# ENAMIDE PHOTOCYCLIZATION AND ITS APPLICATION TO THE SYNTHESIS OF HETEROCYCLES

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Abstract Enamides are class of the conjugated systems which contain two C=C double bonds, irrespective of their olefinic or aromatic nature, on both sides of an amide group, thus forming six π-electron conjugated systems capable of undergoing smooth cyclization under irradiation. The application of enamide photocyclization to the synthesis of a variety of six-membered lactams as exemplified by a number of alkaloid and heterocycle syntheses proved this reaction as of a useful general synthetic tool for the construction of various heterocyclic compounds.

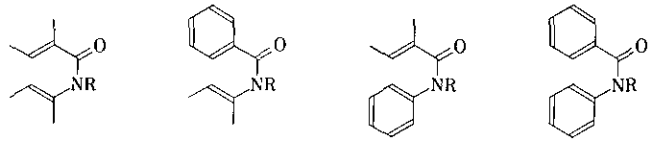
## Introduction

Thermal and photochemical cyclization of hexatrienes with six π-lectron systems to form cyclohexadiene systems may be implicated in the preparation of six-membered rings, which constitute a great part of natural products including terpenes and alkaloids, and have been studied as one of the most important subjects in organic chemistry before and even after the proposal of the generalization by Woodward and Hoffmann[1].

From the same point of view, numerous synthetic studies on the reactions of the six-membered rings including a nitrogen atom which constitutes a characteristic structure in the alkaloids have been thoroughly investigated. However, studies on the nature and application of cyclization of azahexatrienes which are the hexatrienes containing at least one nitrogen atom have not been explored.

During these ten years, we have studied photochemistry of unsaturated amides which contain two double bonds on both sides of the amide group conjugatedly and found that these unsaturated amides, what we called ENAMIDES, underwent facile, non-oxidative and stereospecific photocyclization upon irradiation, thus providing a novel and general approach toward a wide variety of complicated heterocycles from readily available ketones and imines. It is the purpose of this review to summarize the usefulness and synthetic aspects of the photochemical reactions of enamides, particularly their photocyclization.

Enamides can be classified formally into four groups from their structural features of C=C double bonds adjacent to either one of nitrogen atom or carbonyl of amide, that is, by olefinic or aromatic nature and the reactivities of these four types of enamides vary considerably from the most reactive N-acylenamines (enamides-I and II) to the stable acylanilides (enamides-III and IV) as shown in the following structures.



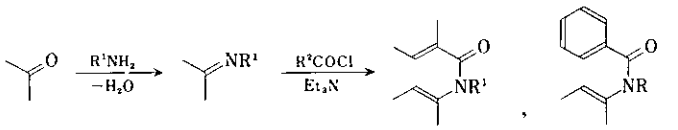
Enamide-I (*N*-Acryloylenamine) Enamide-II (*N*-Benzoylenamine) Enamide-III (Acryloylanilide) Enamide-IV (Benzanilide)

We are going to summarize the enamide photocyclization in this review according to the following items, the general aspects, reaction examples, solvent effect, stereochemistry, mechanism and their application to the synthesis of complex heterocycles. ( The yields cited herein are only of photocyclization )

## (I) Preparation and Property of Enamides

The simplest and most general method of the preparation of enamides is the acylation of an enamine or an aromatic amine with an α,β-unsaturated acid chloride or acid anhydride. Acylation usually takes place only on nitrogen to give the corresponding N-acylenamines or N-acylanilides in good yields, which are rather stable compounds and ready to purify by simple purification, evaporation and recrystallization from the reaction mixture.

( Enamide-I and Enamide-II )

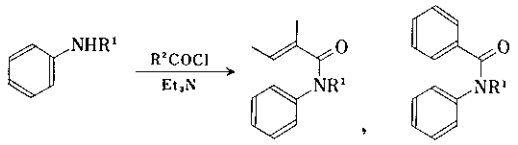


Enamide-I Enamide-II

Acylation of generally unstable imines, which are readily prepared from ketones and primary amines, with α,β-unsaturated acid chlorides such as acryloyl chloride or benzoyl chloride readily gives the corresponding enamide-I or II in good yields, which are comparably stable and crystalline compounds but rather unstable to acid, thus causing hydrolytic cleavage upon heating in acid to give the corresponding carboxamides and ketones depending on the nature of C=C double bond.

Structures of the enamides are easily established from their i.r. spectra which exhibit the peak corresponding to C=C-N-CO grouping at 1650 $cm^{-1}$ and n.m.r. spectra which exhibit signals corresponding to an olefinic proton, which disappears when cyclized.

( Enamide-III and Enamide-IV )



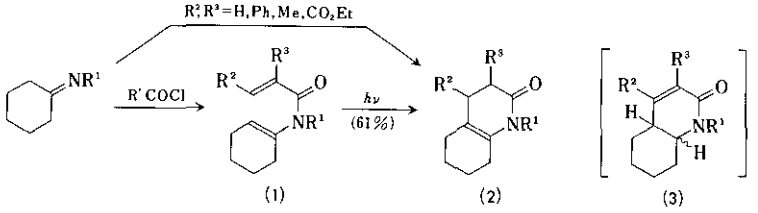
Enamide-III Enamide-IV

As prepared similarly, enamides-III and IV are more stable than their counterparts I and II, because their enamine moieties are the aromatic amines. Acylation of aniline with an α,β-unsaturated acid chlorides affords enamide-III or IV in good yields respectively, which are readily isolated, purified and assigned their structures from i.r. spectra ( absorption at 1650 $cm^{-1}$ for C=C-N-CO grouping) and other spectral evidences.

## (2) Photocyclization of Enamide-I

Irradiation of the enamide (1), prepared from N-cyclohexylidenealkylamine and acryloyl chloride, resulted in the exclusive formation of the hexahydrocarbostyril (2)[2a] and none of the isomeric product (3) was detected in the reaction mixture.

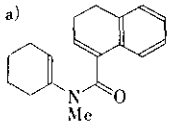
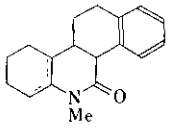
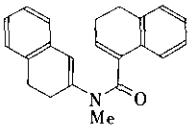
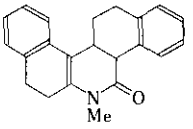
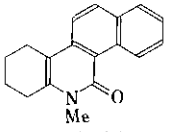
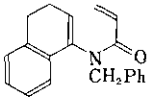
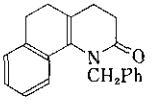
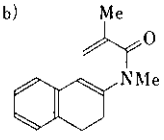
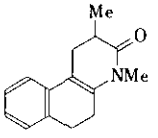
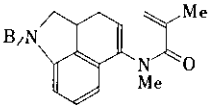
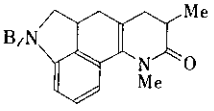
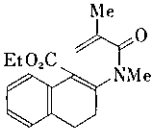
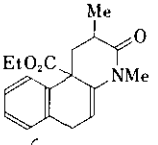
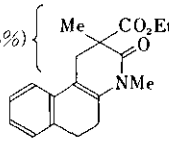
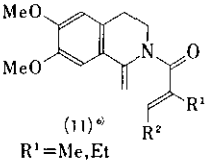
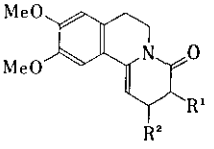
However, the stereochemistry and reaction mechanism including the exclusive formation of (2) remained yet to be studied. Acylation of some imines gave the already cyclized lactams (2)[2] presumably due to the reactivity of an imine or acyl moiety of enamide.




(2-2) Examples of Photocyclization of Enamide-I

Photocyclization of this type of enamides are summarized in Table 1. As seen from the table, the yields of cyclization seem to be depending on the reactivity of the double bonds in the structure of enamides.

Table 1

| Enamide | Photoproduct | Enamide | Photoproduct |
|---|---|---|---|
| a)  (4)[3] |  (12%) |  (8)[5] |  *cis* / *trans* (24%) |
| |  (5) (5%) | c)  (9)[2] |  (42%) |
| b)  (6)[4] |  (45%) |  $B_{\prime}$=COPh (10)[4] |  (28%) |
|  (7)[4] |  (48%)  | d)  (11)[6] $R^1$=Me,Et $R^2$=H,OMe,$CO_2$Me |  (31−57%) |

From the results shown in able 1, the following generalization could be drawn.

a) Stereochemical aspect of the photocyclization of this type of enamides is not clearly understood.

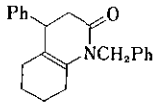
b) The sole formation of the dehydrolactams could be ascribed to the instability of the primary photocyclized products.

c) Photocyclization of enamides prepared from 2-tetraloneimine proceeded very smoothly within relatively short time to give good yields of lactams.

d) The results obtained from enamides from 1-tetraloneimine reflect a great potentiality for the application to ergot alkaloid synthesis.

e) 1-Alkyl-3,4-dihydroisoquinolines, the well-known Bischler-Napieralskıi products, were found to be useful as the starting imines to yield the corresponding enamides just by simple acylation, thus having a potentiality for a general preparation of a number of popular protoberberine alkaloids. Further, introduction of a methoxy group into β-position of the acyl moiety of enamide improved the yield of photocyclization.[6]

High reactivity of this type of enamides was clear from examples of impromptu cyclization to lactams when the corresponding imines were acylated under usual conditions without isolating enamides.[2,7]



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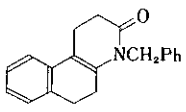

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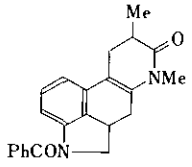
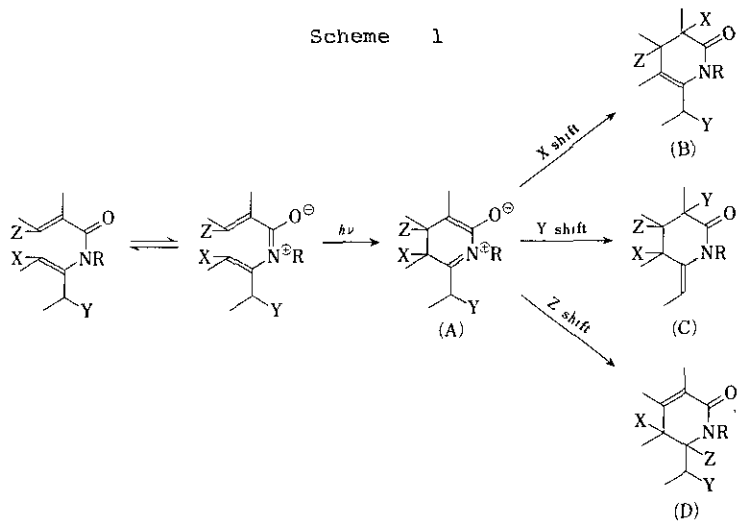



( Reaction Mechanism )

The mechanism of photocyclization of enamide-I can be explained in term of an electrocyclic mechanism as shown in Scheme I as in the case of enamide-II (Scheme 2). There can be expected three types of photoproducts (B), (C), and (D) from a common cyclic intermediate (A). However, the product (D) has not been isolated from the experiments so far carried out.

