Synthesis of Pyrrolo[2,3-*c*]acridines

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The synthesis of 6-amino-3-benzylpyrrolo[2,3-*c*]acridine (**9**) and its 8,9-dimethoxy derivative (**10**) from *N*-benzyl-4,5,6,7-tetrahydroindol-4-one and anthranilonitriles, *via* imine formation followed by cyclization and aromatisation, is described.

Introduction

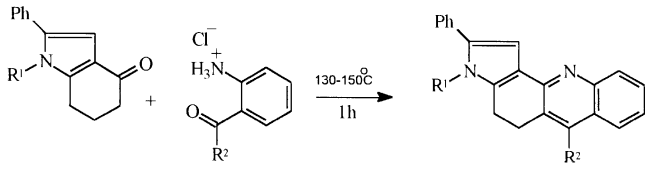
Heterocyclic-fused acridines possess a wide range of biological activities including anti-bacterial, anti-viral and anti-tumour properties.[1] We have recently reported the synthesis of pyrido[2,3-*c*]acridines from 5,6,7,8-tetrahydroquinolin-5-ones.[2] A very similar strategy has been used for the synthesis of pyrrolo[2,3-*c*]acridines in the present work. Although Takagi *et al.*[3] have prepared a series of 4,5-dihydropyrrolo[2,3-*c*]acridines (**2**) from 4,5,6,7-tetrahydroindol-4-ones (**1**), this synthesis is limited to the condensation of 4,5,6,7-tetrahydroindol-4-ones (**1**) with some aromatic ketones (Scheme 1).

Result and Discussion

6-Amino-3-benzylpyrrolo[2,3-*c*]acridine (**9**) and its 8,9-dimethoxy derivative (**10**) were prepared from 4,5,6,7-tetrahydroindol-4-one (**3**) in three steps. *N*-Benzyl-4,5,6,7-tetrahydroindol-4-one (**4**) was prepared by the method of Remers *et al.*[4] by using benzyl bromide as the alkylating agent (Scheme 2).

6-Amino-3-benzyl-4,5-dihydropyrrolo[2,3-*c*]acridine (**7**) and its 8,9-dimethoxy derivative (**8**) were prepared, in 49% and 44% yields respectively, by the one-pot generation/cyclization of the imines, (**5**) and (**6**), from *N*-benzyl-4,5,6,7-tetrahydroindol-4-one (**4**) and the appropriate anthranilonitrile (Scheme 3). The reactants were dissolved in toluene, with a catalytic amount of *para*-toluenesulfonic acid, and refluxed for 100 hours with the azeotropic removal of water. After evaporating the toluene, the residue in dry DME, was treated with 2.5 equivalents of sodium amide, in the presence of 15-crown-5, and refluxed for 24 hours.

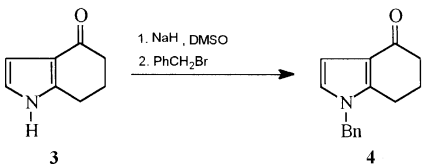
The structures of the isolated products (**7** & **8**) were confirmed by high resolution mass spectroscopy and other spectroscopic data. In the ^{1}H NMR spectra of these compounds, the presence of two different signals around δ 13.0 and δ 8.0,



R¹ = H, Me, Et, Ph, *p*-An, β-Naph; R² = Me, Ph.

