
A New Approach to the Synthesis of 1,2- and 1,4-Dihydropyrido[3,2-*b*]indole Derivatives

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Intramolecular cyclization of α -cyano- β -(3-*p*-nitrophenylaminoindol-2-yl)acrylonitrile yields 1-*p*-nitrophenyl-2-imino-3-cyano-1,2-dihydropyrido[3,2-*b*]indole **7**, methylation of which by methyl iodide in acetone in the presence of potassium carbonate is accompanied by the addition of acetyl anion and formation of 1-*p*-nitrophenyl-2-dimethylamino-3-cyano-4-acetyl-1,4-dihydropyrido[3,2-*b*]indole **9**.

It is known that among the δ -carboline derivatives some compounds with antitumour¹ and antibacterial² activity have been found. On the other hand, much of the literature is devoted to the high biological activity of 1,4-dihydropyridine derivatives.^{3,4}

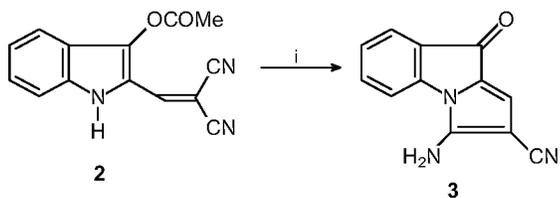
The present paper is aimed at the elaboration of a new approach to δ -carbolines, including those incorporating a 1,4-dihydropyridine fragment into their structure. As the starting compound we have chosen *N*-acetyl-3-*p*-nitrophenylaminoindole **1**.⁵ The nitrile of α -cyano- β -(3-acetoxyindol-2-yl)acrylic acid **2**⁶ is used as a model system for producing (by the method in ref. 7) 2-cyano-3-imino-9-

oxopyrrolo[1,2-*a*]indole **3**,[†] m.p. 325°C (DMF), yield 50% (Scheme 1).

Cyclization at the indole NH group is evidenced by the presence of primary NH₂ group signals in the ¹H NMR and IR spectra of this compound.[‡]

[†]All new compounds gave the expected IR, ¹H NMR and mass spectra and satisfactory elemental analyses.

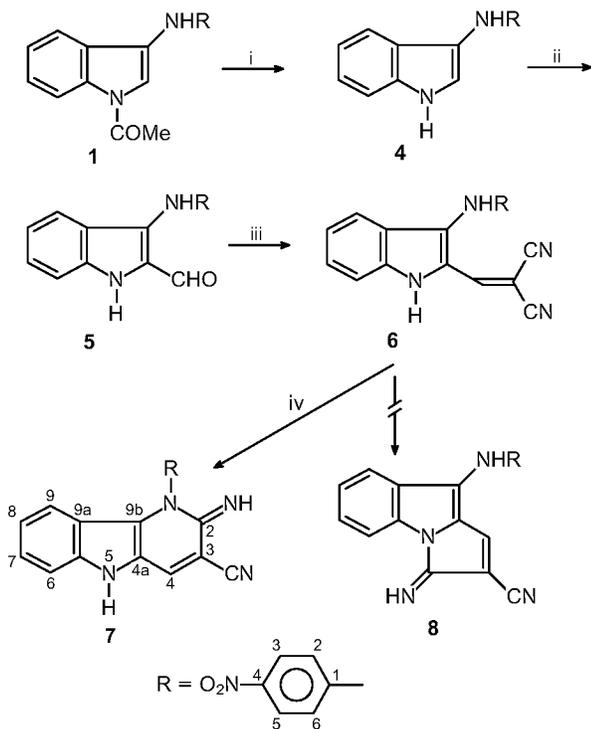
[‡]Spectroscopic data for **3**: IR, ν/cm^{-1} : 3320, 3200, 2210, 1650, 1610. ¹H NMR (²H₆]DMSO), δ : 7.23 (1H, s, CH), 7.73 (2H, br.s, NH₂), 7.27–7.94 (4H, m, arom. protons). MS m/z 209 (M⁺).



