Chemical Transformation of Protoberberines. Part 10.[1] A Novel Synthesis of Sanguilutine and Dihydrosanguilutine, fully Aromatised 2,3,7,8,10-Pentaoxygenated Benzo[*c*]phenanthridine Alkaloids

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2,3,7,8,10-Pentaoxygenated benzo[*c*]phenanthridine alkaloids, sanguilutine (**1**) and dihydrosanguilutine (**2**), were efficiently synthesised from the corresponding 2,3,9,10,12-pentamethoxyprotoberberine (**8**) through a regioselective C(6)–N bond cleavage, followed by recombination between the original C(6) and C(13) positions of compound (**8**) according to a biomimetic route.

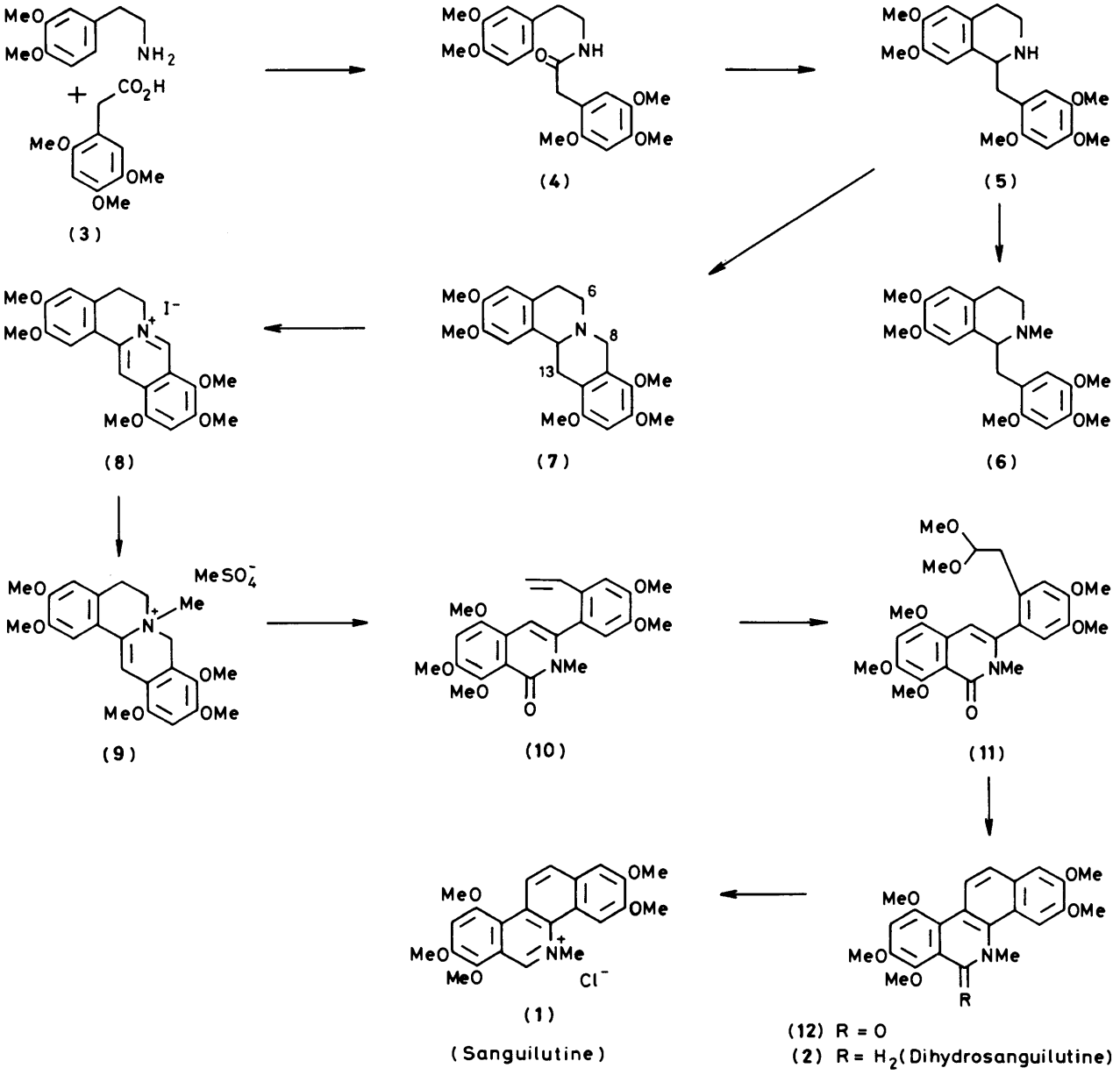
Sanguilutine (**1**), isolated from *Sanguinaria canadensis*[2] and *Papaver oreophilum*,[3] is a representative member of the fully aromatised pentaoxygenated benzo[*c*]phenanthridine alkaloid family.[4] The 2,3,7,8,10-pentamethoxy-substituted structure of this alkaloid has been unambiguously established by its total synthesis.[5,6] Isolation of dihydrosanguilutine (**2**) from *S. canadensis*[7] has also been reported.

