chemically[11,20a] and slightly higher than those estimated from diffusivity.[11,19a,b,49c]

Acknowledgment. Support of this work by the National Science Foundation (Chemical Dynamics Program) is gratefully acknowledged.

Registry No. CDHABr, 20317-32-2; *p*-NPB, 959-22-8; DNFB, 70-34-8; *p*-NPDEP, 311-45-5; *p*-NPDHP, 102494-18-8; CTACl, 112-02-7; CTABr, 57-09-0; CDHACl, 24625-03-4; DNCN, 2401-85-6; DNCB, 97-00-7; *p*-NPDPP, 10359-36-1; *p*-NBP, 20513-28-4; p-$NO_2C_6H_4OC(O)Ph$, 959-22-8; SO_4^{2-}, 14808-79-8; OH^-, 14280-30-9; Cl^-, 16887-00-6; Br^-, 24959-67-9; NO_3^-, 14797-55-8.

Supplementary Material Available: A figure, of variation of k_ψ in the [CTABr] for reactions of *p*-nitrophenyl dialkyl phosphates with 0.01 M NaOH[26c] (2 pages). Ordering information is given on any current masthead page.

Acid-Catalyzed Photooxidation of *m*-Nitrobenzyl Derivatives in Aqueous Solution

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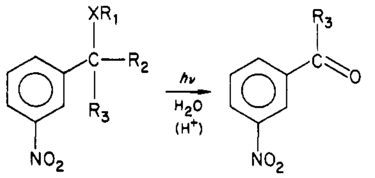
A variety of *m*-nitrobenzyl derivatives including alcohols, alkyl ethers, esters, and an amine undergo photooxidation reactions to produce *m*-nitrobenzaldehyde (or *m*-nitroacetophenone in two cases) as the major isolated product. The reaction is both solvent and pH dependent and only takes place in essentially aqueous media. The quantum efficiency of product formation reaches a maximum (ϕ = 0.3–0.4) in the 20–50% sulfuric acid range, depending on the substrate, although the reaction is reasonably efficient even in neutral aqueous solution. The presence of benzylic hydrogen and a heteroatom (O, N) in the α-position appears to be essential for photooxidation to occur. The multiplicity of the reactive state is T_1. A solvent isotope effect (ϕ_{H_2O}/ϕ_{D_2O} = 1.4) was observed. The proposed mechanism involves rate-determining protonation of T_1 followed by rapid α-hydrogen abstraction by water.

Photochemical reactions of *o*-nitrobenzyl compounds are well-known and have been shown to involve intramolecular oxidation–reduction in several cases. For example, *o*-nitrobenzyl alcohol reacts photochemically[1] in organic solvents to give *o*-nitrosobenzaldehyde, while *o*-nitrobenzaldehyde undergoes photooxidation–reduction in various solvents and even in the solid state to give *o*-nitrobenzoic acid.[2] These reactions do not appear to involve catalysis by either external acids or bases and are clearly intramolecular in origin due to the proximity of the two groups involved.

In contrast, the photoredox reactions of analogous *m*- and *p*-nitrobenzyl derivatives take place only in aqueous media and are subject to catalysis.[3,4] Surprisingly, irradiation of *p*-nitrobenzyl alcohol itself gives *p*-nitrosobenzaldehyde as the major product in a process which is strongly catalyzed by hydroxide ion,[4] whereas the *m*-nitro isomer gives *m*-nitrobenzaldehyde via hydrogen ion catalysis.[5] The detailed mechanism of these reactions has been the subject of several previous reports.[3–5]

We were interested in exploring the generality and possible synthetic utility of such photoredox reactions and because of the greater efficiency of the *m*-nitrobenzyl alcohol reaction,[5] which has absolute quantum yields in the 0.05–0.4 range, depending on the pH, it was decided to concentrate initially on *m*-nitro systems. Their higher reactivity appears to be another example of the well-known meta effect[6] in photochemical reactions.

