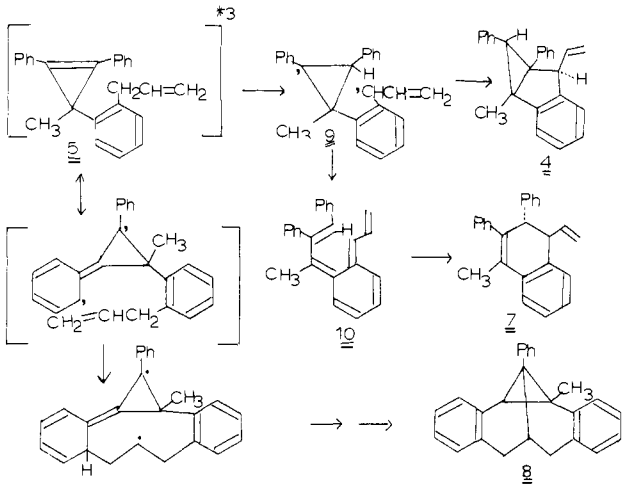
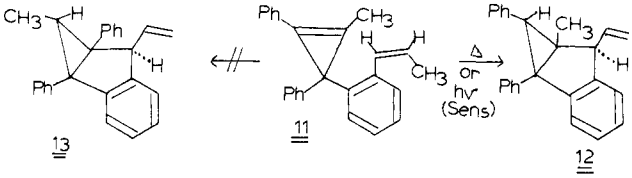
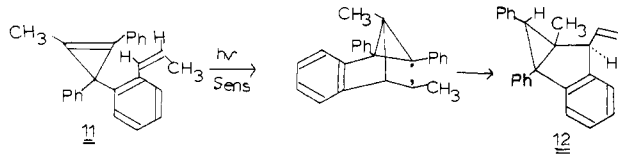


interesting reaction which merits some comment. The mechanism of this transformation may be pictured as proceeding by attack of the ortho position of the triplet state of **5** on the terminal vinyl carbon followed by diradical coupling and subsequent aromatization.[18]

We have also investigated the ene reaction of an unsymmetrically substituted cyclopropene. Thermolysis of (*Z*)-1,3-diphenyl-2-methyl-3-(*o*-1-propenylphenyl)cyclopropene (**11**) gave benzobicyclohexene **12** as the exclusive product in 98% yield: NMR (C_6D_6, 90 MHz) δ 1.35 (s, 3 H), 2.15 (s, 1 H), 4.10 (d, 1 H, J = 8.0 Hz), 5.17–5.46 (m, 2 H), 6.03 (ddd, 1 H, J = 16.7, 9.8, and 8.0 Hz) and 6.51–7.28 (m, 14 H). This reaction is completely regiospecific and involves hydrogen transfer to the carbon bearing the phenyl group. The sensitized irradiation of **11** afforded benzobicyclohexene **12** in 80% yield.[19] No signs of



the isomeric benzobicyclohexane **13** could be detected in the crude photolysate. A mechanism involving hydrogen transfer from the allylic methyl group to the triplet π–π^* excited state followed by diradical coupling cannot rationalize the regiochemistry obtained. This process would be expected to give rise to benzobicyclohexene **13**. We had previously demonstrated that unsymmetrically substituted cyclopropenes transfer hydrogen exclusively to the carbon bearing the methyl group.[17] The regiospecificity associated with the hydrogen-transfer reaction was attributed to formation of the most stable diradical intermediate.[17] The exclusive formation of bicyclohexene **12** in the sensitized irradiation is best explained by a mechanism involving π–π bridging to give the most stable diradical which undergoes a subsequent disproportionation reaction.



Frontier molecular orbital theory nicely rationalizes the exclusive formation of benzobicyclohexene **12** from the thermolysis of **11**. The thermal "ene" reaction has been described in terms of a three-orbital interaction among the HOMO of the π bond in the alkyl olefin, the LUMO of the π bond of the enophile, and the LUMO of the C–H bond of the olefin.[8] Recent MO calculations concerning the ene process suggest that C–C bond formation is much more developed in the transition state than C–H bond formation. According to perturbation theory, the regioselectivity associated with the ene reaction is the result of best orbital overlap,[20] i.e., the atoms with the largest orbital coefficients combine preferentially. The orbital coefficients of the HOMO and LUMO of 1-phenylpropene are presented in generalized form by the size of the orbital lobes in Scheme I. The large coefficient is found at the methyl substituted carbon atom in both the HOMO and LUMO.[20] The coefficient on the carbon end of the ene component is much larger than on the hydrogen atom.[8] Consequently, the MO perturbation treatment of the frontier orbital interaction of 1-phenylpropene with itself predicts that hydrogen transfer will occur on the carbon atom bearing the phenyl group. This is exactly what happens in the thermal ene reaction of the unsymmetrical cyclopropene **11**.