In the previous paper,[1,8] we developed an efficient and convenient method for the synthesis of fully aromatised benzo[*c*]phenanthridine alkaloids according to a biomimetic route, and we succeeded in a synthesis of chelerythrine and dihydrochelerythrine, both tetraoxygenated benzo[*c*]phenanthridine alkaloids, from their biogenetic precursor, berberine. We describe here an alternative total synthesis of sanguilutine (**1**) and dihydrosanguilutine (**2**) from the 2,3,9,10,12-pentamethoxyprotoberberine (**8**) according to our biomimetic method (see Scheme).

Synthesis of 2,3,9,10,12-*Pentamethoxyprotoberberine* (**8**).—The starting protoberberine (**8**) for our synthesis of sanguilutines (**1**) and (**2**) was prepared in the usual manner. 2,4,5-Trimethoxyphenylacetic acid (**3**) was accessible from 2,4,5-trimethoxybenzaldehyde[9] by the conventional procedure involving reduction, chlorination, cyanation, and hydrolysis. The acid (**3**) was heated with 3,4-dimethoxyphenethylamine at 190—200 °C for 4 h to give the amide (**4**) in 85% yield. Treatment of compound (**4**) with phosphoryl trichloride in refluxing benzene, followed by reduction with sodium borohydride, afforded the tetrahydroisoquinoline (**5**) in 85% yield. The structures of compounds (**4**) and (**5**) were easily elucidated from their spectral data. On exposure to Pictet–Spengler conditions (formaldehyde in acetic acid), the isoquinoline (**5**) underwent an unusual *N*-methylation[10,11] to yield the *N*-methyl derivative (**6**) in 70% yield instead of the expected cyclised product (**7**). The structure of the tertiary amine (**6**) was determined from the following spectral evidence: a parent peak at *m/z* 387 in the mass spectrum, and the signals of aromatic protons at δ 6.57 (1 H, s), 6.52 (2 H, s), and 6.01 (1 H, s) together with the *N*-methyl signal at δ 2.55 in its ^{1}H n.m.r. spectrum. The desired tetrahydroprotoberberine (**7**)[12] was obtained in 65% yield by successive treatment of compound (**5**) with acetic formic anhydride, phosphoryl trichloride in refluxing toluene, and $NaBH_4$ in methanol[13] at room temperature. The tetrahydroprotoberberine (**7**) showed a parent peak at *m/z* 385 and a diagnostic base peak at *m/z* 194 attributable to the quinodimethane arising from retro-Diels–Alder reaction in the mass spetrometer, and exhibited three singlets in the aromatic region of its ^{1}H n.m.r. spectrum. Compound (**7**) was subsequently dehydrogenated with iodine in refluxing ethanol in the presence of potassium acetate to provide the protoberberine (**8**)[12] in 89% yield. The characteristic signal due to 8-H appeared at δ 9.82 as a singlet in the ^{1}H n.m.r. spectrum of compound (**8**). As the desired protoberberine (**8**) was conveniently synthesised, we next focussed our efforts on the conversion of this salt (**8**) into sanguilutine (**1**) and dihydrosanguilutine (**2**) according to a biomimetic process (see Scheme).

