Studies on the Syntheses of Heterocyclic Compounds. Part DCXXII.† Total Synthesis of (±)-Mappicine [7-(1-Hydroxypropyl)-8-methylindolizino[1,2-*b*]quinolin-9(11*H*)-one]

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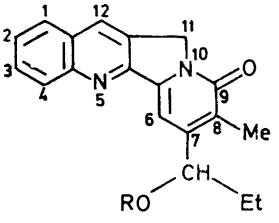
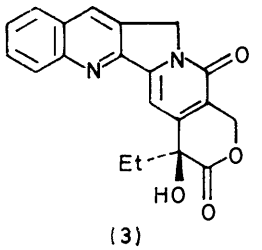
Methyl 9,11-dihydro-9-oxoindolizino[1,2-*b*]quinoline-7-carboxylate (4) was converted into its 8-methyl derivative (5), reduction of which gave 7-hydroxymethyl-8-methylindolizino[1,2-*b*]quinolin-9(11*H*)-one (9). This was converted into (±)-mappicine (1) by way of the 7-carbaldehyde (13) and the 7-propionyl derivative (14).

GOVINDACHARI and his co-workers have recently reported the isolation of a new alkaloid, mappicine (1), as a minor component, in addition to the antileukaemic and antitumour alkaloid (+)-camptothecin (3) from *Mappia foetida*. The structure of mappicine was elucidated by a combination of spectral methods and partial synthesis from camptothecin.[1] The fact that mappicine would be expected to show antitumour activity in the light of its structural relationship to camptothecin,[2] led us to attempt its total synthesis, which we now report. The route involved a new pyridone ring methylation with diazomethane.

Since a large-scale synthesis of methyl 9,11-dihydro-9-oxoindolizino[1,2-*b*]quinoline-7-carboxylate (4) (a popential precursor of camptothecin) was available,[3] we examined the synthesis of mappicine from this ester. The critical step was the introduction of a methyl group on the pyridone ring. Recently, Pelletier and his associates reported a synthesis of 3-methoxycarbonyl-2-methylbut-2-en-4-olide by the reaction of methyl 2,5-dihydro-5-oxofuran-3-carboxylate with diazomethane.[4] Application of this method to compound (4) gave a mixture of the 8-methyl derivative (5) (39%) and the cyclopropane derivative (15) (40%), easily separated by recrystallisation from chloroform–ether. Compound (5) was identified by its spectral and analytical data. The



(1) R = H
(2) R = Ac



(3)

position of the methyl group was determined by comparison of the n.m.r. spectra of the 7-acetates (10) and (11),[5] the former of which was prepared in 0.4% yield

† Part DCXXI, T. Kametani, S. Shibuya, R. Charubala, M. S. Premila, and B. R. Pai, *Heterocycles*, 1975, **3**, 439.

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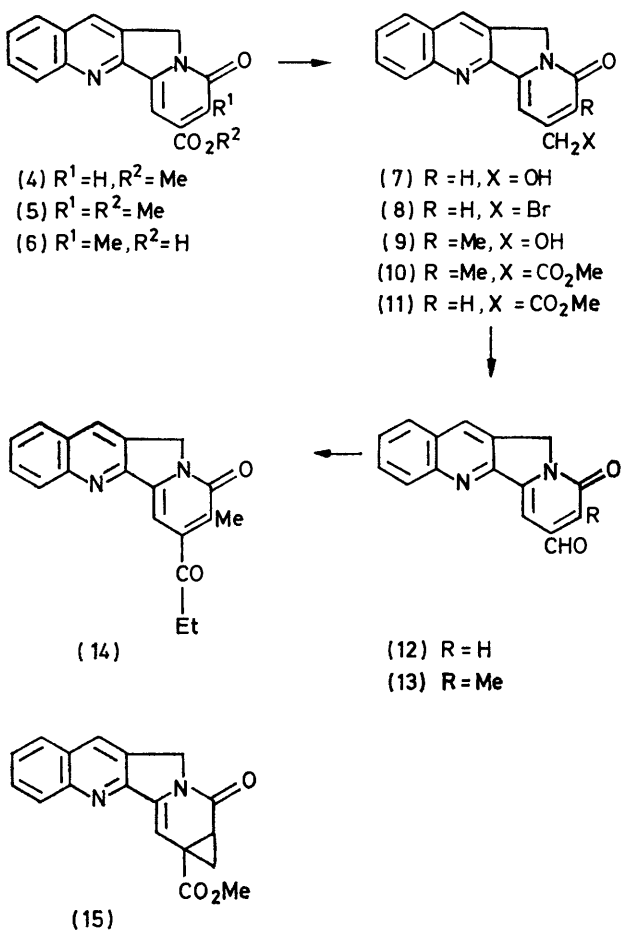
from (5) by Arndt–Eistert reaction *via* the carboxylic acid (6). Compound (11) showed the 8-proton signal at δ 6.6, but this signal was lacking in the spectrum of (10). The presence of a cyclopropane ring in compound (15) was indicated by characteristic n.m.r. signals [6] (see Experimental section); a resonance attributable to a pyridone proton at the 8-position was not observed. This reaction appears to be a useful method for introduction of a methyl group at C-3 of a 2-oxopyridine-4-carboxylate.

