(C), 129.2 (CH), 127.72 (CH), 127.69 (CH), 123.8 (CH), 119.6 (CH), 109.0 (CH), 14.8 ($CH_3$); high-resolution MS *m/e* 209.0840, $C_{14}H_{11}NO$ requires 209.0841.

**4-(Acetylamino)-2-methoxybiphenyl (25).** The crude product was made from 4-(acetylamino)-2-hydroxybiphenyl[12] by the procedure described above for **8**. The material was purified by chromatography on silica gel with EtOAc/hexanes (1/1) as eluent: mp 121–123 °C; IR (KBr) 1655 $cm^{-1}$; $^1H$ NMR (300 MHz, $CD_2Cl_2$) $\delta$ 7.50–7.30 (6H, m) 7.43 (1H, d, $J$ = 1.9 Hz), 7.23 (1H, d, $J$ = 8.2 Hz), 7.01 (1H, dd, $J$ = 8.2, 1.9 Hz), 3.79 (3H, s), 2.16 (3H, s); $^{13}C$ NMR (75.5 MHz, $CD_2Cl_2$) $\delta$ 168.6 (C), 157.2 (C), 139.1 (C), 138.6 (C), 131.1 (CH), 129.8 (CH), 128.3 (CH), 127.0 (CH), 126.6 (C), 111.8 (CH), 103.6 (CH), 55.8 ($CH_3$), 24.8 ($CH_3$); high-resolution MS *m/e* 241.1100, $C_{15}H_{15}NO_2$ requires 241.1103.

**4-(Acetylamino)-3-methoxybiphenyl (26).** This was synthesized from **29**[7] by the procedure described above for **8**. The crude product was recrystallized from MeOH: mp 109–110 °C; IR (KBr) 1662 $cm^{-1}$; $^1H$ NMR (300 MHz, $CD_2Cl_2$) $\delta$ 8.37 (1H, d, $J$ = 8.3 Hz), 7.81 (1H, s, broad), 7.61–7.57 (2H, m), 7.46–7.40 (2H, m), 7.35–7.30 (1H, m), 7.18 (1H, dd, $J$ = 8.3, 1.9 Hz), 7.13 (1H, d, $J$ = 1.9 Hz), 3.96 (3H, s), 2.18 (3H, s); $^{13}C$ NMR (75.5 MHz, $CD_2Cl_2$) $\delta$ 168.4 (C), 148.5 (C), 141.2 (C), 136.8 (C), 129.1 (CH), 127.7 (C), 127.5 (CH), 127.1 (CH), 119.9 (CH), 119.8 (CH), 109.2 (CH), 56.2 ($CH_3$), 25.0 ($CH_3$); high-resolution MS *m/e* 241.1102, $C_{15}H_{15}NO_2$ requires 241.1103.

Decomposition of **2b** in MeOH in the presence of **3** or **4** (0.1 M to 1.0 M) led to a number of adducts (**30–38**) and the reduction product **39**. The latter compound was identified by comparison to an authentic sample.[13] Two of the adducts (**35** and **38**) were identified by synthesis of authentic samples. The others were identified from spectral data after chromatographic separation from the reaction mixtures.

***N*-(4′-Aminophenyl)-4-(acetylamino)biphenyl (30):** mp 172–175 °C; IR (KBr) 3430, 3340, 1650 $cm^{-1}$; $^1H$ NMR (300 MHz, DMSO-$d_6$, 70 °C) $\delta$ 7.63–7.56 (2H, m), 7.59 (2H, d, $J$ = 8.6 Hz), 7.46–7.41 (2H, m), 7.34 (2H, d, $J$ = 8.6 Hz), 7.36–7.29 (1H, m), 7.01 (2H, d, $J$ = 8.7 Hz), 6.60 (2H, d, $J$ = 8.7 Hz), 5.03 (2H, s, broad), 1.93 (3H, s); $^{13}C$ NMR (75.5 MHz, DMSO-$d_6$, 70 °C) 169.3 (C), 156.8 (C), 147.6 (C), 139.3 (C), 137.2 (C), 131.4 (C), 128.4 (CH), 128.3 (CH), 126.9 (CH), 126.5 (CH), 126.4 (CH), 126.1 (CH), 114.0 (CH), 22.9 ($CH_3$); high-resolution MS *m/e* 302.1417, $C_{20}H_{18}N_2O$ requires 302.1419.

***N*-Acetyl-*N*-(4-biphenylyl)-*N*′-phenylhydrazine (31):** recrystallized from EtOAc/ hexanes, mp 214–216 °C; IR (KBr) 3270, 1650 $cm^{-1}$; $^1H$ NMR (300 MHz, DMSO-$d_6$, 70 °C) $\delta$ 8.83 (1H, s), 7.66–7.58 (2H, m) 7.62 (4H, AB quartet, $\Delta\nu$ = 14.5 Hz, $J$ = 9.0 Hz), 7.45–7.40 (2H, m), 7.35–7.30 (1H, m), 7.20–7.15 (2H, m), 6.76–6.72 (3H, m), 2.20 (3H, s); $^{13}C$ NMR (75.5 MHz, DMSO-$d_6$, 70 °C) $\delta$ 172.1 (C), 146.3 (C), 140.8 (C), 139.2 (C), 136.8 (C), 128.9 (CH), 128.4 (CH), 126.9 (CH), 126.2 (CH), 126.1 (CH), 123.2 (CH), 118.9 (CH), 111.5 (CH), 21.8 ($CH_3$); high-resolution MS *m/e* 302.1404, $C_{20}H_{18}N_2O$ requires 302.1419.

**4-(Acetylamino)-3-(phenylamino)biphenyl (32):** recrystallized from EtOAc/hexanes, mp 168–169 °C; IR (KBr) 3380, 3240, 1645 $cm^{-1}$; $^1H$ NMR (300 MHz, $CD_2Cl_2$) $\delta$ 7.88 (1H, d, $J$ = 8.4 Hz), 7.62 (1H, s, broad), 7.55–7.51 (3H, m), 7.42–7.31 (3H, m), 7.35 (1H, dd, $J$ = 8.4, 2.2 Hz), 7.23 (2H, t, $J$ = 8.0 Hz), 6.90–6.85 (3H, m), 5.86 (1H, s, broad), 2.12 (3H, s); $^{13}C$ NMR (75.5 MHz, $CD_2Cl_2$) $\delta$ 169.3 (C), 145.0 (C), 140.6 (C), 138.8 (C), 135.1 (C), 131.3 (C), 129.7 (CH), 129.1 (CH), 127.6 (CH), 127.1 (CH), 123.6 (CH), 123.0 (CH), 121.9 (CH), 120.7 (CH), 116.8 (CH), 24.5 ($CH_3$); high-resolution MS *m/e* 302.1415, $C_{20}H_{18}N_2O$ requires 302.1419.

**4-(Acetylamino)-2-(phenylamino)biphenyl or 5-(acetylamino)-2-(phenylamino)biphenyl (33):** recrystallized from EtOAc/hexanes, mp 156–158 °C; IR (KBr) 3400, 3310, 1675 $cm^{-1}$; $^1H$ NMR (300 MHz, $CD_2Cl_2$) $\delta$ 7.47 (1H, d, $J$ = 1.8 Hz), 7.45–7.40 (4H, m), 7.38–7.33 (1H, m), 7.29–7.24 (2H, m), 7.20 (1H, s, broad), 7.18 (1H, d, $J$ = 8.2 Hz), 7.13 (1H, dd, $J$ = 8.2, 1.8 Hz), 7.08–7.03 (2H, m), 6.97–6.91 (1H, m), 5.71 (1H, s, broad), 2.11 (3H, s); $^{13}C$ NMR (75.5 MHz, $CD_2Cl_2$) 168.4 (C), 143.2 (C), 141.2 (C), 139.0 (C), 138.6 (C), 131.5 (CH), 129.6 (CH), 129.6 (CH), 129.2 (CH), 127.7 (CH), 127.5 (C), 121.8 (CH), 119.1 (CH), 112.5 (CH), 108.2 (CH), 24.8 ($CH_3$); high-resolution MS *m/e* 302.1418, $C_{20}H_{18}N_2O$ requires 302.1419.

**2-(4′-Aminophenyl)-4-phenylacetanilide (34):** recrystallized from EtOAc/hexanes, mp 92–94 °C; IR (KBr) 3450, 3400, 1680 $cm^{-1}$; $^1H$ NMR (300 MHz, $CD_2Cl_2$) $\delta$ 8.30 (1H, d, $J$ = 8.4 Hz), 7.63–7.56 (2H, m), 7.54 (1H, dd, $J$ = 8.4, 2.3 Hz), 7.47 (1H, d, $J$ = 2.3 Hz), 7.45–7.39 (2H, m), 7.34–7.30 (1H, m), 7.28 (1H, s, broad), 7.21 (2H, d, $J$ = 8.3 Hz), 6.80 (2H, d, $J$ = 8.3 Hz), 3.91 (2H, s, broad), 2.02 (3H, s); $^{13}C$ NMR (75.5 MHz, $CD_2Cl_2$) $\delta$ 168.4 (C), 147.1 (C), 140.8 (C), 137.0 (C), 135.0 (C), 133.1 (C), 130.6 (CH), 129.1 (CH), 129.0 (CH), 127.7 (C), 127.5 (CH), 127.1 (CH), 126.3 (CH), 121.8 (CH), 115.6 (CH), 24.8 ($CH_3$); high-resolution MS *m/e* 302.1420, $C_{20}H_{18}N_2O$ requires 302.1419.

