Tetrahedron. Vol 24, pp. 1467 to 1474. Pergamon Press 1968. Printed in Great Britain

1,2-DIHYDROISOQUINOLINES—VII[1]

NEW SYNTHESES OF AVICINE AND NITIDINE DERIVATIVES

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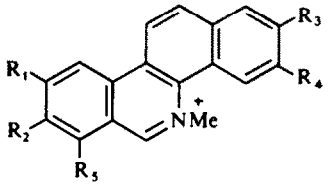
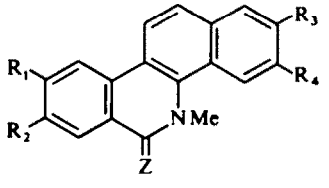
(*Received in the UK* 22 *June* 1967; *accepted for publication* 23 *July* 1967)

Abstract—Synthetic routes to the benzo[c]phenanthridine ring system have been investigated, and new syntheses of oxyavicine (**2a**), 2,3-dimethoxy-8,9-methylenedioxybenzo[c]phenanthridine (**5c**) and 2,3,8,9-tetramethoxybenzo[c]phenanthridine (**5a**) are described.

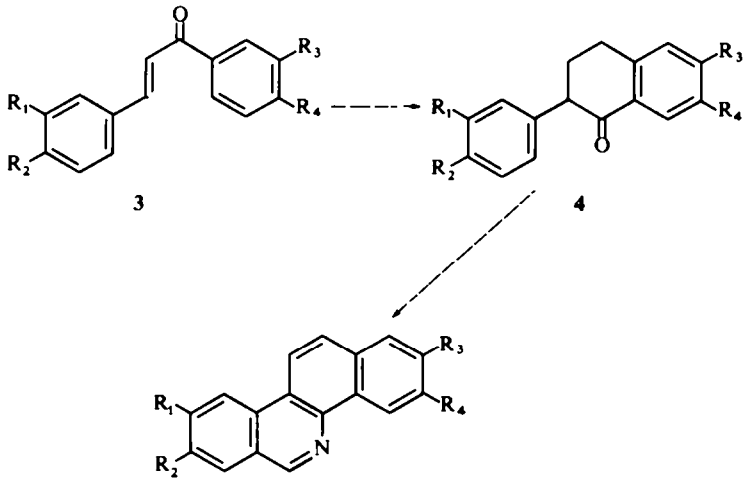
THE benzo[c]phenanthridine alkaloids avicine (**1a**) and nitidine (**1b**) were isolated and characterized by Arthur *et al.*[2] who found that they readily disproportionate into the oxy-forms (**2a** and **2b**) and the corresponding dihydro derivatives (**2c** and **2d**) respectively. Syntheses of oxyavicine (**2a**)[3] and dihydronitidine (**2d**)[4] have been reported by essentially the same method as established by Bailey *et al.*[5] in their synthesis of chelerythrine (**1c**). In this method the necessary chalcone (**3**) was converted via the 2-aryl-1-tetralone (**4**) into the fully aromatic benzo[c]phenanthridine (**5**), which was then N-methylated and either oxidized to oxyavicine (**2a**) or reduced to dihydronitidine (**2d**). Some other oxygenated benzo[c]phenanthridines (**5**) have also been prepared[6] by this method.



1a $R_1, R_2 = R_3, R_4 = CH_2O_2; R_5 = H.$
1b $R_1 = R_2 = OMe; R_3, R_4 = CH_2O_2; R_5 = H.$
1c $R_2 = R_5 = OMe; R_3, R_4 = CH_2O_2; R_1 = H.$

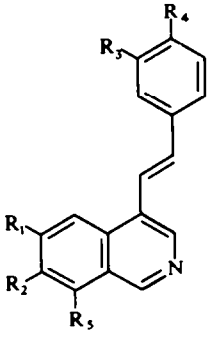


2a $R_1, R_2 = R_3, R_4 = CH_2O_2; Z = O.$
2b $R_1 = R_2 = OMe; R_3, R_4 = CH_2O_2; Z = O.$
2c $R_1, R_2 = R_3, R_4 = CH_2O_2; Z = H_2.$
2d $R_1 = R_2 = OMe; R_3, R_4 = CH_2O_2; Z = H_2.$



5a $R_1 = R_2 = R_3 = R_4 = OMe$.
5b $R_1, R_2 = R_3, R_4 = CH_2O_2$.
5c $R_1 = R_2 = OMe$; $R_3R_4 = CH_2O_2$.
5d $R_1 = R_2 = R_3 = R_4 = H$.

