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BIOMIMETIC SYNTHESIS OF TRICHOTOMINE

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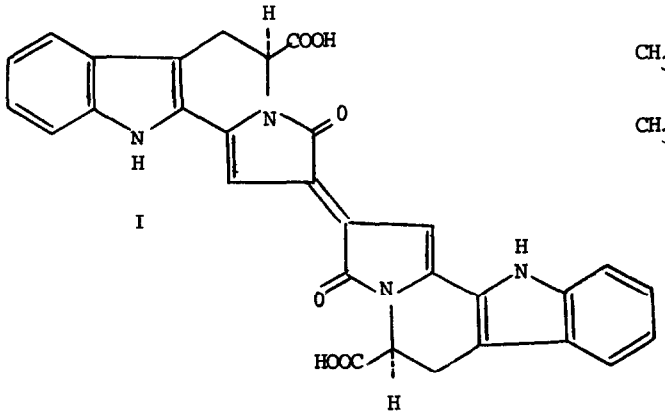
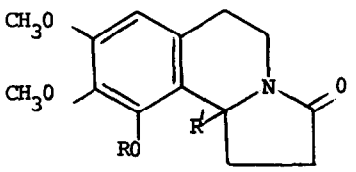
Recently, Iwadare and coworkers reported the isolation and structure elucidation of trichotomine (I), a blue pigment from the fruits of Clerodendron trichotomum (1,2). The structure of this pigment, which possesses a novel chromophore, was confirmed by synthesis (3) and its absolute configuration was assigned by X-ray crystallography (4). These authors proposed that the formation of trichotomine in plants results from oxidative dimerization of the enamine γ-lactam XIII which according to them is biogenetically produced by the condensation of L-tryptophan and succinic acid (2).

In our studies with peyote alkaloids, we recently isolated two lactams II and III (5) whose biosynthesis seemed to involve the condensation of α-ketoglutaric acid with 3-demethylmescaline and mescaline, respectively followed by decarboxylation of the corresponding lactam acids IV and V. We also synthesized these compounds by this route. Subsequently, we showed that C-1 carboxytetrahydroisoquinolines VIII and IX which obviously result from a similar condensation of glyoxylic acid and pyruvic acid with 3-demethylmescaline (6) were precursors of anhalamine (VI) and anhalonidine (VII), respectively. Intermediacy of the Schiff's bases X and XI was suggested by our isolation of XI following the incubation of the precursor IX with peyote slices. Recently, Bobbit and Cheng (7) also implicated similar intermediates based on their facile formation during the electrochemical oxidative decarboxylation of respective 1-carboxylic acids in the benzylisoquinoline series.

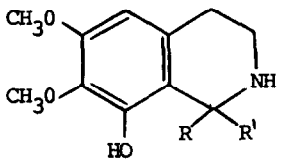
It seemed to us, therefore, that α-ketoglutarate rather than succinate may be a better precursor of the enamine γ-lactam XIII which could be formed via the lactam acid XII. Furthermore, our experience with peyote alkaloids suggested that the entire reaction sequence might occur under the proposed biomimetic conditions even though an oxidation is clearly



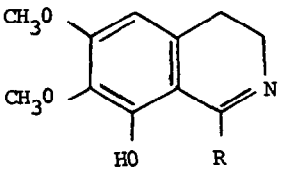
I



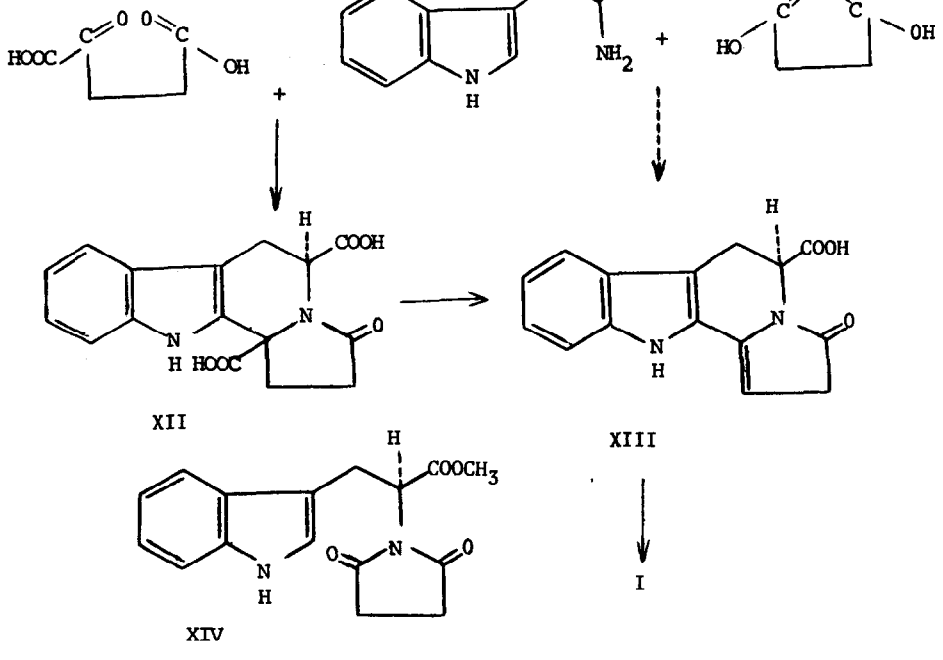
II R=R'=H
III R=CH_3, R'=H
IV R=H, R'=COOH
V R=CH_3, R'=COOH



VI R=R'=H
VII R=CH_3, R'=H
VIII R=H, R'=COOH
IX R=CH_3, R'=COOH



X R=H
XI R=CH_3



XII

XIII

XIV

I

involved.

Accordingly, a mixture of L-tryptophan (0.408 g) and α-ketoglutaric acid (0.320 g) in water (20 ml) was stirred at room temperature for five days. A drop of chloroform was added to inhibit microbial growth. A greenish-blue precipitate observed during the reaction was filtered at the end of the fifth day and washed with water. TLC of the precipitate on silica gel G plate (n-BuOH-AcOH-H_2O, 4:1:5) indicated the presence of a blue spot (R_f 0.84) corresponding to trichotomine. A 42 mg quantity of the blue compound was isolated by preparative TLC using methanol for elution. The isolated product was dissolved in small amount of methanol and treated with diazomethane in ether to form its dimethyl ester. Preparative TLC [silica gel G, EtOAc - C_6H_6 (1:2)] and elution with chloroform-methanol (3:1) afforded 31 mg of the ester as a deep blue product. A reference sample of trichotomine dimethyl ester required for comparison was synthesized following the procedure reported by Iwadare et al. (3) except that the imide ester XIV was obtained by direct treatment of L-tryptophan methyl ester with succinimide. The dimethyl ester from trichotomine prepared by our biomimetic method and the ester obtained following the procedure of Iwadare et al., were identical (TLC, UV, IR, NMR, and mixed m.p.). Identity of the two products was further established by hydrolyzing the esters to trichotomine using the method of Iwadare et al. (3) and by chromatographic and spectral comparison of the two samples obtained from the hydrolysis.

The facile synthesis of trichotomine from L-tryptophan and α-ketoglutaric acid under biomimetic conditions is yet another example of versatile hypothesis, generally attributed to Hahn and coworkers (8-10), and recently proven by us (5,6) and also implicated by others (7,11-14), concerning the involvement of the α-keto acids in the biosynthesis of tetrahydroisoquinoline, 2-carboline and related alkaloids.

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