APPLICATIONS OF ENAMIDE CHEMISTRY TO THE SYNTHESIS OF HETEROCYCLIC COMPOUNDS

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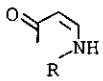
Abstract Photochemical and thermal reactions of enamides with respect to the synthetic application to heterocycles are reviewed. Enamides, N-α,β-unsaturated acylenamines, undergo cyclization under not only photochemical but also thermal conditions to afford a wide variety of heterocyclic compounds, thus proving enamides as potential synthons for the construction of heterocycles.

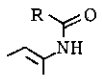
Introduction

Combination of an amide and one or two double bonds provides a couple of useful nitrogen containing conjugated systems such as enacylamines, vinylogous amides, and N-acylenamines as shown below.

Enacylamines

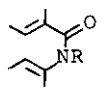


Vinylogous amides

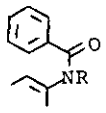


N-Acylenamines (Enamides)

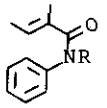
The most attractive system would be N-acylenamines, which are simply called as ENAMIDES, particularly when an additional double bond is involved, thus forming a six π-electron conjugated system. These N-α,β-unsaturated acylenamines can be classified[1] into four groups by the nature of double bonds, either olefinic or aromatic.



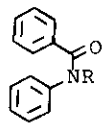
N-Acylenamines
(Enamide-I)



N-Benzoylenamines
(Enamide-II)



N-Acylanilides
(Enamide-III)



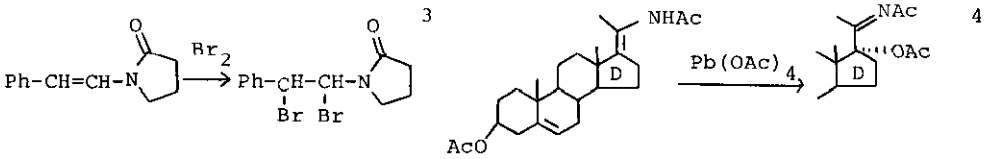
Benzanilides
(Enamide-IV)

As the results of our studies[1] on the chemistry of enamides, it is now established that they are undoubtedly potential synthons for the preparation of heterocyclic compounds. Enamides are readily prepared by simple acylation of imines or

anilines with unsaturated acid chlorides in the presence of a base such as triethylamine. Enamides thus obtained are generally stable compounds but reactive to some extent because they can be regarded as a stabilized form of enamines.

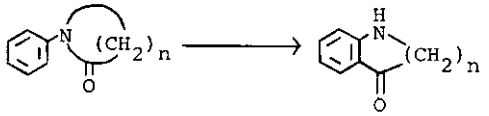
(1) Thermal Reaction of Enamides. ----- (1)

The chemistry of enamides in ground state have considerably been investigated and is well documented by Lenz.[2] As seen from the following examples, it has been found that enamides behave as enamines, thus providing the products expected from the reactions of enamines.



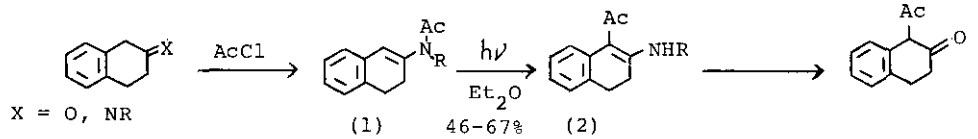
(2) Photochemistry of Enamides ----- (1) Acyl Migration

The major photochemical reaction of simple enamides is a N-C acyl migration[1,2] to form vinylogous amides, which are then capable of undergoing hydrolysis to give 1,3-diketones which are usually prepared by acylation of enamines. However, as Fischer[5] described, this type of acyl migration can be applied to the formation of heterocycles with various ring size.



