Calcd for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 80.09; H, 9.43.

**5-(2-Ethylallyl)-1-methylbicyclo[3.3.1]non-2-en-4-one (13b).** Lithium diisopropylamide (4.25 mmol) was generated in dry THF (20 mL) at -20 °C and cooled to -78 °C. A solution of **11b** (0.90 g, 3.5 mmol) in dry THF (22 mL) was added dropwise over 25 min. After the resulting solution was stirred at -78 °C for 1 h, hexamethylphosphoramide (1.27 g, 7.08 mmol) was added. Stirring was continued at -78 °C for 15 min, and then the cooling bath was removed. The reaction mixture was allowed to warm to room temperature and was stirred for 26 h, after which water was added, and the solvent was removed under reduced pressure. The residue was partitioned between ether (40 mL) and water (20 mL). The combined aqueous layers were extracted with ether (2 × 20 mL). The combined organic extracts were washed with water (4 × 80 mL) and brine (1 × 100 mL) and dried over anhydrous magnesium sulfate. Evaporation of the solvent under reduced pressure provided a yellow oil (0.77 g, quantitative) which appeared to be of good purity by $^1$H NMR analysis. An analytical sample was prepared by HPLC (25:1 hexane–ethyl acetate): 0.6 g, (80%); $^1$H NMR $\delta$ 0.98 (t, 3 H, $J$ = 7 Hz), 1.13 (s, 3 H), 1.23–2.13 (m, 11 H), 2.83 (d, 1 H, $J$ = 16 Hz), 4.71 (d, 2 H, $J$ = 10 Hz), 6.1 (d, 1 H, $J$ = 10 Hz), 6.54 (dd, 1 H, $J$ = 10, 2 Hz); IR (neat) 1675, 1640 cm$^{-1}$; mass spectrum, $m/e$ 218 (M$^+$, 32), 203 (13), 189 (99), 41 (100); UV (MeOH) $\lambda_{max}$ 231 nm ($\epsilon$ 7400). Anal. Calcd for $C_{15}H_{22}O$: C, 82.51; H, 10.16. Found: C, 82.78; H, 10.13.

**5-(2-Ethylallyl)-1-methylbicyclo[3.3.1]nonan-4-one (14a).** A solution of enone **13b** (0.174 g, 0.8 mmol) in dry THF (10 mL) was cooled to -78 °C. K-Selectride (1 M, 0.88 mL) was added dropwise to the reaction mixture. The solution was stirred for 1 h at -78 °C and 1 h at 0 °C. Sodium hydroxide solution (3 N, 1.5 mL) was added, the cooling bath was removed, and hydrogen peroxide (30%, 0.5 mL) was slowly added. The resulting milky white suspension was stirred for 18 h at room temperature. The aqueous layer was separated and extracted with ether (3 × 15 mL). The combined organic fractions were washed with water (2 × 20 mL), 1 N $NaHSO_3$ solution (2 × 20 mL), and brine (2 × 20 mL) and dried over anhydrous magnesium sulfate. Removal of the solvent afforded **14a**, which was chromatographed on HPLC (25:1 hexane–ethyl acetate): 0.136 g (77% isolated yield); $^1$H NMR $\delta$ 0.98 (t, 3 H, $J$ = 7 Hz), 1.03 (s, 3 H), 1.17–2.87 (m, 16 H), 4.72 (d, 2 H, $J$ = 10 Hz); IR (neat) 1700 cm$^{-1}$; mass spectrum, $m/e$ 220 (M$^+$, 62), 191 (100), 163 (90). Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.57; H, 11.00.

**5-Methyl-2-oxo-1-(2-oxobutyl)bicyclo[3.3.1]nonane (14b).** A solution of ketone **14a** (0.093 g, 0.42 mmol) in dry methanol (50 mL) was cooled to -78 °C. Ozone was passed through the solution to saturation as evidenced by development of a deep blue coloration. The reaction mixture was stirred for 30 min at -78 °C, the cold bath was removed, and the mixture was stirred until the blue coloration disappeared. After 20 min, the mixture was recooled to -78 °C, and dimethyl sulfide (3 mL) was slowly added. The reaction mixture was gradually warmed to 0 °C over 1.5 h and stirred for an additional 4 h at 0 °C. After the mixture was stirred for 12 h, the solvent was distilled from the mixture under reduced pressure, and the residue was dissolved in ether (75 mL). The ether extract was washed with water (3 × 50 mL) and brine (1 × 50 mL) and dried over anhydrous magnesium sulfate. Removal of the solvent afforded crude diketone **14b**, which was chromatographed by HPLC (25:1 hexane–ethyl acetate) to give **14b**: 0.046 g (49%); $^1$H NMR $\delta$ 1.01 (t, 3 H, $J$ = 6 Hz), 1.03 (s, 3 H), 1.08–1.94 (m, 10 H), 2.22 (d, 1 H, $J$ = 16 Hz), 2.28–2.45 (m, 3 H), 2.78–3.01 (m, 1 H), 3.08 (d, 1 H, $J$ = 16 Hz); IR (neat) 1710 cm$^{-1}$ (lit.[8a,b] 1710 cm$^{-1}$); mass spectrum, $m/e$ 222 (M$^+$, 39), 207 (64), 193 (100). Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.98. Found: C, 75.63; H, 10.17.

**4-Demethylclov-4-en-3-one (15).** The diketone **14b** (0.028 g, 0.13 mmol) was reacted with KOH in refluxing methanol according to the published procedure.[8a,b] The product was purified by preparative TLC ($SiO_2$, 3:1 hexane–ethyl acetate) to give **15**: 0.016 g (63%); $^1$H NMR $\delta$ 0.90 (s, 3 H), 1.16–2.0 (m, overlapping s at 1.65, 13 H), 2.18 (d, 1 H, $J$ = 18 Hz), 2.28 (d, 1 H, $J$ = 18 Hz), 2.8 (m, 2 H); IR (neat) 1690, 1640 cm$^{-1}$ (lit. 1690, 1630 cm$^{-1}$); UV (EtOH) $\lambda_{max}$ 244 nm ($\epsilon$ 13 900) [lit. 244 (12 800)]. The 2,4-dinitrophenylhydrazone was isolated in the form of red plates: mp 221–223 °C (lit. mp 223–225 °C); UV ($CHCl_3$) $\lambda_{max}$ 395–399 nm ($\epsilon$ 30 400) [lit. 393–397 (30 800)]; $^1$H NMR $\delta$ 0.91 (s, 3 H), 1.19–2.04 (m overlapping s at 1.84, 13 H), 2.37 (d, 1 H, $J$ = 17 Hz), 2.48 (d, 1 H, $J$ = 17 Hz), 2.69 (m, 2 H), 7.37 (s, 1 H), 7.99 (d, 1 H, $J$ = 9.8 Hz), 8.26 (dd, 1 H, $J$ = 10, 2.5 Hz), 9.14 (d, 1 H, $J$ = 2.6 Hz).

**Acknowledgment.** This work was supported by the National Institute of General Medical Science (Grant No. GM 26568). We thank R. A. Raphael and J. S. Roberts for assistance with spectral data relating to the synthesis of *dl*-clovene. NMR spectra were recorded on a Varian XL-200 instrument purchased with funds provided, in part, by a National Science Foundation Department Instrumentation Grant.

**Registry No.** (±)-**9**, 3852-30-0; (±)-**10a**, 85909-15-5; (±)-**10b**, 85909-16-6; (±)-**11a**, 85909-17-7; (±)-*cis*-**11b**, 85909-18-8; (±)-*trans*-**11b**, 85909-19-9; (±)-**12a**, 85909-20-2; (±)-**12b**, 85909-21-3; (±)-**13a**, 85909-22-4; (±)-**13b**, 85909-23-5; (±)-**14a**, 85909-24-6; (±)-**14b**, 85909-25-7; (±)-**15**, 85909-26-8; (±)-**15** 2,4-dinitrophenylhydrazone, 85923-33-7; $ClSiMe_2$-*t*-Bu, 18162-48-6; 1-bromo-3-chloropropane, 109-70-6; 2-(bromomethyl)but-1-ene, 59032-45-0.

# Synthesis of Conformationally Defined Analogues of Norfenfluramine. A Highly Stereospecific Synthesis of Amines from Alcohols in the Benzobicyclo[2.2.1]heptene System[1a,b]

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*Received October 12, 1982*

The synthesis of 5-, 6-, 7-, and 8-(trifluoromethyl)benzonorbornen-2-yl alcohols **6a–9a** (exo) and **11a-14a** (endo) and an examination of the stereospecificity of the conversion to amines via phthalimides are reported. The exo alcohols were prepared from 5-(trifluoromethyl)benzonorbornadiene (**16**) and 6-(trifluoromethyl)benzonorbornadiene (**23**) by hydroboration–oxidation. The endo alcohols were available from the corresponding exo alcohols by oxidation to the benzonorbornen-2-ones **24** (5-$CF_3$), **25** (6-$CF_3$), **26** (7-$CF_3$), and **27** (8-$CF_3$) followed by diborane reduction. While in the presence of the electron-withdrawing $CF_3$ group the exo alcohols gave predominantly the endo amines, the endo alcohols afforded exclusively the exo amines.

