Photochemistry of Alkaloids

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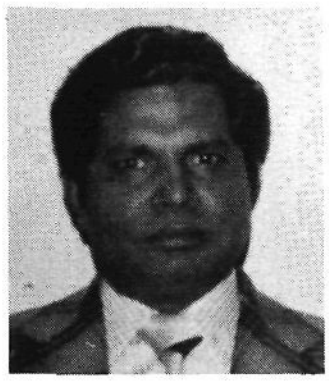

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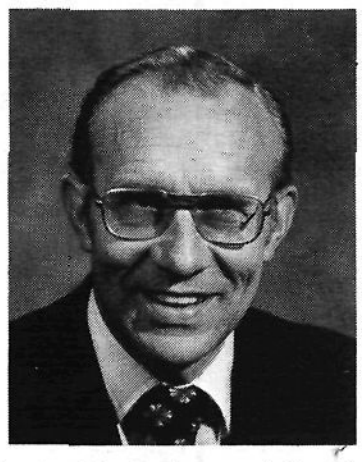

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I. Introduction and Scope

During the last few decades, a number of review articles on the various aspects of organic photochemistry, both mechanistic and preparative, have appeared in the literature. So far reviews have been written on the chemistry and pharmacological properties of the alkaloids, but none of these deals with the photochemistry of the alkaloids. Alkaloids constitute a major segment of organic natural product chemistry and manifest significant pharmacological activity. This review focuses on the fascinating photochemically induced rearrangements and transformations of the alkaloids.

The photochemistry of alkaloids is intriguing because of the wide array of new chemical reactions which are now on record in this group of biologically active compounds. Further, the rigid structure of the alkaloids is excellent for stereochemical analysis of photochemical reactions.

Alkaloid photochemistry includes a wide variety of chromophoric nuclei, pyrrolidine, piperidine, pyridine, quinoline, isoquinoline, and indole, and come from various alkaloid classes, colchicine, isocolchicine, tropane, opium, ergot, rauwolfia, strychnose, and steroid. A rich variety of photochemical reactions on alkaloids, such as oxidation, reduction, dimerization, addition, hydrogen abstraction, dealkylation, epimerization, and degradation, have been observed. Some of these reactions are now unique; that is, they are only known to occur by photochemical means and on the alkaloids.

A few of the reactions have potential for further development as preparative reactions to supplement the organic chemist's repertoire. Others provide challenging mechanistic problems to be solved. Interestingly, some of the photoproducts are also in vivo metabolites, like cocaine → norocaine and slaframine → ketoimine, and others are present in the plant, e.g., colchicine → β-lumicolchicine.

Insofar as mechanisms are concerned, the study of alkaloid photochemistry will feature nitrogen in the key role for both sensitized and direct photooxidations as well as the nonoxidative reactions. There are numerous refinements that can be done on many of the photochemical reactions to broaden the scope of each and optimize the yields.

II. Pyrrolidine, Piperidine, and Pyridine Alkaloids

Weil[1] reported the photochemical oxidation of nicotine (**1**) in presence of methylene blue but was unable to assign the structure of photoproducts of nicotine. However, evidence was presented that the chemical changes were occurring during

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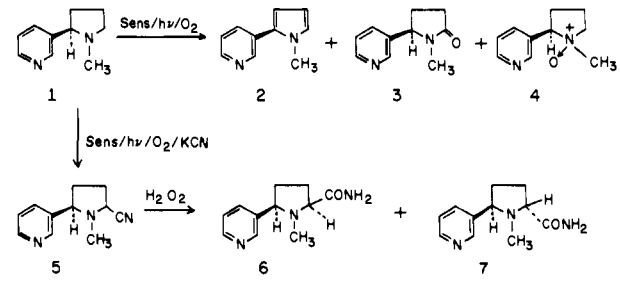
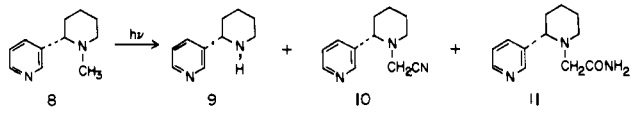
irradiation of nicotine at the *N*-methyl site of the pyrrolidine ring. Hubert-Brierre et al.[2] demonstrated that irradiation of a methanolic solution of nicotine in the presence of methylene blue and oxygen gave nicotyrine (**2**), cotinine (**3**), and nicotine *N*-oxide



4. In the presence of methylene blue, oxygen, and potassium cyanide, the reaction products were α-aminonitrile **5** and two carboxamide epimers, **6** and **7**. The addition of sodium pyruvate to the nicotine solution containing methylene blue, potassium cyanide, and oxygen gave only α-aminonitrile **5**. On the other hand, irradiation of nicotine in methanol under anaerobic conditions in the presence of eosine or eosine and potassium cyanide resulted in the formation of the photoproducts **2** and **5**, respectively. These results indicate that the site of the photochemical oxidation in the nicotine molecule remains the same but the products of oxidation will vary under different experimental conditions.

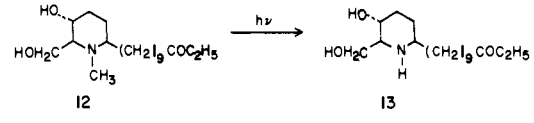
The irradiation of *N*-methylanabasine[2] (**8**), an analogue of nicotine, in methanol in the presence of methylene blue, potassium cyanide, sodium pyruvate, and oxygen gave three photoproducts, identified as a N-demethylated compound (**9**),

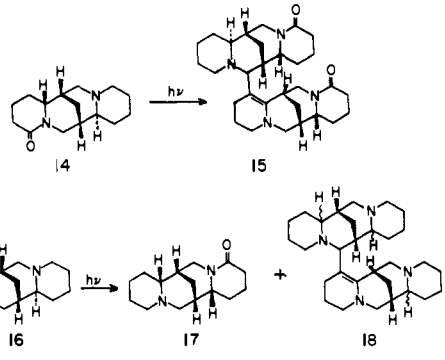


an aminonitrile (**10**), and a carboxamide (**11**). These results indicated that the oxidation of a five-membered heterocyclic ring occurs in an endocyclic fashion while in the six-membered ring it is exocyclic.

The various photoproducts of nicotine have been rationalized[3] and are illustrated in Scheme I.

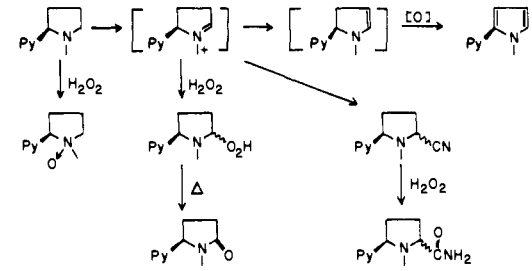
The photoproduct prosopinine (**13**) was obtained by irradiation of *N*-methylprosopinine (**12**) in ethanol in the presence of oxygen.[4] The aerobic irradiation of lupanine[4] (**14**) in methanol resulted in the formation of a dimeric photoproduct (**15**). Under





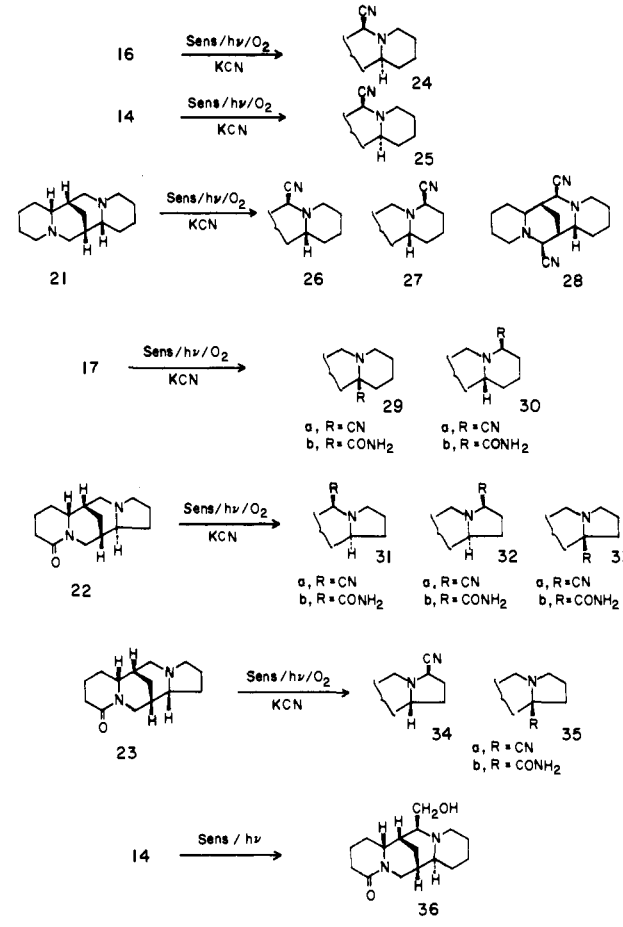
similar experimental conditions, sparteine[4] (**16**) gave isolupanine (**17**) and a dimer (**18**). Lupinine (**19**) on irradiation[5] in benzene

SCHEME I

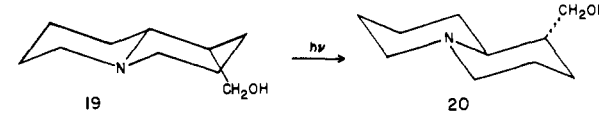


Py = Pyridine

SCHEME II

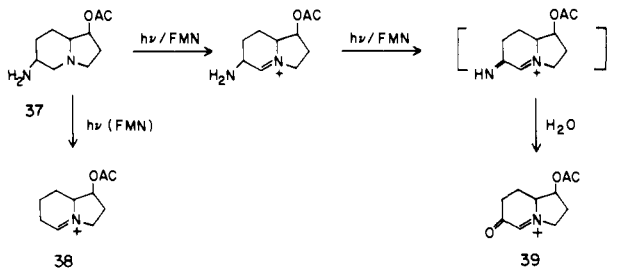


in the presence of benzophenone, acetophenone, or acetone as sensitizers gave epilupine (**20**).



Recently Santamaria and Khuong-Huu[6] irradiated methanolic solutions of sparteine (**16**), lupanine (**14**), α-isosparteine (**21**), α-isolupanine (**17**), camoensidine (**22**), and tetrahydroleontidine (**23**) in the presence of methylene blue, potassium cyanide, and sodium pyruvate under aerobic conditions (Scheme II). They observed that the size of the ring and the ring conformation played an important role during the photochemical oxidation of tertiary amines. The dye sensitized oxidation of amines involved the attack of singlet oxygen on amine followed by the formation of a cation radical.[7] The anaerobic irradiation of lupanin in methanol in the presence of eosine gave an amino alcohol (**36**) which showed the addition of the $\dot{C}H_2OH$ radical on the amine radical –$\dot{C}$HN–.

