Conversion of the Naturally Occurring Amide Alkaloids into O_5 Benzo[*c*]phenanthridinium Alkaloids.[1,†] A New Synthetic Sequence to Antitumour Benzo[*c*]phenanthridine Alkaloids

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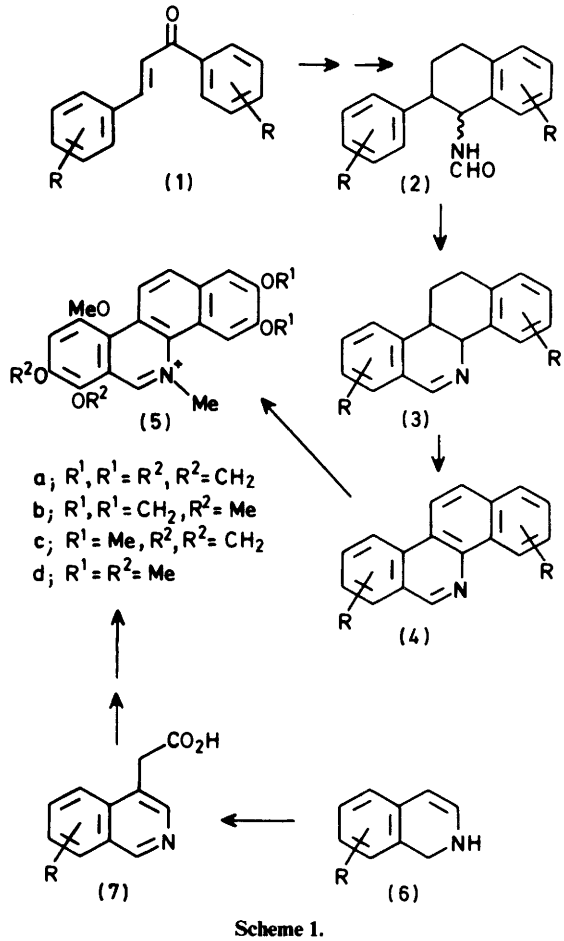
Cyclisation of methyl integriamide (**17a**) and methyl isoarnottianamide (**17b**) by the Bischler–Napieralski reaction gave the naturally occurring O_5 benzo[*c*]phenanthridine alkaloids, chelirubine (**5a**) and chelilutine (**5b**), respectively; this was extended to give a generally applicable, versatile synthesis of benzo[*c*]phenanthridine alkaloids from 2-aryl-3,4-dihydronaphthalen-1(2*H*)-ones (**13**). Treatment of the tetralones (**13**) with methylamine and titanium tetrachloride followed by sodium borohydride provided the *cis*-2-aryl-*N*-methyl-1,2,3,4-tetrahydro-1-naphthylamines (**14**) which were converted into the *N*-formyl derivatives (**15**) with freshly prepared chloral in good yields. Dehydrogenation of the resulting formamides (**15**) with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) gave the fully aromatised amides corresponding to methyl integriamide (**17a**). Bischler–Napieralski reaction of these amides (**17**) furnished the desired quaternary benzo[*c*]phenanthridine alkaloids (**5**).

In 1937, Robinson and co-workers[2] reported a synthetic sequence starting from the chalcone derivatives (**1**) giving compounds with a benzo[*c*]phenanthridine skeleton (**4**); this has become a standard method,[3] with some variations,[3b] for the synthesis of fully aromatised benzo[*c*]phenanthridine alkaloids[4] (**5**) and their derivatives (Scheme 1). In 1967, Dyke *et al.*[5] reported a different route to these alkaloids in which the condensation of the dihydroisoquinoline derivative (**6**) with glyoxylic acid was involved as a key step.

Four fully aromatised O_5 benzo[*c*]phenanthridine alkaloids of this type [chelirubine (**5a**), chelilutine (**5b**), sanguirubine (**5c**), and sanguilutine (**5d**)] were isolated by Slavík *et al.*[4b,6] from several Papaveraceous plants, and tentative structures proposed for them [7] [(**10a**—**d**), respectively]. Independently, Tani *et al.*[8] and Onda *et al.*[9] isolated chelirubine from *Macleaya cordata* (Willd.) R. Br. (*Bocconia cordata* Willd.) and Onda *et al.*[10] proposed another structure (**11**) for chelirubine under the name of bocconine.

On the basis of the spectral data, we reached a different conclusion [formula (**5a**)] for the structure of chelirubine from those of Slavík and of Onda. In order to establish the structure of chelirubine with certainty we undertook the synthesis of compound (**5a**) and (**11**) (Onda's proposed structure) using Robinson's synthetic sequence. However, in the attempted synthesis[11] of compound (**5a**), the Bischler–Napieralski reaction of the 1-formamido-1,2,3,4-tetrahydronaphthalene derivative (alicyclic NH-formamide) (**2a**) resulted in the formation of the 2-aryl-3,4-dihydronaphthalene derivative (stilbene) (**8a**) alone, the product of β-elimination from the formamide molecule, instead of the desired cyclised product (**3a**) (Scheme 2). This observation led us to conclude that for Bischler–Napieralski reaction[11] to take place, the starting NH-formamide (**2**) must have an alkoxy function *para* to the cyclising point in the 2-aryl ring.

It should be added here that, in the synthesis of Onda's structure (**11**), dehydrogenation[11] of the Bischler–Napieralski reaction product (**3b**) stopped at the 11,12-dihydrobenzo-[*c*]phenanthridine derivative (**9**) and did not give the desired, fully aromatised product (**4b**).



Scheme 1.

We also attempted the synthesis of these compounds by Dyke's method.[5] However, we found[12] that the condensation of 1,2-dihydroisoquinoline derivatives (**6**) having an alkoxy group at the 5 position, with glyoxylic acid could not take place because of the *peri*-interaction of the alkoxy group.

