THE SYNTHESIS OF 9-(1-AZETIDINYL)-1,2,3,4-TETRAHYDROACRIDINE

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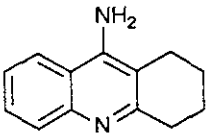
Abstract - Synthesis of analogue (**2**) of tacrine is described in which the primary amino group is replaced by the azetidine moiety. The synthesis was accomplished in two steps from the acridinone derivative **10**. This involved conversion of **10** to triflate **11**, followed by treatment with azetidine to give the target compound **2**.

The recent success of 9-amino-1,2,3,4-tetrahydroacridine (tacrine) (**1**) in the treatment of Alzheimer's disease has inspired our interest in the synthesis of certain related compounds.[1,2,3a] However, the liver toxicity and mutagenicity problems associated with tacrine emphasize the need for safer and more efficacious medicinal agents based on this template. A recent report of a derivative of low toxicity has appeared.[4] Toward this end, we report here the synthesis of several novel 9-amino-1,2,3,4-tetrahydroacridine derivatives.

The primary amino group of tacrine (**1**) may be a source of its toxicity. With this in mind, we concentrated on modifications of the molecule at this point. Based on earlier unrelated studies, azetidine was considered to be a suitable amine substituent, which might lead to inactive and non-toxic tetrahydroacridine metabolites.[3b] Thus, the previously unreported 9-(1-azetidinyl)-1,2,3,4-tetrahydroacridine (**2**) became our target molecule. However, several additional tetrahydroacridine derivatives were synthesized, as various methods of producing the target molecule **2** were explored.



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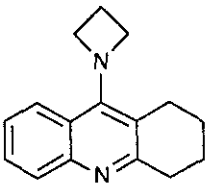
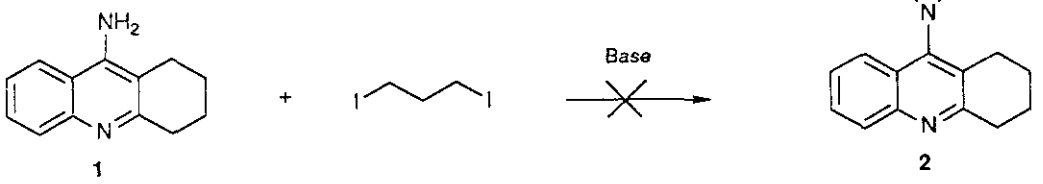


