Synthesis of *trans*-3-carbamoyl-2-(3-pyridyl)-1,2,5,6-tetrahydro-3*H*-pyrrolo[2,1-*a*]isoquinolinium chloride by condensation of 2-carbamoylmethyl-1-methyl-3,4-dihydroisoquinolinium chloride with nicotinaldehyde

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Condensation of 2-carbamoylmethyl-1-methyl-3,4-dihydroisoquinolinium chloride with nicotinaldehyde in the presence of a catalytic amount of piperidine affords *trans*-3-carbamoyl-2-(3-pyridyl)-1,2,5,6-tetrahydro-3*H*-pyrrolo[2,1-*a*]isoquinolinium chloride.0

Keywords: fused isoquinolines, fused pyrroles, nicotinaldehyde, pyridines

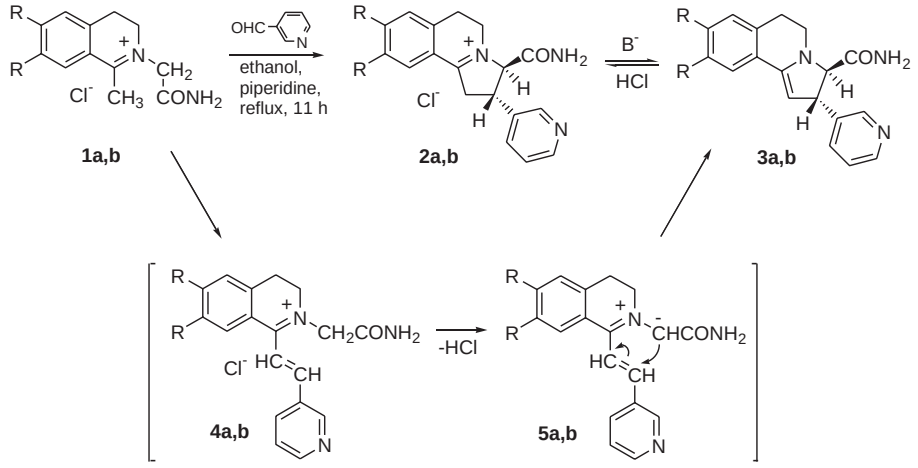
The pyrrolo[2,1-*a*]isoquinoline ring system is present in a variety of natural products and other pharmacologically important compounds. For example, the 5,6-dihydropyrrolo[2,1-*a*]isoquinoline nucleus is closely related to the basic ring system found in the medicinally important lamellarin alkaloids,[1] while 1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline formsts the main skeleton of compounds possessing antidepressant-like activity.[2] A variety of new methods for the synthesis of pyrrolo[2,1-*a*]isoquinoline derivatives have been developed in recent years,[3] including 1,3-cycloaddition of electron deficient dipolarophiles to isoquinolinium-*N*-methylides.[4] Recently, we have shown that 2,3,5,6-tetrahydropyrrolo[2,1-*a*]isoquinoline derivatives can easily be obtained from 10b-styryl-1,5,6,10b-tetrahydroimidazo[2,1-*a*]isoquinolin-2(3*H*)-ones by their rearrangement via azomethine ylide intermediates.[5]

Here we report a novel method for the synthesis of functionalised pyrrolo[2,1-*a*]isoquinoline derivatives employing the condensation of 2-carbamoylmethyl-1-methyl-3,4-dihydroisoquinolinium chlorides with nicotinaldehyde.

The starting salt **1a** (Scheme 1) was obtained by the reaction of 1-methyl-3,4-dihydroisoquinoline with α-chloroacetamide in refluxing acetonitrile[5]. Similar alkylation of 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinole produced the chloride **1b** in 75% yield.

