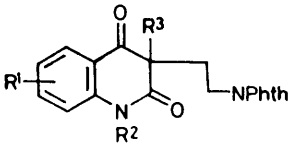
Synthetic Studies on Pyrroloquinolines. Part 5.[1] Preparation of Hydrogenated 3a-Methylpyrrolo[2,3-*b*]quinolines

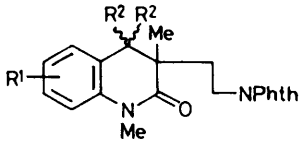
By **Takeo Iwakuma, Michihiko Miyazaki, Kiyohiko Mashimo,** and **Tadasu Tanaka,*** Organic Chemistry Research Laboratory, Tanaba Seiyaku Co. Ltd., Toda, Saitama, Japan
Keiichi Aoe, Masamitsu Nagahashi, Tadamasa Date, and **Keishi Kotera,** Analytical Centre, Tanabe Seiyaku Co. Ltd., Toda, Saitama, Japan

Dissolving-metal reduction of 3-(2-aminoethyl)-1,3-dimethyl-2(1*H*)-quinolone (7a), derived from 7-chloro-1,3-dihydro-1,3-dimethyl-3-(2-phthalimidoethyl)quinoline-2,4-dione (3a) by catalytic hydrogenation followed by removal of the phthaloyl group yielded 2,3,3a,4,9,9a-hexahydro-3a,9-dimethyl-1*H*-pyrrolo[2,3-*b*]quinoline (8a) together with 3-methyl-3-(*o*-methylaminobenzyl)-2-pyrrolidone (9). The latter compound produced starting material (7a) on treatment with dilute acid. The stereochemistry of the B–C ring junction of the 6-methoxy-analogue of (8a) was found to be *cis* by *X*-ray analysis. A facile synthesis of 2,3,3a,4,9,9a-hexahydro-6-methoxy-1,3a-9-trimethyl-1*H*-pyrrolo[2,3-*b*]quinoline (13) has been devised.

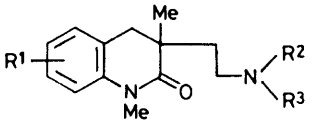
In Part 3 [2] of this series we reported that *C*-methylation occurs in good yield when 7-chloro-1,3-dihydro-3-(2-phthalimidoethyl)quinoline-2,4-dione (1a) is treated with 1 mol of methyl iodide in the presence of anhydrous potassium carbonate in dimethylformamide, giving the 3-methylquinoline-2,4-dione (2). This paper concerns the preparation of hydrogenated 3a-methylpyrrolo-[2,3-*b*]quinolines, having a homologous framework with the basic ring system of physostigma alkaloids, from the quinolone (1a) and its 6-methoxy-analogue (1b).



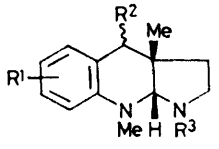
(1a) R^1 = 7-Cl, R^2 = R^3 = H
(1b) R^1 = 6-OMe, R^2 = R^3 = H
(2) R^1 = 7-Cl, R^2 = H, R^3 = Me
(3a) R^1 = 7-Cl, R^2 = R^3 = Me
(3b) R^1 = 6-OMe, R^2 = R^3 = Me



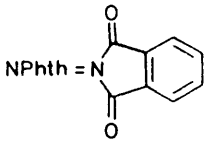
(4a) R^1 = R^2 = R^3 = H
(4b) R^1 = 6-OMe, R^2 = R^3 = H
(5) R^1 = 6-OMe, R^2 = OH, R^3 = H
(6) R^1 = 6-OMe, R^2 = Cl, R^3 = H
(15) R^1 = 6-OMe, R^2 = OMe, R^3 = H



(7a) R^1 = R^2 = R^3 = H
(7b) R^1 = 6-OMe, R^2 = R^3 = H
(11) R^1 = 6-OMe, R^2 = H, R^3 = CO_2Et
(12) R^1 = 6-OMe, R^2 = Me, R^3 = CO_2Et



(8a) R^1 = R^2 = R^3 = H
(8b) R^1 = 6-OMe, R^2 = R^3 = H
(13) R^1 = 6-OMe, R^2 = H, R^3 = Me
(17) R^1 = 6-OMe, R^2 = OMe, R^3 = H



Various attempts for obtaining the 1,3-dimethyldihydroquinolone (4a) from (3a) were unsuccessful, except for catalytic hydrogenation over palladium–charcoal in acetic acid, which gave a poor yield.[3] Therefore, (3b) was converted into the 4-chlorodihydroquinolone (6) by reduction with sodium borohydride in aqueous tetrahydrofuran,[4] followed by chlorination with thionyl chloride in pyridine. Subsequent reductive dechlorination of (6) in hydrogen atmosphere over palladium–charcoal gave the expected (4b) in 40% overall yield from (3b). Removal of the phthaloyl group of (4a) and (4b) by the procedure of Ing and Manske [5] afforded the aminoethyl-dihydroquinolones, (7a) and (7b), almost quantitatively.

