

rect or not. As has already been mentioned, the overlap repulsion has been considered many times previously, but attempts to use VB wave functions^{5,8,9,14,15} omitted difficult but important integrals, and the use of empirical potentials has been uncertain at best.^{5,19,46,47} The type of calculation needed for studying the ethane barrier was essentially impossible in the 1930's, quite difficult in the early 1960's, but with the computers and computational techniques^{48,49} developed by the 1980's, simple enough to be assigned as project in a quantum chemistry course.

Barriers to internal rotation have now been computed in numerous other molecules with use of SCF-MO and more elaborate types of wave functions, with generally good agreement with the experimental values where they are known.³¹ In general it has been found that larger sets of atomic orbitals are needed for molecules whose atoms in the central bond contain lone pairs of electrons and that the effects of bond distance and bond angle relaxation during internal rotation may be important also. For example, in the hydrogen peroxide molecule it has been found that both a larger set of atomic orbitals and consideration of bond angle and bond length changes during rotation were needed⁵⁰ to obtain an accurate description of the internal rotation potential function, whose principal features in this case are the cis barrier, the trans barrier, and the minimum at a skew angle. In retrospect it seems that ethane, with no lone pairs of electrons and only one principal feature in its internal rotation potential function, the barrier height, is one of the simplest molecules to treat, despite the fact that it contains more atoms than some other molecules with internal rotation.

The type of intramolecular force analysis applied to ethane here has also been applied to other molecules

- (46) O. J. Sovers and M. Karplus, *J. Chem. Phys.*, **44**, 3033 (1966).
 (47) M. L. Huggins in "Structural Chemistry and Molecular Biology", A. Rich and N. Davidson, Ed., Freeman, San Francisco, 1968.
 (48) T. H. Dunning, Jr., and P. J. Hay in "Methods of Electronic Structure Theory", H. F. Schaefer, III, Ed., Plenum, New York, 1977.
 (49) M. Dupuis, J. Rys, and H. F. King, *J. Chem. Phys.*, **65**, 111 (1976).
 (50) T. H. Dunning, Jr., and N. W. Winter, *Chem. Phys. Lett.*, **11**, 194 (1971); *J. Chem. Phys.*, **63**, 1847 (1975). D. Cremer, *J. Chem. Phys.*, **69**, 4440 (1978).

such as methanol,^{44,45,51} acetaldehyde,⁴⁴ hydrogen peroxide,⁴⁴ methylamine,⁴⁵ and butadiene.⁵² The conclusions regarding the nature of the forces involved were essentially the same for all of these molecules, although in some cases there were additional complications. The hydrogen peroxide difficulties have already been mentioned; for butadiene a more complicated, correlated wave function was required for the cis portion of the potential although not in determining the barrier height from the lower (trans) minimum.

The nature of the intramolecular forces determining barriers can be probed in even more detail by studying the variation of barrier heights with vibrational excitation. This has been done both theoretically and experimentally for methylsilane,⁵³ and theoretically for BH_3NH_3 .⁵⁴ Good agreement with spectroscopic values of the derivatives of barrier heights with respect to vibrational coordinates is obtained for methylsilane with SCF-MO wave functions but not with empirical non-bonded potential functions, again showing that these simple potential functions are generally not accurate enough to use in internal rotation problems. The study of vibrational motion in methylsilane also provided a value for the effect of the variation in zero-point energy on the internal rotation barrier.

Other points of view have been taken in attempts to understand internal rotational barriers, and extensive references to these may be found in the reviews by Dale,⁵⁵ by Lowe,⁵⁶ by Veillard,²⁹ and by Payne and Allen.³²

I wish to thank Drs. M. Karplus, C. W. Kern, W. N. Lipscomb, O. J. Sovers, W. E. Palke, and K. S. Pitzer for help with work on internal rotation and for helpful comments on this Account.

Registry No. Ethane, 74-84-0.

- (51) C. W. Kern, R. M. Pitzer, and O. J. Sovers, *J. Chem. Phys.*, **60**, 3583 (1974).
 (52) U. Pincelli, B. Cadioli, and B. Levy, *Chem. Phys. Lett.*, **13**, 249 (1972).
 (53) C. S. Ewig, W. E. Palke, and B. Kirtman, *J. Chem. Phys.*, **60**, 2749 (1974).
 (54) W. E. Palke, *J. Chem. Phys.*, **56**, 5308 (1972).
 (55) J. Dale, *Tetrahedron*, **22**, 3373 (1966).
 (56) J. P. Lowe, *Prog. Phys. Org. Chem.*, **6**, 1 (1968); *Science* **179**, 527 (1973).

Photochemical Six-Electron Heterocyclization Reactions

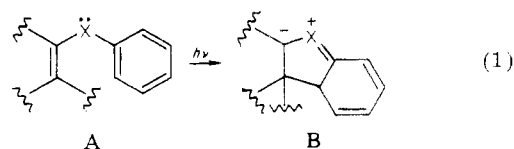
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The equation $A \rightarrow B$ (eq 1) represents a photochemical six-electron cyclization. X is a heteroatom with an unshared electron pair available for participation in the electrocyclicization. The primary synthetic value of this

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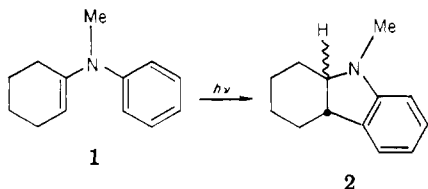
reaction type is the formation of a carbon-carbon bond to an aromatic ring. From a methodological point of view, the heteroatom X functions as a connecting link, which allows the bonding centers to approach each other with the proper trajectory. We have suggested

that the reaction $A \rightarrow B$ be called heteroatom directed photoarylation. In this Account, I present mechanistic, stereochemical, and synthetic aspects of our involvement with this reaction.¹

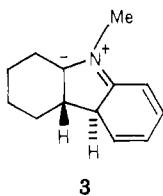
Perspective

It is important to recognize that the type of photo-reaction to be considered in this Account is an example of the 1,5-electrocyclizations² isoelectronic with the *pentadienyl* \rightleftharpoons *cyclopentenyl anion* interconversion. Thermal and photochemical electrocyclizations resulting from the replacement of carbon atoms in the pentadienyl anion with heteroatoms have provided the organic chemist with a rich area for mechanistic and synthetic study. An excellent review of the importance of 1,5-electrocyclizations in heterocyclic chemistry has been provided by Huisgen.³

Before we initiated our studies, we could draw from two important investigations that had been published nearly simultaneously in 1968. Chapman and co-workers reported the "nonoxidative" photocyclization-rearrangement of *N*-aryl enamines to indolines.⁴ With enamines derived from cyclic ketones, the stereoselectivity of photocyclization could be explored. Six- and seven-membered ring enamines gave *trans* indolines as major photoproducts. However, in other examples, substantial quantities of the *cis* isomer were obtained; for example, the *N*-methylaniline enamine of cyclopentanone gave only the *cis*-indoline.

