by ^1H NMR and CMR spectroscopy. These spectra were compared with those of authentic products.

Isolation and Characterization of Iodine Pentoxide. To a solution of *m*-CPBA (12 mmol) in methylene chloride (60 mL) was added *n*-heptyl iodide (1.3791 g, 6 mmol) via syringe (1.0 min) at room temperature (27 ± 2 °C). After 6 min, the reaction mixture was diluted with petroleum ether (60 mL) and cooled to −40 °C (30 min) and later filtered through a Buchner funnel, using Whatman 50 filter paper. The residue was washed repeatedly with ether until all the *m*-chlorobenzoic acid was removed (test with litmus paper). The remaining white solid was isolated, and the following physical, spectral, and chemical characteristics were determined.

The solid decomposed at temperatures >300 °C while we attempted to determine its melting point [cf. I_2O_5 (Alfa-Ventron) >300 °C, d]. An IR spectrum of the residue (KBr pellet) was in all respects identical with that of authentic I_2O_5 (Alfa-Ventron). The oxidation equivalent of the residue was calculated by iodometric titrations against standard thiosulfate. A value of 27.24 g was obtained as the oxidation equivalent (theoretical 27.83 g).

Determination of the Stoichiometry of the M-CPBA–*n*-Heptyl Iodide Reaction. To a solution of *m*-CPBA (12 mmol) in methylene chloride (100 mL, plus 0.2 mL of water) was added *n*-heptyl iodide (6 mmol) via syringe (1.0 min) at room temperature (27 ± 2 °C). After 6 min, an aliquot (50 μL) of the reaction mixture was withdrawn and suitably diluted with methylene chloride and the iodine content was estimated by colorimetry (67 ± 2% based on RI). At the same time, another aliquot (5 mL) was withdrawn and analyzed for its total oxidation equivalent (65 ± 3% based on initial amount of *m*-CPBA used) by standard thiosulfate titration.

The same experiment was repeated with 1.5 and 4 equiv of *m*-CPBA.

Determination of Kinetics (Figures 1 and 2). To a solution of *m*-CPBA (0.6 mmol) in deuterated chloroform (10 mL) containing D_2O (0.1 mL) at 0 °C was added the alkyl iodide (0.3 mmol) via syringe (2 s). At time intervals, an aliquot (0.2 mL) of the reaction mixture was withdrawn and quenched by adding to a solution (0.2 mL) of sulfur dioxide in $CDCl_3$ at 0 °C in an NMR tube. These samples were analyzed via NMR spectroscopy. The relative amounts of alkyl iodide remaining were then calculated and plotted against time, giving Figure 2.

To a solution of *m*-CPBA (3.0 mmol) in deuterated chloroform (50 mL) at 0 °C was added *n*-heptyl iodide (1.5 mmol) via syringe (2 s). At various time intervals, an aliquot (2 mL) of the reaction mixture was withdrawn into a solution of glacial acetic acid (10 mL) and freshly prepared potassium iodide solution (10% solution, 10 mL) and titrated against standard sodium thiosulfate solution (0.024 N), using starch as indicator. At different time intervals, an aliquot (50 μL) of the reaction mixture was withdrawn and diluted with chloroform (5 mL) and the iodine content estimated by colorimetry (500 nm). NMR spectra were recorded from samples withdrawn during the reaction period (refer to experimental procedure in the previous paragraph) and the relative amounts of alcohol determined via integration. These data were plotted as a function of the percentage of the maximum value obtained for alcohol and iodine formation and the disappearance of the total oxidation equivalent (Figure 1).

Acknowledgment. This work was supported by a Center in Toxicology Grant ES00267 to Vanderbilt University from the U.S. Public Health Service.

Photostimulated Nucleophilic Aromatic Substitution for Halides with Carbon Nucleophiles. Preparative and Mechanistic Aspects[1]

M. F. Semmelhack*[2] and Thomas Bargar[3]

Contribution from the Department of Chemistry, Cornell University, Ithaca, New York 14853.
Received August 27, 1979

Abstract: The photo-$S_{RN}1$ reaction operates efficiently with enolate anions derived from simple ketones and esters, but 2-lithio-1,3-dithiane gives low yields. The sluggish and inefficient reaction of dialkyl-substituted ketone and ester enolates is traced to hydrogen atom transfer from the carbon adjacent to the enolate anion to the transient phenyl radical. The first systematic survey of intramolecular coupling of ketone enolate anions shows that six-, seven-, eight-, and ten-membered rings can be formed, although the β-hydrogen transfer becomes important in certain cases.

That radicals can be trapped by nucleophiles is a widely observed phenomenon. The reactions of *p*-nitrobenzylic halides with nucleophiles are known to involve the trapping of benzylic radicals by the nucleophile in a radical chain process.[4] The nucleophile is thought to initiate the chain reaction by transfer of one electron to the aromatic compound. Prior formation of a charge-transfer complex between the nucleophile and the electron-poor arene may be involved since light of relatively long wavelength can initiate certain reactions; quantum yields in excess of 100 are found.[5]

Bunnett and Kim discovered that unactivated aryl halides are attacked by amide ion in liquid ammonia and proposed a radical chain mechanism initiated by one-electron cleavage of the aryl halide; the pathway is labeled $S_{RN}1$.[6] The observations that light can replace solvated electrons as initiator, that acetone enolate anion and other carbanions can serve as the nucleophile, and that heteroatoms other than halogen can be displaced suggest broad application in attachment of carbon units to aromatic rings.[7]

A radical chain mechanism was proposed by Bunnett as presented in Scheme I.[8] When solvated electrons are employed

Scheme I

$$\text{electron source} + \text{PhX} \xrightarrow{h\nu} [\text{PhX}]^{-\cdot} + \text{residue} \quad (1)$$

$$[\text{PhX}]^{-\cdot} \rightarrow \text{Ph}\cdot + \text{X}^- \quad (2)$$

$$\text{Ph}\cdot + \text{R}^- \rightarrow [\text{Ph–R}]^{-\cdot} \quad (3)$$

$$[\text{Ph–R}]^{-\cdot} + \text{PhX} \rightarrow [\text{Ph–X}]^{-\cdot} + \text{Ph–R} \quad (4)$$

(1) Taken from the Ph.D. thesis of Thomas M. Bargar, Cornell University, 1978. Partially published in preliminary form in *J. Org. Chem.*, **42**, 1481 (1977).

(2) To whom correspondence should be addressed at the Chemistry Department, Princeton University, Princeton, NJ 08544.

(3) Public Health Services Graduate Trainee, Cornell University, 1975–1978.

(4) N. Kornblum, *Angew. Chem., Int. Ed. Engl.*, **14**, 734 (1975).

(5) P. D. Wade, Ph.D. thesis, Purdue University, 1973.

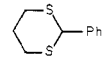
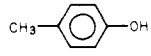
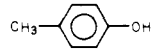
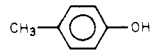
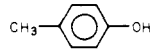
(6) J. K. Kim and J. F. Bunnett, *J. Am. Chem. Soc.*, **92**, 7463, 7464 (1970).

(7) (a) J. F. Bunnett, *Acc. Chem. Res.*, **11**, 413 (1978); (b) J. F. Wolfe and D. R. Carver, *Org. Prep. Proced. Int.*, **10**, 225 (1978).

0002-7863/80/1502-7765$01.00/0

Table I. Reaction of Carbanions with Halobenzene in the Photo-$S_{RN}1$ Process

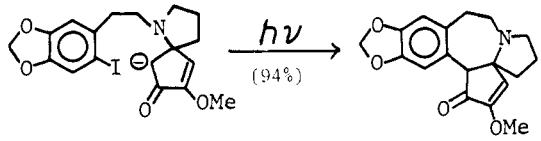
$$PhX + R^- \xrightarrow[NH_3]{h\nu} Ph\text{-}R + X^- \quad (2)$$

entry	RH	base	PhX	products (yield)[d]
1	$(CH_3)COCH_3$	KO-*t*-Bu[a]	PhBr	$(CH_3)_3COCH_2Ph$ (96%), $(CH_3)_3CCOCHPh_2$ (4%)
2	$(CH_3)_2CHCOCH(CH_3)_2$	$NaNH_2$[b]	PhBr	$(CH_3)_3CHCOC(CH_3)_2Ph$ (15%)
3	$(CH_3)_2CHCOCH_3$	KO-*t*-Bu[a]	PhBr	$(CH_3)_2CHCOCH_2Ph$ (79%), $Ph(CH_3)_3CCOCH_3$ (5%)
4	$PhCOCH_3$	KO-*t*-Bu[a]	PhI	$PhCOCH_2Ph$ (11%), PhI (92%)
5	$PhCOCH_3$	KO-*t*-Bu[a]	PhI	$PhCOCH_2Ph$ (67%), PhI (13%)[e]
6	CH_3CO_2-*t*-Bu	$LiNH_2$[c]	PhBr	$PhCH_2CO_2$-*t*-Bu (57%)
7	$CH_3CH_2CO_2$-*t*-Bu	$LiNH_2$[c]	PhBr	$PhCH(CH_3)CO_2$-*t*-Bu (60%)
8	$(CH_3)_2CHCO_2$-*t*-Bu	$LiNH_2$[c]	PhBr	$PhC(CH_3)_2CO_2$-*t*-Bu (11%)
9		$LiNH_2$[c]	PhBr	 (4%)
10	$CH_2(CO_2CH_3)_2$	KO-*t*-Bu[a]	PhBr	$PhCH(CO_2CH_3)_2$ (0%)
11	$CH_3(CO_2CH_3)_2$	KO-*t*-Bu[a]	PhI	$PhCH(CO_2CH_3)_2$ (0%)
12	$CH_3CH_2CH_2C{\equiv}CH$	$NaNH_2$[b]	PhBr	$CH_3CH_2CH_2C{\equiv}C$-Ph (0%)
13		KO-*t*-Bu[a]	PhI	 (93%), PhI (0%)[e]
14		Ag_2O	PhI	 (97%), PhI (84%)

[a] The enolate anion was generated in equilibrium by using this base in threefold molar excess. [b] This base was prepared from Na/K alloy and ammonia; 1 molar equiv was used. [c] This base was prepared from *n*-butyllithium and ammonia; 1 molar equiv was used. [d] External irradiation through Pyrex for 1.5–3 h of a solution in liquid ammonia was used. [e] An immersion well was employed.

to trigger the reaction, then the "electron source" and "residue" in the initiation step (step 1) are obvious. However, in the photoinitiated examples, there is no significant evidence to suggest how the initial radical anion of PhX is generated in step 1.

In the first intramolecular example of this method, one of us reported an efficient ring closure as a key step in the synthesis of cephalotaxine.[9] The success of this reaction (eq 1) in solving



(1)

the problem with high efficiency led us to initiate the present study. The primary goal is the delineation of the scope of Bunnett's reaction in carbon ring closures, with supporting studies on aspects of the general reaction including mechanistic probes. This work complements and partially overlaps with the efforts of Bunnett,[10] Rossi,[11] and Wolfe,[12] among others.

Results and Discussion

A. Intermolecular Examples. At the start of this investigation it was not known whether carbon–carbon bonds could be formed via the photo-$S_{RN}1$ by using carbanions other than acetone enolate and lithioacetonitrile. The results of a study with a selection of anions familiar in organic synthesis are summarized in Table I. The experimental details are included in the appropriate section below; in general, the carbanion (or carbanion precursor) was used in threefold molar excess and irradiation was accomplished by means of a Hanovia medium-pressure mercury arc positioned close to a common Pyrex flask or in the conventional immersion well.

