# Mappicine, a Minor Alkaloid from *Mappia foetida* Miers

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The structure of mappicine, a minor alkaloid isolated from *Mappia foetida* Miers, has been established as (IIa) {7-(1-hydroxypropyl)-8-methylindolizino[1.2-*b*]quinolin-9(11*H*)-one} by partial synthesis from camptothecin (Ia).

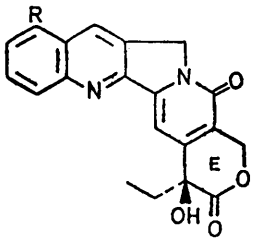
We have previously reported the isolation of the antitumour alkaloid camptothecin (Ia) from *Mappia foetida* Miers (family; Olacaceae).[1,2] A new alkaloid isolated from the plant was shown to be 9-methoxycamptothecin (Ib) by spectral studies. T.l.c. examination of the mother liquors of crystallisation of these alkaloids showed the presence of traces of more polar compounds with green or blue u.v. fluorescence. By repeated chromatography of this material over silica gel we have isolated one new alkaloid in very small yield. This has been named mappicine and we now report evidence leading to structure (IIa) for the alkaloid.

Mappicine, $C_{19}H_{18}N_2O_2$ ($M^+$ 306), has a u.v. spectrum closely resembling that of camptothecin (Ia). Its i.r. spectrum shows bands at 3380, 3280 (OH), 1660, and 1590 $cm^{-1}$ (pyridone) but lacks the δ-lactone peak at 1745 $cm^{-1}$ which is present in camptothecin. Acetylation of mappicine gives a monoacetate. The n.m.r.

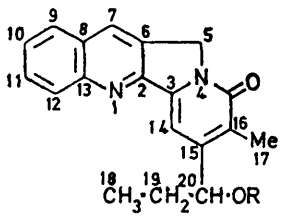
[1] T. R. Govindachari and N. Viswanathan, *Indian J. Chem.*, 1972, **10**, 453.

[2] T. R. Govindachari and N. Viswanathan, *Phytochemistry*, 1972, **11**, 3529.

spectra of mappicine and its acetate are summarised in Tables 1 and 2. The most significant differences between the n.m.r. spectra of mappicine and camptothecin concern the groups present in ring E of camptothecin. Mappicine shows the presence of an aromatic



(I)
a, R=H
b, R=OMe



(II)
a, R=H
b, R=Ac

methyl and a hydroxypropyl group. The triplet at δ 5·14 (C*H*OH) is shifted to δ 5·90 in the acetate. These features indicated the structure of mappicine to be (IIa), the acetate being (IIb).

TABLE 1

N.m.r. spectrum * of mappicine (IIa)

| Chemical shift (δ) | Number of protons | Multiplicity (*J*/Hz) | Assignment |
|---|---|---|---|
| 8·25 | 1 | dd (8 and 1) | 12-H |
| 8·06 | 1 | d (1) | 7-H |
| 7·88 | 1 | s | 14-H |
| 7·80—7·30 | 3 | m | 9-H, 10-H, 11-H |
| 7·68 | 1 | s | OH |
| 5·18 | 2 | s | 5-$H_2$ |
| 5·14 | 1 | t (7) | 20-H |
| 2·37 | 3 | s | 17-$H_3$ |
| 1·88 | 2 | m | 19-$H_2$ |
| 1·16 | 3 | t (7) | 18-$H_3$ |

* Recorded in $C_5D_5N$ at 100 MHz.

TABLE 2

N.m.r. spectrum * of mappicine acetate (IIb)

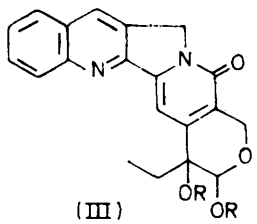
| Chemical shift (δ) | Number of protons | Multiplicity (*J*/Hz) | Assignment |
|---|---|---|---|
| 8·32 | 1 | d (0·8) | 7-H |
| 8·22 | 1 | dd (8 and 0·8) | 12-H |
| 8·0—7·4 | 3 | m | 9-H, 10-H, 11-H |
| 7·36 | 1 | s | 14-H |
| 5·90 | 1 | t (7) | 20-H |
| 5·24 | 2 | s | $H_2$ |
| 2·37 | 3 | s | 17-$H_3$ |
| 2·17 | 3 | s | OAc |
| 1·96 | 2 | m | 19-$H_2$ |
| 1·00 | 3 | t (7) | 18-$H_3$ |

* Recorded in $CDCl_3$ at 100 MHz.