We found that 2-carbamoylmethyl-1-methyl-3,4-dihydroisoquinolinium chloride **1a**, when heated with nicotinaldehyde in ethanol containing a catalytic amount of piperidine, gave *trans*-3-carbamoyl-2-(3-pyridyl)-1,2,5,6-tetrahydro-3*H*-pyrrolo[2,1-*a*]isoquinolinium chloride **2a**. The structure of **2a** was consistent with spectroscopic evidence. A band at 1680 cm^{-1}, assignable to an amide carbonyl group, and bands at 3165 and 3070 cm^{-1}, which correspond to N–H stretching vibrations, are observed in the IR spectrum of **2a**. In the ^{1}H NMR spectrum of **2a**, signals are present which may be assigned to the four protons of the pyrrolinium ring: 3.60 (1H, dd, *J* 19.5, 6.7 Hz, 1-H_a), 3.98 (1H, dd, *J* 19.4, 9.4 Hz, 1-H_b), 4.03–4.22 (1H, m, 2-H) and 5.31 (1H, d, *J* 7.2 Hz, 3-H) ppm. In the ^{13}C NMR spectrum signals of the carbon atoms of the pyrrolinium ring are observed at 43.33 (C-1), 45.20 (C-2), 79.95 (C-3) and 184.12 ppm (C-10*b*).

The relative 2,3-*trans* stereochemistry of **2a** was assigned by the following considerations. From our previous studies of the stereochemistry of 2,3,5,6-tetrahydropyrrolo[2,1-*a*]isoquinoline derivatives by ^{1}H NMR, together with results of MM3 calculations, we concluded that experimental values of the vicinal coupling constants 11.1–11.2 Hz for 2-H and 3-H correspond to their *trans*-orientation.[5] When the salt **2a** was treated with a base, 2,3,5,6-tetrahydropyrrolo[2,1-*a*]-isoquinoline derivative **3a** was formed. In the ^{1}H NMR



1-5a R = H, **b** R = OCH_3

Scheme 1

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spectrum of **3a,** 3-H gives rise to a doublet at 3.62 ppm with $^3J_{2,3}$ = 10.5 Hz due to the vicinal coupling with 2-H. Monte Carlo conformational searches using the MM3 force field followed by energy minimisations gave 151.18° for the dihedral angle H–$C_{(2)}$ –$C_{(3)}$ –H of the optimised structure of **3a**, possessing the relative *trans*-configuration. In this case, the Karplus equation[6] provided the vicinal coupling constant $^3J_{2,3}$ = 10.55 Hz, which is in a good agreement with the experimental data. Analogous searches of **3a** possessing the relative *cis*-configuration gave 25.7° for the dihedral angle H–$C_{(2)}$ –$C_{(3)}$ –H and, correspondingly, 7.9 Hz for $^3J_{2,3}$. We have found that the MM3 force field gives best agreement with experiment in a series of similar heterocyclic systems. Therefore, the compound **3a**, and, correspondingly, the salt **2a** have their 2- and 3-substituents in the relative *trans*-configuration.

Condensation of nicotinaldehyde with 2-carbamoylmethyl-6,7-dimethoxy-1-methyl-3,4-dihydroisoquinolinium chloride **1b** in the presence of piperidine afforded the salt **2b**. The value of 6.9 Hz for $^3J_{2,3}$ found from the ^{1}H NMR spectrum of **2b** is similar to that of **2a** (7.2 Hz); consequently, the relative *trans*-configuration can be assigned for the compound **2b** by analogy to **2a**.

Mechanistically, the present synthesis of pyrrolo[2,1-*a*]isoquinolinium salts may be considered to proceed according to the pathway outlined in Scheme 1. The first step of the reaction involves the formation of 1-azastyrylisoquinolinium chlorides **4a,b**, which after dehydrohalogenation induced by a base afford azomethine ylide intermediates **5a,b**. Intramolecular Michael addition of the ylide carbon atom to the carbon–carbon double bond affords the adducts **3a,b**, that further transform to the final compounds **2a,b**.

In summary, we have demonstrated that base-catalysed condensation of 2-(substituted methylene)-1-methyl-3,4-dihydroisoquinolinium salts with an heteroaromatic aldehyde provides a useful route to the pyrrolo[2,1-*a*]isoquinoline ring system.

