Studies on the Synthesis of Heterocyclic Compounds. Part 832.† A Simple and Efficient Synthesis of Apomitomycin Derivatives; a Potential Intermediate for Mitomycin Synthesis

By **Tetsuji Kametani,* Yoshio Kigawa, Hideo Nemoto, Masataka Ihara,** and **Keiichiro Fukumoto,** Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

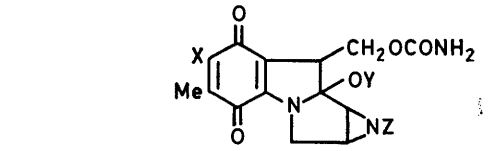
Condensation of pyrrolidine-2-thione (21) with methyl α-bromo-(2-bromo-4,5-dimethoxyphenyl)acetate (15) gave methyl (*Z*)-α-(2-bromo-4,5-dimethoxyphenyl)-α-pyrrolidin-2-ylideneacetate (25) in high yield. Several other methyl (*Z*)-α-aryl-α-[3-acetoxy-4-(*N*-ethoxycarbonyl-*N*-methylamino)pyrrolidin-2-ylidene]acetates (26)—(31) were also synthesised in good yields from reaction of the corresponding phenylacetates (15), (12), and (13) with *trans*-3-acetoxy-4-(*N*-ethoxycarbonyl-*N*-methylamino)pyrrolidine-2-thione (20). Treatment of compounds (25)—(31) with sodium hydride and copper(I) bromide in dimethylformamide afforded methyl 2,3-dihydro-6,7-dimethoxy-1*H*-pyrrolo[1,2-*a*]indole-9-carboxylate (34) and the methyl (±)-*trans*-1-acetoxy-2-(*N*-ethoxycarbonyl-*N*-methylamino)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-9-carboxylates (35)—(37) in good yields. Methyl (±)-*trans*-1-acetoxy-2-(*N*-ethoxycarbonyl-*N*-methylamino)-2,3-dihydro-7-methoxy-6-methyl-1*H*-pyrrolo[1,2-*a*]indole-9-carboxylate (36) was converted into the 5,8-quinone (3), *via* the 8-nitro-compound (38).

DURING the course of synthetic studies directed towards mitomycin derivatives,[1-5] we reported a simple synthesis of 3-benzyl-6-methyl-3,6-diazabicyclo[3.1.0]hexan-2-one (5) from (±)-*trans*-1-benzyl-3-hydroxy-4-methylaminopyrrolidin-2-one (16).[6] On the basis of this finding we have designed a synthetic route to mitomycins (1) *via* compound (2), which should be readily obtained from compound (3).

The quinone (3) has all the structural features of apomitomycins [*e.g.* (4)], except for the C-9 substituent, and could be expected to have biological activity since compound (4) has been reported to show both antitumour and antibacterial activities.[7,8] We now report the easy and efficient synthesis of the apomitomycin type compound (3).

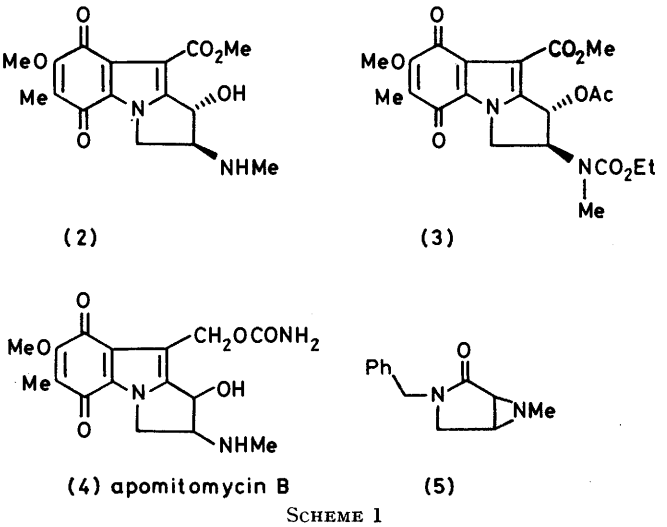
First, condensation of the nitrile (10) with the *O*-methylpyrrolidone (23) was examined in an attempt to obtain compound (24). A preliminary experiment showed that condensation of the nitrile (10) with the *O*-methylpyrrolidone (22), in the presence of 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU), could be carried out successfully, producing compound (32) in high yield. 2-Bromo-5-methoxy-4-methylphenylacetonitrile (10) was prepared as follows. The aldehyde (7), derived from 3-hydroxy-4-methylbenzaldehyde (6)[9] in 87% yield, was reduced with sodium borohydride to give the alcohol (8) in 98.7% yield.

Successive treatment with thionyl chloride and sodium cyanide in the presence of sodium iodide afforded the nitrile (9) in 98.3% overall yield. The bromide (10) was then obtained in 65% yield by bromination of (9). (±)-*trans*-3-Acetoxy-4-(*N*-ethoxycarbonyl-*N*-methylamino)-2-methoxy-Δ[1]-pyrroline (23) was prepared as follows. The sodium alcoholate formed on treatment of (±)-*trans*-1-benzyl-4-(*N*-ethoxycarbonyl-*N*-methylamino)-3-hydroxypyrrolidin-2-one (17)[6] with sodium hydride was reduced with sodium in liquid ammonia at −33 °C to give the debenzylated compound (18), which on acetylation with acetic anhydride in pyridine afforded the acetate (19) in 55% overall yield. The methoxypyrrolidine (23) was then obtained in 94% yield on treatment of the acetate (19) with trimethyloxonium fluoroborate.[10] Attempted condensation between this compound (23) and the bromide (10), under basic conditions involving the use of DBU as already mentioned, failed to produce the expected compound (24).



(1)

	X	Y	Z
mitomycin A	OMe	Me	H
mitomycin B	OMe	H	Me
mitomycin C	NH_2	Me	H
porfiromycin	NH_2	Me	Me



(2) (3) (4) apomitomycin B (5)

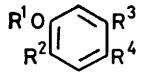
SCHEME 1

† Part 831, K. Kigasawa, M. Hiiragi, H. Ishimaru, N. Wagatsuma, T. Kohagisawa, and T. Nakamura, *Synthesis*, 1980, **14**, 449.

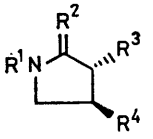
Although the actual product remains undefined, it was shown not to be the pyrroloindole (33). As a result of this unsuccessful reaction, which may be attributable to steric hindrance by the substituents on the pyrrolidine ring of (23), we decided to explore the sulphide condensation method developed by Eschenmoser [11-14] and Felner.[15]

Thus, the dibromide (15), which was obtained in 82% yield on reaction of the ester (14) [16] with *N*-bromosuccimide, was treated with pyrrolidine-2-thione (21) [17] in dry chloroform at room temperature. Subsequent heating of this mixture with DBU afforded the pyrrolidinylideneacetate (25) in 97% yield. Cyclisation of compound (25), effected by sodium hydride and copper(I) bromide in dry dimethylformamide,[1] gave the pyrroloindole (34) in 95% yield.

