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As a part of a search for novel biological active ergoline derivatives, the indole ring present in the ergoline skeleton (indole[4,3-*f,g*]quinoline) was converted into different heterocyclic ring systems such as quinazoline **2**, benzofurane **3** and benzoxazole **4**. Due to the paramount importance of chirality to attain biological activity, natural dihydrolysergic acid **1** was chosen as starting material and a synthetic pathway conservative in term of chirality was followed.

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Ergot alkaloids with their wide spectrum of central and peripheral biological activities have attracted much interest from a pharmacological and synthetic point of view [1]. No other group of natural products exhibits such a wide spectrum of biological action. Moreover, ergot alkaloids have been an important stimulus in the development of new drugs by providing structural prototypes of molecules *e.g.*, the ergolines, with pronounced pharmacological activities. All the ergolines encompass the tetracyclic ergoline skeleton indole-[4,3-*fg*]quinoline that is thought to unselectively interact with the receptors for neurotransmitters, adrenaline, dopamine and serotonin. Notwithstanding the receptorial non-selectivity of most ergolines, compounds such as Nicergoline (Sermion®), Pergolide (Permax®) and Cabergoline (Cabaser®) are effectively employed in the management of neurophysiological disturbances and Parkinson disease [2a,3,4a].

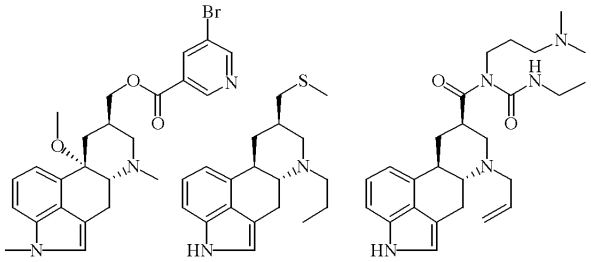
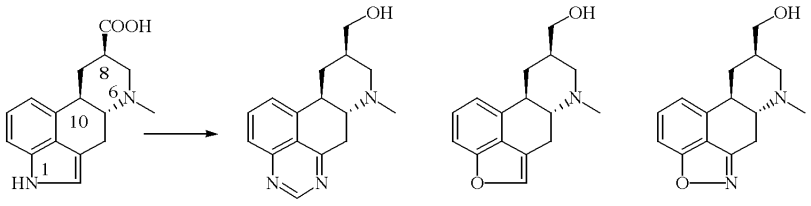



Figure 1

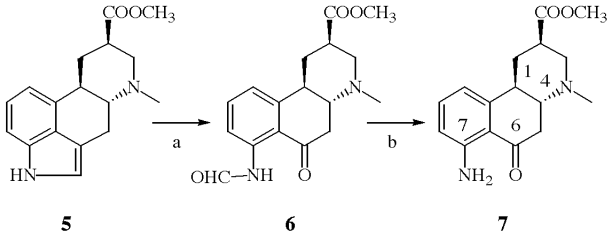
Scheme I




In connection with our research towards the identification of more selective ergolines, the replacement of the indole ring with different heterocyclic ring systems was pursued. The importance of chirality to attain biological activity within the ergolines is well documented; as a result an enantioselective synthetic approach was considered highly attractive. A stereochemical conservative synthetic pathway employing natural (5*R*,8*R*,*10*R) dihydrolysergic acid **1** as starting material was designed. A series of modifications converted the ergoline skeleton into dihydrolysergol analogues such as quinolino[5,6-*ef*]-quinazoline **2**, benzofuro[4,3-*fg*]quinoline **3** and benzisoxazolo[4,3-*fg*]quinoline **4** as shown in Scheme I.

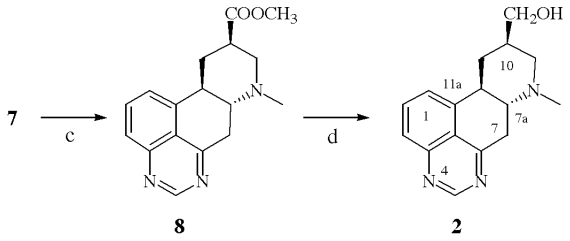
All the compounds were synthesized from the key intermediate **7**, as outlined in Scheme II. Ketone **7** was prepared starting from dihydrolysergic acid methyl ester **5**. Oxidation of 2,3-indole double bond by sodium metaperiodate gave rise to **6** in good yield [5a]. The presence of