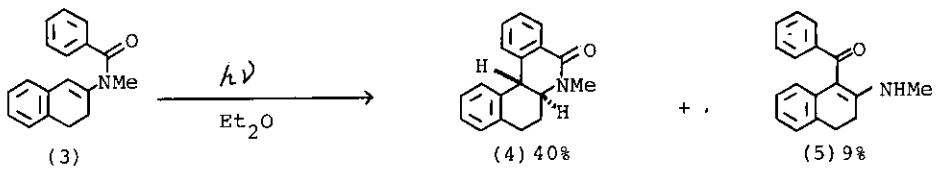
n	5	6	11
Yield(%)	87	83	80

At the beginning of our study[6] on the photochemistry of enamides[1], we also found that this acyl migration proceeds smoothly to give vinylogous amides (2) and then 1,3-diketones upon hydrolysis.



(3) Photochemistry of Enamides ----- (2) Photocyclization

As an extension of the investigation on the enamides, which gave N-C acyl migration products as above, we prepared[6] the corresponding N-benzoylenamines (3) and irradiated. The products obtained were a mixture of the photocyclized lactam (4) as a major and the acyl migrated vinylogous amide (5) as a minor product.



(3) (4) 40% + (5) 9%

Ever since, we have concentrated on the investigation of the photocyclization and established the scope of the new cyclization. At the time when we found a new photocyclization of N-benzoylenamines, there had been known only a few analogous cyclizations as shown below. Thyagarajan[7] reported the cyclizability of benzanilides under oxidative condition, while the first non-oxidative photocyclization of N-acryloylanilides were described by Chapman[8], though no information was available on the stereochemistry.

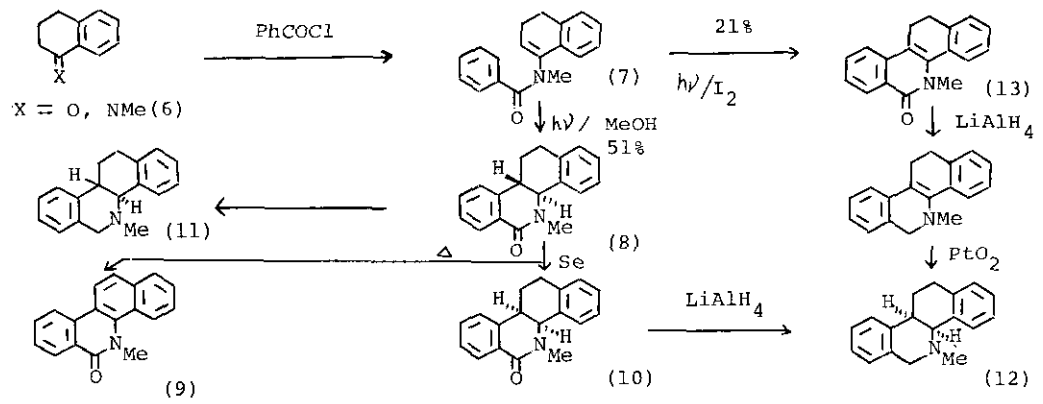
As a substrate for the photocyclization, an enamide has to have a structure forming a conjugated six π-electron system by adding an another double bond in acyl group as in enamides-I, II, III, and IV, of which N-benzoylenamines and N-acylanilides are most important with respect to their application to the synthesis.

(3-1) Photocyclization of N-Benzoylenamines[9] (Enamide-II)

a) Stereochemistry of the Cyclization

Usefulness and potentiality of the enamide photocyclization can be demonstrated by the following example.[9]

1-Tetraloneimine (6) was benzoylated to afford the enamide (7), which was irradiated. The homogeneous lactam (8) was obtained. The nmr peak at δ 4.7 with J=12Hz assigned its trans-structure. The skeleton of the lactam was established by the treatment with selenium to afford the known aromatized lactam (9)[10] along with the unexpected cis-lactam (10) as a major product, which showed the nmr peak at δ 4.75 with J=4.5Hz, thus proving its cis-juncture. Further a pair of the tertiary amines (11 and 12) were prepared and supported the stereochemistries of these products as shown. Further, the fact that irradiation in the presence of iodine afforded the dehydrolactam (13) proved the enamide photocyclization as of non-oxidative nature.



(General Procedure for the Photocyclization of Enamide-II)

Irradiation; on a 0.02 M solution of an enamide in a solvent (MeOH, Et_2O, or C_6H_6) with either low or high pressure mercury lamp at room temp.

