Synthetic Studies on Pyrroloquinolines. Part III.[1] Improved Synthesis of 7-Chloro-2,3-dihydro-4-methoxy-1*H*-pyrrolo[2,3-*b*]quinoline and its Conversion into 3a,10b-Diazacyclopenta[*jk*]phenanthrene Derivatives

By **Tadasu Tanaka,* Ikuo Iijima, Michihiko Miyazaki,** and **Takeo Iwakuma,** Organic Chemistry Research Laboratory, Tanabe Seiyaku Co. Ltd., Toda, Saitama, Japan

3-(2-Aminoethyl)-7-chloro-4-methoxy-2-quinolone (7) was prepared by methylation of 7-chloro-4-hydroxy-3-(2-phthalimidoethyl)-2-quinolone and removal of the phthaloyl group. Cyclization of the 3-(2-acetamidoethyl) derivative (9) gave, after hydrolysis, the pyrrolo[2,3-*b*]quinoline (12). An addition reaction with ethyl acrylate followed by reduction with aluminium hydride led to the pyrroloquinolin-1-ylpropanol (14), which was cyclized to the diazacyclopenta[*jk*]phenanthrene (16) *via* the quaternary salt (15). Hydrolysis of compound (16) gave the 6-ketone (17), whose structure was confirmed by its n.m.r. spectrum.

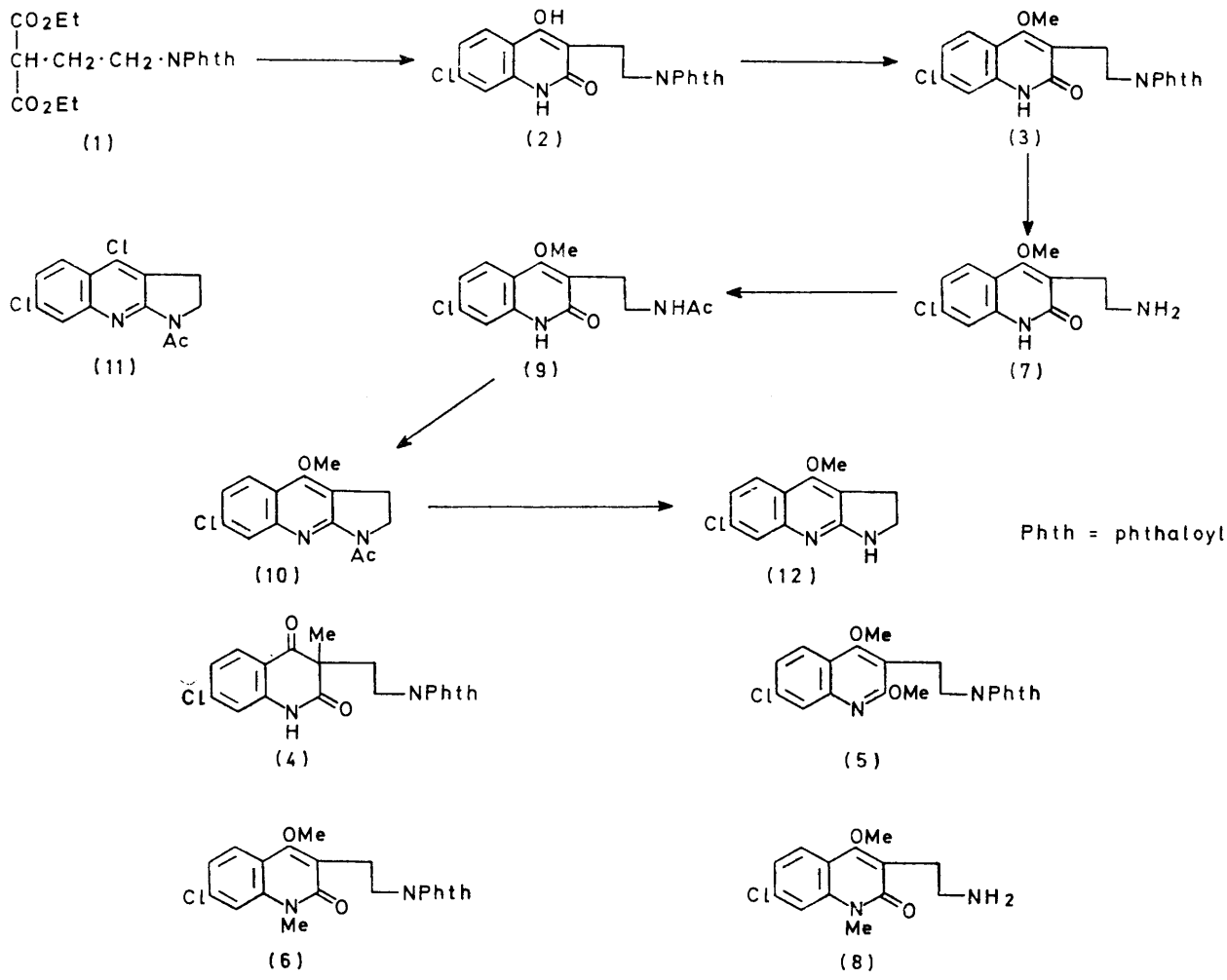
A SERIES of pyrrolo[2,3-*b*]quinoline derivatives[1,2] has been found to possess promising antiphlogistic activity in the rat. We report here an improved method for synthesizing 7-chloro-2,3-dihydro-4-methoxy-1*H*-pyrrolo-[2,3-*b*]quinoline (12), the most active compound of the series, and the preparation from it of 3a,10b-diazacyclopenta[*jk*]phenanthrenes.

