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The Synthesis of a New Heterocyclic System: Pyrido[3′,2′: 4,5]pyrrolo[1,2–*a*]indole

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The first representative of a new heterocyclic system, 2-amino-3-cyano-5*H*-4,5-dihydropyrido[3′,2′:4,5]pyrrolo[1,2–*a*]indole-4,11-dione **5**, has been synthesized based on successive reactions of 2-piperidinomethylene-2*H*-pyrrolo[1,2-*a*]indole-3,9-dione **1** with ethyl cyanoacetate, dimethyl sulfate and ammonia.

Recently we reported on the synthesis of previously inaccessible tricyclic enaminodicarbonyl derivatives,[1] in particular, 2-piperidinomethylene-2*H*-pyrrolo[1,2–*a*]indole-3,9-dione **1**, and have investigated transamination reactions of this compound. Among enamines of this series compounds with cardiotonic activity have been found.[2] We have been further prompted to investigate the reactions of **1** with active methylene compounds and to examine the possibility of the construction of new heterocycles based on this reaction. So, in the present study, the reaction of **1** with ethyl cyanoacetate was carried out. The process proceeded smoothly with formation of the piperidine salt of the ethyl ester of α-cyano-β-{3-hydroxy-9-oxopyrrolo[1,2-*a*]indol-2-yl}acrylic acid **2**,[†,§] yield 95%, m.p. 200–201 °C (**2** was purified by dissolving in acetone followed by addition of ether). The methylation of **2** with Me_2SO_4 proceeds on the oxygen atom at

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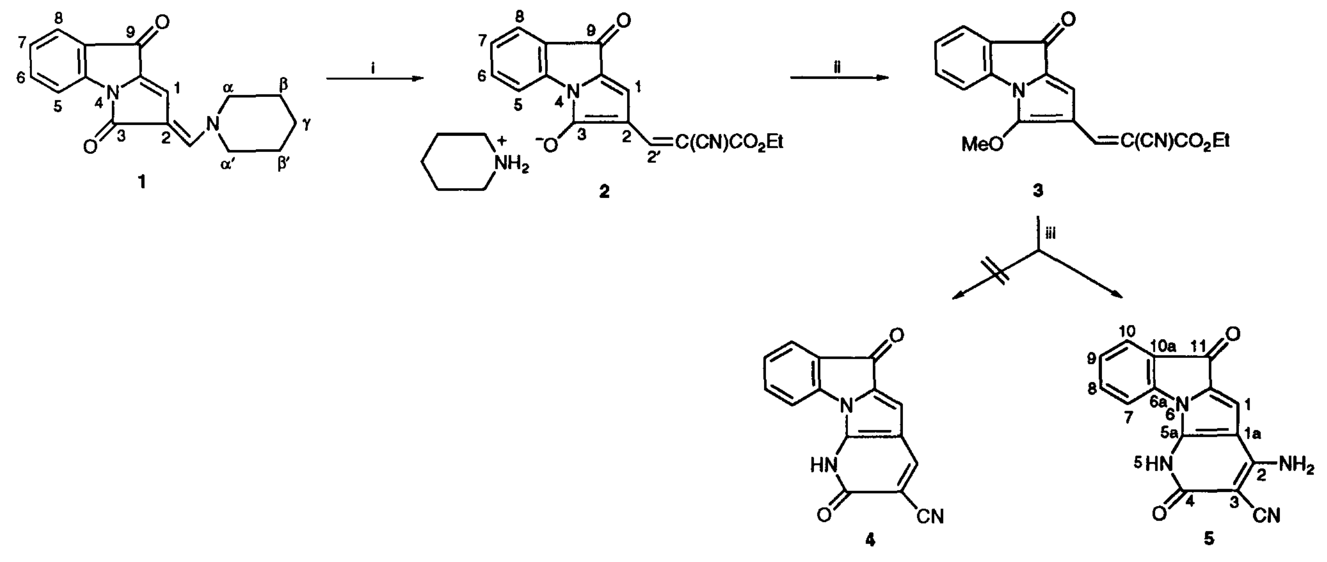
[†] Spectroscopic data for **2**: IR ν/cm^{-1} 2200, 1690, 1630, 1620; ^{1}H NMR ($CDCl_3$) δ 1.27 (tr., 3H,CH_2CH_3), 4.08 (qu., 2H,CH_2CH_3), 1.77 (m., 2H,γ–CH_2), 2.05 (m., 4H,β,β^1–CH_2), 3.41 (tr., 4H,α,α^1–CH_2), 6.94, 7.30–7.50 (m., 4H,arom.protons), 7.50, 7.54 (two s. on 1H,1–CH and 2^1–CH), 9.16 (br. s., 2H,$^+NH_2$); MS *m/z* 308 ($M^{+\cdot}$).