Treatment of (7b) with a large excess of sodium in refluxing ethanol [6] gave the 3a,9-dimethylpyrroloquino-

RESULTS AND DISCUSSION

Methylation of (1a) and (1b) with 2 mol equiv. of methyl iodide in dimethyl sulphoxide gave good yields of the 1,3-dimethylquinolinediones, (3a) and (3b), respectively.

line (8b) in 55.6% yield. Its analytical figures and u.v. behaviour, characteristic of the Ph–N–C–N system[7] [$\lambda_{max.}$ (EtOH): 251 (ε 10 321) and 296 (2 064); $\lambda_{max.}$ (23% HCl–EtOH) 230 (ε 78 600), 235 (7 440), and 286 (7 000) nm] supported the planar structure, and *X*-ray crystallographic analysis determined the stereochemistry. A stereo-view of the hydrochloride of (8a) is given in Figure 1.

The bond distances and angles in the molecule were identical with the values normally found. The pattern of torsion angles in the ring system (Figure 2) indicated

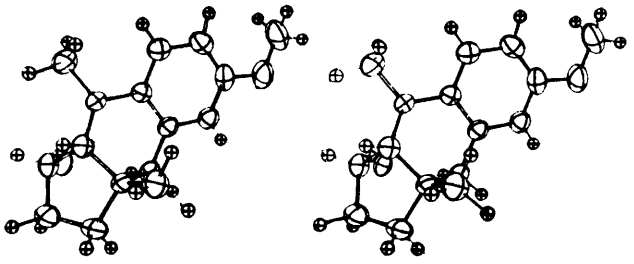


FIGURE 1 Stereoscopic drawing of the molecule (thermal ellipsoids include 50% probability)

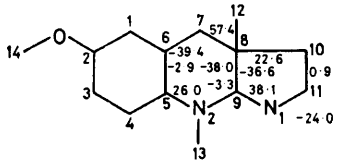
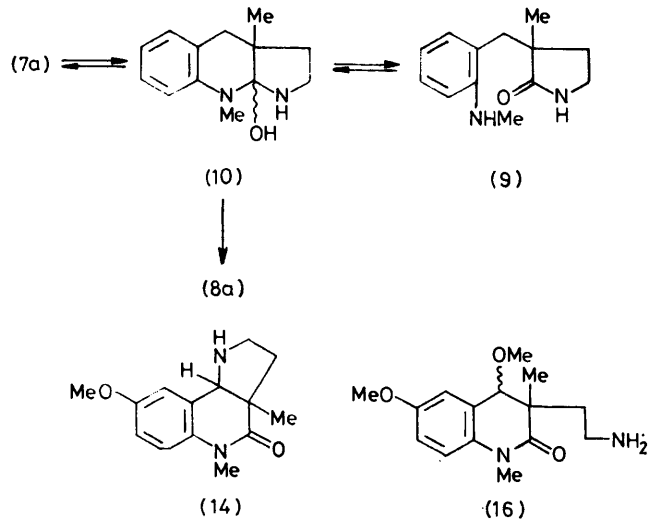


FIGURE 2 Schematic drawing of the ring system showing the torsion angles

that ring B exists in a distorted half-chair conformation and ring C combines with it in an envelope form with a phase angle $\Delta = 32.6$ and a maximum torsion angle $= 39.7°$ [C(11)–N(1)–C(9)–C(8) is taken as ϕ_0].[8] A pair of torsion angles, C(12)–C(8)–C(9)–N(1) (+83.0°) and C(12)–C(8)–C(9)–N(2) (−156.8°), confirmed the B–C ring junction to have a *cis* configuration.

However, the reaction of insufficient sodium with (7a) gave rise to the benzylpyrrolidone (9) in 26.1% yield,



together with 32.1% of (8a). The presence of the pyrrolidone ring was shown by comparison of its i.r. bands [ν(C=O) 1 690 cm^{-1}] with those of the quinolone starting material (7a) [ν(C=O) 1 660 cm^{-1}].[9] Compound (9) quantitatively regenerated (7a) on refluxing in ethanolic hydrochloric acid. This can be explained in terms of *N*–*N'*-transacylation between (7a) and (9) *via* a hypothetical intermediate (10).[10]

Methylation of (8b) by the Clarke–Eschweiler method[11] gave the trimethylpyrroloquinoline (13) in a low yield. This compound was better prepared on the dissolving-metal reduction of the *N*-methylcarbamate (12) derived from (7b) by treatment with ethyl chloroformate in aqueous sodium hydroxide, followed by methylation with methyl iodide in dimethylformamide in the presence of sodium hydride.

