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A New Approach to the Synthesis of Functionally-substituted Pyrido[2,3-*d*]indoles

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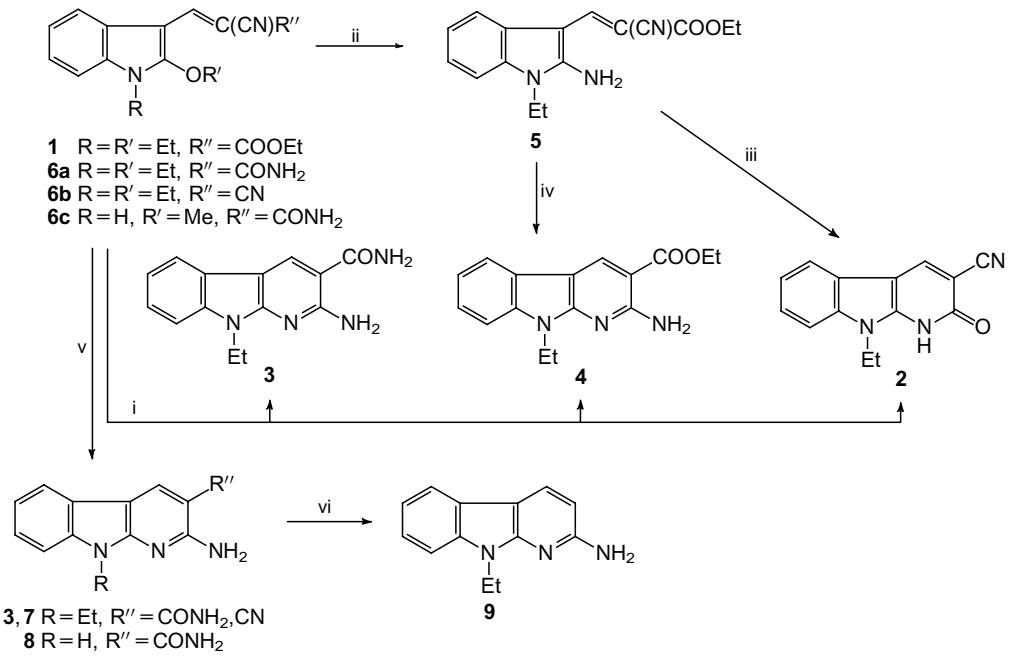
A new approach to the synthesis of 2-oxo- and 2-amino- 3-cyano-(carbamoyl or ethoxycarbonyl)pyrido[2,3-*b*]indole (α-carboline) derivatives based on the cyclization of 2-amino-(alkoxy)-3-(β-cyano-β-ethoxycarbonyl)- or 3-(β-cyano-β-carbamoyl)vinylindole derivatives under different conditions has been developed.

Pyrido[2,3-*b*] indoles (α-carbolines) are a little-studied class of carboline derivatives, and only a limited number of publications have been devoted to the synthesis of α-carbolines possessing 2,3 functional groups.[1–7] Some have been found to possess antiviral, antitumour and psychotropic activity.[2,3,7] The goal of the present investigation is the elaboration of a versatile synthesis for functionally-substituted α-carboline derivatives. Recently we published an article describing the synthesis of 2-alkoxy-3-(β-cyano-β-alkoxycarbonyl)vinylindoles based on the condensation of oxindole derivatives with amide acetals followed by *O*-alkylation of 3-(dimethylamino)methylene indoles by Me_2SO_4 or $Et_3O^+BF_4^-$ and reaction with cyanoacetic esters.[8] It would seem reasonable for a 2-alkoxy group of these compounds to be exchanged for an amino group (due to activation by electronegative substituents at position 3 of the indole molecule) followed by cyclization to α-carbolines. Heating (100 °C) of 1-ethyl-2-ethoxy-3-(β-cyano-β-ethoxycarbonyl)vinylindole **1** with a solution of NH_3 in EtOH results in a mixture of α-carbolin-2-one **2**,† yield 42%, m.p. 307–309 °C (MeCN),‡ 2-amino-3-



Scheme 1 *Reagents and conditions*: i, **1** + 14% solution of NH_3 in EtOH, bomb, 100 °C, 4.5 h; ii, **1** + 14% solution of NH_3 in EtOH, 20 °C, 3 h; iii, AcOH, reflux for 10.5 h; iv, DMF, catalytic amount of *p*-TsOH, reflux for 6 h; v, saturated solution of NH_3 in EtOH, bomb, 115–120 °C, 6 h; vi, 48% solution of HBr, 120 °C, 6.5 h, addition of NaOH.