Conversion of 2,3,9,10,12-*Pentamethoxyprotoberberine* (**8**) *into Sanguilutine* (**1**) *and Dihydrosanguilutine* (**2**).—The protoberberine (**8**) was reduced with lithium aluminium hydride (LAH) in dry tetrahydrofuran (THF) at room temperature, and the dihydrogenated product was then treated with dimethyl sulphate in refluxing benzene to give the methosulphate (**9**) in 80% yield. Hofmann elimination of compound (**9**) with 25% methanolic potassium hydroxide effected C(6)–N bond fission to leave a labile enamine, which was subsequently oxidised with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in chloroform and the product treated with sodium cyanide and sodium hydride in a stream of oxygen in dimethylformamide (DMF)[14] to provide a mixture of the desired enamide (**10**) and an *O*-demethyl derivative. Though the structure of the *O*-demethyl derivative was not characterised, this compound seemed to be the 8-*O*-demethyl product by consideration of the neighbouring carbonyl-group participation.[15] This mixture, without purification, was treated with dimethyl sulphate to afford compound (**10**) in 53% overall yield from (**9**). In this conversion of (**9**) into (**10**), the usual method such as DDQ oxidation–potassium ferricyanide [$K_3Fe(CN)_6$] oxidation[16] was ineffective and gave an intractable mixture. The structure of compound (**10**) was assigned on the basis of its spectral data. The mass spectrum showed a parent peak at *m/z* 411, and the i.r. spectrum revealed an enamide absorption band at 1 645 cm^{-1}. The ^{1}H n.m.r. spectrum exhibited the signals due to the styrene moiety at δ 6.48 (1 H, dd, *J* 17.5 and 10.5 Hz), 5.60 (1 H, dd, *J* 17.5 and 1 Hz), and 5.14 (1 H, dd, *J* 10.5 and 1 Hz), and the *N*-methyl signal at lower field (δ 3.23).

Oxy-functionalisation of the styrene moiety in compound (**10**) was realised by treatment with thallium trinitrate (TTN) trihydrate[17] in methanol at from −10 to −20 °C to furnish the dimethyl acetal (**11**), exposure of which to 10% hydrochloric acid yielded a mixture of oxysanguilutine (**12**) and an *O*-demethyl derivative. The *O*-demethyl derivative in this case seemed to be 7-*O*-(demethyl)oxysanguilutine.[15] This mixture was then treated with dimethyl sulphate to give oxysanguilutine (**12**) in 89% overall yield from compound (**10**). The benzo[*c*]phenanthridine structure of oxysanguilutine (**12**) was apparent from the signals due to 11-H and 12-H at δ 8.95 and 7.52 as an AB quartet (*J* 9 Hz) in its ^{1}H n.m.r. spectrum. Sequential reduction of compound (**12**) with LAH in dry THF, and $NaBH_4$ in methanol, at room temperature afforded dihydrosanguilutine



Scheme.

(**2**) in 86% yield. The structure of compound (**2**) was elucidated from the spectral data. The synthetic dihydrosanguilutine was shown to be identical with natural dihydrosanguilutine by comparison of i.r. and ^{1}H n.m.r. spectra, and t.l.c. behaviour. Since compound (**2**) has already been converted into sanguilutine (**1**) by mercury(II) acetate oxidation,[7] the present synthesis amounts to a formal synthesis of sanguilutine (**1**).

In addition, we have accomplished an alternative transformation of compound (**2**) into compound (**1**). Dihydrosanguilutine (**2**) was oxidised with DDQ in benzene in the presence of 5% sodium hydroxide to furnish sanguilutine chloride (**1**) in 92% yield after treatment with conc. hydrochloric acid. The synthetic sanguilutine was identical with the natural one on comparison of their ^{1}H n.m.r. spectra and by t.l.c. behaviour.

Thus, we have efficiently accomplished a total synthesis of sanguilutine and dihydrosanguilutine from the corresponding protoberberine. The present synthesis showed that our biomimetic method can effectively be applied to a synthesis of fully aromatised pentaoxygenated benzo[*c*]phenanthridine alkaloids in addition to tetraoxygenated ones.

Experimental

M.p.s were determined on a Yanagimoto micro melting point apparatus and are uncorrected. I.r. spectra were measured with a JASCO A-102 spectrometer for chloroform solutions, mass spectra with a Hitachi M-80 mass spectrometer, u.v. spectra with a Hitachi 323 spectrometer for solutions in methanol, and ^{1}H n.m.r. spectra with a JEOL FX-100 spectrometer for solutions in $CDCl_3$ unless stated otherwise, with tetramethylsilane as internal standard. Organic extracts were dried over anhydrous sodium sulphate. Ether refers to diethyl ether unless stated otherwise.

