Studies on the Syntheses of Heterocyclic Compounds. Part 777.† A Synthetic Approach to Seco-mitosane Type of Compound related to Mitomycins

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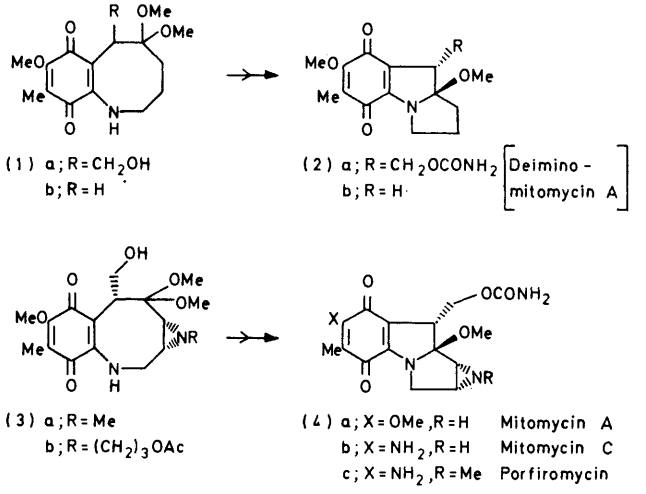
1,2,3,4,5,6-Hexahydro-5,5,8-trimethoxy-9-methyl-1-benzazocine-7,10-dione (1b) has been synthesised from 2,3-dihydro-7-methoxy-6-methyl-1*H*-pyrrolo[1,2-*a*]indole-5,8-dione (10c). The key intermediate, 7,10-diacetoxy-5-trifluoroacetoxy-1-trifluoroacetyl-1,2,3,4,5,6-hexahydro-8-methoxy-9-methyl-1-benzazocine (13b), was prepared by a ring-opening reaction of 5,8-diacetoxy-1,2,9,9a-tetrahydro-7-methoxy-6-methyl-1*H*-pyrrolo-[1,2-*a*]indole (12) with trifluoroacetic anhydride. An alternative route to 1,2,3,4,5,6-hexahydro-1-benzazocine (7d) from 2,3,9,9a-hexahydro-7-methoxy-6-methyl-1*H*-pyrrolo[1,2-*a*]indole (6) has also been devised.

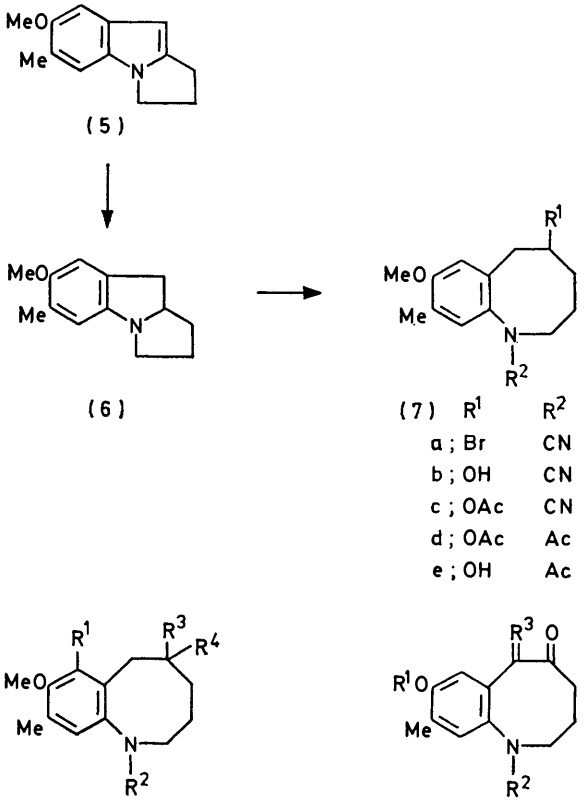
THE first total synthesis of mitomycins [1] (4), anti-tumor antibiotics, was recently accomplished *via* compound (3) by Kishi and his co-workers [2] according to their synthetic route which was used for the synthesis of deiminomitomycin A (2a).[3] During the above reaction the transannular cyclisation of 'the eight-membered quinone' (1a) was thought to be a key step. In a previous paper,[4] we reported the conversion of the pyrrolo[1,2-*a*]indole derivative (5) into 1-cyano-1,3,4,6-tetrahydro-6-methylene-1-benzazocin-5(2*H*)-one (9a) and transannular cyclisation of (9b) into (5). We now wish to describe the synthesis of the eight-membered quinone



SCHEME 1

(1b) from 2,3-dihydro-5,8-dioxo-1*H*-pyrrolo[1,2-*a*]indole-9-carbaldehyde (10a), a precursor of 7-methoxymitosene (10d),[5] by the similar ring-opening method.[4,6]