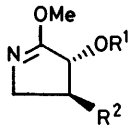
Next, the dibromide (15) and the pyrrolidinethione (20) [obtained in 80% yield by treatment of the pyrrolidone (19) with phosphorus pentasulphide in benzene] when kept in tetrahydrofuran in the presence of DBU, afforded the pyrrolidinylideneacetates (26) and (27) as a diastereoisomeric mixture in 79% yield. In the



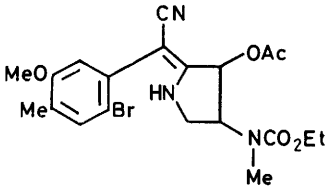
(6) $R^1 = R^4 = H$, $R^2 = Me$, $R^3 = CHO$
(7) $R^1 = R^2 = Me$, $R^3 = CHO$, $R^4 = H$
(8) $R^1 = R^2 = Me$, $R^3 = CH_2OH$, $R^4 = H$
(9) $R^1 = R^2 = Me$, $R^3 = CH_2CN$, $R^4 = H$
(10) $R^1 = R^2 = Me$, $R^3 = CH_2CN$, $R^4 = Br$
(11) $R^1 = R^2 = Me$, $R^3 = CH_2{\cdot}CO_2H$, $R^4 = Br$
(12) $R^1 = R^2 = Me$, $R^3 = CHBr{\cdot}CO_2Me$, $R^4 = Br$
(13) $R^1 = Me$, $R^2 = CH_2OMe$, $R^3 = CHBr{\cdot}CO_2Me$, $R^4 = Br$
(14) $R^1 = Me$, $R^2 = OMe$, $R^3 = CH_2{\cdot}CO_2Me$, $R^4 = Br$
(15) $R^1 = Me$, $R^2 = OMe$, $R^3 = CHBr{\cdot}CO_2Me$, $R^4 = Br$



(16) $R^1 = PhCH_2$, $R^2 = O$, $R^3 = OH$, $R^4 = NH{\cdot}Me$
(17) $R^1 = PhCH_2$, $R^2 = O$, $R^3 = OH$, $R^4 = N(Me)CO_2Et$
(18) $R^1 = H$, $R^2 = O$, $R^3 = OH$, $R^4 = N(Me)CO_2Et$
(19) $R^1 = H$, $R^2 = O$, $R^3 = OAc$, $R^4 = N(Me)CO_2Et$
(20) $R^1 = H$, $R^2 = S$, $R^3 = OAc$, $R^4 = N(Me)CO_2Et$
(21) $R^1 = R^3 = R^4 = H$, $R^2 = S$



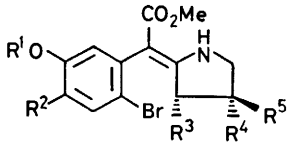
(22) $R^1 = R^2 = H$
(23) $R^1 = OAc$, $R^2 = N(Me)CO_2Et$



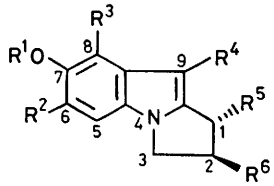
(24)

SCHEME 2

n.m.r. spectrum ($CDCl_3$) of (26) and (27), signals due to the acetoxy group's protons were observed at abnormally high field, δ 1.73 and 1.66, suggesting that the acetoxy and aromatic groups were in a *cis*-arrangement around the double bond so that the acetoxy-groups were shielded by the aromatic ring. The ratio of the intensities of the two sets of acetoxy-protons was found to be *ca.* 1 : 1, as was the ratio of the intensities of the methine protons on C-3, whose signals appeared at δ 6.05 and



(25) $R^1 = Me$, $R^2 = OMe$, $R^3 = R^4 = R^5 = H$
(26) $R^1 = Me$, $R^2 = OMe$, $R^3 = OAc$, $R^4 = H$, $R^5 = N(Me)$-CO_2Et
(27) $R^1 = Me$, $R^2 = OMe$, $R^3 = OAc$, $R^4 = N(Me)CO_2Et$, $R^5 = H$
(28) $R^1 = R^2 = Me$, $R^3 = OAc$, $R^4 = H$, $R^5 = N(Me)CO_2Me$
(29) $R^1 = R^2 = Me$, $R^3 = OAc$, $R^4 = N(Me)CO_2Et$, $R^5 = H$
(30) $R^1 = Me$, $R^2 = CH_2OMe$, $R^3 = OAc$, $R^4 = H$, $R^5 = N(Me)Co_2Et$
(31) $R^1 = Me$, $R^2 = CH_2OMe$, $R^3 = OAc$, $R^4 = N(Me)CO_2Et$, $R^5 = H$



(32) $R^1 = R^2 = Me$, $R^3 = R^5 = R^6 = H$, $R^4 = CN$
(33) $R^1 = R^2 = Me$, $R^3 = H$, $R^4 = CN$, $R^5 = OAc$, $R^6 = N(Me)CO_2Et$
(34) $R^1 = Me$, $R^2 = OMe$, $R^3 = R^5 = R^6 = H$, $R^4 = CO_2Me$
(35) $R^1 = Me$, $R^2 = OMe$, $R^3 = H$, $R^4 = CO_2Me$, $R^5 = OAc$, $R^6 = N(Me)CO_2Et$
(36) $R^1 = R^2 = Me$, $R^3 = HR^4 = CO_2Me$, $R^5 = OAc$, $R^6 = N(Me)CO_2Et$
(37) $R^1 = Me$, $R^2 = CH_2OMe$, $R^3 = H$, $R^4 = CO_2Me$, $R^5 = OAc$, $R^6 = N(Me)CO_2Et$
(38) $R^1 = R^2 = Me$, $R^3 = NO_2$, $R^4 = CO_2Me$, $R^5 = OAc$, $R^6 = N(Me)CO_2Et$
(39) $R^1 = R^2 = Me$, $R^3 = NH_2$, $R^4 = CO_2Me$, $R^5 = OAc$, $R^6 = N(Me)CO_2Et$

SCHEME 3

5.75. Thus the reaction product was shown to be a 1 : 1 mixture of *trans*-(26) and *cis*-(27) as the *Z*-form isomers. As separation of (26) and (27) could not be achieved, the mixture was subjected to the same cyclisation conditions as already described for compound (25), and afforded compound (35) as a single compound in 99% yield. This showed that the *cis*-isomer was epimerised to the thermodynamically more stable *trans*-isomer (35) * under the reaction conditions.

