Nucleophilic Aromatic Substitution on Ester Derivatives of Carcinogenic *N*-Arylhydroxamic Acids by Aniline and *N,N*-Dimethylaniline

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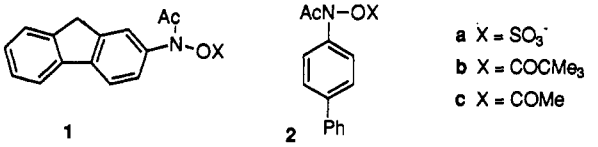
Decomposition of *N*-(pivaloyloxy)-2-(acetylamino)fluorene (**1b**) and *N*-(sulfonatooxy)-4-(acetylamino)-biphenyl (**2a**) in MeOH occurs predominately via N–O bond cleavage to yield oxazoles (**5, 6, 23**), methoxy adducts (**7, 8, 24, 25, 26**), and rearrangement products (**10b, 11b, 28**). Minor ester methanolysis paths lead to the *N*-arylhydroxamic acids (**9, 27**). In the presence of 0.1 M aniline (**3**), **1b** yields a number of adducts (**14–18**) identical to those previously obtained from the reaction of **3** with *N*-(sulfonatooxy)-2-(acetylamino)fluorene (**1a**). This occurs with no change in the rate constant for decomposition of **1b**. At 0.1 M **3** all solvolysis products of **1b**, except the rearrangement products **10b** and **11b**, are reduced below detectable levels. Similar results were obtained for **2a**, which yields the adducts **30–35** in the presence of **3** and **36–38** in the presence of *N,N*-dimethylaniline (**4**). These results are consistent with a mechanism (Scheme V) in which the N–O bond heterolysis leads to a tight ion pair that can undergo internal return to yield the rearrangement products or diffusional separation to yield the free ion. The free nitrenium ion can be trapped by solvent or added nucleophiles. Both the *N*-acetyl-*N*-(4-biphenylyl)nitrenium ion (**45**) and the *N*-acetyl-*N*-(2-fluorenyl)nitrenium ion (**48**) react slowly enough with the solvent to undergo selective reaction with strong nucleophiles. Since **1a**, **1b**, and **2a** span the reactivity range of the ester derivatives of the common *N*-arylhydroxamic acids which undergo N–O bond heterolysis in H_2O, it appears that all of the carcinogenic esters will react with simple aromatic amines via an S_N1 mechanism.

We are interested in the mechanisms of nucleophilic aromatic substitution on esters of *N*-arylhydroxylamines because these reactions are relevant to the problems of chemical carcinogenesis by hydroxylamine derivatives.[1,2] The factors which determine whether S_N1 or S_N2 mechanisms are followed in these nitrogen analogues to the well studied benzyl, 1-phenylethyl, or cumyl systems[3] is also of considerable fundamental interest.

The reactions of carcinogens derived from *N*-arylhydroxylamines with aromatic amines in MeOH serve as simple model systems for the interactions of these materials with the DNA bases.[4-6] We first discovered that a number of *N*-aryl-*O*-pivaloylhydroxylamines react efficiently with aniline or *N,N*-dimethylaniline in MeOH to yield diphenylamines or hydrazines by an S_N2 mechanism.[4] The reaction products were formed by direct nucleophilic attack on the nitrogen of the model carcinogen.[4] Subsequently, other workers demonstrated kinetically bimolecular reactions between a number of hydroxylamine derivatives and simple aromatic amines in THF or MeOH.[5] More recently, we found that the hepatacarcinogen *N*-(sulfonatooxy)-2-(acetylamino)fluorene (**1a**) reacts with



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aniline or *N,N*-dimethylaniline to yield a large number of adducts via an S_N1 pathway.[6] Most of the reaction products isolated in this case were formed by nucleophilic substitution on the aromatic ring.[6] The difference in behavior of these materials was attributed to a steric effect of the *N*-acetyl group which hindered the S_N2 attack of the aromatic amines.[6] The *N*-acetyl group also slows down the generation of the nitrenium ion, but once generated, the *N*-acetyl group has remarkably little effect on the subsequent reactions of the nitrenium ion.[7]