As part of a search for the explanation of the dramatic pharmacological differences between amphetamine and its *m*-(trifluoromethyl)-*N*-ethyl analogue, fenfluramine (**1**, Chart I), and on the basis of our initial highly successful

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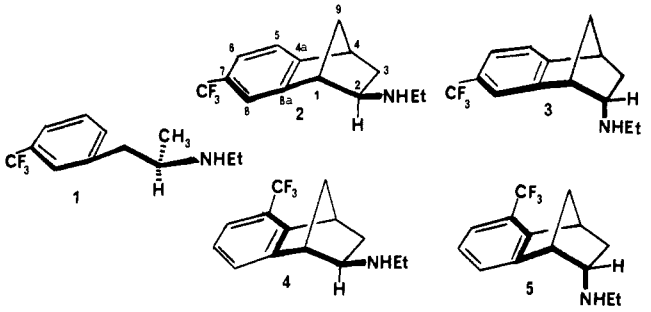
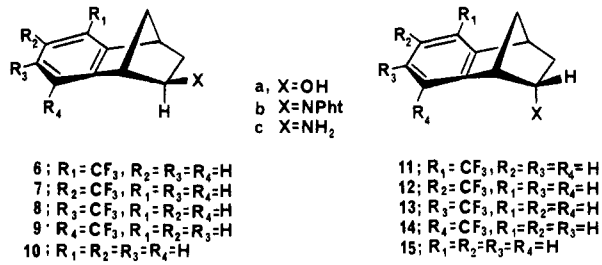
Chart I



use of conformationally defined analogues of amphetamine and methamphetamine,[2] we sought a convenient synthesis of conformationally defined analogues of **1** in the benzobicyclo[2.2.1]heptene skeleton (amines **2** and **4** represent fully extended, trans antiperiplanar conformations of fenfluramine, and amines **3** and **5** represent folded or gauche conformations). We describe in this paper the highly stereospecific synthesis of the bicyclic primary amines **6c–9c** and **11c–13c**, where amines **6c**, **8c**, **11c**, and



a, X=OH
b X=NPht
c X=$NH_2$

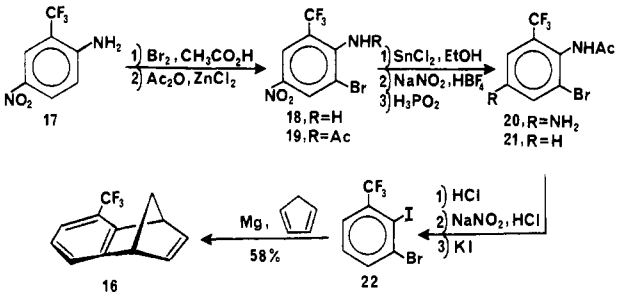
**6**; $R_1$=$CF_3$, $R_2$=$R_3$=$R_4$=H
**7**; $R_2$=$CF_3$, $R_1$=$R_3$=$R_4$=H
**8**; $R_3$=$CF_3$, $R_1$=$R_2$=$R_4$=H
**9**; $R_4$=$CF_3$, $R_1$=$R_2$=$R_3$=H
**10**; $R_1$=$R_2$=$R_3$=$R_4$=H

**11**; $R_1$=$CF_3$, $R_2$=$R_3$=$R_4$=H
**12**; $R_2$=$CF_3$, $R_1$=$R_3$=$R_4$=H
**13**; $R_3$=$CF_3$, $R_1$=$R_2$=$R_4$=H
**14**; $R_4$=$CF_3$, $R_1$=$R_2$=$R_3$=H
**15**; $R_1$=$R_2$=$R_3$=$R_4$=H

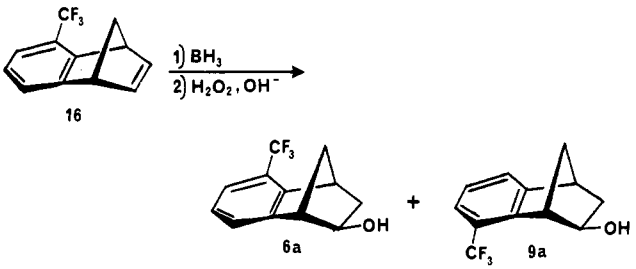
**13c** are conformationally defined analogues of *m*-(trifluoromethyl)amphetamine, amines **7c** and **12c** are analogues of *p*-(trifluoromethyl)amphetamine, and amine **9c** is an analogue of *o*-(trifluoromethyl)amphetamine. The remarkable biochemical activity of these and related compounds as substrates (**6c**, **7c**) or inhibitors (competitive, **8c**, **9c**; uncompetitive, **11c–13c**) of norepinephrine *N*-methyltransferase has recently been reported.[3]

Because alcohols **7a**, **8a**, **12a**, and **13a** were known and alcohols **6a**, **9a**, **11a**, and **14a** could conveniently be prepared, we sought a method for direct and stereospecific conversion of alcohols into amines.[4] Although many

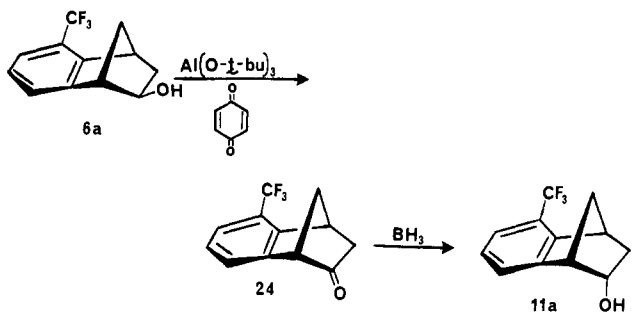
Scheme I



Scheme II



Scheme III



two-step displacement methods are currently available for this transformation, most of them are unattractive in systems which are prone to undergo carbonium ion induced skeletal rearrangements. Mitsunobu et al. have reported a one-pot stereospecific synthesis of amines from alcohols via phthalimides using triphenylphosphine and diethyl azidodicarboxylate (DEAD).[5,6] In spite of the extensive use of this reaction in carbohydrate and nucleoside chemistry and with other simple aliphatic alcohols, there are no reports on the degree of stereospecificity of this reaction in cases such as the benzonorbornene system where carbonium ion induced rearrangements are possible.[6]

## Results and Discussion

**Synthesis of Alcohols.** The exo alcohols **7a**[7] and **8a**[7] were synthesized by hydroboration–oxidation of 6-(trifluoromethyl)benzonorbornadiene[7] (**23**) and separated by medium-pressure liquid chromatography (MPLC, 4:1 hexane/EtOAc on silica gel) as their 3,5-dinitrobenzoate esters. Oppenauer oxidation of the exo alcohols followed by diborane reduction provided the endo alcohols **12a**[7] and **13a**.[7] $^{13}C$ NMR studies on the 6- and 7-(trifluoromethyl)benzonorbornen-2-ones (**25** and **26**) confirmed the positions of the $CF_3$ group,[8] and the results were in agreement with the assignments made by Schubert and

(1) (a) Paper 8 in our series "Conformationally Defined Adrenergic Agents"; for paper 7 see ref 3b. (b) Supported by PHS Research Grants DA 01990, GM 22988, and HL 21887 and by a Grant-in-Aid from the American Heart Association, Kansas Affiliate, Inc. (c) University of Kansas Undergraduate Research Participant, Grant KU 3944. (d) NSF Undergraduate Research Participant, summer 1979, Grant SPI78-2693; Sterling Winthrop Undergraduate Research Fellow, 1980–1981; University of Kansas Undergraduate Research Award, summer 1980. (e) Bennington College, Bennington, VT 05201.

(2) Grunewald, G. L.; Reitz, T. J.; Hallett, A.; Rutledge, C. O.; Vollmer, S.; Archuleta, J. M., III; Ruth, J. A. *J. Med. Chem.* **1980**, *23*, 614.

(3) (a) Rafferty, M. F.; Grunewald, G. L. *Mol. Pharmacol.* **1982**, *22*, 127. (b) Grunewald, G. L.; Pleiss, M. A. Rafferty, M. F. *Life Sci.* **1982**, *31*, 993.

(4) While more direct routes to amines **6c–9c** and **11c–14c** might appear to be available (e.g., methods in ref 2.), all attempted methods that relied on separation of amines or protected amines were unsuccessful. Azidomercuration [$Hg(N_3)_2$]–demercuration ($NaBH_4$)–reduction ($LiAlH_4$) of 6-(trifluoromethyl)benzonorbornadiene (**23**) was stereoselective but not regioselective as both exo amines **7c** and **8c** were obtained in almost equal amounts. Attempts to separate these amines as the free bases, as formamides, or as acetamides were unsuccessful. Also, treatment of the oxime ethers of a mixture of 6- and 7-(trifluoromethyl)benzonorbornen-2-one (**25** and **26**) with $BH_3$/THF afforded a mixture of all four possible isomeric amines **7c**, **8c**, **12c**, and **13c**. The amine mixture was converted to the 3,5-dinitrobenzamide derivatives, and the four amides were separated cleanly by MPLC (silica gel with 4:1 hexane/EtOAc). Unfortunately, the benzamides were either resistant to or decomposed under acidic or basic hydrolysis, and these schemes were abandoned in favor of the method presented in this paper.

(5) Mitsunobu, O.; Wade, M., Sano, T. *J. Am. Chem. Soc.* **1972**, *94*, 679.

(6) For a review of this reaction see: Mitsunobu, O. *Synthesis* **1981**, 1.

(7) Schubert, R. M. Ph.D. Dissertation, Purdue University, West Lafayette, IN, 1972; *Diss. Abstr. Int. B* **1972**, *33*, 645.

