SYNTHESIS OF A POTENTIAL INTERMEDIATE TO APO-MITOMYCINS

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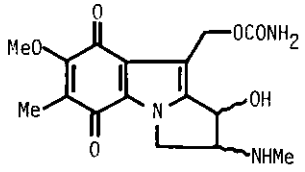
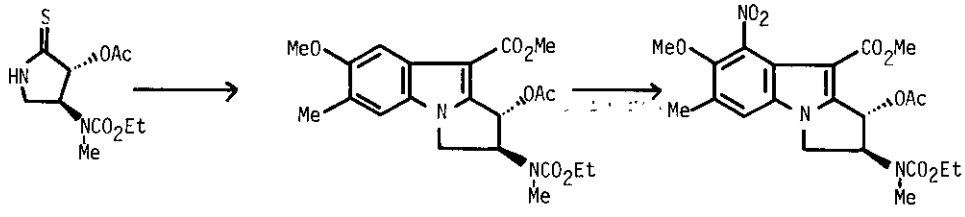
Abstract — Cyclisation of compound (8), which was obtained by condensation of benzyl α-bromo-α-(2-bromo-5-methoxy-4-methylphenyl)acetate (7) with trans-3-acetoxy-4-(N-ethoxycarbonyl-N-methylamino)-2-thiopyrrolidone (2), afforded pyrroloindoles (9) and (10), the former of which on hydrogenolysis gave carboxylic acid (11). Carboxaldehyde (13), which was synthesised from (11) via thioester (12) by successive treatment with oxalyl chloride and ethyl mercaptan, was converted into nitro compound (15). Finally reduction of (15) followed by oxidation of resulting amino compound (16) furnished (±)-1α-acetoxy-2β-[N-ethoxycarbonyl-N-methylamino]-2,3-dihydro-7-methoxy-6-methyl-5,8-dioxo-1H-pyrrolo-[1,2-a]indole-9-carboxaldehyde (17).

During the course of synthetic studies directed towards mitomycin derivatives, we reported a facile synthesis of (±)-methyl 1α-acetoxy-2β-(N-ethoxycarbonyl-N-methylamino)-2,3-dihydro-7-methoxy-6-methyl-5,8-dioxo-1H-pyrrolo[1,2-a]indole-9-carboxylate (5)[1] from trans-3-acetoxy-4-(N-ethoxycarbonyl-N-methylamino)-2-thiopyrrolidone (2) by application of the sulphide condensation method[1].

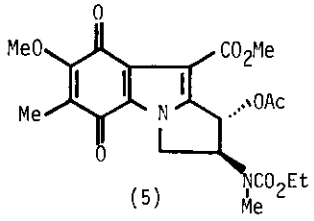
In our envisaged synthesis of apo-mitomycin B (1), an important step is the conversion of this C_9-methoxycarbonyl derivative (5) to the C_9-formyl derivative[2]. However, as we were unable to achieve the direct conversion of quinone (5), or of pyrroloindoles (3) and (4), to the desired formyl compounds by their treatment with metal hydrides such as diisobutylaluminium hydride, we turned our attention to an alternative procedure. The use of the benzyloxycarbonyl group as a protected carboxylic acid is well known and the conversion of a thioester to the aldehyde[3]



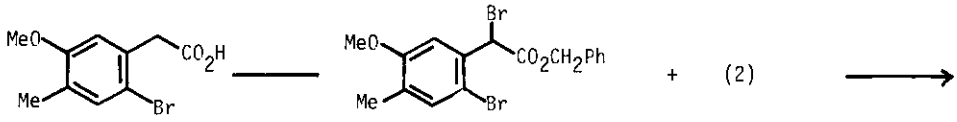
(1) apo-mitomycin B



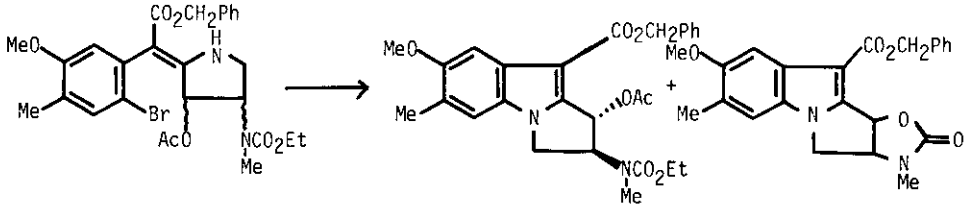
(2) (3) (4)



