

BIOMIMETIC SYNTHESIS OF PROTOBERBERINE ALKALOIDS AND APORPHINE
ALKALOIDS THROUGH N-OXIDE INTERMEDIATES

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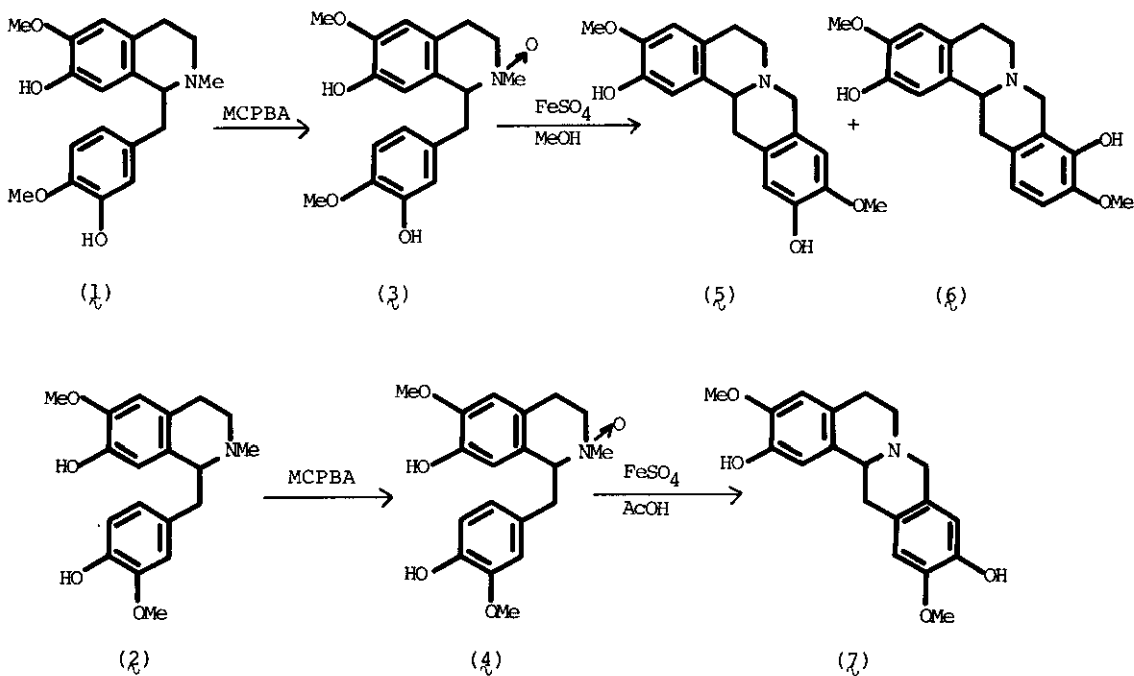
Abstract — Reaction of (\pm)-reticuline N-oxide (3) with cuprous chloride in methanol, followed by treatment with sodium hydro-sulphite, gave (\pm)-corvtuberine (8) in excellent yield, while phenol oxidative coupling of (\pm)-orientaline N-oxide (4) was less effective under the same conditions. Treatment of 3 with ferrous sulphate in methanol afforded (\pm)-coreximine (5) and (\pm)-scoulerine (6), but formation of the protoberberine (7) from 4 with this reagent required acidic conditions.

In recent years there has been an increasing knowledge that tertiary amine N-oxides are involved in biological systems.¹ The natural occurrence of N-oxides in plant and the role of N-oxidation in animal metabolism have posed interesting problems as to the biochemistry and the function of these compounds. In the field of indole alkaloids, the inherent reactivity of N-oxide was demonstrated in the biosynthesis and utilized in the synthesis of a clinically important dimer.²⁻⁴ On the other hand, only few works on N-oxides in the isoquinoline alkaloid field have been reported. An N-oxide intermediate was postulated in the biosynthesis of protoberberine alkaloids⁵ and Norman examined the conversion of laudanosine N-oxide into xylopinine by reaction with a mixture of sulfur dioxide and formic acid.⁶ Transformation of protoberberine N-oxides into protopine type alkaloids was carried out using potassium chromate.⁷

The 1-benzylisoquinoline alkaloids, reticuline (1) and orientaline (2) are known to be key precursors in the biosynthesis of many isoquinoline alkaloids.^{8,9} In order to evaluate the role of N-oxides as intermediates in synthesis and biosynthesis, in

