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FURTHER STUDIES ON LEMOBILINE: PARTIAL SYNTHESIS OF (-)LEMOBILINE AND ITS CONVERSION TO (-)RAVENOLINE

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In a recent communication[1] we reported the isolation and structure (I) of spectabiline, a new dihydrofuroquinol-4-one alkaloid of the leaves of Lemonia spectabilis Lindl. (syn. Ravenia spectabilis Engl.), which has been subsequently renamed as lemobiline[2]. Now we present further evidence of structure (I) proposed earlier[1].

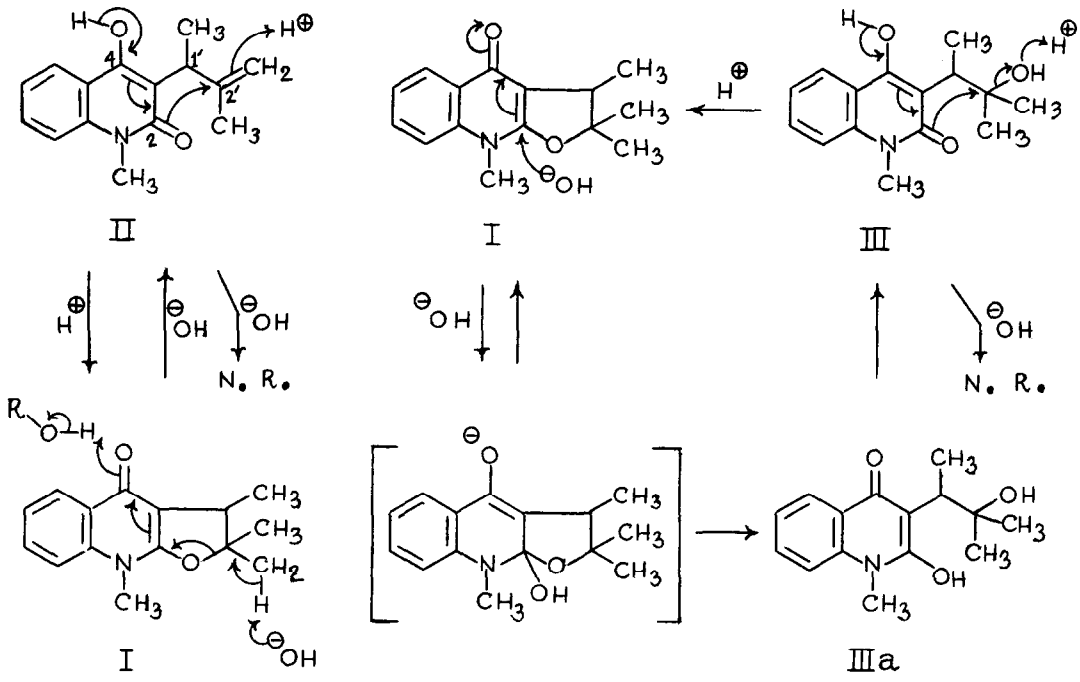
Recently, Chamberlain et al[3] established by feeding experiments that ravenine[4] [N-methyl-4(3',3'-dimethylallyloxy)-2-quinolone[5]] is a biogenetic precursor of ravenoline[4] [N-methyl-3-(1',2'-dimethylallyl)-4-hydroxy-2-quinolone[5]] (II) and also suggested that compound I (≡ lemobiline) isolated by them from Flindersia ifflaiana F. Muell[6] should be formed by cyclisation of ravenoline. These observations prompted us to communicate the results of our investigation.

The chloroform extract of the marc left after the petroleum ether extraction[1] afforded (-)ravenoline[7] (0.02%), $[\alpha]_D$ - 5° ± 1° ($CHCl_3$) and a liberal amount of arborinine (~3%) upon repeated chromatography over silica gel. (-)Ravenoline (II) when treated with 48% HBr or conc. HCl in glacial acetic acid at room temperature for 2 hr. underwent cyclisation to afford (-)lemobiline (I) (65%), $[\alpha]_D$ - 8° ± 1° ($CHCl_3$), identical in all respects (TLC, m.m.p., IR, UV, NMR and rotation[8]) with the natural alkaloid[1]. Ravenoline having been synthesised[4,5] earlier, its acid catalysed cyclisation to lemobiline thus constitutes the total synthesis of the latter. This conversion also suggests the same absolute configuration of the only asymmetric centre in (-)ravenoline and (-)lemobiline [the cyclisation necessarily taking place in a concerted manner (Scheme I) before any epimerisation at C-1' of ravenoline through its $\Delta^{1':2'}$ isomer can occur]. This conversion also strengthens the hypothetical pathway by providing the laboratory analogy for the biosynthesis[3] of lemobiline, which, however, needs final confirmation through feeding experiment.