2,4,5-*Trimethoxyphenylacetic Acid* (**3**).—A solution of 2,4,5-trimethoxybenzaldehyde (5.0 g, 26 mmol) in ethanol (20 ml) was

added to a suspension of $NaBH_4$ (4.8 g, 128 mmol) in ethanol (40 ml) at room temperature and the mixture was stirred for 1 h. The ethanol was evaporated off and the residue was taken up in methylene dichloride, and the extract was washed successively with water and brine, dried, and concentrated to leave the crude alcohol.

Thionyl chloride (6.0 g, 51 mmol) was added dropwise to a solution of the crude alcohol in chloroform (40 ml) at 0 °C, and the reaction mixture was stirred for 2 h at room temperature. The chloroform solution was washed successively with water, 10% aq. sodium hydroxide, and then water, dried, and evaporated under reduced pressure. The residue was dissolved in dimethyl sulphoxide (DMSO) (10 ml) and the solution was added dropwise to a suspension of sodium cyanide (1.9 g, 38 mmol) in DMSO (50 ml) at 50—60 °C. After being stirred for 3 h at the same temperature, the reaction mixture was poured into water (100 ml) and extracted with benzene. The extract was washed successively with water (× 3) and brine, dried, and concentrated to give the crude phenylacetonitrile. Aq. sodium hydroxide (10%; 30 ml) was added to a solution of the above phenylacetonitrile in ethanol (70 ml), and the mixture was heated under reflux for 6 h. Ethanol was evaporated off and the water layer was washed with ether, and then acidified with conc. hydrochloric acid. The acidic solution was extracted with ethyl acetate, and the extract was washed successively with water and brine, dried, and concentrated. The residual solid was recrystallised from propan-2-ol to afford the *acid* (**3**) (2.8 g, 49%), m.p. 83—85 °C (Found: C, 58.3; H, 6.3. $C_{11}H_{14}O_5$ requires C, 58.40; H, 6.24%); $\nu_{max.}$ 1 710 cm^{-1} (carboxylic acid); $\lambda_{max.}$ 230 and 291 nm (log ε 3.60 and 3.36); δ 3.61 (2 H, s, benzylic protons), 3.82 (6 H, s, OMe × 2), 3.88 (3 H, s, OMe), 6.54 and 6.74 (each 1 H, each s, 2 ArH), and 7.25 (1 H, s, CO_2H).

N-(3,4-*Dimethoxyphenethyl*)-2,4,5-*trimethoxyphenylacetamide* (**4**).—A mixture of the acid (**3**) (11 g, 48 mmol) and 3,4-dimethoxyphenethylamine (4.5 g, 80 mmol) was heated at 190—200 °C in a stream of nitrogen for 4 h. Methylene dichloride (100 ml) was added to the cooled reaction mixture and the solution was washed sequentially with 10% hydrochloric acid, 10% aq. sodium hydroxide, and water, dried, and concentrated to dryness. The residual solid was recrystallised from ethyl acetate to give the *amide* (**4**) (16 g, 85%), m.p. 118—120 °C (Found: C, 64.8; H, 7.1; N, 3.6. $C_{21}H_{27}NO_6$ requires C, 64.76; H, 6.99; N, 3.60%); $\nu_{max.}$ 3 425 (NH) and 1 655 cm^{-1} (amide); $\lambda_{max.}$ 231.5, 283.5sh, 286, and 293 nm (log ε 4.22, 3.82, 3.83, and 3.73); δ 2.60 (2 H, t, *J* 7 Hz, CH_2CH_2N), 3.44 (2 H, q, *J* 7 Hz, CH_2CH_2N), 3.45 (2 H, s, CH_2CO), 3.68 (3 H, s, OMe), 3.81 (6 H, s, OMe × 2), 3.86 and 3.89 (each 3 H, each s, OMe × 2), 5.78 (1 H, m, NH), 6.47, 6.61, and 6.72 (each 1 H, each s, 3 ArH), and 6.58 and 6.72 (each 1 H, AB q, *J* 8 Hz, 2 ArH); *m/z* 389 (M^+, 23%), 225 (72), 181 (100), and 164 (87).