Similarly, condensation of the dibromides (12) and (13) with the pyrrolidinethione (20) gave respectively the pyrrolidinylideneacetates (28) and (29) in 70.7% yield, and (30) and (31) in 69% yield, with the ratio of diastereoisomers being *ca.* 1 : 1 in each case. The dibromides (12) and (13) were obtained as follows. Hydrolysis of the nitrile (10) with hot aqueous methanolic

* Since it is difficult to assign the stereochemistry of the substituents on C-1 and C-2 of the pyrrolo[1,2-*a*]indole system with certainty on the basis of a molecular model (W. A. Remers, R. H. Roth, and M. J. Weiss, *J. Org. Chem.*, 1965, **30**, 2910), the stereochemistry of compounds (35)—(39) was assigned for the moment from thermodynamic considerations.

potassium hydroxide solution afforded the acid (11) in 98.7% yield. Successive treatment of the acid (11) with thionyl chloride, *N*-bromosuccinimide and 30% hydrogen bromide in acetic acid, and saturated aqueous sodium hydrogen carbonate, followed by esterification of the resulting acid with methanol and concentrated sulphuric acid, gave a mixture of the dibromides (12) (22%) and (13) (23.3%). Alternatively, the dibromide (12) was prepared in high yield (87.4%) by successive treatment of the acid (11) with thionyl chloride, *N*-bromosuccinimide and 47% aqueous hydrogen bromide, and water, followed by esterification with diazomethane. The mixtures of (28) and (29), and (30) and (31), were subjected to the same cyclisation conditions as already described to give compound (36) in 93.5% yield and (37) in 83% yield, respectively. Hydrogenolysis of (37), with palladium on charcoal in methanol under hydrogen, afforded (36) in 94% yield.

Next, the nitro-compound (38), formed in 91.5% yield by nitration of the ester (36), was reduced with iron and acetic acid to give the amino-compound (39), which on subsequent oxidation with Fremy's salt afforded the quinone (3), in 64% yield from (38).

Thus we have developed a novel method for the preparation of methyl (±)-1α-acetoxy-2β-(*N*-ethoxycarbonyl-*N*-methylamino)-2,3,5,8-tetrahydro-7-methoxy-6-methyl-5,8-dioxo-1*H*-pyrrolo[1,2-*a*]indole-9-carboxylate (3) which is a potential intermediate for mitomycin synthesis.

EXPERIMENTAL

M.p.s were determined with a Yanagimoto Micro apparatus (MP-S2). I.r. and u.v. spectra were obtained with Hitachi 215 and Hitachi 124 recording spectrophotometers respectively. N.m.r. spectra were measured with a JNM-PMX-60 instrument using tetramethylsilane as internal standard. Mass spectra were measured with Hitachi RMU-7, Hitachi M-52, and JMS-01 SG-2 mass spectrometers.

5-Methoxy-4-methylbenzaldehyde (7). The phenolic compound (6) [9] (136 g) was treated with aqueous potassium hydroxide (382.4 ml; 33% w/w) and dimethyl sulphate (186.6 ml), followed by usual work-up, to give the *aldehyde* (7) (130 g, 87%) as needles, m.p. 42—43 °C, b.p. 75—76 °C at 3 mmHg (Found: C, 72.0; H, 6.85. $C_9H_{10}O_2$ requires C, 72.0; H, 6.7%); $\nu_{max.}$ ($CHCl_3$) 1 680 cm^{-1} (C=O); δ(CCl_4) 2.26 (3 H, s, Me), 3.89 (3 H, s, OMe), 7.20 (3 H, s, 3 × ArH), and 9.79 (1 H, s, CHO).

5-Methoxy-4-methylbenzyl Alcohol (8). The aldehyde (7) (220 g) in methanol (1 000 ml) was reduced with sodium borohydride (56 g) to afford the *alcohol* (8) (220 g, 98.7%) as an oil, b.p. 82—83 °C at 0.02 mmHg (Found: C, 70.6; H, 7.95. $C_9H_{12}O_2$ requires C, 71.0; H, 7.95%); δ(CCl_4) 2.12 (3 H, s, Me), 3.92 (3 H, s, OMe), 4.40 (2 H, s, CH_2), 6.60 (1 H, d, *J* 8 Hz, ArH), 6.65 (1 N, s, ArH), and 6.92 (1 H, d, *J* 8 Hz, ArH).

5-Methoxy-4-methylphenylacetonitrile (9). To a stirred solution of the alcohol (8) (220 g) in dry benzene (220 ml) was added thionyl chloride (207 g) in small portions, initially under cooling in ice–water and then at room temperature, over a period of 1.5 h. After addition of all the thionyl chloride, the dark brown solution was stirred for a further 30 min at room temperature, and then refluxed for 30 min. Excess of reagent and solvent were removed by distillation and the residue was taken up in benzene. This extract was washed with water, saturated aqueous sodium hydrogen carbonate, water, and brine, and dried (Na_2SO_4). Evaporation gave a dark brown oil which was dissolved in ethyl methyl ketone (1 000 ml). To this solution was added sodium cyanide (247 g), sodium iodide (247 g), and water (100 ml), and the mixture was refluxed for 3 h. After addition of benzene the organic layer was washed with water, 5% aqueous sodium thiosulphate solution, water, and brine, then dried (Na_2SO_4) and evaporated to give the nitrile (9) (229 g, 98.3%) as a pale brown oil, b.p. 105—106 °C at 3 mmHg; $\nu_{max.}$ ($CHCl_3$) 2 250 cm^{-1} (CN); δ(CCl_4) 2.12 (3 H, s, Me), 3.53 (2 H, s, CH_2), 3.70 (3 H, s, OMe), 6.62br (2 H, s, 2 × ArH), and 6.94 (1 H, d, *J* 8 Hz, ArH).

