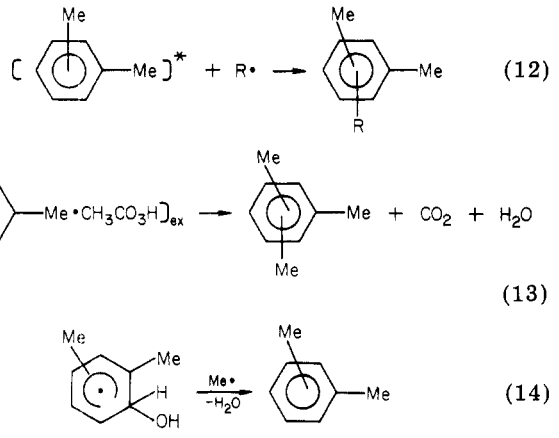

diated immediately after the estimation of peracid concentration. *o*-Methylbenzyl alcohol (**5**) was prepared by bromination of *o*-xylene followed by alkaline hydrolysis:[12] 46%; bp 112–3 °C (15 mm); mp 35–37 °C; NMR ($CDCl_3$) δ 2.26 (s, 3 H, Me), 2.35 (s, 1 H, OH), 4.51 (s, 2 H, CH_2), 7.09 (s, 4 H, aromatic). *m*-Methylbenzyl alcohol (**5b**) was prepared analogously: 38%; bp 117–8 °C (17 mm); NMR ($CDCl_3$) δ 2.27 (s, 3 H, Me), 2.80 (s, 1 H, OH), 4.46 (s, 2 H, CH_2), 7.04 (s, 4 H, aromatic). *p*-Methylbenzyl alcohol (**5c**) was obtained by reduction of *p*-tolualdehyde:[13] 63%; bp 98–100 °C (15 mm); mp 60–62 °C; NMR ($CDCl_3$) δ 2.31 (s, 3 H, Me), 2.43 (s, 1 H, OH), 4.52 (s, 2 H, CH_2), 7.13 (s, 4 H, aromatic). All other reagents were of commercial guaranteed grade.

Photolysis of a Mixture of Peracetic Acid and Xylene. A xylene solution ((4.81–30.4) × 10^{-2} M) of peracetic acid was photolyzed in a quartz vessel (20 × 150 mm) with a 30-W low-pressure Hg lamp or in a Pyrex vessel (20 × 150 mm) with a 300-W high-pressure Hg lamp through a water jacket (20–22 °C). After an estimation of the peracid remaining in the solution, a constant amount of Me_2SO–benzene was added to the photolysate to avoid contamination by the peracid in GLC thermolysis. The products in the solution were analyzed by GLC with FID (Bentone 34-DIDP, PEG 20M-Silicon DC 550, and Uniport HP). The error limit for GLC analysis was within ±5% for the value of product yields; i.e., the true value is in the range of 47.5–52.5% for a 50% yield.

The ratio of bibenzyls, $MeC_6H_4CH_2CH_2C_6H_4Me$ (**7**), to diphenylmethanes, $MeC_6H_4CH_2C_6H_3Me_2$ (**8**), was determined as follows: The solution, treated as stated above, was condensed under reduced pressure (below 30 mm) at 40–50 °C and the condensate was chromatographed on a column packed with Florisil with benzene as a developing solvent. The first eluate was a mixture of **7** and **8**, and benzene was evaporated under vacuum. Its condensate was analyzed by NMR. The ratio of **7** to **8** was determined by the methylene group signals (δ 2.8–2.9 for **7** and δ 3.8–3.9 for **8**).

Registry No. 1, 79-21-0; **2a**, 95-47-6; **2b**, 108-38-3; **2c**, 106-42-3; **3a**, 611-14-3; **3b**, 620-14-4; **3c**, 622-96-8; **4a**, 526-73-8; **4b**, 95-63-6; **4c**, 108-67-8; **5a**, 89-95-2; **5b**, 587-03-1; **5c**, 589-18-4; **6a**, 526-75-0; **6b**, 95-65-8; **6c**, 105-67-9; **6d**, 25134-01-4; **6e**, 108-68-9; **6f**, 95-87-4; **7a**, 952-80-7; **7b**, 4662-96-8; **7c**, 538-39-6; **8**, 32518-89-1.

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A New Synthetic Use of Nucleoside N^1-Oxides

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The use of adenosine N^1-oxide derivatives to prevent intramolecular cyclization during nucleophilic displacement reactions on the sugar moiety is described. This new synthetic use of N^1-oxides is illustrated by the synthesis of 5′-*O*-(*p*-toluenesulfonyl)-2′,3′-*O*-isopropylideneadenosine N^1-oxide (**6**) and subsequent displacement of the 5′ substituent with iodide or azide under conditions which lead exclusively to $N^3 \rightarrow 5'$ intramolecular cyclization in the absence of the N^1-oxide. Similarly, reaction of 2′,3′-*O*-isopropylideneadenosine N^1-oxide with methyltriphenoxyphosphonium iodide produces 5′-iodo-5′-deoxy-2′,3′-*O*-isopropylideneadenosine N^1-oxide (**7**) with no observable cyclization. In addition, 2′,3′-anhydroadenosine N^1-oxide (**17**) is shown to be stable under conditions that lead to complete $N^3 \rightarrow 3'$ intramolecular cyclization in the unprotected 2′,3′-anhydroadenosine (**14**). Reduction of the N^1-oxide to produce the parent nucleoside is readily achieved by using hexachlorodisilane or by hydrogenating over Raney nickel. The mechanistical rationale and implications for additional nucleoside transformations are discussed.

