# THE TOTAL SYNTHESIS OF (±)-MAPPICINE

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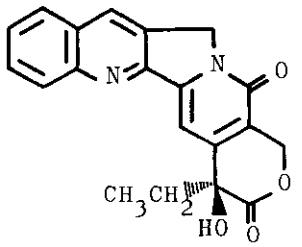
Reduction of 7-methoxycarbonyl-8-methylindolizino[1,2-b]quinolin-9(11H)-one (3), prepared from 7-methoxycarbonylindolizino[1,2-b]-quinolin-9(11H)-one (2), gave the corresponding alcohol (5), which was converted into (±)-mappicine (7) through the aldehyde (6).

Mappicine, a minor alkaloid isolated from Mappia foetida (Olacaceae), 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.[1] 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).[2] 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), $C_{18}H_{14}N_2O_3$, 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 ($\delta$ in $CDCl_3$) 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 ($CDCl_3$) of the pyridone-4-acetates (9 and 10[3]), 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), $C_{18}H_{14}N_2O_3$, m/e 306 ($M^+$), had a cyclopropane ring, whose fact was proved by nmr spectrum [$\delta$ in $CDCl_3$ 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.[4] Moreover, a resonance of C-3 proton in a pyridone system could not be observed in nmr spectrum and ir spectrum ($CHCl_3$) 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.[5]

Reduction of 3 with lithium borohydride in diglyme at 100° for 1 hr gave the alcohol (5) (63 %), mp > 300°, 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 ($CF_3CO_3H$). Dimethyl sulphoxide oxidation of this alcohol (5) in acetic anhydride at 90 - 100° for 4 hr afforded the aldehyde (6) (70 %), mp 257 - 260°, m/e 276 ($M^+$), which showed a formyl group at 1690 $cm^{-1}$ in ir spectrum ($CHCl_3$) and at 10.38 in nmr spectrum ($CDCl_3$) 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° for 2 hr gave the ethyl ketone (11) (90 %) as pale yellow plates, mp 237 - 238°, m/e 304 ($M^+$), which showed the carbonyl groups at 1705 and 1655 $cm^{-1}$ in its ir spectrum ($CHCl_3$) 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° (lit.,[1] mp 270 - 271°), after purification on silica gel chromatography. The ir [$\nu$ max (KBr) 3260$^{br}$, and 1660 $cm^{-1}$], uv [$\lambda$ max (MeOH)



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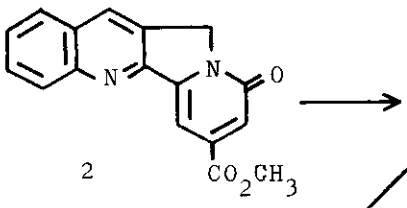

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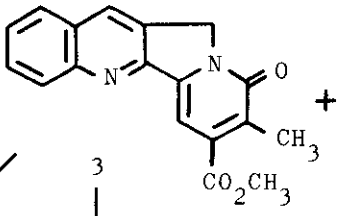

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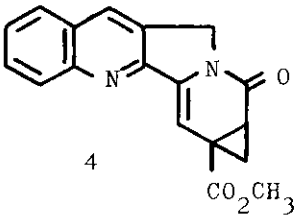

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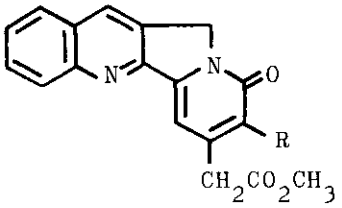
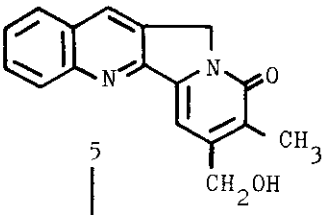


9 R=$CH_3$

10 R=H



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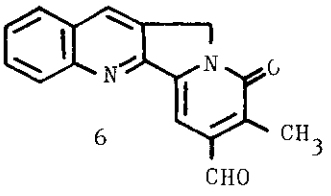

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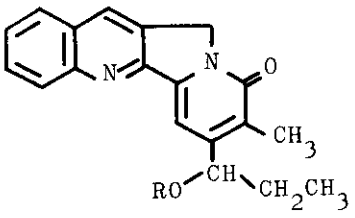
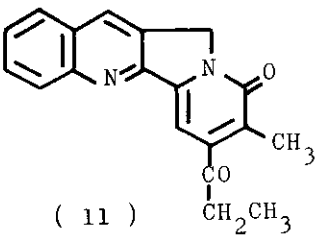


7 R=H

8 R=$COCH_3$



( 11 )

366, 333$^{sh}$, 291, 253, and 246 nm], nmr [δ ($CD_3OD$) 1.03 (3H, t, J 7 Hz, $CH_2\underline{CH_3}$), 1.71 (2H, m, $\underline{CH_2}CH_3$), 2.20 (3H, s, $Ar\underline{CH_3}$), 4.85 (1H, t, J 6 Hz, >CHOH), 5.13 (2H, s, $Ar\underline{CH_2}N$) and 7.5 - 8.4 (ArH)], and mass spectra [m/e 306 ($M^+$), 291, 289, 278, 277, 273, 263, 262, 249, 248, 221, 219, 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° gave (±)-mappicine (7), which was isolated and purified as its acetate (8) (4 %), mp 180 - 181°. 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$^{sh}$, 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, $CH_2\underline{CH_3}$), 1.96 (2H, m, $\underline{CH_2}CH_3$), 2.16 (3H, s, $OCO\underline{CH_3}$), 2.37 (3H, s, $Ar\underline{CH_3}$), 5.27 (2H, broad s, $Ar\underline{CH_2}N$), 6.03 (1H, t, J 7 Hz, $C\underline{H}OAc$) and 7.38-8.32 (Ar$\underline{H}$)] 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.

We thank Professor T. R. Govindachari for providing the spectral data of mappicine.

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Received, 13th December, 1974