Photochemistry of 1-Alkoxy- and 1-(Benzyloxy)-9,10-anthraquinones in Methanol: A δ-Hydrogen Atom Abstraction Process That Exhibits a Captodative Effect

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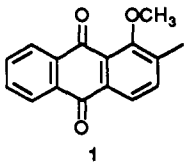
Abstract: The photochemistry of a variety of 1-alkoxy- and 1-(benzyloxy)-9,10-anthraquinones in methanol has been examined. In the absence of oxygen the primary photoproducts of these reactions are 9,10-anthrahydroquinones with $MeOCH_2O$ and ArCH(OMe)O groups at the 1-position, respectively. Quenching studies established the multiplicity of the excited state to be triplet. Deuterium isotope effects, substituent effects, and solvent polarity studies support a mechanism in which a biradical intermediate is formed by an intramolecular δ-hydrogen atom transfer that occurs in one step but not a reaction pathway in which the hydrogen atom transfer is accomplished in two discrete steps via separate electron and proton transfers. Apparent rate constants for the disappearance of 1-(p-$XPhCH_2O$)-2-methyl-9,10-anthraquinone (X = H, Cl, CH_3, NO_2, OCH_3, CF_3, and CN) were measured and found to vary by a factor of 3.4 from the largest ($X = NO_2$) to the smallest ($X = OCH_3$). Captodative interactions account for the small differences in these rate constants.

Introduction

The photochemistry of quinones in general and anthraquinones in particular has been the subject of numerous investigations in recent years.[1] A major mode of photochemical reaction of quinones in good hydrogen-donating solvents is reduction, which is believed to occur by two mechanisms. One involves a hydrogen atom abstraction originating from a n,π^* triplet state. The other accomplishes the equivalent of a hydrogen atom transfer by separate electron and proton transfers and originates from a π,π^* *triplet* state. With anthraquinones the photoreduction pathway that predominates depends upon the relative energies of these two triplet states with the hydrogen atom abstraction reactivity increasing with increasing n,π^* character.[1-4] Since quinones are both good electron and hydrogen atom acceptors, these mechanisms are often difficult to distinguish and quantify.[1] Some success toward that goal, though, has been realized. For example, the rate constants for the reaction of triplet tetrachloro-1,4-benzoquinone with durene via electron and H-atom transfers have recently been measured.[5]

We recently reported that 1-methoxy-2-methyl-9,10-anthraquinone (**1**) undergoes photodemethylation in methanol in the presence of oxygen to give **2**.[6] Although preliminary results presented at that time for this intramolecular bifunctional process were consistent with a δ-hydrogen abstraction leading to 1,5-diradical **3**, a two-step process involving electron and proton transfers could not be ruled out. Related photoprocesses have



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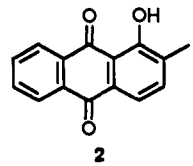

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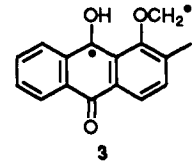

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been observed in alkoxy-substituted naphthoquinones[7] and benzoquinones,[8a] but no attempts were made to distinguish between the hydrogen atom or electron/proton transfer mechanisms.

The conversion of **1** to **2**, which occurs in high yield with either visible or UV light, seemed to us to be an ideal system to explore this mechanistic question in detail. Since this intramolecular oxidation-reduction process bears some resemblance to the photoreduction of carbonyl compounds in alcohols, we anticipated that this study might have broader implications. In this work, then, we describe in detail the photochemistry of **1** and a variety of other 1-alkoxy- and 1-(benzyloxy)-substituted 9,10-anthraquinones. Isotope effects, substituent effects, and solvent polarity studies are used to elucidate not only the general mechanism for this photochemical process but also the precise manner in which the hydrogen atom is transferred.

Results

Exploratory Photochemistry. Irradiation of solutions of **1** in methanol (0.50-1.0 mM) with visible or 308-nm ultraviolet light in the presence of oxygen led to a nearly quantitative yield of **2**. Photolysis under argon followed by exposure to oxygen in the workup gave similar results. The photodemethylation of **1** occurs in other alcohols such as ethanol, 2-propanol, and *tert*-butyl alcohol but not in $CDCl_3$ or CCl_4 or in the absence of solvent.

We were unable to determine the fate of the methyl group using standard analytical techniques. To facilitate the isolation and identification of both cleavage products, anthraquinone **4** was prepared from **2** and 3-(*o*-nitrophenyl)propyl bromide by the Williamson synthesis. Photolysis of **4** in methanol (0.50 mM) with a 300-W tungsten lamp led to greater than 80% isolated yields of **2** and 3-(*o*-nitrophenyl)propanal. By analogy then, the fate of the methyl group in the photolysis of **1** is assumed to be formaldehyde.

Anthraquinone **2** is not the primary photoproduct of **1**. A methanol-d_4 solution of **1** under argon was irradiated with visible light in an NMR tube. Proton NMR spectra of **1** were recorded before and after photolysis. The spectrum of **1** before photolysis is shown in Figure 1a and is assigned as follows: the aromatic hydrogens absorb at 7.6-8.3 ppm (δ) and the methoxy methyl and 2-methyl hydrogens give peaks of equal areas at 3.9 and 2.4 ppm, respectively. Photolysis of **1** gives a single product as shown in

(1) Maruyama, K.: Osuka, A. *The Chemistry of Quinonoid Compounds*; Patai, Zappoport, Eds.; Wiley: London, 1988; Vol. II, Chapter 13.
(2) Hamanoue, K.; Nakayama, T.; Tanaka, A.; Kajiwara, Y.; Teranishi, H. *J. Photochem.* **1986**, *34*, 73.
(3) Hamanoue, K.; Nakayama, T.; Kajiwara, Y.; Yamaguchi, T.; Teranishi, H. *J. Chem. Phys.* **1987**, *86*, 6654.
(4) (a) Wilkinson, F. *J. Phys. Chem.* **1962**, *66*, 2569. (b) Tickle, K.; Wilkinson, F. *Trans. Faraday Soc.* **1965**, *61*, 1981. (c) Carlson, S. A.; Hercules, D. M. *Photochem. Photobiol.* **1973**, *17*, 123.
(5) Kobashi, H.; Funabashi, M.; Kondo, T.; Morita, T.; Okada, T.; Mataga, N. *Bull. Chem. Soc., Jpn.* **1984**, *57*, 3557.
(6) Blankespoor, R. L.; Hsung, R.; Schutt, D. L. *J. Org. Chem.* **1988**, *53*, 2877.
(7) (a) Otsuki, T. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 3089. (b) Maruyama, K.; Osuka, A.; Nakagawa, K.; Jinsenji, T.; Tabuchi, K. *Chem. Lett.* **1988**, 1505.
(8) (a) Edwards, O. E.; Ho, P.-T. *Can. J. Chem.* **1978**, *56*, 733. (b) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*, 3rd ed. Plenum: New York, 1990, p 218.

