Alkaloid Formation through *N*-Oxide Intermediates; Regioselective Synthesis of (±)-Corytuberine by Redox Reaction

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Reaction of (±)-reticuline *N*-oxide (1) with cuprous chloride in methanol followed by treatment with sodium hydrosulphite gave the aporphine alkaloid, (±)-corytuberine (8) in good yield. Protoberberine alkaloids, (±)-coreximine (4) and (±)-scoulerine (5), were obtained by reaction of the *N*-oxide (1) with ferrous sulphate in methanol. On the other hand, formation of the phenol oxidative coupling product, (±)-orientalinone (9), from (±)-orientaline *N*-oxide (2) with cuprous chloride was less effective and formation of the protoberberine (7) from the *N*-oxide (2) with ferrous sulphate required acidic conditions.

RECENT work has revealed that tertiary amine oxides mediate both in the metabolic dealkylation of tertiary amines [1] and in the formation of heterocyclic rings in the biogenesis of certain alkaloids.[2-4] Particularly in the field of indole alkaloids, the inherent reactivity of an *N*-oxide was demonstrated both in the biosynthesis [5-7] and utilized in the synthesis of the clinically important indole dimer.[8-10] Furthermore, a number of alkaloids containing the *N*-oxide moiety have recently been isolated from natural sources, as a result of improvements in chromatographic techniques. For example, the *N*-oxides of morphine, codeine, and thebaine have been found recently.[11] In the field of isoquinoline alkaloids, an *N*-oxide intermediate was postulated in the biosynthesis of protoberberine alkaloids.[12-14] Norman and his co-workers demonstrated the conversion of laudanosine *N*-oxide into xylopinine by reaction with a mixture of sulphur dioxide and formic acid.[15] Further, transformation of protoberberine *N*-oxides into protopine-type alkaloids using potassium chromate was carried out by Bentley and Murray.[16]

The 1-benzylisoquinoline alkaloids (±)-reticuline [17,18] and (±)-orientaline [19] are known to be key precursors in the biosynthesis of many isoquinoline alkaloids,[20,21] and 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 [14,22,23] or enzymic models,[24] we now report our results which interestingly implicate *N*-oxide intermediates in certain phenol oxidative couplings as well as in dealkylation and cyclisation.

(±)-Reticuline and (±)-orientaline were treated with *m*-chloroperbenzoic acid in methylene chloride at room temperature. Separation of the resulting *N*-oxides (1) and (2), from the benzoic acid also formed was achieved by preparative high-pressure liquid chromatography using a reverse-phase packing material (Hitachi gel 3011). The *N*-oxides were thus obtained in quantitative yield.

Several chemical systems have been considered as possible models for biological *N*-dealkylation through *N*-oxides. One of these is reaction of the oxide with iron ion, which is known to involve successive redox reactions in which ferrous ion is the initiator.[25-28] Thus (±)-reticuline *N*-oxide (1) was treated with an excess of hydrated ferrous sulphate in methanol at 10—15 °C for 40 h under a nitrogen atmosphere to give (±)-coreximine (4) (42%) and (±)-scoulerine (5) (23%) together with a mixture of (±)-reticuline and (±)-*N*-nor-reticuline. When the reaction was carried out in a mixture of methanol and acetic acid [16 : 3 (v/v)], (±)-coreximine and (±)-scoulerine were obtained in similar yields (37 and 18% respectively). The reaction proceeded slowly without the catalyst under these acidic conditions, (4) and (5) being obtained in 12 and 6% yields respectively, after 40 h.

On the other hand, none of the protoberberine derivative (7) was obtained from the reaction of (±)-orientaline *N*-oxide (2) with ferrous sulphate in methanol, (±)-orientaline and (±)-*N*-nororientaline being the only products isolated. Cyclisation to protoberberine (7) was however observed in the reaction carried out under acidic conditions. Thus compound (7) was obtained in 55% yield by heating (2) with the catalyst in acetic acid at 70—80 °C for 6 h.