Chelirubine was eventually established as having structure

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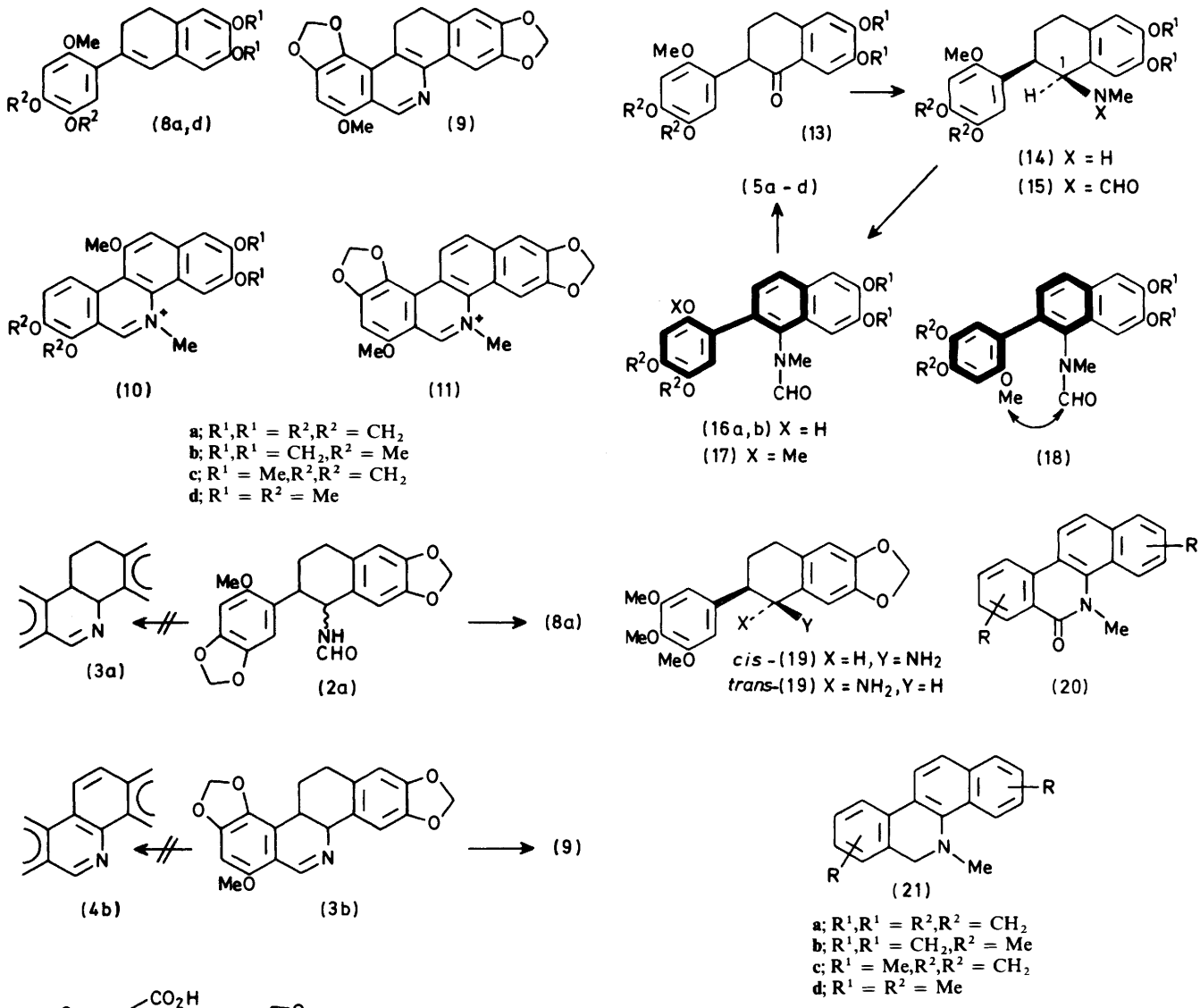

Scheme 2.

Scheme 3.

(**5a**) by synthesis[13] *via* photocyclisation of the enamide derivative (**12**).

In the preceding paper,[1a] we succeeded in establishing the structures of several new naturally occurring amide alkaloids (**16**) by Baeyer–Villiger oxidation of the O_4 quaternary immonium bases (**5**) *in vivo*. We supposed that the *O*-methyl derivatives (aromatic formamides) (**17**) of these alkaloids (**16**) would undergo the Bischler–Napieralski reaction better than alicyclic NH-formamide derivatives (**2**) for the following reasons: (i) the absence of the β-proton of the formamide group in the *O*-methyl alkaloids (**17**) excludes the possibility of β-elimination of an *N*-methylformamide molecule during the reaction; (ii) in the new amide alkaloid, the molecule should be coplanar because of the conjugation between the aryl and the naphthyl rings, giving two conformers (**17**) and (**18**). It may be assumed that the molecule (**17**), having the methoxy and *N*-methylformamide groups on opposite sides of the molecule, is the preferred conformer because of the steric interaction between these functions in (**18**), forcing the formamide group of the aromatic alkaloid into a position closed to the reaction centre (an *ortho* position on the 2-aryl ring); (iii) finally, the reactive species from the *N*-methylformamide group of the aromatic alkaloids (**17**), $^{+}N(Me)=CHOPOCl_2$, was assumed to be more reactive than that ($N=CHOPOCl_2$) of the alicyclic NH-formamides (**2**).

Treatment of integriamide (**16a**) and isoarnottianamide (**16b**) with Rodionow reagent[14] gave the corresponding *O*-methyl derivatives (**17a**) and (**17b**). As expected, treatment of these with phosphorus oxychloride in acetonitrile gave the cyclic quaternary base chlorides in 30.1 and 54.9% yields, respectively.

These materials were identified by comparison with samples of naturally occurring chelirubine (**5a**) and chelilutine (**5b**) chlorides, respectively. It is of interest that, generally speaking, when acetonitrile was used as solvent, Bischler–Napieralski reaction of such aromatic formamides (**17**) proceeded smoothly and provided the desired quaternary base (**5**) in better yield than when xylene was used. However, in the case of the amide (**17a**) having a methylenedioxy group at the 4,5-positions in its 2-aryl substituent, the cyclisation tended to give a tarry substance with the former solvent.

These facts indicated that, if we achieved the synthesis of these aromatic formamide derivatives (**17**) from 2-aryl-1-tetralone derivatives[15] (**13**), Robinson's synthetic sequence could be extended to the synthesis of the fully aromatised O_5 benzo[*c*]phenanthridine alkaloids (**5**). Treatment of the tetralones (**13**) with methylamine in the presence of titanium tetrachloride[16] followed by reduction with sodium borohydride gave the *N*-methyl-1,2,3,4-tetrahydro-1-naphthylamine derivatives (**14**) (Scheme 3). In their ^{1}H n.m.r. spectra, these amines (**14**) show a doublet due to 1-H with *J* 4.0 Hz. In an earlier report,[17] we examined the *J* values of the corresponding signals in the trimethoxy-1,2,3,4-tetrahydro-1-naphthylamines (**19**) in detail and observed that the corresponding signal of the *trans*-isomer [*trans*-(**19**)] has *J* 9.6 Hz, while that of the epimer [*cis*-(**19**)] shows *J* 3.4 Hz. These data suggested that the product (**14**)† has *cis* stereochemistry.