We next examined the conversion of the methoxycarbonyl group into a formyl function on the pyridone



ring, and attempted to synthesise 7-formylindolizino-[1,2-*b*]quinolin-9(11*H*)-one (12) from compound (4) as a model experiment. Reduction of (4) with lithium borohydride [7] in bis-(2-methoxyethyl) ether at 100 °C for 3 h gave the alcohol (7), which was oxidised by manganese dioxide to the aldehyde (12). The alcohol (7) was also converted by hydrobromic acid into the bromide (8), a possible precursor of compound (11) which was transformed into camptothecin (3) by Danishefsky and his co-workers.[5]

Similarly, compound (5) was reduced with lithium borohydride [7] to give the alcohol (9) in 63% yield. Oxidation with dimethyl sulphoxide and acetic anhydride [8] at 90—100 °C for 4 h then afforded the aldehyde (13) in 70% yield. Treatment of the aldehyde (13) with diazoethane [9] in chloroform and ether at 0 °C for 2 h gave the ethyl ketone (14) in 90% yield and reduction of this with sodium borohydride in methanol afforded (±)-mappicine (1) in 70% yield. The i.r. and mass spectra were closely similar to those reported for natural mappicine.[1] Acetylation of (±)-mappicine (1) with acetic anhydride–pyridine gave mappicine acetate (2), identical with an authentic sample provided by Dr. Govindachari. Moreover, a Grignard reaction of the aldehyde (13) with ethylmagnesium bromide in ether–tetrahydrofuran also gave (±)-mappicine (1), isolated and purified as its acetate (2) (0.9%).

EXPERIMENTAL

M.p.s were measured with a Yanagimoto micro-apparatus (MP-S2). I.r. spectra were taken with a Hitachi 215 grating spectrophotometer, n.m.r. spectra with JEOL PMX-60 and JEOL JNM-PS-100 spectrometers (tetramethylsilane as internal standard), mass spectra with a Hitachi RMU-7 spectrometer, and u.v. spectra with a Hitachi 124 spectrometer.

Methyl 9,11-Dihydro-8-methyl-9-oxoindolizino[1,2-b]-*quinoline-7-carboxylate* (5).—To a solution of methyl 9,11-dihydro-9-oxoindolizino[1,2-*b*]quinoline-7-carboxylate (4) [3] (2 g) in chloroform (500 ml) and methanol (100 ml) was added an excess of diazomethane in ether [prepared [10] from *N*-methyl-*N*-nitrosotoluene-*p*-sulphonamide (30 g)] at 0 °C and the mixture was left for 24 h at room temperature. Solvent was distilled off *in vacuo* and the residue was recrystallised from chloroform–ether to give the 8-methyl derivative (5) (800 mg, 39%) as *prisms*, m.p. 251—253° (Found: C, 69.6; H, 4.5; N, 9.35. $C_{18}H_{14}N_2O_3$,0.25H_2O requires C, 69.55; H, 4.55; N, 9.0%), $\nu_{max.}$ (KBr) 1 725 (CO_2Me) and 1 650 cm^{-1} (CO·N), δ ($CDCl_3$) 2.48 (3 H, s, ArMe), 3.95 (3 H, s, CO_2Me), 5.16 (2 H, s, $ArCH_2$·N), 7.45 (1 H, s, 6-H), and 7.53—8.30 (5 H, m, ArH), *m/e* 306 (M^+).

