Neighboring Group Participation by Carbonyl Oxygen. Solvolyses of (9-Ketobenzonorbornen-2-yl)methyl *p*-Bromobenzenesulfonates

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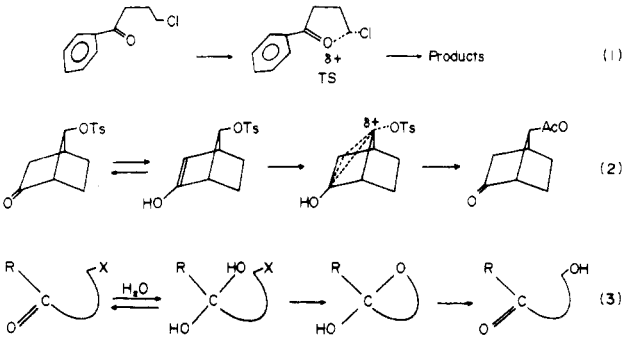
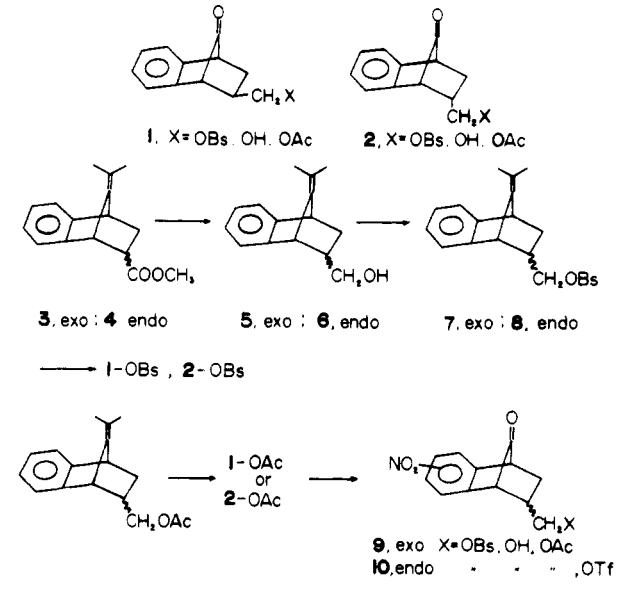
Evidence was obtained for participation due to the hydration equilibrium of a carbonyl compound in hydrolysis. (9-Ketobenzonorbornen-*exo*-2-yl)methyl brosylate (1-OBs) solvolyzed in aqueous acetone affords a single product, the alcohol of retained configuration (1-OH), while the corresponding endo brosylate 2-OBs gives a mixture composed of the alcohol 2-OH, of retained configuration, olefins, and rearranged alcohols. The reaction of 1-OBs is 10^2 times faster than that of 2-OBs, but when poorly nucleophilic solvents such as acetic acid and formic acid are used, 1-OBs is no longer faster than 2-OBs. In accord with this, the acetolysis products of 1-OBS are complex. Methanolysis of 1-OBs in the presence of sodium bicarbonate to prevent the action of the forming bromobenzenesulfonic acid yields the intramolecularly cyclized ketal, 11, as an intermediate.

Although a number of functional groups containing n electrons of heteroatoms have been shown to be capable of neighboring group participation, carbonyl group participation has not attracted sufficient attention.[1,2] Two types of carbonyl participation in solvolyses have thus far been proposed. Pastro and Serve have suggested that in the solvolysis of 4-chlorobutyrophenone in the presence of silver salt, the transition state is stabilized by participation by one of the nonbonded electron pairs in the carbonyl oxygen, as illustrated in eq 1 (Scheme I), causing a rate acceleration.[3,4] Acetolysis of 2-ketonorborn-*anti*-7-yl tosylate was found by Gassman and Marshall to proceed with formation of a product of retained configuration and with a rate 10^7 times faster than that of the parent compound, 7-norbornyl tosylate.[5] The workers explained the results in terms of participation by π electrons of the carbon–carbon double bond in the enol form of 2-keto function (eq 2). The reaction we report here demonstrates a new type of participation, in which a keto group is converted into an intermediate diol with addition of a water molecule and one of the hydroxyl groups formed participates in the transition state of the solvolysis reaction. It may be a special example of the general type of reaction shown in eq 3. This type of participation has been known in the hydrolysis of esters,[6] the reaction center of which is at the sp^2 hybridized carbon atom, but not (to the best of our knowledge) in reactions which take place at the sp^3-hybridized carbon atom, such as solvolytic displacements or S_N2 nucleophilic substitutions. This report describes this type of participation.

Scheme I



Scheme II



Results

Preparations. The model system we chose was (9-ketobenzonorbornen-*exo*- and *endo*-2-yl)methyl derivatives (1 and 2). Syntheses of methyl 9-isopropylidenebenzonorbornene-*exo*- and -*endo*-2-carboxylates (3 and 4) were recently reported[7] (Scheme II). Reductions with lithium aluminum hydride gave the corresponding alcohols 5 and 6, respectively, which were esterified by *p*-bromobenzenesulfonyl chloride to give the brosylates 7 and 8, respectively. Ozone oxidation converted 7 and 8 into the ketones 1-OBs and 2-OBs, respectively. Further, to investigate the effects of an adjacent, strong electronegative group on participation of the 9-keto group, the benzo moiety was transformed into a nitrobenzo moiety. The acetates of 5 and 6 were respectively oxidized by ozone to obtain 1-OAc and 2-OAc, which were treated with fuming nitric acid in acetic anhydride to lead to the aromatic nitro

(1) Capon, B.; McManus, S. P. "Neighboring Group Participation", Vol. 1; Plenum Press: New York and London, 1976.
(2) le Noble, W. J. "Highlights of Organic Chemistry", Marcel Dekker: New York, 1974; Chapter 20.
(3) Pastro, D. J.; Serve, M. P. *J. Am. Chem. Soc.*, **1965**, *87*, 1515–1521. Also, Ward, H. R.; Sherman, Jr., P. D. *ibid.*, **1968**, *90*, 3812-3817.
(4) Similar participation was reported in Oae, S. *J. Am. Chem. Soc.* **1956**, *78*, 4030.
(5) Gassman, P. G.; Marshall, J. L. *J. Am. Chem. Soc.* **1966**, *88*, 2599. Gassman, P. G.; Marshall, J. L.; Hornback, J. M. *Ibid.* **1969**, *91*, 5811–5817.
(6) Bender, M. L.; Silver, M. S. *J. Am. Chem. Soc.* **1962**, *84*, 4589–4590. Bender, M. L.; Reinstein, J. A.; Silver, M. S.; Mikulak, R. *Ibid.* **1965**, *87*, 4545–4553 and references cited therein. Kemp, K. C.; Mieth, M. L. *Chem. Commun.* **1969**, 1260–1261. Bowden, K.; Taylor, G. R. *Ibid.* **1967**, 1112–1113.
(7) Irie, T.; Tanida, H. *J. Org. Chem.* **1979**, *44*, 325–330.