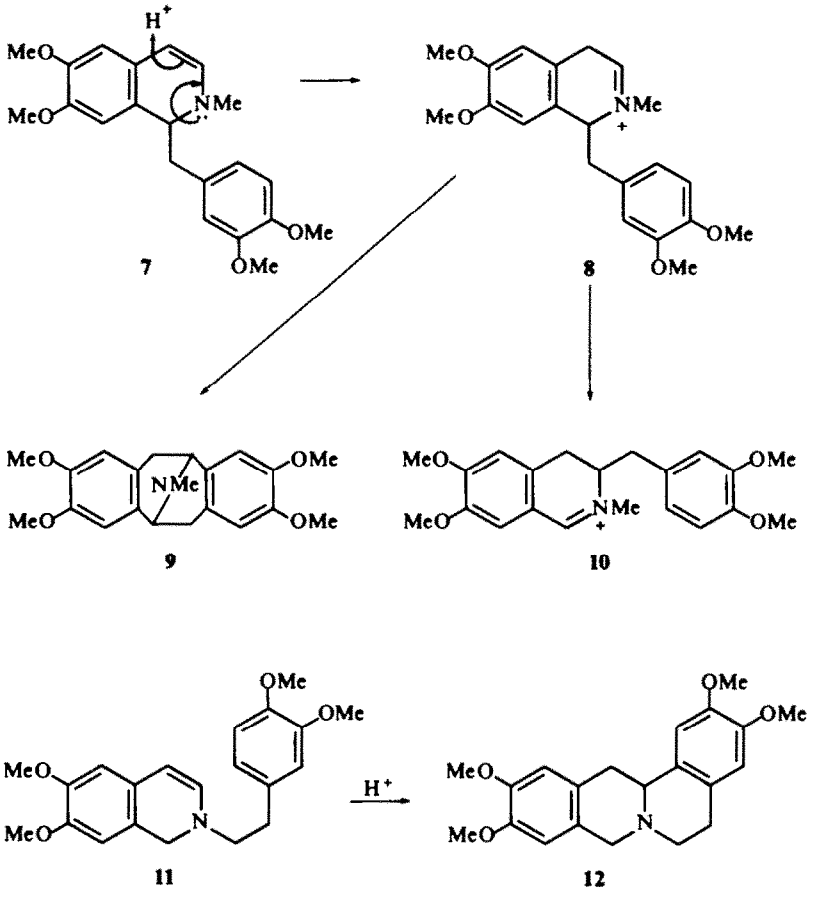
In Part V of this series[7] we described an efficient method for the synthesis of styrenes of the type **6**, which were required for attempted photochemical ring closure to the benzo[c]phenanthridine ring system. We had hoped, in view of the high overall yield of 2,3,8,9-tetramethoxybenzo[c]phenanthridine (**5a**) obtained by the photolysis of the styrene (**6a**), that this synthetic route might prove to be of general value in the preparation of the alkaloids of this group. However, the unsymmetrically substituted styrenes (**6c** and **6d**) have so far proved to be very difficult to cyclise under our conditions and so we have sought alternative synthetic routes to the benzo[c]-phenanthridine ring system.