(8) Reitz, T. J.; Grunewald, G. L., accepted for publication in *Org. Magn. Reson.*

Table I. Conversion of Alcohols to Amines via Phthalimide Formation

| alcohol | time for phthalimide formation, h | % yield phthalimide[a] | % yield amine[b] | amine rel % exo:endo[c] (structure no.) |
|---|---|---|---|---|
| 6a | 48 | 33 | 79 | 11:89[d] (6c/11c) |
| 7a | 36 | 34 | 74 | 7:93 (7c/12c) |
| 8a | 60 | 34 | 85 | 7:93 (8c/13c) |
| 9a | 50 | 13[e] | *f* | 33:67[d,g] (9c/14c) |
| 10a | 36 | 24 | 83 | 72:28[h] (10c/15c) |
| 11a | 43 | 62 | 81 | 100:0[d] (6c/11c) |
| 12a | 56 | 64 | 81 | 100:0 (7c/12c) |
| 13a | 36 | 63 | 63 | 100:0 (8c/13c) |
| 14a | 48 | 36 | 56 | 100:0[d] (9c/14c) |
| 15a | 20 | 53 | 56 | 100:0[h] (10c/15c) |

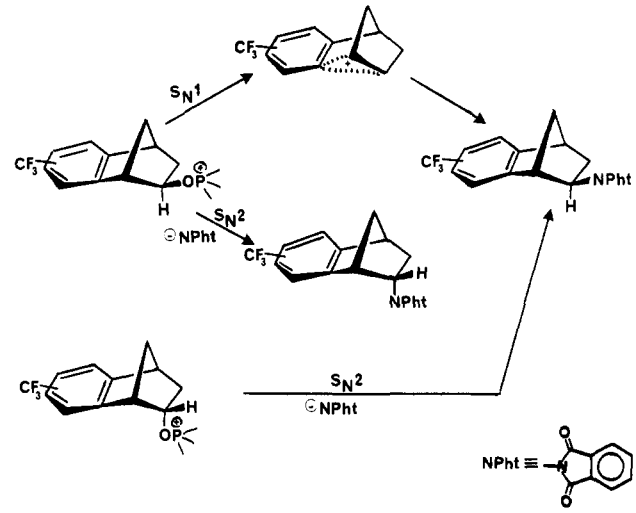
[a] After chromatography. [b] After bulb to bulb distillation (based on starting phthalimide). [c] Ratio determined by GC analysis (6-ft column, 10% Apeizon L, 2% KOH). [d] Ratio determined by GC analysis at the phthalimide stage (6-ft column, 5% SE-30). [e] A substantial amount of unreacted alcohol was recovered. [f] This reaction was not carried out due to an insufficient amount of phthalimide (**14b**). [g] Pure *endo*-phthalimide (**14b**) was obtained by MPLC (silica gel, $CH_2Cl_2$). [h] Identity of these amines was confirmed by comparison with authentic samples.[2]

Brown[7] using europium shift reagents on the endo alcohols.

Access to the 5- and 8-trifluoromethyl-substituted alcohols **6a**, **9a**, **11a**, and **14a** was available through the intermediacy of 5-(trifluoromethyl)benzonorbornadiene (**16**), as illustrated in Scheme I. Treatment of **16** (Scheme II) with diborane followed by an oxidative workup afforded an equimolar ratio of the two exo alcohols **6a** and **9a**. As shown in Scheme III for the 5-$CF_3$ derivative, the endo alcohols **11a** and **14a** were available from the corresponding exo alcohols by oxidation[9] to ketones **24** and **27** followed by reduction with diborane.

**Stereochemical and Positional Assignments.** Stereochemical and positional assignments for the eight alcohols were made on the basis of their $^1H$ NMR and $^{13}C$ NMR characteristics. The four possible sites of attachment of the trifluoromethyl group on the aromatic ring were unambiguously differentiated by utilizing $^{13}C$ NMR substitutent-induced chemical shift (SCS) values (based on spectral data of (trifluoromethyl)benzene[10] and benzonorbornen-2-one).[8,11] The ketones were chosen for $CF_3$ positional assignment due to the large differences in the easily recognizable and assignable 4a- and 8a-carbons[12] (i.e., carbons 4a and 8a resonate at $\delta$ 148.7 and 139.9, respectively, in the parent benzonorbornen-2-one). Assignment of exo and endo orientation of the alcohol (and later phthalimide and amine) substituent was based on $^1H$ NMR spectroscopy.[13] The $^1H$ NMR spectra of 2-substituted benzonorbornenes have been examined at length.[2,14,15] Wilt et al. have shown for the 2-bromo[14a] and 2-chloro[14b] derivatives and Grunewald et al. for the 2-amino and 2-methylamino derivatives[2] that the *exo*-hydrogen attached to the substituted carbon of the endo isomers resonates more than 0.5 ppm downfield from the corresponding *endo*-hydrogen of the exo isomers. Also, in the 2-endo derivatives the *endo*-$C_3$ hydrogen was distinguishable as a high-field doublet of triplets. The $^1H$ NMR spectra of all the synthesized trifluoromethyl 2-substituted benzonorbornenes were consistent with these distinct common features.

Scheme IV




**Alcohol to Amine Conversion.** The results of the Mitsunobu reaction on alcohols **6a–15a** are summarized in Table I. The probable mechanistic pathways for phthalimide formation from alkoxyphosphonium salts are shown in Scheme IV. In the case of an exo alcohol, the alkoxyphosphonium salt can either undergo a phenyl ring assisted $S_N1$-type process to give a positively charged intermediate which then undergoes a nucleophilic attack from the less hindered exo side to afford the N-substituted phthalimide with retention of configuration or an $S_N2$-type displacement to give the N-substituted phthalimide with inversion of configuration. The extent of phenyl ring participation in the ionization of the C–O bond and, to a lesser extent, the site of aromatic substitution determined the exo/endo product ratio. In the case of the endo alcohols (entries **11a–15a** in Table I) the unfavorable orientation of the C–O bond precluded the phenyl ring assisted $S_N1$ process and afforded stereospecifically the expected $S_N2$ product with complete inversion of configuration. For the unsubstituted exo alcohol (**10a** of Table I) the $S_N1$-type process predominated, and the exo phthalimide (and hence the exo amine) was obtained as the major product. However, in the presence of the electron-withdrawing trifluoromethyl group, phenyl ring

(9) Sandman, D.; Mislow, K.; Giddings, W.; Dirlam, J.; Hanson, G. *J. Am. Chem. Soc.* **1968**, *90*, 4877.
(10) Ewing, D. F. *Org. Mag. Reson.* **1979**, *12*, 499.
(11) Chemical shifts may be calculated and compared with observed values. For example, for 6- and 7-(trifluoromethyl)benzonorbornen-2-one (**25** and **26**, respectively), the assignment was conveniently made as follows: **25** ($\delta$ calculated, $\delta$ observed) C-4a (149.0, 149.5), C-8a (143.2, 144.3), C-5 (118.4, 118.5), C-6 (129.9, 129.6), C-7 (123.6, 124.1), C-8 (123.8, 123.6); **26** C-4a (152.0, 152.7), C-8a (140.2, 141.1), C-5 (121.9, 122.0), C-6 (124.2, 125.0), C-7 (129.3, 129.3), C-8 (120.3, 120.4).
(12) Carbons 4a and 8a (see structure **2** for numbering scheme) are easily recognizable since they have no hydrogens and appear as singlets in the off-resonance decoupled spectra.
(13) For a $^{13}C$ NMR study of a series of 2-*exo*- and *endo*-benzonorbornene isomers see: Burn, P. K.; Crooks, P. A.; Meth-Cohn, O. *Org. Magn. Reson.* **1978**, *11*, 370.
(14) (a) Wilt, J. W.; Chenier, P. J. *J. Org. Chem.* **1970**, *35*, 1562. (b) Wilt, J. W.; Gutman, G.; Ranus, W. J., Jr.; Zigman, A. R. *Ibid.* **1967**, *32*, 893.
(15) Cristol, S. J.; Nachtigall, G. *J. Org. Chem.* **1967**, *32*, 3738.

participation was impeded, and exo alcohols **6a–8a** gave predominately the endo amines. The lower yields of phthalimides obtained from the exo (as compared to the endo) alcohols is suggestive of the fact that the $S_N2$-type displacement is much favored from the less hindered (exo) side. The low reactivity of the ortho derivatives, **9a** and **14a**, is likely due to a steric as well as an inductive effect[16] of the 8-trifluoromethyl group.

## Experimental Section

Melting points were determined by using a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were obtained on a Beckman IR-33 spectrophotometer. $^1H$ NMR spectra were determined at 60 MHz by using a Varian T-60 or EM-360 or at 80 MHz by using a Varian FT-80 spectrometer. $^{13}C$ NMR spectra were recorded at 20.11 MHz by using a Bruker WP80-FT spectrometer. All chemical shifts are reported in parts per million ($\delta$) relative to $Me_4Si$. Electron-impact (70 eV) mass spectra were obtained on a Varian CH-5 mass spectrometer. Microanalyses were performed on a Hewlett-Packard Model 185B CHN analyzer at the University of Kansas. Medium-pressure liquid chromatography (MPLC), using an adaptation of the system of Meyers and co-workers,[17] was performed on silica gel 60 (230–400 mesh) at pressures of 20–95 psi. Aniline **17** was obtained from Fairfield Chemical Co.

