counterpart in the Δ^8-THC series was recently synthesized and reported to be extremely active pharmacologically.[13] It is well established that the pharmacological activity in the Δ^8-series parallels that of the naturally occurring Δ^9-THC series.[14] The interest in the synthesis of (-)-**6b** arose because our sequence (Scheme II) allows for easy radiolabeling. Thus treatment of **5b** with tritiated $NaBH_4$ should give tritiated **6b**, which will be used in binding studies of mouse brain homogenates for possible isolation of a THC receptor.

Acknowledgment. This work was carried out with the support of the National Institutes of Drug Abuse (NIDA, Grant No. DA 05488). We are grateful to the Eli Lilly and Co., Indianapolis, for the supply of (1',1'-dimethylheptyl)resorcinol and Prof. J. L. Neumeyer, Northeastern University, for assistance in determination of optical rotations.

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S_N2 Reactions of a Carbon Nucleophile with *N*-Aryl-*O*-pivaloylhydroxylamines: A Model for in Vivo Reactions of Carcinogenic Metabolites of Aromatic Amines

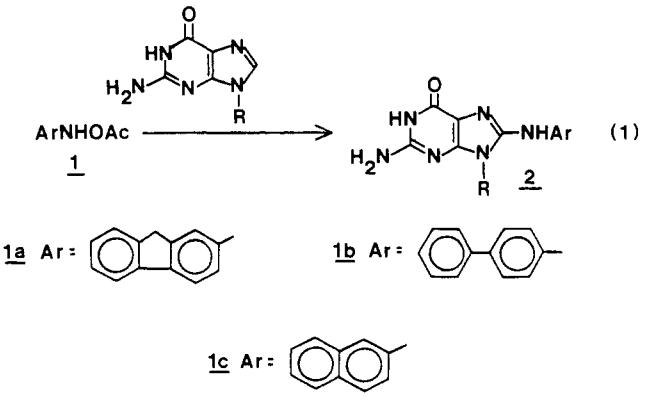
Michael Novak,* Kristy A. Martin, and Julie L. Heinrich

Department of Chemistry, Miami University, Oxford, Ohio 45056

Received August 1, 1989

Summary: The reaction of the *N*-aryl-*O*-pivaloylhydroxylamines **3a–c** with *N,N*-dimethylaniline **4** to generate the diphenylamines **5a–c** and **6a–c**, a model for the in vivo reaction of similar esters of carcinogenic *N*-arylhydroxylamines with C-8 of guanosine, proceeds via an S_N2 mechanism.

Sir: *O*-Acetyl-*N*-arylhydroxylamines such as **1a** are putative carcinogenic metabolites of polycyclic aromatic amines, which are thought to be responsible for the characteristic "C-8 adduct", **2**, obtained from a variety of in vivo and in vitro studies of the metabolism of the corresponding amines or hydroxylamines.[1] Recently it has been shown that **1b** and **1c** do indeed react with deoxyguanosine to form the adducts **2b** and **2c** (R = deoxyribose) in low yields in $EtOH/CHCl_3/H_2O$ (eq 1).[2] The mechanism of this reaction has not been investigated, but a nitrenium ion process is often invoked to explain it.[1] Results from our laboratory and others indicate that aryl nitrenium ions rarely, if ever, undergo nucleophilic attack at nitrogen.[3-5] We have investigated the model reaction of the *N*-aryl-*O*-pivaloylhydroxylamines **3** with *N,N*-dimethylaniline, **4**, in MeOH (eq 2) and found that this process has the characteristics of an S_N2 reaction.



(1)

The decomposition of **3** in 3.7 M **4** in dry MeOH at 25 °C yields the diphenylamines **5** and **6** (Table I). Under these conditions **3a** and **3b** undergo complete reaction within 24 h and appear to be quantitatively converted into **5** and **6**. After 24 h under the same conditions ca. 70% of **3c** is recovered unreacted, and correspondingly low yields of **5c** and **6c** are obtained (Table I). At least one other minor unidentified product is detected in the reaction of **3c**.

Table I. Yields of the Diphenylamines 5a–c and 6a–c and Second-Order Rate Constants for the Reaction of 3a–c and 4 in MeOH at 25 °C

	% yields[a]		
ester	5	6	k_2,[b] M^{-1} s^{-1}
3a	72	10	$(1.1 \pm 0.1) \times 10^{-4}$
3b	60	20	$(3.4 \pm 0.2) \times 10^{-6}$
3c	14	6	$(1.8 \pm 0.3) \times 10^{-6}$

[a] Recovered yields after incubation of **3** in 3.7 M **4** in MeOH at 25 °C for 24 h. See supplementary material for details. [b] See supplementary material for details of kinetic methods.

