

SYNTHESIS OF (±)-KREYSIGINONE, A HOMOAPORPHINE AND HOMOPROTO-BERBERINES VIA N-OXIDE INTERMEDIATES

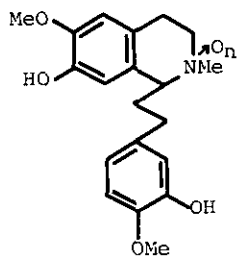
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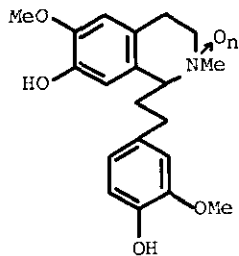
Abstract — Reaction of 1,2,3,4-tetrahydro-7-hydroxy-1-(3-hydroxy-4-methoxyphenethyl)-6-methoxy-2-methylisoquinoline N-oxide (**2**) with ferrous sulfate in methanol gave the 2,9- and 2,11-dihydroxyhomoprotoberberines (**5** and **6**). The 2,10-dihydroxy derivative (**8**) was obtained by the reaction of 1,2,3,4-tetrahydro-7-hydroxy-1-(4-hydroxy-3-methoxyphenethyl)-6-methoxy-2-methylisoquinoline N-oxide (**4**) with ferrous sulfate in hot acetic acid. Reaction of the N-oxides (**2** and **4**) with cuprous chloride in methanol afforded the phenol oxidative coupling products, the homoaporphine (**12**) and (±)-kreysiginones (**13**).

Recently we reported the novel transformation of phenolic 1-benzyl-2-methylisoquinoline N-oxides into protoberberine, aporphine and proaporphine type alkaloids.<sup>1</sup> Here we wish to describe further application of this reaction to the phenolic phenethylisoquinoline derivatives.

The two phenethylisoquinolines (**1**<sup>2</sup> and **3**<sup>3</sup>), substituted with hydroxyl groups at different positions, were oxidized with *m*-chloroperbenzoic acid in methylene chloride at room temperature. The resulting N-oxides (**2** and **4**) were separated from benzoic acid derivatives by reverse phase liquid chromatography.



(1)  $n=0$   
 (2)  $n=1$



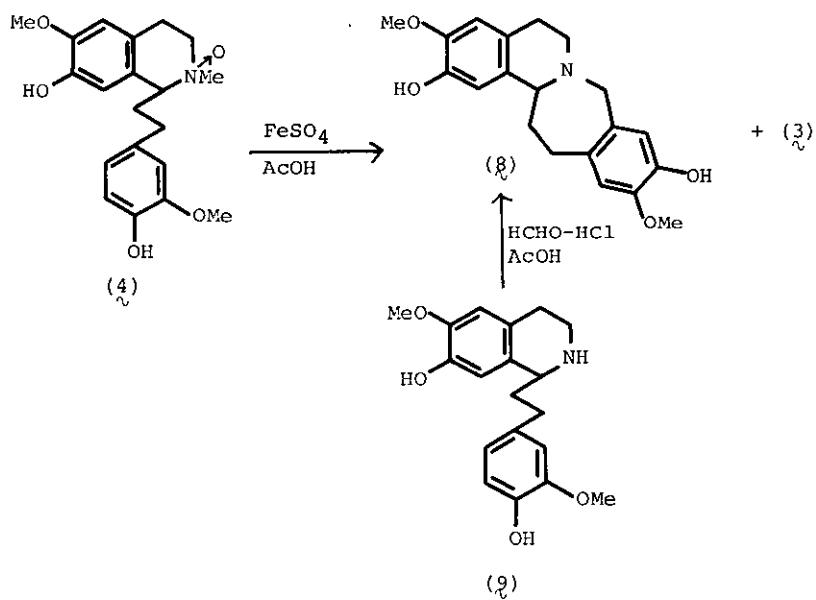
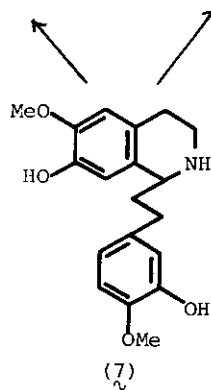
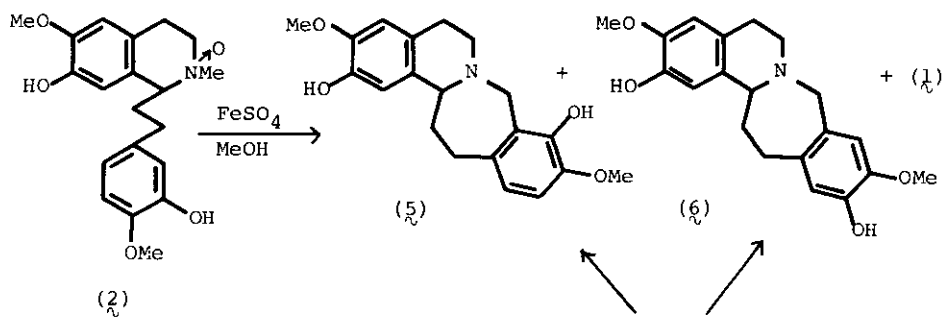
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 (4)  $n=1$