First the introduction of the quinone function into 1-cyano-1-benzazocine derivatives was examined. Namely, oxidation of the phenolic compound (9c), prepared by an ether cleavage of (9b) with boron tribromide, with Fremy's salt gave no desired *o*-quinone but only recovery of the starting material. Then, reduction of the nitro-compounds (8a) and (8b) was attempted. 1-Cyano-1,3,4,6-tetrahydro-7-nitro-1-benzazocin-5(2*H*)-one (8a) was prepared from (9b) by treatment with nitric acid. 5-Acetoxy-1-cyano-1,2,3,-4,5,6-hexahydro-7-nitro-1-benzazocine (8b) was pre-



SCHEME 2

pared as follows. Sodium borohydride reduction of (9b) gave (7b), the acetylation of which followed by nitration of the resulting acetate (7c) with nitric acid afforded (8b). Reduction of the nitro-compounds (8a)

† Part 776, T. Kametani, K. Kigasawa, M. Hiiragi, N. Wagatsuma, T. Kohagizawa, and H. Inone, *J. Pharm. Soc.*, 1979, **99**, 135.

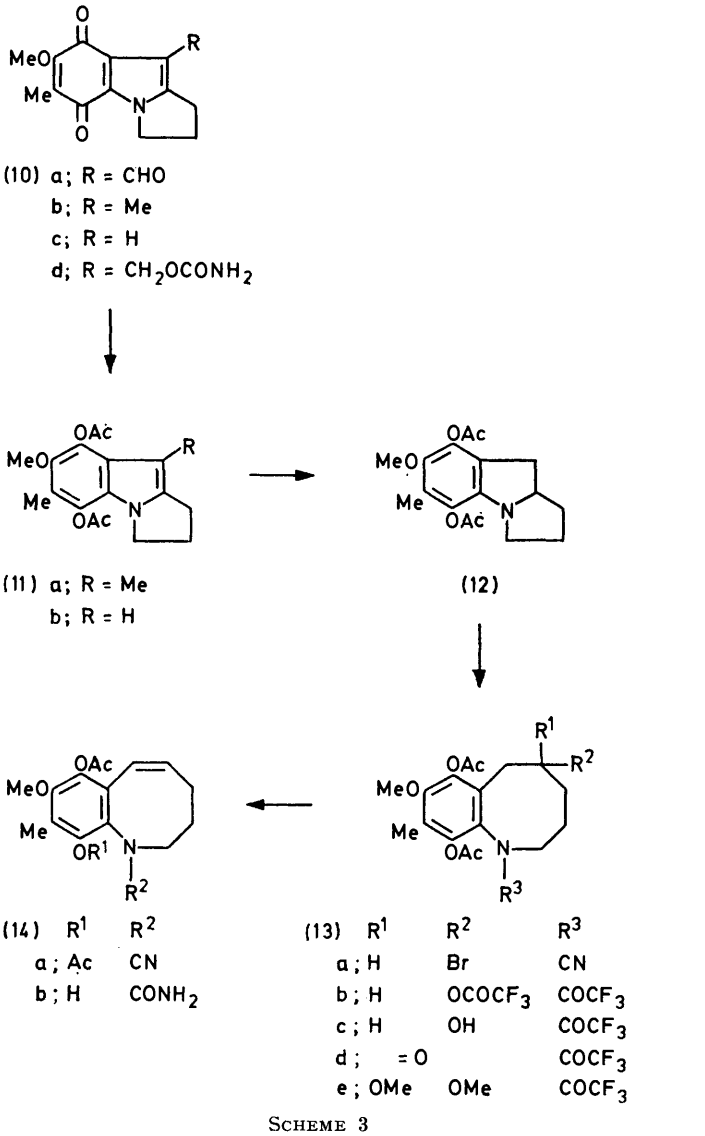
and (8b) gave no desired 7-amino-derivatives but complex mixtures.

Secondly, the transformation of the 1-acetyl-1-benzazocin-5-one (9d) into the quinone was investigated. The eight-membered compound (9d) was synthesised as follows. Heating the indoline (6) with acetic anhydride and sodium acetate yielded the 5-acetoxy-1-acetyl-1,2,3,4,5,6-hexahydro-1-benzazocine (7d). Hydrolysis of the *O*-acetyl groups of this compound (7d) with potassium carbonate in aqueous methanol afforded the alcohol (7e). The n.m.r. spectra of (7d) and (7e) (see Experimental section) indicates the presence of two rotamers [7] about the amide linkage in a ratio of *ca.* 1 : 1. The oxidation of the alcohol (7e) was carried out with chromium trioxide–pyridine complex in dichloromethane at room temperature to give benzazocin-5(2*H*)-one (9d). Although 5-acetoxy-1-acetyl-7-amino-1,2,3,4,5,6-hexahydro-1-benzazocine (8d) could be prepared from (7d) by nitration, followed by reduction of the resulting nitro-compound (8c) in good yield, oxidation of the amine derivative (8d) with Fremy's salt to give the quinone failed.