Diethyl (2-phthalimidoethyl)malonate (1), readily obtainable from 2-phthalimidoethyl bromide and diethyl sodiomalonate,[3] was condensed with *m*-chloroaniline in diphenyl ether at 240—250° to give 7-chloro-4-hydroxy-3-(2-phthalimidoethyl)-2-quinolone (2) in 94% yield. Methylation of compound (2) with methyl toluene-*p*-sulphonate in anhydrous medium at room temperature gave the 4-methoxy-derivative (3) (93%); the 4-methoxy-1-methyl compound (6) was the predominant product of methylation at 50—60°. Use of dimethyl sulphate gave compound (3) in poorer yield. Methylation with methyl iodide gave mainly the 3-methyl derivative (4), whereas diazomethane gave compound (3) and the 2,4-dimethoxy-derivative (5) in the ratio 3 : 1. These methylation products were identified on the basis of analytical figures and i.r. spectroscopy (McCorkindale's generalization[4] on the carbonyl stretching bands of 2- and 4-quinolones was adopted, though some exceptions have been pointed out by Ishii[5]).

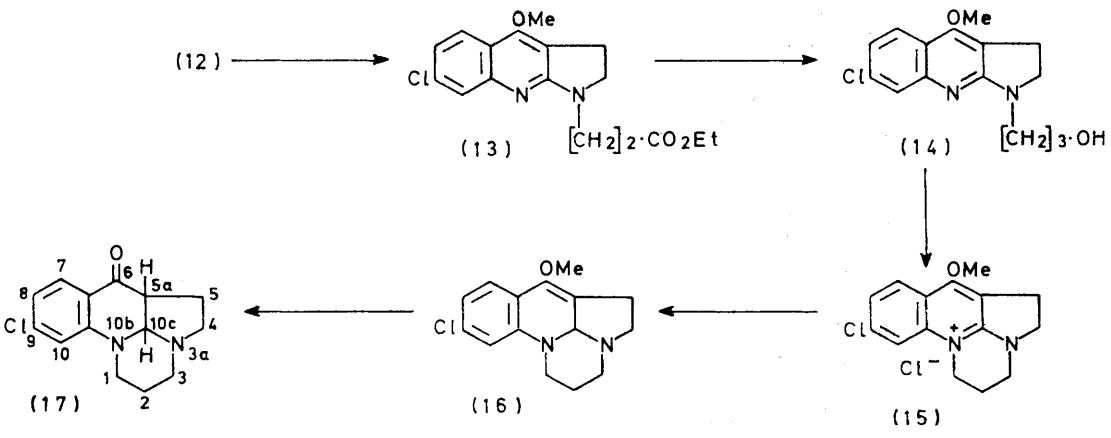
The phthaloyl group of the quinolone (3) was readily removed furnishing the amine (7) (96%). For comparison compound (6) was similarly converted into the amine (8). Although attempted cyclization of the amine (7) with acidic reagents proved fruitless, treatment of its acetyl derivative (9) with phosphoryl chloride containing a few drops of pyridine[7] gave the acetyl compound (10) in 71% yield. Alkaline hydrolysis then led to the pyrroloquinoline (12) in almost quantitative yield. When the pyridine was omitted from the reaction medium, the yield was much lower. Use of more vigorous reaction conditions gave rise to the 4-chloro-compound (11), formed in competition with compound (10).