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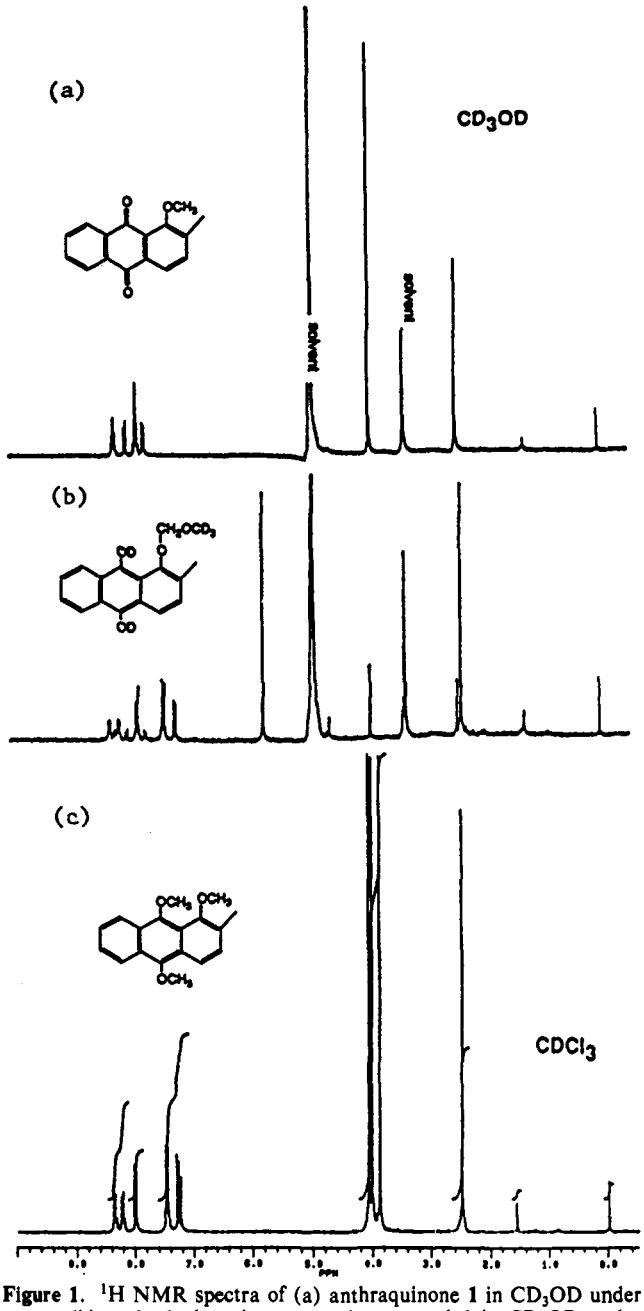
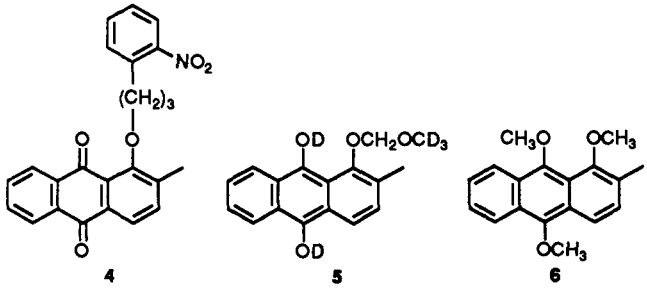


Figure 1. ^1H NMR spectra of (a) anthraquinone **1** in CD_3OD under argon, (b) anthrahydroquinone **5** and unreacted **1** in CD_3OD under argon, and (c) anthrahydroquinone **6** in $CDCl_3$.

Figure 1b. This substance exhibits peaks at 7.1–8.3 (6 H), 5.7 (2 H), and 2.3 (3 H) ppm and is assigned the structure of anthrahydroquinone **5**. Further support for this structural assignment comes from a comparison of the aromatic regions of **5** and the structurally similar anthrahydroquinone **6**, which was synthesized for this purpose and is shown in Figure 1c. Note that the chemical



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shifts and coupling patterns of **5** and **6** are nearly identical between 7.2 and 8.3 ppm, recognizing that one of the three peaks at

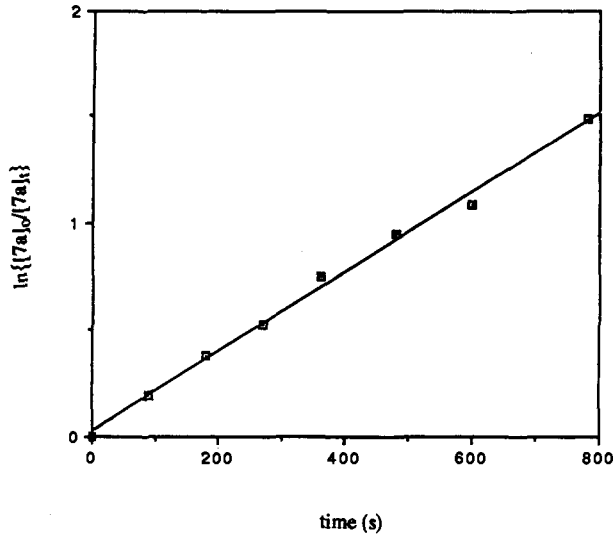


Figure 2. Plot of ln $\{[\mathbf{7a}]_0/[\mathbf{7a}]_t\}$ versus time from the photolysis of 0.30 mM **7a** in CH_3OH using visible light. $R = 0.987$.

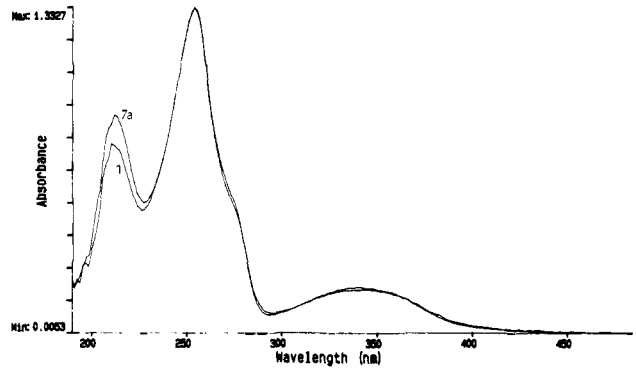
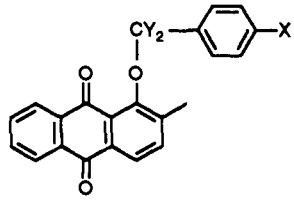


Figure 3. Absorption spectra of 0.0373 mM **1** and **7a** in methanol.

approximately 7.2 in the spectrum of **6** is from $CHCl_3$. When the solution containing **5** is exposed to air, the proton NMR spectrum of **5** is gradually replaced by the one for anthraquinone **2**. Both oxidation of the anthrahydroquinone to the anthraquinone and hydrolysis of the acetal occur under these conditions. The latter observation is surprising but consistent with our inability to isolate the acetal of the anthraquinone. Apparently, strong intramolecular H bonding is occurring in the transition state leading to **2**, making the acetal quite labile.

Substituent Effects. Anthraquinones **7a–h** were prepared from **2** and substituted benzyl halides to probe substituent effects upon the photochemistry of these compounds, which leads to **2** and *p*-XPhCHO in high yields. Dilute, equimolar solutions of these compounds in methanol in Pyrex containers were irradiated simultaneously in a merry-go-round apparatus with a 300-W tungsten lamp at the center. Aliquots were removed at regular intervals and analyzed by HPLC. Plots of ln $\{[7]_0/[7]_t\}$ versus time, as shown in Figure 2 for **7a**, are linear. Since the UV–visible absorption spectra of **7a** (Figure 3) and **7b–h** are nearly identical in the visible and UV regions, the relative slopes from these plots can serve as a quantitative measure of the substituent effects. These slopes are apparent rate constants for the disappearance of **7** (i.e., **7** → products) and correspond to the relative quantum yields of **7**. They are labeled k_{dis} and given in Table I. Quantum yields for the disappearance of **7**, Φ_{dis}, with use of a 308-nm laser are also given in Table I. It should be noted that the quantum yields for **7a–h** were not measured simultaneously, resulting in more error in the measurements. The data show that the substituent effects are quite small with a factor of only 3.4 in k_{dis} separating the fastest anthraquinone **7h** containing the NO_2 group and the slowest anthraquinone **7c** containing the OCH_3 group. The other anthraquinones, **7a** and **7d–7g**, lie in between and have very similar reactivities.

