APPLICATION OF ENAMIDE PHOTOCYCLIZATION TO THE SYNTHESIS OF NATURAL PRODUCTS

Ichiya Ninomiya

Kobe Women's College of Pharmacy

Motoyamakita, Higashinada, Kobe, Japan.

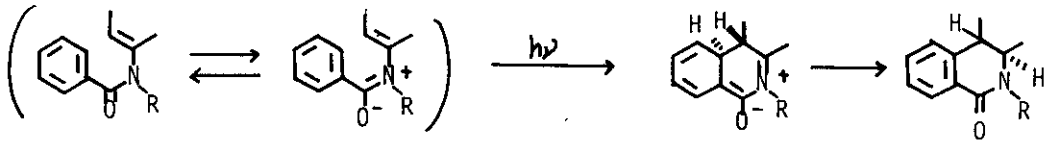
Enamide photocyclization has been shown to be a new and useful tool for the synthesis of various nitrogen-containing heterocyclic systems, particularly alkaloids. By this means, the synthesis of crinan, benzo(c)phenanthridine, aporphine, protoberberine and yohimbine alkaloids has been achieved.

INTRODUCTION

The chemistry of enamines, introduced and developed by G.Stork[1], has been one of the most prolific tools in modern organic synthesis whereas that of imines has not been exploited because of inherent instability and diversity of reactions. However, N-acylenamines, or enamides, which can be regarded as stable derivatives of imines or analogs of enamines, have been employed in photoinduced acyl migration[2a], bromination[2b,2c], reduction[2d], and hydrolysis[2d]. It can therefore be expected that the usefulness of

enamide chemistry will now be expanded.

Recently, a new type of stereospecific photocyclization has been found to occur in the case of enamides with an additional α,β-unsaturated double bond to carbonyl group.[3] Due to the conjugated 6π-electron system, an electrocyclic mechanism has been suggested as follows. The enamide, after excitation (A⟷B), undergoes cyclization in a conrotatory manner to the cyclic intermediate (C) followed by a [1,5]-suprafacial thermal hydrogen shift to afford stereospecifically the trans-lactam (D).



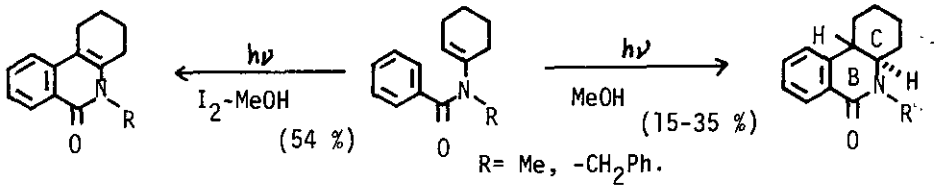
(A) (B) (C) (D)

By applying this enamide photocyclization, various nitrogen-containing heterocyclic systems including a number of isoquinoline alkaloids have been synthesized. This review surveys the utility of enamide photocyclization as applied to the synthesis of natural products, particularly alkaloids and related compounds.

PHENANTHRIDINE ALKALOIDS

A 0.02 M methanolic solution of the N-benzoylenamine (1) of cyclohexanone was irradiated with a low pressure mercury lamp for 40 hr. The reaction mixture, containing a single product as determined by t.l.c. and g.l.c., was evaporated and the resulting solid was recrystallized from alcohol to afford the photocyclized product (2). The B/C trans structure of (2) was assigned from the

n.m.r. data and conversion to a known derivative, thus established the stereospecific course of the photocyclization. On the other hand, irradiation of (1) in the presence of iodine involved an oxidative cyclization to give the dehydrolactam (3).[4]



(3) (1) (2)

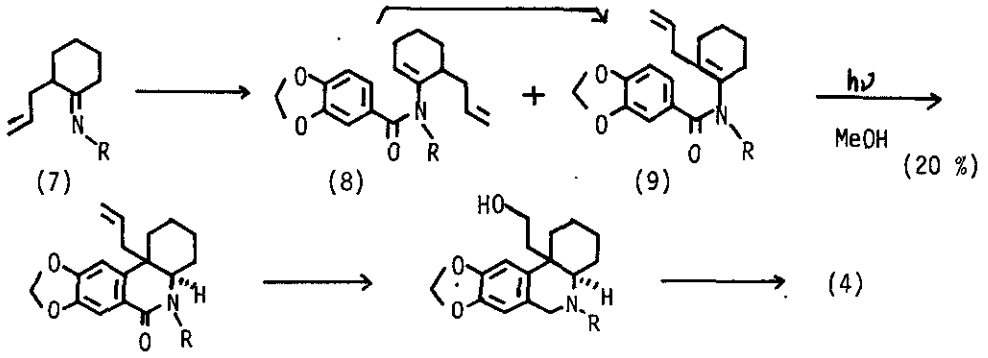
The usefulness of the above enamide photocyclization as a route to alkaloids of the phenanthridine class was demonstrated by the synthesis of crinan (4) and the lactam (5).

