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SYNTHESIS OF N-SUBSTITUTED ISOQUINOLONES

MODEL FOR THE BIOSYNTHESIS OF ISOQUINOLONE ALKALOIDS

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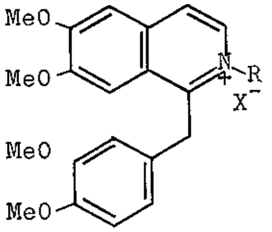
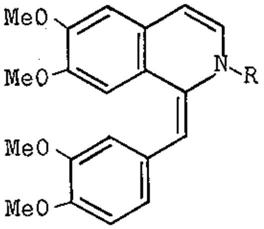
Reactions of enamine intermediate (II) derived from 1-benzylisoquinoline derivative (I) with cuprous chloride/oxygen or singlet oxygen gave isoquinolone derivative (III). The implication of the reaction of enamine intermediate with singlet oxygen to the biosynthesis of isoquinolone alkaloid is discussed.

The isoquinolones[1] are usually synthesized by the oxidation of the isoquinoline salt with potassium ferricyanide or oxidation of the tetrahydroisoquinoline derivative with potassium permanganate in acetone.[2] However, by these methods low yields of isoquinolones are usually obtained. We wish to report the synthesis of N-substituted isoquinolones by the oxidation of the corresponding N-substituted 1-benzylisoquinoline salts and our devised synthesis also gives the insight into the biosynthesis of the isoquinolone alkaloids.

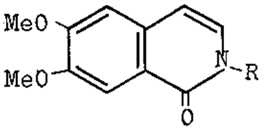
Our approach took the advantages of the known reactivity of 1-benzylisoquinoline salt (I) which exists in the enamine form in the alkaline solution[3] together with the cuprous chloride-catalysed oxidation of enamine with oxygen,[4] where the double bond was cleaved to the corresponding amide and carbonyl compounds.



(I)



(II)

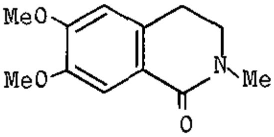


(III)

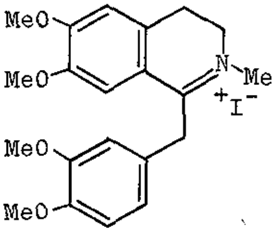
a) R = Me-
b) R = Ph-CH_2-
c) R = $(Me)_2$-C=CH-CH_2-

Reaction of N-methylpapaverinium iodide (Ia, X=I) with aqueous sodium hydroxide solution gave the corresponding enamine (IIa) which was extracted with benzene. Treatment of the benzene solution with cuprous chloride together with continuous flow of stream of oxygen into the solution, the yellow solution changed to colourless solution and the cuprous chloride changed to green cupric salt. The mixture was filtered through celite and the benzene solution was evaporated to dryness, the products were then separated and shown to be the isoquinolone (IIIa, 80% yield) and veratraldehyde (60% yield). Similarly, N-benzylpapaverinium bromide[5](Ib,X=Br) was converted to the corresponding isoquinolone[6](IIIb) in 80% yield and N-3,3-dimethylallylpapaverinium bromide[7] gave the isoquinolone[8](IIIc) in 18% yield.

N-Methyl-3,4-dihydroisoquinolone, for example, compound (IV) is also a natural product, and, therefore, to extend our investigation we decided to study the oxidation of N-methyl-3,4-dihydropapaverinium iodide[9](V). Cuprous chloride-catalysed oxygenation of the enamine derived from compound (V) gave the expected isoquinolone[10](IV) in 10% yield.



(IV)

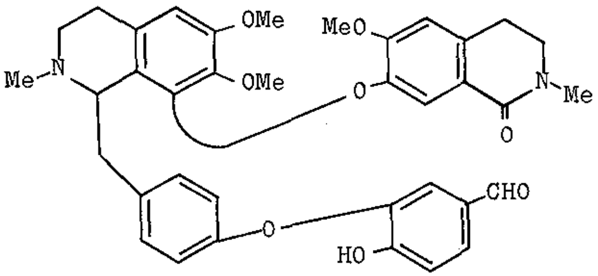


(V)

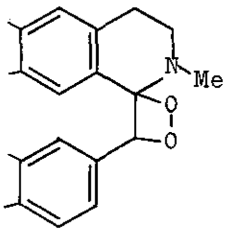
Singlet oxygen[11] has been shown to react with many funtional groups. Lately, increasing interest has been focussed on the reaction of enamine[12] with singlet oxygen, this special interest has been stimulated by the possible implication of the reaction of this type in biological systems. We have also investigated the reaction of singlet oxygen with enamine derived from N-substituted 1-benzylisoquinoline derivative. The photolytic oxidation of tetrahydroisoquinolines to the corresponding isoquinolones and aromatic aldehydes has been previously reported[13].

The reaction was simply carried out by passing stream of oxygen into a methanolic solution of N-substituted 1-benzylisoquinoline derivatives (Ia, b,c and V) containing sodium methoxide and a photosensitizer (Rose bengal), the mixture was then irradiated with a tungsten lamp at room temperature, by this method, the isoquinolones (IIIa,b,c and IV) were successfully synthesized (% yields: 45, 61, 23 and 69 for compounds IIIa,b,c and IV).

The co-occurrence[14] of isoquinolone with the corresponding 1-benzylisoquinoline lends support to the proposal that the isoquinolone is the oxidation product of 1-benzylisoquinoline. The most convincing circumstantial evidence is the isolation of baluchistanamine[14a] (VI) from Berberis baluchistanica. This compound was thought to derive from oxyacanthine which was also isolated from the same plant.



(VI)



(VII)

The mechanistic detail of the in vivo oxidation of 1-benzylisoquinoline to isoquinolone remains unknown. From our study, it is very likely that our devised method followed what happened in nature i.e. the oxidation passed through the enamine and amino-dioxetane intermediate (VII) which could then fragment to the corresponding isoquinolone and carbonyl moieties.

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References and Footnotes

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5 This compound was prepared in 80% yield by the reaction of papaverine with benzyl bromide in acetonitrile under reflux.

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7 This compound was prepared in 50% yield by the reaction of papaverine with freshly distilled 3,3-dimethylallyl bromide in acetonitrile under reflux.

8 This compound has the following physical data: ir: ($CHCl_3$) 1650 cm^{-1}; nmr: ($CDCl_3$) δ 1.80, 1.95 (s, $2xC\underline{H}_3$), 4.06, 4.09 (s, $2xOC\underline{H}_3$), 4.73 (br. d, $N\text{-}C\underline{H}_2$), 5.25-5.65 (m, $\underline{H}C{=}C\text{-}$), 6.57 (d, J=7 Hz, $\underline{H}C{=}$), 7.0 (s, C-5 Ar$\underline{H}$), 7.17 (d, J=7 Hz, C-3 $C\underline{H}\text{-}N$), 8.0 (s, C-8 Ar$\underline{H}$); ms: m/e 273 (M^+, 50%), 205 (100%)

9 This compound was prepared by methylation of 3,4-dihydropapaverine with methyl iodide, cf. A. R. Battersby, R. Binks, R. J. Francis, D. J. McCaldin and H. Ramuz, *J. Chem. Soc.*, 1964, 3600.

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