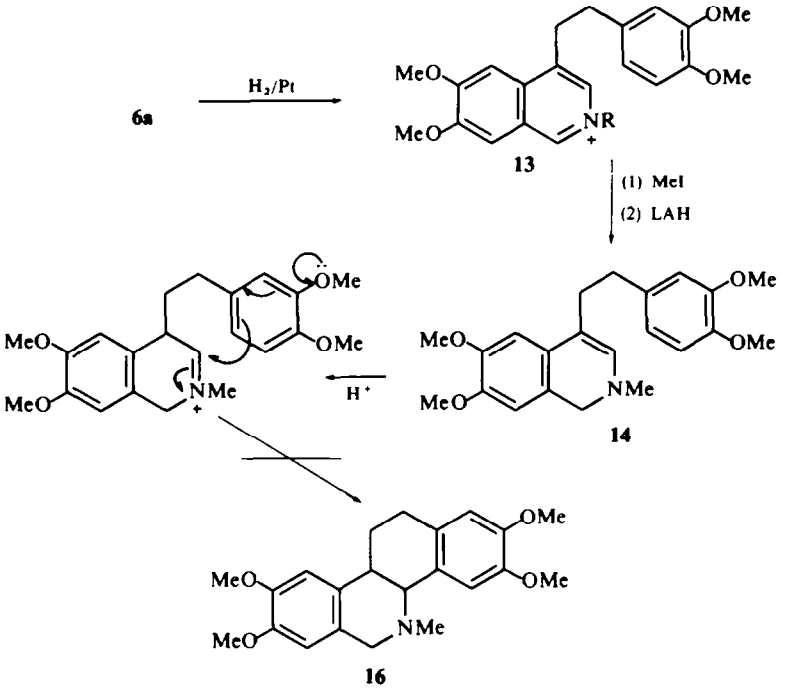
6a $R_1 = R_2 = R_3 = R_4 = OMe$; $R_5 = H$.
6b $R_1, R_2 = R_3, R_4 = CH_2O_2$; $R_5 = H$.
6c $R_1 = R_2 = OMe$; $R_3, R_4 = CH_2O_2$; $R_5 = H$.
6d $R_2 = R_3 = R_4 = R_5 = OMe$; $R_1 = H$.

It is well-known that when a 1,2-dihydroisoquinoline, for example **7**, is treated with mineral acid the C_4-protonated form **8** that results is susceptible to nucleophilic

attack at C_3. Examples of such reactions are provided by the formation of N-methylpavine[8] (**9**), from **7**, the rearrangement of **7** to the 3-benzyl-3,4-dihydroisoquinolinium salt[9] (**10**), and the formation of the berbine skeleton, for example **12** from the N-(β-arylethyl)-1,2-dihydroisoquinoline (**11**).[10]

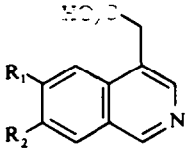


It seemed to us that an analogous synthesis of the benzo[c]-phenanthridine ring system should be possible from a suitably substituted 4-(β-arylethyl)-1,2-dihydroisoquinoline (**14** → **16**), and to test this hypothesis we chose the derivative **14**. This was readily prepared by the catalytic hydrogenation of the styrene **6a** to **13**, (R = H), followed by reduction of the methiodide with LAH. Although the conditions of acid treatment were varied over wide limits, the only observable reaction of the dihydroisoquinoline (**14**) was disproportionation into **13**, (R = Me) and the corresponding 1,2,3,4-tetrahydroisoquinoline. In our experience such a disproportionation occurs extremely readily with 4-substituted -1,2-dihydroisoquinolines.

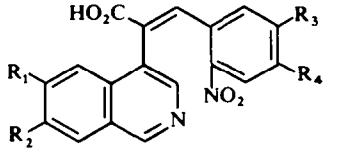


In 1963 Abramovitch and Tertzakian[11] described a new synthesis of benzo[c]-phenanthridine itself (**5d**) that involved the condensation of 4-isoquinolylacetic acid (**17c**) with *o*-nitrobenzaldehyde, reduction of the resulting *cis*-styrene **18d** to the amino acid **19d** followed by a Pschorr-type ring-closure to **20d** and final decarboxylation to **5d**. Unfortunately the starting material **17c** was only available in an 8-stage sequence from isoquinoline, and hence this otherwise attractive route to the benzo[c]-phenanthridines was not further studied.