The examples with ketone enolates (entries 1–5) were included to probe for substituent effects on reactivity and regioselectivity. Under comparable conditions, a primary ketone enolate (entry 1) reacts much more rapidly than a tertiary enolate (entry 2) and the enolate from acetophenone (entry 4). The slow reactions appear to be due to inefficient chain-carrying steps in the radical chain process; more intense and longer irradiation gives complete conversion and reasonable yields (entry 5). With the choice of coupling at a primary or tertiary carbon, isopropyl methyl ketone shows high selectivity for the less substituted site (entry 3). Primary and secondary ester enolates react smoothly, but, again, tertiary ester enolates (entry 8) proceed very slowly. Generation of 2-lithio-1,3-dithiane with lithium amide and irradiation in the presence of bromobenzene led to complete conversion of the halide under the usual conditions, but the yield of $S_{RN}1$ product (2-phenyl-1,3-dithiane) was less than 5%. Both malonate anion and 1-hexyne anion failed to interact with the halobenzene (entries 10–12).

Phenoxide nucleophiles are particularly interesting because the photo-$S_{RN}1$ process would constitute a new technique for phenol-coupling reactions, a powerful biomimetic synthesis strategy. Thiophenoxide[13] has been successfully employed in the electrochemically stimulated $S_{RN}1$ but phenoxide failed in alkali metal-stimulated $S_{RN}1$ reactions.[14] At the same time, numerous examples of halophenols undergoing coupling by halide substitution when being irradiated in aqueous base appeared about the time Bunnett's group reported their first observations.[15] One efficient intramolecular example in a porphine synthesis appeared in 1971.[16] It is not clear whether these reactions proceed via the radical chain mechanism; the primary difference from the conditions developed by Bunnett is the use of water instead of ammonia as the solvent.

We find that in ammonia solution, the sodium salt of *p*-cresol is unreactive when being irradiated in the presence of bromobenzene. Prolonged exposure to Pyrex-filtered light results in slow disappearance of the halobenzene, but the *p*-cresol is recovered. The possibility that the counterion could play a role in initiating radical processes was explored by attempting photostimulation of silver, thallous, and cuprous *p*-cresolates with iodo- or bromobenzene. The results were uniformly negative.

B. Effect of Solvent on the Photo-$S_{RN}1$ Reaction. In the hope of finding a solvent more convenient and more amenable to

(8) (a) J. F. Bunnett and J. E. Sundberg, *J. Org. Chem.*, **41**, 1702 (1976); (b) R. A. Rossi and J. F. Bunnett, *ibid.*, **38**, 1407 (1973).
(9) M. F. Semmelhack, B. P. Chong, R. D. Stauffer, T. D. Rogerson, A. Chong, and L. D. Jones, *J. Am. Chem. Soc.*, **97**, 2507 (1975).
(10) For a recent article and leading references, see: J. F. Bunnett and S. J. Shafer, *J. Org. Chem.*, **43**, 1873 (1978).
(11) For a recent article and leading references, see: A. B. Perini and R. A. Rossi, *J. Organomet. Chem.*, **168**, 163 (1979).
(12) For a recent article and leading references, see: A. P. Komin and J. F. Wolfe, *J. Org. Chem.*, **42**, 2481 (1977).
(13) (a) J. Pinson and J.-M. Saveant, *J. Am. Chem. Soc.*, **100**, 1506 (1978); (b) J. F. Bunnett and X. Creary, *J. Org. Chem.*, **39**, 3173 (1974).
(14) R. A. Rossi and J. F. Bunnett, *J. Org. Chem.*, **38**, 3020 (1973).
(15) For examples, see: K. Omura and T. Matsuro, *Chem. Commun.*, 1394 (1969) and references therein.
(16) R. J. Spangler and D. C. Boop, *Tetrahedron Lett.*, 4851 (1971).

Table II. Irradiation of Pinacolone Enolate and Bromobenzene in Various Solvents

$$MCH_2C(=O)C(CH_3)_3 + PhBr \xrightarrow{h\nu,\ \text{solvent}} \underset{A}{PhCH_2C(=O)C(CH_3)_3} + \underset{B}{Ph_2CHC(=O)(CH_3)_3} + PhH \qquad (3)$$

entry	solvent	counterion, M	conditns	yields % A	% B	% PhH	% PhBr
1	NH_3	K[a]	1.3 h/−33 °C	96	4		0
2	DMF	K[a]	1.3 h/35 °C	57	10	28	
3	Me_2SO	K[a]	1.3 h/35 °C	84	17	3	0
4	THF	K[a]	1.3 h/35 °C	0	0	5	95
5	Me_2SO	Li[b]	1.3 h/35 °C	25	3		56
6	Me_2SO	Li[b]	2.9 h/35 °C	39	13	7	7
7	NH_3	Li[b]	1.3 h/−33 °C	79	14		8
8	NH_3[d]	Na[c]	0.5 h/−33 °C	93			
9	Me_2SO[d]	Na[c]	0.5 h/35 °C	13			high

[a] Potassium *tert*-butoxide (3–6 molar equiv) was used to generate the enolate anion in situ. [b] The lithium enolate was isolated, purified by crystallization and sublimation, and fully characterized. [c] The sodium enolate was isolated and characterized. [d] A uranium-glass filter (passes light of $\lambda > 340$ nm) was employed instead of Pyrex.

Table III. Photostimulated Reactions of 1c with Potassium *tert*-Butoxide at −33 °C in Ammonia

$$1c \xrightarrow[NH_3]{KOBu,\ h\nu} 2c + 5c$$

entry	concn 1c,[c] mM	filter	irradiatn[b] time, min	% 2c	% 5c
1	1.2	none[a]	30	21	11
2	0.5	none[a]	30	35	4
3	0.35	none[a]	30	28	0
4	1.5	Pyrex	30	20	10
5	1.2	Pyrex	12	29	10
6	1.1	Pyrex	1.0	22	10
7	1.1	uranyl glass	1.0	27	8
8	0.12	uranyl glass	1.0	26	8

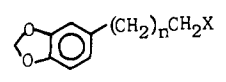
[a] The irradiation source was a Hanovia 450-W medium-pressure lamp in quartz immersion well. [b] Unreached 1c was less than 5% in all examples. [c] The mole ratio of base:1c was 6:1 in all runs.

mechanistic studies than liquid ammonia, we examined the effect of solvent on the photo-$S_{RN}1$ reaction. Parallel studies by Bunnett and co-workers have established that several solvents are effective in the photo-$S_{RN}1$ reaction between potassium diethyl phosphite and iodobenzene.[17] Quantitative studies of this system in Me_2SO produced quantum yields substantially greater than unity and evidence for a low concentration of a charge-transfer complex between the phosphite anion and iodobenzene.[18] In the one example with a carbanion, Me_2SO was shown to be suitable for the photo-$S_{RN}1$ reaction between acetone enolate anion and iodobenzene.[17]

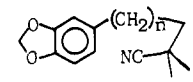
Table II presents our results comparing solvent and counterion effects on the photo-$S_{RN}1$ reaction of pinacolone enolate with bromobenzene. Solvent can slow the reaction by donating hydrogen atoms to chain-carrying radicals, producing benzene as a byproduct. This effect is dramatic comparing DMF with ammonia; under identical irradiation conditions, DMF leads to formation of benzene (28%) in a reasonably fast reaction while ammonia gives no benzene in an exceeding rapid reaction (entries 1 and 2). Me_2SO produces little benzene, but the monophenylation/diphenylation ratio (6:1) is less favorable than in ammonia (20:1). THF almost completely inhibits the photo-$S_{RN}1$ process, leading slowly to benzene as the major product. As observed before,[17] the results are roughly in line with ease of hydrogen atom donation by these solvents. With long wavelength light, the reactions are slower, and then a difference in rate of about sevenfold is noted between Me_2SO and ammonia (entries 8 and 9). The potassium counterion also has a small accelerating effect compared to lithium (factor of more than 3 in Me_2SO, entries 3 and 5).

(17) J. F. Bunnett, R. G. Scamehorn, and R. P. Taber, *J. Org. Chem.*, **41**, 3677 (1976).
(18) S. Hoz and J. F. Bunnett, *J. Am. Chem. Soc.*, **99**, 4690 (1977).

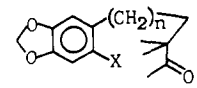
C. Intramolecular Photo-$S_{RN}1$ Reactions of Haloarene Ketones. The synthesis of cephalotaxinone (eq 1) using the photo-$S_{RN}1$ method raised a number of questions relating to the generality of the intramolecular reactions. We have examined compounds which were chosen to test questions of ring size preferences in cyclizations, including regioselectivity with ketones that can give two enolate anions. The simplest cases are compounds **1a–c** where only one enolate anion is possible and the carbonyl group ends up as part of the new ring (**2a–c**). The starting materials were prepared from piperonyl alcohol and 3,4-methylenedioxycinnamic acid via the alkyl halides **3a–c**. Alkylation of the anion of isobutyronitrile gave the nitriles, **4a–c**, and then reaction with methyllithium and hydrolysis produced the ketones **5a–c**. Aromatic iodination with silver trifluoroacetate/iodine gave **1a–c**.



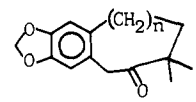
3a: n=0, X=Cl
3b: n=2, X=I
3c: n=4, X=I



4a: n=0
4b: n=2
4c: n=4



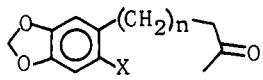
1a: n=0, X=I
1b: n=2, X=I
1c: n=4, X=I
5a: n=0, X=H
5b: n=2, X=H
5c: n=2, X=H



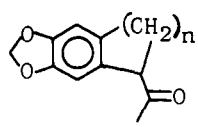
2a: n=0
2b: n=2
2c: n=4

Irradiation of iodo ketone at ~0.05 M in liquid ammonia at −33 °C in the presence of potassium *tert*-butoxide produced a single crystalline product (**2a**), nearly analytically pure, in 99% yield. The structure was established through direct spectral analysis. Under the same conditions of concentration and conditions, iodoketone **1b** produced the eight-membered ring ketone (**2b**) in only 21% yield (95% conversion). At lower concentration (0.001 25 M) with a larger excess of potassium *tert*-butoxide, the yield of **2b** was increased to 73%; the remaining products appeared to be of high molecular weight. Conversion of **1c** to the 10-membered ring (**2c**) proceeded in only 25–35% yield even at high dilution (0.12 mM) and with excess base. In this case, the product from reduction of the iodide (**5c**) was detected, 4–10% yield. A careful study (Table III) showed that there was little variation in yield with wavelength of the irradiation nor much effect of concentration changes over the range 10–0.1 mM in iodo ketone.

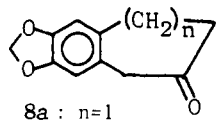
To test questions of regioselectivity, we prepared the series of halo ketones represented by **6a–c** and subjected them to irradiation in the presence of base. Two products were expected, **7** from the internal enolate and **8** from enolization toward the methyl group. Irradiation of **6a** under the usual conditions led to rapid disappearance of starting material, but the only monomeric product isolated (20% yield) was **6d** from reduction of the carbon–iodine



6a: X=I, n=1
6b: X=Br, n=2
6c: X=Br, n=3
6d: X=H, n=1
6e: X=H, n=2
6f: X=H, n=3



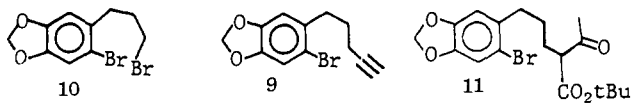
7a: n=1
7b: n=2
7c: n=3



8a: n=1
8b: n=2
8c: n=3

bond; neither of the cyclization products (**7a**, **8a**) was detected.