Scheme II




a) $NaIO_4$, $CH_3SO_3H$, $CH_3OH$, rt b) $CH_3OH$, $H_2SO_4$, rt

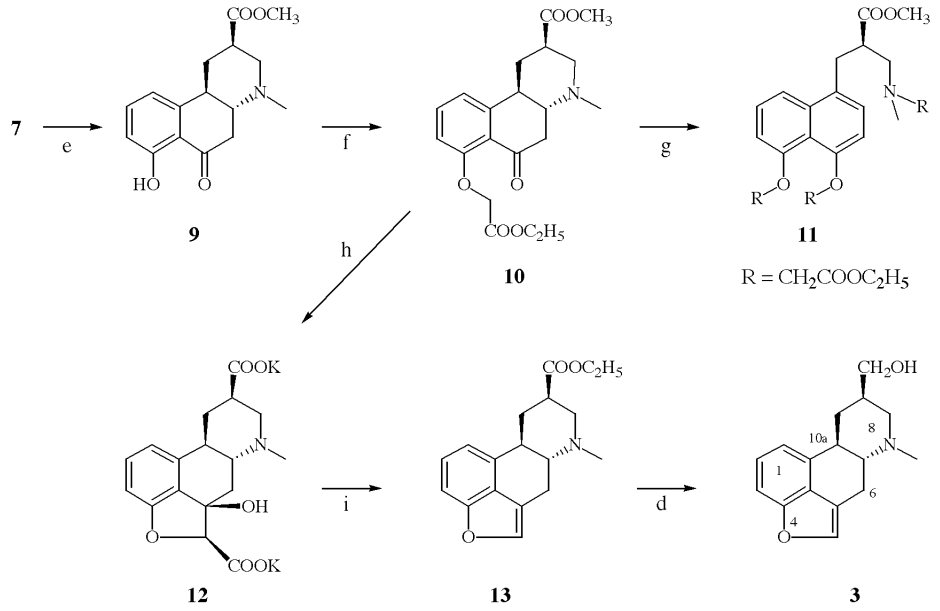
Scheme III




c) $H_2N$-CH=NH· $CH_3COOH$, 180 °C; d) $NaBH_4$, $CH_3OH$, reflux.

accomplished by using cuprous oxide and cupric nitrate that efficiently hydroxylate transient aryl radical intermediates [7a]. The phenolic group of **9** was thereafter *O*-alkylated with ethyl bromoacetate to provide **10** in low yield. Under more forceful conditions, naphthalene **11** was formed as the product. The formation of this compound likely implied quaternarization of the piperidino nitrogen followed by Hoffman elimination. Compound **10** submitted to the action of solid potassium hydroxide in dioxane at reflux afforded dihydrobenzofurane **12** as intermediate, that, without isolation by action of a solution of methanol containing hydrochloric acid, gave rise to benzofurane **13** albeit in low yield, mirroring the ring system constrain impart by the fused ring system [8a].

Scheme IV




e) $NaNO_2$, conc. $H_2SO_4$, $Cu(NO_3)_2$, CuO; f) $BrCH_2CO_2C_2H_5$, NaH, DMF, rt; g) excess $BrCH_2CO_2C_2H_5$, 60% NaH, DMF, 50 °C; h) KOH, dioxane, reflux; i) gaseous HCl, MeOH, reflux.

methanesulphonic acid prevented the formation of 6-*N*-oxide derivatives. Subsequent deformylation with methanol and sulfuric acid provided **7**.

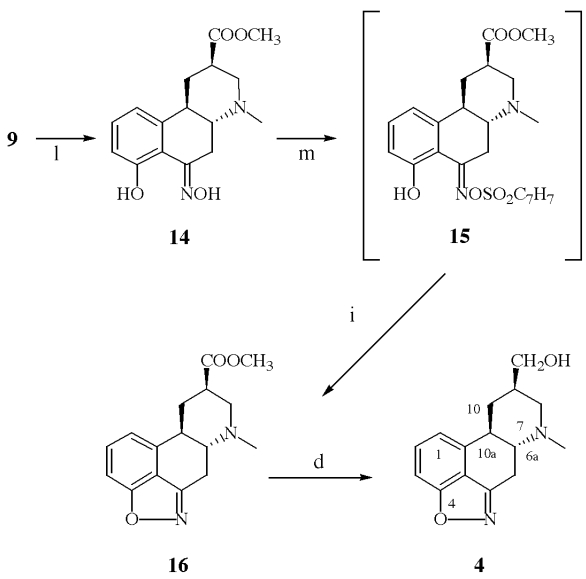
Condensation of **7** with freshly prepared formamidine furnished quinazoline **8** that was further reduced with sodium borohydride to **2**, as depicted in Scheme III [6].