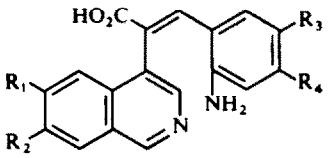
It has been shown[12] that benzaldehyde may be condensed with aminoacetals of the type **21** (R_3 = H) to yield 4-benzylisoquinoline derivatives, and we have examined a large number of other aldehydes in this reaction.[13] We have now found that glyoxylic acid will react with these aminoacetals to yield an easily separable mixture of the corresponding 2- and 4-isoquinolylacetic acids in good yield. By using the N-methyl-aminoacetals **21** (R_3 = Me) yields of the 4-isoquinolylacetic acids approaching



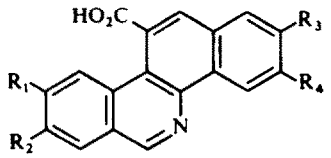
17a $R_1, R_2 = CH_2O_2$.
17b $R_1 = R_2 =$ OMe.
17c $R_1 = R_2 =$ H.



18a $R_1, R_2 = R_3, R_4 = CH_2O_2$.
18b $R_1 = R_2 =$ OMe; $R_3, R_4 = CH_2O_2$.
18c $R_1 = R_2 = R_3 = R_4 =$ OMe.
18d $R_1 = R_2 = R_3 = R_4 =$ H.

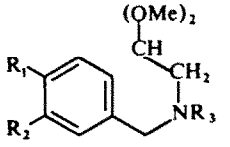


19a $R_1, R_2 = R_3, R_4 = CH_2O_2$.
19b $R_1 = R_2 = OMe$; $R_3, R_4 = CH_2O_2$.
19c $R_1 = R_2 = R_3 = R_4 = OMe$.
19d $R_1 = R_2 = R_3 = R_4 = H$.

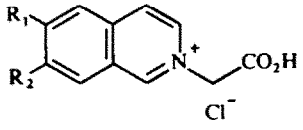


20a $R_1, R_2 = R_3, R_4 = CH_2O_2$.
20b $R_1 = R_2 = OMe$; $R_3, R_4 = CH_2O_2$.
20c $R_1 = R_2 = R_3 = R_4 = OMe$.
20d $R_1 = R_2 = R_3 = R_4 = H$.

90% have been realized. We have thus been able to examine further the scope of the Abramovitch and Tertzakian route to the benzo[c]phenanthridines and report here new syntheses of oxyavicine (**2a**), 2,3-dimethoxy-8,9-methylenedioxybenzo[c]-phenanthridine (**5c**) and 2,3,8,9-tetramethoxybenzo[c]phenanthridine (**5a**).



21a $R_1, R_2 = CH_2O_2$; $R_3 = H$.
21b $R_1 = R_2 = OMe$; $R_3 = H$.



22a $R_1, R_2 = CH_2O_2$

The interaction of the aminoacetal **21a** with glyoxylic acid in HCl solution gave the 4-isoquinolylacetic acid (**17a**) in 68% yield, together with small amounts of the N-substituted isoquinolinium salt (**22a**). Condensation of **17a** with 6-nitropiperonal produced a 74% yield of the styrene **18a** which was reduced with ammoniacal ferrous sulphate to **19a** (60%). Ring-closure of **19a**, essentially as described by Abramovitch and Tertzakian[11] gave **20a**, which, without isolation was decarboxylated thermally to 2,3,8,9-bismethylenedioxybenzo[c]phenanthridine (**5b**). The overall yield of **5b** *from piperonal* was 5%. Finally N-methylation of **5b**, followed by oxidation yielded oxyavicine, identical with an authentic specimen derived[2] from the natural product.

Repetition of the above synthetic sequences with 4-(6,7-dimethoxyisoquinolyl)acetic acid (**17b**) and 6-nitropiperonal gave 2,3-dimethoxy-8,9-methylenedioxybenzo[c]-phenanthridine (**5c**) identified by comparison with an authentic sample.[3]

Finally by using 6-nitroveratraldehyde with **17b**, 2,3,8,9-tetramethoxybenzo[c]-phenanthridine (**5a**) was produced, identical with a sample prepared[7] by photochemical ring-closure of the styrene **6a**.

EXPERIMENTAL

Mps are uncorrected. UV spectra were determined in EtOH soln; IR spectra were measured as nujol mulls and chemical shifts are measured in ppm downfield from TMS as an internal standard.