Condensation of compound (12) with ethyl acrylate in the presence of Triton B yielded the adduct (13) in 70% yield, which was reduced with lithium aluminium hydride in tetrahydrofuran at 5—10°, affording the alcohol (14) in 72% yield [$\nu_{max.}$ 3330 cm^{-1} (OH)]. The alcohol (14) was treated with thionyl chloride in the presence of triethylamine, and the crude product was heated under reflux in benzene to afford the quaternary salt (15). Without purification, the salt was reduced with sodium borohydride in methanol to give the diazacyclopentaphenanthrene (16) in 64% overall yield from the alcohol (14). Its u.v. spectrum indicated that rupture of the quinoline chromophore had occurred and its i.r. spectrum exhibited two sharp Bohlmann bands (2760 and 2720 cm^{-1}) and a band due to C=C stretching conjugated with the benzene ring. Its mass (M^+ 262)

[1] Part II, T. Tanaka, T. Iwakuma, M. Miyazaki, M. Wagatsuma, and I. Iijima, *Chem. and Pharm. Bull. (Japan)*, 1972, **20**, 109.
[2] T. Tanaka, T. Iwakuma, M. Wagatsuma, and I. Iijima, *J. Heterocyclic Chem.*, 1972, **9**, 1355.
[3] R. Riemschneider, K. Brendel, and K. Preuss, *Monatsh.*, 1961, **92**, 1240.
[4] (*a*) N. J. McCorkindale, *Tetrahedron*, 1961, **14**, 223; (*b*) M. F. Grundon, N. J. McCorkindale, and M. N. Rodger, *J. Chem. Soc.*, 1955, 4284; (*c*) B. Witkop, J. P. Patrick, and M. Rosenblum, *J. Amer. Chem. Soc.*, 1951, **73**, 2641.
[5] H. Ishii, *Yagugaku Zasshi*, 1961, **81**, 248.
[6] H. R. Ing and R. F. H. Manske, *J. Chem. Soc.*, 2348, 1926.
[7] N. Ito, K. Irie, Y. Sato, and M. Wada, presented in part at the 93rd Annual Meeting of Pharmaceutical Society of Japan, Tokyo, April 1973.



SCHEME 1



SCHEME 2

and n.m.r. spectra [τ 6·27 (s, OMe) and 6·14 (s, 10c-H)] supported the structure (16).

Finally, the methoxy-derivative (16) was converted into the ketone (17) almost quantitatively by treatment with methanolic 10% hydrogen chloride. The n.m.r. spectrum showed a characteristic downfield shift of the 7-proton signal [τ 2·12 (d, *J* 9 Hz)] in comparison with compound (16), due to the magnetic anisotropy of the newly formed carbonyl group. The 5a,10c-H coupling constant (7 Hz) suggested a *cis* ring junction;[8] addition of deuterium oxide turned the 10c-H signal into a singlet.

