

Enzymatic Oxidative Coupling of optically Active Laudanosoline and Its Methiodide

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Many alkaloids are in principle derived from phenolic precursors by carbon-carbon, carbon-oxygen or carbon-nitrogen coupling with the probable assistance of enzymes.²⁾ While the use of enzymes and enzyme extracts in the synthesis of isoquinoline alkaloids has been reported by Kametani and co-workers,³⁾ Inubushi and associates,⁴⁾ and Frömring,⁵⁾ this approach has been of little preparative value due to formation of complicated mixtures or poor yields. It is therefore not surprising that chemical oxidations have remained the method of choice. For example, FeCl₃ has been used to effect the transformation of racemic laudanosoline (I)⁶⁾ into the quaternary dibenzopyrrocoline (II)⁷⁾ as well as the conversion of racemic laudanosoline methiodide (IV) into the quaternary aporphine (V).⁵⁾ More recently, the preparative value of VOCl₃ in chemical oxidations has been demonstrated.⁸⁾

In contrast, we now report that by the use of the purified enzyme horseradish peroxidase⁹⁾ under controlled reaction conditions, oxidative coupling of (1S)-(+)-laudanosoline hydrobromide (I) and (1R)-(-)-laudanosoline methiodide (IV) could be effected with great facility and in a preparative manner to afford the quaternary dibenzopyrrocoline (II) and the quaternary aporphine (V), respectively, with retention of absolute configuration.

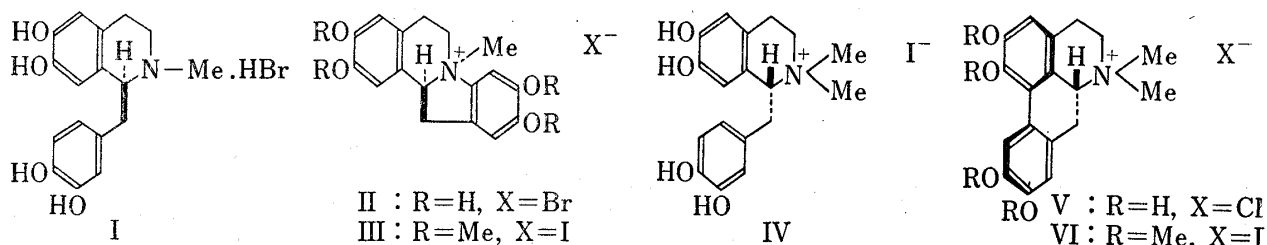


Chart 1

Experimental

To 5 g of (I)¹⁰⁾ and 25 mg of horseradish peroxidase in 250 ml of pH 5 phosphate buffer was added 15 ml of 3% H₂O₂, the mixture stirred for 4 hr, acidified with 24% HBr and the resulting crystals collected to give 3.5 g (81%) of (II): mp 279–280°, [α]_D²⁵ –170° (c=0.5, H₂O). Methylation of (II) according to the procedure

- 1) Location: Nutley, New Jersey, U.S.A.
- 2) A.I. Scott, *Quart. Rev.* (London), **19**, 1 (1965).
- 3) T. Kametani, S. Takano, and T. Kobari, *J. Chem. Soc. (C)*, **9**, 2770 (1969).
- 4) Y. Inubushi, Y. Aoyagi, and M. Matsuo, *Tetrahedron Letters*, **1969**, 2363.
- 5) K.-H. Frömring, *Arch. Pharm.*, **300**, 62 (1967).
- 6) The above structures show one of the two optical isomers in its correct absolute configuration.
- 7) B. Franck and L.-F. Tietze, *Angew. Chem.*, **79**, 815 (1967).
- 8) M.A. Schwartz, R.A. Holton, and S.W. Scott, *J. Am. Chem. Soc.*, **91**, 2800 (1969); M.A. Schwartz, *Synth. Commun.*, **3**, 33 (1973).
- 9) Horseradish peroxidase was obtained from Worthington Biochemical Corp., Freehold, New Jersey, as a lyophilized tan solid, activity grade 3000–4000 units/mg (E.C. 1.11.1.7).
- 10) S. Teitel, J. O'Brien, and A. Brossi, *J. Med. Chem.*, **15**, 845 (1972).