An attempt to replace the chlorine atom at the 4-position of (6) by a methylamino-group resulted in the formation of the pyrrolo[3,2-*c*]quinoline (14); the stereochemistry of an analogue of this was discussed in Part 4.[1]

Compound (6) also reacted with methanol at room temperature yielding the 4-methoxydihydroquinolone (15) quantitatively. Although the expected 4-methoxy-3-aminoethyl compound (16) was readily obtained from (15), subsequent reductive cyclisation did not afford the 4-methoxypyrroloquinoline (17), but instead compound (8b) in a fair yield.

EXPERIMENTAL

Unless otherwise stated i.r. spectra were recorded with a JASCO IR-E spectrometer on Nujol mulls, and n.m.r. spectra on a JEOL JNM-MH-60 spectrometer for solutions in deuteriochloroform with tetramethylsilane as internal standard. U.v. spectra were recorded on a Hitachi EPS 2U spectrometer, and mass spectra on a Hitachi RMS-4 spectrometer. All organic solution were dried over anhydrous sodium sulphate. Solvents were removed with a rotary evaporator.

1,3-Dihydro-6-methoxy-3-(2-phthalimidoethyl)quinoline-2,4-dione (1b).—A solution of *p*-anisidine (18.5 g, 0.15 mol) and diethyl (2-phthalimidoethyl)malonate (50.0 g, 0.15 mol) in diphenyl ether (250 ml) was heated at 250—260 °C for 1.5 h while the ethanol produced was distilled off. The mixture was cooled and the product was filtered off and washed with ether to give (1b) (41.5 g, 91.9%) as sandy crystals, m.p. >270 °C (Found: C, 65.8; H, 4.4; N, 7.6. $C_{20}H_{16}N_2O_5$ requires C, 65.9; H, 4.4; N, 7.6%); $\nu_{max.}$ 3 100, 1 755, and 1 720 cm^{-1}.

1,3-Dihydro-6-methoxy-1,3-dimethyl-3-(2-phthalimidoethyl)quinoline-2,4-dione (3b).—To a stirred mixture of compound (1b) (7.28 g, 0.02 mol) and anhydrous potassium carbonate (20.7 g, 0.15 mol) in dimethyl sulphoxide (150 ml), methyl iodide (42.6 g, 0.30 mol) was added dropwise at 13—18 °C. After stirring for 48 h, the mixture was poured into ice–water, extracted with benzene, and dried. The solvent was removed, and the residue washed with ether to give the quinolinedione (3b) (6.0 g, 76.5%) as pale yellow crystals, m.p. 153—154 °C (ethanol) (Found: C, 67.2; H, 5.2; N, 7.53. $C_{20}H_{22}N_2O_5$ requires C, 67.3; H, 5.1; N, 7.1%); $\nu_{max.}$ 1 772, 1 712, 1 684, and 1 650 cm^{-1}, δ 1.40 (3 H,

s), 2.35—2.75 (2 H, m), 3.30 (3 H, s), 3.10—3.50 (2 H, m), 7.05—7.30 (3 H), and 7.60 (4 H, s); *m/e* 392 (M^+).

7-*Chloro*-1,3-*dihydro*-1,3-*dimethyl*-3-(2-*phthalimidoethyl*)-*quinoline*-2,4-*dione* (3a).—This compound was obtained from 7-chloro-1,3-dihydro-3-(2-phthalimidoethyl)quinoline-2,4-dione (1a) [2] in 74.2% yield by using the same procedure as with (1b)→(3b); m.p. 162—163 °C (Found: C, 63.6; H, 4.2; Cl, 8.5; N, 6.9. $C_{21}H_{17}ClN_2O_4$ requires C, 63.5; H, 4.3; Cl, 8.9; N, 7.0%); $\nu_{max.}$ 1 770, 1 710, 1 690, and 1 660 cm^{-1}; δ 1.40 (3 H, s), 2.35—2.68 (2 H, m), 3.33 (3 H, s), 3.70 (2 H, m), 6.90—7.35 (2 H, m), 7.68 (4 H, s), and 7.73 (1 H, d).

