Synthesis of 9-Amino-, 9-Aminomethyl-1,2,3,4-tetrahydro- and 1,2,3,4,5,6,7,8-Octahydroacridine Derivatives

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This paper describes the synthesis of 9-amino-2- and 4-hydroxy- and 2,4-dihydroxy-1,2,3,4-tetrahydroacridines **2** and of 9-aminomethyl-1,2,3,4-tetrahydro- and 1,2,3,4,5,6,7,8-octahydroacridines **3** starting from the corresponding 9-carboxamido derivatives. A new synthetical pathway to 9-amino-2-hydroxyacridine **9** is also reported.

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Inhibition of acetylcholinesterase may be considered as one of the most promising strategies for the treatment of Alzheimer's disease [1,2]. Among the various acetylcholinesterase inhibitors available for use in humans, the greatest clinical experience has been with Tacrine **1**, approved by Food & Drug Administration in 1993 for treating Alzheimer patients. Tacrine, however, suffers from dose-limiting hepatotoxic complications [3,4], so a considerable number of its derivatives and of its analogues has been synthesized in order to obtain compounds with reduced side effects.

As a further development of our program directed to the preparation of new tacrine-like compounds in order to verify their activity as acetylcholinesterase inhibitors [5,6], in this paper we describe the synthesis of 9-amino-2- and 4-hydroxy- and 2,4-dihydroxy-1,2,3,4-tetrahydroacridines **2** and of 9-aminomethyl-1,2,3,4-tetrahydroacridines and their corresponding 1,2,3,4,5,6,7,8-octahydro derivatives **3**.

The synthetic routes are shown in Scheme 1.

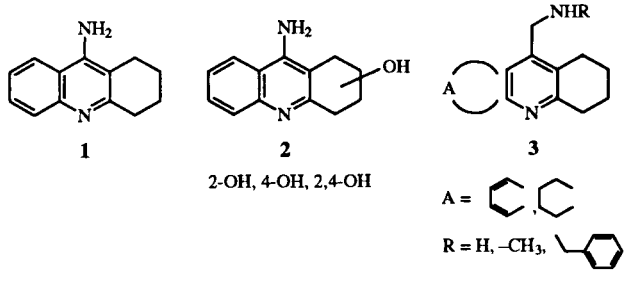


Figure 1.

Amides **4a,b** were prepared by condensation of isatin, cyclohexanone to obtain **4a** or 1,4-cyclohexanedione monoethylene acetal to obtain **4b** and ammonia in ethylene glycol at 150-160°. Treatment of **4b** with diluted hydrochloric acid at 40° readily removed the ethylene group to give an essentially quantitative yield of ketone **4c**, then reduced with sodium borohydride to the corresponding acridinol **4d**. Compounds **4a,b,d,** by reaction with 30% hydrogen peroxide in acetic acid at 80° easily gave the corresponding 10-oxides **5a,b,d** which by a Polonovski rearrangement carried out in acetic anhydride at 90° afforded the acetoxy derivatives **6a,b,e**.

The Hofmann degradation of the amides **4d** and **6** with bromine in a methanolic solution of sodium methoxide provided the methyl carbamates **7d,f-h.** Finally, the hydrolysis of urethanes **7d,f,h** in refluxing 20% potassium hydroxide afforded the expected amines **8**.

The synthetic pathway to 9-amino-2- and 4-hydroxy-1,2,3,4-tetrahydroacridines **8d** and **8f** here described represents a shorter and more suitable approach to prepare these tacrine metabolites [7]. There are no data about the 2,4-diol derivative **8h** in the chemical literature.

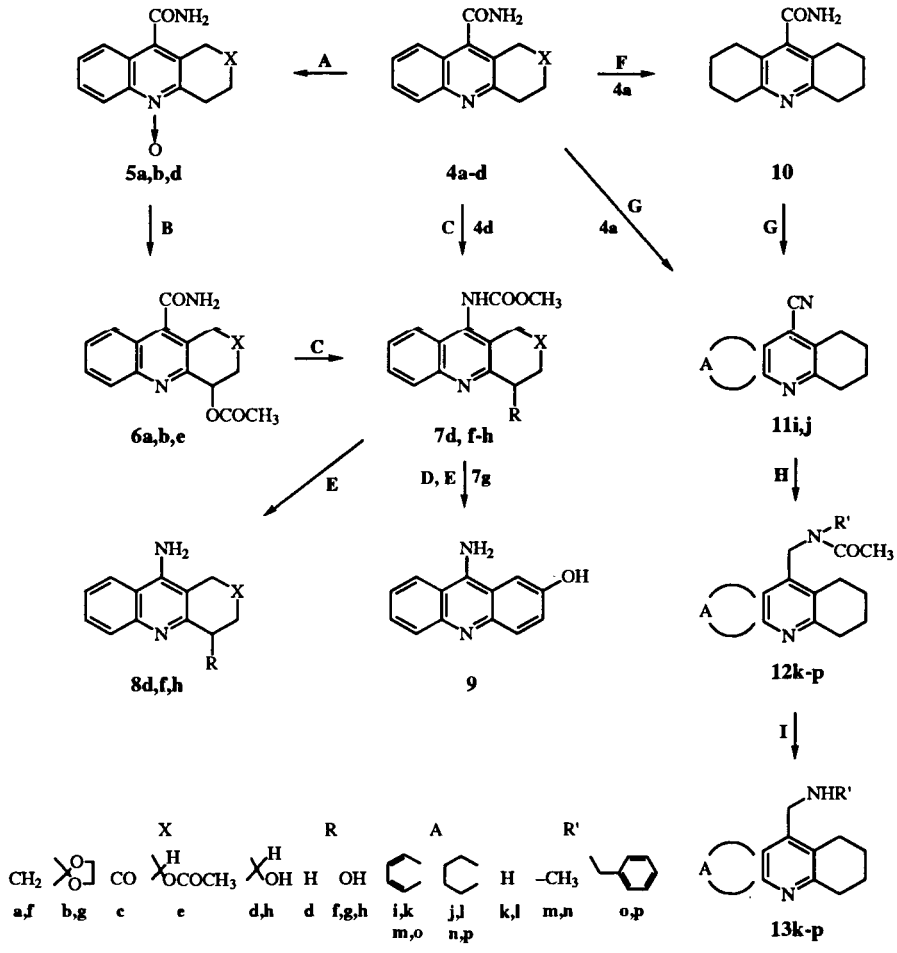
It is important to underline that in the preparation of this latter compound the hydrolysis of the ethylene acetal of **4b** followed by reduction of the corresponding ketone **4c** had to be carried out before the 10*N*-oxidation; in fact, the hydrolysis of compound **7g** with dilute hydrochloric acid afforded only the fully aromatic 2-hydroxy-9-methoxycarbonylaminoacridine, easily hydrolyzed in refluxing 20% potassium hydroxide to the corresponding 9-amino derivative **9**. This sequence could represent an alternative synthetic route to compound **9**, recently prepared by a standard procedure and found to have very strong DNA binding affinity [8].

