Neighboring Group Participation by a Pyridine Ring. 2. Effects of Aromatic Substituents on Solvolysis of 5,8-Methano-5,6,7,8-tetrahydroisoquinoline and Benzonorbornene Derivatives

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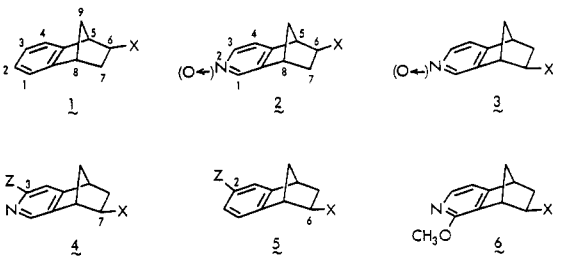
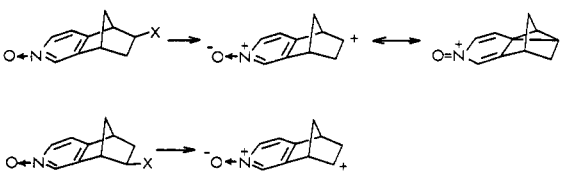
A series of 3-substituted 5,8-methano-5,6,7,8-tetrahydroisoquinolin-7-*exo*-ols (**4**) and 2-substituted benzonorbornen-6-*exo*-ols (**5**) were prepared and the hydrolysis rates of their arenesulfonates were determined in 50% aqueous *tert*-butyl alcohol. The relative rates of CH_3O, CH_3, H, and Cl substituted derivatives at 50 °C were 150, 7.39, 1, and 0.14 for the isoquinoline series and 130, 4.96, 1, and 0.15 for the benzo series, respectively. The products found were the corresponding alcohols with the retained configuration. The $\rho-\sigma^+$ plots for the rates yielded linear correlations with ρ values of −3.19 for the isoquinolines and −3.09 for the benzo series. The data indicate major participation by both aromatic rings.

In benzene chemistry, substituent effects on electrophilic aromatic substitutions have been correlated by the Hammett–Brown $\rho\sigma^+$ linear free energy relationship with solvolyses of α-aryl carbinyl derivatives (electrophilic side chain reactions).[1] In pyridine chemistry, solvolyses of this kind were carried out by Noyce and co-workers,[2] but since then by no others so that the substituent effects have not been based on an energy relationship. We considered that the easy conversion of 2-(halogenomethyl)pyridines into dimers and 4-(halogenomethyl)pyridines into polymers[3,4] could be a problem in such studies. Noyce et al. also reported that the materials used in their kinetic studies, 2-(X-pyridyl)-2-chloropropanes, contained high percentages of 2-(X-pyridyl)propenes formed in their synthesis. We have reported the $\rho\sigma^+$ relationship for the effects of aromatic ring substituents on solvolyses of benzonorbornen-6-*exo*-yl arenesulfonates (**1**)[5] which, though the reaction sites on the bornene ring are β to the aromatic ring, demonstrated the dependence of the solvolysis rate on the nature and extent of aromatic substitution,[6,7] as in α-aryl carbinyl solvolyses. To extend this research to the pyridine system, we synthesized in a previous study[8] 5,8-methano-5,6,7,8-tetrahydroisoquinolin-6(or 7)-yl arenesulfonates and their *N*-oxides (**2** and **3** in Chart I) and found them sufficiently stable for solvolysis studies. It was thought that these compounds might be used in place of the (halogenomethyl)pyridines. Introduction of the *N*-oxide function was found to cause solvolytic rate enhancement by a factor of 28 in 50% aqueous *tert*-butyl alcohol at 50 °C in the homopara exo system (**2**), but rate depression by a factor of 8.6×10^{-2} in the homometa exo system (**3**). These results were ascribed to the electron-donating effects of the *N*-oxide on the cationic transition state of the homopara carbon and to the electron-attracting effects on that of the homometa carbon (Scheme I). To study the effects of aromatic ring substituents other than *N*-oxide, the present paper describes the syntheses and solvolyses of 3-substituted 5,8-methano-5,6,7,8-tetrahydroisoquinolin-7-*exo*-yl derivatives (**4**) and discusses the magnitude of substituent effects on solvolysis in comparison with that in the 2-substituted benzonorbornen-6-*exo*-yl derivatives (**5**). Solvolysis data for 1-methoxy-5,8-methano-5,6,7,8-tetrahydroisoquinolin-7-*exo*-yl tosylate (**6**) are also included.

