

ALKALOID PHOTOCHEMISTRY

(for a nice review of photochemistry of alkaloids prior to 1980 see Singh, A. P.; Stenberg, V. I.; Parmar, S. S. Chem. Rev. 1980, 80, 269-282)

I. Introduction:

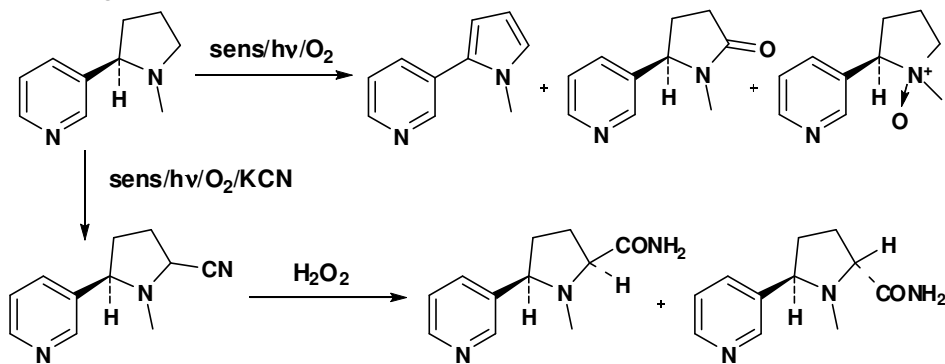
The photochemistry of alkaloids represents a field rich in diversity including oxidation, reduction, dimerization, addition, hydrogen abstraction, dealkylation, epimerization, isomerization and degradation. Yet 60 years after Weil's¹ observation of the photochemical oxidation of nicotine, much remains to be discovered in this field.

Alkaloid photochemistry includes a wide variety of chromophoric substrates including: pyrrolidine, piperidine, pyridine, quinoline, isoquinoline, and indole, and come from a various alkaloid classes, colchicine, isocolchicine, tropane, opium, ergot, strychnose, steroid and others.

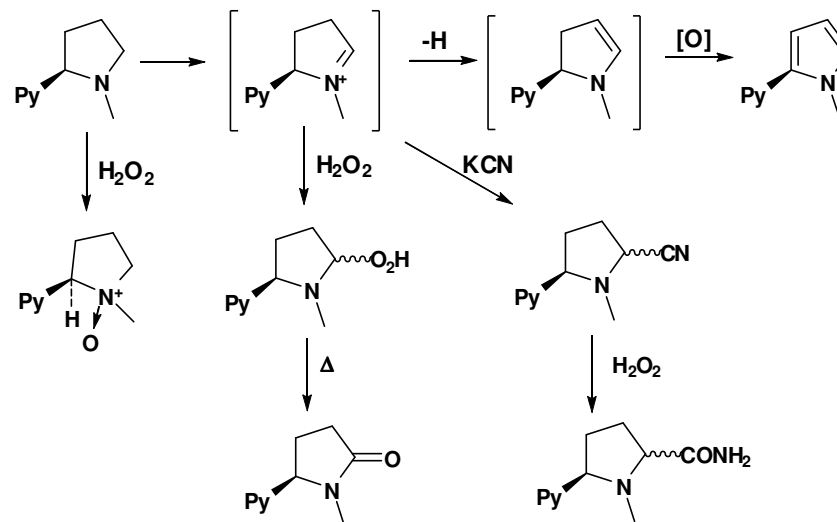
The survey to follow will primarily feature nitrogen as the key participant for both sensitized and direct photochemically induced reactions.

II. Pyrrolidine, Piperidine, and Pyridine Alkaloids:

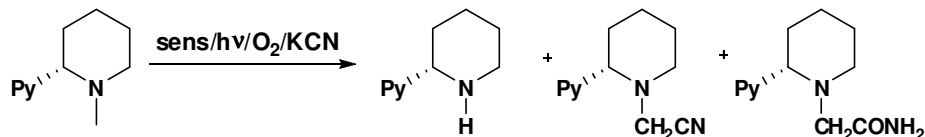
Upon irradiation of a methanolic solution of nicotine in the presence of O₂ and methylene blue, Hubert-Brierre and co-workers observed the formation of nicotyrine, cotinine, and nicotine N-oxide (Hubert-Brierre, Y.; Herlem, D.; Khuong-Huu, F. Tetrahedron 1975, 31, 3049-3054).



The following scheme represents a likely pathway for the observed products (see Santamaria, J. Pure & Appl. Chem., 1995, 67, 141-147).



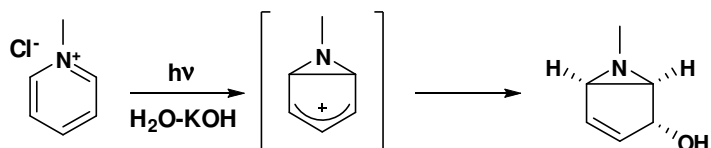
Hubert-Brierre and co-workers also investigated the irradiation of *N*-methyl-anabasine under a similar set of conditions.