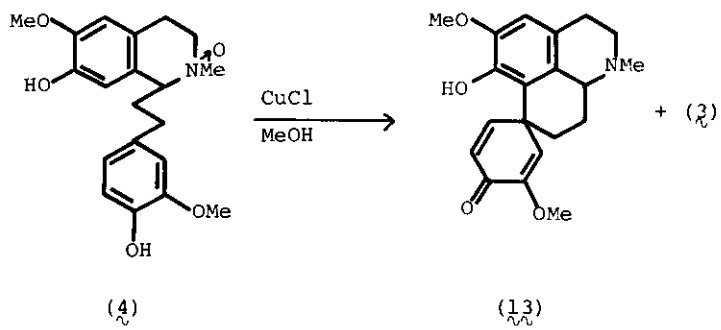
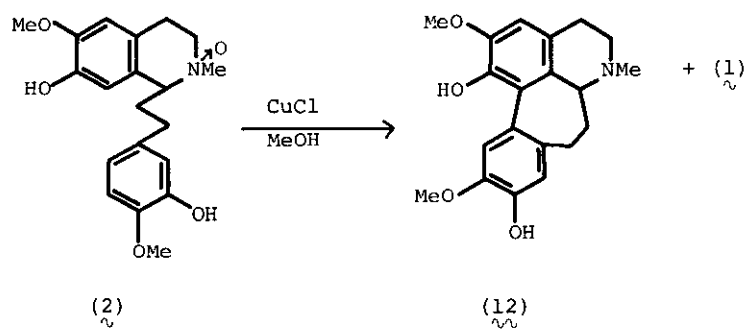
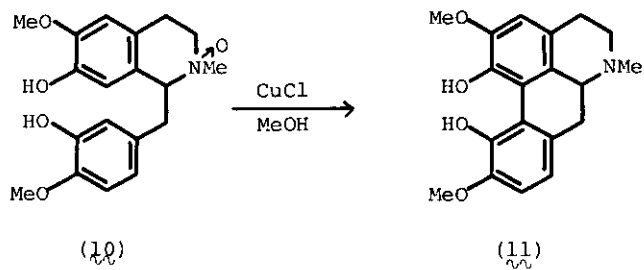
### Reaction of N-Oxide with Ferrous Sulfate

Stirring the 1-(3-hydroxy-4-methoxyphenethyl)isoquinoline N-oxide (2) with hydrated ferrous sulfate in methanol at room temperature produced the 2,9- and 2,11-dihydroxyhomoprotoberberines (5 and 6), together with the reduction product (1). The structures of the homoprotoberberines were established by comparison with authentic samples which were synthesized by phenolic cyclization<sup>4</sup> and the usual Pictet-Spengler reaction. Namely, heating the N-norphenethylisoquinoline (7) with formalin in ethanol yielded the 2,9-dihydroxyhomoprotoberberine (5), which was identified by the presence in its nmr spectrum of two signals ( $\delta$  6.62 and 6.77) with an ortho coupling constant ( $J=8$  Hz) due to the aromatic protons at the 11- and 12-positions. The 2,11-dihydroxyhomoprotoberberine (6) was obtained by treatment of 7 with formalin in the presence of hydrochloric acid.

