A Very Short Route to Fully Aromatic 2,3,8,9- and 2,3,8,9,12-Oxygenated Benzo[*c*]phenanthridines

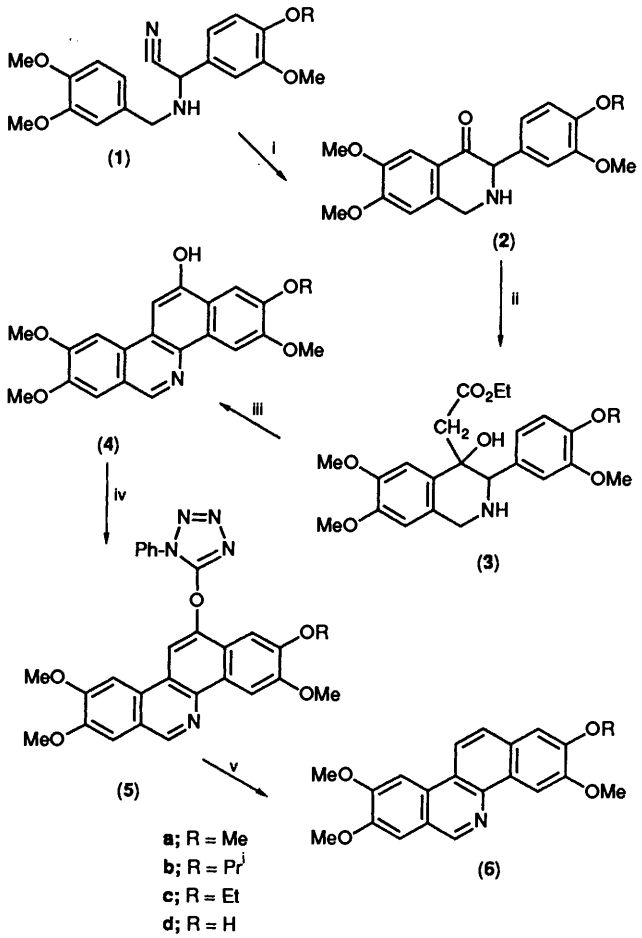
Tiwalade A. Olugbade, Roger D. Waigh,* and Simon P. Mackay
Department of Pharmacy, University of Manchester, Manchester M13 9PL

Cyclisation of suitably substituted 2-benzylamino-2-phenylacetonitriles proceeds by rearrangement, in sulphuric acid or anhydrous hydrogen fluoride, to give 3-aryl-1,2-dihydroisoquinolinones possessing all but two carbons of the benzo[*c*]phenanthridine ring system. These two carbon atoms are introduced in high yield by means of a modified Reformatski reaction and the resulting ester is cyclised in sulphuric acid, with concomitant dehydration and oxidation, to give the fully aromatic four-ring system in only four steps.

Naturally occurring 2,3,8,9-oxygenated benzo[*c*]phenanthridines are of interest for the potent antileukaemic activity (in animals) of their *N*-methyl salts.[1] The published synthetic methods are numerous, but almost without exception are very long, or include one or more photochemical steps which are not amenable to large scale reactions. The number of analogues which have been prepared for structure–action studies is therefore quite small. In contrast to the literature procedures, a two-stage synthesis of a 3-arylisoquinoline provides all but two carbons of the ring system,[2] with suitable functionalisation for the remaining ring to be added. The synthesis has now been completed (Scheme 1).

Attention to detail improved the yield of the isoquinolinone (**2a**) from 24% to 54%, in sulphuric acid, and was further raised to 66% in anhydrous hydrogen fluoride (HF). With a view to the synthesis of analogues of the highly potent antileukaemic alkaloid fagaronine,[3] the isopropyl derivative (**1b**) was prepared and cyclised, giving the phenolic isoquinolinone (**2d**) in both sulphuric acid and HF. Since deprotection was not desired at this early stage, the ethyl analogue (**1c**) was used, giving the *O*-ethyl isoquinolinone (**2c**). The use of HF as cyclising agent resulted in a 68% yield, compared to 29% in sulphuric acid.

