Acknowledgment. The authors would like to thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

Registry No.—**3**, 68423-20-1; **7**, 13429-21-5; **9**, 68423-21-2; **10**, 68423-22-3; **11**, 4515-89-3; **12**, 28974-51-8; **13**, 68423-23-4; **14**, 26921-44-8; **15**, 68423-17-6; **16**, 68423-18-7; **17**, 68423-19-8; **18**, 68423-24-5; spiropentyl *p*-nitrobenzenesulfonate, 68423-25-6; spiropentyl trifluoromethanesulfonate, 68423-26-7; methylenecyclopropane, 6142-73-0; dichloromethyl 2-chloroethyl ether, 13830-34-7; tiglaldehyde, 497-03-0; benzal bromide, 618-31-5; 1-phenylspiropentene, 68438-62-0.

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Neighboring Group Participation by Hydroxyl Oxygen. Intramolecular Cyclization of [(*anti*-9-Hydroxybenzonorbornen-*exo*-2-yl)methyl]-(*p*-nitrophenyl)methylsulfonium Tetrafluoroborate in Water

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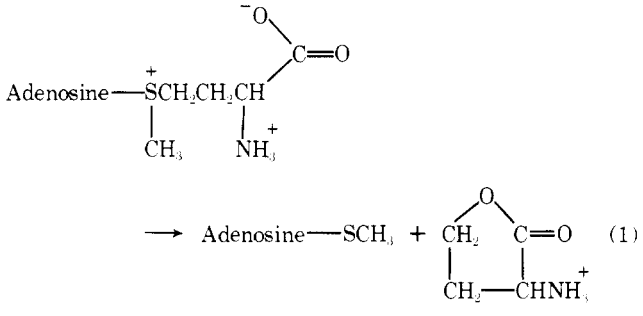
Received July 18, 1978

Gentle warming of the title sulfonium salt **1** in aqueous buffer medium afforded an intramolecularly cyclized ether **2** and *p*-nitro(methylthio)benzene, resulting from attack of the 9-hydroxyl oxygen on the *exo*-2-methylene carbon. This reaction pattern and the conditions required differ from the reported intermolecular nucleophilic attack on a series of aromatic-substituted phenyldimethylsulfonium salts and also, from the hydrolysis of the epimer, (*endo*-2-ylmethyl)sulfonium compound **16**. The reaction of **1**, which may be considered a model reaction of the biological alkylating agent *S*-adenosyl-L-methionine, was subjected to extensive kinetic studies over a wide pH range in aqueous buffered medium. Evidence was obtained for important participation of the *anti*-9-hydroxyl group and for catalysis effects of general bases. The water-catalyzed rate constant for **1** was $k_{H_2O} = 5.13 \times 10^{-7}$ s^{-1} at 25 °C. When this was compared to the rate evaluated for the hydrolysis of (*p*-nitrophenyl)dimethylsulfonium perchlorate (**18**), the effective molarity was calculated to be $\sim 5 \times 10^4$ M.

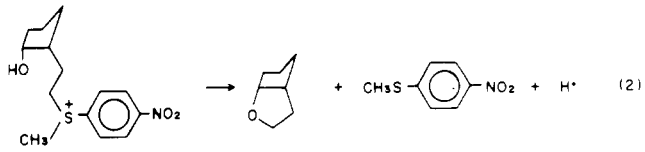
Nucleophilic attack at a carbon atom adjacent to electron-deficient trivalent sulfur (sulfonium compounds) is of biochemical importance. For example, *S*-adenosylmethionine, which is a principal coenzyme associated with biological methylation, undergoes not only methyl transfer, but also nucleophilic attack at the two methylene carbons attached to the sulfur atom.[1-3] An enzymatic reaction of the latter kind has been observed in the conversion of *S*-adenosylmethionine to α-amino-γ-butyrolactone (eq 1). This reaction presumably



(1)

proceeds by intramolecular nucleophilic attack of the carboxylate ion on the four-carbon chain attached to the sulfur.

Study of the enzyme mechanism is considerably aided by mechanistic studies on analogous nonenzymic chemical reactions of appropriate model compounds.[1-4] In studies of this kind, one of the preferred factors for understanding the enzyme reactions is neighboring group participation in intramolecular reactions. Model compounds for adenosylmethionine should undergo nucleophilic attack at the sp^3 carbon α to trivalent sulfur in aqueous media at moderate temperatures. Facile intramolecular nucleophilic substitution was expected, and many model compounds having a substituent capable of participation near the reaction center were synthesized, but the reactions did not proceed as expected.[3] The first success was communicated by Coward et al. in 1976, who found the reaction (eq 2) involving participation by the in-



(2)

tramolecular hydroxyl group. Until some years ago, we studied carbonium ion reactions of the benzonorbornenyl system, in which typical cases for aryl participation were obtained.[6]

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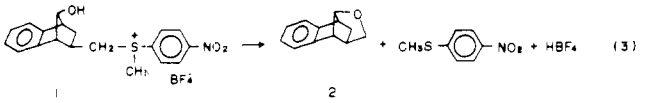
Working with this system, we report here facile intramolecular replacement of the sulfonium group by a hydroxyl group involving general-base catalysis effects.

Results

We converted [(*anti*-9-hydroxybenzonorbornen-*exo*-2-yl)methyl](*p*-nitrophenyl)methylsulfonium tetrafluoroborate (1) into the tricyclic ether **2** (eq 3) in water over a wide pH