End Point; by t.l.c. or g.l.c. until the starting enamide disappears and maximal formation of a new spot of the product.

Product; Evaporation of the solvent followed by recrystallization or chromatography.

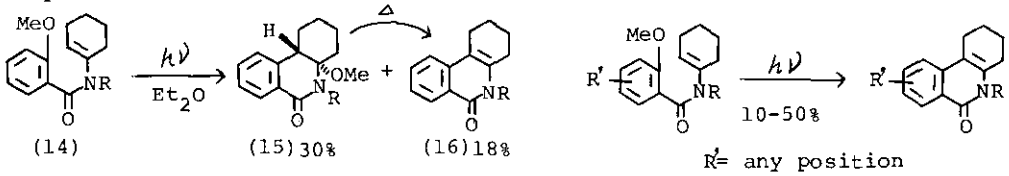
In addition to a facile preparation and stability of enamides, the above convenient procedure with high specificity of the cyclization offers a good chance for its synthetic application.

b) Regiochemistry of the Photocyclization[11]

In order to evaluate the photocyclization to a level of a standard method for the synthesis of heterocycles, the reaction should be regiochemically controlled. This was materialized by the use of the substituent particularly in the ortho-position. From a series of investigations on the substituent effects, some of the most interesting and useful cases are picked as follows.

b-1) Introduction of an ortho-Methoxy-Group[11]

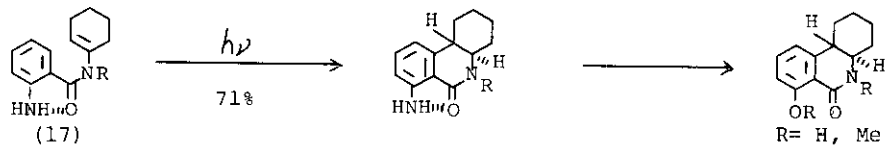
An ortho-methoxy-group in the benzene ring of the enamide (14) brought about a regiospecific cyclization at the root of the methoxy-group, which then underwent 1,5-migration to give the unstable lactam (15) which was readily converted into the dehydrolactam (16) . This specificity, as shown below, was observed without any exception.



When an ortho-methylenedioxy-group was present, a regiospecific cyclization followed by cleavage of a methylene bridge occurred to afford a phenolic product.

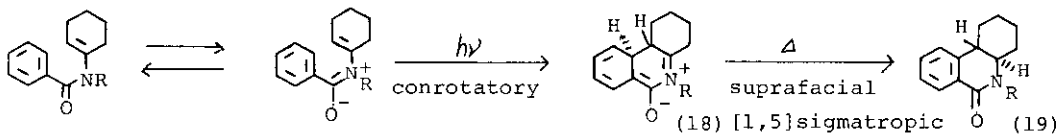
b-c) ortho-Amino-Group[11]

When an amino-group was introduced into the ortho-position of the benzene ring of enamide (17), photocyclization occurred only at the opposite site of the substituent probably due to hydrogen bonding which fixes the conformation of enamide. This regiospecificity would be useful for the application to the synthesis because an amino-group is convertible to popular hydroxy-and methoxy-groups.

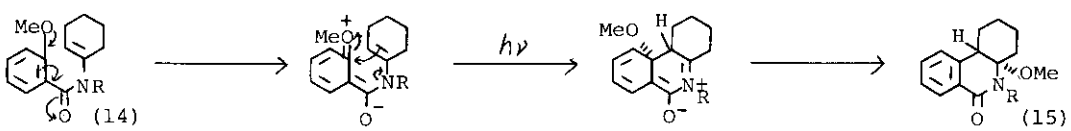


c) The Mechanism of Photocyclization of Enamide-II [6,11]

Stereospecific formation of trans-lactam, no incorporation of the solvent, and non-oxidative nature provided a mechanism of a conrotatory cyclization of six π-electron system as follows. A trans-intermediate (18) would then undergo 1,5-sigmatropic shift of hydrogen suprafacially to give the trans-lactam (19).



A mechanism for the regiospecific cyclization of the ortho-methoxy-substituted enamide (14) can be explained as follows.