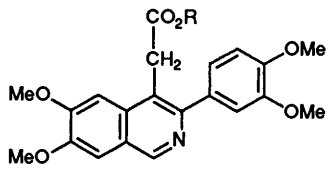
A two-carbon synthon was required, with appropriate substitution for generation of a nucleophile, and with functionality on the other carbon suitable for a subsequent acid-catalysed ring closure. The first choice was an α-halogeno acetal, but these are reported not to form stable Grignard complexes.[4] A Reformatski reaction was an alternative, although giving a different oxidation state. The normal conditions for the Reformatski reaction involve introduction of the halogeno ester and ketone into the reaction mixture together, to minimise self-condensation of the ester and zinc complex. This was not an attractive proposition when using an amino ketone which could react nucleophilically with the halogeno ester, but a modification described by Cure and Gaudemar[5] offered a way round the problem. In their method, the complex between zinc and ethyl bromoacetate is formed in the presence of dimethoxymethane. Addition of the ketone can be delayed until the complex is fully formed. At first we found that very pure zinc had to be used but the use of trimethylsilyl chloride as an initiator[6] avoids even this drawback. The method is a significant improvement and deserves to be more widely known. Using this method the esters (**3a**) and (**3c**) were obtained in yields in excess of 80%. In each case only one of the diastereoisomeric pairs was formed. We presume that attack occurs from the opposite side of the ring from the phenyl substituent, giving the isomers in which the ester and phenyl groups are *trans*. Since the next step involved dehydration the stereochemistry is not significant for the present.



Scheme 1. *Reagents and conditions:* i, H^+; ii, Reformatski; iii, H_2SO_4; iv, 5-chloro-1-phenyl-1*H*-tetrazole, K_2CO_3; v, H_2/Pd.

Cyclisation of the β-hydroxy esters (**3a**) and (**3c**) in sulphuric acid gave the fully aromatic benzo[*c*]phenanthridines (**4a**) and (**4c**) in 52 and 70% yields respectively. There was some de-ethylation in the latter reaction, giving the diphenol (**4d**) in up to 14% yield with longer reaction times. The conversion from β-hydroxy ester into fully aromatic four-ring system must involve

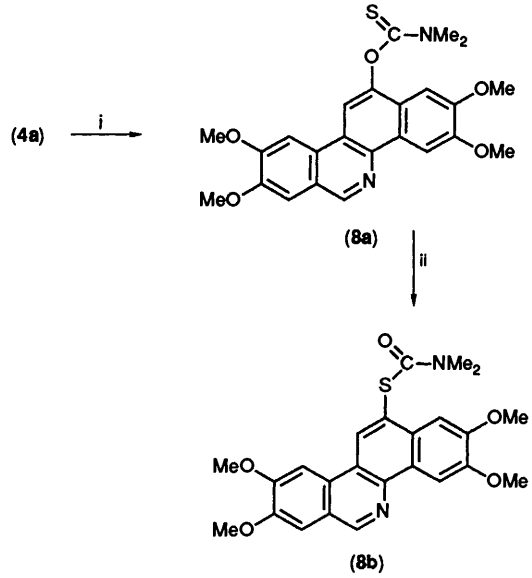
four steps, the preferred order of which is not entirely clear. Cyclisation to give a ketone and dehydration of the tertiary alcohol could occur in either order. Enolisation of the ketone would then be followed by oxidation of the 5,6-dihydrobenzo[*c*]phenanthridine by air or by sulphuric acid; such compounds are known to oxidise readily.[7] The oxidative stage is probably final, since dehydration and spontaneous aromatisation in ethanolic hydrogen chloride gave the ester (**7a**)



(7) **a**; R = Et
b; R = H

which did not cyclise in sulphuric acid. However, when the dihydrobenzo[*c*]phenanthridine was first hydrolysed using hydrochloric acid, to produce the acid (**7b**), the cyclisation in sulphuric acid proceeded readily. The latter procedure offers an alternative (longer) route to the desired benzophenanthridine but is probably not relevant to the cyclisation of the β-hydroxy esters.

In order to establish this route to the major antileukaemic alkaloids, it was necessary to show that the 12-hydroxy group could be removed. Two methods were tried; the first used thermal rearrangement of the dimethylthiocarbamate (**8a**) as a first step prior to desulphurisation (Scheme 2). The rearranged



Scheme 2. *Reagents and conditions:* i, dimethylthiocarbamoyl chloride, KOH; ii, heat.

product was obtained in poor yield, so the dehydroxylation was attempted instead *via* the tetrazolyl ether (Scheme 1). With palladium on charcoal, hydrogenation under pressure gave the de-hydroxybenzo[*c*]phenanthridines (**6a**) and (**6c**). The base (**6c**) is the required intermediate for a simple synthesis of the most potent antileukaemic alkaloid, fagaronine.

Experimental

Solutions of extracted products in organic solvents were dried over anhydrous magnesium sulphate before evaporation. IR spectra were recorded using potassium chloride discs or liquid films as appropriate. Elemental analyses which are quoted as hydrates are the results obtained after thorough drying and repeated combustion.