The introduction of novel functionalities into the sugar moiety of nucleoside derivatives is usually accomplished by nucleophilic displacement of suitable leaving groups with an appropriate nucleophile.[1] In various "one-step" syntheses for the introduction of azide or halogen into the sugar ring, the reaction proceeds via a reactive intermediate which again undergoes nucleophilic displacement.[2-4] When performing such sugar transformations in the adenosine series, one of the major problems has been the concomitant formation of intramolecular cyclization products[1,2,5-7] between N^3 and the sugar moiety. These derivatives have little synthetic usefulness, and various methods have been used to preclude their formation. Jahn has shown that N^6-acylated adenosine 5′-tosylates are effective substrates for nucleophilic displacement reactions,

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whereas the unprotected nucleoside readily formed ($N^3 \rightarrow$-5′)cyclonucleoside under the same conditions.[6] This approach of using N^6-acylated adenosine derivatives to preclude intramolecular cyclization has since been followed by several groups using a variety of leaving groups on the sugar and a whole range of different nucleophiles.[8-10] It should be noted that in cases where the 2′,3′-*O*-isopropylidene group is absent, N^6-acylation of the heterocycle is not required in order to prevent intramolecular cyclization between N^3 and C5′.[11-13] In this regard, the 2′,3′-ketal group has been shown to cause a flattening of the sugar ring,[14] and this presumably enhances the rate of intramolecular cyclization at C5′ when it is present.[15]

Similar problems with cyclonucleoside formation ($N^3 \rightarrow$ 3′) have been encountered with 2′,3′-anhydroadenosine (**14**)[16a] which was shown to decompose in water to yield 5-amino-1-(3-deoxy-β-D-xylofuranosyl)imidazole-4-carboxamidine ($N^5 \rightarrow$3′)-cyclonucleoside hydroformate (**16**) via the ($N^3 \rightarrow$3′)-cyclonucleoside (**15**). Such cyclization precluded facile epoxide transformations without prior acylation of the base. While this paper was in preparation, Robins et al. described a ring opening of **14** with NaN_3 in the presence of NH_4Cl under controlled conditions which did not give appreciable cyclonucleoside formation.[16b]

The use of *N*-acyl derivatives to prevent intramolecular cyclization during nucleophilic displacement on the sugar is presumably related to a decrease in the nucleophilicity of N^3 by the electron-withdrawing effect of the acyl group. Since one could envisage synthetic transformations in which the basic deblocking step for removal of the acyl group would be undersirable, we sought a new functionality which could prevent intramolecular cyclization but which could be removed under nonbasic conditions. This report indicates that adenosine N^1-oxides fulfill these requirements, and several illustrative transformations are described.

The direct oxidation of adenosine derivatives to N^1-oxides has been accomplished by several groups using peracids in a variety of solvents.[17-19] In particular, *m*-chloroperbenzoic acid (MCPBA) has been used extensively for N-oxidation of pyrimidine derivatives, although its use in the purine series has been somewhat limited. A detailed study of the reaction of MCPBA with many nucleic acid components has been described.[20] The N^1-oxidations described in this report were all carried out using MCPBA in triethyl phosphate as solvent, since this combination provided for high yields and simple workups in all of the derivatives studied.

Treatment of 5′-*O*-(*p*-toluenesulfonyl)-2′,3′-*O*-isopropylideneadenosine (**2**)[21] with MCPBA in triethyl phosphate gave the 5′-*O*-(*p*-toluenesulfonyl)-2′,3′-*O*-isopropylideneadenosine N^1-oxide (**6**) in 81% yield (see Scheme I). It was also possible to synthesize **6** by tosylation of 2′,3′-*O*-isopropylideneadenosine N^1-oxide (**5**) (prepared by reaction of 2′,3′-*O*-isopropylideneadenosine (**1**) with MCPBA in triethyl phosphate), but this route usually gave rise to lower yields and colored products. The synthetic usefulness of **6** was demonstrated by its facile conversion to 5′-iodo-5′-deoxy-2′,3′-*O*-isopropylideneadenosine N^1-oxide (**7**) in 87% yield by treatment with NaI in acetone. An identical reaction using **2** gave the cyclonucleoside **3** exclusively. An alternative preparation of **7** was accomplished by reaction of 2′,3′-*O*-isopropylideneadenosine N^1-oxide (**5**) with methyltriphenoxyphosphonium iodide in DMF. This gave **7** in 74% yield, which is somewhat better than that reported earlier using N^6-benzoyl-2′,3′-*O*-isopropylideneadenosine under similar conditions.[10] The use of **1** as starting material has reportedly led to extensive cyclonucleoside formation[2,5] except under carefully controlled conditions.[10]

An additional illustration of the synthetic usefulness of **6** was accomplished by displacement of the 5′-*O*-tosyl function with azide to give 5′-azido-5′-deoxy-2′,3′-*O*-isopropylideneadenosine N^1-oxide (**10**) in 72% yield.

In order to demonstrate the overall effectiveness of the N^1-oxides as substrates for these sugar transformations, it was necessary to show that deoxygenation to the corresponding nucleoside could be readily achieved. In this regard, Stevens et al. have shown that reduction of N^1-oxides can be effectively carried out using Raney nickel.[17] Hydrogenation of 5′-iodo-5′-deoxy-2′,3′-*O*-isopropylideneadenosine N^1-oxide (**7**) in the presence of Raney nickel at room temperature and pressure gave the known 5′-iodo-5′-deoxy-2′,3′-*O*-isopropylideneadenosine (**8**) in 83% yield.[22] Such selective reduction of the N^1-oxide in the presence of the 5′-iodo function may have additional synthetic significance (reduction of the 5′-iodo to the 5′-deoxy has been achieved by several methods,[23-25] including hydrogenation over Raney nickel at elevated pressures[25]). However, such selectivity was not apparent during reduction of 5′-azido-5′-deoxy-2′,3′-*O*-isopropylideneadenosine N^1-oxide (**10**). In this instance, hydrogenation of **10** over Raney nickel at room temperature and pressure gave concomitant reduction of the 5′-azido function as well as the N^1-oxide to produce 5′-amino-5′-deoxy-2′,3′-*O*-isopropylideneadenosine (**11**) (although TLC monitoring of the reaction mixture indicated that reductions of the azide and the *N*-oxide functions were not occurring at the same rate). Similar reductions of azido to amino nucleosides using Raney nickel are well documented.[6,26] Deblocking with hydrochloric acid gave the known 5′-amino-5′-deoxyadenosine hydrochloride (**12**).[6] Kummer and Seshadri have shown that 2,2′-bipyridyl *N*-oxides form adducts with hexachlorodisilane[27] and, very recently, Barton et al.