We used the pentamethoxyamine in (**14d**) to find the optimum conditions for the formylation of the above amines (**14**). Treatment of the pentamethoxyamine (**14d**) with formamide gave a mixture of the desired alicyclic *N*-methylformamide (**15d**) and the stilbene derivative (**8d**) in 56.3 and 11.7% yields, respectively, while formylation was achieved in 87.0% yield on treatment with freshly prepared chloral.[18] The latter conditions also gave good results for the formylation of (**14a—c**). Dehydrogenation of the resulting alicyclic *N*-methylformamides (**15a—d**) to give the desired aromatic formamides (**17**) was achieved in good yield by treatment with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). Of these products (**17a**) and (**17b**) were found to be identical with samples of methyl integriamide and methyl isoarnottianamide, prepared by methylation of the corresponding naturally occurring amide alkaloids.

Finally, we carried out the total syntheses of sanguirubine (**5c**) and sanguilutine (**5d**) from the corresponding 1-tetralone derivatives[15] (**13c**) and (**13d**) by our established pathway. All the quaternary bases (**5**) were characterised as the oxybases (**20**), the dihydrobases (**21**), and/or the ψ-cyanides.

In conclusion, we have established a generally applicable, versatile method for the synthesis of the antileukaemic, active benzo[*c*]phenanthridine alkaloids from the 2-aryl-1-tetralone derivatives (**13**).

Experimental

General directions are given in ref. 1.

Methyl Integriamide [2-(2-*Methoxy*-4,5-*methylenedioxyphenyl*)-6,7-*methylenedioxy*-1-(N-*methylformamido*)*naphthalene*] (**17a**).—The Rodionow reagent[14] prepared from trimethylanilinium toluene-*p*-sulphonate (0.739 g) in dry methanol (1.1 ml) and a solution of sodium metal (0.055 g) in dry methanol (1.5 ml) was added to a suspension of integriamide [2-(2-hydroxy-4,5-methylenedioxyphenyl)-6,7-methylenedioxy-1-(*N*-methylformamido)naphthalene] (**16a**) (0.018 g) in dry toluene (10 ml). The solution was evaporated at 70—80 °C, refluxed for 8 h, and the procedure was then repeated. After addition of a large amount of water, the mixture was evaporated to dryness under reduced pressure, a large amount of water was added, and the residue extracted with chloroform. The chloroform solution was washed with 10% hydrochloric acid, dried (K_2CO_3), and evaporated to dryness under reduced pressure. Recrystallization of the residue from chloroform–methanol gave colourless *prisms* of (**17a**) (0.016 g), m.p. 238—240 °C (Found: C, 66.6; H, 4.45; N, 3.6. $C_{21}H_{17}NO_6$ requires C, 66.5; H, 4.5; N, 3.7%); $\nu_{max.}$ (KBr) 1 675 cm^{-1}; δ 2.97 (3 H, s, NMe), 3.62 (3 H, s, OMe), 5.91 (2 H, s, OCH_2O), 6.01 (2 H, s, OCH_2O), 6.52 (1 H, s, 3′- or 6′-H), 6.55 (1 H, s, 6′-or 3′-H), 7.02 (1 H, s, 5-H), 7.14 (1 H, s, 8-H), 7.18 (1 H, d, *J* 8.5 Hz, 4-H), 7.65 (1 H, d, *J* 8.5 Hz, 3-H), and 8.03 (1 H, s, CHO).

Methyl Isoarnottianamide [1-(N-*Methylformamido*)-6,7-*methylenedioxy*-2-(2,4,5-*trimethoxyphenyl*)*naphthalene*] (**17b**).—A suspension of isoarnottianamide [2-(2-hydroxy-4,5-dimethoxyphenyl)-6,7-methylenedioxy-1-(*N*-methylformamido)naphthalene (**16b**) (0.051 g) in dry toluene (30 ml) was methylated using the Rodionow reagent[14] prepared from trimethylanilinium toluene-*p*-sulphonate (2.06 g) in dry methanol (3 ml) and a solution of sodium metal (0.152 g) in dry methanol (4 ml) in the usual way. Recrystallization of the crude product from chloroform–methanol gave colourless *prisms* of (**17b**) (0.042 g), m.p. 212—214.5 °C (Found: C, 66.75; H, 5.45; N, 3.5. $C_{22}H_{21}NO_6$ requires C, 66.8; H, 5.35; N, 3.55%); $\nu_{max.}$ 1 670 cm^{-1}; δ 2.94 (3 H, s, NMe), 3.68 (3 H, s, OMe), 3.79 (3 H, s, OMe), 3.92 (3 H, s, OMe), 6.03 (2 H, s, OCH_2O), 6.55 (1 H, s, 3′-H), 6.64 (1 H, s, 6′-H), 7.05 (1 H, s, 5-H), 7.16 (1 H, s, 8-H), 7.26 (1 H, d, *J* 8.3 Hz, 4-H), 7.69 (1 H, d, *J* 8.3 Hz, 3-H), and 8.08 (1 H, s, CHO).

Chelirubine {10-*Methoxy*-5-*methyl*-2,3:7,8-*bis*(*methylenedioxy*)*benzo*[c]*phenanthridinium*} (**5a**) *Chloride from Methyl Integriamide* (**17a**).—A mixture of methyl integriamide (**17a**) (0.038 g) and phosphorus oxychloride (0.05 ml) in acetonitrile (1 ml) was refluxed for 3 h. After the solvent had been distilled off under reduced pressure, the residue was basified with 10% sodium hydroxide solution and then extracted with chloroform. The chloroform solution was dried (K_2CO_3) and evaporated to dryness under reduced pressure. A small amount of 10% hydrochloric acid was added to an ice-cooled solution of the residue in a minute amount of chloroform. The precipitates were collected by filtration, washed with benzene, and recrystallized from methanol–isopropyl alcohol to give red purple needles of the chloride (0.012 g), m.p. 295—299 °C (lit., m.p. 282—283 °C[6b]; m.p. 299—302 °C[13]). This material was identical with a sample of chelirubine (**5a**) chloride.[13]