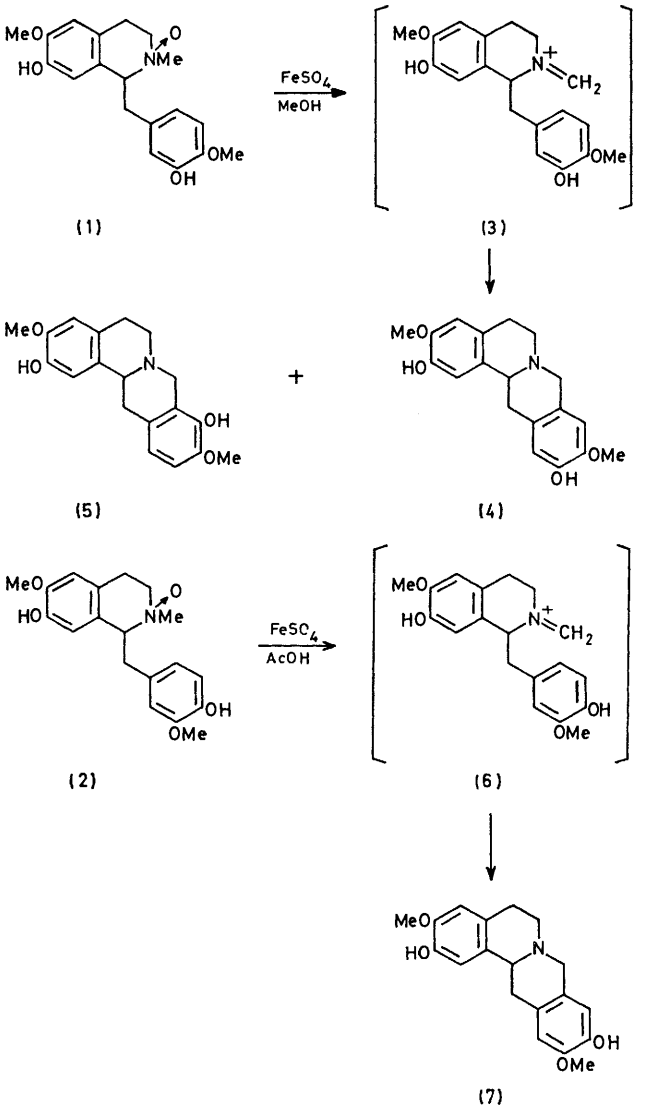
The above results indicate that the imine intermediates (3) and (6) are generated from the oxides (1) and (2) on treatment with ferrous sulphate in neutral protic solvents, or, in acidic solvents without added catalyst.† Cyclisation of this imine intermediate occurs at positions *ortho* and *para* to the phenolic hydroxy-group under neutral conditions, a result of which is in accord with our previous findings on phenol cyclisation.[29] This method provides an alternative synthesis of protoberberine alkaloids.

On the other hand, Ferris and his co-workers have shown that cuprous ion catalyses dealkylation in acetic acid solution only.[26] It was therefore 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 when reticuline *N*-oxide (1) was stirred for 20 h with cuprous chloride in methanol at 10—15 °C, in the absence of oxygen, (±)-corytuberine (8) was isolated in 25% yield by evaporation of the solvent, basification with aqueous sodium hydrogen carbonate, and the usual work-up procedure. The yield of (±)-corytuberine (8) increased to 61%, when the reaction product was treated with sodium hydrosulphite before work-up. No

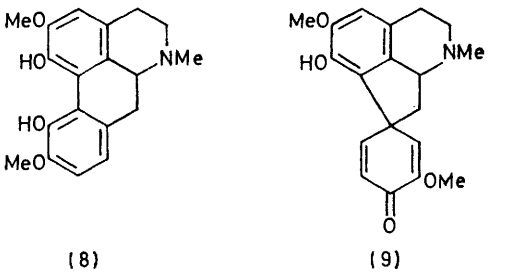
† No decomposition of compounds (1) and (2) in methanol at room temperature was observed.

formation of the other intramolecular coupling products was observed. On the other hand, reaction of (±)-orientaline *N*-oxide (2) with cuprous chloride in methanol for 20 h under the same conditions gave a diastereoisomeric mixture of (±)-orientalinone (9) in only 5.3% yield, after the same work-up without the sodium hydrosulphite treatment. The main product was (±)-orientaline in the above reaction.

Previously we reported that the cuprous chloride–pyridine–molecular oxygen system [30] is the one of choice for phenol oxidative coupling.[24] Reticuline has been converted into corytuberine in 28% yield, along with small amounts of two other phenol oxidation products, by this system. In the reaction, certain divalent copper complexes were thought to be the oxidizing species.[24] Recently Rogić and Demmin studied the mechanism of the cleavage of carbon–carbon bonds by this system and reached a similar conclusion, namely that active divalent copper species act as electron acceptors in the reaction.[31] Reaction of reticuline with cuprous chloride in methanol in the absence of oxygen, followed by treatment with sodium hydrosulphite, gave no detectable amount of corytuberine. It is thus assumed that cuprous chloride is oxidised by the *N*-oxides to give an active cupric species, which is very effective for *ortho–ortho* phenol oxidative coupling in methanol. Thus formation of a favourable copper complex leads to regioselective production of (±)-corytuberine (8). The above reaction could thus be regarded as an intramolecular redox cyclisation.