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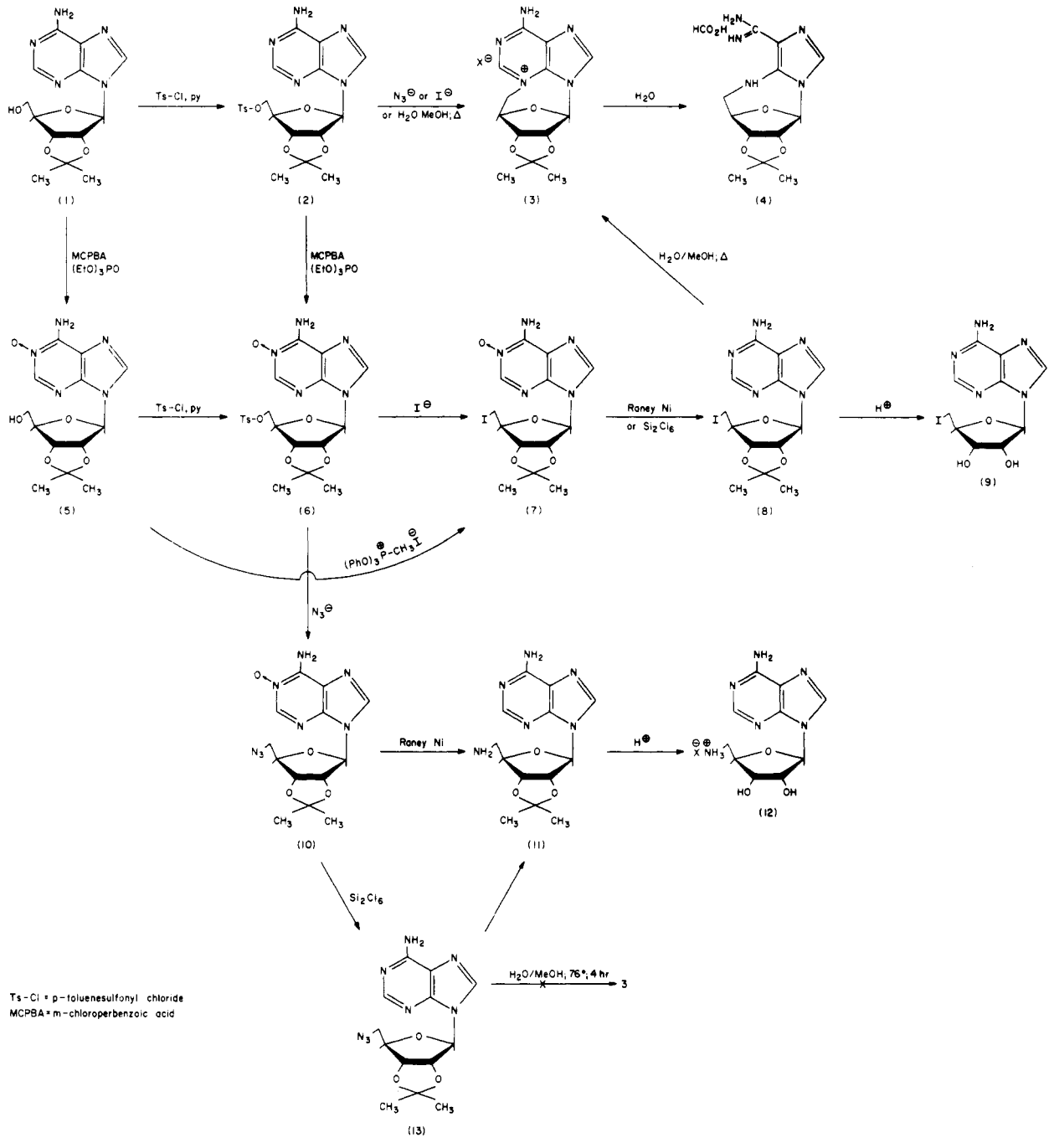
Scheme I



have used the same reagent to deoxygenate α-substituted quinuclidine *N*-oxides.[28] Treatment of **10** with hexachlorodisilane in CH_2Cl_2 gave rapid and smooth reduction of the N^1-oxide function to produce the known 5′-azido-5′-deoxy-2′,3′-*O*-isopropylideneadenosine[29] (**13**) in 73% yield after chromatography on silica gel. Similar treatment of **7** with Si_2Cl_6 gave 5′-iodo-5′-deoxy-2′,3′-*O*-isopropylideneadenosine, also in good yield, thus providing an alternate route to **8**. Acid deblocking of **8** to produce the known 5′-iodo-5′-deoxyadenosine (**9**)[6,10,22] was readily achieved and served as additional structure proof.

The decreased tendency toward intramolecular cyclization that is conferred by the N^1-oxide was further demonstrated by comparison of the relative stabilities of **2** and **6** in H_2O–MeOH (1:1) at 76 °C and of **7** and **8** in the same solvent at 64 °C. Monitoring was by UV[30] (see Figure 1 and Experimental Section) and, in another experiment,

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(30) It should be noted that the λ_{max} of **4** is 286 nm compared to 293 nm for the ($N^3 \rightarrow 3'$)-carboxamidine (**16**).[16a] Whether or not this difference is due to different ring strains in the two chromophores arising from different points of attachment to the sugar ring is not known. That the end product of degradation of **2** in H_2O–MeOH is indeed the carboxamidine **4** and not the cyclonucleoside **3** was confirmed by subjecting **3** (X = tosylate, λ_{max} 272 nm; prepared by intramolecular cyclization of **2** in a nonaqueous medium, by known methods[7]) to the same conditions (H_2O–MeOH, 1:1, 76 °C). The end product [formed instantly, as would be expected from the presence of isosbestic points in the UV spectra during the degradations of **2** and **8** (see Figure 1)] had identical UV spectral data (λ_{max} 286 nm, λ_{min} 248 nm) as that obtained by treatment of **2**. These data would appear to be in agreement with those of others[11] who have shown the intermediacy of the cyclonucleoside **3** in the degradation of adenosine derivatives such as **2** or **8** to their respective carboxamidines.