Chart I



	XR1	R2	R3
1a	OH	H	H
b	OMe	H	H
c	OEt	H	H
d	OH	CH2OH	H
e	OMe	CH2OH	H
f	OCOMe	H	H
g	NH2	H	H
h	OCH2Ph	H	H
i	OH	CH3	H
j	OH	CH2COOEt	H
k	OPh	H	H
l	OPh	CH2OH	H
m	OH	CH2OPh	H
n	OMe	OMe	Me
o	OH	CH2COOEt	Me
p	OH	Me	CH2OH
q	H	COCH3	H
r	H	H	H

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(5) Wan, P.; Yates, K. *J. Org. Chem.* **1985**, *50*, 2881.

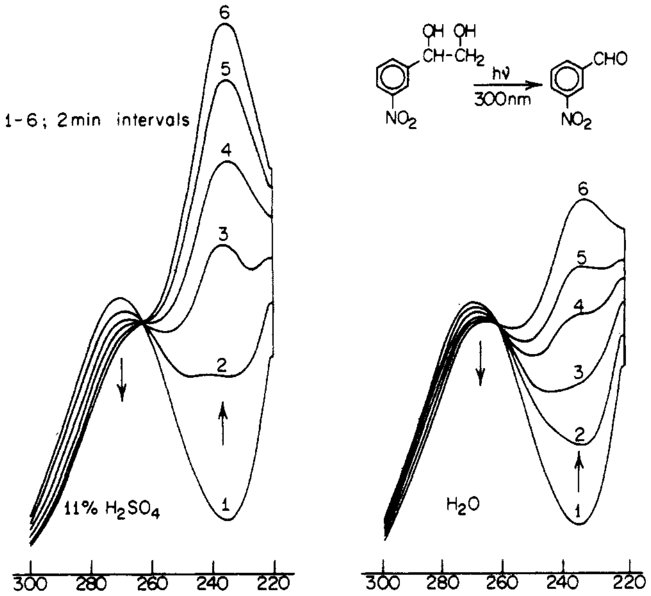

Figure 1. Ultraviolet spectra for photooxidation of *m*-nitrophenyl ethylene glycol **1d** (2×10^{-5} M) to *m*-nitrobenzaldehyde **2** in water and 11% H_2SO_4 at irradiation time as indicated.

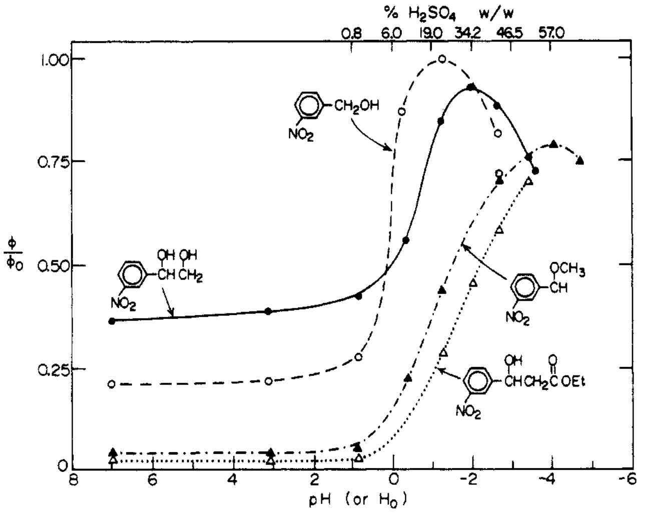

Figure 2. Dependence of the relative quantum efficiency (ϕ/ϕ_0) of photooxidation of *m*-nitrobenzyl derivatives **1a**, **1b**, **1d**, and **1j** at 300 nm on the acid concentration.