As the starting material for the synthesis of 9-aminomethyl compounds **3** we employed the 9-carboxamido-1,2,3,4-tetrahydroacridine **4a**, which, by a short refluxing in phosphorus oxychloride was converted into the hitherto unreported nitrile **11i**.

By catalytic reduction in a Parr apparatus with Raney nickel in acetic acid at 50°, **4a** unexpectedly afforded the related octahydro derivative **10** which was then dehydrated to 9-cyanooctahydroacridine **11j**.

It is noteworthy that the preparation of octahydroacridines by hydrogenation of the corresponding aromatic compounds over noble metal catalysts requires high pressure and temperature, generally with rather poor yields [9]. The high-yield synthesis of 9-carboxamidooctahydroacridine herein reported will allow an easier access to the preparation of such compounds; the anomalous behaviour of **4a** resides probably in the electron-withdrawing effect of the substituent group at position 9, which renders the aromatic ring more susceptible to hydrogenation. Actually, attempts to hydrogenate Tacrine under the same conditions were unsuccessful.

Scheme 1



Reagents: **A**: 30%, H_2O_2, CH_3COOH, 80°; **B**: Ac_2O, 90°; **C**: Br_2, CH_3ONa/CH_3OH; **D**: diluted HCl, 40°; **E**: 20% KOH reflux; **F**: H_2/Ni Raney, 4 atm, 50°, CH_3COOH; **G**: $POCl_3$, reflux; **H**: **12k,l**: H_2/Ni Raney, 4 atm, THF, Ac_2O; **12m-o**: from **12k,l**: CH_3I or $C_6H_5CH_2Br$/NaH, DMF; **I**: 15% H_2SO_4.

Carbonitriles **11**, by lithium aluminium hydride reduction were recovered essentially unchanged, while by Raney nickel catalyzed hydrogenation in the presence of acetic anhydride provided the related 9-acetylamino derivatives **12k,l** in high yields, which were easily hydrolyzed in 15% aqueous sulfuric acid to give the amines **13k,l**. Finally, methylation or benzylation of **12k,l** with methyl iodide or benzyl bromide and sodium hydride in dimethylformamide, followed by hydrolysis, afforded the 9-methylaminomethyl- and 9-benzylaminomethyl-tetrahydro- and octahydroacridines **13m-p**.

In vitro assessment of acetylcholinesterase inhibition, accordingly to the procedure of Ellman [10], showed that the activity (IC_{50}) for rat cerebral cortex are 0.19, 3.55 and 0.50 μM for Tacrine, **8d** and **8f** respectively, while **8h** and aminomethyl derivatives **13** displayed a remarkable decrease in enzyme affinity ($IC_{50} > 50$ μM). Further *in vivo* experiments will be performed and the related pharmacological results, if interesting, will be published elsewhere.

The ir, nmr, ms and microanalytical data supported the structures of the above compounds (see Experimental).

EXPERIMENTAL

Melting points were taken on a Kofler hot stage apparatus and are uncorrected. The ir spectra were determined on a Perkin Elmer 580 spectrophotometer; the ^{1}H-nmr spectra were obtained in dimethyl-d_6 sulfoxide on a Varian Gemini 200 MHz instrument; all values are reported in ppm (δ) and standard abbreviations are used (a = apparent ; b = broad; d = doublet; dd = doublet of doublets; m = multiplet; q = quadruplet; t = triplet; s = singlet, u = unresolved); peak assignments were also based on ^{13}C-APT, ^{1}H-COSY and ^{13}C-^{1}H HETCOR nmr experiments; electron ionization mass spectra were recorded on a HP 59580 B spectrometer operating at 70 eV. Column chromatographic separations were accomplished on Merck silica gel (70-230 mesh) and on Merck aluminium oxide 90. The purity of each compound was checked on Carlo Erba silica gel 60 F_{254} or Merck

aluminium oxide 60 F_{254} (Type E) plates and spots were located by uv light. Sodium sulfate was used to dry organic solutions.

9-Carboxamido-1,2,3,4-tetrahydroacridine **4a.**

9-Carboxamido-3,4-dihydro-1*H*-acridin-2-one Ethylene Acetal **4b.**

A mixture of isatin (14.7 g, 0.1 mole) and cyclohexanone (10.8 g, 0.11 mole to obtain **4a**) or 1,4-cyclohexanedione monoethylene acetal (17.2 g, 0.11 mole to obtain **4b**) in ethylene glycol (100 ml) was heated at 150-160° in an oil bath. Anhydrous ammonia was bubbled into the solution for about 1 hour. After cooling, ice-cold methanol (50 ml) was added to the mixture. The precipitate was collected by filtration, washed with ice-cold methanol and diethyl ether, then dried at 60° at reduced pression.

Compounds **4** were used without further purification. For analytical purposes they were crystallized from dimethylformamide.

Compound **4a,** obtained in 78% yield, had mp 265-267° (lit [11] mp 260-264°); ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 8.12 and 7.97 (d, 2H, $CONH_2$), 7.89 (d, 1H, H-5), 7.72 (d, 1H, H-8), 7.66 (at, 1H, H-6), 7.52 (at, 1H, H-7), 3.03 (t, 2H, H-4), 2.88 (t, 2H, H-1), 1.85 (m, 4H, H-2 and H-3); ms: (m/z) 226, (M^+), 209, 181, 167.

Anal. Calcd. for $C_{14}H_{14}N_2O$: C, 74.31; H, 6.24; N, 12.38. Found: C, 74.55; H, 6.22; N, 12.15.

Compound **4b,** obtained in 62% yield, had mp 300-302°; ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 8.15 and 7.99 (d, 2H, $CONH_2$), 7.92 (d, 1H, H-5), 7.75 (d, 1H, H-8), 7.69 (at, 1H, H-6), 7.58 (at, 1H, H-7), 3.97 (s, 4H, $-O(CH_2)_2O-$), 3.18 (t, 2H, H-4), 3.06 (s, 2H, H-1), 2.07 (t, 2H, H-3); ms: (m/z) 284 (M^+), 212, 167.

Anal. Calcd. for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.66; H, 5.74; N, 9.83.

9-Carboxamido-3,4-dihydro-1*H*-acridin-2-one **4c.**

Compound **4b** (14.2 g, 0.05 mole) in 10% hydrochloric acid (150 ml) was warmed at 40° for 2 hours. The mixture was cooled and neutralized with diluted ammonium hydroxide. The resulting precipitate was collected by filtration, washed with water and ice-cold methanol, then crystallized from ethanol; yield 90%, mp 233-235°; ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 8.19 and 8.07 (d, 2H, $CONH_2$), 7.99 (d, 1H, H-5), 7.81 (d, 1H, H-8), 7.75 (at, 1H, H-6), 7.60 (at, 1H, H-7), 3.78 (s, 2H, H-1), 3.38 (t, 2H, H-4), 2.63 (t, 2H, H-3); ms (m/z) 240 (M^+), 223, 183, 167.

Anal. Calcd. for $C_{14}H_{12}N_2O_2 \cdot H_2O$: C, 65.11; H, 5.46; N, 10.85. Found: C, 64.87; H, 5.36; N, 10.81.

