

Unexpected results in the Friedländer reaction of 4-aryl-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-[1]benzopyran-3-carbonitriles

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In the Friedländer reaction of 4-aryl-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-[1]benzopyran-3-carbonitriles (**1**, **2**), we have detected and isolated the unexpected imidates **5** and **6**, respectively, in addition to the expected tetracyclic tacrine-like derivatives.

Keywords: enamionitriles, chromenes, Friedländer reaction, imidates, Pinner reaction, tacrine analogues

During the past two decades, cholinesterase inhibition has become the most widely studied and effective clinical approaches to treat Alzheimer's disease.¹ In this context, and taking into account that increased levels of intracellular Ca²⁺ ions seem to play a crucial role in neuronal degeneration and death,² in our laboratories we have synthesised and evaluated a number of compounds of types **A** and **B** (Fig. 1), which combine the tetraaminoquinoline moiety of the acetylcholinesterase inhibitor tacrine with a pyridine or a 4H-pyran bearing a substitution pattern similar to that of the related or isosteric calcium channel blockers 1,4-dihydropyridines.³

Continuing with this project, now we have now directed our attention to related molecules of type **C** (Fig. 1), that could be synthesised by a simple Friedländer reaction⁴ from readily available 4-aryl-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-[1]benzopyran-3-carbonitriles.⁵ In this paper, we describe the unexpected isolation and characterisation of imidates (**3a,b**) in the reaction of precursors **1a**⁶ and **1b**⁷ leading to the tetracyclic tacrine-like derivatives **2a** and **2b**, respectively (Scheme 1).

As expected, intermediates **1** on treatment with cyclohexanone, in the presence of aluminium trichloride as promoter, in 1,2-dichloroethane as solvent, at reflux, afforded the target molecules **2a,b**, in 53 and 69% yield respectively. These products gave satisfactory analytical and spectroscopic data, in good agreement with their structures (see Experimental). However, in the reaction of 4H-pyran **1a**, a detailed analysis of the crude reaction mixture allowed us to detect and isolate, in low yield (29%) a new compound to which structure **3a** was assigned (Scheme 1). The mass spectrometry as well as the elemental analysis clearly suggested the presence of a product with C₂₄H₂₇N₃O₅ as molecular formula, while the IR spectrum showed strong broad bands at 3434–3181 cm⁻¹ due to NH (and/or OH) absorptions; in addition, we could observe four strong sharp bands at 1680 (C=O), 1653, 1634 (C=C) and 1530 (C=C) cm⁻¹, attributable to unsaturated carbonyl and aromatic groups. In the ¹H NMR

spectrum, in addition to the expected signals for the aromatic ring, the singlet for H-5 (4.61 ppm), an AB system for H-7 (two doublets at 2.28/2.10 ppm, with a vicinal coupling constant of 16.1 Hz) and the two methyls in the cyclohexane ring (1.03 and 0.92 ppm) also present in compound **2a**, new signals for two NH (and/or OH) groups at 7.50 and 7.15 ppm are present, as well as four groups of signals for six methylenes (CH₂) between 2.55 and 1.05 ppm; this means that, besides a methylene group for 2 H₇/2 H₉, the structure for compound **3a** accounts for five methylene groups that we have found in the ¹³C NMR spectrum at 36.8, 36.4, 24.9, 21.4 and 21.0 ppm, being the signals at 50.3 and 40.2 ppm assigned to C-7 and C-9, respectively. All these assignments were confirmed by HMQC analysis. Analogously, the HMBC experiment allowed us to assign the signals at 81.8, 165.3 and 114.6 ppm to C-4a, C-9a and C-5a, respectively. Only two signals remained to be located in the whole structure: two quaternary carbons at 154.3 and 67.4 ppm, the cross peak in the HMBC experiment between the singlet for H-5 at 4.61 ppm and the signal at 154.3 suggesting a close spatial location between the corresponding carbons. All these data led us to propose as a preliminary structural hypothesis the imidate **3a** (Scheme 1), which is supported by the current spectroscopic values described in literature for this functional group.

Under the same experimental conditions, compound **1b** gave, in addition to the expected Friedländer product **2b**, the imidate **3b** in 22% yield (Scheme 1). This compound showed similar spectroscopic data as described above for the analogous imidate **3a**, and its analytical and mass spectrometry experiment confirmed this proposal.