6,7-Dimethoxy-4-(3,4-dimethoxyphenylethyl)isoquinolinium methiodide (**13**). The styrene **6a** in HCl aq was treated with a molar equiv of $NaClO_4$ in water, and the immediate yellow ppt collected and crystallized from aqueous acetone as needles, m.p. 241–242°, yield 92%; λ_{max} mμ, (ε) 265 (26,900), 350 (10,800), ν_{max} cm^{-1}, 1645 (>C=N<), 1610, 1595 (>C=C<), 1110 (ClO_4^-). (Found: C, 54·3; H, 5·3; N, 3·3. $C_{22}H_{24}NO_8Cl$ requires: C, 54·6; H, 5·4; N, 2·90%.)

This perchlorate (0·2 g) was dissolved in acetone (30 ml) containing water (4 ml) and 1 drop $HClO_4$ (60%) and hydrogenated at 2 atm press over Adam's catalyst (0·02 g) for 6 hr. After removal of the catalyst the acetone was evaporated and the residue cooled to 0°. Collection of the solid product and crystallization from EtOH yielded very pale yellow prisms (0·16 g) m.p. 216–217°; λ_{max} mμ, (ε) 257 (56,200); 318 (11,650); ν_{max} cm^{-1}, 1655 (>C=N<), 1635, 1620, 1600 (>C=C<), 1100 (ClO_4^-); NMR (CF_3CO_2H) ppm, 8·9 doublet [1] J = 5·5 c/s (C_1—H), 7·85 doublet [1] J = 5·5 c/s (C_3—H) 7·5 singlet [1], 7·25 singlet [1], (C_5—H) (C_8—H) ~6·60 complex [3], ~3·30 complex [4] (Ar—CH_2CH_2—). (Found: C, 55·6; H, 5·4; N, 3·2. $C_{21}H_{24}NO_4$, ClO_4 requires: C, 55·5; H, 5·3; N, 3·1%.)

Basification of this material with ammonia gave the free isoquinoline as a pale yellow gum which crystallized on trituration with ether and recrystallized from EtOH as imperfect cubes m.p. 118–120°, yield 82%; λ_{max} mμ, (ε) 240 (32,450), 281 (4570), 313 (2500), 328 (2710). ν_{max} cm^{-1}, 1625 (>C=N<) 1615, 1590 (>C=C<); NMR ($CDCl_3$) ppm, 8·6 singlet [1] (C_1—H), 7·9 singlet [1] (C_3—H), 2·9 complex [4] (—CH_2—CH_2Ar). (Found: C, 71·2; H, 6·45; N, 3·8. $C_{21}H_{23}NO_4$ requires: C, 71·4; H, 6·6; N, 4·0%.)

Methiodide, pale yellow prisms, m.p. 220–222° from $CHCl_3$–EtOH; λ_{max} mμ, (ε) 256 (47,550), 317 (10,850), sh 345 (6795). ν_{max} cm^{-1}, 1650 (>C=N<), 1625, 1600 (>C=C<). (Found: C, 53·4; H, 5·1; N, 3·1. $C_{22}H_{26}NO_4I$ requires: C, 53·3; H, 5·3; N, 2·8%.)

6,7-Dimethoxy-2-methyl-4-(3,4-dimethoxyphenylethyl)1,2-dihydroisoquinoline (**14**). The methiodide (0·2 g) prepared in the previous experiment was carefully dried and pulverized. This material was added in portions to a suspension of LAH (0·2 g) in THF (100 ml). After stirring for 4 hr at room temp the reaction was protected by an atm of N_2 and the excess reagent decomposed by the addition of 33% aqueous sodium potassium tartarate soln. Ether (250 ml) was then added and the combined solvent layer decanted quickly from the solid residue. Water (15 ml) was added to the ethereal layer and the solvents removed under a reduced press of N_2. The solid thus produced was collected and rapidly recrystallized from EtOH, affording pale pink coloured feathery needles (0·11 g), m.p. 89–90°; λ_{max} mμ, (ε) sh 250 (10,233), 285 (4467), 335 (7586). ν_{max} cm^{-1}, 1635, 1600, 1585 (>C=C<). (Found: C, 70·9; H, 7·2; N, 4·2. $C_{21}H_{25}NO_4$ requires: C, 71·0; H, 7·1; N, 3·9%.)