**3-(4′-Aminophenyl)-4-phenylacetanilide (35).** This material was isolated in very low yield from reaction mixtures. An authentic sample was synthesized from 3-(4′-nitrophenyl)-4-phenylaniline (**42**), which was obtained from 4′-nitrodeoxybenzoin and methyl vinyl ketone via a literature procedure.[14] Acetylation with acetyl chloride in the presence of *N*-ethylmorpholine in $CH_2Cl_2$, followed by catalytic reduction in EtOAc with 10% Pd/C at 50 psi of $H_2$, yielded the crude product. The material was purified by chromatography on silica gel with $CH_2Cl_2$/hexanes (1/1) as eluent: mp 224–227 °C; IR (KBr) 3460, 3370, 3320, 1670 $cm^{-1}$; $^1H$ NMR (300 MHz, $CD_2Cl_2$) $\delta$ 7.57 (1H, dd, $J$ = 8.3, 2.2 Hz), 7.41 (1H, d, $J$ = 2.2 Hz), 7.31 (1H, d, $J$ = 8.3 Hz), 7.29 (1H, s, broad), 7.22–7.12 (5H, m), 6.89 (2H, d, $J$ = 8.6 Hz), 6.52 (2H, d, $J$ = 8.6 Hz) 3.70 (2H, s, broad), 2.15 (3H, s); $^{13}C$ NMR (300 MHz, $CD_2Cl_2$) $\delta$ 168.5 (C), 145.9 (C), 141.9 (C), 141.5 (C), 137.8 (C), 136.5 (C), 131.5 (CH), 131.3 (C), 131.0 (CH), 130.1 (CH), 128.1 (CH), 126.5 (CH), 121.7 (CH), 118.4 (CH), 114.6 (CH), 24.8 ($CH_3$); high-resolution MS *m/e* 302.1414, $C_{20}H_{18}N_2O$ required 302.1419.

***N*-[4′-(Dimethylamino)phenyl]-4-(acetylamino)biphenyl (36):** recrystallized from EtOAc/hexanes, mp 132–134 °C; IR (KBr) 1660 $cm^{-1}$; $^1H$ NMR (300 MHz, DMSO-$d_6$, 75 °C) $\delta$ 7.64–7.58 (2H, m) 7.60 (2H, d, $J$ = 8.7 Hz), 7.46–7.41 (2H, m), 7.36 (2H, d, $J$ = 8.7 Hz), 7.36–7.31 (1H, m), 7.17 (2H, d, $J$ = 9.0 Hz), 6.73 (2H, d, $J$ = 9.0 Hz), 2.91 (6H, s), 1.95 (3H, s); $^{13}C$ NMR (75.5 MHz, DMSO-$d_6$, 75 °C) 169.2 (C), 149.1 (C), 142.8 (C), 139.2 (C), 137.3 (C), 131.6 (C), 128.4 (CH), 128.2 (CH), 126.9 (CH), 126.6 (CH), 126.5 (CH), 126.1 (CH), 112.3 (CH), 39.6 ($CH_3$), 22.9 ($CH_3$); high-resolution MS *m/e* 330.1733, $C_{22}H_{22}N_2O$ requires 330.1732.

**2-[4′-(Dimethylamino)phenyl]-4-phenylacetanilide (37):** recrystallized from EtOAc/hexanes, mp 138–140 °C; IR (KBr) 3280, 1650 $cm^{-1}$; $^1H$ NMR (300 MHz, $CD_2Cl_2$) $\delta$ 8.31 (1H, d, $J$ = 8.5 Hz) 7.63–7.59 (2H, m), 7.54 (1H, dd, $J$ = 8.5, 2.3 Hz), 7.49 (1H, d, $J$ = 2.3 Hz), 7.45–7.40 (2H, m), 7.35–7.30 (2H, obscured), 7.31 (2H, d, $J$ = 8.3 Hz), 6.86 (2H, d, $J$ = 8.3 Hz), 3.02 (6H, s), 2.03 (3H, s); $^{13}C$ NMR (75.5 MHz, DMSO-$d_6$, 70 °C) $\delta$ 168.2 (C), 149.5 (C), 139.5 (C), 137.0 (C), 136.2 (C), 134.1 (C), 129.1 (CH), 128.4 (CH), 127.8 (CH), 126.8 (CH), 126.4 (CH), 126.2 (CH), 126.0 (C), 124.5(CH), 112.1 (CH), 39.7 ($CH_3$), 22.8 ($CH_3$); high-resolution MS *m/e* 330.1732, $C_{22}H_{22}N_2O$ requires 330.1732.

**3-[4′-(Dimethylamino)phenyl]-4-phenylacetanilide (38).** This material was isolated in good yield from reaction mixtures of **2a**, but an authentic sample was produced by treatment of **35** with 2 equiv of MeI and $Na_2CO_3$ in dry DMF at 80 °C for 12 h. The crude product contained **35**, the monomethyl and dimethyl compounds, and small amounts of the trimethyl quaternary ammonium salt. Chromatography on silica gel with $CH_2Cl_2$/hexanes (1/1) eluent separated **38** from the reaction mixture: mp 195–197 °C; IR (KBr) 3300, 1660 $cm^{-1}$; $^1H$ NMR (300 MHz, $CD_2Cl_2$) $\delta$ 7.57 (1H, dd, $J$ = 8.3 2.3 Hz), 7.40 (1H, d, $J$ = 2.3 Hz), 7.31 (1H, d, $J$ = 8.3 Hz), 7.29 (1H, s, broad), 7.22–7.12 (5H, m), 6.98 (1H, d, $J$ = 8.9 Hz), 6.56 (1H, d, $J$ = 8.9 Hz), 2.90 (6H, s), 2.16 (3H, s); $^{13}C$ NMR (75.5 MHz, $CD_2Cl_2$) 168.5 (C), 149.8 (C), 142.1 (C), 141.6 (C), 137.8 (C), 136.5 (C), 131.6 (CH), 130.7 (CH), 130.1 (CH), 129.1 (C), 128.2 (CH), 126.5 (CH), 121.7 (CH), 118.3 (CH), 112.1 (CH), 40.5 ($CH_3$), 24.8 ($CH_3$); high-resolution MS *m/e* 330.1729, $C_{22}H_{22}N_2O$ requires 330.1732.

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(14) Kröhnke, F. *Chem. Ber.* **1950**, *83*, 35–50. Kröhnke, F.; Meyer-Delius, M. *Chem. Ber.* **1951**, *84*, 411–423. Kröhnke, F.; Vogt, I. *Ann. Chem.* **1954**, *589*, 26–44. Czerwinska-Fejgin, E.; Polaczkowa, W. *Rocz. Chem.* **1969**, *43*, 577–582. Kolaczkowska, E.; Polaczkowa, W. *Rocz. Chem.* **1971**, *45*, 13–17.

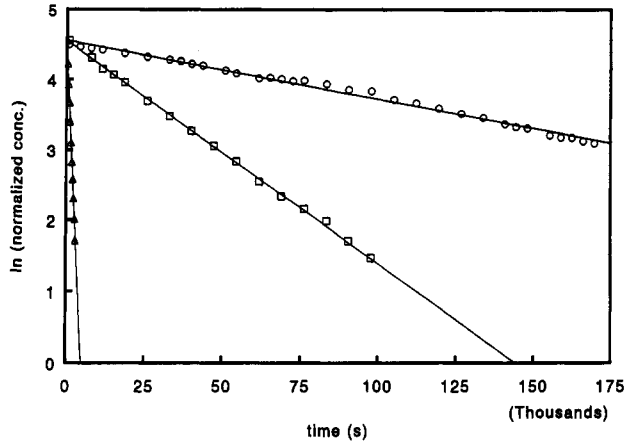



**Figure 1.** Plots of ln of the normalized peak area for the largest singlet in the $^1$H NMR spectra of **1a** (△), **1b** (□), and **2a** (○) vs time at 50 °C. Rate constants were determined from a linear least-squares fit of these data.

**4-(4′-Aminophenyl)-3-phenylacetanilide (40).** This compound was prepared in an analogous manner to **35** from 4-(4′-nitrophenyl)-3-phenylaniline (**43**), which was prepared, in turn, from 4-nitrodeoxybenzoin and methyl vinyl ketone by a published procedure:[15] mp 215–218 °C; IR (KBr) 3380, 3290, 3270, 1665 cm$^{-1}$; $^1$H NMR (300 MHz, $CD_2Cl_2$) δ 7.57 (1H, dd, $J$ = 8.3, 2.3 Hz), 7.43 (1H, d, $J$ = 2.3 Hz), 7.33 (1H, s, broad), 7.31 (1H, d, $J$ = 8.3 Hz), 7.24–7.14 (5H, m), 6.87 (2H, d, $J$ = 8.6 Hz), 6.50 (2H, d, $J$ = 8.6 Hz), 3.65 (2H, s, broad), 2.15 (3H, s); $^{13}$C NMR (75.5 MHz, $CD_2Cl_2$) δ 168.5 (C), 145.6 (C), 142.0 (C), 141.1 (C), 137.2 (C), 136.9 (C), 131.2 (CH), 131.0 (CH), 130.1 (CH), 128.2 (CH), 126.8 (CH), 122.0 (CH), 119.2 (CH), 114.6 (CH), 24.7 ($CH_3$), one signal, for a quaternary carbon, not found; high-resolution MS $m/e$ 302.1421, $C_{20}H_{18}N_2O$ requires 302.1419.