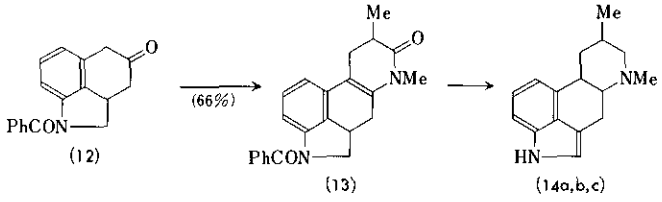
Scheme 1




(2-3) Application to the Synthesis of Alkaloids

Based on the results shown in Table I, the synthesis of Clavine, Ipecac, and Indole alkaloids have been carried out.

(2-3-1) Synthesis of Clavines[7]

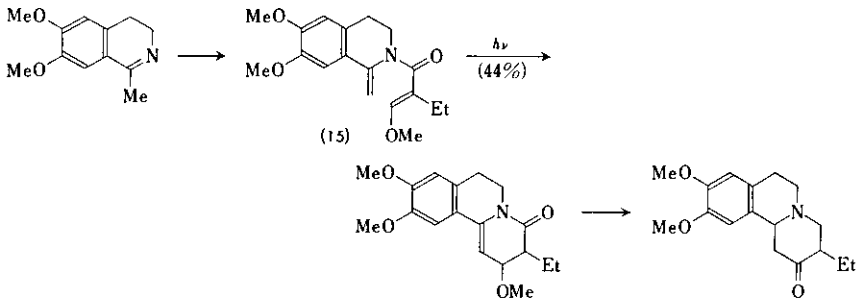



Acylation of the methylimine, which was prepared from the tricyclic ketone (12), with methacryloyl chloride afforded the already-cyclized tetracyclic lactam (13) which contains all the elements of the skeleton of clavine alkaloids and was readily converted into three isomeric clavines, costaclavine (14a), festuclavine (14b), and epicostaclavine (14c)[7], the latter of which was a new isomer hitherto not isolated. Comparison of their n.m.r. spectra firmly established the stereochemistry of costaclavine which had remained to be established.

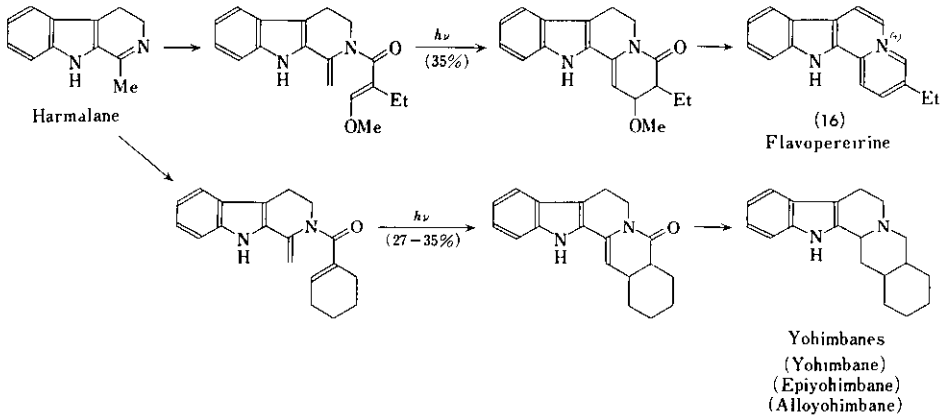
(2-3-2) Synthesis of Ipecac[6] and Indole Alkaloids[8]

1-Alkyl-3,4-dihydroisoquinolines contain a cyclic imine structure, therefore being convertible by simple acylation into the corresponding enamides which were then readily photocyclized to give the lactams as above, though generally in poor

yields.[6] However, introduction of a methoxy group into β-position of the acyl group as shown in the enamide (15) increased the yield of photocyclization as demonstrated by the synthesis of a key intermediate for the synthesis of the alkaloid emetine.[6]




As an extension of the above synthesis, the photocyclization of enamides, prepared from harmalane, succeeded in the simplest preparation of Strychnos alkaloid flavopereirine (16)[8] and in the synthesis of yohimbanes[8], which are basic structures of the alkaloid yohimbine, thus suggesting a potentiality of the application of enamide photocyclization to total synthesis of yohimbine.

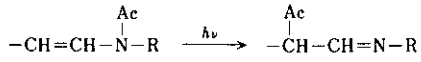



(3) Photocyclization of Enamide-II

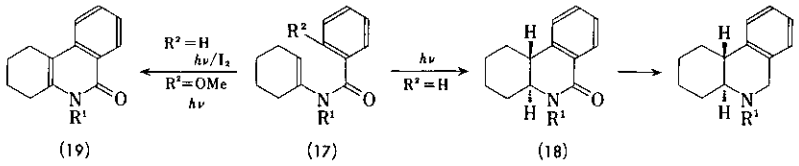
(3-1) Basic Reaction

Photocyclization of enamide-II of N-benzoylenamine type provided the most useful application to the synthesis of a variety of heterocyclic compounds including the naturally abundant isoquinoline alkaloids mainly because of the characteristic structures and reactivities of this type of enamides.

Some simple enamides which are prepared from saturated aliphatic ketones and amines had already been known to undergo ready Photo-Fries rearrangement to give the vinylogous amides as shown below.



However, in 1969, we have discovered a new type of stereospecific photocyclization of N-benzoylenamines (17)[10a,b], which had an additional unsaturation in the acyl moiety, upon irradiation in methanol yielding the homogeneous trans-lactams (18) in good yields. Since irradiation of the enamides (17) under an oxidative condition afforded the dehydrolactams (19), this new photocyclization was found to be of non-oxidative nature. The stereochemistry of photocyclization, that is, the B/C-trans-structure of the photocyclized products (18), was established from n.m.r. spectra, particularly a large coupling constant (J=11Hz) between two protons at the ring junction. The solvent effect on the photocyclization of this type of enamides was observed only on the yields.[37]



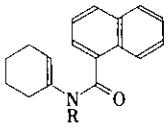
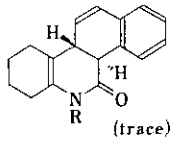
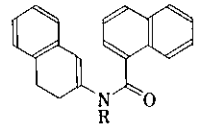
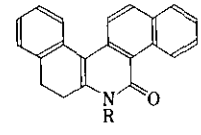
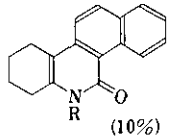
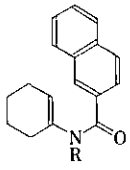
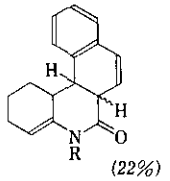
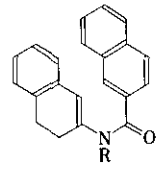
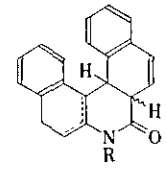
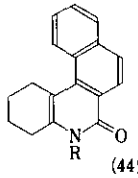
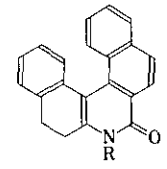
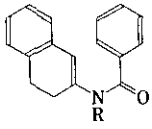
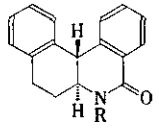
(19) (17) (18)

(3-2) Examples of Photocyclization of Enamide-II

( Synthesis of Basic Structures of Alkaloids and Reaction Mechanism )

Examples of photocyclization of this type of enamides are summarized in Table 2. These enamides were readily prepared by simple acylation of the imines of ketones such as cyclohexanone, 1- and 2-tetralones, with benzoyl, 1- and 2-naphthoyl chlorides respectively. As seen from Table 2, the aromaticity of the benzoyl group would play an important role on the structure of the photoproducts except the cases of the N-naphthoylenamines (20, 21, and 24), which yielded the lactams containing 1,2-dihydronaphthalene structure.

Table 2

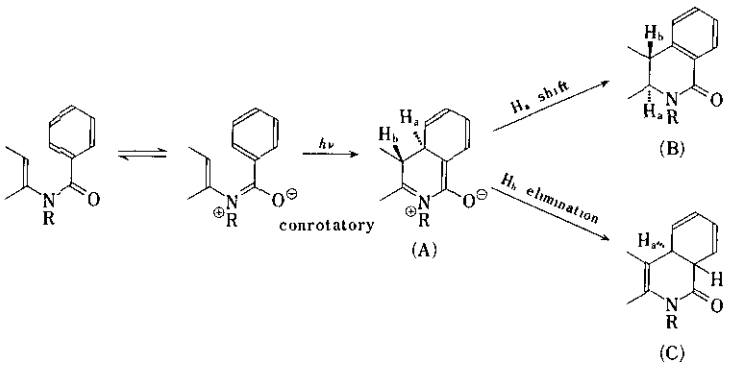
| Enamide | Photoproduct | Enamide | Photoproduct |
|---|---|---|---|
|  (20)[3] |  (trace) |  (23)[5] |  (31%) |
| |  (10%) | | |
|  (21)[4] |  (22%) |  (24)[1] |  (16%) |
| |  (44%) | |  (5%) |
|  (22)[12a b] |  (40–71%) | R=Me,$CH_2$Ph | |

( *Reaction Mechanism* )

From the results summarized in Table 2, the reaction mechanism of photocyclization of enamide-II can be explained as follows; upon irradiation, N-benzoylenamine (enamide-II) undergoes cyclization after excitation in a conrotatory manner to form a cyclic trans-intermediate (A), which then undergoes a thermally allowed suprafacial [1,5] shift of $H_a$ to give the trans-lactam (B) stereospecifically.

However, in the case of the N-naphthoylenamines (20, 21, and 24), the migration of $H_b$ in (A) occurs predominantly to afford the product (C), thus loosing the aromaticity of the naphthalene ring. A driving force of the predominant formation of the product (C) over (B) might be ascribed to lower resonance energy of the naphthalene than the benzene ring.