Experimental

Melting points were determined in an open capillary on a Kleinfeld melting point apparatus. IR spectra were recorded on a Perkin Elmer Spectrum BXII spectrophotometer (KBr pellets). ^{1}H NMR spectra were recorded at 300 MHz and ^{13}C NMR spectra were recorded at 75 MHz on a Varian Gemini 2000 instrument. Chemical shifts, in ppm, were measured relative to tetramethylsilane (TMS).

The molecular mechanics calculations were performed using the MM3* force fields of the Macromodel program version 6.5, using default parameters.[7] The calculations were carried out on a Silicon Graphics O2 workstation. The Polak-Ribiere conjugate gradient algorithm was applied in all minimizations with 300 iterations limit and a cut-off of 12 Å was used for the non-bonded interactions and energy convergence criterion of 0.05 kJ/mol.

2-Carbamoylmethyl-6,7-dimethoxy-1-methyl-3,4-dihydroisoquinolinium chloride (**1b**): A mixture of 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline (8.21 g, 40 mmol) and α-chloroacetamide (5.61 g, 60 mmol) in acetonitrile (10 ml) was heated to reflux for 5h. The reaction mixture was left for 18 h at room temperature. The crystalline solid that separated was filtered off and recrystallised from ethanol to give 8.96 g (75 %) of the title compound, m.p. 237–238 °C. IR (KBr): 3230 (N–H), 3100 (N–H), 1690 cm^{-1} (C=O). ^{1}H NMR spectrum (CF_3COOD): 2.49 (3H, s, 1-CH_3), 2.80–2.95 (2H, m, 4-H_2), 3.63–3.78 (2H, m, 3-H_2), 3.66 (3H, s, OCH_3), 3.70 (3H, s, OCH_3), 4.71 (2H, m, CH_2CO), 6.64 (1H, s, CH), 7.13 ppm (1H, s, CH). ^{13}C NMR spectrum (CF_3COOD): 21.0 (CH_3), 28.5 (C-4), 55.6 (C-3), 58.95 (OCH_3), 59.1 (OCH_3), 60.9 (*C*H_2CO), 113.7 (CH), 116.4 (CH), 122.7 (C), 138.5 (C), 151.5 (C), 160.7 (C), 172.3 (C=O), 181.5 ppm (C-1). Calcd. for $C_{14}H_{19}ClN_2O_3$: C, 56.28; H, 6.41; N, 9.38. Found: C, 56.43; H, 6.61; N, 9.47 %.

(2R,3S*)-3-Carbamoyl-2-(3-pyridyl)-1,2,5,6-tetrahydro-3H-pyrrolo[2,1-a]isoquinolinium chloride* (*trans*-**2a**): A mixture of **1a** (1.60 g, 6.7 mmol), nicotinaldehyde (0.79 g, 7.4 mmol) and three drops of piperidine was heated to reflux in ethanol (15 ml) for 11 h. After reducing the solvent in volume to 5 ml, the solution was kept at 3 °C for 24 h. The precipitated crystals were collected by suction filtration and recrystallised from ethanol to afford **2a** (0.70 g, 32%); m.p. 236–237 °C. IR (KBr): 3165 (N–H), 3070 (N–H), 1680 cm^{-1} (C=O). ^{1}H NMR spectrum (CF_3COOD): 2.91–3.07 (2H, m, 6-H_2), 3.60 (1H, dd, *J* 19.5, 6.7 Hz, 1-H_a), 3.56–3.80 (2H, m, 5-H_2), 3.98 (1H, dd, *J* 19.4, 9.4 Hz, 1-H_b), 4.03–4.22 (1H, m, 2-H), 5.31 (1H, d, *J* 7.2 Hz, 3-H), 7.05–8.85 ppm (8H, m, Ar–H). ^{13}C NMR spectrum (CF_3COOD): 28.0 (C-6), 43.3 (C-1), 45.2 (C-2), 48.5 (C-5), 79.95 (C-3), 124.5, 131.15, 131.7, 131.9, 134.5, 140.2, 141.5, 143.0, 144.15, 144.4, 150.5 (11C-Ar), 172.5 (C=O), 184.1 ppm (C-10*b*). Calcd. for $C_{18}H_{18}ClN_3O$: C, 65.95; H, 5.53; N, 12.82; Cl, 10.82. Found: C, 66.00; H, 5.69; N, 13.08; Cl, 10.73 %.