CRINAN (4)

(6) (4)

Crinan (4), the basic structure of the Amaryllidaceae alkaloid crinine (6), has been synthesized by a route involving the Diels-Alder reaction which required the separation of two isomeric products[5]. In contrast, benzoylation of the imine (7) derived from 2-allylcyclohexanone afforded a mixture of two enamides (8 and 9) which was unseparable by chromatographic means but was converted into the thermally stable isomer (9) by heating the mixture at elevated temperature or, more conveniently, by irradiation with

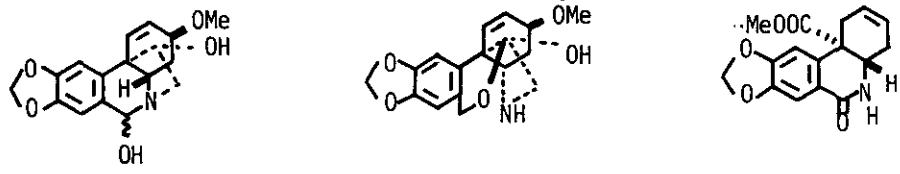
a high pressure mercury lamp for a short time. Photocyclization of the enamide (9) gave the lactam (10) in 20 % yield which was readily converted into crinan (4) by modifying the allyl side chain via (11).[6] (9→10→11→4)



(7) (8) (9) (10) (11)

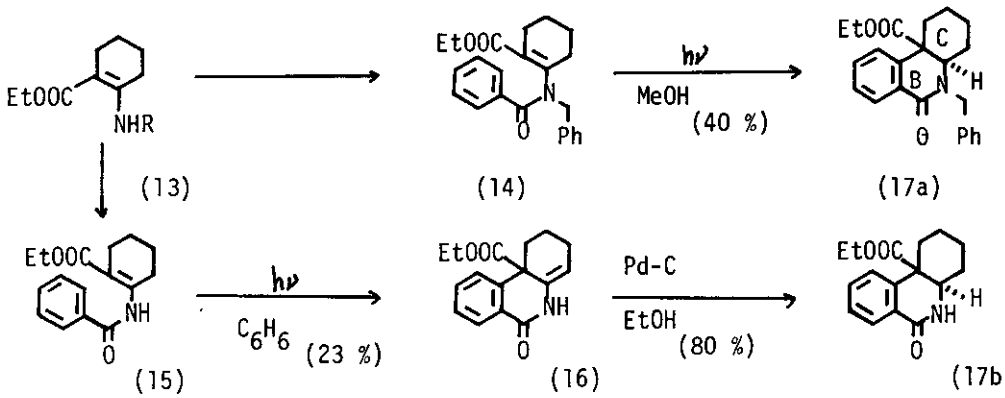
A KEY INTERMEDIATE (5) TO HAEMANTHIDINE

The lactam (5), a key precursor in the first total synthesis of haemanthidine (12a) and nortazettine (12b) by Hendrickson[7], is structurally suitable for enamide photocyclization.

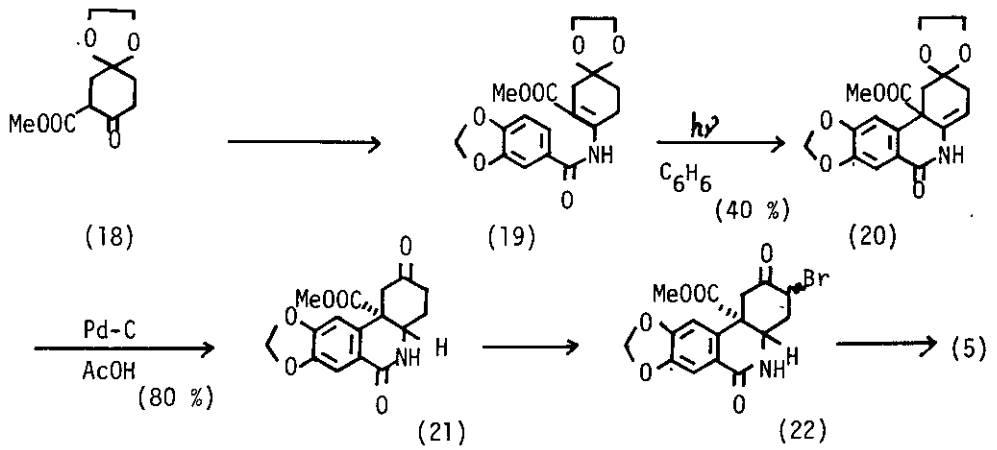


(12a) (12b) (5)

In preliminary experiments, photocyclization of the conjugated enamides (14 and 15), which were readily prepared from the vinylogous carbamate (16), established that an ester group could be introduced at the C_{10a} position.[6b]



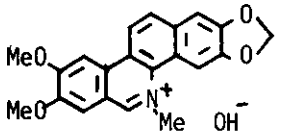
Based on this finding and starting from the substituted cyclohexanone (18), the enamide (19) was prepared and irradiated to give the dehydrolactam (20) followed by stereospecific hydrogenation to afford the B/C trans-lactam (21) in excellent yield. Transformation of (21) by standard methods via the bromo intermediate (22) furnished a convenient route to the key alkaloid precursor (5).[8] (19→20→21→22→5)



