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

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Removal of the phthaloyl group from 7-chloro-3-methyl-3-(2-phthalimidoethyl)quinoline-2,4-dione (2) followed by cyclization gave 7-chloro-3,5-dihydro-3a-methyl-2*H*-pyrrolo[3,2-*c*]quinolin-4(3a*H*)-one (3), the C=N bond of which was reduced stereospecifically to give the 3a,9b-*trans*-compound (4) with sodium borohydride at −30 to −20°. Although treatment of compound (4) with lithium aluminium hydride mainly afforded the abnormal reduction product, 7-chloro-3,3a,4,5-tetrahydro-3a-methyl-2*H*-pyrrolo[3,2-*c*]quinoline (7), treatment with aluminium hydride simply reduced the oxo-group to give the *trans*-hexahydropyrroloquinoline (9). The *cis*-isomer (10) was obtained, along with the *trans*-isomer (9), by reduction of compound (7) with sodium borohydride.

In Part III [1] we reported that methylation of 7-chloro-4-hydroxy-3-(2-phthalimidoethyl)-2(1*H*)-quinolone (1) with methyl iodide in the presence of anhydrous potassium carbonate in dimethylformamide gave a good yield of the 3-methyl derivative (2). This paper describes the preparation of hydrogenated 3a-methylpyrrolo[3,2-*c*]-quinolines from compound (2).

The phthaloyl group of compound (2) was readily removed by Ing and Manske's procedure [2] to give the amine hydrochloride, which cyclized to the imino-lactam (3) on neutralization with aqueous sodium hydroxide. Compound (3) was then hydrogenated in ethanol over platinum oxide. Of the three products, two were the stereoisomeric amino-lactams (5) and (6); both showed a mass spectral molecular ion at *m/e* 202, and their i.r. spectra were closely similar in the carbonyl region. Their n.m.r. data are summarized in the Table. Dreiding models disclosed that the isomer showing a methyl signal at higher field was the *trans*-isomer (6), since its methyl group is shielded by the benzene nucleus.[3] The signal of the 9a-proton of the *cis*-isomer appears at high field owing to the diamagnetic anisotropy of the adjacent C(3a)–CH_3 bond,[4] and one of the 3-protons resonates at lower field presumably because it lies in the plane of the amide carbonyl group.[5]

^{1}H N.m.r. data (τ values)

Compound	3-H_a	3-H_b	3a-CH_3	9a-H
(5)	8·05 (m)	7·00 (m)	8·76	6·21
(6)	8·00 (2H, m)		9·10	5·92
(9)			9·30	6·43
(10)			8·96	6·48