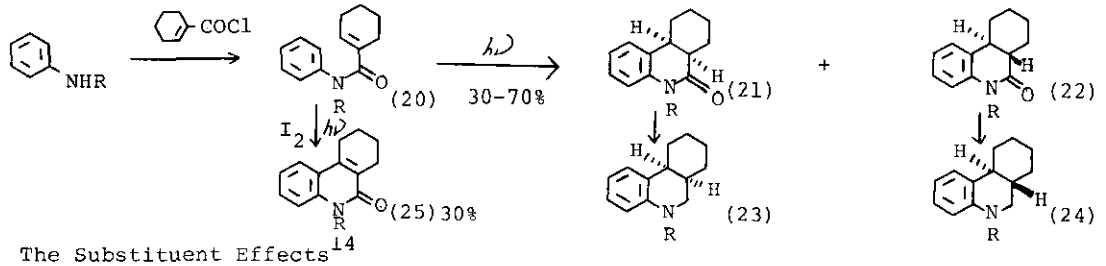
Clear from these results, it is established that photocyclization of N-benzoyl-enamines is of a great value as a potential synthetic method for the construction of various nitrogen containing heterocycles particularly isoquinoline alkaloids.

(3-2) Photocyclization of N-Acylanilides (Enamide-III)

Though Chapman[8] and Ogata[12] reported non-oxidative photocyclization of some N-acryloylanilides forming tetrahydroquinolones, details of the cyclization have remained to be clarified. Therefore, we prepared N-cyclohexenoylanilide (20) for the study of this type of photocyclization.

a) A Typical Example of Photocyclization of Enamide-III[13]

N-Cyclohexenoylanilide (20) was irradiated in a solvent such as MeOH, Et_2O, or C_6H_6 at room temperature. The cyclization proceeded smoothly to give a good yield of a mixture of cis- (21) and trans-lactams (22) with ratios which vary by the solvent employed (solvent effect). In a protic solvent (MeOH), the cis-lactam (21) predominates while the trans-isomer (22) becomes predominant in an aprotic solvent (Et_2O). Reduction of these isomeric lactams gave the known tertiary amines (23 and 24) respectively. Irradiation under oxidative condition afforded the dehydrolactam (25).

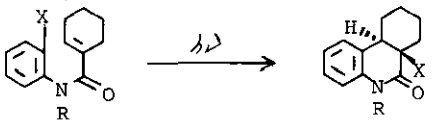


b) The Substituent Effects[14]

One of the most interesting features of this type of cyclization is the substituent effects by which regiospecific synthesis of the specifically substituted heterocycles can be achieved.

b-1) Electron Withdrawing Groups (X= -COOMe, -CN, -Ac, $-CONH_2$)

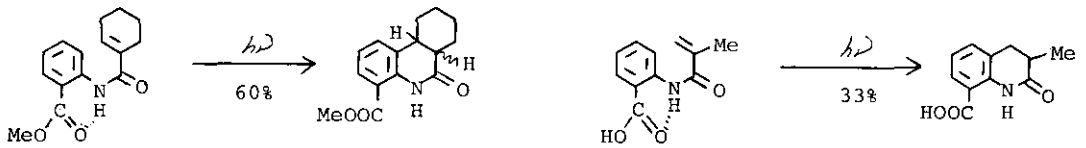
Some electron withdrawing groups such as ester, cyano, acetyl, and carbamoyl groups presenting in the ortho-position brought about the cyclization exclusively at the root of the substituent followed by 1,5-migration to give the migrated lactams in good yields respectively. These are the first examples of the acyl migration occurred at room temperature.



X	COOMe	CN	Ac	$CONH_2$
Yield(%)	71	40	45	53

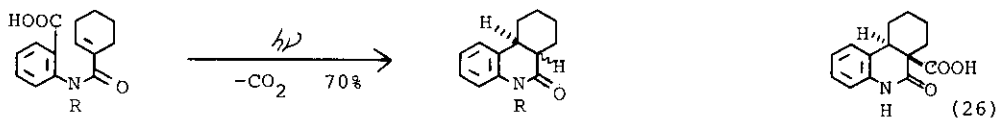
b-2) Hydrogen Bonding

As previously mentioned in the case of enamide-II, the compounds having an ortho-substituent capable of forming hydrogen bonding with N-hydrogen of enamide also undergo smooth regiospecific cyclization at the opposite site of the substituent as shown.