Reaction of the 1-(4-hydroxy-3-methoxyphenethyl)isoquinoline N-oxide (4) with ferrous sulfate in methanol afforded none of the homoprotoberberines and gave only the reduction product (3). However, heating 4 with ferrous ion in acetic acid produced the desired homoprotoberberine (8) together with 3. The structure of 8 was confirmed by comparison with a sample prepared alternatively by reaction of the hydrochloride of 9 with formalin in acetic acid.

The above results are consistent with those obtained for the 1-benzylisoquinolines.<sup>1</sup> Treatment of the N-oxides with trifluoroacetic anhydride<sup>5</sup> in order to obtain the protoberberine type compounds gave poorer results than in the above reactions.





Reaction of N-Oxides with Cuprous Chloride

Previously we observed that reticuline N-oxide (10) was converted to corytuberine (11) in 61 % yield by treatment with cuprous chloride in methanol.<sup>1</sup> However the homo analog (2) on such treatment gave the ortho-para coupling product (12) in 10.2 % yield, together with 1. No ortho-ortho coupled derivative was in the product after reaction of 2 with cuprous chloride in methanol followed by treatment with sodium hydrosulfite. It is assumed that formation of a copper complex, expected to lead to the ortho-ortho coupled product, is difficult in the case of the phenethylisoquinoline.<sup>6</sup>

Reaction of the 1-(4-hydroxy-3-methoxyphenethyl)isoquinoline N-oxide (4) with cuprous chloride in methanol afforded a mixture of (±)-kreysiginone and its diastereoisomer, (13), in 10.3 % yield.

## EXPERIMENTAL

All melting points are uncorrected. Uv spectra were recorded on a Hitachi 124 spectrometer, ir spectra on a Hitachi 215 spectrometer, nmr spectra on a JNM-PMX-60 spectrometer (tetramethylsilane as internal reference), and mass spectra on Hitachi M-52 and JEOL JMS-01SG-2 spectrometers. High pressure liquid chromatography was carried out using a Hitachi 635 instrument equipped with a column (8 mm x 25 cm) packed with Hitachi gel 3011 and monitored by uv absorption and refractive index measurements.

1,2,3,4-Tetrahydro-7-hydroxy-1-(3-hydroxy-4-methoxyphenethyl)-6-methoxy-2-methylisoquinoline N-Oxide (2).

A solution of the phenethylisoquinoline (1) (417 mg, 1.22 mmol) and *m*-chloroperbenzoic acid (250 mg, 1.45 mmol, freshly purified by washing with a phosphate buffer<sup>7</sup>) in dry methylene chloride (10 ml) was stirred for 1.5 hr at room temperature under nitrogen. After evaporation of the solvent, the residue was purified by high pressure liquid chromatography using water-methanol (1 : 9 v/v) as solvent. The faster fraction yielded the N-oxide (2) (413 mg, 95 %) as a pale yellowish solid: nmr  $\delta$  [CDCl<sub>3</sub> - CD<sub>3</sub>OD (2 : 1 v/v)] 3.23 (3H, s, NMe), 3.78 (6H, s, 2 x OMe); mass *m/e* 359 (M<sup>+</sup>), 357, 342, 300; exact mass Calcd. for C<sub>20</sub>H<sub>25</sub>NO<sub>5</sub> : M<sup>+</sup> *m/e* 359.1733. Found : M<sup>+</sup> *m/e* 359.1744. The slower fraction gave *m*-chlorobenzoic acid.

1,2,3,4-Tetrahydro-7-hydroxy-1-(4-hydroxy-3-methoxyphenethyl)-6-methoxy-2-

methylisoquinoline N-Oxide (4).

A solution of the amine (3) (275 mg, 0.80 mmol) and m-chloroperbenzoic acid (165 mg, 0.96 mmol) in methylene chloride (10 ml) was stirred for 2 hr at room temperature under nitrogen. The same work-up as above afforded the N-oxide (4) (258 mg, 90 %) as a pale yellowish solid: nmr  $\delta$  [ $\text{CDCl}_3$  -  $\text{CD}_3\text{OD}$  (2 : 1 v/v)] 3.13 (3H, s, NMe), 3.9 (6H, w, 2 x OMe): mass m/e 359 ( $\text{M}^+$ ), 357, 342, 300; exact mass Calcd. for  $\text{C}_{20}\text{H}_{25}\text{NO}_5$ :  $\text{M}^+$  m/e 359.1733. Found:  $\text{M}^+$  m/e 359.1681.