Chelilutine (7,8,10-*Trimethoxy*-5-*methyl*-2,3-*methylenedioxybenzo*[c]*phenanthridinium*) (**5b**) *Chloride from Methyl Isoarnottianamide* (**17b**).—A mixture of methyl isoarnottianamide (**17b**) (0.040 g) and phosphorus oxychloride (0.2 ml) in acetonitrile (2 ml) was treated in the usual way. Recrystallization of the crude material from aqueous methanol gave orange needles of the chloride (0.023 g), m.p. 184—186 °C;† $\nu_{max.}$ (KBr) 1 640 cm^{-1}; δ (CF_3CO_2H) 4.22 (3 H, s, OMe), 4.30 (6 H, s, OMe × 2), 4.98 (3 H, s, N^+Me), 6.20 (2 H, s, OCH_2O), 7.46 (1 H, s, 9-H), 7.62 (1 H, s, 1-H), 7.91 (1 H, s, 4-H), 8.12 (1 H, d, *J* 8.5 Hz, 12-H), 9.52 (1 H, d, *J* 8.5 Hz, 11-H), and 9.70 (1 H, s, 6-H). This material

† Reduction of an iminium compound with sodium borohydride has been reported to give a *cis*-amine (R. Sarges, *J. Org. Chem.*, 1975, **40**, 1216).

† Although the m.p. of chelilutine (**5b**) chloride was reported as 197—198 °C,[6b] the authentic sample melted at 186—192 °C when measured in our laboratory.

was identical with an authentic sample (m.p. 186—192 °C) of chelilutine (**5b**) chloride (donated by Professor Slavík).

Chelilutine (**5b**) ψ-*Cyanide*†.—A mixed solution of chelilutine (**5b**) chloride (0.023 g) and potassium cyanide (0.008 g) in aqueous methanol [methanol (2 ml) and water (3 ml)] was heated at 50 °C for 1 h. After the precipitates had been filtered off, the filtrate was extracted with chloroform and the chloroform solution dried (K_2CO_3) and evaporated to dryness under reduced pressure. The precipitates were combined with the residue. Purification of the combined mixture by preparative t.l.c. with chloroform–methanol (30:1, v/v) gave colourless prisms of the cyanide (0.010 g), m.p. 258—260 °C (lit.,[6b] m.p. 270.5—271 °C), which were recrystallized from chloroform–methanol (Found: C, 67.7; H, 5.0; N, 6.55. Calc. for $C_{23}H_{20}N_2O_5$: C, 68.3; H, 5.0; N, 6.95%); δ [$(CD_3)_2SO$] 2.53 (3 H, s, NMe), 3.82 (3 H, s, OMe), 3.95 (6 H, s, OMe × 2), 5.79 (1 H, s, 6-H), 6.12 (2 H, s, OCH_2O), 6.91 (1 H, s, 9-H), 7.29 (1 H, s, 1-H), 7.51 (1 H, s, 4-H), 7.57 (1 H, d, *J* 9.0 Hz, 12-H), and 8.25 (1 H, d, *J* 9.0 Hz, 11-H).

Oxychelilutine {7,8-*Dimethoxy*-5-*methyl*-2,3-*methylenedioxybenzo*[c]*phenanthridin*-6(5H)-*one*} (**20b**).—To a stirred solution of chelilutine (**5b**) ψ-cyanide (0.013 g) in hexamethylphosphoric triamide (0.4 ml) was added sodium hydride (52.9% in mineral oil; 0.005 g) at room temperature. The mixture was stirred at room temperature in air for 3 h and then diluted with saturated sodium chloride solution and extracted with ethyl acetate. The organic layer was washed with water, dried (K_2CO_3), and evaporated to dryness under reduced pressure. The residue was purified by preparative t.l.c. with chloroform–methanol (30:1, v/v) and gave colourless *needles* of (**20b**) (0.008 g), m.p. 202—204.5 °C, which were recrystallized from chloroform–methanol (Found: C, 66.7; H, 4.85; N, 3.5. $C_{22}H_{19}NO_6$ requires C, 67.15; H, 4.85; N, 3.55%); $\nu_{max.}$ (KBr) 1 665 cm^{-1}; δ 3.83 (3 H, s, NMe or OMe), 3.98 (3 H, s, NMe or OMe), 4.05 (6 H, s, OMe × 2), 6.04 (2 H, s, OCH_2O), 6.94 (1 H, s, 9-H), 7.13 (1 H, s, 1-H), 7.45 (1 H, s, 4-H), 7.47 (1 H, d, *J* 8.5 Hz, 12-H), and 8.92 (1 H, d, *J* 8.5 Hz, 11-H).

Dihydrochelilutine (7,8-*Dimethoxy*-5-*methyl*-2,3-*methylenedioxy*-5,6-*dihydrobenzo*[c]*phenanthridine*) (**21b**).—A mixture of chelilutine (**5b**) chloride (0.021 g) and sodium borohydride (0.020 g) in methanol (6 ml) was stirred at room temperature for 1 h and evaporated to dryness under reduced pressure. After addition of 10% sodium hydroxide solution, the residue was extracted with chloroform and the chloroform solution was dried (K_2CO_3) and evaporated to dryness under reduced pressure. Column chromatography of the residue on aluminium oxide with chloroform gave colourless *prisms* of (**21b**) (0.016 g), m.p. 139—142 °C, which were recrystallized from acetone–methanol (Found: C, 69.75; H, 5.6; N, 3.6. $C_{22}H_{21}NO_5$ requires C, 69.65; H, 5.6; N, 3.7%); δ 2.54 (3 H, s, NMe), 3.79 (3 H, s, OMe), 3.89 (3 H, s, OMe), 3.93 (3 H, s, OMe), 4.19 (2 H, s, 6-H_2), 5.98 (2 H, s, OCH_2O), 6.53 (1 H, s, 9-H), 7.07 (1 H, s, 1-H), 7.66 (1 H, s, 4-H), 7.42 (1 H, d, *J* 8.0 Hz, 12-H), and 8.26 (1 H, d, *J* 8.0 Hz, 11-H).