6,7-Dimethoxy-3-(3,4-dimethoxyphenyl)-1,2-dihydroisoquinolin-4(3H)-one (**2a**) *Hydrochloride.*—3,4-Dimethoxybenzylamine (16.7 g) in water (200 ml) was treated with dilute HCl until just acid. A solution of 3,4-dimethoxybenzaldehyde (16.6 g) in ethanol (100 ml) was added and the mixture heated on a steam bath for 30 min. Potassium cyanide (10 g) in water (50 ml) was added dropwise with vigorous stirring and the mixture stirred for a further 2 days, after which 2-(3,4-dimethoxybenzylamino)-2-(3,4-dimethoxyphenyl)acetonitrile (30.1 g, 88%) was collected by filtration and thoroughly washed with water. The amino nitrile (**1a**) had m.p. 55–57 °C (lit.,[2] 60–61 °C); IR, ^{1}H NMR and MS were in accord with those of authentic samples.

Cyclisation in hydrogen fluoride. The amino nitrile (27.4 g) in anhydrous hydrogen fluoride (150 ml) was stirred in a stoppered plastic bottle for 24 h. The reaction mixture was transferred to a plastic beaker and the HF allowed to evaporate. After 2 h the residue was diluted by the addition of crushed ice, stirred for 10 min and basified with solid sodium hydrogen carbonate while bubbling with nitrogen. The product was extracted with chloroform, the solution dried over anhydrous magnesium sulphate, diluted with ether and the isoquinoline hydrochloride (20.1 g, 66%) precipitated by addition of ethereal hydrogen chloride. The hydrochloride was sufficiently pure for further use and could be crystallised from water (m.p. 250–252 °C; lit.,[2] 255–256 °C).

Cyclisation in sulphuric acid. The aminonitrile (27.4 g) in chloroform (50 ml) was added to conc. sulphuric acid (100 ml) over a period of 10 min, the mixture stirred for 15 min, and the acid layer separated and diluted with crushed ice (*ca.* 500 g). The resulting greenish solution was stirred for 5 min and basified carefully with conc. ammonium hydroxide while cooling externally with an ice-bath and by addition of more ice. Nitrogen was bubbled through the reaction mixture during basification. The isoquinolinone was extracted with chloroform, and the solution washed with water and dried ($MgSO_4$). After filtration, excess ethereal hydrogen chloride was added to the chloroform solution and the crude isoquinolinone hydrochloride collected by filtration. Purification was effected by boiling with 96% ethanol which, on cooling, gave a white powder (16.4 g, 54%).

3-(4-Hydroxy-3-methoxyphenyl)-6,7-dimethoxy-1,2-dihydroisoquinolin-4(3H)-one (**2d**) *Hydrochloride.*—The method described above, using 4-isopropoxy-3-methoxybenzaldehyde in place of 3,4-dimethoxybenzaldehyde gave 2-(4-isopropoxy-3-methoxyphenyl)-2-(3,4-dimethoxybenzylamino)acetonitrile (**1b**), by chloroform extraction as an uncrystallisable gum in 97% yield; ν_{max} 2 240 (C≡N) and 3 320 cm^{-1} (NH); δ_H(300 MHz; $CDCl_3$) 1.35 (6 H, d, *J* 7 Hz, Me_2C), 1.90 (1 H, br s, exch., NH), 3.80 (9 H, s, OMe), 3.90 (2 H, s, CH_2N), 4.45 (1 H, sept, *J* 7 Hz, CHO), 4.65 (1 H, s, CH–N), and 6.7–7.1 (6 H, m, Ar); *m/z* 343.1784 ($M^+ - 27$, 18%. $C_{20}H_{25}NO_4$ requires 343.1783).

The aminonitrile (5 g) cyclised in anhydrous hydrogen fluoride, using the procedure described above, to give the *isoquinolinone hydrochloride*, m.p. 185–188 °C from water, in 31% yield (Found: C, 58.7; H, 5.5; N, 3.6. $C_{18}H_{20}ClNO_5$ requires C, 59.1; H, 5.5; N, 3.8%); ν_{max} 1 680 (C=O) and 3 460 cm^{-1} (OH); δ_H(300 MHz; [$^2H_6$]DMSO) 3.78 (3 H, s, OMe), 3.86 (3 H, s, OMe), 3.92 (3 H, s, OMe), 4.43 and 4.66 (2 H, AB system, *J* 15 Hz, 1-H), 5.46 (1 H, s, 3-H), 6.82–6.90 (2 H, m, Ar), 7.25 (1 H, br s, Ar), 7.26 (1 H, s, 8-H), and 7.47 (1 H, s, 5-H); *m/z* 329 (M^+, 27%), 327 (11), 300 (32), 178 (100), and 150 (15). The yield from sulphuric acid was 11%.