5,6,8,13,14,14a-Hexahydro-2,9-dihydroxy-3,10-dimethoxydibenzo[a,g]pyrido[1,2-a]-azepine(5).

A mixture of the amine (7) (100 mg, 0.3 mmol) and 37 % formalin (1 ml) in ethanol (10 ml) was refluxed for 2 hr. The solvent was evaporated and the residue was diluted with water and extracted with chloroform. This extract was dried over  $\text{Na}_2\text{SO}_4$  and evaporated to give a powder which on recrystallization from methanol afforded the homoprotoberberine (5) (40 mg, 38.5 %) as crystals, mp 259 - 260°: nmr  $\delta$  ( $\text{CDCl}_3$ ) 3.87 (3H, s, OMe), 3.92 (3H, s, OMe), 6.6 (1H, s, ArH), 6.62 (1H, d, J = 8 Hz, ArH), 6.77 (1H, d, J = 8 Hz, ArH), 6.8 (1H, s, ArH); mass m/e 341 ( $\text{M}^+$ ). Anal. Calcd. for  $\text{C}_{20}\text{H}_{23}\text{NO}_4 \cdot 0.25 \text{H}_2\text{O}$ : C, 69.38; H, 6.85; N, 4.05. Found: C, 69.06; H, 7.00; N, 3.98.

5,6,8,13,14,14a-Hexahydro-2,11-dihydroxy-3,10-dimethoxydibenzo[a,g]pyrido[1,2-a]-azepine (6).

A mixture of the amine (7) (150 mg, 0.46 mmol), 37 % formalin (1 ml), and concentrated hydrochloric acid (1.5 ml) in ethanol (15 ml) was refluxed for 3.5 hr. After evaporation of the solvent, the residue was basified with 10 % ammonia and extracted with chloroform. This extract was dried over  $\text{Na}_2\text{SO}_4$  and evaporated to give a powder which was recrystallized from methanol to afford the homoprotoberberine (6) (40 mg, 25.8 %) as crystals, mp 223 - 225°: nmr  $\delta$  ( $\text{CDCl}_3$ ) 3.87 (3H, s, OMe), 3.92 (3H, s, OMe), 6.6 (1H, s, ArH), 6.71 (1H, s, ArH), 6.8 (2H, s, 2 x ArH); mass m/e 341 ( $\text{M}^+$ ). Anal. Calcd. for  $\text{C}_{20}\text{H}_{23}\text{NO}_4$ : C, 70.36; H, 6.79. Found: C, 70.40; H, 7.00.

5,6,8,13,14,14a-Hexahydro-2,10-dihydroxy-3,11-dimethoxydibenzo[a,g]pyrido[1,2-a]-azepine (8).

A mixture of the hydrochloride of the amine (9) (60 mg, 0.16 mmol), 37 % formalin (2 ml), and acetic acid (3 ml) was stirred and heated at 80 - 100° for 17 hr. After evaporation of the solvent, the residue was basified with 10 % ammonia and extracted with chloroform. This extract was dried over  $\text{Na}_2\text{SO}_4$  and evaporated to

give a gum which was crystallized from methanol to afford the homoprotoberberine (8) (15 mg, 25 %) as crystals, mp 240 - 242<sup>o</sup>: nmr  $\delta$  (CDCl<sub>3</sub>) 3.81 (3H, s, OMe), 3.84 (3H, s, OMe), 6.5 (1H, s, ArH), 6.6 (1H, s, ArH), 6.63 (1H, s, ArH), 6.73 (1H, s, ArH); mass m/e 341 (M<sup>+</sup>). Anal. Calcd. for C<sub>20</sub>H<sub>23</sub>NO<sub>4</sub>; C, 70.36; H, 6.79; N, 4.10. Found: C, 70.16; H, 6.40; N, 4.04.

Reaction of 1,2,3,4-Tetrahydro-7-hydroxy-1-(3-hydroxy-4-methoxyphenethyl)-6-methoxy-2-methylisoquinoline N-Oxide (2) with Ferrous Sulfate.

