

ENAMIDE PHOTOCYCLIZATION IN THE SYNTHESIS
OF BENZO[c]PHENANTHRIDINE ALKALOIDS

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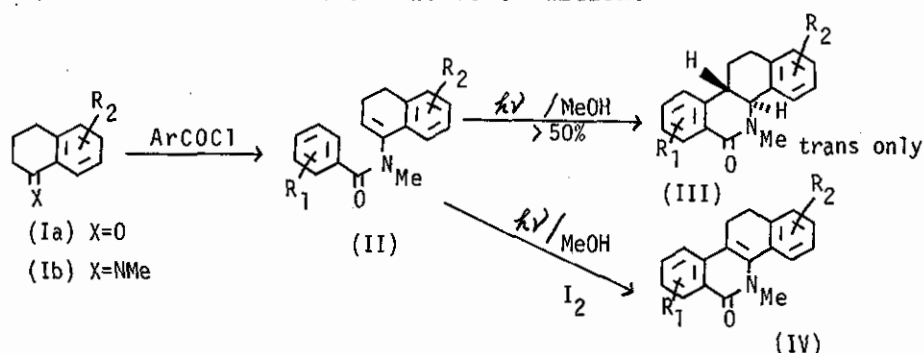
As a target for total synthesis, benzo[c]phenanthridine alkaloids have recently attracted attention because of their potent antileukemic activity. Although a couple of synthetic routes for these alkaloids have been established as reviewed¹⁾, however there still remained untouched alkaloids due to their structural inaccessibility at the time when we started our study.

We, by applying enamide photocyclization, have completed a couple of total syntheses of these alkaloids. This is to summarize the contribution of enamide photocyclization in the synthesis of benzo[c]phenanthridine alkaloids.

§ 1 Preparation of the Skeleton of Benzo[c]phenanthridines²⁾

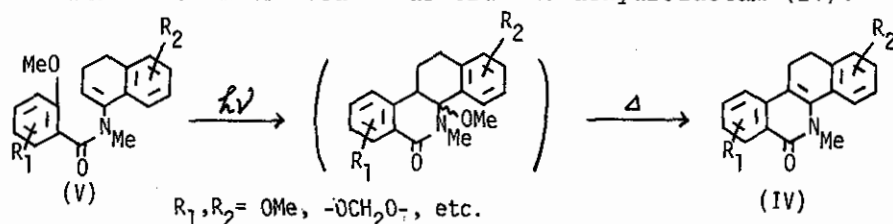
Following the finding of enamide photocyclization in 1969^{2),3)}, we extended the reaction to the enamide (II), which was prepared from 1-tetraloneimine (Ib) by acylation with benzoyl chloride.

The photocyclization was carried out by irradiating a 0.02 M methanolic solution of the enamide (II) with a low pressure mercury lamp at room temperature until the starting enamide disappeared on t.l.c. This simple procedure provided the benzo[c]phenanthridone (III) in good yield. The photocyclization was of stereospecific and non-oxidative nature, thus the product being a homogeneous BC-trans-lactam. Further, the corresponding dehydrolactam (IV) was obtained under oxidative condition.³⁾



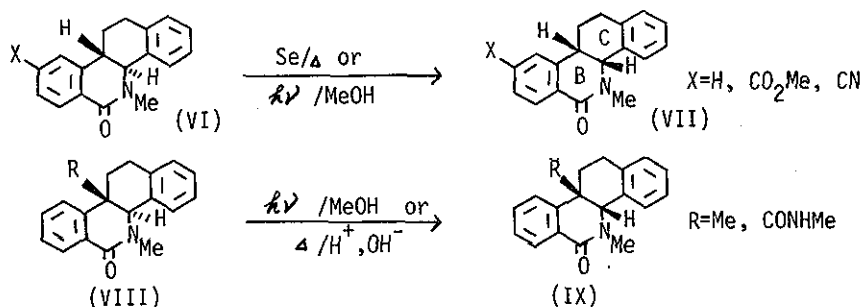
§ 2 Controlling the Direction of the Cyclization⁴⁾

The regiospecificity of the cyclization was established by introducing an additional leaving group such as methoxy- or bromo-group on an ortho-position of N-benzoyl enamine (V). The ortho-methoxy group, for example, forced the cyclization to occur specifically at the root of the group which underwent 1,5-sigmatropic shift and then eliminated to afford the dehydrolactam (IV).