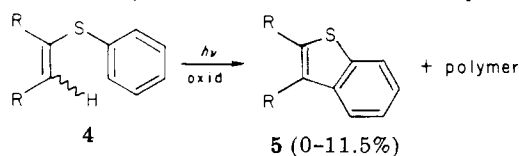


The formation of *trans*-indoline was explained by conrotatory photocyclization to give a *trans*-dihydro ylide, 3. Deuterium-labeling experiments revealed that ylide rearrangement occurred by two competing processes: a 1,4-hydrogen shift and a sequence of two 1,2-shifts.



Wynberg's group in the Netherlands reported a study of the oxidative-photocyclization of a series of phenyl vinyl sulfides 4 to benzothiophenes 5 in low yield.⁵ Polymer formation was extensive and was suggested to be a result of carbon-sulfur bond cleavage in the photo-

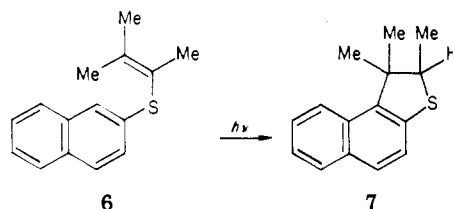
excited state of 4. Rather high energy UV irradiation (quartz glass) was employed because of the absence of long-wavelength absorption in the electronic spectra of 4 and other vinyl sulfides used in this study.



While of obvious chemical interest, the work of Chapman and Wynberg also suggested that two technical considerations might prove valuable in our studies: (1) Cyclizations performed in the absence of oxidation reagents such as dissolved oxygen should allow the stereoselectivity of the process to be studied. (2) A suitable chromophore should be available so that relatively low-energy Pyrex-filtered light could be employed. We have been delighted to find that by following these principles *photoreactions may be taken to completion and high chemical yields of isolated photoproducts may be obtained.*

The 2-Naphthyl Vinyl Sulfide System

Our studies began with an investigation of the photochemistry of 2-naphthyl vinyl sulfides.⁶ We found that Pyrex-filtered irradiation under degassed conditions gave dihydronaphthothiophenes. For example, vinyl sulfide 6 (prepared by acid-catalyzed condensation of 2-naphthalenethiol with 3-methyl-2-butanone) gives 7 in 89% isolated yield.⁷ Significantly, cyclizations were found to be regiospecific to give only the [2,1-*b*] isomer.



The stereochemistry of photocyclizations of 2-naphthyl vinyl sulfides was clearly revealed in studies with 8. Irradiation of 8 in degassed benzene solution gives 10 in 78% isolated yield; on the other hand, irradiation of 8 in the presence of the dipolarophile *N*-phenylmaleimide (NPMI, 2 equiv) results in formation of cycloadduct 11 in 90% yield.⁸ The structure of 11 was unambiguously determined by X-ray analysis. A consideration of the geometry of naphthyl vinyl sulfide 8 and relative configuration of C(5) and C(6) in adduct 11 demonstrates that cyclization of 8 is conrotatory.

The formation of adduct 11 from the presumed intermediate ylide 9 is significant in the context of a reaction mechanism for photochemical heteroatom 1,5-electrocyclizations. For the first, and as far as we know, only time, the stereochemistry of cyclization could be observed before hydrogen migration. Orbital symmetry rules² tell us that a concerted, conrotatory cyclization of 8 must occur from the photoexcited state. Furthermore, *trans* dihydro stereochemistry in 10 requires

(6) A. G. Schultz and M. B. DeTar, *J. Am. Chem. Soc.*, **98**, 3564 (1976); M.Sc. Dissertation of M. B. DeTar, Cornell University, Ithaca, NY, 1973.

(7) A. G. Schultz and M. B. DeTar in "Organic Photochemical Synthesis", R. Srinivasan, Ed., Wiley, New York, 1976, Vol. 2, p 47.

(8) A. G. Schultz and M. B. DeTar in "Organic Photochemical Synthesis", R. Srinivasan, Ed., Wiley, New York, 1976, Vol. 2, p 101.

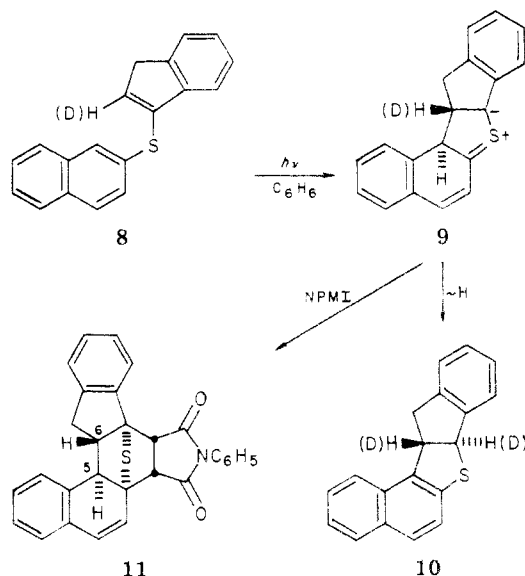
(1) A more comprehensive review is the subject of a contribution to "Organic Photochemistry", A. Padwa, Ed., Marcel Dekker, New York, 1983, Vol. 6, p 1.

(2) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry", Academic Press, New York, 1970.

(3) R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **19**, 947 (1980); for an earlier review of 1,5-electrocyclizations of 1,3-dipoles, see E. C. Taylor and I. J. Turchi, *Chem. Rev.*, **79**, 181 (1979).

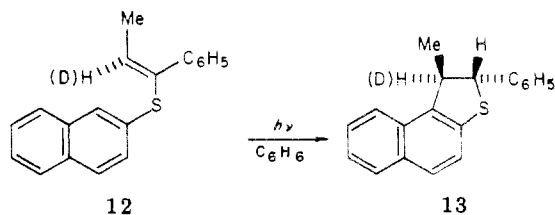
(4) O. L. Chapman and G. L. Eian, *J. Am. Chem. Soc.*, **90**, 5329 (1968); O. L. Chapman, G. L. Eian, A. Bloom, and J. Clardy, *ibid.*, **93**, 2918 (1971).

(5) S. H. Groen, R. M. Kellogg, J. Buter, and H. Wynberg, *J. Org. Chem.*, **33**, 2218 (1968).



that intramolecular hydrogen migration in **9** must be suprafacial.

For the suprafacial hydrogen migration in **9**, both [1,4] and two consecutive [1,2] hydrogen shifts are possible.⁹ Both processes are thermally allowed, and both were found to operate in the earlier enamine photocyclizations.⁴ With monodeuterio **8**, we have found that both mechanisms operate to an approximately equal extent.¹⁰ On the other hand, with the closely related vinyl sulfide **12** only the [1,4] hydrogen shift is important in formation of dihydrothiophene **13**.⁶ The factors responsible for these differences in ylide reactivity are not as yet clearly understood.



Flash photolysis techniques have been used to study the photoproduction of thiocarbonyl ylides.¹⁰ With a series of five 2-naphthyl vinyl sulfides, transient species with absorption maxima near 630 nm were observed.¹¹ The rates of disappearance of these transients are on the order of tens of milliseconds in degassed benzene but are shortened to the microsecond scale in air-saturated solution. While the kinetic analysis for disappearance of transients is complex,¹¹ we feel that the species absorbing at 630 nm are thiocarbonyl ylide intermediates corresponding to **9**. These intermediates would be expected to undergo reactions with dissolved oxygen.¹²

The formation of thiocarbonyl ylide **9** can be sensitized by triplet state sensitizers with triplet energies near or greater than that of vinyl sulfide **8** ($E_T = 60.9$ kcal/mol).¹⁰ On direct irradiation of **8**, some quenching

(9) For a theoretical treatment of [1,4] and [1,2] shifts, see M. T. Reetz, *Tetrahedron*, **29**, 2189 (1973).