1,2,3,4-*Tetrahydro*-6,7-*dimethoxy*-1-(2,4,5-*trimethoxybenzyl*)*isoquinoline* (**5**).—Phosphoryl trichloride (77 ml) was added to a solution of the amide (**4**) (16 g, 41 mmol) in dry benzene (150 ml), and the resulting mixture was heated under reflux for 2 h. Benzene and excess of $POCl_3$ were evaporated off. Water was added to the residue, and the mixture was neutralised with 10% aq. sodium hydroxide and extracted with methylene dichloride. The extract was washed successively with water and brine, dried, and concentrated to afford a residual oil, which was dissolved in methanol (50 ml), and $NaBH_4$ (3.8 g, 1.0 mol) was added portionwise. After the mixture had been stirred for 1 h at room temperature, methanol was evaporated off and the residue was taken up in methylene dichloride. The solution was washed successively with water and brine, dried, and concentrated to dryness. Chromatography of the residue on alumina with chloroform as eluant provided the *benzylisoquinoline* (**5**) (13 g, 85%), m.p. 90—92 °C (from di-isopropyl ether) (Found: C, 66.5; H, 7.3; N, 3.7. $C_{21}H_{27}NO_5 \cdot \frac{1}{4}H_2O$ requires C, 66.73; H, 7.33; N, 3.71%); $\nu_{max.}$ 3 525 cm^{-1} (NH); $\lambda_{max.}$ 233.5 and 291 nm (log ε 4.23 and 3.96); δ 2.63—3.36 (6 H, m, CH_2CH_2N and CH_2Ar), 3.81 (3 H, s, OMe), 3.83 (6 H, s, OMe × 2), 3.86 and 3.90 (each 3 H, each s, OMe × 2), 4.17 (1 H, dd, *J* 9.5 and 4 Hz, 1-H), and 6.56, 6.59, 6.68, and 6.72 (each 1 H, each s, 4 ArH); c.i.m.s. *m/z* 374 ($M^+ + 1$, 45%) and 192 (100).

1,2,3,4-*Tetrahydro*-6,7-*dimethoxy*-2-*methyl*-1-(2,4,5-*trimethoxybenzyl*)*isoquinoline* (**6**).—A mixture of the tetrahydroisoquinoline (**5**) (2.4 g, 6.4 mmol) and 37% aq. formaldehyde (formalin) (20 ml) in acetic acid (60 ml) was heated under reflux for 4 h. The solution was concentrated and the residue was taken up in methylene dichloride. The solution was washed successively with 5% aq. potassium carbonate, water, and brine, dried, and concentrated to give a residue, which was chromatographed on alumina with chloroform as eluant to afford the *title product* (**6**) (1.74 g, 70%), m.p. 106—107 °C (from propan-2-ol) (Found: C, 68.1; H, 7.7; N, 3.6. $C_{22}H_{29}NO_5$ requires C, 68.19; H, 7.57; N, 3.62%); $\lambda_{max.}$ 228sh, 290, and 300 nm (log ε 4.19, 3.91, and 3.64); δ 2.55 (3 H, s, NMe), 2.61—3.32 (6 H, m, CH_2CH_2N and CH_2Ar), 3.55, 3.72, 3.75, 3.83, and 3.88, (each 3 H, each s, OMe × 5), 6.01 (1 H, s, ArH), 6.52 (2 H, s, 2 ArH), and 6.57 (1 H, s, ArH); *m/z* 387 (M^+, 1.2%) and 206 (100).

5,8,13,13a-*Tetrahydro*-2,3,9,10,12-*pentamethoxy*-6H-*dibenzo*[a,g]*quinolizine* (**7**).—The tetrahydroisoquinoline (**5**) (120 mg, 0.32 mmol) was dissolved in acetic formic anhydride (20 ml) and the mixture was kept overnight at room temperature. After evaporation of the mixed anhydride under reduced pressure, water was added to the residue, and the mixture was extracted with methylene dichloride. The extract was washed successively with 10% aq. sodium hydroxide, water, and brine, dried, and concentrated to afford the *N*-formyl derivative.

