# SYNTHESIS OF FAGARONINE

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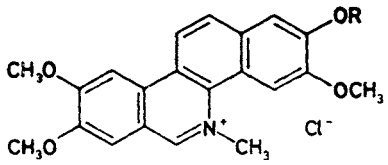
Alkaloids fagaronine (*I*), dihydrofagaronine (*XXV*) and oxyfagaronine (*XXVI*) were synthesized from 2,3-dihydroxynaphthalene (*II*) and 2-bromo-4,5-dimethoxybenzaldehyde (*XI*), the key synthetic steps being the preparation of 2-hydroxy-3-methoxy-5-nitronaphthalene (*VI*) by partial methylation of 2,3-dihydroxy-5-nitronaphthalene (*V*) and formation of benzo[*c*]phenanthridone *XXI* by photocyclization of amide *XVI*.

In our previous paper we described synthesis of the alkaloid sanguinarine and chelerythrine[1]. We tried to prepare in an analogous way the alkaloid fagaronine (*I*). This alkaloid was isolated from *Fagara zanthoxyloides* LAM. by Farnsworth and collaborators[2] and later synthesized by Stermitz[3,4] and Ishii[5,6]. Fagaronine (*I*) exhibits significant activity against mice L1210 and P388 leukemia. To obtain greater amounts for biological studies we tried to synthesize this compound in a more effective way.

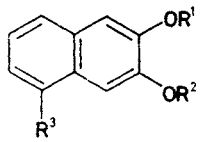
Our synthesis started from 2,3-dihydroxynaphthalene (*II*) which was converted into 2,3-dimethanesulfonyloxy-5-nitronaphthalene (*IV*) via 2,3-dimethanesulfonyloxynaphthalene (*III*) according to Stermitz and collaborators[4]. The compound *IV* was hydrolyzed with sodium hydroxide to give 2,3-dihydroxy-5-nitronaphthalene (*V*) which on methylation with excess of diazomethane afforded a mixture of the desired 2-hydroxy-3-methoxy-5-nitronaphthalene (*VI*), its isomer *VII*, starting compound *V* and dimethoxy derivative *VIII*. Extraction with sodium hydroxide removed the alkali-insoluble dimethoxy derivative *VIII* and the mixture of *V*, *VI* and *VII* was separated by chromatography on silica gel. The isomer *VI* was alkylated with 2-bromopropane to give the isopropyl derivative *IX* which was reduced to 5-amino-2--isopropoxy-3-methoxynaphthalene (*X*).

Fagaronine (*I*) was prepared from the amine *X* in three ways. The first consisted in the reaction of *X* with 2-bromo-4,5-dimethoxybenzaldehyde[7] (*XI*) followed by reduction of the obtained Schiff base *XII* with sodium borohydride to the amine *XIII*. The amine *XIII* was then simultaneously photocyclized and dehydrogenated and the resulting benzo[*c*]phenanthridine *XIV* was quaternized with dimethyl sulfate with simultaneous removal of the isopropyl group to afford fagaronine (*I*).

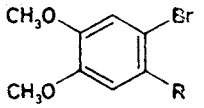
In the second synthesis the amine *X* reacted with 2-bromo-4,5-dimethoxybenzoyl chloride (*XV*) to afford amide *XVI*. The required 2-bromo-4,5-dimethoxybenzoic acid (*XVII*) was prepared by oxidation of the aldehyde *XI* with potassium perman-



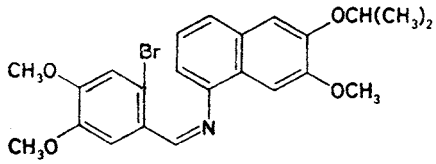
*I*, R = H
*XXIV*, R = $CH(CH_3)_2$



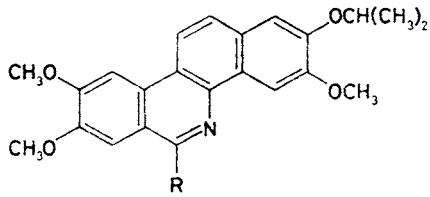
*II*, $R^1$ = H ; $R^2$ = H ; $R^3$ = H
*III*, $R^1$ = $CH_3SO_2$ ; $R^2$ = $CH_3SO_2$ ; $R^3$ = H
*IV*, $R^1$ = $CH_3SO_2$ ; $R^2$ = $CH_3SO_2$ ; $R^3$ = $NO_2$
*V*, $R^1$ = H ; $R^2$ = H ; $R^3$ = $NO_2$
*VI*, $R^1$ = H ; $R^2$ = $CH_3$ ; $R^3$ = $NO_2$
*VII*, $R^1$ = $CH_3$ ; $R^2$ = H ; $R^3$ = $NO_2$
*VIII*, $R^1$ = $CH_3$ ; $R^2$ = $CH_3$ ; $R^3$ = $NO_2$
*IX*, $R^1$ = $CH(CH_3)_2$ ; $R^2$ = $CH_3$ ; $R^3$ = $NO_2$
*X*, $R^1$ = $CH(CH_3)_2$ ; $R^2$ = $CH_3$ ; $R^3$ = $NH_2$