Scheme 1 Reagents and conditions: i, Et₃N, MeOH, reflux, 5 h.

Compound **1** is deacylated by action of Et₃N in methanol with the formation of 3-*p*-nitrophenylaminoindole **4**, yield 80%, m.p. 220–222 °C (MeOH), IR ν/cm^{-1} : 3350, 1590; MS m/z 253 (M⁺). Formylation of the latter by treatment with Vilsmeier reagent gives rise to 2-formyl derivative **5**, yield 96%, m.p. 237–238 °C (DMF–H₂O, 2:1); IR ν/cm^{-1} : 3290, 1640, 1600, 1575; ¹H NMR ([²H₆]DMSO), δ : 9.88 (1H, s, CHO), 11.85, 9.41 (2H, 2s, NH, NHC₆H₄NO₂), 7.48 (4H, A₂B₂ system, C₆H₄NO₂), 6.95–7.59 (4H, m, arom. protons); MS m/z 281 (M⁺). Condensation of aldehyde **5** with the dinitrile of malonic acid (both in the presence of Et₃N at 20 °C or without Et₃N but under reflux) leads to dinitrile **6**, yield 80% and 71%, respectively; a distinct m.p. is absent, m.p. >270 °C (dioxane); IR, ν/cm^{-1} : 3390, 3290, 2210, 1570; ¹H NMR ([²H₆]DMSO), δ : 8.19 (1H, s, CH), 11.17, 9.68 (2H, 2s, NH, NHC₆H₄NO₂), 7.52 (4H, A₂B₂ system, C₆H₄NO₂), 7.11, 7.67 (4H, m, arom. protons); MS m/z 329 (M⁺). Cyclization of dinitrile **6** can occur in either of two directions: with participation of *endo* (indole) or *exo* (at position 3) cyclic NH groups.

Heating of **6** in DMF–MeOH (1:1) gives rise to intramolecular cyclization with formation of **7**, yield 60%, m.p. 280 °C (decomp., DMF–MeOH, 1:1), isolated as the semi-hydrate (Scheme 2).

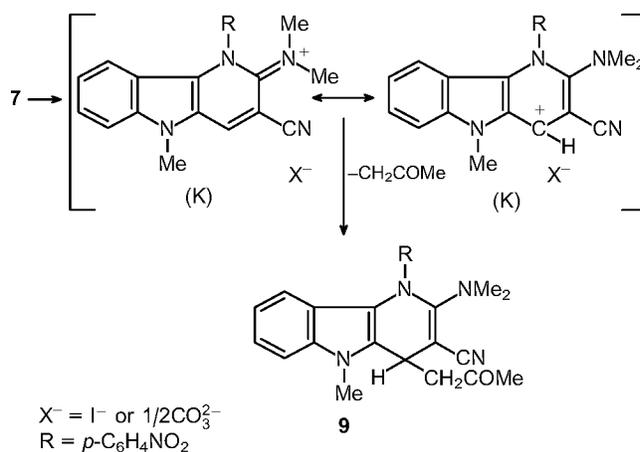


Scheme 2 Reagents and conditions: i, Et₃N, MeOH, reflux, 2 h; ii, POCl₃–DMF, 5–10 °C, 0.25 h, addition of solution of **3** in DMF, standing of the mixture (20 °C, 18 h); iii, PrⁱOH, CH₂(CN)₂, reflux, 5 h or PrⁱOH, CH₂(CN)₂, Et₃N, 5 h, 20 °C; iv, DMF–MeOH, 1:1, reflux, 0.25 h.

A comparison of the ¹H NMR spectra of **3** and **7** (for a description of the spectra of **3**, see above) allows us to draw conclusions about the direction of **6** → **7** cyclization with participation of the basic 3-NH group.