6,7-Dimethoxy-2-methyl-4-(3,4-dimethoxyphenylethyl)1,2,3,4-tetrahydroisoquinoline. 6,7-Dimethoxy-4-(3,4-dimethoxyphenylethyl)isoquinoline methiodide (0·2 g) in EtOH (25 ml) containing water (1 ml) was treated with $NaBH_4$ (0·2 g). After heating for 1 hr on a water-bath the solvent was removed and the tetrahydro-base extracted into ether. Evaporation of the ether gave a colourless gum, which was not obtained crystalline even after chromatography upon alumina, eluting with benzene. TLC showed one spot r.f. 0·7 (silica gel; solvent: 20% diethylamine in $CHCl_3$). NMR ($CDCl_3$) ppm, 6·50 singlet [3] (3 aromatic protons), 6·35 singlet [1] and 6·20 singlet [1] (C_5—H, C_8—H), 3·25 quartet [2] J = 14 c/s, (Ar·CH_2—N<), 2·25 singlet [3] (NCH_3). Methiodide, m.p. 103–105° from MeOH. (Found: C, 52·8; H, 6·35; H, 2·5. $C_{23}H_{32}NO_4I$, CH_3OH requires: C, 52·8; H, 6·65; H, 2·6%.)

3,4-Methylenedioxybenzylaminoacetaldehydedimethylacetal (**21a**). Piperonal (80 g) and aminoacetaldehydedimethylacetal (56 g) in benzene (500 ml) were heated under a Dean Stark head at reflux until the theoretical volume of water had been collected. After removal of the solvent the residue was dissolved in EtOH (500 ml) and hydrogenated at atm press over Adams' catalyst until one mol equiv of H_2 had been taken up. The EtOH was then removed and the residual oil distilled under reduced press to give **21a** as a colourless oily liquid (120 g, 94% yield) b.p. 130–135/l. mm; ν_{max} cm^{-1}, 3330 (NH); NMR (CCl_4) ppm, 6·37 complex [3] (aromatic protons), 5·48 singlet [2] (—O—CH_2—O—), 4·13 triplet [1] (—CH—CH_2—), 3·40 singlet [2] (Ar—CH_2—NH—) 3·07 singlet [6] (2 × OMe), 2·47 doublet [2] (—CH_2—CH—), 1·40 singlet, removed on deuteration [1] (—NH—).

In a similar experiment, **21b** (b.p. 134–135/0·15 mm) was prepared from veratraldehyde in 90% yield.

4-(6,7-Methylenedioxyisoquinolyl)acetic acid hydrochloride (**17a**). 3,4-Methylenedioxybenzylaminoacetaldehydedimethylacetal (20 g) in 6N HCl (400 ml) was stirred at room temp under a N_2 atm for 20 hr. The soln was then warmed on a water-bath for 10 min and glyoxalic acid (8·5 g) in 2N HCl (20 ml) introduced; after heating for a further hr the soln was set aside to cool overnight. The crystalline product was then collected and recrystallized from 2N HCl to give 6,7-methylenedioxyisoquinolyl-4-acetic acid hydrochloride (15·2 g; 68% yield) as yellow needles, m.p. 274° (dec); λ_{max} mμ, (ε) 246 (41,400); ν_{max} cm^{-1}, 1700

(—CO_2H); NMR (CF_3CO_2H) ppm, 8·75 doublet [1] J = 2 c/s (C_1—H), 8·05 doublet [1] J = 2 c/s (C_3—H), 7·30 singlet [1] (C_8—H), 7·27 singlet [1] (C_5—H), 6·10 singlet [2] (—OCH_2O—), 4·20 singlet [2] (—CH_2—CO_2H). (Found: C, 53·7; H, 3·8; N, 5·4. $C_{12}H_{10}NO_4Cl$ requires: C, 53·8; H, 3·7; N, 5·2%.)