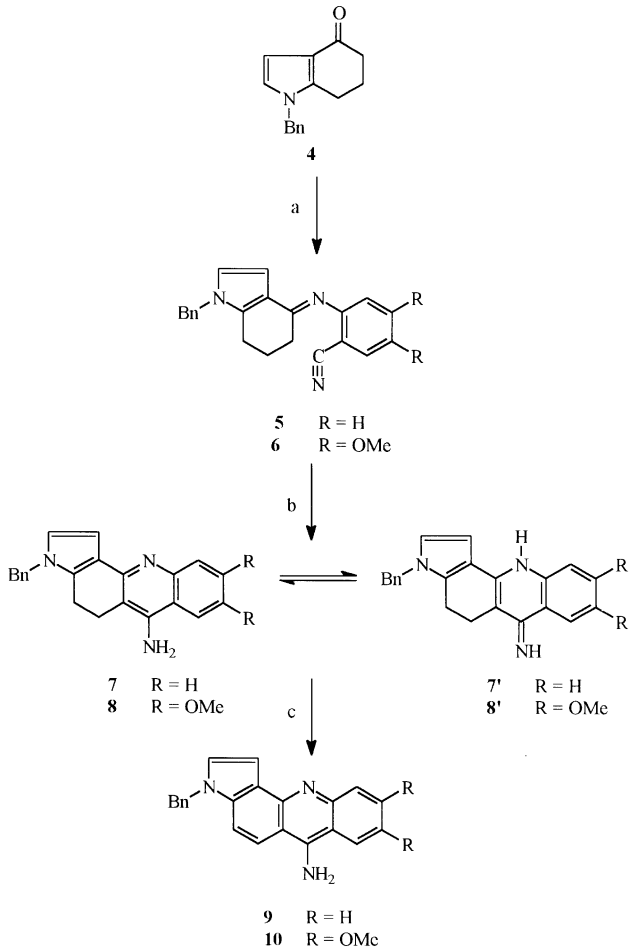
1 **2**

Scheme 1



3 **4**

Scheme 2



Scheme 3. *Reagents and conditions*: -(a) Anthranilonitrile or 4,5-dimethoxyanthranilonitrile, PTSA, toluene, reflux, 100 h. (b) $NaNH_2$, DME, 15-crown-5, N_2, reflux, 24 h. (c) MnO_2, DMF, reflux, 24h.

each integrating to one proton and exchangeable with D_2O, indicates that they exist as the imine, (**7'**) and (**8'**), rather than the tautomeric amine (**7**) and (**8**) in solution. The most important features of these ^1H NMR spectra are the presence of two doublets around δ 7.0 corresponding to the pyrrole protons, a singlet at δ 5.2 corresponding to the methylene protons of the benzyl group, and a mulitiplet at δ 3.0 corresponding to the methylene protons at C-4 and C-5. The ^{13}C NMR spectra were also fully consistent with these structures. Although the IR spectra can be attributed to the imine structures of these compounds they are less indicative due to the common absorption region for C=N stretching and NH_2 bending. The mass spectrum of compound (**7**) shows a very intense molecular ion peak (*m z* 325) and, as expected, the *m z* 91 ion (tropylium ion) as the base peak. Surprisingly, the mass spectrum of the compound (**8**) shows a very weak molecular ion peak and is completely dominated by the tropylium ion (*m z* 91).

Dehydrogenation of 6-amino-3-benzyl-4,5-dihydropyrrolo[2,3-*c*]acridine (**7**) (47%) and its 8,9-dimethoxy derivative (**8**) (34%) was carried out by the methodology developed for dihydropyrido[2,3-*c*]acridines. (10 : 1, w/w, ratio of MnO_2 to substrate in refluxing DMF).[2] The structures of the resultant fully aromatic pyrrolo[2,3-*c*]acridines, (**9**) and (**10**), were confirmed by high resolution mass spectroscopy and other spectroscopic analysis. In the ^1H NMR spectra, the absence of signals near δ 3.00 corresponding to the methylene protons in dihydropyrroloacridines, (**7**) and (**8**), and downfield shifting of all the aromatic protons, due to the extended conjugation, are the most indicative features. The appearance of broad singlets, integrating to two protons and corresponding to the NH_2, confirms the amino structures. The IR spectra of these compounds can also be attributed to the amine structures. However, they are, once again, less indicative due to the common region of C=N stretching and NH_2 bending absorption bands. The mass spectrum of the compound (**9**) is simple and is dominated by the tropylium ion (*m z* 91). The mass spectrum of compound (**10**) shows a very intense peak at *m z* 91 and a molecular ion peak as base peak at m/z 383. The fragmentation process (M^+-Me-CO) characteristic of the *ortho*-substituted dimethoxy compounds, can also be observed in the spectrum.