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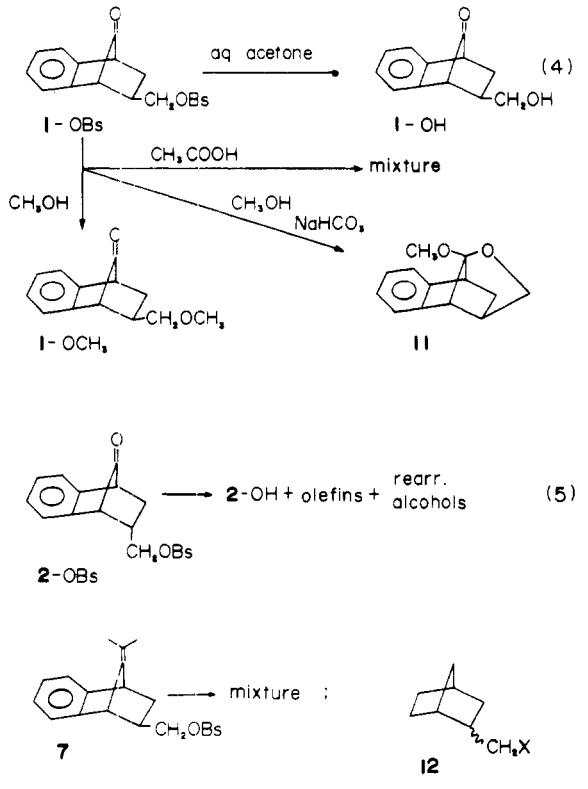
Scheme III



derivatives **9** and **10**. The nitro groups are believed to be at one of the positions β to the bornane moiety.[8] A similar introduction of a nitro group to the β positions was recently used in our study.[9] Acid hydrolyses of **9**-OAc and **10**-OAc followed by esterifications with *p*-bromobenzenesulfonyl chloride or trifluoromethanesulfonic anhydride yielded **9**-OBs, **10**-OBs, and **10**-OTf, respectively.

Hydrolyses and Acetolyses. Solvolyses of 1-OBs in 70–90% aqueous acetone were found to proceed with formation of a single product in nearly quantitative yield. The product was identified as 1-OH of retained structure by comparison of IR spectra and GLC with an authentic sample (eq 4). The absence of other detectable products was confirmed by TLC. In contrast, the reactions of the endo epimer, **2**-OBs, required severe conditions and the product composition was not simple. In a run (in 60% aqueous acetone at 120 °C for 60 h), five products were observed by TLC. VPC analyses indicated that they were **2**-OH of retained configuration in about 40% yield, olefins, and traces of rearranged alcohols (eq 5). Attempts were made to characterize the olefins, but without success. Their high volatilities caused serious technical difficulties in separation and isolation. In the same solvent at 180 °C for 0.5 h the amounts of rearranged alcohols were increased, but still minor. Worthy of note was the fact that the acetolysis of 1-OBs was no longer simple and gave several kinds of products. Also, acetolysis of **2**-OBs gave a mixture of products. A related compound, the 9-isopropylidene brosylate (**7**), was hydrolyzed in aqueous acetone and gave a mixture of products.

Methanolyses. Solvolysis of 1-OBs in absolute methanol gave predominantly the corresponding ether, 1-OCH_3 (Scheme III). However, when this reaction was carried out in the presence of sodium bicarbonate to eliminate the action of the forming bromobenzenesulfonic acid, the product was predominantly the intramolecularly cyclized ketal **11**, the structure of which was determined mainly by ^1H and ^{13}C NMR (see Experimental Section). Treatment of **11** by *p*-toluenesulfonic acid in water afforded 1-OH quantitatively. On the other hand, 1-OCH_3 proved to be stable upon treatment with acid or sodium bicarbonate, even when warmed at 100 °C for 20 h in methanol with or without them.

Rates of solvolyses of 1-OBs, **2**-OBs, **9**-OBs, **10**-OBs, and reference compounds were determined by titration of the produced *p*-bromobenzenesulfonic acid. Hydrolysis in aqueous acetone and trifluoroethanolysis were carried out without addition of base. Acetolysis and formolysis were performed in buffered media (in the presence of an equivalent amount of sodium salt of the corresponding acid).[10] Theoretical infinity values were obtained in all runs after about 10 half-lives at the reaction temperature. The rate constants and activation parameters obtained are listed in Tables I and II. For discussion, the observed rates were extrapolated to 100 °C and the exo/endo rate ratios ($k_{1\text{-OBs}}/k_{2\text{-OBs}}$ and $k_{9\text{-OBs}}/k_{10\text{-OBs}}$) were calculated. As reference compounds, isobutyl brosylate and triflate were solvolyzed in the same solvents, and their rates are listed in Table III.

Discussion

The most significant observation in this study is that the reaction process of 1-OBs in aqueous acetone is unusually simple and affords only an alcohol with configuration retention, 1-OH (eq 4). The reaction of epimer **2**-OBs is not as simple and is accompanied by eliminations (olefins) and rearrangements (eq 5). A related system may be (norborn-*exo*-and -*endo*-2-yl)methyl derivatives (**12** in Scheme III). A detailed study by Berson et al. of carbonium ion reactions in this sytem showed that the process consisted almost entirely of ring-enlarging rearrangements (conversion of the [2.2.1] system into [3.2.1] or [2.2.2].[11] We also found that solvolysis of the 9-isopropylidene compound, **7**, in aqueous acetone resulted in a complex mixture of products. These data imply that the simple product formation in the solvolysis of 1-OBs is due to the presence of the 9-keto group if it takes a proper conformation. However, when 1-OBs was solvolyzed in glacial acetic acid, the product was no longer simple but a mixture.