A mixture of the N-oxide (2) (70 mg, 0.19 mmol) and ferrous sulfate heptahydrate (200 mg) in methanol (20 ml) was stirred for 20 hr at 10 - 15<sup>o</sup> under a nitrogen atmosphere. After evaporation of the solvent, the residue was partitioned between chloroform and a saturated aqueous solution of sodium bicarbonate. The aqueous layer was further extracted with chloroform. The combined organic extracts were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated to give a powder.

Recrystallization from methanol-chloroform afforded the 2,9-dihydroxyhomoprotoberberine (5) (23.3 mg, 32 %) as crystals, mp 259 - 260<sup>o</sup>, whose spectral data and tlc behavior were identical to those of the above sample (5). The residue from the mother liquor was further purified by preparative tlc on silica gel, developing with 10 % methanol in chloroform. The upper zone yielded the 2,10-dihydroxyhomoprotoberberine (6) (15.6 mg, 23.4 %), mp 223 - 225<sup>o</sup> (from methanol), whose spectral data and tlc behavior were identical to those of the above sample (6).

The middle zone gave the 2,9-dihydroxyhomoprotoberberine (5) (5 mg, 7.5 %). The lower zone afforded the 2-methylphenethylamine (1) (14.7 mg, 22 %) as a yellowish gum.

Reaction of 1,2,3,4-Tetrahydro-7-hydroxy-1-(3-hydroxy-4-methoxyphenethyl)-6-methoxy-2-methylisoquinoline N-Oxide (2) with Cuprous Chloride.

A solution of the N-oxide (2) (51 mg, 0.14 mmol) and cuprous chloride (100 mg) in methanol (10 ml) was stirred for 24 hr at 10 - 15<sup>o</sup> under a nitrogen atmosphere. After evaporation of the solvent, water (3 ml) and solid sodium hydrosulfite (50 mg) were added. After sitting for 10 min at room temperature, the mixture was basified with a saturated aqueous solution of sodium bicarbonate and extracted with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated. The resulting gummy residue was purified by preparative tlc on silica gel, developing with 10 % methanol in chloroform, to give the 2-methylphenethylamine (1) (26.4 mg, 55 %) and the 1,10-dihydroxyhomoaporphine (12) (4.9 mg, 10.2 %), mp 241 - 242<sup>o</sup> (from methanol), whose spectral data and tlc

behavior were identical to those of an authentic sample (12)<sup>3</sup>.

Reaction of 1,2,3,4-Tetrahydro-7-hydroxy-1-(4-hydroxy-3-methoxyphenethyl)-6-methoxy-2-methylisoquinoline N-Oxide (4) with Ferrous Sulfate.

A mixture of the N-oxide (4) (110 mg, 0.309 mmol) and ferrous sulfate heptahydrate (150 mg) in acetic acid (10 ml) was stirred for 24 hr at 70° under a nitrogen atmosphere. After evaporation of the solvent, the residue was basified with 10 % ammonia and extracted with chloroform. This extract was dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated to give a brown gum, which was subjected to preparative tlc on silica gel developing with 10 % methanol in chloroform. The upper zone yielded the 2,10-dihydroxyhomoprotoberberine (8) (16 mg, 16 %) as crystals, mp 240 - 242° (from methanol), whose spectral data and tlc behavior were identical to those of the above sample (8).

The lower zone gave the 2-methyl compound (3) (58 mg, 55 %).

Reaction of 1,2,3,4-Tetrahydro-4-hydroxy-1-(4-hydroxy-3-methoxyphenethyl)-6-methoxy-2-methylisoquinoline N-Oxide (4) with Cuprous Chloride.

A mixture of the N-oxide (4) (67 mg, 0.19 mmol) and cuprous chloride (136 mg) in methanol (10 ml) was stirred for 24 hr at room temperature under a nitrogen atmosphere. After evaporation of the solvent, 10 % ammonia was added to the residue which was then extracted with chloroform. This extract was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated. The resulting brown gum was purified by preparative tlc on silica gel developing with 10 % methanol in chloroform. The upper zone yielded an epimeric mixture of the dienones (13)<sup>5</sup> (6.6 mg, 10.3 %) as a yellowish syrup, whose nmr spectrum (CDCl<sub>3</sub>) indicated it to be a mixture of (±)-kreysiginone and its epimer in a ratio of 3 : 7. The lower zone afforded the N-methylphenethylisoquinoline (3) (19.6 mg, 30 %).

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