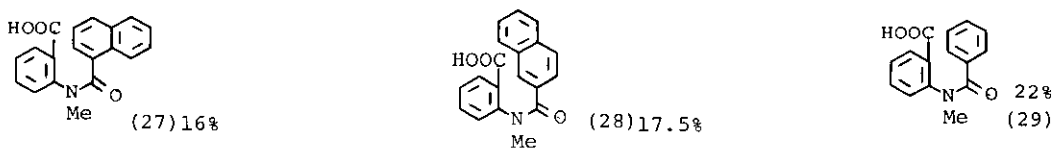


b-3) Cyclization-Decarboxylation by Introduction of an ortho-Carboxy-Group[14]

The introduction of an ortho-carboxy-group in the enamide-III caused not only a regiospecific cyclization at the root of a carboxy-group but also spontaneous decarboxylation to yield the decarboxylated lactams as a mixture of cis- and trans-lactams in a great favor of the former. However, decarboxylation was not observed from the carboxy-substituted lactam (26) under a similar condition.

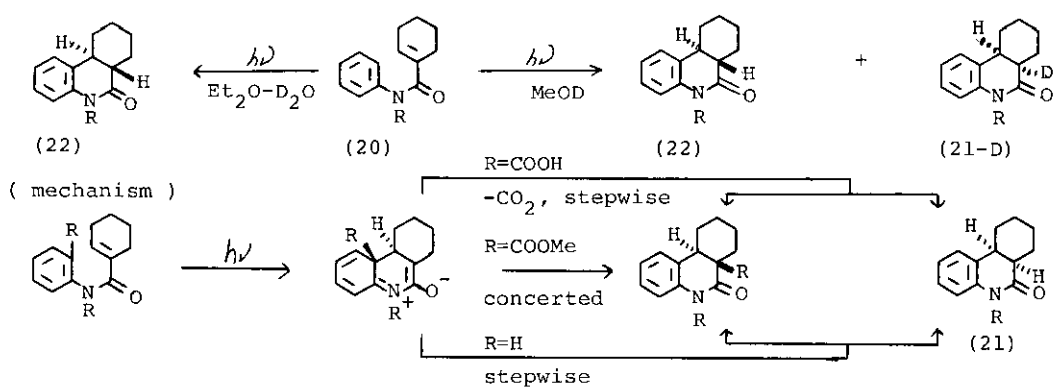


Interestingly, non-oxidative photocyclization was materialized even in the cases of benzanilides (27, 28 and 29) which have been known to undergo cyclization only under oxidative condition.



c) The Mechanism of Photocyclization of Enamide-III[13,14]

In addition to the above results, experiments with deuterated solvents were carried out in order to clarify the mechanism. Though no deuterium incorporation was observed in the photocyclized product from enamide-II, over 90 % of D-incorporation in the cis-lactam (21) while only 12 % in the trans-lactam (22) were observed in the photocyclization of enamide-III (20), thus suggesting a great contribution of a stepwise ionic mechanism in the case of enamide-III as proposed below. In addition, the regiospecific photocyclization of enamide-III carrying an ortho-carboxy- or ester-group would proceed by the mechanism as shown.



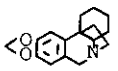
(3-3) Summary of the Photocyclization of Enamide-II and III.

Through ten years investigation on the photocyclization of various types of enamides, the enamide photocyclization has now been established as a potential synthetic method for the construction of heterocycles. From the standpoint of its synthetic application, the enamide photocyclization is summarized as in the Table (p 9) for the convenience of heterocyclic chemists.

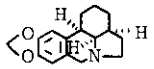
(3-4) Application of Enamide Photocyclization to the Synthesis of Heterocycles[1]

Enamide photocyclization has been successfully applied to the synthesis of various types of nitrogen containing heterocyclic compounds including various isoquinoline alkaloids which are abundant in nature. These results clearly show the usefulness of this cyclization. The followings are the list of the heterocyclic compounds prepared by enamide photocyclization.