Effects of solvents on the exo/endo rate ratios are presented in Table I. The ratios are significantly large in 70–90% aqueous acetone, being in the order of 2×10^2 at 100 °C. However, they decrease with decreasing nucleophilicities of the solvents. In 97% trifluoroethanol, the ratio is 31. In acetic acid and formic acid, the exo rate is not much different from the endo rate; $k_{exo}/k_{endo} = 3.0$ (acetic acid), 0.36 (formic acid). The disappearance of product simplicity in the acetolysis of 1-OBs parallels that of the diminishing rate ratio. Looking at the reaction centers, 1-OBs and **2**-OBs can be regarded as isobutyl derivatives. Thus, isobutyl brosylate was solvolyzed in the same solvents, as presented in Table III. When logarithms of the rates at 100 °C of 1-OBs and **2**-OBs were plotted against logarithms of the rates of isobutyl brosylate (Figure 1), a linear relationship was found between the rates of **2**-OBs and those of isobutyl brosylate. This linearity and

(8) (a) Tanida, H.; Muneyuki, R. *J. Am. Chem. Soc.* **1965**, *87*, 4794–4804. (b) Tanida, H.; Ishitobi, H.; Irie, T.; Tsushima, T. *Ibid.* **1969**, *91*, 4512–4520. (c) Tanida H.; Ishitobi, H. *Tetrahedron Lett.* **1964**, 807–811.

(9) Irie, T.; Tanida, H. *J. Org. Chem.* **1979**, *44*, 1002–1003.

(10) Regarding the standard procedure for rate measurements, see Tanida, H.; Yamamoto, S.; Takeda, K. *J. Org. Chem.* **1973**, *38*, 2077–2084, 2792–2797.

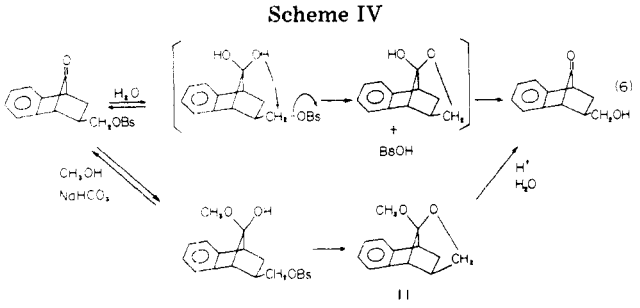
(11) Berson, J. A.; Reynolds-Warnhoff, P. *J. Am. Chem. Soc.* **1964**, *86*, 595–609. Berson, J. A.; Willner, D. *Ibid.* **1964**, *86*, 609–616; *Angew. Chem. Int. Ed. Engl.*, **1968**, *7*, 779–791.

Table I. Solvolysis Rates of (9-Ketobenzonorbornen-*exo*- and *endo*-2-yl)methyl (1 and 2) Brosylates (Triflates) and Exo/Endo Rate Ratios[a]

compd	solvent	temp, °C	k_1, s^{-1}	$\Delta H^{\ddagger}$, kcal/mol^{-1}	$\Delta S^{\ddagger}$, eu	$k_{exo/endo}$ 100 °C
exo-OBs	$(CH_3)_2CO-H_2O$					
	70[b]	100	$(7.75 \pm 0.22) \times 10^{-4}$	14.3	−34.9	274
		75	$(1.81 \pm 0.07) \times 10^{-4}$			
	80[b]	100	$(3.56 \pm 0.07) \times 10^{-4}$	13.0	−39.9	262
		75	$(9.41 \pm 0.30) \times 10^{-5}$			
	90[b]	125	$(3.38 \pm 0.11) \times 10^{-4}$	12.7	−43.1	251
		100	$(1.08 \pm 0.06) \times 10^{-4}$			
	$CF_3CH_2OH-H_2O$					
	97[c]	150	$(2.04 \pm 0.04) \times 10^{-4}$	14.2	−42.7	31
		125	$(6.67 \pm 0.34) \times 10^{-5}$			
		100	1.89×10^{-5} [d]			
	CH_3COOH	150	$(6.17 \pm 0.71) \times 10^{-5}$	25.5	−18.3	3.0
		125	$(8.66 \pm 0.20) \times 10^{-6}$			
		100	9.38×10^{-7} [d]			
	HCOOH	100	8.76×10^{-6} [e]			
exo-OTf	HCOOH	45	$(1.18 \pm 0.04) \times 10^{-4}$	19.3	−15.7	0.36
		70	$(1.19 \pm 0.04) \times 10^{-3}$			
		100	1.27×10^{-2} [d]			
endo-OBs	$(CH_3)_2CO-H_2O$					
	70[a]	150	$(1.60 \pm 0.09) \times 10^{-4}$	24.5	−18.6	
		125	$(2.41 \pm 0.16) \times 10^{-5}$			
		100	2.83×10^{-6} [d]			
	80[b]	165	$(2.03 \pm 0.09) \times 10^{-4}$	24.2	−21.0	
		140	$(3.56 \pm 0.15) \times 10^{-5}$			
		100	1.36×10^{-6} [d]			
	90[b]	175	$(1.18 \pm 0.04) \times 10^{-4}$	25.0	−21.5	
		150	$(2.12 \pm 0.12) \times 10^{-5}$			
		100	4.30×10^{-7} [d]			
	$CF_3CH_2OH-H_2O$					
	97[c]	150	$(2.54 \pm 0.14) \times 10^{-5}$	22.7	−26.7	
		125	$(4.40 \pm 0.15) \times 10^{-6}$			
		100	6.05×10^{-7} [d]			
	CH_3COOH	150	$(3.45 \pm 0.17) \times 10^{-5}$	28.8	−11.7	
		125	$(3.79 \pm 0.04) \times 10^{-6}$			
		100	3.11×10^{-7} [d]			
	HCOOH	100	2.41×10^{-5} [e]			
endo-OTf	HCOOH	45	$(1.54 \pm 0.02) \times 10^{-4}$	22.6	−5.1	
		70	$(2.24 \pm 0.11) \times 10^{-3}$			
		100	3.49×10^{-2} [d]			

[a] Error limits for rate constants are 95% confidence limits [degree of freedom, $f = n - 2$]. $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ were calculated by the Eyring equation. [b] Volume % of first named component. [c] Weight % of first named component. [d] Extrapolated from the observed rate. [e] Derived from the rate of triflate at 100 °C using the k_{OTf}/k_{OBs} rate ratio (1.45×10^3 at 100 °C) which was obtained from isobutyl brosylate and triflate.