§ 3 Trans-Cis Isomerization^{2), 5)}

During the course of study, we found trans-cis isomerization characteristic to benzo[c]phenanthridones, which, coupled with enamide photocyclization, furnished a couple of total synthesis of alkaloids. Under thermal or photochemical condition, trans-benzo[c]phenanthridones (VI and VIII) underwent irreversible isomerization into the corresponding cis-isomers (VII and IX). This reaction is particularly useful because most of the BC-hydro alkaloids so far isolated from plants have BC-cis-configuration.

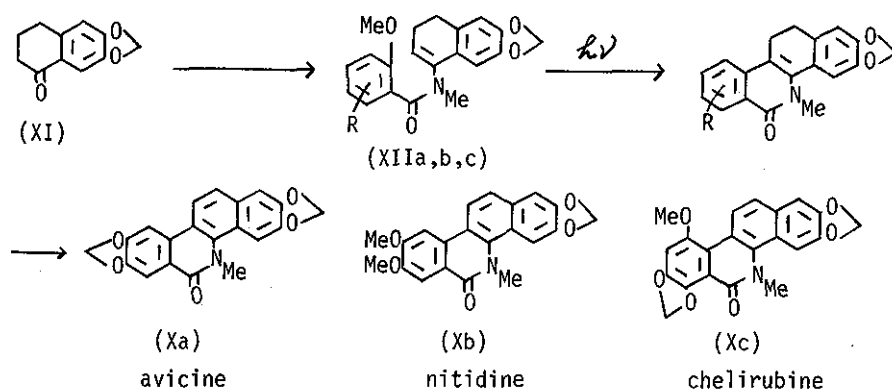


§ 4 Application to Total Synthesis of Alkaloids.

The enamide photocyclization has been successfully applied to total synthesis of the following alkaloids.

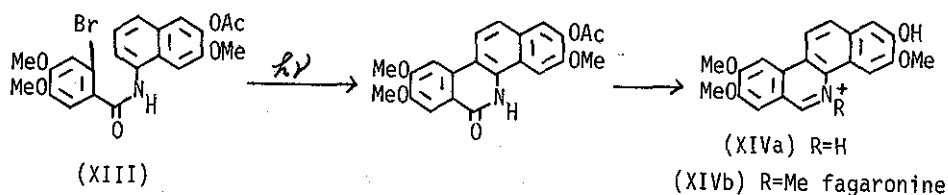
AVICINE (Xa), NITIDINE (Xb), and CHELIRUBINE (Xc)^{4), 6)}

These alkaloids (Xa,b,c), as their oxo-forms, were readily prepared in three steps from the common 1-tetralone (XI) via the enamides (XIa,b,c) which carried an additional ortho-methoxy group, thus brought about regiospecific cyclization respectively.



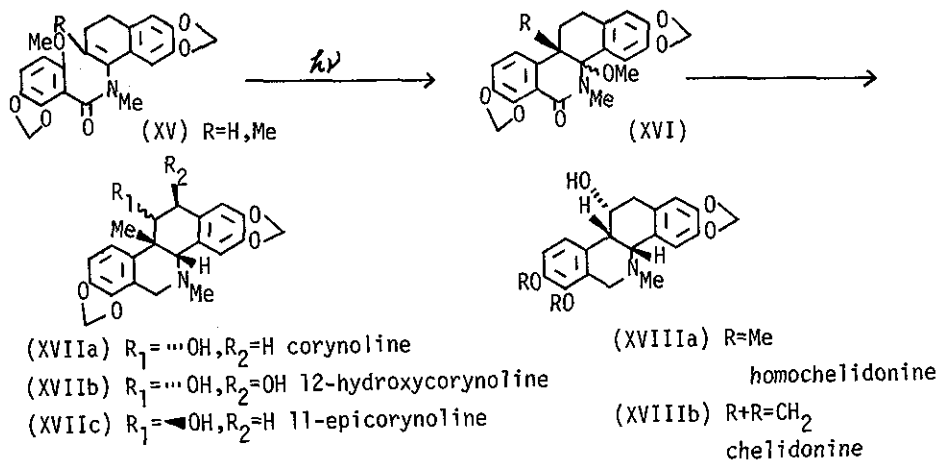
DEMETHYLFAGARONINE (XIVa)⁷⁾

The enamide (XIII) of *N*-naphthylanilide type underwent regio-specific photocyclization.



BC-HYDRO ALKALOIDS (CORYNOLINES and CHELIDONINES)^{8),9),10),11)}

The enamides (XV) were photocyclized to afford the lactams (XVI) respectively, which were converted into the alkaloids containing oxygen functions at 11- and 12-positions, such as corynoline (XVIIa), 12-hydroxycorynoline (XVIIb), 11-epicorynoline (XVIIc) and homochelidonine (XVIII).



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