PHENOL OXIDATION OF ISOQUINOLINE ALKALOIDS WITH CUPROUS CHLORIDE AND OXYGEN IN PYRIDINE AS AN ENZYMATIC MODEL. BIOMIMETIC TOTAL SYNTHESIS OF CORYTUBERINE, ISOBOLDINE, PALLIDINE, ORIENTALINONE AND KREYSIGINONE

Tetsuji Kametani,* Yoshinari Satoh, Makoto Takemura, Yohko Ohta, Masataka Ihara, and Keiichiro Fukumoto
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai, Japan

Phenol oxidaiton of (+)-reticuline (1) perchlorate with cuprous chloride and oxygen in pyridine gave (+)-corytuberine (2), (+)-isoboldine (3), and pallidine (4). Under the same reaction conditions, (±)-orientaline (5) perchlorate yielded (±)-orientalinone (6) and its epimer (7), while (±)-1,2,3,4-tetrahydro-7-hydroxy-1-(4-hydroxy-3-methoxyphenethyl)-6-methoxyisoquinoline (8) hydrochloride furnished (±)-kreysiginone (9) and the diastereoisomer (10). Oxidation with cupric chloride and potassium superoxide in pyridine gave rise to the similar results.

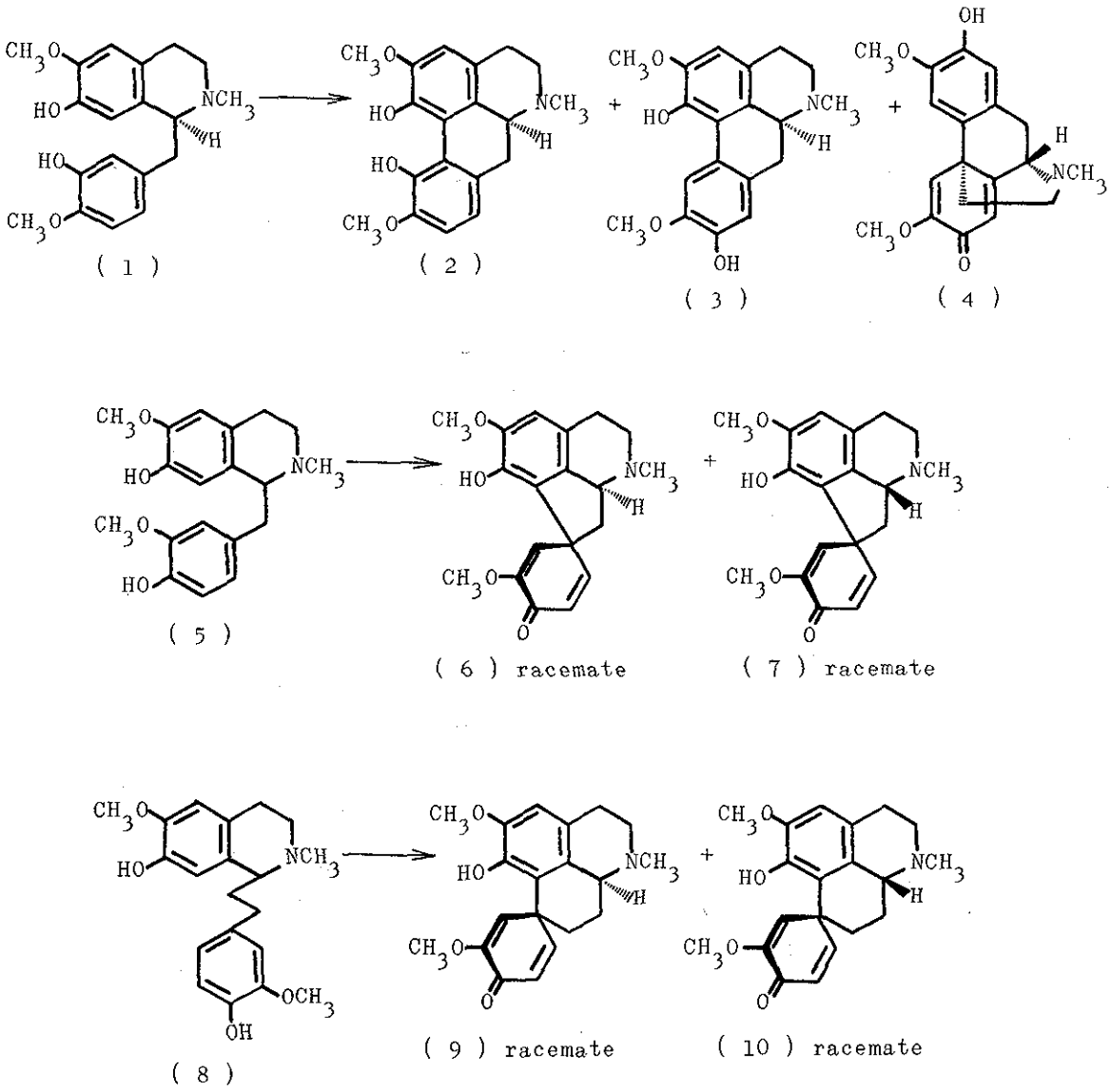
The oxidation and coupling of phenols is a subject of great importance in biochemistry and organic chemistry.[1] Particularly, in an isoquinoline alkaloid field, biosynthetic pathways to a variety of the alkaloid groups, for example, aporphines, morphines, proaporphines, cularines, bisbenzylisoquinolines and phenethylisoquinolines,[2,3] involve phenol oxidative coupling as a key reaction. The three main