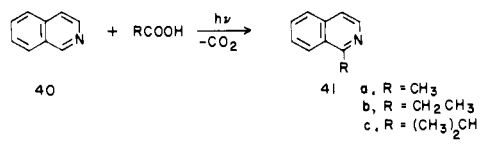
The photochemical activation of slaframine (**37**) in potassium phosphate buffer in the presence of flavine mononucleotide (FMN) and oxygen gave two major photoproducts[8] (**38**, **39**).



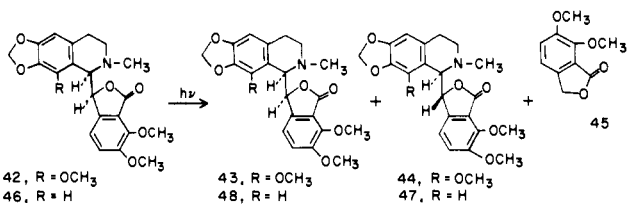
Photoproduct **38**, a cyclic imine, was generated by deamination and rearrangement of **37** while **39**, a keto imine, was formed by electron transfer and hydrolysis.

III. Isoquinoline Alkaloids

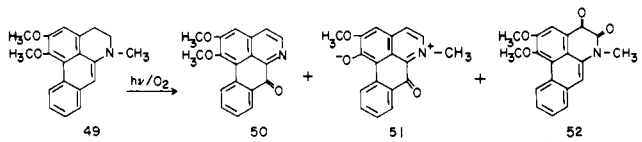
Equimolar quantities of isoquinoline (**40**) and the appropriate carboxylic acids in benzene on irradiation, in quartz vessel under nitrogen atmosphere, resulted in the formation of the corresponding 1-alkylisoquinolines (**41**) in low yields.[9,10]



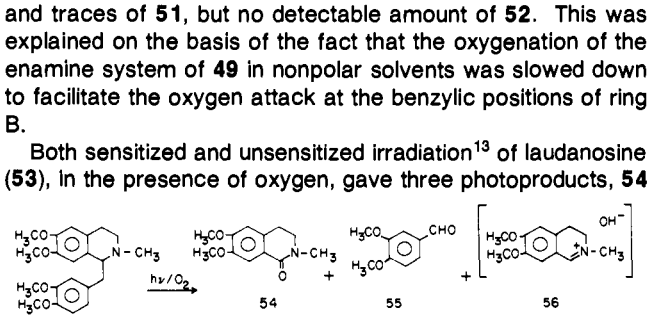
Two photoepimers, (±)-α-narcotine (**43**) and (±)-β-narcotine (**44**), along with a small amount of 6,7-dimethoxyphthalide (**45**) were obtained by irradiating (−)-α-narcotine (**42**) in dry tetrahydrofuran through Pyrex with a 450-W mercury lamp.[11] But the irradiation of (−)-α-narcotine in methanol yielded only 6,7-dimethoxyphthalide. Under similar experimental conditions, (−)-β-hydrastine (**46**) in dry tetrahydrofuran gave (±)-α-hydrastine (**47**), (±)-β-hydrastine (**48**), and **45**.



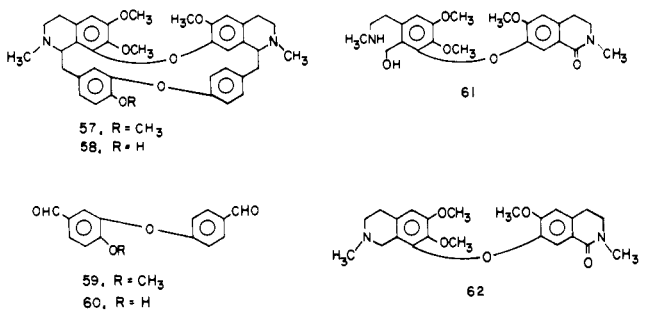
The aerobic photolysis of dehydronuciferine (**49**) in hexane was carried out by using a Hanovia 450-W lamp with a Vycor filter.[12] The photoreaction mixture gave lysicamine (**50**), blue-green zwitterion **51**, and cepharadione B (**52**). The irradiation of a methanolic solution of **49** yielded **50** in higher yield and traces of **51**, but no detectable amount of **52**. This was explained on the basis of the fact that the oxygenation of the enamine system of **49** in nonpolar solvents was slowed down to facilitate the oxygen attack at the benzylic positions of ring B.



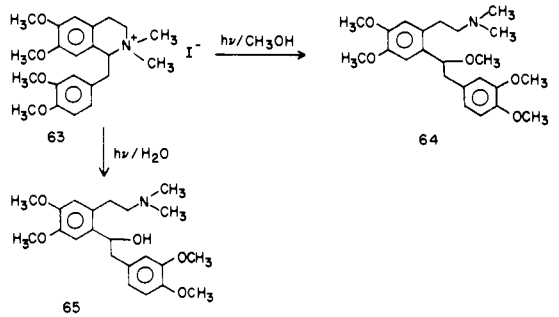
Both sensitized and unsensitized irradiation[13] of laudanosine (**53**), in the presence of oxygen, gave three photoproducts, **54** (45%), veratraldehyde (**55**, 67%), and carbinolamine **58**.



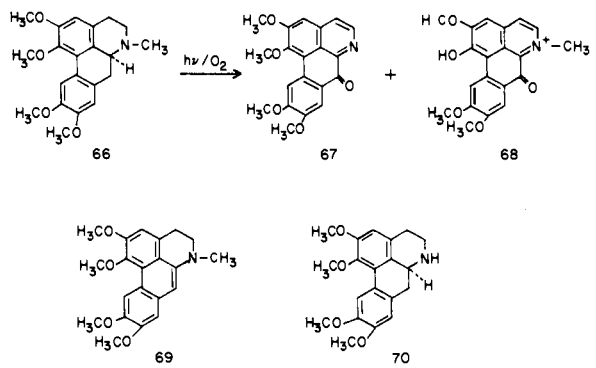
Photoproduct **58** was isolated from the reaction mixture either as its hydrochloride or as its $NaBH_4$ reduction product 6,7-dimethoxy-*N*-methyltetrahydroisoquinoline (42%). The related compounds, isotetrandrine (**57**) and berbamine (**58**), were also studied in the presence of oxygen.[13] Both alkaloids gave a dialdehyde (**59** or **60**), **61**, isolated after the reduction of intermediate, and the tertiary amine **62**. The formation of photoproduct **61** is most probably an artifact of the sodium borohydride reduction.



Ultraviolet irradiation of laudanosine methiodide (**63**) in methanol using a quartz vessel with Corex filter sleeve for 3 h gave the photosolvolysis product (**64**) in 80% yield. An amino alcohol (**65**) was obtained as photoproduct when **63** was irradiated in water acidified to pH 1–2 with dilute sulfuric acid.[14]

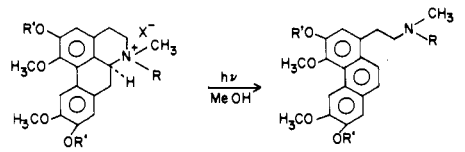


The direct photooxidation[15,18] of glaucine (**66**) gave 85% *O*-methylatheroline (**67**) and 10% corunnine (**68**). The eosine-sensitized photooxidation of **66** and dehydroglaucine (**69**) resulted in the formation of **67** in 85% and 76% yields, respectively, along with small quantity of **68**. The 90% yield of **67** was achieved by the irradiation of norglaucine (**70**).



Photoinduced elimination products were obtained in moderate to high yield when the methanolic solution of the quaternary salts of (+)-glaucine (**71a–d**), (+)-boldine (**71e,f**) and (−)-*O*,*O*′-dimethylapomorphine (**73a,b**) were irradiated.[17] Mechanistically, the formation of phenanthrenes (**72a–f**) and **74** could be explained via the formation of a carbonium ion by photoinduced cleavage of a C–N bond[18] followed by elimination. The extension of aromaticity provides a potent driving force for elimination[19,20] rather than solvolysis.

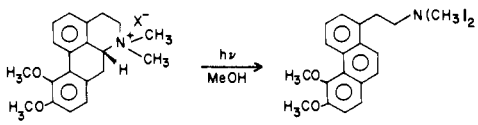
Stermitz et al.[21,22] studied the photochemical reaction of papaverine (**75**) in detail and proposed a mechanism for the



71 72

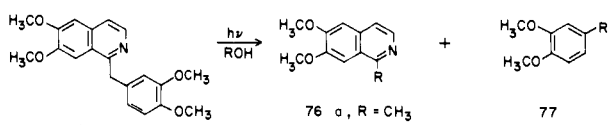
a, X = I; R = CH_3; R' = CH_3
b, X = I; R = C_2H_5; R' = CH_3
c, X = Br, $CH_2C_6H_5$; R' = CH_3
d, X = Cl; R = H; R' = CH_3
e, X = I; R = CH_3; R' = H
f, X = Cl; R = H; R' = H

a, R = CH_3; R' = CH_3
b, C_2H_5; R' = CH_3
c, R = $CH_2C_6H_5$; R' = CH_3
d, R = H; R' = CH_3
e, R = CH_3; R' = H
f, R = H; R' = H



73 a, X = CH_3SO_4
b, X = I

74

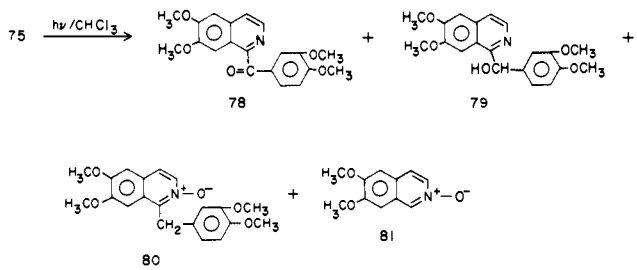


75 76 a, R = CH_3
b, R = CH_2CH_3 77

a, R = CH_3
b, R = CH_2OCH_3
c, R = H
d, R = OCH_3
e, R = CHO
f, R = $COOCH_3$
g, R = $CH_2OCH_2CH_3$
h, R = $COOCH_2CH_3$

incorporation of alcohols in imine photochemistry (Scheme III). Irradiation of methanolic or ethanolic solutions of papaverine or its hydrochloride in quartz vessel under nitrogen atmosphere gave 1-methyl-6,7-dimethoxyisoquinoline (**76a**) or 1-ethyl-6,7-dimethoxyisoquinoline (**76b**), respectively, as a basic photoproduct. Nonbasic photoproducts isolated from the reaction mixture were homoveratrole (**77a**), methyl veratryl ether (**77b**), veratrol (**77c**), 1,3,4-trimethoxybenzene (**77d**), veratraldehyde (**77e**), and methyl veratrate (**77f**) in the case of methanol and **77a**, **77c**, ethyl veratryl ether (**77g**), and ethyl veratrate (**77h**) with ethanol as the solvent.