Experimental Section

Melting points (uncorrected) were determined on Gallenkamp melting point apparatus. IR spectra were recorded on a Perkin-Elmer 1600 series FT-IR spectrophotometer. Samples were taken as nujol mulls on sodium chloride plates. ^1H and ^{13}C NMR spectra were obtained on Bruker W360 at 360 and 90 MHz respectively. Coupling constants are reported in hertz and chemical shifts are reported with respect to TMS (δ = 0). Mass spectra were recorded on Fison Instruments VG Plateform II and high-resolution spectra were recorded on VG ZAB-E spectrometer (EPSRC National Mass Spectrometry Service Centre, Swansea, UK). Microanalyses for carbon, nitrogen, and hydrogen were performed on Perkin-Elemer 240 Elemental Analyzer. Thin layer chromatrography was carried out on Merck silica gel $60F_{254}$ plates. Dimethyl sulfoxide was dried over calcium hydride and distilled under reduced pressure. 1,2-Dimethoxyethane (DME) was dried over sodium wire with benzophenone. Toluene was distilled and stored over molecular sieves.

***N*-Benzyl-6,7-dihydroindol-4(5*H*)-one (4)[4].** Dry dimethyl sulfoxide (16.6 mL) was added to sodium hydride (60% w/v in mineral oil; 1.93 g, 40 mmol), under nitrogen, and the mixture was heated at 70 °C for 1 h with continous stirring, then cooled to room temperature. 6,7-Dihydroindol-4(5*H*)-one (**3**) (5.41 g, 40 mmol) in dimethyl sulfoxide (16.6 mL) was added and stirring was continued for 2 h. Benzyl bromide (6.84 g, 4.75 mL, 0.04 mmol) was added and stirring was continued for further 20 h. The reaction mixture was diluted gradually with water (200 mL). The precipitate was filtered, washed with water (100 mL) and dissolved in dichloromethane (100 mL). The resulting solution was washed with water (100 mL), dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was recrystallized from ethyl acetate to give the title compound (**4**) (4.65 g, 52%), m.p. 80-82 °C (lit.[4] 80-81.5 °C). (Found: C, 79.8; H, 6.6; N, 6.05; $C_{15}H_{15}NO$ requires C, 80.0; H, 6.7; N, 6.2%); ν_{max} (Nujol/cm $^{-1}$) 1652 (C=O), 1606 (aromatic) and 1505; ^1H NMR ($CDCl_3$) δ: 2.08-2.14 (2H, quin, *J* = 6.4, 6-*H*) 2.46 (2H, t, *J* = 6.4, 7-*H*), 2.63 (2H, t, *J* = 6.4, 5-*H*), 5.04 (2H, s, PhCH_2), 6.59 (1H, d, *J* = 3.1, 2-*H* or 3-*H*), 6.62 (1H, d, *J* = 3.1, 2-*H* or 3-*H*), 7.06 (2H, d, *J* = 7.8, 2'-*H*, 6'-*H*), 7.26-7.37 (3H, m, 3'-*H*, 4'-*H*, 5'-*H*); ^{13}C NMR ($CDCl_3$) δ: 21.72 (CH_2), 23.63 (CH_2), 37.63 (CH_2), 50.55 (CH_2), 105.65 (CH), 121.23 (quat), 122.91 (CH), 126.5 (2CH), 127.91 (CH), 128.95 (2CH), 136.52 (quat), 143.54 (quat), 194.16 (quat, C=O); *m z* (EI) 226 (M^++1, 14%), 225 (M^+, 53), 197 (57), 169 (22), 168 (27), 106 (30), 91 (100), 78 (20), 65 (65) and 52 (20).

