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PHOTO-OXIDATION OF SOME BENZYLISOQUINOLINE-DERIVED ALKALOIDS

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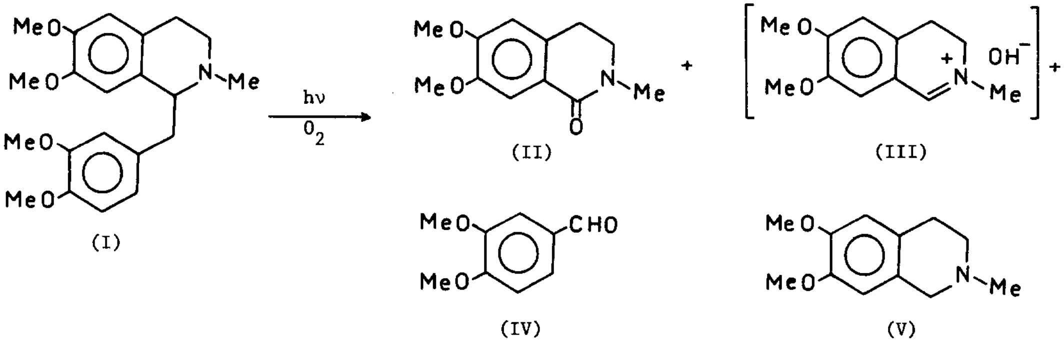
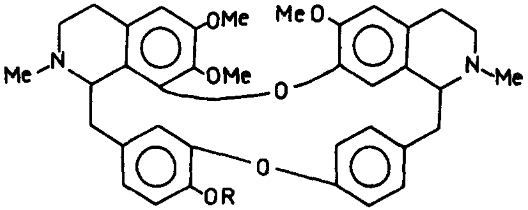
We wish to report a photo-oxidative cleavage reaction of some benzylisoquinoline-based alkaloids, which should be particularly useful in structural studies of bisbenzylisoquinolines not readily amenable to the usual degradative methods.

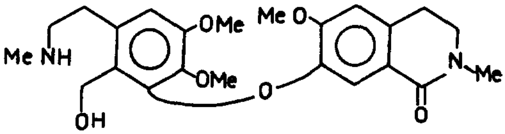
Ultraviolet irradiation[1] of laudanosine (I) in the presence of oxygen gave (II)(45%), veratraldehyde (IV)(67%), and the carbinolamine (III), isolated as its chloride salt[2] or as its reduction ($NaBH_4$) product (V)(42%). The same products were obtained using methylene blue as sensitiser (45 mins; uranyl oxalate filter sleeve), but in lower yield: (II), 32%; (IV), 39%; (V), 15%. No noticeable oxidation of laudanosine occurred in the dark.



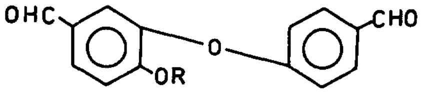
While similar products have been obtained from simple benzylisoquinolines when oxidised with[3] or without[2,4] irradiation, such methods have had only limited success when applied to the more complicated bisbenzylisoquinolines; in particular, few examples of the isolation of isoquinoline-based fragments from direct oxidation have been recorded.[5] We have found, however, that photolysis (15 hrs.) of isotetrandrine (VIa) in the presence of oxygen gave as major products the dialdehyde[6] (VIIIa)(50%), and (VII)(30%), isolated after reduction of the amide-carbinolamine intermediate. The structure of (VII) follows from its p.m.r. spectrum and its ready dehydration to (IX), which could also be obtained directly depending on the reduction conditions. Compound (IX) had m.p. 128-130° (dec.); M.W. (m.s.) 412.198461 ($C_{23}H_{28}O_5N_2$); i.r. : 1645 (s), 1100 cm^{-1} (s); p.m.r. ($CDCl_3$), δ ppm: 7.25 (s, 1H, H_c); 6.73 (d, J $\simeq$ 1 cps, 1H, H_a or H_b); 6.56 (d, J $\simeq$ 1 cps, 1H, H_a or H_b); 3.99, 3.84, 3.77 (three singlets, 3H each, 3 x OCH_3); 3.60 - 3.40 (m, 2H, H_d); 3.45 (s, 2H, H_e); 3.07 (s, 3H, amide $N-CH_3$); 3.05 - 2.55 (m, 6H, aliphatic CH_2) and 2.48 (s, 3H, amine $N-CH_3$). On reductive cleavage (Na; liquid NH_3; toluene), (IX) gave a mixture of products from which (V) was isolated in nearly quantitative yield. The amide group in (IX) is evidently part of ring D since no (V) could be detected when (II) was reduced by the same method.



(VI)

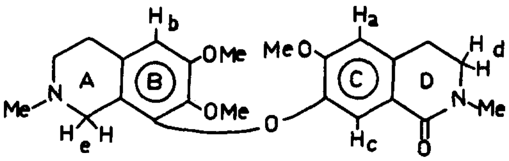


(VII)



(VIII)

a) R = Me b) R = H



(IX)

These reactions have been successfully applied to a range of other bisbenzylisoquinoline alkaloids including tenuipine[7] and micranthine[8], which are difficult to degrade by standard methods. The presence of phenolic groups complicates the reaction, although with berbamine (VIb) the expected products were still obtained but in diminished yield: (VIIIb)(35%, m.p. 135 - 136°) and (IX)(15%).

The mechanism of oxidation of these alkaloids is still uncertain, and further studies are in progress to distinguish between the singlet oxygen pathway[9] and the route involving reaction of ground-state oxygen with substrate radicals[10]. The question of the selective formation of carbinolamine and lactam residues in the cleavage products of (VIa) and (VIb) also remains to be resolved.

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REFERENCES AND FOOTNOTE

1. At 25° for 3 hours in 0.003-0.008 M MeOH; Hanovia 450 watt Hg lamp, water-cooled quartz probe with a pyrex filter sleeve. Products were separated by P.T.L.C. on silica gel.
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