3-(4-*Ethoxy*-3-*methoxyphenyl*)-6,7-*dimethoxy*-1,2-*dihydroisoquinolin*-4(3H)-*one* (**2c**) *Hydrochloride*.—The aminonitrile synthesis described above, using 4-ethoxy-3-methoxybenzaldehyde, gave the desired product (**1c**) in 90% yield, m.p. 55–59 °C; ν_{max} 2 220 (C≡N) and 3 320 cm^{-1} (NH); δ_H(300 MHz; $CDCl_3$) 1.45 (3 H, t, *J* 7 Hz, CH_3C), 1.90 (1 H, br s, exch., NH), 3.85 (9 H, s, OMe), 3.90 (2 H, s, CH_2N), 4.05 (2 H, q, *J* 7 Hz, CH_2–O), 4.65 (1 H, s, CH–N), and 6.7–7.1 (6 H, m, Ar); *m/z* 329.1623 (M^+ − 27, 18%; $C_{19}H_{23}NO_4$ requires 329.1627) and 151 (100). The 2-(4-ethoxy-3-methoxyphenyl)-2-(3,4-dimethoxybenzylamino)acetonitrile thus obtained cyclised in anhydrous hydrogen fluoride, as described above, to give the *isoquinolinone hydrochloride*, m.p. 170–172 °C from aqueous ethanol, in 68% yield (Found: C, 58.6; H, 5.9; N, 3.4. $C_{20}H_{24}ClNO_5 \cdot H_2O$ requires C, 58.3; H, 6.4; N, 3.4%); ν_{max} 1 670 cm^{-1} (C=O); δ_H(300 MHz; $CDCl_3$; free base) 1.30 (3 H, t, *J* 7 Hz, CH_3C), 2.50 (1 H, br s, exch., NH), 3.70 (3 H, s, OMe), 3.77 (3 H, s, OMe), 3.81 (3 H, s, OMe), 3.95 (2 H, q, *J* 7 Hz, CH_2–O), 3.95 (2 H, s, 1-H), 4.40 (1 H, s, 3-H), 6.65–7.0 (4 H, m, Ar), and 7.40 (1 H, s, 5-H); *m/z* 357 (M^+, 16%), 355 (25), 339 (100), 328 (16), 310 (60), 178 (41), and 150 (15). The yield from sulphuric acid was 29%.

4-*Ethoxycarbonylmethyl*-6,7-*dimethoxy*-3-(3,4-*dimethoxyphenyl*)-1,2,3,4-*tetrahydroisoquinolin*-4-*ol* (**3a**).—Zinc powder (98%) was washed with dry ether and dried under reduced pressure at 80 °C for 2 h. Ethyl bromoacetate was freshly distilled under reduced pressure. Dimethoxymethane was treated with sodium wire daily until no more reaction occurred and then distilled. Dioxane and benzene were dried over sodium wire and glassware was dried at 150 °C overnight. The isoquinolinone hydrochloride was converted into the free base, dried under reduced pressure for 3 h, and used fresh.

Zinc powder (19.22 g), dimethoxymethane (60 ml), and chlorotrimethylsilane (3 ml) were placed in a flask fitted with a dropping funnel, condenser, and drying tubes and stirred at room temperature for 15 min. The flask contents were heated to reflux and stirred while ethyl bromoacetate (30 ml) in dimethoxymethane (60 ml) was added dropwise: addition was halted after the addition of 10 ml of solution to ensure that the reaction started smoothly. The remaining solution was added slowly with the reaction temperature maintained at 90–100 °C, and the mixture stirred for 3 h. The heat was turned off and a solution of isoquinolinone (**2a**) (25.0 g) in dioxane (200 ml) added and the mixture stirred for 20 h. Saturated aqueous ammonium chloride (100 ml) and sufficient chloroform to form two layers were added and after filtration the organic layer was separated, washed with saturated aqueous ammonium chloride solution (2 × 30 ml) and water (2 × 20 ml), dried, and evaporated. The residue was redissolved in chloroform (50 ml) and added dropwise to light petroleum (b.p. 40–60 °C; 250 ml), to give the *tetrahydroisoquinolinol* (97%) as a white powder, m.p. 185–186 °C (from EtOAc) (Found: C, 63.9; H, 6.7; N, 3.6. $C_{23}H_{29}NO_7$ requires C, 64.0; H, 6.8; N, 3.3%); ν_{max} 1 715 (C=O) and 3 280 cm^{-1} (NH); δ_H(300 MHz; $CDCl_3$) 1.16 (3 H, t, *J* 7 Hz, CH_3C), 1.88 (2 H, br, OH and NH), 2.75 and 3.12 (2 H, AB system, *J* 15 Hz, 4-CH_2), 3.90 (6 H, s, OMe), 3.92 (6 H, s, OMe), 4.05 (2 H, q, *J* 7 Hz, O–CH_2), 4.04 and 4.26 (2 H, AB system, *J* 15 Hz, 1-H), 4.48 (1 H, s, 3-H), 6.60 (1 H, s, 8-H), 6.90 (1 H, d, *J* 9 Hz, Ar), 7.07 (1 H, dd, *J* 2 and 9 Hz, Ar), 7.08 (1 H, s, 5-H), and 7.12 (1 H, d, *J* 2 Hz, Ar); *m/z* 431 (M^+, 0.4%), 343 (17), 314 (19), 178 (40), 166 (100), and 150 (17).