*XI*, R = CHO
*XV*, R = COCl
*XVII*, R = COOH



*XII*

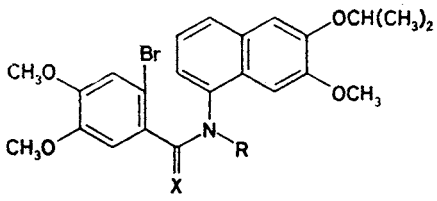


*XIV*, R = H
*XXII*, R = $OCH_3$

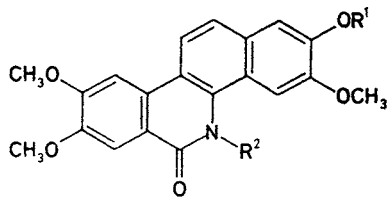
ganate in acetone. This procedure is more advantageous than the previously described one[8] that used pyridine as solvent. Methylation of amide *XVI* with dimethyl sulfate in aqueous acetone gave N-methylamide *XVIII* which was photocyclized in a quartz apparatus to give benzo[*c*]phenanthridone *XIX* in a 7 % yield. As a side product we isolated the phenylnaphthalene derivative *XX*. A simila. rearrangement was observed already earlier in photocyclizations of analogous compounds[9] or in their cyclizations by electroreduction[8].

In the third reaction scheme the photocyclization was carried out directly with the amide *XVI*. This reaction could be performed in a Pyrex reactor, required shorter time and the yield of the phenanthridone *XXI* was 92%. Methylation of *XXI* in the same polar solvent (aqueous acetone) which was used for the uncyclized amide *XVI*,

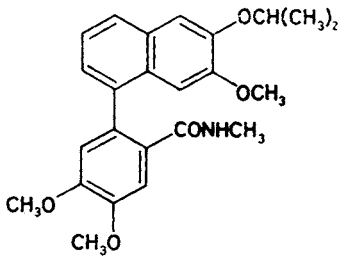
afforded predominantly the O-methyl derivative *XXII* whereas the desired N-methylamide *XIX* was obtained only as a minor product. This result can be explained as follows. In the uncyclized amide *XVI* both the aromatic systems are not coplanar and therefore the enol form is not preferred. On the other hand, the molecule of benzo[*c*]phenanthridone *XXI* is entirely planar, so that the enol form is preferred.



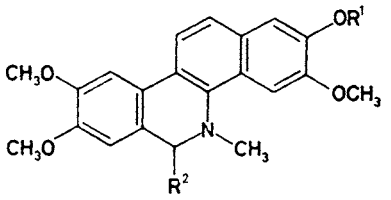
*XIII*, R = H ; X = H,H
*XVI*, R = H ; X = O
*XVIII*, R = $CH_3$ ; X = O



*XIX*, $R^1$ = $CH(CH_3)_2$ ; $R^2$ = $CH_3$
*XXI*, $R^1$ = $CH(CH_3)_2$ ; $R^2$ = H
*XXVI*, $R^1$ = H ; $R^2$ = $CH_3$



*XX*



*XXIII*, $R^1$ = $CH(CH_3)_2$ ; $R^2$ = H
*XXV*, $R^1$ = H ; $R^2$ = H
*XXVII*, $R^1$ = H ; $R^2$ = CN

Methylation of sodium salt of *XXI* in a non-polar medium afforded N-methylbenzo[*c*]phenanthridone *XIX* whereas the O-methyl derivative was obtained only in negligible amounts. Compound *XIX* was reduced with lithium aluminium hydride in tetrahydrofuran to give dihydro derivative *XXIII* which was oxidized with dichlorodicyanobenzoquinone to quaternary salt *XXIV*. Finally, *XXIV* was O-dealkylated with sulfuric acid to furnish fagaronine (*I*). The alkaloid *I* was converted into dihydrofagaronine (*XXV*), oxyfagaronine (*XXVI*) and fagaronine pseudocyanide (*XXVII*). The synthesized compound *I* was identical with a sample isolated from natural material. This third synthetic pathway is suitable for a large-scale preparation of fagaronine.

