Tetrahedron Letters No.28, pp. 2363-2366, 1969. Pergamon Press. Printed in Great Britain.

THE ENZYMATIC OXIDATION OF ISOQUINOLINE ALKALOIDS

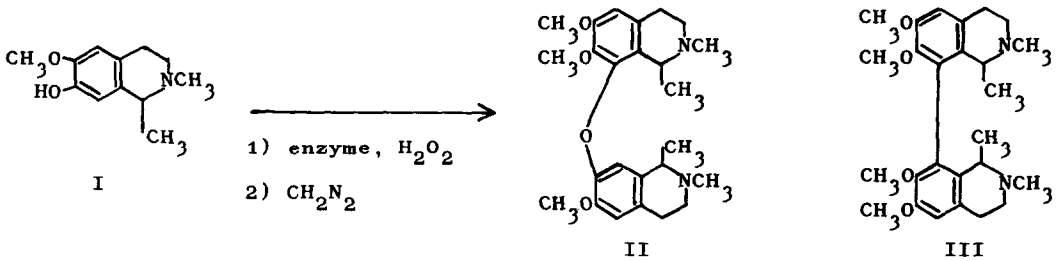
Y. Inubushi, Y. Aoyagi, and M. Matsuo

(Faculty of Pharmaceutical Sciences, Kyoto University, Kyoto, Japan)

(Received in Japan 28 April 1969; received in UK for publication 6 May 1969)

Phenol oxidative coupling reaction has been recognized as an important pathway in plant product biosynthesis; and in physiological conditions, this reaction has been understood to be catalysed by peroxidase. We now wish to report here *in vitro* oxidations of some phenolic isoquinolines with hydrogen peroxide and phyto-peroxidase*.

dl-N-Methylisosalsoline (I, 900 mg.) was oxidized in 3 % aqueous ammonium acetate solution (pH 7.0, 100 ml.) with peroxidase** (10 mg.) and 3 % aqueous H_2O_2 (6 ml.) at 20-25° for 14 hr. After conventional work-up, the collected basic product was methylated with diazomethane to afford an oily dimer (II, a mixture of diastereoisomers, 78 mg.) and crystalline dimer (III, colourless pillars, m.p. 160-161°, 52 mg.). The structure of II was confirmed by spectroscopic comparison with the authentic sample[3]; and the structure III of the



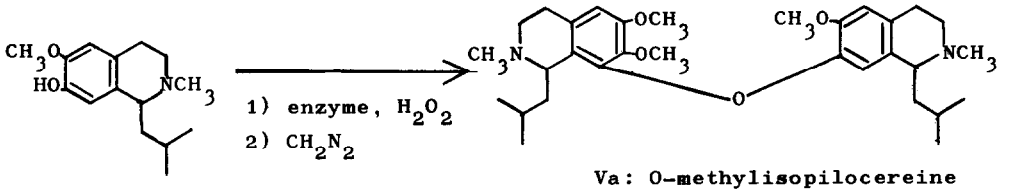
I II III

* Recently, K.H.Flömming[1] reported a peroxidase oxidation of laudanosoline methobromide to an aporphine type compound. We observed, however, that, in case of oxidations of quaternary ammonium bromide and iodide, halogenation of phenolic nucleus occurred predominantly. More recently, T.Kametani *et al.*[2] reported an oxidation of phenolic phenethylisoquinoline using plant homogenate and H_2O_2 as an oxidant, in which a diphenyl ether type dimer was obtained.

** Peroxidase (Horse-radish), crude. Sigma Chemicals Company. Activity: Approximately 44-50 purpurogallin units per mg.

crystalline compound was based on its n.m.r. and mass spectral data.

The oxidation of dl-lophocerine (IV, 1.0 g.) by the same way as above followed by O-methylation yielded two diphenyl ether type dimers, Va (colourless oil, 18 mg.) and Vb (colourless oil, 14 mg.), whose structures were confirmed by comparison of their i.r. and n.m.r. spectra with those of the authentic O-methylisopilocereine and its diastereoisomer[4], respectively.