Table I. NMR (220 MHz) Spectral Data[a,b]

Compound (Solvent)	H1'	H2'	H3'	H4'	H5'5"	H2[c]	H8[c]	Others
1 (D_2O)	6.20 (d) $J_{1'2'}$=3.5	5.39 (d of d) $J_{2'1'}$=3.5 $J_{2'3'}$=6.2	5.11 (d of d) $J_{3'2'}$=6.2 $J_{3'4'}$=2.4	4.50 (m)	3.80 (m)	8.18 (s)	8.27 (s)	1.68, 1.45 (CMe_2)
5 (D_2O)	6.29 (d) $J_{1'2'}$=2.9	5.48 (d of d) $J_{2'1'}$=3.0 $J_{2'3'}$=6.1	5.13 (d of d) $J_{3'2'}$=6.2 $J_{3'4'}$=2.7	4.50 (m)	3.78 (m)	8.56 (s)	8.41 (s)	1.66, 1.44 (CMe_2)
2 ($CDCl_3$)	6.05 (d) $J_{1'2'}$=2.0	5.33 (d of d) $J_{2'1'}$=1.9 $J_{2'3'}$=6.2	5.06 (d of d) $J_{3'2'}$=6.2 $J_{3'4'}$=3.1	4.48 (m)	4.25 (m)	7.85 (s)	8.24 (s)	7.62, 7.17 (d's, J=8.2; Aromatic H's); 2.40 (Ph-Me); 1.59, 1.37 (CMe_2)
6 ($CDCl_3$)	6.08 (d) $J_{1'2'}$=2.3	5.28 (d of d) $J_{2'1'}$=2.4 $J_{2'3'}$=6.3	4.98 (d of d) $J_{3'2'}$=6.3 $J_{3'4'}$=2.8	4.51 (m)	4.23 (m)	8.64 (s)	8.03 (s)	7.68, 7.27 (d's, J=8.2, Aromatic H's); 2.43 (Ph-Me); 1.60, 1.38 (CMe_2)
8[d]	6.13 (d) $J_{1'2'}$=2.0	5.48 (d of d) $J_{2'1'}$=2.1 $J_{2'3'}$=6.1	5.11 (d of d) $J_{3'2'}$=6.2 $J_{3'4'}$=2.6	4.44 (m)	3.40 (m)	8.03 (s)	8.42 (s)	1.64, 1.43 (CMe_2)
7 ($CDCl_3$ or [d])	6.11 (d) $J_{1'2'}$=2.5	5.42 (d of d) $J_{2'1'}$=2.4 $J_{2'3'}$=6.4	5.00 (d of d) $J_{3'2'}$=6.3 $J_{3'4'}$=3.2	4.40 (m)	3.30 (m)	8.73 (s)	8.10 (s)	6.97 (NH_2) 1.64, 1.43 (CMe_2)
13[d]	6.12 (d) $J_{1'2'}$=2.3	5.45 (d of d) $J_{2'1'}$=2.3 $J_{2'3'}$=6.3	5.07 (d of d) $J_{3'2'}$=6.3 $J_{3'4'}$=3.4	4.39 (m)	3.61 ("d")	7.95 (s)	8.34 (s)	6.26 (NH_2) 1.63, 1.40 (CMe_2)
10 ($CDCl_3$ or [d])	6.11 (d) $J_{1'2'}$=2.4	5.36 (d of d) $J_{2'1'}$=2.4 $J_{2'3'}$=6.4	5.00 (d of d) $J_{3'2'}$=6.3 $J_{3'4'}$=3.5	4.39 (m)	3.57 (m)	8.74 (s)	8.06 (s)	7.57 (NH_2) 1.61, 1.39 (CMe_2)
14 (D_2O)	6.33 (s)	4.62 (d) $J_{2'3'}$=2.6	4.35 (d) $J_{3'2'}$=2.7	4.48 ("t")	3.71 ("d")	8.11 (s)	8.27 (s)	
17 (D_2O)	6.41 (s)	4.67 (d) $J_{2'3'}$=2.6	4.34 (d) $J_{3'2'}$=2.6	4.47 ("t")	3.71 ("d")	8.62 (s)	8.48 (s)	

[a] Shifts measured in ppm from internal TSP for 1, 5, 14, and 17, from internal Me_4Si for all others. [b] First-order couplings measured in Hz. [c] Assignment was made by deuterium exchange of H8 [heating of sample in D_2O or CD_3OD-D_2O (1:1) at 75 °C > 4 h] for 1, 5, 7, 10, 13, and 17. Assignments for 2 and 8 are based on those of the parent nucleoside 1 and are not unequivocal. Assignment for 6 is based on that of 5, 7, and 10. [d] CD_3OD-$CDCl_3$ (3:97).

by NMR and TLC (see Experimental Section).[31] Both 5'-azido compounds **10** and **13** showed no degradation at 76 °C for 4 h. NMR and TLC monitoring of the relative stabilities of the N^1-oxides **6**, **7**, and **10** [in CD_3OD-D_2O (1:1) at 76 °C] for extended periods of time (see Experimental Section) showed the order of stability to be **10** > **7** > **6**, and TLC's of the hydrolysates from **6** and **7** indicated several products which were not isolated. Since the rate of hydrolysis was evidently related to the nature of the leaving group present at C5' in **6**, **7**, and **10**, it is tempting to suggest that the above-mentioned products from degradation of **6** and **7** arise from intramolecular cyclization ($N^3 \rightarrow C5'$) followed by hydrolysis to produce ring-opened, unstable 5-amino-1-(5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranosyl)imidazole-4-carboxamidoxime ($N^5 \rightarrow 5'$)-cyclonucleoside derivatives,[17b] which are in turn hydrolyzed further.

To demonstrate further the potential synthetic usefulness of N^1-oxides, we prepared 2',3'-anhydroadenosine N^1-oxide (**17**) from 2',3'-anhydroadenosine (**14**) in 77% yield using MCPBA in triethyl phosphate (see Scheme II). Again, this material proved to be stable by NMR, UV, and TLC under conditions (H_2O, 80 °C, 4 h) which caused complete degradation of the parent epoxide (**14**).[16a]

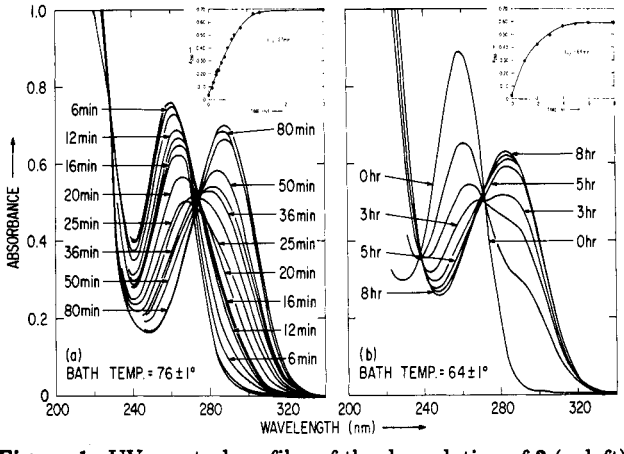

Figure 1. UV spectral profiles of the degradation of **2** (a, left) and **8** (b, right) in MeOH/H_2O (1:1) at elevated temperature. Inserts show a plot of absorbance at 290 nm vs. time for the same experiment.