6-Amino-3-benzyl-4,5-dihydropyrrolo[2,3-*c*]acridine (7). A mixture of *N*-benzyl-6,7-dihydroindol-4(5*H*)-one (**4**) (1.125 g, 5 mmol), anthranilonitrile (0.59 g, 5 mmol) and *p*-toluenesulfonic acid (96 mg, 0.5 mmol) in toluene (60 mL) was refluxed for 100 h with azeotropic removal of water. The solvent was evaporated and the residue was suspended in dry DME (60 mL). Sodium amide (0.49 g, 12.5 mmol) and 15-crown-5 (20 drops) were added and the reaction mixture was refluxed under nitrogen for 24 h. The solvent was evaporated under vaccum and the residue was treated with saturated ammonium chloride solution (50 mL). The precipitate was filtered, washed with water (50 mL) and recrystallized from ethanol to give the title compound (**7**) (0.8 g, 49%), m.p. 265-268 °C (decomp.). (Found: M^+, 325.1579; $C_{22}H_{19}N_3$ requires *M*, 325.1579); ν_{max} (Nujol/cm $^{-1}$) 3320 (NH), 3170 (NH), 1655 (C=N), 1627 and 1582 (aromatic); ^1H-NMR (DMSO-d_6) δ: 2.92-2.98 (4H, m, 4-*H* and 5-*H*), 5.23 (2H, s, PhCH_2), 7.05 (1H, d, *J* = 2.9, 1-*H*), 7.13 (1H, d, *J* = 2.9, 2-*H*), 7.19 (2H, m, *J* = 7.1, 2'-*H* and 6'-*H*), 7.28 (1H, t, *J* = 7.1, 4'-*H*), 7.35 (2H, t, *J* = 7.1, 3'-*H* and 5'-*H*), 7.52 (1H, t, *J* = 7.6, 8-*H*), 7.78 (1H, t, *J* = 7.6, 9-*H*), 8.11 (1H, br s, exchangeable with D_2O, N*H*), 8.2 (1H, d, *J* = 8.4, 7-*H* or

10-*H*), 8.4 (1H, d, J = 8.4, 7-*H* or 10-*H*).13.35 (1H, br s, exchangeable with D_2O, N*H*); ^{13}C NMR (DMSO-d_6) δ: 19.23 (CH_2), 21.41 (CH_2), 50.04 (CH_2), 103.32 (quat), 106.08 (CH), 112.18 (quat), 116.14 (quat), 119.5 (CH), 123.57 (CH), 124.46 (CH), 125.46 (CH), 127.56 (2×CH), 128.06 (CH), 129.21 (2×CH), 132.47 (CH), 137.47 (quat), 137.8 (quat), 138.67 (quat), 146.21 (quat), 153.23 (quat); *m z* (EI) 326 (M^++1, 28%), 325 (M^+, 93), 324 (35), 248 (12.5), 234 (29), 232 (12.5), 205 (7), 117 (10), 91 (100), and 65 (25).

6-Amino-3-benzyl-4,5-dihydro-8,9-dimethoxypyrrolo-[2,3-*c*]acridine (8). The title compound (**8**) (0.845 g, 44%) was prepared from *N*-benzyl-6,7-dihydroindol-4(5*H*)-one (**4**) (1.125 g, 5 mmol), and 4,5-dimethoxyanthranilonitrile (0.89 g, 5 mmol) using the above procedure, and recrystallized from methanol, m.p. 230-232 °C. (Found: 385.179, $C_{24}H_{23}N_3O_2$ requires: 385.179); ν_{max} (Nujol/cm $^{-1}$) 3327 (NH), 3184 (NH), 1639 (C=N), 1580 and 1509 (aromatic); ^1H NMR (DMSO-d_6) δ: 2.87-2.92 (4H, m, 4-*H* and 5-*H*), 3.87 (6H, s, 2×OCH_3), 5.19 (2H, s, PhCH_2), 6.99 (1H, d, J = 2.6, 1-*H*), 7.07 (1H, d, J = 2.6, 2-*H*), 7.17 (2H, d, J = 7.5, 2'-*H* and 6'-*H*), 7.26 (1H, t, J = 7.5, 4'-*H*), 7.33 (2H, t, J = 7.5, 3'-*H* and 5'-*H*), 7.67 (1H, s, 7-*H* or 10-*H*), 7.73 (1H, s, 7-*H* or 10-*H*), 7.87 (1H, br s, exchangeable with D_2O, N*H*), 13.14 (1H, br s, exchangeable with D_2O, N*H*); ^{13}C NMR (DMSO-d_6) δ: 19.26 (CH_2), 21.6 (CH_2), 49.97 (CH_2), 56.24 (CH_3), 56.79 (CH_3), 100.13 (CH), 102.18 (quat), 103.51 (CH), 105.67 (CH), 110.02 (quat), 112.27 (quat), 123.95 (CH), 127.52 (2×CH), 127.99 (CH), 129.15 (2×CH), 133.72 (quat), 137.1 (quat), 137.95 (quat), 143.89 (quat), 148.18 (quat), 152.31 (quat), 153.4 (quat); *m z* (EI) 385 (M^+, 0.3%), 294 (1), 165 (1), 135 (1), 91 (100), 77 (5), 65 (15).