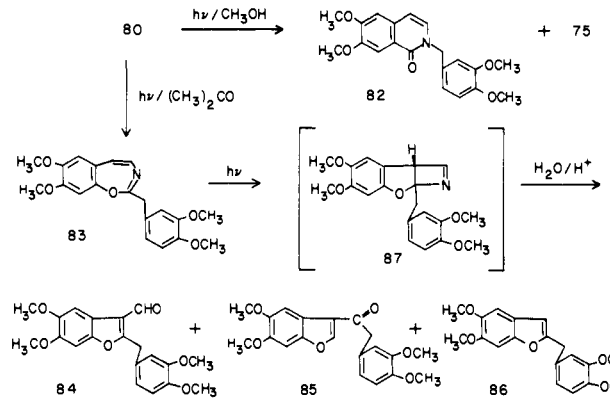
Exposing[23] the chloroform solution of papaverine (**75**) to sunlight gave papaveraldine (**78**), papaverinol (**79**), papaverine *N*-oxide (**80**), and 6,7-dimethoxyisoquinoline *N*-oxide (**81**).



78 79

80 81

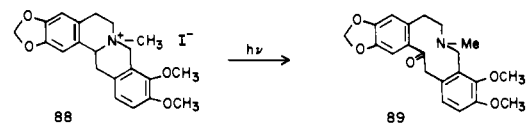
Photolysis of papaverine *N*-oxide (**80**) in different solvents resulted in the formation of several photoproducts.[24] Papaverine and 6,7-dimethoxy-2-(3,4-dimethoxybenzyl)isocarbostyril (**82**) were the only photoproducts when **80** was irradiated in methanol under an argon atmosphere with an Hanovia 450-W medium-pressure mercury lamp and uranyl oxide glass filter sleeve. Under similar experimental conditions, the irradiation of **80** in acetone resulted in the formation of 7,8-dimethoxy-2-(3,4-dimethoxybenzyl)-1,3-benzoxazepine (**83**), 5,6-dimethoxy-2-(3,4-dimethoxybenzyl)benzofuran-3-carboxaldehyde (**84**), 5,6-dimethoxybenzofuran-3-yl 3,4-dimethoxybenzyl ketone (**85**), 5,6-dimethoxy-2-(3,4-dimethoxybenzyl)benzofuran (**86**), and **75**. These investigators have given evidence that neither the aldehyde **84** nor the ketone **85** is a photoproduct of **80**. These



82 83 87 84 85 86

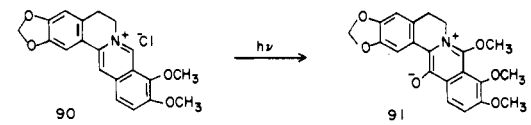
compounds were obtained from the valence tautomer (**87**) of **83** by acid-catalyzed hydrolysis and rearrangement during the preparative chromatography.

Photooxygenation[25] of tetrahydroberberine methiodide (**88**) gave allocryptopine (**89**).

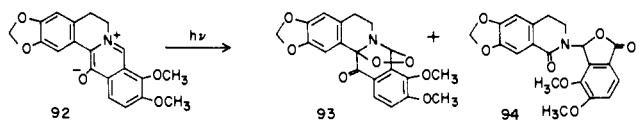


88 89

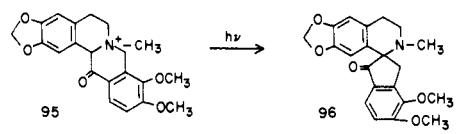
Irradiation[26] of berberium chloride (**90**) in the presence of oxygen gave 8-methoxyberberine phenol betaine (**91**) which is



90 91



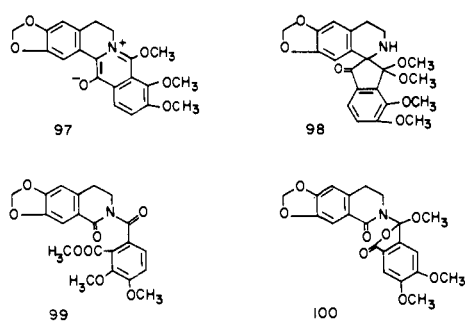
92 93 94



95 96

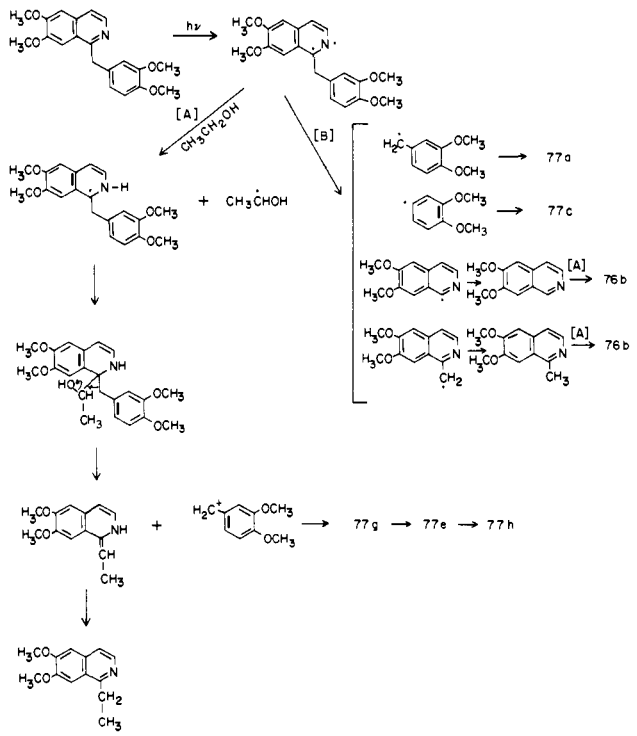
a precursor for the synthesis of (±)-α- and (±)-β-hydrastine, (±)-ophiocarpine, and (±)-13-epiophiocarpine. The photooxygenation[27] of berberinium betaine (**92**) (>0.1% concentration) gave the epidioxydibenzoquinolizidine (**93**) while at <0.1% concentration, the photoproduct berberal (**94**) was isolated from the reaction mixture. The photolysis of 13-oxotetrahydroprotoberberine (**95**) in the presence of sodium hydride and ethanol under nitrogen atmosphere resulted in the formation of a spirobenzylisoquinoline (**98**) in 45% yield.[28]

The photooxygenation[29] of berberine phenol betaine (**97**) gave the spirobenzylisoquinoline **98**, the imide ester **99**, and meth-

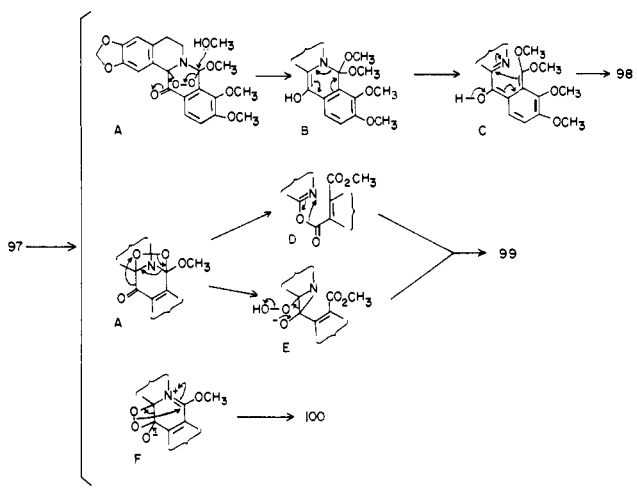


97 98 99 100

SCHEME III

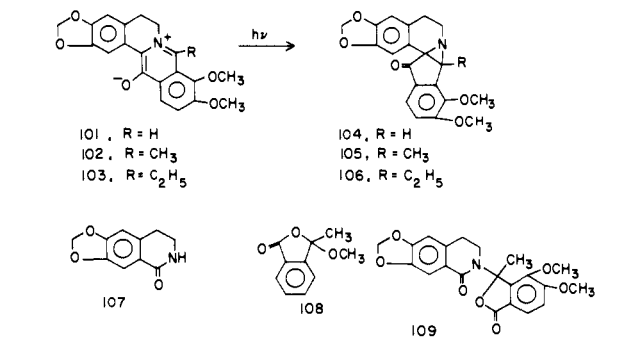


SCHEME IV

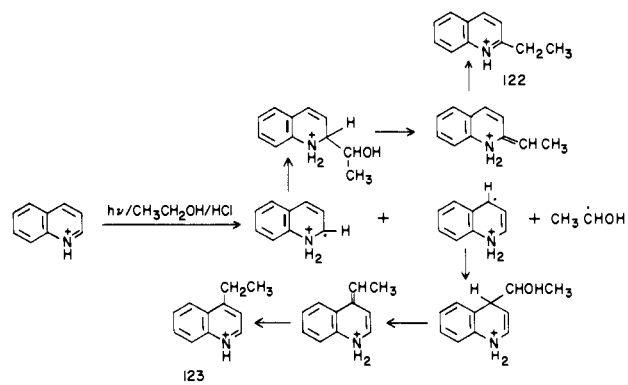


oxyberberal **100**. The formation of the photooxygenation products of **97** are represented mechanistically in Scheme IV.

Recently Hanaoka et al.[30] reported an elegant method for the synthesis of the spirobenzylisoquinoline alkaloids by the photochemical reaction of berberine phenol betaines followed by regioselective C–N bond cleavage of the photoproduct. Irradiation of the methanolic solution of berberine phenol betaines (**101**–**103**) in a Pyrex vessel under nitrogen atmospheres gave

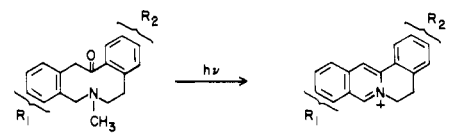


SCHEME V



over 70% yield of 8,14-cycloberbines **104**, **105**, and **106**, respectively, aziridine derivatives. Irradiation of 8,14-cycloberbine (**104**) in methanol under the above conditions produced the starting betaine (**101**) in 55% yield. This confirmed the existence of photoequilibrium between betaines (**101**–**103**) and 8,14-cycloberbines (**104**–**106**). The regioselective C–N bond cleavage of the aziridine ring of 8,14-cycloberbines (**104**–**106**) gave spirobenzylisoquinoline. On the other hand, aerobic irradiation of **102** afforded the 8,14-cycloberbine **105** along with the oxygenated photoproducts **99**, **107**, **108**, and **109**.