Acknowledgment. We gratefully acknowledge support of this work by the National Science Foundation.

(18) An alternate possibility involves initial bond formation via a six-membered transition state to give a primary radical which undergoes subsequent cyclization onto the ortho position of the aromatic ring.

(19) Benzotricycloheptene **12** was obtained as a mixture of exo and endo isomers. In addition, a 20% yield of a [2 + 2] intramolecular cycloadduct was obtained as the minor component. Complete details will be provided in a later publication.

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Azide Photoaffinity Analogues for Acridine Dye Binding Sites[1]

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The antimalarial agent and flavin antagonist quinacrine[2] (I, 3-chloro-9-[[4-(diethylamino)-1-methylbutyl]amino]-7-methoxyacridine) interacts with enzyme active sites, notably those which use flavin as a cofactor, e.g., D-amino acid oxidase.[3-5] We report here the synthesis and some chemical and photochemical properties of a quinacrine analogue (II, 3-azido-9-[[4-(diethylamino)-1-methylbutyl]amino]-7-methoxyacridine). This molecule may act as a photoaffinity label at quinacrine binding sites. Also there is potential for the use of the acridine azide intermediates in the synthesis of compounds which can act both as photoaffinity labels in enzyme systems binding quinacrines or similar acridines and as photoactivatable mutagenic agents.[6,7]

Quinacrine and a variety of related acridine derivatives exhibit changes in intrinsic fluorescence on binding with enzymes and other macromolecular systems. These and subsequent changes in fluorescence of the bound acridine associated with interactions at other nearby sites in a macromolecular complex provide useful information about the system. For example, the fluorescence changes for quinacrine associated with energy transducing membranes, e.g., submitochondrial particles,[8,9] chloroplasts, and chromatophores,[10] appear to report on an energy-linked function

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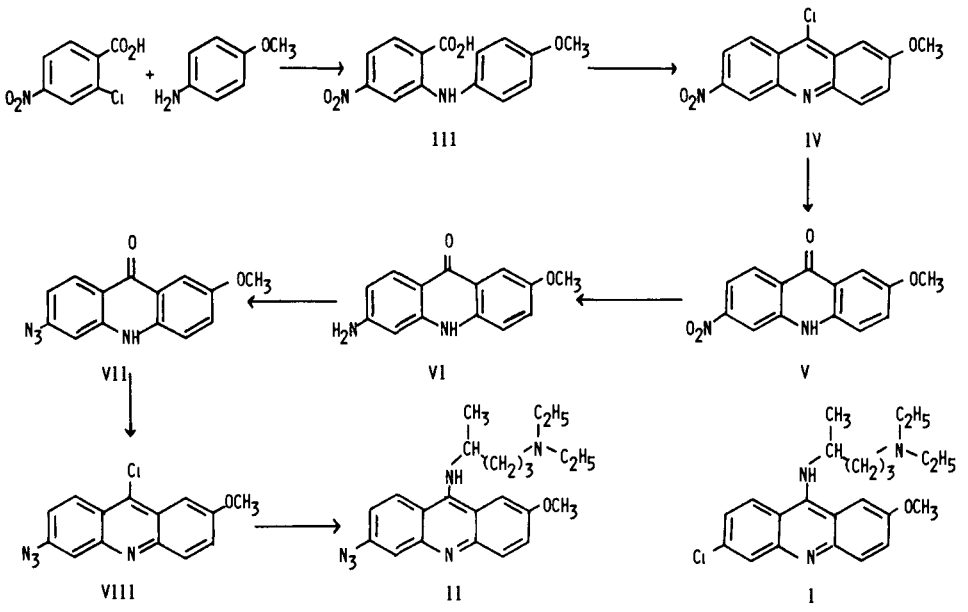

Figure 1. Synthesis of 3-azido-9-[[4-(diethylamino)-1-methylbutyl]amino]-7-methoxyacridine.

associated with the generation of a proton gradient. Also, quinacrine bound to the local anesthetic site of the nicotinic acetylcholine ionophore in membrane vesicles from the electric organ of *Torpedo marmorata* has provided a fluorescent probe useful in the analysis of the coupling of the ionophore with the acetylcholine receptor system.[11,12] In addition to its interaction with protein sites, quinacrine also functions as an intercalating dye, and the specific nature of its interaction with DNA structure is a matter of continuing interest.[13-17] The biological action of acridines in some systems has been suggested to be primarily due to their ability to complex with intracellular DNA.[18] Indeed, quinacrine complexation with DNA in vivo has been inferred from its use as a chromosomal fluorescence stain and from its ability to eliminate bacterial plasmids.[19] We have synthesized II in order to covalently label and identify the metabolic, energy-linked binding sites for the dye in submitochondrial particles. Preliminary accounts[20,21] of this work have shown that the fluorescence properties of the azide analogue monitor the energy-linked function and irradiation of the azide bound to submitochondrial particles results in photoinduced cross-linking reactions between the quinacrine azide and protein components of the membrane.

