Neighboring Group Participation by Pyridine Rings and N-Oxides. Synthesis and Solvolysis of 5,8-Dihydro-5,8-methanoisoquinoline Derivatives

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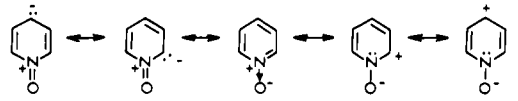
Cycloaddition of cyclopentadiene with glutinic acid (3) followed by multistep synthesis gave 5,8-dihydro-5,8-methanoisoquinoline (13) and its *N*-oxide (14). The alcohols for solvolyses were prepared by hydroboration. Rate and product studies were carried out in 50% aqueous *tert*-butyl alcohol with the arenesulfonates of 5,8-methano-5,6,7,8-tetrahydroisoquinolin-6-*exo*- (19) and -7-*exo*-ols (21) and their *N*-oxides 20 and 22 and with the corresponding endo trifluoromethanesulfonates. When k_{rel} for 2-*exo*-benzonorbornenyl sulfonate is assigned as 1, 21 reacts with a rate factor of 5.9×10^{-3} producing the alcohol of retained configuration, while 19 reacts with a rate factor of 1.8×10^{-5} producing a 61:39 mixture of retained and inverted configurations. The rate factor and products for 22 are 5.1×10^{-6} and a 1:1 mixture of the alcohols of retained and inverted configurations, respectively, and those for 20 are 5.1×10^{-4} and only the alcohol of retained configuration, respectively. When the results from 20 are compared to those from 19, the introduction of an *N*-oxide function at the 6-exo position increases the solvolysis rate and brings about stereoelectronic control for product formation. These provide evidence for increasing participation by the pyridine ring at the 6-carbon. However, comparison of the results from 21 with those from 22 indicates that the *N*-oxide greatly retards the participation at the 7-carbon.

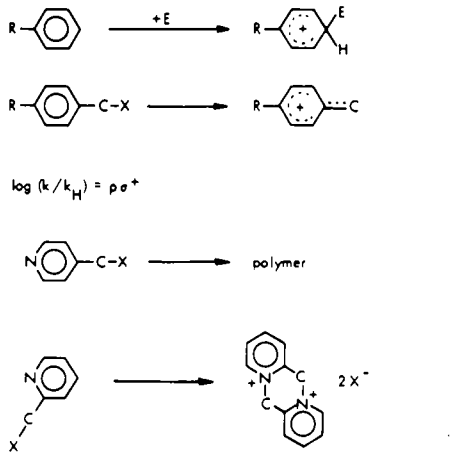
The chemistry of aromatic amine oxides, of which pyridine *N*-oxide is a representative compound, has received much attention for several decades.[1] From the standpoint of organic reactions theory, the fundamental issue in *N*-oxide substituent effects is that the substituent has an electron-supplying effect for the pyridine ring due to the resonance A and an electron-withdrawing effect due to B.[2] The α and γ positions of the ring are said to be



A B

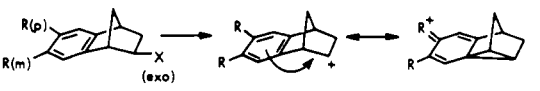
activated toward the electrophilic aromatic substitutions as a result of the A effect. In fact, the nitration for pyridine itself requires very drastic conditions and affords the β-nitro derivative in a very minor yield, but that for pyridine *N*-oxide proceeds under relatively milder conditions yielding the γ-nitro derivative satisfactorily. Although this result greatly stimulated the development of *N*-oxide chemistry, other typical electrophilic substitutions have thus far not given the γ-derivatives.[3] Therefore, it may be said that the A effect has been advocated only on the basis of the nitration results and insufficient evidence. So we wanted another type of confirmative experimental evidence. In contrast, ample support has been found for the B effect from nucleophilic aromatic substitutions.[1] Thus, we tried to obtain experimental evidence to confirm the existence of the A effect.

In benzene chemistry, a linear free energy relationship (Hammett–Brown) has been established between the substituent effects on the electrophilic aromatic substitutions and those on the solvolyses of α-phenylcarbinyl derivatives (the electrophilic side chain reactions). Elec-



tron-supplying substituents directing ortho and para positions in the electrophilic aromatic substitutions accelerate the rate in side chain solvolyses and, in some cases, cause stereospecific control over the product. With the pyridine system, several unsuccessful attempts have been made to solvolyze the α-(pyridyl)alkyl derivatives. Problems resulted from the labile nature of the suitable compounds: 2-(halomethyl)pyridines are easily converted into the dimers and 4-(halomethyl)pyridines into the polymers.[4]

Previously we synthesized the benzonorbornene derivatives and carried out solvolyses to study the effects of benzene substituents upon the cationic transition state forming in the bornane ring. For example, the relative rates for the exo series vary by a factor of more than 10^7 (k_{rel} for the unsubstituted benzo derivative is assigned as 1).[5,6] The rates were found to be linearly correlated with



k_{rel}: H, 1; *p*-CH_3O, 178; *m*-CH_3O, 0.72; *m*-CH_3O-*p*-NO_2, 1.1×10^{-3}; *m,p*-$(NO_2)_2$, 1.1×10^{-5} s^{-1}.

(1) For examples, (a) Ochiai, E. "Aromatic Amine Oxides"; Elsevier: New York, 1967. (b) Katritzky, A. R.; Lagowski, J. M. "Chemistry of the Heterocyclic *N*-Oxides"; Academic Press: New York, 1971. (c) Abramovitch, R. A.; Smith, E. M. "The Chemistry of Heterocyclic Compounds, V 14, Pyridine and Its Derivatives, Supplement Part Two"; Abramovich, R. A., Ed.; Wiley: New York, 1974; Chapter IV. (d) Jones, G.; Baty, D. J. "The Chemistry of Heterocyclic Compounds, V. 32, Quinolines Part II"; Jones, G., Ed.; Wiley: New York, 1982; Chapter 3.

(2) Streitwieser, A.; Meathcock, C. H. "Introduction to Organic Chemistry"; Macmillan Publishing Co., Inc.: New York, 1976; Chapter 35.

(3) Special cases were reported as successful; γ-bromination of quinoline *N*-oxide and some lutidine and picoline *N*-oxides with Br_2-Tl(OAc)$_3$ in acetic acid. Saito, H.; Hamana, M. *Heterocycles* **1979**, *12*, 475. The authors thank Prof. Hamana for this information.