SCHEME 1



SCHEME 2

In conclusion, from consideration of the ease of oxidation of nitrogen to its oxide, *N*-oxide intermediates may play a bigger role in the biogenesis of alkaloids, and in the metabolism of compounds containing nitrogen, than previously expected.

EXPERIMENTAL

All melting points are uncorrected. U.v. spectra were recorded on a Hitachi 124 spectrometer, i.r. spectra on a Hitachi 215 spectrophotometer, n.m.r. spectra on a JNM-PMX-60 spectrometer (tetramethylsilane as internal reference), and mass spectra on a Hitachi M-52 spectrometer. High-pressure liquid chromatography was carried out using a Hitachi 635 instrument equipped with a column packed with Hitachi gel 3011 and monitored by u.v. absorption and refractive index measurements.

(±)-*Reticuline* N-*Oxide* (1).—A solution of (±)-reticuline [14] (443 mg, 1.35 mmol) and 70% *m*-chloroperbenzoic acid (342 mg, 1.39 mmol) in dry methylene chloride (10 ml) was stirred for 5 h at 10—15 °C under nitrogen. After evaporation of the solvent, the residue was purified by high-pressure liquid chromatography using methanol as solvent, concentration of the first fraction, followed by trituration with ether, gave the N-*oxide* (1) * (423 mg, 91%) as a colourless solid, m.p. 151—155 °C (Found: C, 62.85; H, 6.7; N, 3.55. $C_{19}H_{23}NO_5 \cdot H_2O$ requires C, 62.8; H, 6.95; N, 3.85%); δ [$CDCl_3$–CD_3OD (2 : 1, v/v)] 3.20 (3 H, s, NMe) and 3.88 (6 H, s, 2 × OMe); *m/e* 345 (M^+).

(±)-*Orientaline* N-*Oxide* (2).—A solution of (±)-orientaline [24] (337 mg, 1.024 mmol) and *m*-chloroperbenzoic acid (252 mg, 1.024 mmol) in dry methylene chloride (10 ml) was stirred overnight at 10—15 °C under nitrogen. The same work up as above gave the *N*-oxide (2) * (207 mg, 87%) as a *colourless solid*, m.p. 145—147 °C (Found: C, 59.7; H, 6.8; N, 3.25. $C_{19}H_{23}NO_5 \cdot 2H_2O$ requires C, 59.5; H, 7.15; N, 3.65%); δ [$CDCl_3$–CD_3OD (2 : 1, v/v)] 3.22 (3 H, s, NMe)

* The *N*-oxides (1) and (2) seemed to be a stereoisometic mixture but the isomers were used in the next reaction.

and 3.82 and 3.90 (each 3 H, each s, 2 × OMe); *m/e* 345 (M^+).

Reaction of (±)-*Reticuline* N-*Oxide* (1) *with Ferrous Sulphate in Methanol.*—A mixture of the *N*-oxide (1) (69 mg, 0.2 mmol) and $FeSO_4 \cdot 7H_2O$ (112 mg, 0.4 mmol) in methanol (10 ml) was stirred for 40 h at 10—15 °C under a nitrogen atmosphere. After evaporation of the solvent, the residue was partitioned between chloroform and a saturated aqueous solution of sodium hydrogen carbonate. The aqueous layer was further extracted with chloroform. The combined chloroform layers were washed with brine, dried (Na_2SO_4), and evaporated to give a syrup which was purified by preparative t.l.c. on silica gel, using chloroform–methanol (9 : 1, v/v) as eluant. The less-polar fraction gave (±)-scoulerine (5) (15.2 mg, 23%), which on recrystallisation from methanol afforded crystals, m.p. 183—185 °C (lit.,[32] m.p. 183—185 °C), i.r. ($CHCl_3$) and n.m.r. ($CDCl_3$) identical to those of an authentic sample.[32]

A more-polar fraction gave (±)-coreximine (4) (27.7 mg, 42%), which on recrystallisation from methanol afforded prisms, m.p. 238—239 °C (lit.,[33] m.p. 238—239 °C), i.r. (KBr) and n.m.r. ($CDCl_3$) superimposable on those of an authentic sample.[33] The most-polar fraction gave a mixture (15 mg) of reticuline and *N*-nor-reticuline.