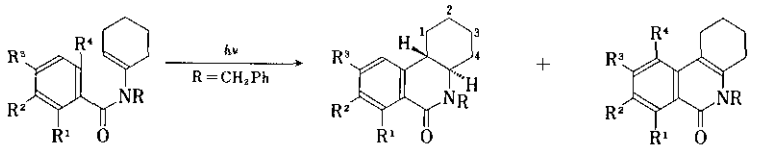
Scheme 2




(3-3) Substituent Effect

A wide variety of N-benzoylenamines were prepared and irradiated to afford the results summarized in Table 3.

Table 3




| | | | |
|---|---|---|---|
| (25)[13] | $R^1=R^3=R^4=H$, $R^2=OMe$ | $R^1=R^3=H$, $R^2=OMe$ (42%) | |
| (26)[13] | $R^1=R^2=R^4=H$, $R^3=OMe$ | $R^1=R^2=H$, $R^3=OMe$ (29%) | |
| (27)[13] | $R^1=R^2=R^4=H$, $R^3=CO_2Me$ | $R^1=R^2=H$, $R^3=CO_2Me$ (10%) | $R^1=R^2=R^4=H$, $R^3=CO_2Me$ (15%) |
| (28)[13] | $R^1=R^2=R^4=H$, $R^3=NO_2$ | | $R^1=R^2=R^4=H$, $R^3=NO_2$ (14%) |
| (29)[14] | $R^2=R^3=R^4=H$, $R^1=OMe$ | $R^1=R^2=R^3=H$, 4a-OMe (30%) | $R^1=R^2=R^3=R^4=H$ (18%) |
| (30)[13] | $R^2=R^3=H$, $R^1=R^4=OMe$ | | $R^2=R^3=R^4=H$, $R^1=OMe$ (10%) |
| (31)[13] | $R^3=R^4=H$, $R^1=R^2=OMe$ | | $R^1=R^2=R^3=H$, $R^4=OMe$ (15%) |
| (32)[14] | $R^3=R^4=H$, $R^1=OCH_2O=R^2$ | | $R^1=R^2=R^3=H$, $R^4=OH$ (14%) |
| (33)[14] | $R^2=R^3=R^4=H$, $R^1=NH_2$ | $R^2=R^3=H$, $R^1=NH_2$ (71%) | |
| (34)[14] | $R^2=R^3=R^4=H$, $R^1=CO_2Me$ | | $R^2=R^3=R^4=H$, $R^1=CO_2Me$ (2.5%)<br>$R^1=R^2=R^3=R^4=H$ (1 5%) |

From the results shown in the above table, the following generalization could be drawn.

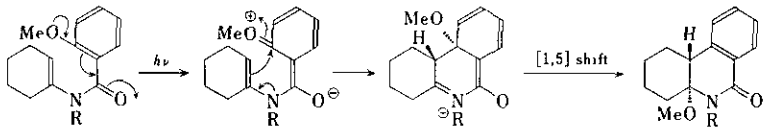
a) Introduction of an electron-donating group into a benzene ring accelerates the photocyclization to a great extent as exemplified by the cases of enamides (25 and 33).

b) On the other hand, the presence of an electron-attracting group suppresses the reaction and increases the yield of the dehydrolactam as in the cases of (27 and 28).

c) Introduction of either an ortho-methoxy or methylenedioxy group facilitates regiospecific photocyclization at the root of the substituent as exemplified by the cases of (29-32).

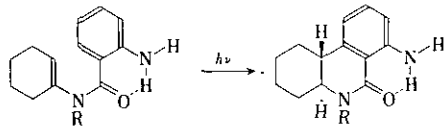
These results in Table 3 clearly indicate the synthetic usefulness of this type of photocyclization. In particular, a regiospecific photocyclization of ortho-methoxy-substituted enamides has been found extremely useful in total synthesis of a variety of alkaloids.[14]

The most likely explanation for the regiospecific photocyclization in the case of the ortho-methoxy-substituted enamides would be as shown in the following scheme.




Because of the contribution of the excited state which involves the ortho-methoxy group, a photo-induced conrotatory cyclization would occur specifically at the root of the substituent to yield the trans-intermediate. Then a thermally allowed suprafacial [1,5]shift of the methoxy group would follow to give the homogeneous product.

Regiospecific photocyclization of the ortho-amino-substituted enamides, which however give cyclization exclusively at the opposite site of the amino group, would be ascribed to strong hydrogen bonding between the amino and carbonyl groups, thus fixing the conformation of the enamide in a form favorable to cyclization as shown.

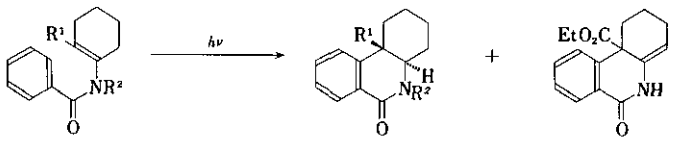



(3-4) Synthesis of Phenanthridines and Application to the Synthesis of Alkaloids

Photocyclization of enamide-II has been most typically applied to the syntheses of phenanthridine and benzo[c]phenanthridine alkaloids. Since phenanthridine is a popular skeleton abundantly occurred in alkaloids particularly of Amarylidaceae such as lycorine and crinine, our synthetic examples shown in Table 4 would provide a great potentiality of this cyclization as a synthetic tool.

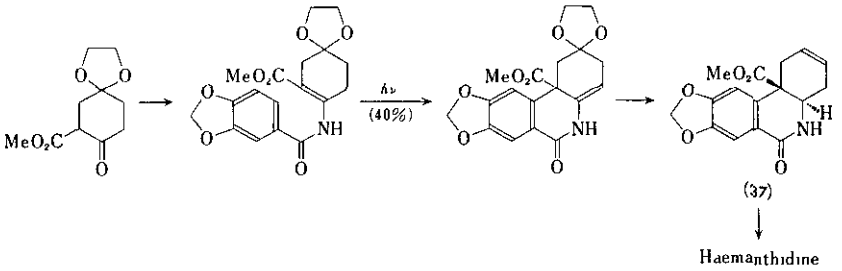
As examples of its application, syntheses of crinan, which is a basic structure of the alkaloid crinine, and γ-lycoran, which is also a basic structure of the alkaloid lycorine, are shown along with a convenient synthesis of a key intermediate (37) for the synthesis of the alkaloid haemanthidine.

Table 4



| | | |
|---|---|---|
| (35)[10b] $R^1$=Me, $R^2$=$CH_2Ph$ | $R^1$=Me, $R^2$=$CH_2Ph$ (55%) | ——— |
| (36)[10b] $R^1$=$CO_2Et$, $R^2$=$CH_2Ph$ | $R^1$=$CO_2Et$, $R^2$=$CH_2Ph$ (40%) | ——— |
| $R^1$=$CO_2Et$, $R^2$=H | ——— | (23%)[16] |

(3-4-1) Synthesis of a Key Intermediate (37) for Haemanthidine[16]

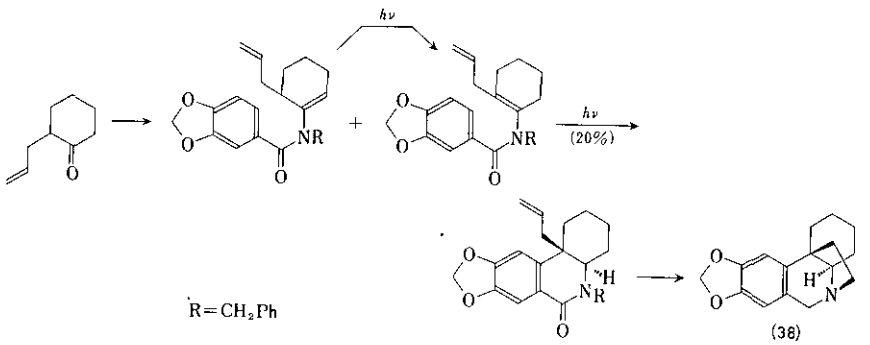


(37)

↓

Haemanthidine

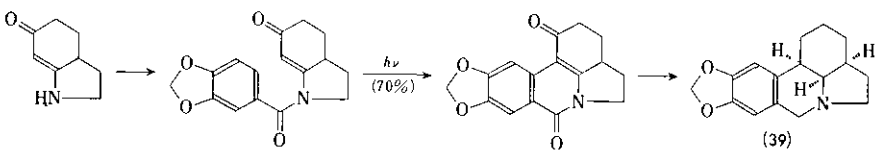
(3-4-2) Synthesis of Crinan (38)[17]



R=$CH_2Ph$

(38)

(3-4-3) Synthesis of γ-Lycoran (39)[18]

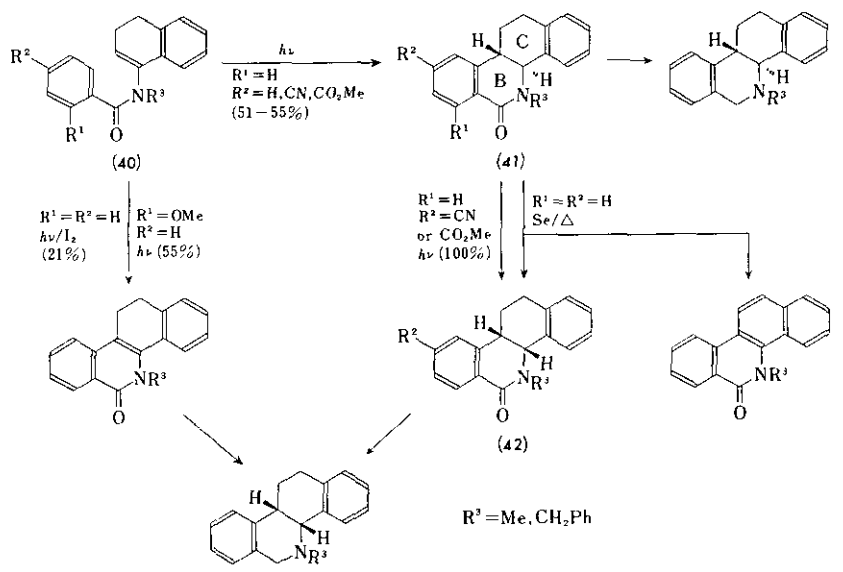


(39)

(3-5) Synthesis of Benzo[c]phenanthridines and Application to the Synthesis of Alkaloids

Acylation of 1-tetraloneimines with benzoyl chloride yielded homogeneous and comparably stable enamides (40) in good yields, which underwent smooth and stereo-

Scheme 3




specific photocyclization to afford the B/C-trans-hexahydrobenzo[c]phenanthridones (41) in over 50 % yields[19]. The structures of the photocyclized products (41) were established from their n.m.r. spectra and chemical reactions as shown in Scheme 3.