4-*Ethoxycarbonylmethyl*-3-(4-*ethoxy*-3-*methoxyphenyl*)-6,7-*dimethoxy*-1,2,3,4-*tetrahydroisoquinolin*-4-*ol* (**3c**).—Using the above method, the isoquinolinone (**2c**) gave the *tetrahydroisoquinolinol* (86%), m.p. 169–170 °C (from EtOH) (Found: C, 64.5; H, 7.0; N, 3.1. $C_{24}H_{31}NO_7$ requires C, 64.7; H, 7.0; N, 3.1%); ν_{max} 1 715 (C=O) and 3 280 cm^{-1} (NH); δ_H(90 MHz; $CDCl_3$) 1.10 (3 H, t, *J* 7 Hz, ester Me), 1.44 (3 H, t, *J* 7 Hz, ether Me), 2.95 (2 H, br, OH and NH), 2.66 and 3.07 (2 H, AB system, *J* 15 Hz, 4-CH_2), 3.80 (3 H, s, OMe), 3.82 (3 H, s, OMe), 3.84 (3 H, s, OMe), 3.95 (2 H, q, *J* 7 Hz, ether CH_2), 4.05 (2 H, q, *J* 7 Hz, ester CH_2), 3.88 and 4.15 (2 H, AB system, *J* 15 Hz, 1-H), 4.38 (1 H, s, 3-H) 6.48 (1 H, s, 8-H), 6.78 (1 H, d, *J* 9 Hz, Ar), 6.95 (1 H, dd, *J* 2 and 9 Hz, Ar), 7.00 (1 H, s, 5-H), and 7.04 (1 H, d, *J* 2 Hz, Ar); *m/z* 445 (M^+, 0.2%), 357 (17), 328 (21). 180 (100), 178 (54), and 150 (24).

2,3,8,9-*Tetramethoxybenzo*[c]*phenanthridin*-12-*ol* (**4a**).—Concentrated sulphuric acid (40 ml) was added to the β-hydroxy ester (**3a**) (8.2 g), whereupon heat was evolved initially. After being stirred for 4 days the reaction mixture was poured onto ice and the yellow *benzo*[c]*phenanthridine sulphate* (4.6 g, 52%) collected by filtration. The free base crystallised from chloroform–ethanol and could be recrystallised from pyridine–ethanol, m.p. > 320 °C, softening at 204 °C (Found: C, 68.8; H, 5.3; N, 3.7. $C_{21}H_{19}NO_5$ requires C, 69.0; H, 5.2; N, 3.8%); λ_{max}(MeOH) 232 (ε 35 700 $dm^3\ mol^{-2}\ cm^{-1}$), 250 (25 500), 286 (79 600), 340 (12 200), 358 (9 200), 380 (5 100) shifted to 294 (69 400), and 396 nm (12 200) with NaOH; δ_H(80 MHz; [$^2H_6$]DMSO) 3.97 (3 H, s, OMe), 4.00 (3 H, s, OMe), 4.03 (3 H, s, OMe), 4.10 (3 H, s, OMe), 7.63 (2 H, s, Ar), 7.73 (1 H, s, Ar), 7.80 (1 H, s, Ar), 8.60 (1 H, s, Ar), 9.13 (1 H, s, 6-H), and 10.38 (1 H, br, OH); *m/z* 365 (M^+, 100%), 364 (24), 350 (10), and 336 (12).

2-*Ethoxy*-3,8,9-*trimethoxybenzo*[c]*phenanthridin*-12-*ol* (**4c**) *and* 3,8,9-*Trimethoxybenzo*[c]*phenanthridine*-2,12-*diol* (**4d**).—Concentrated sulphuric acid (60 ml) was added to the β-hydroxy ester (**3c**) (12.0 g). The mixture was stirred for 24 h, diluted with ice, basified and extracted to give the crude benzo[*c*]phenanthridine. Chromatography on neutral alumina, eluting with chloroform–ethanol (9:1) gave the pure 2-*ethoxybenzo*[c]*phenanthridine* (**4c**) (70%) m.p. > 320 °C (from $CHCl_3$–EtOH) (Found: C, 67.9; H, 5.6; N, 3.5. $C_{22}H_{21}NO_5 \cdot 0.5H_2O$) requires C, 68.0; H, 5.7; N, 3.6%); λ_{max}(MeOH) 233 (ε 25 000 $dm^3\ mol^{-1}\ cm^{-1}$), 251 (19 400), 287 (58 900), 342 (8 900), 359 (7 800), 378 (4 400) shifted to 294 (52 800), and 396 nm (9 400) with NaOH; δ_H(90 MHz; [$^2H_6$]DMSO) 1.40 (3 H, t, *J* 7 Hz, CH_3C), 3.97 (3 H, s, OMe), 4.03 (3 H, s, OMe), 4.07 (3 H, s, OMe), 4.20 (2 H, q, *J* 7 Hz, O–CH_2), 7.63 (2 H, s, Ar), 7.73 (1 H, s, Ar), 7.80 (1 H, s, Ar), 8.62 (1 H, s, Ar), 9.13 (1 H, s, 6-H), and 10.36 (1 H, br, OH); *m/z* 379 (M^+, 100%), 378 (13), 350 (38), and 322 (14).