2-Bromo-5-methoxy-4-methylphenylacetonitrile (10). To a stirred solution of the nitrile (9) (161 g) and sodium acetate (123 g) in chloroform (800 ml) was added bromine (192 g) dropwise over a period of 1.5 h with cooling in ice–water. After addition of the bromine the mixture was stirred for 1 h at room temperature. After addition of water the organic layer was separated off, washed with water, saturated aqueous sodium hydrogen carbonate, 5% aqueous sodium thiosulphate solution, water, and brine, and dried (Na_2SO_4). Evaporation afforded a brown mass, recrystallisation of which from ether gave the bromide (10) (156 g, 65%) as needles, identical (mixed m.p., i.r., and n.m.r. spectra) to an authentic sample.[1]

2-Bromo-5-methoxy-4-methylphenylacetic Acid (11). The hydrolysis of the nitrile (10) (24.1 g) was effected with 0.85N methanolic potassium hydroxide (1 000 ml) and water (100 ml) under reflux for 36 h in the usual way to give the *carboxylic acid* (11) (25.49 g, 98.4%) as needles, m.p. 130.5—131.5 °C (Found: C, 46.6; H, 4.35. $C_{10}H_{11}BrO_3$ requires C, 46.35; H, 4.3%), $\nu_{max.}$ ($CHCl_3$) 1 710 cm^{-1} (C=O); δ($CDCl_3$) 2.16 (3 H, s, Me), 3.77 (5 H, s, OMe and CH_2), 6.72 and 7.30 (each 1 H, each s, 2 × ArH), and 9.00br (1 H, s, disappeared on addition of D_2O); *m/e* 258 (M^+) and 260 ($M^+ + 2$).

Bromination of the Carboxylic Acid (11).—(a) A mixture of the carboxylic acid (11) (5.2 g), thionyl chloride (9.6 g), and carbon tetrachloride (80 ml) was heated at 75—80 °C with vigorous stirring for 2 h. *N*-Bromosuccinimide (11.36 g) and 30% hydrogen bromide in acetic acid (10 drops) were then added. The stirring under reflux was continued for 24 h, with protection from light and in a current of nitrogen. Succinimide was removed by filtration through Celite and the solid washed with carbon tetrachloride. Evaporation of the combined filtrate gave a residue which was basified with saturated aqueous sodium hydrogen carbonate. After addition of ether the two-phase mixture was stirred for 1 h at 0 °C, and then acidified with 10% aqueous hydrochloric acid. After addition of solid sodium chloride, the organic layer was separated, washed with brine, and dried (Na_2SO_4). Evaporation gave a residue, to which was added methanol (250 ml) and concentrated sulphuric acid (10 drops), and the mixture was refluxed for 20 h. Evaporation gave a residue which was taken up in ether and the solution was washed with saturated aqueous sodium hydrogen carbonate and brine, and dried (Na_2SO_4). Evaporation gave a residue (6.58 g) which was chromatographed on silica gel (197 g). Elution with hexane–benzene (1 : 1 v/v) afforded *methyl α-bromo-(2-bromo-5-methoxy-4-methylphenyl)acetate* (12) (1.557 g, 22%)

as a syrup which failed to crystallise (Found: M^+, 349.913 3. $C_{11}H_{12}Br_2O_3$ requires M^+, 349.915 3), $\nu_{max.}$ ($CHCl_3$) 1 750 cm^{-1} (C=O); δ($CDCl_3$) 2.18 (3 H, s, Me), 3.78 and 3.87 (each 3 H, each s, 2 × OMe), 5.74 (1 H, s, CH), 7.27 and 7.31 (each 1 H, each s, 2 × ArH); *m/e* 350 (M^+) and 354 ($M^+ + 4$). Elution with benzene afforded *methyl α-bromo-(2-bromo-5-methoxy-4-methoxymethylphenyl)acetate* (13) (1.786 g, 23.3%) as a syrup (Found: C, 38.0; H, 3.6. $C_{12}H_{14}BrO_4$ requires C, 37.7; H, 3.7%), $\nu_{max.}$ ($CHCl_3$) 1 745 cm^{-1} (C=O), δ($CDCl_3$) 3.45, 3.82, and 3.87 (each 3 H, each s, 3 × OMe), 4.47 (2 H, s, CH_2), 5.91, 7.36, and 7.60 (each 1 H, s, CH and 2 × ArH); *m/e* 380 (M^+) and 384 ($M^+ + 4$).

(b) A mixture of the carboxylic acid (11) (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% aqueous hydrobromic acid (0.375 ml) were then added. Stirring under reflux was continued for 3 h with protection from light and in a current of nitrogen. *N*-Bromosuccinimide (0.63 g) and thionyl chloride (0.5 ml) were then added and stirring under reflux was continued for 3 h. *N*-Bromosuccinimide (0.6 g) and thionyl chloride (0.5 ml) were again added. 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 gave a residue which was dissolved in methanol (60 ml) and treated with a solution of diazomethane in ether (100 ml) [prepared from *p*-tolylsulphonylmethylnitrosamide (10.75 g)]. After 2 h at 0 °C, excess of diazomethane was decomposed with acetic acid. The solvent was removed by evaporation and the residue taken up in ether. This solution was washed with water, cold saturated aqueous sodium hydrogen carbonate, water, and brine, and dried (Na_2SO_4). Evaporation gave a residue (2.7 g) which was chromatographed on silica gel (81 g). Elution with hexane–benzene (1 : 1 v/v) afforded the dibromide (12) (1.545 g, 87.4%) which was identical to the sample prepared by method (a) (i.r., n.m.r., and mass spectral data).

Methyl α-Bromo-(2-bromo-4,5-dimethoxyphenyl)acetate (15).—A mixture of methyl 2-bromo-4,5-dimethoxyphenylacetate (14) (7.148 g) and *N*-bromosuccinimide (4.84 g) in carbon tetrachloride (50 ml) was refluxed for 8 days under irradiation with a 40 W lamp and in a current of nitrogen. Succinimide was removed by filtration through Celite and the solid washed with carbon tetrachloride. The combined filtrate was evaporated and the residue chromatographed on silica gel (220 g). Elution with benzene–hexane (10 : 1 v/v) afforded the *dibromide* (15) (7.469 g, 82%) as a glass which failed to crystallise (Found: C, 36.0; H, 3.25. $C_{11}H_{12}Br_2O_4$ requires C, 35.9; H, 3.3%), $\nu_{max.}$ ($CHCl_3$) 1 750 cm^{-1} (C=O); δ($CDCl_3$) 3.80, 3.87, and 3.90 (each 3 H, each s, 3 × OMe), 5.87 (1 H, s, CH), and 7.02 and 7.37 (each 1 H, each s, 3- and 6-H); *m/e* 366 (M^+) and 370 ($M^+ + 4$).

(±)-*1-Benzyl-4β-(N-ethoxycarbonyl-N-methylamino)-3α-hydroxypyrrolidin-2-one* (17).—To a two-phase mixture of the pyrrolidine [6] (16) (11.282 g), benzene (641 ml), and saturated aqueous sodium hydrogen carbonate (641 ml) at 5 °C was added ethyl chloroformate (9.74 ml). The mixture was stirred for 13 h at room temperature. The organic layer was separated, washed with brine, and dried (Na_2SO_4). Evaporation gave the urethane (17) (14.9 g, 99%) as a pale yellow oil whose spectral data (i.r. and n.m.r.) and behaviour on t.l.c. were identical to those of an authentic sample.[6] This product was used in the next step without further purification.