Fortunately, the B/C-cis-benzo[c]phenanthridones (42) were obtained by both the photo-induced isomerization[20] and thermal treatment with selenium[19] on the trans-lactams (41), presumably due to relative stability of the cis-isomers (42) over the trans-counterparts (41) in this particular series of compounds. Thus, direct comparisons of both cis- and trans-derivatives as shown in Scheme 3 established their structures unambiguously.

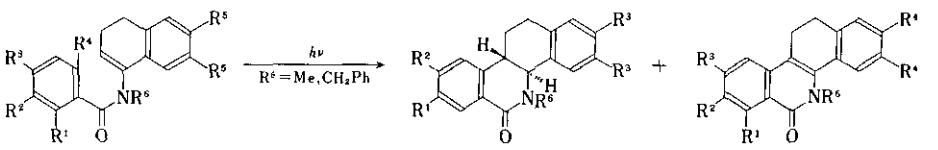
As a result, photocyclization of this type of enamides was found to be of non-oxidative and stereospecific nature, therefore proving the usefulness as a synthetic tool.

(3-5-1) Substituent Effect in the Photocyclization to Benzo[c]phenanthridones

The effects of the substituents on the yields of photocyclization to benzo[c]-phenanthridones are summarized in Table 5.

Most important of all is a regiospecific photocyclization of the ortho-methoxy-substituted enamides which can be expected to have a great potentiality for the application to the alkaloid synthesis as shown in the following chapter (3-5-3). When the enamide bearing an electron-attracting group on the benzene ring was irradiated, a considerable amount of the dehydrolactam was obtained.

Table 5

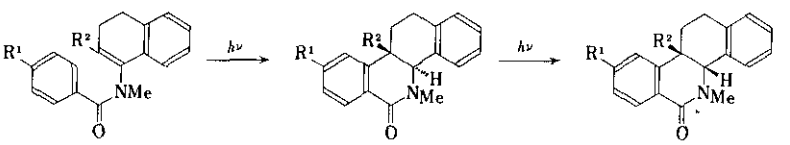


| | | |
|---|---|---|
| (43)[21] $R^1=R^4=H, R^2+R^3=R^5=OCH_2O$ | $R^1+R^2=R^3=OCH_2O$ (52%) | |
| (44)[21] $R^1=R^4=H, R^2=R^3=OMe, R^5=OCH_2O$ | $R^1=R^2=OMe, R^3=OCH_2O$ (60%) | |
| (45)[13,20] $R^1=R^2=R^4=R^5=H, R^3=OMe$ | $R^1=R^3=H, R^2=OMe$ (30%) | $R^1=R^2=R^3=H, R^4=OMe$ (50%) |
| (46)[13] $R^1=R^2=R^4=R^5=H, R^3=OAc$ | $R^1=R^3=H, R^2=OAc$ (33%) | $R^3=H, R^1+R^2=R^4=OCH_2O$ (30%) |
| (47)[13] $R^1=R^3=R^4=R^5=H, R^2=CO_2Me$ | $R^2=R^3=H, R^1=CO_2Me$ (24%) | $R^1=R^2=R^4=H, R^3=NO_2$ (8%) |
| (48)[22] $R^2=R^3=R^4=H, R^1=R^5=OMe$ | | $R^2=R^3=R^4=H, R^1=CO_2Me$ (5%) |
| (49)[4] $R^3=H, R^1+R^2=R^5=OCH_2O, R^4=OMe$ | | |
| (50)[4] $R^1=R^2=R^4=R^5=H, R^3=NO_2$ | | |
| (51)[4] $R^2=R^3=R^4=R^5=H, R^1=CO_2Me$ | | |

(3-5-2) Photo-Induced Isomerization of B/C-trans-Benzo[c]phenanthridones to Their cis-Isomers

It was found that further irradiation on the photocyclized product, B/C-trans-benzo[c]phenanthridones (41), resulted in the irreversible formation of the cis-isomers (42)[20, 23] as shown in Table 6. In addition to the facts that some benzo-[c]phenanthridones underwent smooth thermal isomerization upon heating with selenium as described previously[19], this photoisomerization suggests that the cis-isomers would be more stable than their counterparts in this particular series of heterocycles.

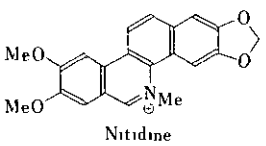
Table 6

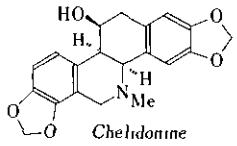


| | | |
|---|---|---|
| $R^2=H, R^1=CO_2Me$ | (52)[20] (20%) | (100%) |
| $R^2=H, R^1=CN$ | (53)[20] (20%) | (100%) |
| $R^1=H, R^2=Me$ | (54)[23] (8%) | (100%) |
| $R^1=H, R^2=CONHMe$ | (55)[23] (77%) | (100%) |

(3-5-3) Synthesis of Benzo[c]phenanthridine Alkaloids

Benzo[c]phenanthridine alkaloids can be divided into two groups[15b], the fully aromatized and B/C-hexahydro alkaloids. The former group of alkaloids such as nitidine and fagaronine are known for their potent antitumor activity[24], therefore having been challenging targets for their syntheses, which have been achieved by several groups.[15a] However, the synthesis of the B/C-hexahydro alkaloids have been almost unexploited except the work by Oppolzer on total synthesis of chelidonine


Nitidine

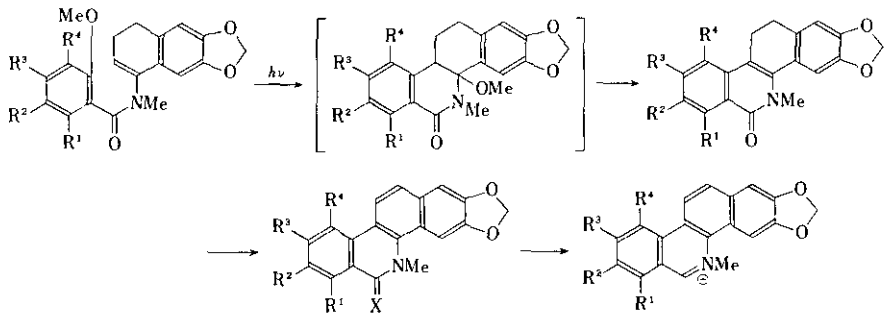

Chelidonine

because of their complicated stereochemistry.

a) Synthesis of the Fully Aromatized Alkaloids

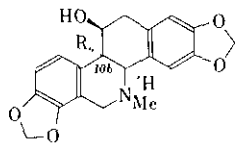
Based on the results shown in Scheme 3, synthetic usefulness of enamide photocyclization was clearly demonstrated by total synthesis of the alkaloids such as avicine, nitidine[21], sanguinarine, chelerythrine, and chelirubine, of which the total synthesis of chelirubine[25] has solved the pending ambiguity on its structure. Outline of the synthetic pathway of this group of alkaloids is summarized in Scheme 4.

Scheme 4



| (X=O,H$_2$) | R$^1$ | R$^2$ | R$^3$ | R$^4$ | |
|---|---|---|---|---|---|
| | H | $-OCH_2O-$ | | H | Dihydroavicine (41%)[21] |
| | H | OMe | OMe | H | Dihydronitidine (50%)[21] |
| | $-OCH_2O-$ | | H | H | Oxysanguinarine (30%)[4] |
| | OMe | OMe | H | H | Oxychelerythrine (19%)[26] |
| | $-OCH_2O-$ | | H | OMe | Chelirubine (38%)[25] |

b) Synthesis of the B/C-Hexahydro Alkaloids


R=H Chelidonine
R=Me: Corynoline

The alkaloid corynoline and its congeners, which were isolated from the Corydalis plants, have a common structural feature of B/C-cis-hexahydro-10b-methylbenzo[c]phenanthridine with an additional hydroxy group in the ring C.

On the other hand, the chelidonine group of alkaloids, which occur in the papaverous plants, have a closely resembled structure with corynoline but lacking a methyl group at C-10b.

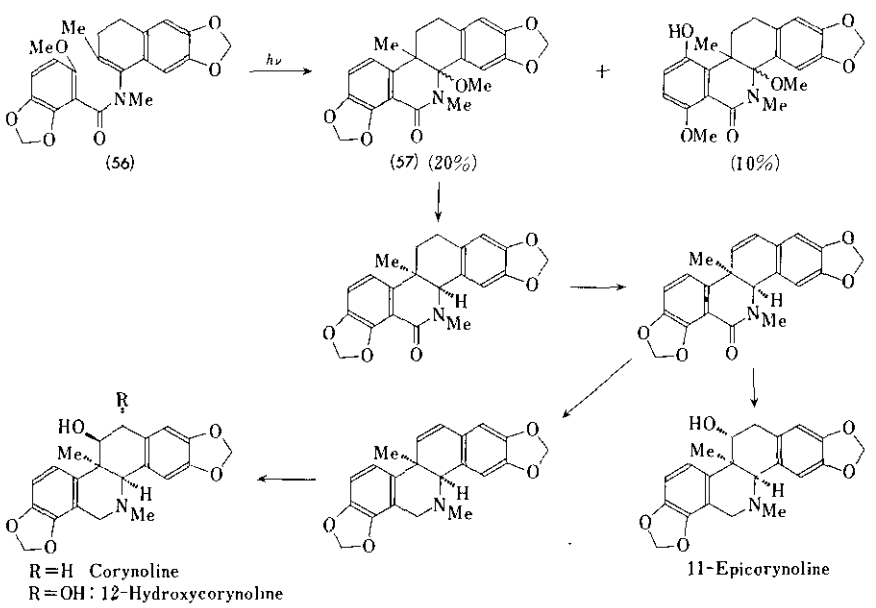
Since these two groups of alkaloids had been almost untouched from attack by chemists except the work by Oppolzer[27], we have picked these alkaloids as our targets to prove usefulness of enamide photocyclization and succeeded in their total synthesis as shown below.

i) Total Synthesis of Corynoline Group of Alkaloids[23, 28]

Due to the structure of enamide (56) requisite for the synthesis of these alkaloids by means of enamide photocyclization, an additional ortho-methoxy group had to be introduced into the enamide (56) as a bait in addition to a methylenedioxy group on the other side. Photocyclization of (56) therefore showed no regiospecificity, thus affording a mixture of two lactams. However, the major product (57) was a compound required for the total synthesis of the alkaloids, corynoline, 12-hydroxycorynoline, and 11-epicorynoline.[28]

Total synthesis of these alkaloids was achieved by the reaction course shown in Scheme 5, which included the construction of a B/C-cis ring junction by isomerization of the trans-photocyclized product (57) and the stereoselective introduction of a hydroxy group into ring C as the most crucial steps.