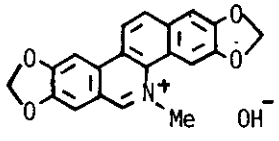
BENZO(c)PHENANTHRIDINE ALKALOIDS

Acylation of the 1-tetralone imines (23) yielded the homogeneous enamide (24) which underwent facile and stereospecific

photocyclization to afford the B/C trans-benzo(c)phenanthridones (25) in better than 50 % yield, while irradiation in the presence of iodine gave the dehydrolactam (26) in good yield. Dehydrogenation of these lactams (25 and 26) provided the aromatic lactam (27), thus indicating a facile route to the synthesis of alkaloids such as nitidine (30) and avicine (31)

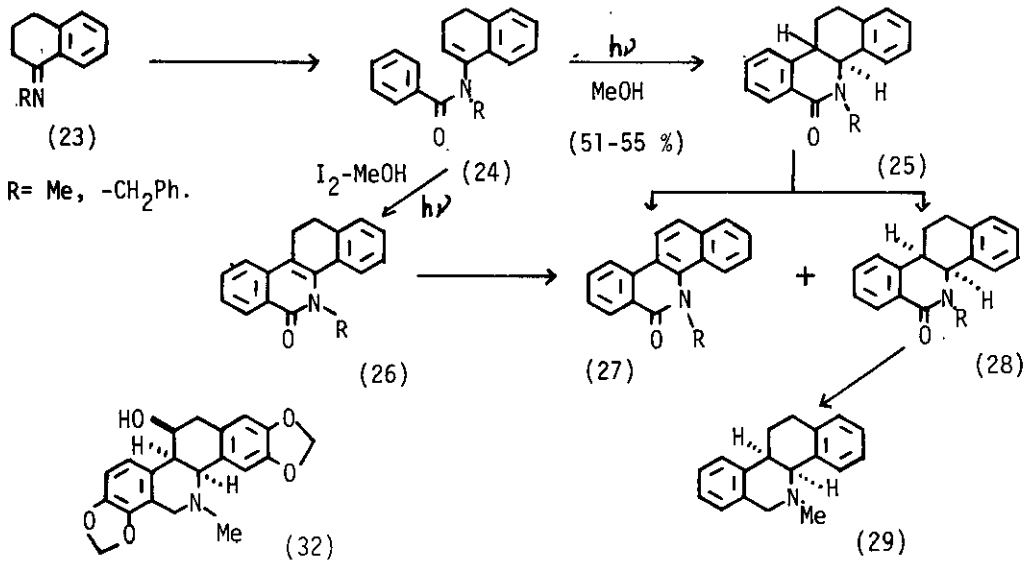


(30)



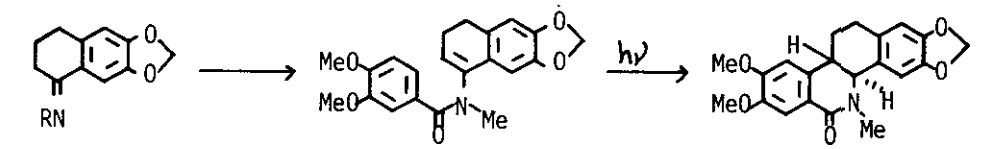
(31)

In addition, selenium dehydrogenation of the photocyclized lactam (25) effected isomerization to yield as the major product the corresponding cis-lactam (28), which was then reduced to the tertiary amine (29). The latter constitutes the same skeletal structure as chelidonine (32), a major alkaloid of Chelidonium majus.[2c]

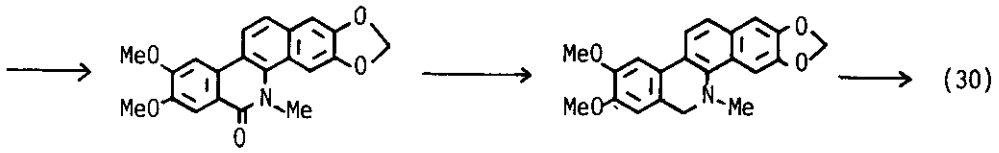


NITIDINE (30)

As an extension of the above reactions, alkaloids such as nitidine (30) can be readily prepared by using enamide photocyclization. The enamide (34), obtained by benzoylation of the imine (33), was subjected to facile photocyclization to yield the homogeneous trans-lactam (35) in 53 % yield which was then dehydrogenated with 30 % Pd-C in p-cymene to oxynitidine (36), though in a poor yield, followed by reduction to the known dihydronitidine (37)[9,10]



(33) (34) (35)