Reaction of (±)-*Reticuline* N-*Oxide* (1) *with Ferrous Sulphate in a Mixture of Methanol and Acetic Acid.*—A mixture of (1) (69 mg, 0.2 mmol) and $FeSO_4 \cdot 7H_2O$ (112 mg, 0.4 mmol) in a mixture of methanol (16 ml) and acetic acid (3 ml) was stirred for 40 h at 10—15 °C under a nitrogen atmosphere. After evaporation of the solvent, the residue was worked up as above to give (±)-coreximine (4) (24.4 mg, 37%) and (±)-scoulerine (5) (11.9 mg, 18%).

Reaction of (±)-*Reticuline* N-*Oxide* (1) *in a Mixture of Methanol and Acetic Acid.*—A solution of (1) (69 mg, 0.2 mmol) in a mixture of methanol (16 ml) and acetic acid (3 ml) was stirred for 40 h at 10—15 °C under a nitrogen atmosphere and the resulting mixture was worked up as above to afford (±)-coreximine (4) (8 mg, 12%) and (±)-scoulerine (5) (4 mg, 6%).

Reaction of (±)-*Reticuline* N-*Oxide* (1) *with Cuprous Chloride in Methanol.*—A solution of the *N*-oxide (1) (69 mg, 0.2 mmol) in methanol (10 ml) was degassed under reduced pressure and CuCl (20 mg, 0.2 mmol) was added in one portion. The resulting mixture was stirred for 20 h at 10—15 °C under a nitrogen atmosphere. After evaporation of the solvent, water (3 ml) was added followed by solid sodium hydrosulphite (50 mg). After being stirred for 10 min at room temperature, the mixture was basified with a saturated aqueous solution of sodium hydrogen carbonate and extracted several times with chloroform. The combined extracts were washed with brine, dried (Na_2SO_4), and evaporated to give a powder, which was recrystallised from methanol–chloroform to afford (±)-corytuberine (8) (40 mg, 61%) as colourless crystals, m.p. 236—240 °C (Found: C, 66.05; H, 6.35; N, 3.8. $C_{19}H_{21}NO_4 \cdot H_2O$ requires C, 66.05; H, 6.7; N, 4.05%); u.v. (MeOH), n.m.r. (CF_3CO_2D) and mass spectra identical to those of the natural alkaloid.

Reaction of (±)-*Orientaline* N-*Oxide* (2) *with Ferrous Sulphate in Hot Acetic Acid.*—A mixture of the *N*-oxide (2) (69 mg, 0.2 mmol) and $FeSO_4 \cdot 7H_2O$ (112 mg, 0.4 mmol) in acetic acid (20 ml) was stirred for 6 h at 70—80 °C under a nitrogen atmosphere. After evaporation of the solvent, the residue was taken up in a saturated aqueous solution of sodium hydrogen carbonate and extracted several times with chloroform. The combined chloroform extracts were washed with brine, dried (Na_2SO_4), and evaporated to give a syrup, which was purified by preparative t.l.c. on silica gel, using chloroform–methanol (9 : 1, v/v) as eluant, to give the protoberberine (7) (36 mg, 55%). Recrystallisation from chloroform afforded crystals, m.p. 207—210 °C (lit.,[35] m.p. 207—210 °C), i.r. ($CDCl_3$) and n.m.r. ($CDCl_3$) spectra consistent with those of an authentic sample.[35]

Reaction of (±)-*Orientaline* N-*Oxide* (2) *with Cuprous Chloride in Methanol.*—A solution of the *N*-oxide (2) (69 mg, 0.2 mmol) in methanol (20 ml) was degassed under reduced pressure and CuCl (100 mg, 1 mmol) was added. The mixture was stirred for 20 h at room temperature under a nitrogen atmosphere. After evaporation of the solvent, the residue was partitioned between a saturated aqueous solution of sodium hydrogen carbonate and chloroform. The aqueous layer was further extracted with chloroform. The combined chloroform extracts were washed with brine and evaporated to give a syrup (38 mg) which was purified by preparative t.l.c. on silica gel, using chloroform–methanol (9 : 1, v/v) as eluant. From the less-polar fraction an epimeric mixture (3.5 mg, 5.3%) of (±)-orientalinone (9) was obtained as a syrup, i.r. ($CHCl_3$) absorption and t.l.c. behaviour identical to those of an authentic sample.[24] The n.m.r. ($CDCl_3$) spectrum indicated it to be a mixture of (±)-orientalinone and its epimer in a ratio of approximately 3 : 1. The more polar fraction afforded (±)-orientaline (23 mg, 35%) as a syrup.

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