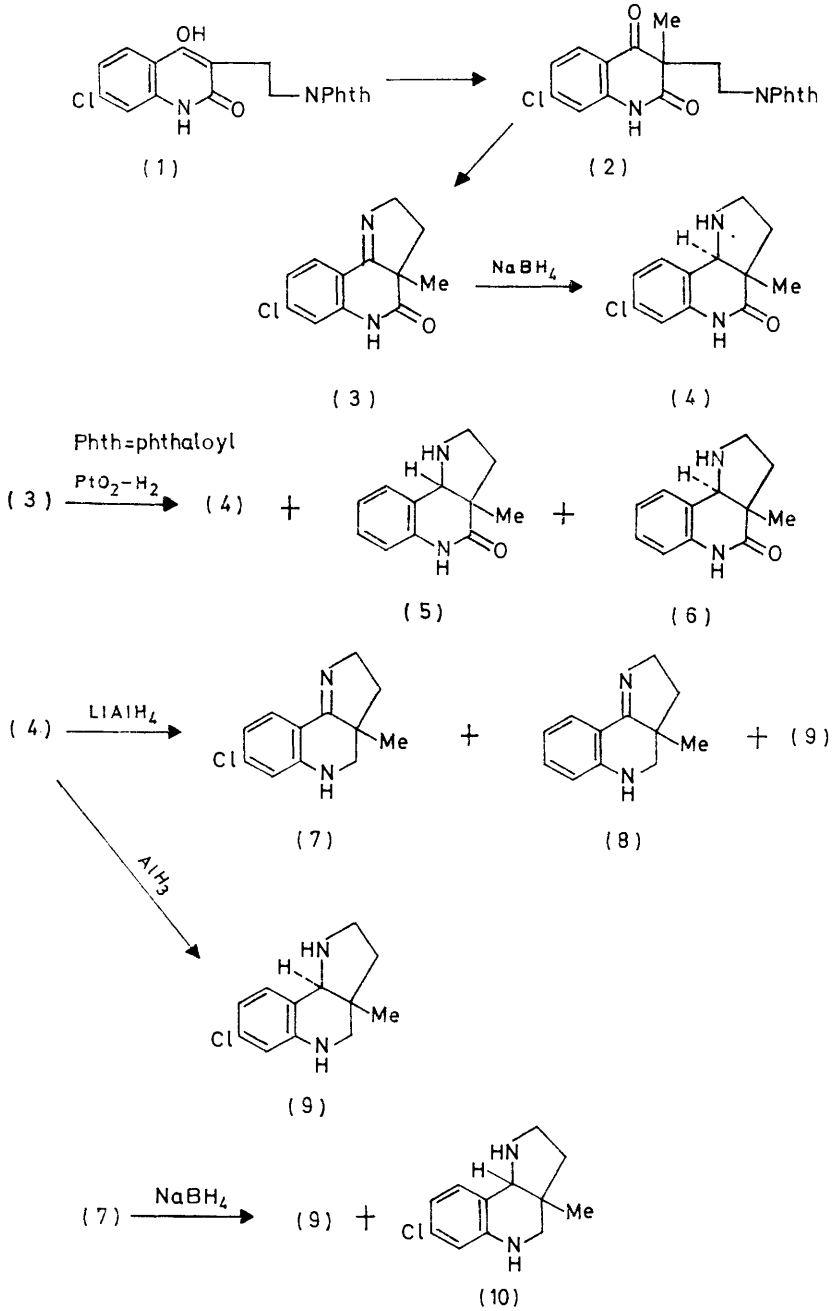
By analogy with the spectral data of the amino-lactam (6), the third product was identified as the 7-chloro-compound (4) with a *trans*-ring junction. This compound was obtained almost quantitatively by reduction

[1] Part III, T. Tanaka, I. Iijima, M. Miyazaki, and T. Iwakuma, *J.C.S. Perkin I*, 1974, 1593.
[2] H. R. Ing and R. F. H. Manske, *J. Chem. Soc.*, 1926, 2348.
[3] L. M. Jackman and S. Sternhell, 'Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry,' Pergamon, Oxford, 1969, p. 94.
[4] (*a*) A. P. Stoll, P. Niklaus, and F. Troxler, *Helv. Chim. Acta*, 1971, **54**, 1992; (*b*) W. Oppolzer and K. Keller, *Tetrahedron Letters*, 1970, 1117.
[5] A. N. Kurtz, W. E. Billups, R. B. Greenlee, H. F. Hamil, and W. T. Pace, *J. Org. Chem.*, 1965, **30**, 1476.

with sodium borohydride in methanol at −30 to −20°; reduction at 20—30° gave a much lower yield. This stereospecific reduction can be explained in terms of attack of borohydride ion on one side only of the C=N bond; attack from the other side would be hindered by the methyl group. The low reaction temperature would favour steric approach control.[6a]

the lack of i.r. absorption in the carbonyl region. The n.m.r. spectrum exhibited a characteristic AMX pattern with peaks centred at τ 3·45 (d, *J* 2 Hz), 3·39 (q, *J* 2 and 9 Hz), and 2·29 (d, *J* 9 Hz) for the 5-, 6-, and 8-protons, respectively, the 8-proton being deshielded by the C=N bond. The third product (5%) was the dechloro-analogue (8).