The spectral data for all new N^1-oxide derivatives synthesized in this study are tabulated in Tables I and II. All

(31) Although the UV spectra of 6, 7, and 10 indicated no degradation after heating in MeOH–H_2O (1:1) at 76 °C for 90 min, it was important to verify that fact by other means since hydrolysis of certain adenosine N^1-oxide derivatives to ring-opened 5-aminoimidazole-4-carboxamidoxime analogues have been shown to occur with no major changes in the UV spectrum except for a diminished intensity.[17b]

Scheme II

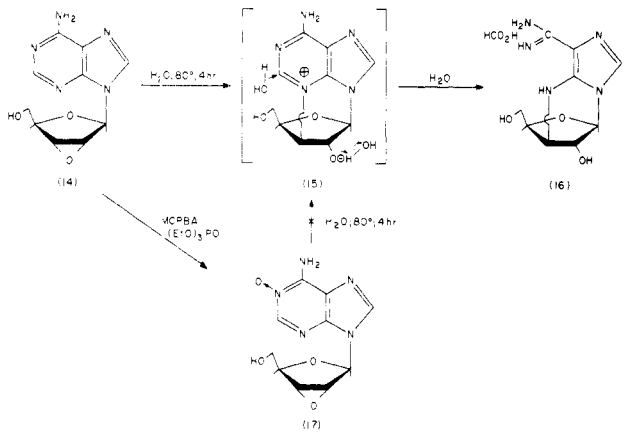

Table II. UV and IR Spectral Data

compd	UV[a] max, nm (ϵ)	IR,[b] cm^{-1}
5	(i) 257 (12 000) (ii) 299 (1920), 261 (7300), 233 (38 000) (iii) 311 (4000), 267 (7900), 231 (24 600)	N→O (1495)
6	(i) 258 (11 400) (ii) 297 (2520), 261 (8100), 229 (37 800) (iii) 310 (3600), 266 (8100), 226 (30 000)	N→O (1495)
7	(i) 257 (11 100) (ii) 296 (2400), 261 (8100), 233 (37 800) (iii) 314 (3600), 267 (7300), 233 (21 300)	N→O (1495)
10	(i) 257 (12 300) (ii) 297 (2300), 261 (7500), 234 (38 100) (iii) 312 (4000), 267 (7300), 233 (21 300)	N→O (1495) N_3 (2100)
17	(i) 258 (12 700) (ii) 299 (2300), 261 (7900), 233 (39 500) (iii) 310 (3900), 267 (8000), 231 (25 800)	N→O (1495)

[a] (i) MeOH/0.1 M methanolic HCl, 1:9; (ii) MeOH; (iii) MeOH/0.1 M methanolic NaOH, 1:9. [b] KBr disk.

show characteristic adenosine N^1-oxide UV spectra[32] and also exhibit absorbances in the IR spectra at 1495 cm^{-1}. Examination of the NMR chemical shift data (Table II) for the N^1-oxide derivatives shows that in all instances, the H2 resonance is shifted downfield (0.38–0.79 ppm) relative to the same proton in the parent nucleoside, making H2 the downfield resonance of the base protons in **5–7**, **10**, and **17**. Such a uniform deshielding is presumably related to the presence of the electronegative oxygen situated at N^1.[33] Examination of the coupling constants for the sugar ring protons indicates that formation of an N^1-oxide induces no pronounced change in the sugar conformation. In addition, the criterion developed by Imbach and co-workers[34] for determining the anomeric configuration of ribonucleosides by observation of the chemical shift difference between the isopropylidene methyl resonances ($\Delta\delta > 0.15$ ppm for β-anomers) and also the H4′ multiplicity criterion[35] (triplet for α-anomers, higher multiplet for β-anomers) in the same compounds can both be seen to remain valid in these isopropylidene derivatives having an N^1-oxide and a substituent at C5′—at least for the β-anomers.

The work described herein permits nucleophilic displacement reactions to be carried out on the sugar moiety of adenosine derivatives without concomitant N^3→sugar intramolecular cyclization. This new synthetic use of N^1-oxides allows the introduction of novel functionalities into the sugar without the requirement of using base-labile blocking groups on the heterocycle.

Experimental Section

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. NMR spectra were recorded on a Varian HR-220 spectrometer, operating in the FT mode, with either Me_4Si ($CDCl_3$, C_5D_5N, or CD_3OD) or trimethylsilylpropanesulfonate (D_2O) as internal reference. UV spectra were recorded on a Beckman Model 25 spectrophotometer and IR spectra on a Beckman IR-4 or a Perkin-Elmer 457 instrument. Elemental analyses were determined by Galbraith Laboratories, Knoxville, TN, or at the Chemistry Department, Northern Illinois University, Dekalb, IL. Evaporations were effected using Büchi rotating evaporators under aspirator or mechanical oil pump vacuum at 40 °C or lower. Thin-layer chromatography (TLC) was performed on Merck silica gel 60, F-254, in solvent A ($CHCl_3$–MeOH, 9:1) or solvent B ($CHCl_3$–MeOH, 4:1). UV-absorbing compounds were detected by visualization under a UV lamp (254 nm). Column chromatography was effected using Merck silica gel 60 (70–230 mesh) or J. T. Baker silica gel 5-3405 (60–200 mesh). *m*-Chloroperbenzoic acid was purchased from Aldrich and purified before use.[36] Hexachlorodisilane was purchased from Alfa. All solvents were distilled before use.

2′,3′-*O*-Isopropylideneadenosine N^1-Oxide (5).[17,37] To a stirred solution of dry **1** (2.00 g, 6.5 mmol) in triethyl phosphate (100 mL) was added MCPBA (4.20 g, 23.5 mmol). After 24 h at room temperature, TLC (solvent A) showed complete reaction. The solvent was removed by distillation in vacuo (0.05 mmHg, oil bath 45–55 °C) until a viscous liquid remained. After dilution with triethyl phosphate (ca. 5 mL), addition of petroleum ether–diethyl ether (1:1, 100 mL) led to precipitation of the crude product. This was recrystallized from absolute EtOH in three crops to give colorless crystals which were dried over P_2O_5 in vacuo at 61 °C for 18 h: 1.78 g (85%); mp 240–241 °C (with partial decomposition at ~175 °C). Anal. Calcd for $C_{13}H_{17}N_5O_5 \cdot 0.8\ H_2O$: C, 46.37; H, 5.57; N, 20.80. Found: C, 46.45; H, 5.66; N, 20.45.