**2-Bromo-4-nitro-6-(trifluoromethyl)aniline (18).** A solution of 122.6 g (768 mmol) of $Br_2$ in 670 mL of glacial acetic acid was added dropwise over a 2.5-h period to a solution of 150 g (723 mmol) of 2-(trifluoromethyl)-4-nitroaniline (**17**) in 750 mL of glacial acetic acid at 45 °C. The mixture was refluxed for 4.75 h, allowed to cool, and then poured into 3.6 L of $H_2O$ to give a beige precipitate which was filtered and recrystallized from 95% EtOH to afford 168.5 g (81%) of **18** as light brown needles: mp 138–140 °C; $^1H$ NMR ($CDCl_3$) $\delta$ 8.25 (d, 1 H, $J$ = 3 Hz, Ar H-3), 8.10 (d, 1 H, $J$ = 3 Hz, Ar H-5), 5.20 (br m, 2 H, $NH_2$); IR (KBr) 3500, 3400 (NH), 1510, 1350 ($NO_2$) $cm^{-1}$; mass spectrum, $m/e$ (relative intensity) 286 (100, $M^{+\cdot}$), 284 (100). Anal. Calcd for $C_7H_4BrF_3N_2O_2$: C, 29.50; H, 1.44; N, 9.83. Found: C, 29.70; H, 1.60; N, 9.80.

**2-Bromo-4-nitro-6-(trifluoromethyl)acetanilide (19).** To a solution of 15.7 g (55 mmol) of **18** in 400 mL of benzene were added 22.7 g (166 mmol) of freshly fused $ZnCl_2$ and 17.3 g (170 mmol) of acetic anhydride. The reaction mixture was refluxed for 32 h and then cooled to room temperature at which time 50 mL of $H_2O$ was slowly added with stirring. The mixture was filtered and the precipitate washed with $CHCl_3$. The filtrate was washed successively with $H_2O$, saturated aqueous $NaHCO_3$, and $H_2O$ and finally dried ($MgSO_4$). Evaporation of the solvent left a brown solid which on recrystallization from MeOH afforded 10.0 g (56%) of **19** as colorless prisms: mp 175–176.5 °C; $^1H$ NMR ($CD_3COCD_3$) $\delta$ 8.67 (br s, 1 H, NH), 8.20 (d, 1 H, $J$ = 3 Hz, Ar H-3), 7.97 (d, 1 H, $J$ = 3 Hz, Ar H-5), 2.03 (s, 3 H, $CH_3CO$); IR (KBr) 3250, 3200, 3115 (NH), 1665 (C=O), 1425 ($NO_2$) $cm^{-1}$; mass spectrum, $m/e$ (relative intensity) 328 (10, $M^{+\cdot}$), 327 (98), 326 (10), 325 (100). Anal. Calcd for $C_9H_6BrF_3N_2O_3$: C, 33.05; H, 1.85; N, 8.56. Found: C, 32.98; H, 2.12; N, 8.40.

**2-Bromo-4-amino-6-(trifluoromethyl)acetanilide (20).** To a slurry of 520 g (2.3 mol) of $SnCl_2 \cdot 2H_2O$ in 940 mL of EtOH was added 103 g (315 mmol) of **19** with stirring. The mixture was refluxed for 0.5 h, stirred at room temperature for 13 h, and then basified to pH 11 with 2 N ethanolic NaOH. The slurry was filtered and the solid $SnO_2$ washed with ether. The aqueous layer was separated and extracted with ether. The combined ethereal extracts were dried ($MgSO_4$), and the ether was evaporated to yield 80.5 g (86%) of **20** as a yellow powder, mp 202–205 °C. Recrystallization from MeOH (2×) afforded colorless needles: mp 211.5–213 °C; $^1H$ NMR ($CD_3COCD_3$) $\delta$ 8.95 (br s, 1 H, NHCO), 7.13 (d, 1 H, $J$ = 3 Hz, Ar H-3), 6.93 (d, 1 H, $J$ = 3 Hz, Ar H-5), 5.30 (br s, 2 H, $NH_2$), 2.10 (s, 3 H, $CH_3CO$); IR (KBr) 3340, 3290, 3230 (NH), 1670 (C=O); mass spectrum, $m/e$ (relative intensity) 298 (15, $M^{+\cdot}$), 296 (15), 256 (98), 254 (100), 236 (73), 234 (73), 217 (84). Anal. Calcd for $C_9H_8BrF_3N_2O$: C, 36.38; H, 2.71; N, 9.43. Found: C, 36.24; H, 2.83; N, 9.30.

**2-Bromo-6-(trifluoromethyl)acetanilide (21).** To a mixture of 80.0 g (269 mmol) of **20** in 125 mL of 48% fluoroboric acid[18] and 40 mL of $H_2O$ at 0 °C was added a solution of 22.3 g (323 mmol) of $NaNO_2$ in 50 mL of $H_2O$. The thick slurry which was formed was stirred at 0 °C for 2.5 h. The mixture was filtered and the solid fluoborate salt washed sequentially with small amounts of cold 5% fluoboric acid, MeOH, and ether. The salt was then stirred into 500 mL of $CHCl_3$ in an ice bath. To this was added dropwise 171 mL of 50% hypophosphorous acid, and the mixture was stirred at room temperature for 24 h. The solution was made basic with $Na_2CO_3$ and then poured into 200 mL of $H_2O$. The organic layer was separated and washed with $H_2O$. The combined organic fractions were dried ($Na_2SO_4$) and evaporated to afford 70.0 g (92%) of **21** as tan crystals which were recrystallized from $EtOH/H_2O$ (3:1) to give white needles: mp 181–183 °C; $^1H$ NMR ($CD_3COCD_3$) $\delta$ 8.67 (br s, 1 H, NHCO), 7.05–7.76 (m, 3 H, Ar H), 2.10 (s, 3 H, $CH_3CO$); IR (KBr) 3240, 3200 (NH), 1670 (C=O); mass spectrum, $m/e$ (relative intensity) 283 (0.4, $M^{+\cdot}$), 241 (82), 239 (86), 221 (77), 219 (81), 202 (100). A sample for elemental analysis was prepared by sublimation (100 °C, 0.1 mm); mp 182–183 °C. Anal. Calcd for $C_9H_7BrF_3NO$: C, 38.32; H, 2.50; N, 4.97. Found: C, 38.50; H, 2.50; N, 5.10.

**1-Bromo-2-iodo-3-(trifluoromethyl)benzene (22).** To a solution of 70 g (248 mmol) of **21** in hot EtOH was added 100 mL of concentrated HCl. The mixture was refluxed for 75 h, allowed to cool and then basified with 20% aqueous NaOH. The resulting black solution was extracted with $CHCl_3$ (3 × 150 mL) and then ether (2 × 200 mL). The combined organic layers were dried ($Na_2SO_4$) and the solvents removed in vacuo to give a black oil. The oil was distilled (52 °C, 1.3 mm) to afford 41 g (69%) of 2-bromo-6-(trifluoromethyl)aniline as a colorless oil which was used without further purification: $^1H$ NMR ($CDCl_3$) $\delta$ 7.37 (d, 1 H, $J$ = 8 Hz, Ar H-3), 7.20 (d, 1 H, $J$ = 8 Hz, Ar H-5), 6.40 (t, 1 H, $J$ = 8 Hz, Ar H-4), 4.55 (br s, 2 H, $NH_2$); IR (film) 3530, 3420 (NH).

To a mixture of 39 mL of concentrated HCl and 26 g of ice was added 20 g (83 mmol) of the above prepared amine. The mixture was maintained at 0–5 °C, and a solution of 6.33 g (91 mmol) of $NaNO_2$ in 26 mL of $H_2O$ was slowly added. The resulting mixture was then added to a cold (0–5 °C) solution of 46.9 g (283 mmol) KI in 150 mL of $H_2O$. The mixture was stirred at room temperature for 22 h and then extracted with $CHCl_3$ (5 × 75 mL). The combined $CHCl_3$ extracts were washed sequentially with $H_2O$, 5% $NaHSO_3$ and $H_2O$. The organic layer was dried ($Na_2SO_4$), and the solvents were removed in vacuo to leave an oily orange solid which was distilled to give 25.5 g (87%) of **22** as a light pink oil which crystallized on prolonged standing: bp 85 °C (1.5 mm); $^1H$ NMR ($CDCl_3$) $\delta$ 7.80 (dd, 1 H, $J$ = 8, 2 Hz, Ar H-6), 7.53 (dd, 1 H, $J$ = 8, 2 Hz, Ar H-4), 7.27 (t, 1 H, $J$ = 5, Ar H-5); IR (film) 3105, 1570, 1400, 1300, 1190, 1170, 1130, 1060, 1000, 780 $cm^{-1}$; mass spectrum, $m/e$ (relative intensity) 352 (7.5, $M^{+\cdot}$), 225 (20), 223 (25), 144 (100). A sample for elemental analysis was prepared by sublimation at room temperature (0.1 mm); mp 34.5–36 °C. Anal. Calcd for $C_7H_3BrF_3I$: C, 23.96; H, 0.86. Found: C, 23.85; H, 0.84.