The mechanism shown in the Scheme seems to account

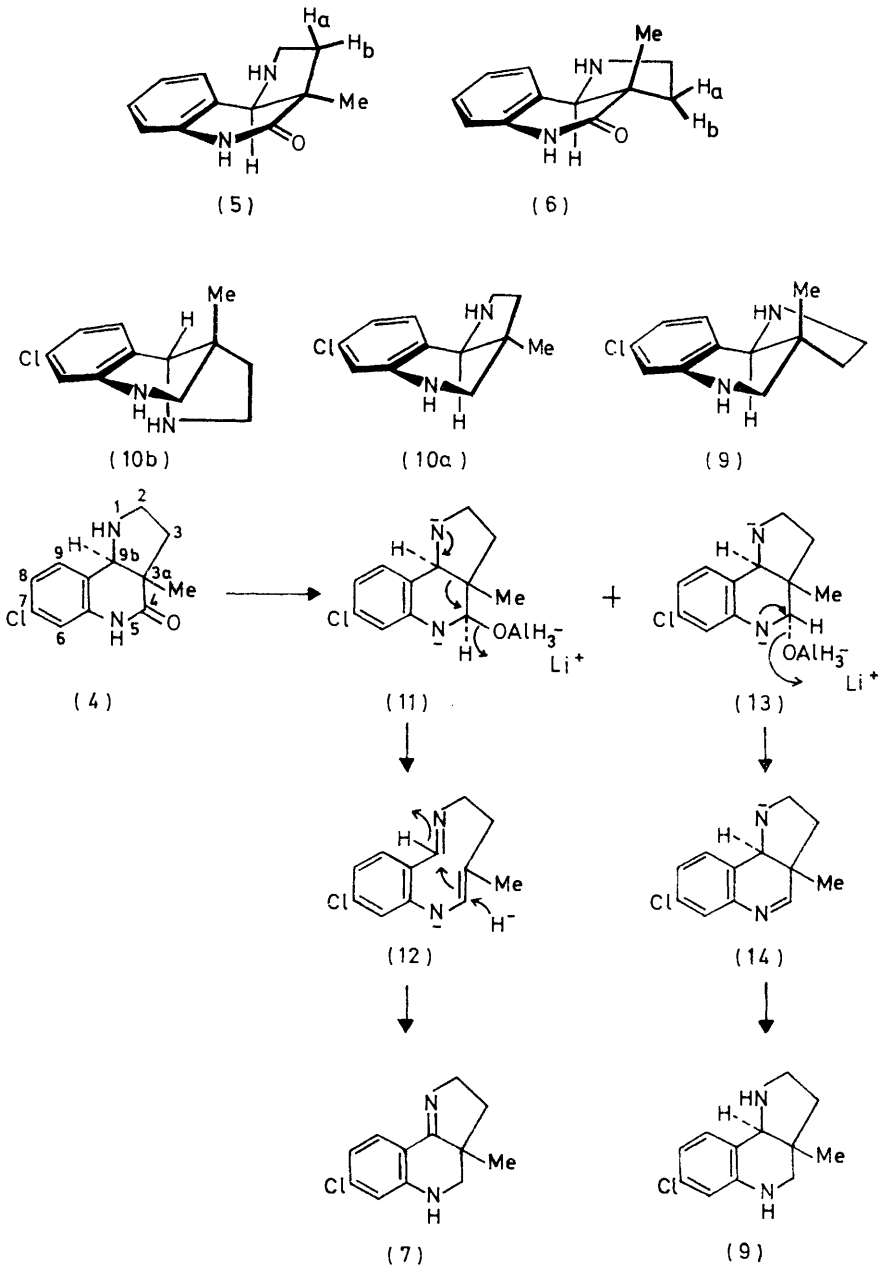


Reduction of the amino-lactam (4) with an excess of lithium aluminium hydride in ether–tetrahydrofuran at reflux temperature gave three products. The expected amine (9) was isolated only as a minor product. The major product (42% yield) was assigned structure (7) on the basis of a mass spectral molecular ion at *m/e* 220 and

best for the results. Attack of the aluminium hydride ion on the amino-lactam (4) would produce two stereoisomeric intermediates, (11) and (13). The one (13) with a quasi-axial $OAlH_3^-$ group would afford the amine (9),