The irradiation of ethanolic solutions of α-allocryptopine (**110**), cryptopine (**111**), and protopine (**112**) under nitrogen atmosphere

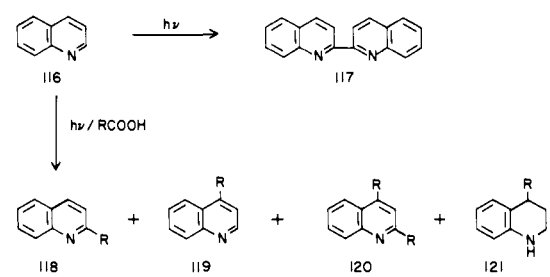


110, $R_1 = OCH_3, OCH_3$; $R_2 = CH_2O_2$
111, $R_1 = CH_2O_2$; $R_2 = OCH_3, OCH_3$
112, $R_1 = R_2 = CH_2O_2$
113, R_1 and R_2 as in **111**
114, R_1 and R_2 as in **112**
115, R_1 and R_2 as in **113**

for 100 h gave berberine (**113**), epiberberine (**114**), and coptisine (**115**), respectively.[31] These authors noticed that the rate of photolysis and the yield of photoproducts increased by using chloroform as a solvent in place of ethanol or methanol.

IV. Quinoline Alkaloids

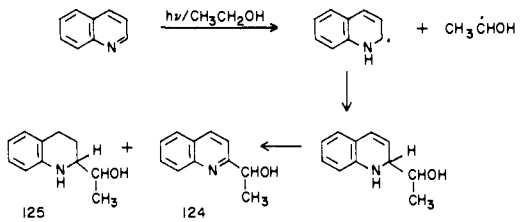
Quinoline (**118**) in 1-propanol undergoes dimerization to 2,2′-diquinoline (**117**) in the presence of ultraviolet light.[32]



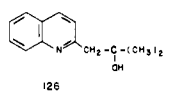
Equimolar quantities of quinoline and the appropriate carboxylic acids in benzene solution were irradiated in a quartz vessel under nitrogen atmosphere using a 200-W high-pressure Hg lamp.[9,10] In all cases, 2-alkylquinoline (**118**) was isolated as a major photoproduct and 4-alkylquinoline (**119**) and 2,4-dialkylquinoline (**120**) as minor photoproducts. In some cases, 4-alkyltetrahydroquinoline (**121**) was also obtained as a photoproduct of **116**.

Stermitz et al.[33,34] studied the photochemical reaction of quinoline in various alcohols and proposed a mechanism for the photoalkylation of quinoline at position 2 or 4 (Scheme V).

SCHEME VI



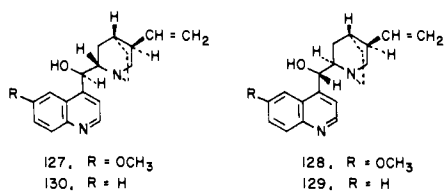
Irradiation of the ethanolic solution of quinoline containing hydrochloric acid in a Pyrex container, under nitrogen atmosphere using Hanovia lamp, yielded 2-ethylquinoline (**122**) and 4-ethylquinoline (**123**). On the other hand, 2-(1-hydroxyethyl)-quinoline (**124**) and traces of 2-(1-hydroxyethyl)-1,2,3,4-tetrahydroquinoline (**125**) were isolated from the irradiated solution of quinoline in ethanol under the above conditions but in the absence of hydrochloric acid (Scheme VI). No photoproduct could be isolated from the irradiation of a similar, neutral reaction mixture of quinoline in 2-propanol; however, in the presence of hydrochloric acid a dimer was obtained. The structure of the dimer at present remains unassigned. Quinoline, on irradiation in *tert*-butyl alcohol, gave 2-(2-hydroxy-2-methylpropyl)quinoline (**126**). Also, photosubstitution products of quinoline at positions



2 and 4 were obtained by irradiating quinoline in the presence of cyclohexane or ether.[35]

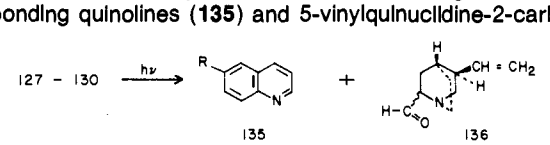
Macht and Teagarden[36] observed an increase in the pharmacological activity of an irradiated solution of quinine (**127**). Later on, several other workers[37-39] reported an increase in the toxicity of the irradiated solution of quinine while others[40,41] found no significant change in the activity of the irradiated solution of quinine.

An increase in the antimalarial activity of an irradiated quinine solution was observed by two independent research groups.[42,43] None of these workers could isolate the photoproducts of quinine and other cinchona alkaloids. Stenberg et al.[44,45] isolated the photoproducts of cinchona alkaloids and investigated the antimalarial activity of the photoproducts. They found that the photoproducts were less active pharmacologically than their precursor. The irradiation of quinine (**127**), quinidine (**128**),

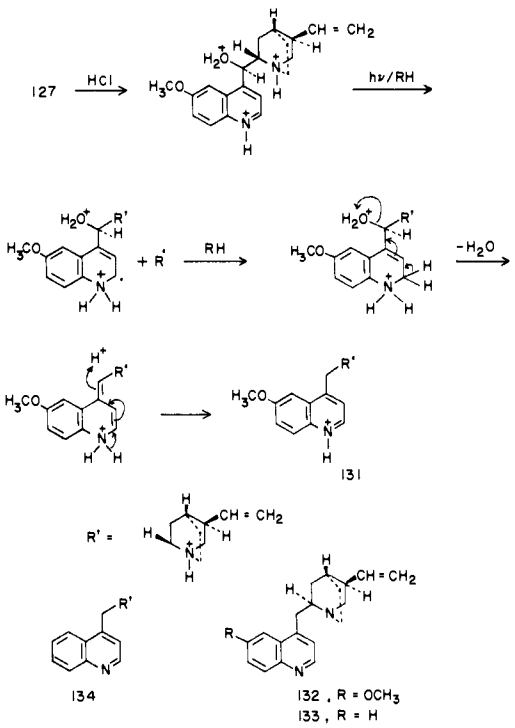


cinchonine (**129**), and cinchonidine (**130**) in 2 M HCl and 2-propanol was carried out in quartz or Pyrex vessels under nitrogen atmosphere with a Hanovia 550-W medium-pressure lamp. All the cinchona alkaloids gave their corresponding deoxy derivatives (**131–134**) as photoproducts. They proposed the mechanism illustrated in Scheme VII for the photochemical conversion of **127–130** into their deoxy derivatives (**131–134**).

Recently, Epling and Yoon[46] reported the photolysis of cinchona alkaloids in neutral solvent by the irradiation of the methanolic solution of quinine, quinidine, cinchonine, and cinchonidine in nitrogen atmosphere using a Hanovia medium-pressure mercury lamp. All cinchona alkaloids gave the corresponding quinolines (**135**) and 5-vinylquinuclidine-2-carbox-



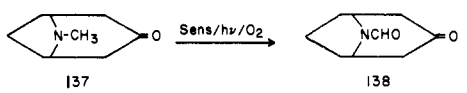
SCHEME VII



aldehyde (**136**). It was also observed that the reaction of cinchonidine and quinidine was faster as compared to cinchonine and quinine.

V. Tropane Alkaloids

The photolysis of pseudopelletierine (**137**) in benzene solution saturated with oxygen or in the presence of Rose Bengal as a sensitizer[47-49] gave *N*-formamidonorpseudopelletierine (**138**).



N-Methylgranatinine, i.e., pseudopelletierine, with the carbonyl removed, gave the same reaction as **137** but at a faster rate, which illustrates that the presence of a carbonyl group is not essential in such a reaction.[48]

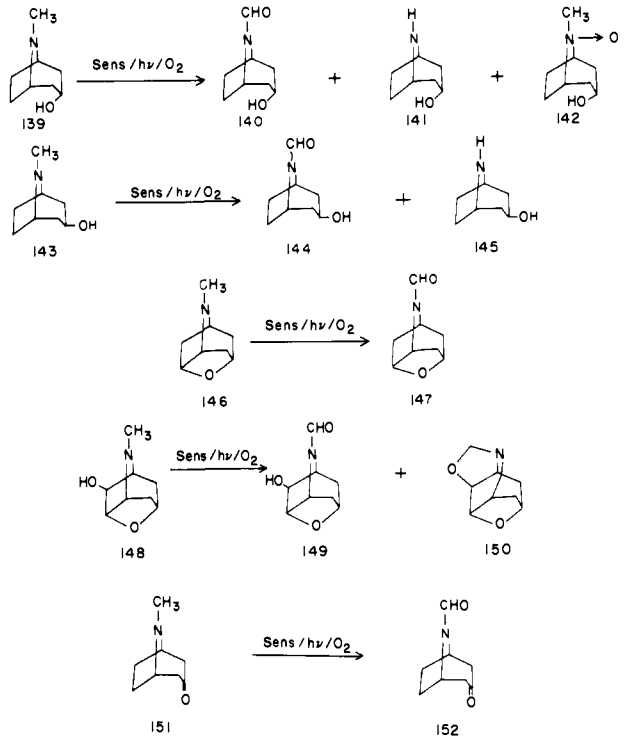
The irradiation of a methanolic solution of tropanol (**139**) and pseudotropanol (**143**), in the presence of methylene blue as a sensitizer, gave formamido and demethylated photoproducts[4,50] (see Scheme VIII). However, tropanol gave *N*-oxytropanol (**142**) as a third photoproduct.[4] Under similar experimental conditions deoxyscopoline (**148**) produced only the formamido photoproduct **147**, whereas scopoline (**148**) gave the formamido product **149** and the cyclic tetrahydrooxazine **150**.

The photolysis[47,48,51] of the benzene solution of tropinone (**151**) in the presence of Rose Bengal as a sensitizer resulted in the formation of *N*-formamidonortropinone (**152**).

Fisch et al.[48] proposed that the *N*-methyl oxidation reaction proceeds via the singlet oxygen originating from the sensitizers on the basis of the facts that the reaction does not proceed in the absence of oxygen or light, the reaction can be quenched by 1,4-diazabicyclooctane, the disappearance of starting amine is linear, and the reaction exhibits an internal filter effect.