of Robinson and Sugasawa¹¹⁾ provided (III), identical in mp and optical rotation with (S)-(-)-O-methyl-cryptaustoline iodide.¹²⁾

To a mixture of 500 mg of IV [mp 219—220°, $[\alpha]_D^{25} -90.3^\circ$ ($c=1$, MeOH)], obtained by quaternization of (R)-(-)-laudanosine¹³⁾ and 0.1 mg of horseradish peroxidase in 200 ml of H₂O was added 200 ml of 0.02% H₂O₂ over 1 hr while maintaining neutral pH by the addition of 0.1M Et₃N as needed. Acidification with dil HCl followed by concentration to 10 ml afforded on cooling 210 mg (60%)¹⁴⁾ of crystalline (V): mp 80—82°, $[\alpha]_D^{25} -40^\circ$ ($c=0.5$, H₂O). The absolute configuration of (V) was established by its conversion into the known (R)-(-)-glaucine methiodide (VI).¹⁵⁾

The above transformations¹⁶⁾ show that enzymatic coupling is at least as efficient as chemical methods for the practical preparation of certain types of alkaloids. The studies, which so far have been preliminary in nature, are now being expanded into a thorough investigation with different substrates and enzymes.

- 11) R. Robinson and S. Sugasawa, *J. Chem. Soc.*, **1932**, 789.
- 12) G.H. Hughes, E. Ritchie, and W.C. Taylor, *Aust. J. Chem.*, **6**, 315 (1953).
- 13) A. Pictet and B. Athanescu, *Chem. Ber.*, **33**, 2346 (1900).
- 14) Optimization of the yield on a smaller scale produced values of 80—90%.
- 15) J. Go, *Yakugaku Zasshi*, **50**, 933 (1930) [*C. A.*, **25**, 518 (1931)].
- 16) We gratefully acknowledge the technical assistance of Messrs. S. Roy and J. Van Burik.

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Studies on Ketene and Its Derivatives. LVII.¹⁾ Reaction of Diketene with β -Diketones

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Though the literature contains many references to synthesis of heterocyclic compounds from diketene, the formation of benzene ring system from diketene had not been described. However, in the previous paper of this series³⁾ we reported that diketene reacted with β -ketoesters such as ethyl acetoacetate in the presence of sodium hydride giving β -resorcinol derivatives such as ethyl orsellinate (V).

The present investigation was undertaken to see if diketene could react with β -diketones such as acetylacetone (Ia), benzoylacetone (Ib), dimedone (Ic) and dibenzoylmethane (Id) in a similar fashion as above to give β -resorcinol derivatives or not.

Concerning this reaction Hamamoto, *et al.*⁴⁾ reported that diketene reacted with acetylacetone (Ia) in the presence of acid such as sulfuric acid to give 3-acetyl-2,6-dimethyl-4-pyrone (IV), but did not react in the presence of a basic catalyst such as pyridine to result in the dimerization of diketene to dehydroacetic acid.

In view of the above fact, first we reinvestigated the reaction of acetylacetone (Ia) with diketene, and we found that reaction was affected under a variety of reaction conditions to give different products. When acetylacetone (Ia) was allowed to react with diketene in tetrahydrofuran (THF) in the presence of sodium hydride, colorless crystals of mp 158—159° (II) were obtained. On the other hand, when the reaction was carried out in water in the presence

- 1) Part LVI: T. Kato and T. Hozumi, *Yakugaku Zasshi*, **93**, 1084 (1973).
- 2) Location: *Aobayama, Sendai, 980, Japan.*
- 3) T. Kato and T. Hozumi, *Chem. Pharm. Bull.* (Tokyo), **20**, 1574 (1972).
- 4) K. Hamamoto, T. Isoshima, and M. Yoshioka, *Nippon Kagaku Zasshi*, **79**, 840 (1958).