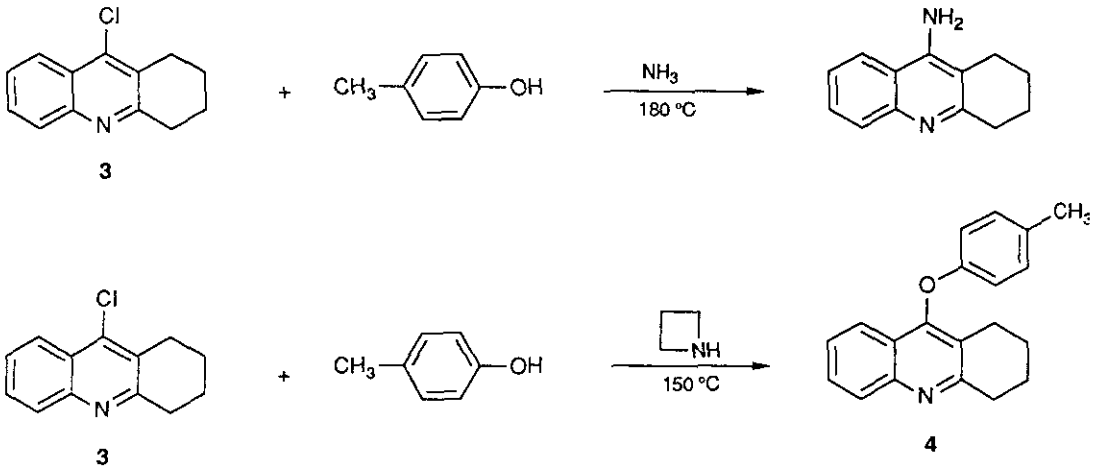
2

A straightforward approach to 9-(1-azetidinyl)-1,2,3,4-tetrahydroacridine (**2**) began with tacrine (**1**) itself. The reaction of tacrine (**1**) with 1,3-diiodopropane in the presence of potassium carbonate in acetonitrile at room temperature or at reflux produced no reaction. The amino group of tacrine is apparently quite unreactive as a nucleophile.

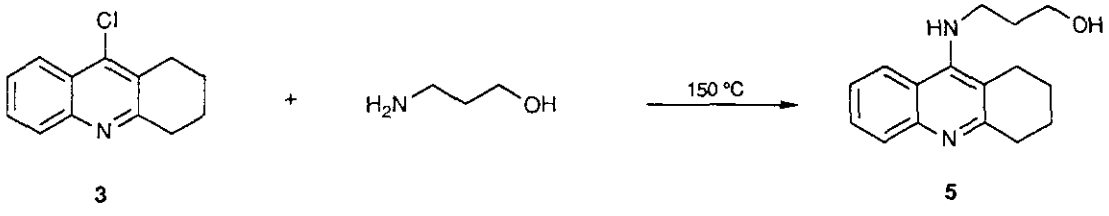


1 2

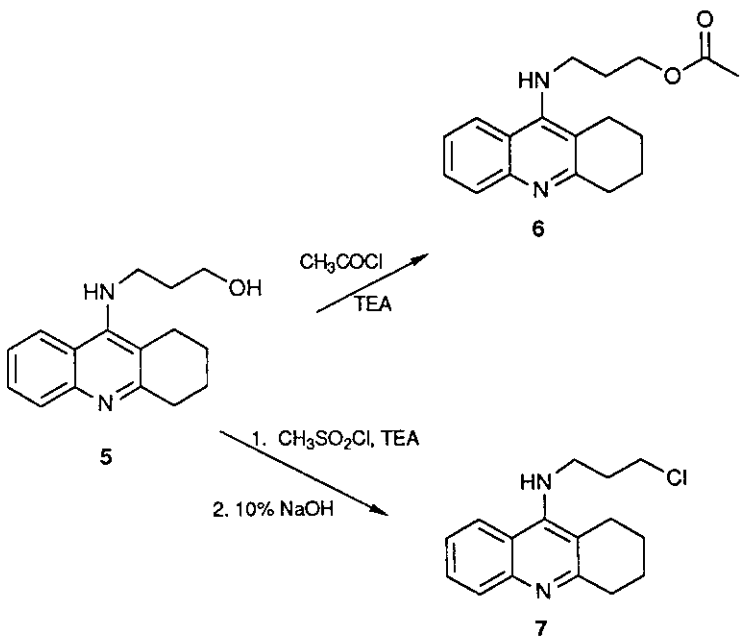
The literature[5,6] regarding the synthesis of tacrine (**1**) was instructive at this point. Tacrine (**1**) is produced by the reaction of 9-chloro-1,2,3,4-tetrahydroacridine (**3**) with *p*-cresol and ammonia at 180 °C.[5,6] The reaction proceeds via 9-(4-methylphenoxy)-1,2,3,4-tetrahydroacridine (**4**). Ammonia displaces the 9-phenoxy substituent, thus forming tacrine (**1**). It was thought that the desired azetidine-substituted compound might be formed by simply replacing ammonia with azetidine. However, when this experiment was performed, only the intermediate, 9-(4-methylphenoxy)-1,2,3,4-tetrahydroacridine (**4**), was isolated. Apparently, azetidine did not survive the rigorous reaction conditions.