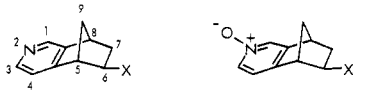
(4) Sorm, F.; Sedivy, L. *Collect. Czech. Chem. Commun.* **1948**, *13*, 289. Reference 1c, Chapter VI, p 474.

(5) Tanida, H.; Ishitobi, H.; Irie, T.; Tsushima, T. *J. Am. Chem. Soc.* **1969**, *91*, 4512.

0022-3263/84/1949-2527$01.50/0

the Hammett–Brown equation: $\log (k/k_0) = \rho\sigma^+$ (ρ = −3.26, 77.6 °C). The results demonstrate the pronounced susceptibility of the solvolysis rate to the nature and extent of aromatic substitution.

We tried to extend this kind of research to the heteroaromatic system, at first to the pyridonorbornene derivatives (5,8-methano-5,6,7,8-tetrahydroisoquinolines) (1).[7] Of particular interest was whether or not the substituent *N*-oxide would facilitate solvolysis.



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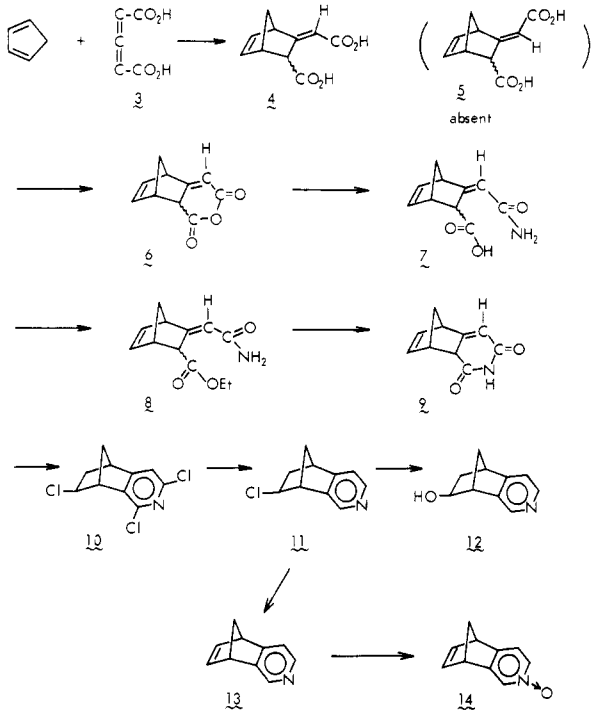
Results

Syntheses. The cycloaddition of cyclopentadiene with glutinic acid (3) previously reported[8] was applied to obtain the adducts (4, a mixture of the endo and exo carboxylic acids) in 91% yield. Treatment of the adducts with warm



3 4 5 6 7 8 9 10 11 12 13 14

acetic anhydride gave the anhydride 6 in a quantitative yield, which indicated no formation of the adduct 5 isomeric in the α,β-unsaturated acid grouping, because 5 cannot be led to the anhydride. The anhydride 6 was transformed into the acid amide 7 with ammonia, the ester amide 8 with ethanol–sulfuric acid, and then the cyclic imide 9 with *n*-butyllithium. The reaction of 9 with phosphorous oxychloride in a sealed tube led to the pyridine derivative 10, which was subjected to catalytic reduction with palladium charcoal giving 7-*exo*-chloro-5,8-methano-5,6,7,8-tetrahydroisoquinoline (11). An X-ray analysis of 10 indicated the 7-exo position (homometa to the ring nitrogen) for the chloro substituent. Hydrolysis of 11 in 50% aqueous acetone in the presence of sodium bicarbonate gave the 7-exo alcohol 12, which was led to the *p*-nitrobenzoate. The benzoate was shown to be in the exo and homometa position to the ring nitrogen by X-ray analysis. Treatment of 11 with potassium *tert*-butoxide in dimethyl sulfoxide

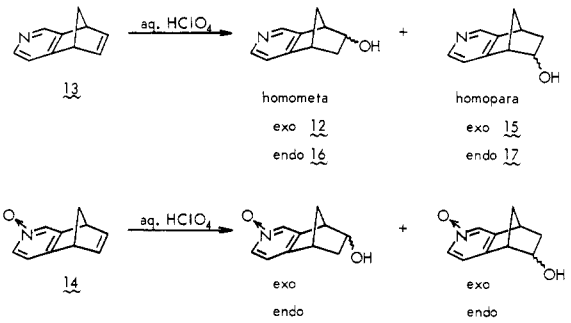
(6) Refer to: (a) Tanida, H.; Irie, T.; Tsushima, T. *J. Am. Chem. Soc.* **1970**, *92*, 3404. (b) Tanida, H.; Ishitobi, H.; Irie, T. *Ibid.* **1968**, *90*, 2688. (c) Tanida, H. *Acc. Chem. Res.* **1968**, *1*, 239.
(7) The numbering used in this paper is shown in the compound 1.
(8) Agosta, William C. *J. Am. Chem. Soc.* **1962**, *84*, 110.

Table I. Products and Ratios on Hydrations and Hydroboration with 13 and 14

	hydration		hydroboration
product alcohol	13	14	13
homopara exo	17.5	30.2	40.3
homopara endo	10.1	12.7	13.9
homometa exo	64.0	48.1	34.7
homometa endo	8.3	9.0	11.1

afforded the desired 5,8-dihydro-5,8-methanoisoquinoline (13). Oxidation of 13 with an equivalent amount of *m*-chloroperbenzoic acid in chloroform afforded the *N*-oxide 14, with no attack of the double bond.

Acid-Catalyzed Hydration. The olefin 13 was warmed in 70% aqueous perchloric acid to obtain the water-addition products. The results were regioselective in favor of addition from the exo side and production of the homometa alcohol, as shown in Table I. Identification and product ratios were determined by HPLC with comparison with authentic samples of the four kinds of alcohols. The same additions with the *N*-oxide 14 were carried out under

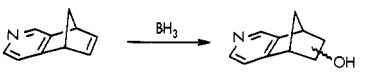


13 14

identical conditions and the product ratios were compared with the results from 13. The increased yield of the homopara exo alcohol and the decreased yield of the homometa exo alcohol should be noted.

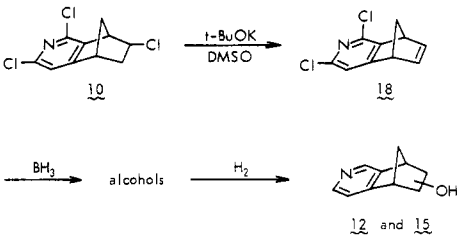
Additions of hydrochloric acid and hydrobromic acids to 13 gave the corresponding four kinds of chlorides and bromides with the same regioselectivity as the above hydration, but the precise yields were not determined because isolation of authentic samples of pure halogenides was very difficult.