Chart I



Scheme I



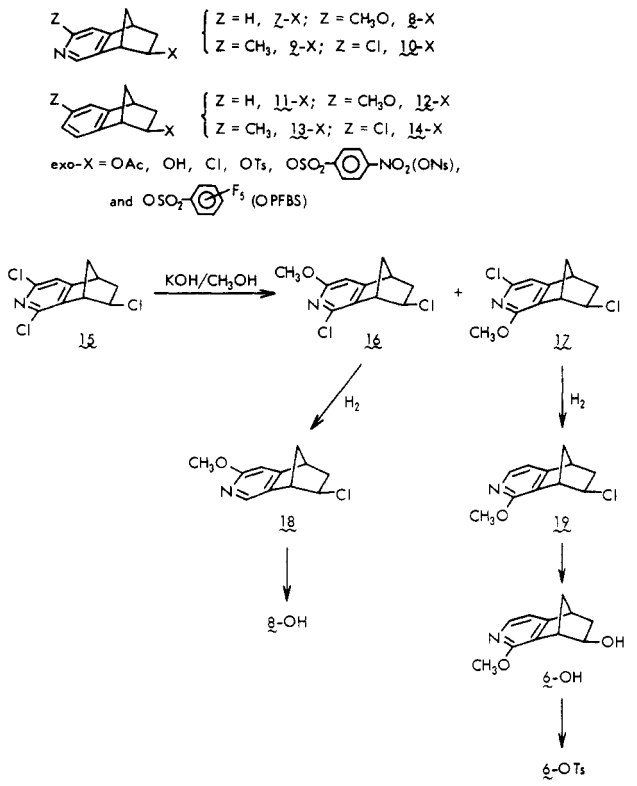
Results

Preparations. For both benzene and pyridine systems, the unsubstituted parent and the methoxy-, methyl-, and chloro-substituted compounds were prepared as shown in Scheme II. 1,3,7-Trichloro-5,8-methano-5,6,7,8-tetrahydroisoquinoline (**15**)[8] was treated with potassium hydroxide in refluxing methanol to obtain a 55:45 mixture of 3-methoxy-1,7-dichloro and 1-methoxy-3,7-dichloro compounds (**16** and **17**), which were separated by silica gel chromatography. Catalytic reductions of both compounds yielded monochlorides **18** and **19**, which were hydrolyzed to the alcohols 8-OH and 6-OH. For solvolysis studies, the *p*-nitrobenzenesulfonate and tosylate were prepared from 8-OH and the tosylate from 6-OH. The acetate of 5,8-methano-5,6,7,8-tetrahydroisoquinolin-7-*exo*-ol (7-OAc)[8] was converted into its *N*-oxide **20**, which was treated with methyl iodide and then with methylmagnesium iodide to

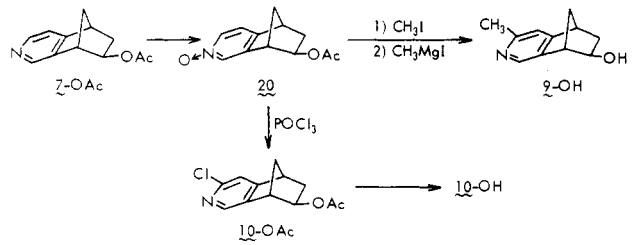
(1) Stock, L. M.; Brown, H. C. "Advances in Physical Organic Chemistry"; Gold, V., Ed.; Academic Press: New York, 1962; Vol. I, pp 35–154.
(2) (a) Noyce, D. S.; Virgilio, J. A.; Bartman, B. *J. Org. Chem.* **1973**, *38*, 2657. (b) Noyce, D. S.; Virgilio, J. A. *Ibid.* **1973**, *38*, 2660.
(3) Sorm, F.; Sedivy, L. *Collect. Czech. Chem. Commun.* **1948**, *13*, 289.
(4) Abramovitch, R. A.; Smith, E. M. "The Chemistry of Heterocyclic Compounds, Pyridine and Its derivatives"; Abramovich, R. A., Ed.; Wiley: New York, 1974; Vol. 14, Chapter IV, Supplement Part 2.
(5) The numbering used in this paper is shown in Chart I. A different numbering from that of previous papers[6,7] was used for the benzonorbornene system in order to preserve uniformity with the present benzo and pyridino systems.
(6) Tanida, H.; Ishitobi, H.; Irie, T.; Tsushima, T. *J. Am. Chem. Soc.* **1969**, *91*, 4512.
(7) 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.
(8) Tanida, H.; Irie, T.; Hayashi, Y. *J. Org. Chem.* **1984** *49*, 2527.

0022-3263/85/1950-0821$01.50/0

Scheme II

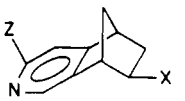


give the 3-methyl derivative **9**-OH. This alcohol was transformed into the *p*-nitrobenzenesulfonate **9**-ONs. Reaction of **20** with phosphorus oxychloride gave the 3-chloro 7-acetate **10**-OAc, which was hydrolyzed to give **10**-OH. The pentafluorobenzenesulfonate **10**-OPFBS was made for kinetics.



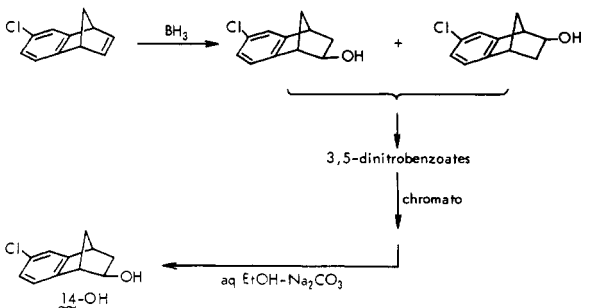
We previously reported the preparation of 2-methoxybenzonorbornen-6-*exo*-yl chloride and 2-methoxybenzonorbornen-6-*exo*-ol (**12**-Cl and **12**-OH).[6] Essentially the same method, based on the reactivity difference between the homopara 6-exo and the homometa 7-exo derivatives, was used to prepare 2-methylbenzonorbornen-6-*exo*-ol (**13**-OH). Addition of hydrochloric acid to 2-methylbenzonorbornadiene[9] gave a mixture of 2-methylbenzonorbornen-6-*exo*- and 7-*exo*-yl chlorides, which was subjected to hydrolysis under conditions in which the 6-*exo*-chloride mainly reacted and the 7-*exo*-chloride remained almost unreacted. Silica gel chromatography separated the crude 6-*exo*-alcohol from the 7-*exo*-chloride. This crude alcohol was again converted by treatment with thionyl chloride into the chloride, which was hydrolyzed once more under the above conditions resulting in the formation of a pure sample of **13**-OH. Solvolysis was studied with the chloride and tosylate derived from this sample.

