(-)-DEHYDRONORCHELIDONINE AND (-)-ISODIDEHYDROCHELIDONINE, TWO PROBABLE BIOGENETIC PRECURSORS IN THE BENZOPHENANTHRIDINE SERIES OF ISOQUINOLINE ALKALOIDS

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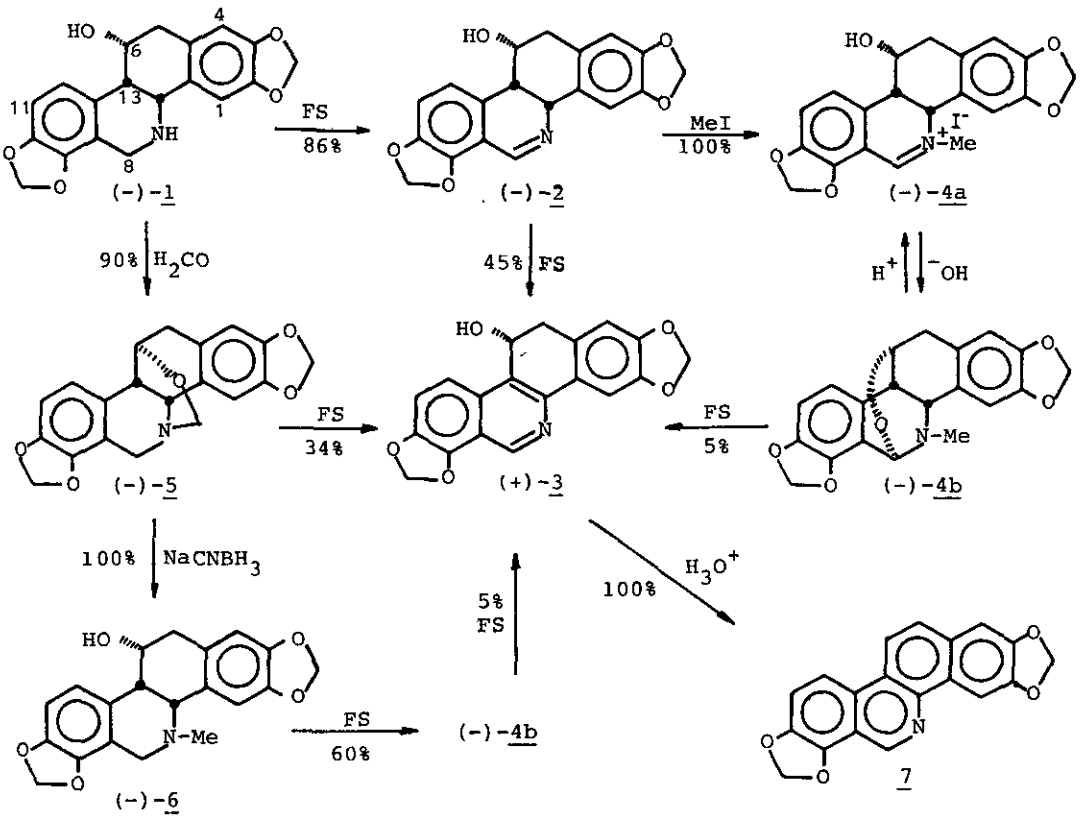
Abstract- The preparation of the title compounds 2 and 5 is described. Their probable biogenetic role is suggested on the basis of chemical evidence obtained by oxidation studies with a one electron oxidant.

The biogenesis of N-methylated benzophenanthridines such as chelidonine and sanguinarine has recently been established in *Chelidonium majus* by Battersby et al.[1] Their well supported conclusions come from incorporation of adequate precursors. However, to our knowledge there is no parallel study concerning the origin of norbenzophenanthridines, e.g. norchelidonine 1 and luguine 3.

We have found that Fremy's salt (FS) oxidation of some aporphine and cularine alkaloids is accompanied by N-demethylation affording the corresponding oxoaporphines[2] and oxocularines.[3] To account for the observed results aminium radicals were proposed. This type of intermediates have also been suggested for oxidation of amines by the flavin-dependent enzyme MAO.[4] To investigate the likely "in vitro" formation of N-demethylated benzophenanthridines such as luguine 3 and norsanguinarine 7, FS[5] oxidation of norchelidonine 1, chelidonine 6, didehydrochelidonine 4b[6] and the new compound isodidehydrochelidonine 5 was carried out. Treatment of (-)-norchelidonine 1 with FS[7] under phase transfer conditions[8] ($CHCl_3$/4% aq. $NaCO_3$, methyltrialkyl(C_8-C_{10})ammonium chloride) for 6 h gave an 86% yield of (-)-dehydronorchelidonine 2.[9] Longer reaction time (7 days) yielded the known (+)-luguine 3 in a 45% yield, identical with an authentic sample in all respects.[10] (+)-Luguine 3 easily dehydrates in acidic media to give norsanguinarine 7. On this basis it looks very likely that this latter compound was derived biogenetically from (-)-norchelidonine 1, via the sequence 1 ⟶ 2 ⟶ 3 ⟶ 7. This is also supported by the fact that 1 and 3 are major products (0.13% and 0.04% respectively) in *Glaucium flavum Cr. var. vestitum*,[10] 7 also being present although in minor proportions (0.002%).



The next target was the N-methylated series. (-)-Dehydronorchelidonine 2 was treated with MeI in $CHCl_3$, to give the corresponding (-)-methiodide 4a in a quantitative yield.[9] Treatment of 4a with 10% NaOH gave (-)-didehydrochelidonine 4b having identical properties to those reported for the dextrorotatory compound, obtained earlier by permanganate oxidation of (+)-chelidonine.[11] A new simple and effective alternative preparation of 4b is thus available. FS oxidation (Py/2% aq. Na_2CO_3) of 4b gave (+)-luguine 3 in 5% isolated yield among a very complex mixture of unidentified products.