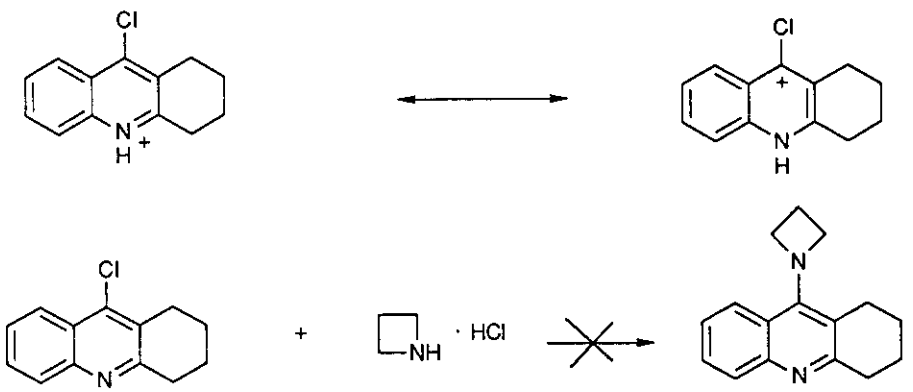
A different approach to the target was then implemented for the addition of the azetidine moiety. 3-Amino-1-propanol and 9-chloro-1,2,3,4-tetrahydroacridine (**3**) were combined and heated to 150 °C for several hours.



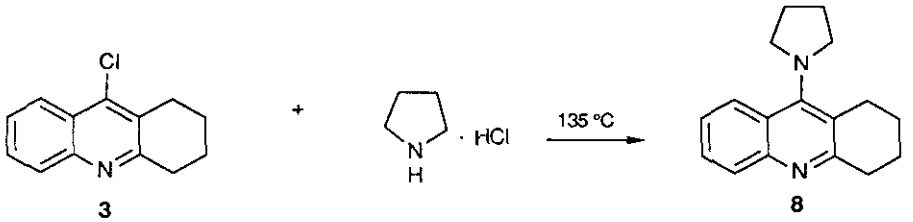
The exclusive product of this reaction was 9-(3-hydroxypropylamino)-1,2,3,4-tetrahydroacridine (**5**). This structure was confirmed by the formation of its acetoxy derivative (**6**) using one equivalent each of acetyl chloride and triethylamine (TEA). The problem of cyclization to the azetidine derivative remained to be solved. Hydroxy compound (**5**) was treated with mesyl chloride and triethylamine. Removal of the solvent and heating the residue with 10% aqueous NaOH provided only the primary chloro compound **7**, and none of the desired cyclization product. Subsequent treatment of the chloro derivative **7** with n-BuLi gave a very complex mixture of products. These experiments served to underscore the fact that the 9-amino functionality (primary or secondary) does not react readily with electrophiles. The same chloro derivative was also produced by reaction of hydroxy compound **5** with triphenylphosphine in carbon tetrachloride.[7]



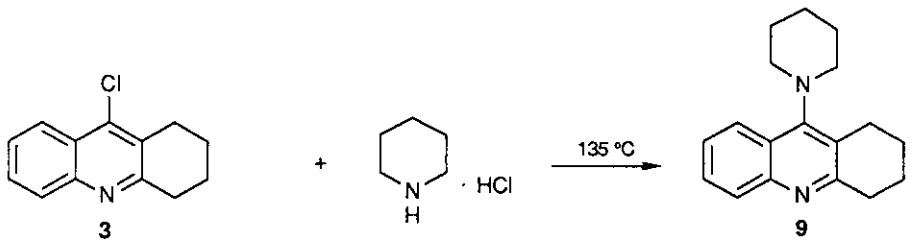
The activation of 9-chloro-1,2,3,4-tetrahydroacridine toward nucleophilic attack using an acid catalyst was considered. Protonation of the ring nitrogen was expected to enhance the electrophilic character of the 9-position (see below). Thus, azetidine hydrochloride was prepared and combined with 9-chloro-1,2,3,4-tetrahydroacridine (**3**). The mixture was heated in a sealed tube for several hours. However, only the starting material was isolated. Once again, under rigorous conditions, the azetidine seemed to decompose.