The mother liquor from recrystallisation was evaporated to afford *methyl* 6a,7,7a,10-*tetrahydro*-8-*oxocyclopropa*[6,7]-*indolizino*[1,2-b]*quinoline*-6a-*carboxylate* (15) (820 mg, 40%) as prisms (from methanol), m.p. 213—215° (Found: C, 70.45; H, 4.55; N, 8.95. $C_{18}H_{14}N_2O_3$ requires C, 70.6; H, 4.6; N, 9.15%), $\lambda_{max.}$ (MeOH) 290sh, 246, 231, and 224 nm, $\nu_{max.}$ ($CHCl_3$) 1 730 (CO_2Me) and 1 655 cm^{-1} (CO·N), δ ($CDCl_3$) 1.05 (1 H, q, *J* 4 and 6 Hz, cyclopropane H), 2.30 (1 H, q, *J* 4 and 10 Hz, cyclopropane H), 2.83 (1 H, *J* 6 and 10 Hz, cyclopropane H), 3.87 (3 H, s, CO_2Me), 4.97 and 5.03 (each 1 H, d, *J* 16 Hz, $ArCH_2$·N), 6.90 (1 H, s, 6-H), and 7.36—8.36 (5 H, m, ArH), *m/e* 306 (M^+).

Methyl 9,11-Dihydro-8-methyl-9-oxoindolizino[1,2-b]-*quinolin-7-ylacetate* (10).—A mixture of the methyl ester

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(5) (70 mg) and 10% hydrochloric acid (10 ml) was refluxed for 1 h and then the excess of hydrochloric acid was removed by distillation *in vacuo* to give the crude carboxylic acid (6). Thionyl chloride (3 ml) was added and the mixture was heated under reflux for 1 h. The excess of reagent was distilled off *in vacuo* and the residue was dissolved in chloroform (100 ml). To this solution was added an excess of diazomethane in ether [10] at 0 °C; the mixture was stirred for 1 h at 0 °C and then left at room temperature overnight. The solvent was removed and the residue was dissolved in methanol (200 ml). Silver oxide (50 mg) was added and the mixture was heated at 55—60 °C with stirring for 3 h in a current of nitrogen. Undissolved material was then filtered off and the filtrate was evaporated; the residue was subjected to silica gel thick-layer chromatography in chloroform–methanol (10 : 1 v/v) to give the homo-ester (10) (1 mg) as pale yellow prisms (from methanol), m.p. 289—290°, $\nu_{max.}$ ($CHCl_3$) 1 730 (CO_2Me) and 1 660 cm^{-1} (CO·N), δ ($CDCl_3$) 2.30 (3 H, s, ArMe), 3.75 (2 H, s, CH_2·CO_2Me), 3.78 (3 H, s, CO_2Me), 5.28 (2 H, s, $ArCH_2$·N), 7.30 (1 H, s, 6-H), and 7.55 and 8.26 (5 H, m, ArH), *m/e* 320 (M^+).

7-*Hydroxymethylindolizino*[1,2-b]*quinolin*-9(11H)-*one* (7).—The ester (4) (500 mg) was added to a solution of lithium borohydride in bis-(2-methoxyethyl) ether (75 ml) [from sodium borohydride (120 mg) and lithium chloride (135 mg)] [7] and the mixture was stirred for 3 h at 100 °C in a current of nitrogen. The solvent was removed by distillation *in vacuo* and the residue was diluted with water. The solid which separated was collected and washed with water and methanol to give the alcohol (7) (370 mg, 81%) as *needles* (from chloroform–methanol–ether), m.p. >300° (Found: C, 72.15; H, 4.65; N, 10.25. $C_{16}H_{12}N_2O_2$ requires C, 72.7; H, 4.55; N, 10.6%), $\nu_{max.}$ (KBr) 3 280 (OH) and 1 660 cm^{-1} (CO·N), δ (CF_3·CO_2H) 5.13 (2 H, s, $ArCH_2$·OH), 5.90 (2 H, s, $ArCH_2$·N), 7.61—8.70 (5 H, m, ArH), and 9.37 (1 H, s, ArH), *m/e* 264 (M^+).

