Synthesis of the Difluorides 6c and 6t. The reactions were done as reported in the literature.[8] The following data are presented here because the published synthesis does not indicate whether *cis*- or *trans*-1,4-dichloro-2-butene was used, nor were spectral data reported.[8] Thus, *trans*-1,4-difluoro-2-butene (**6t**) was prepared from *trans*-1,4-dichloro-2-butene in 64% yield, bp 75–76 °C, with the following spectral properties: IR (CCl_4) 3040 and 2950 (CH), 1680 (weak C=C), 1080 (CF), 980 (C=H) cm^{-1}; ^1H NMR 60 MHz (CCl_4) δ 4.93 (d, m, J = 45 Hz, 4 H), 5.60–6.30 (m, 2 H); ^{19}F NMR (254-MHz, neat) ϕ −159.1 (t, m, J = 45 Hz); mass spectrum, m/e (relative intensity) 92 (9). Similarly, *cis*-1,4-difluoro-2-butene (**6c**) was prepared from *cis*-1,4-dichloro-2-butene in 60% yield, bp 75–76 °C with the following spectral properties: IR (CCl_4) 3040, 2960, and 2890 (CH), 1660 (weak C=C), 1005 (CF), 890 (CH) cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 4.97 (d, m, J = 46 Hz, 4 H), 5.53–6.10 (m, 2 H); ^{19}F NMR (254 MHz, CCl_4) ϕ −159.2 (t, m, J = 46 Hz); mass spectrum, m/e (relative intensity) 92 (5).

Reaction of XeF_2 with 2,3-Dimethyl-1,3-butadiene (2). The reaction was done (25 mg of XeF_2) as described for **1** above with the following variations: temperature, 25 °C; 0.02 equiv of BF_3·ether; reaction time, 20 min. Analysis on a 17.5 ft × $^1/_8$ in. stainless steel column, 2.5% of FFAP on 80/100-mesh Chromosorb W at room temperature, showed >99% **7** and <1% **8** (80% yield) with retention times of 7 and 10 min, respectively. Compound **7** was collected by preparative VPC on a 14 ft × $^1/_4$ in. SS stainless steel column of 2.5% FFAP on 80/100-mesh Chromosorb W and gave the following spectral data: IR (CCl_4) 3010 and 2990 (CH), 1660 (C=C), 1040 (CF), 890 (CH) cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 1.47 (dd, J = 20.8, J = 2.2 Hz, 3 H), 1.87 (dd, J = 7.0, J = 1.0 Hz, 3 H), 4.33 (dd, J = 48.4, J = 18.4 Hz, 2 H), 5.10–5.30 (m, 2 H); mass spectrum, m/e (relative intensity) parent 120 (27), P - HF 100 (3.5), P - CH_2F 87 (100). Compound **8** was formed in less than 1% in methylene chloride but was formed in almost equal amounts in methanol as solvent. Attempted isolation of **8** formed in methanol was unsuccessful since it was too unstable. GC–mass spectral data for **8** at 20 eV gave prominent peaks at m/e (relative intensity) 99 (1), 70 (13), 61 (28), 45 (28), and 43 (100). Support for the existence of **8** was obtained by isomerization of **8** to **7**. A mixture of **7** and **8** (4:1) in methylene chloride with toluene as internal standard was found to rearrange to **7** at room temperature ca. 10 h.

