16, 1.99 (2 s, 3, Ac), 2.12, 2.12 (2 s, 2, 3, Ac), 3.84, 3.85 (2 s, 3, OCH3), 4.06 (d, J = 2.3 Hz, 0.5 H, H4'), 4.96 (d, J = 2.5 Hz, H3', 1H'), 5.01-5.05 (m, 2, Ar), 5.22 (br s, 2, NHz'), 5.34-5.40 (m, 1, H8'), 5.98 (d, J = 8.5 Hz, 1, H1'), 6.39 (s, 1, H2'), 6.97 (d, J = 8.5 Hz, 1, H4'), 7.42 (d, J = 8.5 Hz, 1, H5'), 7.56 (dd, J = 8.5 Hz, 1, H5'), 7.89-7.97 (m, 2, Ar), 8.16 (s, 2, H8), 8.38 (s, 1, H5); MS CI (NH3) m/z 406 (51, MH+). Anal. Calc'd for C12H11ClN3O5S: C, 45.75; H, 4.37; N, 15.92. Found: C, 45.50; H, 4.37; N, 15.88.

5'-Deoxy-5'-(4-methoxyphenyl)sulfinyl(S'R)adenosine [3b(Sa)]. Deacetylation of 2a(Sa) (96 mg, 0.2 mmol) as described for 2b(Sa) gave 3b(Sa) (64 mg, 79%): mp 212-213 °C dec; UV max 255 nm (e, 229 mm, 7190); 'H NMR δ 3.86 (s, 3, OCH3), 3.90 (d, J = 4.9 Hz, H1'), 5.01-5.07 (m, 1, H2'), 5.07 (d, J = 4.9 Hz, H3'), 5.18 (s, 1, H4'), 5.48 (d, J = 4.9 Hz, H5'), 5.56 (d, J = 2.1 Hz, H2'), 5.62 (d, J = 2.1 Hz, H1'), 5.67 (d, J = 2.1 Hz, H5'), 6.04 (d, J = 4.9 Hz, H3'), 6.17 (d, J = 4.9 Hz, H4'), 6.22 (s, 2, NHz'), 6.34-6.4 (m, 1, H8'), 6.56 (s, 1, H7'), 7.00 (m, 3, Ar), 7.3 (s, 1, H8), 8.2 (s, 1, H1'), 8.31 (s, 1, H5); MS CI (NH3) m/z 340 (51, MH+). Anal. Calc'd for C11H11ClN3O4S: C, 45.67; H, 4.38; N, 15.80. Found: C, 45.10; H, 4.40; N, 15.84.
of chloro sulfoxides after chromatographic purification (8a/6a; 10 mg, 0.29 mmol) chromatography (10 mL) containing EtN(Ot-Bu)2 (150 mg, 0.24 mmol) and evaporated in vacuo (150 °C) (bath temperature) for 5 h, workup, and chromatography gave 9a(Z) (62 mg, 58%) as a slightly yellow foam: 1H NMR (CDCl3) δ 2.04, 2.15 (s, 3, Hs), 3.56 (d, JH2-H3 = 6.5 Hz, 1H), 5.37 (br s, 2, NH2), 6.08 (dd, JH2=H3 = 6.0 Hz, 1H), 6.15 (dd, 1, H1, Hs), 6.43 (d, 1, H1), 7.92 (d, 1, Hs), 8.35 (s, 1, Hs); MS m/z 389 (M+HCl), 537 (M+2HCl), 536 (M+2HCl), 530 (M+2HCl), 520 (272), 490 (265), 475 (250), 178 (76), 177 (73), 136 (65), 133 (85), 118 (82).

Thermolysis of the Mixed Chloro Sulfoxides. A solution of chloro sulfoxides after chromatographic purification (8a/6a/6s iso forms—7,2-7,7, 100 mg, 1.34 mmol) in diglyme (35 mL) containing EtN(OHt-Bu)2 (893 mg, 0.93 mL, 5.36 mmol) was purged (N2) for 30 min and then heated at 245 ± 2 °C (bath temperature) for 4.5 h. Volatiles were evacuated in vacuo (50 °C), and the residue was transferred to a C18 column (35 cm × 1.8 cm, 300 A, Phenomenex), and eluted (MeOH/H2O (22:1)) with a 0.1% aqueous solution of TFA for 12 h. The residue was rechromatographed on a silica column. Elution gave 8a(9)(E) (9a(E) (1.16 mmol) at 145 °C, 40 mg, 0.72 mmol) in DMSO (10 mL) containing EtN(OHt-Bu)2 (372 mg, 0.50 mL, 2.88 mmol) was heated at 145 ± 2 °C (bath temperature) for 2.5 h. Workup and silica column chromatography gave 7a/10a (1~:1.5) (plus ~5 % of impurities, 1H NMR); 67 mg, 23% as a yellow foam: MS m/z 407 (M+HCl), 405 (48), 403 (88), 401 (83, M+2HCl), 398 (100), 395 (100), 393 (60), 388 (100, 139, 139 (84), 136 (131, 120, 120, 116 (120, 116 (117, 113). 10a: 1H NMR (CDCl3) δ 1.51 mixture of 7a/10a) δ 2.02, 2.17, 2.17 (s, 3, 3, Ac1), 4.55 (dd, JH2=H3 = 4.9 Hz, JH2=H3 = 3 Hz, 1H), 5.48 (br s, 2, NH2), 5.48 (dd, JH2=H3 = 6.9 Hz, 1H, 7.21 (s, 1, H1), 7.39 (s, 1, H1), 7.83 (s, 1, H1). The use of diglyme as solvent under these conditions gave 7a/10a (1~:1.2 (plus ~5 % impurities); 21%). With both solvents ~26 % of the starting dichloro sulfoxides [diastereomer ratio now = 5:7:1; 1H NMR doublets at δ 4.96 and 4.56 (Hf H4, respectively) were recovered. More vigorous thermolysis in diglyme (150 ± 2 °C) gave 7a/10a (1~:1.6; 2%). A minor amount of the unchanged monochloro sulfoxide 8a (~6%–8%) also was recovered from these thermolyses as the last fraction eluted from silica columns.