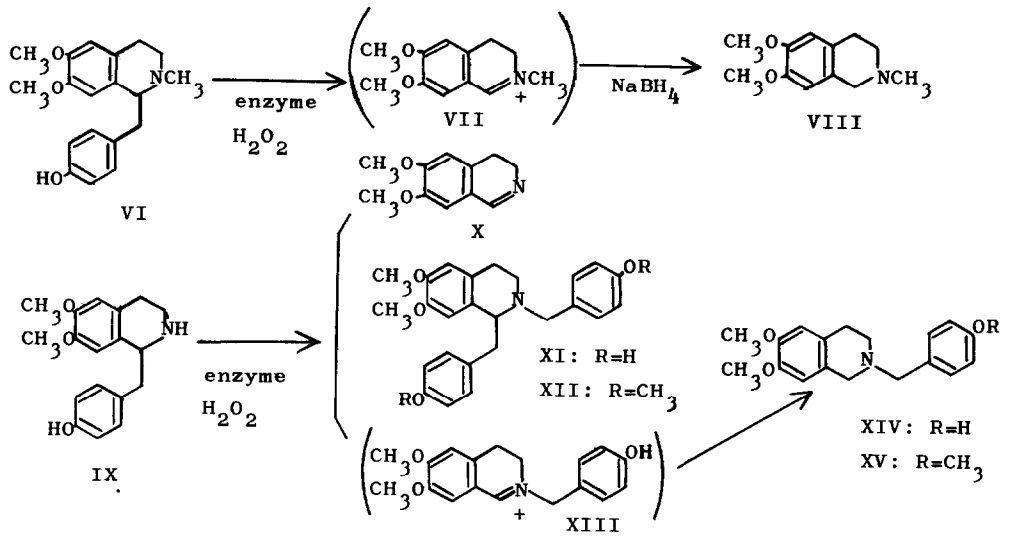
IV

Va: O-methylisopilocereine
Vb: diastereoisomer of Va

In the oxidation of dl-armepavine (VI, 350 mg.) in pH 7.0 buffer solution, a crystalline product, O-methylcorypalline (VIII, colourless pillars, m.p. 69-71°, 72 mg.), was isolated from the quaternary base fraction after borohydride reduction. The structure of the primary quaternary base could be drawn as formula VII from its u.v. spectral observation.

The oxidation of dl-N-norarmepavine (IX, 1.0 g.) in pH 6.5 buffer solution gave a somewhat different result: From the tertiary base fraction, a non-phenolic base (X, pale-yellow oil, 45 mg.) and a phenolic base (XI, colourless oil, 11 mg.) were isolated. The structure of the non-phenolic base (X) was ascertained on the basis of the i.r., n.m.r., and u.v. spectral data, and the corresponding methyl ether (XII) of the phenolic product (XI) was identified with the authentic sample of XII (oxalate, m.p. 181-183°) synthesized through an unambiguous route. From the quaternary base fraction, a crystalline tertiary base (m.p. 201-204°, 62 mg.) was isolated after borohydride reduction. Mass and n.m.r. spectral data of this base agreed with the structure XIV. Furthermore, the corresponding methyl ether (XV, colourless pillars, m.p. 98-99°) was identified with the authentic O-methylsendaverine by mixed melting point determination and comparison of i.r., n.m.r., and mass spectral data.