If exposure to sulphuric acid was extended to 2 days, chromatography as above gave first the 2-ethoxybenzo[*c*]phenanthridine (**4c**) (21%). Elution with chloroform–ethanol (1:4) then gave the *benzo*[c]*phenanthridine*-2,12-*diol* (**4d**) (14%), m.p. 225–227 °C (from $CHCl_3$–EtOH) (Found: C, 66.7; H, 4.8; N, 3.8. $C_{20}H_{17}NO_5 \cdot 0.5H_2O$ requires C, 66.7; H, 5.1; N, 3.9%); λ_{max}(MeOH) 235 (ε 31 500 $dm^3\ mol^{-1}\ cm^{-1}$), 251 (20 700), 289 (53 200), 343 (8 100), 356 (6 300), 380 (4 000) shifted to 296 (39 200), and 359 nm (9 000) with NaOH; δ_H 3.97 (3 H, s, OMe), 4.03 (3 H, s, OMe), 4.07 (3 H, s, OMe), 7.60 (1 H, s, Ar), 7.63 (1 H, s, Ar), 7.70 (1 H, s, Ar), 7.80 (1 H, s, Ar), 7.80 (1 H, s, Ar), 8.60 (1 H, s, Ar), 9.13 (1 H, s, 6-H), and 10.36 (2 H, br, OH); *m/z* 351 (M^+, 100%), 350 (29), and 308 (10).

3-(3,4-*Dimethoxyphenyl*)-4-*ethoxycarbonylmethyl*-6,7-*dimethoxyisoquinoline* (**7a**).—The β-hydroxy ester (**3a**) (2.06 g) was heated under reflux in ethanolic hydrogen chloride (55 ml) for 3 h. The mixture was concentrated to one-fifth volume and the crystalline isoquinoline hydrochloride (1.2 g, 56%; ν_{max} 1 720 cm^{-1}) collected by filtration. The *isoquinoline* was obtained by basification and extraction with chloroform, m.p. 123–125 °C

[from EtOAc–light petroleum (b.p. 60–80 °C)] (Found: C, 67.0; H, 6.1; N, 3.4. $C_{23}H_{25}NO_6$ requires C, 67.1, H, 6.1; N, 3.4%); *m/z* 411 (M^+, 100%), 396 (17), 382 (6), and 338 (43).

When the isoquinoline hydrochloride (0.6 g) was dissolved in concentrated sulphuric acid (4 ml), stirred and monitored by TLC daily, no benzo[*c*]phenanthridine (**4a**) was detected in 22 days.

4-*Carboxymethyl*-3-(3,4-*dimethoxyphenyl*)-6,7-*dimethoxyisoquinoline Hydrochloride* (**7b**) *and Its Conversion into* 2,3,8,9-*tetramethoxybenzo*[c]*phenanthridin*-12-*ol* (**4a**).—The ester hydrochloride (**7a**) (0.3 g) was boiled under reflux in 5M hydrochloric acid for 5 h. Evaporation to dryness gave the 4-*carboxymethylisoquinoline hydrochloride* (0.22 g, 79%). The analytical sample was crystallised from ethanol–ether, m.p. 169–174 °C (Found: C, 58.9; H, 5.2; N, 3.7. $C_{21}H_{21}NO_6 \cdot 0.5H_2O$ requires C, 58.8; H, 5.4; N, 3.3%); ν_{max} 1 700 cm^{-1}.

The carboxymethyl isoquinoline hydrochloride (0.14 g) was added to concentrated sulphuric acid (5 ml) and stirred overnight. Dilution with ice, basification with sodium carbonate and extraction with chloroform gave 2,3,8,9-tetramethoxybenzo[*c*]phenanthridin-12-ol (80 mg, 66%).