[6] H. O. House, 'Modern Synthetic Reactions,' Benjamin, Menlo Park, California, 1972, (*a*) p. 61; (*b*) p. 79.

according to the general pattern of amide reduction; [6b] the other (11), with a quasi-equatorial $OAlH_3^-$ group would undergo Grob fragmentation,[7] because its C(3a)–C(9b) bond, in conjugation with the *N*-electron pair



SCHEME

at the 1-position, can be antiparallel to the C(4)–O bond, forming an unsaturated nine-membered ring (12). Subsequent recyclization would yield the abnormal product (7), with elimination of hydride ion from C-9b.

The amino-lactam (4) was eventually reduced smoothly with aluminium hydride (alane) to give a 74% yield of the amine (9).

Finally, reduction of the imine (7) with sodium boro-hydride gave, after chromatographic separation, the *cis*-(10) and the *trans*-amine (9) in the ratio 2 : 3. The stereochemistry of these isomers was confirmed by comparison of their n.m.r. data (Table) and by consideration of the pattern of reduction from the amide (4) to the amine (9). The low field methyl signal of the *cis*-form led us to attribute the conformation (10a) to this compound.

[7] C. A. Grob, *Angew. Chem. Internat. Edn.*, 1969, **8**, 535.

EXPERIMENTAL

I.r. spectra were recorded with a JASCO IR-E spectrometer (for Nujol mulls), u.v. spectra with a Hitachi EPS-2U spectrometer, n.m.r. spectra with a JEOL JNM-MH-60 spectrometer (tetramethylsilane as internal standard), and mass spectra with a Hitachi RMS-4 spectrometer.

7-*Chloro*-3,5-*dihydro*-3a-*methyl*-2H-*pyrrolo*[3,2-c]*quinolin*-4(3aH)-*one* (3).—To a solution of compound (2) (20·0 g) in dioxan (450 ml) and methanol (240 ml), hydrazine hydrate (80%; 26·0 g) was added in one portion. The solution was refluxed for 3 h, then evaporated *in vacuo*, and the residue was dissolved in acetic acid (450 ml) at 80°. To this solution was added hydrochloric acid (10%; 70 ml), and the resulting solution was refluxed for 20 min, then cooled at room temperature for several hours. The separated solids were filtered off and the filtrate was basified with aqueous 50% sodium hydroxide. The deposited solids were extracted with chloroform. The organic layer was washed with water, dried, and evaporated to give *compound* (3) (9·7 g, 78%), which afforded prisms, m.p. 265—267° (decomp.) (from ethyl acetate) (Found: C, 61·4; H, 4·8; Cl, 14·85; N, 11·8. $C_{12}H_{11}ClN_2O$ requires C, 61·4; H, 4·7; Cl, 15·1; N, 11·9%), $\nu_{max.}$ 3200, 3100, 3050, 1680, and 1635 cm^{-1}, τ ($CDCl_3$) 8·65 (3H, s, CH_3), 7·55—8·00 (2H, m, 3-H_2), 5·75—6·25 (2H, m, 2-H_2), 2·64—3·11 (2H, 6-H and 8-H), 2·20 (1H, d, J 9 Hz, 9-H), and 0·65 (1H, s, 5-H).

trans-7-*Chloro*-1,2,3,3a,5,9b-*hexahydro*-3a-*methyl*-1H-*pyrrolo*[3,2-c]*quinolin*-4-*one* (4).—To a solution of compound (3) (4·69 g) in methanol (400 ml), sodium borohydride (0·76 g) was added gradually at −30°. After being stirred at the same temperature for 2 h, the mixture was poured into water (200 ml) and extracted with chloroform (50 ml × 3). The combined extracts were washed with water, dried (Na_2SO_4), and evaporated. The *product* (4) crystallized from ether as prisms (4·50 g, 95·1%), m.p. 194—195° (Found: C, 60·95; H, 5·45; Cl, 14·75; N, 11·7. $C_{12}H_{13}ClN_2O$ requires C, 60·9; H, 5·55; Cl, 15·0; N, 11·85%), $\nu_{max.}$ 3195, 3070, and 1690 cm^{-1}, *m/e* 236 (M^+), τ ($CDCl_3$) 9·11 (3H, s, CH_3), 7·52—8·35 (4H, 3-H_2, 1- and 5-H), 6·71 (2H, m, 2-H_2), 5·96 (1H, s, 9b-H), and 2·66—3·17 (3H, 6-, 8-, and 9-H).