Reaction of XeF_2 with *cis*- and *trans*-1,3-Pentadienes (3c and 3t). The reactions were as described for **2** above except boron trifluoride was not required as catalyst. Reactions proceeded smoothly at 0 °C for **3t** and **3c**. The reactions were complete in 10–15 min. Analysis by VPC (FFAP column above at room temperature gave **9t**, **10**, **11**, and **12** with retention times 4.3, 12, 14, and 17 min, respectively. Compound **9c**, retention time 5.4 min, was formed when the mixture was allowed to stand overnight at room temperature. The kinetic product distributions are given in Table II. Products **9c**, **9t**, and **12** were isolated by preparative VPC on the $^1/_4$ in. FFAP column above. The following spectral data were obtained. **9t**: ^1H NMR (360 MHz, $CDCl_3$) δ 1.72 (d, d, J = 6.4, J = 1.1 Hz, 3 H), 2.49 (t, m, J = 16.0 Hz, 2 H), 5.3–5.9 complex multiplets (However, when the methyl at δ 1.72 was decoupled the following data were obtained: δ 5.36 (d, t, J = 14.8, J = 6.2 Hz, 1 H), 5.63 (d, J = 14.8 Hz, 1 H), 5.68 (d, t, J = 14.8, J = 6.2 Hz, 1 H), 5.63 (d, J = 14.8 Hz, 1 H), 5.68 (t, t, J = 57, J = 4.7 Hz, 1 H). **9c**: ^1H NMR (360 MHz, $CDCl_3$) δ 1.67 (d, J = 7.0 Hz, 3 H), 2.58 (t, m, J = 16.0 Hz, 2 H), 5.35–5.43 (m, 2 H), 5.72 (t, t, J = 57, J = 4.7 Hz, 1 H). **12**: ^1H NMR (60 MHz, $CDCl_3$) δ 1.42 (d, d, J = 26.1, J = 7.1 Hz, 3 H), 5.05 (d, m, J = 50 Hz, 1 H), 6.00–6.40 (m, 2 H). Although **10** and **11** were stable to the mild reaction conditions, they rearranged to the 1,4-product **12** during isolation by preparative gas chromatography or when a mixture of the products remained overnight at room temperature in methylene chloride as solvent (toluene as internal standard).

Reaction of $C_6H_5IF_2$ with Dienes 1, 2, 3c, and 3t. (Difluoroiodo)benzene was prepared from (dichloroiodo)benzene in methylene chloride as described in the literature,[2] and its molarity (≈0.3 M) was determined by titration with thiosulfate. The $C_6H_5IF_2$ solution contains significant amounts of hydrogen fluoride which is required as catalyst. The hydrogen fluoride was removed by shaking the methylene chloride solution of $C_6H_5IF_2$ with anhydrous KF.[15] To 3.0 mL of the scrubbed $C_6H_5IF_2$ solution at 0 °C with stirring in a 10-mL polyethylene bottle was added a twofold excess of diene. Several drops of unscrubbed $C_6H_5IF_2$ solution were added to introduce hydrogen fluoride catalyst if the reaction did not proceed as indicated by titration with thiosulfate. The mixture was poured into an aqueous solution of sodium sulfite after 30 min at 0 °C. The organic layer was dried over anhydrous magnesium sulfate. Analysis by gas chromatography with the columns and internal standards used for the XeF_2 reactions above gave the kinetic distribution of products listed in Tables I and II. The yields were found to be 40–60% except for diene **1** which was found to be 20%.

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Registry No. **1**, 106-99-0; **2**, 513-81-5; **3c**, 1574-41-0; **3t**, 2004-70-8; **5**, 92901-60-5; **6c**, 92901-61-6; **6t**, 92901-62-7; **7**, 92901-63-8; **8**, 92901-64-9; **9c**, 92901-65-0; **9t**, 92901-66-1; **10**, 92901-67-2; **11**, 92901-68-3; **12**, 92901-69-4; XeF_2, 13709-36-9; $C_6H_5IF_2$, 26735-53-5.

(15) Anhydrous KF is an efficient scrubber of hydrogen fluoride. The insoluable HKF_2 is formed.

Nucleophilic Substitution by Sulfite Ion on a Thiamin Analogue Having a Good Leaving Group

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1′-Methylthiaminium ion[1,2] **1a** and its analogues having pyridine,[3,4] phenol,[3,5] or thiol[3,6] leaving groups (X in **1**) react with sulfite ion to give sulfonic acid betaine **2**. The mechanism of substitution is multistep,[2] Scheme I, rather than S_N2. The first step is the addition of the nucleophile to the pyrimidine ring to give intermediate **3** that expels the leaving group to produce resonance-stabilized cation **4**. Reaction of this cation with a second equivalent of nucleophile gives **5**, and this is followed by aromatization to yield the observed sulfonic acid substitution product **2**.

Because of the nature of the leaving groups employed to date it may be suggested that this complex mechanism is merely a consequence of the selection of departing groups ranked among those labeled "poor" and that an extra driving force may be necessary for their expulsion.