Phosphoryl trichloride (0.5 ml) was added to a solution of the *N*-formyl derivative in dry toluene (5 ml), and the mixture was heated under reflux for 3 h. Toluene was evaporated off, the residue was dissolved in methanol (10 ml), and $NaBH_4$ (400 mg, 10.6 mmol) was added. The methanol solution was stirred for 2 h at room temperature and then concentrated to afford an oily residue, which was taken up in methylene dichloride; the solution was washed successively with water and brine, dried, and concentrated to dryness. Chromatography of the residue on silica gel with ethyl acetate as eluant furnished the pentamethoxyberbine (**7**) (80 mg, 65%), m.p. 191—193 °C (from AcOEt) (lit.,[12] m.p. 187—189 °C) (Found: C, 68.3; H, 7.2; N, 3.5. Calc. for $C_{22}H_{27}NO_5$: C, 68.55; H, 7.06; N, 3.63%); $\lambda_{max.}$ 228sh and 286 nm (log ε 4.24 and 3.91); δ 2.42—3.63 (7 H, m, 5-H_2, 6-H_2, 8-H, 13-H_2, and 13a-H), 3.80 and 3.82 (each 3 H, each s, OMe × 2), 3.87 (6 H, s, OMe × 2), 3.90 (3 H, s, OMe), 4.21 (1 H, d, *J* 16 Hz, 8-H), and 6.40, 6.61, and 6.79 (each 1 H, each s, 3 ArH); *m/z* 385 (M^+, 32%), 194 (100), and 179 (49).

5,6-*Dihydro*-2,3,9,10,12-*pentamethoxydibenzo*[a,g]*quinolizinium Iodide* (**8**).—A solution of iodine (2.6 g, 20 mmol) in ethanol (160 ml) was added to a refluxing suspension of the tetrahydroprotoberberine (**7**) (4.3 g, 11 mmol) and potassium acetate (5.5 g, 56 mmol) in ethanol (80 ml), and the mixture was refluxed for a further 2 h. After the reaction mixture had cooled to room temperature, the precipitates were collected by filtration. Sulphur dioxide gas was passed through a stirred suspension of the precipitates in water (150 ml) for 2 h. The orange precipitates were collected by filtration and dried to give the salt (**8**) (5.0 g, 89%), m.p. 241—243 °C (decomp.) (from EtOH) (lit.,[12] m.p. 230—234 °C) (Found: C, 51.8; H, 4.8; N, 2.45. Calc. for $C_{22}H_{24}INO_5$: C, 51.87; H, 4.75; N, 2.75%); $\lambda_{max.}$ 225, 242sh, 282, 366, and 452 nm (log ε 4.59, 4.39, 4.41, 4.37, and 3.80); δ

[$(CD_3)_2SO$] 3.20—3.53 (2 H, m, 5-H_2), 3.89, 3.96, 4.01, 4.13, and 4.17 (each 3 H, each s, OMe × 5), 4.96 (2 H, t-like, *J* 5.5 Hz, 6-H_2), 7.07, 7.53, 7.67, and 8.75 (each 1 H, each s, 4 ArH), and 9.82 (1 H, s, 8-H).

5,6,7,8-*Tetrahydro*-2,3,9,10,12-*pentamethoxy*-7-*methyldibenzo*[a,g]*quinolizinium Methyl Sulphate* (**9**).—The protoberberine (**8**) (1.0 g, 1.96 mmol) was added portionwise to a stirring suspension of LAH (360 mg, 5.88 mmol) in dry THF (50 ml) in a stream of nitrogen at 0 °C, and the mixture was stirred for a further 2 h at room temperature. Water was added to the reaction mixture, and the precipitates were filtered off.

The filtrate was concentrated to give the dihydrogenated derivative, which was dissolved in dry benzene (100 ml) and the solution was heated under reflux. Dimethyl sulphate (1.45 ml, 5.88 mmol) was added to the refluxing benzene solution and the mixture was refluxed for a further 1.5 h. After the mixture had cooled, the resulting precipitates were collected by filtration and dried to afford the *title methosulphate* (**9**) (795 mg, 80%), m.p. 263—265 °C (from propan-2-ol) (Found: C, 52.6; H, 6.4; N, 2.2. $C_{24}H_{31}NO_9S{\cdot}2H_2O$ requires C, 52.83; H, 6.46; N, 2.57%); $\lambda_{max.}$ 254.5, 262, 291, 305, 368, and 386 nm (log ε 4.15, 4.08, 3.98, 4.00, 4.51, and 4.44); δ[$(CD_3)_2SO$] 3.08 and 3.41 (each 3 H, each s, NMe and $MeSO_4^-$), 3.77, 3.84, and 3.89 (each 3 H, each s, OMe × 3), 3.97 (6 H, s, OMe × 2), 4.04—4.20 (2 H, m, 6-H_2), 4.88 and 5.07 (each 1 H, AB q, *J* 15 Hz, 8 H_2), and 6.83, 6.91, 7.31, and 7.53 (each 1 H, each s, 4 ArH).