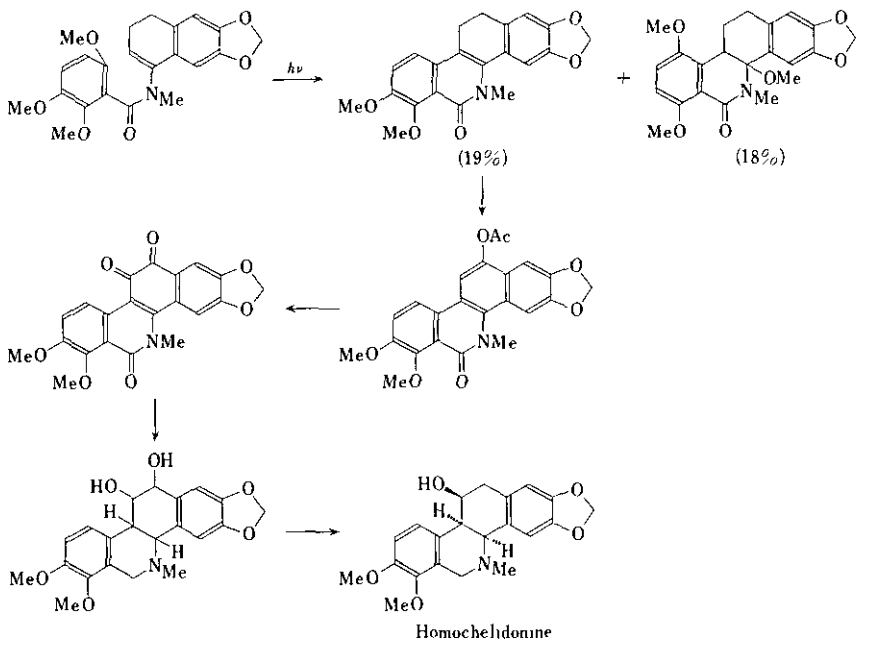
Scheme 5



ii) Total Synthesis of Homochelidonine[22, 26]

Since Oppolzer[27] had already succeeded in the initial total synthesis of chelidonine, we have picked homochelidonine[15] as our target to challenge and completed it by the route shown in Scheme 6.

Scheme 6




The absence of 10b-methyl group in this group of alkaloids enhanced a possibility of aromatization of the compounds appeared during the course of synthesis. This was overcome by preparing the ortho-quinone intermediate followed by a combination of reductions.

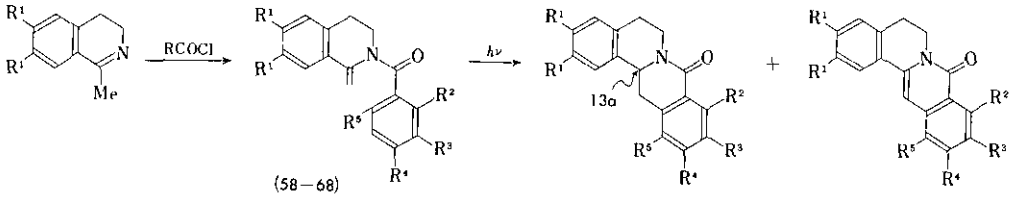
(3-6) Synthesis of Berbines and Application to the Synthesis of the Protoberberine Alkaloids.

Berbine is a basic structure of the popular protoberberine alkaloids and has a structural feature most suitable as a target for the synthesis by enamide photocyclization. The enamides were prepared readily from the Bischler-Napieralski products by simple acylation on nitrogen with benzoyl chloride.

Since the variety of many protoberberine alkaloids is on the number and location of substituents mostly oxygen function, such as hydroxy, methoxy, or methylenedioxy group, we have investigated the photocyclization of various enamides carrying

various substituents as summarized in Table 7.[30, 31]

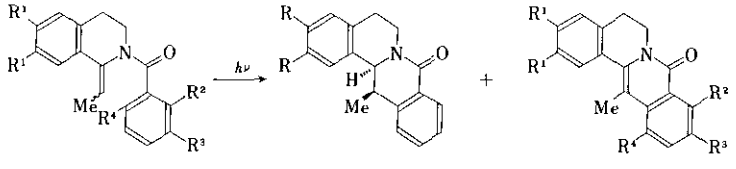
Table 7




| | | |
|---|---|---|
| (58) $R^1=R^2=R^3=R^4=R^5=H$ | $R^1=R^2=R^3=R^4=R^5=H$ (40%) | $R^1=R^2=R^3=R^4=R^5=H$ (20%) |
| (59) $R^2=R^3=R^4=R^5=H$, $R^1=OMe$ | $R^2=R^3=R^4=R^5=H$, $R^1=OMe$ (18%) | $R^2=R^3=R^4=R^5=H$, $R^1=OMe$ (24%) |
| (60) $R^2=R^5=H$, $R^1=R^3=R^4=OMe$ | $R^2=R^5=H$, $R^1=R^3=R^4=OMe$ (5%) | $R^3=R^5=H$, $R^1=R^3=R^4=OMe$ (40%) |
| | | $R^2=R^3=H$, $R^1=R^4=R^5=OMe$ (5%) |
| (61) $R^1=R^3=R^4=R^5=H$, $R^2=OMe$ | | $R^1=R^2=R^3=R^4=R^5=H$ (50%) |
| (62) $R^3=R^4=R^5=H$, $R^1=R^2=OMe$ | | $R^2=R^3=R^4=R^5=H$, $R^1=OMe$ (46%) |
| (63) $R^3=R^4=H$, $R^1=R^2=R^5=OMe$ | | $R^3=R^4=R^5=H$, $R^1=R^2=OMe$ (56%) |
| (64) $R^1=R^4=H$, $R^2=R^3=R^5=OMe$ | | $R^1=R^4=R^5=H$, $R^2=R^3=OMe$ (25%) |
| | | $R^1=R^3=R^4=H$, $R^2=R^5=OMe$ (10%) |
| (65) $R^4=H$, $R^1=R^2=R^3=R^5=OMe$ | | $R^4=R^5=H$, $R^1=R^2=R^3=OMe$ (20%) |
| | | $R^5=R^4=H$, $R^1=R^2=R^5=OMe$ (8%) |
| (66) $R^4=H$, $R^1=R^5=OMe$, $R^2=OCH_2O=R^3$ | | $R^4=R^5=H$, $R^1=OMe$, $R^2=OCH_2O=R^3$ (44%) |
| | | $R^3=R^4=H$, $R^1=R^2=OMe$, $R^5=OH$ (21%) |
| (67) $R^2=R^3=R^5=H$, $R^1=OMe$, $R^4=NO_2$ | | $R^2=R^3=R^5=H$, $R^1=OMe$, $R^4=NO_2$ (8%) |
| (68) $R^3=R^4=R^5=H$, $R^1=OMe$, $R^2=CO_2Me$ | $R^2=R^3=R^4=R^5=H$, $R^1=OMe$, 13a-$CO_2Me$ (8%) | $R^3=R^4=R^5=H$, $R^1=OMe$, $R^2=CO_2Me$ (5%) |

Versatility of the enamide photocyclization was also demonstrated by the ready synthesis of 13-methylberbines as shown in Table 8. The enamides for the 13-methylberbine synthesis were readily prepared from 1-ethyl-3,4-dihydroisoquinolines. Therefore, this synthesis can be further extendable to a wide variety of the Bischler-Napieralskii products having an alkyl or aralkyl group at C-1.

Table 8



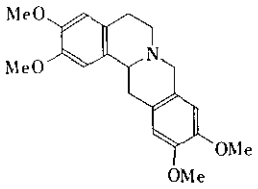

| | | |
|---|---|---|
| (61) $R^1=R^2=R^3=R^4=H$ | R=H (30%) | $R^1=R^2=R^3=R^4=H$ (4%) |
| (62) $R^1=R^3=R^4=H$, $R^2=OMe$ | R=H 13a-OMe (25%) | |
| (63) $R^2=R^3=R^4=H$, $R^1=OMe$ | R=OMe (37%) | $R^2=R^3=R^4=H$, $R^1=OMe$ (9%) |
| (64) $R^3=R^4=H$, $R^1=R^2=OMe$ | | $R^2=R^3=R^4=H$, $R^1=OMe$ (35%) |
| (65) $R^3=H$, $R^1=R^2=R^4=OMe$ | | $R^3=R^4=H$, $R^1=R^2=OMe$ (34%) |
| (66) $R^1=R^4=OMe$, $R^2=OCH_2O=R^3$ | | $R^4=H$, $R^1=OMe$, $R^2=OCH_2O=R^3$ (41%) |
| | | $R^3=H$, $R^1=R^2=OMe$, $R^4=OH$ (29%) |

However, as clear from Table 8, the dehydrolactams became the major products in the photocyclization of enamides from 1-alkyl-3,4-dihydroisoquinolines.

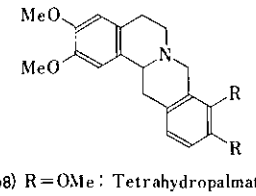
By applying the above results, total syntheses of protoberberine alkaloids

such as xylopinine (67)[30], tetrahydropalmatine (68)[30b], sinactine (69)[30b, 31], and cavidine (70)[31, 32a] were achieved in only four steps respectively, of which the synthesis of cavidine was the initial one which solved the pending problem on structure. As a further extension, we have synthesized the aza-analogs of berbines (71) by irradiation of the pyridine analogs of enamides.[31, 32a]

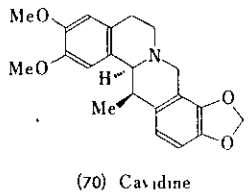
Lenz and Kametani added another examples of berbine synthesis by enamide photocyclization.[32]



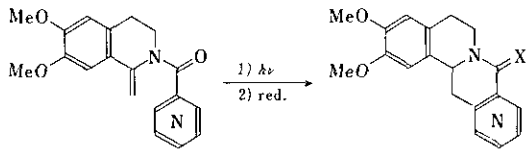
(67) Xylopinine



(68) R=OMe: Tetrahydropalmatine
(69) R=$OCH_2O$=R' Sinactine



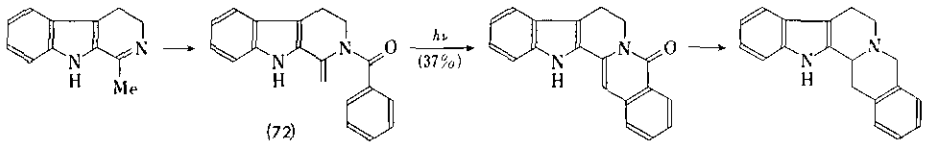
(70) Cavidine



(71) X=O, $H_2$

(3-7) Synthesis of the Yohimbine Skeleton and Application to the Synthesis of Alkaloids.

