polarities and the presence of each as a stereoisomeric mixture.

3-(Phenylsulfonyl)cyclohexanol Acetate (10). A solution of 748 mg (3.11 mmol) of hydroxy sulfone **9**,[16,23] 2.00 mL (21.2 mmol) of acetic anhydride, and 71 mg (0.58 mmol) of 4-(*N*,*N*-dimethylamino)pyridine in 3.00 mL of triethylamine was stirred at room temperature for 18 h, after which it was poured into a mixture of 20 mL of 10% aqueous sodium hydroxide and 20 g of crushed ice to destroy excess acetic anhydride. Subsequent dilution of this mixture with 60 mL of 15% (w/v) aqueous sodium chloride, extraction with 3:1 (v/v) ether/dichloromethane, and washing of the latter extracts with 15% aqueous sodium chloride (1 × 60 mL), 1:1 (v/v) 2 M aqueous hydrochloric acid/saturated brine (2 × 60 mL), 1:1 (v/v) 1 M aqueous sodium hydroxide/saturated brine (1 × 60 mL), and saturated brine (1 × 60 mL) in successive order afforded 789 mg (90%) of sulfone ester **10** as a 5:1 mixture of cis/trans stereoisomers: bp 185–198 °C (bath temperature), 0.30 mm; ^{1}H NMR δ 7.97 (m, 2 aryl H), 7.71 (m, 3 aryl H), 5.43–5.11 (m, C*H*OAc, trans stereoisomer), 5.00–4.39 (m, C*H*OAc, cis stereoisomer), 3.10 (br m, CHS), 2.03 [s, OC(=O)CH_3]; IR ν_{max} (film) 1730 (C=O), 1305, 1240, 1145, 1030, 720, 690 cm^{-1}. Anal. Calcd for $C_{14}H_{18}SO_4$: C, 59.55; H, 6.42; S, 11.36. Found: C, 59.49; H, 6.35; S, 11.32.

Alkylation of [(Phenylsulfonyl)methylene]dilithium (13). To a solution of 312 mg (2.0 mmol) of methyl phenyl sulfone (**15**)[17] in 10.0 mL of anhydrous tetrahydrofuran (THF) cooled to 0 °C (ice/water bath) was added dropwise 3.00 mL of a 1.35 M solution of *n*-butyllithium in hexane. The resulting mixture was stirred at 0 °C for 60 min, after which a solution of 0.37 mL (4.07 mmol) of 1-bromopropane and 0.28 mL (4.00 mmol) of propylene oxide in 3.0 mL of hexane was added dropwise over 2 min. After an additional 20 min at 0 °C, the reaction was quenched by rapid addition of 5 mL of saturated aqueous ammonium chloride. Dilution of this mixture with 60 mL of 15% (w/v) aqueous sodium chloride and 5 mL of 2 M aqueous hydrochloric acid, followed by extraction with 3:1 (v/v) ether/dichloromethane and the usual isolation procedure, afforded 331 mg of crude product. Chromatography of the latter on Florisil (20 mL) gave 247 mg (79%) of recovered starting material (**15**, elution with 1:1 ether/hexane), accompanied by 40 mg of 4-(phenylsulfonyl)-2-butanol (**17**, elution with ether) as the only other identifiable component. The ^{1}H NMR spectral properties[24] of the latter (**17**) were identical with those exhibited by an authentic sample[16] of the same compound.

Acknowledgment. I thank Professor John J. Eisch of the State University of New York at Binghamton for a copy of his ^{1}H NMR spectrum of 3-(phenylsulfonyl)-cyclohexanol.

(23) The same procedure was used to acetylate in quantitative yield the cyclization product (i.e., a mixture of **6** and **9**), thereby verifying cyclohexanoid **9** as the major component as well as confirming its identity.

(24) Hydroxy sulfone **17** exhibited the following spectral properties: ^{1}H NMR δ 3.91 (m, C*H*OH), 3.30 (br t, J = 7 Hz, CH_2S), 1.17 (d, J = 6 Hz, CH_3); IR ν_{max} (film) 3490 (OH), 1295, 1148, 1090, 735, 690 cm^{-1}.