9-Carboxamido-2-hydroxy-1,2,3,4-tetrahydroacridine **4d.**

To a suspension of **4c** (12 g, 0.05 mole) in methanol (100 ml) sodium borohydride (3.8 g, 0.1 mole) was added in several portions during 30 minutes. The mixture was stirred until tlc on silica gel (ethyl acetate/5% methanol) indicated that the starting material had disappeared (about 2 hours). The methanol was evaporated *in vacuo* below 40°. Water was added to the residue and the white precipitate which had formed was filtered and crystallized from methanol; yield 82%, mp 247-250°; ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 8.11 and 7.97 (d, 2H, $CONH_2$), 7.89 (d, 1H, H-5), 7.73 (d, 1H, H-8), 7.67 (at, 1H, H-6), 7.52 (at, 1H, H-7), 5.00 (d, 1H, deuterium oxide-exchangeable, OH), 4.07 (bm, 1H, H-2), 3.28-2.90 (m, 3H, H-4 and H-1eq), 2.78 (dd, 1H, H-1ax, J_{gem} = 16.8 Hz, $J_{1ax,2}$ = 7.3 Hz), 2.02 (m, 1H, H-3eq), 1.88 (m, 1H, H-3ax); ms: (m/z) 242 (M^+), 224, 207, 180.

Anal. Calcd. for $C_{14}H_{14}N_2O_2 \cdot 0.5\ H_2O$: C, 66.91; H, 6.02; N, 11.15. Found: C, 66.70; H, 5.94; N, 11.08.

General Procedure for the Preparation of 9-Carboxamido-1,2,3,4-tetrahydroacridine 10-Oxides **5a,b,d.**

To a stirred solution of each compound **4a, 4b** and **4d** (0.1 mole) in glacial acetic acid (100 ml) was added dropwise 30% hydrogen peroxide (20 ml). The mixture was stirred and maintained at 80° for 5 hours, whereupon tlc on silica gel (ethyl acetate/5% methanol) indicated that all of **4** had reacted. The mixture was diluted with water (50 ml), evaporated to about half of its volume and allowed to cool to room temperature. The precipitated solid, collected by filtration and washed with methanol and diethyl ether, was used in the subsequent reaction without further precipitation. An analytical sample was obtained by recrystallization.

9-Carboxamido-1,2,3,4-tetrahydroacridine 10-Oxide **5a.**

This compound was obtained from **4a** in 90% yield, mp 264-266° (methanol); ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 8.52 (d, 1H, H-5), 8.13 and 8.01 (d, 2H, $CONH_2$), 7.82 (d, 1H, H-8), 7.80 (at, 1H, H-6), 7.72 (at, 1H, H-7), 2.98 (t, 2H, H-4), 2.85 (t, 2H, H-1), 1.85 (m, 2H, H-3), 1.76 (m, 2H, H-2); ms: (m/z) 242 (M^+), 225, 208, 180, 167.

Anal. Calcd. for $C_{14}H_{14}N_2O_2 \cdot H_2O$: C, 66.91; H, 6.02; N, 11.15. Found: C, 66.87; H, 5.85; N, 11.27.

9-Carboxamido-3,4-dihydro-1*H*-acridin-2-one 10-Oxide Ethylene Acetal **5b.**

This compound was obtained from **4b** in 87% yield, mp 272-274° (methanol); ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 8.53 (d, 1H, H-5), 8.19 and 8.04 (d, 2H, $CONH_2$), 7.84 (d, 1H, H-8), 7.78 (at, 1H, H-6), 7.72 (at, 1H, H-7), 3.96 (s, 4H, $-O(CH_2)_2O-$), 3.13 (t, 2H, H-4), 3.03 (s, 2H, H-1), 2.04 (t, 2H, H-3); ms: (m/z) 300 (M^+), 284, 266, 240, 212, 194, 167.

Anal. Calcd. for $C_{16}H_{16}N_2O_4$: C, 63.99; H, 5.37; N, 9.33. Found: C, 64.11; H, 5.37; N, 9.19.

9-Carboxamido-2-hydroxy-1,2,3,4-tetrahydroacridine 10-Oxide **5d.**

This compound was obtained from **4d** in 68% yield, mp 278-281° (ethanol); ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 8.52 (d, 1H, H-5), 8.13 and 8.03 (d, 2H, $CONH_2$), 7.83 (d, 1H, H-8), 7.76 (at, 1H, H-6), 7.68 (at, 1H, H-7), 5.00 (d, 1H, deuterium oxide-exchangeable, OH), 4.02 (um, 1H, H-2), 3.05 (dd, 1H, H-1eq, J_{gem} = 16.8 Hz, $J_{1eq,2}$ = 2.8 Hz), 3.04 (m, 2H, H-4), 2.77 (dd, 1H, H-1ax, J_{gem} = 16.8 Hz, $J_{1ax,2}$ = 7.6 Hz), 1.96 (m, 1H, H-3eq), 1.88 (m, 1H, H-3ax); ms: (m/z) 258 (M^+), 224, 207, 180.

Anal. Calcd. for $C_{14}H_{14}N_2O_3$: C, 65.10; H, 5.46; N, 10.85. Found: C, 65.08; H, 5.29; N, 10.79.

General Procedure for the Preparation of 4-Acetoxy- and 2,4-Diacetoxy-9-carboxamido-1,2,3,4-tetrahydroacridines **6a,b,e.**

A mixture of each compound **5a, 5b** and **5d** (10 g) in acetic anhydride (100 ml) was stirred at 90° until all solid had dissolved (about 1 hour). After cooling the solution was vigorously stirred in an ice-water bath until crystallization was complete (about 1 hour). The precipitate was collected by filtration, washed with water and dried under reduced pressure at 50°.

From the mother liquor, on cooling at -10° an additional crop of equally pure material was obtained.

4-Acetoxy-9-carboxamido-1,2,3,4-tetrahydroacridine **6a.**

This compound was obtained from **5a** in 72% yield, mp 238-241° (ethanol); ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 8.16 and 7.99 (d, 2H, $CONH_2$), 7.97 (d, 1H, H-5), 7.78 (d, 1H, H-8), 7.73 (at, 1H, H-6), 7.61 (at, 1H, H-7), 6.00 (t, 1H, H-4), 2.93 (m, 2H, H-1), 2.11 (m, 2H, H-3), 2.06 (s, 3H, CH_3), 1.90 (m, 2H, H-2); ms: (m/z) 284 (M^+), 241, 225, 207, 180.

Anal. Calcd. for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.77; H, 5.50; N, 9.95.