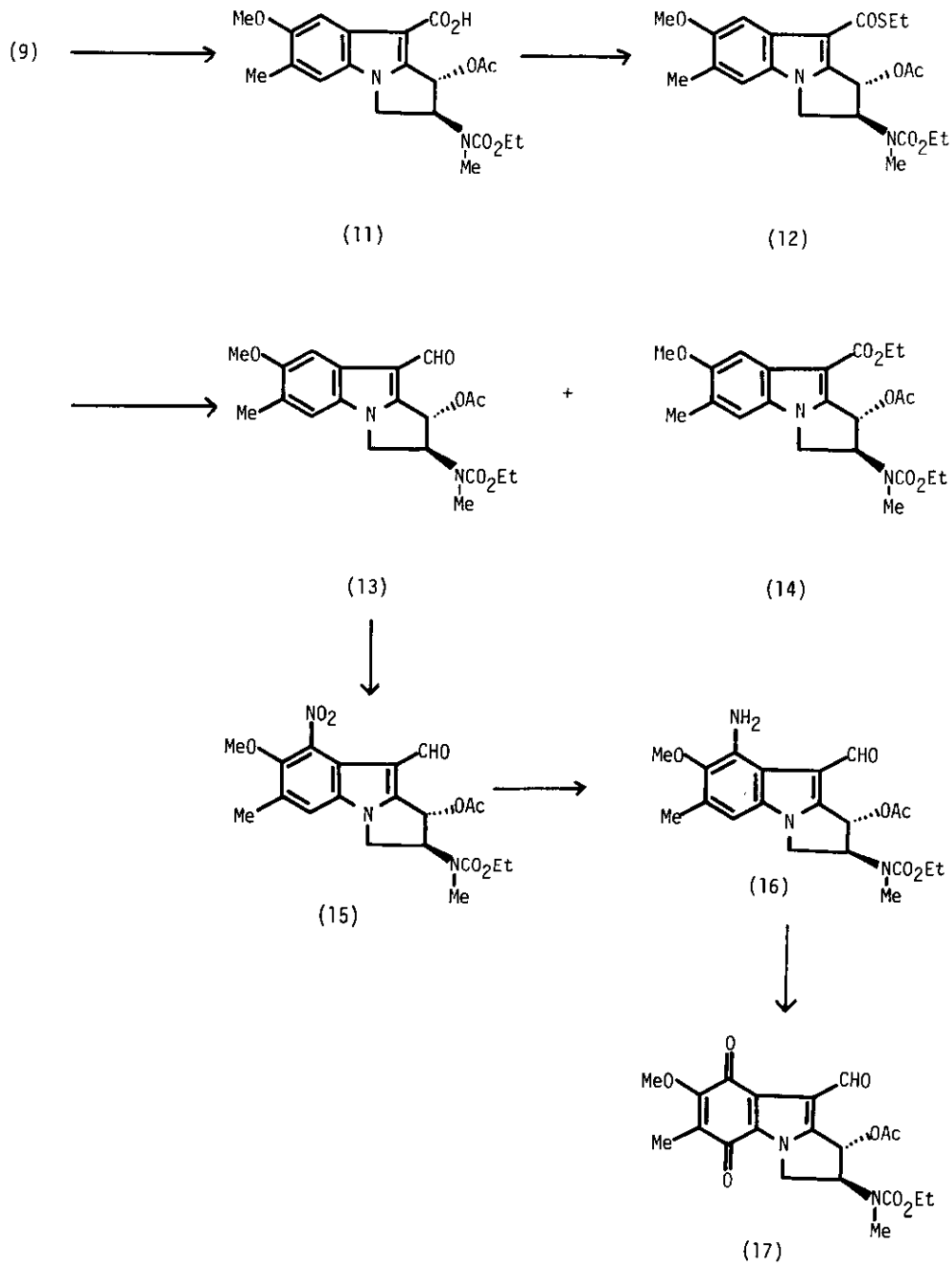
(5)



(6) (7) (2)



(8) (9) (10)


(9)
MeO
Me
CO2H
OAc
N
NCO2Et
Me
(11)
COSEt
(12)
CHO
(13)
CO2Et
(14)
NO2
(15)
NH2
(16)
O
(17)

is readily accomplished by hydrogenolysis. It was therefore envisaged that utilisation of the benzyl ester (9), rather than the methyl ester (4), would enable us to obtain the required C_9-formyl compounds.