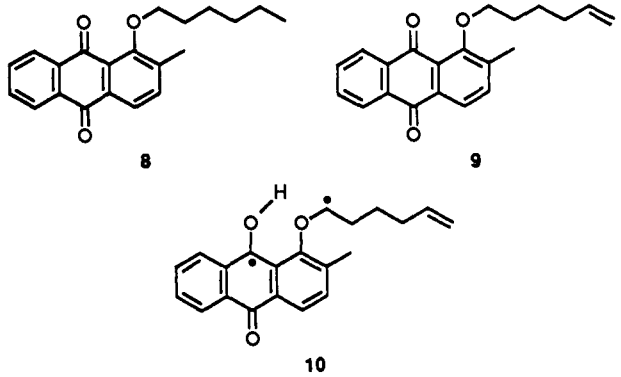


7a: Y = H; X = H
b: Y = D; X = H
c: Y = H; X = OCH_3
d: Y = H; X = CN
e: Y = H; X = CF_3
f: Y = H; X = CH_3
g: Y = H; X = Cl
h: Y = H; X = NO_2

Deuterium Isotope Effects. From the k_{dis} values of 1.92×10^{-4} and 0.883×10^{-4} s^{-1} for **1** and its 1-OCD_3 derivative, respectively, a k_H/k_D ratio of 2.2 is obtained. A similar k_H/k_D value of 2.5 is realized from the quantum values of these compounds (0.020 and 0.0080, respectively) by using the 308-nm light source. The k_H/k_D value of over 2 for **1** suggests that the bond to the isotopically substituted hydrogen atom is being broken in the rate-determining step of the reaction of photoexcited **1**.[8b] The isotope effect is considerably smaller when the OCH_3 group in **1** is replaced with OCH_2Ph as can be seen from the k_{dis} values for **7a** and **7b** in Table I, which give k_H/k_D = 1.2.

Solvent Polarity Studies. Equimolar solutions of **7a** in mixtures of either CH_3OH/water or CH_3OH/hexanol in the presence of oxygen were irradiated simultaneously with a tungsten lamp to determine the effect of solvent polarity upon the rate of photodebenzylation. With each solvent mixture k_{dis} increased with increasing polarity, but not dramatically, as is shown in Figure 4 for aqueous CH_3OH. This is not a general trend for **7**, however. Anthraquinone **7h** reacts faster as the percentage of water in aqueous CH_3OH increases, whereas **7c** actually reacts more slowly.

Photolysis of 1-(5-Hexenyloxy)-2-methyl-9,10-anthraquinone (9). Given the likelihood that biradicals are intermediates in the photochemistry of **1** and **7**, anthraquinones **8** and **9** were prepared. A δ-hydrogen abstraction in **9** gives biradical **10**, which contains a 5-hexenyl radical. Since the 5-hexenyl radical is known to



8 **9**

10

cyclize to the cyclopentylmethyl radical with a rate constant of 1×10^5 s^{-1} at 25 °C,[9] biradical **10** has cyclization as an alternative mode of reaction that is not available to the biradical from **8**. Anthraquinones **8** and **9** were irradiated with visible light in CD_3OD under argon and monitored by NMR. Conversion to anthrahydroquinone occurred in each case, but without a decrease in the area of the vinyl hydrogen peaks in the proton spectrum of **9**. Thus, cyclization of the 5-hexenyl group in **9** did not occur to any appreciable extent. Also, k_{dis} values for **8** and **9** were measured and found to be identical within experimental error.

Effect of Quenchers. Equimolar solutions of **1** (0.13 mM) in methanol under argon were irradiated simultaneously with visible light in the absence and presence of anthracene (0.89 mM). The results, which are shown in Figure 5, show that anthracene is very effective in quenching the photoreaction. Not surprisingly, a triplet excited state for **1** is indicated.

Scope of the Reaction. A variety of other anthraquinones were irradiated with both visible and 308-nm light. These are shown in Table II along with k_{dis} values obtained by using the former light source. It is important to note that no reaction occurs when the methoxy group is at the 2-position. Furthermore, when **1** is reduced to its anthrahydroquinone prior to photolysis, no demethylation is observed even after irradiation for 20 min with the 308-nm laser. Thus, it is apparent that a carbonyl must be in close proximity to the methoxy group for photodemethylation to occur.

(9) Lal, D.; Griller, D.; Husband, S.; Ingold, K. U. *J. Am. Chem. Soc.* **1974**, *96*, 6355.

Table I. Quantum Yields and Apparent Rate Constants for the Disappearance of 7 during Photolysis in Methanol

anthraquinone	Φ_{dis}[a]	$k_{dis} \times 10^3$, s^{-1} [b]
7a	0.39	1.94 ± 0.18
7b	0.34	1.70 ± 0.01
7c	0.11	0.668 ± 0.06
7d	0.39	1.70 ± 0.10
7e	0.34	1.77 ± 0.05
7f	0.34	1.82 ± 0.05
7g	0.49	1.97 ± 0.03
7h	*c*	2.30 ± 0.13

[a] Light source is a 308-nm laser. [b] Slopes from linear plots of ln $\{[7]_0/[7]_t\}$ versus t using a tungsten light source. These apparent rate constants correspond to the relative quantum yields of **7**. Ranges in values are based upon three measurements. [c] Low solubility made analysis difficult.

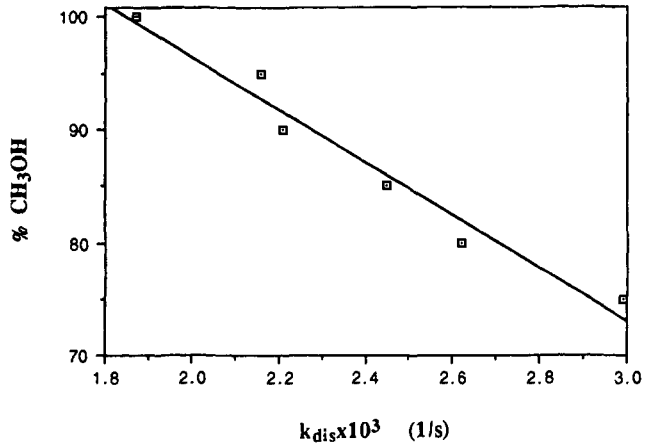


Figure 4. Plot of percent CH_3OH versus k_{dis} from the photolysis of **7a** in aqueous CH_3OH using visible light. R = 0.965.