5′-*O*-(*p*-Toluenesulfonyl)-2′,3′-*O*′-isopropylideneadenosine N^1-Oxide (6). A solution of MCPBA (1.15 g, 6.50 mmol) in triethyl phosphate (25 mL) was cooled to 2–3 °C and dry **2**[21] (0.865 g, 1.88 mmol) was then added with stirring and exclusion of moisture. After 24 h, TLC (solvent A) indicated complete reaction. The solvent was removed by distillation in vacuo (0.05 mmHg, oil bath 50–70 °C) until a yellow viscous material remained. A small amount of triethyl phosphate was added and this solution was added dropwise into petroleum ether–diethyl ether (7:1, 400 mL). The precipitate so formed was filtered and this crude product was dissolved in $CHCl_3$ (75 mL) and extracted with cold saturated aqueous $NaHCO_3$ (3 × 80 mL) followed by H_2O (3 × 80 mL). The $CHCl_3$ layer was reduced to a small volume (5 mL) and then added dropwise to petroleum ether–diethyl ether (7:1, 400 mL). The precipitated product was collected by filtration to yield 0.725 g (81%). This product can be used directly in

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further transformations without additional purification. An analytical sample (200 mg) was prepared by chromatography on a column of Merck silica gel (30 g, 3.5 × 9.5 cm) packed in $CHCl_3$ and developed with a stepwise gradient of $CHCl_3$–MeOH, adding MeOH in 2% increments. The product eluted in 8% MeOH and was collected by precipitation from a $CHCl_3$ solution into petroleum ether–diethyl ether (7:1) and dried in vacuo over P_2O_5 at 61 °C for 20 h; mp 166–167 °C (dec). Anal. Calcd for $C_{20}H_{23}N_5O_7S·0.5H_2O$: C, 49.37; H, 4.97; N, 14.40; S, 6.59. Found: C, 49.47; H, 4.93; N, 14.25; S, 6.49.

5′-Iodo-5′-deoxy-2′,3′-*O*-isopropylideneadenosine N^1-Oxide (7). Method A. To a solution of **6** (0.220 g, 0.46 mmol) in dry acetone (8 mL) was added dry NaI (0.190 g, 1.27 mmol). The reaction was refluxed at 80–85 °C (oil bath) for 2.5 h, at which time TLC (solvent B) indicated complete reaction. Solvent was evaporated to yield a light-colored foam which was dissolved in $CHCl_3$ (50 mL) and washed with 0.1 M $Na_2S_2O_3$ (2 × 50 mL) followed by H_2O (3 × 50 mL). The aqueous layers were back-washed with $CHCl_3$ (3 × 20 mL), and the organic layers were dried over Na_2SO_4. After concentation of the $CHCl_3$ solution to small volume, the crude product was precipitated from $CHCl_3$ into petroleum ether–diethyl ether (7:1) to yield **7**, 0.174 g (87%). An analytical sample was prepared by chromatography on Merck silica gel (40 g, 3.0 × 18.0 cm) packed in $CHCl_3$ and developed with a stepwise gradient of $CHCl_3$–MeOH, with MeOH added in 2% increments. The product was obtained by precipitation as described above to yield 0.164 g (82%) after drying at room temperature in vacuo over P_2O_5 for 18 h; mp 129–130 °C. Anal. Calcd for $C_{13}H_{16}N_5O_4I$: C, 36.04; H, 3.72; N, 16.17. Found: C, 36.43; H, 4.10; N, 16.09.

Method B. To a solution of **5** (0.250 g, 0.77 mmol) in dry DMF (10 mL) was added methyltriphenoxyphosphonium iodide[2] (0.770 g, 1.54 mmol). After the solution was stirred at room temperature for 24 h, the solvent was evaporated (oil pump) to give a yellow-brown gum. This was dissolved in $CHCl_3$ (20 mL) and extracted with 5% aqueous $Na_2S_2O_3$ (2 × 25 mL) followed by H_2O (2 × 25 mL). The aqueous layers were back-washed with $CHCl_3$ (4 × 25 mL) and the combined organic layers were dried over Na_2SO_4 and evaporated to dryness. This foam was dissolved in a minimum volume of $CHCl_3$ and added to petroleum ether. The precipitate so formed was filtered off to yield 0.248 g (74%) of crude **7**. Further purification on a silica gel column gave material identical with that prepared by method A.

5′-Iodo-5′-deoxy-2′,3′-*O*-isopropylideneadenosine (8).[22] Method A. To a stirred solution of **7** (0.085 g, 0.2 mmol) in CH_2Cl_2 (1 mL) was added Si_2Cl_6 (0.053 g, 0.2 mmol). After 45 min the reaction was evaporated to dryness and the residue was dissolved in 4 mL of MeOH/$CHCl_3$ (2:98) and applied to a column of Merck silica gel (35 g, 2.0 × 20.5 cm), which was wet-packed and developed in the same solvent. Fractions containing the required product were pooled and evaporated to dryness in vacuo. Drying at room temperature over P_2O_5 and paraffin wax for 14 h gave a stiff white foam (0.046 g, 56%): mp 103–104 °C dec; UV (MeOH), max 259 nm (ε 14000); IR showed no absorbance at 1495 cm^{-1}. Anal. Calcd for $C_{13}H_{16}N_5O_3I·CH_3OH$: C, 37.42; H, 4.49; N, 15.59. Found: C, 37.63; H, 4.28; N, 15.18.

Method B. To a solution of **7** (0.064 g, 0.13 mmol) in MeOH (5 mL) in a centrifuge tube was added 200 mg (wet) of Raney nickel (W2 activity), and hydrogen gas was bubbled through the suspension for 6 h. Monitoring by TLC (solvent A) showed complete reaction at this point, and the mixture was centrifuged. The supernatant and washings (MeOH) were filtered through Hyflo-Super Cel and the filtrate was evaporated to dryness under reduced pressure to yield a stiff white foam (0.051 g, 83%). This TLC homogeneous product was further purified on a Merck silica gel column (10 g, 3.0 × 4.5 cm) packed in $CHCl_3$. Application of the sample and elution was carried out by using MeOH/$CHCl_3$ (1:99) and pure **8**, 0.046 g (75%), was eluted in the first 200 mL. This product was identical by NMR, UV, and TLC with material prepared by method A.