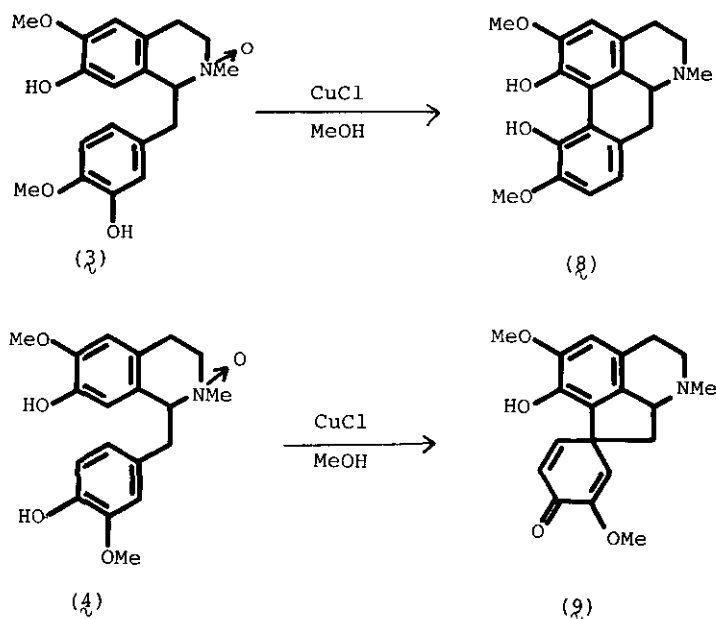
relation to our previous work involving oxidative enzymes from rat liver^{10,11} or enzymic models¹², we studied the reactivity of the N-oxides of the two alkaloids with various metallic ions and wish to report here our interesting findings. N-Oxides (3 and 4) of (±)-reticuline (1) and (±)-orientaline (2) were easily prepared by treatment of the bases with m-chloroperbenzoic acid in methylene chloride, followed by purification using preparative high pressure liquid chromatography. Several chemical systems have been considered as possible models for biological N-dealkylation through N-oxides. Ferrous ion is known to involve successive redox reactions.¹³ When (±)-reticuline N-oxide (3) was treated with excess ferrous sulphate in methanol at 10 - 15°C for 40 hr, (±)-coreximine (5) and (±)-scoulerine (6) were obtained in 42 % and 23 % yield, respectively, together with a mixture of (±)-reticuline and (±)-N-norreticuline. On the other hand, none of the protoberberine derivative was formed from reaction of (±)-orientaline N-oxide (4) with this reagent in methanol. Cyclisation to protoberberine (7) was observed in the reaction carrying out under acidic conditions, compound (7) being obtained in 55 % yield on heating 4 with the catalyst in acetic acid at 70 - 80°C for 6 hr. Thus these reaction of 1-benzylisoquinoline N-oxides with ferrous ion provide an alternative synthesis of protoberberine alkaloids according to the biomimetic route.

Scheme 1



Since cuprous ion catalyses dealkylation in acidic solution only,¹³ it was expected that phenolic N-oxides would undergo phenolic oxidation without dealkylation on treatment with cuprous ion under neutral conditions, and this was found to be the case. Thus, reaction of (\pm)-reticuline N-oxide (3) with cuprous chloride in methanol for 20 hr at 10 - 15°C in the absence of oxygen, followed by treatment with sodium hydrosulphite, afforded (\pm)-corytuberine (8) in 61 % yield along with a small amount of reticuline (1). (\pm)-Orientaline N-oxide (4) furnished a diastereoisomeric mixture of (\pm)-orientalinone (9) in 5.3 % yield by the same reaction as above, without the sodium hydrosulphite treatment. It is assumed that cuprous chloride is oxidised by these N-oxides to give an active cupric species, which is very effective for orth-ortho phenol oxidative coupling as our previous findings with reactions using cuprous chloride-pyridine-molecular oxygen or cupric chloride-pyridine-potassium superoxide have shown.¹² Thus formation of a favourable copper complex leads to regioselective production of (\pm)-corytuberine (8). The above reaction could be regarded as an intramolecular redox cyclisation. It is considered that N-oxide intermediates may play a bigger role in the biogenesis of alkaloids, and in the metabolism of compounds containing nitrogen, than previously expected.

Scheme 2



REFERENCES

1. J. D. Phillipson and S. S. Handa, Lloydia, 1978, 41, 385 and references cited therein.
2. N. Langlois, F. Guéritte, Y. Langlois, and P. Potier, J. Amer. Chem. Soc., 1976, 98, 7017.
3. J. P. Kutney, T. Hibino, E. Jahngen, T. Okumati, A. H. Ratcliffe, A. M. Treasurywala, and S. Wunderly, Helv. Chim. Acta, 1976, 59, 2858.
4. Atta-ur-Rahman, A. Basha, and M. Ghazala, Tetrahedron Letters, 1976, 2351.
5. A. R. Battersby, R. J. Francis, M. Hirst, and J. Staunton, Proc. Chem. Soc., 1963, 268; D. H. R. Barton, R. H. Hesse, and G. W. Kirby, J. Chem. Soc., 1965, 6379.
6. P. A. Bather, J. R. L. Smith, and R. O. C. Norman, J. Chem. Soc. C, 1971, 3060.
7. K. W. Bentley and A. W. Murray, J. Chem. Soc., 1963, 2497.
8. M. Shamma, 'The Isoquinoline Alkaloids, Chemistry and Pharmacology' Academic Press, New York, 1972, M. Shamma and J. Moniot 'The Isoquinoline Alkaloids, Chemistry and Pharmacology' Vol. 2, Academic Press, New York, 1978.
9. T. Kametani, 'The Chemistry of the Isoquinoline Alkaloids' Hirokawa Publishing Co., Tokyo and Elsevier, Amsterdam, 1968; T. Kametani, 'The Chemistry of the Isoquinoline Alkaloids' Vol. 2, The Sendai Institute of Heterocyclic Chemistry, Sendai, 1974.
10. T. Kametani, M. Takemura, M. Ihara, K. Takahashi, and K. Fukumoto, J. Amer. Chem. Soc., 1976, 98, 1956.
11. T. Kametani, Y. Ohta, M. Takemura, M. Ihara, and K. Fukumoto, Bioorg. Chem., 1977, 6, 249.
12. T. Kametani, M. Ihara, M. Takemura, Y. Satoh, H. Terasawa, Y. Ohta, K. Fukumoto and K. Takahashi, J. Amer. Chem. Soc., 1977, 99, 3805.
13. J. P. Ferris, R. D. Gerwe, and G. R. Gapski, J. Amer. Chem. Soc., 1967, 89, 5270; J. Org. Chem., 1968, 33, 3493.

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