Attempts to condense **7** either with urea or guanidine carbonate were unsuccessful and led to complex mixtures. The preparation of benzofurane **3** was accomplished as illustrated in Scheme IV.

Diazotisation of **7** under careful conditions afforded phenol **9** in high yield which was not accompanied by reduction and coupling side products. This was Subsequent reduction of the ester moiety with sodium borohydride, led to **3**. On the other hand, by treatment with hydroxylamine hydrochloride in pyridine, ketone **9** quantitatively led to oxymino derivative **14** as depicted in Scheme V.

This compound underwent a smooth tosylation by exposure to tosyl chloride in pyridine in presence of potassium hydroxide to afford tosylate **15** as transient intermediate, that spontaneously collapsed to the fused ring **16**. Ultimately, reduction of **16** provided benzoxazole **4** [9]. In conclusion, a concise synthesis of novel ring systems related to the ergoline skeleton has been achieved using readily available dihydrolysergic acid **1**.

Scheme V




l) $NH_2OH$•HCl, Py, 75 °C m) $C_7H_7SO_2Cl$, Py, 35 °C

The new ergoline-like scaffolds presented herein, could offer useful tools for a better understanding of the delicate balance between structure and biological activity for ergoline derivatives.

## EXPERIMENTAL

The $^1$H-nmr spectra were recorded on a Varian VXR 400 S MHz spectrometer using TMS as an internal standard. Melting points were determined on a Büchi capillary melting point apparatus and are uncorrected. Electron impact mass spectra were recorded in the form of m/z (intensity to base = 100) on a Finnigan MAT SSQ 7000 mass spectrometer. Microanalyses were performed on a Carlo Erba autoanalyser and were within 0.4% of the calculated values.

(2*R*,4a*R*,10b*R*)-7-Formamido-4-methyl-6-oxo-1,2,3,4,4a,5,6,10b-octahydrobenz[*f*]quinoline-2-carboxylic Acid Methyl Ester (**6**).

A solution of sodium metaperiodate (121 g, 57 mmol) in water (100 ml) was slowly added dropwise to a stirred solution of dihydrolysergic acid methyl ester (**5**) (65 g, 229 mmol) in methanol (550 ml) and methanesulphonic acid (87 g, 910 mmol) at room temperature. After stirring for 3 hours, the sodium iodate was filtered off and the solvent was removed *in vacuo*. The residue taken up in ethyl acetate was thoroughly washed with 0.1 *M* $Na_2CO_3$ solution, then with brine and dried over $Na_2SO_4$. Concentration to small volume afforded (**6**) as shining yellow crystals (59 g, 82% yield), mp 138-141°C; $^1$H nmr (Pyridine-$d_5$): δ (ppm) 1.46 (ddd, J = 11.8, 11.8, 11.8 Hz, 1 H, H1-ax), 1.96 (ddd, J = 4.3, 10.2, 12.4 Hz, 1 H, H4-ax), 2.17 (dd, J = 11.4, 11.4 Hz, 1 H, H3-ax), 2.18 (s, 3 H, $CH_3$-N), 2.52 (dd, J = 12.4, 17.3 Hz, 1 H, H5-ax), 2.6-2.8 (m, 2 H, H1-eq, H10b-), 2.90 (m, 1 H, H5-eq, H3-eq), 3.72 (s, 3 H, $COOCH_3$), 7.07 (t, J = 8.0 Hz, 1 H, H9), 8.77 (bs, 1 H, CHO), 9.1 (bd, J = 8.0 Hz, 1 H, H8); ms: (m/z) 316 (66, $[M]^+$), 298 (24), 288 (28), 273 (30), 257 (14), 239 (33), 187 (39), 159 (100), 130 (69).