EXPERIMENTAL

I.r. spectra were recorded with a JASCO 1R-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-4-hydroxy-3-(2-phthalimidoethyl)-2(1H)-quinolone (2).—A solution of diethyl (2-phthalimidoethyl)malonate (40·0 g, 0·12 mol) and *m*-chloroaniline (15·6 g, 0·12 mol) in diphenyl ether (240 ml) was heated at 250—260° for 3 h while the ethanol produced was distilled off. The solution was cooled and the product was filtered off and washed with ether to give the *quinolone* (2) (41·6 g, 94%), m.p. >270°, as rhombs (Found: C, 61·75; H, 3·65; Cl, 9·7; N, 7·65. $C_{19}H_{13}ClN_2O_4$ requires C, 61·9; H, 3·55; Cl, 9·6; N, 7·6%), $\nu_{max.}$ 3280 (NH), 1755, and 1690 cm^{-1}, τ (CF_3·CO_2D) 1·77 (1H, d, *J* 9 Hz, H-5), 2·26 (1H, d, *J* 2 Hz, H-8), and 2·40 (1H, q, *J* 2 and 9 Hz, H-6).

Methylation of the Quinolone (2).—(a) *With methyl toluene-p-sulphonate and with dimethyl sulphate.* To a stirred mixture of the quinolone (2) (180·0 g, 0·488 mol) and anhydrous potassium carbonate (67·2 g, 0·488 mol) in dimethylformamide (2·5 l), methyl toluene-*p*-sulphonate (197·2 g, 1·07 mol) was added dropwise at 20—25° and stirring was continued for 17 h. After addition of glacial acetic acid (100 g) the mixture was poured into ice–water (*ca.* 1 kg) and the solid was collected, washed with water and benzene, and dried to give *7-chloro-4-methoxy-3-(2-phthalimidoethyl-2(1H)-quinolone* (3) (173 g, 93%), m.p. 258—260° (from methanol–chloroform) (Found: C, 63·05; H, 3·95; Cl, 9·35; N, 7·35. $C_{20}H_{15}ClN_2O_4$ requires C, 62·75; H, 3·95; Cl, 9·5; N, 7·3%), $\nu_{max.}$ 1640 cm^{-1}, τ [$(CD_3)_2SO$] 6·15 (3H, s). When a large excess of this methylating agent was used and the reaction mixture was kept at 50—60°, *7-chloro-4-methoxy-1-methyl-3-(2-phthalimidoethyl)-2(1H)-quinolone* (6) was obtained as the major product (31·7%), accompanied by *7-chloro-2,4-dimethoxy-3-(2-phthalimidoethyl)quinoline* (5) (10·9%) and the quinolone (3) (26·1%), separated by column chromatography on alumina with chloroform as eluant. Compound (5) had m.p. 137—139° (from methanol) (Found: C, 63·8; H, 4·45; Cl, 8·7; N, 7·0. $C_{21}H_{17}ClN_2O_4$ requires C, 63·55; H, 4·3; Cl, 8·95; N, 7·05%), $\nu_{max.}$ 1620 cm^{-1} (C=N), τ [$(CD_3)_2SO$] 6·25 (3H, s, 4-OMe) and 6·10 (3H, s, 2-OMe). Compound (6) had m.p. 212—213° (from acetic acid) (Found: C, 63·65; H, 4·4; Cl, 9·1; N, 7·25. $C_{21}H_{17}ClN_2O_4$ requires C, 63·55; H, 4·3; Cl, 8·95; N, 7·05%), $\nu_{max.}$ 1634 cm^{-1}, τ [$(CD_3)_2SO$] 6·18 (3H, s, OMe) and 6·42 (3H, s, NMe). When methyl toluene-*p*-sulphonate was replaced by dimethyl sulphate under the same reaction conditions, compound (3) (53·7% yield) was the only separable product.