Scheme IV



slope of near unity (1.02) suggest similar mechanisms for both the brosylates. Such a line through all six points does not exist between the rates of 1-OBs and those of isobutyl brosylates. Instead, a likely change of mechanism for solvolysis of 1-OBs in nucleophilic solvents compared to nonnucleophilic solvents is demonstrated in Figure 1. Activation parameters in Table I also appear to reflect this change in mechanism. The $\Delta S^{\ddagger}$ of 1-OBs in nucleophilic solvents are exceptionally large negative and differ markedly from those in nonnucleophilic solvents. Thus, the results obtained from 1-OBs led us to propose the mechanism outlined in eq 6 (Scheme IV), which involves transformation of the 9-keto group into the diol with addition of water (hydration equilibrium of a carbonyl

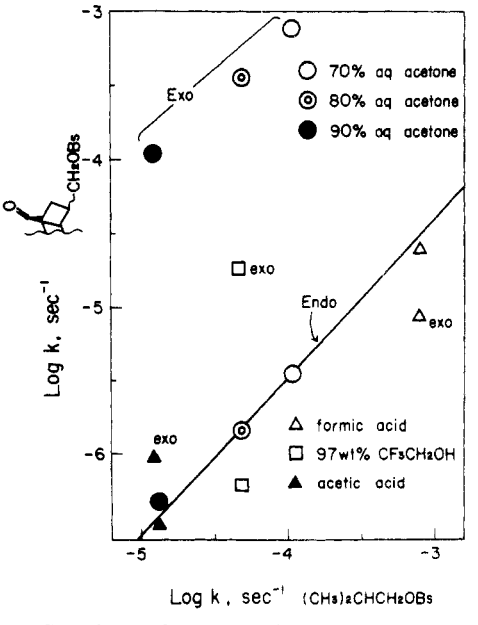


Figure 1. Correlation between solvent effects on rates of (9-ketobenzonorbornen-*exo*- and -*endo*-2-yl)methyl (1 and 2) brosylates and those of isobutyl brosylate at 100 °C: regression line for 2 shows slope of 1.02 and correlation coefficient of 0.976.

Table II. Solvolysis Rates of Aromatic Nitro Derivatives of (9-Ketobenzonorbornen-*exo*- and -*endo*-2-yl)methyl (9 and 10) Brosylates[a]

compd	solvent	temp, °C	k_1, s^{-1}	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, eu	$k_{exo/endo}$ 100 °C
exo	$(CH_3)_2CO$-H_2O					
	70[b]	100	$(1.60 \pm 0.06) \times 10^{-3}$	12.2	−39.0	442
		75	$(4.56 \pm 0.24) \times 10^{-4}$			
	80[b]	100	$(7.98 \pm 0.44) \times 10^{-4}$	11.8	−41.5	
		75	$(2.37 \pm 0.04) \times 10^{-4}$			
	90[b]	125	$(8.21 \pm 0.21) \times 10^{-4}$	11.4	−44.6	
		100	$(2.93 \pm 0.13) \times 10^{-4}$			
endo	70[b]	150	$(1.64 \pm 0.03) \times 10^{-4}$	23.1	−21.8	
		125	$(2.74 \pm 0.10) \times 10^{-5}$			
		100	3.62×10^{-6} [c]			

[a] Error limits for rate constants are indicated in footnote *a* in Table I. [b] Volume % of first named component. [c] Extrapolated from the observed rates.

Table III. Solvolysis Rates of Isobutyl Brosylate (Triflate or Tosylate)[a]

compd	solvent	temp, °C	k_1, s^{-1}	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, eu
OBs	$(CH_3)_2CO$-H_2O				
	70[b]	125	$(6.83 \pm 0.41) \times 10^{-4}$	21.5	−19.7
		100	$(1.04 \pm 0.03) \times 10^{-4}$		
	80[b]	125	$(3.30 \pm 0.16) \times 10^{-4}$	22.0	−19.8
		100	$(4.80 \pm 0.14) \times 10^{-5}$		
	90[b]	125	$(9.58 \pm 0.46) \times 10^{-5}$	22.9	−19.9
		100	$(1.29 \pm 0.07) \times 10^{-5}$		
	CF_3CH_2OH-H_2O				
	97[c]	125	$(3.42 \pm 0.12) \times 10^{-4}$	22.4	−18.7
		100	$(4.81 \pm 0.10) \times 10^{-5}$		
	CH_3COOH	125	$(1.45 \pm 0.09) \times 10^{-4}$	28.5	−5.2
		100	$(1.22 \pm 0.07) \times 10^{-5}$		
	HCOOH	45	$(2.17 \pm 0.02) \times 10^{-6}$	24.6	−7.3
		70	$(3.98 \pm 0.07) \times 10^{-5}$		
		100	7.86×10^{-4} [d]		
OTf	HCOOH	15	$(3.38 \pm 0.12) \times 10^{-4}$	19.8	−5.8
		40	$(5.78 \pm 0.06) \times 10^{-3}$		
		100	1.14[d]		
OTs	CH_3COOH	99.68	3.79×10^{-6} [e]	28.2[e]	−8.0[e]
		74.71	2.30×10^{-7} [e]		

[a] Errors limits for rate constants are indicated in footnote *a* in Table I. [b] Volume % of first named component. [c] Weight % of first named component. [d] Extrapolated from the observed rates. [e] S. Winstein and H. Marshall, *J. Am. Chem. Soc.*, **1952**, *74*, 1120.

compound) followed by participation of the thus-formed hydroxyl group with the cationic reaction center (the transition state involves a five-membered ring) leading to an intramolecularly cyclized hemiketal intermediate.[12] Participation of this type is geometrically impossible for **2**-OBs. In order to isolate an intermediate of the proposed type, methanolysis of **1**-OBs was undertaken with the idea that the methanolysis will proceed via a ketal instead of the above hemiketal and, in general, ketals are stable toward hydrolysis in alkaline solution. Thus, the ketal **11** was successfully isolated from the methanolysis in the presence of sodium bicarbonate, which was added to neutralize the forming sulfonic acid, and then it was quantitatively converted into **2**-OH by treatment with *p*-toluenesulfonic acid in water. This experimental success strongly supports the above mechanism.