classes of enzymes known as catalyst for phenol oxidation and coupling are the laccase, the tyrosinase, and the peroxidase. However, success in demonstrating the intramolecular coupling with enzymes in vitro has so far been limited.[4,5] On the other hand, there are many examples of the phenol oxidations using potassium ferricyanide,[6a-g] ferric chloride,[6f] vanadium oxychloride,[6e,h] thallium tristrifluoroacetate[6i] and so on as chemical oxidizing agents, although most of them gave unsatisfactory yields. We examined phenol oxidation of some isoquinoline alkaloids by a mixture of cuprous chloride and oxygen in pyridine as an enzymatic model, which has already been used for intermolecular coupling of some simple phenols such as 2,6-dimethylphenol,[7] and here wish to report the total synthesis of corytuberine (2), isoboldine (3), pallidine (4), (±)-orientalinone (6), and (±)-kreysiginone (9).

A solution of (+)-reticuline (1)[8] perchlorate (126 mg, 0.3 mmol) in pyridine (6 ml) was added dropwise over 10 min at 20° with efficient stirring under an oxygen atmosphere to a dark green mixture, which was prepared by the absorption of oxygen into a mixture of cuprous chloride (60 mg, 0.3 mmol) in pyridine (6 ml). After 30 min, crystalline ammonium chloride was added. Then the mixture was partitioned between chloroform and dilute ammonia. The chloroform extract was purified by a preparative t.l.c. on silica gel to afford (+)-corytuberine (2)[9-11] (27.4 mg, 28 %), (+)-isoboldine (3)[12] (7.8 mg, 8 %) and pallidine (4)[11] (7.7 mg, 6 %).

A similar reaction of (±)-orientaline (5) perchlorate[13] gave (±)-orientalinone (6 or 7)[13,14] (19.4 %) and (±)-iso-orientalinone (7 or 6) (6.5 %), while a racemic phenethylisoquinoline (8) hydrochloride[6f,g] provided (±)-kreysiginone (9)[6f,g] (11.4 %) and the diastereoisomer

Scheme 1



of (10)[6f,g] (26.6 %) under the similar conditions as above.