**4-[4′-(Dimethylamino)phenyl]-3-phenylacetanilide (41).** This material was prepared from **40** in the same manner that **38** was made from **35**. Purification by chromatography on silica gel ($CH_2Cl_2$/hexanes (1/1)) provided **41** contaminated with ca. 5% of the monomethyl compound. This was of sufficient purity for comparison purposes: mp 190–195 °C; IR (KBr) 3290, 1665 cm$^{-1}$; $^1$H NMR (300 MHz, $CD_2Cl_2$) δ 7.57 (1H, dd, $J$ = 8.3, 2.3 Hz), 7.42 (1H, d, $J$ = 2.3 Hz), 7.33 (1H, d, $J$ = 8.3 Hz), 7.30 (1H, s, broad), 7.25–7.15 (5H, m), 6.96 (2H, d, $J$ = 8.9 Hz), 6.56 (2H, d, $J$ = 8.9 Hz), 2.89 (6H, s), 2.15 (3H, s); $^{13}$C NMR (75.5 MHz, $CD_2Cl_2$) δ 168.4 (C), 149.5 (C), 142.2 (C), 141.0 (C), 137.0 (C), 136.9 (C), 131.3 (CH), 130.7 (CH), 130.1 (CH), 129.1 (C), 128.2 (CH), 126.8 (CH), 122.1 (CH), 119.2 (CH), 112.1 (CH), 40.6 ($CH_3$), 24.7 ($CH_3$); high-resolution MS $m/e$ 330.1729, $C_{22}H_{22}N_2O$ requires 330.1732.

## Results

Kinetics of the decomposition of **1a**, **1b**, and **2a** were monitored at 50 ± 1 °C by $^1$H NMR. Plots of the ln of the normalized peak area for the largest singlets of each compound vs time were linear for at least 4 half-lives for **1a** and **1b** and at least 2 half-lives for **2a** (Figure 1). Reactions of **2a** were generally not followed to the same degree of completion as the other two compounds because of the long half-lives ($t_{1/2} \geq 24$ h) for the decomposition of this ester. Rate constants determined under various conditions from the slopes of these plots are collected in Table I. More extensive kinetic data for **1a** at 35 °C were presented in an earlier paper.[6] The results show that **1b** and **2a** are considerably less reactive than **1a** under these conditions. We previously showed that in the presence of the aromatic amines aniline (**3**) and *N*,*N*-dimethylaniline (**4**) the rate constant for the decomposition of **1a** was unchanged, but these two amines efficiently trapped the nitrenium ion derived from N–O bond heterolysis of **1a** to generate a number of adducts.[6] It is clear from the data of Table I that moderate concentrations of **3** have little effect on the rate of decomposition of **1b** and the rate of decomposition of **2a** is actually decreased by ca. 25% in the presence of 0.1–0.2 M **3** or **4**. The rate constants for solvolysis of **1a** and **2a** are considerably depressed in MeOH, compared to $H_2O$. At $\mu$ = 0.5 M in 5 vol % $CH_3CN$–$H_2O$ at 20 °C the rate constant for hydrolysis of **1a** is 3.8 × 10$^{-2}$ s$^{-1}$.[9] Under the same conditions the rate constant for hydrolysis of **2a** is 4.0 × 10$^{-4}$ s$^{-1}$.[7]

**Table I. Rate Constants for the Decomposition of Esters of Carcinogenic *N*-Arylhydroxamic Acids at 50 °C in MeOD-$d_4$**

| ester | condns[a] | $k_{obs}$[b] (s$^{-1}$) |
|---|---|---|
| **1a** | MeOD-$d_4$ | (9.2 ± 0.1) × 10$^{-4}$ |
| **1b** | MeOD-$d_4$ | (3.2 ± 0.1) × 10$^{-5}$ |
| **1b** | MeOD-$d_4$, 4 mM $KHSO_4$ | (3.6 ± 0.1) × 10$^{-5}$ |
| **1b** | 0.1 M **3** | (3.4 ± 0.2) × 10$^{-5}$ |
| **2a** | MeOD-$d_4$ | (8.3 ± 0.3) × 10$^{-6}$ |
| **2a** | 0.1 M **3** | (6.1 ± 0.1) × 10$^{-6}$ |
| **2a** | 0.2 M **3** | (6.1 ± 0.1) × 10$^{-6}$ |
| **2a** | 0.1 M **4** | (6.3 ± 0.2) × 10$^{-6}$ |

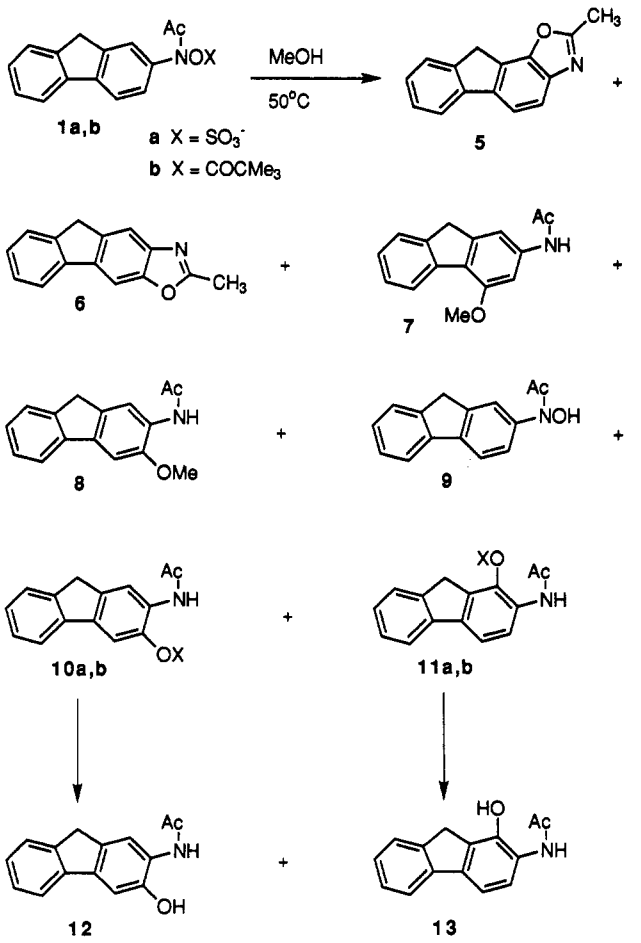
[a] Initial ester concentration is ca. 4 mM. [b] Determined by a linear fit of ln (normalized peak area) for the $^1$H NMR acyl methyl peak of **1a** and **2a**, or the *tert*-butyl peak of **1b**, vs time. Error limits are 2.5 standard deviations of the slope.

Normalized peak area data for all solvolysis products of **1a**, **1b**, and **2a**, except **12**, **13**, and **29**, also fit the first-order rate equation. These three materials are not initial solvolysis products of **1a** and **2a** but are formed from the decomposition of the sulfuric acid esters **10a**, **11a**, and **28**, which can be detected by $^1$H NMR at early reaction times. Control experiments previously showed that **10a** and **11a** decompose into **12** and **13**, respectively, under these conditions,[6] and experiments with authentic **28** also show that it decomposes into **29** under these conditions.

Solvolysis products of the three carcinogenic esters are shown in Schemes I and III, and their yields, determined by $^1$H NMR in MeOD-$d_4$ at 50 °C, are shown in Table II. The product yields shown for **1a** are very similar to those reported earlier at 35 °C, with the exception of the 3-methoxy product **8**. This compound was not identified previously, but examination of the earlier data shows that it was present in the mixtures in a yield similar to that reported here. The product yields for **1b** are very different from those for **1a**. The oxazoles **5** and **6** are not major products of the solvolysis of **1b**, and the pivalic acid esters **10b** and **11b** are considerably less labile than their sulfuric acid counterparts **10a** and **11a**. Only traces (≤2%) of **12** and **13** were found in solvolysis mixtures of **1b**. If 4 mM $KHSO_4$, the byproduct of solvolysis of **1a**, is added to the reaction mixture prior to solvolysis of **1b**, the relative yields of the products **5**–**8** become very similar to those observed for **1a** (Table II). This occurs with very little change in the rate constant for decomposition of **1b** (Table I). The combined yields of the rearrangement products **10b** and **11b** (ca. 55%) are considerably larger than the combined yields of the analogous sulfuric acid esters **10a** and **11a** (ca. 33%), which are the precursors of **12** and **13**.