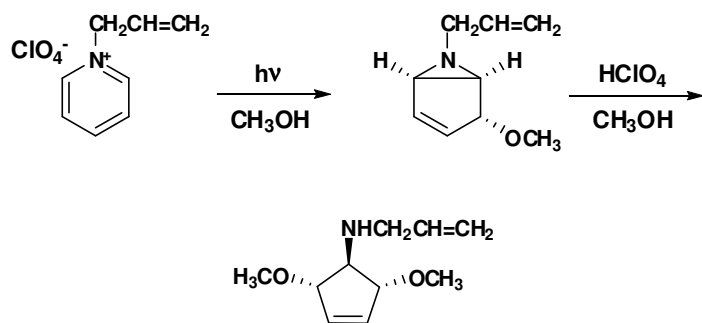
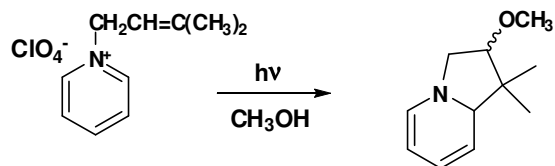
The observation of the *N*-demethylated compound, an aminonitrile and a carboxamide lead to the conclusion that the oxidation with the six membered ring is exocyclic vs. the five membered ring which was endocyclic.

Photohydration of Pyridinium ions first observed by Kaplan and Wilzbach (Kaplan, L.; Pavlik, J. W.; Wilzbach, K. E. *J. Am. Chem. Soc.* 1972, 94, 3283-3284) went nearly unnoticed for 10 years before Mariano and co-workers described their observations of the divergent photochemical behavior of *N*-allylpyridinium perchlorates (Yoon, U. C.; Quillen, S. L.; Mariano, P. S.; Swanson, R.; Stavinoha, J. L.; Bay, E. J. *J. Am. Chem. Soc.* 1983, 105, 1204-1218).

Kaplan (1972):



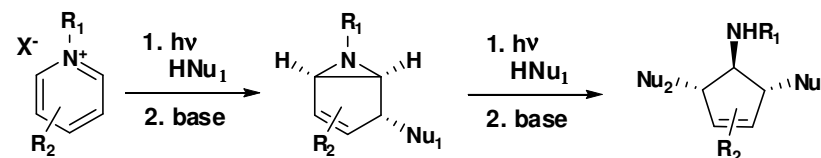
Mariano (1983):



Thirteen years after their first observations with the pyridinium salt photocyclization process, Mariano and co-workers returned to this area and have subsequently reported on several occasions their investigations into the potential synthetic power of a tandem sequences involving:

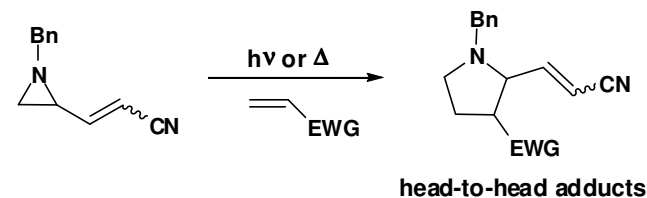
- (1) photoinduced cyclization of pyridinium cations
- (2) stereocontrolled nucleophile addition to produce bicyclic aziridines, and
- (3) stereocontrolled nucleophilic cleavage of the bicyclic aziridine to produce highly functionalized aminocyclopentenes.

(Ling, R.; Yoshida, M.; Mariano, P. S. *J. Org. Chem.* 1996, 61, 4439-4449, Song, L.; Duesler, E. D.; Mariano, P. S. *J. Org. Chem.* 2004, 69, 7284-7293).



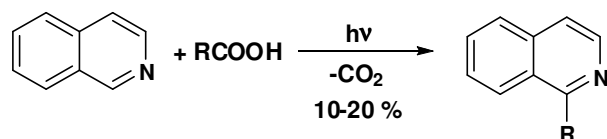
Ila. β -aziridinylacrylonitriles and acrylates:

It has been well established that heating or irradiating aziridines, usually bearing an adjacent electron-withdrawing group, results in the formation of azomethane ylides. The 1,3-dipolar cycloaddition of azomethane ylides with alkenes plays an important role in the synthesis of nitrogen containing five-membered rings (see Ishii, K. et. al. *Tetrahedron* 2004, 60, 10887-10898 and references within for some examples).