Hydroboration. Treatments of 13 with borane–methyl sulfide complex in methylene dichloride followed by oxidation with H_2O_2–NaOH afforded the four isomeric alcohols, the compositions of which were determined by HPLC



13

and are shown in Table I. Preference of the homopara is in contrast to the results from the hydration. Quantitative treatment of 14 with borane was not possible due to the reactive nature of the *N*-oxide to this reagent. The hydroboration of 1,3-di-chloro-5,8-dihydro-5,8-methanoisoquinoline (18) followed by catalytic hydrogenation gave



10 18

a 1:1 mixture of the homopara and the homometa exo alcohols with very minor formation of the endo alcohols.

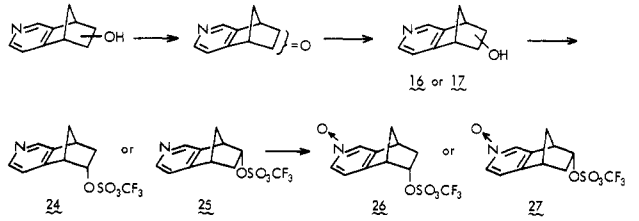
Table II. Rates of Solvolysis in 50% (v/v) Aqueous *tert*-Butyl Alcohol

material		temp, °C	k_{obsd}, s^{-1}	k_{rel} (50 °C)[a]	exo:endo[b] rate ratio
			Exo Series		
	$-O_3S-Ph-CH_3$	50	6.82×10^{-4}	1	
		30	5.26×10^{-5}		
	$-O_3S-Ph-NO_2$	50	5.28×10^{-2} (calcd)		
		30	4.07×10^{-3}		
	$-O_3S-Ph-F_5$	50	4.12×10^{-5}	1.8×10^{-5}	
		30	2.80×10^{-6}		
	$-O_3S-Ph-F_5$	50	1.16×10^{-3}	5.1×10^{-4}	
		30	6.33×10^{-5}		
	$-O_3S-Ph-NO_2$	50	3.14×10^{-4}	5.9×10^{-3}	
		30	1.61×10^{-5}		
	$-O_3S-Ph-F_5$	50	1.36×10^{-2} (calcd)		
		30	6.98×10^{-4}		
	$-O_3S-Ph-F_5$	50	1.17×10^{-5}	5.1×10^{-6}	
			Endo Series		
	$-O_3S-Ph-F_5$	50	2.52×10^{-3}	1	908
		30	5.94×10^{-4}		
	$-O_3S-CF_3$	50	1.32×10^{-3}	4.04×10^{-3}	4
		30	1.24×10^{-4}		
	$-O_3S-CF_3$	50	9.08×10^{-4}	2.78×10^{-3}	166
		30	1.13×10^{-4}		
	$-O_3S-Ph-F_5$	50	1.22×10^{-5}	4.84×10^{-3}	1127[c]
	$-O_3S-CF_3$	50	1.58×10^{-3}		
		30	1.59×10^{-4}		
	$-O_3S-CF_3$	50	5.29×10^{-4}	1.62×10^{-3}	3
		30	5.60×10^{-5}		

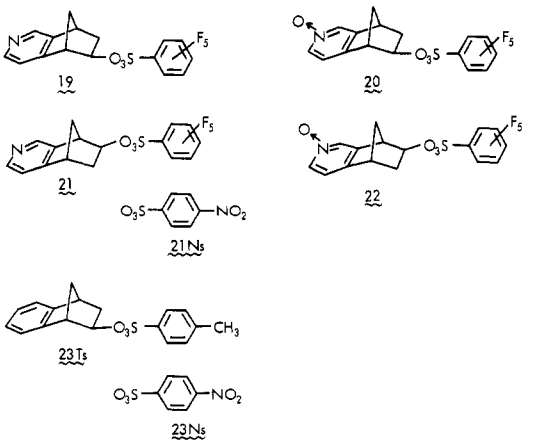
[a] Based on the rates of pentafluorobenzenesulfonates and, in turn, trifluoromethanesulfonate. Conversion factors are 77.4 between *p*-nitrobenzenesulfonate and tosylate, 43.4 between pentafluorobenzenesulfonate and *p*-nitrobenzenesulfonate, and 129.5 between trifluoromethanesulfonate and pentafluorobenzenesulfonate. [b] Based on the rates of the same sulfonates used for calculation of k_{rel}. [c] Reference 10.

The homopara *exo*-**15** isolated in pure form by silica gel chromatography was led to the *p*-nitrobenzoate, which was subjected to X-ray analysis to confirm its structure. The endo and exo configurations of substituents on the bornane ring were determined by ^1H NMR spectra, but the homometa and homopara positions with respect to the ring nitrogen by X-ray analyses.

Preparation of Sulfonates. For solvolysis studies, the exo alcohols were converted into pentafluorobenzene- or *p*-nitrobenzenesulfonates, which were oxidized to the *N*-oxide derivatives. Oxidation of the exo alcohols into the ketones with chromic anhydride followed by reduction with lithium aluminum hydride gave the corresponding endo alcohols **16** and **17**, which were led to the trifluoromethanesulfonates, **24** or **25**, for solvolyses and then, to the *N*-oxides, **26** and **27**. The structures of these compounds were confirmed by ^1H NMR.



Rates of Hydrolysis. To study the participation by the pyridine ring and its *N*-oxide in the cationic transition state in solvolysis requires that the pyridine moiety be maintained in an unprotonated basic form. Thus the conditions must be sufficiently more basic than the pK_a of the substrates, although acidic or neutral solvents are common for solvolysis. The reference pK_a is 5.2 for pyridine in water at 20–25 °C, 6.2 for 3,5-dimethylpyridine as an example of dialkylpyridines, and 1.90 for pyridine *N*-oxide.[1c] Also, the sulfonic acid, once formed during the reaction, should be neutralized to maintain a constant basicity of the reaction medium. Thus, the rates of hydrolysis were determined in 50% (v/v) aqueous *tert*-butyl alcohol which was maintained at pH 7.5 by immediate titration of the forming sulfonic acid with a sodium hydroxide solution of 50% aqueous *tert*-butyl alcohol. The rate data were summarized in Table II. As a standard system, *exo*-2-benzonorbornenyl-*p*-toluenesulfonate (**23Ts**)



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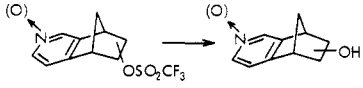
to 48.1%. This suggests increasing stability of the homopara cationic intermediate **29**. However, since no meaningful change of the endo alcohol composition was observed in the reactions of **13** (10.1 vs. 8.3) and **14** (12.7 vs. 9.0), we concluded that there is no effect by the *N*-oxide upon a water attack from the endo side.