Thus, successive treatment of the acid (6) with thionyl chloride, N-bromosuccinimide and 47 % hydrobromic acid, and water, followed by esterification of the product with phenyldiazomethane gave the α-bromoacetate (7) in 69.3 % yield. Compound (7) was converted to the required benzyl ester (9) by the method which we have already described[1]. Condensation of (7) with the 2-thiopyrrolidone (2) in dry dimethylformamide in the presence of 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) afforded the pyrrolidinylidene acetate (8), in 80.9 % yield, as a 1 : 1 diastereoisomeric mixture of trans and cis Z-form isomers. Cyclisation of (8), effected by treatment with sodium hydride and cuprous bromide in dry dimethylformamide, gave a mixture of the pyrroloindoles (9) and (10) in 81.5 % and 10 % yield, respectively. Hydrogenolysis of (9) using palladium on charcoal in methanol under a hydrogen atmosphere afforded the carboxylic acid (11) in 99 % yield. The thioester (12), obtained in 99 % yield from treatment of the acid chloride of (11) with ethyl mercaptan in pyridine, was hydrogenolised using Raney nickel (W_2) in ethanol to produce a mixture of the required aldehyde (13) (28.5 %) and the ethyl ester (14) (9.3 %). Nitration of the aldehyde (13) with 80 % nitric acid afforded the nitro compound (15) in 92.1 % yield which on reduction with iron powder in aqueous acetic acid followed by oxidation with Fremy's salt furnished the quinone (17) in 32.2 % yield.

Thus we have developed a synthetic route to (±)-1α-acetoxy-2β-(N-ethoxycarbonyl-N-methylamino)-2,3-dihydro-7-methoxy-6-methyl-5,8-dioxo-1H-pyrrolo[1,2-a]indole-9-carboxaldehyde (17) which is a potential synthetic intermediate to the apo-mitomycins.

EXPERIMENTAL

Melting points were determined with a Yanagimoto Micro apparatus (MP-S2) and are uncorrected. Ir spectra were obtained with Hitachi 215 recording spectrophotometers. Nmr spectra were measured with a JNM-PMX-60 instrument using tetramethylsilane as internal standard. Mass spectra were measured with Hitachi M-52G and JMS-01SG-2 mass spectrometers.

Benzyl α-Bromo-α-(2-bromo-5-methoxy-4-methylphenyl)acetate (7). —— A mixture of the carboxylic acid (6)[1] (1,3 g), thionyl chloride (1.75 ml), and dry carbon tetrachloride (20 ml) was refluxed for 2 h. N-Bromosuccinimide (1.35 g) and 47 % hydrobromic acid (0.375 ml) were then added to the above reaction mixture. Stirring under reflux was

continued for 3 h with protection from light under a current of nitrogen. N-Bromosuccinimide (0.63 g) and thionyl chloride (0.5 ml) were then added to the reaction mixture and stirring under reflux continued for 3 h. N-Bromosuccinimide (0.6 g) and thionyl chloride (0.5 ml) were again added, and after the mixture had been stirred under reflux for a further 5 h, succinimide was removed by filtration through celite and the solid washed with carbon tetrachloride. The combined filtrate was concentrated and the residue stirred with water for 2 h at 0°C. After addition of solid sodium chloride, the mixture was extracted with ether, and the extract dried (Na_2SO_4). Evaporation of the solvent gave a residue which was dissolved in ether (100 ml) and treated with a solution of phenyldiazomethane[4] in ether (50 ml) [prepared from N-benzyl-N-nitroso-p-toluenesulphonamide (4.35 g)]. After standing for 6 h at room temperature, the solvent was removed by evaporation and the residue (4 g) was chromatographed on silica gel (100 g). Elution with n-hexane-benzene (1 : 1) afforded the dibromide (7) (1.489 g, 69.3 %) as a syrup (Found: C, 47.41; H, 3.72. $C_{17}H_{16}O_3Br_2$ requires C, 47.69; H, 3.77 %), ν_{max} ($CHCl_3$) 1745 cm^{-1} (C=O); δ ($CDCl_3$) 2.14 (3H, s, $ArCH_3$), 3.70 (3H, s, $ArOCH_3$), 5.23 (2H, s, CH_2), 5.92 (1H, s, CH), 7.19 and 7.32 (each 1H, each s, 2 x ArH), 7.35 (5H, s, 5 x ArH); m/e 426 (M^+), 428 ($M^+ + 2$), 430 ($M^+ + 4$).