In an effort to determine if decreasing the reactivity of **1a** would lead to a change in the mechanism of this reaction, we have examined the reactions of *N*-(pivaloyloxy)-2-(acetylamino)fluorene (**1b**) and *N*-(sulfonatooxy)-4-(acetylamino)biphenyl (**2a**) with aromatic amines in MeOH. Both of these compounds are considerably less

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labile than **1a**.[7-9] Replacement of the SO_4^{2-} leaving group of **1a** with the pivalate leaving group of **1b** leads to a decrease in the rate of hydrolysis of about 400-fold,[8] and **2a** undergoes hydrolysis 95-fold more slowly than **1a** at 20 °C in 5% CH_3CN–H_2O.[7,9]

In spite of the decreased reactivity of **1b** and **2a**, the results reported in this paper show that the mechanism of reaction of these materials with aromatic amines is the same as that of the more reactive **1a**. These three compounds show remarkable similarity in their solvolysis in MeOH and their reactions with aniline or *N,N*-dimethylaniline which provides evidence for a common reaction mechanism under these conditions for all esters of carcinogenic *N*-arylhydroxamic acids. These results also have implications for the *in vivo* reactions of ester derivatives of *N*-arylhydroxamic acids.

Experimental Section

The synthesis of **1a** and **2a**, as their K^+ salts, the purification of the amines **3** and **4**, and the solvent MeOH have been described previously.[4,7,10]

***N*-(Pivaloyloxy)-2-(acetylamino)fluorene (1b).** A solution of 78.9 mg (0.33 mmol) of *N*-hydroxy-2-(acetylamino)fluorene (**9**)[11] and 38.4 μL (0.33 mmol) of *N*-ethylmorpholine in 2 mL of dry CH_2Cl_2 was stirred under a N_2 atmosphere at 0 °C, while a solution of 40.6 μL (0.33 mmol) of pivaloyl chloride in 0.5 mL of CH_2Cl_2 was added in a dropwise fashion. The reaction mixture was stirred for an additional 6 h at room temperature. The reaction mixture was washed with 5% aqueous $NaHCO_3$ (1 × 3 mL) and then with distilled H_2O (2 × 3 mL). The organic material was dried over Na_2SO_4, and the solvent was then removed by rotary evaporation. The gummy residue which remained was subjected to column chromatography on silica gel with a CH_2Cl_2/EtOAc (9/1) eluent. After evaporation of solvent, 85 mg (80%) of material was recovered: mp 96–98 °C; IR (KBr) 1771, 1688 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6, 70 °C) δ 7.93 (1H, d, J = 8.2 Hz), 7.89 (1H, d, J = 7.0 Hz), 7.65 (1H, d, J = 1.9 Hz), 7.58 (1H, d, J = 7.5 Hz), 7.44 (1H, dd, J = 8.2, 1.9 Hz), 7.39 (1H, t, J = 7.0 Hz), 7.33 (1H, t, J = 7.4 Hz), 3.92 (2H, s), 2.06 (3H, s), 1.26 (9H, s); ^{13}C NMR (75.5 MHz, DMSO-d_6, 70 °C) δ 174.5, 166.5, 143.5, 143.1, 140.7, 139.7, 137.6, 126.8, 126.5, 124.7, 123.9, 122.0, 119.9, 119.8, 37.4, 36.1, 26.1, 20.9; high-resolution MS *m/e* 323.1558, $C_{20}H_{21}NO_3$ requires 323.1521.