(b) *With methyl iodide.* A mixture of compound (2) (3·68 g, 0·01 mol), anhydrous potassium carbonate (1·38 g, 0·01 mol), and methyl iodide (1·70 g, 0·012 mol) in dimethylformamide (50 ml) was stirred at room temperature for 18 h, then poured into ice–water. The product was filtered off, washed with water, dried, dissolved in chloroform, and purified by column chromatography on alumina (chloroform as eluant). Compound (3) (0·72 g, 18·8%) was eluted first, followed by *7-chloro-3-methyl-3-(2-phthalimidoethyl)-quinoline-2(1H),4(3H)-dione* (4) (2·56 g, 67·0%), m.p. 222—224° (from chloroform) (Found: C, 62·5; H, 3·8; Cl, 9·65; N, 7·25. $C_{20}H_{15}ClN_2O_4$ requires C, 62·75; H, 3·95; Cl, 9·25; N, 7·3%), $\nu_{max.}$ 1760, 1708, 1680, and 1644 cm^{-1}, τ ($CDCl_3$) 8·55 (3H, s, Me).

(c) *With diazomethane.* To a suspension of compound (2) (0·92 g, 0·0025 mol) in anhydrous methanol (14 ml) and chloroform (40 ml), a large excess of ethereal diazomethane (*ca.* 0·025 mol) was added, and the mixture was left at room temperature. After 3 days, insoluble material was filtered off and the filtrate was evaporated *in vacuo*. The residue was purified by fractional recrystallization from chloroform–methanol to give compound (3) (0·21 g, 22·1%), m.p. 260—262° and compound (5) (0·05 g, 5·05%), m.p. 137—139°.

3-(2-Aminoethyl)-7-chloro-4-methoxy-2(1H)-quinolone (7).—To a boiling solution of compound (3) (160·0 g, 0·418 mol) in dioxan (4·80 l) and methanol (2·40 l), 90% hydrazine hydrate (150·0 g, 2·70 mol) was added all at once, and refluxing was continued for 1·5 h. The solvent was evaporated off *in vacuo* and the residue was dissolved in acetic acid (4·0 l) at 80—90°. To the solution was added 10% hydrochloric acid (530 ml) in one portion and the resulting solution was kept at 30° for 16 h. The separated solid was collected, washed with acetone, and dried in air to give the crude *hydrochloride* of *compound* (7) (115 g, 95·1%), m.p. 264—266° (decomp.) (from methanol) (Found: C, 49·4; H, 4·8; Cl, 24·55; N, 9·55. $C_{12}H_{14}Cl_2N_2O_2$ requires C, 49·85; H, 4·9; Cl, 24·5; N, 9·7%), $\nu_{max.}$ 1645 cm^{-1}; the free *base* (7) had m.p. 164—165° (from methanol) (Found: C, 57·3; H, 5·25; Cl, 14·0; N, 11·2. $C_{12}H_{13}ClN_2O_2$ requires C, 57·05; H, 5·2; Cl, 14·05; N, 11·1%).

3-(2-Aminoethyl)-7-chloro-4-methoxy-1-methyl-2(1H)-quinolone (8).—By using the same procedure as described in the preparation of compound (7), compound (6) was converted into the *hydrochloride* of the *quinolone* (8) (87% yield), m.p. 204—205° (Found: C, 51·35; H, 5·5; Cl, 23·5; N, 9·3. $C_{13}H_{16}Cl_2N_2O_2$ requires C, 51·5; H, 5·3; Cl, 23·4; N, 9·25%); the free *base* (8) had m.p. 129—132° (from n-hexane) (Found: C, 58·4; H, 5·8; Cl, 13·4; N, 10·6. $C_{13}H_{15}ClN_2O_2$ requires C, 58·55; H, 5·65; Cl, 13·3; N, 10·5%), $\nu_{max.}$ 1640 cm^{-1}.

3-(2-Acetamidoethyl)-7-chloro-4-methoxy-2(1H)-quinolone (9).—To a stirred solution of compound (7) (20·2 g, 0·08 mol) in glacial acetic acid (50 ml) was added acetic anhydride (12·3 g, 0·12 mol) at 40°. The mixture was stirred for 20 min, the solvent was evaporated off *in vacuo*, and the residue was triturated with methanol (100 ml). The solid was filtered off and dried to give the *product* (9), m.p. 283—285° (decomp.) (from acetic acid–methanol) (Found: C, 56·9; H, 5·2; Cl, 11·9; N, 9·55. $C_{14}H_{15}ClN_2O_3$ requires C, 57·05; H, 5·15; Cl, 12·05; N, 9·5%), τ (CF_3·CO_2D) 5·80 (3H, s, OMe) and 7·72 (3H, s, Ac).