12-(*Dimethylthiocarbamoyloxy*)-2,3,8,9-*tetramethoxybenzo*[c]*phenanthridine* (**8a**).—The benzo[*c*]phenanthridin-12-ol (**4a**), (1.0 g) was dissolved in aqueous potassium hydroxide (10%; 15 ml). Tetrahydrofuran (3 ml) was added and the solution cooled to below 10 °C with an ice-bath. Dimethylthiocarbamoyl chloride (1.7 g) in tetrahydrofuran (5 ml) was added dropwise, with cooling. Stirring was continued for 15 min after which the mixture was diluted with water (20 ml) and the crude product collected by filtration. Crystallisation ($CHCl_3$–MeOH) gave the *thiocarbamate* (0.41 g, 42%), m.p. 274–276 °C (Found: C, 61.3; H, 5.4; N, 5.8. $C_{24}H_{24}N_2O_5 \cdot H_2O$ requires C, 61.3; H, 5.6; N, 6.0%); δ_H 3.65 (6 H, s, NMe_2), 4.05 (3 H, s, OMe), 4.10 (3 H, s, OMe), 4.15 (3 H, s, OMe), 4.20 (3 H, s, OMe), 7.18 (1 H, s, Ar), 7.38 (1 H, s, Ar), 7.78 (1 H, s, Ar), 8.00 (1 H, s, Ar), 8.75 (1 H, s, Ar), and 9.23 (1 H, s, 6-H); *m/z* 452 (M^+, 61%), 365 (14), 88 (100), and 72 (81).

12-(*Dimethylcarbamoylthio*)-2,3,8,9-*tetramethoxybenzo*[c]-*phenanthridine*.—The *O*-arylthiocarbamate described above (**8a**) (42 mg) in digol (1 ml) was heated at 250 °C for 1.5 h, cooled, and refrigerated for 1 week. The supernatent was decanted and the residue triturated with ether. The solid was collected by filtration and crystallised (EtOH) to give the *benzophenanthridine* (10 mg, 24%), m.p. 235–240 °C, recrystallising at 222 °C. There was insufficient material for microanalysis, but IR, ^1H NMR, and MS confirmed the structure: ν_{max}(KCl) 1 660 cm^{-1} (C=O); δ_H 3.18 (6 H, br, NMe_2), 4.08 (6 H, s, OMe), 4.15 (3 H, s, OMe), 4.18 (3 H, s, OMe), 7.35 (1 H, s, Ar), 7.73 (1 H, s, Ar), 7.83 (1 H, s, Ar), 8.60 (1 H, s, Ar), 8.73 (1 H, s, Ar), and 9.23 (1 H, s, 6-H); *m/z* 452.1416 (68%; $C_{24}H_{24}N_2O_5S$ requires 452.1406), 380 (16), and 72 (100).

2,3,8,9-*Tetramethoxy*-12-(1-*phenyl*-1H-*tetrazol*-5-*yloxy*)-*benzo*[c]*phenanthridine* (**5a**).—A mixture of dry acetone (20 ml), anhydrous potassium carbonate (3 g) and the benzo[*c*]phenanthridinol (**4a**) sulphate (2.48 g) was stirred and warmed for 15 min. 5-Chloro-1-phenyl-1*H*-tetrazole (1.4 g) was added and the mixture heated under reflux for 24 h. After cooling and addition of aqueous sodium hydroxide (5%; 20 ml) the solid product was collected by filtration and washed with water. The *tetrazolyl ether* crystallised from MeOH–$CHCl_3$ as long white needles (2.033 g, 75%), m.p. 258–260 °C (decomp.) (Found: C, 64.9; H, 4.3; N, 13.3. $C_{28}H_{23}N_5O_5 \cdot 0.5H_2O$ requires C, 64.9; H, 4.7; N, 13.5%); *m/z* 509.1703 (M^+; $C_{28}H_{23}N_5O_5$ requires 509.1699); δ_H(80 MHz; $CDCl_3$), 3.85 (3 H, s, OMe), 4.09 (3 H, s, OMe), 4.14 (3 H, s, OMe), 4.17 (3 H, s, OMe), 7.24 (1 H, s, Ar), 7.36 (1 H, s, Ar), 7.59–7.75 (4 H, s, and m, Ar), 7.91–7.98 (2 H, m, Ar), 8.73 (2 H, s, Ar), and 9.19 (1 H, s, 6-H).

2,3,8,9-*Tetramethoxybenzo*[c]*phenanthridine* (**6a**).—The above tetrazolyl ether (**5a**) (2.0 g) in dioxane (100 ml) was hydrogenated over palladium-on-charcoal (5%; 1.0 g) at 60 °C for 24 h., at 10 atm. The cooled mixture was filtered and the solid collected, placed on a short column of silica gel and eluted with $CHCl_3$–EtOH (9:1) to give the *benzophenanthridine* (0.9 g, 66%). A sample recrystallised from pyridine had m.p. 307–310 °C (lit.,[8] m.p. varies from 299–301 °C to 306–308 °C); δ_H 4.08 (3 H, s, OMe), 4.09 (3 H, s, OMe), 4.15 (3 H, s, OMe), 4.20 (3 H, s, OMe), 7.29 (1 H, s, Ar), 7.37 (1 H, s, Ar), 7.85 (1 H, s, *J* 9 Hz, Ar), 7.90 (1 H, s, Ar), 8.29 (1 H, d, *J* 9 Hz, Ar), 8.74 (1 H, s, Ar), and 9.24 (1 H, s, Ar), and 9.24 (1 H, s, 6-H); *m/z* 349 (M^+, 100%).