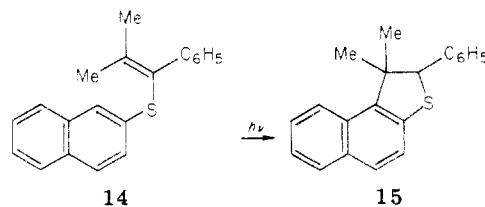
(10) W. G. Herkstroeter and A. G. Schultz, manuscript submitted for publication.

(11) Wolff has reported studies with some of the same vinyl sulfides; T. Wolff, *J. Am. Chem. Soc.*, **100**, 6157 (1978).

(12) For reports of the reaction of thiocarbonyl ylides with oxygen, see K. T. Potts and D. McKeough, *J. Am. Chem. Soc.*, **96**, 4268 (1974), and references cited therein.

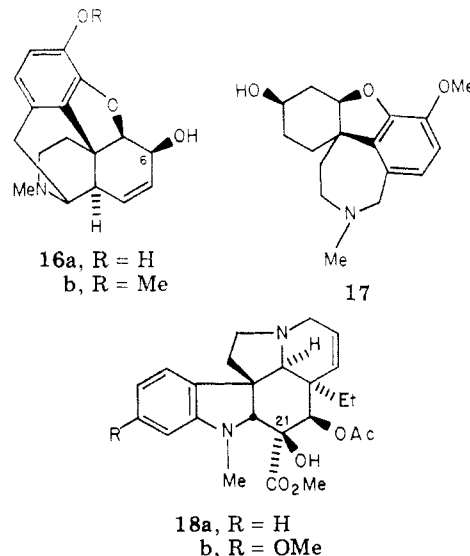
is observed with isoprene, *cis*-piperylene, and 2,5-dimethyl-2,4-hexadiene. However, the Stern-Volmer plots created from quenching data all show substantial curvature. Such observations are in accord with both singlet and triplet reactivity for photoexcited **8**. Trial and error reconstruction of Stern-Volmer plots gives a straight line when 50% of the photoreaction of **8** is assumed to occur through the singlet manifold and the remainder through the triplet state.

Similar quenching experiments were attempted with **14**, but none of the three dienes at concentrations as high as 0.2 M reduced the yields of photoproduct **15**.



This result must mean either that the photoproduct of **14** is formed exclusively in the singlet manifold where the singlet lifetime is too short to permit quenching or that the triplet state is also photoreactive but too short-lived for quenching.

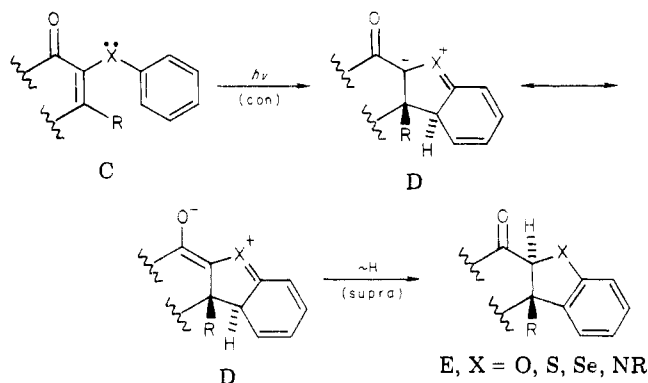
The ylide-trapping experiment may hold considerable synthetic promise. In this ring annelation process, three carbon-carbon bonds and six chiral centers are generated in one experimental operation. However, we decided to focus our initial attention on the ylide rearrangement, e.g., **9** → **10**. We took this path because we felt that photoarylation might furnish a conceptually new approach to medicinally important alkaloids such as morphine (**16a**), codeine (**16b**), lycoramine (**17**), vindrosine (**18a**), and vindoline (**18b**).



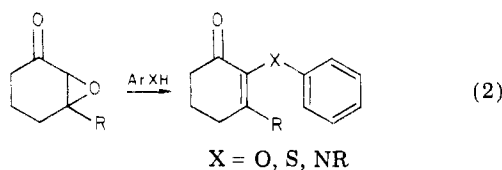
Photoarylation and the Enone Chromophore

While the naphthalene ring in vinyl sulfides of type **8** provides a convenient long-wavelength chromophore, this tactic would not foster broad synthetic scope. A chromophore distinct from the aromatic ring with good synthetic utility is needed, and, for this role, the α,β -unsaturated carbonyl group has proven to be an excellent choice. With the CO group cross-conjugated to the heteroatom as shown in C, stabilization of the intermediate ylide D may result; furthermore, hydrogen migration to give E can be coupled with epimerization

α to the CO group to extend stereochemical control. Happily, this kind of carbonyl group placement is compatible with substitution at C(6) in morphine and C(21) in vindoline.

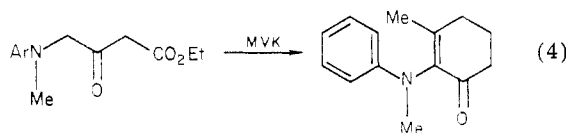
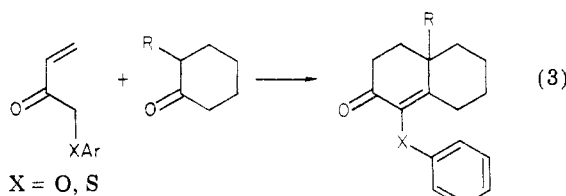


Three general methods for synthesis of photosubstrates have been developed. Epoxides derived from cycloalkenones react with phenols and thiophenols in the presence of a catalytic amount of base (eq 2). This

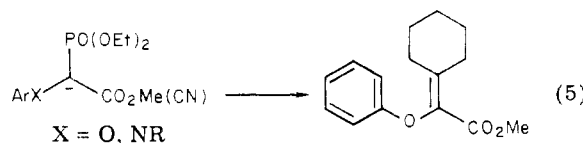


condensation process has good generality, and a variety of substituents are compatible with the reaction conditions.^{13,14} Selenium analogues cannot be made by this process, and only secondary aryl amines react at the epoxide site.

Much of our alkaloid-directed work has required the synthesis of fused bicyclic synthetic intermediates. Annulation reagents that incorporate the heteroatom-connected aryl nucleus have played an important role in synthesis plans. The Robinson-type approach^{13,14} is shown in eq 3; a "three carbon" annulation reagent¹⁵ is used in *N*-aryl enamine construction (eq 4).