In a similar fashion, pyrrolidine hydrochloride was prepared and mixed with 9-chloro-1,2,3,4-tetrahydroacridine (**3**). Heating this mixture in a sealed tube at 135 °C for 12 hours provided 9-(1-pyrrolidinyl)-1,2,3,4-tetrahydroacridine (**8**) in excellent yield. When the same procedure was followed using piperidine hydrochloride, the expected product, 9-(1-piperidinyl)-1,2,3,4-tetrahydroacridine (**9**) was isolated in about 30% yield.[8]

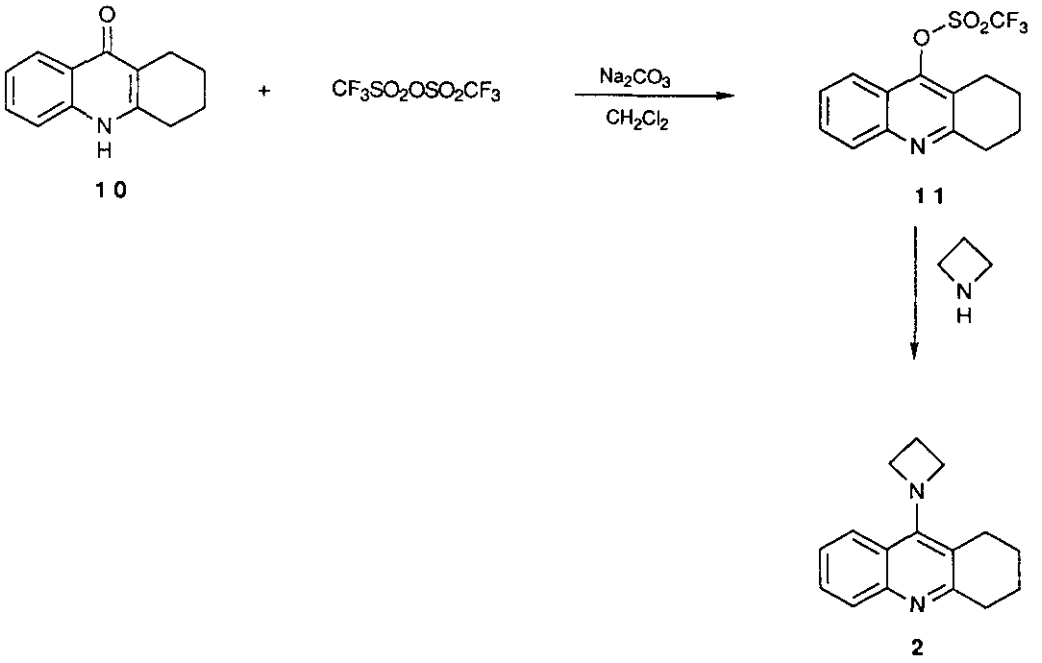


3 **8**



3 **9**

At this point, the placement of a superior leaving group at the 9-position was considered to be a requirement for the synthesis of 9-(1-azetidinyl)-1,2,3,4-tetrahydroacridine (**2**). The reaction of azetidine with such a molecule was expected to provide the long-sought target compound. The triflate **11** was thought to be a suitable candidate for the 9-azetidinyl precursor. As a result, 1,2,3,4-tetrahydro-9-acridinone (**10**) was treated with trifluoromethanesulfonic anhydride and sodium carbonate in methylene chloride.[9,10a] After the triflate had formed completely, azetidine was added and the mixture was heated for several hours. The azetidine-substituted tetrahydroacridine product (**2**)[10b] was isolated from the reaction mixture in 51% yield.