† All new compounds gave the expected IR, ^{1}H NMR and mass spectra and satisfactory elemental analyses.

carbamoyl- and 2-amino-3-ethoxycarbonyl-1-ethyl-α-carbolines **3** and **4**, respectively, which were identified (TLC, mass spectra) by comparison with pure samples obtained under other conditions (see below). A more unambiguous α-carboline synthesis is realized by initial transformation of **1** to 2-amino derivatives **5**,§ yield 85%, m.p. 167–170 °C (EtOH), which gives **2** in 70% yield on heating in AcOH. On the contrary, refluxing a solution of **5** in DMF in the presence of TsOH as catalyst leads to cyclization with participation of the cyano group and formation of 2-amino derivative **4**,¶ yield 55%, m.p. 176–178 °C (MeCN). For information about a similar cyclisation at position 2 of the pyrrole ring in a different series of compounds, see ref. 8.

Amide **3*** is obtained by the interaction of 1-ethyl-2-ethoxy-3-(β-cyano-β-carbamoyl)vinylindole **6a**[9] with NH_3, yield 78%, m.p. 273–276 °C (Pr^iOH). Analogously, α-carbolines **7** and **8** are synthesized from the corresponding alkoxyindoles **6b**,**c**:[9] **7**,† yield 100%, m.p. 201–202 °C (MeCN), **8**‡ (isolated as the hydrochloride), yield 58%, m.p. 276–279 °C (MeOH).

A study of **7** has shown that it can be easily transformed to **9**§ by means of hydrolysis of the cyano group and subsequent decarboxylation (heating of **7** in 46% aqueous HBr), yield 97%, m.p. 145–148 °C (EtOH–H_2O, 1:1), followed by the addition of 2 M NaOH. Thus, a versatile method for the synthesis of 2,3- (or 2-) functionally-substituted α-carbolines from oxindole derivatives has been developed.

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‡ Spectral data for **2**: MS *m*/*z* 237 (M^+); ^1H NMR ([$^2H_7$]DMF): δ 1.41 (t, 3H, CH_2CH_3), 4.46 (q, 2H, CH_2CH_3), 3.50 (br.s, NH-2-pyridone and water of solvent), 7.31 (1H, m), 7.49 (1H, m), 7.68 (1H, d) and 8.14 (1H, d) (arom. protons), 8.85 (s, 1H, C_4H).

§ For **5**: IR: ν/cm^{-1} 3250, 3360 (NH_2), 2220 (CN), 1670 (CO).

¶ For **4**: IR: ν/cm^{-1} 3350, 3460 (NH_2), 1680 (CO); MS *m*/*z* 283 (M^+); ^1H NMR ([$^2H_6$]DMSO): δ 1.31 (t, 3H, NCH_2CH_3), 4.33 (q, 2H, NCH_2CH_3), 1.36 (t, 3H, OCH_2CH_3), 4.32 (q, 2H, OCH_2CH_3), 7.18 (t, 1H), 7.35 (t, 1H), 7.50 (d, 1H) and 8.00 (d, 1H) (arom. protons), 7.25 (br. signal, 2H, NH_2), 8.77 (s, 1H, 4-CH).

* Spectral data for **3**: IR: ν/cm^{-1} 3200, 3300, 3420 (NH_2), 1620 (CO); MS *m*/*z* 254 ($M^{+\cdot}$); ^1H NMR ([$^2H_7$]DMF): δ 1.36 (3H, t, CH_2CH_3), 4.38 (2H, q, CH_2CH_3), 7.69 (2H, br.s, $CONH_2$), 7.20 (1H, t), 7.35 (1H, t), 7.53 (1H, d), 7.84 (1H, d) (arom. protons), 8.89 (1H, s, 4-CH), 7.50 (strong broad signal, NH_2).

† For **7**: IR: ν/cm^{-1} 3220, 3320, 3405, 3460 (NH_2), 2200 (CN); MS *m*/*z* 236 ($M^{+\cdot}$); ^1H NMR ([$^2H_7$]DMF): δ 1.37 (3H, t, CH_2CH_3), 4.39 (2H, q, CH_2CH_3), 6.94 (2H, br.s, NH_2), 7.27 (1H, m), 7.41 (1H, m), 7.57 (1H, d), 8.04 (1H, d) (arom. protons), 8.62 (1H, s, 4-CH).

‡ For **8**: IR: ν/cm^{-1} 3160, 3330 (NH, NH_2), 1670 (CO); MS *m*/*z* 226 ($M^{+\cdot}$); ^1H NMR ([$^2H_7$]DMF): δ 7.31 (1H, t), 7.43 (1H, t), 7.62 (1H, d), 7.95 (1H, d) (arom. protons), 8.40 (broad signal of $CONH_2$ and NH_2 protons), 9.37 (1H, s, C_4H), 13.04 (1H, br.s, NH^+).

§ For **9**: MS *m*/*z* 211 ($M^{+\cdot}$); ^1H NMR ([$^2H_6$]DMSO): δ 1.28 (t, 3H, CH_2CH_3), 4.32 (q, 2H, CH_2CH_3), 6.19 (br.s, 2H, NH_2), 6.33 (d, 1H, 3-CH), 8.04 (d, 1H, 4-CH), 7.10 (t, 1H), 7.24 (t, 1H), 7.44 (d, 1H) and 7.83 (d, 1H) (arom. protons).

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