**5-(Trifluoromethyl)benzonorbornadiene (16).** Benzonorbornadiene **16** was prepared by the general procedure used by Tanida et al.[19] for the preparation of related benzonorbornadienes. To 1.85 g (76 mmol) of powdered Mg in a flame-dried flask was added under $N_2$ 15 mL of a solution of 25 g (71 mmol) of **22** and 4.8 g (72 mmol) of freshly cracked cyclopentadiene dissolved in 135 mL of dry THF. The flask was heated gently to initiate reaction, and then the rest of the solution was added at such a rate as to maintain a slow reflux. The resulting brown mixture was refluxed for an additional 1 h and then allowed to cool. Most of the THF was removed and the residue taken up in ether. The ether was washed with saturated aqueous $NH_4Cl$ (2 × 125 mL),

(16) Note the field and resonance values of 0.63 and 0.19, respectively, for the $CF_3$ group. Values are those given by: Swain, C. G.; Lupton, E. C., Jr. *J. Am. Chem. Soc.* **1968**, *90*, 4328.

(17) Meyers, A. I.; Slade, J.; Smith, R. K.; Mihelich, E. D.; Hershenson, E. M.; Liang, C. D. *J. Org. Chem.* **1979**, *44*, 2247.

(18) Korzeniowski, S. H.; Blum, L.; Gokel, G. W. *J. Org. Chem.* **1977**, *42*, 1469.

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

and the combined aqueous layers were back extracted with ether. The combined organics were washed with 5% aqueous $NaHSO_3$, dried ($Na_2SO_4$), and evaporated. The residue was distilled [bp 58–61.5 °C (3.9 mm)] and then chromatographed on silica gel (hexane) to afford 8.7 g (58%) of **16** as a clear oil: $^1H$ NMR ($CDCl_3$) $\delta$ 6.90–7.47 (m, 3 H, Ar H), 6.70 (m, 2 H, olefinic), 4.23 (m, 1 H, bridgehead H-4), 3.87 (m, 1 H, bridgehead H-1), 2.29 (m, 2 H, $CH_2$); $^{13}C$ NMR ($CDCl_3$)[20] $\delta$ 154.0 (C-8a), 150.9 (C-4a), 144.1 and 142.7 (olefinic C's, C-2 and C-3), 124.8 (C-7), 124.8 (C-8), 120.8 (C-6), 69.6 (C-9), 50.4 and 49.5 (bridgeheads); IR (film) 3100, 3020, 2970, 2900, 1610, 1455, 1430, 1345, 1320, 1300, 1150, 1120, 1070, 1045, 1000, 847, 830, 800, 785, 760, 720, 695 $cm^{-1}$; mass spectrum, *m/e* (relative intensity) 211 (11), 210 (82, $M^{+\cdot}$), 209 (22), 184 (13), 142 (15), 141 (100), 115 (36); high-resolution mass measurement, obsd *m/e* 210.0626, $C_{12}H_9F_3$ requires 210.0656.

**6-(Trifluoromethyl)benzonorbornadiene (23).**[7] Olefin **23** was prepared by the procedure of Schubert:[7] $^1H$ NMR ($CDCl_3$) $\delta$ 7.10–7.57 (m, 3 H, Ar H), 6.76 (m, 2 H, olefinic), 3.94 (m, 2 H, bridgeheads), 2.28 (m, 2 H, $CH_2$); $^{13}C$ NMR ($CDCl_3$)[20] $\delta$ 156.6 (C-8a), 153.2 (C-4a), 143.3 and 142.9 (olefinic C's, C-2 and C-3), 122.3 (C-7), 121.5 (C-8), 118.4 (C-5), 70.4 (C-9), 50.5 (C-1 and C-4); IR (film) 3100, 3010, 2960, 2890, 1620, 1420, 1345, 1315, 1270, 1160, 1110, 1065, 1040, 880, 815, 725, 715, 695 $cm^{-1}$.

***exo*-5-(Trifluoromethyl)benzonorbornen-2-ol (6a) and *exo*-8-(Trifluoromethyl)benzonorbornen-2-ol (9a).** To a solution of 8.0 g (38 mmol) of **16** in 50 mL of THF at 0 °C was slowly added diborane (38 mmol). The resulting mixture was stirred under $N_2$ for 16 h at room temperature. The reaction was then quenched by the sequential addition of 4 mL of $H_2O$, 5.2 mL of 3 N NaOH, and 5.2 mL of 30% $H_2O_2$. An addition 1 mL of each of the peroxide and hydroxide solutions was added and the solution stirred for 4 h. Water (50 mL) was added and the mixture extracted with ether (3 × 50 mL). The organic portion was dried ($Na_2SO_4$), and the solvents were evaporated to give 8.6 g of an oily white solid. Chromatography (MPLC; 2:1 hexanes/EtOAc) of 4.0 g of the solid showed the solid to contain 1.73 g (43%) of **6a**, 1.72 g (43%) of **9a**, and 0.40 g (10%) of starting olefin **16**. Analytical samples of each alcohol were prepared by sublimation (40 °C, 0.1 mm).

Alcohol **6a**: colorless crystals; mp 84–86 °C; $^1H$ NMR ($CDCl_3$) $\delta$ 6.93–7.50 (m, 3 H, Ar H), 3.95 (m, 1 H, CHOH), 3.72 (m, 1 H, bridgehead), 3.30 (br s, 1 H, bridgehead), 3.17 (br s, 1 H, OH, exchangeable in $D_2O$), 1.63–2.33 (m, 4 H, methylenes); IR (KBr) 3270 (OH) $cm^{-1}$; mass spectrum, *m/e* (relative intensity) 228 (13, $M^{+\cdot}$), 185 (14), 184 (100), 115 (42). Anal. Calcd for $C_{12}H_{11}F_3O$: C, 63.15; H, 4.86. Found: C, 63.36; H, 4.94.

Alcohol **9a**: colorless crystals; mp 106–107 °C; $^1H$ NMR ($CDCl_3$) $\delta$ 7.00–7.43 (m, 3 H, Ar H), 3.95 (m, 1 H, CHOH), 3.60 (br s, 1 H, bridgehead), 3.47 (br s, 1 H, OH, exchangeable in $D_2O$), 3.36 (br s, 1 H, bridgehead), 1.60–2.33 (m, 4 H, methylenes); IR (KBr) 3300 (OH) $cm^{-1}$; mass spectrum, *m/e* (relative intensity) 228 (13, $M^{+\cdot}$), 185 (14), 184 (100), 115 (48). Anal. Calcd for $C_{12}H_{11}F_3O$: C, 63.15; H, 4.86. Found: C, 63.40; H, 4.86.

***exo*-6-(Trifluoromethyl)benzonorbornen-2-ol (7a) and *exo*-7-(Trifluoromethyl)benzonorbornen-2-ol (8a).**[7] Alcohols **7a** and **8a** were prepared and separated as 3,5-dinitrobenzoates as reported by Schubert.[7]

Alcohol **7a**: colorless oil; $^1H$ NMR ($CDCl_3$) $\delta$ 7.08–7.40 (m, 3 H, Ar H), 3.92 (m, 1 H, CHOH), 3.28 (m, 2 H, bridgeheads), 2.93 (br s, 1 H, OH, exchangeable in $D_2O$), 1.57–2.30 (m, 4 H, methylenes).

Alcohol **8a**: colorless oil; $^1H$ NMR ($CDCl_3$) $\delta$ 7.43 (br s, 1 H, Ar H), 7.07–7.33 (m, 2 H, Ar H), 3.95 (m, 1 H, CHOH), 3.30 (m, 2 H, bridgeheads), 2.47 (s, 1 H, OH, exchangeable in $D_2O$), 1.57–2.30 (m, 4 H, methylenes); IR (film) 3190 (OH) $cm^{-1}$.

**General Procedure for the Preparation of Ketones 24–27.**[7] A solution of 1.20 g (5.3 mmol) of the appropriate exo alcohol, 0.71 g (6.6 mmol) of benzoquinone, and 2.60 g (10.6 mmol) of aluminum tri-*tert*-butoxide in 35 mL of benzene was refluxed under $N_2$ for 36–40 h. The reaction mixture was allowed to cool and was then washed with 4 N $H_2SO_4$ (3 × 35 mL) followed by 3 N aqueous NaOH (3 × 50 mL). The organic layer was then dried ($Na_2SO_4$) and the solvent evaporated to give a light yellow oil. The crude product was chromatographed ($SiO_2$, $CH_2Cl_2$) to afford pure ketone.

**5-(Trifluoromethyl)benzonorbornen-2-one (24)** was obtained in 92% yield from **6a** as a colorless oil: $^1H$ NMR ($CDCl_3$) $\delta$ 7.03–7.57 (m, 3 H, Ar H), 3.87–4.17 (m, 1 H, bridgehead), 3.60 (br s, 1 H, bridgehead), 1.67–2.63 (m, 4 H, methylenes); $^{13}C$ NMR ($CDCl_3$) $\delta$ 210.9 (C-2), 146.5 (C-4a), 141.8 (C-8a), 126.9 (C-7), 126.5 (C-8), 124.5 (C-5), 124.2 ($CF_3$), 123.5 (C-6), 57.5 (C-1), 49.9 (C-9), 40.8 (C-4), 38.8 (C-3); IR (film) 3030, 3000, 2970, 1755 (C=O), 1600, 1460, 1430, 1410, 1320, 1290, 1260, 1235, 1200, 1160, 1115, 1070, 970, 820, 775, 760, 740, 700, 600 $cm^{-1}$. Anal. Calcd for $C_{12}H_9F_3O$: C, 63.72; H, 4.01. Found: C, 63.95; H, 4.00.