General Method for the Preparation of the cis-2-*Aryl*-N-*methyl*-1,2,3,4-*tetrahydro*-1-*naphthylamines* (**14**) *from the* 2-*Aryl*-3,4-*dihydronaphthalen*-1(2H)-*one Derivatives* (**13**).—A solution of the dihydronaphthalenone derivative (**13**) and methylamine in dry chloroform was gradually added to a solution of titanium tetrachloride[16] in dry chloroform under ice-cooling and the mixture was then refluxed. The resulting precipitates were then filtered off, the filtrate was evaporated to dryness under reduced pressure, and the residue was dissolved in methanol or in dimethylformamide (DMF)–methanol and treated with sodium borohydride at room temperature. The reaction mixture in methanol was diluted with a large amount of water and extracted with chloroform, while that in DMF–methanol was evaporated to dryness, a large amount of water was added to the residue, and it was then extracted with chloroform. The chloroform solution in each case was dried (K_2CO_3) and evaporated to dryness under reduced pressure. Recrystallization of the residue from an appropriate solvent gave the desired *cis*-tetrahydro-1-naphthylamine (**14**).

cis-2-(2-*Methoxy*-4,5-*methylenedioxyphenyl*)-N-*methyl*-6,7-*methylenedioxy*-1,2,3,4-*tetrahydro*-1-*naphthylamine* (**14a**). A solution of the tetralone[15] (**13a**) (colourless prisms; m.p. 162—165 °C) (2.00 g) and methylamine (5.0 g) in dry chloroform (40 ml) was treated as above with a solution of titanium tetrachloride (0.65 ml) in dry chloroform (20 ml) and refluxed for 0.5 h. The crude iminium salt was dissolved in DMF (70 ml)–methanol (7 ml) and reduced with sodium borohydride (0.340 g) for 0.5 h. Ethyl acetate was used as the solvent for extraction, giving colourless *prisms* of (**14a**) (1.72 g), m.p. 156—158 °C (ethyl acetate–ethanol or chloroform–methanol) (Found: C, 67.45; H, 5.9; N, 3.8. $C_{20}H_{21}NO_5$ requires C, 67.6; H, 5.95; N, 3.95%); δ 1.04 (1 H, br s, NH), 1.56—2.60 (2 H, m, 3-H_2), 2.15 (3 H, s, NMe), 2.72—3.00 (2 H, m, 4-H_2), 3.34—3.60 (1 H, m, 2-H), 3.63 (1 H, d, *J* 4.0 Hz, 1-H), 3.74 (3 H, s, OMe), 5.85 (4 H, s, OCH_2O × 2), 6.50 (1 H, s, Ar H), 6.56 (1 H, s, Ar H), 6.69 (1 H, s, Ar H), and 6.75 (1 H, s, Ar H).

cis-N-*Methyl*-6,7-*methylenedioxy*-2-(2,4,5-*trimethoxyphenyl*)-1,2,3,4-*tetrahydro*-1-*naphthylamine* (**14b**). A solution of the tetralone[15] (**13b**) (colourless prisms; m.p. 137—139 °C) (2.00 g) and methylamine (12.0 g) in dry chloroform (40 ml) was treated as above with a solution of titanium tetrachloride (0.62 ml) in dry chloroform (30 ml) and refluxed for 0.5 h. The crude iminium salt was dissolved in DMF (30 ml)–methanol (5 ml) and reduced with sodium borohydride (0.321 g) for 0.5 h to give colourless *prisms* of (**14b**) (1.73 g), m.p. 156—158 °C (chloroform–methanol) (Found: C, 67.7; H, 6.85; N, 3.75. $C_{21}H_{25}NO_5$ requires C, 67.9; H, 6.8; N, 3.75%); δ 1.10 (1 H, br s, NH), 1.64—1.96 (1 H, m, 3-H_A), 2.04—2.62 (1 H, m, 3-H_B), 2.14 (3 H, s, NMe), 2.72—3.00 (2 H, m, 4-H_2), 3.36—3.60 (1 H, m, 2-H), 3.64 (1 H, d, *J* 4.0 Hz, 1-H), 3.78 (6 H, s, OMe × 2), 3.87 (3 H, s, OMe), 5.84 (2 H, s, OCH_2O), 6.51 (1 H, s, Ar H), 6.57 (1 H, s, Ar H), 6.70 (1 H, s, Ar H), and 6.79 (1 H, s, Ar H).

cis-6,7-*Dimethoxy*-2-(2-*methoxy*-4,5-*methylenedioxyphenyl*)-N-*methyl*-1,2,3,4-*tetrahydro*-1-*naphthylamine* (**14c**). A solution of the tetralone[15] (**13c**) (colourless prisms; m.p. 209—211 °C) (5.27 g) and methylamine (7.5 g) in dry chloroform (80 ml) was treated as above with a solution of titanium tetrachloride (1.62 ml) in dry chloroform (50 ml) and refluxed for 1 h. The crude iminium salt was dissolved in DMF (100 ml)–methanol (20 ml) and reduced with sodium borohydride (1.13 g) for 4 h to give colourless *prisms* of (**14c**) (4.55 g), m.p. 147—149 °C (chloroform–methanol) (Found: C, 67.5; H, 6.8; N, 3.7. $C_{21}H_{25}NO_5$ requires C, 67.9; H, 6.8; N, 3.75%); δ 1.23 (1 H, br s, NH), 1.60—1.90 (1 H, m, 3-H_A), 2.04—2.58 (1 H, m, 3-H_B), 2.17 (3 H, s, NMe), 2.74—2.96 (2 H, m, 4-H_2), 3.38—3.62 (1 H, m, 2-H), 3.69 (1 H, d, *J* 4.0 Hz, 1-H), 3.76 (3 H, s, OMe), 3.84 (3 H, s, OMe), 3.86 (3 H, s, OMe), 5.87 (2 H, s, OCH_2O), 6.52 (1 H, s, Ar H), 6.60 (1 H, s, Ar H), and 6.76 (2 H, s, Ar H × 2).

cis-6,7-*Dimethoxy*-N-*methyl*-2-(2,4,5-*trimethoxyphenyl*)-1,2,3,4-*tetrahydro*-1-*naphthylamine* (**14d**). A solution of the tetralone[15] (**13d**) (colourless prisms; m.p. 152—154 °C) (5.00 g) and methylamine (10.0 g) in dry chloroform (65 ml) was treated as above with a solution of titanium tetrachloride (1.5 ml) in dry chloroform (50 ml) and refluxed for 0.5 h. The crude iminium salt was reduced with sodium borohydride (1.033 g) in methanol (30 ml) for 1 h to give colourless *prisms* of (**14d**) (4.78 g), m.p. 144—146 °C (ethanol) (Found: C, 67.9; H, 7.7; N, 3.5.

† ψ-Cyanide refers to the neutral 6-cyano derivative.