The equilibrium constant for addition of water to the carbonyl group is favored with highly electronegative groups.[13] Therefore, if the hydration equilibrium (eq 6) is important in the solvolysis of **1**-OBs, introduction of an electronegative nitro substituent into the benzo moiety of **1**-OBs might favor water addition to form the diol and, consequently, accelerate the solvolysis rate by participation of the diol hydroxyl group. But such an acceleration should be absent in the endo solvolyses. We indeed found that the rate of nitro derivative, **9**-OBs, in 70% aqueous acetone is 1.7 times faster than that of the parent **1**-OBs (Table II), in spite of increased electronegative inductive effects due to the nitro introduction. In contrast, only a slight change was observed between the rates of **2**-OBs and **10**-OBs. Therefore, the exo/endo rate ratio increases from 274 for the parent **1**- and **2**-OBs to 442 for the nitro **9**- and **10**-OBs. Thus, it can be concluded that the present exo brosylates, when highly nucleophilic aqueous acetone is used, are solvolyzed via the participation mechanism, shown in eq 6, with rate acceleration and simple product formation.

Experimental Section

Melting points were taken by capillary and are corrected. Infrared spectra were determined with a 215 Hitachi grating infrared spectrometer, ^1H NMR spectra with a Varian T-60A, ^{13}C NMR spectra with a Varian NV-14 at 15.087 MHz, and mass spectra with a Hitachi RMU-6 spectrometer.

(9-Isopropylidenebenzonorbornen-*exo*-2-yl)methanol (5). A solution of 4.3 g (17.8 mmol) of methyl 9-isopropylidenebenzonorbornene-*exo*-2-carboxylate (**3**)[7] in dry ether was treated with 1.35 g (35.6 mmol) of lithium aluminum hydride. The usual workup gave 3.8 g of **5**: mp 92–93 °C (from hexane–ether); IR ($CHCl_3$) 3600 cm^{-1} (OH); ^1H NMR ($CDCl_3$) δ 1.7 (s, 6, CH_3), 1.2–2.2 (m, 3, C_2C_3), 3.6 (m, 1, at C_4), 3.7 (br s, 1, C_1), 3.8 (m, 2, CH_2OH), and 7.20 (4, aromatic). Anal. Calcd for $C_{15}H_{18}O$: C, 84.07; H, 8.47. Found: C, 84.10; H, 8.38.

(12) The present type of mechanism was considered for the solvolysis of 7-ketonorborn-2-yl tosylates, but rejected. Gassman, P. G.; Marshall, J. L. *J. Am. Chem. Soc.* **1965**, *87*, 4648–4649.

(13) For example, see Carey, F. A.; Sundberg, R. J. "Advanced Organic Chemistry", Part A; Plenum Press: New York, 1977, pp 326–328.

(9-Isopropylidenebenzonorbornen-*endo*-2-yl)methanol (6) was similarly prepared from the epimer carboxylate 4[7] and showed: mp 119–120 °C; IR ($CHCl_3$) 3620 cm^{-1} (OH); ^1H NMR ($CDCl_3$) δ 0.7 (m, 1, C_3 endo), 1.7 (s, 6, CH_3), ~2.1 (m, 1, C_3 exo), 2.9 (m, 1, C_2), 3.30 (m, 2, CH_2OH), 3.8 (m, 1, C_4), 3.95 (m, 1, C_1), and 7.2 (4, aromatic). Anal. Calcd for $C_{15}H_{18}O$: C, 84.07; H, 8.47. Found: C, 84.25; H, 8.53.

(9-Isopropylidenebenzonorbornen-*exo*-2-yl)methyl *p*-bromobenzenesulfonate (7): mp 137–138 °C (from ether); ^1H NMR ($CDCl_3$) δ 1.2–2.2 (m, 3, C_2C_3), 1.5 (s, 3, CH_3), 1.6 (s, 3, CH_3), 3.8 (m, 2, C_1C_4), 4.0 (m, 2, CH_2OBs), 7.2 (4, benzo), and 7.8 (4, OBs). Anal. Calcd for $C_{21}H_{21}O_3BrS$: C, 58.20; H, 4.88; Br, 18.44; S, 7.40. Found: C, 58.31; H, 4.93; Br, 18.49; S, 7.26.

(9-Isopropylidenebenzonorbornen-*endo*-2-yl)methyl *p*-bromobenzenesulfonate (8): mp 129–130 °C; ^1H NMR ($CDCl_3$) δ 0.6 (m, 1, C_3endo), 1.5 (s, 6, CH_3), ~2.1 (m, 1, C_3 exo), 3.1 (m, 1, C_2), 3.6–3.9 (m, 4, C_1, C_4, and CH_2OBs), 7.0 (4, benzo), and 7.7 (4, OBs). Anal. Calcd for $C_{21}H_{21}O_3BrS$: C, 58.20; H, 4.88; Br, 18.44; S, 7.40. Found: C, 58.38; H, 4.99; Br, 18.16; S, 7.33.

(9-Ketobenzonorbornen-*exo*-2-yl)methyl *p*-Bromobenzenesulfonate (1-OBs). Ozone was absorbed at −20 °C by a solution of 1 g of 7 in 14 mL of dichloromethane. The usual workup gave a crude ketone which was purified by elution chromatography (silica gel, benzene) followed by recrystallization from dichloromethane–hexane: mp 145–146 °C; IR ($CHCl_3$) 1790 cm^{-1} (CO); ^1H NMR ($CDCl_3$) δ 1.6–1.9 (m, 3, C_2, C_3), 3.3 (m, 1, C_1), 3.4 (m, 1, C_4), 4.2 (m, 2, CH_2OBs), 7.3 (4, benzo), and 7.8 (4, OBs). Anal. Calcd for $C_{18}H_{15}O_4BrS$: C, 53.08; H, 3.71; Br, 19.62; S, 7.87. Found: 53.05; H, 3.80; Br, 19.88; S, 7.81.