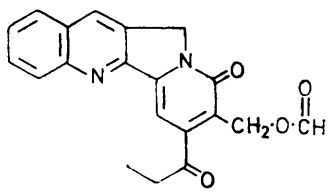
The mass spectral fragmentation pattern of mappicine furnished additional support for the structure. The peaks at *m/e* 291, 289, 248, 219, 205, 191, 181, 167, and 140 are also present in camptothecin.

Structure (IIa) for mappicine has been confirmed by a partial synthesis from camptothecin (Ia) whose structure has been established by an *X*-ray study [3] and by several syntheses.[4,5]

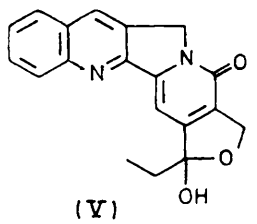
Reduction of camptothecin with sodium borohydride yielded the diol (IIIa) which was among several derivatives of camptothecin which were tested for anti-cancer activity and found to be inactive.[6] The diol was cleaved by lead tetra-acetate to the keto-ester (IV). Alkaline hydrolysis of the latter yielded a product, lacking i.r. carbonyl absorption, which is formulated as the internal hemiacetal (V). This was unsuitable for conversion into mappicine. Reduction of the keto-ester (IV) with sodium borohydride under vigorous conditions yielded a mixture of the diol (VI) and the hydrogenolysis product (IIa) which were separated by chromatography. The latter was identical with mappicine in t.l.c., u.v., n.m.r., and mass spectra. Its i.r. spectrum in KBr showed slight differences in the fingerprint region from that of mappicine. The i.r. spectra could not be run in solution owing to poor solubility.



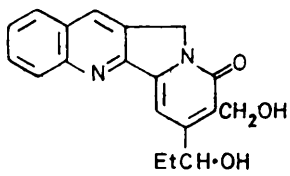
(III)
a, R=H; b, R=Ac



(IV)



(V)



(VI)

The o.r.d. and c.d. of mappicine show negative Cotton effects in the region 300—400 nm suggesting the *S*-configuration at C-20.[7] An attempt to reduce the keto-ester (IV) with lithium aluminium hydride–3-*O*-benzyl-1,2-*O*-cyclohexylidene-α-D-glucofuranose complex [8] to the (20*S*)-alcohol gave only the racemic diol (VI) which did not show any optical activity in o.r.d. and c.d. studies.

## EXPERIMENTAL

U.v. spectra were taken in 95% ethanol on a Beckman DK 2A spectrophotometer. I.r. spectra were run on a Perkin-Elmer Infracord and n.m.r. spectra on a Varian A-60 or XL-100 instrument at 60 or 100 MHz. Mass spectra were determined on a Varian MAT CH7 instrument using the direct inlet at 70 eV.

*Isolation of Mappicine.*—The acetone and methanol

[3] A. T. MacPhail and G. A. Sim, *J. Chem. Soc.* (*B*), 1968, 923.
[4] M. Shamma, D. A. Smithers, and V. St. Georgiev, *Tetrahedron*, 1973, **29**, 1949, and references cited therein.
[5] A. G. Schultz, *Chem. Rev.*, 1973, **73**, 385.
[6] G. H. Svoboda in 'Pharmacognosy and Phytochemistry,' eds. H. Wagner and L. Hörhammer, Springer-Verlag, Berlin, 1971, p. 183.
[7] P. Crabbé, 'O.R.D. and C.D. in Chemistry and Biochemistry,' Academic Press, New York, 1972, p. 61.
[8] S. R. Landor, B. J. Miller, and A. R. Tatchell, *J. Chem. Soc.* (*C*), 1966, 1822, 2280; 1967, 197.