6-Amino-3-benzylpyrrolo[2,3-*c*]acridine (9). A mixture of 6-amino-3-benzyl-4,5-dihydropyrrolo[2,3-*c*]acridine (**7**) (0.5 g, 1.54 mmol) and activated MnO_2 (5.0 g) in DMF (150 mL) was heated at reflux, under nitrogen, for 24 h. The reaction mixture was filtered through Celite® and the solvent was evaporated. The residue was recrystallized from ethyl acetate to give the title compound (**9**) (0.24 g, 47%), m.p.163-165 °C (Found: M^-, 323.1450, $C_{22}H_{17}N_3$ requires, M, 323.1423); ν_{max} (Nujol/cm $^{-1}$) 3334 and 3205 (NH_2), 1652 (NH_2 bending), 1633 and 1597 (aromatic); ^1H NMR (DMSO-d_6) δ: 5.5 (2H, s, PhCH_2), 7.16 (1H, d, J = 2.7, 1-*H*), 7.21-7.33 (6H, m, 2'-*H*, 6'-*H*, and 8-*H*), 7.45 (1H, d, J = 2.7, 2-*H*), 7.51 (1H, d, J = 9, 4-*H* or 5-*H*), 7.55 (2H, br s, exchangeable with D_2O, NH_2), 7.61 (1H, m, 9-*H*), 7.85 (1H, d, J = 8.4, 7-*H* or 10-*H*), 8.0 (1H, d, J = 9, 4-*H* or 5-*H*), 8.37 (1H, d, J = 8.4, 7-*H* or 10-*H*); *m z* (EI) 323 (M^+, 3%), 232 (7), 91 (100), 65 (31), and 51 (8).

4,7,46-Amino-3-benzyl-8,9-dimethoxypyrrolo[2,3*c*]-acridine (10). The title compound (**10**) (0.203 g, 34%) was prepared from 6-amino-3-benzyl-8,9-dimethoxy-4,5-dihydropyrrolo[2,3-*c*]acridine (**8**) (0.6 g, 1.56 mmol) by using the above procedure and recrystallized from methanol, m.p. 263-265 °C (decomp.). (Found: M^+, 383.1634. $C_{24}H_{21}N_3O_2$ requires M, 383.1634); ν_{max} (Nujol/cm $^{-1}$) 3341 and 3198 (NH_2), 1650 (NH_2 bending), 1637, and 1606 (aromatic); ^1H NMR (DMSO-d_6) δ: 3.92 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 5.56 (2H, s, PhCH_2), 7.2-7.35 (5H, m, 2'-*H* and 6'-*H*), 7.55 (1H, d, J = 2.8, 1-*H*), 7.64 (1H, d, J = 2.8, 2-*H*), 7.7 (1H, s, 7-*H* or 10-*H*), 7.8 (1H, d, J = 9, 4-*H* or 5-*H*), 7.9 (1H, s, 7-*H* or 10-*H*), 8.16 (1H, d, J = 9, 4-*H* or 5-*H*), 8.95 (2H, br s, exchangeable with D_2O, NH_2); ^{13}C NMR (DMSO-d_6) δ: 49.91 (CH_2), 56.40 (CH_3), 56.75 (CH_3), 100.1 (CH), 102.95 (CH), 103.49 (CH), 105.54 (quat), 106.45 (quat), 110.03 (CH), 116.70 (quat), 117.40 (CH), 127.51 (2×CH), 128.01 (CH), 128.77 (CH), 129.06 (2×CH), 135.74 (quat), 136.97 (quat), 137.38 (quat), 138.2 (quat), 147.45 (quat), 154.25 (quat), 155.38 (quat); *m z* (EI) 384 (M^++1, 29%), 383 (M^-, 100), 368 (18), 340 (6), 292 (19), 249 (8), 91 (90), and 65 (20).

Acknowledgment. We thank the government of Pakistan for C.O.T. Scholarship (to M. A. M) and EPSRC National Mass Spectrometry Service Centre, Swansea, UK, for high resolution mass spectra.

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