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

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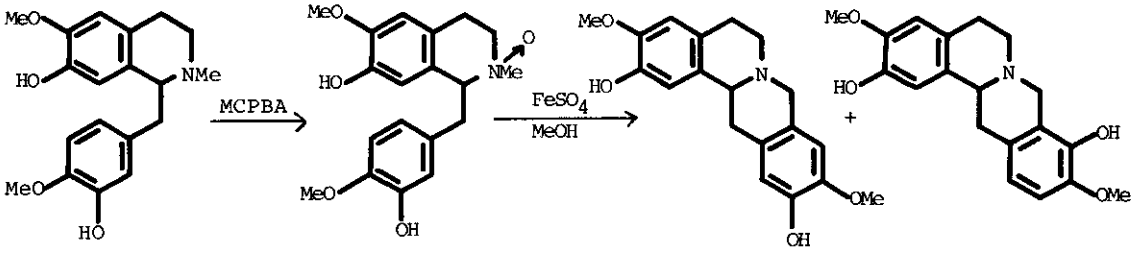
Abstract —— Reaction of (±)-reticuline N-oxide (3) with cuprous chloride in methanol, followed by treatment with sodium hydrosulphite, gave (±)-corytuberine (8) in excellent yield, while phenol oxidative coupling of (±)-orientaline N-oxide (4) was less effective under the same conditions. Treatment of 3 with ferrous sulphate in methanol afforded (±)-coreximine (5) and (±)-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 alkaloids[5] 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]

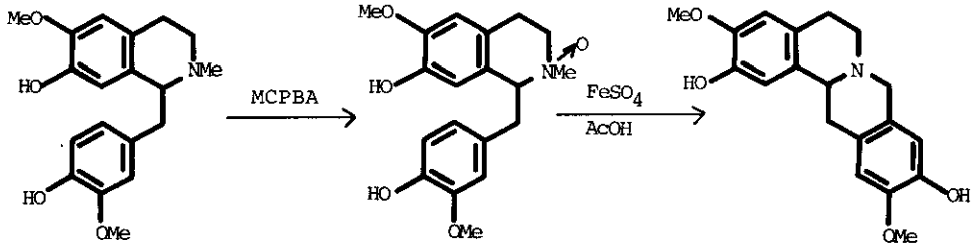
The 1-benzylisoquinoline alkaloids, reticuline (1) and orientaline (2) are known to be key precursors in the biosynthesis of many isoquinoline alkaloids.[8,9] In order to evaluate the role of N-oxides as intermediates in synthesis and biosynthesis, in

relation to our previous work involving oxidative enzymes from rat liver[10,11] or enzymic models[12], 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 biomimitic route.

Scheme 1



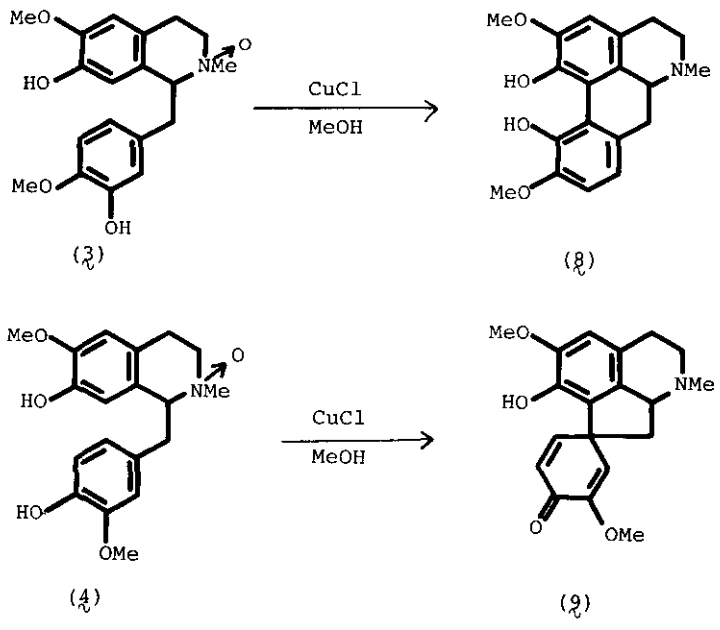
(1) (3) (5) (6)



(2) (4) (7)

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 (±)-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 (±)-corytuberine (8) in 61 % yield along with a small amount of reticuline (1). (±)-Orientaline N-oxide (4) furnished a diastereoisomeric mixture of (±)-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 (±)-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 metalolism of compounds containing nitrogen, than previously expected.

Scheme 2



(3) (8) (4) (9)

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