3,4-*Dihydro*-1,3-*dimethyl*-3-(2-*phthalimidoethyl*)-2(1H)-*quinolone* (4a).—A solution of (3a) (1.20 g, 0.003 mol) in acetic acid (75 ml) was shaken in a hydrogen atmosphere over 10% palladium–charcoal (1.2 g) at 20—25 °C (uptake 173 ml). The catalyst was filtered off, the solvent was removed, and the residue was purified by preparative t.l.c. (chloroform; silica gel). Two bands developed. From the upper band, (4a) (0.25 g, 24.0%) was obtained as colourless plates, m.p. 136.5—138.5 °C (Found: C, 72.1; H, 5.8; N, 8.0. $C_{21}H_{20}N_2O_3$ requires C, 72.3; H, 5.7; N, 8.0%); $\nu_{max.}$ 1 770, 1 715, and 1 600 cm^{-1}; δ 1.23 (1 H, s), 1.6—2.0 (2 H, m), 2.80—2.88 (2 H, m), 3.28 (3 H, s), 3.55—3.90 (2 H, m), 6.7—7.4 (4 H, m), and 7.40—7.85 (4 H, m). From the lower band, the starting material (0.22 g) was recovered.

3,4-*Dihydro*-4-*hydroxy*-6-*methoxy*-1,3-*dimethyl*-3-(2-*phthalimidoethyl*)-2(1H)-*quinolone* (5).—To a stirred solution of compound (3b) (1.96 g, 0.005 mol) in tetrahydrofuran (30 ml) and water (3 ml), sodium borohydride (0.05 g, 0.0013 mol) was added. After stirring for 24 h at 13—18 °C, the pH of the mixture was adjusted to 6.0 with 10% hydrochloric acid and the solvent was evaporated off. The residue was extracted with chloroform, the extract was washed with water, and then dried. Removal of the solvent left a gum which was triturated with ether giving (5) (1.56 g, 79.1%) as colourless needles, m.p. 163—165 °C (ethyl acetate) (Found: C, 66.8; H, 5.6; N, 7.0. $C_{22}H_{22}N_2O_5$ requires C, 66.9; H, 5.6; N, 7.1%); $\nu_{max.}$ 3 480, 1 762, 1 702, and 1 662 cm^{-1}, δ[$CDCl_3$–$(CD_3)_2SO$] 1.22 (3 H, s), 1.50—2.00 (2 H, m), 3.24 (3 H, s), 3.75 (3 H, s), 3.50—3.90 (2 H, m), 4.45 (1 H, d, *J* 6 Hz), 5.61 (1 H, d, *J* 6 Hz), 6.72—7.05 (3 H), and 7.73 (4 H, s); *m/e* 394 (M^+).

4-*Chloro*-3,4-*dihydro*-6-*methoxy*-1,3-*dimethyl*-3-(2-*phthalimidoethyl*)-2(1H)-*quinolone* (6).—Compound (5) (23.64 g, 0.06 mol) was dissolved in pyridine (100 ml) and thionyl chloride (35.6 g, 0.3 mol) was added dropwise below 20 °C. The mixture was stirred at 15—20° for 3 h, and then poured into ice–water and the separated oil was extracted with benzene. The extract was washed with water, 5% hydrochloric acid, and saturated sodium chloride, and dried. Evaporation of the solvent left crude (5), which was crystallised from benzene–hexane as colourless prisms (16.9 g, 68.4%), m.p. 146—148 °C (Found: C, 63.7; H, 5.2; Cl, 8.3; N, 7.0. $C_{22}H_{21}ClN_2O_4$ requires C, 63.9; H, 5.1; Cl, 8.5; N, 6.7%); $\nu_{max.}$ 1 775, 1 710, 1 668, and 1 650 cm^{-1}; δ 1.20 (3 H, s), 2.00—2.45 (2 H, m), 3.31 (3 H, s), 3.64—4.65 (2 H, m), 3.75 (3 H, s), 4.85 (1 H, s), 6.87 (3 H, s), and 7.50—7.90 (4 H).

3,4-*Dihydro*-6-*methoxy*-1,3-*dimethyl*-3-(2-*phthalimidoethyl*)-2(1H)-*quinolone* (4b).—A solution of compound (6) (0.842 g, 0.002 mol) in monoglyme (25 ml) was shaken with hydrogen in the presence of 10% palladium–charcoal (0.5 g) at room temperature (uptake 46 ml). After filtering off the catalyst, benzene (40 ml) was added to the filtrate and the solution was washed with saturated sodium hydrogencarbonate and dried. Evaporation of the solvent left a gum which was purified by t.l.c. on silica gel [ethyl acetate–hexane (2 : 3)] to give compound (4b) as a colourless resin (0.561 g, 73.1%); $\nu_{max.}$ 1 778, 1 715, and 1 662 cm^{-1}; δ 1.25 (3 H, s), 1.82 (2 H, t, *J* 7 Hz), 2.65 (1 H, d, *J* 16 Hz), 2.97 (1 H, d, *J* 16 Hz), 3.28 (3 H, s), 3.73 (3 H, s), 3.72 (2 H, t, *J* 7 Hz), 6.65 (1 H, d, *J* 7, 5 Hz), 6.70 (1 H, d, *J* 7.5 Hz), 6.75 (1 H, s), and 7.45—7.90 (4 H); *m/e* 378 (M^+).