The four kinds of *endo*-trifluoromethanosulfonates, **24–27**, which were studied solvolyzed with almost the same rates (within a rate factor of 3 at 50 °C) and with almost all of the alcohol formed taking the inverted configuration. The results clearly show the absence of the *N*-oxide effect in the endo sulfonate solvolyses. As criteria for partici-



pation, the exo:endo rate ratios in the last column of Table II increase from a factor of 4 to 166 with the transformation into the *N*-oxide in the homopara series and, on the other hand, decrease from 1127 to 3 in the homometa series.

Consequently, all the present results consistently indicate that the *N*-oxide function exerts an electron-supplying effect on the cationic transition state at the homopara carbon (the "A" effect) and an electron-withdrawing effect on that at the homometa carbon. Evidence consists of the contrast in rate variation due to the introduction of *N*-oxide between the 10^{-3} times slower rate of the homometa exo derivative and the 28 times faster rate of the homopara exo derivative, the significant difference between the exo:endo rate ratios for the homometa and homopara *N*-oxides systems (3 vs. 166), the product formation in favor of the alcohol with inverted configuration from the homometa exo derivative and with retained configuration from the homopara exo derivative, and also the increased formation of the homopara alcohol with the acid-catalyzed hydration.

Experimental Section

Melting points were taken in capillary tubes and are corrected. ^{1}H NMR spectra were determined with a Varian T-60A and infrared spectra with a 215 Hitachi grading infrared spectrophotometer. All HPLC analyses were carried out by using a system comprised of the following components: Waters 6000-A pump, UVIDEC-100 UV detector, and Reodyne 7120 injector.

Cycloaddition of Cyclopentadiene with Glutinic Acid (3). To a solution of 9.32 g of glutinic acid (**3**) in 180 mL of ether was added a solution of 14.43 g of cyclopentadiene in 20 mL of ether at 0 °C with stirring and the mixture was left standing overnight. The adducts **4** were separated as crystals (12.10 g, 85.6%, mp 209–213 °C dec) and the mother liquor gave the second crop (0.71 g, 5.0%). ^{1}H NMR (Me_2SO-d_6) δ 1.0–2.0 (m, 2 H, methano bridge), 3.2 and 3.4 (m, 2 H, bridgeheads), 3.7 (m, 1 H, α to carboxylic acid), 5.9, 6.1, and 6.3 (m, 3 H, olefin).

The Acid Amide 7. Treatment of 2.95 g of **4** with 15 mL of acetic anhydride was carried out at 105 °C for about 30 min with stirring until the crystals were dissolved in a transparent brown solution. Distillation of acetic anhydride under reduced pressure left a crystallized residue, which was dissolved in 50 mL of xylene. Treatment with ammonia gas immediately turned the solution cloudy and then the insoluble compounds were separated, removed by filtration, washed with ether, and dissolved in water. The water solution was washed with ether and acidified with dilute hydrochloric acid to separate the crystals, which were obtained by filtration and dried: 2.07 g (70.5%); mp 181–185 °C dec (from methanol–ether); ^{1}H NMR (Me_2SO-d_6) δ 1.3–1.7 (m, 2 H, methano bridge), 3.3 and 3.5 (m, 2 H, bridgeheads), 3.7 (m, 1 H, α to carboxylic acid), 5.9 and 6.1 (m, 3 H, olefin), and 6.5–6.9 (m, 2 H, amide). Anal. Calcd for $C_{10}H_{11}O_3N$: C, 62.16; H, 5.74; N, 7.25. Found: C, 62.28; H, 5.82; N, 7.45.

The Amide Ester 8. To a solution of 2.07 g of **7** in 50 mL of ethanol were added five drops of sulfuric acid and the mixture was left overnight under reflux with stirring. Distillation of ethanol under reduced pressure left a residue, which was dissolved in ethyl acetate. The solution obtained was washed with saturated sodium bicarbonate solution and then with saturated sodium chloride, dried, and distilled, leaving 1.66 g (70.0%) of crystals: mp 96–101 °C (from ether); ^{1}H NMR (acetone-d_6) δ 1.2 (t, 3 H, $COOCH_2CH_3$), 1.4–1.8 (m, 2 H, methano bridge), 3.3–3.6 (m, 2 H, bridgeheads), 3.8–4.0 (m, 1 H, α to COOR), 4.1 (q, 2 H, $COOCH_2CH_3$), 6.0 and 6.3 (m, 3 H, olefin), and 6.0–6.4 (m, 2 H, amide). Anal. Calcd for $C_{12}H_{15}O_3N$: C, 65.14; H, 6.83; N, 6.33. Found: C, 64.95; H, 6.77; N, 6.30.

The Cyclic Imide 9. To a solution of 3.8 g of **8** in 40 mL of monoglyme was added dropwise 17.6 mL of a 14% solution of *n*-butyllithium in hexane at 0 °C with stirring under nitrogen atmosphere and the mixture was stirred at room temperature for 1.5 h. Distillation of the reaction solvent under reduced pressure left a residue, which was dissolved in ice water. The water solution was washed with chloroform and acidified with cold diluted hydrochloric acid to separate the crystals. After filtration, the crystals were recrystallized from methanol. The yield was 1.48 g (49.2%): mp 188.5–192 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 1.7 and 2.0 (m, 2 H, at C_9), 3.4 and 3.7 (m, 2 H, bridgeheads), 3.9 (m, 1 H, juncture proton), 5.9, 6.2, and 6.6 (m, 3 H, olefin). Anal. Calcd for $C_{10}H_9O_2N$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.33; H, 5.27; N, 8.15.

1,3,7-*exo*-Trichloro-5,8-methano-5,6,7,8-tetrahydroisoquinoline (10). A mixture of 33.3 g of **9** and 150 mL of phosphorus oxychloride was placed in a sealed tube and warmed at 200 °C overnight. After cooling, the reaction mixture was concentrated by distilling with excess phosphorus oxychloride and the resulting residue was decomposed by being added slowly to ice water and extracted with ether. The ether solution was dried, treated with charcoal, concentrated, and subjected to silica gel chromatography with benzene as a solvent. The benzene elute gave 39.0 g (82.5%) of crystals: mp 88–89.5 °C (from hexane); ^{1}H NMR ($CDCl_3$) δ 1.7–2.4 (m, 4 H, at C_6 and C_9), 3.5 and 3.6 (m, 2 H, bridgeheads), 3.9 (m, 1 H, *endo*-H at C_7), and 7.1 (s, 1 H, at C_4). Anal. Calcd for $C_{10}H_8NCl_3$: C, 48.32; H, 3.24; N, 5.64; Cl, 42.80. Found: C, 48.15; H, 3.29; N, 5.62; Cl, 42.55.