extracts of the stem of the plant were worked up as described previously.[8] After the removal of camptothecin and 9-methoxycamptothecin by crystallisation, the combined mother liquor was evaporated and the residual gum triturated with methanol. The solid obtained was chromatographed over silica gel in chloroform. Mappicine, which showed a bright green fluorescence in u.v. light, was eluted by chloroform–methanol (97 : 3). Crystallisation from methanol yielded the *alkaloid* (IIa) as pale yellow crystals, m.p. 251—252°, $\lambda_{max.}$ 218, 245sh, 253, 290, 333sh, and 366 nm (log ε 4·48, 4·32, 4·35, 3·74, 4·00, and 4·17) (Found: C, 66·2; H, 6·8; N, 8·1. $C_{19}H_{16}N_2O_2,2H_2O$ requires C, 66·7; H, 6·5; N, 8·2%), *m/e* 306 ($M^+$, 43%), 291 (43), 289 (53), 278 (35), 277 (64), 273 (45), 263 (18), 262 (20), 249 (48), 248 (57), 221 (53), 219 (100), 218 (59), 217 (29), 206 (50), 205 (49), 192 (26), 191 (29), 181 (33), 168 (20), 167 (24), 166 (20), 140 (27), and 110 (27), o.r.d. (*c* 0·024, dioxan) $[\Phi]_{590}$ − 89°, $[\Phi]_{401}$ − 1651°, $[\Phi]_{350-345}$ + 1079° (broad), $[\Phi]_{340-335}$ + 1016° (broad), $[\Phi]_{325}$ + 2159°; $[\Phi]_{260}$ 0°, $[\Phi]_{247}$ + 3301°, and $[\Phi]_{240}$ 0°, c.d. (*c* 0·024, dioxan) $[\theta]_{410}$ 0°, $[\theta]_{375}$ − 1524°, and $[\theta]_{300}$ + 889°, n.m.r. spectrum in Table 1.

*Mappicine Acetate* (IIb).—Mappicine (25 mg) was heated with pyridine (0·5 ml) and acetic anhydride (3 ml) at 60—70° for 6 h. The solution was evaporated to dryness *in vacuo* and the residue crystallised from methanol to yield the acetate (15 mg), m.p. 191—192°, $\nu_{max.}$ (KBr) 1730 and 1660 cm$^{-1}$, *m/e* 348 ($M^+$, 70%), 305 (45), 290 (40), 289 (100), 288 (92), 287 (65), 277 (60), 274 (60), 273 (95), 259 (25), 248 (42), 245 (40), 231 (23), 219 (75), 218 (55), 205 (25), 191 (23), 181 (20), and 140 (30), n.m.r. spectrum in Table 2.

*Dihydrocamptothecin* (IIIa).—Sodium borohydride (2 g) was added in portions, during 10 min, to a suspension of camptothecin (Ia) (2 g) in methanol (150 ml). The solution was warmed on a water-bath for 10 min and left overnight at room temperature. The solution was concentrated *in vacuo*, diluted with water, and brought to pH 6 by addition of dilute acetic acid. The solid was filtered off to give the diol (1·6 g), m.p. 280—283° (decomp.) (from dimethylformamide), $\nu_{max.}$ (Nujol) 3480, 3300br, and 1660 cm$^{-1}$ (Found: C, 68·1; H, 5·7. Calc. for $C_{20}H_{18}N_2O_4$: C, 68·6; H, 5·2%), *m/e* 350 (50%), 332 (10), 319 (8), 305 (25), 304 (100), 303 (38), 302 (37), 289 (41), 287 (52), 276 (33), 275 (45), 261 (11), 249 (15), 248 (82), 247 (62), 219 (80), 218 (35), 217 (30), 205 (25), 191 (18), 190 (17), and 140 (16). The diol gave a positive periodic acid test for 1,2-glycols. Acetylation of the diol with pyridine–acetic anhydride gave the *diacetate* (IIIb), m.p. 220° (from methanol), $\nu_{max.}$ (Nujol) 1780, 1760, 1660, and 1240 cm$^{-1}$ (Found: C, 66·0; H, 5·4. $C_{24}H_{22}N_2O_6$ requires C, 66·4; H, 5·1%), *m/e* 434 ($M^+$).