(9-Ketobenzonorbornen-*endo*-2-yl)methyl *p*-bromobenzenesulfonate (2-OBs) was similarly prepared by ozone oxidation of 8: mp 107–108 °C; IR ($CHCl_3$) 1790 cm^{-1} (CO); ^1H NMR ($CDCl_3$) δ 0.8 (m, 1, C_3 endo), 2.4 (m, 1, C_3 exo), 3.2 (m, 1, C_2), 3.2–3.8 (m, 4, C_1, C_4, and CH_2OBs), 7.2 (4, benzo), and 7.7 (4, OBs). Anal. Calcd for $C_{18}H_{15}O_4BrS$: C, 53.08; H, 3.71; Br, 19.62; S, 7.87. Found: C, 53.06; H, 3.72; Br, 19.59; S, 8.08.

(9-Isopropylidenebenzonorbornen-*exo*-2-yl)methyl acetate was obtained by treatment of 5 with acetic anhydride in pyridine: mp 91–92 °C (from hexane). Anal. Calcd for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86; O, 12.48. Found: C, 79.50; H, 7.94; O, 12.72.

(9-Isopropylidenebenzonorbornen-*endo*-2-yl)methyl acetate was derived from 6: mp 62–63 °C (from hexane). Anal. Calcd for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86; O, 12.48. Found: C, 79.64; H, 7.85; O, 12.50.

(9-Ketobenzonorbornen-*exo*-2-yl)methyl Acetate (1-OAc). Ozone was absorbed at −20 °C by a solution of 150 mg of the above acetate in 6 mL of dichloromethane. The usual workup gave a crude ketone which was purified by elution chromatography (silica gel, benzene) followed by recrystallization from ether–hexane: mp 82–83 °C; IR ($CHCl_3$) 1740 cm^{-1} ($COOCH_3$) and 1790 (CO); ^1H NMR ($CDCl_3$) δ 1.6–2.0 (m, 3, C_2, C_3), 2.1 (s, 3, OAc), 3.2–3.4 (m, 2, C_1, C_4), 3.8–4.5 (m, 2, CH_2OAc), and 7.2 (4, aromatic). Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.02; H, 6.13. Found: C, 72.92; H, 6.16.

(9-Ketobenzonorbornen-*endo*-2-yl)methyl acetate (2-OAc) was prepared in the same way and showed: mp 60–61 °C; IR ($CHCl_3$) 1740 cm^{-1} (OAc) and 1790 (CO); ^1H NMR ($CDCl_3$) δ 0.9 (m, 1, C_3 endo), 2.1 (s, 3, OAc), ~2.4 (m, 1, C_3 exo), ~2.5 (m, 1, C_2), 3.2–3.9 (m, 4, C_1, C_4, and CH_2OAc), and 7.3 (4, aromatic). Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.02; H, 6.13. Found: C, 72.86; H, 6.09.

(9-Ketobenzonorbornen-*exo*-2-yl)methanol (1-OH) was obtained by treatment of 1-OAc with *p*-toluenesulfonic acid in water and showed: mp 83.5–84.5 °C (from ether–hexane); IR ($CHCl_3$) 1790 cm^{-1} (CO); ^1H NMR ($CDCl_3$) δ 2.2 (br s, 1, OH), 1.5–2.1 (m, 3, C_2, C_3), 3.4 (m, 2, C_1, C_4), 3.8 (m, 2, CH_2OH), and 7.3 (4, aromatic). Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.33; H, 6.43.

Nitrations of 1-OAc and 2-OAc. To a solution of 266 mg of 1-OAc in 2 mL of acetic anhydride was added dropwise a solution of 440 mg of fuming nitric acid under ice cooling. The reaction mixture was allowed to stand overnight and then poured into chilled water and extracted with ether. The ether solution was washed with aqueous sodium bicarbonate and water, dried, and evaporated, leaving 277 mg of crystals. Recrystallization from ether gave the nitro acetate 9-OAc: mp 100–105 °C; IR ($CHCl_3$) 1350 and 1530 cm^{-1} (NO_2), 1745 (OAc), and 1800 (CO); ^1H NMR ($CDCl_3$) δ 1.7–2.1 (m, 3, C_2, C_3), 2.2 (s, 3, OAc), 3.5–3.7 (m, 2, C_1, C_4), 3.9–4.7 (m, 2, CH_2OAc), 7.5–7.7 (m, 1, aromatic β to NO_2), and 8.1–8.4 (m, 2, aromatic α to NO_2). Anal. Calcd for $C_{14}H_{13}O_5N$: C, 61.09; H, 4.76; N, 5.09; O, 29.06. Found: C, 61.01, H, 4.75; N, 5.01; O, 29.21. This acetate was hydrolyzed by warming with *p*-toluenesulfonic acid in water to give oily alcohol 9-OH: IR ($CHCl_3$) 1350 and 1520 cm^{-1} (NO_2), 1800 (CO), and 3500–3600 (OH).

Nitration of 2-OAc was performed in the same way. The nitro acetate 10-OAc showed: mp 88–95 °C (from ether); IR ($CHCl_3$) 1350 and 1520 cm^{-1} (NO_2), 1740 (OAc), and 1795 (CO); ^1H NMR ($CDCl_3$) δ 0.9 (m, 1, C_3 endo), 2.1 (s, 3, OAc), ~2.4 (m, 1, C_3 exo), 2.5 (m, 1, C_2), 3.2–3.9 (m, 4, C_1, C_4, and CH_2OAc), 7.4–7.7 (m, 1, aromatic β to NO_2), and 8.1–8.3 (m, 2, aromatic α to NO_2). Anal. Calcd for $C_{14}H_{13}O_5N$: C, 61.09; H, 4.76; N, 5.09; O, 29.06. Found: C, 60.99; H, 4.76; N, 5.07; O, 29.28. The alcohol 10-OH: oil; IR ($CHCl_3$) 1520 and 1350 cm^{-1} (NO_2), 1800 (CO), and 3550–3600 (br OH).