Benzyl (Z)-α-[3-Acetoxy-4-(N-ethoxycarbonyl-N-methylamino)pyrrolidin-2-ylidene]-α-(2-bromo-5-methoxy-4-methylphenyl)acetate (8). — A mixture of the thiopyrrolidone (2)[1] (260 mg), the dibromide (7) (428 mg), DBU (0.228 ml), and dry DMF (5 ml) was heated at 60 - 70°C for 2 days, and then at 100°C for 3 days, under an atmosphere of nitrogen. The reaction mixture was directly chromatographed on silica gel (60 g). Elution with benzene-ethyl acetate (1 : 1) and evaporation of the solvent gave a residue (657 mg) which was again chromatographed on silica gel (20 g). Elution with benzene-ethyl acetate (10 : 1) afforded the diastereoisomeric compounds (8) (465 mg, 80.9 %) as a pale brown gum, ν_{max} ($CHCl_3$) 3375 (NH), 1740, 1690, and 1665 cm^{-1} (C=O); δ ($CDCl_3$) 1.24 (3H, t, J 7.2 Hz, $CH_2\underline{CH_3}$), 1.63 (3H, s, $COCH_3$), 2.18 (3H, s, $ArCH_3$), 2.93 (3H, s, NCH_3), 3.77 and 3.78 (3H, each s, $ArOCH_3$), 4.18 (2H, q, J 7.2 Hz, $\underline{CH_2}CH_3$), 4.4 - 5.0 (1H, m, C_4-H), 5.20 (2H, s, $CO_2\underline{CH_2}Ar$), 5.91 and 6.11 (1H, each d, J 5.0 and 6.0 Hz, C_3-H), 6.70 and 6.80 (1H, each s, ArH), 7.40 (1H, s, ArH), 7.45 (5H, s, 5 x ArH); m/e 574 (M^+), 576 ($M^+ + 2$).

(±)-Benzyl 1α-Acetoxy-2β-(N-ethoxycarbonyl-N-methylamino)-2,3-dihydro-7-methoxy-6-methyl-1H-pyrrolo[1,2-a]indole-9-carboxylate (9) and Benzyl 2,3,3a,4,10a,10b-Hexahydro-8-methoxy-3,7-dimethyl-2-oxo-10H-oxazolo[4',5'-3,4]pyrrolo[1,2-a]indole

10-carboxylate (10). — A mixture of compounds (8) (785 mg), 50 % sodium hydride in mineral oil (164 mg), cuprous bromide (316 mg), 3Å molecular sieves 1/16 (393 mg) and dry DMF (7.8 ml) was heated at 95 - 100°C for 24 h with stirring under an atmosphere of nitrogen. After excess ammonium chloride had been added, the reaction mixture was extracted with benzene. This extract was washed with 10 % ammonia, water, and brine, and dried (Na_2SO_4). Evaporation of the solvent gave a residue (1 g) which was chromatographed on silica gel (30 g). Elution with benzene-ethyl acetate (10 : 1) afforded the carboxylate (9) (550 mg, 81.5 %), which was recrystallised from isopropyl alcohol as needles, mp 131 - 133°C (Found: C, 65.81; H, 6.13; N, 5.43. $C_{27}H_{30}N_2O_7$ requires C, 65.57; H, 6.11; N, 5.67 %), ν_{max} ($CHCl_3$) 1740, 1705^{sh} and 1695 cm^{-1} (C=O); δ ($CDCl_3$) 1.28 (3H, t, J 7.2 Hz, $CH_2\underline{CH_3}$), 1.87 (3H, s, $COCH_3$), 2.37 (3H, s, $ArCH_3$), 2.94 (3H, s, NCH_3), 3.91 (3H, s, OCH_3), 4.20 (2H, q, J 7.2 Hz, $\underline{CH_2}CH_3$), 4.2 - 4.8 (2H, m, C_3-H_2), 4.9 - 5.4 (1H, m, C_2-H), 5.27 and 5.61 (each 1H, each d, J 12.8 Hz, $CO_2\underline{CH_2}Ar$), 6.69 (1H, d, J 3.2 Hz, C_1-H), 7.17 - 7.77 (7H, m, 7 x ArH); m/e 494 (M^+).