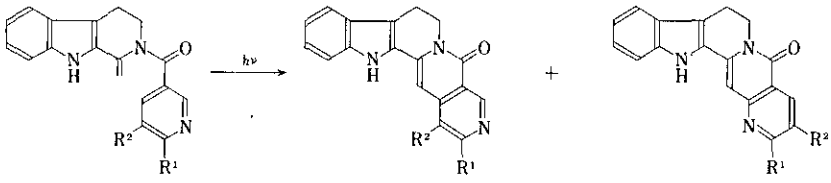
The above successful berbine synthesis prompted us to extend this reaction to harmalane therefore giving rise to provide a novel and facile synthesis of polycyclic heterocycles such as yohimbine group of compounds. Tryptamine was benzoylated followed by cyclization to give harmalane in good yield, which was further acylated to afford the enamide (72). The enamide (72) underwent smooth photocyclization to give a dehydrogenated pentacyclic lactam which constitutes a basic skeleton of yohimbine.



(72)

During the course of this study, some new types of alkaloids, nauclefine (73), naucletine (75), angustidine (76), and angustoline (77)[34] were isolated from the Nauclea and Strychnos plants and have a common azayohimbine structure which is the structure ideal for applying enamide photocyclization to their synthesis. Thus, just a month work completed total synthesis of these alkaloids by the route as summarized in Table 9.

Table 9



$R^1=R^2=H$
$R^2=H, R^1=Me$
$R^1=H, R^2=Ac$
$R^1=H, R^2=CH(Cl)Me$

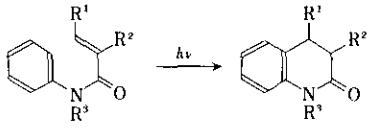
(73) $R^1=R^2=H$ (Naucléfine) (48%)
(74) $R^2=H, R^1=Me$ (Angustidine) (21%)
(75) $R^1=H, R^2=Ac$ (Nauclétine) (30%)
$R^1=H, R^2=CH(OMe)Me$ (5%)
(76) $R^1=H, R^2=CH=CH_2$ (Angustine)
(77) $R^1=H, R^2=CH(OH)Me$ (Angustoline)

$R^1=R^2=H$ (12%)
$R^2=H, R^1=Me$ (13%)
$R^1=H, R^2=Ac$ (8%)
$R^1=H, R^2=Et$ (6%)
$R^1=H, R^2=CH(OMe)Me$ (1%)

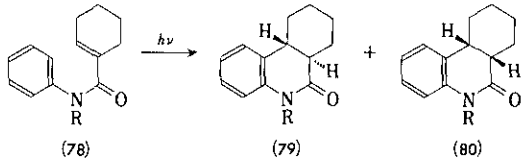
(4) Photocyclization of Enamide-III

(4-1) Basic Reaction

Chapman[11] and Ogata[35] reported the first non-oxidative photocyclization of some N-acryloylanilides , resulting in the formation of carbostyrils. However they described no information on the stereochemistry of the cyclization.



Since N-acylanilides can be regarded as enamide-III in our sense, we have investigated the stereochemistry of photocyclization of this type of enamides systematically in order to evaluate the reaction to a level of a useful synthetic tool,[36] by employing N-cyclohexenoylanilides (78).



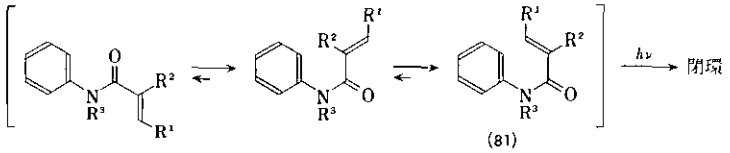
(78) (79) (80)

Irradiation of the readily prepared *N*-cyclohexenoylanilide (78)[36] gave a mixture of epimeric lactams, trans-(79) and cis-(80), the ratio of which were found to be strongly solvent-dependent. The trans-lactam (79) was predominant when an aprotic solvent such as benzene and ether was employed for irradiation, while the cis-(80) became predominant in a protic solvent such as methanol. Ratios of the formation of epimeric lactams (79 and 80) were not changed even under thermal and photochemical conditions. Of course, as Chapman and Ogata reported, the photocyclization of these N-acylanilides is of non-oxidative nature, since irradiation under oxidative condition afforded only the dehydrolactam.

(4-2) Substituent Effect

(4-2-1) Substituent on the Acyl Moiety

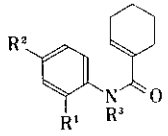
Investigation on the photocyclization of the N-alkylacryloylanilides (81) with substituents on α- and β-positions of the acyl moiety revealed that the substituent at α-position bettered the yields of cyclization[4, 14], while α-unsubstituted enamides gave only a poor yield of the photocyclized lactam, therefore suggesting that a steric repulsion between the benzene ring and α-substituent would force the molecule to take a conformation favorable for cyclization, that is, α,β-unsaturated carbonyl group and the benzene ring in *S*-trans configuration.




(81)
*S-trans*

(4-2-2) Substituent on the Benzene Ring[14, 37]

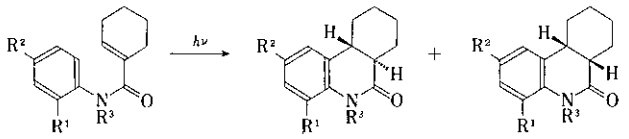
The results of the investigation on the photocyclization of variously substituted N-cyclohexenoylanilides (82) are summarized in Table 10[37].




(82)

It is clear that the enamides (82) undergo smooth photocyclization to give a mixture of cis- and trans-lactams, whose ratios being affected by the solvent employed as stated above. Particularly, photocyclization of the acylanilides with an electron-attracting group proceeded very smoothly to give excellend yields of lactams.

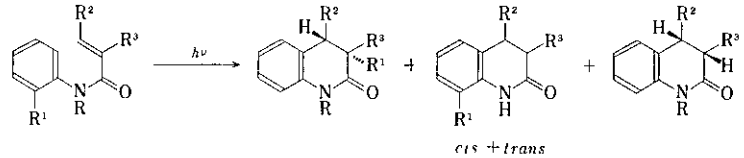
Table 10



| | yield (%) (*cis*+*trans*) | time (hr) | solvent effect (*trans*/*cis*) Et$_2$O | benzene | MeOH |
|---|---|---|---|---|---|
| (83) R$^1$=H, R$^2$=OMe, R$^3$=CH$_2$Ph | 60–65 | 40 | 9 2 | 1.2 | 0 2 |
| (84) R$^1$=H, R$^2$=CO$_2$Me, R$^3$=CH$_2$Ph | 50–60 | 9 | 34.5 | 8 7 | 0 5 |
| (85) R$^2$=H, R$^1$=OMe, R$^3$=CH$_2$Ph | 52–65 | 35 | 20.8 | 1.9 | 0.3 |
| (86) R$^2$=R$^3$=H, R$^1$=CO$_2$Me | 60 | 10 | 2.0 | 0.5 | — |

Regioselectivity of the photocyclization of this type of enamides was controlled by the introduction of an ortho-electron-attracting group such as ester and carbonyl groups as summarized in Table 11.[14, 37]

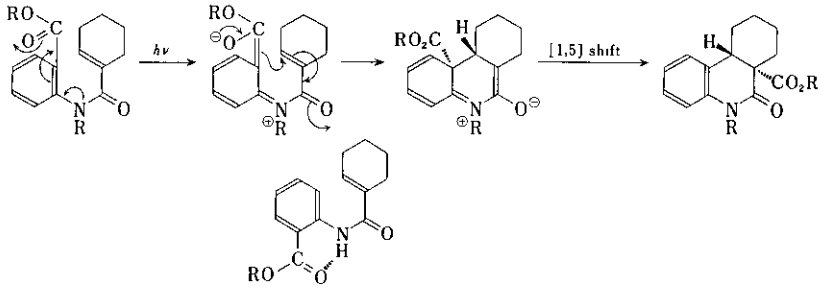
Table 11



*cis* +*trans*

| | | | | |
|---|---|---|---|---|
| (87) R$^2$=H, R$^1$=CO$_2$Me, R$^3$=Me, R=CH$_2$Ph | (40%) | | | |
| (88) R$^2$=H, R$^1$=Ac, R$^3$=Me, R=CH$_2$Ph | (25%) | | | |
| (89) R$^1$=CO$_2$Me, R$^2$=(CH$_2$)$_4$ =R$^3$, R=CH$_2$Ph | (71%) | | | |
| (90) R$^1$=Ac, R$^2$=(CH$_2$)$_4$ =R$^3$, R=CH$_2$Ph | (45%) | | | |
| (91) R$^1$=CN, R$^2$=(CH$_2$)$_4$ =R$^3$, R=CH$_2$Ph | (40%) | | | |
| (92) R$^2$=R=H, R$^1$=CO$_2$Me, R$^3$=Me | | (61%) | | |
| (93) R=H, R$^1$=CO$_2$Me, R$^2$=(CH$_2$)$_4$ =R$^3$ | | (60%) | | |
| (94) R$^2$=R=H, R$^1$=CO$_2$H, R$^3$=Me | | (33%) | | |
| (95) R$^2$=H, R$^1$=CO$_2$H, R$^3$=Me, R=CH$_2$Ph | | | | (41%) |
| (96) R$^1$=CO$_2$H, R$^2$=(CH$_2$)$_4$ =R$^3$, R=CH$_2$Ph | | | | (70%) |
| (97) R$^2$=H, R$^1$=CONH$_2$, R$^3$=Me, R=CH$_2$Ph | | | | (50%) |
| (98) R$^1$=CONH$_2$, R$^2$=(CH$_2$)$_4$ =R$^3$, R=CH$_2$Ph | | | | (53%) |

N-Alkylacylanilides (87-91) which carry an electron-attracting group underwent smooth photocyclization exclusively at the root of the substituent followed by the migration of the substituent in a [1,5] manner to give the product as shown. This regiospecific cyclization can be explained as in the following scheme.[14]

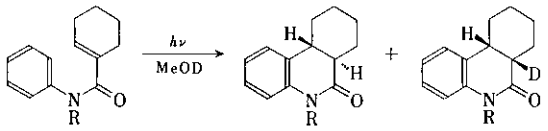


On the other hand, failure of the migration of substituent in the case of N-noracylanilides (92-94) would be ascribed to strong hydrogen bonding between NH- and substituent, thus fixing the conformation of enamide in a form favorable to cyclization to the opposite site of the substituent.[37]

Furthermore, photocyclization of the N-alkylacylanilides (95-98) which bear an ortho-carboxy or carbamoyl group occurred exclusively at the root of the substituent followed by elimination of the substituent to yield the cis-lactam predominantly[14, 37] as a result of either decaroxylation or decarbamoylation.