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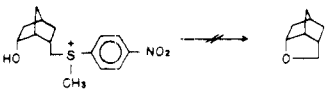
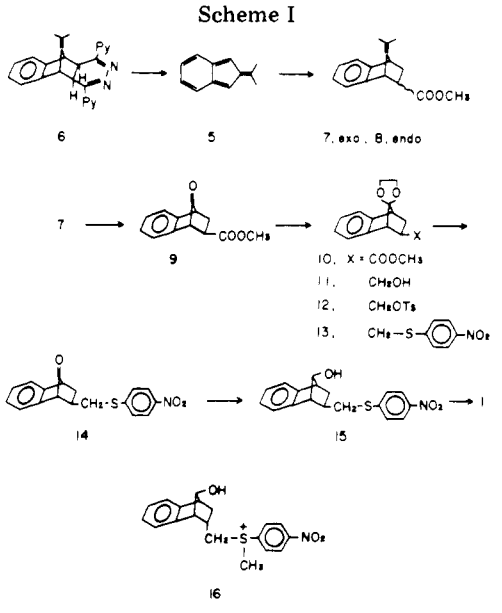


range. Evidence for the structure of **2** was mainly obtained from NMR spectra. The related compound, [(*endo*-6-hydroxynorborn-*endo*-2-yl)methyl](*p*-nitrophenyl)methylsulfonium salt (**3**), does not yield the corresponding ether **4** under similar conditions, but rather reacts in a different way.[3] The marked contrast between the reactions of **1** and **3** is of considerable interest and may be due to the strict stereochemical requirements involved in the S_N2 type process at the sp^3 carbon.[7]

Syntheses. To prepare 1, 8,8-dimethylisobenzofulvene (**5**) was trapped with a dienophile, methyl acrylate or acrylonitrile. We have previously reported similar trapping experiments.[8] When **5** was generated by thermal decomposition of **6** [the addition product of 9-isopropylidenebenzonorbornadiene to 3,6-di(2′-pyridyl)-*S*-tetrazine[8]] in the presence of a large excess of methyl acrylate, methyl 9-isopropylidenebenzonorbornene-*exo*- and -*endo*-2-carboxylates (**7** and **8**) were formed in a ratio of 7:3 and isolated in pure form by elution chromatography followed by recrystallization (Scheme I). The reaction with acrylonitrile also gave a mixture of the corresponding *exo*- and *endo*-2-nitriles, but when this mixture was hydrolyzed in an alkali medium, the carboxylic acid produced was entirely the *exo*-carboxylic acid (COOH instead of $COOCH_3$ in **7**) due to epimerization at C-2. Ozone oxidation transformed **7** into the ketone **9**, which was subsequently led to the ketal **10**, the alcohol **11** with lithium aluminum hydride reduction, the tosylate **12**, the thioether **13** by treatment with *p*-nitrothiophenol and sodium hydride, and the keto thioether **14**. Reduction of **14** with sodium borohydride predominantly gave the anti alcohol **15** in a manner similar to previously reported results.[9] Treatments of **15** with methyl iodide and silver tetrafluoroborate in nitromethane afforded the desired sulfonium salt **1**. The same reaction sequence starting from the endo compound **8** afforded the *endo*-sulfonium salt **16**.

Scheme I



Kinetics. The reactions of **1** were performed in water medium in the pH range of 4.65–10.91. The rates were followed by the increasing intensities at the UV maximum (350 nm) due to *p*-nitro(methylthio)benzene formation. Effects of varying the buffer ion concentration at a constant ionic strength (μ = 1.0 M) at several pH values were determined and summarized in Table I. The rate constants, k_1, extrapolated to 25.0 °C, are used for discussion.

Calculations. Based on general acid–base catalysis, the rate constant, k_1, in the acetate buffer may be defined by

$$k_1 = k_{Ac}[CH_3COO^-] + k_{HAc}[CH_3COOH] + k_{OH}[OH^-] + k_{H_2O} + k_H[H^+] \quad (4)$$

At constant pH, substituting k_0 for the last three terms reduces eq 4 to

$$k_0 = k_{OH}[OH^-] + k_{H_2O} + k_H[H^+] \quad (5)$$

$$k_1 = \{k_{Ac} + (k_{HAc}/K_a')[H^+]\}[CH_3COO^-] + k_0 \quad (6)$$

$$= k_{Ac}'[CH_3COO^-] + k_0 \quad (7)$$

where the K_a' is the dissociation constant of acetic acid, 1.753×10^{-5}, at 25.0 °C.[10]

Figure 1 plots k_1 in reciprocal seconds of Table I against acetate ion concentration for three different pH values. Ionic strength remained constant at a given pH. The linearity of the plots confirmed the expectation of eq 7 that k_1 depends on acetate concentration. The slopes, k_{Ac}', and intercepts, k_0, of such plots are given in Table II.

Plots of k_{Ac}' vs. the hydrogen ion concentrations, $[H^+] = 10^{-pH}$, for the three given pH values, as shown in Figure 2, permit the evaluation of k_{HAc}/K_a' and k_{Ac} by eq 8 at 25.0 °C,

$$k_{Ac}' = (k_{HAc}/K_a')[H^+] + k_{AC} = 1.825 \times 10^{-2}[H^+] + 3.25 \times 10^{-7} \quad (8)$$

where $k_{Ac} = 3.25 \times 10^{-7}\ M^{-1}\ s^{-1}$, $k_{HAc} = 3.20 \times 10^{-7}\ M^{-1}\ s^{-1}$, and $K_a' = 1.753 \times 10^{-5}$.

The same treatments of k_1 obtained from the phosphate and carbonate buffers and the 0.001 N NaOH solution (Table I, B–D), when extrapolated to the zero buffer concentrations,

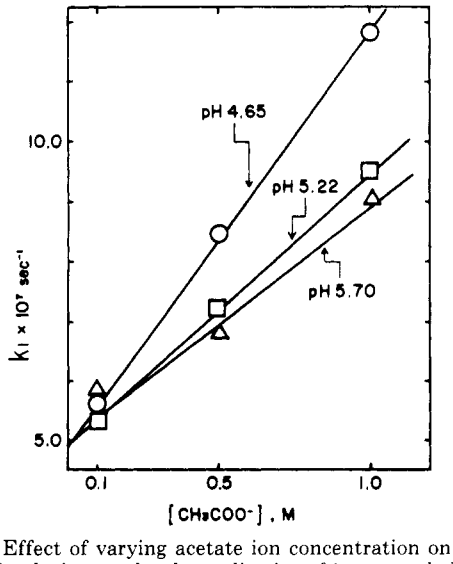


Figure 1. Effect of varying acetate ion concentration on the rate constants for the intramolecular cyclization of **1** at several pH values, 25 °C, and μ = 1.0 M.

