A NOVEL AND BIOMIMETIC SYNTHESIS OF CHELILUTINE AND SANGUILUTINE

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2,3,7,8,10-Pentaoxygenated benzo[c]phenanthridine alkaloids, chelilutine and sanguilutine, were synthesized from 2,3,7,8-tetraoxygenated benzo[c]phenanthridines derived from protoberberine alkaloids, berberine and palmatine respectively, through oxidative methoxylation.

KEYWORDS benzo[c]phenanthridine alkaloid; protoberberine alkaloid; chelilutine; sanguilutine; biomimetic synthesis; oxygen; salcomine; methoxylation

Several 2,3,7,8,10-pentaoxygenated benzo[c]phenanthridine alkaloids¹⁾ such as chelirubine (1) have been isolated and shown to be biosynthesized²⁾ from protoberberine alkaloids, e.g. stylopine (2), through 2,3,7,8-tetraoxygenated benzo[c]phenanthridine alkaloids such as sanguinarine (3). Various syntheses of these pentaoxygenated alkaloids have so far been developed.³⁻⁶⁾ We describe here a first, convenient conversion of 2,3,7,8-tetraoxygenated benzo[c]phenanthridine alkaloids into pentaoxygenated alkaloids, chelilutine (4a) and sanguilutine (4b) on the basis of the above biosynthesis.

7-O-Demethyldihydrochelerythrine (6a)⁷⁾ derived from berberine (5a) was oxidized with molecular oxygen in tetrahydrofuran in the presence of salcomine⁸⁾ at room temperature for 3 h to afford the p-quinone (7a) [m/z 349(M^+); ν 1650, 1620; 8.15 d, 7.46 d] in 94% yield. Reduction of 7a with sodium hydrosulfite in aqueous acetone, followed by O-methylation with diazomethane gave dihydrochelilutine (8a) [mp 145-147°C (lit.⁵⁾ 139-142°C] in 53% yield. Alternatively, catalytic hydrogenation of 7a over 5% Pd-C in the presence of methyl sulfate and barium hydroxide effected reductive O-methylation⁹⁾ to furnish 8a more efficiently in 81% yield. Regioselective methoxylation at C-10 was thus accomplished by introduction of oxygen at the para position of the phenolic hydroxyl group. Dihydrochelilutine (8a) was oxidized with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone to provide chelilutine (4a) [mp 194-195°C (lit. 184-186°C⁵⁾, 197-198°C³⁾] in 90% yield. Synthetic chelilutine was identical with natural chelilutine.

Similarly, sanguilutine (4b) was synthesized from palmatine (5b). Palmatine (5b) was converted to the phenolic benzo[c]phenanthridine (6b)¹⁰⁾ according to our method⁷⁾ for 6a from 5a. Salcomine-catalyzed oxygen oxidation of 6b gave the p-quinone (7b) [94%; m/z 365(M^+); ν 1650, 1620; 8.17 d, 7.50 d]. Reductive O-methylation of 7b afforded dihydrosanguilutine (8b) [90%; mp 152-154°C (lit.⁶⁾ 154-155°C], which was already converted to sanguilutine (4b).⁶⁾ Synthetic dihydrosanguilutine was identical with the authentic sample.

Thus, we have succeeded in a biomimetic synthesis of the pentaoxygenated benzo[c]phenanthridine alkaloids chelilutine (4a) and sanguilutine (4b) from protoberberine alkaloids, berberine (5a) and

palmitine (5b), via 2,3,7,8-tetraoxygenated benzo[c]phenanthridines (6a and 6b), respectively, through regioselective methoxylation. The present synthesis suggests a possible biosynthetic pathway to penta-oxygenated benzo[c]phenanthridine alkaloids from the corresponding tetra-oxygenated ones.

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