Phenylation of the Starting Dichloro Sulfoxides [Diastereomer 12:1; 47 mg, 5.86 mmol) at 145 °C (bath temperature) for 2.5 h. Workup and silica column chromatography gave 7a/10a (1~:1.5) (plus ~5 % of impurities, 1H NMR); 67 mg, 23% as a yellow foam: MS m/z 407 (M+HCl), 405 (48), 403 (88), 401 (83, M+2HCl), 398 (100), 395 (100), 393 (60), 388 (100, 139, 139 (84), 136 (131, 120, 120, 116 (120, 116 (117, 113). 10a: 1H NMR (CDCl3) δ 1.51 mixture of 7a/10a) δ 2.02, 2.17, 2.17 (s, 3, 3, Ac1), 4.55 (dd, JH2=H3 = 4.9 Hz, JH2=H3 = 3 Hz, 1H), 5.48 (br s, 2, NH2), 5.48 (dd, JH2=H3 = 6.9 Hz, 1H, 7.21 (s, 1, H1), 7.39 (s, 1, H1), 7.83 (s, 1, H1). The use of diglyme as solvent under these conditions gave 7a/10a (1~:1.2 (plus ~5 % impurities); 21%). With both solvents ~26 % of the starting dichloro sulfoxides [diastereomer ratio now = 5:7:1; 1H NMR doublets at δ 4.96 and 4.56 (Hf H4, respectively) were recovered. More vigorous thermolysis in diglyme (150 ± 2 °C) gave 7a/10a (1~:1.6; 2%). A minor amount of the unchanged monochloro sulfoxide 8a (~6%–8%) also was recovered from these thermolyses as the last fraction eluted from silica columns.

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Inhibition of S-Adenosyl-L-homocysteine Hydrolase

chloro sulfoxides were thermolyzed.\(^{7b}\) mp 175-183 °C dec; UV max 258 nm (ε 10 000), min 235 nm (ε 7700); \(^1\)H NMR \(\delta 4.73\) (dd, \(J_{3-\gamma} = 5.2\) Hz, \(J_{OH-\gamma} = 5.5\) Hz, 1, H3), 5.11 (ddd, \(J_{3-\gamma} = 7.7\) Hz, \(J_{OH-\gamma} = 5.9\) Hz, 1, H2'), 5.96 (d, 1, OH3'), 5.99 (d, 1, OH2'), 6.34 (d, 1, H1'), 7.42 (br s, 2, NH2), 8.18 (8, 1, H2), 8.50 (s, 1, H8); MS \(m/z\) 321 (3.8, M+ [W121), 319 (28, M+ [W1, W1]), 317 (44, 41), 136 (54, BH, 103 (42), 59 (100). Anal. Calcd for C\(_{3}H_7Cl_2N_5O_3\) (318.1): C, 37.49; H, 2.93; N, 22.31.

Stannyl Radical-Mediated Hydrodechlorination of Chloro Sulfoxides. A solution of \(S_a(5'S, S_s)\) (35 mg, 0.067 mmol) in benzene (5 mL) was deoxygenated (Ar) for 45 min. Bu\(_3\)SnH (118 mg, 0.108 mL, 0.4 mmol) and AIBN (5 mg) were added, and the mixture was refluxed for 5 h. Volatiles were evaporated, and the residue was chromatographed (alumina; MeOH/EtOAc (1:3)) to give 2a (22 mg, 67%) and recovered 5a (5'S, S_s) (6 mg, 17%) (\(^1\)H NMR). Identical treatment of 6a (5'R, S_s) (35 mg, 0.067 mmol) gave 3a (S_s) (23 mg, 70%) and recovered 6a (9 mg, 26%).

Identical independent treatment of 2a (S_s) and 3a (S_s) resulted in quantitative recovery of unchanged starting materials without detected (\(^1\)H NMR) alteration of stereochemistry at sulfur.

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