In a similar experiment, **17b** was prepared from 3,4-dimethoxybenzylaminoacetaldehydedimethylacetal in 67% yield as colourless fine needles from 2N HCl, m.p. 228–230°. (Found: C, 55·2; H, 4·90; N, 4·75; Cl, 12·15. $C_{13}H_{14}NO_4Cl$ requires: C, 55·0; H, 5·0; N, 4·9; Cl, 12·5%.)

Trans-α-[4′-(6′,7′-*Methylenedioxy)isoquinolyl*]2-*nitro*-4,5-*methylenedioxycinnamic acid* (**18a**). 6,7-Methylenedioxyisoquinolyl-4-acetic acid hydrochloride (10·0 g), 6-nitropiperonal (7·0 g), AcONa (3·0 g), Ac_2O (150 ml) and $MeNH_2$ (100 ml) were heated under reflux for 4 hr. The resultant hot soln was poured into boiling water (500 ml) and heated with rapid stirring at 100° for a further 10 min. On cooling *trans*-α-[4′-(6′,7′-methylenedioxy)isoquinolyl]2-nitro-4,5-methylenedioxycinnamic acid separated and was collected (11.3 g; 74% yield). This material as the hydrochloride was crystallized from 2N HCl as pale yellow prisms, m.p. > 340° (68%); λ_{max} mμ, (ε) 247 (39,600), 317 (10,000), 331 (9630); ν_{max} cm^{-1}, 2650 ($\overset{+}{N}H$), 1725 (—CO_2H); NMR (CF_3CO_2H) ppm, 8·73 multiplet [1] (C_1—H), 8·47 singlet [1] (C_3—H), 7·87 multiplet [1] (C_3—H), 7·33 singlet [1] (C_6—H), 7·23 singlet [1] (C_8—H), 7·13 singlet [1] (C_5—H), 6·15 singlet [1] (—CH=C<), 6·07 singlet [2] and 5·77 singlet [2] (2 × —OCH_2O—). (Found: C, 53·7; H, 3·2; N, 6·6. $C_{20}H_{13}N_2O_8Cl$ requires: C, 54·0; H, 2·9; N, 6·3%.)

In similar experiments, **18b** was prepared in 64% yield from 6,7-dimethoxyisoquinolyl-4-acetic acid hydrochloride and 2-nitropiperonal as yellow needles, m.p. > 340° from 2N HCl. Compound **18c** was obtained in 62% yield from 4-(6,7-dimethoxy)isoquinolylacetic acid hydrochloride and 2-nitroveratraldehyde.

(Unique NMR spectra and satisfactory analytical figures were obtained for both of these compounds.)

Trans-α-[4′-(6′,7′-*Methylenedioxy)isoquinolyl*]2-*amino*-4,5-*methylenedioxycinnamic acid*. Ferrous sulphate (24 g) in hot water (80 ml) was added to a hot soln of *trans*-α-[4′-(6′,7′-methylenedioxy)isoquinolyl]-2-nitro-4,5-methylenedioxycinnamic acid hydrochloride (4·0 g) in 0·880 ammonia (100 ml) with vigorous stirring. The mixture was heated for 10 min on the water-bath and then filtered and the filtrate neutralized (pH 8) with glacial AcOH. After 24 hr, solid *trans*-α-[4′-(6′7-methylenedioxy)isoquinolyl]-2-amino-4,5-methylenedioxycinnamic acid was collected (2·2 g, 60%). Recrystallization of this material or its hydrochloride salt was not achieved; ν_{max} cm^{-1}, 3430, 3330 (—NH_2), 1675 (—CO_2H); NMR (CF_3CO_2H) ppm, 8·37 multiplet [1] (C_1—H), 8·13 multiplet [1] (C_3—H), 7·27 singlet [1] (C_8—H), 7·17 broad singlet [2] (C_3—H and C_5—H), 6·95 singlet [1] (C_6—H), 6·72 singlet [1] (—CH=C<), 5·97 singlet [2] and 5·77 singlet [2] (2 × —OCH_2O—).