4-Acetoxy-9-carboxamido-3,4-dihydro-1*H*-acridin-2-one Ethylene Acetal **6b.**

This compound was obtained from **5b** in 78% yield, mp 230-232° (methanol); ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 8.21 and 8.05 (d, 2H, $CONH_2$), 7.97 (d, 1H, H-5), 7.80 (d, 1H, H-8), 7.75 (at, 1H, H-6), 7.63 (at, 1H, H-7), 6.12 (dd, 1H, H-4ax, $J_{4ax,3ax}$ = 9.3 Hz, $J_{4ax,3eq}$ = 6.5 Hz), 4.00 (m, 4H, -O(CH_2)$_2$O-), 3.23 (d, 1H, H-1, J_{gem} = 16.8 Hz), 3.05 (d, 1H, H-1, J_{gem} = 16.8 Hz), 2.49 (overlapped with dimethyl sulfoxide, m, 1H, H-3eq), 2.27 (uq, 1H, H-3ax, J_{gem} = 12.2 Hz, $J_{3ax,4ax}$ = 9.3 Hz), 2.14 (s, 3H, CH_3); ms: (m/z) 343 (M^++1), 300, 282, 265, 238, 210, 193, 167.

Anal. Calcd. for $C_{18}H_{18}N_2O_5$: C, 63.15; H, 5.30; N, 8.18. Found: C, 63.43; H, 5.33; N, 8.32.

9-Carboxamido-2,4-diacetoxy-1,2,3,4-tetrahydroacridine **6e.**

This compound was obtained from **5d** in 58% yield, mp 236-238° (ethyl acetate); ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 8.23 and 8.09 (d, 2H, $CONH_2$), 8.00 (d, 1H, H-5), 7.83 (d, 1H, H-8), 7.77 (at, 1H, H-6), 7.65 (at, 1H, H-7), 6.11 (t, 1H, H-4eq, $J_{4eq,3eq}$ = 6.0 Hz, $J_{4eq,3ax}$ = 6.4 Hz), 5.27 (bm, 1H, H-2eq), 3.28 (dd, 1H, H-1eq, J_{gem} = 16.0 Hz, $J_{1eq,2eq}$ = 4.6 Hz), 3.07 (dd, 1H, H-1ax, J_{gem} = 16.0 Hz, $J_{1ax,2}$ = 6.0 Hz), 2.50 (overlapped with dimethyl sulfoxide, m, 1H, H-3eq), 2.36 (m, 1H, H-3ax, J_{gem} = 15.5 Hz, $J_{3ax,4eq}$ = 6.4 Hz, $J_{3ax,2eq}$ = 6.7 Hz), 2.10 (s, 3H, 4-OCOCH_3), 1.99 (s, 3H, 2-OCOCH_3); ms: (m/z) 299 (M^+ - $COCH_3$), 239, 222, 206, 194.

Anal. Calcd. for $C_{18}H_{18}N_2O_5$: C, 63.15; H, 5.30; N, 8.18. Found: C, 63.40; H, 5.41; N, 8.21.

General Procedure for the Preparation of 2- and 4-Hydroxy- and 2,4-Dihydroxy-9-methoxycarbonylamino-1,2,3,4-tetrahydroacridines **7d,f-h.**

Compounds **4d** or **6** (0.05 mole) were mixed to a solution of sodium (2.5 g, 0.11 mole) in anhydrous methanol (200 ml). Bromine (16 g, 0.1 mole) in methanol (100 ml) was then added with stirring during 20 minutes, the temperature being kept below 25°. After the addition was completed, the mixture was refluxed for 20 minutes, after which it was separated from a small amount of insoluble material by filtration, then neutralized with acetic acid. The solvent was evaporated at reduced pressure and the resulting solid, thoroughly rinsed with water to remove sodium bromide, was directly crystallized.

2-Hydroxy-9-methoxycarbonylamino-1,2,3,4-tetrahydroacridine **7d.**

This compound was obtained from **4d** in 68% yield, mp 221-223° (methanol); ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 9.55 (s, 1H, deuterium oxide-exchangeable, NH), 7.88 (d, 1H, H-5), 7.85 (d, 1H, H-8), 7.65 (at, 1H, H-6), 7.50 (at, 1H, H-7), 4.95 (d, 1H, deuterium oxide-exchangeable, OH), 4.04 (bm, 1H, H-2), 3.68 (s, 3H, OCH_3), 3.13 (m, 2H, H-4), 2.99 (dd, 1H, H-1eq, J_{gem} = 17.2 Hz), 2.68 (dd, 1H, H-1ax, J_{gem} = 17.2 Hz, $J_{1ax,2}$ = 7.1 Hz), 1.99 (m, 1H, H-3eq), 1.85 (m, 1H, H-3ax); ms: (m/z) 273 (M^+ + 1), 254, 240, 223, 211.

Anal. Calcd. for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 65.98; H, 5.79; N, 10.13.

4-Hydroxy-9-methoxycarbonylamino-1,2,3,4-tetrahydroacridine **7f.**

This compound was obtained from **6a** in 76% yield, mp 177-179° (ethanol); ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 9.53 (s, 1H, deuterium oxide-exchangeable, NH), 7.97 (d, 1H, H-5), 7.88 (d, 1H, H-8), 7.69 (at, 1H, H-6), 7.55 (at, 1H, H-7), 5.32 (d, 1H, deuterium oxide-exchangeable, OH), 4.73 (q, 1H, H-4), 3.67 (s, 3H, OCH_3), 2.80 (m, 2H, H-1), 1.95 (m, 3H, H-2eq and H-3), 1.76 (m, 1H, H-2ax); ms: (m/z) 272 (M^+), 254, 239, 211, 184, 155.

Anal. Calcd. for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.26; H, 5.65; N, 10.26.

4-Hydroxy-9-methoxycarbonylamino-3,4-dihydro-1*H*-acridin-2-one Ethylene Acetal **7g.**

This compound was obtained from **6b** in 69% yield, mp 191-193° (methanol); ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 9.67 (s, 1H, deuterium oxide-exchangeable, NH), 8.00 (d, 1H, H-5), 7.91 (d, 1H, H-8), 7.73 (at, 1H, H-6), 7.57 (at, 1H, H-7), 5.47 (bs, 1H, deuterium oxide-exchangeable, OH), 4.85 (t, 1H, H-4ax, $J_{4ax,3eq}$ = 6.6 Hz, $J_{4ax,3ax}$ = 10.0 Hz), 3.97 (m, 4H, -O(CH_2)$_2$O-), 3.68 (s, 3H, OCH_3), 3.01 (at, 2H, H-1), 2.37 (dd, 1H, H-3eq, J_{gem} = 12.9 Hz, $J_{3eq,4ax}$ = 6.6 Hz), 2.01 (at, 1H, H-3ax, J_{gem} = 12.9 Hz, $J_{3ax,4ax}$ = 10.0 Hz); ms: (m/z) 331 (M^++1), 269, 241, 209, 184, 155.

Anal. Calcd. for $C_{17}H_{18}N_2O_5$: C, 61.81; H, 5.49; N, 8.48. Found: C, 61.90; H, 5.60; N, 8.55.