EXPERIMENTAL

All moisture- or oxygen-sensitive reactions were conducted under a nitrogen atmosphere. Melting points were taken on a Thomas Hoover apparatus and are uncorrected. Nmr spectra were recorded (δ, ppm) on Magnachem-200, GN-300 or , Varian 300 spectrometers with TMS as an internal reference and deuterated chloroform as a solvent. Mass spectra were obtained on MAT CH-5-DF(FAB), FINNIGAN 8230 B(EI), KRATOS MS-80 (H.R.EI) and MAT CH-7(CI) mass spectrometers unless otherwise specified. Infrared spectra (ν, cm^{-1}) were obtained on a Perkin-Elmer 1420 Ratio Recording IR spectrophotometer. N,N-Dimethylformamide (Fisher), THF (Fisher), ether (Fisher) and methylene chloride (Fisher) were used without purification.

9-Chloro-1,2,3,4-tetrahydroacridine[11,12]

1,2,3,4-Tetrahydroacridinone (Aldrich) (1.99 g, 10.0 mmol) was added in portions to phosphoryl chloride (10.0 ml, 107 mmol). The mixture was then refluxed (120 °C) for 2 h.

After cooling to room temperature, the reaction mixture was cautiously quenched by the dropwise addition of water. The pH of the resulting solution was then adjusted to about 10 by the addition of conc. NH_4OH, and a solid precipitated. It was collected by suction filtration and was then dissolved in acetone. The yellow solution was concentrated until it became cloudy. Cooling provided yellow crystals (1.85 g, 85%); mp 65-67 °C (lit.[11] mp 68 °C); ^1H nmr (200 MHz, $CDCl_3$) δ 8.17 (d, 1H, ArH, J=9 Hz), 8.02 (d, 1H, ArH, J=8 Hz), 7.70 (dd, 1H, ArH, J=8, 7 Hz), 7.57 (dd, 1H, ArH, J=9, 7 Hz), 3.14 (broad m, 2H, CH_2), 3.02 (broad m, 2H, CH_2), 1.94 (m, 4H, 2xCH_2); ir ($CHCl_3$) 3065, 2940, 2865, 1580, 1555, 1480, 1430, 1395, 1365, 1310, 1250, 1222, 1162, 1135 cm^{-1}; ms (EI, 70 eV), M^+ 217 (100%), 182.

9-(3-Hydroxypropylamino)-1,2,3,4-tetrahydroacridine (5)

9-Chloro-1,2,3,4-tetrahydroacridine (1.09 g, 5.0 mmol) and 3-amino-1-propanol (1.12 g, 15.0 mmol) were combined in a thick-walled tube. The tube was flushed with nitrogen, sealed, and heated to 150 °C for 10 h. After cooling to room temperature, the brown residue was taken up in 50 ml of CH_2Cl_2 and washed with saturated Na_2CO_3 and brine. Drying over $MgSO_4$, filtering, and evaporation of the solvent provided 1.2 g (94%) of an off-white solid, mp 130-133 °C; ^1H nmr (200 MHz $CDCl_3$) δ 7.97 (d, 1H, ArH, J=9 Hz), 7.84 (d, 1H, ArH, J=8 Hz), 7.46 (dd, 1H, ArH, J=9, 6 Hz), 7.24 (dd, 1H, ArH, J=8, 6 Hz), 4.72 (broad s, 1H, NH), 4.30 (broad 1H, OH), 3.85 (t, 2H, CH_2, J=7 Hz), 3.66 (m, 2H, CH_2), 2.96 (broad s, 2H, CH_2), 2.63 (broad s, 2H, CH_2), 1.80 (m, 6H, 3xCH_2); ir ($CHCl_3$) 3340 (broad), 2935, 2870, 1575, 1560, 1495, 1420, 1335, 1290, 1270 cm^{-1}; ms (EI, 70 eV), M^+ 256, 211, 198(100), 197. Anal. Calcd for $C_{16}H_{20}N_2O$: C, 75.0; H, 7.81; N, 10.94. Found: C, 74.93; H, 7.82; N, 10.98.