The kinetics of this process were monitored by ^1H NMR spectroscopy in methanol-d_4 under pseudo-first-order conditions for **3a** and **3b** in the concentration range 0.05–0.20 M in **4**, and by UV methods for **3c** at concen-

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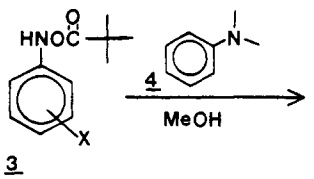
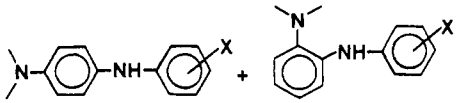


3

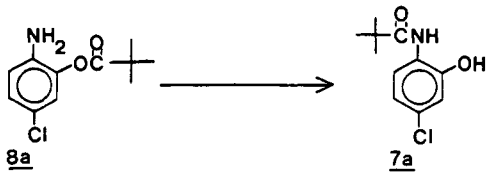
a X = 4-Cl
b X = 3,4-diCl
c X = 4-NO_2



5 6 (2)

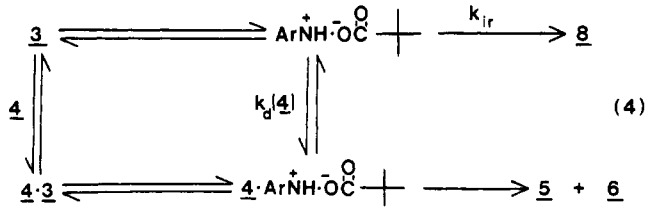
trations of 4 of 0.5 and 1.0 M (**3c** has significant absorbance at longer wavelengths than that of the cutoff for solutions of 4 in MeOH of about 350 nm). Rate constants were linear in 4, and second-order rate constants for reaction of 3 and 4, k_2, are included in Table I. This is the first documented example of substitution with bimolecular kinetics in these systems.

The solvolysis rate constant for **3a**, k_s, is $(1.0 \pm 0.2) \times 10^{-6}$ s^{-1} under these conditions, but solvolysis of **3b** and **3c** could not be detected over a period of 72 h at 25 °C. The major solvolysis product (>85%) is **7a**, which is also a significant hydrolysis product of **3a** in H_2O where it was shown to be derived from an intramolecular acyl transfer in the initially formed **8a** (eq 3).[3a]



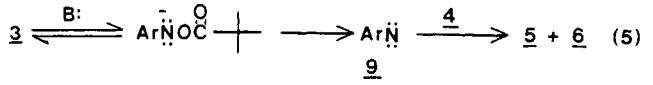
8a 7a (3)

The kinetic behavior is inconsistent with nucleophilic attack of 4 on a free nitrenium ion formed by rate-limiting N–O bond heterolysis. In addition to S_N2 substitution, second-order kinetics could be given by rate-limiting trapping of an ion pair intermediate or by a preassociation mechanism (nucleophile assisted ionization), eq 4.[6] The ratio k_2/k_s of 110 M^{-1} for **3a** would require that $k_d[4] \approx 10^2 k_{ir}$. We have previously shown in aqueous solution that nucleophiles and other trapping agents do not compete effectively with internal return of a tight ion pair for aryl nitrenium ion–sulfate or pivalate ion pairs,[3] so rate-limiting trapping by 4 is not likely. The preassociation mechanism, which would operate if the nitrenium ion is relatively unstable,[6] would require that 4 be ca. 3.0×10^3 fold more effective at assisting ionization than MeOH. The sensitivity to substituent effects for k_2 ($\rho^+ = -2.6$) is also significantly lower than that observed for nitrenium ion processes in H_2O or alcohols ($\rho^+ \approx -5.0$ to -7.0) and suggests significant bond formation in the rate-limiting step.[3,4,7] We conclude that all available data are most consistent with an S_N2 mechanism. The S_N2 mechanism previously was favored for the reaction of activated aromatics with arylhydroxylamines in trifluoroacetic acid which also generates diphenylamines, but this conclusion was based on little experimental evidence.[8]



3 8 4 4·3 5 + 6 (4)

One other mechanistic possibility, base-induced α-elimination to generate a nitrene, followed by trapping of the nitrene, **9**, with 4 (eq 5), a known reaction of electron-



3 5 + 6 (5)

9

deficient nitrenes,[9] is not supported by the experimental data. The pK_a of **3c** in MeOH is 13.2,[10] and **3a** and **3b** will be less acidic than **3c**, so very little deprotonation can occur in the presence of the weakly basic 4. When aryl nitrenes are trapped in this fashion the *o*-diphenylamine, **6**, predominates.[9] In our case the para isomer **5** is always formed in greater yield. It has also not been demonstrated that less electron-deficient nitrenes such as **9a** can undergo this trapping reaction.

The present data cannot preclude a change of mechanism to S_N1 for more reactive *N*-aryl-*O*-acylhydroxylamines,[6] although the nature of the products derived from their reaction with guanosine argue against it. Preliminary kinetic results indicate no change in mechanism for **3** when X = 4-Me.[7]

Acknowledgment. This work is supported by a grant from the American Cancer Society (BC-348).

Supplementary Material Available: Complete characterization of **5a–c** and **6a–c** (4 pages). Ordering information is given on any current masthead page.

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(7) Preliminary kinetic results for the 4-methyl and unsubstituted esters (3, X = 4-Me and X = H) follow the same pattern observed for **3a–c**. Values of ρ^+ based on these data and those reported herein are −7.5 for k_s and −2.5 for k_2. Details of the kinetic studies and product analyses for these compounds will be reported at a later date.

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