The singlet oxygen interpretation was questioned by Bartholomew and Davidson[51] on the basis of the results reported by Fisch et al. that the chemical generation of singlet oxygen from sodium hypochlorite and hydrogen peroxide[52] did not give similar results to the photooxidation, the tropinone reaction was not sensitized by naphthalene or triphenylene but was by Rose Bengal, and that tropinone was efficiently reduced by Rose

SCHEME VIII



Bengal in methanol solution in the absence of oxygen. The alternative mechanism is outlined in reactions 1–8, where D = dye, AH = amine, and A· = α-amino radical.

$$D_T + AH \rightarrow D^{-}\cdot\ AH^{+}\cdot \quad (1)$$

$$D_T + O_2 \rightarrow D_0 + O_2 \quad (2)$$

$$D^{-}\cdot AH^{+}\cdot \rightarrow D_0 + AH \quad (3)$$

$$D^{-}\cdot AH^{+}\cdot \rightarrow \dot{D}H + \dot{A} \quad (4)$$

$$\dot{D}H + O_2 \rightarrow D_0 + HO\cdot_2 \quad (5)$$

$$\dot{A} + O_2 \rightarrow A\dot{O}_2 \quad (6)$$

$$A\dot{O}_2 + AH \rightarrow AO_2H + \dot{A} \quad (7)$$

$$AO_2H \rightarrow \text{products} \quad (8)$$

Herlem et al.[4] further expanded the charge-transfer mechanism concept in accordance with reactions 9–13 where A = the sensitizer.

$$A_3{}^{*} + R_2\ddot{N}CH_3 \rightarrow A^{-}\cdot + R_2\dot{N}^{+}CH_3 \quad (9)$$

$$A^{-}\cdot + R_2\dot{N}^{+}CH_3 \rightarrow AH\cdot + R_2NCH_2\cdot \quad (10)$$

$$2AH\cdot \rightarrow A + AH_2 \quad (11)$$

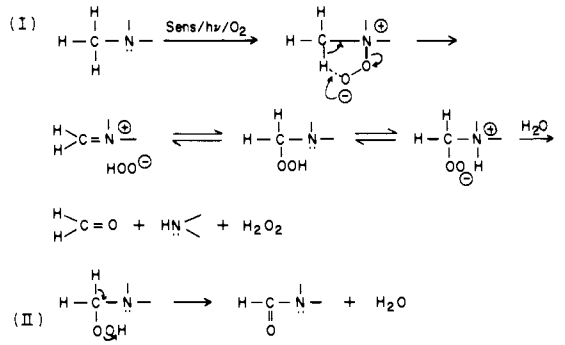
$$R_2N\dot{C}H_2 + A \rightarrow A^{-}\cdot + R_2N^{+}{=}CH_2 \quad (12)$$

$$R_2N^{+}{=}CH_2 \rightarrow R_2NH + H_2CO \quad (13)$$

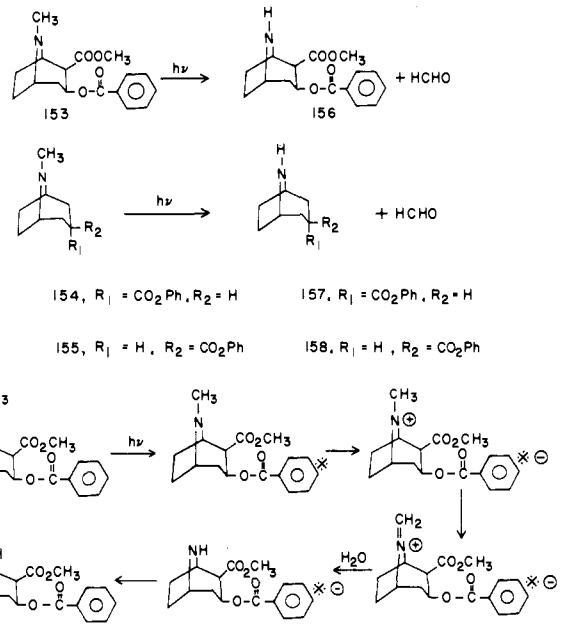
The formation of dealkylated amine and *N*-formamido derivative during the irradiation of these tertiary amines could be explained on the basis of Scheme IX.[7]

Recently Singh et al.[53,54] studied the photochemical reaction of cocaine (**153**), benzoyltropine (**154**), and benzoylpseudotropine (**155**). The methanolic solutions of all these compounds were irradiated in quartz vessel with a Corex filter under nitrogen atmosphere. All compounds gave corresponding N-demethylated products (**156–158**) and formaldehyde. Since the demethylation also occurs for benzoyltropine, where the benzoyl group does not come in close proximity to the *N*-methyl reaction center in

SCHEME IX. Mechanism of Formaldehyde and Formamide Formation



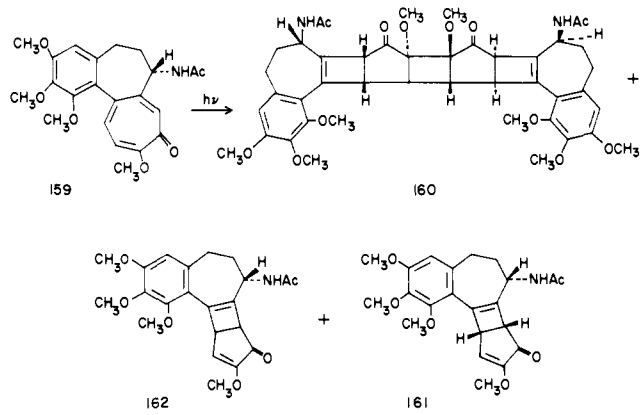
SCHEME X



any conformer, the reaction must be intermolecular in character at least in part. No demethylated products were obtained during the irradiation of tropanol and atropine under similar experimental conditions.[55] Scheme X[54] was proposed to account for the products.

VI. Colchicine and Isocolchicine Alkaloids

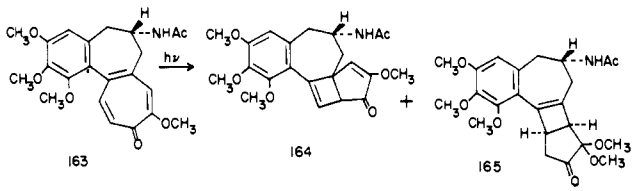
The aqueous solution of colchicine (**159**) in the presence of ultraviolet light yielded a crystalline material which was assumed to be lumicolchicine.[56] Later on, three crystalline photoproducts, α-lumicolchicine (**160**), β-lumicolchicine (**161**), and γ-lumi-



colchicine (**162**), were isolated from the irradiated solution of

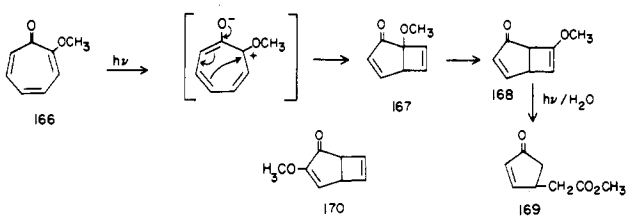
colchicine[57-60] and their structures have been assigned by various workers.[59-63] β-Lumicolchicine (**161**), which is found in small amounts in various plant species, undergoes photodimerization in the presence of ultraviolet light[63] and gives α-lumicolchicine (**160**).

Similarly, irradiation of isocolchicine (**163**) gave lumiisocolchicine (**164**) as a major photoisomer[64,65] and methanol adduct



165 as a minor photoproduct.[64] The formation of photoproducts **161** and **162** from colchicine and **164** from isocolchicine during their irradiation is evidence that the trimethoxystyryl system in the photoproducts is playing an important role in the electronic control of the product formation.

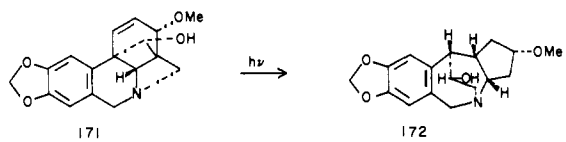
The photolysis[66] of α-tropolone methyl ether (**166**) resulted in the formation of photoproducts, 1-methoxybicyclo[3.2.0]-hepta-3,6-dien-2-one (**167**), 7-methoxybicyclo[3.2.0]hepta-3,6-



dien-2-one (**168**), and methyl 4-oxo-2-cyclopentene-1-acetate (**169**). The formation of the photoproduct **167** could be explained by assuming that the excited state of **166** is dipolar in character.[67] The absence of 3-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (**170**) as a photoproduct during the irradiation of **166** could be explained by the lack of methoxyl stabilization in the excited state. Thus, the formation of photoproduct analogues of **170**, **161** and **162** from colchicine and **164** from isocolchicine is evidence that the trimethoxystyryl chromophore in the photoproducts (**161**, **162**, and **164**) is essential in electronic control of product formation.

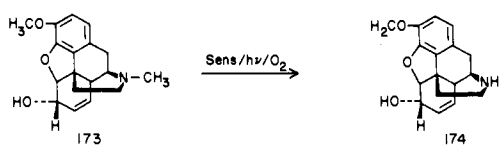
VII. Amaryllidaceae Alkaloids

The photolysis[68] of crinamine (**171**) in methanol under nitrogen with a high-pressure mercury lamp for 1.5 h yielded a crystalline product, photocrinamine (**172**).

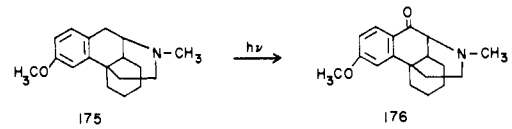


VIII. Opium Alkaloids

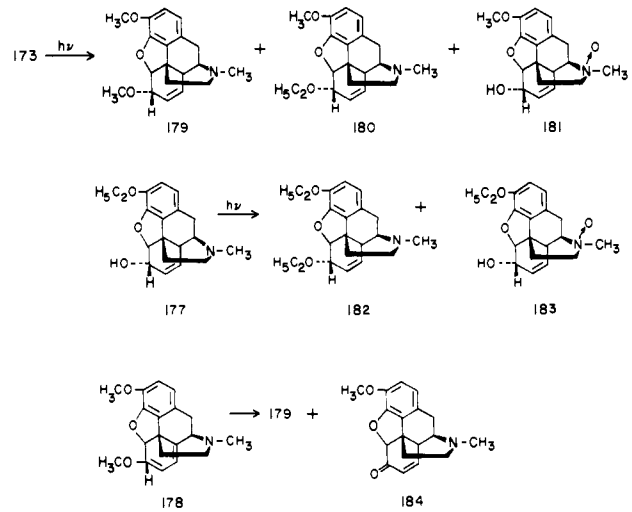
The Rose Bengal sensitized oxidative demethylation of codeine (**173**) to norcodeine (**174**) was achieved by Lindner et al.[69] The



oxygen uptake during the photooxidation of codeine was 50 times slower in *tert*-butyl alcohol as compared to 2,5-dimethylfuran. Neither the *N*-formyl nor the *N*-oxide photoproduct of **173** was isolated from the reaction mixture. Photooxidation[70] of (+)-3-methoxy-*N*-methylmorphinan hydrobromide (**175**) gave (−)-3-methoxy-10-oxo-*N*-methylmorphinan (**176**).