Further elution with ethyl acetate afforded the carboxylate (10) (55 mg, 10 %), which was recrystallised from benzene as needles, mp 258 - 259°C (Found: C, 67.85; H, 5.34; N, 6.89. $C_{23}H_{22}N_2O_5$ requires C, 67.96; H, 5.46; N, 6.89 %), ν_{max} ($CHCl_3$) 1755 and 1696 cm^{-1} (C=O); δ ($CDCl_3$) 2.34 (3H, s, $ArCH_3$), 3.00 (3H, s, NCH_3), 3.95 (3H, s, $ArOCH_3$), 4.1 - 4.5 (2H, m, C_4-H_2), 4.7 - 5.1 (1H, m, C_{3a}-H), 5.45 (2H, s, $CO_2\underline{CH_2}Ar$), 6.06 (1H, d, J 8.0 Hz, C_{10b}-H), 7.1 - 7.7 (7H, m, 7 x ArH); m/e 406 (M^+).

(±)-1α-Acetoxy-2β-(N-ethoxycarbonyl-N-methylamino)-2,3-dihydro-7-methoxy-6-methyl-1H-pyrrolo[1,2-a]indole-9-carboxylic Acid (11). — A mixture of the compound (9) (100 mg), 30 % palladium on charcoal (150 mg), and methanol (30 ml) was stirred at room temperature under a hydrogen atmosphere for 2 h. After removal of the palladium on charcoal by filtration, the solvent was evaporated to give the carboxylic acid (11) (81 mg, 99 %) as a viscous oil (Found: M^+, 404.1572. $C_{20}H_{24}N_2O_7$ requires M^+, 404.1582), ν_{max} ($CHCl_3$) 1735 and 1680^{br} cm^{-1} (C=O); δ ($CDCl_3$) 1.19 (3H, t, J 7.2 Hz, $CH_2\underline{CH_3}$), 2.15 (3H, s, $COCH_3$), 2.33 (3H, s, $ArCH_3$), 2.93 (3H, s, NCH_3), 3.95 (3H, s, C_2-H), 6.67 (1H, d, J 3.8 Hz, C_1-H), 7.03 and 7.61 (each 1H, each s, 2 x ArH), 9.75 br (1H, s, CO_2H); m/e 404 (M^+). All attempts at crystallisation failed.

(±)-Ethyl 1α-Acetoxy-2β-(N-ethoxycarbonyl-N-methylamino)-2,3-dihydro-7-methoxy-6-methyl-1H-pyrrolo[1,2-a]indole-9-thiocarboxylate (12). — A mixture of the carboxylic acid (11) (81 mg), oxalyl chloride (1 ml), and dry methylene chloride (15 ml) was stirred for 5 h at room temperature under a nitrogen atmosphere. Evaporation of