2,4-Dihydroxy-9-methoxycarbonylamino-1,2,3,4-tetrahydroacridine **7h.**

This compound was obtained from **6e** in 50% yield, mp 209-211° (methanol); ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 9.58 (s, 1H, deuterium oxide-exchangeable, NH), 7.97 (d, 1H, H-5), 7.89 (d, 1H, H-8), 7.70 (at, 1H, H-6), 7.56 (at, 1H, H-7), 5.40 (d, 1H, deuterium oxide-exchangeable, 4-OH, $J_{4,OH}$ = 4.3 Hz), 4.92 (d, 1H, deuterium oxide-exchangeable, 2-OH, $J_{2,OH}$ = 4.2 Hz), 4.88 (m, 1H, H-4eq, $J_{4,OH}$ = 4.3 Hz, $J_{4,3ax}$ = 4.6 Hz), 4.24 (m, 1H, H-2ax), 3.68 (s, 3H, OCH_3), 3.12 (dd, 1H, H-1eq, J_{gem} = 17.1 Hz, $J_{1eq,2ax}$ = 5.2 Hz), 2.59 (dd, 1H, H-1ax, J_{gem} = 17.1 Hz, $J_{1ax,2ax}$ = 8.2 Hz), 2.1 (dt, 1H, H-3eq, J_{gem} = 13.0 Hz, $J_{3eq,2ax}$ = 3.8 Hz, $J_{3eq,4eq}$ = 3.8 Hz), 1.94 (dq, 1H, H-3ax, J_{gem} = 13.0 Hz, $J_{2ax,3ax}$ = 9.4 Hz, $J_{3ax,4eq}$ = 4.6 Hz); ms: (m/z) 288 (M^+), 270, 241, 209, 184, 155.

Anal. Calcd. for $C_{15}H_{16}N_2O_4$•0.25 H_2O: C, 61.53; H, 5.68; N, 9.57. Found: C, 61.50; H, 5.83; N, 9.64.

General Procedure for the Preparation of 9-Amino-2- and 4-Hydroxy- and 2,4-Dihydroxy-1,2,3,4-tetrahydroacridines **8d,f,h.**

A suspension of the urethanes **7d, 7f** or **7h** (10 mmoles) in a 20% (1:1) hydroalcoholic solution of potassium hydroxide (60 ml) was refluxed for 4 hours. After cooling, ice water was added to the mixture and the precipitated solid was collected, washed with water until neutral to litmus, then dried at 60° at reduced pressure and finally crystallized. Compounds **8d** and **8h** (1 g)

were acetylated in a stirred 1:1 mixture of acetic anhydride and pyridine (20 ml) at 40-50° for 3 hours. After cooling, water was added and the precipitated solid collected, washed with water, then dried at 60° under reduced pressure. Compound **8h** afforded the 2-*O*-acetyl- and the 2,4-*O*-diacetyl-derivatives, which were separated by column chromatography on alumina, by eluting with ethyl acetate.

9-Amino-2-hydroxy-1,2,3,4-tetrahydroacridine **8d.**

This compound was obtained from **7d** in 70% yield, mp 246-248° (methanol) (lit [7] maleate mp 225° dec); ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 8.12 (d, 1H, H-8), 7.62 (d, 1H, H-5), 7.47 (t, 1H, H-6), 7.25 (t, 1H, H-7), 6.32 (s, 2H, deuterium oxide-exchangeable, NH_2), 4.91 (d, 1H, deuterium oxide-exchangeable, OH, $J_{2,OH}$ = 3.8 Hz), 4.04 (um, 1H, H-2), 3.00-2.78 (m, 3H, H-4 and H-1eq), 2.43 (partially overlapped with dimethyl sulfoxide, 1H, H-1ax, J_{gem} = 16.6 Hz, $J_{1ax,2}$ = 7.1 Hz), 1.92 (m, 1H, H-3eq), 1.78 (m, 1H, H-3ax); ^{13}C-nmr (dimethyl-d_6 sulfoxide): 156.9 (C-4a), 148.4 (C-9), 146.5 (C-10a), 127.9 (C-5 and C-6), 122.6 (C-7), 121.9 (C-8), 116.9 (C-9a), 107.3 (C-8a), 65.2 (C-2), 33.2 (C-4), 31.2 (C-1), 30.8 (C-3); ms: (m/z) 214 (M^+), 197, 185, 158, 130.

Anal. Calcd. for $C_{13}H_{14}N_2O$•0.25 H_2O: C, 71.37; H, 6.68; N, 12.80. Found: C, 71.56; H, 6.79; N, 13.01.

The *O*-Acetyl derivative had mp 173-175° (ethyl acetate); ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 8.13 (d, 1H, H-8), 7.62 (d, 1H, H-5), 7.49 (t, 1H, H-6), 7.27 (t, 1H, H-7), 6.43 (s, 2H, NH_2), 5.21 (m, 1H, H-2), 2.91 (m, 3H, H-4 and H-1eq), 2.61 (dd, 1H, H-1ax, J_{gem} = 16.8 Hz, $J_{1ax,2}$ = 6.2 Hz), 2.02 (s, 3H, CH_3), 1.99 (m, 2H, H-3); ms: (m/z) 256 (M^+).

9-Amino-4-hydroxy-1,2,3,4-tetrahydroacridine **8f.**

This compound was obtained from **7f** in 64% yield, mp 175-177° (methanol) (lit [7] hemifumarate mp 225° dec); ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 8.17 (d, 1H, H-8), 7.71 (d, 1H, H-5), 7.53 (t, 1H, H-6), 7.32 (t, 1H, H-7), 6.45 (s, 2H, deuterium oxide-exchangeable, NH_2), 5.09 (bs, 1H, deuterium oxide-exchangeable, OH), 4.53 (ut, 1H, H-4), 2.55 (ut, partially overlapped with dimethyl sulfoxide, 2H, H-1), 2.01 (m, 2H, H-3), 1.75 (m, 2H, H-2); ^{13}C-nmr (dimethyl-d_6 sulfoxide): 158.7 (C-4a), 148.6 (C-9), 146.1 (C-10a), 128.2 (C-5 and C-6), 123.2 (C-7), 122.0 (C-8), 117.3 (C-9a), 107.9 (C-8a), 68.7 (C-4), 30.8 (C-3), 23.6 (C-1), 17.9 (C-2); ms: (m/z) 214 (M^+), 195, 185, 158, 130.

Anal. Calcd. for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.08. Found: C, 72.85; H, 6.59; N, 13.07.

9-Amino-2,4-dihydroxy-1,2,3,4-tetrahydroacridine **8h.**

This compound was obtained from **7h** in 63% yield, mp 233-235° (methanol);. ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 8.17 (d, 1H, H-8), 7.72 (d, 1H, H-5), 7.52 (t, 1H, H-6), 7.32 (t, 1H, H-7), 6.45 (s, 2H, deuterium oxide-exchangeable, NH_2), 5.72 and 4.91 (bs, 2H, deuterium oxide exchangeable, 4-OH and 2-OH), 4.71 (t, 1H, H-4, $J_{4,3}$ = 4.8 Hz), 4.29 (m, 1H, H-2eq), 2.90 (dd, 1H, H-1eq, J_{gem} = 16.6 Hz, $J_{1eq,2eq}$ = 5.4 Hz), 2.38 (dd, 1H, H-1ax, J_{gem} = 16.6 Hz, $J_{1ax,2eq}$ = 7.2 Hz), 1.96 (m, 2H, H-3); ^{13}C-nmr (dimethyl-d_6 sulfoxide): 158.0 (C-4a), 148.8 (C-9), 146.4 (C-10a), 128.3 (C-5), 128.1 (C-6), 123.2 (C-7), 122.0 (C-8), 117.2 (C-9a), 106.6 (C-8a), 68.0 (C-4), 62.1 (C-2), 33.2 (C-1 and C-3); ms: (m/z) 230 (M^+), 213, 201, 183, 158, 130.