9-(3-Acetoxypropylamino)-1,2,3,4-tetrahydroacridine (6)

9-(3-Hydroxypropylamino)-1,2,3,4-tetrahydroacridine (0.050 g, 0.20 mmol) and triethylamine (0.020 g, 0.20 mmol) were dissolved in 2 ml of CH_2Cl_2 under N_2 and cooled to -80 °C. Acetyl chloride (0.016 g, 0.20 mmol) was then added dropwise using a syringe. The resulting homogeneous yellow solution was stirred at -80 °C for 30 min, and was then allowed to gradually warm to ambient temperature. The reaction mixture was stirred for a total of 4 h. Additional CH_2Cl_2 (25 ml) was added and the organic layer was washed with brine. Drying over $MgSO_4$, filtering, and evaporation provided an orange oil.

Chromatography on silica gel (95% $CHCl_3$, 4% MeOH, 1% NH_4OH) provided 0.050 g (83%) of the product as a colorless oil; ^1H nmr (200 MHz, $CDCl_3$) δ 7.96 (d, 1H, ArH, J=8 Hz), 7.90 (d, 1H, ArH, J=6 Hz), 7.55 (dd, 1H, ArH, J=6, 8 Hz), 7.34 (dd, 1H, ArH, J=8, 8 Hz), 4.21 (t, 2H, CH_2, J=6 Hz), 3.53 (m, 2H, CH_2), 3.06 (broad s, 2H, CH_2), 2.71 (broad s, 2H, CH_2), 2.07 (s, 3H, CH_3), 1.93 (m, 6H, 3xCH_2); ir ($CHCl_3$) 3380(NH), 3045, 2920. 2845, 1725(s), 1605, 1572, 1550, 1488, 1410, 1355, 1230(s) cm^{-1}; ms (FAB) M^+ 299 (100%). High resolution mass spectrum calcd for $C_{18}H_{23}N_2O_2$ 299.1759; found 299.1788.

9-(3-Chloropropylamino)-1,2,3,4-tetrahydroacridine (7)

9-(3-Hydroxypropylamino)-1,2,3,4-tetrahydroacridine (0.43 g, 1.7 mmol) and triethylamine (0.19 g, 0.19 mmol) were dissolved in 7 ml of CH_2Cl_2 and cooled to 0 °C under a nitrogen atmosphere. Methanesulfonyl chloride (0.21 g, 1.9 mmol), diluted with 2 ml of CH_2Cl_2, was added dropwise using a syringe. The homogeneous yellow solution was stirred for 1 h at 0 °C and 1 h at room temperature. A solution of 10% aqueous NaOH (3 ml) was then added to the reaction mixture, and it was heated to 80 °C for 3 h. After cooling to room temperature, the reaction mixture was diluted with 50 ml of CH_2Cl_2 and washed with saturated Na_2CO_3 and brine. An orange oil was recovered after drying over $MgSO_4$, filtering and evaporating to dryness. Separation by preparative centrifugal thin-layer chromatography (silica gel; 95% $CHCl_3$,4% MeOH,1% NH_4OH as eluent) provided 0.19 g (63%) of **7** as a colorless oil; ^1H nmr (300 MHz, $CDCl_3$) δ 7.93 (dd, 1H, ArH J=5, 1 Hz), 7.91 (dd, 1H, ArH, J=4, 1 Hz), 7.56 (dt, 1H, ArH, J=7, 1 Hz), 7.37 (m, 1H, ArH), 4.00 (broad s, 1H, NH), 3.65 (m, 4H, 2xCH_2), 3.07 (broad s, 2H, CH_2), 2.75 (broad s, 2H, CH_2), 2.10 (quintet, 2H, CH_2, J=7 Hz), 1.93 (m, 4H, 2xCH_2); ir ($CHCl_3$) 3070, 2945, 2875, 1618, 1585, 1563, 1500, 1422, 1358, 1300, 1173, 1120 cm^{-1}; ms (EI, 70 eV) M^+ 274, 239, 211 (100%). High resolution mass spectrum (FAB, $[M+H]^+$) calcd for $C_{16}H_{20}N_2Cl$ 275.1315; found 275.1306.