Results

The *m*-nitrobenzyl alcohol derivatives **1a–r** were chosen for study and were synthesized by using standard literature methods or were available commercially (Chart I). These include one amine, benzylamine (**1g**), which was chosen to investigate the effect of a more basic α-heteroatom, and toluene (**1r**). Direct irradiation (300 nm) of a 10^{-3} M solution, in either water or sulfuric acid–water mixtures up to 50% acid, of compounds **1a–h** gave *m*-nitrobenzaldehyde **2** as the major isolated product.[7] The *p*-nitro isomers of these substrates gave no detectable oxidation product under identical reaction conditions.

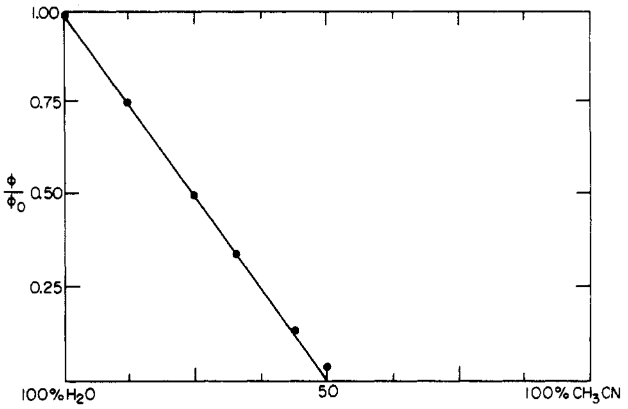

Figure 3. Effect of added MeCN to water (v/v) on the relative quantum efficiency of photooxidation of *m*-nitrophenyl ethylene glycol **1d** to *m*-nitrobenzaldehyde at 300 nm.

Table I. Measured and Estimated Quantum Yields

compd	$\phi_{\text{pH 7}}$	ϕ_{max} (% H_2SO_4)
1a	0.085	0.42 (20)
1b	0.011	0.31 (57)
1d	0.140	0.36 (34)
1j	0.070	

The formation of *m*-nitrobenzaldehyde was followed by UV spectrophotometry, based on appearance of a new band at 234 nm, as shown in Figure 1. Product formation was also monitored for compounds **1b** and **1d** by extraction from the irradiated solution and analysis by GC. The reaction was found to be strongly pH dependent and the isolated yield of product could be increased by raising the acidity of the solution irradiated. Figure 2 shows a plot of relative quantum yield of product formation ϕ/ϕ_0 (where ϕ_0 is the quantum yield at pH 7) vs. acid concentration or pH (H_0) for substrates **1a**, **1b**, **1d**, and **1j**. It can be seen from Figure 2 that although the relative quantum yield increases more or less sigmoidally up to an acid concentration of 20–55% ($H_0 = -1.1$ to -3.3), depending on the substrate, the efficiency of the reaction falls off at higher acidities. This occurs even earlier for benzylamine (**1g**) which gave **2** only from pH 7 to pH 5. Apparently the protonated form of this substrate ($pK_{BH^+} = 9.33$)[8] is unreactive upon irradiation.

The absolute quantum yield for **1d** at pH 7 was determined by ferrioxalate actinometry[9] to be $\phi = 0.14 \pm 0.02$ (at 300 nm). This was the most reactive substrate investigated in neutral solution and the absolute quantum yields for several of the other substrates were estimated by comparison of their ϕ_0 values with that of **1d**. These are shown in Table I.

The estimated values for **1a** compare reasonably well with previously reported[3b] quantum yields for this compound of 0.055 (at pH 7) and 0.34 (at maximum acidity) determined by using a malachite green leucocyanide actinometer.

The photooxidation reaction was found to take place only in purely aqueous or predominantly aqueous media. Addition of organic solvents such as MeOH, EtOH, isopropyl alcohol, or acetonitrile reduced the quantum efficiency drastically. This is shown in Figure 3, where the relative quantum yield ϕ/ϕ_0 for compound **1d** is plotted against the percentage solvent composition for acetonitrile–water mixtures. As 50% acetonitrile is approached,

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(6) Cornelisse, J.; Havinga, E. *Chem. Rev.* **1975**, 353. Havinga, E.; De Jongh, R. O.; Dorst, W. *Recl. Trav. Chim.* **1956**, *75*, 378. Zimmerman, H. E.; Somasekhara, S. *J. Am. Chem. Soc.* **1963**, *85*, 922. For a review, see: Cristol, S. J.; Bindel, T. H. In *Organic Photochemistry*; Padwa, A., Ed.; Marcel Dekker: New York, 1983; Vol. 6, Chapter 5.