**6-(Trifluoromethyl)benzonorbornen-2-one (25)**[7] was obtained in 79% yield from **7a** as a colorless oil: $^1H$ NMR ($CDCl_3$) $\delta$ 7.40 (br s, 1 H, Ar H), 7.13–7.33 (m, 2 H, Ar H), 3.65 (m, 1 H, bridgehead), 3.53 (br s, 1 H, bridgehead), 1.60–2.60 (m, 4 H, methylenes); $^{13}C$ NMR ($CDCl_3$) $\delta$ 211.7 (C-2), 149.5 (C-4a), 144.3 (C-8a), 129.6 (C-6), 124.3 ($CF_3$), 124.1 (C-7), 123.6 (C-8), 118.5 (C-5), 58.1 (C-1), 50.9 (C-9), 41.8 (C-4), 39.6 (C-3); IR (film) 3040, 3000, 2975, 2950, 1755 (C=O), 1625, 1460, 1430, 1415, 1345, 1320, 1290, 1270, 1255, 1215, 1160, 1110, 1060, 1045, 975, 925, 895, 850, 835, 810, 745, 715 $cm^{-1}$.

**7-(Trifluoromethyl)benzonorbornen-2-one (26)**[7] was obtained in 66% yield from **8a** as a colorless oil: $^1H$ NMR ($CDCl_3$) $\delta$ 7.42 (br s, 1 H, Ar H), 7.10–7.35 (m, 2 H, Ar H), 3.65 (m, 1 H, bridgehead), 3.50 (br s, 1 H, bridgehead), 1.60–2.60 (m, 4 H, methylenes); $^{13}C$ NMR ($CDCl_3$) $\delta$ 212.0 (C-2), 152.7 (C-4a), 141.1 (C-8a), 129.3 (C-7), 125.0 (C-6), 124.3 ($CF_3$), 122.0 (C-5), 120.4 (C-8), 58.0 (C-1), 51.0 (C-9), 41.9 (C-4), 39.7 (C-3); IR (film) 3040, 3000, 2975, 2900, 1755 (C=O), 1620, 1455, 1425, 1410, 1345, 1315, 1280, 1270, 1160, 1145, 1110, 1080, 1065, 1040, 970, 920, 890, 855, 830, 805, 745, 730, 705 $cm^{-1}$.

**8-(Trifluoromethyl)benzonorbornen-2-one (27)** was obtained in 56% yield from **9a** as a colorless oil: $^1H$ NMR ($CDCl_3$) $\delta$ 7.07–7.57 (m, 3 H, Ar H), 3.90 (br s, 1 H, bridgehead), 3.75 (m, 1 H, bridgehead), 1.67–2.67 (m, 4 H, methylene); $^{13}C$ NMR ($CDCl_3$) $\delta$ 210.5 (C-2), 150.6 (C-4a), 138.1 (C-8a), 127.6 (C-6), 126.0 (C-8), 125.1 (C-5), 124.0 ($CF_3$), 123.2 (C-7), 56.6 (C-1), 50.4 (C-9), 41.6 (C-4), 39.4 (C-3); IR (film) 3030, 3010, 2970, 1755 (C=O), 1605, 1465, 1430, 1410, 1320, 1290, 1260, 1245, 1210, 1165, 1120, 1070, 975, 935, 910, 860, 805, 770, 730, 700 $cm^{-1}$; mass spectrum, *m/e* (relative intensity) 227 (3), 226 (16, $M^{+\cdot}$), 185 (11), 184 (100), 129 (12), 115 (46). Anal. Calcd for $C_{12}H_9F_3O$: C, 63.72; H, 4.01. Found: C, 63.68; H, 4.12.

**General Procedure for the Preparation of Endo Alcohols 11a–14a.** A solution of 1.0 mmol of the appropriate ketone in 5 mL of anhydrous THF was cooled under $N_2$ in an ice bath. Two equivalents of 1 M diborane in THF was added and the reaction mixture allowed to stir at room temperature for 3.5 h, at which time 5 mL of $H_2O$ and 10 mL of ether were added. The ether layer was washed with 3 N NaOH solution (2 × 30 mL) and with brine (25 mL). The aqueous extracts were then extracted with ether. The combined organics were dried ($Na_2SO_4$) and the solvents evaporated to afford the desired alcohol.

***endo*-5-(Trifluoromethyl)benzonorbornen-2-ol (11a)** was obtained in 93% yield from **24** as a white solid. A sample for elemental analysis was sublimed (40 °C, 0.1 mm) to afford white crystals: mp 68–70 °C; $^1H$ NMR ($CDCl_3$) $\delta$ 7.00–7.53 (m, 3 H, Ar H), 4.48 (br m, 1 H, CHOH), 3.70 (m, 1 H, bridgehead), 3.33 (m, 1 H, bridgehead), 2.33 (ddd, 1 H, $J$ = 13, 8, 4 Hz, *exo*-$C_3$ methylene), 1.80 (s, 1 H, OH, exchangeable in $D_2O$), 1.50–1.95 (m, 2 H, $C_9$ methylene), 0.80 (dt, 1 H, $J$ = 13, 3 Hz, *endo*-$C_3$ methylene); IR (KBr) 3380 (OH) $cm^{-1}$; mass spectrum, *m/e* (relative intensity) 228 (2.5, $M^{+\cdot}$), 184 (100), 115 (52). Anal. Calcd for $C_{12}H_{11}F_3O$: C, 63.15; H, 4.86. Found: C, 63.50; H, 5.10.

***endo*-6-(Trifluoromethyl)benzonorbornen-2-ol (12a)**[7] was obtained quantitative yield from **25** as a white solid: mp 65–66 °C (lit.[7] mp 62–63 °C); $^1H$ NMR ($CDCl_3$) $\delta$ 7.12–7.55 (m, 3 H, Ar H), 4.44 (br m, 1 H, CHOH), 3.30 (m, 2 H, bridgeheads), 2.28 (ddd, 1 H, *exo*-$C_3$ methylene), 1.45–1.95 (m, 2 H, $C_9$ methylene), 1.53 (br s, 1 H, OH), 0.72 (dt, 1 H, *endo*-$C_3$ methylene).

***endo*-7-(Trifluoromethyl)benzonorbornen-2-ol (13a)**[7] was obtained in 99% yield from **26** as a white solid: mp 79.0–79.5 °C (lit.[7] mp 80.5–81 °C); $^1H$ NMR ($CDCl_3$) $\delta$ 7.38 (s, 1 H, Ar H), 7.00–7.30 (m, 2 H, Ar H), 4.40 (br m, 1 H, CHOH), 3.27 (m, 2 H, bridgeheads), 2.27 (ddd, 1 H, *exo*-$C_3$ methylene), 1.45–1.93 (m,

(20) Carbon resonances for the $CF_3$ group and the carbon adjacent to the $CF_3$ group for olefins **16** and **23** were not located.

2 H, $C_9$ methylene), 1.40 (br s, 1 H, OH), 0.73 (dt, 1 H, *endo*-$C_3$ methylene).

***endo*-8-(Trifluoromethyl)benzonorbornen-2-ol (14a)** was obtained in quantitative yield from **27** as a white solid. A sample for elemental analysis was sublimed (40 °C, 0.1 mm) to afford white crystals: mp 58–60 °C; $^1$H NMR ($CDCl_3$) $\delta$ 6.97–7.50 (m, 3 H, Ar H), 4.48 (br m, 1 H, CHOH), 3.70 (m, 1 H, bridgehead), 3.27 (m, 1 H, bridgehead), 2.27 (ddd, 1 H, $J$ = 13, 8, 4 Hz, *exo*-$C_3$ methylene), 1.50–1.93 (m, 3 H, $C_9$ methylene and OH, 1 H exchangeable in $D_2O$), 0.80 (dt, 1 H, $J$ = 13, 3 Hz, *endo*-$C_3$ methylene); IR (film) 3430 (OH) cm$^{-1}$; mass spectrum, $m/e$ (relative intensity) 228 (11, M$^{+\cdot}$), 185 (16), 184 (100), 164 (15), 115 (59). Anal. Calcd for $C_{12}H_{11}F_3O$: C, 63.15; H, 4.86. Found: C, 63.00; H, 5.05.

**General Procedure for the Preparation of Phthalimides.**[5] To 0.5 g (2.2 mmol) of the alcohol dissolved in 10 mL of anhydrous THF were added under $N_2$ 1.1 equiv of phthalimide and 1.1 equiv of triphenylphosphine. Diethyl azidodicarboxylate (1.1 equiv) was then slowly added to the white slurry, resulting in a clear orange solution. The mixture was stirred at room temperature for 20–60 h. The reaction was quenched by the addition of 15 mL of brine. The layers were separated, and the aqueous layer was washed with 5 mL of ether. The combined organic fractions were dried ($Na_2SO_4$), and the solvent was evaporated. The crude phthalimide was purified by chromatography ($SiO_2$, $CH_2Cl_2$), followed by recrystallization from EtOH and in some cases sublimation (100–120 °C, 0.1 mm). C, H, and N analyses for four of the phthalimides were unsatisfactory for carbon; in each case high-resolution mass spectral peak matching gave satisfactory results [$\Delta$(calcd – obsd) < 0.002], and in all cases the resulting amines gave acceptable C, H, and N analyses.