## EXPERIMENTAL

The melting points were determined on a Boetius microblock and are uncorrected. The analytical samples were dried over phosphorus pentoxide at 14 Pa and room temperature or at 77°C for 6 h. Purity of the compounds was checked by TLC on silica gel (Silufol $UV_{254}$, Kavalier, or plates $GF_{254}$, Merck), UV-detection at 254 and 366 nm. UV spectra were obtained with a Unicam SP 8000 spectrometer ($\lambda_{max}$, nm; log $\varepsilon$, $m^2$ $mol^{-1}$), IR spectra with a Unicam SP 2000 G instrument ($\nu$, $cm^{-1}$). Proton NMR spectra were taken on a Tesla BS 487C spectrometer (80 MHz; $\delta$, ppm; $J$, Hz) with tetramethylsilane as internal standard.

### 2,3-Dihydroxy-5-nitronaphthalene (*V*)

2,3-Dimethanesulfonyloxy-5-nitronaphthalene[4] (*III*; 72·1 g; 0·20 mol) was added to a solution of sodium hydroxide (48 g; 1·2 mol) in water (1 400 ml) and the mixture was refluxed under argon for 1·5 h. After cooling and acidification with hydrochloric acid (1 : 1), the mixture was extracted with ether (3 × 500 ml) and the combined extracts were dried over sodium sulfate. Evaporation of the solvent afforded the dihydroxy derivative *V* (32·9 g; 80%) as dark yellow needles, m.p. 206—208 °C. An analytical sample was crystallized from benzene–ether and melted at 207—209°C. For $C_{10}H_7NO_4$ (205·2) calculated: 58·84% C, 3·44% H, 6·83% N; found: 58·38% C, 3·46 H, 6·68% N.

### 2-Hydroxy-3-methoxy-5-nitronaphthalene (*VI*)

A solution of diazomethane (467 ml; 0·224 mol) was added at 0°C to a stirred solution of *V* (32·8 g; 0·16 mol) in ether (300 ml) during 1 h. After stirring for another hour, the ethereal solution was extracted with 5% NaOH (3 × 300 ml). The ethereal phase was washed with water, dried over sodium sulfate and the solvent was evaporated. Crystallization of the residue from ethyl acetate afforded 11·2 g (30%) of 2,3-dimethoxy-5-nitronaphthalene (*VIII*), m.p. 158—160°C (reported m.p. 158—159°C (ref.[3]), m.p. 157—158°C (ref.[10])).

The combined alkaline extracts were acidified with hydrochloric acid (1 : 1) to pH 1 and extracted with ether (3 × 400 ml). The combined extracts were dried over sodium sulfate and taken down, leaving a mixture (24 g) of *V*, *VI* and *VII* which was chromatographed on silica gel (400 g, Kieselgel 60, Merck). Elution with benzene–chloroform (95 : 5) gave 9·9 g (28%) of *VI*, m.p. 126—128°C (reported[3] m.p. 126—127°C) which was used in the next reaction without purification. Benzene–chloroform (70 : 30) eluted 5·8 g (16·5%) of the isomer *VII*, m.p. 163—165C° (reported[3] m.p. 159—160°C).

### N-(2′-Bromo-4′,5′-dimethoxybenzyl)-2-isopropoxy-3-methoxy-5-naphthylamine (*XIII*)

A mixture of 2-bromo-4,5-dimethoxybenzaldehyde (*XI*; 2·46 g; 10 mmol), 2-isopropoxy-3-methoxy-5-naphthylamine (*X*; 2·31 g; 10 mmol) and benzene (50 ml) was refluxed for 4 h under simultaneous removal of water. The solvent was evaporated and the dry Schiff's base *XII* (m.p. 150—152°C; reported[3] m.p. 153—154°C) was dissolved in dimethylformamide (60 ml). The solution was heated to 90°C, sodium borohydride (0·46 g; 12 mmol) was added and the mixture was stirred and heated to 110°C for 1 h. After cooling, the solution was poured into water (150 ml), the precipitate was collected, washed with water and dissolved in chloroform (50 ml). The chloroform solution was washed with water, dried over sodium sulfate and taken down. Crystallization of the residue from ethanol afforded amine *XIII* (2·4 g; 51%), m.p. 189—191°C. For $C_{23}H_{26}BrNO_4$ (460·4) calculated: 60·00% C, 5·69% H, 17·36% Br, 3·04% N; found: 60·31% C,

5·61% H, 17·25% Br, 3·09% N. UV spectrum ($CH_3OH$): 207 (3·83); 221 (3·82); 260 (3·58); 318 (2·87). IR spectrum ($CHCl_3$): 2 845 ($CH_3O$); 3 450 (NH). $^1$H NMR spectrum ($CDCl_3$): 7·10 m, 6 H (arom.); 6·50 m, 1 H (H-6); 4·70 m, 1 H (OCH); 4·48 s + bs, 3 H ($CH_2$ + NH); 3·98 s, 3 H ($OCH_3$); 3·85 s, 3 H ($OCH_3$); 3·71 s, 3 H ($OCH_3$); 1·48 d, $J$ = 6·0, 6 H ($C(CH_3)_2$).