The products of solvolysis of **2a** are quite similar, in general, to those obtained from **1a**. The major quantitative differences include a larger yield of the *N*-arylhydroxamic acid (20% for **27** vs 2.1% for **9**) and the rearrangement product (44% for **28**, measured as **29** vs 33% for **10a** and **11a**, measured as **12** and **13**). The hydrolysis products previously reported for **2a** are analogous in many cases to the methanolysis products reported here.[7,12] The hydroxy

**Scheme I**




analogues to the methoxy adducts **24**–**26** are found among the hydrolysis products of **2a**, but the relative yields of these products are very different.[7,12] In particular, the hydroxy analogue of **26** is generated in much lower relative yield than reported here.[7] The sulfuric acid ester **28** is also generated under hydrolysis conditions, but is a minor product in aqueous solution.[7] The oxazole **23** and the hydroxamic acid **27** were not observed among the hydrolysis products of **2a**.[7,12]

For all three compounds there are minor solvolysis products (≤3% for individual products) which can be detected by their $^1$H NMR peaks in the acyl methyl or *tert*-butyl regions of the spectrum. These products have not been identified either because of difficulty in separating them from the reaction mixtures or isolation of too little product for complete identification.

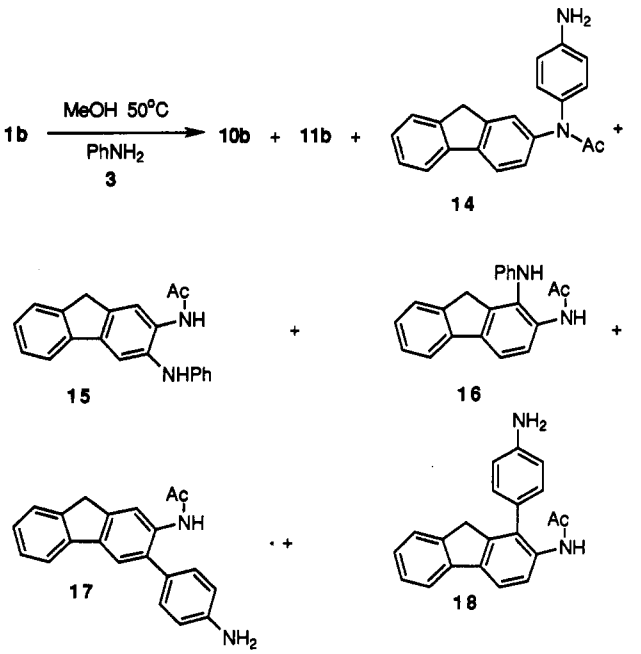
Although the rate constant for decomposition of **1b** is not affected by added **3** (Table I), the product distribution is greatly altered. Scheme II and Table III show that in 0.1 M solutions of **3** in MeOD-$d_4$ all the normal solvolysis products except **10b** and **11b** are no longer detectable. These products are replaced by a series of adducts that were also observed in the reaction of **1a** with **3**.[6] The conditions for the two experiments are somewhat different (35 °C vs 50 °C) but the relative yields of the products **14**–**18** are very similar to those previously reported for **1a**.[6] The rearrangement products **10b** and **11b** are produced in the same yield in the presence of 0.1 M **3** as they are in its absence. An increase in the concentration of **3** to 0.2 M has no discernible effect on the yields of any of the reaction products, with the possible exception of **9**. It appears from the data in Tables II and III that **3** may

**Table II. Yields of Solvolysis Products for 1a, 1b, and 2a at 50 °C in MeOD-$d_4$**

| 1a | | 1b | |
|---|---|---|---|
| product | % yield[a] | product | % yield[a] |
| **5** | 20 ± 2 | **5** | 0.8 ± 0.2 |
| **6** | 18 ● 2 | **6** | 1.2 ± 0.2 |
| **7** | 15 ± 1 | **7** | 9 ± 2 |
| **8** | 6 ± 1 | **8** | 3.5 ± 0.5 |
| **9** | 2.1 ± 0.5 | **9** | 1.8 ± 0.2 |
| **10a** | *b* | **10b** | 27 ● 3 |
| **11a** | *b* | **11b** | 26 ± 3 |
| **12** | 20 ± 2 | **12** | *c* |
| **13** | 13 ± 2 | **13** | *c* |
| **1b, 4 mM $KHSO_4$** | | **2a** | |
| product | % yield[a] | product | % yield |
| **5** | 13 ± 1 | **23** | 5.3 ± 0.5 |
| **6** | 12 ± 1 | **24** | 15 ± 1 |
| **7** | 7 ± 1 | **25** | 6.4 ● 0.5 |
| **8** | 3.0 ● 0.5 | **26** | 3 ± 1 |
| **9** | 2.2 ● 0.2 | **27** | 20 ± 3 |
| **10b** | 30 ● 3 | **28** | *d* |
| **11b** | 25 ± 3 | **29** | 44 ± 4 |
| **12** | *c* | | |
| **13** | *c* | | |

[a] Determined by NMR peak integration at completion of the kinetic run. These data are averages of duplicate or triplicate runs. Initial concentration of esters was ca. 4 mM. [b] Both **10a** and **11a** can be detected at early reaction times, but they decompose into **12** and **13**, respectively. See Results. [c] There are traces of these materials (≤2%) which are apparently derived from methanolysis of **10b** and **11b**. See Results. Their yields were summed into those of their precursors. [d] This material can be detected at early reaction times, but it decomposes into **29** under the reaction conditions.

**Scheme II**




weakly catalyze the acyl transfer reaction that generates the *N*-arylhydroxamic acid.

The effect of **3** and **4** on the reactions of **2a** is somewhat more complicated than appears to be the case for **1b**. Concentrations of these amines as low as 0.1 M cause a ca. 25% decrease in the rate constant for solvolysis of **2a**. Higher concentrations have no further effect. This appears to be due to the suppression of the S–O bond cleavage reaction previously described for **1a**.[6] We noted in the earlier paper that addition of either **3** or **4** to solvolysis reaction mixtures of **1a** halted the S–O bond cleavages

**Scheme III**

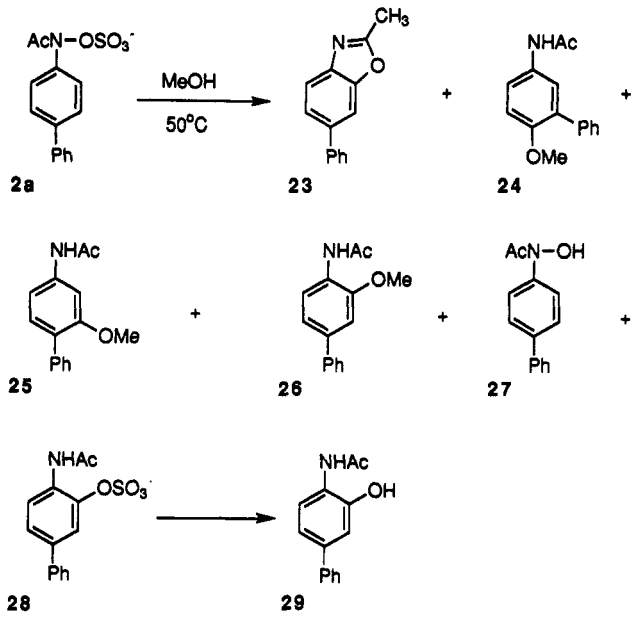



**Table III. Yields of Reaction Products for 1b in the Presence of 3 in MeOD-$d_4$ at 50 °C**

| product | % yield[a] 0.1 M 3 | % yield[a] 0.2 M 3 |
|---|---|---|
| 9 | 3.5 ± 0.5 | 5.0 ± 0.5 |
| 10b[b] | 29 ± 3 | 27 ± 3 |
| 11b[b] | 27 ± 3 | 26 ± 3 |
| 14 | 17 ± 2 | 15 ± 2 |
| 15 | 13 ± 1 | 13 ± 2 |
| 16 | 5 ± 1 | 4 ± 1 |
| 17 | 4 ± 1 | 4 ± 1 |
| 18 | t[c] | t[c] |

[a] Determined by NMR peak integration at completion of the kinetic run. These data are averages of duplicate runs. Initial concentration of 1b was ca. 4 mM. [b] Low yields of the respective hydroxy compounds 12 and 13 are summed into the yields of the rearrangement products. [c] Less than 1%, but detectable by comparison with an authentic sample.

that resulted in the formation of 9, 12, and 13.[6] This is apparently caused by an increase in the pH of the solution upon addition of the mildly basic amines. This does not lead to a noticeable change in the rate constant for decomposition of 1a because the reaction which forms 9 is a negligible part (ca. 3%) of the solvolysis of 1a in the absence of the amines. There is a noticeable effect in the case of 2a because the *N*-arylhydroxamic acid 27 accounts for 20 ± 3% of the overall solvolysis products in the absence of the amines (Table II). Support for this explanation is provided by the behavior of the rearranged product 28. In the absence of 3 or 4 it decomposes into 29 rapidly enough that after 10 half-lives of the solvolysis reaction it can no longer be detected (Table II). During the reaction in the presence of 0.1 M 3 or 4, 28 is still produced, but under these conditions it undergoes only very slow decomposition (Table IV). About 5% of 28 is converted into 29 after 10 half-lives of the decomposition of 2a under these conditions. This is consistent with previous observations concerning the stability of 10a and 11a under these reaction conditions.[6] Table IV also shows that no 27 is detected among the products of decomposition of 2a in the presence of the aromatic amines.