Kinetics. The kinetics of the decomposition of **1b** and **2a** were monitored in MeOD-d_4 (99.8% deuterated) at 50 °C in the presence or absence of **3** or **4** (0.1–0.2 M) by ^1H NMR spectroscopy at 300 MHz as previously described for **1a**.[6] Initial concentrations of **1b** and **2a** were ca. 4 mM. For **1b**, the singlets due to the *tert*-butyl group of the starting material and its decomposition products, which appear in the range from ca. δ 1.5 to 1.2, were used to monitor concentrations. For **2a**, the singlets of the acyl methyl groups of the starting material and its decomposition products, which appear from ca. δ 2.6 to 1.9, were utilized. In one experiment, 4 mM $KHSO_4$ was added to the MeOD-d_4 prior to monitoring the decomposition of **1b**. Kinetic data were handled as described in the earlier paper.[6]

Products. Reaction products were isolated from larger scale reactions (ca. 5 mM in **1b** or **2a**, 50 mL volume) in the presence or absence of 1.0 M **3** or **4** in dry MeOH. The reactions were performed under a N_2 atmosphere at 50 °C. Reactions were allowed to continue for 7–10 half-lives as determined from the kinetics experiments described above. Details of product separations were described in the earlier paper.[6] Characterization of individual reaction products for **1b** and **2a** is described below.

Quantification of reaction products was performed by ^1H NMR of the kinetic reaction mixtures after 10 half-lives, as calculated from the kinetic data. ^1H NMR spectra of each of the reaction products were taken in MeOD-d_4 under the kinetic conditions to provide reliable chemical shift standards. Identification of products in the kinetic mixtures was based on chemical shift coincidences of at least two well resolved peaks for each compound. In all cases agreement between the standard and reaction mixture resonances was ±0.005 ppm. Identities of reaction products were also confirmed by HPLC comparison with authentic samples as described earlier.[6]

Products of 1b. Most of the reaction products observed for **1b** were identical to those previously reported for **1a**.[6] Only the two rearrangement products **10b** and **11b** and the 3-methoxy compound **8** were not previously reported. The isomers **10b** and **11b** were not easily separated by chromatography, so authentic samples of each were prepared from the corresponding hydroxy compounds. An authentic sample of **8** was also prepared.

3-Methoxy-2-(acetylamino)fluorene (8). Treatment of 25 mg of 3-hydroxy-2-(acetylamino)fluorene[9] dissolved in 5 mL of EtOH with a large excess of diazomethane for 24 h led to recovery of 26 mg of crude product after the reaction mixture was quenched with AcOH and evaporation of all solvents. The material was purified by chromatography on silica gel with CH_2Cl_2/EtOAc (3/1) eluent to provide 23 mg (87%) of product: mp 155–156 °C; IR (KBr) 1662 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.55 (1H, s), 7.84 (1H, s, broad), 7.65 (1H, d, J = 7.4 Hz), 7.49 (1H, d, J = 7.3 Hz), 7.33 (1H, t, J = 7.3 Hz), 7.25 (1H, s), 7.23 (1H, t, J = 7.3 Hz), 3.96 (3H, s), 3.82 (2H, s), 2.21 (3H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 168.1 (C), 147.3 (C), 144.0 (C), 141.7 (C), 136.8 (C), 135.8 (C), 126.8 (C), 126.6 (CH), 126.0 (CH), 124.9 (CH), 119.0 (CH), 116.2 (CH), 101.5 (CH), 55.9 (CH_3), 36.7 (CH_2), 25.0 (CH_3); high-resolution MS *m/e* 253.1107, $C_{16}H_{15}NO_2$ requires 253.1103.

