MODEL REACTIONS FOR THE BIOSYNTHESIS OF SOME ALKALOIDS

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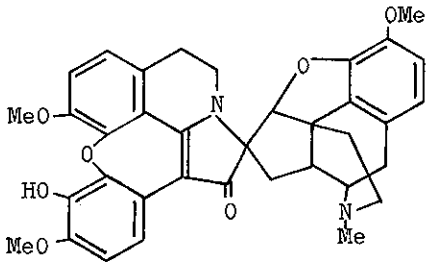
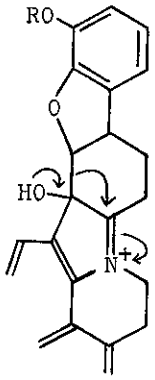
Reactions of 3,4-dihydropapaverine with 1,2-cyclohexanedione and Triton B/pyridine gave the spiro compound (V) representing a model reaction for the fusion of cularine and morphine alkaloids in the proposed biosynthesis of cancentrine (I). The enamine intermediates derived from 1-benzylisoquinolines were converted to the corresponding isoquinolones by photosensitized oxygenation or cuprous chloride-catalysed oxygenation. A method for the hydroxylation at β position of the amino group is also described.

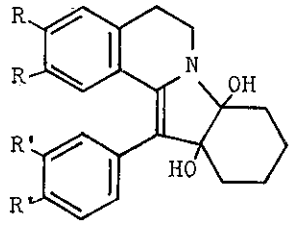
Cancentrine (I), a cularine-morphine dimer, was isolated from Dicentra canadensis (Goldie) Wald. The key step proposed for the biosynthesis[1] of this interesting alkaloid involved the fusion of cularine and morphine alkaloids and proceeded through the iminium intermediate (partial structure II). In order to study the feasibility of the proposed rearrangement in a model system, we have studied the reaction of carbanion α to imine in the 3,4-dihydroisoquinoline derivatives with 1,2-diketones. We reasoned that the reaction of carbanion at the α position to the



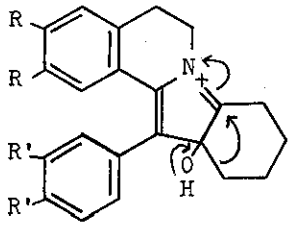
(I)



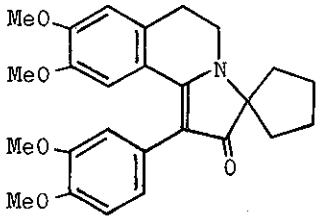
(II)



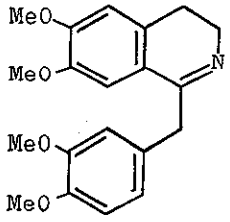
(III)



(IV)



(V)

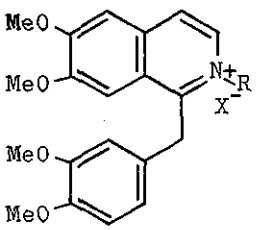


(VI)

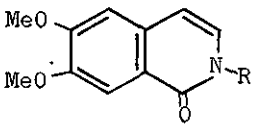
imine group with 1,2-diketones, for example, 1,2-cyclohexanedione would lead to intermediate (III). Elimination of the hydroxyl group facilitated by a lone pair electrons on nitrogen would give intermediate (IV) which could further rearrange to compound (V). Indeed, on heating 3,4-dihydropapaverine (VI) or the corresponding hydrochloride with 1,2-cyclohexanedione and Triton B in pyridine under reflux for 5 hr., the spiro compound[2](V) was isolated in 62% yield. Other diketones, for example, benzil and furil were found to undergo similar rearrangement[3]. Triton B in pyridine was found to be the most suitable combination of base and solvent for the generation of this type of carbanion, from this finding a convenient synthesis of 1-aroylisoquinolines was developed[4].

The isoquinolone alkaloids were proposed to be the oxidation product of 1-benzylisoquinoline derivatives because of the co-occurrence of these two types of alkaloids[5-6]. We have found that in vitro 1-benzylisoquinoline derivatives (VII) could be transformed to the corresponding isoquinolones[5](VIII). The transformation could be effected by converting compounds (VII) to the corresponding enamine intermediates which were then reacted with singlet oxygen (Method A) or cuprous chloride/oxygen (Method B). The percentage yields of the reactions are shown in the table.

Compound	Product	Method A	Method B
VII a	VIII a	45	80
VII b	VIII b	61	80
VII c	VIII c	23	18



(VII)

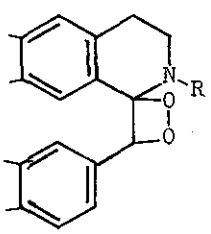


(VIII)

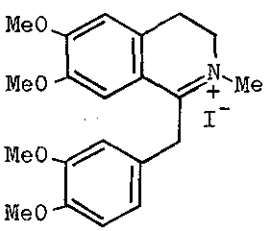
a) R = Me-

b) R = Ph-CH_2-

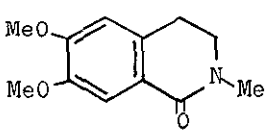
c) R = $(Me)_2$-C=CH-CH_2-



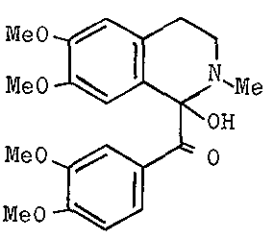
(IX)



(X)



(XI)



(XII)

It is most likely that the amino-dioxetane (IX) is the intermediate in the cleavage reaction and we think that the amino-dioxetane intermediate is responsible for the biosynthesis of the isoquinolone alkaloids.

Photosensitized oxygenation of the enamine intermediate of compound (X) gave the corresponding isoquinolone (XI) in 69% yield, while cuprous chloride-catalysed oxygenation gave the isoquinolone in 10% yield, and the main product of this reaction was found to be the hydroxy-ketone (XII, ca 55% yield). Sodium borohydride reduction of compound (XII) gave α-hydroxylaudanosine and β-hydroxylaudanosine in the ratio of 1:1. The transformation of compound (X) to hydroxylaudanosine illustrated a method to introduce a hydroxyl group β to amino group. The occurrences of alkaloids[7] with hydroxyl group β to amino group are widespread and compounds of this type have also been inferred to be the intermediate in the biosynthesis of some alkaloids from feeding experiments[8]. It is possible that in the biosynthesis[9] of some of these alkaloids the amino-dioxetane was the intermediate which could be reduced to the corresponding β-hydroxyamino compound. It is interesting to note the similarity of our method of hydroxylation and the *in vivo* hydroxylation[10], in our method molecular oxygen and a reducing agent (sodium borohydride) were used whereas *in vivo*, molecular oxygen and a reducing agent (typically NADPH) were required.

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