THERMAL CYCLIZATION OF ENAMIDES

Takeaki Naito and Ichiya Ninomiya*
Kobe Women's College of Pharmacy
Motoyamakita, Higashinada, Kobe 658, Japan.

Abstract----- Enamides of N-aroylenamine type (2) and (7a), which contain an electron deficient aromatic ring, undergo facile cyclization not only photochemically but also thermally to afford the corresponding azaberbines (3), (4), (5), and (8) in good yields respectively.

Photocyclization[1] of unsaturated enamides has made a considerable contribution to the synthesis of nitrogen-containing heterocycles, particularly alkaloids. During our study[1] on the photocyclization of enamide containing an electron deficient aromatic ring, we found that some enamides could also undergo facile cyclization even under thermal condition to give the corresponding dehydrolactams in good yields.

Although acylation of the 3,4-dihydroisoquinoline (1) with an equimolar amount of nicotinoyl chloride in the presence of triethylamine yielded the N-nicotinoyl-enamine (2), treatment with an excessive amount of the acid chloride led to the formation of the N-nicotinoyldihydropyridine (3) in 60 % yield, which exhibited the following spectral data, m/e 415 (M^+); ν 1650, 1600, 1585, and 1570 cm^{-1}; δ 8.77 (2H, m, 2'- and 6'-H), 7.93 (1H, dt, J=8 and 2Hzs, 4'-H), 7.47 (1H, dd, J=8 and 5 Hzs, 5'-H), 7.17 (1H, s, 13-H), 6.97 (1H, br.d, J= 8Hz, 11-H), 6.77 (1H, s, 1-H), 6.37 (1H, s, 4-H), 5.67 (1H, d, J=8Hz, 12-H), 4.97 (2H, s, 9-H_2), 4.30 (2H, t, J=6Hz, 6-H_2), 3.97 (6H, s, OMe × 2), and 2.90 (2H, t, J=6Hz, 5-H_2).

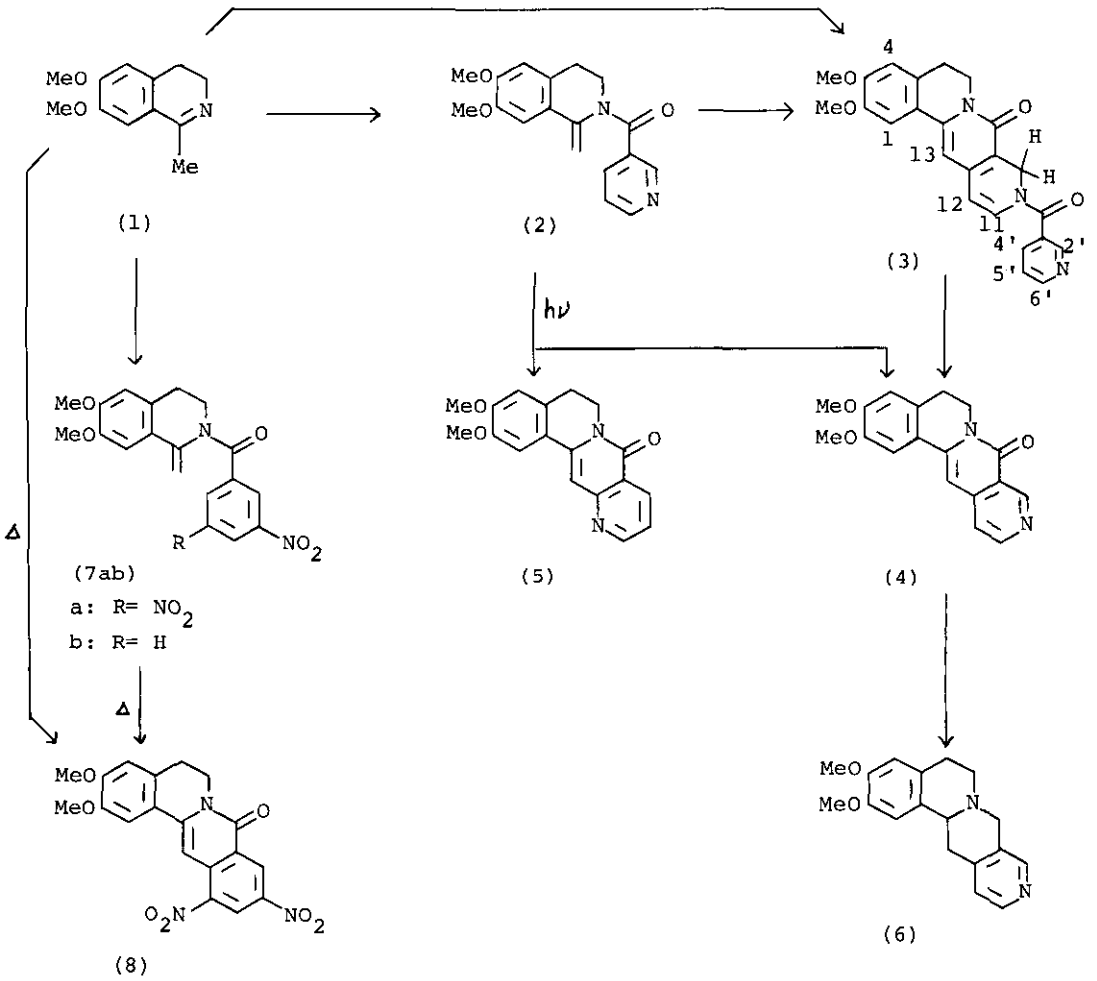
The n.m.r. data, particularly peaks for the N-nicotinoyldihydropyridine chromophore, are similar to those for the analogous dihydropyridine moiety reported by Sainsbury and coworkers.[2] When the enamide (2) was treated with an excessive amount of nicotinoyl chloride, the cyclized product (3) was also obtained in a good yield.