(2R,3S*)-3-Carbamoyl-8,9-dimethoxy-2-(3-pyridyl)-1,2,5,6-tetrahydro-3H-pyrrolo[2,1-a]isoquinolinium chloride* (*trans*-**2b**): The reaction of **1b** (2.00 g, 6.7 mmol) and nicotinaldehyde (0.79 g, 7.4 mmol) was carried out according to the procedure described for the compound **2a** and gave 1.12 g (43%) of the title compound **2b**; m.p. 242–243 °C (ethanol). IR (KBr): 3230 (N–H), 3080 (N–H), 1695 cm^{-1} (C=O). ^{1}H NMR spectrum (CF_3COOD): 2.89–2.99 (2H, m, 6-H_2), 3.45–3.71 (3H, m, 1-H, 5-H_2), 3.54 (3H, s, OCH_3), 3.64 (3H, s, OCH_3), 3.93 (1H, dd, *J* 19.5, 9.4 Hz, 1-H), 4.11–4.19 (1H, m, 2-H), 5.21 (1H, d, *J* 6.9 Hz, 3-H), 6.63–8.84 ppm (6H, m, Ar-H). ^{13}C NMR spectrum (CF_3COOD): 28.6 (C-6), 43.4 (C-1), 45.6 (C-2), 48.1 (C-5), 59.0 (OCH_3), 59.0 (OCH_3), 79.5 (C-3), 114.3, 116.3 (C-10, C-7), 117.6 (C), 131.4 (CH), 138.9 (C), 142.0 (C), 144.4 (CH), 144.55 (CH), 150.6 (CH), 151.8 (C), 162.8 (C), 173.2 (C=O), 181.7 ppm (C-10*b*). Calcd. for $C_{20}H_{22}ClN_3O_3$: C, 61.93; H, 5.72; N, 10.83; Cl, 9.14. Found: C, 61.86; H, 5.84; N, 10.79; Cl, 9.14 %.

(2R,3S*)-2-(3-pyridyl)-2,3,5,6-tetrahydropyrrolo[2,1-a] isoquinoline-3-carboxamide* (*trans*-**3**): To a solution of chloride **2a** (0.50 g, 1.5 mmol) in ice-cooled water (10 ml) was added saturated sodium carbonate solution until pH 9 was attained. The aqueous solution was extracted with ether (3 × 10 ml), and the combined organic extracts were washed with water and dried over magnesium sulfate. The solvent was removed at reduced pressure and the residue was crystallised from ethanol to afford the title compound **3** (0.35 g, 78%); m.p. 155–157 °C. IR (KBr): 3420 (N–H), 3150 (N–H), 1675 cm^{-1} (C=O). ^{1}H NMR ($CDCl_3$): 2.91–2.96 (2H, m, 6-H_2), 3.23–3.37 (2H, m, 5-H_2), 3.62 (1H, d, *J* 10.5 Hz, 3-H), 4.26 (1H, d, *J* 10.5 Hz, 2-H), 5.34 (1H, s, 1-H), 5.90 (1H, br. s, NH), 6.96 (1H, br. s, NH), 7.23–8.64 ppm (8H, m, Ar–H). ^{13}C NMR ($CDCl_3$): 29.9 (C-6), 48.2 (C-2), 51.7 (C-5), 77.2 (C-3), 99.6 (C-1), 123.4 (CH), 125.0 (CH), 126.5 (CH), 127.1 (C), 128.6 (CH), 128.7 (CH), 133.4 (C), 135.7 (CH), 139.0 (C), 146.5 (C), 148.5 (CH), 149.7 (CH), 174.8 ppm (C=O). Calcd. for $C_{18}H_{17}N_3O$: C, 74.20; H, 5.88; N, 14.42. Found: C, 74.03; H, 5.59; N, 14.10 %.

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