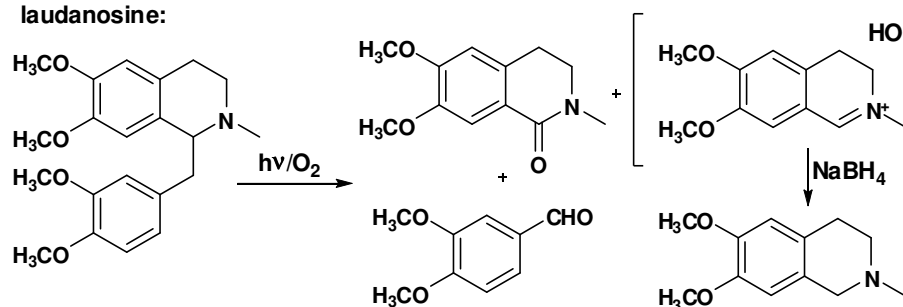
III. Isoquinoline Alkaloids:

Noyori and co-workers observed that irradiation of equimolar quantities of isoquinoline and the appropriate carboxylic acids in benzene resulted in the formation of the corresponding 1-alkylisoquinolines in poor yield (Noyori, R.; Lato, M.; Kawanisi, M.; Nozaki, H. *Tetrahedron* 1969, 25, 1125-1169).

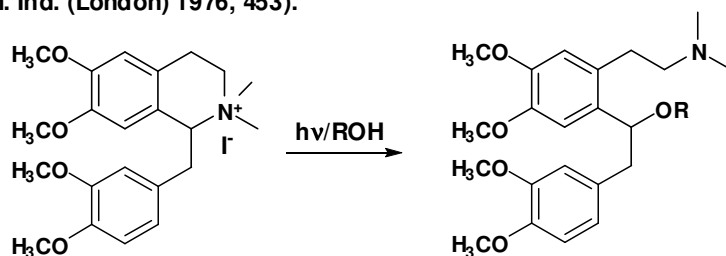


Bick and co-workers reported the photo-oxidative cleavage of some benzylisoquinoline-based alkaloids (Bick, I. R. C.; Bremner, J. B.; Wiriyaichitra, P. *Tet. Lett.* 1971, 50, 4795-4797).

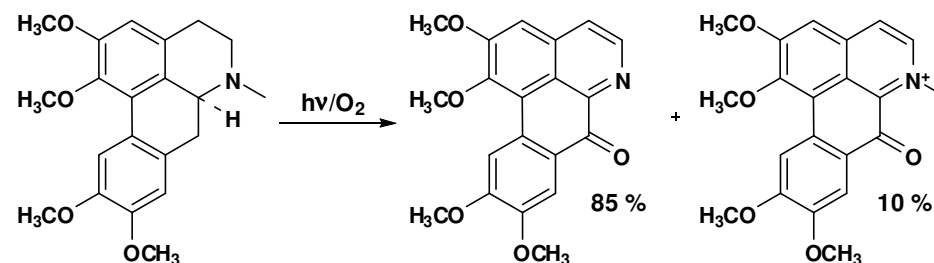
laudanosine:



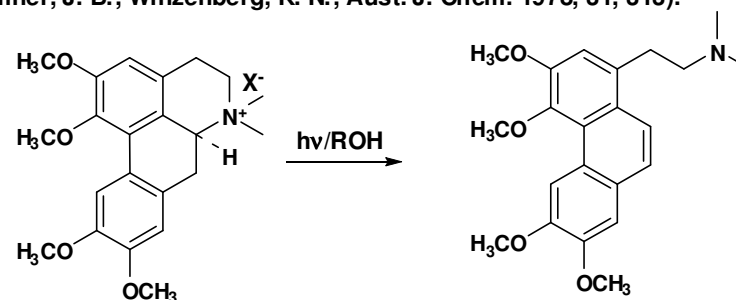
Photosolvolysis of laudanosine methylidide (Bremner, J. B.; Thuc, L. V. *Chem. Ind. (London)* 1976, 453).



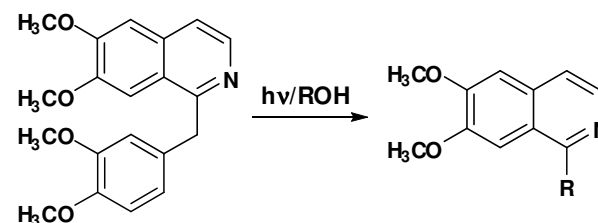
Direct photooxidation of glaucin gave *O*-methylatheroline (85 %) and corunnine (10 %) (Castedo, L.; Suau, R.; Mourino, A. *An. Quim.* 1977, 73, 290).



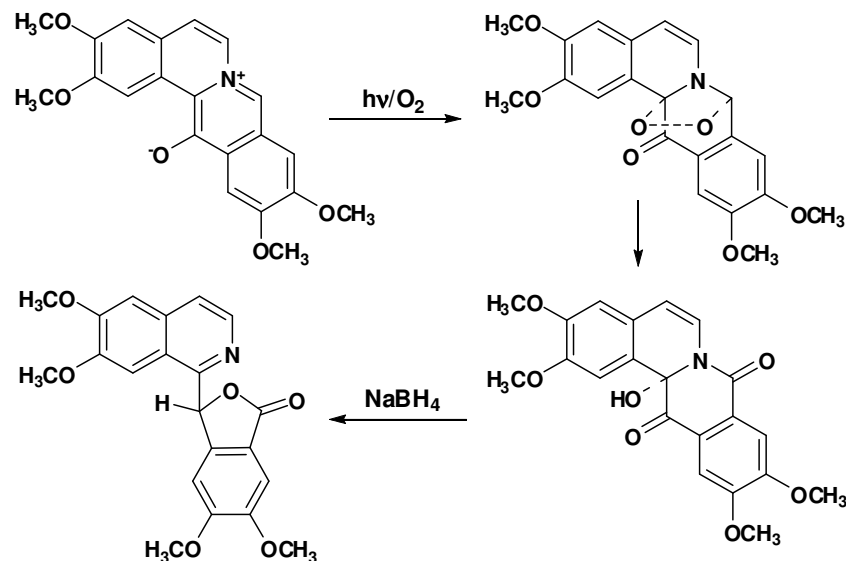
Photoinduced elimination products were obtained in moderate to high yield upon irradiation of a methanolic solution of the quaternary salt of glaucine (Bremner, J. B.; Winzenberg, K. N.; *Aust. J. Chem.* 1978, 31, 313).