*Anal*. Calcd. for $C_{17}H_{20}N_2O_4$: C, 64.54; H, 6.37; N, 8.05. Found: C, 64.43; H, 6.21; N, 8.23.

(2*R*,4a*R*,10b*R*)-7-Amino-4-methyl-6-oxo-1,2,3,4,4a,5,6,10b-octahydrobenz[*f*]quinoline-2-carboxylic Acid Methyl Ester (**7**).

A solution of concentrated sulfuric acid (100 ml) in methanol (ml 100) was added dropwise to a stirred solution of (**6**) (50 g, 15.8 mmol) in methanol (500 ml) at 5 °C. After set aside at room temperature for 5 hours, the reaction mixture was diluted with ethyl acetate and carefully treated with a dilute ammoniun hydroxide solution. After partitioning and washing with brine, the organic phase was dried over $Na_2SO_4$. The solvent was removed *in vacuo* and the residue crystallized from ethyl acetate to provide (**7**) (38 g, 85% yield) as yellow crystals, mp 118-122 °C; $^1$H nmr ($CDCl_3$): δ (ppm) 1.50 (ddd, J= 11.8, 11.8, 11.8 Hz, 1 H, H1-ax), 2.15 (m, 1 H, H4-ax), 2.23 (dd, J= 11.4, 11.4 Hz, 1 H, H3-ax), 2.34 (s, 3 H, $CH_3$-N), 2.48 (dd, J= 12.2, 16.8 Hz, 1 H, H5-ax), 2.6-2.8 (m, 2 H, H1-eq, H10b-ax), 2.86 (m, 1 H, H2-ax), 3.10 (dd, J = 4.0, 16.8 Hz, 1 H, H5-eq), 3.17 (ddd, J = 2.0, 4.0, 11.4 Hz, 1 H, H3-eq), 3.72 (s, 3 H, $COOCH_3$), 6.50 (bs, 2 H, $NH_2$), 6.54-6.65 (two d, J = 8.0 Hz, 2 H, H8, H10), 7.23 (dd, J = 8.0, 8.0 Hz, 1 H, H9); ms: (m/z) 288 (86, $[M]^+$), 273 (16), 257 (11), 229 (9), 213 (10), 187 (8), 173 (28), 159 (100), 147 (25), 130 (21).

*Anal*. Calcd. for $C_{16}H_{20}N_2O_3$: C, 66.65; H, 6.99; N, 9.72. Found: C, 66.34; H, 7.21; N, 9.57.

(10*R*,7a*R*,11a*R*)-8-Methyl-7a,8,9,10,11,11a-hexahydro-7*H*-4,6,8-triazabenzo[*de*]anthracen-10-carboxylic Acid Methyl Ester (**8**).

A stirred mixture of (**7**) (10 g, 35 mmol) and freshly prepared formamidine acetate (7.2 g, 70 mmol) was slowly brought to melting at 180°C and maintained for 15 minutes. After cooling, the residue was taken up in ethyl acetate and thoroughly washed with a 0.1 *M* $Na_2CO_3$ solution then brine. After drying over $Na_2SO_4$, the solvent was removed *in vacuo* and the residue filtered on a small pad of [silica gel, cyclohexane/acetone (3/2)] to afford after crystallization from ethylacetate (**8**) (5.2 g, yield 51%), mp 120-122 °C; $^1$H nmr ($CDCl_3$): δ (ppm) 1.62 (ddd, J = 13.7, 13.7, 13.7 Hz, 1 H, H11-ax), 2.30 (ddd, J = 4.1, 10.0, 12.0 Hz, 1 H, H7-ax), 2.34 (dd, J = 11.4, 11.4 Hz, 1 H, H9-ax), 2.50 (s, 3 H, $CH_3N$), 2.9-3.0 (m, 3 H, H10-ax, H11-ax, H11-eq), 3.12 (dd, J = 12.0, 17.0 Hz, 1 H, H7-ax), 3.28 (ddd, J = 1.8, 3.8, 11.4 Hz, H9-eq), 3.68 (dd, J = 4.1, 11.7 Hz, 1 H, H7-eq), 3.76 (s, 3 H, $COOCH_3$), 7.5-7.9 (m, 3 H, H1, H2, H3), 9.20 (s, 1 H, H5); ms: (m/z) 297 (100, $[M]^+$), 282 (20), 266 (14), 238 (10), 210 (8), 195 (5), 181 (12), 168 (75), 140 (9), 128 (3).