Table I. Rates for Hydrolyses of [(*anti*-9-Hydroxybenzonorbornen-*exo*-2-yl)methyl](*p*-nitrophenyl)methylsulfonium Tetrafluoroborate (1)

A. acetate buffer, CH_3COONa–CH_3COOH, μ = 1.0 M with KCl, pH at 26.5 °C

pH	[B]/[BH]	[B][a]	k_{obsd}, s^{-1}, at °C 75.0	55.0	$k_1^{25.0°C}$,[b] s^{-1}
4.65	1:1	1.0	6.00×10^{-4}	6.21×10^{-5}	1.18×10^{-6}
		0.5	4.57×10^{-4}	4.63×10^{-5}	8.46×10^{-7}
		0.1	3.40×10^{-4}	3.30×10^{-5}	5.59×10^{-7}
5.22	3:1	1.0	5.71×10^{-4}	5.56×10^{-5}	9.48×10^{-7}
		0.5	4.38×10^{-4}	4.25×10^{-5}	7.20×10^{-7}
		0.1	3.55×10^{-4}	3.35×10^{-5}	5.40×10^{-7}
5.70	9:1	1.0	5.46×10^{-4}	5.36×10^{-5}	9.27×10^{-7}
		0.5	4.40×10^{-4}	4.19×10^{-5}	6.87×10^{-7}
		0.1	3.49×10^{-4}	3.45×10^{-5}	6.04×10^{-7}

B. phosphate buffer, Na_2HPO_4–KH_2PO_4, μ = 1.0 M with KCl, pH at 26.0 °C

pH	[B]/[BH]	[B][a]	k_{obsd}, s^{-1}, at °C 75.0	55.0	$k_1^{25.0°C}$,[b] s^{-1}
7.16	3:1	0.3	9.32×10^{-4}	8.87×10^{-5}	1.45×10^{-6}
		0.15	7.35×10^{-4}	6.47×10^{-5}	9.24×10^{-7}
		0.03	5.60×10^{-4}	4.97×10^{-5}	7.20×10^{-7}
7.68	9:1	0.3	1.62×10^{-3}	1.40×10^{-4}	1.94×10^{-6}
		0.15	1.16×10^{-3}	9.62×10^{-5}	1.24×10^{-6}
		0.03	8.88×10^{-4}	7.34×10^{-5}	9.39×10^{-7}

C. carbonate buffer, Na_2CO_3–$NaHCO_3$, μ = 1.0 M with KCl, pH at 25.5 °C

pH	[B]/[BH]	[B][a]	k_{obsd}, s^{-1}, at °C 60.0	40.0	$k_1^{25.0°C}$,[b] s^{-1}
8.85	1:9	0.3	1.02×10^{-3}	6.96×10^{-5}	7.36×10^{-6}
		0.15	9.95×10^{-4}	6.82×10^{-5}	7.24×10^{-6}
		0.03	9.60×10^{-4}	6.55×10^{-5}	6.92×10^{-6}
			45.0	25.0	
9.80	1:1	0.3	1.16×10^{-3}	5.36×10^{-5}	5.36×10^{-5}
		0.15	1.06×10^{-3}	5.09×10^{-5}	5.09×10^{-5}
		0.03	9.01×10^{-4}	4.54×10^{-5}	4.54×10^{-5}

D. 0.001 N NaOH solution, μ = 1.0 M with KCl, pH at 25.0 °C

pH	[B]/[BH]	[B][a]	k_{obsd}, s^{-1}, at 25.0 °C	$k_1^{25.0°C}$,[b] s^{-1}
10.91			6.36×10^{-4}	6.36×10^{-4}

[a] [B] and [BH] are molar concentration of base and acid, respectively. [b] Extrapolated by a FACOM computer. But rates at pH 9.80 and 10.91 were the observed data.

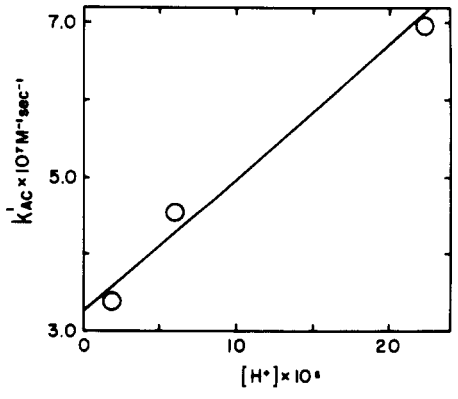


Figure 2. Dependence on hydrogen ion concentrations of the observed acetetate ion catalytic constants, k_{Ac}', in eq 8, at 25 °C and μ = 1.0 M.

Table II. Dependence of Rate Constants at 25.0 °C on Acetate Ion[a]

pH	$[H^+] \times 10^6$[b]	$k_{Ac}' \times 10^7$, M^{-1} s^{-1}	$k_0 \times 10^7$, s^{-1}
4.65	22.4	6.98	4.92
5.22	6.03	4.58	4.92
5.70	2.0	3.35	5.45

[a] See Figure 1. [b] $[H^+] = 10^{-pH}$.

Table III. Rate Constants, k_0, at Zero Concentration of Buffers Other than Acetate at 25.0 °C

pH	$[OH^-]$[a]	k_0, s^{-1}
7.16	1.46×10^{-7}	6.12×10^{-7}
7.68	4.83×10^{-7}	8.15×10^{-7}
8.85	7.14×10^{-6}	6.86×10^{-6}
9.80	6.36×10^{-5}	4.42×10^{-5}
10.91	8.19×10^{-4}	6.36×10^{-4}

[a] $\log [OH^-] = pH - pK_w$.