Table I. Rates of Solvolyses of 5,8-Methano-5,6,7,8-tetrahydroisoquinoline Derivatives



Z	X	temp, °C	k_1, s^{-1}	k_{rel} at 50 °C[a]
H	OSO_2-C$_6$H$_4$-NO_2	50	3.14×10^{-4}	1
		30	1.61×10^{-5}	
	OSO_2-C$_6$F$_5$	50	1.36×10^{-2}	
		30	6.98×10^{-4} (calcd)[b]	
CH_3O	OTs	50	1.04×10^{-3}	150
		30	7.57×10^{-5}	
	OSO_2-C$_6$H$_4$-NO_2	50	4.70×10^{-2} (calcd)[c]	
		25	2.16×10^{-3}	
		5	1.24×10^{-4}	
CH_3	OSO_2-C$_6$H$_4$-NO_2	50	2.32×10^{-3}	7.39
		30	1.90×10^{-4}	
Cl	OSO_2-C$_6$F$_5$	50	1.95×10^{-3}	0.14
		30	1.37×10^{-4}	

[a] Based on the rates of *p*-nitrobenzenesulfonates and, in turn, pentafluorobenzenesulfonate. Conversion factors are calculated with the parent compound (Z = H) as 43.3 between pentafluorobenzenesulfonate and *p*-nitrobenzenesulfonate. [b] See text for calculation. [c] Conversion factor between *p*-nitrobenzenesulfonate and tosylate was determined as 45.2 at 50 °C.



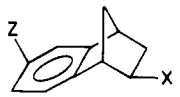
Hydroboration of 2-chlorobenzonorbornadiene[9] with borane–methyl sulfide complex gave a mixture of the corresponding 6-*exo*- and 7-*exo*-ols, which were converted into 3,5-dinitrobenzoates. The formation of exo alcohols is a result of the sterically favored exo attack. Silica gel chromatography separated the 6-*exo*- and 7-*exo*-yl 3,5-dinitrobenzoates in pure states, and each was hydrolyzed in aqueous ethanol containing sodium carbonate to give the 6-*exo*-ol **14**-OH and the 7-*exo*-ol. The structure of the 7-*exo*-yl 3,5-dinitrobenzoate was established by X-ray analysis, so that the structure of the 6-*exo*-yl dinitrobenzoate was presumed. The tosylate **14**-OTs was prepared for solvolysis studies.

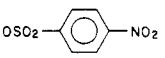
Rates of Solvolysis. Under the conditions described in the previous paper,[8] solvolyses were carried out in 50% (v/v) aqueous *tert*-butyl alcohol maintaining a constant pH of 7.5 during the reaction, and the rate data are summarized in Tables I and II. To make rate measurements possible under ordinary conditions and by a simple procedure, the above mentioned alcohols were converted into three different arenesulfonates (tosylate, *p*-nitrobenzenesulfonate, and pentafluorobenzenesulfonate) and the chlorides. The most reactive methoxy-substituted compound 8-X in the pyridine system was solvolyzed with two

(9) Tanida, H.; Muneyuki, R.; Tsuji, T. *Bull. Chem. Soc. Jpn.* **1964**, *37*, 40.

(10) It is noted that the relative leaving group ability obtained here is significantly large in this system. For example, the corresponding factor was reported as 11.9 in the solvolyses of 1-phenylethyl esters in 80% aqueous ethanol at 75 °C. Noyce, D. S.; Virgilio, J. A. *J. Org. Chem.* **1972**, *37*, 2643.

Table II. Rates of Solvolyses of Benzonorbornene Derivatives



Z	X	temp, °C	k_1, s^{-1}	k_{rel} at 50 °C
H	OTs	50	6.82×10^{-4}	1
		30	5.26×10^{-5}	
		50	5.28×10^{-2} (calcd)[b]	
		30	4.07×10^{-3}	
CH_3O	Cl	50	1.39×10^{-4}	130
CH_3	OTs	50	3.38×10^{-3}	4.96
		30	2.89×10^{-4}	
	Cl	80	1.64×10^{-4}	
		60	1.78×10^{-5}	
		50	5.30×10^{-6} (calcd)	
Cl	OTs	50	9.98×10^{-5}	0.15

[a] Based on the rates of tosylates. Conversion factors are calculated with the parent compound (Z = H) as 77.4 between *p*-nitrobenzenesulfonate and tosylate and with the methyl-substituted compound as 637.7 between tosylates and chlorides. [b] See text for calculation.

kinds of leaving groups, *p*-nitrobenzenesulfonate and tosylate, and the ratio of the rates was determined extrapolating the rates observed with the *p*-nitrobenzenesulfonate at 25 and 5 °C to the rate at 50 °C (ref *c* in Table I). The rate ratio for the benzene **13**-X tosylate and chloride was similarly determined. The rates of the pyridine **7**-X pentafluorobenzenesulfonate and the benzene **11**-X *p*-nitrobenzenesulfonate at 50 °C were calculated involving the assumption that the temperature dependence of the rates in the range 30–50 °C is the same between **7**-X pentafluorobenzenesulfonate and *p*-nitrobenzenesulfonate and between **11**-X *p*-nitrobenzenesulfonate and tosylate. The relative rates in Tables I and II are based on assigning the rates for the unsubstituted pyridino *p*-nitrobenzenesulfonate (**7**-ONs) and the benzo tosylate (**11**-OTs) as unity.