*Anal*. Calcd. for $C_{17}H_{19}N_3O_2$: C, 68.67; H, 6.44, N, 14.13. Found: C, 68.49; H, 6.57; N, 14.21.

(10*R*,7a*R*,11a*R*)-8-Methyl-7a,8,9,10,11,11a-hexahydro-7*H*-4,6,8-triazabenzo[*de*]anthracen-10-methanol (**2**).

Sodium borohydride (2.5 g, 67 mmol) was added portionwise to a stirred solution of (**8**) (5 g, 16.8 mmol) and sodium methoxide (0.1 g, 1.8 mmol) in methanol (200 ml) at room temperature. After heating at reflux for 30 minutes, the solvent was removed and the residue was thoroughly washed with water, then crystallized from a small volume of methanol to provide (**2**) (3.7 g, 81%), mp 189-192 °C; $^1$H nmr (DMSO-$d_6$): δ (ppm), 1.92

(m, 2 H, H9-ax, H10), 2.32 (ddd, J = 4.2, 10.1, 12.1 Hz, 1 H, H7-ax), 2.49 (s, 3 H, $CH_3N$), 3.11 (dd, J = 12.1, 17.0 Hz, 1 H, H7-ax), 3.27 (ddd, J = 1.8, 3.7, 11.3 Hz, H9-eq), 3.41 (m, 1 H, CH(*H*)OH), 3.73 (m, 1 H, C*H*(H)OH), 4.52 (t, J = 5.1 Hz, $CH_2OH$), 3.68 (dd, J = 4.2, 11.7 Hz, 1 H, H7-eq), 7.4-7.9 (m, 3 H, H1, H2, H3), 9.19 (s, 1 H, H5); ms: (m/z) 269 (100, $[M]^+$), 238 (10), 210 (18), 182 (15), 167 (75), 157 (29), 128 (13).

*Anal.* Calcd. for $C_{16}H_{19}N_3O$: C, 71.35; H, 7.11, N, 15.60. Found: C, 71.57; H, 7.24; N, 15.68.

(2*R*,4a*R*,10b*R*)-7-Hydroxy-4-methyl-6-oxo-1,2,3,4,4a,5,6,10b-octahydrobenz[*f*]quinoline-2-carboxylic Acid Methyl Ester (**9**).

A solution of sodium nitrite (7 g, 102 mmol) in ice water (35 ml) was added dropwise to a stirred ice cooled solution of (**7**) (25 g, 87 mmol) dissolved in 35% sulfuric acid (50 ml) and water (300 ml) at such a rate as to maintain the temperature at 0-5 °C. After the solution has been stirred for additional 15 minutes, urea was added to decompose any excess sodium nitrite. To the resulting cold solution of the diazonium salt was added a solution of cupric nitrate trihydrate (48 g, 199 mmol) in water (300 ml). Under vigorous stirring, cuprous oxide (10.5 g, 73 mmol) was added to the solution. After the evolution of nitrogen has ceased, the resulting green solution was set aside at room temperature for 15 minutes then alkalinized with dilute ammonia solution and thoroughly partitioned with ethyl acetate. The organic phase was washed with brine and dried. After removal of the solvent, the residue was filtered on a small pad of silica gel [cyclohexane/-acetone (5/2)] to provide after crystallisation from ethyl acetate (**9**) (21.3 g, 85% yield), mp 101-103 °C; $^1$H nmr ($CDCl_3$): δ (ppm) 1.51 (ddd, J = 12.0, 12.0, 12.0 Hz, 1 H, H1-ax), 2.22 (m, 1 H, H4-ax), 2.25 (dd, J = 11.6, 11.6 Hz, 1 H, H3-ax), 2.35 (s, 3 H, $CH_3$-N), 2.55 (dd, J = 12.4, 17.1 Hz, 1 H, H5-ax), 2.7-3.0 (m, 3 H, H1-eq, H2-ax, H10b, ax), 3.1-3.2 (m, 2 H, H3-eq, H5-eq), 3.73 (s, 3 H, $COOCH_3$), 6.88 (m, 2 H, H8, H10), 7.45 (dd, J = 8.0, 8.0 Hz, H9), 12.5 (s, 1 H, OH); ms: (m/z) 289 (43, $[M]^+$), 274 (40), 258 (31), 230 (25), 212 (28), 160 (100), 144 (40), 132 (31), 128 (18), 115 (53).