7-*Bromomethylindolizino*[1,2-b]*quinolin*-9(11H)-*one* (8).—A suspension of the alcohol (7) (300 mg) in concentrated hydrobromic acid (50 ml) was refluxed for 20 h and the excess of reagent was then distilled off *in vacuo*. The residue was basified with saturated sodium hydrogen carbonate solution and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated to give the *bromide* (8) (120 mg, 32%) as yellow prisms (from chloroform–methanol), m.p. 279—281° (Found: C, 58.55; H, 3.2. $C_{16}H_{11}BrN_2O$ requires C, 58.75; H, 9.4%), $\nu_{max.}$ (KBr) 1 660 cm^{-1} (CO·N), δ ($CDCl_3$–CF_3·CO_2H) 4.50 (2 H, s, $ArCH_2Br$), 5.75 (2 H, s, $ArCH_2$·N), 7.32 (1 H, s, ArH), 7.98—8.55 (5 H, m, ArH), and 9.28 (1 H, s, ArH), *m/e* 326 (M^+) and 328 ($M^+ + 2$, isotope ion).

7-*Formylindolizino*[1,2-b]*quinolin*-9(11H)-*one* (12).—A mixture of the alcohol (7) (17 mg), manganese dioxide (80 mg), and chloroform (70 ml) was refluxed for 20 h in a current of nitrogen. The manganese dioxide was then filtered off and washed with hot methanol. The filtrate and washing were combined and evaporated *in vacuo* and the residue was subjected to silica gel thick-layer chromatography [chloroform–methanol (20 : 1 v.v)] to afford the aldehyde (12) (1 mg, 6%) as an amorphous powder, $\nu_{max.}$ (KBr) 1 700 (CHO) and 1 660 cm^{-1} (CO·N), *m/e* 262 (M^+).

7-*Hydroxymethyl*-8-*methylindolizino*[1,2-b]*quinolin*-9(11H)-*one* (9).—To a solution of lithium borohydride [from sodium borohydride (100 mg) and lithium chloride (110 mg)] [7] in bis-(2-methoxyethyl) ether (50 ml) was added the methyl ester (5) (400 mg), and the mixture was stirred at 100 °C for 1 h in a current of nitrogen. The solvent was distilled off and saturated aqueous ammonium chloride was added to the residue; the separated material was collected and washed with water and methanol to give the *alcohol* (9) (230 mg, 63%) as a powder, m.p. >300°, $\nu_{max.}$ (KBr) 3 270 (OH) and 1 650 cm^{-1} (CO·N), δ (CF_3·CO_2H–$CDCl_3$) 2.30 (3 H, s, ArMe), 5.03 (2 H, s, $ArCH_2$·OH), and 5.73 (2 H, s, $ArCH_2$·N), *m/e* 278 (M^+). The *acetate* gave pale yellow prisms, m.p. 281—282° (from chloroform–ether) (Found: C, 70.15; H, 4.95; N, 8.6. $C_{19}H_{16}N_2O_3$,-$0.33H_2O$ requires C, 70.25; H, 5.1; N, 8.6%).

7-*Formyl*-8-*methylindolizino*[1,2-b]*quinolin*-9(11H)-*one* (13).—A mixture of the alcohol (9) (100 mg), dimethyl sulphoxide (2 ml), and acetic anhydride (1.5 ml) was heated at 90—100 °C for 4 h in a current of nitrogen and then made basic with 10% ammonia and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated and the residue was chromatographed on silica gel. Elution with chloroform–methanol (99 : 1 v/v) gave the *aldehyde* (13) (70 mg, 70%) as yellow prisms (from methanol), m.p. 257—260° (Found: C, 71.45; H, 4.55; N, 9.7. $C_{17}H_{12}N_2O_2$,$0.5H_2O$ requires C, 71.55; H, 4.6; N, 9.8%), $\nu_{max.}$ ($CHCl_3$) 1 690 (CHO) and 1 650 cm^{-1} (CO·N), δ ($CDCl_3$) 2.62 (3 H, s, ArMe), 5.31 (2 H, s, $ArCH_2$·N), and 10.38 (1 H, s, CHO), *m/e* 276 (M^+).