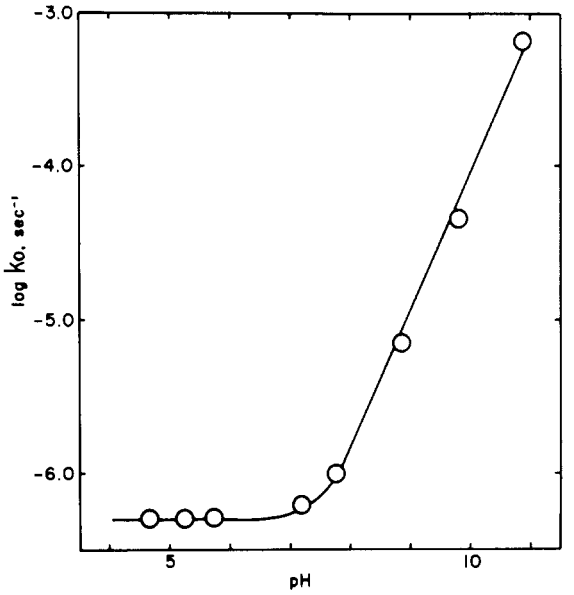


Figure 3. pH–rate profile for the intramolecular cyclization of 1 in water at zero buffer concentration, 25 °C, and μ = 1.0 M.

give k_0 in Table III. Figure 3 shows the dependence of the logarithms of the k_0 on pH.

From eq 5, the k_0 value in the area independent of pH in Figure 3 is k_{H_2O}, 5.13×10^{-7} s^{-1}. Inspection of the k_0 values in Table II indicates that the $k_H[H^+]$ contribution to k_0 is absent so that a plot of k_0 against the hydroxyl ion concentration [OH], [$\log [OH^-] = -(pK_w - pH)$], as shown in Figure 4, permits evaluation of the slope, k_{OH}, and the intercept, k_{H_2O}. Since the pK_w of water at 25.0 °C is 13.997, the treatment gives k_{OH} = 0.8 M^{-1} s^{-1}.[11]

A solvent isotope effect was determined for the reaction of 1 in deuterium oxide buffered with acetic acid–sodium acetate. The data are listed in Table IV and the same calculations as above give $k_{D_2O} = 4.00 \times 10^{-7}$ s^{-1}. Therefore, $k_{H_2O}/k_{D_2O} = 5.13 \times 10^{-7}$ $s^{-1}/4.00 \times 10^{-7}$ s^{-1} = 1.28.

As a reference compound, the epimeric [(*anti*-9-hydroxybenzonorbornen-*endo*-2-yl)methyl](*p*-nitrophenyl)methylsulfonium tetrafluoroborate (**16**) was hydrolyzed in the acetate buffer under the following conditions: pH 4.65, $[CH_3COONa]/[CH_3COOH]$ = 1:1, $[CH_3COONa]$ = 1.0 M (μ = 1.0 M). The reaction proceeded with a rate constant of $k_{obsd} = 2.59 \times 10^{-5}$ s^{-1} at 75.0 °C, forming the thioether **17**, as shown in eq 9. Therefore, the reaction pattern is totally dif-

Table IV. Rates of 1 in D_2O Buffered with CH_3COOH–CH_3COONa, μ = 1.0 M with KCl, pH at 27 °C

pH[a]	[B]/[BH]	[B][b]	k_{obsd}, s^{-1}, at °C 67.0	50.4	$k_1^{25°C}$,[c,d] s^{-1}
5.2	1:1	1.0	3.88×10^{-4}	4.60×10^{-5}	1.12×10^{-6}
		0.5	2.79×10^{-4}	3.03×10^{-5}	6.32×10^{-7}
		0.1	2.23×10^{-4}	2.42×10^{-5}	5.04×10^{-7}

[a] For determination of pH in D_2O, refer to M. O. Funk and E. T. Kaiser, *J. Am. Chem. Soc.*, **99**, 5336–5340 (1977) and ref 29 cited therein. [b] [B] and [BH] are molar concentration of CH_3COONa and CH_3COOH, respectively. [c] Extrapolated by a FACOM computer. [d] Plots of k_1 vs. $[CH_3COO^-]$ give $k_{D_2O} = 4.00 \times 10^{-7}$ s^{-1}.

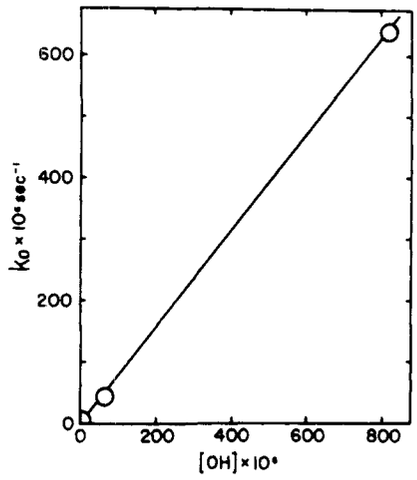
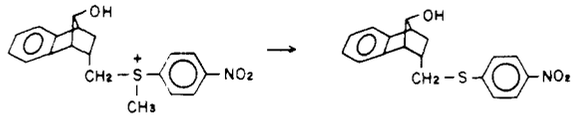


Figure 4. Dependence on hydroxyl ion concentration of the rate constants for the intramolecular cyclization of 1 at zero buffer concentration, 25 °C, and μ = 1.0 M.



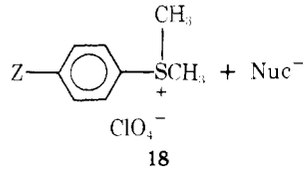
(9)

16 17

ferent from that of 1. The apparent k_{exo}/k_{endo} ratio is 23 at 75 °C.