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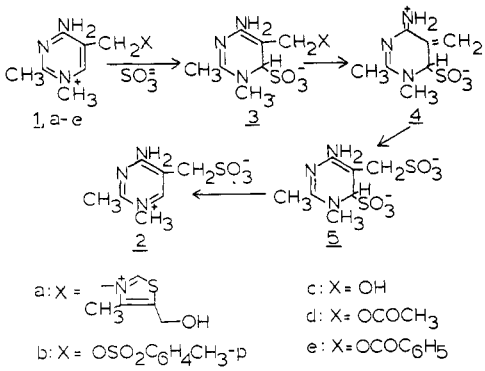
0022-3263/84/1949-5018$01.50/0

Scheme I



Such is achieved when the electron-withdrawing cationic pyrimidine ring is converted into the strongly electron-donating entity **3** on addition of the nucleophile.

We now report that an analogue having tosylate ion as a nucleofuge shows rapid but not exceptional reactivity toward sulfite ion, and this is consistent with the mechanism in Scheme I. The tosylate ion generally is acknowledged to be a "good" leaving group. Hence, the multistep mechanism must be an intrinsic property of the substituted pyrimidine ring and not a characteristic imposed by the departing group.

Results and Discussion

Synthesis of Tosylate 1b. Substrate **1b** having the tosylate leaving group was synthesized from tosyl chloride and alcohol **1c**. It was necessary to employ 2,6-dimethylpyridine instead of pyridine as solvent in order to hinder the facile, subsequent substitution of the tosylate to give the corresponding pyridine analogue **1** (X = pyridine)[3] and to avoid the usual aqueous workup to remove the heterocyclic solvent. The product is a highly water soluble salt difficult to recover from aqueous solution.

Our synthesis of known alcohol **1c**[7] is interesting and avoids exposure of the investigator to the unquaternized precursor alcohol as in the reported method. The uncharged carbinol is known as toxopyrimidine because of its toxicity.[8] An inexpensive, readily available source of the highly substituted pyrimidine ring of **1c** is thiamin (vitamin B_1), which is easily methylated at the 1′ position.[1] Hydrolysis of 1′-methylthiaminium ion, however, does not provide desired alcohol **1c**; instead the thiazolium ring is rapidly cleaved and subsequent hydrolysis is very difficult.[9] We have found a simple way to achieve the desired "hydrolysis" by using methanol rather than water as a solvent and a nucleophile, acetate ion, that furnishes the oxygen atom of the alcohol.

When **1a** is briefly heated in methanol with fused potassium acetate, substitution takes place. The thiazole ring is replaced by an acetoxy group to give **1d**. This acetate ester then undergoes a transesterification reaction with solvent to liberate the desired alcohol. This sequence of substitution–transesterification can easily be followed by examining the reaction mixture using NMR, signals for the ring protons being especially convenient. There is no need to isolate the intermediate acetate ester. Should an ester be desired, however, the benzoate **1e**, synthesized by using sodium benzoate, is easy to prepare and isolate.

The substitution reaction to give acetate ester probably takes place by a variation of the mechanism given in Scheme I. A nucleophile, probably methoxide ion formed in a solvolysis reaction with acetate base, adds to the pyrimidine ring in place of sulfite ion and thereby initiates replacement of the thiazole by acetate ion.

Table I. Conditions and Results of the Substitution of Tosylate 1b by Sulfite Ion at 25.0 °C and 1.0 M Ionic Strength

pH	$10^3SO_3^{2-}{}_{free}$,[a] M		k_2, M^{-1} s^{-1}
6.08	1.08		2.41
6.64	3.62		2.39
6.64	2.42		2.32
6.71	7.72		2.49
7.07	3.44		2.49
		av	2.42 ± 0.07

[a] Calculated by using pK_a = 6.59 for bisulfite ion.

Although NMR analysis of reaction mixtures indicates the formation of alcohol **1c** to be quantitative, considerable effort had to be expended in order to find conditions to isolate the product free of contaminating salt. Our reported conditions provide a convenient synthesis of the quaternized alcohol which is likely to be a useful starting material for the preparation of other thiamin analogues.

Kinetics and Product Studies. Tosylate **1b** underwent facile substitution in the presence of sulfite ion. The results in Table I show that the second-order rate constant is independent of pH, thus eliminating the possibility of a competing hydroxide ion initiated hydrolysis of the sulfonate ester or of hydrolytic substitution[10] by a variation of Scheme I during reaction with sulfite ion.

That reaction involves cleavage of the CH_2–OTs bond was demonstrated on a preparative scale by isolation of the expected sulfonate substitution product **2** in essentially quantitative yield.