7-*Propionyl*-8-*methylindolizino*[1,2-b]*quinolin*-9(11)-*one* (14).—A solution of diazoethane in ether [from *N*-nitrosoethylurea (50 mg)] [9] was added to the aldehyde (13) (20 mg) at 0 °C. The mixture was set aside for 1.5 h, and the solvent was then distilled off to give the ethyl ketone (14) (20 mg, 90%) as pale yellow *plates* (from methanol), m.p. 237—238° (Found: C, 74.55; H, 5.25; N, 9.3. $C_{19}H_{16}N_2O_2$ requires C, 75.0; H, 5.3; N, 9.2%), $\nu_{max.}$ ($CHCl_3$) 1 705 ($ArCO_2Et$), and 1 660 cm^{-1} (CO·N), δ ($CDCl_3$) 1.37 (3 H, t, *J* 7 Hz, CH_2·CH_3), 2.26 (3 H, s, ArMe), 2.97 (2 H, q, *J* 7 Hz, CH_2·CH_3), 5.23 (2 H, s, $ArCH_2$·N), 7.19 (1 H, s, 6-H), and 7.40—8.47 (5 H, m, ArH), *m/e* 304 (M^+).

(±)-*Mappicine* (1).—Sodium borohydride (10 mg) was added in small portions to a solution of the ethyl ketone (14) (10 mg) in methanol (10 ml) with stirring at room temperature and the mixture was stirred for 3 h at the same temperature, then evaporated. The residue was diluted with aqueous ammonium chloride and extracted with chloroform–methanol (20 : 1 v/v). The extract was washed with water, dried (Na_2SO_4), and evaporated *in vacuo* to afford (±)-mappicine (1) (7 mg, 70%) as pale yellow *prisms* (from methanol), m.p. 271—273° (Found: C, 73.2; H, 5.7; N, 8.85. $C_{19}H_{18}N_2O_2$,$0.33H_2O$ requires C, 73.05; H, 6.0; N, 8.95%), $\nu_{max.}$ (KBr) 3 260 (OH) and 1 660 cm^{-1} (CO·N); $\lambda_{max.}$ (MeOH) 366, 333sh, 291, 253, and 246 nm, δ ($CDCl_3$–CD_3OD) 1.03 (3 H, t, *J* 7 Hz, CH_2·CH_3), 1.71 (2 H, m, CH_2·CH_3), 2.20 (3 H, s, ArMe), 4.85 (1 H, t, *J* 6 Hz, CH·OH), 5.13 (2 H, s, $ArCH_2$·N), and 7.50—8.42 (6 H, m, ArH), *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.

(±)-*Mappicine Acetate* (2).—(a) *From* (±)-*mappicine* (1). A mixture of (±)-mappicine (1) (2 mg), acetic anhydride (1 ml), and one drop of pyridine was heated at 70 °C for 6 h in a current of nitrogen and the excess of reagent was distilled off *in vacuo*. The residue was basified with 10% ammonia and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated to give (±)-mappicine acetate (2) (1 mg) as

pale yellow prisms (from methanol), m.p. 180—181°, $\nu_{max.}$ ($CHCl_3$) 1 730 (OAc) and 1 655 cm^{-1} (CO·N), $\lambda_{max.}$ (MeOH) 366, 333sh, 293, 254, and 247 nm, δ ($CDCl_3$) 0.99 (3 H, t, *J* 7 Hz, CH_2·CH_3), 1.98 (2 H, m, CH_2·CH_3), 2.17 (3 H, s, OAc), 2.37 (3 H, s, ArMe), 5.30 (2 H, s, $ArCH_2$·N), 5.95 (1 H, t, *J* 7 Hz, CHOAc), and 7.37—8.36 (6 H, m, ArH), *m/e* 348 (M^+).

(b) *From the aldehyde* (13). To a solution of the aldehyde (13) (90 mg) in anhydrous tetrahydrofuran (30 ml) was added dropwise an excess of ethylmagnesium bromide in ether at 0 °C with stirring in a current of nitrogen. The mixture was stirred for 4 h at room temperature and then decomposed with saturated aqueous ammonium chloride. The solvent was removed and the residue was extracted with chloroform; the extract was washed with water, dried (Na_2SO_4), and evaporated *in vacuo* to give crude (±)-mappicine, which was acetylated as above to give (±)-mappicine acetate (2) (1 mg), identical with the sample prepared by method (a).

We thank Dr. T. R. Govindachari for spectral data of mappicine and mappicine acetate. We also thank Mrs. H. Hori, Miss A. Ujie, Miss R. Kato, Miss R. Suenaga, and Mr. K. Kawamura, Pharmaceutical Institute, Tohoku University, for microanalyses and spectral measurements, and Dr. K. Okui, Research Laboratories, Chugai Pharmaceutical Co. Ltd., for microanalyses.

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