3-(Pivaloyloxy)-2-(acetylamino)fluorene (10b). This compound was synthesized from 3-hydroxy-2-(acetylamino)fluorene[9] as described above for **1b**. The crude product was purified by chromatography on silica gel with EtOAc/hexanes (1/1) eluent: mp 182–184 °C; IR (KBr) 1748, 1653 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.28 (1H, s), 7.65 (1H, d, J = 7.3 Hz), 7.50 (1H, d, J = 7.3 Hz), 7.45 (1H, s), 7.33 (1H, t, J = 7.3 Hz), 7.27 (1H, t, J = 7.3 Hz), 7.16 (1H, s, broad), 3.86 (2H, s), 2.16 (3H, s), 1.43 (9H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 176.4 (C), 167.9 (C), 143.7 (C), 141.1 (C), 140.8 (C), 140.2 (C), 138.6 (C), 128.3 (C), 126.7 (CH), 126.7 (CH), 125.0 (CH), 119.7 (CH), 119.3 (CH), 113.3 (CH), 39.4 (C), 36.8 (CH_2), 27.2 (CH_3), 24.5 (CH_3); high-resolution MS *m/e* 323.1516, $C_{20}H_{21}NO_3$ requires 323.1521.

1-(Pivaloyloxy)-2-(acetylamino)fluorene (11b). This material was synthesized as described above for **1b** from 1-hydroxy-2-(acetylamino)fluorene.[9] The crude product was purified by chromatography on silica gel with EtOAc/hexanes (1/1) eluent: mp 178–180 °C; IR (KBr) 1750, 1650 cm^{-1}; ^1H NMR (300 MHz), $CDCl_3$) δ 8.03 (1H, d, J = 8.2 Hz), 7.72 (1H, d, J = 7.5 Hz), 7.62 (1H, d, J = 8.2 Hz), 7.47 (1H, d, J = 7.3 Hz), 7.35 (1H, t, J = 7.3 Hz), 7.27 (1H, t, J = 7.4 Hz), 7.08 (1H, s, broad), 3.70 (2H, s), 2.15 (3H, s), 1.46 (9H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 175.6 (C), 168.0 (C), 142.5 (C), 141.0 (C), 140.2 (C), 138.6 (C), 135.2 (C), 128.4 (C), 126.9 (CH), 126.8 (CH), 124.9 (CH), 122.8 (CH), 120.0 (CH), 117.9 (CH), 39.6 (C), 34.5 (CH_2), 27.2 (CH_3), 24.4 (CH_3); high-resolution MS *m/e* 323.1524, $C_{20}H_{21}NO_3$ requires 323.1521.

Products of 2a. Products of the solvolysis of **2a** included three methoxy adducts **24–26**. An authentic sample of one of these (**24**) was available from an earlier study.[12] Authentic samples of the other two were independently synthesized. Authentic samples of **27–29** were available from previous studies.[7,12] Characterization of **23** and synthesis of **25** and **26** follows.

2-Methyl-6-phenylbenzoxazole (23). After initial recovery from reaction mixtures, this material was purified by recrystallization from MeOH: mp 58–61 °C; IR (KBr) 1611, 1580 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 7.70 (1H, d, J = 1.7 Hz), 7.67 (1H, d, J = 8.3 Hz), 7.67–7.61 (2H, m), 7.55 (1H, dd, J = 8.3, 1.7 Hz), 7.49–7.43 (2H, m), 7.39–7.33 (1H, m), 2.63 (3H, s); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 164.8 (C), 152.1 (C), 141.5 (C), 141.2 (C), 138.5

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(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) δ 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) δ 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) δ 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) δ 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) δ 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) δ 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) δ 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) δ 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) δ 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) δ 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) δ 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) δ 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) δ 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) δ 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) δ 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) δ 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) δ 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) δ 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.

(13) Miller, E. C.; Sandin, R. B.; Miller, J. A.; Rusch, H. P. *Cancer Res.* **1956**, *16*, 525–534.

(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.