Finally, the synthesis of the eight-membered quinone (1b) was achieved by the conversion of the indoloquinone (10c) into 7,10-diacetoxy-1-trifluoroacetyl-5,5,8-trimethoxy-1-benzazocine (13e) followed by the removal of the protecting groups. Reduction of the indoloquinone (10b) [8] with sodium borohydride and acetylation of the crude product with acetic anhydride–pyridine yielded (11a). In the same way, the indoloquinone (10c), prepared from the aldehyde (10a) by decarbonylation of the 9-formyl group with tris(triphenylphosphine)chlororhodium, was transformed into the 5,8-diacetoxy-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole (11b). Although sodium borohydride reduction of (11b) in acetic acid had given the indoline (12) in low yield, catalytic hydrogenation of (11b) in the presence of platinum and tetrafluoroboric acid afforded (12) almost quantitatively. A von Braun reaction of the indoline (12) gave 5-bromo-1-cyano-1-benzazocine (13a). On treatment of (13a) with 1,5-diazabicyclo[5.4.0]undec-1-ene, 1-aminocarbonyl-10-hydroxy-1,2,3,4-tetrahydro-1-benzazocine (14b) was obtained in low yield instead of the desired (14a).

At this stage, we selected an alternative route to the benzazocine from the indoline (12). Thus, heating the indoline (12) with trifluoroacetic anhydride in a sealed tube at 150—160 °C for 1.5 h afforded the ring-cleaved compound (13b) in good yield. Hydrolysis of the *O*-trifluoroacetyl group with a solution of sodium hydrogencarbonate in aqueous methanol afforded the alcohol (13c). On treatment of the alcohol (13c) with chromium trioxide–pyridine complex in dichloromethane, the ketone (13d) was obtained. Acetalisation of (13d) was achieved with trimethyl orthoformate in methanol in the presence of boron trifluoride–diethyl ether to give the acetal (13e). Treatment of the acetal (13e) with potassium carbonate in aqueous methanol at room temperature gave only starting material and unidentified products. Removal of the two kinds of acyl groups of (13e) to (1b) was accomplished by treatment of (13e) with lithium aluminium hydride in tetrahydrofuran at room temperature.

Thus, transformation of the indoloquinone (10a), a precursor of 7-methoxymitosene (10d) into the eight-membered quinone has been completed. Furthermore, it was found that transannular cyclisation of (1b) with tetrafluoroboric acid [2] in dichloromethane did not yield (2b) but (10c).



SCHEME 3

EXPERIMENTAL

M.p.s were taken with a Yanagimoto micro-apparatus (MP-S2) and are uncorrected. I.r. spectra were measured with a Hitachi 215 recording spectrophotometer, n.m.r. spectra with a JEOL JNM-PMX 60 spectrophotometer, and mass spectra with a Hitachi M-52G and a JEOL D-300 spectrometers.

1-*Cyano*-1,3,4,6-*tetrahydro*-8-*hydroxy*-9-*methyl*-1-*benzazocin*-5(2H)-*one* (9c).—To a stirred solution of (9b) (24 mg) in dichloromethane (5 ml) was added boron tribromide (5 drops) at −20 °C. After stirring at −20 °C for 3 h,

methanol (1 ml) was added and the reaction mixture was washed with aqueous sodium chloride solution, dried (Na_2SO_4), and evaporated. The residual syrup was chromatographed on alumina (neutral, grade III) with chloroform–methanol (98 : 2 v/v) as an eluant to afford (9c) (13 mg, 57%) as *prisms* (from ethanol), m.p. 164—165 °C (Found: C, 67.65; H, 6.4; N, 12.25. $C_{13}H_{14}N_2O_2$ requires C, 67.8; H, 6.15; N, 12.15%); $\nu_{max.}$ ($CHCl_3$) 3 610 (OH), 2 210 (CN), and 1 705 cm^{-1} (C=O); δ($CDCl_3$) 2.20 (3 H, s, 9-Me), 3.70 (2 H, s, Ar·CH_2·CO), 5.00—5.70br (1 H, OH), and 6.66 and 7.10 (each 1 H, each s, 2 × ArH); *m/e* 230 (M^+).

1-*Cyano*-1,3,4,6-*tetrahydro*-8-*methoxy*-9-*methyl*-7-*nitro*-1-*benzazocin*-5(2H)-*one* (8a).—To a solution of the ketone (9b) (24 mg) in dichloromethane (10 ml) was added fuming nitric acid (*d* 1.50) (0.5 ml) at −20 °C, and the mixture was stirred at −20 °C for 15 min. The reaction mixture was washed with water, dried (Na_2SO_4), and evaporated to give (8a) (25 mg, 88%) as *prisms* (from ethanol), m.p. 136—137 °C (Found: C, 58.05; H, 5.3; N, 14.5. $C_{14}H_{15}N_3O_4$ requires C, 58.1; H, 5.25; N, 14.55%); $\nu_{max.}$ ($CHCl_3$) 2 220 (CN) and 1 715 cm^{-1} (C=O); δ($CDCl_3$) 2.36 (3 H, s, 9-Me), 3.66 (2 H, s, Ar·CH_2·CO), 3.86 (3 H, s, OMe), and 7.44 (1 H, s, ArH); *m/e* 289 (M^+).