1-Acetyl-7-chloro-2,3-dihydro-4-methoxy-1H-pyrrolo[2,3-b]-quinoline (10).—A stirred suspension of compound (9) (60·0

[8] M. G. Karplus, *J. Chem. Phys.*, 1959, **30**, 11.

g, 0·203 mol) in phosphoryl chloride (180 ml) was kept at room temperature for 46 h, and the excess of phosphoryl chloride was then distilled off *in vacuo* below 30°. Cold aqueous 10% sodium hydroxide (1 l) was added to the residue and the mixture was extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated, and the residue in benzene (40 ml) was chromatographed on alumina (chloroform as eluant). 1-*Acetyl*-4,7-*dichloro*-2,3-*dihydro*-1H-*pyrrolo*[2,3-b]*quinoline* (11), eluted first, was obtained as rhombs, m.p. 191—192° (from benzene) (Found: C, 55·5; H, 3·55; N, 9·85; Cl, 24·75. $C_{13}H_{10}Cl_2N_2O$ requires C, 55·55; H, 3·6; N, 9·95; Cl, 25·2%). Further elution gave *compound* (10) (15·8 g, 26·7%), isolated as needles, m.p. 175—177° (from benzene) (Found: C, 61·0; H, 4·75; Cl, 12·75; N, 10·05. $C_{14}H_{13}ClN_2O_2$ requires C, 60·75; H, 4·75; Cl, 12·8; N, 10·2%), $\nu_{max.}$ 1655 and 1620 cm^{-1}, τ ($CDCl_3$) 5·90 (3H, s, OMe) and 7·25 (3H, s, Ac), followed by 4,7-dichloro-2,3-dihydro-4-methoxy-1H-pyrrolo[2,3-*b*]quinoline, and finally 7-chloro-2,3-dihydro-4-methoxy-1H-pyrrolo[2,3-b]quinoline (12), isolated as sandy crystals, m.p. 224° (decomp.) (from chloroform) (Found: C, 61·1; H, 4·85; Cl, 15·3; N, 11·85. Calc. for $C_{12}H_{11}ClN_2O$: C, 61·4; H, 4·7; Cl, 15·1; N, 11·95%), $\nu_{max.}$ 1628 (C=N), τ [$(CD_3)_2SO$] 5·97 (3H, s, OMe), 2·33 (1H, d, *J* 9 Hz, 5-H), 3·05 (1H, q, *J* 2 and 9 Hz, 6-H), and 2·75 (1H, d, *J* 2 Hz, 8-H), $\lambda_{max.}$ (95% EtOH) 227 (ε 16,800), 246 (24,600), 251 (25,000), 335 (4100), and 343 nm (3900), *m/e* 234 (M^+), identical (i.r. spectrum) with authentic material.[2]

Ethyl 3-(7-*Chloro*-2,3-*dihydro*-4-*methoxy*-1H-*pyrrolo*[2,3-b]*quinolin*-1-*yl*)*propionate* (13).—A mixture of compound (12) (50 g), ethyl acrylate (10 ml), and Triton B (1 drop) was heated in an oil-bath at 100° for 20 h, then cooled. Chloroform (250 ml) was added and the resulting solution was extracted with cold 1% sulphuric acid (4 times). The aqueous layer was neutralized with 3% sodium hydrogen carbonate solution and the separated oil was extracted with chloroform. The extract was evaporated and the residue was crystallized from di-isopropyl ether to give the *product* (13) (5·00 g, 70%) as needles, m.p. 95—97° (Found: C, 60·85; H, 5·7; Cl, 10·65; N, 8·25. $C_{17}H_{19}ClN_2O_3$ requires C, 60·8; H, 5·7; Cl, 10·6; N, 8·35%), $\nu_{max.}$ 1720 cm^{-1}.