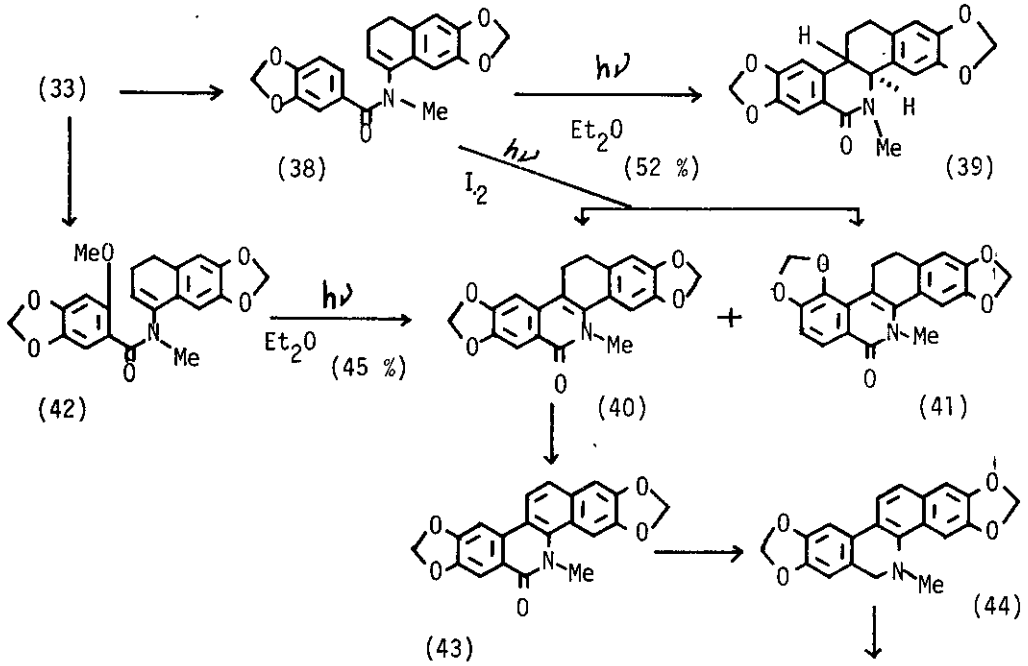


(36) (37)

AVICINE (31)

The enamide (38), also obtained from the imine (33), was photocyclized in ether to the trans-lactam (39) in 52 % yield. However , due to the poor conversion of (39) to oxyavicine (43) by the above sequences, an oxidative photocyclization was applied to the enamide (38) to afford a mixture of the dehydrolactams (40 and 41) in 25 and 6 % yields, respectively. In view of poor regiospecificity of this result, the additionally ortho-methoxy-substi-

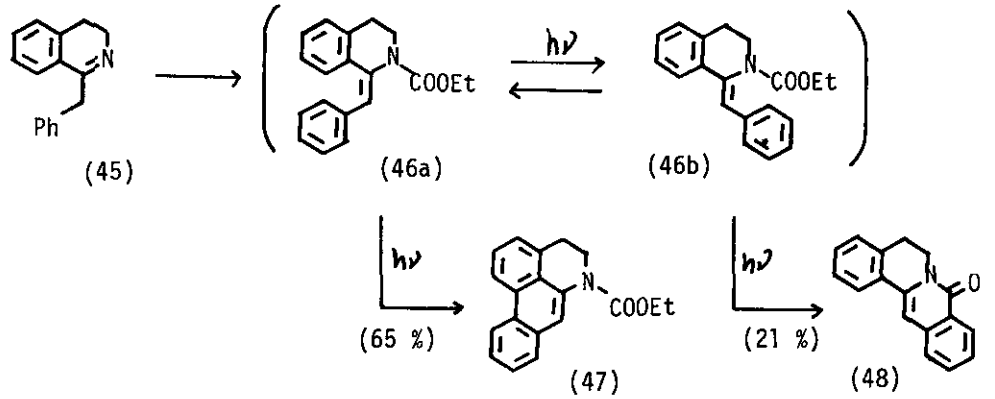
tuted enamide (42) was subjected to photocyclization to give by elimination of the methoxyl group the single dehydrolactam (40) in 45 % yield. Conversion of (40) to oxyavicine (43), dihydroavicine (44)[10] and avicine (31) was readily accomplished by standard methods and thus provided a facile route to this group of alkaloids.[9]



APORPHINE ALKALOIDS

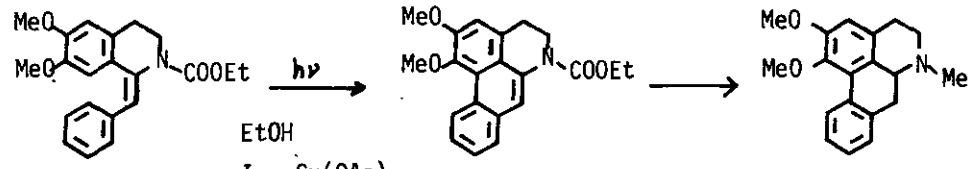
The first examples which demonstrated the utility of enamide photocyclization were described by Cava[11] and Yang[12] for the synthesis of aporphines.