3-(2-*Aminoethyl*)-3,4-*dihydro*-1,3-*dimethyl*-2(1H)-*quinolone* (7a).—To a solution of compound (4a) (0.98 g, 0.002 8 mol) in dioxan (20 ml) and methanol (10 ml), was added 90% hydrazine (1.8 g, 0.050 mol) and the mixture was refluxed for 3 h. The solvent was removed and the residue was dissolved in acetic acid (20 ml) at 100 °C. To this was added 5% hydrochloric acid (8 ml) and the solution was set aside at room temperature for 16 h. Separated crystals were filtered off, the filtrate was made alkaline with 30% sodium hydroxide, and the separated oil was taken up in chloroform. Evaporation of the solvent gave (7a) as a yellow oil (0.56 g, 92.1%); $\nu_{max.}$ (liquid) 3 550, 3 360, 3 300, 3 190, 1 660, and 1 600 cm^{-1}; δ 1.15 (5 H, s, 2 H were exchangeable with D_2O), 1.4—1.8 (2 H, m), 2.5—3.0 (4 H, m) 6.90 (3 H, s), and 6.75—7.4 (4 H); the hydrochloride had m.p. 200—202 °C (isopropyl alcohol) (Found: C, 61.2; H, 7.3; Cl, 13.8; N, 10.8. $C_{13}H_{19}ClN_2O$ requires C, 61.2; H, 7.5; Cl, 13.9; N, 11.0%).

3-(2-*Aminoethyl*)-3,4-*dihydro*-6-*methoxy*-1,3-*dimethyl*-2(1H)-*quinolone* (7b).—By using the same procedure described above, compound (4b) was converted into (7b), a yellow oil (90.0%); $\nu_{max.}$ (liquid) 3 360, 3 300, and 1 662 cm^{-1}; δ 1.16 (3 H, s), 1.56 (2 H, t, *J* 7 Hz), 1.72 (2 H, br, s exchangeable with D_2O), 2.60—3.00 (2 H, m), 2.71 (2 H, s), 3.26 (3 H, s), 3.74 (3 H, s), and 6.55—6.90 (3 H); *m/e* 248 (M^+).

Reductive Cyclisation of Compound (7a).—To a refluxing solution of compound (7a) (0.50 g, 0.002 3 mol) in anhydrous ethanol (80 ml), sodium (3.45 g, 0.15 g atom) was added in small portions in 1.5 h. The mixture was cooled, water (40 ml) was added and the ethanol was evaporated off. The separated oil was taken up in chloroform and purified by column chromatography on silica gel with chloroform as eluant. The first fraction gave 3-*methyl*-3-(o-*methylaminobenzyl*)-2-*pyrrolidone* (9) (0.13 g, 26.0%), as an oil; $\nu_{max.}$ (liquid) 3 340, 3 220, 2 810, and 1 690 cm^{-1}; δ 1.20 (3 H, s), 1.5—3.6 (6 H, m), 2.68 (3 H, s), 4.2—4.9 (1 H, br s, exchangeable with D_2O), and 6.3—7.3 (5 H, 1H was exchangeable with D_2O). The second fraction afforded 2,3,3a,4,9,9a-*hexahydro*-3a,9-*dimethyl*-1H-*pyrrolo*[2,3-b]-*quinoline* (8a) as a colourless oil (0.14 g, 30.0%); $\nu_{max.}$ (liquid) 3 330, and 1 605 cm^{-1}; δ 1.05 (3 H, s), 1.55 (2 H, t, *J* 6 Hz), 2.45 (3 H, s, 1 H, was exchangeable with D_2O), 2.80 (2 H, t, *J* 6 Hz), 2.83 (3 H, s), 3.90 (1 H, s), and 6.4—7.2 (4 H); *m/e* 202 (M^+); the hydrochloride had m.p. 212.5—213.5 °C (decomp.); the picrate had m.p. 183—184.5 °C (decomp.) (Found: C, 52.6; H, 4.8; N, 16.2. $C_{19}H_{21}N_5O_7$ requires C, 52.9; H, 4.9; N, 16.2%); $\lambda_{max.}$ (EtOH) 244 (ε 13 800), 289 (2 770), 296 (sh.) (2 390), and 327 (390) nm. From the third fraction, the starting material (7a) was recovered (0.12 g).