The formation of these imidates (**3**) was totally unexpected. In fact, this is the first time that we have isolated³ such a type of molecules in the Friedländer reaction.⁴ Similarly, we are not aware of this type of reactivity in related substrates.⁹

In Scheme 2 we propose a simple mechanism for the formation of compounds **3**. As shown, the presumed intermediate **D** preferentially eliminates water to give

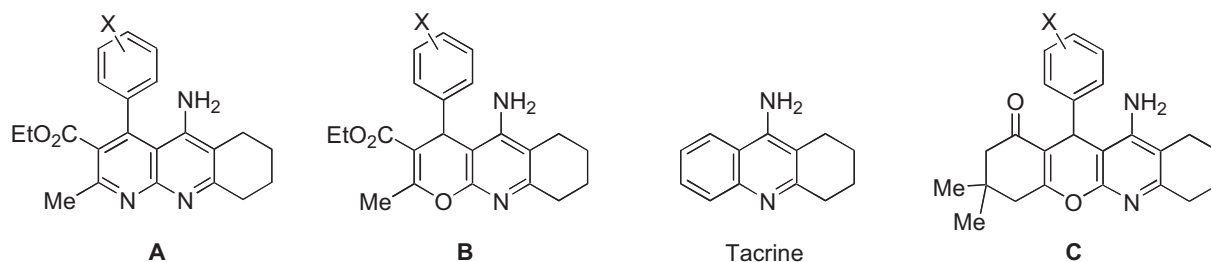
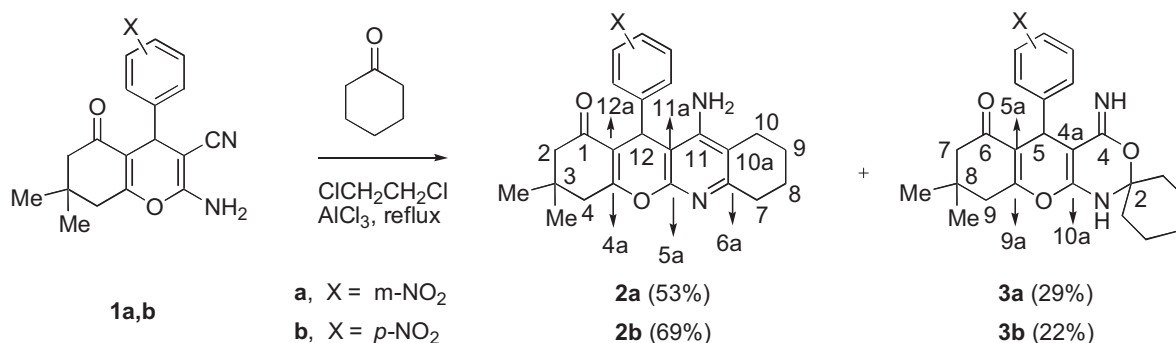


Fig. 1

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Scheme 1

an imine/enamine **E** that leads to the major products the [1]benzopyrano[2,3-*b*]quinolines **2**, but the hydroxyl group in intermediate **D** could also attack the nitrile moiety as in the Pinner reaction¹⁰ to afford the imidates **3**.

The intriguing possibility that these imidates might be the true intermediates in the reaction of β -enaminonitriles and/or *o*-aminobenzonitriles with a carbonyl compound containing a reactive α -methylene group, remains to be investigated, as well as the generality of this protocol for the synthesis of cyclic imidates. These issues are being investigated in our laboratory, and will be reported in due course.