7-*exo*-Chloro-5,8-methano-5,6,7,8-tetrahydroisoquinoline (11). To a solution of 27 mg of sodium metal in 20 mL of ethanol were added 146 mg of **10** and 50 mg of 5% palladium on charcoal and the mixture was stirred under a hydrogen atmosphere. After absorption of 2 mol equiv of hydrogen, the mixture was filtered and concentrated under reduced pressure. The residue was extracted with ether. The ether solution was washed with aqueous sodium hydroxide and saturated sodium chloride solution, dried, treated with charcoal, and concentrated leaving 89 mg (84.7%) of **11**: mp 36–37.5 °C (from hexane); ^{1}H NMR ($CDCl_3$) δ 1.8–2.5 (m, 4 H, at C_6 and C_9), 3.3 and 3.5 (m, 2 H, bridgeheads), 3.9 (m, 1 H, *endo*-H at C_7), 7.1 (d, 1 H, at C_4), 8.55 (d, 1 H, at C_3), and 8.6 (s, 1 H, at C_1). Anal. Calcd for $C_{10}H_{10}NCl$: C, 66.85; H, 5.61; N, 7.80; Cl, 19.74. Found: C, 66.91; H, 5.60; N, 7.86; Cl, 19.59.

7-*exo*-Hydroxy-5,8-methano-5,6,7,8-tetrahydroisoquinoline (12). A mixture of 163 mg of **11** and 92 mg of sodium bicarbonate in 4 mL of 50% (v/v) aqueous acetone was placed in a sealed tube and heated at 150 °C for 20 h. Concentration of the reaction mixture under reduced pressure gave a residue, which was extracted with ether. The ether solution was washed with water, dried, decolorized with charcoal, and distilled leaving 113 mg (77.3%) of **12**: mp 99–100 °C (from ether–hexane); ^{1}H NMR ($CDCl_3$) δ 1.7–2.4 (m, 4 H, at C_6 and C_9), 3.4 (m, 2 H, bridgeheads), 4.0 (m, 1 H, *endo*-H at C_7), 5.4 (s, 1 H, OH), 7.1 (d, 1 H, at C_4), and 8.1–8.5 (overlapping broad s, 2 H, at C_1 and C_3). Anal. Calcd for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.72; H, 6.94; N, 8.88.

7-*exo*-*p*-Nitrobenzoate. A mixture of 71 mg of **12**, 98 mg of *p*-nitrobenzoyl chloride, and 1 mL of pyridine was warmed at 100 °C for 30 min. The usual workup[11,12b] gave 115 mg (84.1%) of

(11) Fieser, L. F.; Fieser, M. "Reagents for Organic Synthesis"; Wiley: New York, 1967; pp 958–959.

(12) (a) "Organic Syntheses"; Wiley: New York; 1955; Collect. Vol. III, p 366. (b) "Organic Syntheses"; Wiley: New York; 1963; Collect. Vol. IV, p 478. (c) "Organic Syntheses"; Wiley: New York; 1973; Collect. Vol. V, p 294.

crystals: mp 170–171 °C (from dichloromethane–hexane); ^{1}H NMR ($CDCl_3$) δ 2.1 (m, 4 H, at C_6 and C_9), 3.5 and 3.7 (m, 2 H, bridgeheads), 5.0 (m, 1 H, *endo*-H at C_7), 7.1 (d, 1 H, at C_4), 8.2 (s, 4 H, benzene), and 8.7 (broad s, 2 H, at C_1 and C_3). Anal. Calcd for $C_{17}H_{14}N_2O_4$: C, 65.80; H, 4.55; N, 9.03. Found: C, 65.92; H, 4.62; N, 9.07.

5,8-Dihydro-5,8-methanoisoquinoline (13). To a solution of 390 mg of potassium *tert*-butoxide in 1 mL of dimethyl sulfoxide was added at 10 °C a solution of 312 mg of **11** in 2 mL of dimethyl sulfoxide and the mixture was left at room temperature for 30 min. The reaction mixture was poured into ice water and extracted with *n*-pentane. The *n*-pentane solution was washed with water, dried, and distilled leaving 215 mg (86.5%) of **13**, an oil: ^{1}H NMR ($CDCl_3$) δ 2.0–2.4 (m, 2 H, at C_9), 3.9 (m, 2 H, bridgeheads), 6.7 (m, 2 H, olefin), 7.1 (d, 1 H, at C_4), 8.15 (d, 1 H, at C_3), and 8.35 (s, 1 H, at C_1). Picrate, mp 135–137 °C (from methanol). Anal. Calcd for $C_{16}H_{12}O_7N_4$: C, 51.62; H, 3.25; N, 15.05. Found: C, 51.54; H, 3.13; N, 14.90.

1,3-Dichloro-5,8-dihydro-5,8-methanoisoquinoline (18). To a solution of 347 mg of potassium *tert*-butoxide in 3 mL of dimethyl sulfoxide was added at 0 °C with stirring a solution of 512 mg of 1,3,7-*exo*-trichloro-5,8-methano-5,6,7,8-tetrahydroisoquinoline (**10**) in 2 mL of dimethyl sulfoxide and the mixture was left at room temperature for 1 h. The mixture was poured into ice water and extracted with *n*-pentane. The *n*-pentane solution was washed with water, dried, and distilled leaving 379 mg of an oil. Purification with silica gel in benzene gave 308 (70.5%) mg of the product: ^{1}H NMR ($CDCl_3$) δ 2.2–2.5 (m, 2 H, at C_9), 4.0 (m, 2 H, bridgeheads), 6.6–7.0 (m, 2 H, olefin), and 7.1 (s, 1 H, at C_4). When the amount of potassium *tert*-butoxide was increased, introduction of the *tert*-butoxy group into the pyridine ring was observed. The products and their composition varied with the amount of potassium *tert*-butoxide and the reaction temperature due to the susceptibility of the 1- and 3-chloro substituents toward *tert*-butoxide.