1-*Cyano*-1,2,3,4,5,6-*hexahydro*-5-*hydroxy*-8-*methoxy*-9-*methyl*-1-*benzazocine* (7b).—To a stirred solution of the ketone (9b) (244 mg) in methanol (20 ml) was added sodium borohydride (40 mg) at room temperature within 30 min. The solvent was evaporated and the residue was extracted with dichloromethane. The extract was washed with aqueous sodium chloride solution. The organic layer was dried (Na_2SO_4) and evaporated to give the alcohol (7b) (240 mg, 98%) as a *syrup*, $\nu_{max.}$ ($CHCl_3$) 2 210 cm^{-1} (CN); δ(CCl_4) 2.14 (3 H, s, 9-Me), 3.75 (3 H, s, OMe), and 6.64 and 7.00 (each 1 H, each s, 2 × ArH); *m/e* 246 (M^+).

5-*Acetoxy*-1-*cyano*-1,2,3,4,5,6-*hexahydro*-8-*methoxy*-9-*methyl*-1-*benzazocine* (7c).—A mixture of the alcohol (7b) (240 mg), acetic anhydride (2 ml), and pyridine (2 ml) was stirred at room temperature in a current of nitrogen for 15 h. The reaction mixture was poured into ice–water and extracted with dichloromethane. The extract was washed with 10% aqueous hydrochloric acid solution, aqueous sodium hydrogencarbonate solution, and aqueous sodium chloride solution, and then dried (Na_2SO_4) and evaporated. The residue was recrystallised from diethyl ether–n-hexane to afford (7c) (235 mg, 82%) as *prisms*, m.p. 93—95 °C (Found: C, 66.85; H, 7.0; N, 9.75. $C_{16}H_{20}N_2O_3$ requires C, 66.65; H, 7.0; N, 9.7%), $\nu_{max.}$ ($CHCl_3$) 2 210 (CN) and 1 725 cm^{-1} (C=O); δ(CCl_4) 2.00 (3 H, s, Ac), 2.18 (3 H, s, 9-Me), 3.84 (3 H, s, OMe), and 6.62 and 7.06 (each 1 H, each s, 2 × ArH); *m/e* 288 (M^+).

5-*Acetoxy*-1-*cyano*-1,2,3,4,5,6-*hexahydro*-8-*methoxy*-9-*methyl*-7-*nitro*-1-*benzazocine* (8b).—To a stirred solution of the acetate (7c) (30 mg) in dichloromethane (5 ml), fuming nitric acid (*d* 1.50; 0.2 ml) was added at −20 °C. The reaction mixture was stirred at −20 °C for 10 min, washed with water, dried, and evaporated. The residue was recrystallised from n-hexane to give (8b) (31 mg, 89%) as *needles*, m.p. 108—109 °C (Found: C, 57.65; H, 5.7; N, 12.25. $C_{16}H_{19}N_3O_5$ requires C, 57.65; H, 5.75; N, 12.6%); $\nu_{max.}$ ($CHCl_3$) 2 210 (CN), 1 730 (C=O), and 1 530 and 1 370 cm^{-1} (NO_2); δ(CCl_4) 1.98 (3 H, s, OAc), 2.40 (3 H, s, 9-Me), 3.90 (3 H, s, OMe), and 7.54 (1 H, s, ArH); *m/e* 333 (M^+).

5-*Acetoxy*-1-*acetyl*-1,2,3,4,5,6-*hexahydro*-8-*methoxy*-9-*methyl*-1-*benzazocine* (7d).—A mixture of the indoline (6) (3.0 g), sodium acetate (3.0 g), and acetic anhydride (50 ml) was refluxed for 15 h under the nitrogen atmosphere. The reaction mixture was poured into ice–water and extracted with dichloromethane. The organic layer was washed with aqueous sodium hydrogencarbonate solution, dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel to afford (7d) (1.7 g, 38%) as *prisms*, m.p. 126—128 °C (from n-hexane) (Found: C, 67.0; H, 7.7; N, 4.4. $C_{17}H_{23}NO_4$ requires C, 66.85; H, 7.6; N, 4.6%), $\nu_{max.}$ ($CHCl_3$) 1 725 and 1 640 cm^{-1} (C=O); δ(CCl_4) 1.64 and 1.66 (each 1.5 H, each s, >N·$COCH_3$), 2.00 (3 H, s, OAc), 2.18 (3 H, s, 9-Me), 3.86 (3 H, s, OMe), 6.60 and 6.80 (each 0.5 H, each s, ArH), and 6.90 (1 H, s, ArH); *m/e* 305 (M^+).