## (4-3) Solvent Effect and Reaction Mechanism[36]

The solvent effect on the photocyclization of this type of enamides was investigated by employing the deuterated solvents[36].

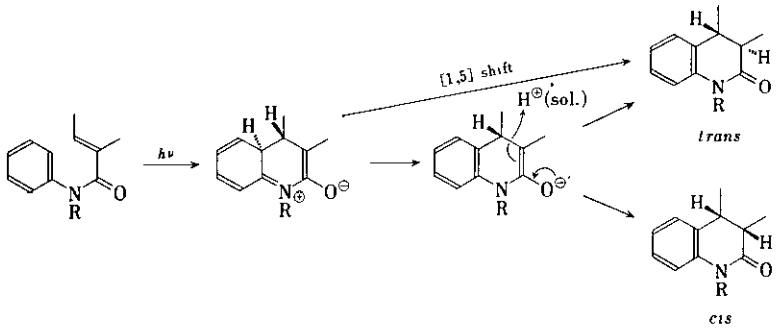



(78)

Photocyclization of the acylanilide (78) in deuterium methoxide gave a mixture of cis- and trans-lactams in 36 % yield in the ratio of 10 to 1 in favor of the cis-lactam, in which deuterium incorporation was over 90 %. On the other hand, under the condition that is known to afford the trans-lactam predominantly, the photocyclized product obtained in 53 % yield was incorporated by only 12 % of deuterium.

Therefore, it would be strongly suggested that the photocyclization of this type of enamides would proceed mainly by a stepwise mechanism concurrent with a minor participation of concerted mechanism as shown in Scheme 7.

Scheme 7

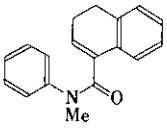
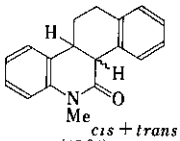
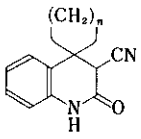
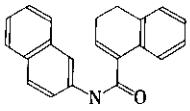
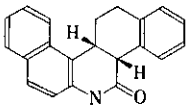
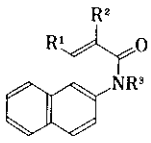
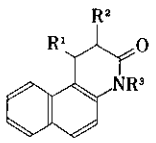
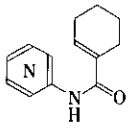
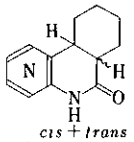
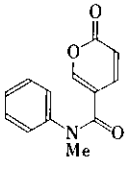
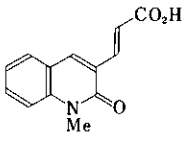
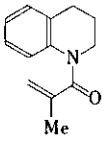
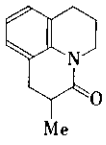


(4-4) Examples of Photocyclization of Enamide-III

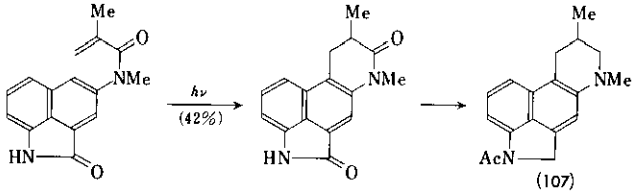
( Synthesis of Basic Skeleton of Alkaloids )

In contrast to the naturally abundant isoquinoline alkaloids, there are only a few alkaloids which have the structure suitable for applying the enamide photocyclization for their synthesis. Therefore, syntheses of some heterocyclic compounds including basic skeletons of alkaloids such as clavine are summarized in Table 12.

Table 12

| Enamide | Photoproduct | Enamide | Photoproduct |
|---|---|---|---|
|  (99)[36] |  *cis* + *trans* (43%) |  (104)[41] $n$ = 4,5 |  (18–20%) |
|  (100)[5] |  (101) (54–60%) |  (105)[39] $R^1$=H,Ph, $R^2$=$R^3$=H,Me |  (50–59%) |
|  (102)[38] |  *cis* + *trans* (29–88%) |  (106)[40] |  (33%) |
|  (103)[4] |  (40%) | | |

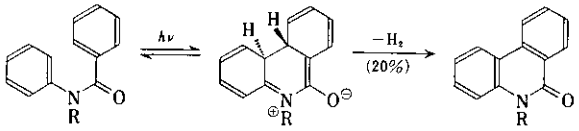
Irradiation of the naphthalide (100)[39], which belongs to enamide-III, leads to the cis-pentacyclic lactam (101) as a sole product probably due to severe steric hindrance existing in a new polycyclic ring system formed.



## (5) Photocyclization of Enamide-IV

### (5-1) Basic Reaction

This chapter deals with the photocyclization of benzanilide type of enamides in which two benzene rings are present adjacent to an amide group. Photocyclization of benzanilides, first reported by Thyagarajan[41a], can be explained as follows. Upon irradiation, benzanilide would cyclize to form a presumably trans-oriented cyclic intermediate (108), from which the cyclized product can be obtained only when an oxidizing agent is present for dehydrogenolysis[41]. Therefore, the photocyclized product is the dehydrogenated aromatic lactam, phenanthridone. However, it seems that the photocyclization of this type of enamides would be depending on the structure, that is, the reactivity of the aromatic rings.

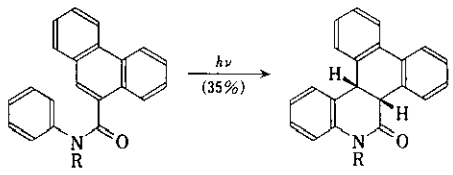



(108)

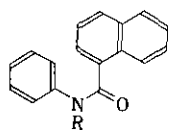
### (5-2) Photocyclization of Enamide-IV Containing Polycyclic Aromatic and Heteroaromatic Rings

In the case of enamide-IV containing a polycyclic aromatic ring, such as naphthalene and phenanthrene, a C=C double bond next to carbonyl group shows comparably high reactivity similar to that of aliphatic double bond. Therefore, irradiation of phenanthrenecarboxanilide brought about smooth cyclization even under non-oxidative condition.

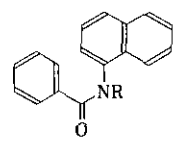
Further, it is shown that the N-naphthoylanilide (110) underwent photocyclization whereas the N-benzoylnaphthalide (111) did not, probably due to the difference in their reactivities of the C=C double bonds in the rings adjacent to the amide group.[44]




(109)



(110)



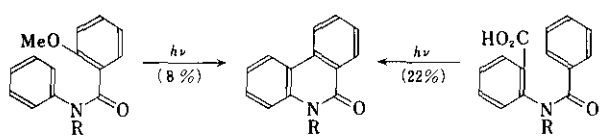
(111)

Kanaoka[45] reported some examples of non-oxidative photocyclization of enamide-IV containing heteroaromatic rings.

Therefore, it is clear that in the photocyclization of enamide-IV, the structure of enamides, particularly the nature of aromatic rings, would play the most important role of determining the cyclization.

(5-3) Photocyclization of Enamide-IV Bearing ortho-Substituent

Even in the case of enamide-IV which carries either an ortho-methoxy group[42] on the benzene ring next to the amide carbonyl or an ortho-carboxy group[43] on the benzene ring next to the amide nitrogen, the photocyclization occurred even under non-oxidative condition thus affording the phenanthridone as the product. Driving force in these cyclization would be a feasibility of elimination of the substituent as a simple fragment such as methanol or carbon dioxide respectively. Further examples of this type of non-oxidative photocyclization are collected in Table 13.

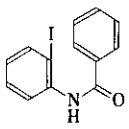
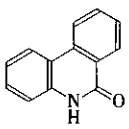
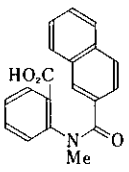
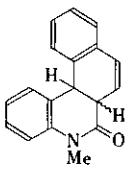
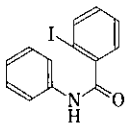
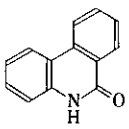
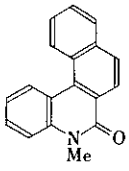
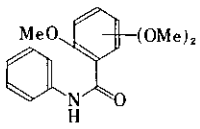
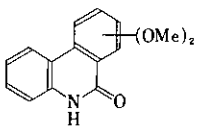
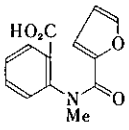
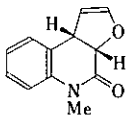
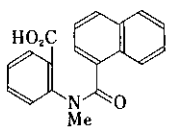
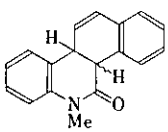
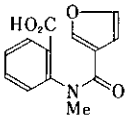
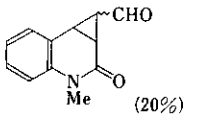
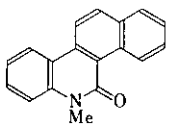
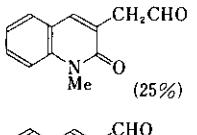
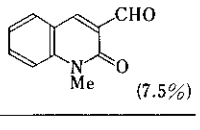


(112) (113)

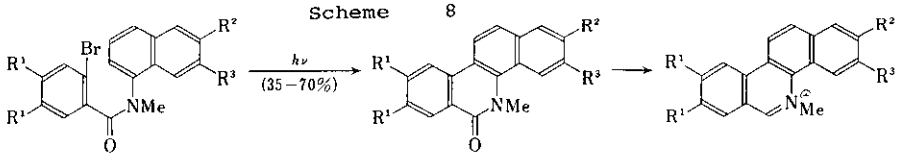
(5-4) Application to the Synthesis of Alkaloids

By applying photocyclization of enamide-IV, the following alkaloids and related compounds, N-demethylfagaronine (118)[46], nitidine (119)[47], avicine (120)[47a], narciprimine (121)[41c], and anhydrolycorine (122)[48] were synthesized as shown in the following schemes.