Discussion

A survey of the literature indicates that intermolecular nucleophilic attack on sulfonium compounds takes place only under forced conditions and such a water attack is exceedingly slow. As a reference, the reaction of a series of aromatic-substituted phenyldimethylsulfonium perchlorates with various nucleophiles (eq 10) was studied by Coward and Sweet.[12] The



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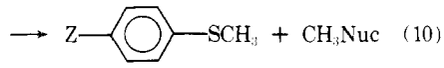


(10)

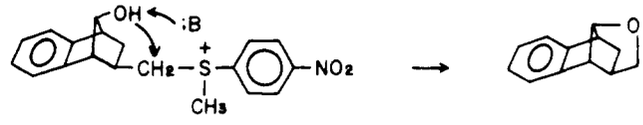
reaction rate follows the law

$$dP/dt = k_2[S][Nuc] \quad (11)$$

which yields

$$k_{obsd} = k_{OH}[OH] \quad (12)$$

when hydroxide is used as the nucleophile under pseudo-first-order conditions. It has been reported that the k_{OH} term for the hydrolysis of (*p*-chlorophenyl)dimethylsulfonium perchlorate (Z = Cl in 18) is 2.45×10^{-4} M^{-1} s^{-1} at 78.8 °C, the activation parameters are $\Delta F^{\ddagger}$ = 26.3 kcal/mol, $\Delta H^{\ddagger}$ = 24.8 kcal/mol, and $\Delta S^{\ddagger} = -5.0$ eu, and the Hammett ρ value, as an indication of the substituent effect at the para position of the aryl ring, is 1.60 at 78.8 °C under the condition $[OH^-]$ = 1.0 M. Further, the slope, β, of Brønsted plots has been reported to be 0.36 for the reactions of (*p*-nitrophenyl)dimethylsulfonium perchlorate with various amines. On the basis of these data, one can calculate, for the hydrolysis of (*p*-nitrophenyl)dimethylsulfonium perchlorate, that $k_{OH}^{25°C}$ is $\sim 10^{-6}$ M^{-1} s^{-1} and $K_{H_2O}^{25°C}$ is $\sim 10^{-11}$ M^{-1} s^{-1}.[13] Therefore, the k_{OH} (= 0.8 M^{-1} s^{-1}) for the present reaction is 10^6 times greater than that for (*p*-nitrophenyl)dimethylsulfonium perchlorate and also 41 times greater than that (1.92×10^{-2} M^{-1} s^{-1} at 25 °C) reported for the more flexible cyclopentyl derivative in eq 2. Comparison between the k_{H_2O} values for 1 and (*p*-nitrophenyl)dimethylsulfonium perchlorate gives an effective molarity (EM) of $\sim 5 \times 10^4$ M, which is slightly less than the value of 5×10^5 M reported for the reaction in eq 2. These facts suggest important participation of the intramolecular hydroxyl group at the 9 position in 1. In addition, the epimer **16**, in which hydroxyl participation is geometrically impossible, was found to undergo a completely different type of reaction, as shown in eq 9, with a slower rate.



2

Of significant interest is the evidence for general-base catalysis effects in the acetate buffer medium. The second-order rate constants obtained were 3.20×10^{-7} M^{-1} s^{-1} for CH_3COOH and 3.25×10^{-7} M^{-1} s^{-1} for CH_3COO^-. In the cases of the phosphate and carbonate buffers, the rate constants at zero buffer concentrations, k_0, are placed in the pH-dependent area in Figure 3. Thus, the above-mentioned calculation does not lead to reliable rate constants, k_B and k_{BH} M^{-1} s^{-1}.[14]

The solvent isotope effect found as k_{H_2O}/k_{D_2O} = 1.28 is compatible with the value, 1.37, obtained from the reaction[5] in eq 2, which suggests a nucleophilic reaction catalyzed by general bases with a transition state early on the reaction coordinate.

Consequently, the present study provides evidence for the participation of the neighboring hydroxyl group and catalysis effects of general bases on nucleophilic attack at the sp^3 carbon over a wide pH range in aqueous media.

Experimental Section

Melting points were taken by capillary and are corrected. Infrared spectra were determined with a 215 Hitachi grating infrared spectrophotometer, ^1H NMR spectra with a Varian T-60A, and ultraviolet spectra with an EPS-3T Hitachi recording spectrophotometer.

Methyl 9-Isopropylidenebenzonorbornene-*exo*- and -*endo*-2-carboxylates (7 and 8). To a solution of 775 mg (4.25 mmol) of 9-isopropylidenebenzonorbornadiene in 60 mL of methanol was added 36.6 g (425 mmol) of methyl acrylate and then, at 10 °C with stirring, 1 g (4.25 mmol) of 3,6-di(2′-pyridyl)-1,2,4,5-tetrazine. The reaction mixture was allowed to stand overnight at room temperature and then concentrated under reduced pressure and extracted with ether to remove the insoluble 3,6-dipyridylpyridazine produced. VPC indicated a 7:3 composition for the product mixture. The ether solution was evaporated and subjected to elution chromatography (solvent, 1:1 benzene–hexane). The first fraction was predominantly composed of the *exo*-carboxylate **7** (690 mg) and the second fraction of the *endo*-**8** (280 mg). Both carboxylates were purified by recrystallization from *n*-pentane.

For **7**: mp 52–53 °C; IR ($CHCl_3$) 1730 cm^{-1} ($COOCH_3$); NMR ($CDCl_3$) δ 1.6–2.6 (m, 3, at C_2, C_3), 1.65 (s, 6, CH_3), 3.80 (s, 3, $COOCH_3$), 3.85 (m, 1, at C_4), 4.15 (br s, 1, at C_1), and 7.2 (4, aromatic).

For **8**: mp 102–103 °C; IR ($CHCl_3$) 1730 cm^{-1}; NMR ($CDCl_3$) δ 1.65 (s, 6, CH_3), 1.5–1.8 (m, 1, at C_3 endo), 1.9–2.4 (m, 1, at C_3 exo), 3.2 (m, 1, at C_2), 3.60 (s, 3, $COOCH_3$), 3.85 (m, 1, at C_4), 4.2 (doubling d, 1, at C_1), and 7.2 (4, aromatic). Anal. Calcd for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 79.22; H, 7.60.