1-*Acetyl*-1,2,3,4,5,6-*hexahydro*-5-*hydroxy*-8-*methoxy*-9-*methyl*-1-*benzazocine* (7e).—A mixture of the acetate (7d) (305 mg), potassium carbonate (150 mg), water (1 ml) and methanol (30 ml) was stirred at room temperature for 15 h. The reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was dried (Na_2SO_4) and evaporated to leave (7e) (205 mg, 78%) as *needles* (from diethyl ether), m.p. 167—168 °C (Found: C, 68.0; H, 8.2; N, 5.25. $C_{15}H_{21}NO_3$ requires C, 68.4; H, 8.05; N, 5.3%); $\nu_{max.}$ ($CHCl_3$) 1 630 cm^{-1} (C=O); δ(CCl_4) 1.64 and 1.66 (each 1.5 H, each s, >N·$COCH_3$), 2.14 (3 H, s, 9-Me), 3.80 (3 H, s, OMe), 6.70 and 6.76 (each 0.5 H, each s, ArH), and 6.82 (1 H, s, ArH); *m/e* 263 (M^+).

1-*Acetyl*-1,3,4,6-*tetrahydro*-8-*methoxy*-9-*methyl*-1-*benzazocin*-5(2H)-*one* (9d).—To a solution of the chromium trioxide–pyridine complex [prepared from chromium trioxide (0.6 g)] in dichloromethane (20 ml) was added the alcohol (7e) (200 mg) in dichloromethane (30 ml), and the resulting mixture was stirred at room temperature for 10 min. The reaction mixture was washed with 5% aqueous hydrochloric acid solution and aqueous sodium chloride solution, dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel with benzene as an eluant to yield (9d) (165 mg, 83%) as *prisms*, m.p. 148—149 °C (from ethanol–diethyl ether) (Found: C, 69.2; H, 7.55; N, 5.4. $C_{15}H_{19}NO_3$ requires C, 68.95; H, 7.35; N, 5.35%); $\nu_{max.}$ ($CHCl_3$) 1 705 (C=O) and 1 650 cm^{-1} (>N·CO); δ($CDCl_3$) 1.68 (3 H, s, Ac), 2.18 (3 H, s, 9-Me), 3.66 (2 H, s, $ArCH_2$·CO), 3.84 (3 H, s, OMe), and 6.68 and 6.92 (each 1 H, each s, 2 × ArH); *m/e* 261 (M^+).

5-*Acetoxy*-1-*acetyl*-1,2,3,4,5,6-*hexahydro*-8-*methoxy*-9-*methyl*-7-*nitro*-1-*benzazocine* (8c).—A mixture of the acetate (7d), fuming nitric acid (*d* 1.50; 10 ml), and dichloromethane (50 ml) was stirred at room temperature for 2 h. The reaction mixture was washed with water, dried (Na_2SO_4), and evaporated to give a solid, the recrystallisation of which from diethyl ether afforded (8c) (0.98 g, 85%) as *prisms*, m.p. 123—124 °C (Found: C, 58.1; H, 6.3; N, 8.15. $C_{17}H_{22}N_2O_6$ requires C, 58.25; H, 6.35; N, 8.0%); $\nu_{max.}$ ($CHCl_3$) 1 735 (C=O), 1 655 (>N·CO), and 1 530 and 1 375 cm^{-1} (NO_2); δ(CCl_4) 1.66 (3 H, s, >NAc), 1.96 (3 H, s, OAc), 2.36 (3 H, s, 9-Me), 3.86 (3 H, s, OMe), and 7.16 (1 H, s, ArH); *m/e* 350 (M^+).

5-*Acetoxy*-1-*acetyl*-7-*amino*-1,2,3,4,5,6-*hexahydro*-8-*methoxy*-9-*methyl*-1-*benzazocine* (8d).—To a stirred solution of the nitro-compound (8c) (300 mg) in 50% aqueous acetic acid (20 ml) was added iron powder (1 g) during 30 min at 80 °C and the mixture was stirred at 80 °C for 1 h. The mixture was extracted with dichloromethane. The organic layer was washed with water and aqueous sodium hydrogencarbonate solution, dried (Na_2SO_4), and evaporated to leave (8d) (210 mg, 77%) as a *syrup*, $\nu_{max.}$ ($CHCl_3$) 3 500,

3 420 (NH_2), 1 720 (OAc), and 1 640 (>NAc); δ(CCl_4) 1.75 (3 H, s, >NAc), 2.10 (3 H, s, OAc), 2.26 (3 H, s, 9-Me), 3.78 (3 H, s, OMe), 4.60br (2 H, s, NH_2, disappeared with D_2O), and 6.30 (1 H, s, ArH). A portion of this compound was acetylated with acetic anhydride and pyridine in a usual method to yield the acetamide (8e) as *prisms* (from ethanol–diethyl ether), m.p. 156—157 °C (Found: C, 63.1; H, 7.35; N, 7.75. $C_{19}H_{26}N_2O_5$ requires C, 62.95; H, 7.25; N, 7.75%); $\nu_{max.}$ ($CHCl_3$) 3 450 (NH), 1 720 (C=O), and 1 690 and 1 640 cm^{-1} (>N·CO); δ(CCl_4) 1.66 (3 H, s, >N·Ac), 2.00 (3 H, s, OAc), 2.12 (3 H, s, NH·Ac), 2.26 (3 H, s, 9-Me), 3.72 (3 H, s, OMe), 6.90 (1 H, s, ArH), and 8.26br (1 H, s, NH); *m/e* 362 (M^+).