2-Isopropoxy-3,8,9-trimethoxybenzo[*c*]phenanthridine (*XIV*)

A solution of sodium hydroxide (80 mg; 2 mmol) in water (50 ml) was added to the amine *XIII* (0·47 g; 1 mmol) in acetonitrile (450 ml) and the mixture was irradiated for 6 h with a medium-pressure mercury lamp (125 W) through a Pyrex filter with simultaneous introduction of argon. The mixture was concentrated almost to dryness in vacuo and partitioned between chloroform (100 ml) and water (50 ml). The organic phase was separated, washed with water, dried over sodium sulfate and the solvent was evaporated. Crystallization of the residue from nitromethane (8 ml) gave 147 mg (38%) of fenanthridine *XIV* as colourless needles, m.p. 269—271°C (reported[3] m.p. 270—272°C).

2-Hydroxy-3,8,9-trimethoxy-5-methylbenzo[*c*]phenanthridinium Chloride (Fagaronine, *I*)

The phenanthridine *XIV* was quaternized with dimethyl sulfate with simultaneous dealkylation as described[3]. The obtained fagaronine methosulfate was converted[3] into the chloride *I* which on crystallization from methanol–ethyl acetate was obtained in 8% yield (from *XIV*); m.p. 194—196°C (then solidified and remelted at 266—268°C). The product was identical (m.p., TLC, UV, IR and $^1$H NMR) with an authentic natural sample of *I* as well as with the material obtained by other procedures (vide infra).

2-Bromo-4,5-dimethoxybenzoic Acid (*XVII*)

A solution of potassium permanganate (19 g; 120 mmol) in water (360 ml) was added dropwise during 2 h to a boiling solution of 2-bromo-4,5-dimethoxybenzaldehyde (*XI*; 19·7 g; 80 mmol) in acetone (200 ml). After refluxing for 1 h, acetone was evaporated in vacuo, the formed manganese dioxide was filtered, washed with hot 5% NaOH (100 ml) and with hot water (100 ml). The filtrate was extracted with ether (300 ml) and acidified with 18% hydrochloric acid. The separated crystals were filtered, air-dried and crystallized from methanol–benzene to furnish 15·6 g (74%) of acid *XVII*, m.p. 184—185°C (reported[8] m.p. 182—185°C).

2′-Bromo-4′,5′-dimethoxybenzoic Acid 2-Isoproxy-3-methoxy-5-naphthylamide (*XVI*)

A mixture of acid *XVII* (13·1 g; 50 mmol), chloroform (50 ml) and thionyl chloride (7.3 ml; 100 mmol) was stirred and refluxed for 1 h. After evaporation to dryness, the remaining benzoyl chloride *XV* was coevaporated with benzene (40 ml), dissolved in dichloromethane (30 ml) and added dropwise at 0°C during 30 min to a stirred mixture of amine *X* (9·24 g; 40 mmol), dichloromethane (80 ml) and triethylamine (13·8 ml; 100 mmol). The mixture was stirred for 1 h at 0°C and then let attain room temperature during another hour. 3-Dimethylaminopropylamine (5 ml) was added with stirring which was then continued for 30 min. The reaction mixture was washed with 6% hydrochloric acid (2 × 80 ml), water (1 × 80 ml) and 3% sodium hydrogen carbonate (2 × 80 ml). The organic phase was dried over sodium sulfate, taken down and the residue was crystallized from methanol–benzene to give 15·3 g (81%) of amide *XVI*, m.p. 196—198°C. For $C_{23}H_{24}BrNO_5$ (474·4) calculated: 58·23% C, 5·10% H, 16·85% Br, 2·95% N; found: 58·44% C, 5·21% H, 17·23% Br, 3·12% N. UV spectrum ($CH_3OH$): 210 (3·72); 238 (3·81); 295 (3·00); 330

(2·58). IR spectrum ($CHCl_3$): 1 666 (CO); 2 845 ($CH_3O$); 3 418 (NH). $^1$H NMR spectrum ($CDCl_3$): 8·30 bs, 1 H (NH); 6·80—7·80 m, 7 H (arom); 4·70 m, 1 H (OCH); 3·89 s, 3 H ($OCH_3$); 3·82 s, 6 H (2 × $OCH_3$); 1·42 d, $J$ = 6·5, 6 H ($C(CH_3)_2$).