Comparisons of second-order rate constants for tosylate **1b** with those for other thiamin analogues show it to be one of the most reactive analogues studied in sulfite ion substitution reactions. But its reactivity is not unusual. The tosylate is only 28 times more reactive than a substrate having *p*-nitrophenoxide ion as a leaving group[5] and is equally as reactive as that having nicotinamide (3-carbamoylpyridine) as the nucleofuge.[4] The comparison substrates are the most reactive members of their classes studied to date and both are known to react by multistep Scheme I.

We have suggested that for aryloxide ion leaving groups addition of sulfite ion to the ring is rate limiting and subsequent departure of the phenoxide ion is fast.[5] The tosylate now may be added to this class of substrates. Its moderately greater reactivity over that of the *p*-nitrophenoxy compound is entirely consistent with the expected greater electron-withdrawing field effect of the tosyloxy group that activates the pyrimidine ring for attack by a nucleophile.

A linear three-point plot of σ_1 vs. the logarithm of the second-order rate constants for sulfite ion reacting with substrates having tosylate, *p*-nitrophenoxide, and phenoxide ion leaving groups is consistent with the claim that leaving groups activate by their inductive effects. The inductive substituent parameters for the respective oxygen-substituted groups are 0.56, 0.47, and 0.40.[11] The ρ_I of this limited correlation is a very large 14.2 (correlation coefficient, 0.998), indicating a remarkable sensitivity to inductive effects.

That the tosylate and nicotinamide analogues have the same reactivity is an interesting coincidence which is un-

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derstandable if the rate-limiting step is different for each. The ground-state electrostatic destabilization present in the nicotinium dication is expected to facilitate addition of sulfite ion to the charged pyrimidine ring. This would make the dicationic substrate more reactive than the monocationic tosylate were it not for the additional energy barrier added by the rate-limiting loss of the nicotinamide. In the case of the singly charged tosylate addition of sulfite ion to the pyrimidine ring is slower, but this step is associated with the entire energy barrier since subsequent loss of the tosylate ion is fast. It is merely fortuitous that both substrates have the same total energy barrier. This analysis is consistent with our claim that all thiamin analogues studied to date react by the same mechanism, some with different rate-limiting steps.

The multistep mechanism given in Scheme I is a consequence of the structure of the substituted pyrimidine ring. It is not a pathway required by the nature of the leaving group.

Depending on the identity of the nucleofuge it is possible in the sulfite ion reactions to make any one of three steps rate limiting: (1) addition of sulfite ion to the ring to give **3** in the case of aryloxides[5] and the tosylate, (2) loss of a pyridine substituent to form **4** following addition,[4] and (3) addition of a second sulfite nucleophile to cationic intermediate **4** resulting from expulsion of a thiolate ion leaving group.[6] Can a leaving group be found for a thiamin analogue having structure **1** that will change not the rate-limiting step but the mechanism of substitution with sulfite ion? It would be interesting to learn how substituents on the pyrimidine ring may be modified to produce a mechanism change.

Experimental Section

4-Amino-1,2-dimethyl-5-[(tosyloxy)methyl]pyrimidinium Chloride (1b). To 2.0 g (7.9 mmol) of 4-amino-5-(hydroxymethyl)-1,2-dimethylpyrimidinium perchlorate (**1c**) dissolved in 40 mL of 2,6-dimethylpyridine and cooled to 0 °C was added 3.3 g (16 mmol) of *p*-toluenesulfonyl chloride with rapid stirring. The violet solution was allowed to stand at room temperature for 15 h to give a precipitate. One portion of 40 mL of CH_2Cl_2 was added, and the recovered solid was washed twice with 40-mL portions of CH_2Cl_2. The resultant crystalline residue was dissolved in a small volume of cold dimethylformamide and a 15–20-fold excess of hot toluene was added to give 0.87 g (2.5 mmol, 32%) of colorless crystals of the chloride which were recrystallized from acetonitrile: mp 195 °C dec; ^{1}H NMR (Me_2SO-d_6, Me_4Si) δ 9.20, 8.64 (NH_2), 8.51 (6-H), 7.46, 7.06 (tosyl), 4.69 (CH_2), 3.76 (NCH_3), 2.55 (2-CH_3), 2.26 (tosyl-CH_3). Anal. Calcd for $C_{14}H_{18}ClN_3O_3S$: C, 48.91; H, 5.28, N, 12.22. Found: C, 48.59; H, 5.28; N, 12.54.