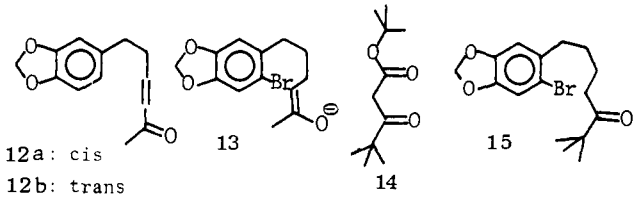
The higher homologue **6b** was prepared from **9** which, in turn, arose from dibromide **10** by coupling with lithium acetylide.



10 9 11

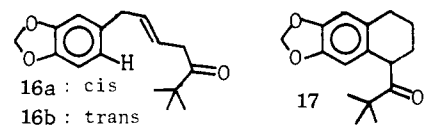
Irradiation of **6b** with a sixfold excess of potassium *tert*-butoxide in liquid ammonia as usual produced several minor products and a major product (GC analysis) which was identified as the seven-ring cyclization product, **8b**, in 34% yield after isolation by medium-pressure liquid chromatography. Minor products were **6e** (4%) and **7b** (19%).

Bromo ketone **6c** was prepared from dibromide **10** by the alkylation of *tert*-butyl acetoacetate (to give **11**) followed by decarboxylation. Irradiation under the usual conditions produced four monomeric products. They were identified as the reduction product (**6f**, 3%), the six-ring cyclization product (**7c**, 3%), the eight-ring cyclization product (**8c**, 19%), and an α,β-unsaturated ketone (**12**, 7% yield).

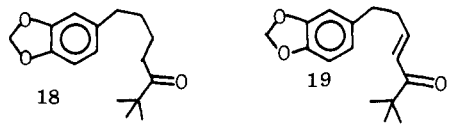


12a: cis
12b: trans
13 14 15

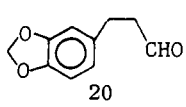
The low efficiency of cyclizations with compounds **6** and the detection of **12** led us to suspect that some important competing pathway operated when an "internal" enolate (i.e., **13**) was available. From dibromide **10** and β-ketoester **14**, we obtained bromo ketone **15**, where only the "internal" enolate is possible. Irradiation of **15** under the usual conditions produced two monomeric products, the β,γ-unsaturated ketone **16** (65% yield;



16a: cis
16b: trans
17

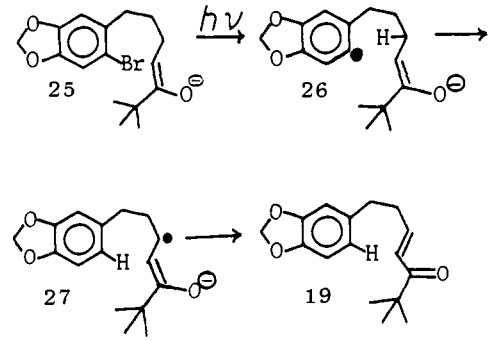


18 19



20

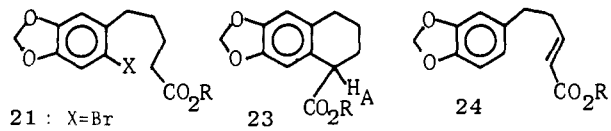
Scheme II



25 26 27 19

identified by hydrogenation to **18** and by comparison with a sample of **16** prepared by an alternate route) and a minor product (ca. 13% yield) which could not be obtained free of **16**. In addition, the alternative structure **19** was prepared starting from **20**, by aldol reaction with pinacolone, and shown to be different from **16**. Remarkably, treatment of **19** under the conditions of the photo-$S_{RN}1$ (but without irradiation) produced **16** quantitatively. The minor product was tentatively assigned structure **17**, the result of cyclization, on the basis of GC–MS and interpretation of spectral data on a partially purified sample; it showed GC retention time identical with that of the major product from an intramolecular benzyne ring closure from **15**. We postulate that **19** is the first formed product during irradiation of **15** in base, but rapid base-promoted double-bond isomerization produces the more stable β,γ-isomer, **16**. Cyclization is a minor pathway, and the loss of halide/introduction of a double bond, seen earlier as a minor process, now is strongly preferred.

In a single attempt to induce cyclization of ester enolates onto aromatic rings, we prepared the bromoester **21** (from di-*tert*-butyl



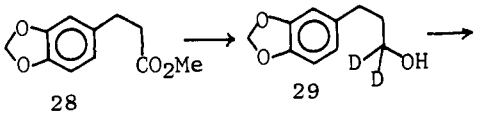
21: X=Br
22: X=H
23 24

malonate and dibromide **10**). Under the usual conditions of excess potassium *tert*-butoxide in liquid ammonia, irradiating through Pyrex, a slow reaction ensued to give several products. The reduction product (**22**) was tentatively identified, and the presence of the cyclization product (**23**) could be ruled out (<5% yield) on the basis of the absence of characteristic absorption (δ 3.5–4.0) for proton H_A in **23**, in the ^1H NMR spectrum. Generation of the enolate anion with potassium amide instead of potassium *tert*-butoxide gave similar results. Neither an α,β-unsaturated ester (i.e., **24**) nor the cyclization product (**23**) was detected.

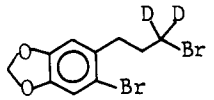
With the hope of understanding the process leading to dehydrogenation of the side chain well enough to avoid this reaction, we considered possible mechanisms. An attractive possibility is the intramolecular hydrogen atom transfer from the β position of the carbonyl unit to the proposed phenyl radical, as outlined in Scheme II. The enolate anion **25** is converted to **26** by the initiation mechanism (unspecified), and then a hydrogen is transferred through a six-atom transition state to give the radical anion **27**, the one-electron reduction product of an α,β-unsaturated ketone. Then transfer of one electron away from **27** would produce the initial product, **19**, and could serve as a propagation step. This mechanism is consistent with the fact that gem-dimethyl-substituted ketones (**1a–c**) undergo smooth cyclization while their unmethylated analogues can give an enolate (e.g., **25**) which activates adjacent hydrogen atoms toward transfer to the aryl radical. It is noteworthy that the cephalotaxinone precursor, which cyclized in high yield, also has the gem-dialkyl substitution pattern where no hydrogens can be activated by enolization (eq 1).

Direct evidence for the proposed pathway was obtained from a simple deuterium-labeling experiment. Reduction of **28** with lithium aluminum deuteride produced **29** with >95% isotopic

purity at the positions indicated with deuterium (eq 4). Con-

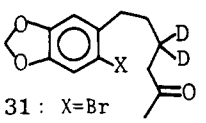


28 29

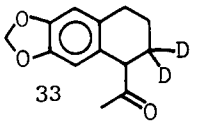


30

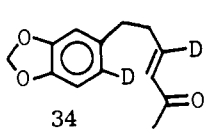
version to dibromide **30** followed by reaction with *tert*-butyl acetoacetate and decarboxylation as before provided the deuterium-labeled ketone **31**. Mass spectral analysis using the parent ion peaks for **31** showed the molecule to contain 0% d_0, 3% d_1, and 97% d_2. Under the usual photo-$S_{RN}1$ conditions, four products were obtained for which the major monomeric species are represented by **32–35**. The first three are minor products (2–5%



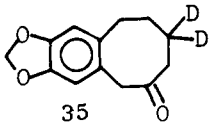
31 : X=Br
32 : X=H



33

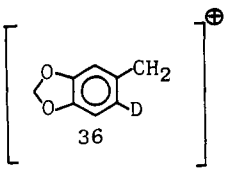


34



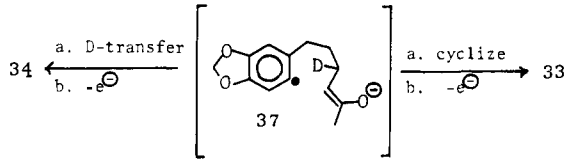
35

yield for each) while **35** is formed in amounts 10-fold larger. Mass spectral analysis of all four products show >95% d_2. For **34**, a major fragmentation pathway produces the ion of *m/e* 136, consistent with the benzyl cation, **36**. The corresponding ion at



36

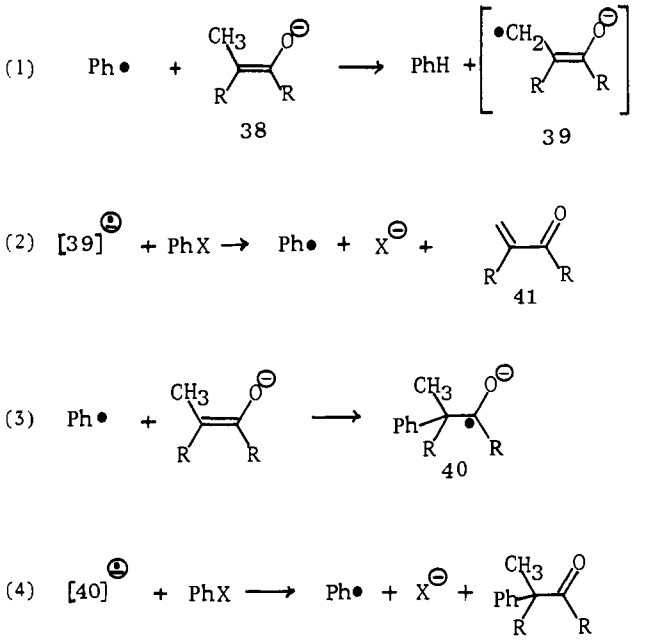
m/e 135 is the base peak in the electron-impact spectrum of the unlabeled analogue **12**. Although precise quantities were not measured, it is clear from GC peak areas that the ratio of six-ring product:enone is much larger for the labeled case (**33**:**34** ≈ 5:1) than for the unlabeled case (**7c**:**12** ≈ 1:2). This change can be interpreted as an isotope effect on the partitioning of radical anion **37** toward cyclization (no primary isotope effect) and toward D atom transfer (eq 5, slowed by primary isotope effect).



The radical chain mechanism (Scheme I) has not been established for the intramolecular examples presented here, and we have no specific experiments which bear on the question. In the cyclizations where H atom transfer occurs (i.e., **6** and **15**), conversion of starting material is similar in rate to the efficient cyclizations (i.e., with **1a–c**). This suggests that either the H atom transfer is not a termination step (the radical anion **27** can transfer an electron in a chain-carrying step) or that cyclization is not a chain process.

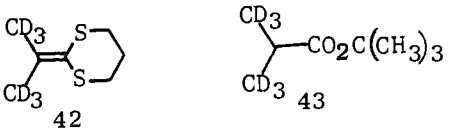
Observations concerning the transfer of hydrogen atoms activated by enolization in the attempted cyclization of ketone enolates suggested that an analogous *inter*molecular pathway might be operating in the $S_{RN}1$ reaction of simple alkyl-substituted

Scheme III. General Mechanism for H Atom Transfer



ketone and ester enolate anions. As shown in this work (Table I, entries 2 and 8) and by others,[8a] alkyl substituents in the 2-position of the reactive enolate have a severe rate-retarding effect and lead to reduced yields. Phenyl substituents have no such effect.[8a] It is also clear that the simple photo-$S_{RN}1$ reaction is relatively insensitive to steric effects.[19] Based on our results with intramolecular examples, we propose a general mechanism for hydrogen atom transfer with appropriate substrates in the photo-$S_{RN}1$ reaction (Scheme III). In this scheme, the enolate anion **38** can react by H atom transfer (step 1) or carbon–carbon coupling (step 3). In both cases, a radical anion is produced (**39**, **40**) which is formally capable of chain propagation via electron transfer to PhX (steps 2 and 4). But a product (**41**) appears in step 2 which is prone to radical and anionic polymerization and presumably gives high molecular weight products under the reaction conditions.