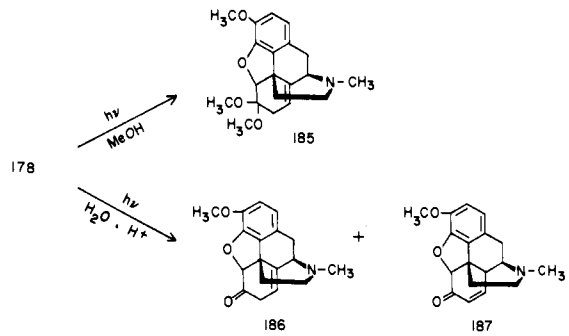


The exposure of solutions of codeine (**173**), ethylmorphine (**177**), and thebaine (**178**) in organic solvents to diffused sunlight resulted in the formation of various photoproducts.[71] Methylcodeine (**179**), 3-*O*-methyl-6-*O*-ethylmorphine (**180**), and codeine



N-oxide (**181**) were isolated from the photoreaction mixture of **173**. Diethylmorphine (**182**) and ethylmorphine *N*-oxide (**183**) were photoproducts of **177**. Thebaine gave codeinone (**184**) and methylcodeine (**179**).

Recently, Dauben et al.[72] reported the synthesis of codeine from thebaine via the photochemical pathway. The methanolic solution of **178**, on irradiation, with a Hanovia 450-W lamp through a Corex filter under nitrogen atmosphere gave neopinone dimethyl ketal (**185**). On the other hand, a mixture of two

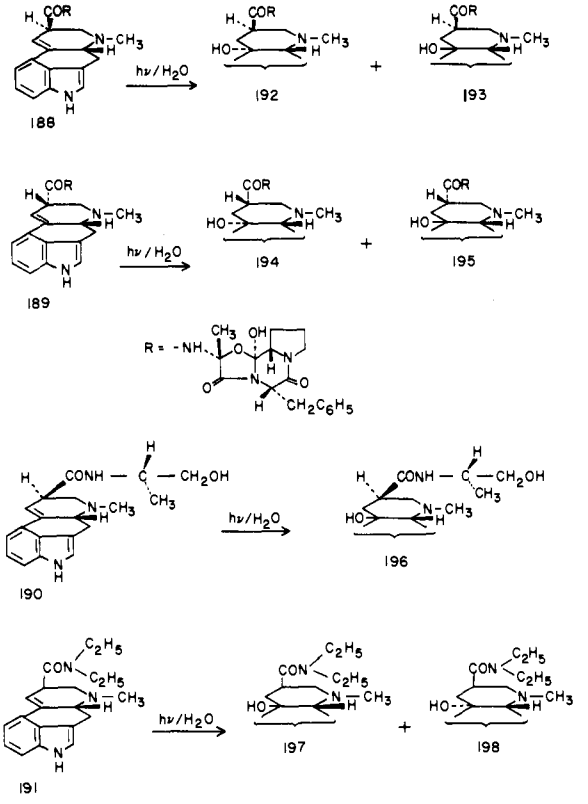


photoproducts, neopinone (**186**) and codeinone (**187**), was obtained by irradiating the acidic aqueous solution of **178**. The acidic hydrolysis of **185** gave a mixture of **178**, **186**, and **187**. Both products **186** and **187** could be converted readily to codeine.[73]

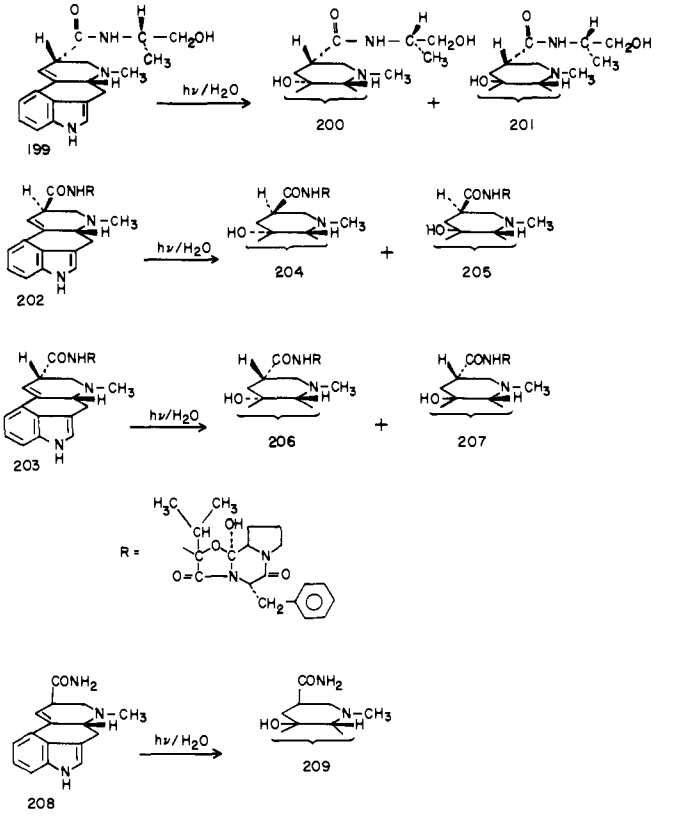
IX. Indole Alkaloids

Stoll and Schlientz[74] observed that during the exposure of the appropriate ergot alkaloids in acetic acid–water solution to ultraviolet light, a molecule of water is added across the double bond present in ring D of the lysergic acid or isolysergic acid moiety. The irradiation of ergotamine (**188**), ergotaminine (**189**), ergometrine (**190**), and lysergic acid diethylamide (**191**) in acetic acid–water solution under the atmosphere of carbon dioxide gave lumiergotamine epimers (**192**, **193**), lumiergotaminine epimers (**194**, **195**), lumiergometrine (**196**), and lumilysergic acid diethylamide epimers (**197**, **198**), respectively (Scheme XI).

SCHEME XI

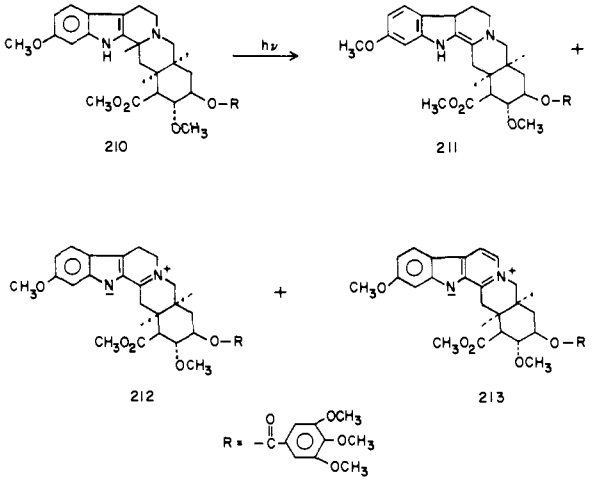


SCHEME XII



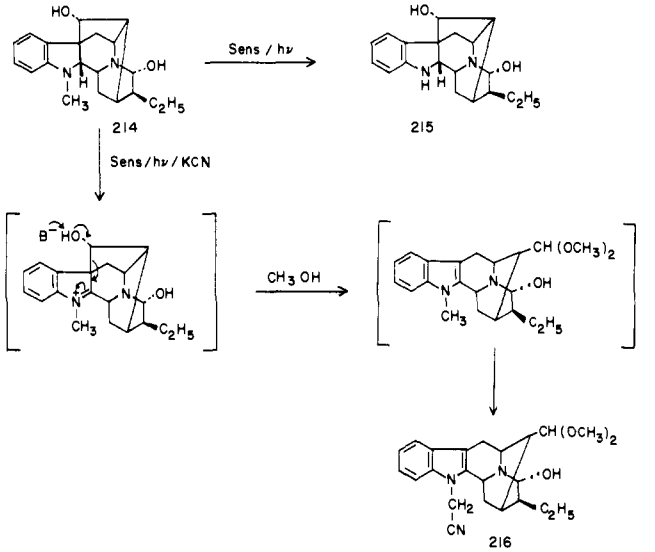
Hellberg[75,76] extended the work of Stoll and Schlientz to ergometrinine (**199**), ergocristine (**202**), ergocristinine (**203**), and ergine (**208**) (Scheme XII). Ergometrinine was irradiated in 0.1 M HCl in a quartz vessel under nitrogen atmosphere. The reaction mixture yielded two lumiergometrinine epimers (**200**, **201**). Similarly, the irradiation of ergocristine in 0.1 M methanesulfonic acid and ergocristinine in 0.1 M acetic acid gave lumiergocristine epimers (**204**, **205**) and lumiergocristinine epimers (**206**, **207**), respectively. Lumiisolysergic amide (**209**) was the only photoproduct isolated from the irradiated solution of ergine (**208**) in 0.1 M HCl. On the other hand, the irradiation of ergine in dilute acetic acid gave two photoproducts. The structure of one photoproduct could not be assigned due to its instability while the other photoproduct was found to be lumiisolysergic amide (**209**).

Earlier studies have reported that the irradiated solution of reserpine (**210**) in chloroform or methanol gave three spots on



paper chromatography.[77-80] Two spots on paper chromatography were found to be 3-isoreserpine (**211**) and 3,4-dehydroreserpine (**212**) while the third spot was assumed to be lumireserpine. Wright and Tang[81] irradiated reserpine in chloroform by using mercury arc lamp. These investigators detected 3-isoreserpine and 3,4-dehydroreserpine on TLC. The third major photoproduct after 120 h of irradiation was isolated by column chromatography and its structure, which previously was assumed to be lumireserpine, was assigned to be 3,4,5,6-tetradehydroreserpine (**213**).

The anaerobic photolysis of the methanolic solution of ajmaline (**214**) in the presence of methylene blue as a sensitizer gave norajmaline[4] (**215**) while in the presence of KCN and eosine as

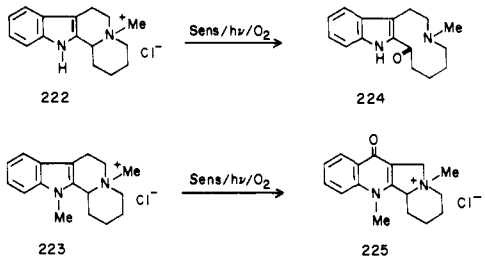


a sensitizer the endolic aminonitrile[2] **216** was formed. In a later case, the stereochemistry of C-2 substituents in **214** did not influence the site of oxidation.[2]

Bernauer et al.[82,83] observed an unusual photooxygenation reaction of C-toxiferine I (**217**) and deoxycalebasine (**218**). The irradiation of **217** in the presence of oxygen gave C-alkaloid (**219**) while in the presence of oxygen and ammonium eosine gave

C-alkaloid A (**220**) (Scheme XIII). Alkaloid C-calebasine (**221**) was the only photoproduct when deoxycalebasine was irradiated in the presence of oxygen and ammonium eosine as a sensitizer.

