Available online at www.sciencedirect.com
ScienceDirect
Mendeleev Commun., 1995, **5**(**3**), 107–109

Mendeleev
Communications

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

Svetlana Yu. Ryabova, Lyudmila M. Alekseeva and Vladimir G. Granik*

Centre for Medicinal Chemistry, All-Russian Research Chemical-Pharmaceutical Institute, 119815 Moscow, Russian Federation. Fax: +7 095 246 7805

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 acetonyl anion and formation of 1-*p*-nitrophenyl-2-dimethylamino-3-cyano-4-acetonyl-1,4-dihydropyrido[3,2-*b*]indole **9**.

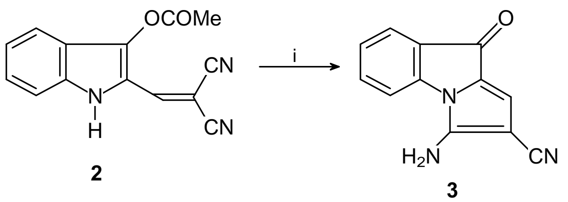
It is known that among the δ-carboline derivatives some compounds with antitumour[1] and antibacterial[2] activity have been found. On the other hand, much of the literature is devoted to the high biological activity of 1,4-dihydropyridine derivatives.[3,4]

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 NH_2 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.

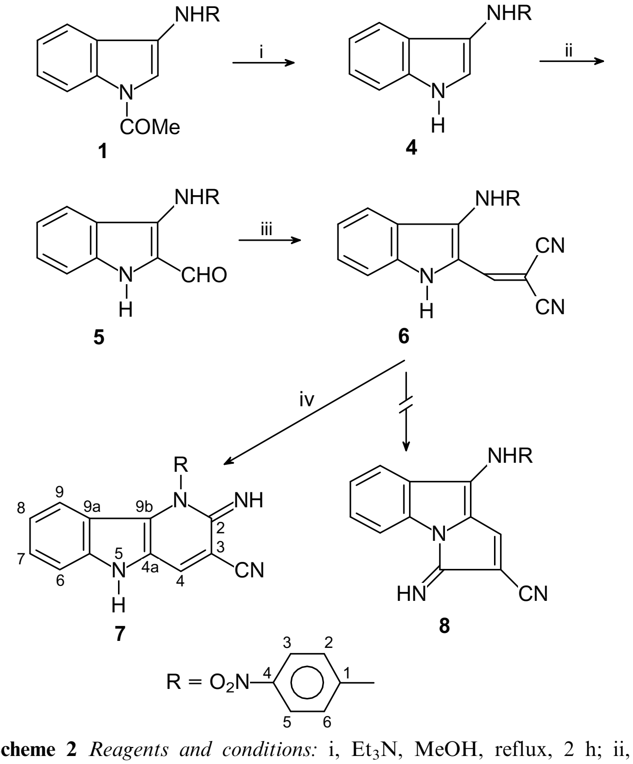
[‡] *Spectroscopic data for* **3**: IR, ν/cm^{-1}: 3320, 3200, 2210, 1650, 1610. ^1H NMR ([$^2H_6$]DMSO), δ: 7.23 (1H, s, CH), 7.73 (2H, br.s, NH_2), 7.27–7.94 (4H, m, arom. protons). MS *m*/*z* 209 (M^+).



Scheme 1 *Reagents and conditions:* i, Et_3N, MeOH, reflux, 5 h.

Compound **1** is deacylated by action of Et_3N 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–H_2O, 2:1); IR ν/cm^{-1}: 3290, 1640, 1600, 1575; ^{1}H NMR ([$^2H_6$]DMSO), δ: 9.88 (1H, s, CHO), 11.85, 9.41 (2H, 2s, NH, $NHC_6H_4NO_2$), 7.48 (4H, A_2B_2 system, $C_6H_4NO_2$), 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 Et_3N at 20 °C or without Et_3N 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; ^{1}H NMR ([$^2H_6$]DMSO), δ: 8.19 (1H, s, CH), 11.17, 9.68 (2H, 2s, NH, $NHC_6H_4NO_2$), 7.52 (4H, A_2B_2 system, $C_6H_4NO_2$), 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 semihydrate (Scheme 2).