Anal. Calcd. for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.72; H, 6.13; N, 12.25.

The 2-*O*-Acetyl derivative had mp 130-132° (methanol); ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 8.17 (d, 1H, H-8), 7.72 (d, 1H, H-5), 7.54 (t, 1H, H-6), 7.33 (t, 1H, H-7), 6.57 (s, 2H, deuterium oxide-exchangeable, NH_2), 5.43 (m, 1H, H-2), 5.30 (d, 1H, deuterium oxide-exchangeable, 4-OH), 4.70 (dd, 1H, H-4), 3.10 (dd, 1H, H-1eq, J_{gem} = 16.6 Hz, $J_{1eq,2}$ = 5.7 Hz), 2.54 (partially overlapped with dimethyl sulfoxide, dd, 1H, H-1ax), 2.09 (m, 2H, H-3), 2.04 (s, 3H, CH_3); ms: (m/z) 272 (M^+).

The 2,4,-*O*-Diacetyl derivative had dec 225° (methanol); ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 8.19 (d, 1H, H-8), 7.70 (d, 1H, H-5), 7.55 (t, 1H, H-6), 7.35 (t, 1H, H-7), 6.69 (s, 2H, deuterium oxide-exchangeable, NH_2), 5.93 (m, 1H, H-4), 5.30 (bm, 1H, H-2ax), 3.12 (dd, 1H, H-1eq, J_{gem} = 16.8 Hz, $J_{1eq,2ax}$ = 8.2 Hz), 2.56 (dd, 1H, partially overlapped with dimethyl sulfoxide, H-1ax, J_{gem} = 16.8 Hz, $J_{1ax,2ax}$ = 8.2 Hz), 2.26 (m, 2H, H-3), 2.05 (s, 6H, CH_3); ms: (m/z) 314 (M^+).

9-Amino-2-hydroxyacridine **9.**

Compound **7g** (3.3 g, 10 mmoles) in 10% hydrochloric acid (50 ml) was stirred at 40° for 1 hour. After a few minutes, a yellow precipitate began to separate from the initially clear solution. The mixture was filtered, while still hot, to afford a yellow solid which was rinsed with methanol and crystallized from dimethylformamide to obtain 2.5 g (92%) of 2-hydroxy-9-methoxycarbonylaminoacridine, mp >300°; ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 10.35 (s, 1H, deuterium oxide-exchangeable, OH), 9.98 (bs, 1H, deuterium oxide-exchangeable, NH), 8.08 (d, 1H, H-8), 8.04 (d, 2H, H-4 and H-5), 7.72 (t, 1H, H-6), 7.57 (t, 1H, H-7), 7.48 (dd, 1H, H-3), 7.28 (d, 1H, H-1), 3.71 (s, 3H, CH_3); ms: (m/z) 268 (M^+), 236, 208, 181, 153.

Anal. Calcd. for $C_{15}H_{12}N_2O_3$: C, 67.15; H, 4.51; N, 10.44. Found: C, 67.26; H, 4.26; N, 10.68.

This urethane (2.0 g, 7.5 mmoles) was hydrolized by refluxing for 1 hour in aqueous 20% potassium hydroxide under nitrogen atmosphere. After cooling, the solution was carefully acidified to *p*H 4 with diluted hydrochloric acid. The yellowish-brown hydrochloride salt which had separated was collected by filtration, washed with water and crystallized from dimethylformamide, yield 1.0 g (54%), mp >300°; ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 14.13 (s, 1H, 10-NH^+), 10.40 (s, 1H, deuterium oxide-exchangeable, OH), 9.80 and 9.60 (d, 2H, deuterium oxide-exchangeable, NH_2), 8.66 (d, 1H, H-8), 7.90 (m, 4H, H-1, H-4, H-5 and H-6), 7.68 (dd, 1H, H-3), 7.50 (t, 1H, H-7); ms: (m/z) 210 (M^+), 181, 154, 127.

Anal. Calcd. for $C_{13}H_{10}N_2O$•HCl•0.5 H_2O: C: 61.06; H, 4.73; N, 10.96. Found: C, 61.02; H, 4.73; N, 10.73.

9-Carboxamido-1,2,3,4,5,6,7,8-octahydroacridine **10.**

A solution of **4a** (10 g, 0.044 mole) in glacial acetic acid (200 ml) was hydrogenated over Raney nickel (2 g) at 4 atmospheres of pressure and 50° for 10 hours. The catalyst was removed by filtration and the solution was evaporated to dryness. The residue was made alkaline with diluted ammonium hydroxide and the resulting precipitate was collected by filtration, rinsed with water until rinsings were neutral, then dried under reduced pressure. The dried crude material of good purity grade weighed 8.1 g (80%) and had mp 283-285° (2:1 ethanol/water); ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 7.80 and 7.60 (d, 2H, $CONH_2$), 2.71 (t, 4H, H-4 and H-5), 2.61 (t, 4H, H-1 and H-8), 1.72 (m, 8H, H-2, H-3, H-6 and H-7); ^{13}C-nmr

(dimethyl-d_6 sulfoxide): 169.3 (CO), 153.5 (C-4a and C-10a), 145.6 (C-9), 124.0 (C-8a and C-9a), 32.1 (C-4 and C-5), 25.0 (C-1 and C-8), 22.6 (C-3 and C-6), 22.3 (C-2 and C-7); ms: (m/z) 230 (M^+), 213, 185, 170.

Anal. Calcd. for $C_{14}H_{18}N_2O \cdot 0.5\ H_2O$: C, 70.26; H, 8.00; N, 11.71. Found: C, 69.99; H, 8.27; N, 11.68.

9-Cyano-1,2,3,4-tetrahydroacridine **11i.**

9-Cyano-1,2,3,4,5,6,7,8-octahydroacridine **11j.**

Compound **4** or **10** (15 g) was added in small portions with stirring to phosphorus oxychloride (90 ml) and the mixture was refluxed until a complete solution was obtained. The heating was stopped and the mixture was rapidly cooled in an ice-water bath in order to avoid low yields owing to the formation of dark tar material. The solvent was evaporated under reduced pressure at no more than 40°. The residue was carefully treated with cracked ice and made alkaline with diluted ammonia. The resulting suspension was stirred at room temperature for about 1 hour, then filtered. The solid obtained, thoroughly washed with water, was directly crystallized.

Compound **11i** was obtained from **4a** in 87% yield, mp 95-97° (methanol); ir: ν CN 2223 cm^{-1}; ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 7.94 (d, 1H, H-8), 7.87 (dd, 1H, H-5), 7.77 (t, 1H, H-6), 7.67 (t, 1H, H-7), 3.01 (m, 4H, H-1 and H-4), 1.86 (m, 4H, H-2 and H-3); ms: (m/z) 208 (M^+), 193, 180, 140.