Hydroboration of 5,8-Dihydro-5,8-methanoisoquinoline (13). To a solution of 3.37 g of **13** in 70 mL of dichloromethane was added 63.5 mL of a 1 molar solution of diborane–dimethyl sulfide complex (BMS) in dichloromethane at room temperature under nitrogen atmosphere with stirring. The mixture was stirred for 1.5 h and left standing overnight. To the mixture were added 58 mL of ethanol with gas evolution, 21 mL of 3 N aqueous sodium hydroxide, and then 22 mL of 30% hydrogen peroxide. After being refluxed for 1 h, the mixture was acidified with dilute aqueous hydrochloric acid and distilled under reduced pressure to remove dichloromethane and ethanol. The aqueous residue was washed with dichloromethane, made alkaline with aqueous sodium hydroxide, and extracted with dichloromethane. After drying, distillation of the dichloromethane gave 3.97 g of a residue, which was shown by HPLC to be composed of four isomeric alcohols as described in the text. The alcohols were isolated by silica gel chromatography: 0.85 g (22.4%) of 6-exo, 0.18 g (4.7%) of 6-endo, 0.80 g (21.1%) of 7-exo, and 0.12 g (3.2%) of 7-endo.

6-*exo*-Hydroxy-5,8-methano-5,6,7,8-tetrahydroisoquinoline (15): mp 67–68 °C (from ether–hexane); ^{1}H NMR ($CDCl_3$) δ 1.8–2.4 (m, 4 H, at C_7 and C_9), 3.3–3.5 (m, 2 H, bridgeheads), 4.0 (m, 1 H, *endo*-H at C_6), 4.3 (1 H, OH), 7.1 (d, 1 H, at C_4), 8.3 (d, 1 H, at C_3), and 8.4 (s, 1 H, at C_1). Anal. Calcd for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.63; H, 6.67; N, 8.90.

6-*exo*-*p*-Nitrobenzoate was prepared as described for the above 7-exo alcohol: mp 123–124 °C (from ether–hexane); ^{1}H NMR ($CDCl_3$) δ 1.9–2.3 (m, 4 H, at C_7 and C_9), 3.5–3.7 (m, 2 H, bridgeheads), 4.9–5.1 (m, 1 H, endo-H at C_6), 7.2 (d, 1 H, at C_4), 8.2 (s, 4 H, benzene), and 8.4 (broad s, 2 H, at C_1 and C_3). Anal. Calcd for $C_{17}H_{14}N_2O_4$: C, 65.80; H, 4.55; N, 9.03. Found: C, 65.87; H, 4.51; N, 9.03.

6-*exo*-Pentafluorobenzenesulfonate 19. To a solution of 108 mg of the 6-exo alcohol **15** in 8 mL of THF was added 0.8 mL of a 15% hexane solution of *n*-butyllithium with stirring and ice cooling under nitrogen atmosphere and the mixture was further stirred for 0.5 h with ice cooling. A solution of 268 mg of pentafluorobenzenesulfonyl chloride in 2 mL of tetrahydrofuran was added to the mixture, which was then left standing for 30 min. The mixture was extracted with ether, and the solution was dried and distilled leaving 127 mg of an oil. The oil was purified with preparative thick-layer chromatography and gave crystals: 28 mg (10.7%); mp 111–112 °C dec (from ether–hexane); ^{1}H NMR ($CDCl_3$) δ 1.9–2.3 (m, 4 H, at C_7 and C_9), 3.5 and 3.7 (m, 2 H, bridgeheads), 4.9 (m, 1 H, *endo*-H at C_6), 7.2 (m, 1 H, at C_4), and 8.3–8.5 (m, 2 H, at C_1 and C_3). Anal. Calcd for $C_{16}H_{10}NO_3SF_5$: C, 49.11; H, 2.58; N, 3.58; S, 8.19; F, 24.28. Found: C, 49.27; H, 2.62; N, 3.65; S, 8.37; F, 24.11.

***N*-Oxide of 6-*exo*-Pentafluorobenzenesulfonate 20.** To a solution of 40 mg of **19** in 5 mL of chloroform was added 1.5 equiv of *m*-chloroperbenzoic acid and the mixture was left standing at room temperature for 4 h. The mixture was washed with cold aqueous sodium carbonate, dried, and distilled leaving 37.5 mg (90.1%) of crystals: mp 168 °C dec (from hexane–dichloromethane); ^{1}H NMR ($CDCl_3$) δ 1.9–2.3 (m, 4 H, at C_7 and C_9), 3.5 and 3.7 (m, 2 H, bridgeheads), 4.9 (m, 1 H, *endo*-H at C_6) and 7.2 (m, 1 H, at C_4), and 8.3–8.5 (m, 2 H, at C_1 and C_3). Anal. Calcd for $C_{16}H_{10}NO_4SF_5$: C, 47.18; H, 2.47; N, 3.44; S, 7.87; F, 23.32. Found: C, 47.04; H, 2.73; N, 3.48; S, 7.83; F, 23.38.

7-*exo*-Pentafluorobenzenesulfonate 21. The same procedure as that given above was applied to the 7-exo alcohol: mp 104.5–105.5 °C dec (from ether–hexane); ^{1}H NMR ($CDCl_3$) δ 1.9–2.3 (m, 4 H, at C_6 and C_9), 3.5 and 3.7 (m, 2 H, bridgeheads), 4.9 (m, 1 H, *endo*-H at C_7), 7.1 (d, 1 H, at C_4), 8.3 (d, 1 H, at C_3), and 8.4 (s, 1 H, at C_1). Anal. Calcd for $C_{16}H_{10}NO_3SF_5$: C, 49.11; H, 2.58; N, 3.58; S, 8.19; F, 24.28. Found: C, 49.18; H, 2.63; N, 3.59; S, 8.42; F, 24.00.

***N*-Oxide of 7-*exo*-pentafluorobenzenesulfonate 22** was prepared as above: crystals; mp 170 °C dec (dichloromethane–hexane); ^{1}H NMR ($CDCl_3$) δ 1.9–2.3 (m, 4 H, at C_6 and C_9), 3.5 and 3.7 (m, 2 H, bridgeheads), 4.9 (m, 1 H, *endo*-H at C_7), 7.1 (d, 1 H, at C_4), 8.0 (d, 1 H, at C_3), and 8.1 (s, 1 H, at C_1). Anal. Calcd for $C_6H_{10}NO_4SF_5$: C, 47.18; H, 2.47; N, 3.44; S, 7.87; F, 23.32. Found: C, 46.92; H, 2.44; N, 3.70; S, 7.94; F, 23.33.