2,3-*Dihydro*-7-*methoxy*-6-*methyl*-1H-*pyrrolo*[1,2-a]*indole*-5,8-*dione* (10c).—A mixture of the aldehyde (10a) (104 mg), tris(triphenylphosphine)chlororhodium (500 mg) and toluene (100 ml) was refluxed under the nitrogen atmosphere for 4 h. The solvent was evaporated and the residue was chromatographed on silica gel with benzene as an eluant to give (10c) (86 mg, 93%) as *red needles* (from ethanol), m.p. 148—149 °C (Found: C, 67.1; H, 5.7; N, 5.8. $C_{13}H_{13}NO_3$ requires C, 67.5; H, 5.65; N, 6.05%); $\nu_{max.}$ ($CHCl_3$) 1 665 and 1 640 cm^{-1} (C=O); δ($CDCl_3$) 1.94 (3 H, s, 6-Me), 2.40—3.10 (4 H, m, 1- and 2-H_2), 4.00 (3 H, s, OMe), 4.24 (2 H, t, *J* 7 Hz, 3-H_2), and 6.24 (1 H, s, 9-H); *m/e* 231 (M^+).

5,8-*Diacetoxy*-2,3-*dihydro*-7-*methoxy*-6-*methyl*-1H-*pyrrolo*-[1,2-a]*indole* (11b).—To a mixture of the quinone (10c) (231 mg), dichloromethane (20 ml), and methanol (2 ml) was added sodium borohydride (100 mg). The reaction mixture was washed rapidly with water and the organic layer was added dropwise to a mixture of acetic anhydride (10 ml) and pyridine (10 ml) in a current of nitrogen. The reaction mixture was stirred at room temperature for 5 h and poured onto ice. The resulting mixture was extracted with dichloromethane. The organic layer was washed with 10% aqueous hydrogen chloride, aqueous sodium hydrogencarbonate solution, and aqueous sodium chloride solution and then dried (Na_2SO_4). Evaporation of the solvent afforded a solid, the recrystallisation of which gave (11b) (265 mg, 80%) as *needles*, m.p. 123—124 °C (from diethyl ether) (Found: C, 64.2; H, 6.1; N, 4.35. $C_{17}H_{19}NO_5$ requires C, 64.35; H, 6.05; N, 4.4%); $\nu_{max.}$ ($CHCl_3$) 1 760 cm^{-1} (C=O); δ($CDCl_3$) 2.16 (3 H, s, 6-Me), 2.38 (6 H, s, 2 × Ac), 3.78 (3 H, s, OMe), 4.06 (2 H, t, *J* 7 Hz, 3-H_2), and 5.98 (1 H, s, 9-H); *m/e* 317 (M^+).

5,8-*Diacetoxy*-2,3-*dihydro*-7-*methoxy*-6,9-*dimethyl*-1H-*pyrrolo*[1,2-a]*indole* (11a).—To a mixture of the quinone (10b) (125 mg), dichloromethane (10 ml), and methanol (2 ml) was added sodium borohydride (40 mg). The reaction mixture was washed rapidly with water and the organic layer was added dropwise to a mixture of acetic anhydride (5 ml) and pyridine (5 ml) in a current of nitrogen. Work-up as above afforded (11a) (126 mg, 75%) as *needles* (from diethyl ether), m.p. 152—153 °C (Found: C, 65.2; H, 6.3; N, 4.2. $C_{18}H_{21}NO_5$ requires C, 65.2; H, 6.4; N, 4.25%); $\nu_{max.}$ 1 760 cm^{-1} (C=O); δ($CDCl_3$) 2.16 and 2.20 (each 3 H, each s, 6- and 9-Me), 2.36 (6 H, s, 2 × Ac), 3.74 (3 H, s, OMe), and 4.02 (2 H, t, *J* 7 Hz, 3-H_2); *m/e* 331 (M^+).

