# Anodic Oxidation of the Bridged Ether Derivative of (±)-Reticuline

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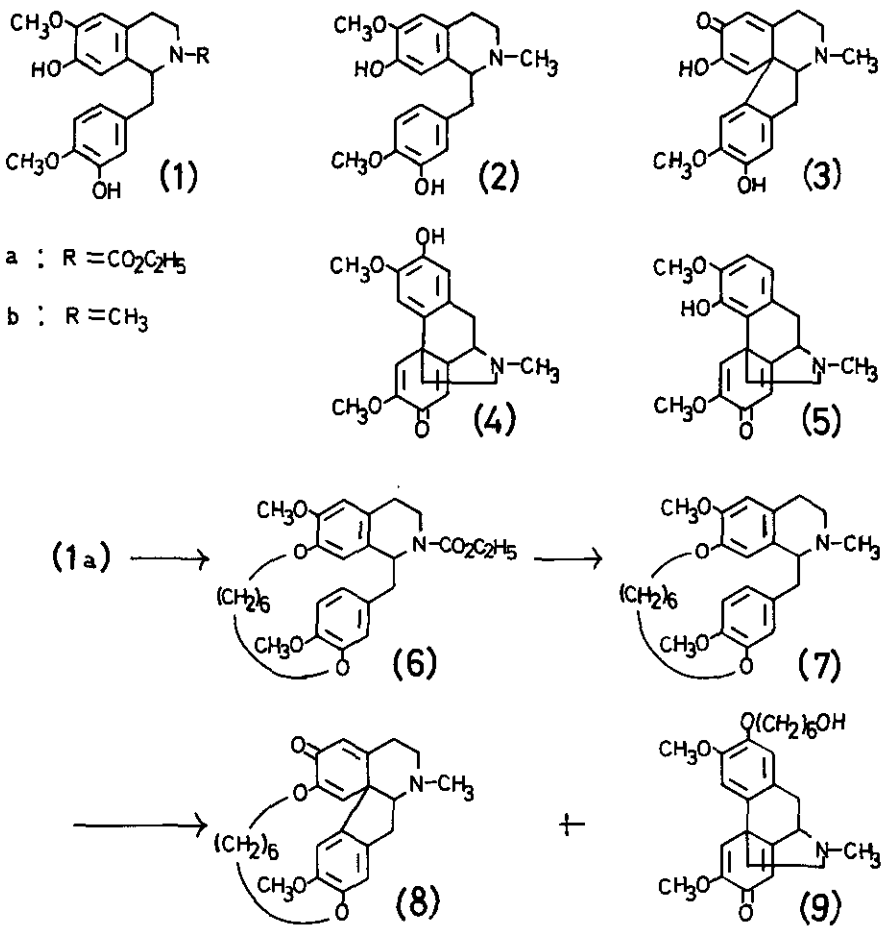
Anodic oxidation of the bridged ether derivative (7) of (±)-reticuline (1b), synthesized from the N-carbethoxy-1-benzyl-tetrahydroisoquinoline (1a), afforded the proerythrinadienone type coupling product (8) and the morphinadienone type coupling product (9).

1-Benzyl-tetrahydroisoquinolines are not only the most simple natural isoquinoline alkaloids but also the precursor of various types of these alkaloids, biogenetically. Amoung the isoquinoline alkaloids, for instance, the aporphine alkaloids, isoboldine (2), the proerythrinadienone alkaloids (3), the morphinadienone alkaloids, pallidine (4), and the morphine alkaloids, salutaridine (5) may be synthesized from reticuline (1b) by the oxidative phenol coupling reaction in living cell. A number of biomimetic synthesis of these types alkaloids have been reported by the oxidative phenol and non-phenol coupling reactions by the oxidation with metal salts and complexes, photochemical reactions, and other chemical reactions [1].

In the preceding communication [2], we reported that the biomimetic oxidation of the bridged ether derivatives of norbelladine gave the site selective coupling products by the oxidation with $VOF_3$. This paper deals with the continuative investigation of the oxidative coupling reaction of the bridged ether derivative (7) of a 1-benzyl-tetrahydroisoquinoline, (±)-reticuline (1b), mimicking enzymatic control of reaction sites, as the preceding report.

The bridged ether derivative (6), mp. 127-130°, was prepared by the reaction of the N-crbethoxy-tetrahydroisoquinoline (1a) with hexamethylene dibromide in the presence of $K_2CO_3$ in DMF at 80-85° for 12 Hr in 84.5% yield. $LiAlH_4$ reduction of




(6) afforded the bridged ether derivative (7) of (±)-reticuline (1b), mp. 101-103°, in nearly quantitative yield.

Although anodic oxidation of the bridged ether derivative (6) did not gave any coupling products, the N-methyl derivative (7) yield two coupling products in fairly good yield. Anodic oxidation was carried out in $CH_3CN$ in the presence of $HBF_4$ as the supporting electrolyte [3] to give a proerythrinadienone type coupling product (8); mp. 171-172° (sublimed at 150°), nmr ($CDCl_3$) ppm: 5.39, 6.26, 7.01 (each s, 3H), and 6.41 (d, J=1.5 Hz, 1H) (2 olefinic and 2 aromatic protons), as a major product, and a morphinadienone type coupling product (9), oil, nmr ($CDCl_3$) ppm: 6.31, 6.33, 6.6 (each s, 3H), and 6.8 (s, 1H) (2 olefinic and 2 aromatic protons), as a minor product [4].

Previous reports on the anodic oxidation of 1-benzyl-tetrahydroisoquinolines have shown that the oxidative coupling products are the morphinadienone type compounds [3]. In comparison, the anodic oxidation of the bridged ether derivatives (7) of (±)-reticuline (1b), as described, produced a proerythrinadienone type compound (8) as a major product along with a morphinadienone type compounds (9) by the steric restriction between two aromatic rings as anticipated. These result demonstrates that biochemical selectivity, as shown in the case of the isoquinoline alkaloids biosynthesis, could be the result of the geometry of enzyme-substrate complexes [5].

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2) M. Murase, T. Takeya and S. Tobinaga, Heterocycles, preceding communication.

3) S. Tobinaga, Bioorg. Chem., 4, 110 (1975), and refs. cited therein.

4) The structure of (8) and (9) were characterized by comparison of the ir and nmr spectra with those reported in ref. (T. Kametani, R. Charubala, M. Ihara, M. Koizumi, T. Takahashi, and K. Fukumoto, J. Chem. Soc. (C), 3315 (1971)).

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Received, 13th August, 1980