

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

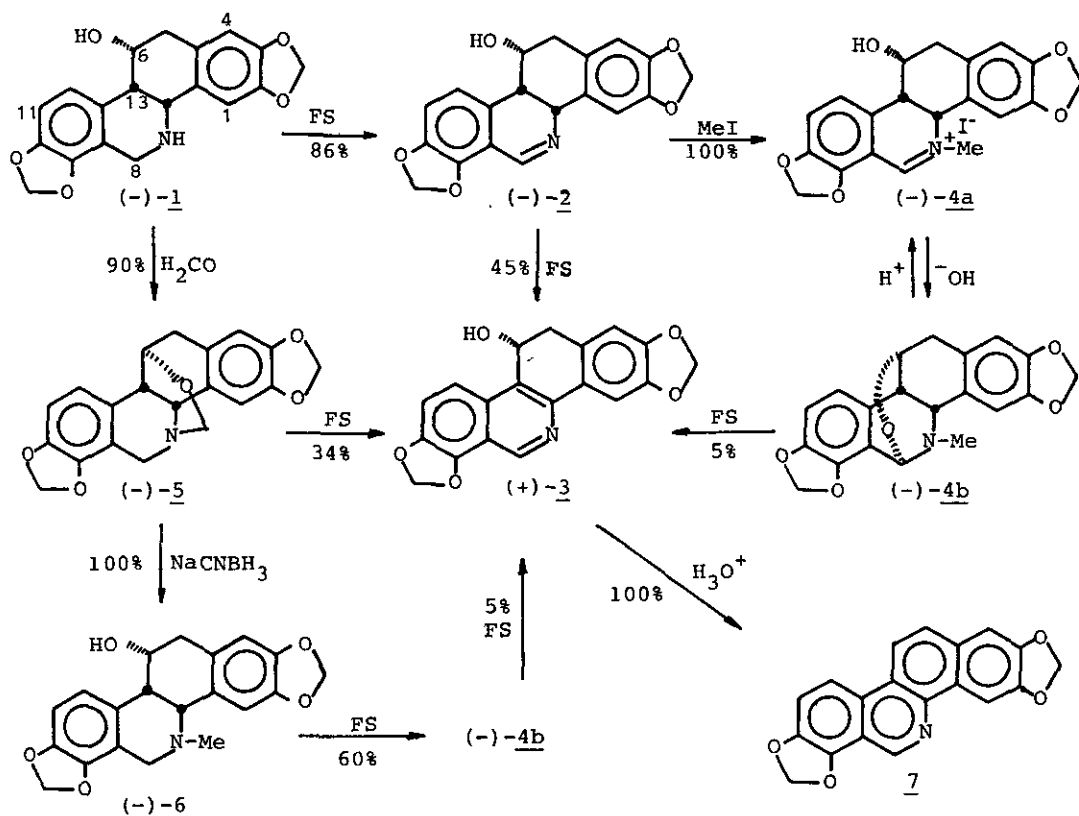
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Abstract- The preparation of the title compounds 2 and 5 is
described. Their probable biogenetic role is suggested on the
basis of chemical evidence obtained by oxidation studies with
a one electron oxidant.

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 nor-benzophenanthridines, 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 oxoaporphines² 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, FS⁵ oxidation of norchelidonine 1, chelidonine 6, didehydrochelidonine 4b⁶ and the new compound isodidehydrochelidonine 5 was carried out. Treatment of (-)-norchelidonine 1 with FS⁷ under phase transfer conditions⁸ (CHCl₃/4% aq. NaCO₃, methyltrialkyl(C₈-C₁₀) 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 CHCl₃, 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. Na₂CO₃) of 4b gave (+)-luguine 3 in 5% isolated yield among a very complex mixture of unidentified products.

In an attempt to obtain (-)-chelidonine 5, 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 was envisaged as the result of an internal Mannich reaction with the hydroxyl group at C₆ 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 NaCNBH₃ 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 \rightarrow 2 \rightarrow 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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(-)-Dehydronorchelidonine 2: yellow prisms, mp 252-254°C (CHCl₃); $[\alpha]_D^{20}$ -318° (c:0.14, CHCl₃); $\lambda_{\max}^{\text{EtOH}}$ (log ϵ): 227(4.41), 234(sh,4.38), 270(3.99), 288(sh, 3.89) and 338(3.61) nm; $\lambda_{\max}^{\text{EtOH+HCl}}$ (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 (CDCl₃): 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-CH₂-O), 5.91 and 5.89 (AB_q, J=1, 1H each, O-CH₂-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); $\lambda_{\max}^{\text{EtOH}}$: 234, 300 and 398 nm; $\lambda_{\max}^{\text{EtOH+Na}_2\text{CO}_3^{4\%}}$: 228 and 290 nm;

ν_{\max} (KBr): 3300, 1650, 1490, 1460 and 1250 cm^{-1} ; $\delta(\text{CDCl}_3+\text{TFA}-d_1)$: 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-CH₂-O), 6.00 (s, 2H, O-CH₂-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); $\lambda_{\max}^{\text{EtOH}}$ (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} ; $\delta(\text{CDCl}_3)$: 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-CH₂-O), 5.92 (s, 2H, O-CH₂-O), 4.79 and 4.19 (AB_q , $J=11$, 2H, N-CH₂-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 $\delta(\text{CDCl}_3)$: 77.76 (t) (N-CH₂-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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