The nitro *exo*-brosylate (9-OBs) showed: mp 120–123 °C (from CH_2Cl_2–hexane); IR ($CHCl_3$) 1350 and 1525 cm^{-1} (NO_2) and 1800 (CO); ^1H NMR ($CDCl_3$) δ 1.5–2.0 (m, 3, C_2, C_3) 3.4–3.7 (m, 2, C_1, C_4), 4.1–4.4 (m, 2, CH_2OBs), 7.7–7.9 (m, 1, aromatic β to NO_2), and 8.1–8.4 (m, 2, aromatic α to NO_2). Anal. Calcd for $C_{18}H_{14}O_6BrSN$: C, 47.80; H, 3.12; Br, 17.67; N, 3.10. Found: C, 47.86; H, 3.00; Br, 17.71; N, 3.07.

The nitro *endo*-brosylate (10-OBs) showed: mp 75–80 °C (from CH_2Cl_2–hexane); IR ($CHCl_3$) 1350 and 1520 cm^{-1} (NO_2) and 1800 (CO); ^1H NMR ($CDCl_3$) δ 0.8 (m, 1, C_3 endo), 2.2–2.8 (overlapping m, 2, C_2, C_3 exo), 3.1–3.9 (m, 4, C_1, C_4, and CH_2OBs), 7.7–7.9 (m, 1, aromatic β to NO_2), and 8.1–8.3 (m, 2, aromatic α to NO_2). Anal. Calcd for $C_{18}H_{14}O_6BrSN$: C, 47.80; H, 3.12; Br, 17.67; N, 3.10. Found: C, 47.76; H, 3.04; Br, 17.96; N, 3.14.

The nitro *endo*-triflate (10-OTf) was prepared by treatment with trifluoromethanesulfonic anhydride in dichloromethane–pyridine and showed mp 67–68 °C (from hexane). Anal. Calcd for $C_{13}H_{11}O_4F_3S$: C, 48.75; H, 3.45. Found: C, 49.14; H, 3.16.

Hydrolysis Products from 1-OBs. A solution of 163 mg of **1-OBs** in 20 mL of 70% aqueous acetone was sealed into an ampule which was warmed at 110 °C for 2 h. The reaction mixture was concentrated under reduced pressure, neutralized with sodium bicarbonate, and extracted with ether. The ether solution was washed with water, dried, and evaporated, leaving 73 mg of crystals (97% yield) of 1-OH, which was identified with the above-described sample. Thin-layer chromatography and VPC indicated no other product.

Hydrolysis Products from 2-OBs. A solution of 325.8 mg of 2-OBs in 40 mL of 60% aqueous acetone was sealed into an ampul which was warmed at 120 °C for 60 h. The reaction mixture was concentrated under reduced pressure and extracted with ether. The ether solution was washed with aqueous sodium bicarbonate and water, dried, and evaporated, leaving 168.8 mg of a residue (oil). Thin-layer chromatography showed at least five components. VPC analysis showed the most important peak was 2-OH (BDS 15 m, 150 °C, retention time of 13 min), and showed the existence of olefins and traces of other alcohols. The yield of 2-OH was estimated as 40% by VPC (1% XE60 1 m, 140 °C) using an internal reference (*n*-docosane, $CH_3(CH_2)_{20}CH_3$). Acetylation of the above residue followed by VPC analysis showed 2-OAc as the most important compound. Although the olefins and 2-OH were separated on preparative layer chromatography, isolation and purification of the olefins were unsuccessful because of the high volatilities. In a run, the above residue was treated with sodium borohydride in ether–methanol to reduce the carbonyl group, which might be a factor of the volatilities. However, the olefinic components on preparative layer chromatography extracted by ether were run away with solvent evaporation.

The hydrolysis of 2-OBs was carried out in 60% aqueous acetone at 180 °C for 0.5 h. VPC analysis of the products showed the formation of 2-OH and other alcohols in an approximate ratio of 2:1, besides olefins.

Methanolysis Products from 1-OBs. (i) A solution of 550 mg of 1-OBs in 25 mL of methanol was sealed into an ampule which was warmed at 100 °C for 20 h. After evaporation of the solvent, the residue was extracted with dichloromethane. The dichloromethane solution was washed with aqueous sodium bicarbonate and water, dried, and evaporated, leaving 238 mg

(86%) of an oil. Treatment of the oil by preparative layer chromatography (benzene–ethyl acetate 3:1) gave 190 mg of 1-OMe and 20 mg of the intramolecularly cyclized ketal [*endo*-2-methoxy-3-oxa-7,8-benzotricyclo[4.2.1^{1,5}.0^{2,6}]non-7-ene (**11**)]. (ii) A solution of 209 mg of 1-OBs in 10 mL of methanol and 210 mg of powdered $NaHCO_3$ were sealed into an ampule and warmed at 100 °C for 20 h. The same workup as above gave 100 mg (98%) of an oil. Treatment by preparative layer chromatography yielded 5 mg of 1-OMe and 85 mg of 11. Treatment by *p*-toluenesulfonic acid in water converted the major 11 into 1-OH. The ether 1-OMe showed: IR ($CHCl_3$) 1790 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$) δ 1.5–2.2 (m, 3, C_2, C_3), 3.4 (s, 3, OCH_3), 3.3–3.5 (m, 4, C_1, C_4, and CH_2OCH_3), and 7.4 (4, aromatic). The ketal 11 showed: *m/e* 202, M$^+$; ^{1}H NMR ($CDCl_3$) δ 1.1 (m, 1, C_3 exo), 2.2 (m, 1, C_3 endo), 2.3 (m, 1, C_2), 3.2 (m, 1, C_4), 3.3 (s, 3, OCH_3), 3.5 (br s, 1, C_1), 4.2 (m, 2, C_2–CH_2–O), and 7.2 (4, aromatic); ^{13}C NMR ($CDCl_3$) δ 49.3 (C-1), 36.8 (C-2), 35.0 (C-3), 51.2 (C-4), 138.3[a] (C-4a), 123.9[b] (C-5), 125.9[b] (C-6), 126.8[b] (C-7), 120.3[b] (C-8), 146.7[a] (C-8a), 126.8 (C-9), 77.1 (C_9–OCH_2–C_2), and 53.7 (OCH_3) (a and b may be exchanged).

