A NOVEL AND BIOMIMETIC SYNTHESIS OF CHELILUTINE AND SANGUILUTINE

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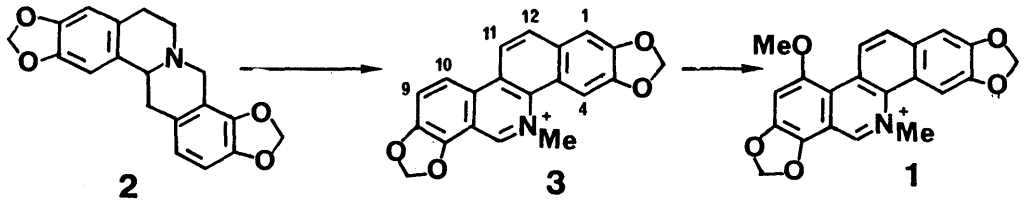
2,3,7,8,10-Pentaoxygenated benzo[c]phenanthridine alkaloids, chelilutine and sanguilutine, were synthesized from 2,3,7,8-tetraoxygenated benzo[c]phenanthridines derived from protoberberine alkaloids, berberine and palmatine respectively, through oxidative methoxylation.

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

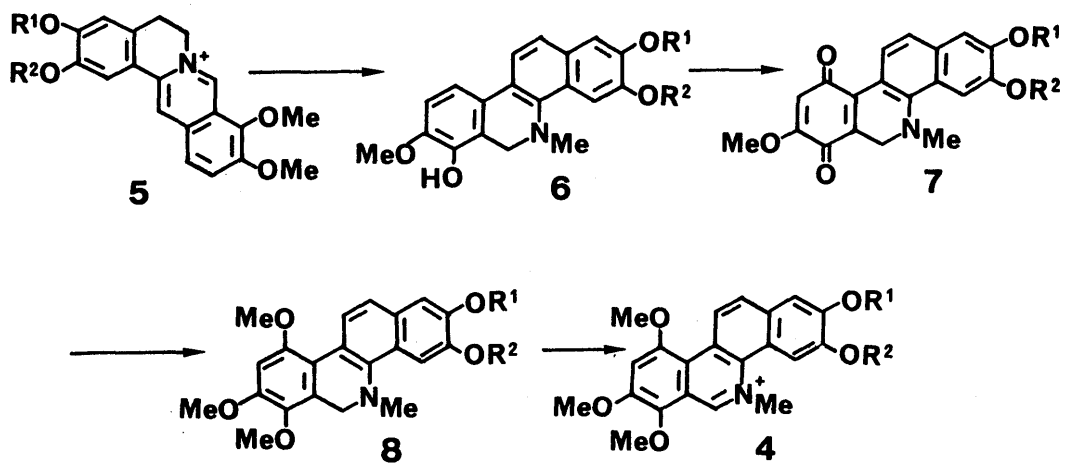
Several 2,3,7,8,10-pentaoxygenated benzo[c]phenanthridine alkaloids[1] such as chelirubine (**1**) have been isolated and shown to be biosynthesized[2] from protoberberine alkaloids, e.g. stylopine (**2**), through 2,3,7,8-tetraoxygenated benzo[c]phenanthridine alkaloids such as sanguinarine (**3**). 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 salcomine[8] 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-methylation[9] 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°C[5], 197-198°C[3])] 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 method[7] 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



a: $R^1+R^2=CH_2$ **b**: $R^1=R^2=CH_3$

palmatine (**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 pentaoxygenated benzo[c]phenanthridine alkaloids from the corresponding tetraoxygenated ones.

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