2,3,3a,4,9,9a-*Hexahydro*-6-*methoxy*-3a,9-*dimethyl*-1H-*pyrrolo*[2,3-b]*quinoline* (8b).—To a boiling solution of compound (7b) (0.50 g, 0.002 mol) in ethanol (200 ml), sodium (6.0 g, 0.26 g atom) was added in small portions during 1 h. After 1 h of refluxing, sodium (3.5 g) was added

again during 30 min, and refluxing continued for a further 30 min. Water was then added to the mixture, the ethanol was evaporated off, and the residue was taken up in benzene. Removal of solvent left an oil; column chromatography on alumina, with chloroform as eluant, yielded compound (8b) as a yellow oil (0.26 g, 55.5%); $\nu_{max.}$ (liquid) 3 360 and 1 592 cm^{-1}; δ 1.08 (3 H, s), 1.48 (2 H, t, *J* 6 Hz), 2.17 (1 H, s, exchangeable with D_2O), 2.42 (2 H, s), 2.74 (2 H, t, *J* 6 Hz), 2.78 (3 H, s), 3.77 (3 H, s), 3.85 (1 H, s), and 6.30—6.70 (3 H); the hydrochloride had m.p. 194—195 °C (decomp.) (Found: C, 62.4; H, 7.7; N, 10.4. $C_{14}H_{21}Cl{\cdot}N_2O$ requires C, 62.5; H, 7.8; N, 10.4%).

Ethyl [2-(1,3-*Dimethyl*-2-*oxo*-1,2,3,4-*tetrahydro*-3-*quinolyl*)-*ethyl*]*methylcarbamate* (12).—To a stirred mixture of compound (7b) (0.87 g, 0.003 5 mol) and 5% sodium hydroxide (24 ml) in benzene (20 ml), was added dropwise ethyl chloroformate (0.90 g, 0.008 3 mol) below 20 °C, and stirring was continued for 1 h. The benzene layer was separated and the solvent was evaporated off to give (11) (1.05 g, 90.5%) as an oil; $\nu_{max.}$ (liquid) 3 330, 1 710, and 1 669 cm^{-1}; *m/e* 320 (M^+). Sodium hydride (66% oil dispersion, 0.20 g, 0.005 mol) was added to a solution of compound (11) (0.8 g, 0.002 5 mol) in dimethylformamide (10 ml) at 12—18 °C. To this was added methyl iodide (0.284 g, 0.005 mol) and the reaction was stirred for 1 h at 20—25 °C. The mixture was poured into ice–water and the separated oil was taken up in benzene. Removal of the benzene gave (12) (0.77 g, 92.2%) as an oil; $\nu_{max.}$ (liquid) 1 695 and 1 660 cm^{-1}; δ 1.17 (3 H, s), 1.22 (3 H, t, *J* 7.5 Hz), 1.72 (2 H, t, *J* 7 Hz), 2.87 (3 H, s), 3.37 (3 H, s), 3.35 (2 H, d, *J* 7 Hz), 3.84 (3 H, s), 4.14 (2 H, q, *J* 7.5 Hz), and 6.70—7.10 (3 H); *m/e* 334 (M^+).

2,3,3a,4,9,9a-*Hexahydro*-6-*methoxy*-1,3a,9-*trimethyl*-1H-*pyrrolo*[2,3-b]*quinoline* (13).—To a boiling solution of compound (12) (0.50 g, 0.001 5 mol) in ethanol (200 ml), was added, during 4.5 h, sodium (12.0 g, 0.52 g atom) in small portions, and refluxing was continued for 1 h. After cooling, water (70 ml) was added to the mixture, and the ethanol was evaporated off. Column chromatohraphy of the residue on silica gel (ethyl acetate as eluant) yielded (13) (0.155 g, 40.1%) as a yellow oil; the oxalate had m.p. 125—128 °C (decomp.) (ethanol–ether) [Found: C, 64.2; H, 8.2; N, 9.2. $C_{15}H_{22}N_2O{\cdot}0.5(COOH)_2{\cdot}0.5H_2O$ requires C, 63.9; H, 8.0; N, 9.3]; $\nu_{max.}$ 2 200—2 700 cm^{-1}; δ 1.11 (3 H, s), 1.90 (2 H, t, *J* 7 Hz), 2.45 (3 H, s), 2.40—2.75 (2 H, m), 3.20 (3 H, s), 3.10—3.40 (2 H, m), 3.82 (3 H, s), 4.46 (1 H, s), and 6.78 (3 H); *m/e* 246 (M^+).