2-*Ethoxy*-3,8,9-*trimethoxy*-12-(1-*phenyl*-1H-5-*tetrazol*-5-*yloxy*)*benzo*[c]*phenanthridine* (**5c**).—A mixture of the benzo[*c*]phenanthridinol (**4c**) 0.8 g dry dimethylformamide (10 ml), and potassium t-butoxide (0.33 g) was stirred under nitrogen until the phenol dissolved (3 min). 5-Chloro-1-phenyl-1*H*-tetrazole (0.5 g) was added and the mixture stirred under nitrogen for 20 min. The cloudy solution was poured onto ice and the *tetrazolyl ether* (0.7 g, 64%) collected by filtration. The analytical sample crystallised as long needles, m.p. 260–266 °C (MeOH–$CHCl_3$) (Found: C, 66.2; H, 5.0; N, 13.4. $C_{29}H_{25}N_5O_5$ requires C, 66.5; H, 4.8; N, 13.4%); *m/z* 523 (M^+, 8%), 495 (49), 453 (32), and 379 (100); δ_H(80 MHz; CF_3COOD) 1.39 (3 H, t, *J* 7.8 Hz, CH_3C), 4.14 (6 H, s, OMe), 4.25 (3 H, s, OMe), 4.08 (2 H, q, *J* 7.8 Hz, CH_2C), 7.45 (1 H, s, Ar), 7.61–7.85 (6 H, m and s, Ar), 8.08 (1 H, s, Ar), 8.20 (1 H, s, Ar), 8.84 (1 H, s, Ar), and 9.42 (1 H, s, 6-H).

2-*Ethoxy*-3,8,9-*trimethoxybenzo*[c]*phenanthridine* (**6c**).—The above tetrazolyl ether (**5c**) (0.56 g) was hydrogenated as described to give the *benzo*[c]*phenanthridine* (155 mg, 40%), m.p. 271–274 °C, recrystallising at 233–238 °C (from $CHCl_3$–MeOH); δ_H 1.60 (3 H, t, *J* 8 Hz, CH_3C), 4.10 (3 H, s, OMe), 4.17 (3 H, s, OMe), 4.20 (3 H, s, OMe), 4.33 (2 H, q, *J* 8 Hz, CH_2O), 7.30 (1 H, s, Ar), 7.40 (1 H, s, Ar), 7.87 (1 H, d, *J* 9 Hz, Ar), 7.93 (1 H, s, Ar), 8.33, (1 H, d, *J* 9 Hz, Ar), 8.77 (1 H, s, Ar), and 9.27 (1 H, s, 6-H); *m/z* 363.1467 (100%; $C_{22}H_{21}NO_4$ requires 363.1470), 348 (6.1), 334 (40.6), and 318 (5.7).

Acknowledgements

We thank the Nigerian Government for support of T. A. O. and the SERC for support of S. P. M.

References

1 M. Suffness and G. A. Cordell in 'The Alkaloids,' ed. A. Brossi, Academic Press, New York, 1985, vol. 25, p. 178.
2 D. N. Harcourt and R. D. Waigh, *J. Chem. Soc. C*, 1971, 967.
3 G. A. Cordell and N. R. Farnsworth, *Heterocycles*, 1976, **4**, 393.
4 C. Feugeas, *Bull. Soc. Chim. Fr.*, 1963, 2568; J. C. Stowell, *J. Org. Chem.*, 1976, **41**, 560.
5 J. Cure and M. Gaudemar, *Bull. Soc. Chim. Fr.*, 1969, 2471; M. W. Rathke, *Org. React.* 1975, **22**, 423.
6 G. Picotin and P. Miginiae, *J. Org. Chem.*, 1987, **52**, 4796.
7 R. H. F. Manske in 'The Alkaloids,' ed. R. H. F. Manske, Academic Press, New York, 1954, vol. 4, p. 256.
8 A. S. Bailey, R. Robinson, and R. S. Staunton, *J. Chem. Soc.*, 1950, 2277; S. F. Dyke and M. Sainsbury, *Tetrahedron*, 1967, **23**, 3161; S. F. Dyke, M. Sainsbury, and B. J. Moon, *ibid.*, 1968, **24**, 1467.

Paper 0/00913J
Received 27*th February* 1990
Accepted 2*nd May* 1990