*Anal.* Calcd. for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62, N, 4.84. Found: C, 66.21; H, 6.79; N, 5.01.

(2*R*,4a*R*,10b*R*)-7-Ethoxycarbonylmethyl-4-methyl-6-oxo-1,2,3,4,4a,5,6,10b-octahydrobenz[*f*]quinoline-2-carboxylic Acid Methyl Ester (**10**).

Sodium hydride (60 %) (1.83 g, 46 mmol) was slowly added portionwise to a stirred solution of (**9**) (12 g, 41 mmol) in dimethylformamide (250 ml) at 0-5 °C under nitrogen. After stirring for 1 hour at room temperature, ethyl bromoacetate (5.1 ml, 46 mmol) was added dropwise and the reaction set aside overnight at 30-40 °C. The solution was carefully quenched with of 1 *M* ammonium chloride solution (75 ml), then after dilution with ethyl acetate was thoroughly washed with brine. After drying over sodium sulfate, the solvent was evaporated off and the oily residue was chromatographed over silica gel [cyclohexane/acetone (4/1)], to furnish after crystallization from diethylether, (**10**) (4.3 g, 27%), mp 118-121 °C; $^1$H nmr ($CDCl_3$): δ (ppm) 1.26 (t, J = 7.1 Hz, $COOCH_2CH_3$), 1.53 (ddd, J = 12.0, 12.0 Hz, 1 H, H1-ax), 2.20 (m, 1 H, H4-ax), 2.22 (dd, J = 11.5, 11.5 Hz, 1 H, H3-ax), 2.32 (s, 3 H, $CH_3$-N), 2.47 (dd, J = 12.0, 17.1 Hz, 1 H, H4-ax), 2.70-3.0 (m, 3 H, H1-eq, H2-ax, H10b-ax), 3.14 (dd, J = 4.6, 17.1 Hz, 1 H, H5-eq), 3.18 (m, 1 H, H3-eq), 3.73 (s, 3 H, $COOCH_3$), 4.13 (q, J = 7.1 Hz, 2 H, $COOCH_2CH_3$), 4.74 (m, 2 H, $OCH_2COO$), 6.78 (d, J = 8.4 Hz, 1 H, H10), 7.10 (d, J = 8.0 Hz, 1 H, H8), 7.45 (dd, J = 8.0, 8.4 Hz, 1 H, H9); ms: (m/z) 375 (7, $[M]^+$), 360 (30), 344 (18), 302 (16), 288 (100), 185 (27), 173 (69), 144 (64), 155 884).

*Anal.* Calcd. for $C_{19}H_{23}NO_4$: C, 63.15, H, 6.41, N, 3.88. Found: C, 63.21; H, 6.69; N, 4.07.

(9*R*,6a*R*,10a*R*)-7-Methyl-6a,7,8,9,10,10a-hexahydro-6*H*-4-oxa-7-aza-acephenanthrylene-9-carboxylic Acid Methyl Ester (**13**).

Powdered potassium hydroxide (2.13 g, 53 mmol) was added portionwise to a stirred suspension of (**10**) (4 g, 11 mmol) in dioxane (200 ml) and oven dried 4 Å molecular sieves. After stirring 1 hour at room temperature, the suspension was refluxed for 5 hours. After cooling, the suspension was filtered and the solution was evaporated to dryness. The residue was taken up in methanol (300 ml) and gaseous hydrochloric acid was bubbled. After heating at reflux for 2 hours, the solvent was removed and the residue taken up in ethyl acetate was thoroughly washed with 1 *N* $Na_2CO_3$ solution then with brine. After drying over sodium sulfate, the solvent was removed and the crude material was chromatographed over silica gel [cyclohexane/ethylacetate (5/1)], to provide (**13**) (0.85 g, 28% yield), mp 178-181 °C; $^1$H nmr ($CDCl_3$): δ (ppm) 1.31 (ddd, J = 12.7, 12.7, 12.7 Hz, 1 H, H10 Ax), 2.0 (ddd, J = 4.2, 9.1, 13.1 Hz, 1 H, H6a-ax), 2.16 (dd, J = 11.4, 11.4 Hz, 1 H, H8-ax), 2.34 (s, 3 H, $CH_3$-N), 2.42 (m, 1 H, H-6ax), 2.78 (m, 3 H, H9-ax, H10-eq, H10a-ax), 3.09 (ddd, J = 2.8, 3.8, 11.4 Hz, H8-eq), 3.31 (dd, J = 4.2, 15.3 Hz, 1 H, H6-eq), 3.83 (s, 3 H, $COOCH_3$), 7.0-7.3 (m, 3 H, H1, H2, H3), 7.63 (d, J = 1.9 Hz, 1 H, H5); ms: (m/z) 285 (100, $[M]^+$), 256 (36), 226 (100), 185 (19), 173 (85), 144 (71), 155 (39).