1,2,3,3a,5,9b-*Hexahydro*-8-*methoxy*-3a,5-*dimethyl*-1H-*pyrrolo*[3,2-c]*quinoline* (14).—A solution of compound (6) (2.06 g, 0.005 mol) and 40% methylamine (4.0 g, 0.051 6 mol) in monoglyme (50 ml) was set aside at room temperature for 30 h. The solvent was then evaporated off and the residue was taken up in benzene. The benzene layer was extracted with 10% hydrochloric acid (3 × 30 ml) and the combined acidic layer was made alkaline with 10% sodium hydroxide. The oil which separated was taken up in benzene; this was removed and the remaining oil was triturated with cold ether to give (14) (0.718 g, 58.3%) as colourless crystals, m.p. 124—125 °C (isopropyl ether) (Found: C, 67.9; H, 7.4; N, 11.3. $C_{14}H_{18}N_2O_2$ requires C, 68.2; H, 7.3; N, 11.3%); $\nu_{max.}$ 3 335 and 1 650 cm^{-1}, δ 1.16 (3 H, s), 1.60—2.15 (1 H, m), 2.40—3.20 (3 H, m), 3.40 (3 H, s), 3.70 (1 H, s), 3.83 (3 H, s), and 6.95 (3 H, s); *m/e* 246 (M^+).

3,4-*Dihydro*-4,6-*dimethoxy*-1,3-*dimethyl*-3-(2-*phthalimido-ethyl*)-2(1H)-*quinolone* (15).—A solution of compound (6) (0.412 g, 0.001 mol) in methanol (10 ml) was set aside at room temperature for 4 h and the solvent was then removed. Trituration of the oily residue gave (15) (0.326 g, 80.0%) as colourless prisms, m.p. 131—133 °C (from ethyl acetate–ether) (Found: C, 67.6; H, 6.1; N, 6.9. $C_{23}H_{24}N_2O_5$ requires C, 67.6; H, 5.9; N, 6.8%); $\nu_{max.}$ 1 765, 1 712, and 1 662 cm^{-1}; δ 1.45 (3 H, s), 1.78 (2 H, t, *J* 8 Hz), 3.18 (2 H, t, *J* 8 Hz), 3.35 (6 H, s), 3.84 (3 H, s), 3.90 (1 H, s), 6.82 (1 H, d, *J* 2.5 Hz), 6.97 (1 H, d, *J* 2.5 Hz), 6.97 (1 H, s), and 7.73 (4 H).

3-(2-*Aminoethyl*)-3,4-*dihydro*-4,6-*dimethoxy*-1,3-*dimethyl*-2(1H)-*quinolone* (16).—By using the same procedure as described in the preparation of (7b) from (4b), compound (15) was converted into (16), an oil (91.7% yield); $\nu_{max.}$ (liquid) 3 370, 3 300, and 1 660 cm^{-1}; *m/e* 278 (M^+).

Reductive Cyclisation of Compound.—(16).—To a refluxing solution of (16) (1.25 g, 0.004 5 mol) in anhydrous ethanol (800 ml), was added sodium (3.0 g, 0.136 g atom) in small portions in 8 h. After the solution had been refluxed for a further 1 h, water was added and the solvent was removed. The residue was dissolved in benzene, the solution was washed with water, and then dried. Removal of the solvent left an oil, which was purified by column chromatography on alumina (chloroform eluant). The eluted product (0.59 g, 43.6%) was converted to the hydrochloride and identified with an authentic specimen of (8b) hydrochloride by mixed m.p. and i.r. comparisons.

Crystal Structure Analysis of (8b) *Hydrochloride.*—*Crystal data.* $C_{14}H_{21}ClN_2O$, $M = 268.79$. Ortho rhombic, space group *Pcab*, $a = 12.023(2)$, $b = 30.993(5)$, $c = 7.640(1)$ Å, $U = 2\,847.08$ Å^3; $D_c = 1.254$ g cm^{-3}, $Z = 8$; Cu-K_α radiation (λ 1.541 Å); μ(Cu-K_α) = 6.97 cm^{-1}.

Refinement and solution. A colourless needle crystal elongated along the *c* axis was mounted on a goniometer. Accurate cell parameters were determined by least-squares method using 19 2θ values measured on an automatic four-circle diffractometer AFC/3 (Rigaku). Three-dimensional intensity data were collected on this diffractometer using graphite-monochromated Cu-K_α radiation to $2\theta_{max.} = 130°$. Of 2 803 independent reflections measured, 1 390 having $|F_o| > 3\sigma(|F_o|)$ were considered as observed and were used in the analysis.