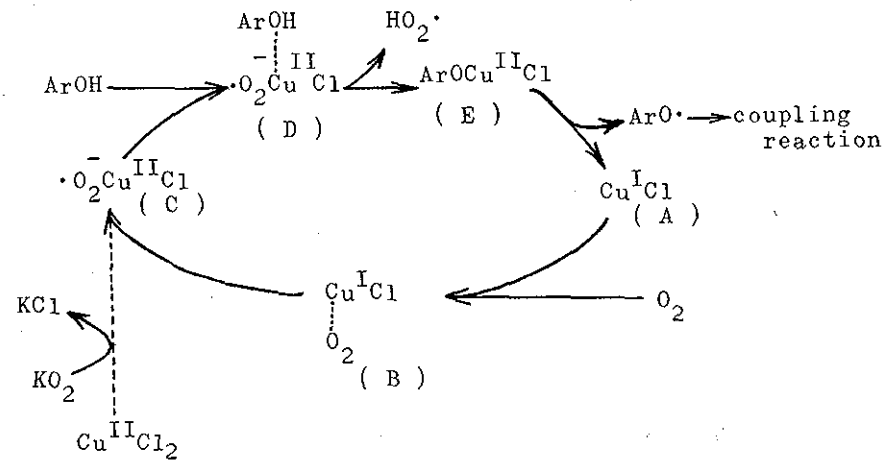
The above reactions have the following characteristic features.

The ortho-ortho oxidative coupling of reticuline to corytuberine with chemical reagent is the first example. An equimolar amount of cuprous chloride for the substrate was required for the consumption of the substrate. The use of the salts as the substrates for the reaction appears to be favorable. The oxidation using free base yielded a more tarry material. The work-up of this reaction is easy comparing with the use of the other oxidizing agents.

The use of the other solvent such as dimethylformamide in palce of pyridine for the above reaction gave a poor result and longer reaction time. Cuprous bromide gave a similar result as cuprous chloride, but the use of divalent copper salts such as cupric chloride instead of cuprous chloride gave no oxidized product.

Two mechanisms could be considered for the above oxidation. The first one resembles to the tysosinase[1,15] in which the copper would

Scheme 2



be in the cuprous state throughout the reaction and phenols are oxidized directly with activated molecular oxygen to aryloxy radicals as in the following equation.

$$ArOH + O_2 \longrightarrow ArO\cdot + HO_2\cdot$$

The second one is relevant to that for the laccase,[1,16] in which one electron of one phenol group is transfered to molecular oxygen *via* copper, the valence of which changed during the reaction as shown in the Scheme 2.

Tsuji and his co-workers found an oxidative cleavage of catechol or phenol to monomethyl muconate under the similar reaction conditions as above except the presence of methanol and regarded the oxidation as the model reaction of pyrocatechase.[17] Moro-oka and Foote demonstrated that superoxide acts in the similar way of pyrocatechase and metapyrocatechase.[18] In order to clarify the mechanism of the above oxidation, the following reactions were studied. When a mixture of cupric chloride and an excess of potassium superoxide in pyridine was stirred for several hours at room temperature under nitrogen atmosphere, the color of the solution changed to dark green. With this mixture, (±)-reticuline (racemate of 1) perchlorate was converted into (±)-corytuberine (racemate of 2) (32.5 %), (±)-isoboldine (racemate of 3) (8.5 %) and (±)-pallidine (racemate of 4) (6.5 %), whereas (±)-orientaline (5) perchlorate was transformed to a mixture of (±)-orientalinone (6) and isoorientalinone (7) (25 % yield), the ratio of two components of which was nearly consistent with the case of the mixture of cuprous chloride and oxygen in pyridine. Neither potassium superoxide in pyridine nor potassium superoxide and cuprous chloride in pyridine under nitrogen atmosphere oxidized the above

substrates, but the starting material was recovered. It is thus presumed that the stage such as C in Scheme 2 would operate on the above oxidation, although cupric chloride could be reduced with potassium superoxide to cuprous salt as shown in the following equation.

$$2CuCl_2 + 2KO_2 \longrightarrow Cu_2Cl_2 + 2O_2 + 2KCl$$

Furthermore, on the oxidation in pyridine using a divalent copper complex, [pyridine $CuCl(OCH_3)]_2$, prepared according to the reported procedure,[7b] (±)-reticuline (racemate of 1) and (±)-orientaline (5) perchlorates afforded the same reaction products as above. Therefore, the above oxidizing system, cuprous chloride-oxygen-pyridine, would be regarded as a laccase enzymatic model involving redox copper.