(±)-*3α-Acetoxy-4β-(N-ethoxycarbonyl-N-methylamino)-pyrrolidin-2-one* (19).—To a mixture of the urethane (17) (16.56 g), 50% sodium hydride in mineral oil (8.17 g), and dry tetrahydrofuran (100 ml), cooled in solid carbon dioxide–acetone, was added freshly distilled liquid ammonia (400 ml). To the resulting mixture at −33 °C was added metallic sodium (3 g) with stirring. Stirring was continued for a further 5 h at −33 °C under nitrogen. After addition of absolute ethanol (100 ml) and ammonium chloride (18 g), the ammonia was allowed to evaporate off and a precipitate was removed by filtration through Celite. The filtrate was evaporated to dryness to give the crude debenzylated compound (18) as a syrup which was used in the next step without further purification. A mixture of compound (18), acetic anhydride (13.8 ml), and pyridine (74 ml) was stirred at 0 °C for 5 days under nitrogen. Evaporation gave a residue which was acidified with 10% aqueous hydrochloric acid and extracted with ethyl acetate. This extract was washed with brine and dried (Na_2SO_4). Evaporation gave a residue (15 g) which was chromatographed on silica gel (200 g). Elution with ethyl acetate–methanol (6 : 1 v/v) afforded the crude acetate (19). Recrystallisation from benzene–ether afforded the pure *acetate* (19) (7.623 g, 55%) as needles, m.p. 108 °C (Found: C, 49.15; H, 6.45; N, 11.2. $C_{10}H_{16}N_2O_5$ requires C, 49.15; H, 6.6; N, 11.45%), $\nu_{max.}$ ($CHCl_3$) 3 460 (NH), 1 720, and 1 690 cm^{-1} (C=O); δ($CDCl_3$) 1.28 (3 H, t, *J* 7.2 Hz, CH_2Me), 2.15 (3 H, s, Ac), 2.93 (3 H, s, NMe), 3.1—3.7 (2 H, m, 5-H_2), 4.17 (2 H, q, *J* 7.2 Hz, CH_2Me), 4.83 (1 H, dd, *J* 9.3 and 9.0 Hz, 4-H) 5.66 (1 H, d, *J* 9.3 Hz, 3-H), and 7.05br (1 H, s, NH); *m/e* 244 (M^+).

(±)-*3α-Acetoxy-4β-(N-ethoxycarbonyl-N-methylamino)-pyrrolidin-2-thione* (20).—To a stirred suspension of phosphorus pentasulphide (1.65 g) in refluxing dry benzene (25 ml) under a current of nitrogen was added dropwise a hot solution of the acetate (19) (2.44 g) in dry benzene (30 ml). The mixture was refluxed for 2 h in a current of nitrogen. The suspended solid was removed by filtration of the hot mixture through Celite and the solid washed with chloroform. The combined filtrate was evaporated and the residue chromatographed on silica gel (120 g). Elution with ethyl acetate afforded the crude thiolactam (20). Recrystallisation from ether afforded the pure *thiolactam* (20) (2.088 g, 80%) as needles, m.p. 115—116 °C (Found: C, 46.05; H, 6.35; N, 10.6. $C_{10}H_{16}N_2O_4S$ requires C, 46.15; H, 6.2; N, 10.75%), $\nu_{max.}$ ($CHCl_3$) 3 440 (NH), 1 745, 1 705sh, and 1 695 cm^{-1} (C=O); δ($CDCl_3$) 1.27 (3 H, t, *J* 7.2 Hz, CH_2Me), 2.16 (3 H, s, Ac), 2.93 (3 H, s, NMe), 3.66 (2 H, d, *J* 8.3 Hz, 5-H_2), 4.14 (2 H, q, *J* 7.2 Hz, CH_2-Me), 4.78 (1 H, dd, *J* 8.7 and 8.3 Hz, 4-H), 5.83 (1 H, d, *J* 8.7 Hz, 3-H), and 9.00br (1 H, s, NH); *m/e* 260 (M^+).

(±)-*3α-Acetoxy-4β-(N-ethoxycarbonyl-N-methylamino)-2-methoxy-Δ¹-pyrroline* (23).—A mixture of the pyrrolidone (19) (122 mg), trimethyloxonium tetrafluoroborate [10] (222 mg), molecular sieves 3A 1/16 (200 mg), and methylene chloride (2 ml) was stirred for 24 h at room temperature in a current of nitrogen. After addition of excess of 50% aqueous potassium carbonate, the mixture was stirred at 0 °C for 1 h and then extracted with ether. The organic extract was washed with brine and dried (Na_2SO_4). Eva-

poration afforded the *iminoether* (23) (121 mg, 94%) as an oil (Found: C, 51.2; H, 7.25; N, 10.4. $C_{11}H_{18}N_2O_5$ requires C, 51.15; H, 7.05; N, 10.85%); $\nu_{max.}$ ($CHCl_3$) 1 740 and 1 685 (C=O), and 1 655 cm^{-1} (C=N); δ($CDCl_3$) 1.27 (3 H, t, *J* 7.2 Hz, CH_2Me), 2.12 (3 H, s, Ac), 2.92 (3 H, s, NMe), 3.87 (3 H, s, OMe), 4.20 (2 H, q, *J* 7.2 Hz, CH_2Me), 4.56—4.93 (1 H, m, 4-H), and 5.95 (1 H, d, *J* 6.6 Hz, 3-H), *m/e* 258 (M^+).

Methyl (*Z*)-α-(2-*Bromo*-4,5-*dimethoxyphenyl*)-α-*pyrrolidin*-2-*ylideneacetate* (25).—A mixture of the pyrrolidinethione (21) [17] (507 mg), the dibromide (15) (1.846 g), and molecular sieves 3A 1/16 (5 g) in dry chloroform (30 ml) was stirred at room temperature for 31 h. After addition of DBU (1.53 g), the resulting mixture was refluxed for 88 h in a current of nitrogen. Molecular sieves were removed by filtration through Celite, and the solid washed with chloroform. The combined filtrate was evaporated and the residue chromatographed on silica gel (180 g). Elution with benzene–ethyl acetate (20 : 1 v/v) afforded compound (25) (1.732 g, 97%) as a pale brown gum, $\nu_{max.}$ ($CHCl_3$) 3 400 (NH) and 1 655 cm^{-1} (C=O); δ($CDCl_3$) 1.66—2.13 (2 H, m, 4-H_2), 2.32 (2 H, t, *J* 6 Hz, pyrrolidine 3-H_2), 3.5—3.72 (2 H, m, 5-H_2), 3.57, 3.77, and 3.83 (each 3 H, each s, 3 × OMe), 6.73 and 7.07 (each 1 H, each s, 2 × ArH), and 8.42br (1 H, s, NH); *m/e* 355 (M^+) and 357 ($M^+ + 2$).