Acylation of the well-known Bischler-Napieralskii product (45) with ethyl chloroformate gave the carbamates (46a and 46b), which were photocyclized upon irradiation in the presence of iodine to afford the aporphine (47) as the major product and the berbine (48) as the minor component.[12a]



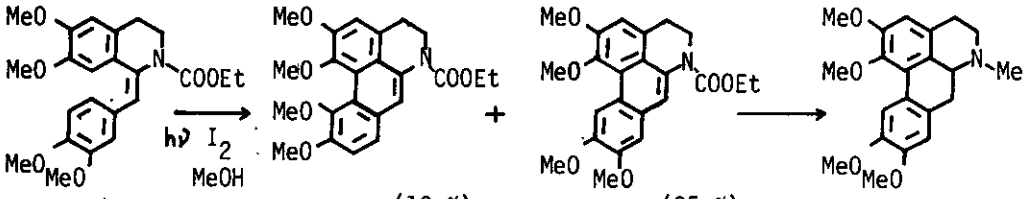
(45) (46a) (46b) (47) (48)

Although the regiospecificity of the cyclization was not extensively studied, photocyclization of other carbamates has been employed in the synthesis of aporphines. Thus, irradiation of (49) in the presence of iodine afforded the aporphine (50) which was then reduced to nuciferine (51).[11]



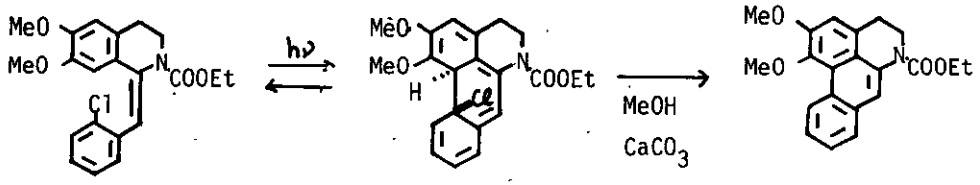
(49) (50) (51)

Similar treatment of the carbamate (52) afforded a mixture of two photocyclized products (53 and 54) which indicated a lack of regiospecificity on cyclization. Reduction of (54) then provided glaucine (55).[11b, 12]



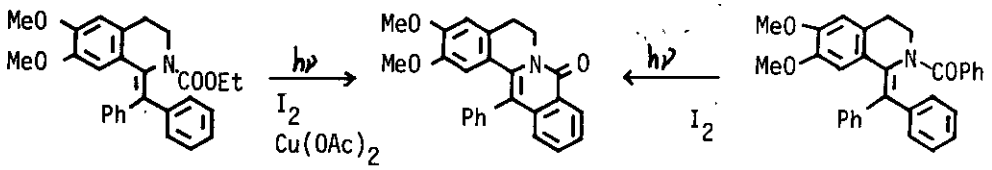
(52) (53) (54) (55)

Although the products from the above photocyclizations had the ydrolactam structure, this reaction proved to be a non-oxidative nature as shown by the following sequences. (56→57→50)[11b]

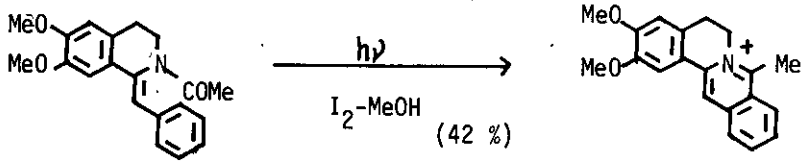


(56) (57) (50)

Carbamate photocyclization has also been extended to the synthesis of berbine-type alkaloids. (58→59, 60→59[13], 61→62[14])

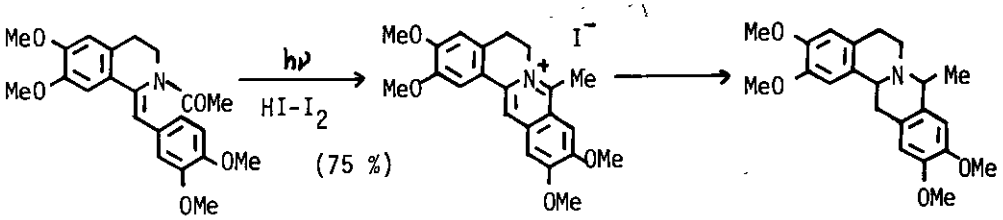


(58) (50 %) (59) (60)



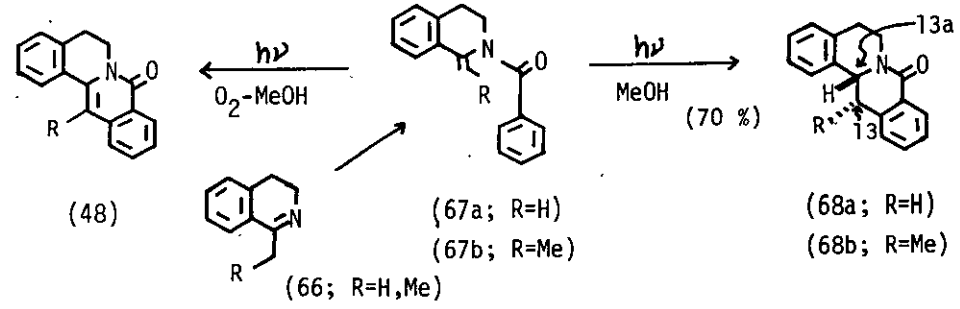
(61) (62)