Discussion

Substituent effects on the solvolysis rates were significantly large in the benzene and pyridine systems studied. As shown in Tables I and II, the electron-donating methoxy substituent raises the relative rate at 50 °C by a factor of 150 in the pyridine system and 130 in the benzene system. The electron-withdrawing chloro substituent lowers the rate to 0.15 in both systems. Plots of the relative rates vs. the σ^+ constants yield satisfactorily linear correlations as shown in Figure 1. The reaction constants, ρ, were −3.19 for the pyridine system and −3.09 for the benzene system. In consequence of the very similar ρ values, a plot of the rate constants at 50 °C between the pyridine system and the benzene system yields a straight line with a slope of 45°. Therefore, substituent effects on the free energy of activation are nearly identical in both the systems. Accordingly, the discussion previously presented for the transition state and the subsequently formed intermediate in the benzene system[6,7,11] can be applied to the present pyridine derivatives (eq 1). The

(1)

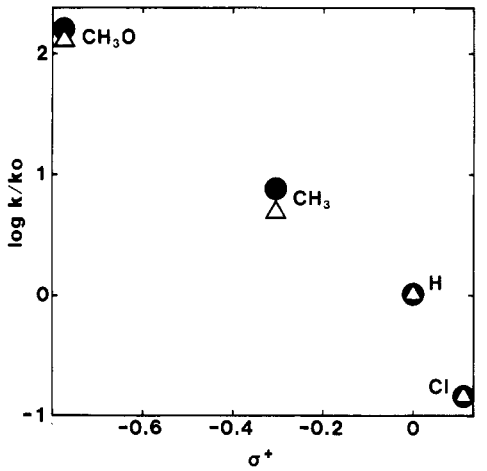
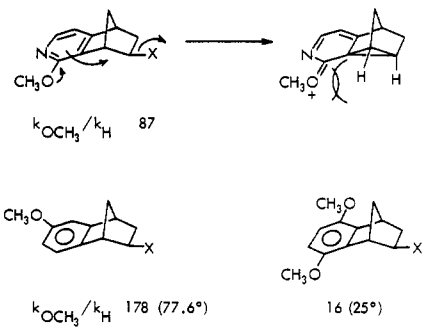
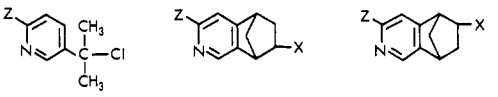


Figure 1. The ρ–σ^+ treatment of the relative solvolysis rates, k_Z/k_H, in 50% aqueous *tert*-butyl alcohol: 3-substituted 5,8-methano-5,6,7,8-tetrahydroisoquinolin-7-*exo*-yl arenesulfonates, ●, ρ = −3.19; 2-substituted benzonorbornen-6-*exo*-yl arenesulfonates, △, ρ = −3.09.

Scheme III



major factor is clearly participation by the aromatic rings in both systems. In the solvolysis study of 2-(X-pyridyl)-2-chloropropanes, Noyce et al.[2b] observed satisfactory correlation with the σ^+ constants of 4- and 5-substituted 2-(2-pyridyl)-2-chloropropanes and 5-substituted 2-(3-pyridyl)-2-chloropropanes, but an absence of such correlation for 6-substituted 2-(2-pyridyl)-2-chloropropanes. Our system essentially corresponds to their 6-substituted 2-(3-pyridyl)-2-chloropropanes (**22**) in which



22, Z = CH_3 Z = CH_3O, CH_3, H, Cl **23**

the 6-methyl-substituted compound was solvolyzed for rate measurement showing no deviation from the σ^+ treatment. Our results show that the σ_p^+ constants can be applied even if the substituents are ortho to the pyridine nitrogen. This is inconsistent with the opinion that such a situation would require a different substituent constant than σ^+.[2b,12] It is impossible to test the applicability of the σ_m^+ constants in the present system, because the substituents must be located on the pyridine nitrogen. Solvolysis of 3-substituted 5,8-methano-5,6,7,8-tetrahydroisoquinolin-6-*exo*-yl arenesulfonates (**23**) would be of interest to see whether the σ_m^+ constants or other defined constants are applicable. However, we have not yet found a practical synthesis for **23**.

(11) Tanida, H.; Ishitobi, H. *J. Am. Chem. Soc.* **1966**, *88*, 3663. Tanida, H.; Tsuji, T.; Ishitobi, H. *Ibid.* **1964**, *86*, 4904.

(12) Tomashik, P.; Johnson, C. D. "Advances in Heterocyclic Chemistry"; Katritzky, A. R., Boulton, A. J., Ed.; Academic Press: New York, 1976; Vol. 20, Chapter 1.

The solvolysis rate of the 1-methoxy derivative **6** was determined to be $k = 3.51 \times 10^{-4}$ s^{-1} at 50 °C under the same conditions. Thus the rate-enhancing effect of the 1-methoxy group ($k_{rel} = 50.6$) is smaller than that (150) of the 3-methoxy substituent. We have observed similar facts as shown in Scheme III, in which the 2-methoxy substituent in the benzonorbornene system accelerates the acetolysis rate by a factor of 178 at 77.6 °C,[6] but the 1,4-dimethoxy substituents accelerate it only by a factor of 16 at 25 °C.[13] When the reaction progresses toward the bridged transition state, the 1-methoxy substituent will have steric interference with the bridgehead hydrogen and the hydrogen α to the leaving group (a kind of ortho effect), so that the participation effect of the methoxy substituent is greatly perturbed.

Experimental Section

Melting points were taken in capillary tubes and are corrected. ^{1}H NMR spectra were determined with a Varian T-60A with tetramethylsilane as an internal standard, and infrared spectra were obtained with a Hitachi 260-10 spectrophotometer. All HPLC analyses were carried out with a system comprised of the components: Waters 6000-A pump, UVIDEC-100 UV detector, and Reodyne 7120 injector.