9-(1-Azetidinyl)-1,2,3,4-tetrahydroacridine (2)

Method A. 1,2,3,4-Tetrahydro-9-acridinone (0.40 g, 2.0 mmol) and sodium carbonate (0.23 g, 2.2 mmol) were suspended in CH_2Cl_2 (8 ml) under a nitrogen atmosphere. Trifluoromethanesulfonic anhydride (0.37 ml, 2.2 mmol) was then added using a syringe, and the colorless suspension was stirred at ambient temperature for 4.5 h. Azetidine (0.27 ml, 4.0 mmol) was then added, and the solution was decanted into a thick-walled and

threaded tube. The tube was flushed with N_2, sealed and heated to 50 °C for 18 h. After cooling to room temperature, the reaction mixture was diluted with 25 ml of CH_2Cl_2 and washed with 25 ml of saturated aqueous Na_2CO_3. Drying the organic layer over $MgSO_4$, filtering, and evaporating to dryness gave an oily yellow solid. Separation by radial chromatography followed by evaporation of the eluent (silica gel; 95% $CHCl_3$, 4% MeOH,1% NH_4OH) provided 0.24 g (51%) of the desired product as an off-white solid, mp 68 °C; ^1H nmr (200 MHz, $CDCl_3$) δ 8.08 (d, 1H, ArH, J=8 Hz), 7.84 (d, 1H, ArH, J=8 Hz), 7.56 (dd, 1H, ArH, J=8, 8 Hz), 7.28 (dd, 1H, ArH, J=8, 8 Hz), 4.71 (t, 4H, 2xNCH_2, J=8 Hz), 3.12 (dd, 2H, CH_2, J=6, 8 Hz), 2.71 (dd, 2H, CH_2, J=4, 8 Hz), 2.46 (quintet, 2H, CH_2, J=8 Hz), 1.88 (m, 2H, CH_2), 1.69 (m, 2H, CH_2); ir (KBr) 2940, 2850, 1620, 1553, 1500, 1460, 1378, 1355 cm^{-1}. Anal. Calcd for $C_{16}H_{18}N_2$: C, 80.67: H, 7.56; N, 11.76. Found: C, 80.76; H, 7.47; N, 11.63; ms (FAB); 239 (M^+ +1, 100%), 238, 211. High resolution mass spectrum calcd for $C_{16}H_{19}N_2$ 239.1548; found 239.1536.

Method B. The triflate **11** was generated in situ as described in method A. Azetidine (0.27 ml, 4.0 mmol) was added dropwise to the reaction mixture, and the resultant solution was heated in a sealed tube at 45-48 °C for 18 h. The reaction mixture was cooled to ambient temperature, and an additional equivalent of azetidine (0.14 ml, 2 mmol) was added. Stirring was then continued at 45-48° C in the sealed tube for 18 h. Product isolation proceeded as described in method A to give 200 mg (42%) of **2** as an off-white solid. The spectral data (^1H nmr, ir) obtained for this material were identical with that recorded above. This relatively pure (>95%) material was purified further by dissolving it in 60 ml of diethyl ether, filtering, washing the filtrate with saturated aqueous Na_2CO_3, drying ($MgSO_4$) the organic phase and concentrating it in vacuo to give 140 mg (30%) of **2** as a white solid; mp 93-94 °C. Needles were obtained from methanol; mp 97 °C.