A Comment on the Structure and Proton NMR Spectrum of 2,8,17-Trithia[4^{5,12}][9]metacyclophane

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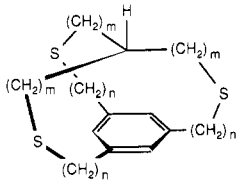
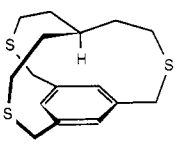
Ricci et al.[1] reported in 1976 the syntheses of several macrocyclic thioethers, which were assigned structures **1a–d**. The compounds were characterized by their melting points, elemental analyses, and 60-MHz ^{1}H NMR spectra. The complete assignments of the NMR spectra were not included in the Experimental Section of this paper, but the actual spectra were reproduced in the region from 0 to 8 ppm (δ). The spectrum of 2,8,17-trithia[4^{5,12}][9]-metacyclophane (**1b**) showed four resonances in this region, which were easily assigned to the aromatic ring protons and the three types of methylene groups; however, no methine resonance was visible. There are two possible stereoisomers of 2,8,17-trithia[4^{5,12}][9]metacyclophane, the "out" isomer **1b** and the "in" isomer **2**, but Ricci et al. apparently did not consider that the methine proton might lie *inside* the macrocycle as illustrated in structure **2**. Were this the case, the methine proton resonance would surely fall below 0 ppm due to the strong shielding effect of the benzene ring current.



1a n = 1, m = 3
1b n = 1, m = 2
1c n = 2, m = 3
1d n = 2, m = 2



2

We have been interested in compounds exhibiting short nonbonded distances between hydrogens and aromatic rings,[2,3] and the distance between the methine hydrogen and the aromatic ring plane in isomer **2** would be exceptionally short. Accordingly, we prepared 2,8,17-trithia-[4^{5,12}][9]metacyclophane using a minor modification of the method of Ricci et al.[1] The 250-MHz ^{1}H NMR spectrum of this material is essentially identical with that of Ricci et al. in the region from δ 0 to 8; however, an examination of the very high field region of the spectrum reveals the methine proton resonance as a septet at δ −1.68. This resonance is observed at a higher field than even the most highly shielded methylene protons of [9]- (δ 0.33), [8]- (0.19), [7]- (−0.3 to −0.9), [6] (−0.6),[4] and [5]paracyclophane (0.01).[5] This substance must therefore be the "in" isomer **2**. No material with spectral properties consistent with structure **1b** was isolated from the reaction mixture.[6]

Experimental Section

2,8,17-Trithia[4^{5,12}][9]metacyclophane. A solution of 1,3,5-tris(mercaptomethyl)benzene[8] (1.09 g, 5.0 mmol) and tris-(2-bromoethyl)methane[9] (1.69 g, 5.0 mmol) in benzene (100 mL) and a solution of KOH (1.03 g, 18 mmol) in ethanol (100 mL) were added simultaneously and dropwise over 3 h to rapidly stirred, refluxing ethanol (500 mL) under an argon atmosphere. After heating for 15 h, the reaction mixture was cooled and acidified with concentrated HCl (1 mL). The solvent was evaporated, and the solid residue was extracted twice with 50 mL portions of CCl_4. The extracts were combined, concentrated, and chromatographed

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(6) In this regard, we note that MM2(85)[7] calculations yield a steric energy for the "in" isomer **2** that is ca. 7 kcal/mol lower than that of the "out" isomer **1b**. In the calculated structure of compound **2**, the distance from the inside hydrogen to the mean plane of the aromatic ring is 2.21 Å.

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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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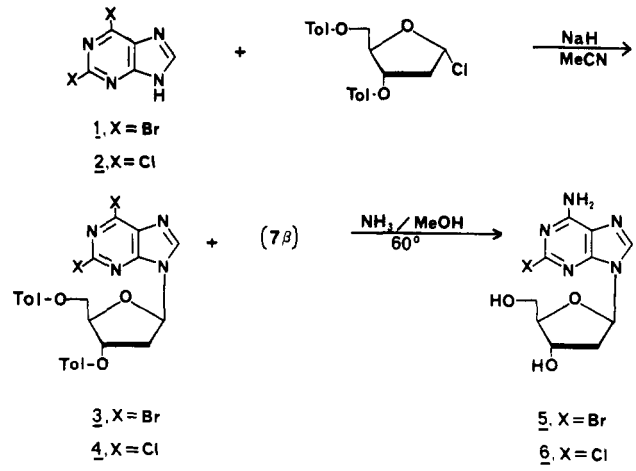
2-Halo-2′-deoxyadenosines show significant cytotoxicity against human T cells[1,2] and melanoma cells[3] in culture. The increased toxicity relative to deoxyadenosine is due to the presence of a halogen at the 2-position, a feature that prevents enzymatic deamination but allows phosphorylation in cells.[4] 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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(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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