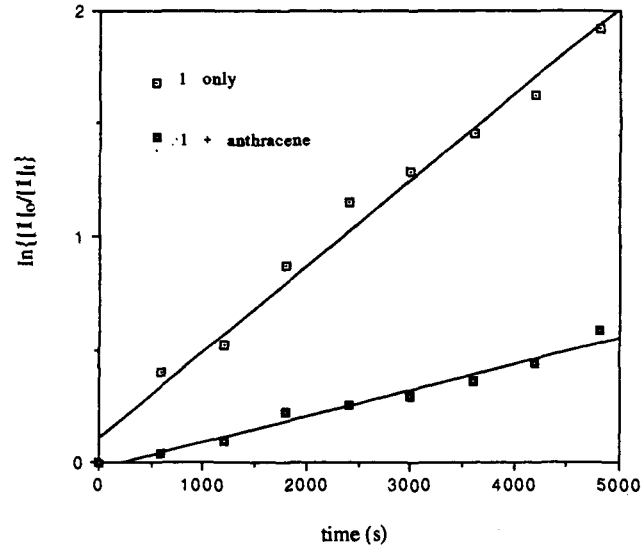


Figure 5. Plots of ln $\{[1]_0/[1]_t\}$ versus time from the photolysis of 0.13 mM **1** in CH_3OH and under argon using visible light in the absence (R = 0.984) or presence (R = 0.973) of 0.89 mM anthracene.

Scheme I

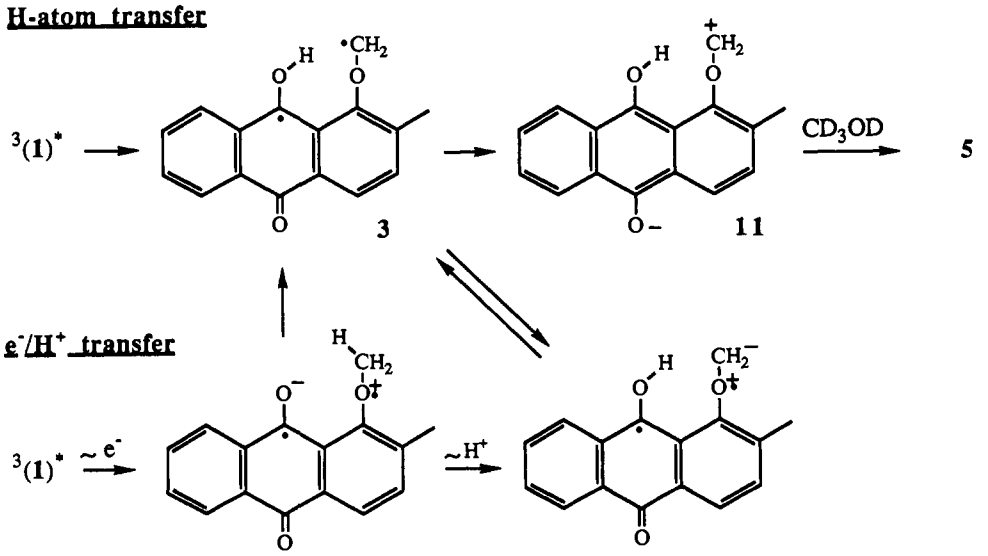


Table II also shows that reaction does not occur when the oxygen at the 1-position is substituted with other heteroatoms. Both 1-(methylamino)- and 1-(thiomethoxy)-9,10-anthraquinone failed to undergo photodemethylation.

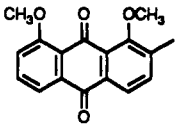
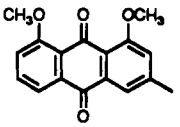
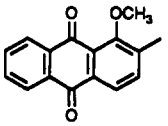
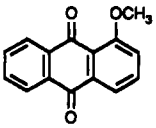
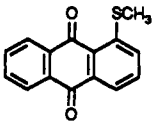
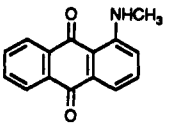
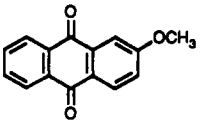
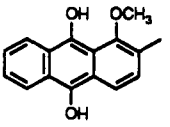
Discussion

The formation of **5** as the primary photoproduct of **1** in CD_3OD can be viewed as an intramolecular redox process in which the anthraquinone is reduced by the methoxy group at its 1-position. As was pointed out earlier, this transformation bears, then, some resemblance to the photoreduction of anthraquinones in alcohol.

Possible Mechanisms. In Scheme I two mechanisms are considered for the photoconversion of **1** to **5**. The first one is a hydrogen atom transfer from the methoxy group to the excited carbonyl. This intramolecular δ-hydrogen abstraction, which has been observed in the photochemistry of ketones,[10-17] leads to biradical **3**. In the second mechanism consecutive electron and proton transfers, hereafter referred to as e^-/H^+, accomplish the transfer of a hydrogen atom. After convergence of the two mechanisms at biradical **3**, an intramolecular electron transfer presumably occurs to give zwitterion **11**, an intermediate that would be expected to react with CD_3OD to give **5**. Zwitterions resulting from intramolecular electron transfer have been postulated as intermediates in the photochemistry of quinones.[8,18]

There is experimental support for assuming that a common mechanism is operating in the photochemistry of the anthraquinones in this study that have different alkoxy and benzyloxy substituents at the 1-position. The k_{dis} values for **1**, **8**, and **7a** are 1.90×10^{-4}, 6.00×10^{-4}, and 19.2×10^{-4} s^{-1}, respectively. With homolytic bond dissociation energy (BDE) estimates for the OCH_2-H, $OCH(C_5H_{11})$-H, and OCH(Ph)-H bonds of 100, 95, and 85 kcal/mol, respectively, there is good correlation between ln (k_{dis}) and BDE, demonstrating Arrhenius behavior as would be expected if a common mechanism were operative. Another observation that supports a common mechanism is that the absorption spectra of these anthraquinones are virtually identical at wavelengths above 240 nm as shown in Figure 3 for **1** and **7a**. This implies a common photoexcited state. Each of the two mechanisms in Scheme I will now be considered in detail.

Table II. Apparent Rate Constants for the Disappearance of a Variety of Anthraquinones during Photolysis in Methanol

anthraquinone/anthrahydroquinone	$k_{dis} \times 10^4$, s^{-1} [a]
	0.239
	0.208
	1.92
	0.239
	no reaction[b]
	no reaction[b]
	no reaction[b]
	no reaction[b]

[a] Slopes from linear plots of ln $\{[AQ]_0/[AQ]_t\}$ versus time using a tungsten light source. These apparent rate constants correspond to the relative quantum yields of these anthraquinones. [b] Under argon.

(10) (a) Wagner, P. J.; Giri, B. P.; Scaiano, J. C.; Ward, D. L.; Gabe, E.; Lee, F. L. *J. Am. Chem. Soc.* **1985**, *107*, 5483 and references therein. (b) Wagner, P. J.; Meador, M. A.; Park, B.-S. *J. Am. Chem. Soc.* **1990**, *112*, 5199. (c) Paquette, L. A.; Ternansky, R. J.; Balogh, D. W.; Kentgen, G. *J. Am. Chem. Soc.* **1983**, *105*, 5446.
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(14) Pappas, S. P.; Zehr, R. D.; Blackwell, J. E., Jr. *J. Heterocycl. Chem.* **1970**, 1215.
(15) Coyle, D. J.; Peterson, R. V.; Heicklen, J. *J. Am. Chem. Soc.* **1964**, *86*, 3850.
(16) Stephenson, L. M.; Parlett, J. L. *J. Org. Chem.* **1971**, *36*, 1093.
(17) Yates, P.; Pal, J. M. *J. Chem. Soc. D* **1970**, 553.
(18) Baldwin, J. E.; Brown, J. E. *J. Chem. Soc., Chem. Commun.* **1969**, 167.