Stermitz and co-workers made the following observation of the irradiation of alcoholic solutions of papaverine (Stermitz, F. R.; Seiber, R. P.; Nicodem, D. E.; *J. Org. Chem.* 1968, 33, 1136-1140).

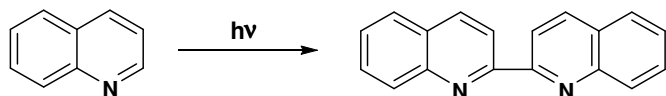


Many have observed the biogenetic conversion protoberberine-type alkaloids into phthalideisoquinoline alkaloids (see Kondo, Y.; Imai, J.; Nozoe, S. *J. Chem. Soc. Perkin Trans. I* 1980, 919-923).

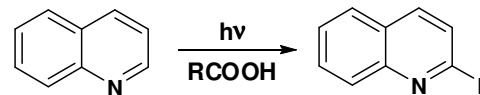


IV. Quinoline Alkaloids:

Quinoline suffers dimerization upon irradiation in alcoholic solution (Pfordte, K.; Leuschner, G. *Justus Liebigs Ann. Chem.* 1061, 30, 646).

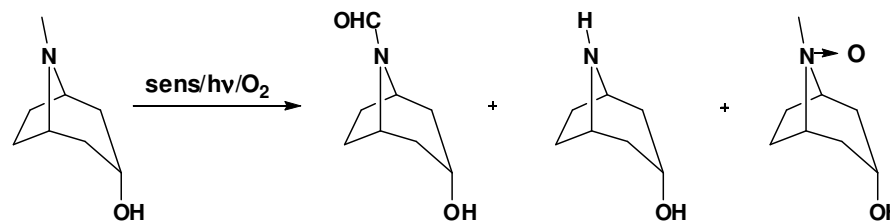


Noyori and co-workers observed that irradiation of equimolar quantities of quinoline and equimolar quantities of the appropriate carboxylic acids in benzene resulted in the formation of the corresponding 2-alkylquinolines in low yield (Noyori, R.; Lato, M.; Kawanisi, M.; Nozaki, H. *Tetrahedron* 1969, 25, 1125-1169).



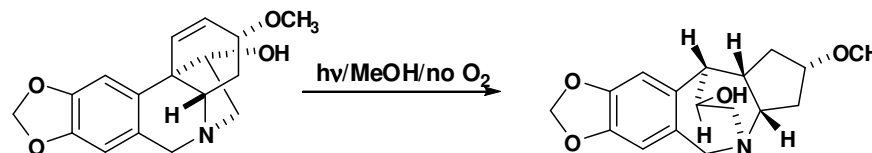
V. Tropane alkaloids:

The irradiation of a methanolic solution of tropanol in the presence of a sensitizer gave formamido, demethylated and *N*-oxytropanol products (Herlem, D.; Hubert-Briere, Y.; Khuong-Huu, F.; Goutarel, R. *Tetrahedron* 1973, 29, 2195-2202).