Experimental

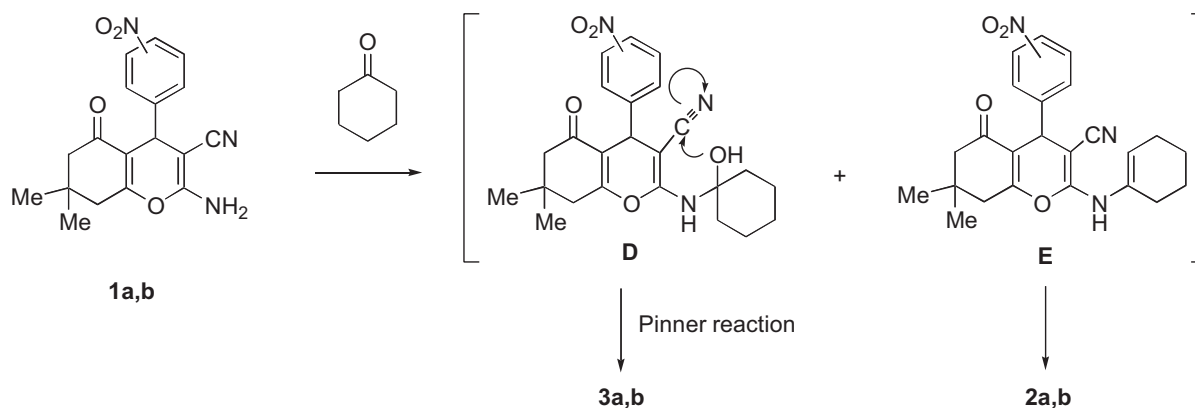
Reactions were monitored by TLC using precoated silica gel aluminium plates containing a fluorescent indicator (Merck, 5539). Detection was done by UV (254 nm) followed by charring with sulfuric-acetic acid spray, 1% aqueous potassium permanganate or 0.5% phosphomolybdic acid in 95% EtOH. Anhydrous Na₂SO₄ was used to dry organic solutions during work-up and the removal of solvents was carried out under vacuum with a rotary evaporator. Flash column chromatography was performed using silica gel 60 (230–400 mesh, Merck). Melting points were determined on a Kofler block. IR spectra were obtained on a Perkin-Elmer Spectrum One spectrophotometer. ¹H NMR spectra were recorded with a Varian VXR-200S spectrometer, using tetramethylsilane as internal standard and ¹³C NMR spectra were recorded with a Bruker WP-200-SY. Chemical shifts are in δ (p.p.m.; values with * can be interchanged). All the assignments for protons and carbons were in agreement with 2D COSY, gHSQC, gHMBC, and 1D NOESY spectra. Elemental analyses were conducted on a Carlo Erba EA 1108 apparatus.

General method for the Friedländer reaction

Aluminium chloride (1.2–1.7 equiv) was suspended in dry 1,2-dichloroethane (10 ml) at RT under argon. The corresponding 4*H*-benzopyran (1 equiv) and cyclohexanone (1.2–1.7 equiv) were added. The reaction mixture was heated under reflux (10–24 h). Then, a mixture of THF/H₂O (1: 1) was added at RT. Aqueous sodium hydroxide (10%) was added dropwise to the mixture until the aqueous layer was basic. After stirring for 30 min, the mixture was

extracted three times with dichloromethane. The organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and the solvent was evaporated. The resultant solid was separated and purified by silica gel flash chromatography.