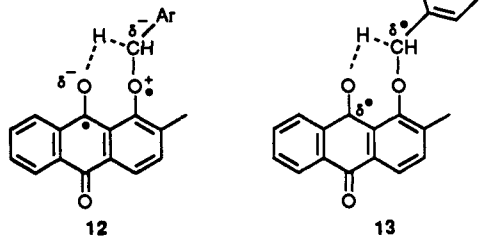
Isotope Effects. The deuterium isotope effect of 2.2 for **1** is not only consistent with the hydrogen atom transfer mechanism in which the transfer step is rate-determining but also supports the e^-/H^+ transfer mechanism in which the proton transfer step is rate-determining. It is not consistent, however, with the e^-/H^+ transfer mechanism in which the electron transfer step is rate-determining. With either mechanism the **3** to **11** transformation would have to be very fast. The absence of cyclized anthrahydroquinone in the photolysis of the structurally similar **9** suggests that the rate constant for the **3** to **11** transformation is greater than 10^5 s^{-1}.

Substituent Effects. Substituent effects in the photodebenzylation of **7** are relatively small with a factor of only 3.4 in k_{dis} between the fastest anthraquinone **7h**, which possesses the electron-withdrawing NO_2 group, and the slowest anthraquinone **7c**, which possesses a OCH_3 group. The other anthraquinones with structure **7** have similar reactivities even though their substituents vary appreciably in their electron-donating and -withdrawing abilities (i.e., σ or σ^-). There is poor correlation, therefore, between k_{dis} and either σ or σ^-.

Although the e^-/H^+ transfer mechanism with a rate-determining electron transfer step has already been eliminated on the basis of the deuterium isotope effect, it is also inconsistent with the substituent effect data. Clearly, a rate-determining step in which positive charge is developing in the transition state at a site β to the aryl group would be expected to go faster as the substituents become more electron donating.

The e^-/H^+ transfer mechanism with a slow proton transfer step is not supported by the data either. A likely transition state for this step is **12** with partial negative charge developing at the carbon α to the aryl group. This is consistent with **7h** and **7c** having the largest and smallest k_{dis}, respectively, but does not account for the poor correlation of the remaining substituents with σ and σ^-. Furthermore, the ratio of only 3.4 in the k_{dis} values for **7h** and **7c** is quite small considering that the reaction site is adjacent to the aromatic ring. This corresponds to a ρ value of only 0.4 if $\sigma-$ values for these two anthraquinones are used.

Captodative Effects. Structure **13** is the transition state for the hydrogen atom transfer step in the photodebenzylation of **7**.



12 **13**

Substituent effects upon homolytic processes and free radical stabilities have been examined and appear to be both electronic and steric in their origin.[19,20] A number of investigators have suggested that a radical center, bonded to both electron-donating and electron-withdrawing groups, is synergistically stabilized via a captodative effect.[21-24] This synergistic or captodative effect has been estimated to be 4–5 kcal/mol in radicals such as $ROCHCOPh$, $R_2NCHCOPh$, and $R_2NC(CN)_2$.[24] The developing radical at the 1-position in **13** lies between an oxygen atom that can donate electron density and an aromatic ring that can accept electron density. Consequently, a captodative interaction could account for **7h** having the largest k_{dis} and **7c** having the smallest one.

Solvent Polarity Effects. The solvent polarity studies also lend support to a hydrogen atom transfer mechanism that exhibits a captodative effect. Figure 4 shows the effect of solvent polarity upon the photodebenzylation of **7a**. As noted earlier, the absence of a common trend for **7** is consistent with a homolytic process in which little charge separation is developing in the transition step. When the NO_2 group is present, charge separation is enhanced due to the captodative effect, resulting in a k_{dis} for **7h** that increases with increasing solvent polarity. In contrast, charge separation is minimized when the OMe group is present such that k_{dis} for **7c** actually decreases with increasing solvent polarity.

The solvent polarity data do not support the e^-/H^+ transfer mechanism with a slow proton-transfer step. In the proton-transfer step, charge is delocalized as reaction proceeds through transition state **12**. Consequently, not only would a general trend of decreasing k_{dis} with increasing solvent polarity be expected, but the effect would likely be the most pronounced with **7h**, in which charge delocalization is enhanced by the NO_2 group.

Summary

In this work we have examined the photochemistry of a variety of 9,10-anthraquinones substituted with alkoxy or benzyloxy groups at the 1-position. In methanol and in the absence of oxygen these compounds undergo an intramolecular oxidation–reduction reaction, giving anthrahydroquinones. Quenching studies establish the multiplicity of the excited state to be triplet. Deuterium isotope effects, substituent effects, and solvent polarity studies support a mechanism in which a biradical intermediate is formed by an intramolecular δ-hydrogen atom transfer that occurs in one step but not a reaction pathway in which the hydrogen atom transfer is accomplished in two discrete steps via separate electron and proton transfers.

Experimental Section

General. Melting points were determined in open capillary tubes with a Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ. IR spectra were obtained with a Sargent-Welch Pye Unicam 3-200 IR or Mattson Galaxy 4020 FT-IR spectrometer. Mass spectra were recorded on a Hewlett-Packard 5971A GC/MS. HPLC analyses were made with a Rainin Model 81-NM pump, Rainin C-18 reverse-phase column, and Milton Roy 3100 detector using methanol–water mixtures as the eluting solvent. Proton and ^{13}C NMR spectra were recorded on a Bruker 250-MHz AC-E spectrometer.

Measurement of Quantum Yields. Quantum yield measurements were made with a Lambda Physik EMG 50 Laser using xenon chloride at 308 nm. The number of photons absorbed by the sample were counted by using a Scientech 372 power meter and concentrations were monitored by a Perkin-Elmer Lambda Array 3840 UV/visible spectrophotometer.

Measurement of Apparent Rate Constants (k_{dis}). Samples were irradiated simultaneously in a merry-go-round apparatus using a 300-W tungsten light source. Aliquots were removed at various times and sample concentrations were determined by HPLC at a wavelength of 260 nm. Plots of $\ln\{[AQ]_0/[AQ]_t\}$ versus time (AQ = reactant anthraquinone) were linear and the slopes correspond to the apparent rate constants for the disappearance of AQ (k_{dis}).

1-Methoxy-2-methyl-9,10-anthraquinone (1) was prepared by the method of Savard and Brassard:[25] mp 164–165 °C (lit.[26] mp 166–167 °C). Anal. Calcd for $C_{16}H_{12}O_3$: C, 76.18; H, 4.79. Found: C, 76.00; H, 5.08.

1-(Trideuteriomethoxy)-2-methyl-9,10-anthraquione (1-d_3) was prepared from **2** and diemthyl-d_6 sulfate in 81% yield by the method of Kelly and Ghoshal:[27] mp 164-165 °C; MS, *m/e* (rel intensity) 255 (100), 238 (32), 225 (48), 207 (22), 179 (24), 166 (40), 152 (33).