$C_{22}H_{29}NO_5$ requires C, 68.2; H, 7.55; N, 3.6%); δ 1.00—1.36 (1 H, m, NH), 1.64—2.64 (2 H, m, 3-H_2), 2.17 (3 H, s, NMe), 2.72—3.00 (2 H, m, 4-H_2), 3.40—3.64 (1 H, m, 2-H), 3.70 (1 H, d, *J* 4.0 Hz, 1-H), 3.76 (3 H, s, OMe), 3.78 (3 H, s, OMe), 3.83 (3 H, s, OMe), 3.84 (3 H, s, OMe), 3.87 (3 H, s, OMe), 6.50 (1 H, s, Ar H), 6.60 (1 H, s, Ar H), 6.75 (1 H, s, Ar H), and 6.78 (1 H, s, Ar H).

Formylation of cis-6,7-*Dimethoxy*-N-*methyl*-2-(2,4,5-*trimethoxyphenyl*)-1,2,3,4-*tetrahydro*-1-*naphthylamine* (**14d**) *with Formamide*.—A solution of the pentamethoxyamine (**14d**) (0.204 g) in formamide (1.0 ml) was heated at 150 °C for 1.5 h, poured into ice–water, and extracted with chloroform. The chloroform solution was dried (K_2CO_3) and evaporated to dryness under reduced pressure. The residue was chromatographed on silica gel with benzene–ethyl acetate (1:1, v/v).

(*i*) 6,7-*Dimethoxy*-2-(2,4,5-*trimethoxyphenyl*)-3,4-*dihydronaphthalene* (**8d**). The first eluate gave colourless *prisms* of (**8d**) (0.022 g), m.p. 121—125 °C, which were recrystallized from benzene–n-hexane (Found: C, 70.5; H, 6.75. $C_{21}H_{24}O_5$ requires C, 70.75; H, 6.8%); δ 2.52—3.00 (4 H, m, 3- and 4-H_2), 3.85 (3 H, s, OMe), 3.91 (6 H, s, OMe × 2), 3.93 (3 H, s, OMe), 3.95 (3 H, s, OMe), 6.55 (2 H, s, Ar H and 1-H), 6.66 (1 H, s, Ar H), 6.71 (1 H, s, Ar H), and 6.86 (1 H, s, Ar H).

(*ii*) cis-6,7-*Dimethoxy*-1-(N-*methylformamido*)-2-(2,4,5-*trimethoxyphenyl*)-1,2,3,4-*tetrahydronaphthalene* (**15d**). The second eluate gave colourless *prisms* of (**15d**) (0.123 g), m.p. 161—162 °C, which were recrystallized from isopropyl alcohol (Found: C, 66.35; H, 7.1; N, 3.55. $C_{23}H_{29}NO_6$ requires C, 66.5; H, 7.05; N, 3.35%); $\nu_{max.}$ 1 665 cm^{-1}; δ 1.58—2.64 (2 H, m, 3-H_2), 2.48 (3 H, s, NMe), 2.80—3.04 (2 H, m, 4-H_2), 3.40—3.70 (1 H, m, 2-H), 3.80 (6 H, s, OMe × 2), 3.82 (3 H, s, OMe), 3.88 (6 H, s, OMe × 2), 4.88 (1 H, d, *J* 5.8 Hz, 1-H), 6.50 (2 H, s, Ar H × 2), 6.63 (2 H, s, Ar H × 2), and 7.67 (1 H, s, CHO).

General Method for the Formylation of the cis-2-*Aryl*-N-*methyl*-1,2,3,4-*tetrahydro*-1-*naphthylamines* (**14**) *with Freshly Prepared Chloral to give the* cis-2-*Aryl*-1-(N-*methylformamido*)-1,2,3,4-*tetrahydronaphthalene* (**15**).—A mixture of the amine (**14**) and freshly prepared chloral[19]† in chloroform was refluxed. The reaction mixture was washed with water, dried (K_2CO_3), and evaporated to dryness under reduced pressure. Purification of the residue by column chromatography on silica gel with chloroform followed by recrystallization from an appropriate solvent gave the desired 1-formamido-1,2,3,4-tetrahydronaphthalene (**15**). In some cases, the product was obtained as a mixture of rotational isomers.

cis-2-(2-*Methoxy*-4,5-*methylenedioxyphenyl*)-6,7-*methylenedioxy*-1-(N-*methylformamido*)-1,2,3,4-*tetrahydronaphthalene* (**15a**). A mixture of the amine (**14a**) (1.38 g) and freshly prepared chloral (0.76 ml) in chloroform (10 ml) was treated as above, refluxing for 1 h, to give colourless *prisms* of (**15a**) (1.29 g), m.p. 236.5—239 °C (chloroform–methanol) (Found: C, 65.5; H, 5.45; N, 3.6. $C_{21}H_{21}NO_6$ requires C, 65.8; H, 5.5; N, 3.65%); $\nu_{max.}$ 1 655 cm^{-1}; δ 1.65—2.32 (2 H, m, 3-H_2), 2.46 (3 H, s, NMe), 2.76—3.00 (2 H, m, 4-H_2), 3.28—3.64 (1 H, m, 2-H), 3.75 (3 H, s, OMe), 4.84 (1 H, d, *J* 5.0 Hz, 1-H), 5.81 (1 H, d, *J* 2.0 Hz, OCH_2O), 5.85 (1 H, d, *J* 2.0 Hz, OCH_2O), 5.86 (2 H, s, OCH_2O), 6.47 (2 H, s, Ar H × 2), 6.55 (1 H, s, Ar H), 6.58 (1 H, s, Ar H), and 7.64 (1 H, s, CHO).

cis-6,7-*Methylenedioxy*-1-(N-*methylformamido*)-2-(2,4,5-*trimethoxyphenyl*)-1,2,3,4-*tetrahydronaphthalene* (**15b**). A mixture of the amine (**14b**) (8.01 g) and freshly prepared chloral (3.16 ml) in chloroform (40 ml) was treated as above, refluxing for 2 h, to give colourless *prisms* of (**15b**) (8.08 g), m.p. 168—171 °C (isopropyl alcohol) (Found: C, 66.35; H, 6.35; N, 3.6. $C_{22}H_{25}NO_6$ requires C, 66.15; H, 6.3; N, 3.5%); $\nu_{max.}$ 1 675 cm^{-1}; δ 1.76—2.30 (2 H, m, 3-H_2), 2.45 (3 H, s, NMe), 2.76—3.10 (2 H, m, 4-H_2), 3.36—3.64 (1 H, m, 2-H), 3.78 (3 H, s, OMe), 3.80 (3 H, s, OMe), 3.85 (3 H, s, OMe), 4.82 (1 H, d, *J* 5.8 Hz, 1-H), 5.88 (2 H, s, OCH_2O), 6.49 (2 H, s, Ar H × 2), 6.60 (2 H, s, Ar H × 2), and 7.64 (1 H, s, CHO).