Anal. Calcd. for $C_{14}H_{12}N_2$: C, 80.74; H, 5.81; N, 13.45. Found: C, 80.78; N, 5.77; N, 13.54.

Compound **11j** was obtained from **10** in 85% yield, mp 62-64° (ethyl acetate/*n*-hexane); ir: ν CN 2226 cm^{-1}; ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 2.73 (bm, 8H, H-1, H-4, H-5 and H-8), 1.75 (bm, 8H, H-2, H-3, H-6 and H-7); ms: (m/z) 212 (M^+), 197, 184, 169.

Anal. Calcd. for $C_{14}H_{16}N_2 \cdot 0.25\ H_2O$: C, 77.56; H, 7.67; N, 12.92. Found: C, 77.37; H, 7.96; N, 12.99.

9-Acetylaminomethyl-1,2,3,4-tetrahydroacridine **12k.**

9-Acetylaminomethyl-1,2,3,4,5,6,7,8-octahydroacridine **12l.**

Each nitrile **11i** or **11j** (0.05 mole), dissolved in a mixture of tetrahydrofuran (100 ml) and acetic anhydride (30 ml), was hydrogenated with Raney nickel (2 g) at 4 atmospheres of pressure and 40° for 4 hours. After filtration, the solvent was evaporated; the residue made alkaline with aqueous potassium carbonate was extracted with chloroform. The solvent was removed and the crude product crystallized.

Compound **12k** was obtained from **11i** in 68% yield, mp 210-213° (ethyl acetate); ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 8.15 (t, 1H, deuterium oxide-exchangeable, NH), 8.06 (d, 1H, H-5), 7.86 (d, 1H, H-8), 7.63 (t, 1H, H-6), 7.49 (t, 1H, H-7), 4.65 (d, 2H, 9-CH_2), 3.01 (as,4H, H-1 and H-4), 1.85 (as, 4H, H-2 and H-3), 1.80 (s, 3H, CH_3); ms: (m/z) 254 (M^+), 195, 183, 167.

Anal. Calcd. for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13; N, 11.02. Found: C, 75.66; H, 7.28; N, 10.74.

Compound **12l** was obtained from **11j** in 74% yield, mp 212-214° (ethyl acetate); ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 7.85 (bt, 1H, deuterium oxide-exchangeable, NH), 4.13 (d, 2H, 9-CH_2), 2.70 (bs, 4H, H-4 and H-5), 2.67 (bs, 4H, H-1 and H-8), 1.78 (s, 3H, CH_3), 1.72 (bs, 8H, H-2, H-3, H-6 and H-7); ms: (m/z) 258 (M^+), 199, 184, 170.

Anal. Calcd. for $C_{16}H_{22}N_2O$: C, 74.38; H, 8.58; N, 10.84. Found: C, 74.51; H, 8.66; N, 10.89.

General Procedure for the Preparation of 9-*N*-Acetyl-*N*-methyl(or benzyl)aminomethyl-1,2,3,4-tetrahydro- and 1,2,3,4,5,6,7,8-Octahydroacridines **12m-p.**

To a stirred suspension of sodium hydride (0.6 g, 50% oil dispersion, 12 mmoles) in anhydrous dimethylformamide (50 ml), a solution of **12k** or **12l** (10 mmoles) in dimethylformamide was added dropwise. After stirring for 1 hour at room temperature, methyl iodide (17 g, 12 mmoles, to obtain **12m** and **12n**) or benzyl bromide (2.1 g, 12 mmoles, to obtain **12o** and **12p**) in dimethylformamide (10 ml) was added, the mixture stirred for 4 hours at room temperature, then poured into water and extracted with ethyl acetate. The crude material resulting from the solvent evaporation was purified by chromatography on a silica gel column with ethyl acetate as eluant.

9-*N*-Acetyl-*N*-methylaminomethyl-1,2,3,4-tetrahydroacridine **12m.**

This compound, obtained by reaction of **12k** with methyl iodide in 72% yield, had mp 93-95°(ethyl acetate/*n*-hexane); ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 8.05 (d, 1H, H-5), 7.86 (d, 1H, H-8), 7.61 (t, 1H, H-6), 7.46 (t, 1H, H-7), 4.97 (s, 2H, 9-CH_2), 3.01 (t, 2H, H-4), 2.90 (t, 2H, H-1), 2.58 (s, 3H, N-CH_3), 2.03 (s, 3H, $COCH_3$), 1.83 (bs, 4H, H-2 and H-3); ms: (m/z) 268 (M^+), 195, 180, 167.

Anal. Calcd. for $C_{17}H_{20}N_2O$: C, 76.08; H, 7.51 N, 10.44. Found: C, 76.24; H, 7.69; N, 10.28.

9-*N*-Acetyl-*N*-methylaminomethyl-1,2,3,4,5,6,7,8-octahydroacridine **12n.**

This compound, obtained by reaction of **12l** with methyl iodide in 76% yield, had mp 77-79° (diethyl ether/*n*-hexane); ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 4.48 (s, 2H, 9-CH_2), 2.72 (bs, 4H, H-4 and H-5), 2.58 (bs, 7H, H-1, H-8 and N-CH_3), 2.00 (s, 3H, $COCH_3$), 1.71 (bs, 8H, H-2, H-3, H-6 and H-7); ms: (m/z) 272 (M^+), 199, 184, 170.

Anal. Calcd. for $C_{17}H_{24}N_2O \cdot 0.5\ H_2O$: C, 72.56; H, 8.96; N, 9.96. Found: C, 72.70; H, 8.99; N, 9.71.

9-*N*-Acetyl-*N*-benzylaminomethyl-1,2,3,4-tetrahydroacridine **12o.**

This compound, obtained by reaction of **12k** with benzyl bromide in 77% yield, had mp 97-100° (diethyl ether/*n*-hexane); ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 7.94 (d, 1H, H-5), 7.77 (d, 1H, H-8), 7.56 (t, 1H, H-6), 7.34 (t, 1H, H-7), 7.26 (as, 3H, 3',4' and 5' phenyl protons), 6.92 (d, 2H, 2' and 6' phenyl protons), 5.14 (s, 2H, 9-CH_2), 4.10 (s, 2H, benzyl CH_2), 3.06 (t, 2H, H-4), 2.49 (t, 2H, overlapped with dimethyl sulfoxide, H-1), 2.18 (s, 3H, CH_3), 1.82 (m, 2H, H-3), 1.64 (m, 2H, H-2); ms: (m/z) 344 (M^+), 253, 195, 180.

Anal. Calcd. for $C_{23}H_{24}N_2O$: C, 80.20; H, 7.02; N, 8.13. Found: C, 80.13; H, 7.20; N, 8.17.