Nitrile- and ester-stabilized phosphonate carbanions provide a third type of photosubstrate (eq 5).¹⁶⁻¹⁸



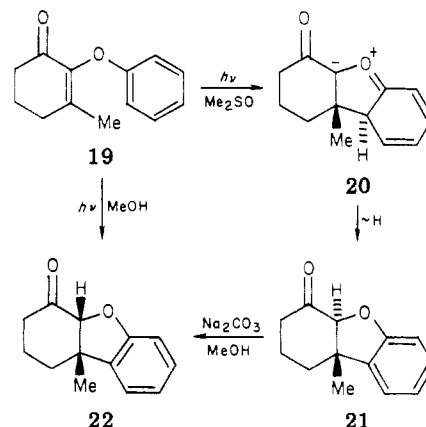
(13) A. G. Schultz, W. Y. Fu, R. D. Lucci, B. G. Kurr, K. M. Lo, and M. Boxer, *J. Am. Chem. Soc.*, **100**, 2140 (1978).

(14) A. G. Schultz, R. D. Lucci, W. Y. Fu, M. H. Berger, J. Erhardt, and W. K. Hagmann, *J. Am. Chem. Soc.*, **100**, 2150 (1978).

(15) A. G. Schultz and I-Ching Chiu, *J. Chem. Soc., Chem. Commun.*, 29 (1978).

Because of only moderate reactivity, these reagents are most useful with aldehydes and unhindered cyclic ketones.

Photocyclization-rearrangement of 2-aryloxy and 2-arylthio enones is highly stereoselective and generally occurs in excellent chemical yield. Pyrex-filtered irradiation of **19** in the polar, aprotic solvent Me₂SO gives trans-fused dihydrofuran **21**; in protic solvents, **19** gives the more stable cis-fused epimer.¹⁹



A wide range of substituents on the aromatic ring is compatible with photocyclization.²⁰ Regiochemical control for meta-substituted aryl derivatives can be moderate to excellent (2:1 for alkyl and CO₂R to >50:1 for OCH₃, with 1,2,3-aryl substitution predominating) but is, at present, somewhat unpredictable from system to system.¹⁴ However, with mono ortho substitution, cyclization always occurs at the unsubstituted ortho position.²¹ *o*-Chloro¹⁴ and bromo derivatives²² undergo cyclization without cleavage of the aryl-halogen bond. This result, coupled with the fact that halogen may be removed from aromatic rings by hydrogenolysis, means that halogen may serve as a blocking group to control regioselectivity of meta-substituted aryloxy enone photocyclizations.

Ring-fused aryloxy enones such as **23** provide an interesting test of stereoselectivity in the photochemical bond-forming step.^{14,23} In benzene solution, **23** gives only **25** in 80–90% isolated yield; in methanol, both **25** and epimer **26** are produced. Irradiation in methanol-*d* gives **25** with no incorporation of deuterium and **26** with complete deuterium incorporation at C(1); control experiments demonstrate that deuterium incorporation in **26** is the result of a kinetically controlled process.

In photocyclizations of **19** and **23**, product stereochemistry is fully compatible with a reaction mechanism involving a conrotatory electrocyclic process to give a carbonyl ylide (e.g., **20** and **24**); suprafacial 1,4 hydrogen migration gives a trans-fused dihydrofuran, while pro-

(16) A. G. Schultz and C.-K. Sha, *Tetrahedron*, **36**, 1757 (1980).

(17) A. G. Schultz, J. J. Napier, and R. Ravichandran, *J. Org. Chem.*, in press.

(18) Ph.D. Dissertation of J. J. Napier, Cornell University, Ithaca, NY, 1981.

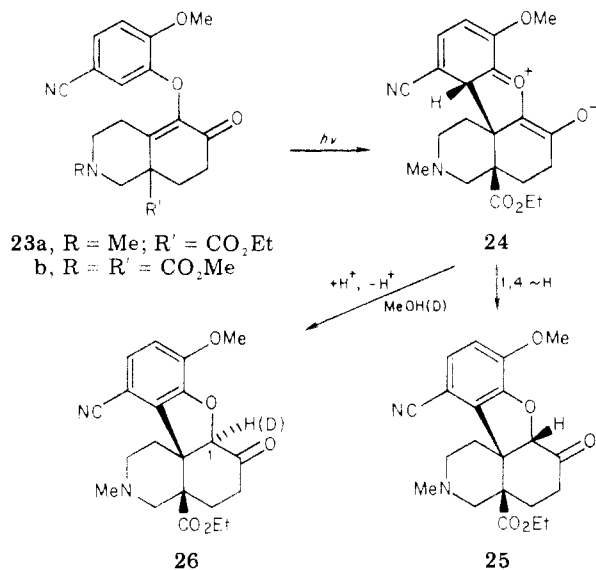
(19) See ref 13 and 14 for discussion of hydrogen-atom rearrangement.

(20) *m*-Dialkylamino and *p*-nitro substituents on analogues of **19** gave slow photodecomposition rather than cyclization.

(21) By contrast, cyclization with loss of HX or HOME seems to be the dominant reaction pathway on irradiation of *o*-halo- and *o*-methoxy-substituted diaryl ethers; see J. A. Elix and D. P. Murphy, *Aust. J. Chem.*, **28**, 1559 (1975).

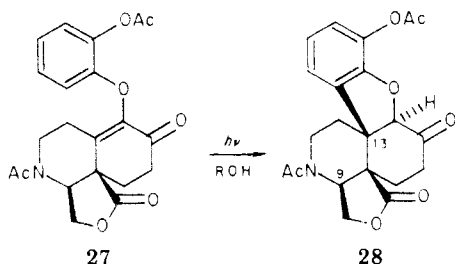
(22) Unpublished result from Rensselaer Polytechnic Institute by R. Ranganathan.

(23) A. G. Schultz and R. D. Lucci, *J. Chem. Soc., Chem. Commun.*, 925 (1976).



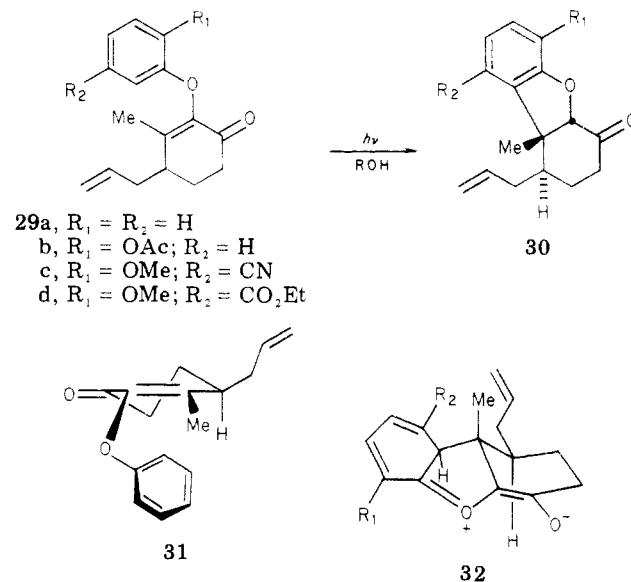
ton transfer from solvent (methanol-*d*)²⁴ to ylide gives a *cis*-fused dihydrofuran. It is noteworthy that protonation of the ylide occurs to give the more stable epimer. Recent flash photolysis studies support the hypothesis of carbonyl ylide involvement in the photocyclization process.²⁵