Kinetic Materials. In a series of compounds synthesized for solvolyses, elementary analyses were carried out with crystalline derivatives: alcohols, benzoates, or sulfonates. Solvolysis materials that were oils (**6**-OTs, **8**-OTs, **10**-OPFBS, **13**-Cl, **13**-OTs, and **14**-OTs) were either purified by preparative thick-layer chromatography or shown to be single compounds by thin-layer chromatography. Kinetic measurements with analyzed compounds (**9**-ONs and in the previous work, **7**-ONs) confirmed the identity of rate constants within experimental error obtained from analytically pure material and material purified by chromatography. Also, studies by HPLC indicated no meaningful difference between the materials.

Kinetic Measurements. Rates were determined at pH 7.5 in 50% (v/v) aqueous *tert*-butyl alcohol by using a pH stat, as described in the previous paper.[8] An exception was 2-chlorobenzonorbornen-6-*exo*-yl chloride, for which the amount of remaining chloride was measured by HPLC during the reaction by using pentamethylbenzene as an internal standard. The rate constants were calculated by the Guggenheim method.

3-Methoxy-1,7-*exo*-dichloro- and 1-Methoxy-3,7-*exo*-dichloro-5,8-methano-5,6,7,8-tetrahydroisoquinolines (16 and 17). A mixture of 2.9 g of potassium hydroxide in 40 mL of methanol and 2.6 g of 1,3,7-*exo*-trichloro-5,8-methano-5,6,7,8-tetrahydroisoquinoline (**15**) was warmed under reflux for 6 h. The mixture was concentrated by distilling the methanol under reduced pressure, diluted with water, and extracted with ether. The ether solution was dried and distilled leaving 2.5 g of a mixture of the methoxy derivatives. Silica gel chromatography with a 1:4 mixture of benzene and hexane gave 1.07 g (41.9%) of **17** and then 1.31 g (51.3%) of **16**. **16**: mp 58.5–60 °C (*n*-hexane); ^{1}H NMR ($CDCl_3$) δ 1.9–2.4 (m, 4 H at C_6, C_9), 3.4, 3.6 (m, 2 H, bridgeheads), 3.9 (s, 3 H, OCH_3), 4.0 (m, 1 *endo*-H at C_7), and 6.5 (s, 1 H at C_4). Anal. Calcd for $C_{11}H_{11}NOCl_2$: C, 54.12; H, 4.54; N, 5.74; Cl, 29.05. Found: C, 53.90; H, 4.35; N, 5.86; Cl, 28.89. **17**: mp 79.5–80.5 °C (*n*-hexane); ^{1}H NMR ($CDCl_3$) δ 1.9–2.4 (m, 4 H at C_6, C_9), 3.4, 3.6 (m, 2 H, bridgeheads), 3.9 (m, 1 *endo*-H at C_7), 4.0 (s, 3 H, OCH_3), and 6.8 (s, 1 H at C_4). Anal. Found: C, 54.04; H, 4.31; N, 5.75; Cl, 29.21.

7-*exo*-Chloro-3-methoxy-5,8-methano-5,6,7,8-tetrahydroisoquinoline (18). To a solution of 222 mg of sodium metal in 150 mL of methanol were added 1.6 g of **16** and 0.4 g of 5% palladium on charcoal. Catalytic reduction followed by the usual workup gave 1.3 g (94.6%) of **18** as crystals, mp 61–63 °C (*n*-hexane); ^{1}H NMR ($CDCl_3$) δ 1.8–2.4 (m, 4 H at C_6, C_9), 3.4, 3.5 (m, 2 H, bridgeheads), 3.9 (s, 3 H, OCH_3), 3.9 (m, 1 *endo*-H at C_7), 6.6 (s, 1 H at C_4), and 8.0 (s, 1 H at C_1). Anal. Calcd for $C_{11}H_{12}ONCl$: C, 63.01; H, 5.77; N, 6.88; Cl, 16.91. Found: C, 62.99; H, 5.90; N, 6.75; Cl, 16.93.

7-*exo*-Chloro-1-methoxy-5,8-methano-5,6,7,8-tetrahydroisoquinoline (19). Catalytic reduction was carried out with **17** as described above to obtain **19** as an oil: ^{1}H NMR ($CDCl_3$) δ 1.9–2.4 (m, 4 H at C_6, C_9), 3.5, 3.8 (m, 2 H, bridgeheads), 4.0 (m, 1 *endo*-H at C_7), 4.0 (s, 3 H, OCH_3), 6.8 (d, 1 H at C_4), and 8.0 (d, 1 H at C_3).

3-Methoxy 7-ol 8-OH. A mixture of 897 mg of **18**, 431 mg of sodium bicarbonate, and 35 mL of 50% (v/v) aqueous acetone was warmed under reflux for 23 h. The mixture was concentrated under reduced pressure and extracted with ether. The ether solution was washed with saturated aqueous sodium chloride, dried, and distilled leaving 800 mg (97.8%) of **8**-OH: mp 55–58 °C (ether–hexane); ^{1}H NMR ($CDCl_3$) δ 1.6–2.3 (m, 4 H at C_6, C_9), 3.1 (s, 1 H, OH), 3.3 (m, 2 H, bridgeheads), 3.9 (s, 3 H, OCH_3), 4.0 (m, 1 *endo*-H at C_7), 6.6 (s, 1 H at C_4), and 7.9 (s, 1 H at C_1). Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33. Found: C, 69.10; H, 6.89; N, 7.48.

***p*-Nitrobenzenesulfonate 8-ONs.** A mixture of 81 mg of **8**-OH, 102 mg of *p*-nitrobenzenesulfonyl chloride, and 0.5 mL of pyridine was left overnight in a refrigerator. The usual workup[14,15a] gave 136 mg of crude crystals. Recrystallization from dichloromethane–hexane gave 120 mg (75.9%) of pure crystals: mp 132–133 °C; ^{1}H NMR ($CDCl_3$) δ 1.7–2.2 (m, 4 H at C_6, C_9), 3.3, 3.5 (m, 2 H, bridgeheads), 3.8 (s, 3 H, OCH_3), 4.6 (m, 1 *endo*-H at C_7), 6.5 (s, 1 H at C_4), 7.9 (s, 1 H at C_1), 8.1, 8.4 (2 sets of d, 4 H, arom.). Anal. Calcd for $C_{17}H_{16}N_2O_6S$: C, 54.25; H, 4.29; N, 7.44; S, 8.52. Found: C, 54.26; H, 4.23; N, 7.48; S, 8.44.