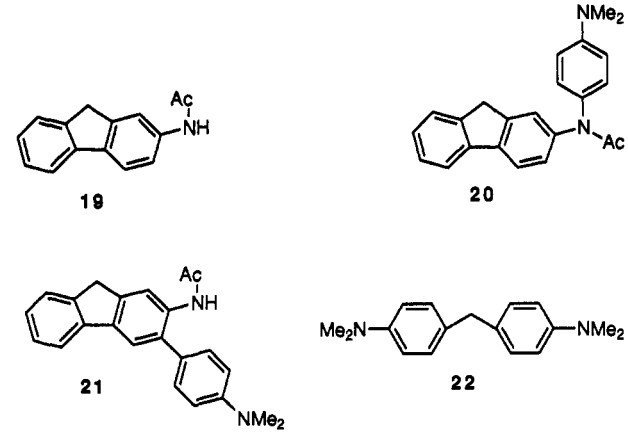
A variety of products are generated when 2a undergoes decomposition in the presence of 3 and 4 (Scheme IV). These compounds have structures which are analogous to

**Table IV. Yields of Reaction Products for 2a in the Presence of 0.1 M 3 or 0.1 M 4 in MeOD-$d_4$ at 50 °C**

| 0.1 M 3 product | 0.1 M 3 % yield[a] | 0.1 M 4 product | 0.1 M 4 % yield[a] |
|---|---|---|---|
| 28[b] | 62 ± 4 | 28[b] | 61 ± 4 |
| 30 | 2.3 ± 0.4 | 36 | 3.5 ± 0.4 |
| 31 | 2.1 ± 0.4 | 37 | 2.5 ± 0.4 |
| 32 | 9 ± 1 | 38 | 15 ± 1 |
| 33 | 7 ± 1 | 39 | 7 ± 1 |
| 34 | 2.0 ± 0.6 | | |
| 35 | 1.8 ± 0.4 | | |

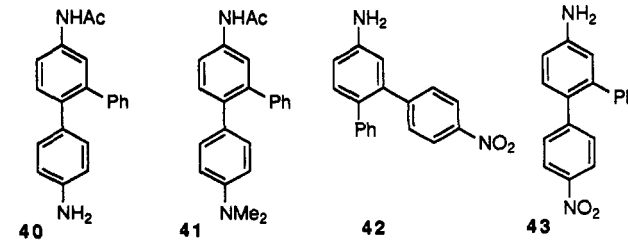
[a] Determined by NMR peak integration at completion of the kinetic run. Results reported are averages of two determinations. Initial concentration of 2a was 4 mM. [b] A small amount (ca. 5%) of 28 decomposes during these reactions into 29. This yield of 29 is included in the overall yield of 28.

the materials isolated from the reaction of 1a with 3 (14–18) and 4 (19–22).[6] The data of Table IV show that these




materials are generated at the expense of the normal solvolysis products, except 28. The yield of 28 observed under these conditions, 62 ± 4%, is consistent with the calculated yield of 59 ± 5% expected for 28 based on the product yield data of Table II and the correction of the overall solvolysis rate for the 25% of the reaction that leads to S–O bond cleavage in the absence of the aromatic amines.

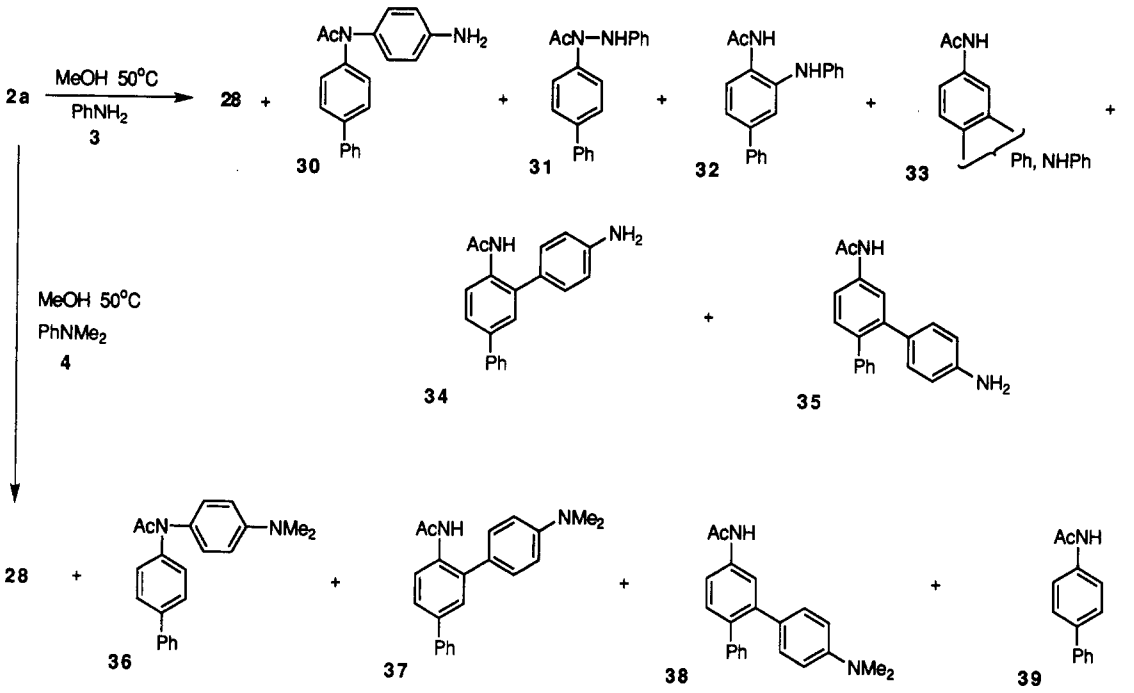
Identification of the structures of these adducts was based on $^1$H and $^{13}$C NMR data and independent synthesis. Both 35 and 38 were synthesized from 42, which was obtained from 4′-nitrodeoxybenzoin and methyl vinyl ketone via a procedure described in the literature.[14] The synthesis of 40 and 41 from 43, which was also available




from a literature procedure,[15] was instrumental in identifying 34 and 37. The structures 34, 35, and 40 represent all the chemically reasonable structures for adducts in which the para carbon of aniline is bound to the aromatic ring of the biphenyl nucleus that bears the nitrogen.[6,7,12]

(15) Czerwinska-Fejgin, E.; Polaczkowa, W. *Rocz. Chem.* **1966**, *40*, 421–428; **1966**, *40*, 615–620; **1967**, *41*, 1759–1766.

**Scheme IV**




The analogous structures in the *N*,*N*-dimethylaniline series are **37**, **38**, and **41**. All of these compounds can be distinguished from the other isomers by their characteristic $^1$H NMR spectra, so the identification of **34** and **37** is based on a process of elimination.

A second factor used to identify **34** and **37** depends on an unusually high-frequency chemical shift previously noted for the aromatic hydrogen ortho to the *N*-acetyl group of ortho-substituted acetanilides.[16] This effect has been attributed to a sterically induced conformational restriction of the *N*-acetyl group, which maximizes the anisotropic deshielding at the ortho-hydrogen.[16] This shift also occurs in similarly substituted derivatives of 4-(acetylamino)biphenyl.[7,12] The chemical shifts of these hydrogens in the $^1$H NMR spectra of **34** and **37** are $\delta$ 8.30 and 8.31, respectively, in $CD_2Cl_2$. These shifts are at ca. 0.7 ppm higher frequency than any of the chemical shifts for aromatic hydrogens of **35**, **38**, **40**, or **41**.

The availability of **40** and **41** by independent synthetic routes made it possible to search for these materials in the reaction mixtures of **2a** with **3** and **4**. It was not possible to confirm the presence of these materials in the reaction mixtures. If they are generated, their yields must be below the threshold for detection by $^1$H NMR (ca. 0.3–0.5%).

The N-substituted adducts **30**, **31**, and **36** are readily distinguishable from the other adducts because they have only 12 aromatic carbon resonances in their $^{13}$C NMR. All of the other adducts have 14.[17] The structural assignment for **32** is based on the high frequency $^1$H NMR shift ($\delta$ 7.88 in $CD_2Cl_2$) for the hydrogen ortho to the *N*-acetyl group, as described above. The two remaining chemically reasonable structures for **33**, 4-(acetylamino)-2-(phenylamino)biphenyl or 5-(acetylamino)-2-(phenylamino)biphenyl, cannot be distinguished by NMR data. There is precedent for both substitution patterns among the methoxy adducts of **2a**. Crystals suitable for X-ray analysis have not yet been grown.

Both **1a** and **2a** yield significant amounts of the reduction products **19** and **39**, respectively, in the presence of **4**. The oxidation byproduct, **22**, is formed in yields approximately equivalent to **19** for **1a**.[6] This material was not searched for in the present case.