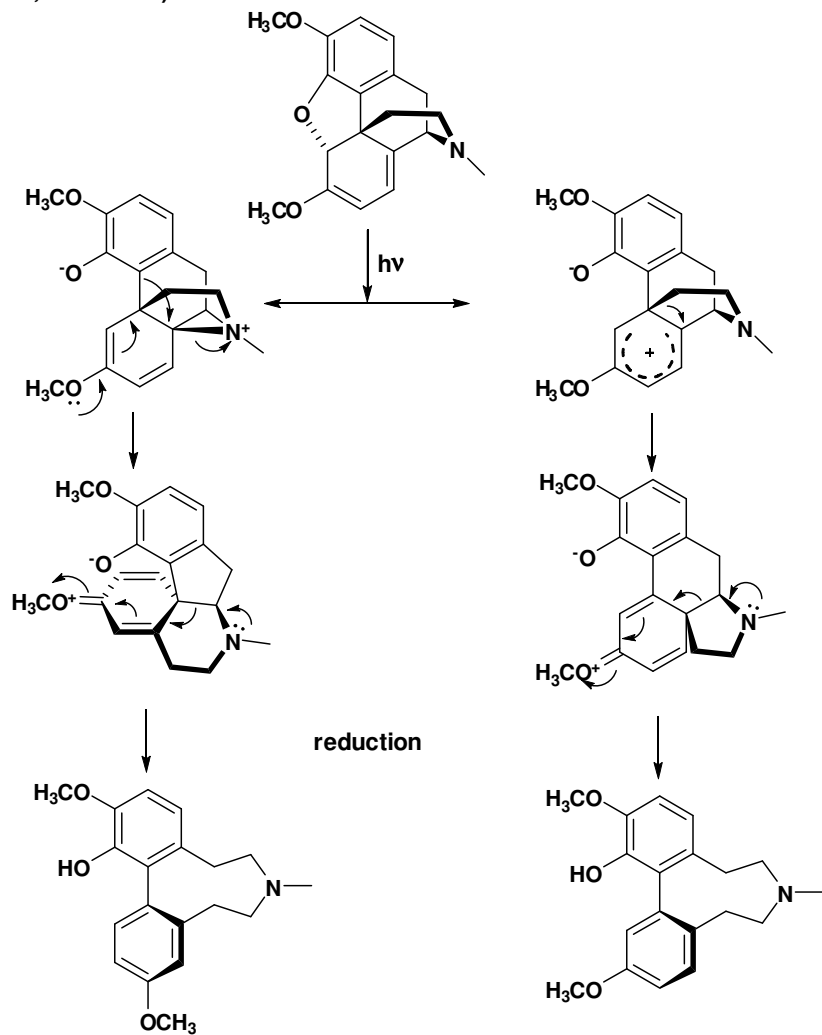
VI. Amaryllidaceae Alkaloids:

The photolysis of crinamine in MeOH under N_2 gave the following result (Tsuda, Y.; Kanede, M.; Takagi, S.; Yamaki, M.; Iitaka, Y. *Tet. Lett.* 1978, 19, 1199-1200).

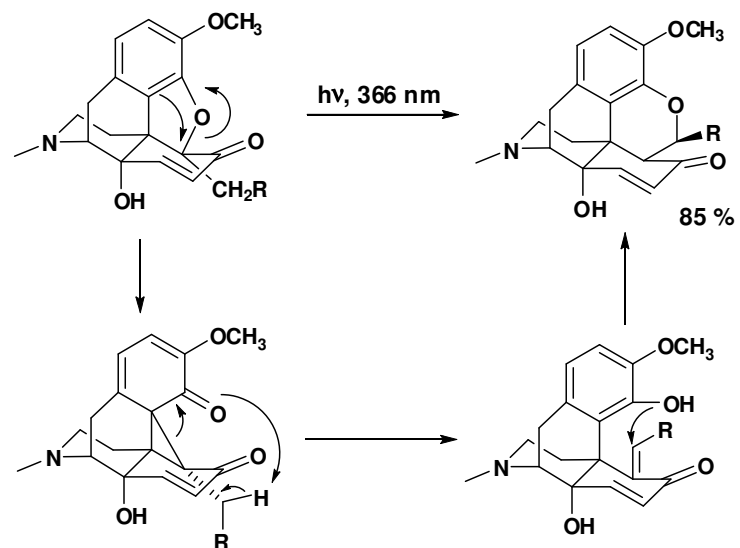


VII. Opium Alkaloids:

Theuns and co-workers reported the biomimetic synthesis of neodihydrothebaine and bractazonine via simple irradiation of thebaine and subsequent reduction (Theuns, H. B.; Vos, G. F.; ten Noever de Braw, M. C.; Salemink, C. A.; *Tet. Lett.* 1984, 25, 4161-4162).

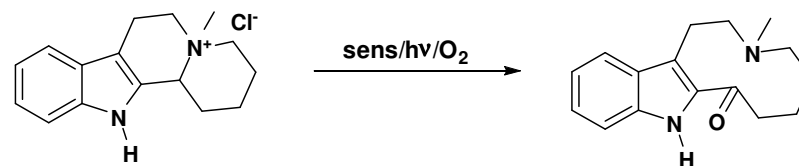


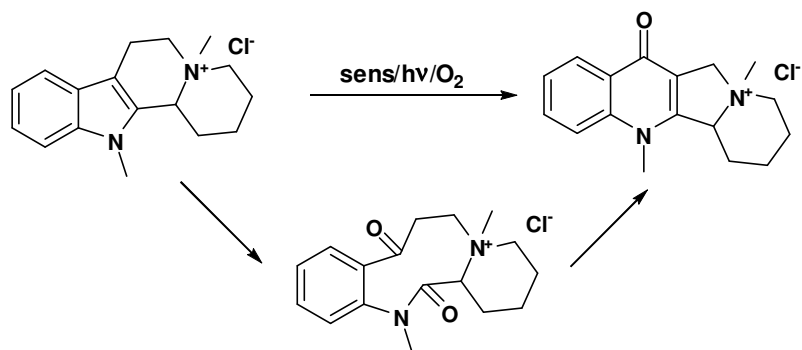
Lotfy and co-workers have recently disclosed their observations of the irradiation of variably substituted codeinones and morphinones (Lotfy, H. R.; Schultz, A. G.; Metwally, M. A.; *Russ. J. Org. Chem.* 2003, 39, 1261-1263).