Tosylate 8-OTs was prepared with *p*-toluenesulfonyl chloride in pyridine as described for **8**-ONs: an oil; ^{1}H NMR ($CDCl_3$) δ 1.7–2.3 (m, 4 H at C_6, C_9), 2.5 (s, 3 H, $ArCH_3$), 3.4, 3.5 (m, 2 H, bridgeheads), 3.9 (s, 3 H, OCH_3), 4.6 (m, 1 *endo*-H at C_7), 6.5 (s, 1 H at C_4), 7.4, 7.8 (2 sets of d, 4 H, aromatic), and 7.9 (s, 1 H at C_1).

1-Methoxy 7-ol 6-OH. Hydrolysis of **19** (517 mg) was carried out for 3 days in boiling 50% (v/v) aqueous acetone in the presence of sodium bicarbonate to obtain 442 mg (93.7%) of **6**-OH: oil; ^{1}H NMR ($CDCl_3$) δ 1.7–2.3 (m, 4 H at C_6, C_9), 3.2 (s, 1 H, OH), 3.3, 3.4 (m, 2 H, bridgeheads), 4.0 (m, 1 *endo*-H at C_7), 4.0 (s, 3 H, OCH_3), 6.8 (d, 1 H at C_4), and 7.9 (d, 1 H at C_3).

Tosylate 6-OTs: ^{1}H NMR ($CDCl_3$) δ 1.7–2.2 (m, 4 H at C_6, C_9), 2.5 (s, 3 H, $ArCH_3$), 3.4, 3.6 (m, 2 H, bridgeheads), 4.0 (s, 3 H, OCH_3), 4.6 (m, 1 *endo*-H at C_7), 6.8 (d, 1 H at C_4), 7.4, 7.8 (2 sets of d, 4 H, arom.) and 7.9 (d, 1 H at C_3).

5,8-Methano-5,6,7,8-tetrahydroisoquinolin-7-*exo*-yl Acetate (7-OAc). A mixture of 846 mg of **7**-OH, 804 mg of acetic anhydride, and 4 mL of pyridine was warmed at 100 °C for 1 h. The mixture was poured into ice water, made alkaline, and extracted with ether. The ether solution was dried and decolorized with charcoal, and the solvent was distilled leaving 1.034 g (96.9%) of an oil: ^{1}H NMR ($CDCl_3$) δ 1.8–2.2 (m, 4 H at C_6, C_9), 2.1 (s, 3 H, OAc), 3.4, 3.5 (m, 2 H, bridgeheads), 4.8 (m, 1 *endo*-H at C_7), 7.1 (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 7-OAc (20).** To a solution of 1.034 g of **7**-OAc in 17 mL of chloroform was added 1.646 g of 80% *m*-chloroperbenzoic acid at 0 °C with stirring. The mixture was left overnight in a refrigerator, washed with aqueous sodium carbonate, dried, and distilled leaving 0.999 g (89.6%) of an oil: ^{1}H NMR ($CDCl_3$) δ 1.9–2.2 (m, 4 H at C_6, C_9), 2.1 (s, 3 H, OAc), 3.5 (m, 2 H, bridgeheads), 4.8 (m, 1 *endo*-H at C_7), 7.1 (d, 1 H at C_4), 8.1 (d of d, 1 H at C_3) and 8.2 (broad s, 1 H at C_1).

3-Methyl 7-*exo*-ol 9-OH. A mixture of 999 mg of **20** and 3 mL of methyl iodide was stirred at room temperature for 3 h. The solution composed of two layers was distilled to remove excess methyl iodide. The residue was suspended in 5 mL of ether and to the mixture was added an ether solution containing methylmagnesium iodide in 10-fold excess with stirring at room temperature. The mixture became homogeneous with stirring for 30 min and then was refluxed for 2 h, mixed with water and saturated aqueous ammonium chloride, and extracted with ether. The ether solution was shaken with dilute hydrochloric acid and this acid layer was made alkaline by adding aqueous sodium hydroxide and

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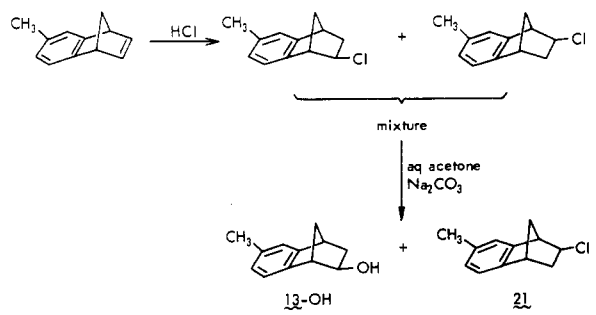
Scheme IV



again extracted with ether. The ether solution was dried, decolorized with charcoal, and distilled leaving 351 mg of a residue. Silica gel chromatography gave 280 mg (35.1%) of **9-OH** with acetone solvent: ^{1}H NMR ($CDCl_3$) δ 1.7–2.3 (m, 4 H at C_6, C_9), 2.5 (s, CH_3), 3.4 (m, 2 H, bridgeheads), 4.0 (m, 1 *endo*-H at C_7), 4.9 (s, 1 H, OH), 7.0 (s, 1 H at C_4) and 8.2 (s, 1 H at C_1).