1-[3-(*o*-Nitrophenyl)propyl]-2-methyl-9,10-anthraquinone (4). A mixture of 46.0 mg (0.193 mmol) of 1-hydroxy-2-methyl-9,10-anthraquinone (**2**),[25] *o*-(3-iodopropyl)nitrobenzene (354 mg, 1.22 mmol), and

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K_2CO_3 (533 mg, 3.86 mmol) in 10 mL of 2-butanone was heated to reflux for 15 h. The reaction mixture was cooled, diluted with 50 mL of acetone, and filtered. Removal of solvent in a rotary evaporator gave a red solid. Chromatography of this material on silica gel followed by elution with benzene/hexane (15:85) gave excess iodide. Elution with benzene gave **4** as a yellow solid, which was recrystallized from heptane/toluene, giving 60.2 mg (78%) of yellow needles: mp 162–163 °C; IR (Nujol) 1562, 1460, 1176, 1155, 1130, 1090, 1055, 950, 927, 906, 870, 829, 783, 760, 748, 710, 690, 652, 638, 625, 611, cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.27–2.38 (m, 2 H), 2.43 (s, 3 H), 3.19–3.26 (m, 2 H), 4.06 (t, 2 H), 7.34–7.41 (m, 1 H), 7.51–7.61 (m, 3 H), 7.70–7.81 (m, 2 H), 7.92–7.95 (dd, 1 H), 8.02–8.05 (d, 1 H), 8.19–8.29 (m, 2 H); ^{13}C NMR (250 MHz, $CDCl_3$) δ 17, 30, 31, 73, 123, 125, 126, 127 (2), 132, 133 (4), 134 (2), 135, 136, 137, 141, 150, 158, 183 (2); MS, *m/e* (rel intensity) 401 (36), 366 (6), 251 (9), 238 (100). Anal. Calcd for $C_{24}H_{19}NO_5$: C, 71.81; H, 4.77; N, 3.49. Found: C, 71.69; H, 5.03; N, 3.49.

Photolysis of 4. A solution of **4** (124 mg, 0.309 mmol) in approximately 400 mL of HPLC grade methanol and under argon was irradiated for 46 with a 300-W tungsten lamp. The methanol was removed in a rotary evaporator and the residue was chromatographed on silica gel. Elution with hexane–benzene (80:20) gave 60.2 mg (82%) of **2**. Elution with hexane–toluene–ethyl acetate (70:20:10) gave 50 mg (83%) of 3-(*o*-nitrophenyl)propanal as a viscous liquid, which gave spectra data identical in all respects with those of a sample of 3-(*o*-nitrophenyl)-propanal prepared from 3-(*o*-nitrophenyl)-1-propanol by using pyridinium chlorochromate: IR (film) 3035, 2815, 2720, 1711, 1605, 1511, 1440, 1345, 1167, 1060, 960, 858, 790, 740, 708, 660 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 2.70–2.32 (m, 4 H), 7.20-7.90 (m, 4 H), 9.70 (s, 1 H).

1-(Hexyloxy)-2-methyl-9,10-anthraquinone (8). A mixture of **2** (80.0 mg, 0.336 mmol), 1-iodohexane (480 mg, 2.26 mmol), and K_2CO_3 (800 mg, 5.80 mmol) in 50 mL of 2-butanone was heated to reflux for 50 h during which time the color changed from deep red to orange. The reaction mixture was cooled, diluted with 80 mL of acetone, and vacuum filtered. The solvent was removed in a rotary evaporator giving a solid that was chromatographed on silica gel and eluted with toluene. Recrystallization from heptane gave 70.3 mg (65%) of **8** as yellow needles: mp 98 °C; IR (Nujol) 1670, 1580, 1329, 1315, 1275, 1245, 1194, 1160, 1070, 1051, 1010, 985, 978, 920, 900, 888, 860, 821, 800, 755, 715, 686, 659 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.93 (t, 3 H), 1.37–1.57 (m, 6 H), 1.90–2.01 (m, 2 H), 2.43 (s, 3 H), 3.97 (t, 2 H), 7.58–7.61 (d, 1 H), 7.70–7.81 (m, 2 H), 8.02–8.05 (d, 1 H), 8.22–8.31 (m, 2 H); ^{13}C NMR (250 MHz, $CDCl_3$) δ 14, 17, 23, 26, 30, 31, 74, 123, 127 (3), 133 (4), 134, 136, 141, 158, 183 (2); MS, *m/e* (rel intensity) 322 (2), 320 (5), 251 (70), 238 (100). Anal. Calcd for $C_{21}H_{22}O_3$: C, 78.23; H, 6.88. Found: C, 78.54; H, 6.89.

1-(5-Hexenyloxy)-2-methyl-9,10-anthraquinone (9). A mixture of **2** (50.0 mg, 0.210 mmol), 6-iodo-1-hexene (100 mg, 0.467 mmol), and K_2CO_3 (1.0 g, 7.2 mmol) in 20 mL of 2-butanone was heated to reflux for 40–50 h during which time the color changed from deep red to yellow. After cooling, the mixture was diluted with 45 mL of acetone and vacuum filtered. The solvent was removed in a rotary evaporator and the yellow solid residue was chromatographed on silica gel and eluted with toluene. Recrystallization of the resulting solid from heptane gave 48.0 mg of **9** (71%) as yellow needles: mp 110 °C; IR (Nujol) 1710, 1672, 1640, 1580, 1465, 1411, 1380, 1324, 1275, 1260, 1249, 1195, 1160, 1100, 1050, 1015, 915, 890, 854, 717, 700, 660 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.61–1.73 (m, 2 H), 1.92–2.03 (m, 2 H), 2.15–2.23 (m, 2 H), 2.41 (s, 3 H), 3.97 (t, 2 H), 4.96–5.11 (m, 2 H), 5.80–5.96 (m, 1 H), 7.56–7.59 (dd, 1 H), 7.69–7.80 (m, 2 H), 8.00–8.03 (d, 1 H), 8.18–8.27 (m, 2 H); ^{13}C NMR (250 MHz, $CDCl_3$) δ 17, 25, 30, 34, 74 (2), 115, 123, 126 (2), 127, 133, 134 (2), 135, 136, 139, 141, 158, 183 (2); MS, *m/e* (rel intensity) 320 (4), 251 (17), 238 (100), 181 (7), 152 (11). Anal. Calcd for $C_{21}H_{20}O_3$: C, 78.73; H, 6.29. Found: C, 78.74; H, 6.02.

1-(Benzyloxy)-2-methyl-9,10-anthraquinone (7a). A mixture of **2** (26.0 mg, 0.109 mmol), 650 mg of benzyl bromide, and K_2CO_3 (1 g, 7.25 mmol) in 45 mL of 2-butanone was heated to reflux for 19 h during which time the reaction mixture changed from yellow to red. After cooling, the mixture was diluted with 35 mL of H_2O and extracted with 35 mL of CH_2Cl_2. The CH_2Cl_2 extract was washed with 25 mL of H_2O and dried over Na_2SO_4. After removal of solvent in a rotary evaporator the solid residue was recrystallized from heptane giving 24.2 mg (68%) of **7a** as yellow needles: mp 150–151 °C; IR (Nujol) 1670, 1325, 1276, 1242, 1192, 1160, 1045, 1013, 975, 956, 915, 892, 850, 760, 725, 696 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.36 (s, 3 H), 5.05 (s, 2 H), 7.34–7.47 (m, 3 H), 7.60–7.64 (m, 3 H), 7.72–7.83 (m, 2 H), 8.07–8.10 (d, 1 H), 8.24–8.33 (m, 2 H); ^{13}C NMR (250 MHz, $CDCl_3$) δ 17, 76, 124, 127 (4), 128 (4), 133 (3), 134 (3), 137, 142, 157, 183 (2); MS, *m/e* (rel intensity) 314 (31), 139 (9), 91 (100). Anal. Calcd for $C_{22}H_{16}O_3$: C, 80.47; H, 4.91. Found: C, 80.68; H, 5, 5.30.