5,8-*Diacetoxy*-2,3,9,9a-*tetrahydro*-7-*methoxy*-6-*methyl*-1H-*pyrrolo*[1,2-a]*indole* (12).—(*a*) A mixture of the pyrroloindole (11b) (1.5 g), platinum oxide (0.1 g), 42% tetrafluoroboric acid (10 ml), ethanol (100 ml), and ethyl acetate (100 ml) was stirred in a current of hydrogen at room temperature for 45 min. The catalyst was filtered off, and the filtrate was diluted with water and extracted with dichloromethane. The organic layer was washed with water and 5% aqueous ammonia solution, dried (Na_2SO_4), and evaporated to give (12) (1.5 g, 99%) as a *syrup*, $\nu_{max.}$ ($CHCl_3$) 1 760 cm^{-1} (OAc); δ(CCl_4) 2.04 (3 H, s, 6-Me), 2.34 (6 H, s, 2 × Ac), and 3.76 (3 H, s, OMe); *m/e* 319 (M^+).

(*b*) To a stirred solution of the pyrroloindole (11b) (31 mg) in acetic acid (2 ml) was added sodium borohydride (300 mg) during 3 h, and the mixture was stirred for additional 15 h. The reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was washed with water, aqueous sodium hydrogencarbonate, and aqueous sodium chloride solution and then dried and evaporated. The product was separated on silica gel thick-layer chromatography to give (12) (8 mg, 26%), which was identical with the above sample.

7,10-*Diacetoxy*-5-*bromo*-1-*cyano*-1,2,3,4,5,6-*hexahydro*-8-*methoxy*-9-*methyl*-1-*benzazocine* (13a).—A mixture of the indoline (12) (1.5 g), cyanogen bromide (1.0 g), and benzene (100 ml) was stirred under nitrogen atmosphere at room temperature for 15 h. The mixture was evaporated and the residue was chromatographed on silica gel with n-hexane–ethyl acetate (85 : 15 v/v) as eluant to afford a solid, the recrystallisation of which gave (13a) (0.97 g, 56%) as *prisms*, m.p. 117—118 °C (from ethanol) (Found: C, 50.85; H, 4.85; N, 6.5. $C_{18}H_{21}BrN_2O_5$ requires C, 50.85; H, 5.0; N, 6.6%); $\nu_{max.}$ ($CHCl_3$) 2 200 (CN) and 1 760 cm^{-1} (OAc); δ(CCl_4) 2.06 (3 H, s, Ar·Me), 3.36 and 3.40 (each 3 H, each s, 2 × OAc), and 3.75 (3 H, s, OMe); *m/e* 426/424 (M^+).

7-*Acetoxy*-1-*aminocarbonyl*-1,2,3,4-*tetrahydro*-10-*hydroxy*-8-*methoxy*-9-*methyl*-1-*benzazocine* (14b).—A mixture of the bromide (13a) (70 mg), 1,5-diazabicyclo[5.4.0]undec-5-ene (50 mg), and dimethyl sulphoxide (5 ml) was stirred at room temperature under a nitrogen atmosphere for 15 h. The reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was dried and evaporated and the residue was chromatographed on silica gel with n-hexane–ethyl acetate (70 : 30 v/v) as eluant to give (14b) (33 mg, 63%) as *needles* (from diethyl ether), m.p. 137—138 °C (Found: C, 60.05; H, 6.15; N, 8.8. $C_{16}H_{20}N_2O_5$ requires C, 60.0; H, 6.3; N, 8.75%); $\nu_{max.}$ ($CHCl_3$) 3 400 (OH), 1 770 (OAc), and 1 690 ($CONH_2$); δ($CDCl_3$) 2.30 and 2.34 (each 3 H, each s, Ac and 9-Me), 3.76 (3 H, s, OMe), 5.50—6.10 (1 H, m, 5-H), and 6.50 (1 H, d, *J* 11 Hz, 6-H); *m/e* 320 (M^+).

7,10-*Diacetoxy*-1,2,3,4,5,6-*hexahydro*-8-*methoxy*-9-*methyl*-5-*trifluoroacetoxy*-1-*trifluoroacetyl*-1-*benzazocine* (13b).—A solution of the indoline (12) (0.8 g) in trifluoroacetic anhydride (25 ml) was heated in a sealed tube at 150—160 °C for 1.5 h. The mixture was evaporated and the residue was chromatographed on silica gel with n-hexane–ethyl acetate (94 : 6 v/v) as eluant to afford a solid, the recrystallisation of which from diethyl ether–n-hexane gave (13b) (1.05 g, 79%) as *needles*, m.p. 106—106.5 °C (Found: C, 47.55; H, 4.15; N, 2.7. $C_{21}H_{21}NO_8F_6$ requires C, 47.65; H, 4.0; N, 2.65%); $\nu_{max.}$ ($CHCl_3$) 1 780 (OAc and $OCOCF_3$) and 1 700 cm^{-1} (>N·CO); δ(CCl_4) 2.06 (3 H, s, Ar·Me), 2.20 and 2.40 (each 1.5 H, each s, OAc),[7] 2.24 (3 H, s, OAc), and 3.76 (3 H, s, OMe); *m/e* 529 (M^+).