## Discussion

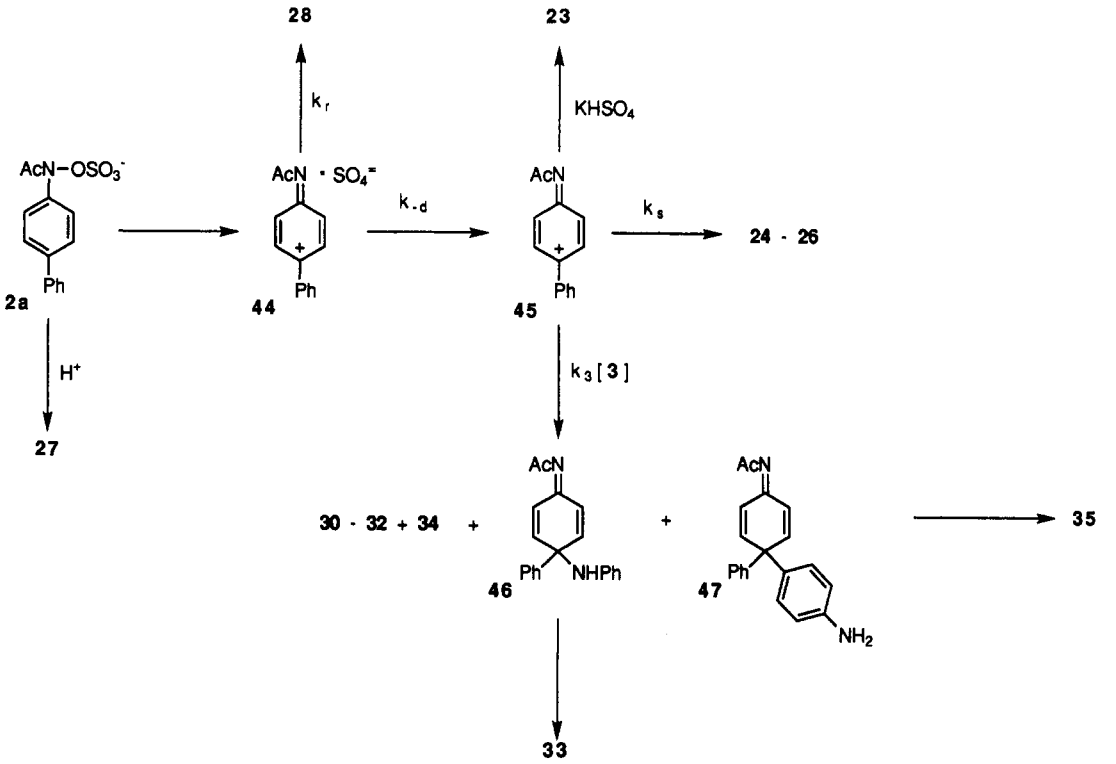
The behavior of **1b** and **2a** in MeOH in the presence or absence of **3** or **4** is similar, in general terms, to the results previously reported for **1a**.[6] After correction for the significant acid-catalyzed S–O bond cleavage process of **2a** which leads to **27**, it is clear that the two aromatic amines trap an intermediate generated after the rate limiting transition state for N–O bond cleavage for both **1b** and **2a**. Since the yields of the rearrangement products **10b**, **11b**, and **28** cannot be reduced by addition of **3** or **4** it is apparent that they are generated by a pathway different from the other major solvolysis products. All other solvolysis products, except the *N*-arylhydroxamic acids **9** and **27**, are generated from the same intermediates which react with the aromatic amines. The solvolysis product data for **1b** in the presence and absence of $KHSO_4$ indicate that the formation of significant amounts of the oxazoles **5**, **6**, and **23** is dependent on this salt. It is not presently clear why this is the case. A mechanism consistent with these results is shown for **2a** in Scheme V. A very similar mechanism was written for **1a**,[6] which could be adapted with minor changes for **1b**.

In the mechanism, the initially generated tight ion pair **44** can undergo internal return with rearrangement to form **28** or diffusional separation to generate the free ion **45**. In aqueous solution **45** reacts with the solvent with a first-order rate constant, $k_s$, of $4.9 \times 10^6$ s$^{-1}$ at 20 °C.[7] The second-order rate constant for its reaction with $H_2O$, $k_{H_2O}$, is then $8.8 \times 10^4$ M$^{-1}$ s$^{-1}$. The reactivity ratio $k_{MeOH}/k_{H_2O}$ for the 1-(4-methoxyphenyl)ethyl cation which has similar

(16) Ribera, A.; Rico, M. *Tetrahedron Lett* **1968**, 535–539. Zanger, M.; Simons, W. W.; Gennaro, A. R. *J. Org. Chem.* **1968**, *33*, 3673–3675.

(17) In fact, **33** and **40** show 13 $^{13}$C NMR resonances in the aromatic region. For **33**, integration of $^{13}$C NMR peaks shows that two tertiary carbon signals at $\delta$ 129.6 coincide. For **40** one of the quaternary carbon signals apparently is superimposed on another peak.

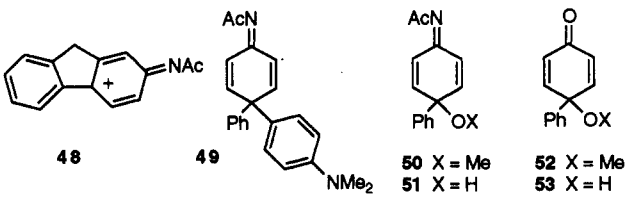
**Scheme V**




overall reactivity to **45**, is ca. 20,[18] so a reasonable estimate of $k_{MeOH}$ for **45** is $1.8 \times 10^6$ $M^{-1}$ $s^{-1}$. In neat MeOH the first-order rate constant for reaction of **45** with the solvent then is estimated to be $4.4 \times 10^7$ $s^{-1}$ at 20 °C. The accuracy of this estimate is admittedly fairly low, but it does serve to demonstrate that **45** will have sufficient lifetime, even in the nucleophilic solvent MeOH, to react selectively with nucleophiles as required by the mechanism of Scheme V. Since the *N*-acetyl-*N*-(2-fluorenyl)nitrenium ion **48** is somewhat less reactive with $H_2O$ than **45**,[7,9] it should have a longer lifetime in MeOH than **45** and react even more selectively with added nucleophiles. The lack of detectable trappable solvolysis products for **2a** at 0.1 M **3** indicates that $k_3/k_s \geq 300$ $M^{-1}$ for **45** in MeOH. The ratio $k_4/k_s$ must have a similar value. This suggests that the second-order rate constant for the reaction of **3** or **4** with **45** must be at or near the diffusion-controlled limit. The low regioselectivity of these reactions (Table IV) is consistent with this conclusion. Similar results for **1a** and **1b** indicate that **48** also reacts with **3** and **4** with a rate constant near the diffusion-controlled limit.

In aqueous solution ion pairs such as **44** have a finite lifetime if the counterion is a relatively weak nucleophile because the reaction of **45** with such species is activation limited.[7] In MeOH, $k_r$ must be approximately equal to $k_{-d}$ to account for the large yield of **28** (ca. 60% of solvolysis products due to N–O bond cleavage). The ion pair **44** does have a finite lifetime, but collapse of the tight ion pair to rearranged product is very fast. Similar conclusions must be made for the ion pair generated from **1b** since the combined yield of the rearrangement products **10b** and **11b** in that case is ca. 55%. An $^{18}O$ labeling study of this rearrangement is in progress and will be reported at a later date.

Several of the adducts formed between **45** and **3** or **4** are most easily explained by rearrangement of an initial unstable adduct. Specifically, **35** appears to arise from rearrangement of **47** and **33** from **46** (Scheme V). The *N*,*N*-dimethyl analogue of **35**, **38**, is most easily explained by rearrangement of **49**. The two methoxy adducts **24** and **25** appear to be derived from **50**. Although none of these initial adducts were directly observed, there is precedent for these arrangements. The unstable *N*-acetyl quinol ether imine **50** can be generated by anodic oxidation of **39** in MeOH.[12] It undergoes rapid acid catalyzed decomposition in aqueous solution to generate **24** and the hydroxy analogue of **25**, as well as the ketone **52**.[12] The kinetics of the formation of **24** are most easily explained by an acid-catalyzed dienone–phenol rearrangement, while the hydroxy analogue of **25** must be formed by an addition–elimination mechanism.[12,19] During the hydrolysis of **2a** an unstable intermediate, identified by $^1H$ NMR as **51**, builds up to detectable levels.[7,12] This material decomposes rapidly in an aqueous environment in a manner analogous to **50** to generate the hydroxy analogues of **24** and **25** and the ketone **53**.[7,12]




**48** **49** **50** X = Me **51** X = H **52** X = Me **53** X = H

As expected from the aqueous solution studies, in MeOH the product of the dienone–phenol rearrangement, **24**, predominates over **25** (Table II). In this case **25** does not have to be formed by an addition–elimination sequence, but our data provide no means of distinguishing between

(18) Richard, J. P.; Rothenberg, M. E.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 1361–1372. Richard, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 1373–1383.

(19) Gassman, P. G.; Granrud, J. E. *J. Am. Chem. Soc.* **1984**, *106*, 2448–2449.

the two alternative mechanisms. The generation of **35** and **38** in our reaction mixtures without the formation of detectable amounts of **40** and **41** is consistent with the expected relative migratory ability of the two aromatic groups in **47** and **49**. Since **50** and **51** undergo predominately the dienone–phenol rearrangement in acidic to neutral solution, we expect that **46** suffers a similar fate. On the basis of that precedent, we tentatively identify **33** as 5-(acetylamino)-2-(phenylamino)biphenyl.