1-[(α,α-Dideuteriobenzyl)oxy]-2-methyl-9,10-anthraquinone (7b) was prepared from benzyl-d_2 bromide (by $LiAlD_4$ reduction of ethyl benzoate and treatment of the resulting $PhCD_2OH$ with concentrated HBr) and **2** by using the above method for **7a**: mp 151–152 °C; MS, *m/e* (rel intensity) 330 (46), 238 (11), 152 (13), 93 (100).

1-[(*p*-Chlorobenzyl)oxy]-2-methyl-9,10-anthraquinone (7g). A mixture of **2** (21.9 mg, 0.092 mmol), K_2CO_3 (1.1 g, 7.97 mmol), and *p*-chlorobenzyl chloride (878 mg, 5.45 mmol) in 55 mL of 2-butanone was heated to reflux for 23 h. After cooling, the reaction mixture was diluted with 30 mL of H_2O and extracted with 50 mL of CH_2Cl_2. The CH_2Cl_2 extract was washed with 20 mL of H_2O, dried over Na_2SO_4, and evaporated to dryness. The residue was recrystallized from heptane/toluene giving 21.3 mg of **7g** (64%) as yellow crystals: mp 170–1 °C; IR (Nujol) 1670, 1513, 1460, 1380, 1320, 1280, 1250, 1178, 1030, 950, 860, 719 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.36 (s, 3 H), 4.99 (s, 2 H), 7.38–7.43 (dt, 2 H), 7.56–7.63 (m, 3 H), 7.72–7.82 (m, 2 H), 8.06–8.10 (d, 1 H), 8.23–8.30 (m, 2 H); ^{13}C NMR (250 MHz, $CDCl_3$) δ 17, 25, 111, 124, 126, 127 (3), 129 (2), 133 (3), 134 (2), 136 (3), 141, 158, 183 (2); MS, *m/e* (rel intensity 364 (7), 362 (20), 237 (9), 152 (10), 127 (34), 125 (100). Anal. Calcd for $C_{22}H_{15}O_3Cl$: C, 72.83; H, 4.17; Cl, 9.77. Found: C, 72.37; H, 4.46; Cl, 9.66.

1-[(*p*-Methoxybenzyl)oxy]-2-methyl-9,10-anthraquinone (7c). A mixture of **2** (26.3 mg, 0.110 mmol), *p*-methoxybenzyl chloride (390 mg, 2.49 mmol), and K_2CO_3 (1.3 g, 9.42 mmol) in 35 mL of 2-butanone was heated to reflux for 6 h during which time the color changed from red to yellow. The mixture was diluted with 35 mL of acetone and vacuum filtered. Removal of solvent in a rotary evaporator gave a viscous liquid residue that was treated with cold hexane to remove excess *p*-methoxybenzyl chloride. The resulting yellow solid was recrystallized from heptane giving 26.1 mg (66%) of **7c** as yellow needles: mp 167–168 °C; IR (Nujol) 1670, 1513, 1460, 1380, 1320, 1280, 1250, 1178, 1030, 950, 930, 860, 719 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.34 (s, 3 H), 3.84 (s, 3 H), 4.98 (s, 2 H), 6.93–6.97 (d, 2 H), 7.52–7.62 (m, 3 H), 7.73–7.82 (m, 2 H), 8.06–8.09 (d, 1 H), 8.24–8.33 (m, 2 H); ^{13}C NMR (250 MHz, $CDCl_3$) δ 17, 53, 75, 114, 116, 123, 126, 127 (2), 130 (2), 133 (3), 134 (3), 136, 143, 157, 160, 183 (2); MS, *m/e* (rel intensity) 358 (100), 250 (70), 238 (60), 121 (38). Anal. Calcd for $C_{23}H_{18}O_4$: C, 77.08; H, 5.06. Found: C, 76.92; H, 5.24.

1-[(*p*-Nitrobenzyl)oxy]-2-methyl-9,10-anthraquinone (7h). A mixture of **2** (16.0 mg, 0.0672 mmol), *p*-nitrobenzyl bromide (242 mg, 1.12 mmol), and K_2CO_3 (1.1 g, 7.97 mmol) in 25 mL of 2-butanone was heated to reflux for 1 h during which time the mixture changed color from red to yellow. The reaction mixture was diluted with 30 mL of acetone and vacuum filtered. Removal of solvent in a rotary evaporator gave a light yellow solid. Most of the excess *p*-nitrobenzyl bromide was removed by sublimation leaving a yellow solid that was recrystallized from heptane/toluene to give 12.0 mg (60%) of **7h** as yellow crystals: mp 238–239 °C; IR (Nujol) 1670, 1460, 1380, 1280, 1156, 1060, 980, 900, 852, 730 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.42 (s, 3 H), 5.14 (s, 2 H), 7.65–7.69 (dd, 1 H), 7.77–7.85 (m, 4 H), 8.12–8.15 (d, 1 H), 8.26–8.34 (m, 4 H); ^{13}C NMR (250 MHz, $CDCl_3$) δ 17, 73, 124 (2), 127 (3), 128, 133, 135 (4), 136, 140, 141, 145, 147, 154, 157, 183 (2); MS, *m/e* (rel intensity) 373 (14), 356 (7), 239 (16), 238 (100), 237 (47), 181 (16), 152 (19). Anal. Calcd for $C_{22}H_{15}NO_5$: C, 70.77; H, 4.05; N, 3.75. Found: C, 70.55; H, 4.07; N, 3.76.

1-[(*p*-Methylbenzyl)oxy]-2-methyl-9,10-anthraquinone (7f). A mixture of **2** (49.6 mg, 0.208 mmol), K_2CO_3 (2.2 g, 15.9 mmol), and *p*-methylbenzyl bromide (1.92 g, 10.4 mmol) in 50 mL of 2-butanone was heated to reflux for 80 min. After cooling, the reaction mixture was diluted with 60 mL of H_2O and extracted with CH_2Cl_2 (2 × 50 mL). The CH_2Cl_2 extracts were combined and dried over Na_2SO_4. Removal of solvent in a rotary evaporator gave a viscous yellow liquid. Chromatography of this residue on silica gel and elution (in order) with hexane, hexane/toluene (5:1), toluene, toluene/CH_2Cl_2 (1:1), and CH_2Cl_2 gave excess *p*-methylbenzyl bromide followed by **7f**. Recrystallization (twice) from heptane/toluene gave 41.3 mg (58%) of **7f** as yellow crystals: mp 157–158 °C; IR (nujol) 1675, 1590, 1570, 1465, 1380, 1330, 1320, 1280, 1250, 1050, 1020, 960, 940, 860, 810, 780, 720 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.35 (s, 3 H), 2.39 (s, 3 H), 5.01 (s, 2 H), 7.24–7.28 (m, 4 H), 7.47–7.81 (m, 4 H), 8.05–8.18 (m, 2 H); ^{13}C NMR (250 MHz, $CDCl_3$) δ 17, 21, 75, 124, 126, 127, 128, 129 (2), 130 (2), 133, 134 (3), 135 (2), 136, 138, 142, 158, 183 (2); MS, *m/e* (rel intensity) 342 (17), 238 (7), 152 (7), 105 (100). Anal. Calcd for $C_{23}H_{18}O_3$: C, 80.68; H, 5.30. Found: C, 80.10; H, 5.22.