5′-Iodo-5′-deoxyadenosine (9).[6,10,22] Deblocking of **8** was carried out as described by Moffatt and co-workers[10] to yield **9**. This material had identical melting point and NMR spectrum as quoted in the literature.[10]

5′-Azido-5′-deoxy-2′,3′-*O*-isopropylideneadenosine N^1-Oxide (10). To a solution of **6** (0.110 g, 0.23 mmol) in dry DMF (5 mL) was added LiN_3 (0.044 g, 0.9 mmol) and the reaction was heated at 74–80 °C (oil bath) with stirring for 2.25 h. The solvent was removed using a rotary evaporator (oil pump) and coevaporated three times with absolute ethanol. The yellowish residue so obtained was partitioned between $CHCl_3$ (50 mL) and H_2O (50 mL). The aqueous phase was extracted with $CHCl_3$ (3 × 50 mL) and the combined organic extracts were washed with H_2O (3 × 80 mL) and dried over Na_2SO_4 for 16 h. After filtration, the filtrate was evaporated to a light brown residue. This TLC homogeneous compound was recrystallized from acetone (5 crops) to yield 0.058 g (72.3%). On some occasions crystallization did not occur readily, and the product was chromatographed on Merck silica gel (developed in $CHCl_3$–MeOH, 98:2). An analytical sample was prepared by recrystallization from acetone and dried in vacuo over P_2O_5 at 61 °C for 16 h; mp 169–170 °C. Anal. Calcd for $C_{13}H_{16}N_8O_4·0.5H_2O$: C, 43.69; H, 4.80; N, 31.36. Found C, 43.44; H, 4.79; N, 31.20.

5′-Azido-5′-deoxy-2′,3′-*O*-isopropylideneadenosine (13).[29] To a stirred solution of **10** (0.049 g, 0.14 mmol) in CH_2Cl_2 (3 mL) was added Si_2Cl_6 (0.038 g, 0.14 mmol). After 45 min, the solution was evaporated to dryness to yield a stiff white foam. This was dissolved in 4 mL of MeOH/$CHCl_3$ (2:98) and applied to a Merck silica gel column (30 g, 2.5 × 14.0 cm) packed and developed in the same solvent. Fractions containing the required product were pooled and evaporated to dryness to yield 0.034 g (73%) of **13**. An analytical sample was obtained by crystallization from methyl ethyl ketone/*n*-pentane by diffusion to yield white crystals which were filtered and dried over P_2O_5 and paraffin wax in vacuo at 61 °C for 20 h: mp 140–141 °C (lit.[29] mp 137–138.5 °C); UV (MeOH) max 259 nm (ε 14300); the IR spectrum showed an absorbance at 2100 cm^{-1} (N_3) but none at 1495 cm^{-1} (N→O). Anal. Calcd for $C_{13}H_{16}N_8O_3$: C, 46.98; H, 4.82; N, 33.73. Found: C, 47.14; H, 4.95; N, 33.54.

5′-Amino-5′-deoxyadenosine Hydrochloride (12). To a solution of **10** (0.378 g, 1.1 mmol) in MeOH (20 mL) was added ~200 mg (wet) of Raney nickel (W2 activity), and hydrogen gas was bubbled through the suspension for 6 h (with the addition of similar amounts of Raney nickel at 2-h intervals) after which time TLC indicated complete reaction. The catalyst was filtered off and washed well with MeOH. The filtrate was concentrated almost to dryness and 0.1 N HCl (15 mL) was added. This acidified solution was evaporated to dryness several times from H_2O until TLC showed complete deblocking. The slightly colored **12** was dissolved in H_2O and applied to a column of Dowex 1-X2 (OH^- form, 250 mL). Development was with H_2O and then with a stepwise gradient of H_2O–MeOH, with MeOH added in 10% increments, the product being eluted at 50% aqueous MeOH. Fractions containing the required product were evaporated to dryness and the residue was dissolved in MeOH (10 mL). Hydrogen chloride gas was bubbled into the solution, the solvent was evaporated to a small volume, and crystallization (3 crops) was induced by addition of acetone to yield 0.222 g (74%), mp 144–145 °C. A recrystallized sample had mp 154–155 °C dec (lit.[6] 150 °C) and had NMR, UV, and TLC properties consistent with those of 5′-amino-5′-deoxyadenosine hydrochloride.

2′,3′-Anhydroadenosine N^1-Oxide (17). To a solution of **14**[16a] (0.100 g, 0.4 mmol) in triethyl phosphate (5 mL) was added MCPBA (0.277 g, 1.6 mmol) and the solution was stirred at room temperature for 24 h. At this point TLC (solvent B) indicated complete reaction and the solvent was removed by distillation in vacuo (0.1 mmHg, oil bath 45–50 °C) until the volume remaining was ca. 1 mL. Addition of low-boiling petroleum ether (~20 mL) yielded a precipitate which was filtered off, dissolved in a small volume of MeOH/$CHCl_3$ (1:4), and chromatographed on a column of Baker silica gel (20 g, 2.5 × 12.5 cm). The column was packed and developed in the same solvent mixture. Fractions containing the required product were pooled and evaporated to dryness. The residue so obtained was crystallized from absolute EtOH in 2 crops to yield 0.082 g (77%), mp 160–161 °C. Anal. Calcd for $C_{10}H_{11}N_5O_4·0.5H_2O$: C, 43.80; H, 4.41; N, 25.54. Found C, 43.96; H, 4.65; N, 25.15.

Stability Studies. Small amounts (~12–15 mg) of **2** or **8** were dissolved in $CHCl_3$–MeOH (96:4) (10 mL) and extracted with cold saturated aqueous $NaHCO_3$ (2 × 10 mL) followed by H_2O (2 × 10 mL). The organic layer was evaporated to dryness and a 20-mL solution of ca. 1 OD_{260} unit was made up using MeOH–H_2O (1:1).