The aerobic photolysis of indoloquinolizidine chloride (**222**) and its 1-methyl derivative (**223**) in the presence of Rose Bengal as

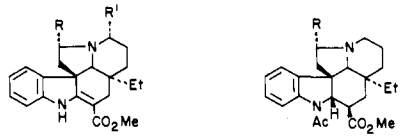


222 224

223 225

a sensitizer gave 2-acylindole (**224**) and 1,2,3,4,6,7,12,12b-octahydroindolizino[1,2-*b*]quinolin-7-one methochloride (**225**), respectively.[84]

Dye-sensitized photooxidation[85] of vincadifformine (**226**) in methanol in the presence of KCN gave two isomeric nitriles (**227**, **228**). Under similar experimental conditions *N*-acetyl-2,16-



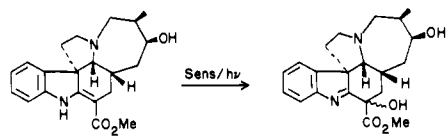
226, R = R' = H
227, R = CN, R' = H
228, R = H, R' = CN

229, R = H
232, R = CN

dihydrovincadifformine (**229**), tabersonine (**230**), and *N*-acetyl-2,16-dihydrotabersonine (**231**) gave **232**, **233**, and **234**

230, R = H
233, R = CN

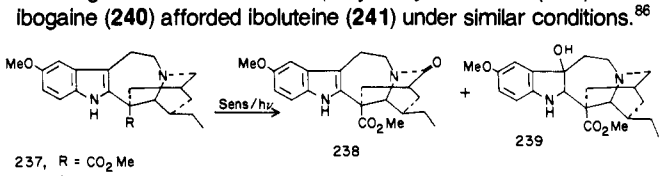
231, R = H
234, R = CN



235 236

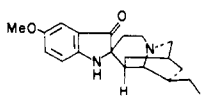
nitriles, respectively. Similarly, iboxyphylline (**235**) on irradiation yielded hydroxyindolenine (**236**). The site of oxidation depends on the stability of the intermediate immonium ions which is dependent on the molecular structure and stabilization by conjugation.

The irradiation of voacangine (**237**) in the presence of sensitizer gave lactam **238** and β-hydroxyindolenine (**239**) while ibogaine (**240**) afforded iboluteine (**241**) under similar conditions.[86]



237, R = CO_2Me
240, R = H

238 239



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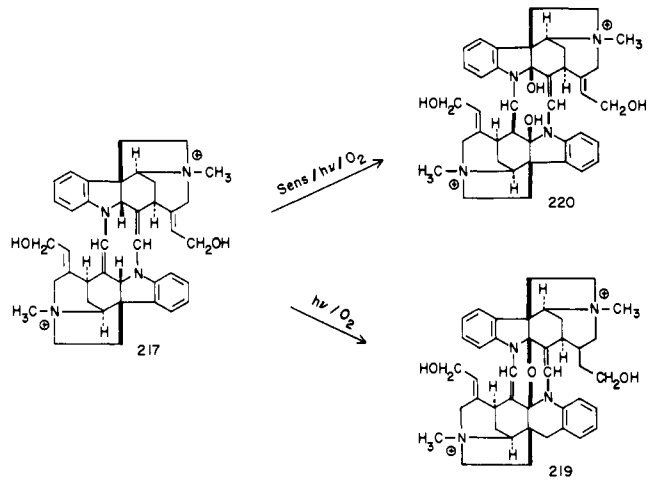
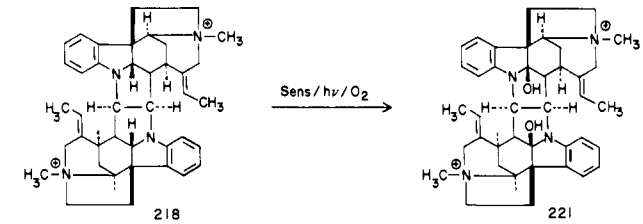
Though physostigmine (**242**) has been reported to be sensitive to ultraviolet light,[87] the photoproducts were not been isolated

SCHEME XIII

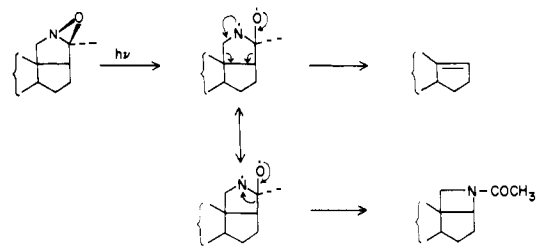


217 220 219

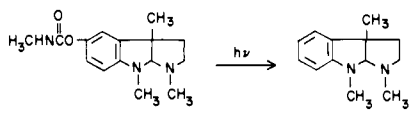


218 221

SCHEME XIV



and identified. The irradiation of physostigmine in 2-propanol produced 10% of deoxyeseroline[88] (**243**). Both sensitizing and



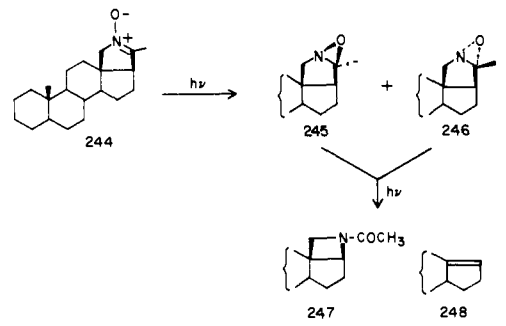
242 243

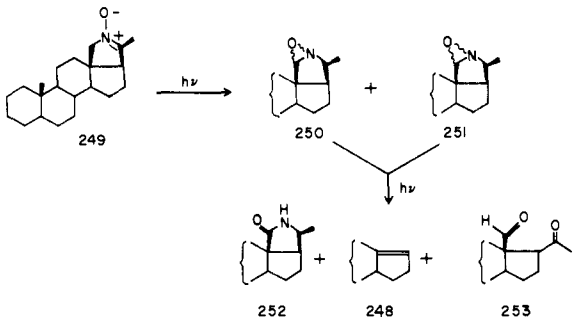
quenching studies were unsuccessful for the formation of **243**. This interesting reaction may be useful for the conversion of phenols to the corresponding benzene derivatives through their carbamate esters.

X. Steroidal Alkaloids

The irradiation of the steroidal alkaloid nitrone[89] (**244**) in acetonitrile gave stereoisomeric oxaziranes **245** and **246**, *N*-acetylazetidine (**247**), and an ethylenic derivative (**248**). Similarly, the nitrone **249**, which is an epimer of **244**, gave the mixture of stereoisomer of oxaziranes **250** and **251**, lactone **252**, ethylenic derivative **248**, and aldehydic acetone **253**. The formation of photoproducts **247**, **248**, **252**, and **253** could be represented mechanistically as in Schemes XIV and XV.

The irradiation[4,90-92] of 20α-(dimethylamino)-5α-pregnane (**254**) in the presence of eosine or methylene blue and oxygen gave a secondary amine (**255**) whereas in the presence of eosine and oxygen, 20α-pregnanone (**256**), 20α-(methylformamido)-5α-pregnane (**257**), and 20α-formamido-5α-pregnane (**258**) were

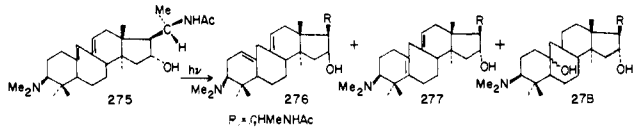




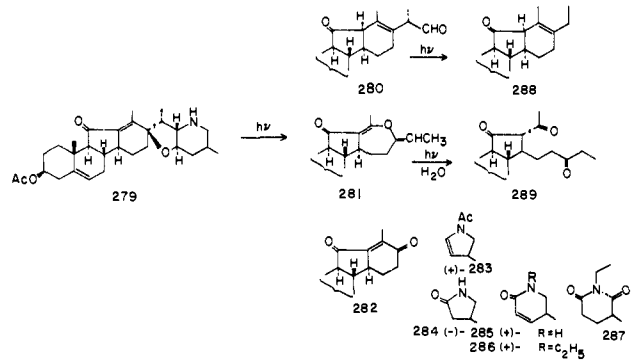
formed (Scheme XVI). Furthermore, a series of steroidal alkaloids were irradiated in the presence of methylene blue and oxygen. 3α-(Dimethylamino)-5α-pregnane (**259**) gave a secondary amine (**260**) and a ketone (**261**) while two derivatives, 3β-(dimethylamino)cyclolaudane (**262**) and **263**, showed the formation of both **264** and **265** and **266**, respectively, during their photolysis.

The photochemical reaction of conanine (**267**) was investigated in detail under various experimental conditions[4,50,90-92] (Scheme XVII). The irradiation of conanine in benzene–methanol gave an imine (**268**). Two lactones (**269** and **270**) were obtained from the photochemical reaction mixture of **267** when methylene blue and oxygen were used during irradiation. Under similar experimental conditions but with eosine as a photosensitizer in place of methylene blue, four photoproducts (**269–272**) were isolated from the reaction mixture of **267**. The irradiation of **267** in the presence of eosine, oxygen, and potassium cyanide gave **270**, **273**, and **274**.

On irradiation of *N*-acetylbuxaminol (**275**), two deconjugated dienes (**276** and **277**) and a tertiary homoallylic alcohol (**278**) were isolated from the photoreaction mixture.[93]

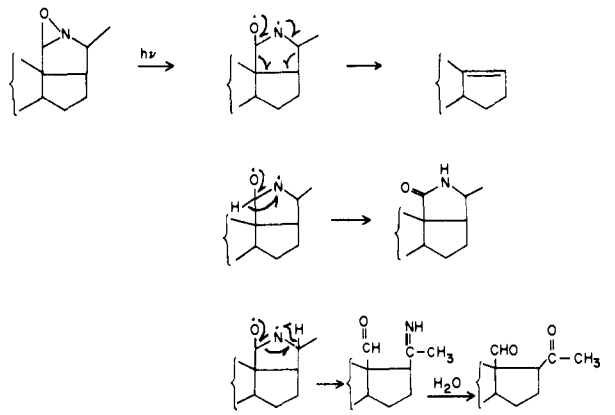


The irradiation of *O*-acetyljervine (**279**) in various solvents[94] gave three alicyclic photoproducts, **280–282**, and five heterocyclic compounds, **283–287**. Photoproducts **280** and **281**