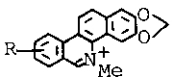
Alkaloids



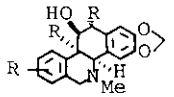
crinan



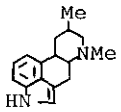
γ-lycoran



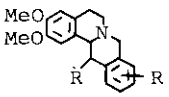
avicine
nitidine
sanguinarine
chelirubine



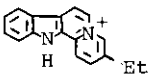
corynoline
homochelidonine
12-hydroxycorynoline
11-epicorynoline



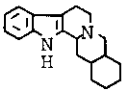
three clavines



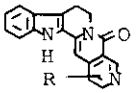
xylopinine
4H-palmatine
sinactine
cavidine



flavopereirine

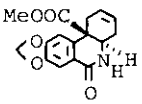


three yohimbanes

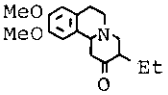


naucléfine
angustine
angustidine
naucléfine
angustoline

Intermediates to Alkaloids

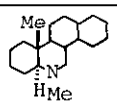


to haemanthidine

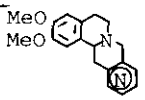


to emetine

Miscellaneous Heterocycles



azasteroid



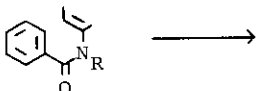
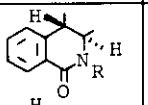
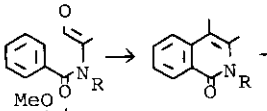
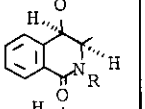
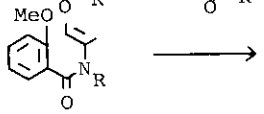
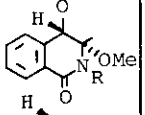
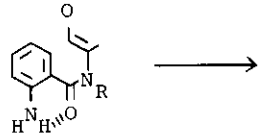
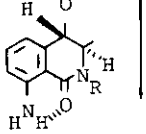
azaberbine

naphthyridine

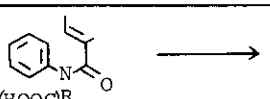
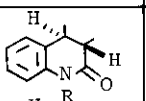
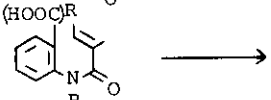
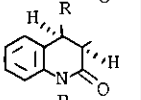
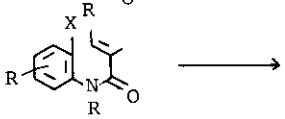
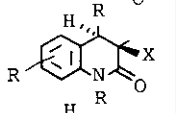
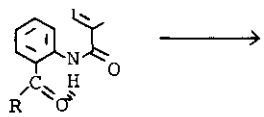
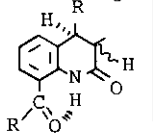
naphthyridine

Table

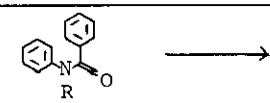
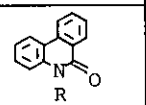
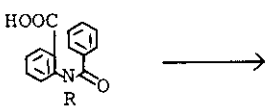
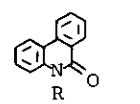
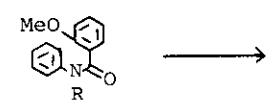
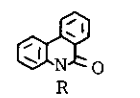
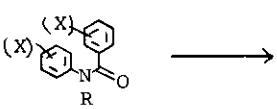
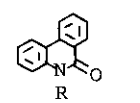
(Synthesis of Isoquinoline Derivatives)

Enamide-II	Products	Condition	Products to be Synthesized
		non-oxidative	3,4-trans-Isoquinolines
		1) oxidative 2) catalytic hydrogenation	3,4-cis-Isoquinolines
		ortho-OMe	Regiocontrolled
		ortho-NH_2	Regiocontrolled

(Synthesis of Quinoline Derivatives)