The structure was solved by the multi-solution method with the program MULTAN [12] based on 331 reflections with $|E| > 1.60$. The structure was refined by block-diagonal least-squares methods. The quantity minimized was

Atomic co-ordinates for non-hydrogen atoms, with estimated standard deviations in parentheses

Atom	*x*	*y*	*z*
C(1)	5 425(1)	2 972(0)	1 365(2)
C(1)	4 068(4)	4 512(2)	4 338(7)
C(2)	2 991(5)	4 669(1)	4 352(7)
C(3)	2 146(4)	4 416(2)	4 962(7)
C(4)	2 371(4)	3 994(1)	5 526(7)
C(5)	3 449(4)	3 833(1)	5 500(6)
C(6)	4 305(4)	4 097(1)	4 868(6)
C(7)	5 471(4)	3 921(1)	4 881(7)
C(8)	5 659(4)	3 662(1)	6 569(7)
C(9)	4 786(4)	3 306(1)	6 651(6)
C(10)	6 761(4)	3 415(2)	6 510(8)
C(11)	6 519(4)	2 963(2)	5 827(8)
C(12)	5 587(5)	3 956(2)	8 162(7)
C(13)	2 803(4)	3 137(2)	6 745(7)
C(14)	1 773(6)	5 244(2)	3 625(10)
N(1)	3 689(3)	3 411(1)	6 045(5)
N(2)	5 287(3)	2 956(1)	5 471(5)
O	2 869(3)	5 090(1)	3 790(6)

$\Sigma w(|F_o| - |F_c|)^2$. In the final refinement cycles, the anisotropic thermal factors and the isotropic thermal factors were used for the non-hydrogen atoms and the hydrogen atoms, respectively. The refinement was terminated when all shifts were $<0.2\sigma$. In this calculation, four reflections [(0,0,2), (0,1,2), (0,10,0), and (2,2,0)], were deleted because the lack of accuracy was indicated by the counting statistics. Refinement terminated at $R = \Sigma(|F_o|^2 - |F_c|^2)/\Sigma(|F_o^2|)\}$ 0.057 and $R'\{=[\Sigma w||F_o| - |F_c||^2/\Sigma w|F_o|^2]^{1/2}\}$ 0.056. Unit weights were used because a systematic tendency was found for the distribution of $|\Delta|F_1||$. The atomic scattering factors were taken from International Tables.[13]

An ORTEP [14] perspective view of the molecule along the *c* axis, is shown in Figure 1. Calculations were performed on a UNIVAC 1108 computer system. Atomic fractional co-ordinates are in the Table. Observed and calculated structure factors, isotropic and anisotropic thermal parameters, and bond lengths and angles are in SUP 22450.*

We thank Emeritus Professor S. Sugasawa, Tokyo University, and Dr. S. Saito, director of this laboratory, for encouragement, and the staff for instrumental analysis and spectral measurements.

[8/949 *Received*, 22*nd May*, 1978]

* For details see Notice to Authors No. 7, *J.C.S. Perkin I*, 1977, Index issue.

REFERENCES

[1] T. Tanaka, N. Taga, M. Miyazaki, and I. Iijima, *J.C.S. Perkin I*, 1974, 2110.
[2] T. Tanaka, I. Iijima, M. Miyazaki, and T. Iwakuma, *J.C.S. Perkin I*, 1974, 1593.
[3] R. G. Melton, E. J. Eisenbraun, P. W. K. Flanagan, and M. C. Hamming, *Org. Prep. and Procedures*, 1970, **2**, 37.
[4] J. C. Hubert, W. N. Speckamp, and H. O. Huisman, *Tetrahedron Letters*, 1972, **4493**; Z. Horii, C. Iwata, and Y. Tamura, *J. Org. Chem.*, 1961, **26**, 2273.
[5] H. R. Ing and R. F. H. Manske, *J. Chem. Soc.*, 1926, 2348.
[6] P. L. Julian and J. Pikl, *J. Amer. Chem. Soc.*, 1935, **57**, 539.
[7] A. Z. Britten, W. G. Bardsley, and C. M. Hill, *Tetrahedron*, 1971, **27**, 5631; A. H. Jackson and A. E. Smith, *J. Chem. Soc.*, **1964**, 5510.
[8] C. Altona, H. J. Geise and C. Romers, *Tetrahedron*, 1967, **24**, 13.
[9] K. Nakanishi, 'IR Absorption Spectroscopy,' Nankodo, Kyoto, Japan, 1976, p. 51.
[10] P. A. Thio and M. J. Kornet, *J. Heterocyclic Chem.*, 1971, **8**, 479.
[11] A. C. Cope, E. Ciganek, L. J. Fleckenstein, and M. A. P. Meisinger, *J. Amer. Chem. Soc.*, 1960, **82**, 4651.
[12] P. Main, M. M. Woolfson, and G. Germain, 'MULTAN. A Computer Program for Automatic Solution of Crystal Structures,' University of York, 1971.
[13] 'International Tables for *X*-Ray Crystallography,' Kynoch Press, Birmingham, 1974, vol. V, pp. 73—83.
[14] C. K. Johnson, 'ORTEP,' Report ORNL 3794, Oak Ridge National Laboratory, Tennessee, 1965.