9-Isopropylidenebenzonorbornene-*exo*- and -*endo*-2-nitriles. When added to a solution of 986 mg (5.56 mmol) of 9-isopropylidenebenzonorbornadiene in 100 mL of dioxane at 10 °C, 1.31 g (5.56 mmol) of 3,6-di(2′-pyridyl)-1,2,4,5-tetrazine dissolved with evolution of nitrogen gas. The mixture was left to stand for 3 h, added to 5.9 g (111.2 mmol) of acrylonitrile, left to stand overnight at 70 °C, concentrated under reduced pressure, and extracted with ether to remove insoluble 3,6-dipyridylpyridazine. The ether solution was evaporated and subjected to elution chromatography. The first component was the benzoisofulvene dimer (120 mg), the structure of which was reported previously.[8] The second component was mostly the *exo*-nitrile (460 mg) and the third was the *endo*-nitrile (260 mg). The nitriles were purified by recrystallization from *n*-hexane–ether.

exo-Nitrile: mp 99–100 °C; IR ($CHCl_3$) 2240 cm^{-1} (CN); NMR ($CDCl_3$) δ 1.5–2.5 (m, 3, at C_2, C_3), 1.65 (s, 3, CH_3), 1.7 (s, 3, CH_3), 3.9 (m, 1, at C_4), 4.15 (br s, 1, at C_1), and 7.20 (4, aromatic). Anal. Calcd for $C_{15}H_{15}N$: C, 86.08; H, 7.22; N, 6.69. Found: C, 85.94; H, 7.13; N, 6.86.

endo-Nitrile: mp 128.5–129.5 °C; IR ($CHCl_3$) 2240 cm^{-1}; NMR ($CDCl_3$) δ 1.5 (s, 6, CH_3), 1.2–1.7 (m, 1, at C_3 endo), 2.1–2.6 (m, 1, at C_3 exo), 2.9–3.2 (m, 1, at C_2), 3.85 (m, 1, at C_4), 4.0 (doubling d, 1, at C_1), and 7.20 (4, aromatic). Anal. Calcd for $C_{15}H_{15}N$: C, 86.08; H, 7.22; N, 6.69. Found: C, 85.94; H, 7.13; N, 6.66.

9-Isopropylidenebenzonorbornene-*exo*-2-carboxylic Acid. The above-described reaction mixture (500 mg) produced by the reaction of 8,8-dimethylisobenzofulvene (**5**) with acrylonitrile, before the chromatographic treatment, was heated at 200 °C in 13 mL of 90% aqueous ethylene glycol containing 200 mg of sodium hydroxide. The mixture was washed with ether, acidified with dilute HCl, and extracted with ether. The ether solution was dried and evaporated. The residue was recrystallized to obtain 350 mg of the *exo*-2-acid, mp 154–155 °C, which was identified with a sample derived from the ester **7**: IR ($CHCl_3$) 1720 cm^{-1} (COOH); NMR ($CDCl_3$) δ 1.7 (s, 6, CH_3), 1.7–2.6 (m, 3, at C_2, C_3), 3.95 (m, 1, at C_4), 4.15 (br s, 1, at C_1), and 7.2 (4, aromatic). Anal. Calcd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06. Found: C, 79.04; H, 7.12.

Hydrolysis of the *endo*-nitrile, described above, under identical conditions gave the same *exo*-acid.

(9-Ethylenedioxybenzonorbornen-*exo*-2-yl)methyl *p*-Toluenesulfonate (12). Ozone was absorbed by a solution of 5 g of the *exo*-carboxylate **7** in 60 mL of methylene dichloride. Usual workup gave a crude ketone **9** (4.1 g): IR ($CHCl_3$) 1790 (C=O) and 1730 cm^{-1} ($COOCH_3$).

A solution of 4.1 g of the crude ketone in 50 mL of ethylene glycol and 200 mL of toluene containing 0.4 g of *p*-toluenesulfonic acid was refluxed with stirring and subjected to azeotropic dehydration for 16 h. Water was added to the reaction mixture cooled to room temperature. The organic layer was separated and the water layer was extracted with ether. The organic layer and the ether solution were combined, washed with aqueous Na_2CO_3, dried, and evaporated, leaving a residue (**10**, 5.17 g): IR ($CHCl_3$) 1730 cm^{-1} ($COOCH_3$).

The residue was reduced with $LiAlH_4$ in 150 mL of ether. The usual workup afforded 4.21 g of alcohol **11**: IR ($CHCl_3$) 3450 cm^{-1} (OH); NMR ($CDCl_3$) δ 1.2–2.1 (m, 3, at C_2, C_3), 2.5 (s, 1, OH), 3.1 (s overlapped with d, 2, at C_1, C_4), 3.6–4.1 (overlapping m, 6, CH_2OH and ethylene ketal), and 7.1 (4, aromatic).

The alcohol was treated with 3.45 g of tosyl chloride in 10 mL of pyridine at 0 °C. The usual workup gave tosylate **12**: mp 168–169 °C (from *n*-hexane–methylene dichloride); NMR ($CDCl_3$) δ 1.3–2.2 (m, 3, at C_2, C_3), 2.45 (s, 3, CH_3), 3.0 (s overlapped with d, 2, at C_1, C_4), 3.8 (m, 4, ethylene ketal), 4.1–4.7 (m, 2, CH_2OTs), 7.2 (4, aromatic), and 7.35, 7.85 (4, aromatic). Anal. Calcd for $C_{21}H_{22}O_5S$: C, 65.26; H, 5.74; S, 8.30. Found: C, 65.15; H, 5.68; S, 8.40.

Conversion of 12 into Thioether 13. A suspension of 786 mg of sodium hydride (50% in oil) in 30 mL of tetrahydrofuran was stirred at −60 °C under nitrogen atmosphere and to this was added 1 g of tosylate **12** and 2.55 g of *p*-nitrothiophenol. The mixture was refluxed for 3 h with stirring, concentrated under reduced pressure, and extracted with ether by adding water. The ether solution was washed with water, dried, distilled, and chromatographed over silica gel. Following *p*-nitrophenyl disulfide, 0.9 g of **13** was eluted with 1:1 *n*-hexane–benzene and recrystallized from ether–hexane: mp 125–126 °C; IR ($CHCl_3$) 1340 and 1510 cm^{-1} (NO_2); NMR ($CDCl_3$) δ 1.5–2.2 (m, 3, at C_2, C_3), 3.1 (s overlapped with d, 2, at C_1, C_4), 3.4–3.6 (m, 2, at CH_2S), 3.7–4.2 (m, 4, ethylene ketal), 7.2 (4, aromatic), and 7.3, 8.1 (4, aromatic). Anal. Calcd for $C_{20}H_{19}NO_4S$: C, 65.02; H, 5.18; N, 3.79; S, 8.68. Found: C, 64.97; H, 5.13; N, 3.73; S, 8.73.