Therefore, it is assumed that N-acylation of a pyridine ring of the enamide (2) forms an electron deficient pyridinium structure, thus facilitating a thermal cyclization of the enamide (2) to yield the cyclized product (3).

In order to evaluate the above thermal cyclization of enamide, we next investigated the reactions of the N-nicotinoyldihydropyridine (3) for its application. N-Deacylation was readily achieved by heating (3) in either 5% KOH-MeOH or c-HCl, affording the corresponding naphthyridine (4)[3] in a good yield. For an alternative synthesis of the naphthyridine (4), the enamide (2) was irradiated in methanol with a high pressure mercury lamp at room temperature for 10 h. The products were a mixture of two types of naphthyridines (4) and (5) in 20 and 10 % yields respectively, of which the former was found to be identical with the sample obtained from (3) upon hydrolysis. Thus, photocyclization of the enamide (2) gave two naphthyridines (4) and (5), while thermal cyclization proceeded siteselectively to give the 2,7-naphthyridine (4) presumably due to steric hindrance of nicotinoyl group in an intermediary dihydro-1,6-naphthyridine ring system. Since the lactam (4) can be regarded as a despyrrole derivative of naucléfine,[2] an antitumor alkaloid from Nauclea plants, it was reduced with lithium aluminum hydride to afford the corresponding amine, azaberbine (6), for its testing of pharmacological activity.

Then, we prepared the N-(3,5-dinitrobenzoyl)enamine (7a) from the 3,4-dihydroisoquinoline (1) and 3,5-dinitrobenzoyl chloride at room temperature and investigated its thermal reaction. The enamide (7a) was thus thermally cyclized upon refluxing in benzene to afford the corresponding lactam (8) in 95 % yield, which was also obtained from (1) by acylation with 3,5-dinitrobenzoyl chloride in benzene under refluxing condition in 70 % yield. However, the mono-nitrobenzoylenamine (7b), which was prepared from (1) and 3-nitrobenzoyl chloride, gave no cyclized lactam even under strong acylating conditions. These results clearly suggest that a considerable electron deficiency in an aromatic ring of the enamide is required for its thermal cyclization.

ACKNOWLEDGEMENT This work was supported by a Grant-in-Aid from the Ministry of Education, Science and Culture, Japan.



REFERENCES

1) I. Ninomiya and T. Naito, Kagaku no Ryoiki, Zokan 123, 69 (1979)

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

3) G. R. Lenz, J. Heterocyclic Chem., 16, 433 (1979)

Received, 19th April, 1980