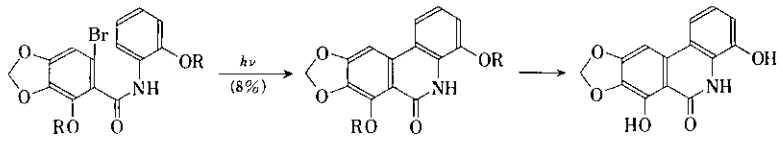
Table 13

| Enamide | Photoproduct | Enamide | Photoproduct |
|---|---|---|---|
|  |  (48%)[41a] |  (115)[43] |  (16%) |
|  |  (9%)[41a] | |  (1.5%) |
|  |  (37−80%)[42] |  (116)[40] |  (5%) |
|  (114)[43] |  (4%) |  (117)[40] |  (20%) |
| |  (12%) | |  (25%) |
| | | |  (7.5%) |

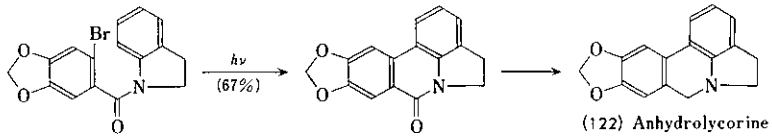
Scheme 8



(118) $R^1=R^3=OMe$, $R^2=OH$: Fagaronine
(119) $R^1=OMe$, $R^2=OCH_2O=R^3$: Nitidine
(120) $R^1=R^2+R^3=OCH_2O$ Avicine



R=COPh (121) Narciprimine



(122) Anhydrolycorine

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REFERENCES

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

2 a) I. Ninomiya, T. Naito, and S. Higuchi, Chem. Commun., 1970, 1662

b) P. W. Hickmott and G. Sheppard, J. Chem. Soc. (C), 1971, 1358.

3 I. Ninomiya, A. Shinohara, T. Kiguchi, and T. Naito, J.Chem. Soc. Perkin I, 1976, 1868.

4 I. Ninomiya and T. Kiguchi, unpublished result.

5 I. Ninomiya, S. Higuchi, and T. Naito, Abstr. Papers, 92nd Congress of Pharmaceutical Society of Japan, Osaka, 1972, II-53.

6 I. Ninomiya, T. Kiguchi, and Y. Tada, Heterocycles, 1977, 6, 1799.

7 I. Ninomiya and T. Kiguchi, J. Chem. Soc. Chem. Commun., 1976, 624.

8 I. Ninomiya, Y. Tada, T. Kiguchi, O. Yamamoto, and T. Naito, Heterocycles, 1978, 9, 1527.

9 a) E. Bertele, H. Boos, J. D. Dunitz, E. Elsinger, A. Eschenmoser, I. Felner, H. P. Gribi, H. Gschwent, E. F. Meyer, M. Pesaro, and R. Scheffold, Angew. Chem., 1964, 76, 393.

b) N. C. Yang and G. R. Lenz, Tetrahedron Letters, 1967, 4897.

c) P. T. Izzo and A. S. Kende, Tetrahedron Letters, 1966, 5731.

d) R. W. Hoffmann and K. R. Eicken, Chem. Ber., 1969, 102, 2987.

10a) I. Ninomiya, T. Naito, and T. Kiguchi, Tetrahedron Letters, 1970, 4451.

b) I. Ninomiya, T. Naito, and T. Kiguchi, J. Chem. Soc. Perkin I, 1973, 2257.

11 O. L. Chapman and W. R. Adams, J. Amer. Chem. Soc., 1968, 90, 2333.

12a) I. Ninomiya, T. Naito, and T. Mori, J. Chem. Soc. Perkin I, 1973, 505.

b) I. Ninomiya, T. Naito, and T. Mori, Tetrahedron Letters, 1969, 2259.

13 I. Ninomiya, T. Kiguchi, O. Yamamoto, and T. Naito, J. Chem. Soc. Perkin I, 1979, 1723.

14 I. Ninomiya, T. Kiguchi, and T. Naito, J. Chem. Soc. Chem. Commun., 1974, 81.

15a) T. Kametani, " The Chemistry of the Isoquinoline Alkaloids " Hirokawa, Tokyo, 1968, p 176.

15b) M. Shamma, " The Isoquinoline Alkaloids " Academic Press, New York, 1972

16 I. Ninomiya and T. Naito, Abstr. Papers, 22nd. Kinki Regional Meeting, Pharmaceutical Society of Japan, Osaka, 1972, p 23.

17a) I. Ninomiya, T. Naito, and T. Kiguchi, J. Chem. Soc. Perkin I, 1973, 2261.

b) I. Ninomiya, T. Naito, and T. Kiguchi, Chem.Commun., 1970, 1669.

18 H. Iida, S. Aoyagi, and C. Kibayashi, J. Chem. Soc. Chem. Commun., 1974, 499.

19a) I. Ninomiya, T. Naito, and T. Mori, J. Chem. Soc. Perkin I, 1973, 1696.

b) I. Ninomiya, T. Naito, and T. Mori, Tetrahedron Letters, 1969, 3643.

20 I. Ninomiya, T. Kiguchi, O. Yamamoto, and T. Naito, Heterocycles, 1976, 4, 467.

21 I. Ninomiya, T. Naito, H. Ishii, T. Ishida, M. Ueda, and K. Harada, J. Chem. Soc. Perkin I, 1975, 762.

22 I. Ninomiya, O. Yamamoto, and T. Naito, Heterocycles, 1977, 7, 131.

23 I. Ninomiya, O. Yamamoto, and T. Naito, Heterocycles, 1976, 4, 743.

24 F. R. Stermitz, J. P. Gillespie, L. G. Amoros, R. Romero, and T. A. Stermitz, J. Medicin. Chem., 1975, 18, 708.

25a) H. Ishii, E. Ueda, K. Nakajima, T. Ishida, T. Ishikawa, K. Harada, I. Ninomiya, T. Naito, and T. Kiguchi, Chem. Parm. Bull. (Japan), 1978, 26, 864.

b) H. Ishii, K. Harada, T. Ishida, E. Ueda, K. Nakajima, I. Ninomiya, T. Naito, and T. Kiguchi, Tetrahedron Letters, 1975, 319.

26 I. Ninomiya, O. Yamamoto, and T. Naito, Heterocycles, 1977, 7, 137.

27 W. Oppolzer and K. Keller, J. Amer. Chem. Soc., 1971, 93, 3836.

28 I. Ninomiya, O. Yamamoto, and T. Naito, J. Chem. Soc. Chem. Commun., 1976, 437.

29 M. Onda, K. Yuasa, and J.Okada, Chem. Pharm. Bull. (Japan) 1974, 22, 2365.

30a) I. Ninomiya and T. Naito, J. Chem. Soc. Chem. Commun., 1973, 137.

b) I. Ninomiya, T. Naito, and H. Takasugi, J. Chem. Soc. Perkin I, 1975, 1720.

31 I. Ninomiya, H. Takasugi, and T. Naito, Heterocycles, 1973, 1, 17.

32a) I. Ninomiya, T. Naito, and H. Takasugi, J. Chem. Soc, Perkin I, 1975, 1791.

b) G. R. Lenz, J. Org. Chem., 1974, 39, 2839, 2846.

c) G. R. Lenz, J. Org. Chem., 1976, 41, 2201.

d) G. R. Lenz, J. Org. Chem., 1977, 42, 1117.

e) T. Kametani, T. Sugai, Y. Shoji, T. Honda, F. Satoh, and K. Fukumoto, J. Chem. Soc. Perkin I, 1977, 1151.

33a) I. Ninomiya, H. Takasugi, and T. Naito, J. Chem. Soc. Chem. Commun., 1973, 732.

b) I. Ninomiya, T. Naito, and H. Takasugi, J. Chem. Soc. Perkin I, 1976, 1865.

c) I. Ninomiya, and T. Naito, Heterocycles, 1974, 2, 607.

d) M. Sainsbury and N. L. Uttley, J. Chem. Soc.Perkin I, 1976, 2416.

e) M. Sainsbury and N. L. Uttley, J. Chem. Soc. Perkin I, 1977, 2109.

34a) T. Y. Au, H. T. Cheung, and S. Sternhell, J. Chem. Soc., Perkin I, 1973, 13.

b) J. D. Phillipson, S. R. Hemingway, N. G. Bisset, P. J. Houghton, and E. J. Shellard, Phytochemistry, 1974, 13, 973.

c) F. Hotellier, P. Delaveau, and J. L. Pousset, Phytochemistry, 1975, 14, 1407.

35a) Y. Ogata, K. Takagiri, and I. Ishino, J. Org. Chem., 1971, 36, 3975.

b) M. Ogata and H. Matsumoto, Chem. Pharm. Bull. (Japan), 1972, 20, 2264.

36 I. Ninomiya, S. Yamauchi, T. Kiguchi, A. Shinohara, and T. Naito, J. Chem. Soc. Perkin I, 1974, 1747.

37 T. Kiguchi, Dissertation Thesis, Osaka University, 1977.

38 I. Ninomiya, T. Kiguchi, S. Yamauchi, and T. Naito, J. Chem. Soc., Perkin I, 1976, 1861.

39 I. Ninomiya, T. Kiguchi, and T. Naito, Heterocycles, 1976, 4, 973.

40 I. Ninomiya, T. Kiguchi, and T. Naito, Heterocycles, 1978, 9, 1023.

41a) B. S. Thyagarajan, N. Kharasch, H. B. Lewis, and W. Wolf, Chem. Commun., 1967, 614.

b) D. H. Hey, G. H. Jones, and M. J. Perkins, J.Chem. Soc. (C), 1971, 116.

c) A. Mondon and K. Krohn, Chem. Ber., 1972, 105, 3726.

42 Y. Kanaoka and K. Ito, J. Chem. Soc. Chem. Commun., 1973, 647.

43 I. Ninomiya, T. Kiguchi, S. Yamauchi, and T. Naito, J. Chem. Soc. Perkin I, 1980, 198.

44 I. Ninomiya, T. Kiguchi, and T. Naito, Abstr. Papers, 92nd. Congress of Pharmaceutical Society of Japan, Osaka, 1972, II-50.

45a) Y. Kanaoka, K. Ito, Y. Hatanaka, J. L. Flippen, I. L. Karle, and B. Witkop, J. Org. Chem., 1975, 40, 3001.

b) E. Winterfeldt and H. J. Altman, Angew. Chem., 1968, 80, 486.

46 I. Ninomiya, T. Naito, and H. Ishii, Heterocycles, 1975, 3, 307.

47a) S. V. Kessar, G. Singh, and P. Palakrishnan, Teterahedron Letters, 1974, 2269.

b) W. J. Begley and J. Grimshaw, J. Chem. Soc. Perkin I, 1977, 2324.

48 H. Hara, O. Hoshino, and B. Umezawa, Tetrahedron Letters, 1972, 5031.

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