(-)Lemobiline when refluxed with 10% methanolic KOH for 40 hr. was partly converted into (-)ravenoline (16% yield), identical (m.m.p., TLC, rotation, IR, UV, NMR and MS) with the natural alkaloid, and a tertiary alcohol (III) (16% yield), m.p. 220° ($C_{15}H_{19}O_3N$) (M^+ 261, 4%), λ_{max} (EtOH) 257sh nm (log ϵ, 3.84), 278 (3.70), 289 (3.80), 315 (3.95). The structure of III was fully consistant with its PMR and mass spectra. PMR ($CDCl_3$, 60 MHz): δ (ppm) 1.30 and 1.55 [each 3H, s; $(CH_3)_2COH$], 1.33 (3H, d, J = 7.5 Hz; CH-CH_3), 3.73 (3H, s, N-CH_3), 7.15-7.7 (3H, m, H-7 and H-8); 8.09 (1H, q d, J_o 8.5 Hz, J_m 3 Hz, J_p 1 Hz, H-5). An ill-defined quartet around δ 3.78 (J = 7.5 Hz), partially hidden in the N-CH_3 singlet at δ 3.73, is assigned to the secondary methine proton at C-1'. Appearance of the H-5 signal (deshielded by the peri C-O bond) near δ 8 indicates that the tertiary alcohol possesses in solution the 4-hydroxy-2-quinolone (III) (and not 2-hydroxy-4-quinolone, IIIa) structure like ravenoline which shows the H-5 signal at δ 7.97 as a quartet of doublet (J_o 8.5 Hz, J_m 2.5 Hz and J_p 1.25 Hz). In 4-quinolone system the H-5 experiences much more deshielding effect of the peri carbonyl group as in the case of lemobiline[1] (H-5 appears at δ 8.47). Mass spectrum: m/e 261 (4%, M^+), 246 (3.5%, $M^+ - CH_3$), 228 (13%, $M^+ - CH_3 - OH$), 203 (base peak, $M^+ - Me_2COH + H$), 202 (32%, $M^+ - Me_2COH$), 188 (4%, base peak - CH_3), 59 (14%, $Me_2C{=}\overset{+}{O}H$).

Both ravenoline and the tertiary alcohol III remained unchanged after refluxing with 10% methanolic KOH separately for nearly 40 hr. This observation suggests that ravenoline is not formed through the intermediacy of the tertiary alcohol III or vice versa during the base induced reaction of lemobiline. Two independent routes may, therefore, be postulated for the formation of ravenoline (II) and the tertiary alcohol (III) from lemobiline (I) by a concerted and a stepwise mechanism respectively, as shown in Scheme I.

Like ravenoline, the alcohol III under similar acid catalysed condition also gave lemobiline in good yield. Both ravenoline and the tertiary alcohol were found to be resistant to acetylation (Ac_2O/Py, R.T., 24 hr.). This inert nature of the peri phenolic OH may be ascribed to the presence of a bulky side chain in the ortho position offering significant steric hindrance to the approach of the reagent (pyridine-Ac_2O complex).



Scheme I

Lemobiline being optically active can not arise by rearrangement of optically inactive ravenine during isolation. We believe that the following evidence unambiguously eliminate the possibility of its being an artifact arising out of cyclisation of (-)ravenoline during its isolation.

a) (-)Ravenoline was submitted to the same isolation procedure as that of lemobiline but no trace of the latter could even be detected by TLC from the dilute HCl (2N) extract and ravenoline was recovered unchanged from the non-basic part in almost quantitative yield.

b) From the petroleum ether extract of the plant materials lemobiline could be isolated directly by exhaustive chromatography over alumina prior to any acid treatment.

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2. See Errata of Ref. 1, Tetrahedron Letters, 2730 (1970).
3. T. R. Chamberlain, J. F. Collins and M. F. Grundon, Chem.Comm., 1269 (1969).
4. B. D. Paul and P. K. Bose, Indian J. Chem., 7, 678 (1969).
5. T. R. Chamberlain and M. F. Grundon, Tetrahedron Letters, 3547 (1967).
6. No name, physical data or properties of this alkaloid was, however, reported by the authors[3].
7. Apparently we have isolated the optical antipode of (+)ravenoline, $[\alpha]_D$ + 6° ($CHCl_3$), reported earlier by Paul and Bose[4].
8. Natural lemobiline was found to have $[\alpha]_D$ - 7° ± 1° ($CHCl_3$) on careful redetermination (previous report[1] $[\alpha]_D$ - 5.9°).