(7) In these reactions small quantities of orange-colored materials were always isolated in addition to *m*-nitrobenzaldehyde. These may be the products of a subsequent photochemical reaction of initially formed *m*-nitrosobenzaldehyde,[5] since nitroso compunds are often unstable and can undergo further ground and excited state transformations.[15]

(8) Perrin, D. P. *Dissociation Constants of Organic Bases in Aqueous Solutions*; Butterworths: London, 1965.

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the photoreaction is essentially stopped. Irradiation of compounds **1a–h** in pure organic solvents such as DMF, hydrocarbons (hexanes, cyclohexane, benzene), and acetonitrile did not give any oxidation products, and the unreacted substrate could be recovered in greater than 95% yield.

It is interesting that whereas most active *m*-nitrobenzyl substrates **1d** gave **2** as the major product, compounds **1i** and **1j** gave *m*-nitroacetophenone instead. In contrast, substrates **1k–m**, containing β-phenoxy groups, were not photochemically reactive under the same reaction conditions as **1a–j**. Also, substrates with no α-hydrogens (**1n–p**) did not react under identical reaction conditions to those of **1a–j**, although the ketal **1n** did cleave thermally in acid solution to give the corresponding ketone.

The presence of heteroatom on C_α of the substrate was also found to be important, since substrates **1g** and **1r** did not produce any oxidation product under similar reaction conditions. However, as pointed out previously, **1g** with an α-nitrogen reacted similarly to **1a–h** to give **2**.

The multiplicity of the reactive excited state of these photooxidations was found to be T_1[10] by using a triplet sensitizer (acetone E_t = 79 K cal mol^{-1})[9] which gave the same product as on direct irradiation and by effective triplet quenching using potassium sorbate. It was found that the presence of molecular oxygen did not reduce the quantum efficiency of the product formation, but when deliberately introduced by saturating the solvent with oxygen, the efficiency of product formation increased by approximately 20%. When an oxygen-saturated solution of compounds **1a–d** was irradiated, the resulting solution oxidized a KI solution immediately, with iodine being detected by starch indicator. This experiment failed to give a positive result for substrates **1n–p**, which have no α-hydrogens. The observation of a positive iodine test for **1a–d** under these conditions indicates that hydrogen peroxide[4] is probably produced under the reaction conditions by an independent (photochemical) radical process, since exclusion of oxygen did not alter the major oxidation product (**2**) but gave no positive test for iodine. As a control, an oxygen-saturated acidified solution of any of the above compounds (**1a-d**) produced no product in the dark even after 48 h, and starting material was recovered quantitatively.

A deuterium solvent isotope effect was observed for substrates **1a–d** with an average value of ϕ_{H_2O}/ϕ_{D_2O} 1.40 ± 0.03. Irradiation of an acidified methanol solution of the same substrates did not give any oxidation product **2**. Also irradiation of **1a** and **1d** in the presence of an electron acceptor (1,4-dicyanobenzene) gave no **2**, and starting material was recovered unchanged.