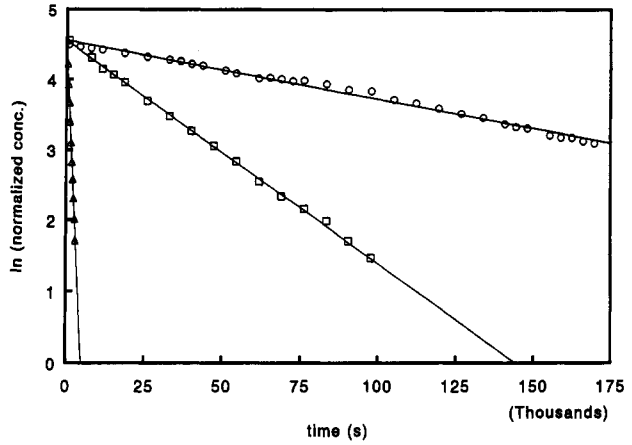


Figure 1. Plots of ln of the normalized peak area for the largest singlet in the ^{1}H NMR spectra of **1a** (△), **1b** (□), and **2a** (○) vs time at 50 °C. Rate constants were determined from a linear least-squares fit of these data.

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 μ = 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}

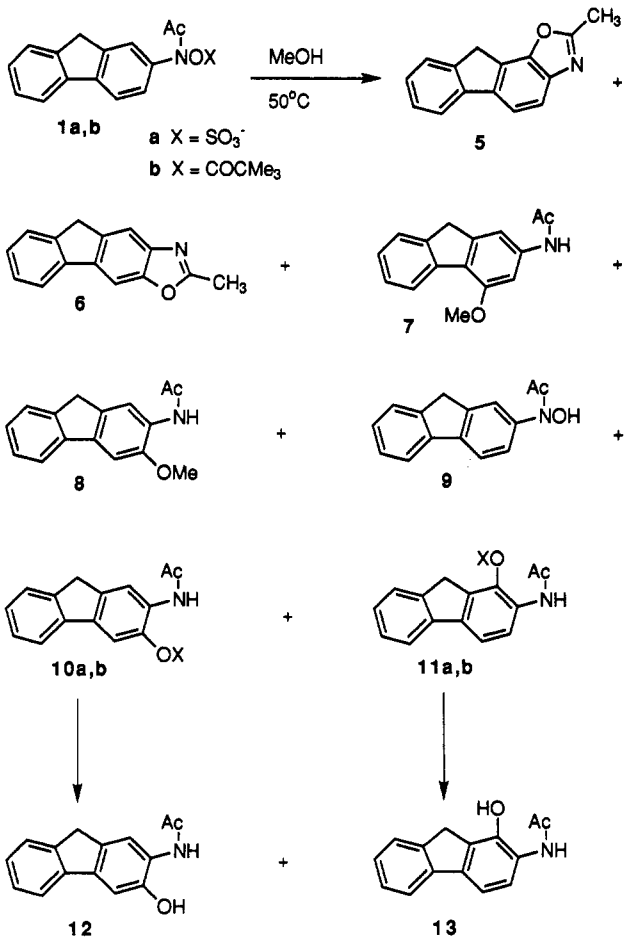
[a] Initial ester concentration is ca. 4 mM. [b] Determined by a linear fit of ln (normalized peak area) for the ^{1}H NMR acyl methyl peak of **1a** and **2a**, or the *tert*-butyl peak of **1b**, vs time. Error limits are 2.5 standard deviations of the slope.

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.