A simple labeling experiment supports this scheme. Reaction of acetone-d_6 with 2-lithio-2-(trimethylsilyl)-1,3-dithiane gave **42** (after elimination of trimethylsilanol[20]). Mercury-promoted hydrolysis of the ketene thioacetal afforded 2-methylpropionic acid-d_6 which was esterified to give **43**. Reaction of **43** with



42 43

lithium diisopropylamide generated the enolate which was irradiated with *p*-bromoanisole in liquid ammonia. The products consisted of *tert*-butyl 2-methyl-2-(*p*-methoxyphenyl)propionate (28% yield) and anisole (54%). The anisole produced was 65% d_0 and 35% d_1 (mass spectral analysis), confirming the occurrence of intermolecular H-atom transfer (step 1, Scheme III). The unlabeled anisole might arise several ways, including the anionic pathway proposed by Bunnett[8a] to account for minor products. For comparison, unlabeled *tert*-butyl 2-methylpropionate enolate anion under identical conditions leads to *tert*-butyl 2-methyl-2-phenylpropionate (5% yield), bromoanisole (34% recovered), and anisole (35% yield). And *tert*-butyl acetate enolate under identical conditions produces *tert*-butyl phenylacetate (67% yield), *tert*-butyl diphenylacetate (29% yield), and less than 5% anisole.

(19) J. F. Bunnett and J. E. Sundberg, *Chem. Pharm. Bull.*, **23**, 2260 (1975).
(20) D. Seebach, M. Kolb, and B.-T. Gröbel, *Chem. Ber.*, **106**, 2277 (1973).

Summary and Conclusions. The results reported here show that the photo-$S_{RN}1$ reaction can be applied to variously substituted enolate anions, that the choice of solvent must be made carefully, and that intramolecular reaction of enolate anions onto aryl halides can be efficient. In each of the points, easy hydrogen atom transfer to a transient phenyl radical is likely to provide the difference between a slow, inefficient substitution reaction and the very fast, nearly quantitative processes which are often observed. Ammonia and dimethyl sulfoxide, as reported for reactions of several anions by Bunnett,[18] appear to be generally good in avoiding quenching by H atom transfer, compared to other common solvents such as hexamethylphosphoric triamide, dimethylformamide, and tetrahydrofuran.

Another source of H atoms was uncovered in the intramolecular reactions and then also detected in an intermolecular case. The hydrogens β to the carbonyl group become activated in the enolate anion and can be transferred to the transient phenyl radical. In the intramolecular cases, this results in low efficiency of cyclization and formation of a byproduct bearing a double bond in the side chain. This reaction is avoided by blocking either the α or the β position with carbon substituents in place of hydrogen. Then cyclizations proceed in 70–90% yields, even for eight-membered rings.

Experimental Section

Apparatus. Unless otherwise stated, all ^1H NMR spectra were recorded on a Perkin-Elmer Model R-24 or Varian A-60A spectrometer at 60 MHz and are reported in ppm downfield from internal tetramethylsilane (δ). IR spectra were obtained on a Perkin-Elmer Model 137 or 237 spectrometer and are expressed in microns (μm). The 6.238-μm line of polystyrene was used as reference. UV spectra were recorded on a Cary Model 1605 spectrometer. Mass spectra data were obtained with the assistance of Dr. Jack Henion and Dr. Tim Wachs using an AEI Model MS 902 (70 eV, electron impact or chemical ionization as specified below). GC–MS analysis was done with Finnegan Model 3300 GC–MS equipped with a Systems Industries datasystem 500.

Analytical GC was performed on a Perkin-Elmer Model 3920 gas chromatograph, flame ionization detection, using 0.125-in. stainless steel columns with nitrogen carrier gas at a flow of 30 mL/min unless otherwise specified. For quantitative analyses, a weighed amount of a standard was added to the product mixture, and the relative peak areas of the product and standard were measured with a disk or electronic integrator. The relative molar responses of product and standard were determined independently by measuring the peak areas of a mixture of weighed authentic product and weighed standard. Preparative GC was accomplished by using a Varian Aerograph 90-P instrument equipped with 0.375-in. aluminum columns at a flow rate of 100 mL/min of helium and thermal conductivity detection.

Preparative liquid chromatography was carried out with standard gravity-flow techniques or a medium-pressure closed apparatus with UV-detection, according to a published design.[21] Preparative layer chromatography (PLC) employed 20 × 20-cm glass plates coated with a 2-mm layer of EM Reagents GF-254 Silica gel with 1% copper–zinc sulfide fluorescent indicator. Analytical thin-layer chromatography (TLC) employed Macherey Nagel and Co. Polygram precoated plastic sheets at 0.25 mm thickness of silica gel (also with a fluorescent indicator).

Photochemical experiments employed a Hanovia 450-watt medium pressure mercury arc (Ace Glass, Inc.) as the light source. Elemental analyses were carried out by Scandinavia Microanalytical Laboratory, Herlev, Denmark, except for metal-containing compounds, which were sent to Pascher Mikroanalytisches Laboratorium, Bonn, West Germany. Melting points were taken on an Electrothermal melting point apparatus. Melting and boiling points are uncorrected.

Materials. All solvents were ACS Reagent Grade. Organic reagents, unless otherwise noted, were obtained from Aldrich Chemical Co., Milwaukee, Wis., and were used as received. Tetrahydrofuran (THF), dioxane, ether, benzene, and hexane for reaction solvents were dried by distillation, just before use, under inert atmosphere, from the purple sodium benzophenone radical anion, and transferred via oven-dried syringe. Diisopropylamine, hexamethylphosphoric triamide (HMPA), acetonitrile, dichloromethane, dimethyl sulfoxide (Me_2SO), and dimethylformamide (DMF) were dried by distillation under inert atmosphere or appropriate vacuum from calcium hydride. They were stored under inert gas in air-tight round-bottom flasks equipped with a stopcock for removal by syringe, over Linde 4A molecular sieves which were activated by heating at 120 °C for 1 week. *n*-Butyllithium was obtained as a 15% solution in hexane from Lithium Corp. of America and was filtered through Celite under argon and stored in air-tight round-bottom flasks equipped with a stopcock for removal by syringe. Alkyllithium reagents were titrated under argon with a standard solution of 2-butanol in xylene by using 1,10-phenanthroline as indicator.[22]

Under Argon. Experiments which required an inert atmosphere were carried out under Airco prepurified argon. The phrase "under argon" means that the reaction vessel was at least three times alternatively evacuated (20–0.01 torr) and refilled with argon at 50 torr positive pressure by means of a mercury bubbler tube. Isolation of air- or moisture-sensitive compounds was accomplished by using the standard double-manifold technique or with the aid of an argon-filled Vacuum Atmosphere Model HE-43-Z Dri-Lab.

Photochemical Experiments. The photochemical experiments using an external light source were done with a standard quartz immersion well assembly (Ace Glass Co.) positioned adjacent to the reaction vessel, a three-necked flask equipped with a solid addition tube, a dry-ice condenser, a serum-stoppered joint, and a three-way stopcock. By means of the three-way stopcock, the system was placed under argon. Then gaseous ammonia, predried by condensation over sodium, was passed into the system and condensed at the dry-ice condenser. When the desired level of ammonia was attained, the reaction flask was again isolated from the distillation flask, reactants were added, and irradiation was begun.

Photo-$S_{RN}1$ Reaction of *tert*-Butyl Lithioacetate with Bromobenzene, Lithium Amide as Base. According to the general procedure, the reaction flask was filled with 30 mL of anhydrous, oxygen-free ammonia and cooled to −78 °C. Then *n*-butyllithium (3.0 mL of a 15% solution in hexane, 6.0 mmol) was added rapidly, dropwise, by syringe. After the vigorous reaction subsided, *tert*-butyl acetate (0.81 mL, 6.0 mmol, distilled from calcium hydride) was added over 3 min by syringe, and the resulting solution was stirred for 0.5 h at −78 °C, and then allowed to warm to reflux. Bromobenzene (0.21 mL, 2.0 mmol) was added rapidly and the lamp positioned approximately 2 in. from the reaction vessel. As irradiation commenced, the mixture became bright yellow; the flask was washed at frequent intervals with a stream of ethyl alcohol to minimize accumulation of frost/ice on the outer surface. After irradiation for 80 min at reflux, excess ammonium chloride was added portionwise as a solid causing the color to discharge. The ammonia was allowed to evaporate, and the residue was partitioned between ether (50 mL) and 5% aqueous hydrochloric acid (25 mL). The ether layer was washed twice with 25-mL portions of 5% aqueous hydrochloric acid, dried over anhydrous magnesium sulfate, and filtered. To the filtrate was added 145.3 mg of 1-methylnaphthalene (GC internal standard), and the solution was analyzed on a 6-ft column of 5% DEGS at 90 °C. The following data were obtained: bromobenzene (4.5 min, <1%), *tert*-butyl phenylacetate (16.5 min, 76% yield), and 1-methylnaphthalene (24.0 min). After 33.5 min, the column temperature was raised to 150 °C rapidly and *tert*-butyl diphenylacetate appeared (51.0 min, 24% yield). The products were identified by comparison of GC retention times and spectral data (pure samples collected by preparative GC) with those of samples obtained by alternative routes or purchased. The *tert*-butyl diphenylacetate has a melting point of 79–80.5 °C (lit. mp 80–81 °C).[23]

The Photo-$S_{RN}1$ Reaction of Pinacolone with Bromobenzene, Potassium *tert*-Butoxide as Base. As before, the reaction vessel was charged with 2.022 g (18.0 mmol) of potassium *tert*-butoxide and ammonia (30 mL). To the solution was added dry pinacolone (distilled from calcium hydride, 0.75 mL, 6.0 mmol) followed by bromobenzene (0.21 mL, 2.0 mmol). Irradiation as before (60 min) followed by the usual extraction procedure provided a crude product which was analyzed by GC exactly as above. The products observed were 1-phenyl-3,3-dimethyl-2-butanone (34.5 min, 96% yield) and 1,1-diphenyl-3,3-dimethyl-2-butanone (4% yield). The first product was identified from spectral data and through the 2,4-dinitrophenylhydrazone, mp 140–141 °C (lit. mp 140–141 °C).[24] The second product showed: ^1H NMR ($CDCl_3$) δ 7.28 (s, 10 H, aryl-H), 5.61 (s, 1 H, Ph_2CH—C=O), 1.18 (s, 9 H, $-C(CH_3)_3$); IR ($CHCl_3$) 3.37 (m), 5.85 (s), 6.21 (m) μm; mp 133.5–134.5 °C; mass spectral mol wt 252, calcd for $C_{18}H_{20}O$ 252.

Anal. Calcd for $C_{18}H_{20}O$: C, 85.67; H, 7.99. Found: C, 85.43; H, 7.96.

The Photo-$S_{RN}1$ Reaction of the Enolate of Diisopropyl Ketone with Bromobenzene using Sodium Amide as Base. A few small crystals of ferric nitrate nonahydrate and ammonia (25 mL) were placed in the usual reaction vessel. Sodium/potassium alloy (0.25 mL, 6.25 mmol)[25]

(21) A. I. Meyers, J. Slade, R. K. Smith, E. D. Mihelich, F. M. Hershenson, and C. D. Liang, *J. Org. Chem.*, **44**, 2247 (1979).

(22) S. C. Watson and J. F. Eastham, *J. Organomet. Chem.*, **9**, 165 (1967).

(23) W. Leake and R. Levine, *J. Am. Chem. Soc.*, **81**, 1627 (1959).