**Phthalimides: Physical and Spectral Data. Phthalimide 11b**: mp 142–143 °C; $^1$H NMR ($CDCl_3$) $\delta$ 6.80–7.80 (m, 7 H, Ar H), 4.88 (dt, 1 H, $J$ = 10, 4 Hz, NCH), 3.77 (m, 2 H, bridgeheads), 1.95–2.80 (m, 2 H, $C_3$ methylene), 1.87 (br s, 2 H, $C_9$ methylene); mass spectrum, $m/e$ (relative intensity) 357 (1.5, M$^{+\cdot}$), 185 (13), 184 (100), 174 (50), 115 (42); high-resolution mass measurement, obsd $m/e$ 357.0976, $C_{20}H_{14}F_3NO_2$ requires 357.0976.

**Phthalimide 6b**: mp 120–121 °C; $^1$H NMR ($CDCl_3$) $\delta$ 6.82–7.93 (m, 7 H, Ar H), 4.13 (m, 1 H, NCH), 3.87 (m, 1 H, bridgehead), 3.60 (br s, 1 H, bridgehead), 2.50–3.05 (m, 2 H, $C_3$ methylene), 1.50–2.12 (m, 2 H, $C_9$ methylene); mass spectrum, $m/e$ (relative intensity) 357 (1.5, M$^{+\cdot}$), 185 (13), 184 (100), 174 (49), 115 (42); high-resolution mass measurement, obsd $m/e$ 357.0974, $C_{20}H_{14}F_3NO_2$ requires 357.0976.

**Phthalimide 12b**: mp 131–132 °C; $^1$H NMR ($CDCl_3$) $\delta$ 6.90–7.77 (m, 7 H, Ar H), 4.85 (dt, 1 H, $J$ = 10, 4 Hz, NCH), 3.80 (m, 1 H, bridgehead), 3.52 (m, 1 H, bridgehead), 2.23–2.80 (m, 2 H, $C_3$ methylene), 1.88 (br s, 2 H, $C_9$ methylene). Anal. Calcd for $C_{20}H_{14}F_3NO_2$: C, 67.23; H, 3.95; N, 3.92. Found: C, 67.30; H, 3.84; N, 3.81.

**Phthalimide 7b**: mp 153–154 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.17–7.92 (m, 7 H, Ar H), 4.17 (m, 1 H, NCH), 3.57 (br s, 2 H, bridgeheads), 2.53–2.98 (m, 2 H, $C_3$ methylene), 1.53–2.10 (m, 2 H, $C_9$ methylene). Anal. Calcd for $C_{20}H_{14}F_3NO_2$: C, 67.23; H, 3.95; N, 3.92. Found: C, 67.00; H, 3.88; N, 3.72.

**Phthalimide 13b**: mp 117–118 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.10–7.73 (m, 7 H, Ar H), 4.90 (dt, 1 H, $J$ = 10, 4 Hz, NCH), 3.77 (m, 1 H, bridgehead), 3.55 (m, 1 H, bridgehead), 2.03–2.83 (m, 2 H, $C_3$ methylene), 1.90 (br s, 2 H, $C_9$ methylene); mass spectrum, $m/e$ (relative intensity) 357 (5.9, M$^{+\cdot}$), 185 (13), 184 (100), 174 (43), 115 (46); high-resolution mass measurement, obsd $m/e$ 357.0965, $C_{20}H_{14}F_3NO_2$ requires 357.0976.

**Phthalimide 8b**: mp 104–105 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.13–7.95 (m, 7 H, Ar H), 4.27 (m, 1 H, NCH), 3.60 (br s, 2 H, bridgeheads), 2.57–3.07 (m, 2 H, $C_3$ methylene), 1.52–2.57 (m, 2 H, $C_9$ methylene). Anal. Calcd for $C_{20}H_{14}F_3NO_2$: C, 67.23; H, 3.95; N, 3.92. Found: C, 67.50; H, 3.91; N, 3.80.

**Phthalimide 14b**: mp 163–164 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.06–7.75 (m, 7 H, Ar H), 5.03 (dt, 1 H, $J$ = 10, 4 Hz, NCH), 3.97 (m, 1 H, bridgehead), 3.56 (m, 1 H, bridgehead), 1.80–2.75 (m, 4 H, methylenes, includes 2 H singlet at 1.91). Anal. Calcd for $C_{20}H_{14}F_3NO_2$: C, 67.23; H, 3.95; N, 3.92. Found: C, 67.10; H, 4.08; N, 4.21.

**Phthalimide 9b**: mp 125–126 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.08–7.97 (m, 7 H, Ar H), 4.25 (m, 1 H, NCH), 3.88 (m, 1 H, bridgehead), 3.60 (m, 1 H, brideghead), 2.50–3.00 (m, 2 H, $C_3$ methylene), 1.53–2.17 (m, 2 H, $C_9$ methylene); mass spectrum, $m/e$ (relative intensity) 357 (3.2, M$^{+\cdot}$), 185 (12), 184 (100), 174 (42), 115 (36); high-resolution mass measurement, obsd $m/e$ 357.0969, $C_{20}H_{14}F_3NO_2$ requires 357.0976.

**General Procedure for the Preparation of Amines.**[5] To a solution of 500 mg (1.4 mmol) of the phthalimide in 20 mL of 95% EtOH was added 250 mg (4.24 mmol) of 85% hydrazine hydrate and the mixture refluxed under $N_2$ for 3 h. The EtOH was evaporated and the residue taken up in 20 mL of 2 N KOH solution. The basic solution was extracted with ether (4 × 15 mL), and the combined ether extracts were washed with brine and dried ($K_2CO_3$). Evaporation of the solvent gave an oil which was purified by bulb to bulb distillation, affording in all cases but **8c** a colorless oil (**8c** was a solid at room temperature). The free amine was converted to the HCl salt by using ethereal HCl followed by recrystallization from 95% EtOH/$Et_2O$ to afford white crystals.

**Amines: Physical and Spectral Data. Amine 11c**: $^1$H NMR ($CDCl_3$) $\delta$ 7.00–7.55(m, 3 H, Ar H), 3.50–3.97 (m, 2 H, bridgehead and NCH), 3.27 (m, 1 H, bridgehead), 2.42 (ddd, 1 H, $J$ = 13, 9, 4 Hz, *exo*-$C_3$ methylene), 1.80 (m, 2 H, $C_9$ methylene), 1.33 (s, 2 H, NH), 0.63 (dt, 1 H, $J$ = 13, 3 Hz, *endo*-$C_3$ methylene); IR (film) 3360 (NH), 2995, 2800, 1605, 1440, 1355, 1325, 1165, 1115, 1080, 1050, 790, 760 cm$^{-1}$. **11c**·HCl: mp 253 °C dec; mass spectrum, $m/e$ (relative intensity) 228 (6), 227 (22, M$^{+\cdot}$), 185 (13), 184 (100), 164 (14), 115 (58). Anal. Calcd for $C_{12}H_{12}F_3N$·HCl: C, 54.66; H, 4.97; N, 5.31. Found: C, 54.40; H, 5.10; N, 5.19.

**Amine 6c**: $^1$H NMR ($CDCl_3$) $\delta$ 6.90–7.47 (m, 3 H, Ar H), 3.65 (m, 1 H, bridgehead), 2.83–3.17 (m, 2 H, NCH and bridgehead, latter centered at 3.06), 1.10–2.17 (m, 6 H, includes $C_9$ methylenes centered at 1.95, $NH_2$ singlet at 1.37, and $C_3$ methylene). **6c**·HCl: mp 290 °C dec; IR (KBr) 3500 (NH), 3000, 1590, 1560, 1515, 1435, 1380, 1320, 1300, 1250, 1220, 1110, 1075, 925, 790, 750, 705 cm$^{-1}$; mass spectrum, $m/e$ (relative intensity) 228 (3), 227 (18, M$^{+\cdot}$), 185 (10), 184 (100), 164 (11), 115 (64). Anal. Calcd for $C_{12}H_{12}F_3N$·HCl: C, 54.66; H, 4.97; N, 5.31. Found: C, 54.28; H, 5.14; N, 5.08.

**Amine 12c**: $^1$H NMR ($CDCl_3$) $\delta$ 7.16–7.53 (m, 3 H, Ar H), 3.66 (dt, 1 H, $J$ = 9, 4 Hz, NCH), 3.27 (m, 2 H, bridgeheads), 2.40 (ddd, 1 H, $J$ = 12, 9, 4 Hz, *exo*-$C_3$ methylene), 1.80 (m, 2 H, $C_9$ methylene), 0.80 (br s, 2 H, $NH_2$), 0.63 (dt, 1 H, $J$ = 12, 3 Hz, *endo*-$C_3$ methylene); IR (film) 3400, 3300, 1620, 1590, 1430, 1350, 1320, 1290, 1275, 1190, 1140, 1100, 1075, 1060, 1045, 945, 890, 820, 710, 645 cm$^{-1}$. **12c**·HCl: mp 263–264 °C; mass spectrum, $m/e$ (relative intensity) 228 (3.5), 227 (23, M$^{+\cdot}$), 210 (6), 185 (11), 184 (100), 164 (7), 115 (54). Anal. Calcd for $C_{12}H_{12}F_3N$·HCl: C, 54.66; H, 4.97; N, 5.31. Found: C, 54.90; H, 5.00; N, 5.10.