1-[[(*p*-Trifluoromethyl)benzyl]oxy]-2-methyl-9,10-anthraquinone (7e). A mixture of **2** (49.9 mg, 0.209 mmol), K_2CO_3 (2.2 g, 15.9 mmol), and a *p*-(trifluoromethyl)benzyl bromide (2.30 g, 9.84 mmol) in 50 mL of 2-butanone was heated to reflux for 75 min. After cooling, the reaction mixture was diluted with 80 mL of H_2O and extracted with CH_2Cl_2 (2

× 50 mL). The CH_2Cl_2 extracts were combined, washed with 25 mL of H_2O, and dried over Na_2SO_4. Removal of solvent in a rotary evaporator gave a solid that was recrystallized (twice) from heptane/toluene giving 56.3 mg (68%) of **7e** as light yellow needles: mp 179–180 °C; IR (Nujol) 1675, 1590, 1575, 1465, 1380, 1335, 1320, 1285, 1270, 1250, 1170, 1110, 1080, 1060, 1025, 990, 900, 855, 845, 830, 720 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.37 (s, 3 H), 5.05 (s, 2 H), 7.61–7.73 (m, 7 H), 8.11–8.30 (m, 3 H); ^{13}C NMR (250 MHz, $CDCl_3$) δ 17, 75, 122, 125 (q, J = 1250 Hz), 126 (3), 127 (2), 128, 129, 130 (2), 132, 134 (4), 142 (2), 158, 183 (2); MS, m/e (rel intensity) 396 (21), 378 (9), 250 (8), 237 (26), 222 (9), 159 (100), 152 (11), 109 (11). Anal. Calcd for $C_{23}H_{15}O_3F_3$: C, 69.70; H, 3.81. Found: C, 69.64; H, 4.11.

1-[(*p*-Cyanobenzyl)oxy]-2-methyl-9,10-anthraquinone (7d). A mixture of **2** (49.5 mg, 0.208 mmol), K_2CO_3 (2.2, 15.9 mmol), and *p*-cyanobenzyl bromide (2.17 g, 11.1 mmol) in 50 mL of 2-butanone was heated to reflux for 75 min. After cooling, the reaction mixture was diluted with 60 mL of H_2O and extracted with CH_2Cl_2 (2 × 50 mL). The CH_2Cl_2 extracts were combined, washed with H_2O (30 mL), and dried over Na_2SO_4. Removal of solvent in a rotary evaporator gave yellow crystals. Excess *p*-cyanobenzyl bromide was removed by sublimation (0.1 mmHg, ~70 °C). The residue was decolorized (norit) and recrystallized from toluene. Recrystallization gave 26.6 mg of **7d** (42%): mp 222–223 °C; IR (Diffuse reflectance in KBr) 2227, 1671, 1580, 1582, 1568, 1324, 1276, 1244, 1192, 1053, 985, 892, 824, 711 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.39 (s, 3 H), 5.05 (s, 2 H), 7.65–7.78 (m, 7 H), 8.10–8.30 (m, 3 H); ^{13}C NMR (250 MHz, $CDCl_3$) δ 17, 73, 112, 118, 123, 126, 127 (2), 128, 129 (2), 132, 133 (2), 134 (4), 136, 139, 141, 156, 183. Anal. Calcd for $C_{23}H_{15}O_3N$: C, 78.18; H, 4.28; N, 3.96. Found: C, 77.89; H, 4.56; N, 3.97.

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Short, Enantiogenic Syntheses of (−)-Indolizidine 167B and (+)-Monomorine†

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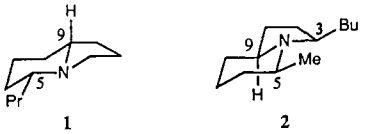
Abstract: The enantiogenic syntheses of (−)-indolizidine 167B (**1**) and (+)-monomorine (**2**) are described. D-Norvaline and L-alanine are converted into their 1-pyrrole derivatives by reaction with 2,5-dimethoxytetrahydrofuran. Thereafter, Arndt–Eistert homologation of the *N*-alkanoic acid substituent, followed by rhodium(II) acetate catalyzed decomposition of its α-diazo ketone derivative, provides the relevant bicyclic precursors, the vested chirality of which directs catalytic hydrogenation affording **1** and **2**. Provision for the 5-butyl side chain in **2** is made by prior Lewis acid catalyzed rearrangement of the mixed anhydride obtained from butyryl chloride and the pyrrole analogue of L-alanine.

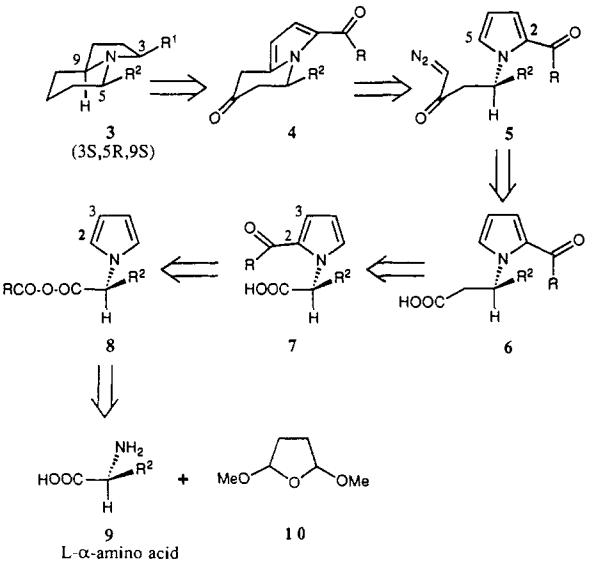
Introduction

Indolizidine alkaloids offer attractive targets for synthesis because of their exotic provenance, scarcity, and marked biological activity.[1] Two typical, but contrasting, examples are indolizidine 167B (**1**), a vanishingly minor constituent of the skin of a dendrobatid frog, caught on Isla de Colón, Panamá,[2,3] and (+)-monomorine (**2**), a trail pheromone of the Pharaoh's ant (*Monomorium pharaonis* L.), a pest in heated buildings.[4] Although frogs of the genus *Dendrobates* were never used as a source of arrow poisons, unlike the Colombian genus *Phyllobates*,[2] several of the constituents contained in their skins and closely related to **1**, are noncompetitive blockers of neuromuscular transmission.[5] Consequently, the practical preparation of these rare and potent substances is of some importance. So far, indolizidine 167B has been synthesized twice in its racemic form[6,7] and once as its (−) enantiomer,[8] whereas many syntheses have been reported for racemic[9,10] and enantiomerically pure monomorine.[11] It might therefore appear that sufficient methods are available for preparing mono- and disubstituted indolizidines. Unfortunately, most are multistep procedures giving the product in poor overall yields. We



1 2

Scheme I



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(1) Lamberton, J. A. *The Alkaloids*; Specialist Periodical Reports; The Royal Society of Chemistry: London, 1976–1983; Vol. 6–13. Gellert, E. *J. Nat. Prod.* **1982**, *45*, 50–73.

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