Catalytic Hydrogenation of Compound (3).—A solution of compound (3) (0·40 g) in anhydrous ethanol (20 ml) was shaken with hydrogen in the presence of platinum oxide (0·10 g) at room temperature (uptake 38 ml). Filtration and evaporation left a syrupy residue, which was basified with aqueous sodium hydrogen carbonate and extracted with chloroform. The extracts were washed with water, dried, and evaporated to give an oil which was chromatographed on silica gel (chloroform). The first fraction gave compound (4) (0·085 g, 21%) as prisms, m.p. 194—196°. From the second fraction, trans-1,2,3,3a,5,9b-*hexahydro*-3a-*methyl*-1H-*pyrrolo*[3,2-c]*quinolin*-4-*one* (6) (0·04 g, 12%) was isolated as prisms, m.p. 162—163° (from ether) (Found: C, 71·0; H, 6·7; N, 13·9. $C_{12}H_{14}N_2O$ requires C, 71·25; H, 7·0; N, 13·85%), $\nu_{max.}$ 3200, 3120, 3060, and 1670 cm^{-1}. The last fraction afforded cis-1,2,3,3a,5,9b-*hexahydro*-3a-*methyl*-1H-*pyrrolo*[3,2-c]*quinolin*-4-*one* (5) (0·069 g, 20%) as prisms, m.p. 178—179° (from benzene) (Found: C, 71·3; H, 6·8; N, 13·7%), $\nu_{max.}$ 3200, 3100, 3050, and 1655 cm^{-1}.

Reduction of Compound (4).—(a) *With lithium aluminium hydride*. To a stirred suspension of lithium aluminium hydride (0·076 g) in anhydrous tetrahydrofuran (5 ml), a solution of compound (4) (0·472 g) in tetrahydrofuran (5 ml) was added dropwise at 2—5°. The ice-bath was removed and the mixture was refluxed at 40° for 7 h. Then more reagent (0·076 g) was added and stirring was continued for 3 h. The mixture was decomposed with water and the separated solids were filtered off. The filtrate was dried (Na_2SO_4) and evaporated to leave an oil, which was purified by t.l.c. on silica gel [chloroform–methanol (10 : 1)]. Four bands developed; from the band of highest R_F (0·7) 7-*chloro*-3,3a,4,5-*tetrahydro*-3a-*methyl*-2H-*pyrrolo*[3,2-c]*quinoline* (7) (0·187 g, 42·6%) was obtained as yellow prisms, m.p. 169—171° (from ethyl acetate) (Found: C, 65·2; H, 5·8; Cl, 16·4; N, 12·6. $C_{12}H_{13}ClN_2$ requires C, 65·3; H, 5·95; Cl, 16·05; N, 12·7%), $\nu_{max.}$ 3230 and 1610 cm^{-1}, $\lambda_{max.}$ (MeOH) 235, 246sh, 266, and 360 nm. The band of R_F 0·6 gave 3,3a,4,5-*tetrahydro*-3a-*methyl*-2H-*pyrrolo*[3,2-c]-*quinoline* (8) (0·02 g, 5·4%) as yellow needles, m.p. 154—155° (from di-isopropyl ether) (Found: C, 77·1; H, 7·5; N, 14·9. $C_{12}H_{14}N_2$ requires C, 77·4; H, 7·6; N, 15·05%), $\nu_{max.}$ 3230 and 1620 cm^{-1}, τ ($CDCl_3$) 8·85 (3H, s, CH_3), 8·04—8·40 (2H, m, 3-H_2), 6·51—6·95 (2H, m, 4-H_2), 5·90—6·26 (2H, m, 2-H_2), 5·86 (1H, s, 5-H), 2·70—3·54 (3H, 6-, 8-, and 7-H), and 2·17 (1H, q, J 2 and 9 Hz, 9-H), *m/e* 186 (M^+). The third band gave the starting material (4) and the band of lowest R_F (0·1) afforded trans-7-*chloro*-2,3,3a,4,5,9b-*hexahydro*-3a-*methyl*-1H-*pyrrolo*[3,2-c]*quinoline* (9) (0·112 g, 25·2%) as prisms, m.p. 163—164° (from ethyl acetate) (Found: C, 64·55; H, 6·95; Cl, 15·6; N, 12·6. $C_{12}H_{15}ClN_2$ requires C, 64·7; H, 6·8; Cl, 15·9; N, 12·6%), $\nu_{max.}$ 3280 cm^{-1}, τ ($CDCl_3$) 9·30 (3H, s, CH_3), 7·9—8·7 (3H, 3-H_2 and NH), 6·56—6·94 (4H, 2- and 4-H_2), 6·43 (1H, s, 9b-H), 6·00 (1H, NH), and 2·70—3·66 (3H, 6-, 8-, and 9-H).