(9-Ketobenzonorbornen-*exo*-2-yl)methyl *p*-Nitrophenyl Sulfide (14). A mixture of 775 mg of **13**, 30 mL of ethanol, and 5 mL of concentrated HCl was refluxed overnight. The mixture was concentrated under reduced pressure and extracted with methylene dichloride. The methylene dichloride solution was washed with water, dried, and evaporated, leaving 753 mg of an oily residue. When treated with *n*-hexane–ether, the oil crystallized: mp 141–142 °C; IR ($CHCl_3$) 1340 and 1510 cm^{-1} (NO_2); NMR ($CDCl_3$) δ 1.7–2.2 (m, 3, at C_2, C_3), 3.2 (d, 2, CH_2S), 3.5 (m, 2, at C_1, C_4), 7.3 (4, aromatic), and 7.4, 8.1 (4, aromatic). Anal. Calcd for $C_{18}H_{15}NO_3S$: C, 66.44; H, 4.65; N, 4.31; S, 9.85. Found: C, 66.63; H, 4.65; N, 4.20; S, 9.77.

(*anti*-9-Hydroxybenzonorbornen-*exo*-2-yl)methyl *p*-Nitrophenyl Sulfide (15). To a solution of 680 mg of **14** in 20 mL of tetrahydrofuran and 20 mL of methanol was added 79 mg of sodium borohydride and the mixture was stirred for 1 h at room temperature. The usual workup gave 658 mg of a crude alcohol, which was recrystallized from *n*-hexane–ether to afford 384 mg of yellow crystals, mp 101–102 °C dec. A small amount of the syn epimer was removed by the recrystallization. The anti configuration of the 9-hydroxyl group was proven by the absence of a hydrogen bond in the infrared spectra and by formation of **2** from **1**: NMR ($CDCl_3$) δ 1.5–2.3 (m, 3, at C_2, C_3), 2.4 (s, 1, OH), 3.2 (br s, 2, at C_1, C_4), 3.5 (d, 2, CH_2S), 3.95 (s, 1, at C_9), 7.1 (4, aromatic), and 7.3, 8.1 (4, aromatic). Anal. Calcd for $C_{18}H_{17}NO_3S$: C, 66.03; H, 5.24; N, 4.28; S, 9.79. Found: C, 66.18; H, 5.31; N, 4.09; S, 9.89.

[(*anti*-9-Hydroxybenzonorbornen-*exo*-2-yl)methyl](*p*-nitrophenyl)methylsulfonium Tetrafluoroborate (1). To a stirred solution of 102 mg of silver tetrafluoroborate in 2 mL of nitromethane was added, at room temperature, a solution of 172 mg of **15** in 2 mL of nitromethane and a solution of 372 mg of methyl iodide in 2 mL of nitromethane. The mixture was stirred for 3 h and the yellow-white crystals which precipitated were removed by filtration. The filtrate was concentrated under reduced pressure, leaving an oil which was treated with methanol, ether, and methylene dichloride to afford 149 mg of yellow crystals: mp 130–131 °C dec (from methanol–ether); IR (Nujol) 3550 cm^{-1} (OH); NMR (CD_3OD) δ 1.5–2.5 (m, 3, at C_2, C_3), 3.3 (m, 2, bridgehead), 3.4 (s, 3, CH_3), 3.8 (s, 1, at C_9), 4.4 (d, 2, CH_2S), 7.1 (4, aromatic), 8.4 (4, aromatic). Anal. Calcd for $C_{19}H_{20}O_3NSBF_4$: C, 53.16; H, 4.70; N, 3.26; S, 7.47. Found: C, 52.88; H, 4.91; N, 3.14; S, 7.71.

Preparation of 9-Substituted (Benzonorbornen-*endo*-2-yl)methyl Derivatives. Starting from **8**, the same reaction sequence as above led to **(9-ketobenzonorbornen-*endo*-2-yl)methyl *p*-nitrophenyl sulfide**: mp 124–125 °C (from *n*-hexane–dichloromethane); IR ($CHCl_3$) 1340 and 1510 (NO_2) and 1790 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.0 (q, 1, C_3 endo), 2.3–3.1 (m, 4, C_2 exo, C_3 exo, CH_2S), 3.5 (m, 2, at C_1, C_4), 7.35 (4, aromatic), and 7.3, 8.1 (4, aromatic). Anal. Calcd for $C_{18}H_{15}NO_3S$: C, 66.44; H, 4.65; N, 4.31; S, 9.85. Found: C, 66.51; H, 4.78; N, 4.26; S, 9.92. This ketone (76 mg) was dissolved in a mixed solvent of 4 mL of methanol and 4 mL of tetrahydrofuran and then reduced by sodium borohydride to **(*anti*-9-hydroxybenzonorbornen-*endo*-2-yl)methyl *p*-nitrophenyl sulfide**: IR (CCl_4) 3630 (OH), 1340 and 1510 cm^{-1} (NO_2); NMR ($CDCl_3$) δ 0.85 (q, 1, C_3 endo), 2.1–3.0 (m, 4, C_2 exo, C_3 exo, and CH_2S), 3.2 (m, 2, at C_1, C_4), 2.3 (s, 1, OH), 3.9 (s, 1, at C_9), 7.2 (4, aromatic), and 7.3, 8.1 (4, aromatic). The sulfonium compound **16** was obtained from this alcohol and used for kinetic studies without purification.

Hydrolysis Products. On hydrolysis of **1** in an acetate buffer medium, the reaction mixture obtained was extracted with ether. The ether solution was dried and evaporated. Preparative thin-layer chromatography of the residual oil afforded *p*-nitro(methylthio)benzene and the cyclized product **2**. The infrared spectrum of **2** was identical with that of a compound which was almost quantitatively obtained upon treatment of (*anti*-9-hydroxybenzonorbornen-*exo*-2-yl)methanol with *p*-bromobenzenesulfonyl chloride in pyridine followed by the usual workup, instead of the expected (*anti*-9-hydroxybenzonorbornen-*exo*-2-yl)methyl *p*-bromobenzenesulfonate. The structure of the oil was clarified by NMR ($CDCl_3$) δ 1.15 (br d of d, 1, C_3 exo), 1.81 (d of d, 1, C_3 endo), 2.3 (br d, 1, at C_2), 3.32 (br d of d, 1, at C_4), 3.5 (br d, 1, at C_1), 4.1 (br s, 2, CH_2O), 4.4 (br t, 1, at C_9), and 7.2 (m, 4, aromatic).