In addition, the synthesis of β-coralydine (65) via the enamide (63) and the protoberberine (64) has been reported.[14]



PROTOBERBERINE ALKALOIDS

1-Alkyl-3,4-dihydroisoquinolines (66) are cyclic imines and readily convertable into the corresponding N-benzoates (67a and 67b). Since the latter corresponds structurally to the enamide (1), their photocyclization to the berbine derivatives (68) would indicate a potential synthetic route to various protoberberine alkaloids.[15]

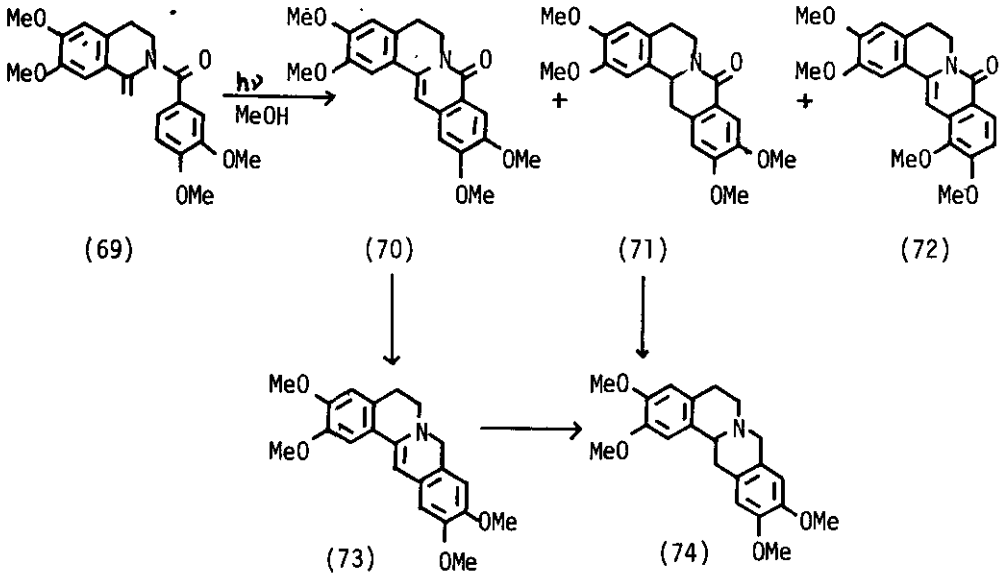


Three hour's irradiation of the enamide (67a), prepared from 1-methyl-3,4-dihydroisoquinoline (66), afforded 8-oxoberbine (68a) in excellent yield while that of the enamide (67b), derived from the 1-ethyl precursor (66), yielded the homogeneous product (68b) with a trans relationship between C_{13}-Me and C_{13a}-H.

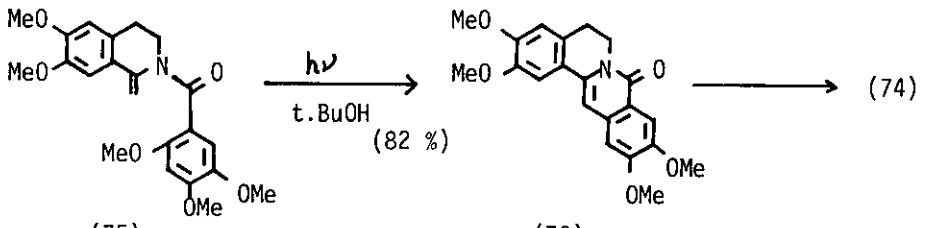
This established that this type of synthesis involves the same stereospecificity as in the case of (1 → 2). Further, oxidative photocyclization of (67a) furnished the dehydrolactam (48) in good yield.[16]

XYLOPININE (74)

Photocyclization of the enamide (69) yielded three photocyclized products (70, 71, and 72) in 40, 5, and 5 % yields respectively. Reduction of (71) with $LiAlH_4$ and (70) with $LiAlH_4$ to the enamine (73) followed by $NaBH_4$ afforded xylopinine (74).[16]



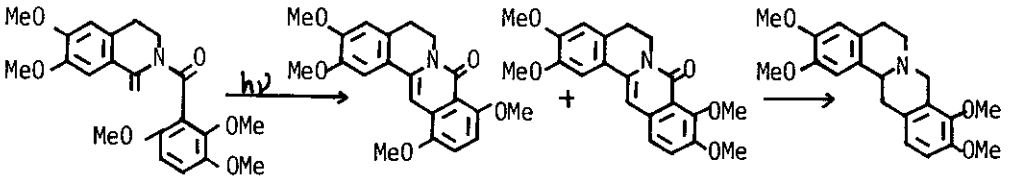
Regiospecificity of the cyclization and therefore its preparative value was demonstrated by Lenz.[17] Photocyclization of the enamide (75) containing an additional methoxyl group at the ortho position induced exclusive cyclization at the root of the methoxyl group to afford the dehydrolactam (70) in excellent yield.[17]