9-(1-Pyrrolidinyl)-1,2,3,4-tetrahydroacridine (8)

Pyrrolidine hydrochloride (1.10 g, 10 mmol) and 9-chloro-1,2,3,4-tetrahydroacridine (0.44 g, 2.0 mmol) were combined in a threaded thick-walled glass tube. The tube was flushed with nitrogen, sealed and heated to 110 °C for 20 h. The resulting brown residue was taken up in 25 ml of CH_2Cl_2 and washed with 25 ml of saturated aqueous Na_2CO_3. A brown oil was obtained after dyring the organic layer over $MgSO_4$, filtering, and evaporation of the solvent.

This oil was filtered through a short silica gel column (95% $CHCl_3$, 4% MeOH,1% NH_4OH), and the baseline impurities were removed. The product was isolated in pure form as an orange oil (0.48 g, 95%) after evaporation of the eluent. This compound slowly decomposes when stored for extended periods at room temperature. ^1H Nmr (200 MHz, $CDCl_3$) δ 7.90 (d, 1H, ArH, J=10 Hz), 7.83 (d, 1H, ArH, J=8 Hz), 7.48 (dd, 1H, ArH, J=8, 8 Hz), 7.30 (dd, 1H, ArH, J=6, 8 Hz), 3.35 (m, 4H, 2xNCH_2), 3.05 (t, 2H, CH_2, J=6 Hz), 2.75 (t, 2H, CH_2, J=7 Hz), 2.04 (m, 4H, 2xCH_2), 1.82 (m, 4H, 2xCH_2); ir ($CHCl_3$) 3078(w), 2950, 2875, 1570, 1486, 1400 cm^{-1}; ms: (EI, 70 eV), M^+ 252(100%), 223, 209.

9-(1-Piperidinyl)-1,2,3,4-tetrahydroacridine (9)

9-Chloro-1,2,3,4-tetrahydroacridine (0.44 g, 2.0 mmol) and phenol (0.38 g, 4.0 mmol) were combined in a threaded thick-walled glass tube. The tube was flushed with nitrogen, sealed, and heated to 110 °C for 1 h. Piperidine (0.40 ml, 4.0 mmol) was then added and heating was continued at 135 °C for 20 h. After cooling to room temperature, the resulting residue was taken up in 25 ml of CH_2Cl_2 and washed with 25 ml of 10% aqueous NaOH. Drying the organic layer over $MgSO_4$, filtering, and evaporation to dryness gave a dark brown oil. This oil was filtered through a short silica gel column (95% $CHCl_3$, 4% MeOH,1% NH_4OH). Evaporation of the solvent provided a crude solid which was crystallized from ethyl ether to give (0.32 g, 60%) of an off-white solid; mp 110-111 °C.

This compound was also prepared in about 30% yield (after chromatography) by the heating of 9-chloro-1,2,3,4-tetrahydroacridine with an excess of piperidine hydrochloride at 135 °C for 24 h.

^1H Nmr (200 MHz, $CDCl_3$) δ 8.13 (d, 1H, ArH, J=6 Hz), 7.95 (d, 1H, ArH, J=8 Hz), 7.57 (dd, 1H, ArH, J=6, 8 Hz), 7.39 (dd, 1H, ArH, J=6, 10Hz), 3.28 (broad s, 4H, 2xNCH_2), 3.12 (t, 2H, CH_2, J=6 Hz), 2.91 (t, 2H, CH_2, J=6 Hz), 1.89 (m, 4H, 2xCH_2), 1.75 (m, 6H, 3xCH_2); ir (KBr) 3065(w), 2940, 2860, 2810, 1562, 1488, 1439, 1405, 1360, 1296, 1255, 1230, 1212, 1145, 1120, 1097 cm^{-1}; ms (EI, 70 eV), M^+ 266(100%), 209. Anal. Calcd for $C_{18}H_{22}N_2$: C, 81.20; H, 8.27; N, 10.53. Found: C, 81.07; H, 8.31; N, 10.46.

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