This solution was distributed (1.5-mL aliquots) into tightly capped vials and suspended in an oil bath. In each instance, a control of the respective N^1-oxides (**6** and **7**) was carried out at the same time. In the case of **2** and **6**, the oil bath was maintained at 76 ± 1 °C and in the case of **7** and **8** at 64 ± 1 °C. At regular intervals, vials were removed and chilled in ice, and the UV spectra recorded (Figure 1). Compounds **2** and **8** showed complete degradation in 90 min ($t_{1/2}$ = 27 min) and 8 h ($t_{1/2}$ = 64 min), respectively, whereas **7** showed no observable degradation by UV, and the UV spectrum of **6** remained essentially unchanged except for a slightly diminished intensity.

The stabilities of **6**, **7**, **10**, and **13** were also examined separately at 76 °C (0.02 M) in CD_3OD–D_2O (1:1), monitoring by UV, NMR, and TLC (solvent B). After 90 min, **6** showed ca. 30% degradation (estimated by NMR and verified by TLC which showed the presence of a faster moving spot) even though the UV spectrum was unchanged except for diminished intensity. NMR indicated that total breakdown had occurred after 22 h (TLC showed several spots and the UV spectrum showed a much decreased intensity). After 90 min, **7** showed no degradation by UV or TLC, NMR indicating ca. 1% breakdown, and after 22 h the UV spectrum showed a slightly diminished intensity, but NMR indicated ca. 35% degradation and TLC showed four spots. **13** showed no degradation by NMR after 4 h, and **10** showed no degradation by UV, NMR, or TLC even after 22 h.

In the case of **17**, carried out in H_2O at 81 °C no breakdown could be detected after 4 h by UV, TLC, or NMR, although some slight discoloration of the NMR sample (0.02 M) was evident; **14** showed complete degradation at this point.[16a]

In the case of **3** (X = tosylate or iodide) complete degradation was noted at the first time point (5 min).

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Registry No. **1**, 362-75-4; **2**, 5605-63-0; **5**, 5167-12-4; **6**, 72525-43-0; **7**, 72525-44-1; **8**, 30685-66-6; **10**, 72525-45-2; **12**, 4137-54-6; **13**, 34245-48-2; **14**, 2627-64-7; **17**, 72525-46-3.

Stereochemistry of Free-Radical Eliminations on β-Phenylsulfonyl Radicals

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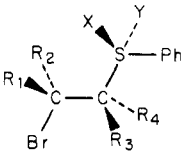
Tributyltin radicals have been allowed to react with *erythro*- and *threo*-2-bromo-3-(phenylsulfonyl)butane (**5a,b**) to generate β-(phenylsulfonyl)-*sec*-butyl radicals **9**. The intermediate **9** eliminates phenylsulfonyl radicals to form 2-butenes in a nonstereospecific manner. The lack of stereospecificity is due to rotation about the C_2–C_3 bond before the loss of the phenylsulfonyl radical can occur and implies that the stabilization of the radical by sulfur bridging is negligible.

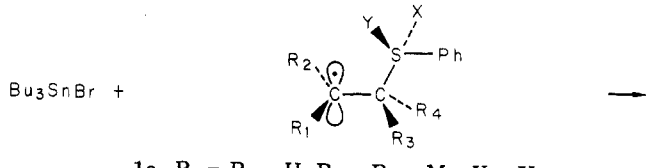
Alkyl radicals, substituted at the β position with a sulfur, often eliminate a sulfur-centered radical to generate an alkene.[1] We have recently investigated the stereochemistry of this elimination when β-phenylthio radicals, **1**,[1a] and β-phenylsulfonyl radicals, **2**,[1b] are generated by reaction of the corresponding bromides with tributyltin radicals (eq 1).

Reaction of either **3a** or **3b** with tributyltin radicals generates the same mixture of (*E*)- and (*Z*)-2-butenes, indicating that the barrier to rotation in **1** is less than the barrier to elimination.[1a] In striking contrast, however, reactions of tributyltin radicals with the four diastereomeric bromo sulfoxides **4a–d** produce (*E*)- and (*Z*)-2-butenes stereoselectively.[1b] The 2-butenes generated are those expected from loss of the phenylsulfinyl radical from nonequilibrium conformations of **2**. Thus, the barrier to rotation in **2** is larger than the barrier to elimination. We have rationalized this result by proposing that the greater kinetic stability of the phenylsulfinyl radical, **7**, as compared to the phenylthio radical, **6**,[2,3] lowers the barrier to elimination in **2** relative to **1**.

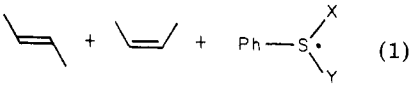
In order to test the hypothesis that the stability of the leaving radical determines the stereochemistry of the elimination, we now report a study of the reaction of the diastereomeric 2-bromo-3-(phenylsulfonyl)butanes (**5a,b**)



3a, $R_1 = R_4 = H$; $R_2 = R_3 = Me$; X = Y = :
3b, $R_1 = R_3 = Me$; $R_2 = R_4 = H$; X = Y = :
4a, $R_1 = R_4 = H$; $R_2 = R_3 = Me$; X = O; Y = :
4b, $R_1 = R_4 = H$; $R_2 = R_3 = Me$; X = :; Y = O
4c, $R_1 = R_3 = Me$; $R_2 = R_4 = H$; X = O; Y = :
4d, $R_1 = R_3 = Me$; $R_2 = R_4 = H$; X = :; Y = O
5a, $R_1 = R_4 = H$; $R_2 = R_3 = Me$; X = Y = O
5b, $R_1 = R_3 = Me$; $R_2 = R_4 = H$; X = Y = O



1a, $R_1 = R_4 = H$; $R_2 = R_3 = Me$; X = Y = :
1b, $R_1 = R_3 = Me$; $R_2 = R_4 = H$; X = Y = :
2a, $R_1 = R_4 = H$; $R_2 = R_3 = Me$; X = O; Y = :
2b, $R_1 = R_4 = H$; $R_2 = R_3 = Me$; X = :; Y = O
2c, $R_1 = R_3 = Me$; $R_2 = R_4 = H$; X = O; Y = :
2d, $R_1 = R_3 = Me$; $R_2 = R_4 = H$; X = :; Y = O
9a, $R_1 = R_4 = H$; $R_2 = R_3 = Me$; X = Y = O
9b, $R_1 = R_3 = Me$; $R_2 = R_4 = H$; X = Y = O



(1)

6, X = Y = :
7, X = :; Y = O
8, X = Y = O

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