In an attempt to obtain (-)-chelidonine 6, treatment of (-)-norchelidonine 1 with formaldehyde followed by sodium borohydride led to the isolation by column chromatography of only a 5% yield of (-)-chelidonine 6,[12] the main product being the new compound (-)-5.[13] The formation of (-)-5[9] was envisaged as the result of an internal Mannich reaction with the hydroxyl group at C_6 on the basis of the following results: a) reaction of (-)-1 with formaldehyde at room temperature without added borohydride gave a 90% yield of (-)-5 as the only product isolated, b) (-)-5 was not reduced by borohydride at room temperature, c) upon refluxing with 98% formic acid or by treatment with $NaCNBH_3$ at a controlled pH 3-4, (-)-5 gave (-)-chelidonine 6 in quantitative yield. When 6 was submitted to FS oxidation at room temperature, (-)-didehydrochelidonine 4b was isolated in a 60% yield. When the reaction was kept going for a longer time, only (+)-luguine could be

isolated in a low yield (5%). However, the above FS oxidation of (-)-isodidehydrochelidonine 5 at room temperature for 7 days led to the isolation of (+)-luguine 3 in 27% yield, along with 22% of starting material.

While no conclusive biogenetic pathways can be proposed on the basis of the above results, they show that in the norbenzophenanthridine series the oxidative conversions 1 ⟶ 2 ⟶ 3 are easily carried out using a one electron oxidant such as Fremy's salt, perhaps, mimetizing the natural process. On the other hand, while the oxidation of benzophenanthridines 4b and 6 to luguine 3 is a low yield process, probably due to competitive reactions, that of isodidehydrochelidonine 5 gives a fair yield of luguine 3. The above results might therefore be considered of some relevance for future incorporation studies on the biogenetic origin of norbenzophenanthridines.

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9. All new compound gave satisfactory elemental analysis.
(-)-Dehydronorchelidonine 2: yellow prisms, mp 252-254°C ($CHCl_3$); $|\alpha|_D^{20}$ -318° (c:0.14, $CHCl_3$); λ_{max}^{EtOH}(log ε): 227(4.41), 234(sh,4.38), 270(3.99), 288(sh, 3.89) and 338(3.61) nm; $\lambda_{max}^{EtOH+HCl}$(log ε): 236(4.26), 296(4.26) and 398 (3.52) nm; ν_{max}(KBr): 3300, 1650, 1490, 1460 and 1260 cm^{-1}; δ($CDCl_3$): 8.45 (d,J=3.2,1H,H-8), 7.10(s,1H,H-1), 6.87 and 6.70(AB_q,J=7.5,1H each,H-11 and H-12), 6.54(s,1H,H-4), 6.05 and 6.00(AB_q,J=1,1H each,O-CH_2-O), 5.91 and 5.89 (AB_q,J=1,1H each,O-CH_2-O), 4.72(dd,J=7 and 3.2,1H,H-14), 4.09(m,1H,H-6), 3.10(m,1H,H-13) and 3.02(m,2H,H-5) ppm (assigned on the basis of decoupling experiments); m/e (%): 337(M^+,100), 320(40), 319(50), 318(80), 317(78), and 293(90).

(-)-Methiodide 4a: Yellow needles, mp 242-244°C (isopropanol); $|\alpha|_D^{20}$ -333° (c:0.1,EtOH); λ_{max}^{EtOH}: 234, 300 and 398 nm; $\lambda_{max}^{EtOH+Na_2CO_3 4\%}$: 228 and 290 nm;

ν_{max}(KBr): 3300, 1650, 1490, 1460 and 1250 cm^{-1}; $\delta(CDCl_3+TFA-d_1)$:8.93(broad s, 1H,H-8), 7.11 and 6.87(AB_q,J=8,1H each,H-11 and H-12), 6.81(s,1H,H-1), 6.69(s, 1H,H-4), 6.22 and 6.15(AB_q,J=1,2H,O-CH_2-O), 6.00(s,2H,O-CH_2-O), 5.22(m,1H,H-14), 4.45(m,1H,H-6), 3.48(s,3H,N^+-Me), 3.43(m,1H,H-13) and 3.18(d,J=2.8,2H,H-5).

(-)-Isodidehydrochelidonine 5: White plates, mp 178-180°C (EtOH); $|\alpha|_D^{20}$ -156° (c:0.025,EtOH); λ_{max}^{EtOH}(log ε): 211(4.33), 238(3.89) and 290(3.86) nm; ν_{max}(KBr): 2900, 1510, 1490, 1460, 1390, 1360 and 1340 cm^{-1}; $\delta(CDCl_3)$: 6.73(s,1H,H-1), 6.73 and 6.60(AB_q,J=8,2H,H-11 and H-12), 6.68(s,1H,H-4), 5.98 and 5.94(AB_q, J=1.5,2H,O-CH_2-O), 5.92(s,2H,O-CH_2-O), 4.79 and 4.19(AB_q,J=11,2H,N-CH_2-O), 4.49 and 4.20(AB_q,J=18,2H,H-8),4.04(m,1H,H-6), 3.96(d,J=2.6,1H,H-14), 3.25 (d,J=3,2H,H-5) and 2.67(m,1H,H-13) ppm; CMR $\delta(CDCl_3)$: 77.76(t)(N-CH_2-O) ppm; m/e (%): 351(M^+,80), 323(13), 322(27), 308(8), 306(8), 293(17), 235(13), 176(26), 175(43), 174(32) and 148(100).

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13. To compound 5 we have given the trivial name of (-)-isodidehydrochelidonine because of its similitude with (-)-4b.

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