(24) H. O. House and E. J. Grubbs, *J. Am. Chem. Soc.*, **81**, 4733 (1959).

was added over a few minutes via syringe. The resulting blue solution was stirred at reflux until it became gray-green. The diisopropyl ketone (0.85 mL, 6.0 mmol) was added, and the mixture was allowed to stir for 5.0 min before bromobenzene (0.21 mL, 2.0 mmol) was added all at once via syringe. The solution was irradiated for 2.0 h, and the products were detected and isolated as before. On a 12-ft Carbowax 20 M column at 120 °C, 2-phenyl-2,4-dimethyl-3-pentanone was detected (41 min, 15% yield). It was identified by comparison with a sample prepared by methylation of 1-phenyl-3-methyl-2-butanone using sodium hydride/methyl iodide. ^{1}H NMR ($CDCl_3$): δ 7.28 (s, 5 H, aryl-H), 2.70 (septet, 1 H, J = 7 Hz, $CH(CH_3)_2$), 1.48 (s, 6 H, $PhC(CH_3)_2$–), 0.88 (d, 6 H, J = 7 Hz, $CH(CH_3)_2$). IR (neat): 3.35 (s), 5.85 (s), 6.22 (w), 6.67 (m), 6.79 (m), 6.89 (m) μm.

The Photo-S_{RN}1 Reaction of 2-Lithio-1,3-dithiane with Bromobenzene. As above for *tert*-butyl acetate, 2-lithio-1,3-dithiane[26] was generated from lithium amide and irradiated with bromobenzene for 1.3 h. Isolation as before produced a crude product in which 2-phenyl-1,3-dithiane was detected by GC analysis, 4% yield. It was compared with a sample prepared from benzaldehyde by using the standard procedure.[26]

Product Analysis for Table I. Following one of the procedures above, the examples reported in entries 1–13 of Table I were carried out. **(a). *tert*-Butyl Propionate.** From lithium amide (6.0 mmol), *tert*-butyl propionate (6.0 mmol), and bromobenzene (2.0 mmol), and irradiation for 2.0 h, GC analysis detected *tert*-butyl 2-phenylpropionate (60% yield). It exhibited an IR spectrum identical with that of a sample prepared by methylation of *tert*-butyl phenylacetate with 1 molar equiv of lithium diisopropyl amide and methyl iodide. ^{1}H NMR ($CDCl_3$): δ 7.19 (s, 5 H, aryl-H), 3.55 (q, 1 H, $PhCHCH_3$, J = 7.0 Hz), 1.45 and 1.35 (methyl doublet overlapping *tert*-butyl singlet, 12 H); cf. lit. NMR spectrum.[27] **(b). *tert*-Butyl 2-Methylpropionate.** From lithium amide (6.0 mmol), *tert*-butyl 2-methylpropionate (6.0 mmol), and bromobenzene (2.0 mmol), and irradiation for 2.0 h, GC analysis detected *tert*-butyl 2-methyl-2-phenylpropionate (11% yield) and bromobenzene (16% unreacted). The ester was isolated by preparative GC and compared with a sample from methylation of *tert*-butyl 2-phenylpropionate using lithium diisopropylamide and methyl iodide. ^{1}H NMR ($CDCl_3$): δ 7.24 (s, 5 H, aryl-H), 1.53 (s, 6 H, CH_3), 1.38 (s, 9 H, $C(CH_3)_3$); cf. lit. NMR.[27] **(c). 3-Methyl-2-butanone.** A mixture of potassium *tert*-butoxide (18 mmol), 3-methyl-2-butanone (6.0 mmol), and bromobenzene (2.0 mmol) was irradiated as above for 1.0 h. Product GC analysis showed 3-phenyl-3-methyl-2-butanone (5%) and 1-phenyl-3-methyl-2-butanone (79% yield). The first product was identified by preparation of a sample from 2-methyl-2-phenylpropionitrile (addition of methyllithium followed by acid hydrolysis) and by comparison of literature spectral data.[28] The second product was identified by comparison with a sample prepared by methylation of 1-(1-ethoxy)ethoxy-1-cyano-2-methylpropane according to Stork[29] and by comparison with literature values: melting point of 2,4-dinitrophenylhydrazone was 113–114 °C;[30] our value was 113.5–114.5 °C. **(d). Acetophenone.** According to the procedure using potassium *tert*-butoxide, acetophenone and bromobenzene were irradiated in ammonia solution for 2.0 h. Analysis by GC indicated the absence of benzyl phenyl ketone (<2% yield) and presence of acetophenone (87%) and bromobenzene (76%). See below for related experiments in an immersion well. **(e). Dimethyl Malonate.** According to the procedure using potassium *tert*-butoxide, dimethyl malonate and bromobenzene were irradiated in ammonia solution for 2.0 h. Analysis by GC indicated the absence of dimethyl phenylmalonate (<2%) and the presence of bromobenzene (75%). **(f). *p*-Cresol with Iodobenzene and Silver Nitrate.** With use of the general procedure with potassium *tert*-butoxide, a mixture of silver nitrate (0.68 g, 4.0 mmol), ammonia (20 mL), *p*-cresol (0.28 mL, 4.0 mmol), iodobenzene (0.40 mL, 3.5 mmol), and potassium *tert*-butoxide was irradiated for 2.1 h. From the crude product was isolated 0.71 g (99%) of iodobenzene and 0.36 g (84%) of *p*-cresol. The expected product, phenyl *p*-tolyl ether, was not detected in the crude product, by using GC and ^{1}H NMR analysis. **(g). With 1-Pentyne.** Following the general procedure with sodium/potassium amide as base (from Na/K alloy), a mixture of 1-pentyne (0.59 mL, 6.0 mmol), bromobenzene (0.21 mL, 2.0 mmol), and the metal amide from 0.24 mL (ca. 6.0 mmol) of sodium/potassium alloy was irradiated for 1.0 h. Isolation as before produced a yellow liquid, 0.60 g, which displayed a ^{1}H NMR spectrum essentially identical with that of bromobenzene; no 1-phenyl-1-pentyne was detected, with an expected sensitivity that would allow detection of a 5% yield.

Photo-S_{RN}1 Experiments in an Immersion Well. The following experiments employed a standard four-necked photochemical immersion well (Ace Glass Co.) equipped with a nitrogen inlet to a glass frit at the bottom of the well to provide inert gas and agitation. To one neck was attached a dry-ice condenser with a U-tube containing oil to serve as an exit bubbler. Another neck was fitted with a three-way stopcock to admit either nitrogen or ammonia, and the third neck was capped with a rubber septum. Through the fourth neck, the jacketed lamp was inserted and the cooling outlets were connected to a circulating pump in series with a 20-ft coil of 0.25-in. copper tubing. When the lamp was turned on, heptane was circulated by the pump and cooled by immersing the copper coil in a large Dewar flask containing dry-ice/acetone slurry. Anhydrous ammonia was condensed over sodium in a preliminary drying operation and then distilled into the immersion well. **(a). Reaction of Acetophenone with Bromobenzene.** The immersion well was charged with potassium *tert*-butoxide (6.07 g, 54.0 mmol) and purged for 0.5 h with nitrogen through the glass frit. The circulating system was turned on and found to maintain a temperature of −52 °C in the cooling jacket of the immersion well. While the ammonia (ca. 125 mL) was being introduced, acetophenone (2.0 mL, 18.0 mmol) was added in 2.0 mL of hexane all at once by syringe through the septum followed by iodobenzene (0.67 mL, 6.0 mmol). The vessel was wrapped with aluminum foil, and a Pyrex light filter was inserted. The lamp was turned on while hanging *above* the apparatus, and, when it reached normal operating intensity, it was lowered into the well. Within a few minutes of operation, the ammonia was at reflux. After 3 h, the lamp was extinguished and the reaction was quenched by careful addition of excess ammonium chloride. The ammonia was allowed to evaporate and the residue was partitioned between 75 mL of ether and 100 mL of 5% aqueous hydrochloric acid, dried over anhydrous magnesium sulfate, and filtered. The filtrate was diluted to 100 mL, and a 5.0-mL aliquot was analyzed by quantitative GC, 1-methylnaphthalene as internal standard. Detected were iodobenzene (13%) and benzyl phenyl ketone (67% yield). The remainder of the ether solution was concentrated by rotary evaporation and the residue distilled in a short path apparatus. At 150 °C (20 torr), the excess acetophenone distilled. At 100 °C (0.01 torr), essentially pure benzyl phenyl ketone distilled (781 mg, 67% yield). Recrystallization from 95% ethyl alcohol provided a sample of mp 56–57 °C (lit. mp 55–56 °C).[31] **(b). Diethyl Malonate.** According to the general procedure above, the immersion well was assembled with potassium *tert*-butoxide (2.02 g, 10.0 mmol), ammonia (125 mL), diethyl malonate (2.72 mL, 18.0 mmol), and iodobenzene (0.67 mL, 6.0 mmol). After irradiation for 3.0 h without the Pyrex filter, addition of ammonium chloride and isolation as before provided the crude product as an ether solution. Analysis by GC (using commercial diethyl phenylmalonate for comparison) indicated the absence of diethyl phenylmalonate (<1%). **(c). *p*-Cresol.** The photochemical immersion well was assembled containing potassium *tert*-butoxide (2.25 g, 20.0 mmol), ammonia (125 mL), *p*-cresol (1.89 mL, 18.0 mmol), and iodobenzene (0.67 mL, 6.0 mmol). The mixture was irradiated without the Pyrex filter for 3.1 h and quenched with ammonium chloride, and the crude product was isolated as an ether solution. Analysis as before by GC indicated the absence (<1%) of both iodobenzene and the expected product, phenyl *p*-tolyl ether. From the ether solution, *p*-cresol was isolated by short path distillation in 80–85% recovery; the residue from the distillation (50 °C (0.01 torr), 170 mg of black solid) was a complex mixture by TLC analysis (silica gel, benzene).

Irradiation of Pinacolone Enolate and Bromobenzene in Various Solvents (Table II). General Procedure—Dimethyl Sulfoxide. A 50-mL three-necked flask containing potassium *tert*-butoxide (0.67 g, 6.0 mmol) and bearing a three-way stopcock and rubber septum was placed under argon. Anhydrous, oxygen-free dimethyl sulfoxide (15 mL) was added all at once via syringe, followed by 0.75 mL (6.0 mmol) of dry pinacolone and 0.21 mL (2.0 mmol) of bromobenzene. The reaction mixture was positioned close to the Hanovia 450-W medium-pressure mercury arc and irradiated for 1.3 h. The reaction temperature was 30–35 °C during irradiation. The mixture was cooled in an ice bath, and 25 mL of 5% aqueous hydrochloric acid was added, followed by a mixture of naphthalene and toluene (GC internal standards). The pale yellow solution was poured into 50 mL of ether and washed with 25 mL of saturated aqueous sodium chloride solution. Analysis of the ether solution on a 6-ft column of 5% FFAP programmed from 60 to 180 °C gave the following data: bromobenzene (2%), 3,3-dimethyl-1-phenyl-2-butanone (84%), and 3,3-dimethyl-1,1-diphenyl-2-butanone (17%). Analysis on a 12-ft column of 5% Carbowax 20 M at 50 °C revealed benzene (3%). Collection of the ketonic products by preparative GC allowed comparison of IR and

(25) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. 1, Wiley, New York, 1967, p 1102.
(26) D. Seebach and E. J. Corey, *J. Org. Chem.*, **40**, 231 (1975).
(27) W. G. Kenyon, E. M. Kaiser, and C. R. Hauser, *J. Org. Chem.*, **30**, 2937 (1965).
(28) A. A. Khalaf and R. M. Roberts, *J. Org. Chem.*, **35**, 3717 (1970).
(29) G. Stork and L. Maldonado, *J. Am. Chem. Soc.*, **93**, 5286 (1971).
(30) H. Cristol, A. Laurent, and M. Mousseron, *Bull. Soc. Chim. Fr.*, 2313 (1961).
(31) C. F. H. Allen and W. E. Barker, "Organic Syntheses", Collect. Vol. II, Wiley, New York, 1943, p 156.