2′-Bromo-4′,5′-dimethoxybenzoic Acid N-Methyl-N-(2-isopropoxy--3-methoxy-5-naphthyl)amide (*XVIII*)

A solution of sodium hydroxide (2·8 g; 70 mmol) in water (28 ml) was added to a solution of amide *XVI* (2·32 g; 5 mmol) in acetone (20 ml). Dimethyl sulfate (2 ml; 21 mmol) was added to the stirred boiling mixture which was then refluxed with stirring for 2 h. After cooling, water (300 ml) was added and the mixture was extracted with chloroform. The extract was washed with 5% ammonium hydroxide and water, dried over sodium sulfate and the solvent was evaporated. Crystallization from ethanol afforded 2·2 g (90%) of methylamide *XVIII*, m.p. 182—184°C. For $C_{24}H_{26}BrNO_5$ (488·4) calculated: 59·02% C, 5·37% H, 16·36% Br, 2·87% N; found: 59·18% C, 5·28% H, 16·12% Br, 2·81% N. UV spectrum ($CH_3OH$): 210 (3·74); 237 (3·75); 291 (2·97); 331 (2·64). IR spectrum ($CHCl_3$): 1 642 (CO), 2 845 ($CH_3O$). $^1$H NMR spectrum ($CDCl_3$): 7·20 s, 1 H (arom); 7·10 s, 1 H (arom).; 6·80 s, 1 H (arom.); 6·41 s, 1 H (arom.); 7·00—7·50 m, 3 H (arom.); 4·70 m, 1 H (OCH); 4·03 s, 3 H ($OCH_3$); 3·70 s, 3 H ($OCH_3$); 3·58 s, 3 H ($OCH_3$); 3·21 s, 3 H ($NCH_3$); 1·48 d, $J$ = 6·5, 6 H ($C(CH_3)_2$).

2-Isopropoxy-3,8,9-trimethoxy-5-methyl-6-oxo-5,6-dihydrobenzo[*c*]phenanthridine (*XIX*) and N-Methyl-2-(5-(2-isopropoxy-3-methoxy)naphthyl)-4,5-dimethoxybenzamide (*XX*)

A mixture of methylamide *XVIII* (1·22 g; 2·5 mmol), triethylamine (1·2 ml) and acetonitrile (500 ml) was irradiated with a medium-pressure mercury lamp (125 W) in a quartz apparatus under argon for 24 h. The mixture was concentrated almost to dryness in vacuo, and the residue was partitioned between chloroform (100 ml) and water (50 ml). The organic phase was dried over sodium sulfate and the solvent was evaporated. The residue which contained two compounds (TLC) was dissolved in chloroform and chromatographed on a column of silica gel (120 g; Kieselgel 60, Merck) in benzene with gradual addition of chloroform. The first fraction on crystallization from acetonitrile afforded 72 mg (7%) of methylamide *XIX*, m.p. 194—196°C, identical (TLC, spectra) with the product of methylation of *XXI*. The second eluted compound was crystallized from methanol (27 mg; 3%); it melted at 123—125°C, and after resolidification again at 176—178°C. It was identified as *XX*. For $C_{24}H_{27}NO_5$ (409·4) calculated: 70·39% C, 6·65% H, 3·42% N; found: 70·36% C, 6·92% H, 3·19% N. UV spectrum ($CH_3OH$): 209 (3·67); 240 (3·78); 288 (3·05). IR spectrum ($CHCl_3$): 1 650 (CO); 3 440 (NH). $^1$H NMR spectrum ($CDCl_3$): 7·68 dd, 1 H (arom.); 7·30 m, 2 H (arom.); 7·60 s, 1 H (arom.); 7·19 s, 1 H (arom.); 6·89 s, 1 H (arom.); 6·80 s, 1 H (arom.); 5·20 bd, 1 H (NH); 4·75 m, 1 H (OCH); 4·01 s, 3 H ($OCH_3$), 3·88 s, 3 H ($OCH_3$); 3·77 s, 3 H ($OCH_3$); 2·32 d, $J$ = 5·0, 3 H ($NCH_3$); 1·50 d, 3 H ($CCH_3$); 1·49 d, 3 H ($CCH_3$).