The compounds described in this and the earlier paper,[6] **1a**, **1b**, and **2a**, span the reactivity range of esters of carcinogenic *N*-arylhydroxamic acids which have been shown to undergo N–O bond cleavage in a predominately aqueous environment. Both **1a** and **2a** undergo solvolysis in $H_2O$ and MeOH by N–O bond heterolysis to generate nitrenium ions.[6,7,9] The 2-fluorenyl group has the most negative $\sigma^+$ of the aryl groups which are commonly found in carcinogenic *N*-arylhydroxamic acids, while the 4-biphenyl group has the least negative $\sigma^+$.[20] Since the rates of these solvolysis reactions correlate reasonably well with $\sigma^+$,[4,9,21] **1a** and **2a** represent the reactivity extremes of sulfuric acid esters of carcinogenic *N*-arylhydroxamic acids. Acetic acid esters of most *N*-arylhydroxamic acids undergo ester hydrolysis in preference to N–O bond heterolysis in aqueous solution.[22] Only **1c** and a few other compounds of similar reactivity undergo N–O bond heterolysis, while less reactive materials such as **2c** undergo ester hydrolysis.[22] Sterically hindered esters have suppressed rates of hydrolysis which make it possible to observe N–O bond heterolysis in less intrinsically reactive systems.[8,23] These synthetic compounds are significantly less reactive than the ultimate carcinogens generated *in vivo* such as **1a** and **2a**.[8,23]

Our results, then, indicate that all the commonly occurring reactive esters of carcinogenic *N*-arylhydroxamic acids will undergo solvolysis to generate nitrenium ions in MeOH, a solvent that is both more nucleophilic than $H_2O$[18] and less able to stabilize the transition state for N–O bond heterolysis to generate nitrenium ions.[6,7,9] Moreover, these compounds will react with simple aromatic amines in MeOH via an $S_N1$ rather than $S_N2$ mechanism. Generation of the nitrenium ion in $H_2O$ will be considerably more facile, and the nitrenium ion, once formed, will be less reactive with the solvent, so these ions should react selectively with simple aromatic amines in an aqueous environment, also. We are currently extending this study to the investigation of the mechanism of reaction of **1a** and **2a** with nucleotides in an aqueous environment. It is clear from this, and our other work with these compounds,[6,7,9] that selective nitrenium ions are generated *in vivo* from these compounds. It is not yet clear that nitrenium ions are responsible for all the *in vivo* reactions of these materials.

**Acknowledgment.** This work was supported by a grant from the American Cancer Society (CN-23J). The 300-MHz $^1H$ and 75.5-MHz $^{13}C$ NMR spectra were obtained at Miami with equipment funded by NSF Grant No. CHE-9021532. High-resolution mass spectra were obtained at the Ohio State University Chemical Instrumentation Center.

**Supplementary Material Available:** $^{13}C$ NMR spectra for **1b**, **8**, **10b**, **11b**, **23**, **25**, **26**, **30–38**, **40**, and **41** (21 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(20) The $\sigma^+$ values for the aryl groups of the common carcinogenic *N*-arylhydroxamic acids are as follows: 2-fluorenyl, –0.49; 4-stilbenyl, –0.41; 2-phenanthryl, –0.2; 2-naphthyl, –0.18; 4-biphenyl, –0.18. Hansch, C.; Leo, A. *Substituent Constants for Correlation Analysis in Chemistry and Biology*; Wiley: New York, 1979.

(21) Novak, M.; Pelecanou, M.; Roy, A. K.; Andronico, A. F.; Plourde, F. M.; Olefirowicz, T. M.; Curtin, T. J. *J. Am. Chem. Soc.* **1984**, *106*, 5623–5631. Gassman, P. G.; Granrud, J. E. *J. Am. Chem. Soc.* **1984**, *106*, 1498–1499.

(22) Underwood, G. R.; Kirsch, R. B. *J. Chem. Soc., Chem. Commun.* **1985**, 136–138. Underwood, G. R.; Davidson, C. M. *J. Chem. Soc., Chem. Commun.* **1985**, 555–556. Underwood, G. R.; Callahan, R. J. *Tetrahedron Lett.* **1987**, *28*, 5427–5430. Nicolaou, C.; Underwood, G. R. *Tetrahedron Lett.* **1989**, *30*, 1479–1482.

(23) Underwood, G. R.; Price, M. F.; Shapiro, R. *Carcinogenesis* **1988**, *9*, 1817–1821.

# Thermal Fragmentation of Trihaloethyl and Hexafluoro-2-propyl (α-Hydroxyiminobenzyl)phosphonates. Solvent Effects and the Trapping of Metaphosphate

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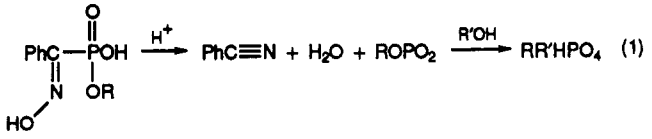
*Received June 29, 1993*•

Reactions of 2,2,2-trihaloethyl or 1,1,1,3,3,3-hexafluoro-2-propyl benzoylphosphonate anions **7** or **10** with hydroxylamine gave the corresponding (α-hydroxyiminobenzyl)phosphonates, **3** or **11**, respectively, as predominantly (*E*)-isomers. Refluxing (*E*)-**3a** or (*E*)-**3b** in EtOH or 2-PrOH caused them to fragment to benzonitrile and mixed phosphodiesters: ethyl trihaloethyl phosphate (**12**) or 2-propyl trihaloethyl phosphate (**13**), respectively. (*E*)-**3a** did not undergo any fragmentation in boiling water or MeOH. Refluxing (*E*)-**3a** in aprotic solvents led to the formation of benzonitrile and *P,P'*-bis-(2,2,2-trifluoroethyl)pyrophosphate (**4a**). The rate of fragmentation increased with solvent polarity. Similar behavior was exhibited by **11**. The fragmentation of anions **3** and **11** is interpreted in terms of a dissociative mechanism leading to the formation of metaphosphate in the first step. The lack of reactivity in water and methanol is rationalized by assuming stabilization of the starting material by H-bond formation, while the rate enhancement by polar solvent is attributed to stabilization of the transition state and solvation of the departing $OH^-$ by the solvent. The metaphosphate formed in the thermal fragmentation of **3a** in MeCN was trapped by styrene oxide, as evidenced by the isolation and identification of 2-oxo-2-(2',2',2'-trifluoroethyl)-4-phenyl-1,3,2-dioxaphospholane as a mixture of diastereoisomers **18** and **19**.

## Introduction

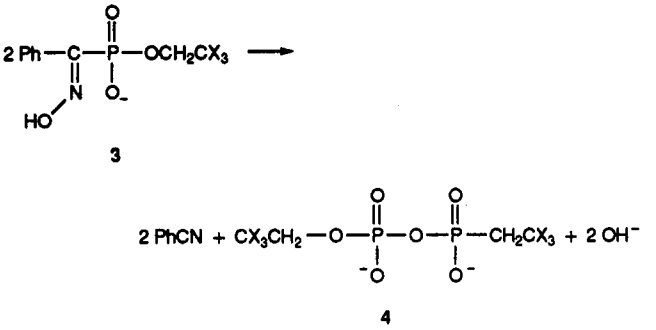
Previously we reported that (α-hydroxyiminophenyl)-phosphonic acids (e.g. **1**) and monoesters (**2**) undergo acid-catalyzed fragmentation to monomeric metaphosphoric acid[1] or ester,[2,3] respectively, and consequently may act as phosphorylating agents (eq 1).[1-4]



**1**, R = H
**2**, R = alkyl

In the course of our studies on the effect of structure on the behavior of this class of compounds, we examined a series of 2,2,2-trihaloethyl (α-hydroxyiminobenzyl)-phosphonates.[5] We found that, in contrast to the anion of methyl ester **2** (R = Me) which is thermally stable, the anion of 2,2,2-trifluoroethyl (α-hydroxyiminobenzyl)-phosphonate (**3a**) yields upon heating in acetonitrile a pyrophosphate derivative (**4a**) (Scheme I). Since this was interpreted in terms fragmentation of **3a** to a metaphosphate, we considered that phosphonates of type **3** could serve as starting materials to mixed phosphates containing 2,2,2-trihaloethyl groups. Such groups are useful for protection of phosphates and they are known to be easily removable under mild conditions.[6] In the present paper we wish to describe results of our studies aimed at determining the synthetic potential of compounds of type **3** under different conditions.

**Scheme I**[a]



[a] **a**, X = F; **b**, X = Cl.

## Results and Discussion

**Synthesis of Polyhaloalkyl (α-Hydroxyiminobenzyl)phosphonate Anions.** The syntheses of compounds **3** are described in our previous paper. Two main approaches can be employed: (1) Demethylation of methyl 2,2,2-trihaloethyl (α-hydroxyiminobenzyl)phosphonates (**5**).[5] These compounds are obtained, usually as predominantly (*Z*)-isomers, by the reaction of the corresponding dialkyl acylphosphonates with hydroxylamine. The oxime stereochemistry is preserved in the dealkylation illustrated

• Abstract published in *Advance ACS Abstracts*, December 1, 1993.