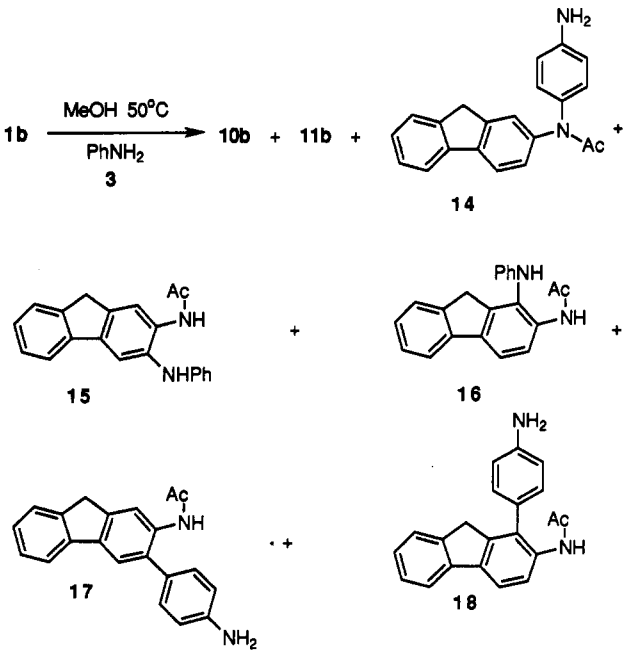
Although the rate constant for decomposition of **1b** is not affected by added **3** (Table I), the product distribution is greatly altered. Scheme II and Table III show that in 0.1 M solutions of **3** in MeOD-d_4 all the normal solvolysis products except **10b** and **11b** are no longer detectable. 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

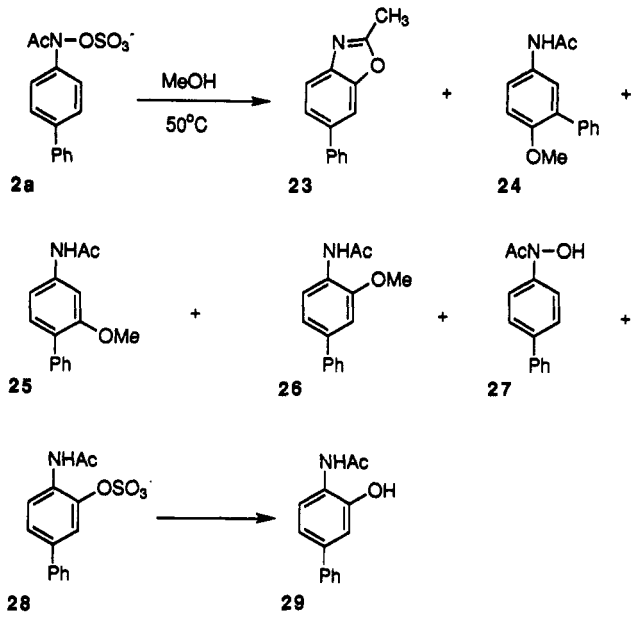


Table III. Yields of Reaction Products for 1b in the Presence of 3 in MeOD-d_4 at 50 °C

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.

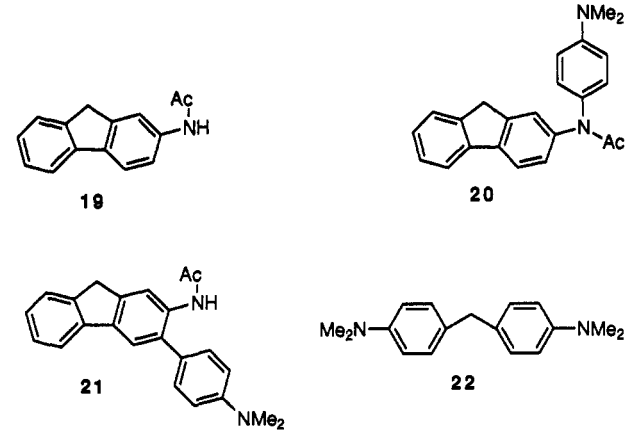
A variety of products are generated when 2a undergoes decomposition in the presence of 3 and 4 (Scheme IV). These compounds have structures which are analogous to

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		

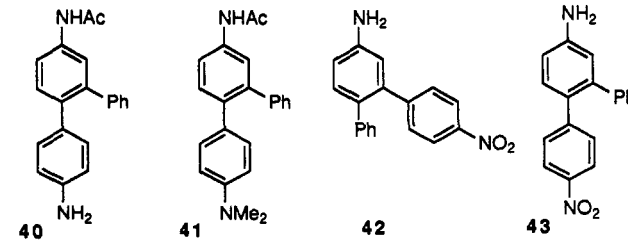
[a] Determined by NMR peak integration at completion of the kinetic run. Results reported are averages of two determinations. Initial concentration of 2a was 4 mM. [b] A small amount (ca. 5%) of 28 decomposes during these reactions into 29. This yield of 29 is included in the overall yield of 28.