Methyl α-[3-*Acetoxy*-4-(N-*ethoxycarbonyl*-N-*methylamino*)-*pyrrolidin*-2-*ylidene*]-α-(2-*bromo*-4,5-*dimethoxyphenyl*)-*acetates* (26) *and* (27).—(a) A mixture of the pyrrolidinethione (20) (130 mg), the dibromide (15) (184 mg), DBU (152 mg), and dry toluene (10 ml) was heated at 80 °C for 22 h, and then refluxed for 24 h, in a current of nitrogen. The solvent was evaporated off to give a residue which was chromatographed on silica gel (18 g). Elution with benzene–ethyl acetate (10 : 1 v/v) afforded the diastereoisomeric compounds (26) and (27) (117 mg, 45.4%) as a pale brown gum, $\nu_{max.}$ ($CHCl_3$) 3 390 (NH), 1 750, 1 695, and 1 672 cm^{-1} (C=O); δ($CDCl_3$) 1.25 (3 H, t, *J* 7.2 Hz, CH_2Me), 1.66 and 1.73 (3 H, each s, Ac), 2.93 (3 H, s, NMe), 3.64, 3.83, and 3.87 (each 3 H, each s, 3 × OMe), 4.16 (2 H, q, *J* 7.2 Hz, CH_2Me), 4.4—4.9 (1 H, m, 4-H), 5.75 and 6.05 (1 H, each d, *J* 4.8 and 5.6 Hz, 3-H), 6.68 and 6.77 (1 H, each s, ArH), and 7.06 (1 H, s, ArH); *m/e* 514 (M^+) and 516 ($M^+ + 2$).

(b) A mixture of the pyrrolidinethione (20) (130 mg), the dibromide (15) (184 mg), molecular sieves 3A 1/16 (2 g), and dry toluene (8 ml) was refluxed for 30 h. Molecular sieves were removed by filtration through Celite and the solids washed with benzene. The combined filtrate was evaporated to afford a residue which was chromatographed on silica gel (18 g) to give a diastereoisomeric mixture of (26) and (27) (125 mg, 48.5%), identical (i.r., n.m.r., and mass spectral data) to the foregoing sample.

(c) A mixture of the pyrrolidinethione (20) (120 mg), the dibromide (15) (169 mg), molecular sieves 3A 1/16 (2 g), DBU (140 mg), and dry tetrahydrofuran (10 ml) was refluxed for one month. Work-up as already described afforded (26) and (27) (188 mg, 79%), identical (i.r., n.m.r., and mass spectral data) to the foregoing samples.

Methyl α-[3-*Acetoxy*-4-(N-*ethoxycarbonyl*-N-*methylamino*)-*pyrrolidin*-2-*ylidene*]-α-(2-*bromo*-5-*methoxy*-4-*methylphenyl*)-*acetates* (28) *and* (29).—A mixture of the pyrrolidinethione (20) (260 mg), the dibromide (12) (352 mg), DBU (304 mg), and dry toluene (20 ml) was heated at 60—70 °C for 38 h, and then heated at 110 °C for 2 days, in a current of nitrogen. Benzene was added, and the solution washed with 10% aqueous hydrochloric acid and brine, and dried (Na_2SO_4). Evaporation gave a residue which was chromatographed on silica gel (15 g). Elution with benzene–ethyl acetate (10 : 1 v/v) gave the diastereoisomeric compounds (28) and (29) (353 mg, 70.7%) as a pale brown gum, $\nu_{max.}$ ($CHCl_3$) 3 390 (NH), 1 745, 1 695, and 1 665 cm^{-1} (C=O); δ($CDCl_3$) 1.27 (3 H, t, *J* 7.2 Hz, CH_2Me), 1.64 and 1.70 (3 H, each s, Ac), 2.20 (3 H, s, ArMe), 2.97 (3 H, s, NMe), 3.69 and 3.83 (each 3 H, each s, 2 × OMe), 4.22 (2 H, q, CH_2Me), 4.5—5.1 (1 H, m, 4-H), 5.85 and 6.14 (1 H, each d, *J* 4.8 and 6.0 Hz, 3-H), 6.71 and 6.81 (1 H, each s, ArH), 7.42 (1 H, s, ArH), and 8.60br (1 H, s, NH); *m/e* 498 (M^+) and 500 ($M^+ + 2$).

Methyl α-[3-*Acetoxy*-4-(N-*ethoxycarbonyl*-N-*methylamino*)-*pyrrolidin*-2-*ylidene*]-α-(2-*bromo*-5-*methoxy*-4-*methoxymethylphenyl*)*acetates* (30) *and* (31).—A mixture of the pyrrolidinethione (20) (150 mg), the dibromide (13) (220 mg), DBU (175 mg), and dry toluene (20 ml) was heated at 70—80 °C for 28 h and then heated at 100—115 °C for 48 h, in a current of nitrogen. The resulting mixture was taken up in benzene. The solution was evaporated and the residue chromatographed on silica gel (12 g). Elution with benzene–ethyl acetate (5 : 1 v/v) gave the diastereoisomeric compounds (30) and (31) (211 mg, 69%) as a pale brown gum, $\nu_{max.}$ ($CHCl_3$) 3 390 (NH), 1 745, 1 695, and 1 665 cm^{-1} (C=O); δ($CDCl_3$) 1.23 (3 H, t, *J* 7.2 Hz, CH_2Me), 1.61 and 1.67 (3 H, each s, Ac), 2.91 (3 H, s, NMe) 3.39, 3.61, and 3.77 (each 3 H, each s, 3 × OMe), 4.13 (2 H, q, *J* 7.1 Hz, CH_2Me), 4.42 (2 H, s, CH_2OMe), 5.74 and 6.04 (1 H, each d, *J* 4.8 and 6.2 Hz, 3-H), 6.64 and 6.73 (1 H, each s, ArH), 7.32 and 7.50 (1 H, each s, ArH), and 8.45br (1 H, s, NH); *m/e* 528 (M^+) and 530 ($M^+ + 2$).