4-Amino-5-(hydroxymethyl)-1,2-dimethylpyrimidinium Salts 1c. A mixture of 47.8 g (0.100 mol) of 1′-methylthiaminium diperchlorate[1] (**1a**) and 19.6 g (0.20 mol) of fused potassium acetate was heated at reflux for 2.5 h in 630 mL of methanol. The cooled mixture was filtered to remove $KClO_4$, reduced to about one-half volume, filtered again, and evaporated. The residue was extracted with three portions of CH_2Cl_2 to yield 16.2 g (76%) of crude acetate product contaminated with $KClO_4$. Recrystallization from 2-propanol gave 8.1 g (38%) of pure acetate (colorless plates): mp 177–179 °C dec; ^{1}H NMR (D_2O, DSS) δ 8.27 (6-H), 4.78 (CH_2), 4.05 (NCH_3), 2.85 (CCH_3), 2.03 (CH_3CO_2). Anal. Calcd for $C_9H_{15}N_3O_3$: C, 50.69; H, 7.09; N, 19.71 Found: C, 50.25; H, 7.02; N, 19.45.

The perchlorate salt was prepared by dissolving 23.3 g (0.109 mol) of pure acetate in 100 mL of water and adding 10.9 mL (0.11 mol) of 60% $HClO_4$. The solution was reduced almost (but not completely, CAUTION) to dryness. The resultant mass was recrystallized from 2-propanol to give 23.3 g (0.0919 mol, 84%) of colorless plates: mp 140–141 °C. Anal. Calcd for $C_7H_{12}ClN_3O_5$: C, 33.15; H, 4.77; N, 16.57. Found: C, 32.93; H, 4.81; N, 16.47.

Preliminary attempts to prepare the tosylate of the alcohol containing acetate ion impurity by a reaction with tosyl chloride in 2,6-dimethylpyridine gave the chloride salt of the alcohol: mp 260 °C, turns brown and then decomposes. The acetate ion reacts with the tosyl chloride. Anal. Calcd for $C_7H_{12}ClN_3O$: C, 44.34; H, 6.38; N, 22.16. Found, C, 44.18, H, 6.49; N, 21.85.

The formation of acetate ester **1d** and its conversion to hydroxy product **1c** in methanol may be followed conveniently by proton magnetic resonance spectroscopy. The pyrimidine ring proton signal of the former appears 7 Hz downfield from that of the latter.

4-Amino-1,2-dimethyl-5-[(benzoyloxy)methyl]pyrimidinium Perchlorate (1e). A suspension of 2.01 g (4.20 mmol) of 1′-methylthiaminium diperchlorate,[1] 1.22 g (8.46 mmol) of sodium benzoate, and 20 mL of methanol was heated at reflux for 45 min to give a milky solution that deposited 1.01 g (2.82 mmol, 67%) of crude product, mp 186–196 °C dec, on cooling. Recrystallization from methanol raised the melting point to 196–201 °C dec. For elemental analysis the sample was recrystallized from ethanol–water: mp 203–205 °C dec. Anal. Calcd for $C_{14}H_{16}ClN_3O_6$, C, 47.00; H, 4.51; N, 11.75. Found: C, 47.27; H, 4.58; N, 11.84.

Product Study for Sulfite Ion Substitution Reaction. When tosyloxy compound **1b** was heated briefly with excess sulfite ion, a precipitate, mp[2] 300 °C, of the betaine **2** formed and was collected. An NMR (Me_2SO-d_6) spectrum was identical with that of an authentic sample.

Kinetics of Substitution by Sulfite Ion. Reactions involving the tosyloxy compound **1b** were followed spectrophotometrically at 294 nm by using a reported method.[2] First-order kinetics was observed for at least 4 half-lives. Sulfite ion concentrations were checked iodometrically. Using a 2.5×10^{-4} M solution of substrate, the absorbance change was 0.240, consistent with a comparison of the spectra of authentic tosylate and sulfonate product.

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Registry No. **1a**, 92844-20-7; **1b**, 92844-21-8; **1c**·ClO_4, 92844-23-0; **1c**·acetate, 92844-24-1; **1c**·Cl, 92844-25-2; **1e**, 92844-27-4; **2**, 92844-28-5; potassium acetate, 127-08-2; perchloric acid, 7601-90-3; sodium benzoate, 532-32-1; sulfite, 14265-45-3; tosyl chloride, 98-59-9.