***p*-Nitrobenzenesulfonate 9-ONs** was prepared as described for 8-ONs: crystals; mp 150–151 °C (dichloromethane–*n*-hexane); ^{1}H NMR ($CDCl_3$) δ 1.8–2.2 (m, 4 H at C_6, C_9), 2.5 (s, 3 H, CH_3), 3.4, 3.6 (m, 2 H, bridgeheads), 4.7 (m, 1 *endo*-H at C_7), 7.0 (s, 1 at C_4), 8.3 (s, 1 H at C_1), and 8.2, 8.4 (2 sets of d, 4 H aromatic). Anal. Calcd for $C_{17}H_{16}N_2O_5S$: C, 56.65; H, 4.48; N, 7.77; S, 8.90. Found: C, 56.49; H, 4.32; N, 7.87; S, 9.09.

3-Chloro 7-*exo*-yl Acetate 10-OAc. A mixture of 1.06 g of **20**, 10 mL of phosphorus oxychloride, and 10 mL of chloroform was warmed under reflux for 3 h and distilled under reduced pressure leaving a residue, to which ice water was added. The mixture was made alkaline and extracted with ether. The ether solution was dried and distilled leaving a residue, which was purified by silica gel chromatography to obtain 0.7 g (60.9%) of **10-OAc**: ^{1}H NMR ($CDCl_3$) δ 1.9–2.2 (m, 4 H at C_6, C_9), 2.1 (s, 3 H, OAc), 3.5 (m, 2 H, bridgeheads), 4.8 (m, 1 *endo*-H at C_7), 7.2 (s, 1 H at C_4), and 8.3 (s, 1 H at C_1).

3-Chloro 7-*exo*-ol 10-OH. A solution of **10-OAc** in 10% aqueous hydrochloric acid was refluxed for 3 h, made alkaline with aqueous sodium hydroxide, and extracted with ether. The ether solution was dried and distilled leaving **10-OH** as crystals: mp 133–134 °C (ether); ^{1}H NMR ($CDCl_3$) δ 1.7–2.3 (m, 4 H at C_6, C_9), 2.9 (s, 1 H, OH), 3.4 (m, 2 H, bridgeheads), 4.0 (m, 1 *endo*-H at C_7), 7.1 (s, 1 H at C_4), and 8.1 (s, 1 H at C_1). Anal. Calcd for $C_{10}H_{10}NOCl$: C, 61.39; H, 5.15; N, 7.16; Cl, 18.12. Found: C, 61.57; H, 5.24; N, 7.20; Cl, 17.91.

Pentafluorobenzenesulfonate 10-OPFBS. To a solution of 51 mg of **10-OH** in 3 mL of tetrahydrofuran was added 0.33 mL of 15% *n*-butyllithium in *n*-hexane at 0 °C with stirring under a nitrogen atmosphere. The mixture was stirred for 10 min and mixed with 174 mg of pentafluorobenzenesulfonyl chloride. After stirring for 30 min, the mixture was poured into ice water and extracted with ether. The ether solution was dried and distilled leaving a residue, which was treated by preparative thick-layer chromatography with a 3:1 mixture of benzene and ethyl acetate. The sulfonate **10-OPFBS** (15 mg, 31.3%) and the alcohol **10-OH** (29 mg) were obtained. ^{1}H NMR ($CDCl_3$) for **10-OPFBS** δ 1.8-2.3 (m, 4 H at C_6, C_9), 3.5, 3.7 (m, 2 H, bridgeheads), 4.9 (m, 1 *endo*-H at C_7), 7.2 (s, 1 H at C_4), and 8.3 (s, 1 H at C_1).

2-Methylbenzonorbornen-6-*exo*-ol (13-OH). A solution of 2.8 g of 2-methylbenzonorbornadiene in 15 mL of concentrated hydrochloric acid was warmed overnight at 80 °C with stirring and the mixture was poured into ice water and extracted with ether. The ether solution was dried, decolorized, and distilled leaving 3.31 g of the chloride mixture (Scheme IV). This residue was dissolved in 100 mL of 50% (v/v) aqueous acetone containing 1.5 g of sodium bicarbonate and the solution was warmed under reflux for 2.5 days. Distillation of the mixture left a residue, which was extracted with ether. The ether solution was dried and distilled leaving a residue, which was treated by silica gel chromatography to recover 0.63 g of the chloride mixture with benzene solvent and to obtain 2.27 g of a crude **13-OH** with ethyl acetate solvent. This crude alcohol was treated with thionyl chloride in ethyl ether to obtain the chloride, which was hydrolyzed by boiling in 70% (v/v) aqueous acetone containing 1.05 g of sodium bicarbonate for 48 h. The reaction mixture was distilled to remove the solvent and extracted with ether. Evaporation of the ether left 2.64 g of a residue, which was subjected to silica gel chromatography to obtain 1.64 g of the chloride **21** with benzene solvent and 0.99 g of the alcohol **13-OH** with ethyl acetate. Recrystallization from *n*-hexane gave pure **13-OH**: mp 58.5–59.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.6–2.2 (m, 4 H at C_7, C_9), 2.1 (s, 1 H, OH), 2.3 (s, 3 H, CH_3), 3.2 (m, 2 H, bridgeheads), 3.9 (m, 1 *endo*-H at C_6), 6.9 (d of d, 1 H at C_3), 7.0 (d, 1 H at C_1), and 7.1 (d, 1 H at C_4). Anal. Calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.47; H, 8.10.