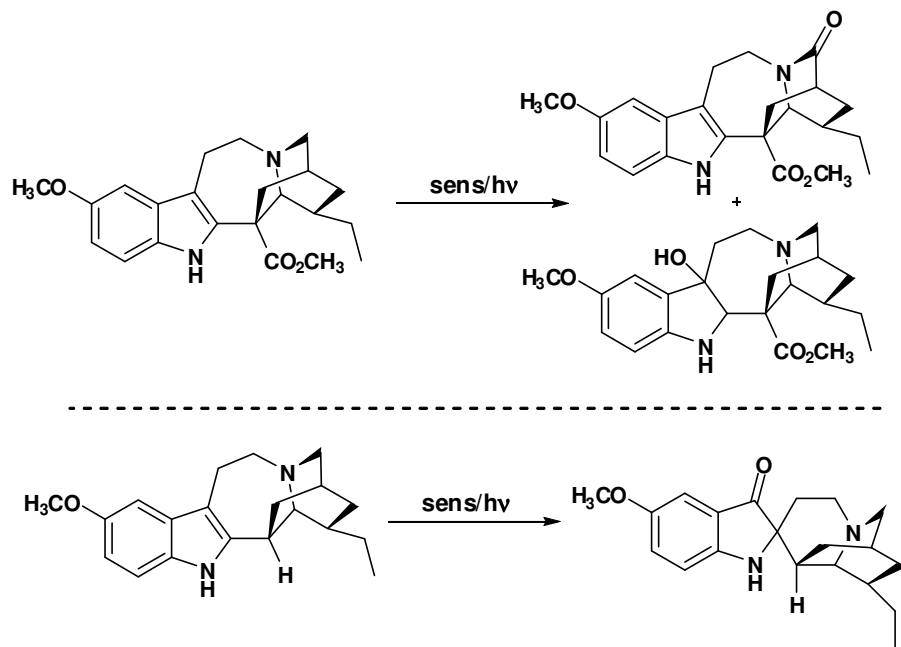
VIII. Indole Alkaloids:

Nakagawa and co-workers reported the results of irradiation of indoloquinolizide chloride and its 1-methyl derivative in the presence of a sensitizer (Nakagawa, M.; Okajima, Y.; Kobayashi, K.; Asaka, T.; Hino, T. *Heterocycles* 1975, 3, 799-803).

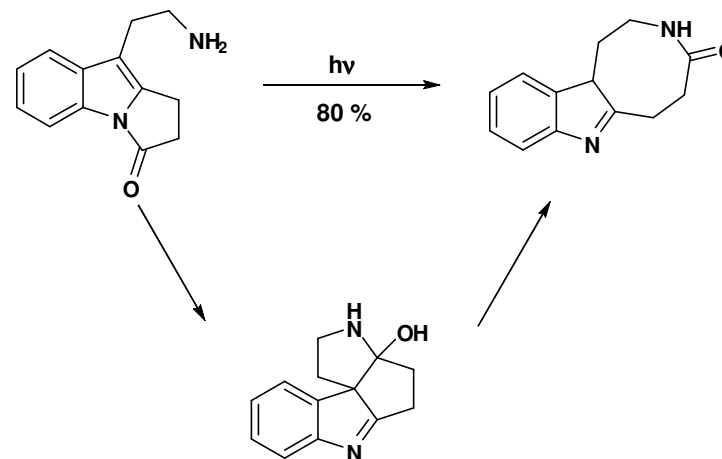
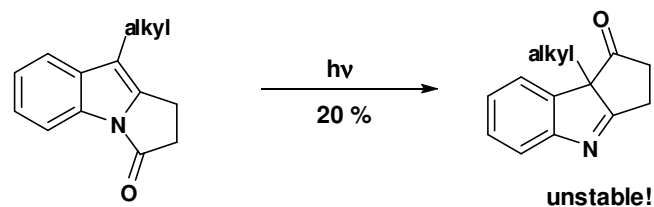
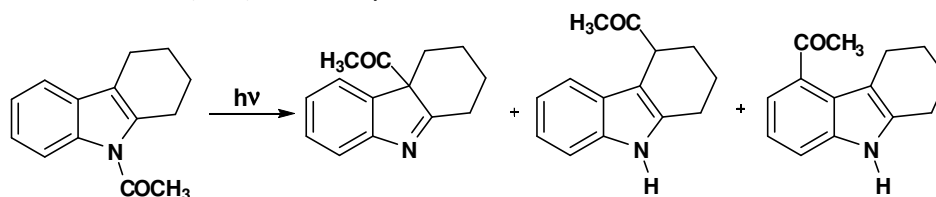