*The Keto-ester* (IV).—A suspension of the diol (IIIa) (0·5 g) in glacial acetic acid (45 ml) was heated with lead tetra-acetate (0·9 g) at 60° for 3 h. The solution was concentrated *in vacuo*, diluted with water, and extracted with chloroform to yield 8-*formyloxymethyl*-7-(1-*oxopropyl*)*indolizino*[1,2-b]*quinolin*-9(11H)-*one* (IV) (320 mg), m.p. 192—194° (decomp.) (from chloroform–methanol), $\nu_{max.}$ (Nujol) 1735, 1715, and 1660 cm$^{-1}$ (Found: C, 68·6; H, 4·9. $C_{20}H_{16}N_2O_4$ requires C, 69·0; H, 4·6%), *m/e* 348 ($M^+$, 10%), 320 (4), 304 (38), 303 (45), 302 (80), 291 (32), 287 (100), 275 (45), 273 (32), 248 (70), 247 (65), 234 (53), 231 (43), 229 (37), 219 (85), 218 (80), 217 (80), 216 (80), 205 (80), 192 (40), 191 (75), and 190 (80), δ[$(CD_3)_2SO$] * 8·55 (1H, s, CHO), 8·2—7·5 (5H, m, aromatic), 7·25 (1H, s, 14-H), 5·22 (4H, s, 17-$H_2$ and 5-$H_2$), 3·0 (2H, q, *J* 7 Hz, 19-$H_2$), and 1·2 (3H, t, *J* 7 Hz, 18-$H_3$). On addition of $C_6D_6$ to the solvent, the singlet at δ 5·22 was resolved into two singlets (2H each) at 5·28 and 5·15.

*Reduction of the Keto-ester* (IV).—A solution of the keto-ester (0·4 g) in 1% methanolic potassium hydroxide (60 ml) was refluxed for 1·5 h with sodium borohydride (0·6 g). The solution was concentrated *in vacuo*, diluted with water, and filtered. Chromatography of the solid over silica gel in chloroform–methanol (97 : 3) gave in the initial fractions, dl-*mappicine* (60 mg), m.p. 270—271° (from methanol), $\nu_{max.}$ (KBr) 3260 and 1660 cm$^{-1}$ (Found: C, 74·0; H, 6·2. $C_{19}H_{18}N_2O_2$ requires C, 74·5; H, 5·9%). This sample was identical in t.l.c., u.v., n.m.r., and mass spectra with the natural alkaloid. Further elution of the column with chloroform–methanol (95 : 5) yielded the *diol* (VI) (17-hydroxymappicine) (60 mg), m.p. 258—260° (decomp.) (from chloroform–methanol), $\nu_{max.}$ (KBr) 3420br, and 1660 cm$^{-1}$ (Found: C, 65·5; H, 6·1. $C_{19}H_{18}N_2O_3,2MeOH$ requires C, 65·3; H, 6·8%), *m/e* 322 ($M^+$, 30%), 304 (30), 293 (30), 289 (60), 286 (25), 275 (25), 261 (40), 249 (20), 248 (100), 247 (20), 219 (40), 218 (30), 205 (25), and 191 (15).

*Attempted Asymmetric Reduction of the Keto-ester* (IV).—Lithium aluminium hydride (180 mg) in ether (20 ml) was refluxed for 1 h with 3-*O*-benzyl-1,2-*O*-cyclohexylidene-α-D-glucofuranose.[7] To the complex was added the keto-ester (IV) (0·5 g) in tetrahydrofuran (25 ml). The solution was refluxed for 2 h and worked up as usual. Chromatography of the product over silica gel in chloroform gave the diol (VI) identical with the foregoing sample.

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* The alkaloid numbering system [see (II)] is used in assigning protons.