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

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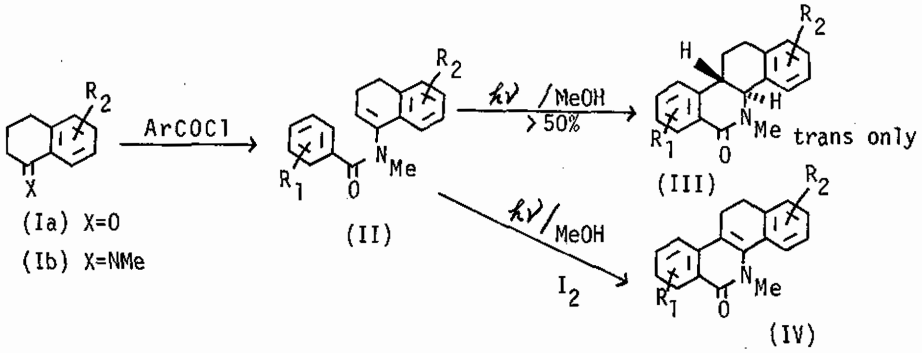
As a target for total synthesis, benzo[c]phenanthridine alkaloids have recently attracted attention because of their potent antileukemic activity. Although a couple of synthetic routes for these alkaloids have been established as reviewed1), however there still remained untouched alkaloids due to their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

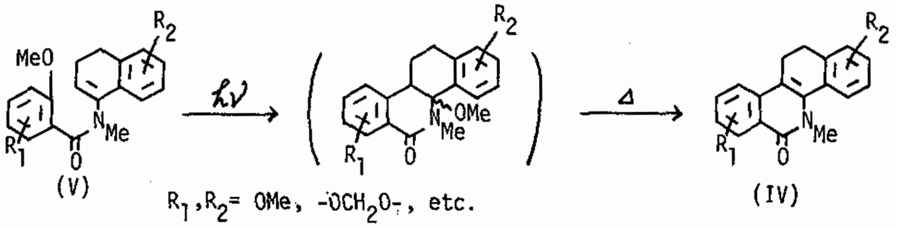
Following the finding of enamide photocyclization in 19692),3), we extended the reaction to the enamide (II), which was prepared from 1-tetraloneimine (Ib) by acylation with benzoyl chloride.

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)

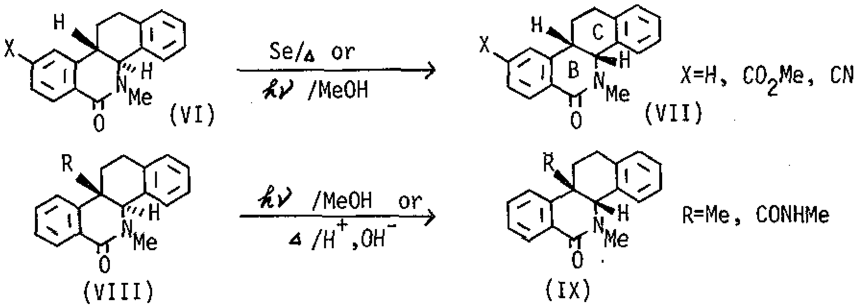
The regiospecificity of the cyclization was established by introducing an additional leaving group such as methoxy- or bromo-group on an ortho-position of N-benzoyl enamine (V). The ortho-methoxy group, for example, forced the cyclization to occur specifically at the root of the group which underwent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



R_1, R_2= OMe, $-OCH_2O-$, etc.

§ 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.

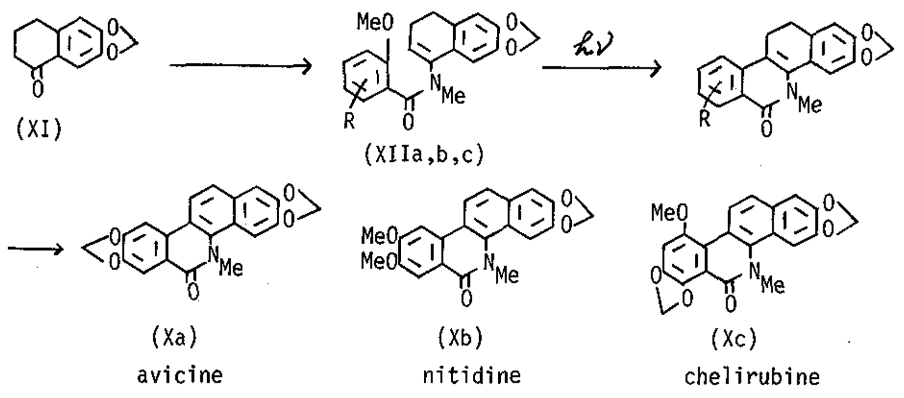


§ 4 Application to Total Synthesis of Alkaloids.

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 (XIIa,b,c) which carried an additional ortho-methoxy group, thus brought about regiospecific cyclization respectively.

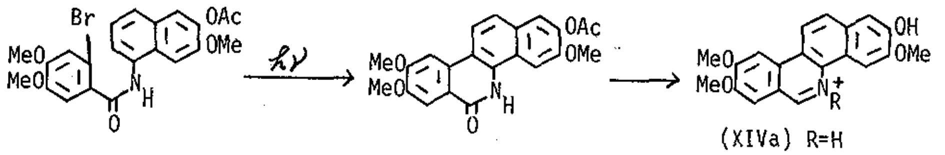


(XI) (XIIa,b,c)

(Xa) avicine (Xb) nitidine (Xc) chelirubine

DEMETHYLFAGARONINE (XIVa)7)

The enamide (XIII) of N-naphthylanilide type underwent regiospecific photocyclization.

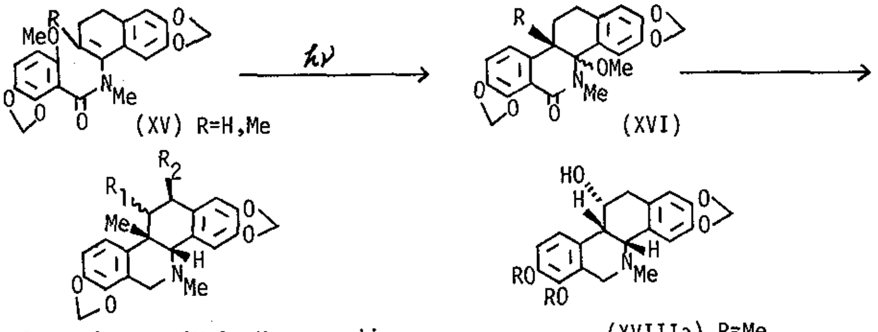


(XIII)

(XIVa) R=H
(XIVb) R=Me fagaronine

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).



(XV) $R=H,Me$

(XVI)

(XVIIa) $R_1=\cdots OH, R_2=H$ corynoline
(XVIIb) $R_1=\cdots OH, R_2=OH$ 12-hydroxycorynoline
(XVIIc) $R_1=\blacktriangleleft OH, R_2=H$ 11-epicorynoline

(XVIIIa) $R=Me$ homochelidonine
(XVIIIb) $R+R=CH_2$ chelidonine

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