2-Methylbenzonorbornen-6-*exo*-yl Chloride (13-Cl). A mixture of 0.25 g of **13-OH**, 0.4 g of thionyl chloride, and 12 mL of ether containing 1 drop of pyridine was warmed under reflux for 3 h. The workup[15b] gave 0.26 g (94.0%) of **13-Cl**: bp 70 °C (2 mmHg); ^{1}H NMR ($CDCl_3$) δ 1.8–2.2 (m, 4 H at C_7, C_9), 2.3 (s, 3 H, CH_3), 3.3, 3.5 (m, 2 H, bridgeheads), 3.9 (m, 1 *endo*-H at C_6), 6.9 (broad d, 1 H at C_3), 7.0 (broad s, 1 H at C_1) and 7.1 (d, 1 H at C_4).

Tosylate 13-OTs: oil; ^{1}H NMR ($CDCl_3$) δ 1.7–2.1 (m, 4 H at C_7, C_9), 2.3 (s, CH_3 at C_2), 2.5 (s, CH_3 in tosyl), 3.3, 3.5 (m, 2 H, bridgeheads), 4.5 (m, 1 *endo*-H at C_6), 6.8 (broad d, 1 H at C_3), 6.9 (broad s, 1 H at C_1), 7.0 (d, 1 H at C_4), 7.3, 7.8 (2 sets of d, 4 H, aromatic in tosyl).

Hydroboration of 2-Chlorobenzonorbornadiene. To a solution of 2.31 g of the diene in 15 mL of dichloromethane was added with stirring under ice cooling 6.5 mL of a 1 M solution of borane–methyl sulfide complex in dichloromethane. The mixture was stirred for 3 h at room temperature and treated with a mixture of 5 mL of ethanol, 1.5 mL of 3 N aqueous sodium hydroxide, and 1.6 mL of 30% aqueous hydrogen peroxide. The usual workup[16] gave a mixture of alcohols, which were transformed into 3,5-dinitrobenzoates. Silica gel chromatography with a 4:1 mixed solvent of *n*-hexane and ethyl acetate gave first 726 mg of 2-chlorobenzonorbornen-6-*exo*-yl dinitrobenzoate and second 752 mg of the 7-*exo*-yl dinitrobenzoate. **The 6-*exo*-yl dinitrobenzoate**: mp 171.5–172.5 °C (*n*-hexane–ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 1.9–2.2 (m, 4 H at C_7, C_9), 3.4, 3.6 (m, 2 H, bridgeheads), 5.1 (m, 1 *endo*-H at C_6), 7.0–7.3 (m, 3 H, aromatic), and 9.2 (m, 3 H, aromatic of benzoate); IR ($CHCl_3$) 1724 cm^{-1} ($\nu_{C=O}$), 1541 and 1341 (ν_{NO_2}). Anal. Calcd for $C_{18}H_{13}N_2O_6Cl$: C, 55.61; H, 3.37; N, 7.21; Cl, 9.12. Found: C, 55.37; H, 3.33; N, 7.22; Cl, 8.77. **The 7-*exo*-yl dinitrobenzoate**: mp 156–157 °C (acetone–water); ^{1}H NMR and IR were identical with those for the 6-*exo*-yl dinitrobenzoate. Found: C, 55.60; H, 3.55; N, 7.18; Cl, 8.75. The structure was established by X-ray analysis.

2-Chlorobenzonorbornen-6-*exo*-ol (14-OH). The above 6-*exo*-yl dinitrobenzoate (185 mg) was hydrolyzed by refluxing overnight in a solution of 100 mg of sodium carbonate in 60 mL of 50% (v/v) aqueous ethanol. The mixture was distilled to remove the ethanol and extracted with ether. The ether solution was dried and evaporated leaving 86 mg (92.8%) of an oil: ^{1}H NMR ($CDCl_3$) δ 1.7–2.2 (m, 4 H at C_7, C_9), 2.6 (s, 1 H, OH), 3.2 (m, 2 H, bridgeheads), 3.9 (m, 1 *endo*-H at C_6), and 6.9-7.2 (m, 3 H, aromatic). **Tosylate 14-OTs**: oil; ^{1}H NMR ($CDCl_3$) δ 1.7–2.2 (m, 4 H at C_7, C_9), 2.5 (s, 3 H, CH_3), 3.3, 3.5 (m, 2 H, bridgeheads), 4.5 (m, 1 *endo*-H at C_6), 7.0 (m, 3 H, aromatic), and 7.3, 7.7 (2 sets of d, 4 H, aromatic of tosyl).

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Registry No. 6-OH, 94706-56-6; **6-OTs**, 94706-57-7; **7-OH**, 90343-61-6; **7-OAc**, 94706-58-8; **7-ONs**, 90343-72-9; **7-OPFBS**, 90343-70-7; **8-OH**, 94706-60-2; **8-ONs**, 94706-61-3; **8-OTs**, 94706-62-4; **9-OH**, 94706-63-5; **9-ONs**, 94706-64-6; **10-OH**, 94706-65-7; **10-OAc**, 94706-66-8; **10-OPFBS**, 94706-67-9; **11-OTs**, 7525-47-5; **11-ONs**, 94706-68-0; **12-Cl**, 94706-69-1; **13-OH**, 58653-85-3; **13-Cl**, 94706-71-5; **13-OTs**, 94706-70-4; **14-OH**, 94706-73-7; **14-OTs**, 94706-72-6; **15**, 90343-59-2; **16**, 94706-74-8; **17**, 94706-75-9; **18**, 94706-76-0; **19**, 94706-77-1; **20**, 94706-59-9; 2-chlorobenzonorbornadiene, 4897-72-7; *exo*-2-chlorobenzonorbornen-6-yl 3,5-dinitrobenzoate, 94706-78-2; *exo*-2-chlorobenzonorbornen-7-yl 3,5-dinitrobenzoate, 94706-79-3; 2-methylbenzonorbornadiene, 4897-73-8.

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