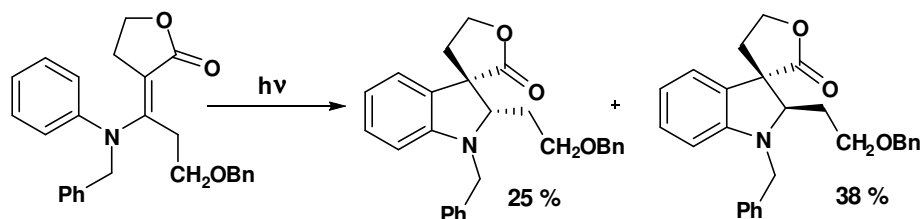
An interesting observation was made by Guise, Ritchie and Taylor regarding the difference in irradiation products of voacangine and ibogaine (Giuse, G. B.; Ritchie, E.; Taylor, W. C.; Aust. J. Chem. Soc. 1965, 18, 279-286).



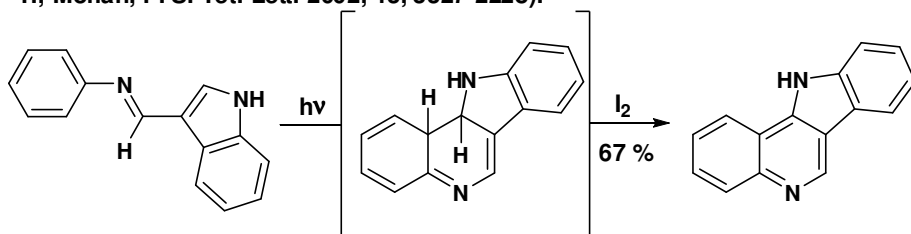
Enamide photochemistry is well known and its useful application has been thoroughly investigated. Simple enamides generally undergo a [1,3]-acyl radical shift to afford vinylogous amides. Below are examples of the photorearrangement of 1-acylindoles to 3-acylindolenines (Ban, Y.; Yoshida, K.; Goto, J.; Oishi, T. J. Am. Chem. Soc. 1981, 103, 6990-6992).



Sinibaldi and co-workers have demonstrated the feasibility for a photochemical approach to 3,3-spiro indolines (Ibrahim-Ouali, M.; Sinibaldi, M. E.; Troin, Y.; Cuer, A.; Dauphin, G.; Gramain, J-C. *Heterocycles* 1995, 41, 1939-1950).

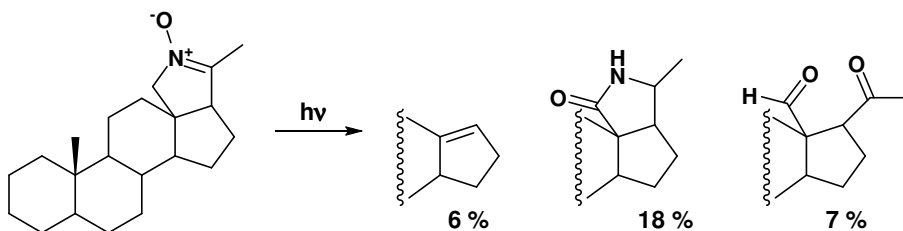


Cryptosanguinolentine was prepared by Mohan and co-workers as part of their program of synthesis of heteroannulated acridines, below is the formation of the tetracyclic system of cryptosanguinolentine (Nandha Kumar, R.; Suresh, T.; Mohan, P. S. *Tet. Lett.* 2002, 43, 3327-2228).



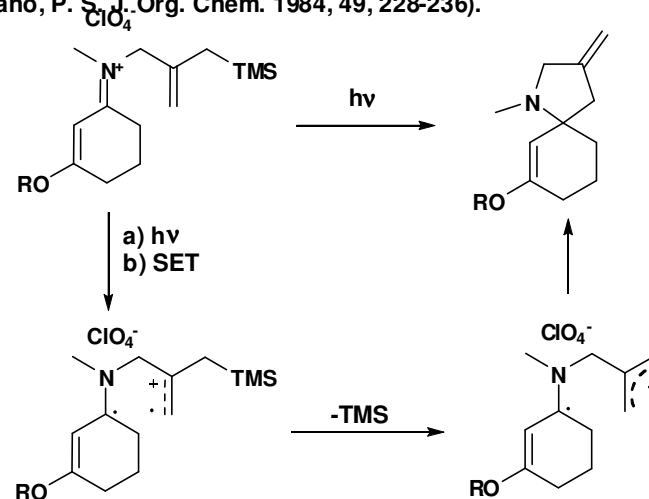
IX. Steroidal Alkaloids:

Irradiation of the steroidal alkaloid nitron in acetonitrile gave the following result (Parelo, J.; Beugelmans, R.; Millient et Xavier Lusinchi, P. *Tet. Lett.* 1968, 10, 5087-5092).