Friedländer reaction of compound 1a: Following general method above, from compound **1a** (250 mg, 0.74 mmol), AlCl₃ (146.3 mg, 1.1 mmol), ClCH₂CH₂Cl (5 ml), cyclohexanone (108.7 mg, 1.11 mmol), after 7 h, products **2a** (167.2 mg, 53%) and **3a** (95 mg, 29%) were obtained. **11-Amino-2,3,4,7,8,9,10,12-octahydro-3,3-dimethyl-12-(3-nitrophenyl)-1*H*-[1]benzopyrano[2,3-*b*]quinolin-1-one (3):** m.p. 293°C; IR (KBr) ν_{max} 3428, 3246, 2934, 2869, 1637, 1528, 1371, 1205 cm⁻¹; ¹H NMR (DMSO, 300 MHz) δ 8.35 (s, 1 H, H2'), 7.96 (d, *J* = 7.9 Hz, 1 H, H4'), 7.64 (d, *J* = 7.9 Hz, 1 H, H6'), 7.49 (t, *J* = 7.9 Hz, 1 H, H5'), 5.82 (s, 2 H, NH₂), 5.19 (s, 1 H, H12), 2.71–2.48 (m, 4 H, 2 H4, 2 H7), 2.30 (m, 1 H, H10A), 2.15 (m, 1 H, H10B), 2.30 (d, *J* = 16 Hz, 1 H, H2A), 2.05 (d, *J* = 16.1 Hz, 1 H, H2B), 1.66 (br s, 4 H, 2 H9, 2 H8), 1.03 [s, 3 H, CH₃(C3)], 0.85 [s, 3 H, CH₃(C3)]; ¹³C NMR (DMSO, 75 MHz) δ 195.6 (C1), 165.3 (C4a), 153.6 (C5a), 152.6 (C1'), 151.5 (C11), 147.1 (C6a), 146.4 (C3'), 134.4 (C6'), 129.5 (C5'), 122.9 (C2'), 121.3 (C4'), 113.3 (C10a), 112.7 (C12a), 97.9 (C11a), 49.9 (C2), 40.4 (C4), 32.5 (C12), 31.9 (2 C, C3, C7), 28.6 [CH₃(C3)], 26.2 [CH₃(C3)], 22.9 (C10), 22.1 (C9)*, 21.9 (C8)*; MS (APCI +) *m/z*: [M + 1]⁺ 420.3; [M + Na]⁺ 442.2; [2M + Na]⁺ 861.5. Found: C, 68.96; H, 6.22; N, 9.94. Calcd. for C₂₄H₂₅N₃O₄ (419.47): C, 68.72; H, 6.01; N, 10.02%. **4-Imino-8,8-dimethyl-5-(3-nitrophenyl)-5,7,8,9-tetrahydro-1*H*-spiro[[1]benzopyrano[2,3-*d*][1,3]oxazine-2,1'-cyclohexan]-6(4*H*)-one (3a):** m.p. 273–275°C; IR (KBr) ν_{max} 3434, 3326, 3181, 3036, 2928, 2869, 1680, 1653, 1634, 1530, 1372, 1349, 1204 cm⁻¹; ¹H NMR (DMSO, 300 MHz) δ 7.97 (m, 2 H, H2', H4'), 7.62 (d, *J* = 7.9 Hz, 1 H, H6'), 7.53 (t, *J* = 7.9 Hz, 1 H, H5'), 7.50 (br s, 1 H NH), 7.15 (s, 1 H, NH), 4.61 (s, 1 H, H5), 2.55 (br s, 2 H, 2 H9), 2.28 (d, *J* = 16.1 Hz, 1 H, H7A), 2.10 (d, *J* = 16.1 Hz, 1 H, H7B), 1.69–1.58 (m, 4 H), 1.39–1.32 (m, 4 H), 1.30–1.05 (m, 2 H) [10 H, (CH₂)₅], 1.03 [s, 3 H, CH₃(C8)], 0.92 [s, 3 H, CH₃(C8)]; ¹³C NMR (DMSO, 75 MHz) δ 196.6 (C6), 165.3 (C10a), 163.8 (C9a), 154.3 (C4, C=NH), 148.7 (C1'), 147.7 (C3'), 134.8 (C6'), 129.8 (C5'), 122.5 (C2'), 121.3 (C4'), 114.6 (C5a), 81.8 (C4a), 67.4 [OC(2)NH], 50.3 (C7), 40.2 (C9), 36.8, 36.4, 24.9, 21.4, 21.0 [5 C, O-(CH₂)₅C(2)-NH], 32.1 (2 C, C8, C5), 28.8 [CH₃(C3)], 26.9 [CH₃(C3)]; EM (APIES +) *m/z*: [M + 1]⁺ 438.3; [M + Na]⁺ 460.3; [2M + 1]⁺ 875.5; [2M + Na]⁺ 897.6. Found: C, 63.68; H, 5.90;



Scheme 2

N, 9.24. Calcd. for $C_{24}H_{27}N_3O_5$ (437.49) + H_2O : C, 63.28; H, 6.42; N, 9.22%.