3-(4,5-*Dimethoxy*-2-*vinylphenyl*)-5,7,8-*trimethoxy*-2-*methylisoquinolin*-1(2H)-*one* (**10**).—The methosulphate (**9**) (500 mg, 0.98 mmol) was added to refluxing 25% potassium hydroxide–methanol (20 ml) and the mixture was heated under reflux for 10 min, then poured into ice–water and extracted with chloroform (40 ml); the extract was washed successively with water and brine, dried, and filtered. To the filtrate was added a solution of DDQ (225 mg, 1.00 mmol) in chloroform (40 ml), and the mixture was stirred for 3 h at room temperature. Chloroform was evaporated off, the residue was dissolved in DMF (25 ml), and sodium hydride (135 mg, 3.09 mmol) and sodium cyanide (135 mg, 2.70 mmol) were added. The reaction mixture was heated in a stream of oxygen at 60 °C for 5 h. Water was added to the reaction mixture, which was then extracted with chloroform. The extract was washed, successively with water and brine, dried, and concentrated to give a mixture of compound (**10**) and its 8-*O*-demethyl derivative. This mixture was dissolved in THF (20 ml), and dimethyl sulphate (620 mg, 4.90 mmol) and 10% aq. sodium hydroxide (4 ml) were added. The THF solution was heated under reflux for 1 h, then water was added, the mixture was extracted with methylene dichloride, and the extract was washed successively with water, 28% aq. ammonium hydroxide, and brine, dried, and concentrated to dryness. Chromatography of the residue on alumina with methylene dichloride–methanol (200:1) as eluant gave the *title compound* (**10**) (212 mg, 53%), m.p. 198—200 °C (from MeOH) (Found: C, 66.5; H, 6.2; N, 3.4. $C_{23}H_{25}NO_6{\cdot}\frac{1}{4}$ MeOH requires C, 66.57; H, 6.25; N, 3.34%); $\nu_{max.}$ 1 645 cm^{-1} (amide); $\lambda_{max.}$ 213.5, 225, 262sh, 308, and 362 nm (log ε 4.59, 4.59, 4.14, 4.11, and 3.90); δ 3.23 (3 H, s, NMe), 3.89, 3.90, and 3.97 (each 3 H, each s, OMe × 3), 3.98 (6 H, s, OMe × 2), 5.14 (1 H, dd, *J* 10.5 and 1 Hz, *Z*-C*H*H=CH), 5.60 (1 H, dd, *J* 17.5 and 1 Hz, *E*-CH*H*=CH), 6.48 (1 H, dd, *J* 17.5 and 10.5 Hz, CH_2=C*H*), and 6.69, 6.75, 6.84, and 7.14 (each 1 H, each s, 4 ArH); *m/z* 411 (M^+, 100%) and 396 (40).