cis-6,7-*Dimethoxy*-2-(2-*methoxy*-4,5-*methylenedioxyphenyl*)-1-(N-*methylformamido*)-1,2,3,4-*tetrahydronaphthalene* (**15c**). A mixture of the amine (**14c**) (4.55 g) and freshly prepared chloral (2.4 ml) in chloroform (30 ml) was treated as above, refluxing for 2 h, to give colourless *prisms* of (**15c**) (4.06 g), m.p. 182.5—185 °C (isopropyl alcohol) (Found: C, 66.3; H, 6.4; N, 3.4. $C_{22}H_{25}NO_6$ requires C, 66.15; H, 6.3; N, 3.5%); $\nu_{max.}$ 1 670 cm^{-1}; δ‡ 1.87—2.28 (2 H, m, 3-H_2), 2.47 ($\frac{6}{7}$ × 3 H, s, NMe), 2.60 ($\frac{1}{7}$ × 3 H, s, NMe), 2.81—3.12 (2 H, m, 4-H_2), 3.37—3.69 (1 H, m, 2-H), 3.79 (6 H, s, OMe × 2), 3.86 and 3.88 (total 3 H, each s, OMe), 4.90 (1 H, d, *J* 5.0 Hz, 1-H), 5.85 and 5.90 (total 2 H, each s, OCH_2O), 6.52 (2 H, s, Ar H × 2), 6.60 (1 H, s, Ar H), 6.64 (1 H, s, Ar H), 7.69 ($\frac{6}{7}$ H, s, CHO), and 7.81 ($\frac{1}{7}$ H, s, CHO).

cis-6,7-*Dimethoxy*-1-(N-*methylformamido*)-2-(2,4,5-*trimethoxyphenyl*)-1,2,3,4-*tetrahydronaphthalene* (**15d**). A mixture of the amine (**14d**) (4.01 g) and freshly prepared chloral (1.6 ml) in chloroform (30 ml) was treated as above, refluxing for 1 h, to give colourless prisms of (**15d**) (3.74 g), m.p. 154—157 °C (isopropyl alcohol). This material was identical with a sample which was prepared from the pentamethoxyamine (**14d**) and formamide.

General Method for the Dehydrogenation of the cis-2-*Aryl*-1-(N-*methylformamido*)-1,2,3,4-*tetrahydronaphthalenes* (**15**) *to give the* 2-*Aryl*-1-(N-*methylformamido*)*naphthalenes* (**17**).—A mixture of the 2-aryl-1-(*N*-methylformamido)-1,2,3,4-tetrahydronaphthalene (**15**) and DDQ in benzene was refluxed. The precipitates were then filtered off, a large amount of 5% sodium hydroxide solution was added to the filtrate, and the mixed solution was extracted with chloroform. The chloroform solution was washed with 5% sodium hydroxide solution, dried (K_2CO_3), and then evaporated to dryness under reduced pressure. Purification of the residue by column chromatography on silica gel with chloroform followed by recrystallization from an appropriate solvent gave the desired 2-aryl-1-(*N*-methylformamido)naphthalene (**17**).

Methyl integriamide (**17a**). A solution of the 1-formamido-1,2,3,4-tetrahydronaphthalene (**15a**) (1.58 g) and DDQ (5.62 g) in benzene (180 ml) was treated as above, refluxing for 3 h, to give colourless prisms of (**17a**) (1.17 g), m.p. 238—240 °C (chloroform–methanol). This material was identical with a sample of methyl integriamide (**17a**) which was prepared by methylation of integriamide (**16a**) obtained from natural sources.

Methyl isoarnottianamide (**17b**). A solution of the 1-formamido-1,2,3,4-tetrahydronaphthalene (**15b**) (8.08 g) and DDQ (13.78 g) in benzene (300 ml) was treated as above, refluxing for 1.5 h, to give colourless prisms of (**17b**) (6.65 g), m.p. 219—221 °C (chloroform–ethanol); $\nu_{max.}$ (KBr) 1 675 cm^{-1}. This material was identical with a sample of methyl isoarnottianamide (**17b**) which was prepared by methylation of isoarnottianamide (**16b**) obtained from natural sources.

6,7-*Dimethoxy*-2-(2-*methoxy*-4,5-*methylenedioxyphenyl*)-1-(N-*methylformamido*)*naphthalene* (**17c**). A solution of the 1-formamido-1,2,3,4-tetrahydronaphthalene (**15c**) (4.06 g) and DDQ (6.93 g) in benzene (190 ml) was treated as above,

† Chloral was prepared by mixing chloral hydrate with the same amount of concentrated sulphuric acid, and then separating the upper layer and distilling it at 98 °C.

‡ In their ^1H n.m.r. spectra some of the partially unsaturated formamides (**15**) and some of the aromatic formamides (**17**) show a complex pattern, indicating that they exist as a mixture of the rotational isomers with respect to the *N*-formyl group.

refluxing for 1 h, to give colourless *prisms* of (**17c**) (2.40 g), m.p. 217—219 °C (chloroform–ethanol) (Found: C, 66.7; H, 5.35; N, 3.5. $C_{22}H_{21}NO_6$ requires C, 66.8; H, 5.35; N, 3.55%); $\nu_{max.}$ 1 690 cm^{-1}; δ 3.03 (3 H, s, NMe), 3.63 (3 H, s, OMe), 3.95 (3 H, s, OMe), 4.01 (3 H, s, OMe), 5.94 (2 H, s, OCH_2O), 6.57 (1 H, s, 3'- or 6'-H), 6.59 (1 H, s, 6'- or 3'-H), 6.98 (1 H, s, 5-H), 7.17 (1 H, s, 8-H), 7.22 (1 H, d, *J* 8.0 Hz, 4-H), 7.71 (1 H, d, *J* 8.0 Hz, 3-H), and 8.11 (1 H, s, CHO).