2-Isopropoxy-3,8,9-trimethoxy-6-oxo-5,6-dihydrobenzo[*c*]phenanthridine (*XXI*)

Triethylamine (1·32 ml; 10·0 mmol) was added to a solution of amide *XVI* (3·80 g; 8·0 mmol) in benzene (450 ml) and methanol (50 ml) and the mixture was irradiated with a medium-pressure mercury lamp (125 W) with a Pyrex filter under argon for 5 h. Reaction mixtures from four batches (total 15·2 g; 32 mmol of *XVI*) were combined, the solvents were evaporated, the residue was dissolved in chloroform (300 ml) and washed with water (2 × 200 ml). After drying over sodium sulfate, the chloroform was evaporated in vacuo and the still liquid residue was immediate-

ly dissolved in boiling acetonitrile (100 ml). The separated colourless crystals were collected on filter, affording 11·6 g (92%) of *XXI*, m.p. 284–286°C. For $C_{23}H_{23}NO_5$ (393·4) calculated: 70·21% C, 5·89% H, 3·56% N; found: 70·18% C, 6·11% H, 3·38 %N. UV spectrum ($CH_3OH$): 250 (3·62); 267 (3·66); 278 (3·67); 289 (3·79); 363 (2·92). IR spectrum ($CHCl_3$): 1 645 (CO), 2 845 ($CH_3O$), 3 420 (NH). $^1$H NMR spectrum ($CDCl_3$): 12·50 bs, 1 H (NH); 8·25 s, 1 H (H-7); 7·82 d, $J$ = 8·0, 1 H (H-11); 7·39 d, $J$ = 8·0, 1 H (H-12); 7·78 s, 1 H (H-4); 7·49 s, 1 H (H-10); 7·10 s, 1 H (H-1); 4·75 m, 1 H (OCH); 4·10 s, 3 H ($OCH_3$); 4·02 s, 3 H ($OCH_3$); 3·92 s, 3 H ($OCH_3$); 1·45 d, $J$ = 6·0, 6 H ($C(CH_3)_2$).

2-Isopropoxy-3,8,9-trimethoxy-5-methyl-6-oxo-5,6-dihydrobenzo[*c*]phenanthridine (*XIX*)

Sodium hydride (1·39 g; 58 mmol) was slowly added to a stirred solution of *XXI* (11·4 g; 29 mmol) in benzene (114 ml) and the mixture was stirred and refluxed for 2 h. After cooling to 60°C, dimethyl sulfate (2·76 ml; 29 mmol) was slowly added, the mixture was stirred and refluxed for 2·5 h, cooled and poured into water. Chloroform (300 ml) was added and the mixture was made alkaline with ammonia. The chloroform phase was washed with water (2 × 200 ml), dried over sodium sulfate, the solvent was evaporated and the dry residue was dissolved in chloroform and chromatographed on a column of silica gel (200 g; Kieselgel 60, Merck). Elution with benzene–chloroform (95 : 5) afforded phenanthridine *XXII* (0·92 g; 8%) as colourless crystals, m.p. 209–211°C (acetonitrile). For $C_{24}H_{25}NO_5$ (407·5) calculated: 70·74% C, 6·18% H, 3·44% N; found: 70·80% C, 6·40% H, 3·40% N. UV spectrum ($CH_3OH$): 227 (3·13); 248 (3·20); 280 (3·66); 309 (3·15); 343 (2·48); 359 (2·33). $^1$H NMR spectrum ($CDCl_3$): 8·50 s, 1 H (H-7); 7·96 d, $J$ = 8·0, 1 H (H-11); 7·53 d, $J$ = 8·0, 1 H (H-12); 7·55 s, 1 H (arom.); 7·50 s, 1 H (arom.); 7·20 s, 1 H (arom.); 4·75 m, 1 H (OCH); 4·21 s, 3 H ($OCH_3$); 4·10 s, 3 H ($OCH_3$); 4·00 s, 6 H (2 × $OCH_3$); 1·50 d, $J$ = 6·0, 6 H ($C(CH_3)_2$).

Elution with benzene–chloroform–ethanol (50 : 49 : 1) gave methylamide *XIX* (10·1 g; 86%) as colourless crystals, m.p. 194–196°C (acetonitrile) (reported[6] m.p. 194–196°C). UV spectrum ($CH_3OH$): 253 (3·65); 266 (3·74); 276 (3·78); 287 (3·87); 320 (3·25); 335 (3·18). IR spectrum ($CHCl_3$): 1 635 (CO). $^1$H NMR spectrum ($CDCl_3$): 7·90 d, $J$ = 8·5, 1 H (H-11); 7·87 s, 1 H (H-7); 7·59 s, 1 H (arom.); 7·48 s, 1 H (arom.); 7·17 s, 1 H (arom.); 7·50 d, $J$ = 8·5, 1 H (H-12); 4·76 m, 1 H (OCH); 4·02 s, 3 H ($OCH_3$); 4·00 s, 9 H (2 × $OCH_3$, $NCH_3$); 1·47 d, $J$ = 6·0, 6 H ($C(CH_3)_2$).