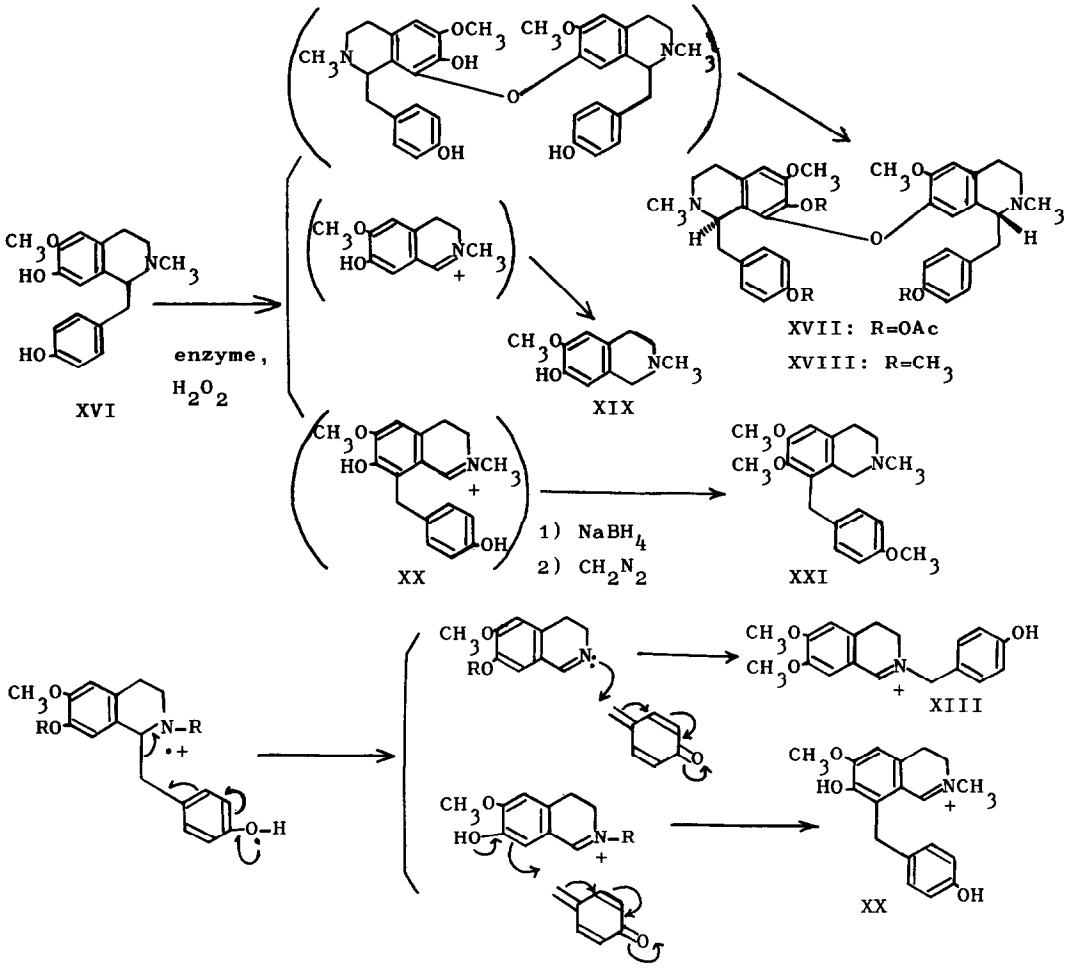
The oxidation of dl-N-methylcoclaurine (XVI, 5.0 g.) was carried out in a similar condition as above. In this reaction, a diphenyl ether type dimer



(XVII, oil, 163 mg.) was isolated from the acetylated tertiary base fraction, and the corresponding methyl ether (XVIII) of this product was identified by i.r. and n.m.r. spectrometry with the optically active authentic sample of XVIII[5]. From the quaternary base fraction, were isolated the following two products after borohydride reduction: One (colourless pillars, m.p. 170-171°, 655 mg.) was identified with corypalline (XIX) by i.r. spectrum and mixed melting point: and the other (oil, 13 mg.), which was isolated after O-methylation, was concluded to be XXI from the fact that the i.r., n.m.r., and mass spectra of this methyl ether were found to be superimposable on those of the authentic sample of XXI synthesized through an alternative route.

Of all the above reactions, stereoselectivity was not observed, and in the parallel blank experiments using boiled enzyme, no oxidation occurred and starting materials were recovered quantitatively.

A possible mechanism for the elimination of p-hydroxybenzyl group in the course of the oxidation might involve a participation of the cation radical on nitrogen atom as well as phenolic hydroxyl group. Further, N-benzylisoquinoline (XI and XIII) and 8-benzylisoquinoline (XX) were assumed to be resulted by the attack of nitrogen lone pair or phenolic nucleus on an unstable quinoid type compound formed in the course of the above elimination reaction.



Acknowledgement We wish to thank Prof. Dr. Masao Tomita, President of Kyoto College of Pharmacy, for his encouragement in this work and supplying the authentic samples of compound II, VIII, XV, XVIII, and XIX.

REFERENCES

1) K. H. Flömming, Arch. Pharm., 300, 977 (1967).
2) T. Kametani, S. Takano, and T. Kobari, J. Chem. Soc.(C), 1969, 9.
3) M. Tomita, Y. Masaki, and K. Fujitani, Chem. Pharm. Bull.(Tokyo), 16, 257 (1968).
4) K. Bessho, Chem. Pharm. Bull.(Tokyo), 11, 1500 (1963).
5) M. Tomita, Y. Masaki, K. Fujitani, and Y. Sakatani, Chem. Pharm. Bull. (Tokyo), 16, 688 (1968).