**Amine 7c**: $^1$H NMR ($CDCl_3$) $\delta$ 7.06–7.50 (m, 3 H, Ar H), 3.30 (m, 1 H, bridgehead), 2.83–3.13 (m, 2 H, NCH and bridgehead, latter centered at 3.03), 1.10–2.15 (m, 6 H, $C_9$ methylene, $C_3$ methylene, $NH_2$ at 1.45); IR (film) 3400, 3300, 1620, 1590, 1435, 1345, 1320, 1290, 1270, 1255, 1160, 1150, 1110, 1045, 960, 885, 820, 765, 750, 725, 695 cm$^{-1}$. **7c**·HCl: mp 245–246 °C; mass spectrum, $m/e$ (relative intensity) 228 (3.6), 227 (20, M$^{+\cdot}$), 210 (8), 185 (12), 184 (100), 164 (10), 115 (69). Anal. Calcd for $C_{12}H_{12}F_3N$·HCl: C, 54.66; H, 4.97; N, 5.31. Found: C, 55.01; H, 5.15; N, 5.17.

**Amine 13c**: $^1$H NMR ($CDCl_3$) $\delta$ 7.10–7.56 (m, 3 H, Ar H), 3.66 (dt, 1 H, $J$ = 9, 4 Hz, NCH), 3.10–3.40 (m, 2 H, bridgeheads), 2.40 (ddd, 1 H, $J$ = 12, 9, 4 Hz, *exo*-$C_3$ methylene), 1.80 (m, 2 H, $C_9$ methylene), 0.80 (br s, 2 H, $NH_2$), 0.60 (dt, 1 H, $J$ = 12, 3 Hz, *endo*-$C_3$ methylene); IR (film) 3400, 3300, 1620, 1590, 1430, 1345, 1320, 1270, 1185, 1155, 1105, 1070, 1060, 1045, 825, 690 cm$^{-1}$. **13c**·HCl: mp 260 °C dec; mass spectrum, $m/e$ (relative intensity) 228 (4), 227 (14, M$^{+\cdot}$), 210 (8), 185 (13), 184 (100), 164 (8), 115 (71). Anal. Calcd for $C_{12}H_{12}F_3N$·HCl: C, 54.66; H, 4.97; N, 5.31. Found: C, 54.85; H, 5.10; N, 5.16.

**Amine 8c**: $^1$H NMR ($CDCl_3$) $\delta$ 7.00–7.46 (m, 3 H, Ar H), 3.30 (m, 1 H, bridgehead), 2.83–3.13 (m, 2 H, NCH and bridgehead, latter centered at 3.04), 1.13–2.23 (m, 6 H, includes $C_9$ methylene centered at 1.93, $NH_2$ singlet at 1.42, and $C_3$ methylene); IR (film) 3400, 3300, 1620, 1590, 1460, 1435, 1345, 1320, 1275, 1255, 1185, 1155, 1140, 1060, 1045, 960, 825, 765, 745, 720, 685, 645, 610 cm$^{-1}$. **8c**·HCl: mp 249–250 °C; mass spectrum, $m/e$ (relative intensity) 228 (3), 227 (19, M$^{+\cdot}$), 210 (11), 185 (11), 184 (100), 164 (7), 115 (50). Anal. Calcd for $C_{12}H_{12}F_3N$: C, 63.43; H, 5.32; N, 6.16. Found: C, 63.80; H, 5.50; N, 6.00.

**Amine 14c.** See footnote *f* of Table I.

**Amine 9c:** $^1$H NMR ($CDCl_3$) $\delta$ 6.90–7.45 (m, 3 H, Ar H), 3.33 (br s, 2 H, bridgeheads), 3.13 (m, 1 H, NCH), 1.10–2.17 (m, 6 H, includes $C_9$ methylene at 1.90, $NH_2$ singlet at 1.60, and $C_3$ methylene); IR (film) 3500, 3400, 3045, 3000, 2890, 1605, 1465, 1430, 1345, 1320, 1300, 1220, 1160, 1120, 1070, 1050, 965, 915, 800, 740, 710 cm$^{-1}$. **9c**·HCl: mp 262–263 °C, mass spectrum, *m/e* (relative intensity) 228 (3), 227 (15, $M^+$·), 210 (5), 185 (12), 184 (100), 164 (8), 115 (63). Anal. Calcd for $C_{12}H_{12}F_3N$·HCl: C, 54.66; H, 4.97; N, 5.31. Found: C, 54.31; H, 5.20; N, 5.18.

**Acknowledgment.** We thank Ruth Pazhenchevsky for technical assistance in the preparation of **22**. Helpful discussions with Professor Richard Givens of the University of Kansas are gratefully acknowledged.

**Registry No.** **6a**, 85977-26-0; **6b**, 86022-65-3; **6c**, 83118-49-4; **6c**·HCl, 86022-69-7; **7a**, 50781-99-2; **7b**, 86022-66-4; **7c**, 83118-50-7; **7c**·HCl, 86022-71-1; **8a**, 50782-00-8; **8b**, 86022-67-5; **8c**, 83118-51-8; **8c**·HCl, 86022-73-3; **9a**, 85977-27-1; **9b**, 86022-68-6; **9c**, 83118-52-9; **9c**·HCl, 86022-74-4; **10a**, 13153-47-4; **10b**, 85977-34-0; **10c**, 62624-26-4; **11a**, 86022-61-9; **11b**, 85977-30-6; **11c**, 83118-47-2; **11c**·HCl, 86023-21-4; **12a**, 86022-62-0; **12b**, 85977-31-7; **12c**, 83118-48-3; **12c**·HCl, 86022-70-0; **13a**, 86022-63-1; **13b**, 85977-32-8; **13c**, 86022-72-2; **13c**·HCl, 86087-02-7; **14a**, 86022-64-2; **14b**, 85977-33-9; **14c**, 86022-76-6; **15a**, 13153-75-8; **15b**, 86022-75-5; **15c**, 58742-04-4; **16**, 85977-24-8; **17**, 121-01-7; **18**, 400-66-8; **19**, 85977-20-4; **20**, 85977-21-5; **21**, 85977-22-6; **21** (amine), 58458-13-2; **22**, 85977-23-7; **23**, 85977-25-9; **24**, 85977-28-2; **25**, 69103-41-9; **26**, 69103-42-0; **27**, 85977-29-3; cyclopentadiene, 542-92-7; phthalimide, 85-41-6.

# 3-Substituted 1-Methoxypyridinium Ions: Substituent Effects on Rates of Hydrogen–Deuterium Exchange

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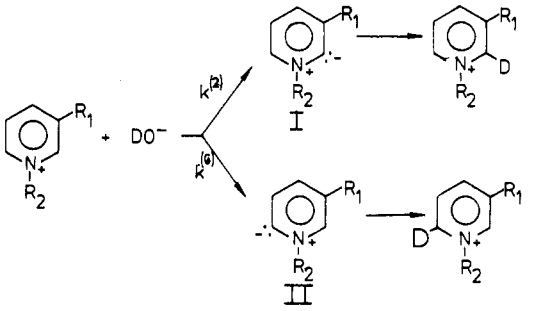
*Received November 1, 1982*

Pyridinium ylides are formed by deprotonation of the 2- and 6-positions of 3-substituted 1-methoxypyridinium ions in $D_2O$ buffer solutions at 75.0 °C in reactions catalyzed by deuterioxide ion. Dual substituent parameter equations employing inductive and resonance effects correlate rate constants very well. Both 1- and 3-substituents have an additive influence on the reactivity of the 2-position even when reactivity approaches a diffusion-controlled limit.

Various N-substituted pyridinium ions and pyridine *N*-oxides form ylides by a simple deprotonation process.[1] The reaction is catalyzed by the deuterioxide ion and not by buffer bases. Pathways are illustrated in Scheme I.

We report the results of hydrogen–deuterium exchange kinetic studies involving 3-substituted 1-methoxypyridinium ions ($R_2$ = $CH_3O$) in aqueous buffers. Reactive centers are situated ortho and para to the ring substituents ($R_1$). Ylides I and II are formed when the carbon acids are deprotonated by deuterioxide ion at the 2- and 6-positions. Our study involving ortho and para substituents in the *N*-methoxypyridinium ions is the most extensive to date. The results of this study along with those presented by Zoltewicz et al.[2,3] allow us to generalize about the effects of substituents on the rates of ylide formation. Some of our substrates are among the most acidic simple carbon acids known.

Scheme I




## Experimental Section

**Chemicals and Stock Solutions.** All common laboratory chemicals were reagent grade. Deuterium oxide was 99.8%.

Deuterated stock solutions of acetic, formic, and boric acids, sodium dihydrogen phosphate, sodium carbonate, sodium acetate, and sodium chloride were prepared by dissolving an appropriate weight of anhydrous reagent in a volumetric flask. Dilute DCl was prepared by diluting commercial concentrated DCl with $D_2O$. Stock sodium deuterioxide solution was prepared by dissolving freshly cut sodium in $D_2O$. Pyridinium perchlorates were prepared as previously.[4]

**Kinetic Procedure.** The pyridinium salt was weighed into a volumetric flask (2 mL). Stock solutions of buffer and NaCl were added by syringe. After dilution to the mark with $D_2O$, the substrate concentration was 0.5 M, and the ionic strength was 1.0 M. Samples in an NMR tube were placed in a constant-temperature bath at 75.0 ± 0.5 °C. Periodically, the tube was removed and quenched in ice, and the NMR spectrum of the solution was recorded. Rate constants for exchange at H-2,6 were obtained in the usual way from plots of log (H-2 and/or H-6/H-5) vs. time.[5] H-5 served as the NMR reference standard.

Following a kinetic run, pD measurements were made at 75.0 ± 0.5 °C on the reaction mixture from the NMR tube as well as on a portion of the original unheated mixture according to the method of Bates[6] by using a Radiometer PHM 61 pH meter and

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