2-Isopropoxy-3,8,9-trimethoxy-5-methyl-5,6-dihydrobenzo[*c*]phenanthridine (*XXIII*)

Lithium aluminium hydride (0·87 g; 23 mmol) was slowly added to a stirred solution of phenanthridone *XIX* (9·36 g; 23 mmol) in tetrahydrofuran (600 ml) at 35°C. The mixture was stirred and refluxed for 3 h. After cooling to 0°C, the stirred mixture was decomposed by addition of water (0·87 ml), followed after 5 min with 15% aqueous sodium hydroxide (0·87 ml) and, again after 5 min, with water (2·6 ml). Stirring was continued for 15 min, the precipitate was filtered, washed thoroughly with ether, the combined extracts were dried over magnesium sulfate and taken down, leaving 8·9 g (98%) of *XXIII* as colourless crystals, m.p. 197–199°C. An analytical sample was crystallized from acetonitrile and melted at 200–202°C (reported[6] m.p. 199–202°C). UV spectrum ($CH_3OH$): 230 (3·53); 276 (3·60); 311 (3·35); 332 (3·29). $^1$H MMR spectrum ($CDCl_3$): 7·70 d, $J$ = 8·5, 1 H (H-11); 7·45 d, $J$ = 8·5, 1 H (H-12); 7·61 s, 1 H (arom.); 7·29 s, 1 H (arom.); 7·10 s, 1 H (arom.); 6·76 s, 1 H (arom.); 4·70 m, 1 H (OCH); 4·15 s, 2 H ($CH_2N$); 4·03 s, 3 H ($OCH_3$); 3·99 s, 3 H ($OCH_3$); 3·92 s, 3 H ($OCH_3$); 2·65 s, 3 H ($NCH_3$); 1·47 d, $J$ = 6·0, 6 H ($C(CH_3)_2$).

2-Isopropoxy-3,8,9-trimethoxy-5-methylbenzo[*c*]phenanthridinium Chloride (*XXIV*)

A solution of *XXIII* (8·8 g; 22·4 mmol) in benzene (440 ml) was mixed with 5% aqueous sodium hydroxide (220 ml), and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (10 g; 44·8 mmol) in benzene (440 ml) was slowly added under vigorous stirring. The mixture was stirred vigorously at 25°C for 2 h. Ethyl acetate (600 ml) was added and, after stirring for 5 min, the organic phase was separated and the aqueous one was extracted with ethyl acetate (200 ml). The combined extracts were dried over sodium sulfate and the solvents were evaporated. The dry residue was dissolved in acetone (100 ml), filtered and the filtrate was treated at 35°C with a mixture of ethanol (15 mol) and conc. hydrochloric acid (15 ml). The precipitate was collected and air-dried to give 8·02 g (84%) of *XXIV*, m.p. 266–270°C. An analytical sample was crystallized from methanol–ethyl acetate to give long bright yellow needles, m.p. 268–270°C (reported m.p. 265–267°C (ref.[3]); m.p. 274–277°C (ref.[6])). UV spectrum ($CH_3OH$): 222 (3·15); 236 (3·12); 273 (3·54); 301 (3·44); 330 (3·41). $^1H$ NMR spectrum ($CF_3COOD$): 9·30 s, 1 H (H-6); 8·52 d, $J$ = 8·5, 1 H (H-11); 8·12 d, $J$ = 8·5, 1 H (H-12); 8·11 s, 2 H (arom.); 7·69 s, 1 H (arom.); 7·60 s, 1 H (arom.); 5·03 s, 3 H ($NCH_3$); 5·00 m, 1 H (OCH); 4·30 s, 3 H ($OCH_3$); 4·18 s, 6 H (2 × $OCH_3$); 1·52 d, $J$ = 6·0, 6 H ($C(CH_3)_2$).

Fagaronine (*I*)

Compound *XXIV* (7·3 g; 17 mmol) was added to a solution of 96% sulfuric acid (7·3 ml) in acetic acid (291 ml) and the mixture was stirred and refluxed for 2·5 h. After standing overnight, the crystals were collected, air-dried and added into a stirred solution of sodium chloride (136 g) in water (1 564 ml). The mixture was stirred for 2 h and set aside in a refrigerator overnight. The bright yellow crystals were collected and crystallized from methanol–ethyl acetate to give 5·4 g (82%) of *I*, m.p. 198–200°C, with resolidification and remelting at 268–270°C. UV spectrum ($CH_3OH$): 221 (3·19); 236 (3·17); 273 (3·58); 301 (3·48); 311 (3·48); 329 (3·36). $^1H$ NMR spectrum ($CF_3COOD$): 9·35 s, 1 H (H-6); 8·28 d, $J$ = 8·5, 1 H (H-11); 7·88 d, $J$ = 8·5, 1 H (H-12); 7·88 s, 2 H (arom.); 7·61 s, 1 H (arom.); 7·40 s, 1 H (arom.); 4·93 s, 3 H ($NCH_3$); 4·22 s, 3 H ($OCH_3$); 4·14 s, 6 H (2 × $OCH_3$).