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.

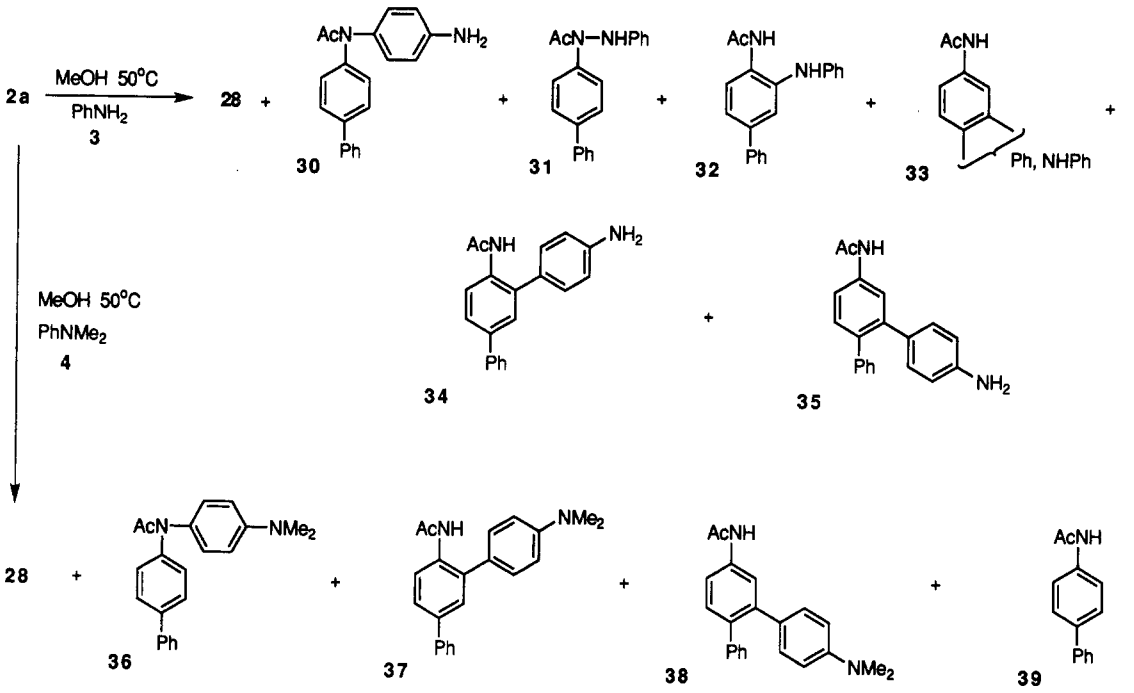
Identification of the structures of these adducts was based on ^{1}H and ^{13}C NMR data and independent synthesis. Both 35 and 38 were synthesized from 42, which was obtained from 4′-nitrodeoxybenzoin and methyl vinyl ketone via a procedure described in the literature.[14] The synthesis of 40 and 41 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 δ 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 (δ 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 4.9×10^6 s^{-1} at 20 °C.[7] The second-order rate constant for its reaction with H_2O, k_{H_2O}, is then 8.8×10^4 M^{-1} s^{-1}. The reactivity ratio k_{MeOH}/k_{H_2O} for the 1-(4-methoxyphenyl)ethyl cation which has similar