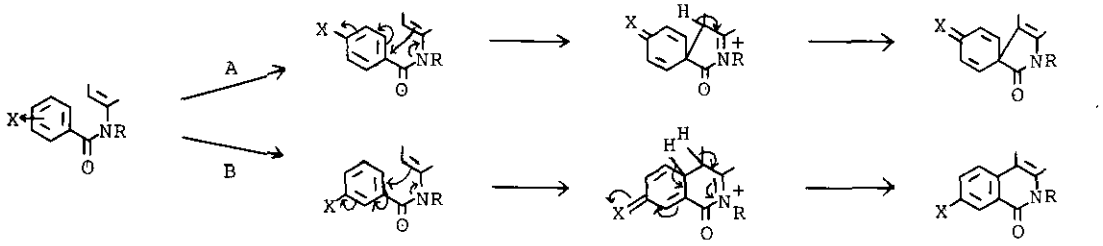
Enamide-III	Products	Condition	Products to be Synthesized
		aprotic solvent	3,4-trans-Quinolines
		protic solvent or ortho-COOH	3,4-cis-Quinolines
		ortho-X (electron with-drawing group)	Regiocontrolled
		N-nor and ortho-COR	Regiocontrolled

(Synthesis of Aromatic Lactams)

Enamide-IV	Products	Condition	Products to be Synthesized
		oxidative	Aromatic Phenanthridones
		ortho-COOH	
		ortho-OMe	
		ortho-halogen (Thyagarajan)	

(4) Thermal Reaction of Enamides ----- (2) Thermal Cyclization

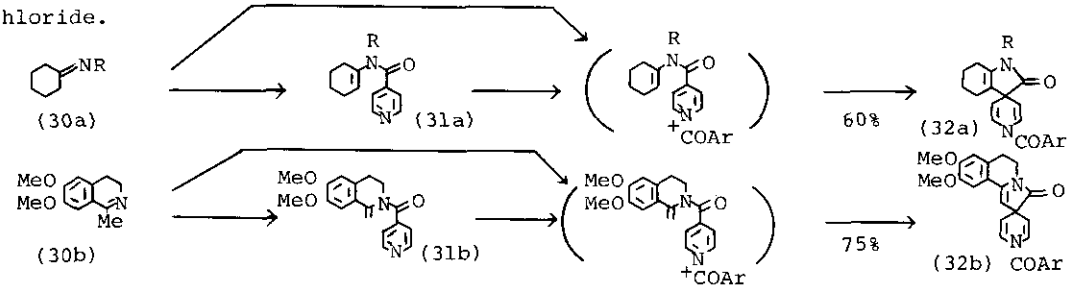
Our recent investigation on the reactivity of enamides which have a pyridinium moiety instead of a benzene ring disclosed a new phase of enamide chemistry which led to a possibility of the cyclization of enamide even under thermal condition. Actually, when an electron withdrawing factor was introduced into the benzene ring,therefore making the aromatic ring strongly electron deficient, there can be expected the cyclization by two routes (A and B) to occur even under thermal condition as assumed in the following scheme.



The above assumption has been materialized by the introduction of a pyridinium moiety or two nitro-groups in enamide-II.

(4-1) Acylation of Imines with Isonicotinoyl Chloride.[15] (Route A)

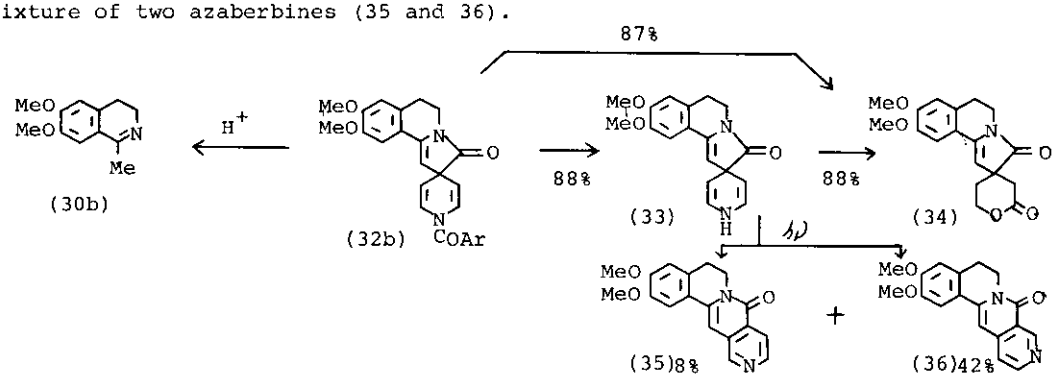
Acylation of the imines (30) with one molar amount of isonicotinoyl chloride yielded the enamides (31) in good yields. However the product obtained from acylation with an excessive amount of the acid chloride was the spirodihydropyridines (32), which were also obtained from the enamides (31) upon treatment with the acid chloride.