6,7-*Dimethoxy*-1-(N-*methylformamido*)-2-(2,4,5-*trimethoxyphenyl*)*naphthalene* (**17d**). A solution of the 1-formamido-1,2,3,4-tetrahydronaphthalene (**15d**) (3.01 g) and DDQ (5.00 g) in benzene (70 ml) was treated as above, refluxing for 2 h, to give colourless prisms (2.40 g), m.p. 211—215 °C (chloroform–ethanol) (Found: C, 66.7; H, 6.1; N, 3.35. $C_{23}H_{25}NO_6$ requires C, 67.15; H, 6.1; N, 3.4%); $\nu_{max.}$ 1 660 cm^{-1}; δ 2.98 (3 H, s, NMe), 3.68 (3 H, s, OMe), 3.80 (3 H, s, OMe), 3.92 (3 H, s, OMe), 3.95 (3 H, s, OMe), 4.01 (3 H, s, OMe), 6.56 (1 H, s, 3'-H), 6.66 (1 H, s, 6'-H), 6.98 (1 H, s, 5-H), 7.17 (1 H, s, 8-H), 7.26 (1 H, d, *J* 8.0 Hz, 4-H), 7.71 (1 H, d, *J* 8.0 Hz, 3-H), and 8.11 (1 H, s, CHO).

General Method for the Bischler–Napieralski Reaction of the 2-*Aryl*-1-(N-*methylformamido*)*naphthalenes* (**17**) *to give the Quaternary Base* (**5**).—A mixture of the 2-aryl-1-(*N*-methylformamido)naphthalene (**17**) and phosphorus oxychloride in acetonitrile or xylene was refluxed, then the solvent was distilled off under reduced pressure, the residue was basified with 10% sodium hydroxide solution and extracted with chloroform. The chloroform solution was dried (K_2CO_3) and evaporated to dryness under reduced pressure. A small amount of 10% hydrochloric acid was added to an ice-cooled solution of the residue in a minute amount of chloroform. The precipitates were collected by filtration and recrystallized from an appropriate solvent to give the desired quaternary base as the chloride. This material was characterized as the dihydrobase (**21**) or the ψ-cyanide.

Sanguirubine (**5c**) *chloride*. A mixture of the 1-formamidonaphthalene (**17c**) (0.509 g) and phosphorus oxychloride (2.40 ml) in xylene (20 ml) was treated as above, refluxing for 20 h, to give red needles of (**5c**) chloride (0.226 g), m.p. 281—284 °C (decomp.) (methanol–ethanol) (lit.,[6b] m.p. 275—276 °C); δ (CD_3OD) 4.04 (3 H, s, OMe), 4.10 (3 H, s, OMe), 4.17 (3 H, s, OMe), 4.90 (3 H, s, N^+Me), 6.45 (2 H, s, OCH_2O), 7.47 (1 H, s, 9-H), 7.68 (1 H, s, 1-H), 7.86 (1 H, s, 4-H), 8.04 (1 H, d, *J* 9.0 Hz, 12-H), 9.26 (1 H, d, *J* 9.0 Hz, 11-H), and 9.72 (1 H, s, 6-H). This material was identical with an authentic sample of sanguirubine (**5c**) chloride (donated by Professor Slavík).

Direct synthesis of dihydrosanguirubine (**21c**) *from the* 1-*formamidonaphthalene* (**17c**). A mixture of the 1-formamidonaphthalene (**17c**) (0.203 g) and phosphorus oxychloride (0.96 ml) in acetonitrile (8 ml) was refluxed for 0.5 h, then the solvent was distilled off under reduced pressure, and the residue was dissolved in anhydrous methanol (10 ml). After the addition of sodium borohydride (0.099 g), the mixture was stirred at room temperature for 3 h, poured into a large amount of water, and extracted with chloroform. The chloroform solution was washed with water, dried ($MgSO_4$), and evaporated to dryness under reduced pressure. Column chromatography of the residue on silica gel with a mixed solvent [chloroform–benzene, 1:1 (v/v)] gave colourless *prisms* of (**21c**) (0.019 g), m.p. 193—196 °C, which were recrystallized from chloroform–methanol (Found: C, 69.7; H, 5.55; N, 3.6. $C_{22}H_{21}NO_5$ requires C, 69.65; H, 5.6; N, 3.7%); δ 2.60 (3 H, s, NMe), 3.86 (3 H, s, OMe), 4.00 (3 H, s, OMe), 4.06 (3 H, s, OMe), 4.12 (2 H, s, 6-H_2), 5.98 (2 H, s, OCH_2O), 6.59 (1 H, s, 9-H), 7.10 (1 H, s, 1-H), 7.12 (1 H, d, *J* 9.0 Hz, 12-H), 7.47 (1 H, d, *J* 9.0 Hz, 11-H), and 7.68 (1 H, s, 4-H).

Sanguilutine (**5d**) *chloride*. A mixture of the 1-formamidonaphthalene (**17d**) (1.37 g) and phosphorus oxychloride (6.20 ml) in acetonitrile (30 ml) was treated as above, refluxing for 0.5 h, to give orange-yellow needles of (**5d**) chloride (0.87 g), m.p. 140—145 °C (decomp.) (water) (lit.,[6b] m.p. 163—164 °C); δ (D_2O) 3.79 (3 H, s, OMe), 3.92 (3 H, s, OMe), 3.96 (3 H, s, OMe), 4.04 (3 H, s, OMe), 4.08 (3 H, s, OMe), 4.48 (3 H, s, N^+Me), 6.60 (1 H, s, 9-H), 7.02 (1 H, s, 1-H), 7.15 (1 H, s, 4-H), 7.20 (1 H, d, *J* 10.0 Hz, 12-H), 8.32 (1 H, d, *J* 10.0 Hz, 11-H), and 9.16 (1 H, s, 6-H). This material was identical with an authentic sample of sanguilutine (**5d**) chloride (donated by Professor Slavík).

Sanguilutine (**5d**) ψ-*cyanide*. A solution of sanguilutine (**5d**) chloride (0.151 g) and potassium cyanide (0.037 g) in water (30 ml) was stirred for 0.5 h. The precipitates were collected by filtration and recrystallized from chloroform–methanol to give colourless prisms of (**5d**) ψ-cyanide (0.078 g), m.p. 228—232 °C (decomp.) (lit.,[6b] m.p. 232—233 °C) (Found: C, 68.45; H, 5.7; N, 6.5. Calc. for $C_{24}H_{24}N_2O_5$: C, 68.55; H, 5.75; N, 6.65%); δ 2.60 (3 H, s, NMe), 3.94 (9 H, s, OMe × 3), 3.98 (3 H, s, OMe), 4.04 (3 H, s, OMe), 5.60 (1 H, s, 6-H), 6.63 (1 H, s, 9-H), 7.09 (1 H, s, 1-H), 7.51 (1 H, d, *J* 9.0 Hz, 12-H), 7.60 (1 H, s, 4-H), and 8.30 (1 H, d, *J* 9.0 Hz, 11-H).

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