^{1}H NMR spectral data with samples prepared earlier (see above).

Preparation of the Sodium Enolate of Pinacolone. To a 100-mL three-neck flask was transferred solid sodium bis(trimethylsilyl)amide[32] (3.29 g, 17.9 mmol) under a flow of argon. The flask was cooled to 0 °C as tetrahydrofuran (25 mL) was added by syringe. The mixture was cooled to −78 °C and pinacolone (2.24 mL, 17.9 mmol) was added dropwise over 0.5 h. Then the solution was allowed to warm to 25 °C; the solvent was removed under vacuum, leaving a fluffy white solid which was maintained at 0.001 torr for 12 h to remove the coordinated solvent. The solid became yellow and liquified after a few minutes exposure to air. ^{1}H NMR (C_6H_6): δ 3.78 (br s, 1 H, methylene H), 3.48 (br s, 1 H, methylene H), 1.20 (s, 9 H, $C(CH_3)_3$). Minor impurity peaks were detected at δ 3.55 and 0.89. Sublimation (150 °C (0.001 torr)) gave good recovery; however, in the ^{1}H NMR spectrum of the sublimate, a new minor peak appeared at δ 1.85 and the peak at δ 3.55 was absent. The crude solid was used in further studies.

Preparation of the Lithium Enolate of Pinacolone. A solution of lithium diisopropylamide in tetrahydrofuran was prepared from *n*-butyllithium (25.4 mL of 1.97 M solution in hexane, 50.0 mmol) and 7.7 mL (55.0 mmol) of diisopropylamine. With the base solution at −78 °C, pinacolone (6.25 mL, 50.0 mmol) was added dropwise over 10 min via syringe. The resulting white suspension was maintained at −78 °C for 0.5 h, and then the volatile material was removed at 25 °C (0.001 torr) (15 h). The resulting free-flowing white powder (3.78 g, 73% yield) could be sublimed at 150 °C (0.001 torr) and recrystallized as its tetrahydrofuran solvate by cooling a saturated solution in tetrahydrofuran to −40 °C under argon and filtering at −40 °C. The coordinated THF was removed by warming at 50 °C (0.001 torr). It was possible to transfer the solid in air without significant decomposition. ^{1}H NMR (C_6D_6): δ 3.99 (d, 1 H, J = 1 Hz, methylene H), 3.89 (br s, 1 H, methylene H), 1.17 (s, 9 H, $C(CH_3)_3$). IR (Nujol): 6.19 (m), 6.37 (w), 6.56 (w), 7.35 (m), 7.65 (m), 8.21 (2), 8.37 (s), 9.72 (w), 9.96 (s), 11.61 (w) μm. Mass spectrum (electron impact, 70 eV): no parent ion, *m/e* 100 (22%), 57 (100%). Chemical ionization (isobutane): no parent ion, *m/e* 101 (100%), 58 (80%).

Anal. Calcd for $C_6H_{11}LiO$: C, 67.93; H, 10.45; Li, 6.54. Found (sublimed): C, 67.15; H, 10.59; Li, 7.33. Found (crystallized and dried at 50 °C (0.001 torr)): C, 66.89; H, 10.48; Li, 6.50.

Entries 5–9 in Table II were carried out by using the standard procedures, except that the appropriate pinacolone salt was added as a solid before irradiation. Product analysis was as before.

Preparative Cyclization via the $S_{RN}1$ Reaction. Exemplified with Iodo Ketone 1a. A solid addition tube was loaded with iodo ketone **1a** (346 mg, 1.00 mmol) and attached to a reaction flask containing potassium *tert*-butoxide (337 mg, 3.0 mmol) under argon, and ammonia was condensed into the flask (ca. 25 mL). With the mixture at reflux, external irradiation (as described before) was allowed for 50 min. The initially pale yellow solution became brown. Excess solid ammonium chloride was added, and the ammonia was allowed to evaporate. The residue was partitioned between ether and water, and the ether layer was washed sequentially with 3 × 25-mL portions of 5% aqueous hydrochloric acid and 2 × 25-mL portions of 5% aqueous sodium thiosulfate. It was then dried over anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporation to leave a red oil, 313 mg. Short path distillation (150 °C (0.001 torr)) produced a colorless solid: mp 69–71 °C, 217 mg, 99% yield. Recrystallization from ether gave the analytical sample of **2a**, mp 72.5–73.5 °C. ^{1}H NMR ($CDCl_3$): δ 6.49 (s, 1 H, aryl-H), 6.42 (s, 1 H, aryl-H), 5.87 (s, 2 H, $-OCH_2O-$), 3.39 (s, 2 H, $ArCH_2CO-$), 2.68 (s, 2 H, $ArCH_2$), 1.00 (s, 6 H, CH_3). IR (CCl_4): 5.88 (s), 6.74 (s), 9.67 (s), 10.66 (s), 11.90 (s) μm. Mass spectral mol wt: 218; calcd for $C_{13}H_{14}O_3$, 218.

Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.33; H, 6.48.

Cyclization of 1b. In the same way, a mixture of iodo ketone **1b** (187 mg, 0.50 mmol), potassium *tert*-butoxide (674 mg, 6.0 mmol), and 400 mL of ammonia was irradiated by an external lamp for 2.2 h. Isolation as before produced 90 mg of pale yellow solid distillate and 78 mg of residue. The distillate cut corresponds to a 73% yield of cyclization products. It showed a single significant component on TLC analysis, and an ^{1}H NMR spectrum entirely consistent with structure **2b**. Recrystallization from ether gave colorless crystals, mp 80–80.5 °C. ^{1}H NMR ($CDCl_3$): δ 6.63 (s, 1 H, aryl-H), 6.52 (s, 1 H, aryl-H), 5.92 (s, 2 H, $-OCH_2O-$), 3.77 (s, 2 H, $ArCH_2CO$), 2.59 (t, 2 H, $ArCH_2-$), 1.58 (m, 4 H, $-CH_2$), 1.09 (s, 6 H, $-CH_3$). IR ($CHCl_3$): 3.39 (s), 5.93 (s), 6.75 (s), 9.60 (s), 10.63 (s) μm. Mass spectral mol wt: 246.1254; calcd for $C_{15}H_{18}O_3$, 246.1251.

Irradiation of 1c (Table III). High dilution provided distinctly higher yields, so an immersion well and large volume vessel were employed. In a typical experiment, a mixture of 0.199 g (0.49 mmol) of iodo ketone **1c** and potassium *tert*-butoxide (0.67 g, 5.99 mmol) in 450 mL of ammonia was irradiated with a Pyrex filter as described in the general procedure for immersion well experiments. The reaction was complete in <13 min. Product isolation as before left 0.142 g of a yellow oil. Preparative layer chromatography (silica gel eluted with 1:1 benzene: dichloromethane) gave a major band (R_f = 0.2–0.35) which was shown to be a mixture of **2c** and **5c**, inseparable by chromatography (^{1}H NMR and GC; see below) in a ratio of 65:25 (**2c**:**5c**). The yield of **2c** is calculated to be 29%. In other runs, **5c** was absent in the product mixture, allowing **2c** to be isolated and characterized. Analysis by GC (6-ft × 0.125-in. column packed with 3% OV-1 on 100/120 Chromasorb W at 177 °C) showed **2c** at 21.6 min and **5c** at 23.0 min. For **2c**, ^{1}H NMR ($CDCl_3$): δ 6.72 (s, 1 H, aryl-H), 6.54 (s, 1 H, aryl-H), 5.86 (s, 2 H, $-OCH_2-$), 3.66 (s, 2 H, $ArCH_2CO-$), 2.56 (t, 2 H, $ArCH_2$), 0.76–1.91 (m, 14 H, $-CH_2-$, $-CH_3$). IR (neat): 3.41 (s), 5.87 (s), 6.75 (s), 8.23 (s), 9.60 (s), 10.63 (s) μm. Mass spectral mol wt: 274; calcd for $C_{17}H_{22}O_3$, 274.

Results under different conditions are presented in Table III.

Irradiation of 6a. With the external irradiation technique through a Pyrex flask, iodo ketone **6a** (318 mg, 1 mmol) and potassium *tert*-butoxide (6.0 mmol) were irradiated in 80 mL of ammonia for 20 min. Isolation as before followed by short path distillation (120 °C (0.001 torr)) produced a colorless oil, 41 mg, identified as the reduction product (**6d**) by comparison of GC retention time and ^{1}H NMR and IR spectral data with a sample prepared by alternate means (see supplementary material).

Irradiation of 6b. With the external irradiation technique through a Pyrex flask, bromo ketone **6b** (285 mg, 1.0 mmol) and potassium *tert*-butoxide (674 mg, 6.0 mmol) in 85 mL of ammonia were irradiated for 1.3 h. Isolation as usual provided 201 mg of a dark oil, which was distilled (short path, 150 °C (0.005 torr)) to give a pale yellow liquid, 116 mg. The distillate was separated into three components by GC (6-ft × 0.375-in. column packed with 5% FFAP on Chromasorb W at 180 °C).

Fraction 1 was identified as the reduction product (**6e**) by comparison of retention time and mass spectral fragmentation pattern with a sample prepared by an alternative route (supplementary material). Mass spectrum: *m/e* 206 (8.8%), 148 (100), 147 (23), 135 (31), 77 (18), 51 (10), 43 (11).

Fraction 2 was obtained by medium-pressure **1c** (silica gel, eluted with benzene/dichloromethane), mp 87–91 °C, and assigned structure **7b**. ^{1}H NMR ($CDCl_3$): δ 6.70 (s, 2 H, aryl-H), 5.93 (s, 2 H, $-OCH_2O-$), 3.95 (t, 1 H, J = 7.5 Hz, $ArCHCO-$), 2.89 (m, 2 H, $ArCH_2-$), 2.1–2.5 (m, superimposed on singlet at δ 2.15, 5 H, $-CH_2-$, $-COCH_3$). IR (CCl_4): 5.83 (s), 6.78 (s), 9.65 (s), 10.53 (s) μm. Mass spectrum: *m/e* 204 (12%, parent), 161 (97%, loss of acetyl), 131 (73), 103 (57), 102 (17), 77 (25), 75 (11), 73 (41), 59 (10), 58 (13), 45 (60), 44 (100), 43 (34).

Fraction 3: preparative **1c** also produced the compound responsible for peak 3 in the GC analysis as colorless crystals, mp 64.5–66.5 °C, and it was assigned structure **8b**. ^{1}H NMR ($CDCl_3$): δ 6.69 (s, 1 H, aryl-H), 6.63 (s, 1 H, aryl-H), 5.93 (s, 2 H, $-OCH_2O-$), 3.70 (s, 2 H, $ArCH_2CO-$), 2.75 (t, 2 H, $-CH_2CH_2CO$), 2.29 (t, 2 H, $ArCH_2CH_2-$), 1.76 (m, 4 H, $-CH_2-$). IR (CCl_4): 5.83 (s), 6.55 (s), 6.62 (s), 9.58 (s), 10.61 (s) μm. Mass spectrum: *m/e* 204 (41%, parent), 175 (10), 149 (57), 148 (100), 147 (46), 118 (10), 117 (12), 115 (15), 91 (13), 90 (10), 89 (25), 77 (12), 63 (16), 44 (11).