*Anal.* Calcd. for $C_{17}H_{19}NO_3$: C, 71.56, H, 6.71, N, 4.91. Found: C, 71.38; H, 6.46; N, 4.99.

(9*R*,6a*R*,10a*R*)-7-Methyl-6a,7,8,9,10,10a-hexahydro-6*H*-4-oxa-7-aza-acephenanthrylene-9-methanol (**3**).

Sodium borohydride (3.3 g, 90 mmol) was added portionwise to a stirred solution of (**13**) (8.6 g, 30 mmol) and sodium methoxide (0.15 g, 1.8 mmol) in methanol (300 ml) at room temperature. After heating at reflux for 45 minutes, the solvent was evaporated off and the residue taken up in dichloromethane was thoroughly washed with brine. After drying, the solvent was removed and the crude reaction product was chromatographed over silica gel [cyclohexane/-acetone (2/1)], and successively crystallized from a small volume of ethanol to afford (**3**) (4.1 g, 52%), mp 178-181 °C; $^1$H nmr (DMSO-$d_6$): δ (ppm) 1.29 (ddd, J = 12.7, 12.7, 12.7 Hz, 1 H, H10-ax), 1.89 (m, 2 H, H7-ax, H8), 2.1 (ddd, J = 4.2, 9.2, 13.1 Hz, 1 H, H6a-ax), 2.14 (dd, J = 11.4, 11.4 Hz, 1 H, H8-ax), 2.34 (s, 3 H, $CH_3$-N), 2.43 (m, 1 H, H-6ax), 2.71 (m, 3 H, H9-ax, H10-eq, H10a-ax), 3.09 (ddd, J = 2.7, 3.8, 11.4 Hz, H8-eq), 3.29 (dd, J = 4.1, 15.3 Hz, 1 H, H6-eq), 3. 36 (m, 1 H, C*H*(H)OH), 3.67 (m, 1 H, CH(*H*)OH), 4.41 (t, J = 5.2 Hz, 1 H, $CH_2OH$), 7.0-7.4 (m, 3 H, H1, H2, H3), 7.59 (d, J = 1.8 Hz, 1 H, H5); ms: (m/z) 257 (100, $[M]^+$), 226 (24), 183 (16), 168 (29), 155 (61), 145 (12).

*Anal.* Calcd. for $C_{16}H_{19}NO_2$: C, 74.68, H, 7.44, N, 5.44. Found: C, 74.41; H, 7.73; N, 5.69.

(2*R*,4a*R*,10b*R*)-4-Methyl-7-hydroxy-6-oxyimino-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline-2-carboxylic Acid Methyl Ester (**14**).

A solution of (**10**) (7.5 g, 26 mmol) and hydroxylamine hydrochloride (9 g, 126 mmol) in pyridine (150 ml) was refluxed for 30 minutes. The solvent was removed and the residue taken up in ethyl acetate was washed with brine and dried. After removal of the solvent, the residue was dissolved in acetone and treated with charcoal. Concentration to a small volume, provided (**14**) (6.1 g, 77% yield), mp 264-266 °C; $^1$H nmr (DMSO-$d_6$): δ (ppm) 1.59 (m, 1 H, H1-ax), 2.3-3.8 (m, 11 H, $CH_2$3, H2, H1-eq, H10b, H4a, $CH_2$5, $CH_3$-N), 3.68 (s, 3 H, $COOCH_3$), 6.62, 6.87 (two d, J = 7.7 Hz, 2 H, H10, H8), 7.25 (dd, J = 7.7 Hz, 1 H, H9), 11.2, 11.6, 12.0 (three bs, 3 H, two N-OH, phenolic OH); ms: (m/z) 304 (27, $[M]^+$), 287 (100), 273 (11), 255 (9), 173 (85), 244 (13).