7-*exo*-*p*-Nitrobenzenesulfonate (21Ns). Treatment of **12** with *p*-nitrobenzenesulfonyl chloride was carried out in the usual way. The workup[11,12a] gave **21Ns** as crystals: mp 124–124.5 °C (from dichloromethane–hexane); ^{1}H NMR ($CDCl_3$) δ 1.7–2.2 (m, 4 H, at C_6 and C_9), 3.4 and 3.6 (m, 2 H, bridgeheads), 4.7 (m, 1 H, *endo*-H at C_7), 7.1 (d, 1 H, at C_4), 8.3 (d, 1 H, at C_3), 8.4 (s, 1 H, at C_1), and 8.1 and 8.4 (two sets of d, 4 H, benzene). Anal. Calcd for $C_{16}H_{14}N_2O_5S$: C, 55.48; H, 4.07; N, 8.09; S, 9.26. Found: C, 55.28; H, 4.17; N, 8.08; S, 9.44.

***N*-Oxide of the 6-Exo Alcohol.** To a solution of 103 mg of the 6-exo alcohol **15** in 10 mL of chloroform was added 2 equiv of *m*-chloroperbenzoic acid with stirring at room temperature and the mixture was stirred for 2 h. Distillation of chloroform from the mixture under reduced pressure left a residue, which was extracted with water. The aqueous solution was washed with ether and concentrated under reduced pressure. Recrystallization of crude crystals (101 mg) from methanol–ether afforded 84 mg (74.2%) of a pure sample: mp 169–171 °C dec; ^{1}H NMR (CD_3OD) δ 1.7–2.4 (m, 4 H, at C_7 and C_9), 3.3 and 3.5 (m, 2 H, bridgeheads), 3.9 (m, 1 H, *endo*-H at C_6), 7.4 (d, 1 H, at C_4), 8.1 (d, 1 H, at C_3), and 8.2 (s, 1 H, at C_1). Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.91. Found: C, 67.65; H, 6.07; N, 7.97.

***N*-Oxide of the 7-Exo Alcohol.** The same procedure as above gave crystals: mp 219–221 °C dec (from methanol–ether); ^{1}H NMR (CD_3OD) δ 1.6–2.4 (m, 4 H, at C_6 and C_9), 3.4 (m, 2 H, bridgeheads), 3.9 (m, 1 H, *endo*-H at C_7), 7.3 (d, 1 H, at C_4), 8.1 (d of d, 1 H, at C_3), and 8.2 (d, 1 H, at C_1). Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.91. Found: C, 67.72; H, 6.40; N, 8.02.

5,8-Methano-5,6,7,8-tetrahydroisoquinolin-6-one. To a solution of 750 mg of chromic anhydride in 7 mL of pyridine was added a solution of 295 mg of the 6-exo alcohol **15** with stirring at room temperature and the mixture was left standing overnight. After addition of ethyl acetate, the mixture was filtered and the filtrate was washed with aqueous sodium carbonate, decolorized with charcoal, dried, and concentrated leaving 192 mg (65.9%) of an oil: ^{1}H NMR ($CDCl_3$) δ 1.8–2.6 (m, 4 H, at C_7 and C_9), 3.6 and 3.8 (m, 2 H, bridgeheads), 7.3 (d, 1 H, at C_4), and 8.3–8.6 (m, 2 H, at C_1 and C_3); IR ($CHCl_3$) 1759 cm^{-1} ($\nu_{C=O}$).

6-*endo*-Hydroxy-5,8-methano-5,6,7,8-tetrahydroisoquinoline (17). Reduction of the above 6-one (192 mg) was carried out with lithium aluminum hydride in the usual manner. The workup[12c] gave a mixture (193 mg) of the corresponding endo and exo alcohols in a ratio of 9 to 1. Separation with preparative

thick-layer chromatography gave 173 mg (89.0%) of the endo alcohol as pure crystals: mp 106–107.5 °C (from ether); ^{1}H NMR ($CDCl_3$) δ 0.8–1.1 (m, 1 H, *endo*-H at C_7), 1.7 (m, 2 H, at C_9), 2.2–2.6 (m, 1 H, *exo*-H at C_7), 3.3 (m, 2 H, bridgeheads), 4.5–4.9 (m, 1 H, *endo*-H at C_6), 7.2 (d, 1 H, at C_4), 8.2 (d, 1 H, at C_3), and 8.3 (s, 1 H, at C_1). Anal. Calcd for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.59; H, 6.90; N, 8.70.

6-*endo*-Trifluoromethanesulfonate 24. A solution of **17** (50 mg), pyridine (49 mg), and CH_2Cl_2 (2 mL) was treated with a solution of trifluoromethanesulfonic anhydride (131 mg) in dichloromethane (1 mL). The usual workup followed by purification with preparative thick-layer chromatography gave a satisfactory sample for solvolysis, an oil: ^{1}H NMR ($CDCl_3$) δ 1.3–1.6 (m, 1 H, *endo*-H at C_7), 1.9–2.1 (m, 2 H, at C_9), 2.3–2.8 (m, 1 H, *exo*-H at C_7), 3.5 and 3.8 (m, 2 H, bridgehead), 5.5–5.8 (m, 1 H, *exo*-H at C_6), 7.2 (d, 1 H, at C_4), 8.4 (d, 1 H, at C_3), and 8.5 (s, 1 H, at C_1).

***N*-Oxide of the 6-Endo Alcohol 26.** According to the procedure described for the exo alcohol, the *N*-oxide was prepared by *m*-chloroperbenzoic acid oxidation: crystals; mp 177–178 °C dec (from methanol–ether); ^{1}H NMR ($CDCl_3$) δ 0.8–1.1 (m, 1 H, *endo*-H at C_7), 1.7 (m, 2 H, at C_9), 2.1–2.6 (m, 1 H, *exo*-H at C_7), 3.3 and 3.5 (m, 2 H, bridgeheads), 4.7 (m, 1 H, *exo*-H at C_6), 7.2 (m, 1 H, at C_4), and 7.7–8.2 (m, 2 H, at C_1 and C_3). Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.91. Found: C, 67.51; H, 6.19; N, 8.02.

Trifluoromethanesulfonate, an oil, was prepared from **17**-OSO_2CF_3 with *m*-chloroperbenzoic acid oxidation.

5,8-Methano-5,6,7,8-tetrahydroisoquinolin-7-one. The 7-exo alcohol **12** (1.01 g) was oxidized with chromic anhydride in pyridine according to the procedure described for the 6-exo alcohol. The yield was 712 mg (71.4%) of an oil: ^{1}H NMR ($CDCl_3$) δ 1.8–2.7 (m, 4 H, at C_6 and C_9), 3.7 (m, 2 H, bridgeheads), 7.3 (d, 1 H, at C_4), 8.4 (d, 1 H, at C_3), and 8.5 (s, 1 H, at C_1); IR ($CHCl_3$) 1757 cm^{-1} ($\nu_{C=O}$).