(b) *With alane*. To a solution of aluminium chloride (0·533 g) in anhydrous ether (20 ml) was added a suspension of lithium aluminium hydride (0·456 g) in ether (15 ml) at −10°, and the mixture was stirred at the same temperature for 20 min. The cooling bath was removed and the solution was allowed to come to room temperature. After 1 h a solution of compound (4) (0·473 g) in anhydrous tetrahydrofuran (10 ml) was added dropwise to the alane solution and stirring was continued for 24 h. The mixture was poured onto ice–water and basified with aqueous ammonia, and the deposited solids were filtered off. The organic layer was separated, dried, and evaporated to leave a solid which was recrystallized from ethyl acetate to give compound (9) (0·34 g, 71·9%) as prisms, m.p. 162—164°.

Reduction of Compound (7) *with Sodium Borohydride*.—Sodium borohydride (0·128 g) was added gradually to a stirred solution of compound (7) (0·15 g) in methanol (5 ml) at 10—15°, and the solution was kept at room temperature for 16 h, then warmed at 50° for 2 h. The solvent was removed *in vacuo*, water (10 ml) was added to the residue, and the mixture was extracted with ethyl acetate (30 ml × 4). The combined extracts were dried (Na_2SO_4) and evaporated to leave an oil which was purified by preparative t.l.c. on silica gel [ethyl acetate–methanol (9 : 1)]. The upper band (R_F 0·6) gave the trans-amine (9), identical with the product obtained from the reduction of compound (4) with alane. The lower band afforded the *cis*-amine (10) (0·03 g, 20%) as an oil, $\nu_{max.}$ ($CHCl_3$) 3440 cm^{-1}, *m/e* 222 (M^+), τ ($CDCl_3$) 8·96 (3H, s, CH_3), 8·05—8·42 (2H, m, 3-H_2), 6·7—7·22 (4H, 2- and 4-H_2), 6·48 (1H, s, 9b-H), 5·82 (2H, 1- and 5-H), and 2·72—3·50 (3H, 6-, 8-, and 9-H). The *monopicrate* formed needles, m.p. 217—220° (decomp.) (from ethanol) (Found: C, 47·8; H, 3·7; Cl, 8·05; N, 15·2. $C_{18}H_{16}ClN_5O_7$ requires C, 48·05; H, 3·6; Cl, 7·9; N, 15·55%).

We thank Professor Emeritus S. Sugasawa, Tokyo University, and Mr. M. Yamazaki, director of this laboratory, for discussions and suggestions. We also thank Dr. K. Kotera and the members of the instrumental analysis room for elemental analyses and spectral measurements.

[4/801 *Received*, 22*nd April*, 1974]