Discussion

It has been demonstrated that the photochemical oxidation of *m*-nitrobenzyl derivatives (**1a–j**) to give either *m*-nitrobenzaldehyde or in some cases *m*-nitroacetophenone is quite a general reaction and gives reasonable quantum yields in aqueous solution, especially when acid is present. It is clear that the structural requirements for this reactivity are that at least one α-hydrogen and at least one α-heteroatom be present in the substrate, since it has been shown that structurally related substrates without both of these features such as **1n–r** do not react at all under similar conditions. The presence of an α-phenoxy group as in **1k–m** also inhibits the reaction, presumably due either to strong UV absorption by this chromophore or by energy dissipation via photophysical processes. (Irradiation of compound **1d** in the presence of equimolar *p*-anisyl alcohol or phenol also suppressed the photooxidation). The reaction appears to be another example of an acid-catalyzed photochemical process according to Wubbels' definition,[11] since the relative quantum yield increases sharply and sigmoidally in the acidity region pH 1 to $H_0 = -2$, in a similar way to that of previously reported photohydration reactions.[12] The fall-off in efficiency at higher acidities is probably due to protonation of the ground-state molecule on the α-oxygen. Presumably the cation so formed is photochemically inactive, since compound **1g** which is fully protonated in the ground state at low pH only oxidizes efficiently in the pH 7 to 5 region. The expected acidity range for significant ground-state protonation of benzyl alcohols and ethers is in the $H_0 = -3$ region, based on reported pK_{BH^+} values for typical alcohols and ethers.[13] Another possibility is that deactivational processes become more important in more concentrated acid solutions and that the reaction is quenched by high concentrations of ionic species.

A detailed mechanism has been proposed recently[5] for the photooxidation of *m*-nitrobenzyl alcohol itself and its methyl ether, but it is not easy to arrive at a unified mechanism which explains all the results. For example, although it is reasonable that **1i**, which is the only reactive substrate with an α-methyl group, gives *m*-nitroacetophenone rather than the aldehyde as major product, it is not obvious why **1j** should also give the ketone, since other substrates (**1d,e**) have groups with α-carbon atoms yet give only the aldehyde. It is also not clear why the reaction produces a nitro rather than a nitroso compound as major product.

It seems reasonable that the general mechanism for these photooxidations involves protonation of the excited state (T_1) on the nitro group, which is possible even at these low acidities due to its enhanced excited-state basicity[14] followed by rapid α-hydrogen abstraction by a water molecule within the solvation shell. This is supported by the observed solvent isotope effect. The following general scheme can be proposed for most of the substrates studied and is reasonable as far as the primary photochemical steps and probable initial photochemical product are involved, but the subsequent (possibly dark) reactions leading to the observed final product are less evident.

The *m*-nitrosocarbonyl compound formed initially (Scheme I) could then undergo either further ground state or photochemical oxidation to the *m*-nitro compound[15] or disproportionate to give a nitro and an azoxy compound, as proposed previously.[3,5] The latter seems more likely since in all of the reactions investigated small quantities of orange-colored dyes are isolated. This material consists of at least four compounds which have not yet been separated or identified. However, in the case of substrate **1a**, *m*-(3-(hydroxymethyl)phenyl)-*NNO*-azoxybenzaldehyde has been isolated in 40% yield (relative to 60% isolated yield of *m*-nitrobenzaldehyde).[3] Further work is in prog-

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(10) Nitroaromatic systems are known to undergo an efficient intersystem crossing to the triplet excited state. For a review, see: (a) Morrison, H. A. In *The Chemistry of Nitro and Nitroso Groups*; Feuer, H., Ed., Wiley: New York, 1969; Chapter 4. (b) Dopp, D. *Top. Curr. Chem.* **1975**, *55*, 49. (c) Frolov, A. N.; Kuznetsova, N. A.; El'Tsov, A. V. *Russ. Chem. Res.* (*Engl. Transl.*) **1976**, *45*, 1024.

