THE TOTAL SYNTHESIS OF (±)-MAPPICINE

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Reduction of 7-methoxycarbonyl-8-methylindolizino[1,2-b]quinolin-9(11H)-one (3), prepared from 7-methoxycarbonylindolizino[1,2-b]quinolin-9(11H)-one (2), gave the corresponding alcohol (5), which was converted into (±)-mappicine (7) through the aldehyde (6).

Mappicine, a minor alkaloid isolated from Mappia foetida (Oleaceae), was assigned the structure (7) on the basis of spectral analysis and a partial synthesis from a co-existed base camptothecin (1) by Govindachari in 1974. We have investigated a total synthesis of mappicine from 7-methoxycarbonylindolizino[1,2-b]quinolin-9(11H)-one (2), which would be a potential precursor to camptothecin (1). Here we wish to report the successful result.

Treatment of 7-methoxycarbonylindolizino[1,2-b]quinolin-9(11H)-one (2) with an excess of diazomethane, prepared from N-methyl-N-nitrosotoluene-p-sulphonamide, in chloroform and methanol at room temperature for 24 hr afforded a mixture of 7-methoxycarbonyl-8-methylindolizino[1,2-b]quinolin-9(11H)-one (3) (40%), mp 251 - 253°, and cyclopropane derivative (4) (38%), mp 213 - 215°, which was easily separated by recrystallisation from chloroform-ether. The former (3), C_{18}H_{14}N_{2}O_{3}, m/e 306 (M^+), showed an amide and an ester carbonyl groups at 1725 and 1650 cm⁻¹.
respectively, in ir spectrum (KBr) and nmr spectrum (δ in CDCl₃) revealed two methyl groups at 2.48 and 3.95, and a C-5 proton on a pyridone ring at 7.45. The position of methyl group was determined by a comparison of nmr spectrum (CDCl₃) of the pyridone-4-acetates (9 and 10), the former of which were prepared in 3% yield from 3 by Arndt-Eistert reaction. Thus, the C-3 proton on pyridone ring in 10 was observed at 6.6, but this chemical shift could not be found in 9. The latter (4), C₁₈H₁₄N₂O₃, m/e 306 (M⁺), had a cyclopropane ring, whose fact was proved by nmr spectrum [δ in CDCl₃ 1.05 (1H, q, J 4 and 6 Hz), 2.30 (1H, q, J 4 and 10 Hz) and 2.83 (1H, q, J 6 and 10 Hz)] showing a characteristic pattern to this ring system. Moreover, a resonance of C-3 proton in a pyridone system could not be observed in nmr spectrum and ir spectrum (CHCl₃) revealed the presence of an amide and an ester functions at 1655 and 1730 cm⁻¹, respectively. Similar reaction with diazomethane was reported by Pelletier.

Reduction of 3 with lithium borohydride in diglyme at 100°C for 1 hr gave the alcohol (5) (63%), mp >300°C, m/e 278 (M⁺), which showed an amide carbonyl at 1650 cm⁻¹ in ir spectrum (KBr) and carbinol-methylene resonance at 5.03 in nmr spectrum (CF₃CO₂H). Dimethyl sulfoxide oxidation of this alcohol (5) in acetic anhydride at 90 - 100°C for 4 hr afforded the aldehyde (6) (70%), mp 257 - 260°C, m/e 276 (M⁺), which showed a formyl group at 1690 cm⁻¹ in ir spectrum (CHCl₃) and at 10.38 in nmr spectrum (CDCl₃) in addition to an amide function at 1650 cm⁻¹. The reaction of an aldehyde (6) with diazoethane, prepared from N-nitrosoethylurea, in chloroform and ether at 0°C for 2 hr gave the ethyl ketone (11) (90%) as pale yellow plates, mp 237 - 238°C, m/e 304 (M⁺), which showed the carbonyl groups at 1705 and 1655 cm⁻¹ in its ir spectrum (CHCl₃) and an ethyl group at 1.25 (t, J 7 Hz) and 2.88 (q, J 7 Hz). Reduction of this ketone with sodium borohydride in methanol afforded (±)-mappicine (7) (70%), mp 271 - 273°C (lit., mp 270 - 271°C), after purification on silica gel chromatography. The ir [ν max (KBr) 3260br, and 1660 cm⁻¹], uv [λ max (MeOH)]
366, 333, 291, 254, and 247 nm], nmr [δ (CD$_3$OD) 1.03 (3H, t, J 7 Hz, CH$_2$CH$_3$), 1.71 (2H, m, CH$_2$CH$_3$), 2.20 (3H, s, ArCH$_3$), 4.85 (1H, t, J 6 Hz, CHO), 5.13 (2H, s, ArCH$_2$N) and 7.5 - 8.4 (ArH)], and mass spectra [m/e 306 (M$^+$), 291, 289, 278, 277, 273, 263, 262, 249, 248, 221, 218, 217, 206, 205, 192, 191, 181, 168, 167, 166, 140 and 110] were closely similar to the reported data of natural mappicine. ¹

Grignard reaction of 6 with ethyl magnesium bromide in ether-tetrahydrofuran for 4 hr at 20°C gave (°)-mappicine (7), which was isolated and purified as its acetate (8) (4%). mp 180 - 181°C. The ir spectrum (CHCl$_3$) showed O-acetyl and amide groups at 1730 and 1655 cm$^{-1}$, and uv spectrum revealed absorption maxima at 366, 333, 293, 254 and 247 nm, whose data were similar to those of mappicine (7). Moreover, the nmr [δ in CDCl$_3$; 0.99 (3H, t, J 7 Hz, CH$_2$CH$_3$), 1.36 (2H, m, CH$_2$CH$_3$), 2.16 (3H, s, OCOCH$_3$), 2.37 (3H, s, ArCH$_3$), 5.27 (2H, broad s, ArCH$_2$N), 6.03 (1H, t, J 7 Hz, COAc) and 7.38 - 8.32 (ArH)] and mass spectra [m/e 348 (M$^+$), 305, 290, 289, 288, 287, 277, 274, 273, 248 and 219] were identical with the reported data of 8. ¹

Thus, we have accomplished the total synthesis of (°)-mappicine.

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