7-*endo*-Hydroxy-5,8-methano-5,6,7,8-tetrahydroisoquinoline (16) was prepared from the 7-one as described for the 6-endo alcohol: crystals; mp 132–133 °C (from dichloromethane–hexane); ^{1}H NMR ($CDCl_3$) δ 0.8–1.1 (m, 1 H, *endo*-H at C_6), 1.8 (m, 2 H, at C_9), 2.2–2.7 (m, 1 H, *exo*-H at C_6), 3.3–3.6 (m, 2 H, bridgeheads), 4.5–4.9 (m, 1 H, *exo*-H at C_7), 7.1 (d, 1 H, at C_4), 8.2 (d, 1 H, at C_3), and 8.4 (s, 1 H, at C_1). Anal. Calcd for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.79; H, 6.91; N, 8.66.

Trifluoromethanesulfonate 25, an oil, was prepared from **16** as described above.

***N*-Oxide of the 7-endo alcohol** was prepared by treatment of the 7-endo alcohol **16** with *m*-chloroperbenzoic acid: crystals; mp 198–199 °C dec (from methanol–ether); ^{1}H NMR (CD_3OD) δ 0.8–1.1 (m, 1 H, *endo*-H at C_6), 1.9 (m, 2 H, at C_9), 2.3–2.7 (m, 1 H, *exo*-H at C_6), 3.3–3.7 (m, 2 H, bridgeheads), 4.6–4.9 (m, 1 H, *exo*-H at C_7), 7.4 (m, 1 H, at C_4), and 8.0–8.4 (m, 2 H, at C_1 and C_3). Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.91. Found: C, 67.95; H, 6.14; N, 7.82.

Trifluoromethanesulfonate 27, an oil, was prepared from **16**-OSO_2CF_3.

5,8-Dihydro-5,8-methanoisoquinoline *N*-Oxide (14). To a solution of 305 mg of 5,8-dihydro-5,8-methanoisoquinoline (**13**) in 30 mL of chloroform was added dropwise a solution of 1 equiv of *m*-chloroperbenzoic acid in chloroform at −10 °C over 20 min with stirring and the temperature of the reaction mixture was raised to 10 °C over 5 h. Washing of the mixture with saturated aqueous sodium carbonate followed by drying and distillation of the chloroform left 308 g of an oily product, which was washed with *n*-pentane to remove a small amount of the remaining starting material. The yield was 262 mg (77.3%). ^{1}H NMR ($CDCl_3$) δ 2.1–2.5 (m, 2 H, at C_9), 4.0 (m, 2 H, bridgeheads), 6.7 (m, 2 H, olefin), 7.1 (d, 1 H, at C_4), 7.9 (d, 1 H, at C_3), and 8.1 (s, 1 H, at C_1).

Acid-Catalyzed Hydration with 5,8-Dihydro-5,8-methanoisoquinoline. The olefin **13** (58.3 mg) was dissolved with 70% aqueous perchloric acid (1 mL) in a tightly stoppered flask to react at 80 °C for 19 h. The reaction mixture was made alkaline, salted out, and extracted with ether. The ether solution gave 62.5 mg (95.2%) of an alcoholic mixture, which when analyzed by HPLC, gave the results shown in Table I.

The olefin *N*-oxide **14** (32.35 mg) was treated in the same way with 70% aqueous perchloric acid (1 mL). The results are shown in Table I.

Kinetic Measurements. The kinetic solutions were prepared by dissolving the sulfonates in 50% (v/v) aqueous *tert*-butyl alcohol at a concentration of 1×10^{-3} mol/L at 25 °C. The solution was placed in a cell maintained at the reaction temperature shown in Table II. The hydrolysis reaction was followed by titration of the forming sulfonic acid with 0.01 N sodium hydroxide in 50% aqueous *tert*-butyl alcohol to maintain a constant pH of 7.5 during the whole reaction process. The measurements were carried out with a pH stat equipped with a Radiometer TTT80 titrator, PHM84 Research pH meter, and ABU80 Autoburett. Titrations were observed by continuous recording. Rate constants were calculated, according to the Guggenheim method, by plotting logarithms of the varying amounts of titration against time.

Solvolysis Products. The four kinds of sulfonates were solvolyzed under the same conditions as to the kinetic measurements for ten half lives and the products analyzed by HPLC. Analysis conditions for products from **19** and **21** were the following: column, Cosmosil $5C_{18}$, 4.6 × 150 (mm); solvent, 800 mL of a buffer solution which was prepared from 1 g of Et_3N and 800 mL of water and adjusted to pH 7.5 by H_3PO_4, 20 mL of tetrahydrofuran, and 12 mL of acetonitrile; speed, 1 mL/min; reference compound, 4-hydroxyquinoline.

Analysis conditions for products from **20** and **22** were as follows: column, Cosmosil $5C_{18}$, 4.6 × 150 (mm); solvent, 800 mL of a buffer solution which was prepared from 1 g of Et_3N and 800 mL of water and adjusted to pH 7.5 by H_3PO_4, 20 mL of methanol, and 1 mL of tetrahydrofuran; speed, 1 mL/min; reference compound, pyridine. The results are shown in Table III.

Registry No. **3**, 32804-68-5; **4** (isomer 1), 90343-55-8; **4** (isomer 2), 90410-08-5; **7**, 90343-56-9; **8**, 90343-57-0; **9**, 90343-58-1; **10**, 90343-59-2; **11**, 90343-60-5; **12**, 90343-61-6; **12** *N*-oxide, 90343-73-0; **12** *p*-nitrobenzoate derivative, 90343-64-9; **13**, 90343-62-7; **14**, 90343-63-8; **15**, 90343-66-1; **15** *N*-oxide, 90343-74-1; **15** *p*-nitrobenzoate derivative, 90343-67-2; **16**, 90410-09-6; **16** *N*-oxide, 90410-11-0; **17**, 90410-10-9; **17** *N*-oxide, 90410-12-1; **18**, 90343-65-0; **19**, 90343-68-3; **20**, 90343-69-4; **21**, 90343-70-7; **21Ns**, 90343-72-9; **22**, 90343-71-8; **24**, 90343-76-3; **25**, 90343-77-4; **26**, 90343-78-5; **27**, 90343-79-6; 1,3-cyclopentadiene, 542-92-7; 5,8-methano-5,6,7,8-tetrahydroisoquinolin-6-one, 90343-75-2; 5,8-methano-5,6,7,8-tetrahydroisoquinolin-7-one, 90343-80-9.