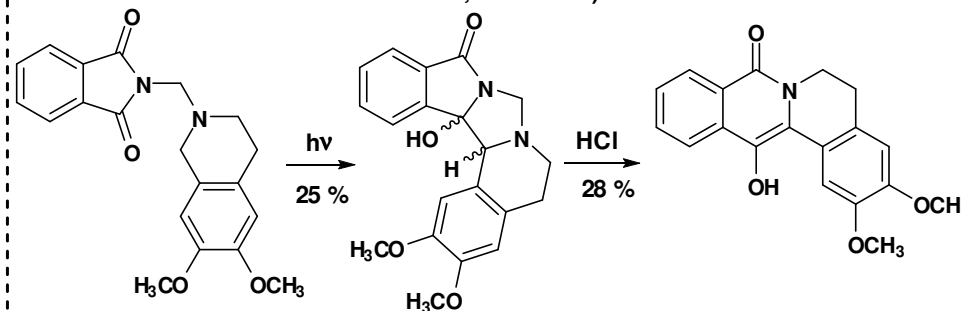


X. Misc. Examples of Photochemical Alkaloid Chemistry:

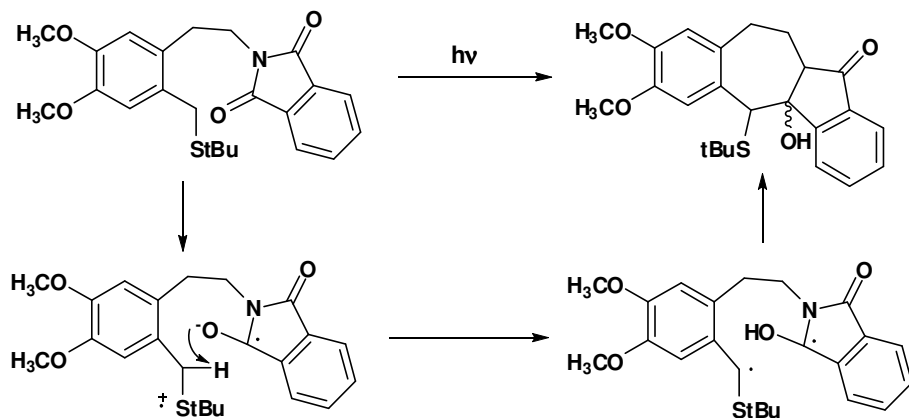
Electron-transfer photochemistry of allylsilane-iminium salt systems have been shown to serve as a viable carbon-carbon forming methodology (Chiu, F-T.; Ullrich, J. T.; Mariano, P. S. *J. Org. Chem.* 1984, 49, 228-236).



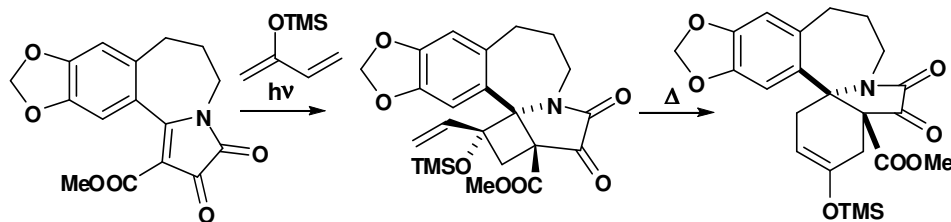
Coyle and co-workers have shown the irradiation of Mannich bases obtained from phthalimides, formaldehyde and 1,2,3,4-tetrahydroisoquinolines carrying methoxy substituents gives pentacyclic photoproducts (Coyle, J. D.; Bryant, L. R. B.; Cragg, J. E. *J. Chem. Soc. Perkin Trans. I* 1985, 1177-1180).



A similar transformation described by Kanaoka (Sato, Y.; Nakai, H.; Misoguchi, T.; Hatanaka, Y.; Kanaoka, Y. *J. Am. Chem. Soc.* 1976, 98, 2349-2350) has been employed by Mazzocchi in the synthesis of the functionalized ring system of Chilinene, a berberine alkaloid (Mazzocchi, P. H.; King, C. R.; Ammon, H. L.; *Tet. Lett.* 1987, 28, 2473-2476).



Tsuda and co-workers have employed a simple [2+2] cycloaddition of an activated butadiene to a dioxopyrroloisoquinoline followed by a 1,3-anionic rearrangement to fashion the core of erythrin alkaloids (Tsuda, Y.; Oshima, T.; Hosoi, S.; Kaneuchi, S.; Kiuchi, F.; Toda, J.; Sano, T. *Chem. Pharm. Bull.* 1996, 44, 500-508, for a review of light induced [2+2] cycloadditions see Crimmins, M. T. *Chem. Rev.* 1988, 88, 1453-1473).



In their investigation of elusive intramolecular hydrogen transfer reactions, Kessar and co-workers investigated the intramolecular photoreactions of 2-formyl benzamides and 2-formylbenzylamines (Kessar, S. V.; Singh Mankotia, A. K.; Agnihotri, K. R. *J. Chem. Soc. Chem. Commun.* 1993, 598-599).