Oxysanguilutine (**12**).—A solution of the enamide (**10**) (45 mg, 0.11 mmol) in methanol (10 ml) was added dropwise to a solution of TTN trihydrate (47 mg, 0.11 mmol) in methanol (10 ml) during 15 min at −10 to −20 °C. The reaction mixture was kept at the same temperature for 20 min, then methylene dichloride (20 ml) was added and the resulting precipitates were filtered off. The methylene dichloride solution was washed successively with 10% aq. sodium hydroxide and water, dried, and concentrated to leave a residue, which was taken up in methanol (10 ml). Hydrochloric acid (10%; 2 ml) was added to the methanol solution, and the mixture was heated at 50 °C for 1.5 h. Methanol was evaporated off, the residue was taken up in methylene dichloride, and the solution was washed with water, dried, and concentrated to dryness. The residual oil was dissolved in THF (10 ml), to which dimethyl sulphate (70 mg, 0.55 mmol) and 10% aq. sodium hydroxide (1 ml) were added. The THF solution was separated, and heated under reflux for 2 h. After the solution had cooled, THF was evaporated off, the residue was taken up in methylene dichloride, and the solution was washed successively with 28% aq. ammonium hydroxide, water, and brine, dried, and concentrated to dryness. Chromatography of the residue on alumina with methylene dichloride–methanol (100:1) as eluant afforded *oxysanguilutine* (**12**) (40 mg, 89%), m.p. 156—158 °C (from MeOH) (Found: M^+, 409.1541. $C_{23}H_{23}NO_6$ requires *M*, 409.1524); $\nu_{max.}$ 1 640 cm^{-1} (amide); $\lambda_{max.}$ 244, 275.5, 284.5, 308sh, 320, 337, and 351 nm (log ε 4.59, 4.65, 4.72, 4.05, 4.10, 4.14, and 4.18); δ 3.89 (3 H, s, NMe), 4.00, 4.02, 4.03, 4.04, and 4.05 (each 3 H, each s, OMe × 5), 6.96, 7.14, and 7.42 (each 1 H, each s, 3 ArH), and 7.52 and 8.95 (each 1 H, AB q, *J* 9 Hz, 12- and 11-H); *m/z* 409 (M^+, 100%), 394 (23), and 366 (21).

Dihydrosanguilutine (**2**).—LAH (46 mg, 1.21 mmol) was added to a solution of oxysanguilutine (**12**) (50 mg, 0.12 mmol) in dry THF (10 ml) under a stream of nitrogen at 0 °C. The reaction mixture was stirred for 1 h at room temperature, then water was added and the precipitates were filtered off. The filtrate was concentrated and the residue was dissolved in methanol (10 ml). $NABH_4$ (46 mg, 1.21 mmol) was added to the methanol solution and the mixture was kept for 30 min at room temperature. Methanol was evaporated off, the residue was taken up in methylene dichloride, and the solution was washed successively with water and brine, dried, and concentrated to dryness. Chromatography of the residue on alumina with methylene dichloride–methanol (100:1) as eluant provided dihydrosanguilutine (**2**) (41 mg, 86%), m.p. 153—156 °C (from MeOH) (lit.,[7] 154—155 °C) (Found: C, 69.9; H, 6.4; N, 3.55. Calc. for $C_{23}H_{25}NO_5$: C, 69.85; H, 6.37; N, 3.54%); $\lambda_{max.}$ 228, 277, 328, and 345 nm (log ε 4.54, 4.62, 4.27, and 4.07); δ 2.60 (3 H, s, NMe), 3.83, 3.93, 3.96, 4.01, and 4.07 (each 3 H, each s, OMe × 5), 4.24 (2 H, s, 6-H_2), 6.58, 7.12, and 7.68 (each 1 H, each s, 3 ArH), and 7.49 and 8.32 (each 1 H, AB q, *J* 8 Hz, 12- and 11-H); *m/z* 395 (M^+, 100%) and 364 (16).

Sanguilutine Chloride (**1**).—DDQ (28 mg, 0.12 mmol) was added to a stirred solution of dihydrosanguilutine (**2**) (29 mg, 0.07 mmol) in benzene (10 ml) in the presence of 5% aq. sodium hydroxide (2 ml) at room temperature, and the mixture was stirred for a further 3 h. The benzene layer was separated and the water layer was extracted with chloroform. The combined organic solution was washed successively with water and brine, dried, and concentrated to dryness. To the residue was added a small amount of conc. hydrochloric acid, and the resulting precipitates were collected by filtration and recrystallised from ethanol to give sanguilutine chloride (**1**) (29 mg , 92%), m.p. 137—138 °C (lit.,[5] 137—138 °C); $\lambda_{max.}$ 240.5, 271, 301, 315, 326, and 396 nm (log ε 4.47, 4.67, 4.29, 4.32, 4.38, and 3.60); δ[$(CD_3)_2SO$] 4.02, 4.07, 4.09, 4.17, and 4.27 (each 3 H, each s, OMe × 5), 5.02 (3 H, s, NMe), 7.74, 7.77, and 8.06 (each 1 H, each s, 3 ArH), 8.27 and 9.42 (each 1 H, AB q, *J* 9 Hz, 12- and 11-H), and 10.04 (1 H, s, 6-H).

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