Kinetic Measurements. For hydrolyses, aqueous acetone was prepared by mixing acetone and water by volume and a sample was dissolved at a concentration of 0.02 N. Portions (2.0 mL), placed in sealed tubes, were withdrawn after appropriate intervals of time and cooled. The rates were determined by titration of the forming sulfonic acid with 0.01 N sodium hydroxide using a Metrohm potentiograph E 336A. Hydrolyses in trifluoroethanol–water (97:3) were carried out in the same way. Acetolyses and formolyses were carried out by the standard procedure.[10]

Registry No. 1-OAc, 70969-18-5; 1-OBs, 70969-19-6; 1-OH, 70969-20-9; 1-OMe, 70969-21-0; 1-OTf, 70969-22-1; 2-OAc, 71030-45-0; 2-OBs, 71030-46-1; 2-OH, 71030-47-2; 2-OTf, 71030-48-3; 3, 68258-49-1; 4, 68330-61-0; 5, 70969-23-2; 6, 71030-49-4; 7, 70969-24-3; 8, 71030-50-7; 9-OAc, 70969-08-3; 9-OBs, 70969-09-4; 9-OH, 70969-10-7; 10-OAc, 71030-42-7; 10-OBs, 71030-43-8; 10-OH, 71030-44-9; 10-OTf, 71000-86-7; isobutyl brosylate, 70969-25-4; isobutyl triflate, 60306-25-4; isobutyl tosylate, 4873-56-7; (9-isopropylidenebenzonorbornen-*exo*-2-yl)methyl acetate, 70969-26-5; (9-isopropylidenebenzonorbornen-*endo*-2-yl)-methyl acetate, 71030-51-8; 11, 70969-27-6.

Diazotization of Nitroanthranilic Acids. Effect of Carboxyl Group on the Nucleophilic Ipso Substitution of the Nitro Group by Chloride Ion

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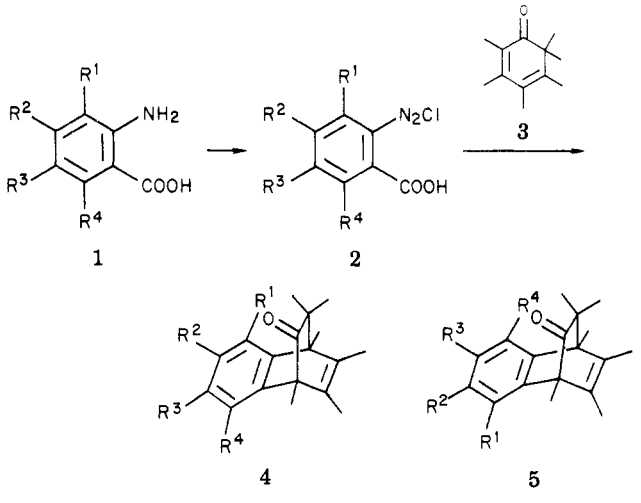
In the diazotization with isoamyl nitrite of four nitro-substituted anthranilic acids, i.e., 3- (**1b**), 4- (**1c**), 5- (**1d**), and 6-nitroanthranilic acid (**1a**), in the presence of hydrochloric acid, only **1a** undergoes a facile ipso nucleophilic substitution of the nitro group by chloride ion. Relative ease of substitution among **1a–d**, methyl 3-nitroanthranilate (**11**), and *o*-nitroaniline (**6**) reveals that the introduction of a carboxyl or methoxycarbonyl group to the 6-position of 6 accelerates the rate of substitution more than 10^2; this effect is ascribed to the buttressing effect of these groups against the adjacent diazonium group which in turn activates the nitro group by disturbing its coplanar conformation.

The nucleophilic substitution of aromatic nitro compounds has been known to take place when an electronegative substituent is present.[1-3] In studying the diazotization of four nitroanthranilic acids to be used as precursors of nitrobenzynes, we found that the diazotization of 3-nitroanthranilic acid (**1a**) resulted in the facile formation of 2-carboxy-6-chlorobenzenediazonium chloride (**2e**). Its formation could be interpreted in terms of nucleophilic substitution of the nitro group by chloride ion, but the rate of substitution was considerably faster than that in the case of *o*-nitroaniline (**6**), implying the presence of a rate-enhancing effect of the carboxyl group.

3-Nitrobenzenediazonium-2-carboxylate, a precursor of 3-nitrobenzyne, can be prepared as the hydrochloride (**2b**) from 6-nitroanthranilic acid (**1b**) by its reaction with isoamyl nitrite in the presence of hydrochloric acid. The structure of **2b** is verified in the forms of the corresponding Diels–Alder adducts **4b** and **5b** (Scheme I).[4] In contrast,

Scheme I



a, $R^1 = NO_2$; R^2-R^4 = H
b, $R^4 = NO_2$; R^1-R^3 = H
c, $R^2 = NO_2$; $R^1 = R^3 = R^4$ = H
d, $R^3 = NO_2$; $R^1 = R^2 = R^4$ = H
e, R^1 = Cl; R^2-R^4 = H

an analogous attempt to prepare 2-carboxy-6-nitrobenzenediazonium hydrochloride (**2a**), the alternative precursor of 3-nitrobenzyne, from 3-nitroanthranilic acid (**1a**) was unsuccessful; however, a diazonium salt was

(1) (a) R. Oda and Z. Yoshida "Dai Yuki Kagaku", Vol. 9, Part I, M. Kotake, Ed., Asakura Shoten, Tokyo, 1963, p 104; (b) P. T. Izzo, *J. Org. Chem.*, **24**, 2026 (1959); (c) E. Havinga, R. O. de Jongh, and M. E. Kronenberg, *Helv. Chim. Acta*, **50**, 2550 (1967).

(2) (a) B. B. Dey, T. R. Govindachari, and S. C. Rajagopalan, *Curr. Sci.*, **15**, 161 (1946) [*Chem. Abstr.*, **40**, 7174 (1946)]; (b) B. B. Dey, R. Krishna, and B. R. Pai, *J. Sci. Ind. Res.*, **10B**, 134, 140 (1951) [*Chem. Abstr.*, **47**, 3256 (1953)].

(3) (a) L. Sihlbom, *Acta Chem. Scand.*, **5**, 872 (1951); **7**, 790, 1197 (1953); (b) E. S. Lewis and H. Suhr, *J. Am. Chem. Soc.*, **82**, 862 (1960).

(4) A. Oku and A. Matsui, *Bull. Chem. Soc. Jpn.*, **50**, 3338 (1977).

0022-3263/79/1944-3342$01.00/0