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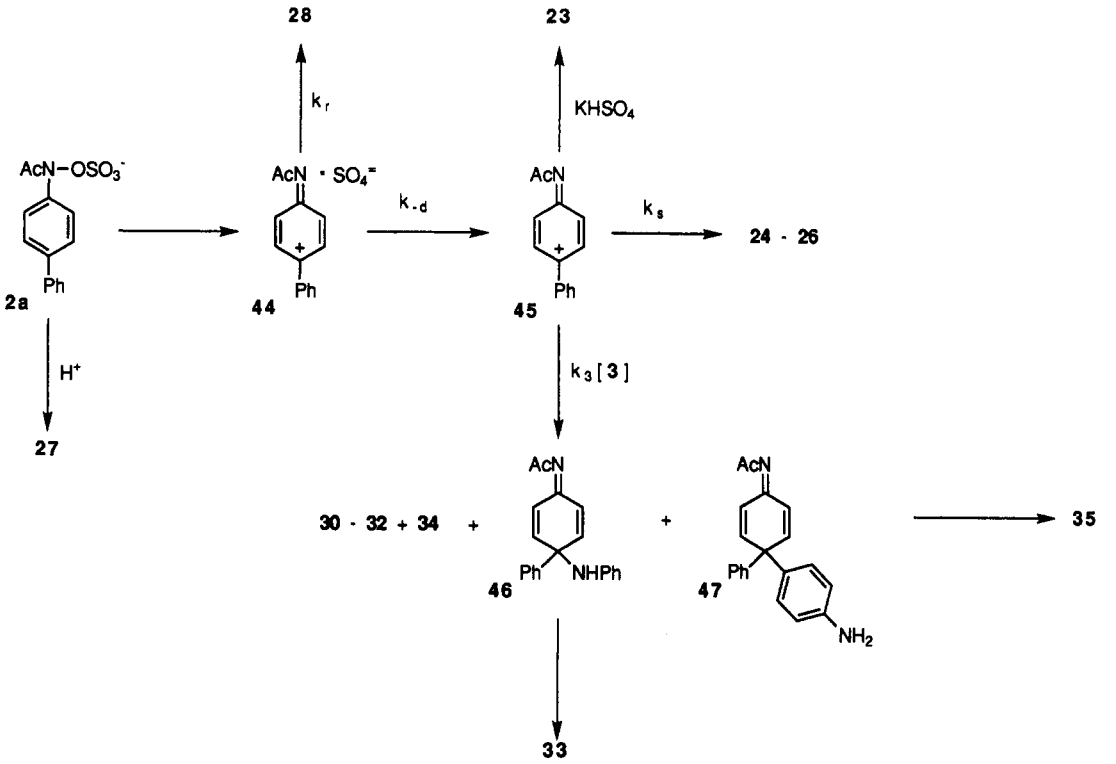
(17) In fact, **33** and **40** show 13 ^{13}C NMR resonances in the aromatic region. For **33**, integration of ^{13}C NMR peaks shows that two tertiary carbon signals at δ 129.6 coincide. For **40** one of the quaternary carbon signals apparently is superimposed on another peak.

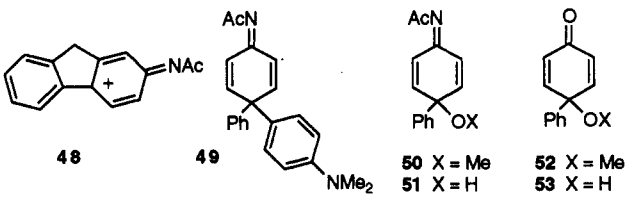
Scheme V



overall reactivity to **45**, is ca. 20,[18] so a reasonable estimate of k_{MeOH} for **45** is 1.8×10^6 M^{-1} s^{-1}. In neat MeOH the first-order rate constant for reaction of **45** with the solvent then is estimated to be 4.4×10^7 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 σ^+ of the aryl groups which are commonly found in carcinogenic *N*-arylhydroxamic acids, while the 4-biphenyl group has the least negative σ^+.[20] Since the rates of these solvolysis reactions correlate reasonably well with σ^+,[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 σ^+ 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.

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(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.