2,3-*Dihydro*-7-*methoxy*-6-*methyl*-1H-*pyrrolo*[1,2-a]*indole*-9-*carbonitrile* (32).—A mixture of 2-methoxy-Δ[1]-pyrrolin-2-ol (22) (18 g), the nitrile (10) (12 g), and DBU (7.5 g) was heated at 95—100 °C for 7 days in a current of nitrogen. After addition of chloroform the solution was washed with 10% aqueous hydrochloric acid, water, and brine, and dried (Na_2SO_4). Evaporation afforded a black crystalline mass, recrystallisation of which from methanol gave (32) (9.6 g, 85%) as needles, m.p. 174—174.5 °C (lit.,[18] 173.5 °C), identical (i.r. and n.m.r.) to the material described in the literature.[18]

Methyl 2,3-*Dihydro*-6,7-*dimethoxy*-1H-*pyrrolo*[1,2-a]*indole*-9-*carboxylate* (34).—A mixture of compound (25) (68 mg), 50% sodium hydride in mineral oil (13.8 mg), copper(I) bromide (30 mg), and dry dimethylformamide (1.5 ml) was heated at 80 °C for 8 h with stirring in a current of nitrogen. After excess of ammonium chloride had been added the mixture was extracted with benzene. The extract was washed with aqueous ammonium chloride, water, and brine, and dried (Na_2SO_4). Evaporation gave compound (34) (50 mg, 95%). Recrystallisation from methanol afforded *needles*, m.p. 162 °C (Found: C, 65.5; H, 6.15; N, 4.9. $C_{15}H_{17}NO_4$ requires C, 65.45; H, 6.2; N, 5.1%), $\nu_{max.}$ ($CHCl_3$) 1 685 cm^{-1} (C=O); δ($CDCl_3$) 2.53—2.87 (2 H, m, 2-H_2), 3.27 (2 H, t, *J* 6.8 Hz, 1-H_2), 3.89, 3.92, and 3.98 (each 3 H, each s, 3 × OMe), and 6.74 and 7.67 (each 1 H, each s, 2 × ArH); *m/e* 275 (M^+).

Methyl (±)-1α-*Acetoxy*-2β-(N-*ethoxycarbonyl*-N-*methylamino*)-2,3-*dihydro*-6,7-*dimethoxy*-1H-*pyrrolo*[1,2-a]*indole*-9-*carboxylate* (35).—A mixture of compounds (26) and (27) (155 mg), 50% sodium hydride in mineral oil (22 mg), copper(I) bromide (47 mg), and dry dimethylformamide

(1.5 ml) was heated at 80 °C for 5 h, followed by the same treatment for compound (25), to give compound (35) (129 mg, 99%). Recrystallisation from methanol afforded the *carboxylate* (35) as needles, m.p. 171.5—172.5 °C (Found: H, 6.05; C, 58.2; H, 6.1; N, 6.25. $C_{21}H_{26}N_2O_8$ requires C, 58.05; N, 6.45%), $\nu_{max.}$ ($CHCl_3$) 1 740 and 1 690 cm^{-1} (C=O); δ($CDCl_3$) 1.20 (3 H, t, *J* 7.2 Hz, CH_2Me), 2.15 (3 H, s, Ac), 2.96 (3 H, s, NMe), 3.88, 3.97, and 4.06 (each 3 H, each s, 3 × OMe), 4.2—4.8 (2 H, m, 3-H), 5.0—5.4 (1 H, m, 2-H), 6.75 (1 H, d, *J* 3.7 Hz, 1-H), and 6.84 and 7.77 (each 1 H, each s, 2 × ArH); *m/e* 434 (M^+).

Methyl (±)-1α-*Acetoxy*-2β-(N-*ethoxycarbonyl*-N-*methylamino*)-2,3-*dihydro*-7-*methoxy*-6-*methyl*-1H-*pyrrolo*[1,2-a]-*indole*-9-*carboxylate* (36).—Similar treatment of a mixture of compounds (28) and (29) (134 mg) with 50% sodium hydride in mineral oil (32 mg), copper(I) bromide (62 mg), and dry dimethylformamide (1.3 ml) under heating at 70—80 °C for 15 h afforded the carboxylate (36) (105 mg, 93.5%). Recrystallisation from hexane gave the *carboxylate* (36) as needles, m.p. 141—142 °C (Found: C, 60.5; H, 6.25; N, 6.7%), $\nu_{max.}$ ($CHCl_3$) 1 740 and 1 690 cm^{-1} (C=O); δ($CDCl_3$) 1.20 (3 H, t, *J* 7.2 Hz, CH_2Me), 2.12 (3 H, s, Ac), 2.33 (3 H, s, ArMe), 2.90 (3 H, s, NMe), 3.83 and 3.92 (each 3 H, each s, 2 × OMe), 4.17 (2 H, q, *J* 7.2 Hz, CH_2Me), 4.2—4.8 (2 H, m, 3-H), 5.0—5.4 (1 H, m, 2-H), 6.68 (1 H, d, *J* 3.7 Hz, 1-H), and 7.08 and 7.97 (each 1 H, each s, 2 × ArH); *m/e* 418 (M^+).

Methyl (±)-1α-*Acetoxy*-2β-(N-*ethoxycarbonyl*-N-*methylamino*)-2,3-*dihydro*-7-*methoxy*-6-*methoxymethyl*-1H-*pyrrolo*-[1,2-a]*indole*-9-*carboxylate* (37).—A mixture of compounds (30) and (31) (105 mg), 50% sodium hydride in mineral oil (19 mg), copper(I) bromide (31 mg), and dry dimethylformamide (1 ml) was heated similarly at 70—80 °C to give compound (37) (74 mg, 83%) as a glass (Found: M^+, 448.182 6. $C_{22}H_{28}N_2O_8$ requires M^+, 448.184 4), $\nu_{max.}$ ($CHCl_3$) 1 742 and 1 695 cm^{-1} (C=O); δ($CDCl_3$) 1.18 (3 H, t, *J* 7.2 Hz, CH_2Me), 2.13 (3 H, s, Ac), 2.91 (3 H, s, NMe), 3.48, 3.84, and 3.92 (each 3 H, each s, 3 × OMe), 4.15 (2 H, q, *J* 7.2 Hz, CH_2Me), 4.62 (2 H, s, CH_2OMe), 4.9—5.4 (1 H, m, 2-H), 6.70 (1 H, d, *J* 3.8 Hz, 1-H), and 7.39 and 7.69 (each 1 H, each s, 2 × ArH); *m/e* 448 (M^+). All attempts at crystallisation failed.

Conversion of (37) *into* (36). A mixture of compound (37) (21 mg), 30% palladium on charcoal (2 mg), and methanol (2 ml) was stirred for 12 h at room temperature under hydrogen. After removal of the palladium on charcoal by filtration through Celite, evaporation gave the carboxylate (36) (18.5 mg, 94%) as needles, m.p. 141—142 °C, which was identical (mixed m.p., i.r., and n.m.r. spectra) to the foregoing sample.