With **23** and several other ring-fused aryloxy^{14,23,26} and thioaryloxy enones,¹³ two conrotatory cyclizations are possible but only one has been observed. In all these examples, photocyclization appears to be governed by product development control to give a relatively strain-free delocalized ylide (e.g., **24**) with *cis*-decalone-like ring fusion. Dreiding stereomodels indicate that the corresponding ylide with a *trans*-decalone-like ring fusion is exceedingly strained. While we are fully aware of the assumptions inherent in an analysis of this type, we do feel that this model will be useful in predicting stereocontrol in related ring-fused systems. The model has been used successfully in photoconversion **27** → **28** where we were interested in remote stereochemical control between centers C(9) and C(13) in one of our approaches to the morphine ring system.²⁷



To determine if product development control would operate for other systems in which the overriding constraint of ring strain is not present, the stereoselectivity of photocyclization of 4-allyl-3-methyl-2-(aryloxy)-2-cyclohexen-1-ones (**29**) was investigated.²⁸ In contrast to the ring-fused aryloxy enones, **29a–29d** seem to undergo cyclization by steric approach control to give mainly the C(4) diastereoisomer shown (>90%); that is, an early transition state with geometry similar to

formula **31** seems to be a good predictive model. Molecular models of the carbonyl ylide intermediate **32** show significant steric interaction between the C(4) allyl group and any aromatic substituent, R₂. Product diastereoisomer distribution does not reflect this situation in the series **29a–29d**. For this reason, a transition state resembling ylide geometry is a less attractive model.



General Synthesis Applications

Photoarylations that involve the α,β -unsaturated carbonyl group are conveniently performed in a conventional preparative Pyrex glass photoreactor under an inert atmosphere. Chemical yields are generally 70–90%, and quantum yields have been estimated to be in the 25–50% range. The process is applicable to large-scale laboratory synthesis, and reactant concentrations ≥ 0.1 M may be employed. On several occasions we have performed photocyclizations on an ~ 100 -g scale using a 2000-mL photoreaction flask; when photostates are reasonably pure, irradiation with a 450-W mercury arc lamp requires ~ 24 h for complete conversion of starting material. It is worth restating that the generally high level of success in enone photoarylation is the result of a combination of efficient photocyclization (quantum yield) and the fact that, under the reaction conditions employed, photoproducts absorb relatively little of the incident light. With regard to this last point, it is important to monitor photo-reactions carefully because in many cases photoproducts possess significant photoreactivity.

A wide range of aromatic ring systems are compatible with photoarylation. Two interesting heteroaromatic examples derived from isophorone epoxide and the corresponding heteroaromatic thiol are **33** and **34**. Selenium analogues also may be prepared (e.g., **35**²⁹ and **36**³⁰), but because of a current lack of efficient and general methods for photostate preparation, we have not vigorously explored the potential of aryl vinyl selenide photochemistry.

An investigation of the modification of photoproducts by simple chemical reactions has extended the utility of photoarylation. Reductive cleavage of the C(2)-heteroatom bond provides β -arylated enones (eq 6).^{13,14}

(24) Reaction of ylides with protic solvents was first discovered in studies with 2-naphthyl vinyl sulfide **12**.

(25) T. Wolff, *J. Org. Chem.*, **46**, 978 (1981).

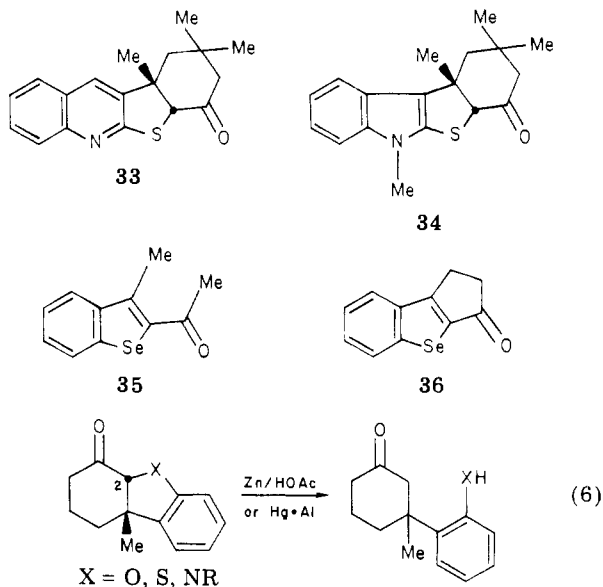
(26) A. G. Schultz and W. Y. Fu, *J. Org. Chem.*, **41**, 1483 (1976).

(27) Unpublished result from Rensselaer Polytechnic Institute by P. Shannon; also see ref 1 and 40.

(28) A. G. Schultz and J. J. Napier, *Tetrahedron Lett.*, **23**, 4225 (1982).

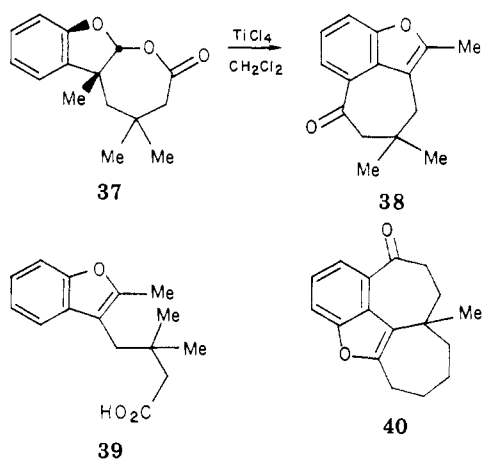
(29) A. G. Schultz, *J. Org. Chem.*, **40**, 3466 (1975).

(30) Unpublished result from Rensselaer Polytechnic Institute by R. Ravichandran.



Because cycloalkenones may serve as precursors to aryloxy enones, the overall process represents a method for enone β -arylation. In contrast to the more direct organocopper methodology, the photochemical process is compatible with a wide range of functionality in the aromatic ring. Certain stereochemical advantages (vide supra) and regiospecific placement of the hetero substituent XH in the final product are other noteworthy features of the photochemical method. When the heteroatom is sulfur, reductive removal with Raney nickel also is possible.³¹

Oxidative cleavage of the C(2)-acyl group in photoannulated benzodihydrofurans is performed in near-quantitative yield by Baeyer-Villiger reaction with *m*-chloroperbenzoic acid,^{14,32} the resulting lactones are formed with retention of C(2) stereochemistry. With lactone 37, we were able to explore the possibility of further aromatic ring annelation via the newly formed lactone acyl group. The acylation, accompanied by rearrangement to a benzofuran, is accomplished by refluxing a methylene chloride solution of lactone 37 with excess titanium tetrachloride to give tricyclic ketone 38 in 94% isolated yield. When the TiCl_4 reaction is performed at -78°C , furan carboxylic acid 39 is the major reaction product isolated after aqueous workup (98%).



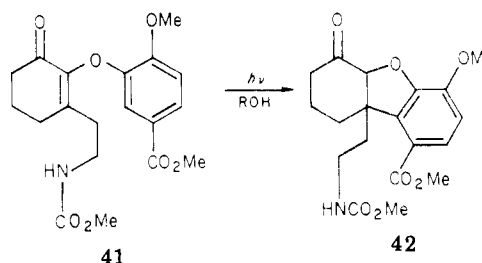
(31) A. G. Schultz, *J. Org. Chem.*, **39**, 3185 (1974).