the solvent and excess reagent gave a residue which was taken up in dry methylene chloride (15 ml). After addition of pyridine (6 ml) and ethyl mercaptan (3 ml), the mixture was stirred at 0°C for 3 h, and then at room temperature for 13 h under nitrogen. Evaporation gave a residue which was chromatographed on silica gel (6 g). Elution with benzene-ethyl acetate (20 : 1) afforded the thiocarboxylate (12) (89 mg, 99 %) as a pale yellowish syrup (Found: M^+, 448.1668. $C_{22}H_{28}N_2O_6S$ requires M^+, 448.1668), ν_{max} ($CHCl_3$) 1735, 1680 and 1625 cm^{-1} (C=O), δ ($CDCl_3$) 1.15 and 1.35 (each 3H, each t, J 7.2 Hz, 2 x $CH_2\underline{CH_3}$), 2.16 (3H, s, $COCH_3$), 2.33 (3H, s, $ArCH_3$), 2.89 (3H, s, NCH_3), 3.08 (2H, q, J 7.2 Hz, $S\underline{CH_2}CH_3$), 3.92 (3H, s, $ArOCH_3$), 4.11 (2H, q, J 7.2 Hz, $O\underline{CH_2}CH_3$), 4.0 - 4.8 (2H, m, C_3-H_2), 5.05 br (1H, s, C_2-H), 6.61 (1H, d, J 2.4 Hz, C_1-H), 7.02 and 7.71 (each 1H, each s, 2 x ArH); m/e 448 (M^+).

(±)-1α-Acetoxy-2β-(N-ethoxycarbonyl-N-methylamino)-2,3-dihydro-7-methoxy-6-methyl-1H-pyrrolo[1,2-a]indole-9-carboxaldehyde (13) and (±)-Ethyl 1α-Acetoxy-2β-(N-ethoxycarbonyl-N-methylamino)-2,3-dihydro-7-methoxy-6-methyl-1H-pyrrolo[1,2-a]indole-9-carboxylate (14). — Thioester (12) (89 mg) was dissolved in ethanol (50 ml) containing Raney nickel (W_2) (1 g) [which had been deactivated by treatment with refluxing acetone for 2 h] and the mixture was refluxed for 3.5 h with vigorous stirring. After removal of the catalyst by filtration, the ethanolic solution was condensed to give a residue which was separated by preparative thick-layer chromatography on silica gel, using benzene-ethyl acetate (3 : 2) as eluant, to afford the carboxaldehyde (13) (22 mg, 28.5 %), which was recrystallised from ethanol as needles, mp 129 - 130°C, Rf = 0.4 (Found: M^+, 388.1596. $C_{20}H_{24}N_2O_6$ requires M^+, 388.1627), ν_{max} ($CHCl_3$) 1745, 1695 and 1655 cm^{-1} (C=O); δ ($CDCl_3$) 1.20 (3H, t, J 7.2 Hz, $CH_2\underline{CH_3}$), 2.14 (3H, s, $COCH_3$), 2.33 (3H, s, $ArCH_3$), 2.93 (3H, s, NCH_3), 3.91 (3H, s, $ArOCH_3$), 4.15 (2H, q, J 7.2 Hz, $C\underline{H_2}CH_3$), 4.1 - 4.7 (2H, m, C_3-H_2), 5.70 br (1H, s, C_2-H), 6.62 (1H, d, J 3.9 Hz, C_1-H), 7.04 and 7.71 (each 1H, each s, 2 x ArH), 9.65 (1H, s, $C\underline{H}O$); m/e 388 (M^+) and the ethyl ester (14) (8 mg, 9.3 %), which was recrystallised from ether-n-hexane as needles, mp 114.5 - 115.5°C, Rf=0.57, (Found: M^+, 432.1897. $C_{22}H_{28}N_2O_7$ requires M^+, 432.1896), ν_{max} ($CHCl_3$) 1740 and 1690 cm^{-1} (C=O); δ ($CDCl_3$) 1.17 and 1.33 (each 3H, each t, J 7.2 Hz, 2 x $CH_2\underline{CH_3}$), 2.10 (3H, s, $COCH_3$), 2.32 (3H, s, $ArCH_3$), 2.87 (3H, s, NCH_3), 3.89 (3H, s, $ArOCH_3$), 4.12 and 4.30 (each 2H, each q, J 7.2 Hz, 2 x $C\underline{H_2}CH_3$), 6.55 (1H, d, J 3.0 Hz, C_1-H), 7.01 and 7.58 (each 1H, each s, 2 x ArH); m/e 432 (M^+).