7,10-*Diacetoxy*-1,2,3,4,5,6-*hexahydro*-5-*hydroxy*-8-*methoxy*-9-*methyl*-1-*trifluoroacetyl*-1-*benzazocine* (13c).—A mixture of the benzazocine (13b) (1.06 g), sodium hydrogencarbonate (170 mg), methanol (100 ml), and water (10 ml) was stirred at room temperature for 2 h. The reaction

mixture was diluted with water and extracted with dichloromethane. The organic layer was dried and evaporated to afford (13c) as a viscous syrup (820 mg, 95%), $\nu_{max.}$ ($CHCl_3$) 1 760 (OAc), and 1 696 cm^{-1} (>N·CO); δ(CCl_4) 2.10 (3 H, s, Ar·Me), 2.28 and 2.32 (each 3 H, each s, 2 × Ac), and 3.84 (3 H, s, OMe); *m/e* 433 (M^+).

7,8-*Diacetoxy*-1,2,3,4,5,6-*hexahydro*-8-*methoxy*-9-*methyl*-1-*trifluoroacetyl*-1-*benzazocin*-5-*one* (13d).—A mixture of the alcohol (13c) (430 mg), chromium trioxide–pyridine complex [prepared from chromium trioxide (600 mg)], and dichloromethane (30 ml) was stirred at room temperature for 10 min. The mixture was washed with aqueous sodium chloride solution, dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel to afford (13d) (280 mg, 65%) as a viscous syrup, $\nu_{max.}$ ($CHCl_3$) 1 760 (OAc) and 1 705 and 1 700 cm^{-1} (CO and >N·CO); δ(CCl_4) 2.14 (3 H, s, Ar·Me), 2.30 and 2.34 (each 3 H, each s, 2 × Ac), 3.50 (2 H, s, Ar·CH_2·CO), and 3.84 (3 H, s, OMe); *m/e* 431 (M^+).

7,10-*Diacetoxy*-1,2,3,4,5,6-*hexahydro*-5,5,8-*trimethoxy*-9-*methyl*-1-*trifluoroacetyl*-1-*benzazocine* (13e).—A mixture of the ketone (13d) (300 mg), trimethyl orthoformate (100 mg), methanol (10 ml), and boron trifluoride–diethyl ether (2 drops) was stirred at room temperature under a nitrogen atmosphere for 24 h. The reaction mixture was poured into aqueous sodium hydrogencarbonate solution. The resulting mixture was extracted with dichloromethane. The organic layer was dried (Na_2SO_4) and evaporated to leave the *acetal* (13e) (286 mg, 86%) as a viscous syrup (Found: *m/e* 477.1621. $C_{21}H_{26}F_3NO_8$ requires *m/e* 477.163 1), $\nu_{max.}$ ($CHCl_3$) 1 760 (Ac) and 1 695 cm^{-1} (>N·$COCF_3$); δ($CDCl_3$) 2.06 (3 H, s, 9-Me), 2.20 (6 H, s, 2 × Ac), 3.00 and 3.24 (each 3 H, each s, 2 × 5-OMe), and 3.76 (3 H, s, 8-OMe); *m/e* 477 (M^+).

1,2,3,4,5,6-*Hexahydro*-5,5,8-*trimethoxy*-9-*methyl*-1-*benzazocine*-7,10-*dione* (1b).—A mixture of the acetate (13e) (280 mg), lithium aluminium hydride (50 mg), and tetrahydrofuran (5 ml) was stirred at room temperature for 3 h under a nitrogen atmosphere. Excess of lithium aluminium hydride was decomposed with aqueous tetrahydrofuran and the reaction mixture was extracted with dichloromethane. The extract was washed with aqueous sodium chloride solution, dried (Na_2SO_4), and evaporated to leave (1b) (143 mg, 83%) as *violet needles* (from methanol–diethyl ether), m.p. 148—149 °C (Found: C, 60.75; H, 7.2; N, 4.6. $C_{15}H_{21}NO_5$ requires C, 61.0; H, 7.15; N, 4.75%); $\nu_{max.}$ ($CHCl_3$) 3 400 (NH), 1 640, and 1 580 cm^{-1} (C=O); δ($CDCl_3$) 1.80 (3 H, s, 9-Me), 3.16 (6 H, s, 2 × 5-OMe), 4.14 (3 H, s, 8-OMe), and 6.30br (1 H, s, NH); *m/e* 264 (M^+ − OMe).

Transannular Cyclisation of 1,2,3,4,5,6-*Hexahydro*-5,5,8-*trimethoxy*-9-*methyl*-1-*benzazocine*-7,10-*dione* (1b).—A solution of the eight-membered quinone (1b) (15 mg) in dichloromethane (2 ml) was treated with 40% tetrafluoroboric acid (0.05 ml) at room temperature for 2 min. The reaction mixture was washed with aqueous sodium hydrogencarbonate solution, dried (Na_2SO_4), and evaporated to give (10c) (11 mg, 94%) as *red needles*, m.p. 148—149 °C, identical with the sample described above.

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