Similarly, the formation of spirodihydropyridines was also observed on the acylation of harmalane and 3-aminocrotonate.

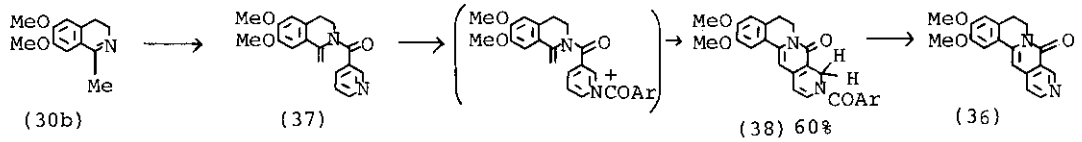
In order to evaluate the formation of spirodihydropyridines, a couple of investigations were carried out. Though spirodihydropyridines were unstable to acid causing fragmentation, alkaline hydrolysis converted them into the corresponding N-norspirodihydropyridines (33) under mild condition (5 % KOH) while the corresponding lactones (34) under strong condition (20 % KOH). Irradiation of the N-norspirodihydropyridines (33) brought about photorearrangement to afford a

mixture of two azaberbines (35 and 36).



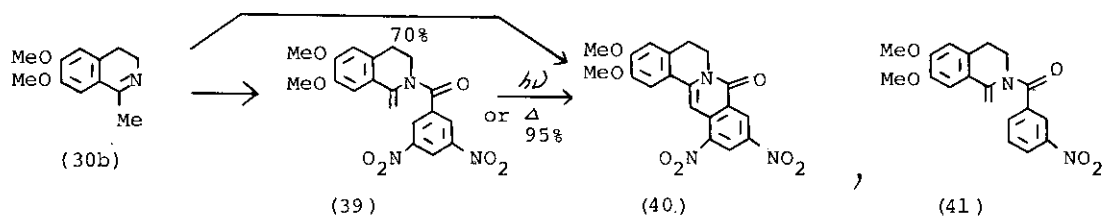
(4-2) Acylation of Imines with Nicotinoyl Chloride.[16] (Route B)

A proposed conversion by the route B was materialized by the use of nicotinoyl chloride. Acylation of the imine (30b) with nicotinoyl chloride afforded the enamide (37) when one molar amount of the acid chloride was employed, while acylation with an excessive amount of the acid chloride yielded the already cyclized dihydroazaberbine (38), which was hydrolyzed to give the corresponding azaberbine (36).



(4-3) Acylation of Imines with 3,5-Dinitrobenzoyl Chloride.[16]

As an electron withdrawing factor, 3,5-dinitrobenzoyl chloride was employed for the acylation of imine. The product obtained under a refluxing temperature was the already cyclized berbinone (40), which was also obtained from the enamide (39) under both thermal and photochemical conditions. On the other hand, acylation with 3-nitrobenzoyl chloride did not give any cyclized product but the enamide (41).



Conclusion

Starting from the various unsaturated acid chlorides, irrespective of acyclic or cyclic and apliphatic or aromatic, and the various imines, irrespective of acyclic or cyclic, and the anilines, stable enamides of four types are readily prepared. By the cyclization of these enamides under either photochemical or thermal condition, a wide variety of nitrogen-containing heterocyclic compounds are readily prepared. Usefulness and potentiality of the enamide chemistry for the synthetic application are exemplified by the synthesis of a number of heterocyclic compounds including various types of isoquinoline alkaloids.

Acknowledgement

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