On hydrolysis of **16** in an acetate buffer medium ($[CH_3COO^-]/[CH_3COOH]$ = 1:1, μ = 1.0 M) at 75 °C, the workup procedure afforded (*anti*-9-hydroxybenzonorbornen-*endo*-2-yl)methyl *p*-nitro-

phenyl sulfide. The absence of *p*-nitro(methylthio)benzene in the products was confirmed. When hydrolysis of **16** was carried out in 1 N NaOH for 5 min at 100 °C, the reaction mixture was colored red and showed an intensive absorption at 400 nm. According to literature,[12] the color may have been due to formation of *p*-nitrophenolate ion and dimethyl sulfide.

Rates of Hydrolysis as Functions of pH and Buffer Concentrations. Hydrolysis studies of **1** were conducted at 1×10^{-4} M in the given buffer system[15] and summarized in Table I. Portions were taken at various times and read spectrometrically at the UV maximum at 350 nm due to forming *p*-nitro(methylthio)benzene. The difference between absorption intensities at infinite time and at any time indicates the amount of remaining **1**. Thus, the pseudo-first-order rate coefficients were calculated with a computer.

Acknowledgments. We thank Dr. Kusuo Horiki for his helpful suggestions and discussions and Miss Takako Nishiya for some of the syntheses.

Registry No.—**1**, 68258-47-9; **2**, 68258-48-0; **5**, 37620-72-7; **7**, 68258-49-1; **8**, 68330-61-0; **9**, 68258-50-4; **10**, 68258-51-5; **11**, 68258-52-6; **12**, 68258-53-7; **13**, 68258-54-8; **14**, 68258-55-9; **15**, 68258-56-0; **16**, 68330-63-2; **17**, 68330-64-3; 9-isopropylidenebenzonorbornene-*exo*-2-nitrile, 68258-57-1; 9-isopropylidenebenzonorbornene-*endo*-2-nitrile, 68330-65-4; 9-isopropylidenebenzonorbornene-*exo*-2-carboxylic acid, 68258-58-2; (9-ketobenzonorbornen-*endo*-2-yl)methyl *p*-nitrophenyl sulfide, 68330-66-5; 9-isopropylidenebenzonorbornadiene, 7350-72-3; 3,6-di(2′-pyridyl)-1,2,4,5-tetrazine, 1671-87-0; acrylonitrile, 107-13-1; silver tetrafluoroborate, 14104-20-2.

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(10) For a similar calculation, see E. R. Garrett, *J. Am. Chem. Soc.*, **80**, 4049–4056 (1958).
(11) If $k_{OH}[OH]$ is negligible, $k_H = (k_0 - k_{H_2O})/[H^+]$. With $k_0 = 5.13 \times 10^{-7}$ s^{-1}, assignments of k_0 at pH 4.65 and 5.22 (Table II) do not permit estimates of k_H, but that at pH 5.70 (5.45×10^{-7} s^{-1}) gives 1.6×10^{-2} M^{-1} s^{-1} for k_H. However, it would be more reasonable to say that $k_H[H^+]$ is absent in the pH area of the experiments.
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(14) Plots of $k_1^{25°C}$ (Table I) vs. [B] result in greater slopes with increasing pH values. Therefore, plots of k_B' vs. $[H^+]$ to obtain k_{HB} (slope) become negative.
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Stereochemistry, Conformational Analysis, and Transannular Cyclizations of Nine-Membered Ring Azaolefins

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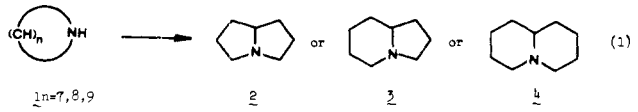
Received September 12, 1978

A transannular route to the indolizidine ring system (**3**) via an intramolecular cyclization of the appropriate azaolefins is described. Treatment of 1*H*-2,3,4,7,8,9-hexahydroazonine (**7b**) with either bromine or mercuric chloride affords, after reduction, the indolizidine alkaloid, δ-coniceine (**15**). The lactam analogue 1,3,4,7,8,9-hexahydro-2*H*-azonin-2-one (**7a**) also undergoes regiospecific ring closure when treated with a suitable electrophile (mercuric acetate) to yield the indolizinone skeleton **21**. Similar alkyl-substituted compounds were prepared and the products cyclized stereoselectively. The synthetic consequence of this reaction as well as the mechanistic implications are discussed.

Medium-ring compounds are often strained due to cross-ring interactions and undergo a variety of transannular reactions.[2] The transannular cyclization of medium-ring nitrogen compounds such as **1** would, in principle, provide a particularly interesting route to pyrrolizidine (**2**), indolizidine (**3**), or quinolizidine type alkaloids[3] (**4**) (eq 1). Transannular



(1)

1 n=7,8,9 2 3 4

reactions in heterocyclic systems were first reported in 1881[4] and many other transannular reactions in nitrogen heterocycles have been reported.[5] The transannular amine/carbonyl interaction has been carefully studied by Leonard,[6] who used such a route in a total synthesis of (±)-isoretronecanol.

We felt that the reaction of an amine or amide nitrogen with a remote (transannular) double bond possessed the most synthetic potential because: (1) additions to C–C double bonds are often stereospecific; and (2) the reaction leading to cyclized products would possess functionality where it is often found in naturally occuring alkaloids. The present paper reports our results on the chemistry of nine-membered ring lactams and amines.

Transannular Cyclizations. In previous communications[7a,b] we have shown that bromination[8] of 1-aza-4-cyclooctene (**5**), for example, leads to transannular ring closure to pyrrolizidines (**2**). The cyclization is stereospecific, yielding exclusively the product (**6**) expected from opening the bro-

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