(75) (70)

TETRAHYDROPALMATINE (79)

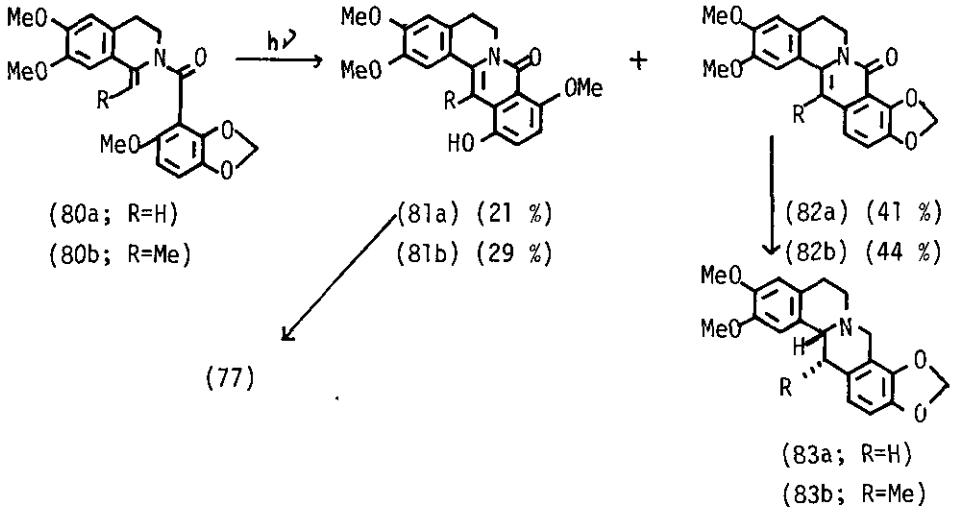
Irradiation of the enamide (76) afforded a mixture of two products (77 and 78). After chromatographic separation, the major product (78) was reduced to give tetrahydropalmatine (79).[18]



(76) (77) (78) (79)

SINACTINE (83a) AND CAVIDINE (83b)

Since many of the protoberberine alkaloids contain a 9,10-methylenedioxy group, the enamides (80a and 80b), which have both methoxyl and methylenedioxy groups at ortho positions, were prepared.[19] Photocyclizations proceeded as expected to furnish the two types of photocyclized products (81a, 81b, and 82a, 82b), respectively. The dehydrolactams (82a and 82b) were reduced to give sinactine (83a) and cavidine (83b)[20], respectively. The by-product (81a) was converted to the compound (77).



(80a; R=H)
(80b; R=Me)

(81a) (21 %)
(81b) (29 %)

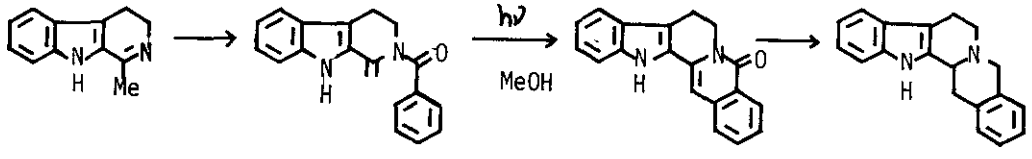
(82a) (41 %)
(82b) (44 %)

(77)

(83a; R=H)
(83b; R=Me)

YOHIMBINE ALKALOIDS

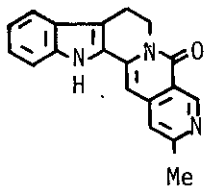
In view of the structural resemblance between 1-alkyl-3,4-dihydroisoquinoline (66) and 1-methyl-3,4-dihydrocarboline, harmalane, (84), the possibility of extending enamide photocyclization to the synthesis of yohimbine alkaloids was investigated. Acylation of harmalane (84) gave the corresponding N-benzoate (85) which was irradiated to yield the dehydrolactam (86) in 36.5 % yield. $LiAlH_4$ and $NaBH_4$ reductions converted (86) into the tertiary amine (87), descarbomethoxydihydrogambirtannine, one of the simplest yohimbine alkaloids.[21]



(84) (85) (86) (87)

ANGUSTIDINE (88)

Recently, three new types of alkaloids, angustidine (88), angustine (89), and angustoline (90), which have a hetero-yohimbine structure, were isolated from Strychnos angustiflora and their structures were determined mainly from the n.m.r. data.[22]