(±)-1α-Acetoxy-2β-(N-ethoxycarbonyl-N-methylamino)-2,3-dihydro-7-methoxy-6-methyl-8-nitro-1H-pyrrolo[1,2-a]indole-9-carboxaldehyde (15) — A mixture of the compound

(13) (51 mg), 80 % aqueous nitric acid (0.007 ml), and dry methylene chloride (10 ml) was stirred for 3 min at 0°C. After addition of ice-cooled water, the layers were separated and the aqueous layer was extracted with chloroform. The combined organic solution was washed with saturated aqueous sodium hydrogen carbonate and brine, and dried (Na_2SO_4). Evaporation of the solvent gave the nitro compound (16) (52.7 mg, 92.6 %), which was recrystallised from ethanol as pale red needles, mp 166 - 167°C (Found: $\underline{M}^+$, 433.1512. $C_{20}H_{23}N_3O_8$ requires $\underline{M}^+$, 433.1486), ν_{max} ($CHCl_3$) 1750 and 1685^{br} cm^{-1} (C=O); δ ($CDCl_3$) 1.21 (3H, t, $\underline{J}$ 7.2 Hz, $CH_2\underline{CH}_3$), 2.13 (3H, s, $COCH_3$), 2.39 (3H, s, $ArCH_3$), 3.01 (3H, s, NCH_3), 3.81 (3H, s, $ArOCH_3$), 4.11 (2H, q, $\underline{J}$ 7.2 Hz, $\underline{CH}_2CH_3$), 4.0 - 4.8 (2H, m, C_3-H_2), 4.8 - 5.2 (1H, m, C_2-H), 6.63 (1H, d, $\underline{J}$ 4.0 Hz, C_1-H), 7.20 (1H, s, ArH), 9.73 (1H, s, $C\underline{H}O$); $\underline{m/e}$ 433 (M^+).

(±)-1α-Acetoxy-2β-(N-ethoxycarbonyl-N-methylamino)-2,3-dihydro-7-methoxy-6-methyl-5,8-dioxo-1H-pyrrolo[1,2-a]indole-9-carboxaldehyde (17). — A stirred solution of the compound (15) (45 mg) in acetic acid (2.25 ml) and water (0.225 ml) was heated with iron powder (100 mg) at 70°C for 30 min, cooled to room temperature, and diluted with ice-cooled water. The mixture was extracted with methylene chloride. This extract was washed with saturated aqueous sodium hydrogen carbonate and brine, and dried (Na_2SO_4). Evaporation of the solvent gave the corresponding 8-amino-aldehyde (16), which was converted directly to the quinone.

A solution of the crude aminoaldehyde in acetone (7.5 ml) was added to a stirred solution of Fremy's salt (100 mg) in a mixture of water (5 ml) and 0.167M potassium dihydrogen phosphate (2.5 ml). The resulting mixture was stirred at room temperature for 16 h, and then diluted with water and extracted with methylene chloride. The extract was dried (Na_2SO_4) and concentrated, and the residue (29 mg) was chromatographed on silica gel (3 g). Elution with benzene-ethyl acetate (10 : 1) afforded the quinone (17) (14 mg, 32.2 %), which was recrystallised from isopropyl alcohol as yellowish prisms, mp 149.5 - 150.5°C (Found: C, 57.19; H, 5.27; N, 6.79. $C_{20}H_{22}N_2O_8$ requires C, 57.41; H, 5.30; N, 6.70 %), (Found: $\underline{M}^+$, 418.1386. $C_{20}H_{22}N_2O_8$ requires $\underline{M}^+$, 418.1385), ν_{max} (MeOH) 415 (ε 823), 326 (ε 5067), 270 (ε 14567), 241 (ε 12844), and 213 (ε 18492); ν_{max} ($CHCl_3$) 1740, 1675^{br} and 1645 cm^{-1} (C=O); δ ($CDCl_3$) 1.20 (3H, t, $\underline{J}$ 7.2 Hz, $CH_2\underline{CH}_3$), 1.97 (3H, s, C_6-Me), 2.12 (3H, s, $COCH_3$), 3.00 (3H, s, NCH_3), 4.03 (3H, s, OMe), 4.09 (2H, q, $\underline{J}$ 7.2 Hz, $\underline{CH}_2CH_3$), 6.39(1H, d, $\underline{J}$ 3.1 Hz, C_1-H), 10.29 (1H, s, $C\underline{H}O$); $\underline{m/e}$ 418 (M^+).

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