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(3) Katzhendler, J.; Karaman, R.; Gibson, D.; Leader, H.; Breuer, E. *J. Chem. Soc., Perkin Trans. 2* **1989**, 589.

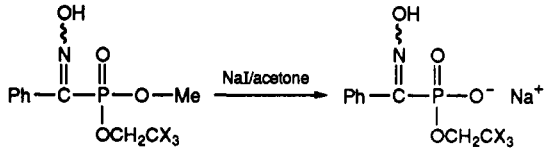
(4) Quin, L. D.; Wu, X.-P.; Breuer, E.; Mahajna, M. *Tetrahedron Lett.* **1990**, *31*, 6281.

(5) Breuer, E.; Mahajna, M. *Heteroat. Chem.* **1992**, *3*, 251.

(6) For use of 2,2,2-trichloroethyl group, see: Denharton, J. A.; Wijnands, R. A.; Van Boom, J. H. *J. Org. Chem.* **1981**, *46*, 2242. For 2,2,2-trifluoroethyl, see: Neilson, P. W.; Neilson, R. H. *Inorg. Chem. Soc.* **1980**, *19*, 1875. For 1,1,1,3,3,3-hexafluoro-2-propyl, see: Hosaka, H.; Suzuki, Y.; Sato, H.; Gug-Kim, S.; Takaku, H. *Nucleic Acids Res.* **1991**, *19*, 2935; and *Tetrahedron Lett.* **1991**, *32*, 785.

0022-3263/93/1958-7822$04.00/0 

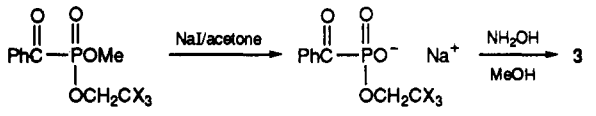
**Scheme II**[a]




5 3

[a] a, X = F; b, X = Cl.

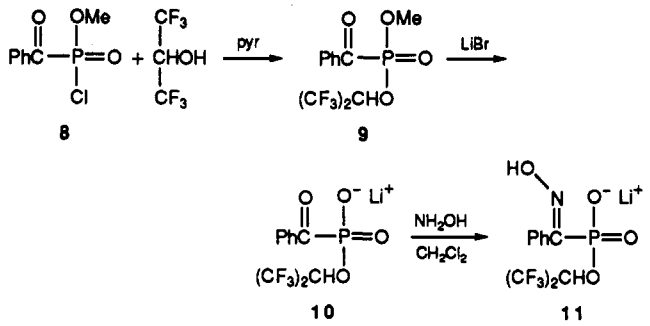
**Scheme III**[a]




6 7

[a] a, X = F, b, X = Cl.

**Scheme IV**




8 9 10 11

in Scheme II.[7] (2) Reaction of trihaloethyl benzoylphosphonate anions 7[5] with hydroxylamine. This synthetic route, which leads predominantly to (*E*)-isomers, is illustrated in Scheme III.

The latter approach was found applicable also for the preparation of lithium 1,1,1,3,3,3-hexafluoro-2-propyl (α-hydroxyliminobenzyl)phosphonate (**11**). Methyl benzoylphosphonochloridate (**8**)[8] was reacted with 1,1,1,3,3,3-hexafluoro-2-propanol in dichloromethane in the presence of pyridine. The resulting benzoylphosphonate mixed ester **9** was dealkylated by lithium bromide in acetonitrile, to yield ester salt **10**, which in turn was converted to the oxime **11** by hydroxylamine in dichloromethane (Scheme IV). In this case too, the product **11** formed was predominantly (*E*).

**Thermal Fragmentation of Polyhaloalkyl (α-Hydroxyiminobenzyl)phosphonate Anions.** We examined the thermal behavior of monoanions **3a** in a series of refluxing solvents. The results are summarized in Table I. It is seen from the data in this table that there was no fragmentation observed in water and in methanol in 12–14 h. In contrast, when a solution of **3a** in ethanol or 2-propanol was refluxed, monitoring the reaction mixture by $^{31}P$ NMR spectroscopy revealed the gradual disappearance of the starting material and the evolvement of a new phosphorus-containing product. In ethanol the new peak was a quintet at 0.45 ppm and in 2-propanol it was a quartet at −0.33 ppm. These chemical shifts and splitting patterns indicate the formation of mixed phosphodiesters **12a** and **13a**, respectively (Scheme V). When the reaction was performed in a mixture of ethanol and 2-propanol (experiment 6, Table I), the formation of two mixed phosphodiesters, **12a** and **13a** was observed in the same ratio as the molar ratio of the two alcohols in the medium. The formation of two mixed phosphodiesters, **12a** and **13a**, in this experiment, in the same molar ratio as that of the two alcohols comprising the medium shows lack of selectivity among the two sterically different alcohols and confirms that the alcohols are not involved in the rate-determining step of the reaction. The absence of steric effect has been applied previously by several research groups as a diagnostic tool to distinguish between associative- and dissociative-type mechanisms.[9,10]

In all aprotic solvents examined the reactions yielded benzonitrile and a single phosphorus-containing product resonating at −11.3 ppm. This chemical shift is consistent with the bis(2,2,2-trifluoroethyl)pyrophosphate (**4a**) structure. We also examined, to a limited extent, the thermal behavior of 2,2,2-trichloroethyl (α-hydroxyiminobenzyl)-phosphonate (**3b**) and 1,1,1,3,3,3-hexafluoro-2-propyl (α-hydroxyiminobenzyl)phosphonate (**11**) anions. The results obtained for **3b** and **11** are summarized in Tables II and III, respectively. Thermal treatment of these compounds led to products of the same type as that of **3a**. Reflux of **3b** in 2-propanol gave mixed phosphodiester **13b**, while reflux in MeCN gave pyrophosphate **4b**. Similarly, heating 1,1,1,3,3,3-hexafluoro-2-propyl (α-hydroxyiminobenzyl)phosphonate (**11**) in EtOH or 2-PrOH gave hexafluoro-2-propyl ethyl or hexafluoro-2-propyl 2-propyl phosphates **15** and **16**, respectively (Scheme VI), while heating **11** in MeCN gave pyrophosphate **17** (Scheme VII).

Although these experiments were all carried out at different temperatures, and therefore cannot be viewed as kinetic studies, some trends are clearly apparent. From the results listed in Tables I–III, two points arise that deserve consideration. These are (i) the solvent effect on the reaction and (ii) the specificity of the (*E*)-oximes, as opposed to the (*Z*)-oximes, to undergo fragmentation.

**(i) Effect of Solvent.** The lack of fragmentation of **3a** in refluxing water and methanol can be attributed to stabilization of the starting material by solvent hydrogen bonding.[11] The variation of the reaction rate with the changing of the hydroxylic solvents in our case is, therefore, in accordance with a concerted dissociative mechanism involving the formation of metaphosphate (**14**, Scheme V) in the first step and its subsequent trapping by the solvent.

Although the solubilities of **3a** in the various aprotic solvents are different, as are the boiling points of the

(7) The assignment of the oxime stereochemistry is based on $^{31}P$ NMR shifts. For correlation of $^{31}P$ NMR shifts with stereochemistry in hydroxyiminophosphonates, see: Breuer, E.; Karaman, R.; Goldblum, A.; Gibson, D.; Leader, H.; Potter, B. V. L.; Cummins, J. H. *J. Chem. Soc., Perkin Trans. 1*, **1988**, 3047.

(8) Breuer, E.; Mahajna, M.; Quin, L. D.; Quin, G. S. *J. Org. Chem.* **1991**, *56*, 4791.

(9) (a) Freeman, S.; Friedman, J. M.; Knowles, J. R. *J. Am. Chem. Soc.* **1987**, *109*, 3166; **1988**, *110*, 1268. (b) Cullis, P. M.; Nicholls, D. *J. Chem. Soc., Chem. Commun.* **1987**, 783. (c) Ramirez, F.; Marecek, J. F. *Tetrahedron* **1979**, *35*, 1581; **1980**, *36*, 3151. (d) Friedman, J. M.; Knowles, J. R. *J. Am. Chem. Soc.* **1985**, *107*, 6126.

(10) The same type of test was applied to other metaphosphate analogs using amines of differing steric requirements: (a) Harger, M. J.; Smith, A. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2507. (b) Coogan, M. P.; Harger, M. J. *J. Chem. Soc., Chem. Commun.* **1990**, 1745.

(11) A similar type of solvent effect was seen in the fragmentation of benzisoxazole-3-carboxylic acids. These undergo quantitative decarboxylation to salicylonitriles via a concerted mechanism. The rate constants of this fragmentation reaction were found to vary over a range of $10^8$ from water to HMPA, water being the slowest: (a) Kemp, D. S.; Cox, D. D.; Paul, K. G. *J. Am. Chem. Soc.* **1975**, *97*, 7312. (b) Kemp, D. S.; Paul, K. G. *Ibid.* **1975**, *97*, 7305. (c) Kemp, D. S.; Reczek, J.; Vellaccio, F. *Tetrahedron Lett.* **1978**, 741.