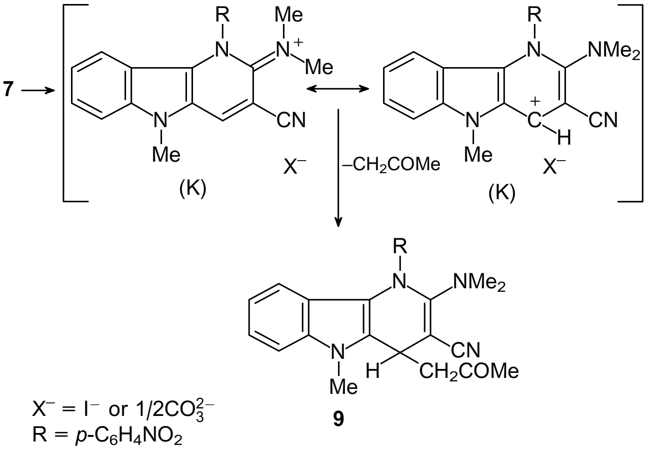


Scheme 2 *Reagents and conditions:* i, Et_3N, MeOH, reflux, 2 h; ii, $POCl_3$–DMF, 5–10 °C, 0.25 h, addition of solution of **3** in DMF, standing of the mixture (20 °C, 18 h); iii, Pr^{i}OH, $CH_2(CN)_2$, reflux, 5 h or Pr^{i}OH, $CH_2(CN)_2$, Et_3N, 5 h, 20 °C; iv, DMF–MeOH, 1:1, reflux, 0.25 h.

A comparison of the ^{1}H 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 ^{1}H NMR and ^{13}C NMR spectroscopy. The ^{1}H NMR spectrum of **7** ([$^2H_6$]DMSO) displays signals: 6.14 (1H, br.s, NH-imine), 5.91 (1H, d, *J* 9 Hz, H-C_9), 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, A_2B_2 system, $C_6H_4NO_2$), 8.25 (1H, s, H-C_4). 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 K_2CO_3 with the addition of acetonyl 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-acetonyl-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 K_2CO_3, 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 acetonyl anion (formed in the reaction mixture in the presence of K_2CO_3) attacks the electron-deficient position 4 of (K) to yield **9**. It is important to note that in the ^{1}H 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. ^{13}C NMR ([$^2H_6$]DMSO) δ: 154.9 (C_2), 99.8 (C_3), 133.9 (C_4), 119.8 (C_{4a}), 114.5 (C_{9b}), 139.9 (C_{5a}), 128.8 (C_{9a}), 113.1, 119.9, 126.2, 127.1 (C_{6-9}), 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. ^{1}H NMR ([$^2H_6$]DMSO) δ: 3.75 (3H, s, NMe-indole), 2.90 (6H, br.s, NMe_2), 2.10 (3H, s, CH_2COMe), 2.69 (2H, AB system, J_{hem} 17 Hz, J^1_{vic} 9 Hz, J^2_{vic} 5 Hz, CH_2COMe), 4.21 (1H, q, H-C_4), 7.89 (4H, A_2B_2 system, $C_6H_4NO_2$), 7.08–7.53 (4H, m, arom. protons). MS *m*/*z* 429 (M^+), 372 (M^+ – CH_2COMe).

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

The research described in this publication was made possible in part by grant no. N 37000 from the International Science Foundation.

References

1 N. N. Suvorov, V. A. Chernov, V. S. Velezheva, Yu. A. Ershova, S. V. Simakov and V. P. Sevodin, *Khim.-Farm. Zh.*, 1981, **9**, 27 (in Russian).

2 Sh. Minami, Sh. Yamade, H. Sakurai and T. Hirose, *Japan Kokai*, 76, 136, 698 (Cl C07D 471/04) (*Chem. Abstr.*, 1977, **87**, 5937s).

3 A. Sausins and G. Duburs, *Heterocycles*, 1988, **27**, 269.

4 A. E. Sausins and G. Ya. Duburs, *Khim. Geterotsikl. Soedin.*, 1992, **4**, 435 [*Chem. Heterocycl. Compd. (Engl. Transl.)*, 1992, **4**, 363].

5 V. S. Velezheva, V. I. Gunar, M. V. Balyakina and N. N. Suvorov, *Khim. Geterotsikl. Soedin.*, 1978, **7**, 939 [*Chem. Heterocycl. Compd. (Engl. Transl.)*, 1978, **7**, 757].

6 S. Yu. Ryabova, Yu. I. Trofimkin, L. M. Alekseeva, L. S. Khabarova and V. G. Granik, *Khim. Geterotsikl. Soedin.*, 1991, **3**, 343 [*Chem. Heterocycl. Compd. (Engl. Transl.)*, 1991, **3**, 278].

7 S. Yu. Ryabova, L. M. Alekseeva and V. G. Granik, *Khim. Geterotsikl. Soedin.*, 1991, **9**, 1199 [*Chem. Heterocycl. Compd. (Engl. Transl.)*, 1991, **9**, 960].

8 V. H. Quast, K.-H. Roß, E. Spiegel, K. Peters and H. G. von Schnering, *Angew. Chem.*, 1977, **B89**, 202.

9 A. F. Mishnev, A. E. Shvec, Ya. Ya. Bleidelis, G. Ya. Duburs, A. E. Sausins and V. K. Lusis, *Khim. Geterotsikl. Soedin.*, 1977, **9**, 1229 [*Chem. Heterocycl. Compd. (Engl. Transl.)*, 1977, **9**, 991].

Received: Moscow, 26th December 1994
Cambridge, 28th February 1995; Com. 5/00038F