9-*N*-Acetyl-*N*-benzylaminomethyl-1,2,3,4,5,6,7,8-octahydroacridine **12p.**

This compound, obtained by reaction of **12l** with benzyl bromide in 80% yield, had mp 122-124° (diethyl ether/*n*-hexane); ^{1}H-nmr (dimethyl-d6 sulfoxide): δ 7.34-7.00 (m, 5H, phenyl protons), 4.52 (d, 2H, 9-CH_2), 4.15 (d, 2H, benzyl CH_2), 2.67 (bs, 4H, H-4 and H-5), 2.29 (bs, 4H, H-1 and H-8), 2.06 (s, 3H, $COCH_3$), 1.65-1.56 (bd, 8H, H-2, H-3, H-6 and H-7); ms: (m/z) 348 (M^+), 199, 184, 170.

Anal. Calcd. for $C_{23}H_{28}N_2O$: C, 79.27; H, 8.10; N, 8.04. Found: C, 79.13; H, 8.39; N, 8.16.

General Procedure for the Preparation of 9-Aminomethyl-1,2,3,4-tetrahydro- and 1,2,3,4,5,6,7,8-Octahydroacridines **13k-p.**

Each compound **12** (2 g) was boiled in 15% aqueous sulfuric acid (20 ml) until starting material had disappeared (about 6 hours). The reaction was controlled by tlc on alumina with ethyl acetate as eluant. After cooling, the reaction mixture was diluted with water, made alkaline with potassium carbonate and extracted with chloroform. The solvent was removed and the resulting residue was directly crystallized, **13k,l**, or converted to the maleate salt, **13m-p**.

9-Aminomethyl-1,2,3,4-tetrahydroacridine **13k.**

This compound was obtained from **12k** in 89% yield, mp 100-102° (ethyl acetate); ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 8.12 (d, 1H, H-5), 7.84 (d, 1H, H-8), 7.60 (t, 1H, H-6), 7.48 (t, 1H, H-7), 4.06 (s, 2H, 9-CH_2), 3.20 (bs, 2H, deuterium oxide-exchangeable, NH_2), 3.01 (as, 4H, H-4 and H-1), 1.84 (m, 4H, H-2 and H-3); ^{13}C-nmr (dimethyl-d_6 sulfoxide): 158.5 (C-9 and C-4a), 146.0 (C-10a), 128.6 (C-5), 128.1 (C-9a), 128.0 (C-6), 125.5 (C-8a), 125.4 (C-7), 123.9 (C-8), 37.0 (CH_2NH_2), 33.9 (C-4), 25.2 (C-1), 22.7 (C-3), 22.3 (C-2); ms: (m/z) 213 (M^+ + 1), 195, 180, 167.

Anal. Calcd. for $C_{14}H_{16}N_2$: C, 79.21; H, 7.60; N, 13.20. Found: C, 79.21; H, 7.87; N, 13.25.

9-Aminomethyl-1,2,3,4,5,6,7,8-octahydroacridine **13l.**

This compound was obtained from **12l** in 84% yield, mp 139-142° (ethyl acetate); ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 3.58 (s, 2H, 9-CH_2), 2.76 (bt, 4H, H-4 and H-5), 2.68 (bt, 4H, H-1 and H-8), 1.87 (s, 2H, deuterium oxide-exchangeable, NH_2), 1.72 (bm, 8H, H-2, H-3, H-6 and H-7); ^{13}C-nmr (dimethyl-d_6 sulfoxide): 172.3 (C-9), 153.1 (C-4a and C-10a), 127.2 (C-8a and C-9a), 37.3 (CH_2NH_2), 32.5 (C-4 and C-5), 24.4 (C-1 and C-8), 22.8 (C-3 and C-6), 22.6 (C-2 and C-7); ms: (m/z) 217 (M^+ + 1), 199, 184, 170.

Anal. Calcd. for $C_{14}H_{20}N_2 \cdot 2\ H_2O$: C, 66.63; H, 9.59; N, 11.10. Found: C, 66.58; H, 9.41; N, 10.90.

9-Methylaminomethyl-1,2,3,4-tetrahydroacridine **13m.**

This compound was obtained from **12m** in 92% yield; maleate: mp 192-194° (ethanol); ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 8.24 (d, 1H, H-5), 7.94 (d, 1H, H-8), 7.73 (t, 1H, H-6), 7.62 (t, 1H, H-7), 6.01 (s, 2H, maleate protons), 4.63 (s, 2H, 9-CH_2), 3.06 (bs, 4H, H-1 and H-4), 2.78 (s, 3H, N-CH_3), 1.89 (m, 4H, H-2 and H-3); ms: (m/z) 226 (M^+), 195, 180, 167.

Anal. Calcd. for $C_{15}H_{18}N_2 \cdot C_4H_4O_4$: C, 66.65; H, 6.48; N, 8.18. Found: 66.68; H, 6.56; N, 8.20.

9-Methylaminomethyl-1,2,3,4,5,6,7,8-octahydroacridine **13n.**

This compound was obtained from **12n** in 74% yield; maleate: mp 179-182° (2-propanol); ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 6.08 (s, 2H, maleate protons), 4.17 (s, 2H, 9-CH_2), 2.84 (bs, 8H, H-1, H-4, H-5 and H-8), 2.75 (s, 3H, CH_3), 1.76 (bs, 8H, H-2, H-3, H-6 and H-7); ms: (m/z) 230 (M^+), 199, 184, 170.

Anal. Calcd. for $C_{15}H_{22}N_2 \cdot C_4H_4O_4$: C, 65.87; H, 7.57; N, 8.09. Found: C, 65.81, H, 7.72; N, 8.14.

9-Benzylaminomethyl-1,2,3,4-tetrahydroacridine **13o.**

This compound was obtained from **12o** in 89% yield; maleate: mp 186-188° (ethanol); ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 8.05 (d, 1H, H-5), 7.92 (d, 1H, H-8), 7.70 (t, 1H, H-6), 7.57 (m, 4H, H-7 and 3',4',5' phenyl protons), 7.48 (d, 2H, 2' and 6' phenyl protons), 6.03 (s, 2H, maleate protons), 4.54 (s, 2H, 9-CH_2), 4.43 (s, 2H, benzyl CH_2), 3.02 (bt, 2H, H-4), 2.87 (bt, 2H, H-1), 1.82 (bs, 4H, H-2 and H-3); ms: (m/z) 302 (M^+), 195, 180, 91.

Anal. Calcd. for $C_{21}H_{22}N_2 \cdot C_4H_4O_4$: C, 71.75; H, 6.26; N, 6.69. Found: C, 71.75; H, 6.24; N, 6.79.

9-Benzylaminomethyl-1,2,3,4,5,6,7,8-octahydroacridine **13p.**

This compound was obtained from **12p** in 86% yield; maleate: mp 177-179° (2-propanol); ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 7.48 (m, 5H, phenyl protons), 6.01 (s, 2H, maleate protons), 4.27 (s, 2H, 9-CH_2), 3.95 (s, 2H, benzyl CH_2), 2.68 (bd, 8H, H-1, H-4, H-5 and H-8), 1.72 (bs, 8H, H-2, H-3, H-6 and H-7); ms: (m/z) 306 (M^+), 199, 184, 170.

Anal. Calcd. for $C_{21}H_{26}N_2 \cdot C_4H_4O_4$: C, 71.06; H, 7.16; N, 6.63. Found: C, 71.02; H, 7.36; N, 6.76.

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