Figure 1 shows the structure of quinacrine (I), quinacrine azide (II), and the intermediates formed in the preparation of the latter. Our choice of the azide analogue shown was motivated by the presumed minimal effect on the properties of the dye brought about by replacement of the chlorine substitutent with the pseudohalogen azide group.[22,23] Since direct nucleophilic displacement of chloride by azide at this relatively inactivated position of the acridine ring system was not feasible, de novo construction of the acridine was considered the only appropriate alternative. This was accomplished by using analogous or known chemistry to obtain intermediate VI as a starting point in the synthesis of II.

2-Chloro-4-nitrobenzoic acid and *p*-anisidine were converted to III (mp 235–237 °C) in 75% yield by a slight modification of the procedure of Albert and Gledhill[24] for the synthesis of the corresponding ethoxy acid. Cyclization gave IV (mp 217–218 °C, lit.[25] 215 °C) in 80% yield. Refluxing IV in 10% aqueous hydrochloric acid gave the intermediate acridone (V) in 95% yield.[25] V was converted to the aminoacridone (VI) by refluxing for 3 h in 5% aqueous hydrochloric acid containing 1.1 equiv of stannous chloride. The product was crystallized from pyridine–water and was obtained in 90% yield, mp 294 °C (lit.[25] 290 °C).

The aminoacridone (VI) was diazotized in aqueous 2.5% hydrochloric acid at 4 °C by addition of 1.3 equiv of sodium nitrite in small portions over a 20-min period. The solution was stirred for an additional hour after which 2.1 equiv of sodium azide were added in small portions in the dark (all synthetic operations from this point were conducted in the dark in a fume hood). The solution was stirred an additional hour, made alkaline with sodium hydroxide, and the precipitated azidoacridone product (VII) filtered and dried over phosphorus pentoxide. The yield of crude product, which was used as such for the next step, was 98%. Recrystallization from pyridine–water gave an analytical sample: mp 200 °C, dec; ν_{max} ($CHCl_3$) 2120 cm^{-1}. Anal. Calcd for $C_{14}H_{10}N_4O_2$: C, 63.15; H, 3.79; N, 21.04. Found: C, 63.15; H, 3.69; N, 20.51.

The azidoacridone (VII) was heated for 3 h at 110 °C in phosphorus oxychloride which contained 3% concentrated hydrochloric acid (v/v). The excess phosphorus oxychloride was removed in vacuo and the reddish residue was dissolved in minimal chloroform and added to a vigorously stirred solution of 10% aqueous ammonium hydroxide. The precipitated product was filtered and dried over phosphorus pentoxide, subsequently taken up in chloroform, and passed through a column of silica gel. The azidochloroacridine product (VIII) was eluted from the column first, and most (ca. 70%) of it was obtained before a second more polar impurity was eluted. The desired product was then crystallized from chloroform–methanol. The polar impurity was

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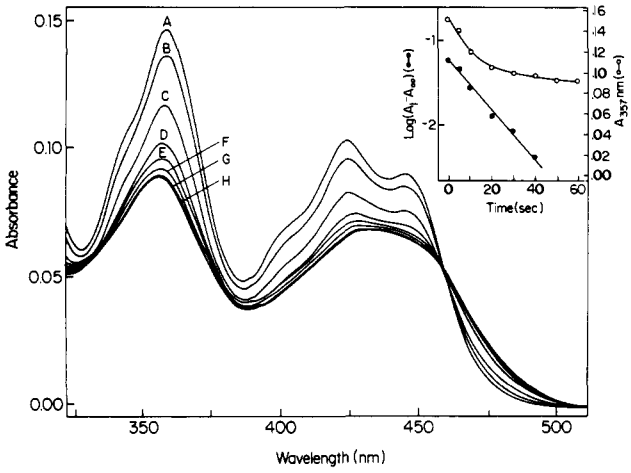

Figure 2. Visible absorption spectra at 25 °C for the photodecomposition of 3-azido-9-[[4-(diethylamino)-1-methylbutyl]amino]-7-methoxyacridine. Spectra A–H correspond to 0, 5, 10, 20, 30, 40, 50, and 60-s irradiations of a 1.078×10^{-5} M solution of the azide in 30 mM phosphate, pH 3.0. The solutions were irradiated in a Rayonet RPR-100 photochemical reactor using four RPR-3500-A lamps. The inset plots show A_{357} (○) and the logarithm of the observed A_{357} minus A_{357} observed at 60-s irradiation time (●) against time.

removed in this way. The yield of crystalline product was 50%: mp 161–162 °C, dec; ν_{max} ($CHCl_3$) 2120 cm^{-1}. Anal. Calcd for $C_{14}H_9N_4ClO$: C, 59.06; H, 3.19; N, 19.68; Cl, 12.45. Found: C, 59.04; H, 3.22; N, 19.53; Cl, 12.40.