(32) A. G. Schultz, J. Erhardt, and W. K. Hagmann, *J. Org. Chem.*, **42**, 3458 (1977).

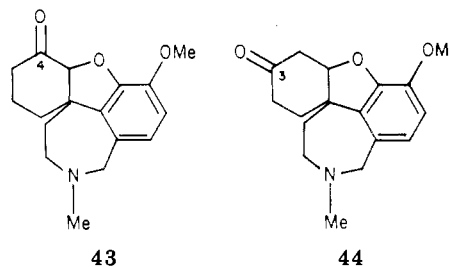
The TiCl_4 -induced rearrangement is highly stereoselective with preferential migration of the group disposed anti to the leaving carboxylate function (e.g., methyl in 37). Similar methodology has resulted in preparation of the novel tetracycle 40, derived from a 10-methyl-2-octalone precursor.³³

Application to Alkaloid Total Synthesis

A total synthesis of the galanthamine-type alkaloid lycoramine (17) represents our first application of photoarylation to natural products synthesis.³⁴ Here, the epoxy ketone route to aryloxy enone 41 provides a convergent approach originating with 1,3-cyclohexanedione and isovanillin.³⁵ The key photocyclization $41 \rightarrow 42$ (>86% isolated yield) establishes the crucial carbon-carbon bond joining an aromatic ring to a quaternary carbon atom located at a ring junction.



Conventional methods were used to develop the azacycloheptane ring in tetracyclic ketone 43 from the appended urethane and ester functions in 42. The last operation in the synthesis required a 1,2-carbonyl transposition in 43 to give lycoramine (44). However,



the chemically labile phenolic ether bond adjacent to the carbonyl group in 43 and 1,3 related to the carbonyl group in 44 placed severe constraints on available transposition methodology. After extensive investigation,³⁶ we developed a highly efficient transposition method based on earlier work by Marshall and Roebke.³⁷ *dl*-Lycoramine (17) could then be obtained by LiAlH_4 reduction of 44 (~10% overall yield from 1,3-cyclohexanedione).

Our method for carbonyl group modification significantly enhances the flexibility of synthesis design with heteroatom-directed photoarylation; 4-oxo- and 3-oxo-hexahydrobenzofurans related to 43 and 44 are now readily available.

(33) The reader is directed to ref 14 for further synthetic studies with lactone-derived intermediates.

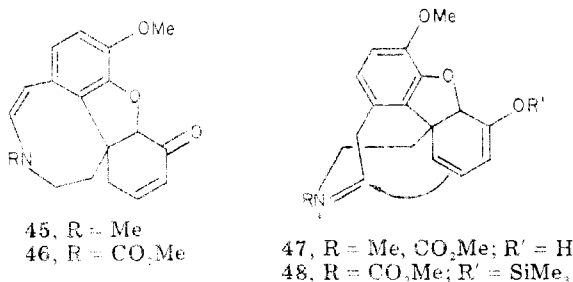
(34) A. G. Schultz, Y. K. Yee, and M. H. Berger, *J. Am. Chem. Soc.*, **99**, 8065 (1977); Ph.D. Dissertation of Y. K. Yee, Cornell University, Ithaca, NY, 1978.

(35) Problems associated with the use of epoxides of 3-alkyl-2-cyclohexen-1-ones are presented in ref 34 and 14. For an interesting rearrangement of a 2-(aryloxy)-2-cyclohexen-1-one, see A. G. Schultz and J. J. Napier, *J. Chem. Soc., Chem. Commun.*, 224 (1981).

(36) Y. K. Yee and A. G. Schultz, *J. Org. Chem.*, **44**, 719 (1979).

(37) J. A. Marshall and H. Roebke, *J. Org. Chem.*, **34**, 4188 (1969).

Upon completion of the lycoramine synthesis, attention was shifted to the more demanding morphine target. A major structural difference between the two alkaloids is that morphine can be considered to be a phenethylamine derivative, while lycoramine, lacking one structural carbon atom relative to morphine, is a benzylamine. By a modification of the lycoramine synthesis plan, we were able to construct the enamine enone systems **45** and **46** and test the concept of an internal Mannich approach to morphine, e.g., via **47**.³⁸

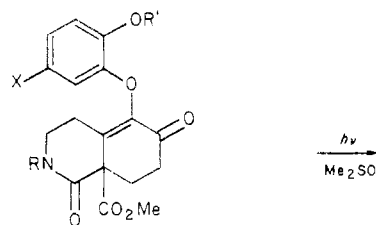


Unfortunately, we could not bring about the desired cyclization to codeinone or *N*-carbomethoxynorcodeinone using a variety of protic or Lewis acid catalysts. Because it was possible that enolization of **45** and **46** was not occurring to give the desired dienol iminium ion **47**, we prepared the corresponding dienol trimethylsilyl ether with the hope that **48** could be generated, but again cyclization did not occur.

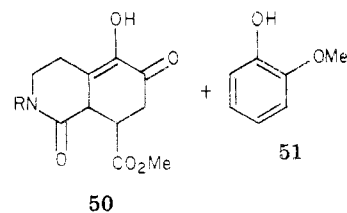
A successful approach to the morphine ring system evolved from a synthesis plan conceived near the beginning of our study in 1974.³⁹ The highly convergent (aryloxy)methyl vinyl ketone annelation was to be used to construct aryloxy enone **49**. Photocyclization, decarboxylation, and lactam reduction was expected to give enamine **53**. The remaining ring was to be constructed in two possible ways: (1) addition of cyanide ion to an iminium ion derived from **53** followed by intramolecular aromatic ring acylation, or (2) incorporation of the required one carbon unit prior to photocyclization in the form of an aryl nitrile functionality (e.g., **49d**). The first alternative has been reduced to practice.

A major obstacle in the development of this plan was the discovery that the *o*-methoxy substituent in **49a** promoted a "photohydrolysis" to give in ~60% yield α -diketone **50** and *o*-methoxyphenol (**51**) and very little of the desired cyclization product.¹⁸ While the origin of water in this process remains obscure, the propensity for photohydrolysis was found to correlate with the presence of strongly electron donating ortho substituents on the aromatic ring. Eventually we found that the mildly electron withdrawing *o*-acetoxy substituent in **49b** and **49c** is compatible with photocyclization and **52** (R = CH₂C₆H₅) may be obtained in 95% yield.⁴⁰

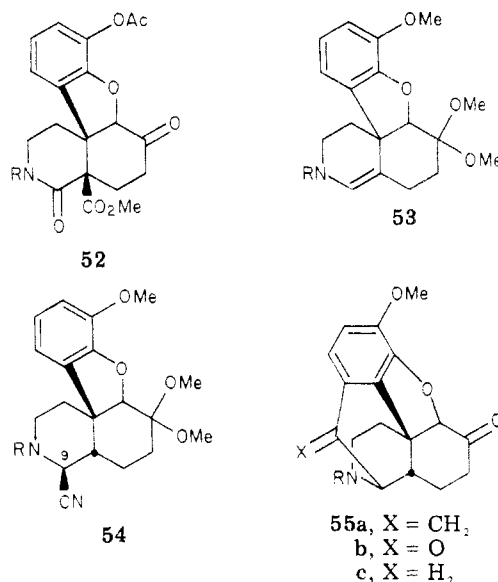
Conversion of **52** to **53** proceeded uneventfully, and while enamine **53** (R = Me) added HCN to give a mixture of epimers at C(9), the benzyl derivative gave a single diastereoisomer **54** in high yield. Many routes