Irradiation of 6c. With the external irradiation technique through a Pyrex flask, bromo ketone **6c** (299 mg, 1.0 mmol) and potassium *tert*-butoxide in 70 mL of ammonia were irradiated for 2.0 h, and the products were isolated as usual. The crude product, 188 mg of brown oil, was

Table IV. GC Analysis of Products from 6b

fractn	time, min	mass spectrum parent, *m/e*	rel area, %	estd yield, %
1	21.6	206	7.0	4
2	26.4	204	33	19
3	49.2	204	60	34

Table V. GC Analysis of Products from 6c

fractn	time, min	mass spectrum parent, *m/e*	rel area, %	estd yield, %
1	27.6	220	9	3
2	32.4	218	9	3
3	40.2	218	22	7
4	50.4	218	60	19

(32) V. Wannagat and H. Niederprün, *Chem. Ber.*, **94**, 1540 (1961).

distilled (short path, 160 °C (0.02 torr)) to give a pale yellow oil, 59 mg. Analysis by GC (6-ft × 0.375-in. column packed with 5% FFAP on Chromasorb W at 180 °C) produced the data presented in Table V.

Fraction 1 was identified as **6f** by comparison of GC retention time and mass spectral fragmentation pattern with a sample prepared by an alternative route (supplementary material). Mass spectrum: *m/e* 220 (14%, parent), 135 (100), 91 (11), 85 (10), 79 (12), 51 (25), 45 (29), 44 (53), 43 (74), 42 (11), 41 (11), 40 (23).

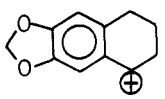
Fraction 2 was obtaned pure as an oil by medium-pressure LC (silica gel, benzene/dichloromethane as eluant) and assigned structure **7c**. ^{1}H NMR ($CDCl_3$): δ 6.60 (s, 1 H, aryl-H), 6.44 (s, 1 H, aryl-H), 5.90 (s, 2 H, $-OCH_2O-$), 3.71 (t, 1 H, $ArCHCO-$), 2.69 (m, 2 H, $ArCH_2CH_2-$), 2.11 (s, 3 H, $-COCH_3$), 1.4–2.1 (m, 4 H, $-CH_2-$). IR (CCl_4): 5.86 (s), 6.63 (s), 6.72 (s), 8.07 (s), 9.59 (s), 10.55 (s). Mass spectrum: *m/e* 218 (12%, parent), 175 (54%, $-CH_3CO$), 145 (54), 131 (12), 117 (62), 116 (18), 115 (61), 103 (16), 102 (16), 91 (31), 40 (100).

Fraction 3 was obtained pure as an oil from medium-pressure LC, as above, and assigned structure **12**. ^{1}H NMR ($CDCl_3$): δ 6.6–6.9 (m, 1 H, $CH_2—CH—CH=C—CO$), 6.70–6.67 (m, 3 H, aryl-H), 5.91–6.20 (m, 1 H, $-CH=CH—CO-$), 5.91 (s, 2 H, $-OCH_2O-$), 2.37–2.83 (m, 4 H, $ArCH_2CH_2—C=C-$), 2.20 (s, 3 H, $-COCH_3$). IR (CCl_4): 5.46 (s), 5.88 (m), 5.96 (s), 6.65 (s), 6.72 (s), 6.92 (s), 7.95 (s), 9.51 (s) μm. Calcd for $C_{13}H_{14}O_3$: mol wt 218. Mass spectrum: *m/e* 218 (4%), 135 (100), 79 (11), 77 (33), 51 (22), 43 (16).

Fraction 4 was obtained pure as a colorless solid, mp 87.5–89.5 °C, by medium-pressure LC as before and was assigned structure **8c**. ^{1}H NMR ($CDCl_3$): δ 6.69 (s, 1 H, aryl-H), 6.62 (s, 1 H, aryl-H), 5.96 (s, 2 H, $-OCH_2O-$), 3.78 (s, 2 H, $ArCH_2CO-$), 2.73 (t, 2 H, $-CH_2CH_2CO-$), 2.31 (t, 2 H, $ArCH_2CH_2-$), 1.2–2.0 (m, 4 H, $-CH_2-$). IR (CCl_4): 3.41 (s), 5.36 (w), 5.88 (s), 6.63 (s), 6.73 (s), 7.90 (s), 9.59 (s), 10.64 (s) μm. Mass spectrum: *m/e* 218 (92%, parent), 190 (20), 189 (25), 175 (16), 162 (85), 161 (59), 160 (21), 149 (86), 148 (44), 147 (37), 145 (30), 135 (50), 132 (35), 131 (75).

Irradiation of 15. With the external irradiation technique through a Pyrex flask, bromo ketone **15** (341 mg, 1.0 mmol) and potassium *tert*-butoxide (674 mg, 6.0 mmol) in 85 mL of ammonia were irradiated for 2.0 h, and then the product mixture was isolated and analyzed as before. Short path distillation (130 °C (0.01 torr)) afforded 205 mg of a pale yellow oil, which contained two products in a 5:1 ratio (GC analysis, 6-ft × 0.275-in. column packed with FFAP, 180 °C, major component at 40 min (yield based on weight of distillate and peak areas, 65%) and minor at 48 min (yield, 15%)). The major component was separated in pure form (GC, TLC) by medium-pressure liquid chromatography and shown to be **16** (cis or trans) by spectroscopic data and hydrogenation to **18**. ^{1}H NMR ($CDCl_3$): δ 6.66 (br s, 3 H, aryl-H), 5.89 (s, 2 H, $-OCH_2O-$), 5.50–5.85 (m, 2 H, $-CH=CH-$), 3.15–3.45 (m, 4 H, $ArCH_2CH=CHCH_2CO-$), 1.17 (s, 9 H, $-CH_3$). IR (neat): 3.37 (s), 3.40 (s), 3.45 (s), 5.86 (s), 6.65 (s), 6.71 (s), 6.92 (s), 8.01 (s), 9.61 (s) μm. Mass spectrum: *m/e* 290 (26%, parent), 262 (100), 261 (65), 260 (11), 161 (15), 135 (27).

Hydrogenation of the distillate (25 mg) in 5.0 mL of ethyl acetate by using 21 mg of 5% Pd/C of 1 atm of hydrogen for 24 h produced a mixture with two components (31.2 min (major) and 45.0 min (minor) retention time from GC analysis as described immediately above). The major component was identified as **18** by comparison of GC retention time (coinjection) and mass spectral fragmentation pattern with a sample produced by an alternate route (supplementary material). The minor component was unchanged during hydrogenation; it was obtained in ca. 90% purity (contaminated with **16**) by medium-pressure LC separation of the original distillation. Mass spectral analysis: parent at *m/e* 200 and base peak at *m/e* 175, assigned to fragment i. Resistance to hydrogenation also supports structure **17**. Reaction of **15** with a solution of lithium diisopropylamide (threefold molar excess) in tetrahydrofuran at 0 °C under argon followed by addition of hexamethylphosphoric triamide and potassium *tert*-butoxide (threefold molar excess) gave, after 17 h at 25 °C, a complex mixture of products. The major product was obtained in 85–90% purity by layer chromatography and shown to be identical with **17** in GC retention time and MS fragmentation pattern.



i

Further confirmation of the structure of **16** was obtained by comparison of GC and spectral data with a sample produced by alternate synthesis (supplementary material).

Irradiation of 21. According to the general procedure for external irradiation through a Pyrex flask, a mixture of bromo ester **21** (204 mg, 0.60 mmol) and lithium amide (prepared by addition of 0.25 mL of a 3.36 M solution of *n*-butyllithium in hexane to ammonia at −78 °C) in 15 mL of ammonia at reflux was irradiated for 1.5 h. Isolation as before produced a crude product (120 mg) which was a mixture. Unreacted **21** was indicated by absorptions at δ 7.15 and 6.65 in the ^{1}H NMR spectrum; the cyclization product (**23**) and the α,β-unsaturated product (**24** or positional isomer) were shown to be absent of signals in the region δ 5.8–3.0 in a high-sensitivity scan of the ^{1}H NMR spectrum.

Preparation of 31, 1-(6-Bromo-3,4-methylenedioxyphenyl)-3,3-dideuterio-5-hexanone. (a). Preparation of 1-(3,4-Methylenedioxyphenyl)-3,3-dideuterio-3-propanol. A solution of methyl 3-(3,4-methylenedioxyphenyl)propanoate (6.16 g, 35.0 mmol) in 25 mL of ether was added to a slurry of lithium aluminum deuteride (798 mg, 19.0 mmol) in 50 mL of ether at a rate which caused the reaction mixture to reflux gently. After addition was complete, the mixture was heated at reflux for 30 min and then cooled in an ice bath during sequential addition of 1 mL of water, 1 mL of 13% aqueous potassium hydroxide solution, and 3 mL of water. From the filtrate was isolated crude alcohol-d_2 as a colorless oil which was purified by simple distillation to yield a center cut of bp 92–100 °C (0.005 torr); 4.11 g, 65%. ^{1}H NMR ($CDCl_3$): δ 6.65 (s, 3 H, aryl-H), 5.87 (s, 2 H, $-OCH_2O-$), 2.4–2.8 (m, 2 H, $ArCH_2CH_2$), 1.5–2.0 (m, 3 H, $-CH_2CD_2OH$). IR (film): 2.97 (s), 3.38 (s), 6.55 (s), 6.61 (s), 6.93 (s), 8.05 (s), 8.41 (s) μm. Integration of the ^{1}H NMR spectrum failed to detect signals due to residual protons at C-3 (<5% H). **(b).** The alcohol was converted to 1-(3,4-methylenedioxyphenyl)-3,3-dideuterio-3-iodopropane and then to **30**, 1-(6-bromo-3,4-methylenedioxyphenyl)-3,3-dideuterio-3-bromopropane, according to the method described for the unlabeled analogue, **10** (see supplementary material). **(c).** Reaction of **30** with *tert*-butyl acetoacetate and subsequent decarboxylation produced **31**, exactly as described for the unlabeled analogue, **6b**. ^{1}H NMR ($CDCl_3$): δ 6.96 (s, 1 H, aryl-H), 6.68 (s, 1 H, aryl-H), 5.92 (s, 2 H, $-OCH_2O-$), 2.3–2.8 (m, 4 H, $ArCH_2CH_2CD_2CH_2CO-$), 2.13 (s, 3 H, $-COCH_3$), 1.3–1.7 (br t, 2 H, $-CH_2CH_2CD_2$). IR (neat): 3.35 (s), 4.44 (m), 4.67 (w), 5.83 (s), 6.65 (s), 6.78 (s), 7.11 (s), 7.37 (s), 8.11 (s), 8.54 (s) μm. Mass spectrum: *m/e* 304 (4.11%), 303 (9.70), 302 (64.5), 301 (11.7), 300 (62.7), 299 (1.8), 298 (0.0). Calcd for $C_{13}H_{13}D_2{}^{79}BrO_3$: parent at *m/e* 300. With use of natural abundances for H, Br, and C, the family of peaks from *m/e* 298 (unlabeled parent) to 304 corresponds to 0% d_0, 3 ± 2% d_1, and 97 ± 3% d_2.

Irradiation of 31. Exactly according to the procedure for irradiation of **6c**, compound **31** (327 mg, 1.09 mmol) was irradiated. Short path distillation of the crude product at 150 °C (0.02) torr produced 58 mg of a colorless oil. Analysis by GC as before indicated the presence of **32** (3%, based on assumption of equal molar response factors for all components), **33** (4%), **34** (5.5%), and **35** (15%).

Compound **33** was identified by GC retention time and mass spectral fragmentation pattern in comparison with **6f**, the unlabeled analogue. Mass spectrum: *m/e* 223 (21.4%), 222 (32.1), 137 (21.4), 136 (71.3), 135 (100), 77 (28.6), 73 (21.4), 44 (3.6), 43 (53.2). From the ratio of abundance for *m/e* 223, 222, 221, and 220, the deuterium distribution is calculated to be >95% d_2. No significant deuterium is detected in the fragment at *m/e* 135 (3,4-methylenedioxybenzyl cation).