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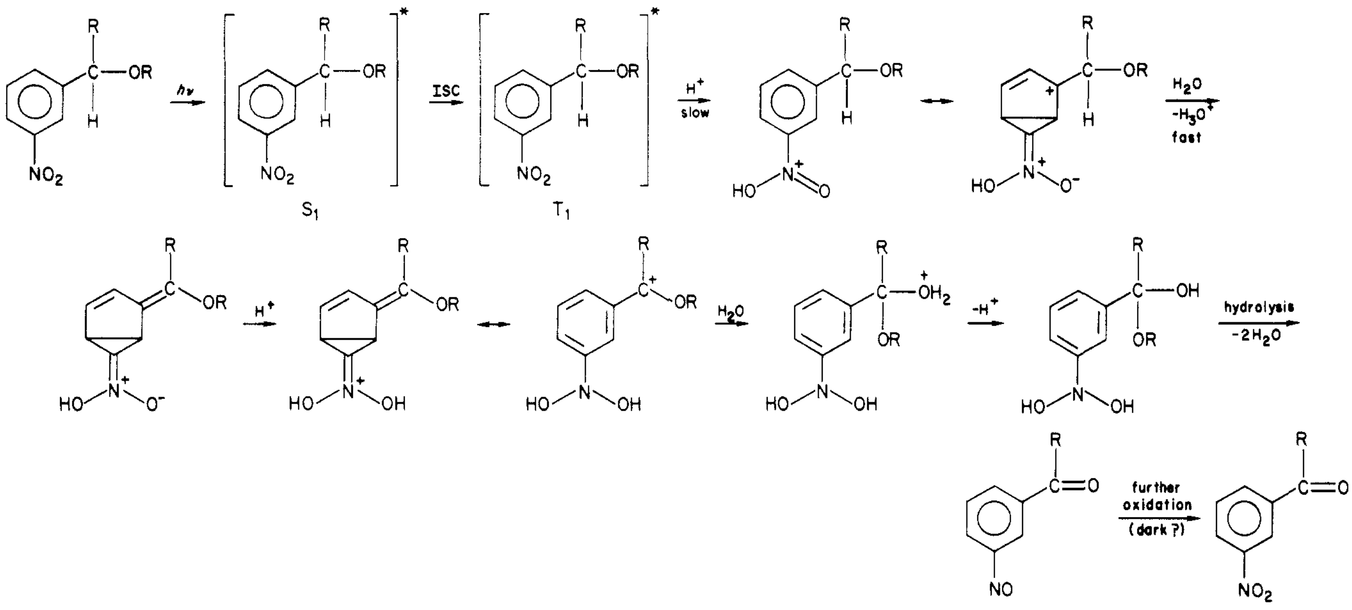
(15) Chow, Y. L. In *The Chemistry of Amino, Nitroso, Nitro Compounds and Their Derivatives*; Patai, S., Ed.; Wiley: Chichester, U.K., 1982; *Vol.* 1, Chapter 4.

Scheme I



ress to elucidate the detailed mechanism of these photooxidations. Although an electron-transfer process has been proposed[16] for the photoisomerization of *p*-nitrobenzaldehyde to *p*-nitrobenzoic acid, we do not consider this likely in the present case since such a reaction should proceed just as easily in organic solvents as in water. Also, the use of an electron acceptor[17] such as 1,4-dicyanobenzene should enhance product formation, whereas we could recover only unreacted starting material in its presence. In addition, we have ruled out bimolecular processes in the primary photochemical steps, since a tenfold increase in substrate concentration had no effect on the quantum yield. Similarly, irradiation of an equimolar mixture of nitrobenzene and benzyl alcohol does not lead to photooxidation.

Experimental Section

Materials. Solvents. Methylene chloride was used for extraction in preparative experiments; the reagent grade was distilled once over a 1-m Vigreux column before use. Distilled water was used for these experiments, and organic solvents employed were ACS grade (Caledon or Fisher) and used without further purification. Sulfuric acid solutions were prepared by diluting the commercial acid (BDH or Fisher) with distilled water and their percent composition by weight of H_2SO_4 was obtained by measuring their densities at 25 °C using a DMA 02C digital precision density meter from Anton Parr Instruments, Graz, Austria, and available tabulated percent composition/density data.[18]