In analogous experiments the reductions of *trans*-α-[4′-(6′,7′-dimethoxy)isoquinolyl]2-nitro-4,5-methylenedioxycinnamic acid and *trans*-α-[4′-(6′,7′-dimethoxy)isoquinolyl]2-nitro-4,5-dimethoxycinnamic acid hydrochloride were achieved. The yields of crude amine were 71 and 65% respectively, these amorphous solids were exceptionally difficult to recrystallize and were used unpurified in the subsequent reactions.

2,3,8,9-*Bismethylenedioxy-benzo*[*c*]*phenanthridine* (**5b**). *trans*-α-[4′-(6′,7′-Methylenedioxy)isoquinolyl]-2-amino-4,5-methylenedioxycinnamic acid (2·0 g) in 2N HCl (120 ml) was treated with a soln of $NaNO_2$ (0·55 g) in water (40 ml). Excess HNO_2 was decomposed by the addition of urea and Cu powder (2·0 g) then added. After stirring at room temp for 5 hr the mixture was filtered. The solid product was dried and then suspended in quinoline (10 ml) and heated at 230° for 20 min, water was then added and most of the quinoline was removed by steam distillation. The solid residue from the steam distillation was continuously extracted with chloroform for 24 hr, the extracts were then combined and evaporated to give the crude benzo[c]phenanthridine. This material was sublimed at 250°/0·05 mm press to yield 0·4 g of the pure benzo[c]phenanthridine which was finally recrystallized from pyridine as cream coloured needles, m.p. 328° dec (lit.[3] 325° dec), yield 18%; λ_{max} mμ, (ε) 230 (25,120), 274 (60,260) 352 (4460, 369 (3020). ν_{max} cm^{-1}, 1635 (>C=N—); NMR (CF_3CO_2H) ppm, 8·83 multiplet [1] (C_6—H), 7·97 doublet [1] J = 10 c/s (C_{11}—H), 7·75 singlet [1] (C_7—H), 7·70 doublet [1] J = 10 c/s. (C_{12}—H) 7·62 singlet [1] (C_{10}—H), 7·37 singlet [1] (C_4—H), 7·08 singlet [1] (C_1—H), 6·22 singlet [2] and 6·05 singlet [2] (2 × —OCH_2O—). (Found: C, 71·9; H, 3·4; N, 4·6. Calc. for $C_{19}H_{11}O_4N$: C, 71·9; H, 3·5; N, 4·4%.)

2,3,8,9-*Tetramethoxybenzo*[*c*]*phenanthridine* (**5a**). In an exactly analogous experiment *trans*-α-[4′-(6′,7′-dimethoxy)isoquinolyl]2-amino-4,5-dimethoxycinnamic acid was converted into 2,3,8,9-tetramethoxybenzo[c]phenanthridine. Sublimation of the crude product at 220°/0·1 mm and recrystallization

from pyridine–EtOH gave colourless plates m.p. 305–307° (lit.[5] 302–304). (Found: C, 72·4; N, 5·5; N, 4·0. Calc. for $C_{21}H_{19}NO_4$: C, 72·2; N, 5·5; N, 4·0%.)

2,3-*Methylenedioxy*-8,9-*dimethoxybenzo*[*c*]*phenanthridine* (**5c**). *trans*-α-[4'-(6',7'-Dimethoxy)isoquinolyl] 2-amino-4,5-methlenedioxycinnamic acid gave a 15% yield of the corresponding **5c** when diazotized and reacted under the conditions described above. Recrystallization from pyridine–EtOH gave colourless needles, m.p. 277–279° (lit.[4] 277–287°); λ_{max} mμ, (ε) 230 (36,300), 275 (63,100), 315 (24,000), 370 (2100). (Found: C, 72·1; H, 4·6; H, 4·7. Calc. for $C_{20}H_{15}NO_4$: C, 72·1; H, 4·5; H, 4·2%.)

Acknowledgements—We are grateful to Professor Arthur for a sample of oxyavicine, and to Professor Govindachari for a sample of 2,3-dimethoxy-8,9-methylenedioxybenzo[c]phenanthridine. We thank the S.R.C. for a studentship (to B. J. M.), and wish to thank Messrs. R. C. Kinsman and J. H. Bugler for some experimental assistance.

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