The structure of **7** as a 1,2-dihydro- δ -carboline derivative (not that of pyrrolo[1,2-*a*]indole derivative **8**) is established by ¹H NMR and ¹³C NMR spectroscopy. The ¹H NMR spectrum of **7** ([²H₆]DMSO) displays signals: 6.14 (1H, br.s, NH-imine), 5.91 (1H, d, *J* 9 Hz, H-C₉), 6.74 (1H, t), 7.23 (1H, t) and 7.42 (1H, d, *J* 9 Hz) (8,7,6 benzene ring protons), 8.20 (4H, A₂B₂ system, C₆H₄NO₂), 8.25 (1H, s, H-C₄). The signal due to indole NH is absent. The characteristic peculiarity of the spectrum of this compound is the significant shift of the 9-H signal to lower field (5.91 as compared with 7.27–7.94 for aromatic protons in **3** and the rest of the aromatic proton signals in **7**). Such a displacement is caused exclusively by the screening influence of the anisotropy of the ring currents of the 1-*p*-nitrophenyl substituent turned from the plane of the tricycle molecule (from Dreiding molecular models).[§]

An interesting and unexpected result is obtained upon methylation of **7**. Reaction of **7** with methyl iodide in acetone in the presence of anhydrous K₂CO₃ with the addition of acetyl anion to the 4 position of the molecule takes place together with tris-alkylation. As a result, 1-*p*-nitrophenyl-2-dimethylamino-3-cyano-4-acetyl-5-methyl-1,4-dihydropyrido[3,2-*b*]indole **9** is obtained, yield 75%, m.p. 198–199 °C (MeOH–dioxane, 3:1)[¶]. Scheme 3 is likely for the formation of **9**.



Scheme 3 Reagents and conditions: i, MeI, acetone, anhydrous K₂CO₃, reflux 56–60 h, MeI added to the reaction mixture every 7–8 h.

In other words, first tris-methylation takes place with formation of a cation (K) and then the acetyl anion (formed in the reaction mixture in the presence of K₂CO₃) attacks the electron-deficient position 4 of (K) to yield **9**. It is important to note that in the ¹H NMR spectrum of **9** (as distinct from **7**) a lower-field shift of the 9-H signal is not observed. It is known that the 1,4-dihydropyridine ring is not a flat system, and some data show that this ring has a boat conformation.^{8,9} Construction of molecular models for **9**, taking into account these data, shows that in this instance the *p*-nitrophenyl ring cannot influence the shape due to the above-mentioned anisotropic effect (as for **7**) and so the

[§] Spectroscopic data for **7**: IR ν/cm^{-1} : 3320, 2200, 1620, 1600, 1580. ¹³C NMR ([²H₆]DMSO) δ : 154.9 (C₂), 99.8 (C₃), 133.9 (C₄), 119.8 (C_{4a}), 114.5 (C_{9b}), 139.9 (C_{3a}), 128.8 (C_{9a}), 113.1, 119.9, 126.2, 127.1 (C₆₋₉), 119.9, 131.1 (C_{2,3,5,6}), 148.1, 144.1 (C_{1,4}), 117.7 (CN). MS m/z 329 (M⁺).

[¶] Spectroscopic data for **9**: IR ν/cm^{-1} : 1720, 2190. ¹H NMR ([²H₆]DMSO) δ : 3.75 (3H, s, NMe-indole), 2.90 (6H, br.s, NMe₂), 2.10 (3H, s, CH₂COMe), 2.69 (2H, AB system, *J*_{hem} 17 Hz, *J*_{vic}¹ 9 Hz, *J*_{vic}² 5 Hz, CH₂COMe), 4.21 (1H, q, H-C₄), 7.89 (4H, A₂B₂ system, C₆H₄NO₂), 7.08–7.53 (4H, m, arom. protons). MS m/z 429 (M⁺), 372 (M⁺ – CH₂COMe).

signals for all the protons in the condensed benzene ring are within the same range (7.08–7.53).

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