Friedländer reaction of compound 1b: Following the general method, from compound **1b** (250 mg, 0.74 mmol), $AlCl_3$ (146.03 mg, 0.11 mmol), $ClCH_2CH_2Cl$ (5 ml), cyclohexanone (108.78 mg, 1.11 mmol), after 5 h, products **2b** (215 mg, 69%) and **3b** (72 mg, 22%) were obtained. **11-Amino-2,3,4,7,8,9,10,12-octahydro-3,3-dimethyl-12-(4-nitrophenyl)-1H-[1]benzopyrano[2,3-b]quinolin-1-one (2b):** m.p. 323–325 °C; IR (KBr) ν_{max} 3390, 3227, 2936, 2869, 1639, 1604, 1568, 1517, 1371, 1345, 1227, 1206 cm^{-1} ; 1H NMR (DMSO, 300 MHz) δ 7.87 (d, J = 8.6 Hz, 2 H, $H3'$, $H5'$), 7.35 (d, J = 8.6 Hz, 2 H, $H2'$, $H6'$), 5.53 (s, 2 H, NH_2), 4.95 (s, 1 H, $H12$), 2.42–2.30 (m, 4 H, 2 $H4$, 2 $H7$), 2.07 (m, 1 H, $H10A$), 1.92 (m, 1 H, $H10B$), 2.07 (d, J = 16 Hz, 1 H, $H2A$), 1.83 (d, J = 16.1 Hz, 1 H, $H2A$), 1.44 (br s, 4 H, 2 $H9$, 2 $H8$), 0.81 [s, 3 H, $CH_3(C3)$], 0.63 [s, 3 H, $CH_3(C3)$]; ^{13}C NMR (DMSO, 75 MHz) δ 195.5 (C1), 165.3 (C4a), 153.7 (C5a)*, 152.6 (C1')*, 151.8 (C11)***, 151.5 (C6a)***, 145.8 (C4'), 129.3 (2 C, C2', C6'), 123.0 (2 C, C3', C5'), 113.4 (C10a), 112.5 (C12a), 97.8 (C11a), 49.9 (C2), 40.3 (C4), 32.8 (C12), 31.9 (C3), 31.8 (C7), 28.6 [$CH_3-(C3)$], 26.4 [$CH_3(C3)$], 22.9 (C10), 22.1 (C9), 21.9 (C8); MS (APCI +) m/z : $[M + 1]^+$ 420.3. Found: C, 68.58; H, 6.12; N, 10.10. Calcd. for $C_{24}H_{25}N_3O_4$ (419.47): C, 68.72; H, 6.01; N, 10.02%. **4-Imino-8,8-dimethyl-5-(4-nitrophenyl)-5,7,8,9-tetrahydro-1H-spiro[[1]benzopyrano[2,3-d][1,3]oxazine-2,1'-cyclohexan]-6(4H)-one (3b):** M.p. 269–271 °C; IR (KBr) ν_{max} 3389, 3202, 2956, 1683, 1667, 1622, 1602, 1520, 1369, 1344, 1205 cm^{-1} ; 1H NMR (DMSO, 300 MHz) δ 8.05 (d, J = 8.7 Hz, 2 H, $H3'$, $H5'$), 7.51 (s, 1 H, NH), 7.41 (d, J = 8.7 Hz, 2 H, $H2'$, $H6'$), 7.14 (s, 1 H, NH), 4.59 (s, 1 H, $H5$), 2.53 (br s, 2 H, 2 $H9$), 2.26 (d, J = 16.1 Hz, 1 H, $H7A$), 2.07 (d, J = 16.1 Hz, 1 H, $H7B$), 1.69–1.58 (m, 4 H), 1.39–1.32 (m, 4 H), 1.30–1.05 (m, 2 H) [10 H, $NH(CH_2)_5O$], 1.03 [s, 3 H, $CH_3(C3)$], 0.92 [s, 3 H, $CH_3(C3)$]; ^{13}C NMR (DMSO, 75 MHz) δ 196.5 (C6), 165.3 (C10a), 163.7 (C9a), 154.2 [2 C, C4', C4 (C=NH)], 145.9 (C1'), 129.3 (2 C, C2', C6'), 123.5 (2 C, C3', C5'), 114.2 (C5a), 81.7 (C4a), 67.3 [OC(2)NH], 50.3 (C7), 40.4 (C9), 36.6, 36.5, 25.0, 21.4, 21.0 [5 C, -O(CH $_2$) $_5$ C(2)N-], 32.5 (C8), 32.1 (C5), 28.8 [$CH_3-(C3)$], 27.0 [$CH_3(C3)$]; MS (APIES +) m/z : $[M + 1]^+$ 438.3; $[M + Na]^+$ 460.2; $[2M + 1]^+$ 875.5; $[2M + Na]^+$ 897.5. Found: C, 65.68; H, 5.88; N, 9.36. Calcd. for $C_{24}H_{27}N_3O_5$ (437.49): C, 65.89; H, 6.22; N, 9.60%.

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