3-(7-*Chloro*-2,3-*dihydro*-4-*methoxy*-1H-*pyrrolo*[2,3-b]*quinolin*-1-*yl*)*propan*-1-*ol* (14).—To a stirring suspension of lithium aluminium hydride (4·90 g) in tetrahydrofuran (70 ml), a solution of compound (13) (4·90 g) in tetrahydrofuran (70 ml) was added dropwise at 5—7°. The mixture was kept at room temperature for 1 h, then cooled in ice and decomposed with water. The separated inorganic matter was filtered off and the filtrate dried (Na_2SO_4) and evaporated. The residue gave *compound* (14) (3·10 g, 72·0%) as needles, m.p. 136—138° (from ethyl acetate) (Found: C, 61·45; H, 5·9; Cl, 12·15; N, 9·7. $C_{15}H_{17}ClN_2O_2$ requires C, 61·55; H, 5·85; Cl, 12·1; N, 9·55%), $\nu_{max.}$ 3330 cm^{-1}.

9-*Chloro*-2,3,4,5-*tetrahydro*-6-*methoxy*-1H,10cH-3a,10b-*diazacyclopenta*[jk]*phenanthrene* (16).—To a mixture of compound (14) (2·10 g), chloroform (15 ml), and triethylamine (3 ml), thionyl chloride (10·0 g) was added dropwise at 4—7°. The mixture was allowed to warm to room temperature and left for 16 h. The solvent and the excess of thionyl chloride were removed *in vacuo* and 3% sodium hydrogen carbonate solution was added to the residue. The separated oil was extracted with benzene (30 ml) and the extract was dried (Na_2SO_4) and refluxed for 1 h, yielding a yellow gum (15) insoluble in the solution. The solvent was decanted and the gum was dissolved in methanol (50 ml). Sodium borohydride (0·8 g) in methanol (20 ml) was added at room temperature and the solution was set aside for 16 h. The solvent was evaporated off and the residue was extracted with chloroform. Evaporation of the extract gave a white solid which afforded *compound* (16) [0·28 g, 37·0% from compound (14)] as rhombs, m.p. 144—146° (from ethyl acetate) (Found: C, 65·35; H, 6·25; Cl, 12·55; N, 10·3. $C_{15}H_{17}ClN_2O$ requires C, 65·1; H, 6·2; Cl, 12·8; N, 10·1%), $\nu_{max.}$ ($CHCl_3$) 2760 and 2720 (Bohlmann bands) and 1670 cm^{-1}, τ ($CDCl_3$) 6·30—8·30 (10H, m), 6·27 (3H, s, OMe), 6·14 (1H, s, 10c-H), 3·60 (1H, d, *J* 2·5 Hz, 10-H), 3·52 (1H, q, *J* 8 and 2·5 Hz, 8-H), and (1H, d, *J* 8 Hz, 7-H), *m/e* 276 (M^+).

9-*Chloro*-2,3,4,5,5a,10c-*hexahydro*-1H-3a,10b-*diazacyclopenta*[jk]*phenanthren*-6-*one* (17).—A solution of compound (16) (0·1 g) in methanolic 10% hydrochloric acid refluxed for 5 min then evaporated *in vacuo*. The residue was neutralized with saturated sodium hydrogen carbonate solution and the separated oil was extracted into chloroform. Evaporation of the extract left a solid which crystallized from di-isopropyl ether to give *compound* (17) (0·09 g, 94·8%) as rhombs, m.p. 135—137° (Found: C, 64·05; H, 5·8; N, 10·95. $C_{14}H_{15}ClN_2O$ requires C, 64·0; H, 5·75; N, 10·65%), $\nu_{max.}$ (CCl_4) 2780 and 2720 (Bohlmann bands) and 1660 cm^{-1}, τ ($CDCl_3$) 6·13 (1H, d, *J* 7 Hz, 10c-H), 3·26 (1H, q, *J* 9 and 1·5 Hz, 10-H), and 2·12 (1H, d, *J* 9 Hz, 7-H), *m/e* 262 (M^+).

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

[4/200 *Received*, 1*st February*, 1974]