Substrates **1a** and **1g** were purchased from Aldrich Chemical Company. All other substrates were prepared following procedures described in the literature; **1b**, **1c**, **1f**, **1h**, and **1k** were prepared by the reaction of equimolar *m*-nitrobenzyl bromide (Aldrich) and the corresponding sodium salt of the alcohol or acid.[19] Substrates **1e**, **1l**, and **1m** were prepared by reaction of *m*-nitrostyrene oxide[20] with the corresponding sodium salt of the alcohol.[21] Substrate **1d** was prepared by hydrolysis of the corresponding nitrostyrene oxide.[22] Compounds **1j** and **1o** were prepared by reaction of *m*-nitrobenzaldehyde or *m*-nitroacetophenone with ethyl bromoacetate in the presence of zinc,[23] and substrate **1g** was prepared as described in a previous report.[24] All starting materials were purified by distillation, recrystallization, or chromatographic methods. Synthesized compounds were purified and identified by their melting point, boiling point, and spectroscopic data which were in all cases in good agreement with literature values.

Irradiations. In a typical preparative scale experiment 100–200 mg of sample was dissolved in 500 mL of water (or appropriate sulfuric acid solution). Enough acetonitrile (10–50 mL) was added to obtain a clear solution, which was placed in a 600-mL quartz tube and purged with N_2 or argon for 30 min. The solution was then irradiated in a Rayonet reactor for 3–6 h using 300 nm (32 W) lamps. The progress of the reaction was monitored by UV spectrophotometry on aliquots of irradiated samples at different times, up to 70–80% conversion. The solution was stirred continuously with a magnetic bar and cooled with a cold finger during the irradiation. After irradiation the reaction mixture was saturated with NaCl and extracted with methylene chloride (3 × 50 mL). The extracts were dried ($MgSO_4$ or Na_2SO_4) and evaporated under reduced pressure to obtain the crude product. NMR was used to check the extent of the reaction, and the yield of product formation was determined on the basis of the integration of the signal of aldehyde product at δ 10.0 and the α-proton(s) of the starting material at δ 4.5–5.5. The pure product was isolated by using preparative TLC (Chromatotron Model 7924). The product was identified by comparison of its IR and NMR spectra and melting point with those of an authentic sample.

Sensitization and Quenching Studies. The following experiment was typical of the procedure employed for the sensitization experiments. A solution of substrate (50–80 mg) and acetone (20 g) and water or acid solution (500 mL) was purged with argon or nitrogen for 30 min and was irradiated for 1–2 h in a Rayonet reactor using 300-nm lamps. The solution was then saturated with NaCl and extracted with CH_2Cl_2. The extracts were collected, dried, and evaporated. NMR of the crude material indicated no starting material and the spectrum was exactly matched with that of *m*-nitrobenzaldehyde.

Triplet quenching experiments were accomplished by dissolving the substrate and known amounts of potassium sorbate in water–acetonitrile in Pyrex vessels (15 mm o.d.). The solutions were degassed and irradiated in a merry-go-round apparatus for

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45 min. After workup (extraction with dichloromethane), the crude material was analyzed on a 3% OV 17 on Chromosorb W/HP column, with *m*-nitrobenzaldehyde as internal standard.

Acknowledgment. The continued financial support of the Natural Sciences and Engineering Research Council of Canada is gratefully acknowledged.

Registry No. **1a**, 619-25-0; **1b**, 1515-84-0; **1c**, 80171-39-7; **1d**, 101999-47-7; **1e**, 101999-48-8; **1f**, 21388-97-6; **1g**, 7409-18-9; **1g**·H^+, 101999-54-6; **1h**, 101999-49-9; **1i**, 5400-78-2; **1j**, 6925-96-8; **1k**, 17414-84-5; **1l**, 101999-50-2; **1m**, 101999-51-3; **1n**, 73585-54-3; **1o**, 101999-52-4; **1p**, 101999-53-5; **1q**, 39896-32-7; **1r**, 99-08-1; *m*-nitrobenzaldehyde, 99-61-6; *m*-nitroacetophenone, 121-89-1; *m*-nitrosobenzaldehyde, 52944-86-2; D_2, 7782-39-0; D_2O, 7789-20-0.