REFERENCES AND NOTES

1 W. I. Taylor and A. R. Battersby, "Oxidative Coupling of Phenols" Marcel Dekker, New York, 1967; T. Kametani and K. Fukumoto, "Phenolic Oxidaiton", Gihodo, Tokyo, 1970.

2 T. Kametani, "The Chemistry of Isoquinoline Alkaloids", Hirokawa Publishing Co. Inc., Tokyo and Elsevier Publishing Co., Amsterdam, 1968; T. Kametani, "The Chemistry of the Isoquinoline Alkaloids", Vol. 2, The Sendai Institute of Heterocyclic Chemistry, Sendai, Japan, 1974.

3 M. Shamma, "The Isoquinoline Alkaloids", Academic Press, New York and London, 1972.

4 A. Brossi, A. Ramel, J. O'Brien, and S. Teitel, Chem. Pharm. Bull., 1973, 21, 1839.

5 T. Kametani, K. Fukumoto, and M. Ihara, Bioorg. Chem., in the press.

6 (a) D. H. R. Barton, D. S. Bhakuni, R. James, and G. W. Kirby, J. Chem. Soc. (C), 1967, 128; (b) W. W.-C. Chan and P. Maitland, J. Chem. Soc. (C), 1966, 753; (c) A. H. Jackson and J. A. Martin, J. Chem. Soc. (C), 1966, 2061; (d) T. Kametani, K. Fukumoto, A. Kozuka, H. Yagi, and M. Koizumi, J. Chem. Soc. (C), 1969, 2034; (e) T. Kametani, A. Kozuka, and K. Fukumoto, J. Chem. Soc. (C), 1971, 1021; (f) T. Kametani, F. Satoh, H. Yagi, and K. Fukumoto, J. Chem. Soc. (C), 1968, 1003; (g) A. R. Battersby, R. B. Bradbury, R. B. Herbert, M. H. G. Munro and R. Ramage, J. C. S. Perkin I, 1974, 1394; (h) M. A. Schwartz, Synth. Commun., 1973, 3, 33; (i) M. A. Schwartz and I. S. Mami, J. Amer. Chem. Soc., 1975, 97, 1239.

7 (a) M. E. Hay, H. S. Blanchard, G. F. Endres, and J. W. Eustance, J. Amer. Chem. Soc., 1959, 81, 6335, (b) H. Finkbeiner, A. S. Hay, H. S. Blanchard, and G. F. Endres, J. Org. Chem., 1966, 31, 549.

8 A. R. Battersby, M. Hirst, D. J. McCaldin, R. Southgate, and J. Staunton, J. Chem. Soc. (C), 1968, 2163.

9 All products were identified on the basis of spectral and t.l.c. comparisons with authentic samples.

10 A. H. Jackson and J. A. Martin, J. Chem. Soc. (C), 1966, 2222.

11 (+)-Corytuberine was recently isolated from Corydalis pallida var. tenuis; T. Kametani, M. Takemura, and M. Ihara, Phytochemistry, in the press.

12 T. Kametani, M. Ihara, and T. Honda, J. Chem. Soc. (C), 1970, 1060.

13 A. R. Battersby, T. H. Brown, and J. H. Clements, J. Chem. Soc. (C), 1965, 4550.

14 T. Kametani, K. Fukumoto, S. Shibuya, H. Nemoto, T. Sugahara,

T. Takahashi, Y. Aizawa, and M. Toriyama, J. C. S. Perkin I, 1972, 1435.

15 D. Kertesz and R. Zito, "Oxygenases", ed. O. Hayaishi, Academic Press, New York, 1962, p. 317.

16 P. D. McDonald and G. A. Hamilton, "Oxidation in Organic Chemistry", Part B, ed. W. S. Trahanovsky, Academic Press, New York, 1973, pp. 126 - 133.

17 J. Tsuji and H. Takayanagi, J. Amer. Chem. Soc., 1974, 96, 7349; Tetrahedron Letters, 1976, 1365; T. Kajimoto, H. Takahashi, and J. Tsuji, J. Org. Chem., 1976, 41, 1389.

18 Y. Moro-oka and C. S. Foote, J. Amer. Chem. Soc., 1976, 98, 1510.

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