- 49a, R = CH₂C₆H₅; R' = Me; X = H
b, R = Me; R' = Ac; X = H
c, R = CH₂C₆H₅; R' = Ac; X = H
d, R = R' = Me; X = CN



from **54** to the B/C trans-fused morphine ring system **55** may be imagined, but we have found that the method developed by Rapoport and Gless⁴¹ in their 6,7-benzomorphan ring synthesis serves admirably.⁴²



Photocyclodehydration Studies. Indole and Indoline Ring Synthesis

2-(*N*-alkylanilino)acetoacetates are conveniently prepared in high yield by reaction of the appropriate aniline derivative with ethyl 2-haloacetoacetates.⁴³ We reasoned that these substances might undergo photocyclization in their enolic form (e.g., **57**). In fact, Pyrex-filtered irradiation of **56** \rightleftharpoons **57** in the absence of acids provides 3-hydroxyindoline **58** in nearly quantitative yield.

A variety of substituents on the benzene ring are compatible with photocyclization. 3-Hydroxyindolines are convertible to indoles on acid-catalyzed dehydration and to oxindoles on oxidative rearrangement with lead tetraacetate-pyridine.⁴⁴ On the other hand, indoles

(38) Ying Yee was the first to test this internal Mannich route to morphine with derivative **45a**; unpublished results, Cornell University, 1978. J. J. Napier pursued this same approach with urethane derivative **45b** in the Rensselaer Polytechnic Institute laboratories; see ref 18 and 40 for details of the Napier work.

(39) Our initial studies appear in ref 23.

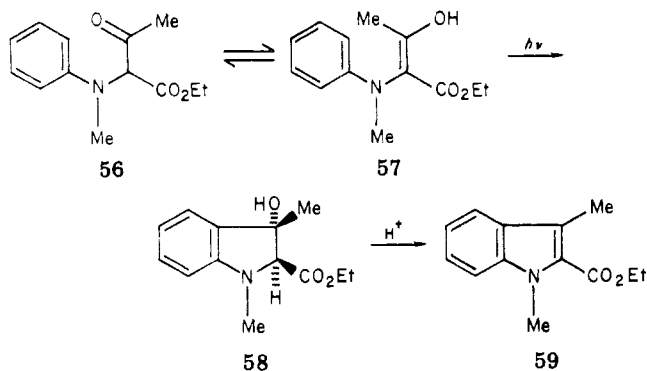
(40) A. G. Schultz, R. D. Lucci, J. J. Napier, H. Kinoshita, R. Ravichandran, P. Shannon, and Y. K. Yee, manuscript in preparation.

(41) R. D. Gless and H. Rapoport, *J. Org. Chem.*, **44**, 1324 (1979).

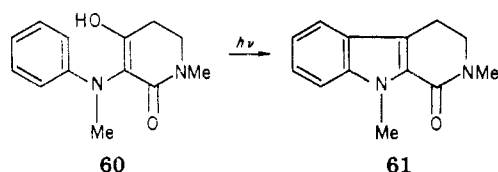
(42) Not all reactions in this synthesis are optimized; however, at present, the overall yield from **49c** to **55a** is ~50%.

(43) A. G. Schultz and W. K. Hagmann, *J. Chem. Soc., Chem. Commun.*, 726 (1976).

(44) A. G. Schultz and W. K. Hagmann, *J. Org. Chem.*, **43**, 4231 (1978).

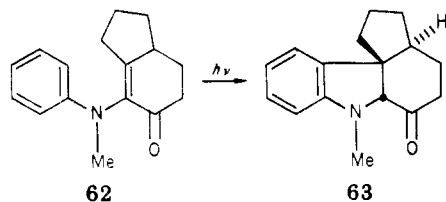


may be isolated directly by irradiation in protic (acidic) solvent. For example, the tetrahydro- β -carboline (61) can be isolated in 71% yield after irradiation of the highly enolic β -keto lactam 60 in degassed benzene-methanol-acetic acid solution.⁴⁵



Acid-catalyzed cyclodehydration of 2-anilino ketones has been used in indole ring construction. Complicating rearrangements often occur; in comparison, the photochemical method proceeds under mild reaction conditions, and yields are generally good to excellent. With some modification in the method of photosubstrate preparation, photocyclodehydration can be applied to N-unsubstituted indole synthesis.⁴⁶ The photoreaction is applicable to large-scale laboratory preparation with use of the equipment already described or, in the form of a student experiment, may be performed with an ordinary 275-W sunlamp.⁴⁷ Photocyclization of oxygen and sulfur analogues of 56 also has been studied.⁴⁵

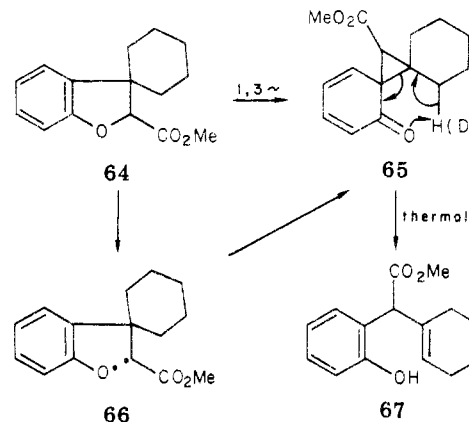
Within the context of developing methods for *Aspidosperma* alkaloid synthesis, we have explored several methods of indoline ring construction.^{16,48} Of particular note is the photocyclization $62 \rightarrow 63$.¹⁵



Secondary Photoreactions

Photoarylation products generally may be isolated in high yield. However, the potential for product photoreactivity must be appreciated. In the conversion of the (aryloxy)acrylic ester shown in eq 5 to dihydrofuran 64 (88% yield), a small amount of phenol 67 also is formed.⁴⁹ Appropriate experiments demonstrate that

67 is not formed directly from the (aryloxy)acrylic ester but rather arises by way of a secondary photoreaction of 64. In fact, rearrangement to phenol 67 occurs in 84% isolated yield ($\sim 50\%$ conversion) on extended irradiation of 64 in ether solution.



Related (aryloxy)acetic acid photorearrangements have been suggested to occur by a "solvent-caged radical mechanism" for ortho- and para-substituted phenol formation.⁵⁰ Photorearrangement of optically active 64 results in "complete" retention of optical activity in phenol 67, suggesting a concerted rearrangement rather than one involving a long-lived diradical such as 66.⁴⁹

Flash photoexcitation of 64 in degassed ether solution produces a long-lived transient absorption band ($\lambda_{\max} \sim 320$ nm), which is very similar to that of stable, alkyl-substituted 2,4-cyclohexadienones.⁵¹ This transient band is thought to be produced by the intermediate spirocyclopropyl-2,4-cyclohexadienone 65.