Displacement of the chloro substituent from VIII to give the quinacrine azide analogue II was carried out by heating a mixture of the 2-amino-5-(diethylamino)pentane (1.33 equiv) with the chloroacridine (VIII) and phenol at 100 °C for 3 h. The mixture was then taken up in ether and dry hydrogen chloride gas bubbled through it to precipitate the hydrochloride salt: mp 173 °C, dec; ν_{max} ($CHCl_3$) 2110 cm^{-1}. Anal. Calcd for $C_{23}H_{29}N_6O \cdot 2HCl \cdot H_2O$: C, 55.53; H, 6.89; N, 16.89; Cl, 14.24. Found: C, 55.37; H, 6.43; N, 16.44; Cl, 13.78.

Figure 2 shows the photosensitivity of the quinacrine azide product which appears to smoothly decompose in a 60-s irradiation with 350-nm light. The inset plot for Figure 2 shows the absorbance plotted for the 357-nm maximum and log (A_i – A) plotted against time. A $t_{1/2}$ of 8–10 s is observed for the first-order photodecomposition. Similar data are obtained from the absorbances at 423 nm. An isosbestic point at 460 nm is also observed for the photodecomposition reaction. The photosensitivity of II is not pH dependent. Photodecomposition kinetics virtually identical with those seen in Figure 2 have been observed at pH 7.2 (30 mM phosphate). We have not investigated the photochemical products for the irradiation of II or any of the other azido intermediates all of which are comparably photosensitive. It is important to note that most biological systems are relatively insensitive to irradiation with 350-nm light of such intensity and duration as is needed to photodecompose II. The photosensitivity of II appears to be comparable to other organic azides which have proven useful in photochemical labeling.[26]

Both work in our laboratory and elsewhere suggest that these azides will prove useful in photochemical labeling experiments. Mair and Stevens[6] have shown that azide in the 3-position on the acridine ring gives rise on irradiation to complex mixtures of products which they assumed to result from a variety of reactions of the generated reactive nitrene. In our more biologically interesting azidoacridines there is a similar photoproduct complexity. In contrast Mair and Stevens showed that the azide in the 9-position of the acridine ring results in a long-lived nitrene. Such nitrenes may survive many collisions with solvent and form an azo dimer as a principal product. Other positions of the acridine ring do not appear to have been investigated.

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Ethylidenation of Olefins Using a Convenient Iron-Containing Cyclopropanation Reagent[1]

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Large numbers of methods have been developed previously for the synthesis of cyclopropanes, usually through use of olefins as starting materials.[2] Among the most commonly used procedures are the Simmons–Smith reaction and related methods.[2e] However, the vast majority of the cases in which these methods are employed involve the transfer of simply the methylene group to olefins to give relatively simple cyclopropanes. Some exceptions are the transfer of the benzylidene group[3] and, in a very few cases, the transfer of the ethylidene group.[3,4] However, these latter reactions commonly occur in disappointingly low yields. Certainly, alkylidene transfer in general has not been shown to be a synthetically attractive operation.

Earlier we had reported the use of reagent **1** for the methylenation of olefins.[5] The development of this methodology was

$$CpFe(CO)_2CH_2S^+(CH_3)_2\ BF_4^-$$
1

$$CpFe^+(CO)_2{=}CH_2$$
2

$$CpFe^+(CO)_2{=}CHCH_2CH_3$$
3

$$CpFe^+(CO)_2(H_2C{=}CHCH_3)$$
4

based upon previous studies of others concerned with the iron–carbene complex **2** and closely related derivatives.[6] Because of

(1) This work was presented in part at the following meetings and symposia: (a) "Abstracts of Papers", 177th National Meeting of the American Chemical Society, Honolulu, HI, April, 1979; American Chemical Society: Washington, DC, 1979; ORGN 255. (b) 9th International Conference on Organometallic Chemistry, Dijon, France, Sept., 1979, Abstract No. B4; (c) 9th Northeast Regional Meeting of the American Chemical Society, Syracuse, NY, Oct, 1979; American Chemical Society: Washington, DC, 1979. ORGN 1. (d) International Symposium on Metallo-organics in Organic Synthesis, Swansea, Wales, July, 1980.

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