A Regioselective Entry to 13-Substituted 8-Oxoprotoberberines. Total Synthesis of (±)-Corydaline

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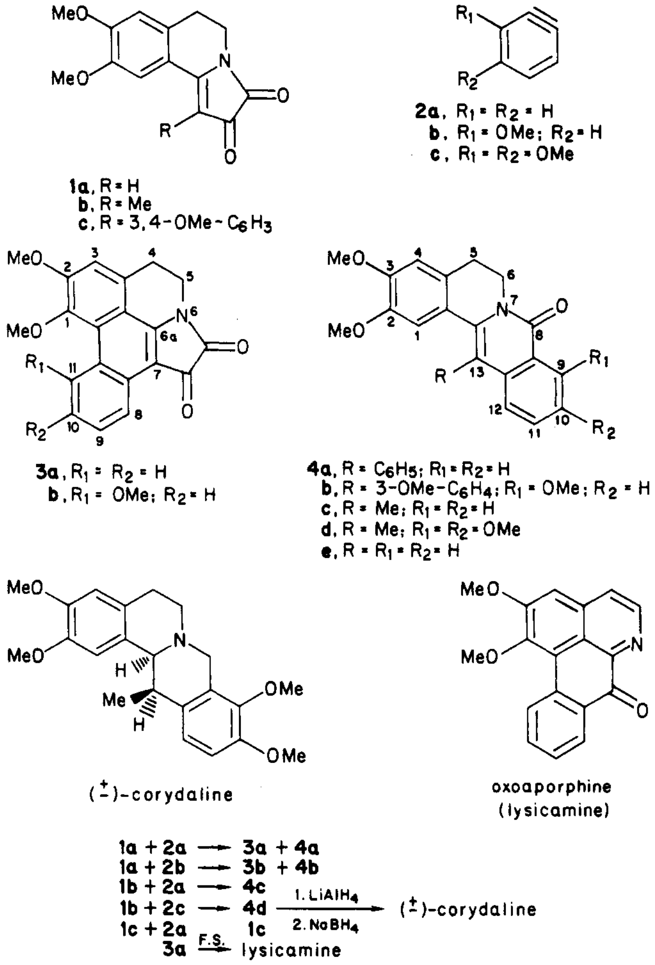
13-Alkyl and 13-aryl substituted 8-oxoprotoberberines were obtained by intermolecular benzyne cycloaddition of isoquinolinopyrrolinediones with arynes. This convergent and highly regioselective reaction has been applied to the synthesis of (±)-corydaline.

During the past few years we have been working on the development of new synthetic approaches to several types of isoquinoline alkaloids.[1] In particular, recognition of the common phenantrene or dihydrophenantrene structures led to our recently devising what appears to be a highly convergent general approach to the quite large aporphinoid subgroup of isoquinolines.[2]

In continuation of our work with benzyne cycloadditions, the reactions of **1** with arynes **2** were investigated and led to an efficient route to **4** (Scheme I). In our opinion, this unexpected route to the pharmacologically important protoberberines[3] shows promise as a synthetic tool both because of its convergence and its high regioselectivity. As a final demonstration, an efficient regioselective synthesis of (±)-corydaline is described.

The isoquinolinopyrrolidinediones **1** were prepared uneventfully by reaction of 1-alkyl-3,4-dihydroisoquinolines[4] with a molar equivalent of oxalyl chloride in pyridine.[5] With large quantities of both these precursors and anthranilic acids **6a**, **6b**,[6] and **6c**[7] we were now prepared to carry out the key intermolecular cycloaddition step.

Scheme I



In the event, reaction of **1a** with in situ generated benzyne[8] led to an easily separable mixture of the expected red-violet [4 + 2] adduct **3a**[9] (readily convertible into the oxoaporphine lysicamine by Fremy's salt oxidation[10]) and

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