We have uncovered some very interesting stereochemical aspects of the benzodihydrofuran photorearrangement. Notably, cis-fused 22 undergoes efficient photorearrangement to give phenol 69, but with use of the same reaction conditions, trans-fused epimer 21 does not give 69. Flash photolysis experiments are compatible with formation of a transient 2,4-cyclohexadienone intermediate from 22, but with 21, no transient absorption spectrum is produced.

The exclusive formation of 69 from 22 may be a result of high stereoselectivity for photorearrangement to give intermediate cyclohexadienone 68. From 68, H-atom transfer can occur only from the methyl substituent. The failure of 21 to undergo photorearrangement may be a result of conformational requirements and/or the concerted nature of the 1,3-migration process; 1,3-migration with retention of stereochemistry in 21 would produce a *diastereoisomer* of 68 with a strained *trans-ring fusion*.⁵²

Fortunately, there is good control of this *secondary photoprocess*. Along with a favorable change in chromophore on conversion of aryloxy enone to benzodihydrofuran, we also have discovered electronic and steric factors that affect the secondary photorearrangement. Electron-donating groups on the hexahydrodibenzofuran aromatic ring facilitate rearrange-

(45) Ph.D. Dissertation of W. K. Hagmann, Cornell University, Ithaca, NY, 1978. For additional examples of this photocyclization in the sulfur series, see T. Sasaki and K. Hayakawa, *Tetrahedron Lett.*, 21, 1525 (1980); T. Sasaki, K. Hayakawa, and H. Ban, *Tetrahedron*, 38, 85 (1982).

(46) A. G. Schultz and W. K. Hagmann, *J. Org. Chem.*, 43, 3391 (1978).

(47) For an undergraduate laboratory experiment, "A Photochemical Preparation of Indoles", see A. G. Schultz and V. Kane, *J. Chem. Educ.*, 56, 555 (1979).

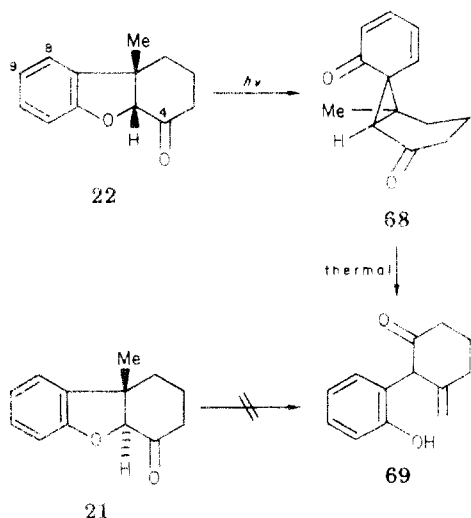
(48) Ph.D. Dissertation of C.-K. Sha, Cornell University, Ithaca, NY, 1981.

(49) A. G. Schultz, J. J. Napier, and R. Lee, *J. Org. Chem.*, 44, 663 (1979).

(50) For example, see D. P. Kelly, J. T. Pinhey, and R. D. G. Rigby, *Aust. J. Chem.*, 22, 977 (1969).

(51) Unpublished results of collaborative efforts with R. L. Strong and K. Wisniewski in the Rensselaer Polytechnic Institute laboratories.

(52) For a related benzodihydrofuran photorearrangement, see Y. Kanaka and K. San-nohe, *Tetrahedron Lett.*, 21, 3893 (1980).



ment to a phenol, while electron-withdrawing groups retard the reaction. In fact, with Pyrex-filtered light, rearrangement is completely suppressed with an acyl substituent at C(8) or C(9) in **22**. A carbonyl substituent at C(4) seems to facilitate photorearrangement, and we have already noted that trans-fused hexa-

hydrodibenzofurans are unreactive (e.g., **21**). The origin of electronic and steric effects as well as the synthetic potential of benzodihydrofuran photochemistry is currently under investigation in our laboratory.

Concluding Remarks

In this Account I have focused attention on our own studies of photochemical six-electron heterocyclization reactions. Potential for stereochemical control, the possibility of intercepting ylide intermediates by dipolar cycloadditions (inter- and intramolecular), and the potential for incorporation of a variety of heteroatoms suggest that photochemical heterocyclizations will provide a rich area of organic chemistry for future consideration.

It is a pleasure to acknowledge the contribution of graduate and postdoctoral students who participated in this research effort; their names are recorded in the references. Continued support from the National Institutes of Health, the National Institute on Drug Abuse, and most recently the National Science Foundation is appreciated. Early support from the Research Corporation, the Petroleum Research Fund, administered by the American Chemical Society, and a Du Pont Young Faculty Grant was instrumental in the initiation of this research program.

Applications of Holography in the Investigation of Photochemical Reactions

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Holography is a method of photography that results in three-dimensional images of the object being photographed.¹ An example of a typical arrangement for producing a hologram is shown in Figure 1. Light from a single coherent source, almost always a laser, is divided into two beams; an object beam that is scattered off the object being photographed and a reference beam. An interference pattern resulting from the overlapping of these two beams is formed in the plane of a photographic plate. As a result of photochemical reactions that occur in the photographic plate, the optical properties of the plate are changed and a permanent record of the interference pattern is produced. To read the hologram, a reconstruction beam, identical with the reference beam, is directed at the recording plate. A portion of this reconstruction beam is diffracted by the recorded hologram and produces a virtual image of the original object. An observer looking at this diffracted light sees a three-dimensional image of the original scene.

Much experimental effort has gone into the development of efficient holographic recording materials.²

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These investigations have primarily been concerned with improving the holographic recording process and only secondarily with the underlying photochemistry. In this account, these priorities will be reversed and the use of holography as a tool for investigating photochemistry will be discussed. Of course, it is sometimes difficult to draw a sharp distinction between the two approaches. Interesting photochemical results have emerged from the search for holographic materials³ and new approaches to holographic recording have resulted from the photochemical investigations.⁴

It would, of course, not be particularly wise to attempt to study photochemistry by studying the time development of holograms of toy trains. The arrangement actually used is much simpler and is shown in Figure 2. The hologram is produced by the interference of two mutually coherent plane waves. The interference pattern is thus a simple sinusoidal variation of light intensity across the sample. The resulting

(1) J. B. DeVelis, and G. O. Reynolds, "Theory and Applications of Holography", Addison-Wesley, Reading, MA, 1967.

(2) W. J. Tomlinson, and E. A. Chandross, *Adv. Photochem.*, **12**, 201 (1980).

(3) W. J. Tomlinson, E. A. Chandross, R. L. Fork, C. A. Pryde, and A. A. Lamola, *Appl. Opt.*, **11**, 533 (1972); A. Bloom, R. A. Bartolini, and D. L. Ross, *Appl. Phys. Lett.*, **24**, 612 (1974); A. Bloom, R. A. Bartolini, P. L. K. Hung, and D. L. Ross, *ibid.*, **29**, 483 (1976).

(4) C. Bräuchle, U. P. Wild, D. M. Burland, G. C. Bjorklund, and D. C. Alvarez, *Opt. Lett.*, **7**, 177 (1982); *IBM J. Res. Dev.*, **26**, 217 (1982).