*Anal*. Calcd. for $C_{16}H_{20}N_2O_4$: C, 63.14, H, 6.62, N, 9.20. Found: C, 63.29; H, 6.41; N, 9.51.

(9*R*,6a*R*,10a*R*)-7-Methyl-6a,7,8,9,10,10a-hexahydro-6*H*-4-oxa-5,7-diaza-acephenanthrylene-9-carboxylic Acid Methyl Ester (**16**).

A solution of *p*-toluenesulphonylchloride (7.2 g, 38 mmol) in tetrahydrofuran (150 ml) was slowly added dropwise to a stirred solution of (**14**) (5.6 g, 18 mmol) in tetrahydrofuran (250 ml) and 20% potassium hydroxide solution (24 ml, 86 mmol) at room temperature. After stirring for 7 hours, the solvent was evaporated off. The residue was taken up in methanol (200 ml) and gaseous hydrochloric acid was bubbled through the mixture. After heating at reflux for 3 hours, the solvent was removed *in vacuo* and the residue taken up in ethyl acetate was thoroughly washed with 1 *N* $Na_2CO_3$ solution, then with brine. After drying over sodium sulfate, the solvent was removed and the residue was chromatographed over silica gel [cyclohexane/ethylacetate (4/1)], to provide **16** after crystallization from diethylether (3.7 g, 70% yield), mp 161-165 °C; $^1$H nmr ($CDCl_3$): δ (ppm) 1.64 (ddd, J = 12.0, 12.0, 12.0 Hz, 1 H, H10-ax), 2.33 (s, 3 H, $CH_3$-N), 3.77 (s, 3 H, $COOCH_3$), 7.34 (d, J = 7.3 Hz, 1 H, H3), 7.56 (d, J = 8.3 Hz, 1 H, H1), 7.68 (dd, J = 7.3, 8.3 Hz, 1 H, H2); ms: (m/z) 286 (38, $[M]^+$), 257 (7), 227 (48), 225 (13), 199 (16), 184 (19), 157 (26), 146 (70), 129 (24), 115 (13).

*Anal*. Calcd. for $C_{16}H_{18}N_2O_3$: C, 67.12, H, 6.34, N, 9.78. Found: C, 66.91; H, 6.69; N, 10.06.

(9*R*,6a*R*,10a*R*)-7-Methyl-6a,7,8,9,10,10a-hexahydro-6*H*-4-oxa-5,7-diaza-acephenanthrylene-9-methanol (**4**).

Sodium borohydride (1.4 g, 39 mmol) was added portionwise to a stirred solution of (**16**) (3.7g, 13 mmol) and sodium methoxide (0.1 g, 1.8 mmol) in methanol (150 ml) at room temperature. After heating at reflux for 1 hour, the solvent was removed and the residue taken up in chloroform was thoroughly washed with brine. After drying, the solvent was removed and the crude reaction product was chromatographed over silica gel [cyclohexane/-acetone (3/1)], then crystallized from a small volume of acetone to furnish (**4**) (1.7 g, 51%), mp 212-215 °C; $^1$H nmr (DMSO-$d_6$): δ (ppm) 1.61 (ddd, J = 12.0, 12.0, 12.0 Hz, 1 H, H10-ax), 2.34 (s, 3 H, $CH_3$-N), 3.37 (m 1 H, C*H*(H)OH), 3 58 (m, 1 H, CH(*H*)OH), 4.21 (t, J = 4.8 Hz, 1 H, $CH_2$OH), 7.35 (d, J = 7.3 Hz, 1 H, H3), 7.48 (d, J = 8.2 Hz, 1 H, H1), 7.69 (dd, J = 7.3, 8.2 Hz, 1 H, H2); ms: (m/z) 258 (100, $[M]^+$), 227 (11), 201 (23), 184 (17), 169 (39), 156 (56), 146 (86).

*Anal*. Calcd. for $C_{15}H_{18}N_2O_2$: C, 69.74, H, 7.02, N, 10.84. Found: C, 69.56; H, 7.31; N, 10.97.

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