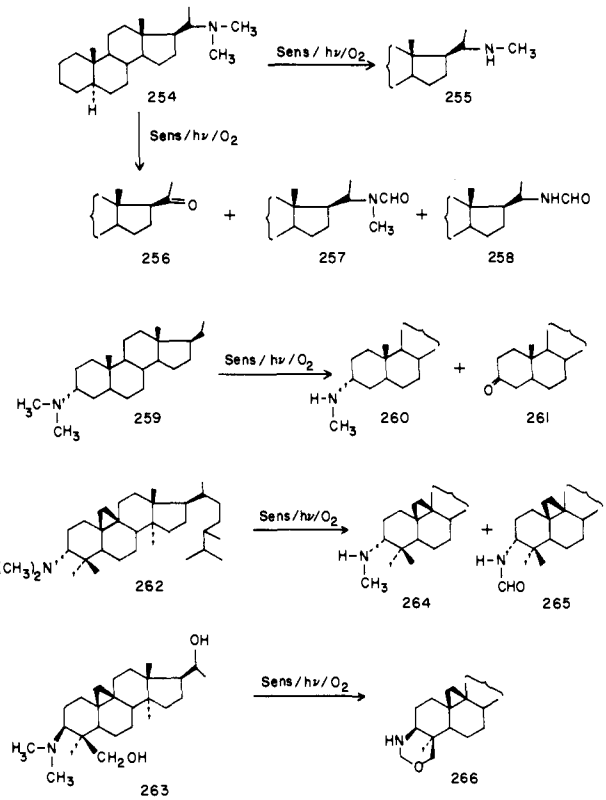


underwent further photochemical reaction and formed **288** and **289**, respectively. These workers also noticed a high degree of photostability on N-protonation of **279** in acetic acid. Furthermore, the photochemical reactivity of *N*-methyl and *N*-acetyl

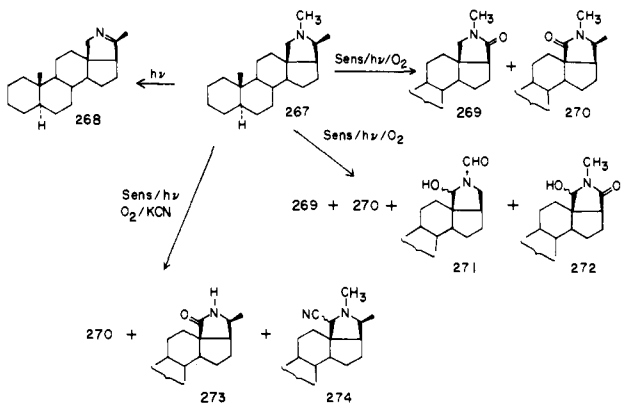
SCHEME XV



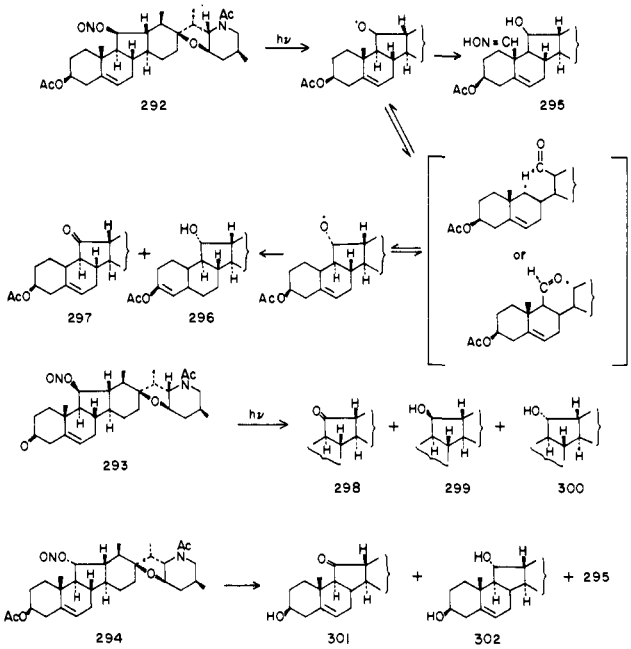
SCHEME XVI



SCHEME XVII

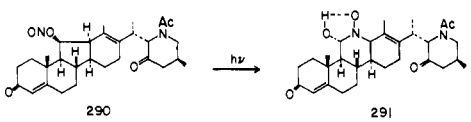


SCHEME XVIII



derivatives of **279** was markedly reduced in neutral solvents. The *N*-chloro derivative of **279** in dioxane gave *O*-acetyljervine hydrochloride.

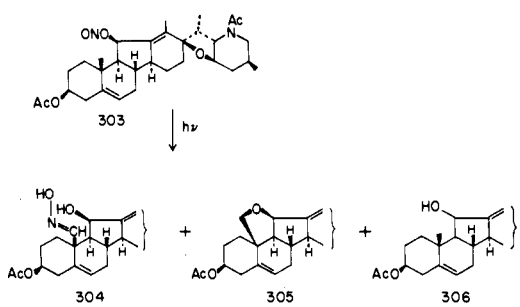
Suginome et al.[95-98] reported the photochemical formation of a cyclic nitrone from the nitrite of a fused five-membered ring alcohol. The nitrite (**290**) of *N*-acetyl-22,27-imino-11β-



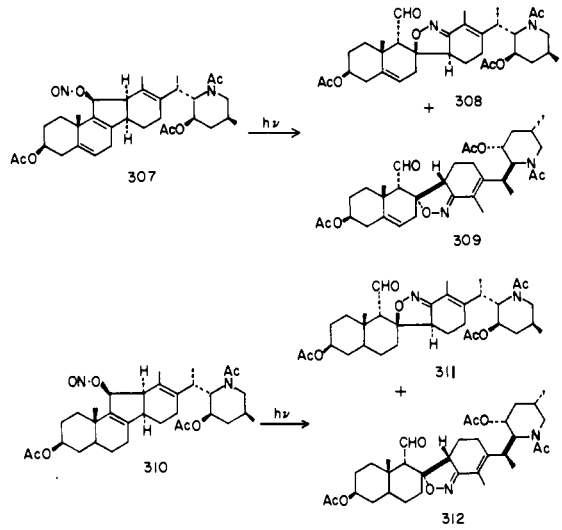
hydroxy-12α-jerv-4,13(17)-diene-3,23-dione, on irradiation in dry toluene using 150-W high-pressure Hg arc lamp, gave stereospecific cyclic nitrone **291**. These workers[98] have shown that the intermolecular migration of nitrito group, generated from the nitro moiety, into the C-12 position of the molecule takes place.

The irradiation of 3-*O*,*N*-diacetyl-22,27-imino-17,23-oxidojerv-5-ene-3β,11β-diol 11-nitrite (**292**), *N*-acetyl-22,27-imino-11β-hydroxy-17,23-oxidojerv-4-en-3-one 11-nitrite (**293**), and 3-*O*,*N*-diacetyl-22,27-imino-17,23-oxidojerv-5-ene-3β,11α-diol 11-nitrite (**294**) in dry toluene under nitrogen atmosphere afforded **295**–**297**, **298**–**300**, and **295**, **301**, and **302** as major photoproducts, respectively[99,100] (Scheme XVIII).

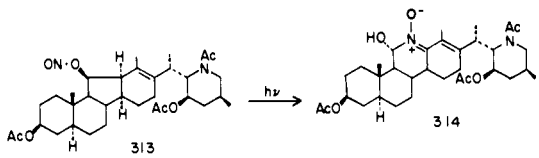
Similarly, veratrobasine 11-nitrite (**303**) on photolysis yielded **304**, **305**, and **306** as photoproducts.[101]



Recently Suginome et al. studied the photoinduced transformation of a series of nitrites. All were irradiated in toluene with Pyrex-filtered light. The photoinduced rearrangement of (22*S*,25*S*)-*N*-acetylveratra-5,8,13(17)-trienine-3β,11β,23β-triol 3,23-diacetate 11-nitrite[102] (**307**) gave the two isomeric spiroisoxazolines **308** and **309**. (22*S*,25*S*)-*N*-Acetyl-5α-veratra-

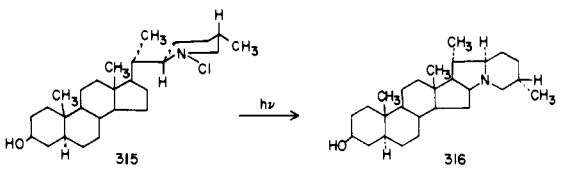


8,13(17)-dienine-3β,11β,23β-triol 3,23-diacetate 11-nitrite[103] (**310**) produced two isomeric spiroisoxazolines, **311** and **312**, while (22*S*,25*S*)-*N*-acetyl-5α-veratr-13(17)-enine-3β,11β,23β-triol 3,23-diacetate 11-nitrite[104,105] (**313**) yielded exclusively a nitrone (**314**). On the basis of these results they concluded that

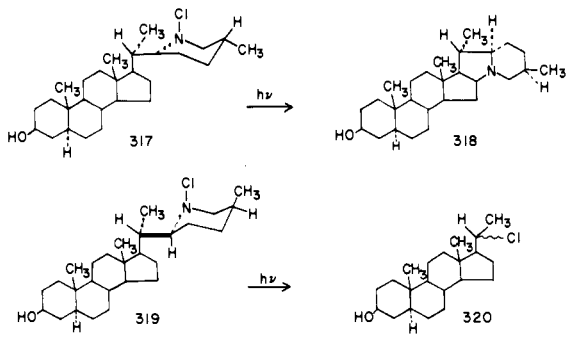


the presence of double bond either at 5,6 or at both 5,6 and 8,9 positions in nitrites is essential for the formation of isomeric isoxazolines.

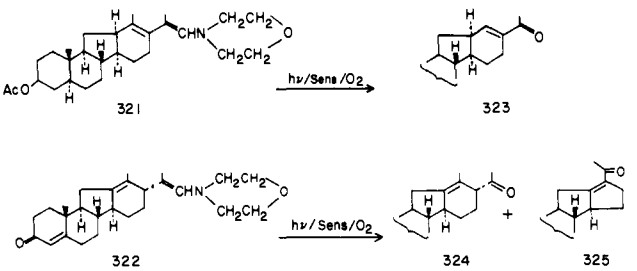
Adam and Schrelber[106,107] synthesized two solanum steroidal alkaloids, demissidine (22*R*,25*S*)-5α-solanidan-3βol (**316**) and



demissidine (22*S*,25*S*)-5α-solanidan-3β-ol (**318**), by irradiating the *N*-chloro derivatives of (22*R*,25*S*)-22,26-imino-5α-cholestan-3β-ol (**315**) and (22*S*,25*R*)-22,26-imino-5α-cholestan-3β-ol (**317**), respectively, in trifluoroacetic acid. Under similar experimental conditions,[108] the irradiation of steroidal alkaloid **319** followed a different photochemical fragmentation path as compared to **315** and **317** and produced the nitrogen-free halogen-containing compound (**320**).



The photooxygenation[109] of enamine **321** in benzene containing Rose Bengal as a sensitizer gave α,β-unsaturated ketone **323** while enamine **322** gave β,γ-unsaturated ketone **324** and α,β-unsaturated ketone with contracted D ring (**325**) under similar experimental conditions.



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