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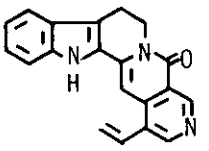
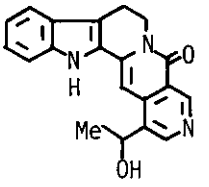
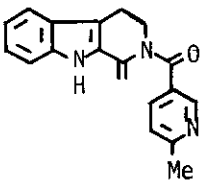
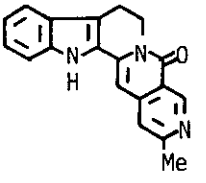
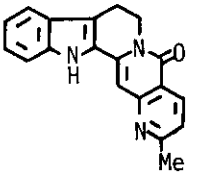


(89)



(90)

These alkaloids have structures suitable as targets for the enamide photocyclization. Thus, the enamide (91), obtained from harmalane (84) by acylation with 6-methylnicotinoyl chloride, was subjected to irradiation. Although the photocyclization was not regiospecific, the anticipated angustidine (88) was obtained as the major product in 20.5 % yield along with its isomer (92) in 13 % yield. Thus the first total synthesis of (88) was achieved.[21]

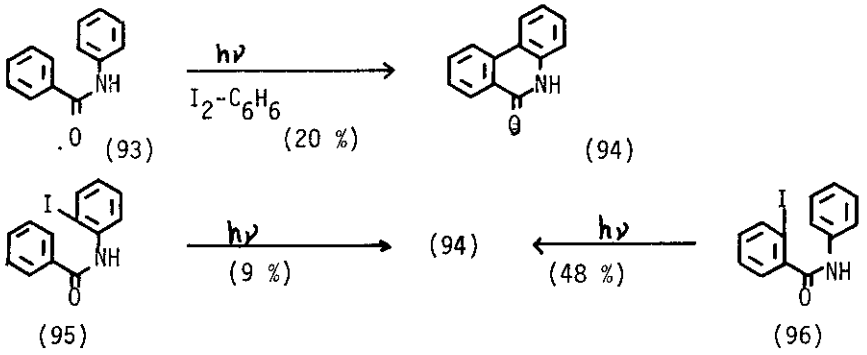
(84) ⟶  $\xrightarrow[\text{MeOH}]{h\nu}$  + 

(91) (88) (92)

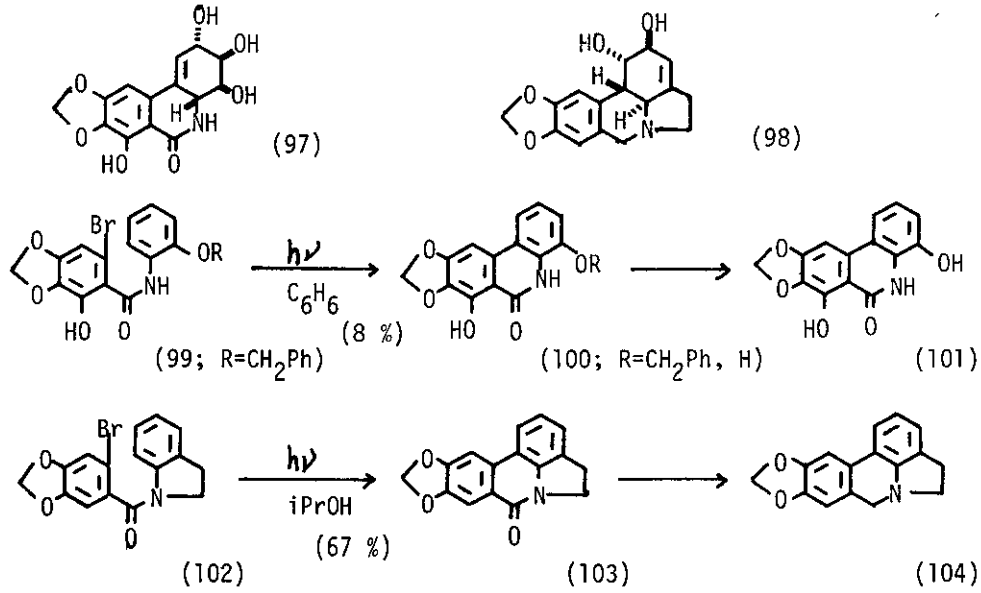
OXIDATIVE PHOTOCYCLIZATION OF BENZANILIDES

In contrast to the above non-oxidative photocyclization, benzanilide (93) underwent cyclization only under oxidative conditions

to afford phenanthridone (94).[23] This type of photocyclization was accelerated by the presence of iodine or by the introduction of halogen (95 and 96) as a substituent at the ortho position as shown below.



This type of cyclization was also applied to the synthesis of narciprimine (101)[24], a degradation product of the mitose poison, narciclasine (or lycoricidinol) (97)[25], (99→100→101), and to the synthesis of anhydrolycorine (104), a degradation product of the Amaryllidaceae alkaloid lycorine (98). (102→103→104)[26]



CONCLUSION

Based on the examples described in this review, the preparative value of enamide photocyclization has been demonstrated. The ready accessibility and stability of enamides as well as the convenient irradiation procedure provides a facile means of synthesizing a variety of isoquinoline alkaloids and related compounds.

ACKNOWLEDGEMENT

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