Methyl (±)-1α-*Acetoxy*-2β-(N-*ethoxycarbonyl*-N-*methylamino*)-2,3-*dihydro*-7-*methoxy*-6-*methyl*-8-*nitro*-1H-*pyrrolo*-[1,2-a]*indole*-9-*carboxylate* (38).—A mixture of compound (36) (380 mg), 70% aqueous nitric acid (0.06 ml), and dry methylene chloride (75 ml) was stirred for 5 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 solutions were washed with saturated aqueous sodium hydrogen carbonate and brine, and dried (Na_2SO_4). Evaporation gave a residue (560 mg) which was chromatographed on silica gel (15 g). Elution with benzene–ethyl acetate (5 : 1 v/v) afforded the nitro compound (38) (385 mg, 91.5%) as a pale yellow glass. Crystallisation from hexane–methylene chloride gave pale yellow *needles*, m.p. 168—169 °C (Found: C, 54.3; H, 5.35; N, 8.95. $C_{21}H_{25}N_3O_9$ requires C, 54.4; H, 5.45; N, 9.05%), $\nu_{max.}$ ($CHCl_3$) 1 740 and 1 695 cm^{-1} (C=O); δ($CDCl_3$) 1.21 (3 H, t, *J* 7.2 Hz, CH_2Me), 2.13 (3 H, s, Ac), 2.45 (3 H, s, ArMe), 2.96 (3 H, s, NMe), 3.76 and 3.86 (each 3 H, each s, 2 × OMe), 4.14 (2 H, q, *J* 7.2 Hz, CH_2Me), 4.58 (2 H, t, *J* 10 Hz, 3-H), 4.8—5.2 (1 H, m, 2-H), 6.64 (1 H, d, *J* 3.4 Hz, 1-H), and 7.21 (1 H, s, ArH); *m/e* 463 (M^+).

Methyl (±)-1α-*Acetoxy*-2β-(N-*ethoxycarbonyl*-N-*methylamino*)-2,3,5,8-*tetrahydro*-7-*methoxy*-6-*methyl*-5,8-*dioxo*-1H-*pyrrolo*[1,2-a]*indole*-9-*carboxylate* (3). A stirred solution of compound (38) (50 mg) in acetic acid (2.5 ml) and water (0.5 ml) was heated with iron powder (300 mg) at 60 °C for 2.5 h. The mixture was then diluted with water and extracted with methylene chloride. The extract was washed with water, saturated aqueous sodium hydrogen carbonate, and brine, and dried (Na_2SO_4). Evaporation gave the crude amine (39), which was used directly in the next step. A solution of the amine (39) 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 14 h, and then diluted with water and extracted with methylene chloride. The extract was dried (Na_2SO_4) and evaporated to give a solid which on recrystallisation from methanol afforded the quinone (3) (13 mg) as yellowish needles, m.p. 169—170 °C (Found: C, 55.35; H, 5.25; N, 6.0. $C_{21}H_{24}N_2O_9,0.5H_2O$ requires C, 55.15; H, 5.5; N, 6.1%), $\lambda_{max.}$ (MeOH) 211 (ε 19 142), 244 (ε 19 142), 286 (ε 12 639), 324sh (ε 5 349), and 410 nm (ε 801); $\nu_{max.}$ ($CHCl_3$) 1 740, 1 690, 1 675sh, and 1 645 cm^{-1} (C=O); δ($CDCl_3$) 1.20 (3 H, t, *J* 7.2 Hz, CH_2Me), 1.96 (3 H, s, 6-Me), 2.12 (3 H, s, Ac), 2.98 (3 H, s, NMe), 3.83 (3 H, s, OMe), 4.10 (3 H, s, 7-OMe), 4.16 (2 H, q, *J* 7.2 Hz, CH_2Me), 4.5—4.9 (1 H, m, 2-H), and 6.46 (1 H, d, *J* 2.5 Hz, 1-H); *m/e* 448 (M^+). A further quantity of the quinone (3) (18 mg; total yield, 64%) was obtained from the mother-liquor by preparative thick-layer chromatography on silica gel using benzene–ethyl acetate (3 : 2 v/v) as developer.

We thank Mr. K. Kawamura, Mrs. C. Koyanagi, Miss K. Mushiake, Mrs. R. Kobayashi, Miss J. Okazaki, Miss Y. Kato, Miss K. Kikuchi, Miss Y. Enomoto, and Miss K. Ohtomo, for microanalyses, spectral measurements, and manuscript preparation.

[9/1246 *Received*, 7*th August*, 1979]

REFERENCES

1 T. Kametani and K. Takahashi, *Heterocycles*, 1978, **9**, 293, and references cited therein.
2 T. Kametani, K. Takahashi, M. Ihara, and K. Fukumoto, *Heterocycles*, 1978, **9**, 435.
3 T. Kametani, K. Takahashi, M. Ihara, and K. Fukumoto, *Heterocycles*, 1978, **9**, 439.
4 T. Kametani, T. Osawa, and M. Ihara, *Heterocycles*, 1979, **12**, 913.
5 T. Kametani, K. Takahashi, M. Ihara, and K. Fukumoto, *Heterocycles*, 1979, **12**, 933.
6 T. Kametani, Y. Kigawa, and M. Ihara, *Tetrahedron*, 1979, **35**, 313.
7 S. Oboshi, M. Matui, S. Ishii, N. Masago, S. Wakai, and K. Uzu, *Gann*, 1967, **58**, 315.
8 S. Kinoshita, K. Uzu, K. Nakano, M. Shimizu, and T. Takahashi, *J. Medicin. Chem.*, 1971, **14**, 103.
9 N. V. Sidgwick and E. N. Allott, *J. Chem. Soc.*, 1923, **123**, 2819.
10 T. J. Curphey, *Org. Synth.*, 1971, **51**, 142.
11 A. Eschenmoser, *Pure Appl. Chem.*, 1969, **20**, 1.
12 P. Dubs, E. Götschi, M. Roth, and A. Eschenmoser, *Chimia* (*Switz.*), 1970, **24**, 34.

[13] Y. Yamada, D. Miljkovic, P. Wehrli, B. Golding, P. Loeliger, R. Keese, K. Mueller, and A. Eschenmoser, *Angew. Chem.*, 1969, **81**, 301.
[14] M. Roth, P. Dubs, E. Götschi, and A. Eschenmoser, *Helv. Chim. Acta*, 1971, **54**, 710.
[15] I. Felner and K. Schenker, *Helv. Chim. Acta*, 1970, **53**, 754.
[16] T. Kametani, O. Umezawa, Y. Satoh, K. Ogasawara, S. Shibuya, M. Ishiguro, and D. Mizuno, *Yakugaku Zasshi*, 1963, **83**, 838.
[17] J. Tafel and P. Lawaczeck, *Ber.*, 1907, **40**, 2842.
[18] G. R. Allen, jun. and M. J. Weiss, *J. Org. Chem.*, 1965, **30**, 2904.