2-Hydroxy-3,8,9-trimethoxy-5-methyl-5,6-dihydrobenzo[*c*]phenanthridine (Dihydrofagaronine, *XXV*)

Sodium borohydride (76 mg; 2 mmol) was slowly added to a stirred solution of *I* (193 mg; 0·50 mmol) in methanol (10 ml), the mixture was refluxed for 3 h, cooled and the solvent was evaporated. The residue was thoroughly partitioned between water (20 ml) and chloroform (50 ml). The organic phase was dried over magnesium sulfate, taken down and the residue was crystallized from chloroform–methanol, affording 98 mg (56%) of *XXV*, m.p. 206–210°C (reported[5,6] m.p. 196–200°C). For $C_{21}H_{21}NO_4$ (351·4) calculated: 71·49% C, 6·02% H, 3·98% N; found: 71·66% C, 6·11% H, 3·92% N. $^1H$ NMR spectrum ($CDCl_3$): 7·69 d, $J$ = 8·5, 1 H (H-11); 7·45 d, $J$ = 8·5, 1 H (H-12); 7·61 s, 1 H (arom.); 7·28 s, 1 H (arom.); 7·20 s, 1 H (arom.); 6·76 s, 1 H (H-1); 4·14 s, 2 H ($CH_2N$); 3·99 s, 3 H ($OCH_3$); 3·97 s, 3 H ($OCH_3$); 3·91 s, 3 H ($OCH_3$); 2·60 s, 3 H ($NCH_3$).

2-Hydroxy-3,8,9-trimethoxy-5-methyl-6-oxo-5,6-dihydrobenzo[*c*]phenanthridine (Oxyfagaronine, *XXVI*)

Compound *XIX* (264 mg; 0·65 mmol) was added to a stirred solution of 96% sulfuric acid (0·5 g) in acetid acid (10 ml). After reflux for 2 h, the cold reaction mixture was poured into water

(50 ml), the precipitate was collected and air-dried. Crystallization from acetonitrile furnished 184 mg (77%) of oxyfagaronine *XXVI*, m.p. 268–270°C (reported[6] m.p. 273–275°C). UV spectrum ($CH_3OH$): 252 (3·55); 266 (3·62); 277 (3·67); 287 (3·76); 320 (3·12); 336 (3·07); 369 (2·81). IR spectrum ($CHCl_3$): 1 638 (CO), 3 540 (OH). $^1$H NMR spectrum ($CD_3SOCD_3$, 80°C): 8·11 d, $J$ = 8·0, 1 H (H-11); 7·51 d, $J$ = 8·0, 1 H (H-12); 7·76 s, 2 H (arom.); 7·70 s, 1 H (arom.); 7·24 s, 1 H (arom.); 4·02 s, 3 H ($OCH_3$); 4·00 s, 3 H ($OCH_3$); 3·96 s, 3 H ($OCH_3$); 3·92 s, 3 H ($NCH_3$).

2-Hydroxy-6-cyano-3,8,9-trimethoxy-5-methyl-5,6-dihydrobenzo[*c*]phenanthridine (*XXVII*)

Potassium cyanide (20 mg; 0·30 mmol) was added to a solution of *I* (96 mg; 0·25 mmol) in water (30 ml) and the mixture was stirred at 25°C for 2 h. The precipitate was taken up in chloroform, the extract was dried over magnesium sulfate, and the solvent was evaporated. Crystallization from chloroform–methanol gave 63 mg (67%) of the title compound *XXVII*, m.p. 217–221°C. For $C_{22}H_{20}N_2O_4$ (376·4) calculated: 70·20% C, 5·36% H, 7·44% N; found: 69·95% C, 5·49% H, 7·28% N. UV spectrum ($CH_3OH$): 232 (3·54); 277 (3·61); 312 (3·40); 428 (3·37). IR spectrum ($CHCl_3$): 3 540 (OH intramolecularly bonded). $^1$H NMR spectrum ($CD_3SOCD_3$): 7·90 d, $J$ = 8·5, 1 H (H-11); 7·58 d, $J$ = 8·5, 1 H (H-12); 7·50 s, 2 H (arom.); 7·23 s, 1 H (arom.); 7·19 s, 1 H (arom.); 5·74 s, 1 H (H-6); 3·99 s, 3 H ($OCH_3$); 3·92 s, 3 H ($OCH_3$); 3·86 s, 3 H ($OCH_3$); 2·60 s, 3 H ($NCH_3$).

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