Compound **35** was identified by GC retention time and mass spectral fragmentation pattern in comparison with **7c**, the unlabeled analogue. Mass spectrum: *m/e* 220 (15.5%), 178 (13.3), 177 (100), 147 (56), 119 (50), 118 (13), 117 (31), 116 (17). From the ratio of abundance for *m/e* 221, 220, 219, and 218, the deuterium distribution is calculated to be >95% d_2.

Compound **36** was identified by GC retention time and mass spectral fragmentation in comparison with the unlabeled analogue, **12**. Mass spectrum: *m/e* 220 (21.6%), 136 (100), 78 (32.3), 43 (71.1), 40 (10.8). From the ratio of the abundances for *m/e* 221, 220, 219, and 218 and *m/e* 135 and 136 (compared to **12**), the overall deuterium content is calculated to be >95% d_2, and the fragment at *m/e* 136 (or 135 in **14**) is 1% d_0, 98% d_1, and 1% d_2, indicating one deuterium in the 3,4-methylenedioxybenzyl cation fragment.

Preparation of 2-(Hexadeuterioisopropylidene)-1,3-dithiane (42). This compound was obtained in 88% yield by using the procedure reported for the unlabeled analogue.[32] ^{1}H NMR ($CDCl_3$): δ 2.6–3.0 (m, 4 H, $-SCH_2CH_2CH_2S-$), 1.8–2.3 (m, 2 H, $-CH_2-$). IR (film): 3.33 (s), 3.37 (s), 4.42 (m), 4.51 (m), 4.63 (m), 4.70 (m), 4.80 (m), 7.82 (s), 9.60 (s), 9.82 (s), 11.04 (s) μm.

Preparation of *tert*-Butyl 2-(Trideuteriomethyl)-3,3,3-trideuteriopropanoate (43). To a slurry of mercuric oxide (32.5 g, 0.15 mol) in 100 mL of tetrahydrofuran was added 18.5 mL (0.15 mol) of boron trifluoride etherate and 20 mL of water. Then a solution of 10.3 g (62 mmol) of **42** in 20 mL of tetrahydrofuran was added, and the mixture was heated at reflux for 4 h. The solvent was decanted, and the pasty residue was triturated with dichloromethane. From the combined organic solutions was isolated 2.41 g (44%) of colorless isobutyric acid-d_3. The

crude acid was dissolved in 3 mL of dichloromethane and 2.2 mL (26 mmol) of oxalyl chloride was added dropwise rapidly at 25 °C. The mixture was stirred at 25 °C for 4 h and then distilled through a 3-in. Vigreux column. The fraction of bp 80–87 °C was collected, 1.69 g (59% yield) of colorless isobutyryl chloride-d_6. The acid chloride was added via syringe to a solution of 1.11 g (15 mmol) of dry *tert*-butyl alcohol and 2.0 mL (15 mmol) of *N,N*-dimethylaniline in 5 mL of ether. The resulting solid mass was allowed to stand at 25 °C for 24 h and was then partitioned between water and ether. From the ether was isolated, after simple distillation, a sample of **43**: bp 122–125 °C, 0.66 g, 29%. ^{1}H NMR ($CDCl_3$): δ 2.15–2.45 (br s, 1 H, –C*H*—CO), 1.44 (s, 9 H, CH_3). IR (neat): 3.29 (s), 3.33 (s), 4.42 (s), 4.62 (w), 4.73 (w), 5.75 (s), 7.29 (s), 7.39 (s), 7.79 (s) μm. Mass spectrum: no parent ion, *m/e* 135 (3.1%), 77 (48.3), 57 (100), 49 (40), 41 (22). Estimation of the percent deuterium was based on the *m/e* 135 fragment (loss of $-CH_3$ from the *tert*-butyl unit): 0.3% d_4, 2.4% d_5, 97.3% d_6.

Irradiation of *tert*-Butyl Lithioisobutyrate-d_6 (Lithium Enolate of 43) with *p*-Bromoanisole. With the external radiation apparatus, a mixture of *p*-bromoanisole (0.25 mL, 2.0 mmol) and the lithium enolate of **43** (prepared from 1.06 mL, 6.0 mmol, of **43** and 1.1 mol equiv of lithium diisopropylamide) in 40 mL of ammonia refluxes for 1.5 h. The products were isolated as before and analyzed by GC (6-ft × 0.25-in. column of 5% FFAP on Chromasorb W, programmed from 60 to 180 °C and with biphenyl as internal standard). The products observed were anisole (54% yield) and *tert*-butyl 3,3,3-trideuteriomethyl-2-(trideuteriomethyl)-2-(*p*-anisyl)propanoate (28% yield, retention time: 34.3 min). The mass spectrum of the anisole produced was compared with the mass spectrum of commercial anisole, under precisely the same conditions. Standard anisole: *m/e* 109 (7.4), 108 (87.4). Anisole from irradiation experiment: *m/e* 109 (53), 108 (82). The data are consistent with a mixture of anisole-d_1 (*m/e* 109, 35%) and anisole-d_0 (*m/e* 108, 65%).

Acknowledgment. We wish to thank the Public Health Service (NIH Grant AI-08687) for generous support of this work, including an NIH traineeship to T.M.B. through the Cornell Chemistry Department. We are grateful to Mr. Jeffrey Hayes for the experiments with compound **1c**.

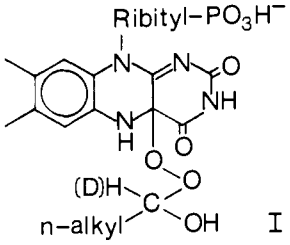
Supplementary Material Available: The preparation of starting materials (**1a–c**, **3a–c**, **4a–c**, **5a–c**, **6a–c**, **10**, **15**, and **21**) and comparison compounds (**6d**, **6e**, **16**, **18**, and **19**) is reported in detail, including six references (16 pages). Ordering information is given on any current masthead page.

Communications to the Editor

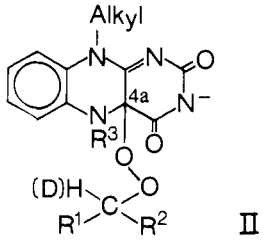
Formation of a Nonchemiluminescent Excited-State Species in the Decomposition of 4a-(Alkylperoxy)flavins

Sir:

Bacterial luciferase chemiluminescence is proposed to arise from chemical transformations of enzyme-bound I.[1] Previous model



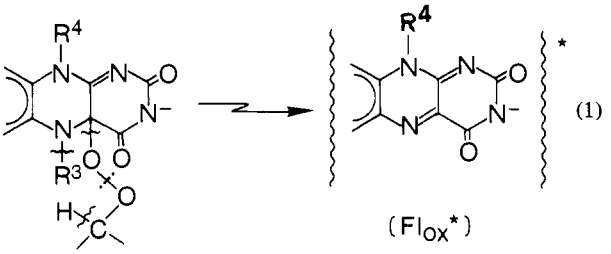
I



II

studies[2] have employed N^5-alkyl-4a-(alkylperoxy)flavins (II). The minimal requirements for chemiluminescence (CL) in the model reactions requires R^1 = alkyl or aryl, R^2 = OH or H, and R^3 = alkyl.[2] In the DMF solvent employed in the present study the substitution of OH for H as R^2 alters the kinetics of the peroxide decomposition but not the quantum yield (Φ) of CL. CL arises from a minor reaction path for the disappearance of II.[2] For this reason [II] is controlled by a non-CL reaction(s), and $-d[II]/dt$ and the exponential decay in light emission share a common rate constant.[3] We now describe experiments which support the formation of two excited species on decomposition of II (R^1 = $C_6H_4CH_3$-*p*; R^2 = H (D), OH; R^3 = C_2H_5).[4]

CL, in the absence of added fluorescer, is due to excited flavin (Fl_{ox}*) (eq 1; II = **1–6**) as shown by the fact that chemilumi-



(1)

1, R^3 = Et; R^4 = Me
2, R^3 = *m*-$CH_3OC_6H_4CH_2CH_2$; R^4 = Me
3, R^3 = Et; R^4 = *m*-$HOC_6H_4CH_2CH_2$
4, R^3 = Et; R^4 = *m*-$CH_3OC_6H_4CH_2CH_2$
5, R^3 = Et; R^4 = C_6H_5
6, R^3 = Et; R^4 = 2′,6′-$(CH_3)_2C_6H_3$

nescent emissions are identical with the fluorescence emissions of Fl_{ox}.[5] Particularly convincing evidence for this is the identity of the chemiluminescent emission spectra obtained on decomposition of **1** and **2**. Though these two 4a-(alkylperoxy)flavins possess different structures, they provide the same Fl_{ox}. Also when R^4 is aromatic (**5** and **6**), there is very little chemiluminescent emission

(1) (a) Hastings, J. W.; Balny, C.; LePeuch, C.; Douzou, P. *Proc. Natl. Acad. Sci. U.S.A.* **1973**, *70*, 3468. (b) Hastings, J. W.; Balny, C. *J. Biol. Chem.* **1975**, *250*, 7288. (c) Balny, C.; Hastings, J. W. *Biochemistry* **1975**, *14*, 4719. (d) Hastings, J. W.; Gibson, Q. H.; Friedland, J.; Spudich, J. In "Bioluminescence in Progress"; Johnson, F. H., Haneda, Y., Eds.; Princeton University Press: Princeton, NJ, 1966; p 151.

(2) (a) Kemal, C.; Bruice, T. C. *Proc. Natl. Acad. Sci. U.S.A.* **1976**, *73*, 995. (b) Kemal, C.; Chan, T. W.; Bruice, T. C. *Ibid.* **1977**, *74*, 405. (c) Kemal, C.; Bruice, T. C. *J. Am. Chem. Soc.* **1977**, *99*, 7066.

(3) Maskiewicz, R.; Sogah, D.; Bruice, T. C. *J. Am. Chem. Soc.* **1979**, *101*, 5347.

(4) For experimental procedures, see ref 1b,c. (In this study the solvent has been dry DMF unless stated otherwise, 30 °C.) Quantum yields are based on initial concentrations of compounds II which are formed quantitatively on mixing excess (10^{-2} M) *p*-methylbenzyl hydroperoxide or 1′-(*p*-methylbenzyl) hydroxyperoxide with the appropriate N^5-ethylflavinium cation (10^{-4} M). The presence of alkyl peroxides in excess of that required to generate II does not influence the time course or Φ. All reactions are carried out under dry and anaerobic conditions. Quantum yields for chemiluminescent reactions were determined from the areas under plots of c.p.s. vs. time. Measurements were made with a PAR quantum photometer Model 1140A calibrated by use of the standard luminol reaction [Lee, J.; Wesley, A. S.; Ferguson, J. F.; Seliger, H. H. In ref 1d, pp 35–43]. Chemiluminescence emission spectra and fluorescence emission spectra (corrected) were recorded on a Perkin–Elmer MPF-3 spectrofluorophotometer. The fluorescence quantum efficiency of Rhodamine-B in *t*-BuOH was determined by employing the reported value in EtOH [Parker, C. A.; Rees, W. T. *J. Chem. Soc.* **1960**, 596] as standard.

(5) The fluorescent emissions of compounds Fl_{ox} are as follows: R^4 = Me (518 nm), R^4 = *m*-$HOC_6H_4CH_2CH_2$ (526 nm), R^4 = *m*-$CH_3OC_6H_4CH_2CH_2$ (512 nm).

0002-7863/80/1502-7774$01.00/0