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

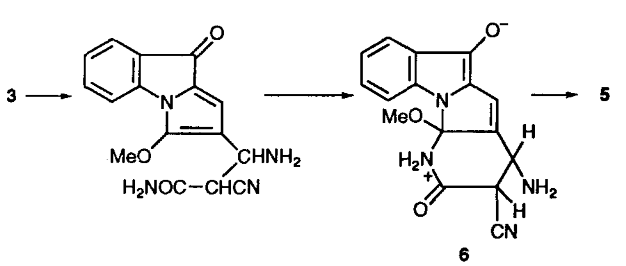


Scheme 1 *Reagents and conditions*: i, NCCH$_2$COOEt, Et$_3$N, DMF, 20 °C, 24 h; ii, Me$_2$SO$_4$, MeOH, b.p., 10 h; iii, 14% sol. NH$_3$ in MeOH, autoclave, 90–100 °C, 5 h.

position 3 of the tricycle and 3-methoxy derivative **3**[‡] is obtained, yield 47%, m.p. 204–206 °C (benzene). Nucleophilic substitution of the 3-methoxy group in compound **3** is facilitated due to the electron-attracting 2-ethoxycarbonylcyanovinyl- and 9-carbonyl- groups. Owing to this an attempt has been made to build up the pyridine cycle by heating **3** with ammonia. In this case, cyclization with participation of the ethoxycarbonyl group and the C$_3$-atom of the tricycle to form tetracyclic derivative **4** was supposed to be possible. But, unexpectedly, addition of ammonia to the vinyl fragment took place. The subsequent cyclization resulted in 2-amino-3-cyano-5*H*-4,5-dihydropyrido[3′,2′: 4,5]pyrrolo[1,2–*a*]indole-4,11-dione **5**,[¶] yield 27%, m.p. > 300 °C (DMF), Scheme 1.

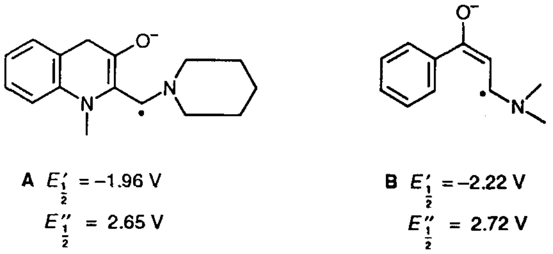
The data obtained give no grounds on which to make a conclusion about the relative rate of processes taking place on treatment of **3** with ammonia. Hence, it is impossible to establish the sequence of stages by which **5** is formed and to estimate which reaction (the change of OMe to NH$_2$, amide formation or addition of NH$_3$ to the double bond) is the first to take place.

One of the alternative schemes for the formation of **5** is given in Scheme 2. Aromatization at the last stage (**6**→**5**), probably due to a disproportionation reaction, occurs besides MeOH cleavage.



Scheme 2

Evidently, either during the formation of **5** according to Scheme 2, or under the initial change of OMe to NH$_2$ group, there is an obligatory desaromatization of the pyrrole ring with the formation of compounds such as **6**. The loss of energy in this case is probably compensated by the formation of an aromatic indole ring. An investigation of the electrochemical reduction of enamines is in favour of this conclusion.[3] In fact, a significant facilitation of the electrochemical reduction of enaminoketones of the indole series in comparison with acyclic enaminoketones is explained by the stabilization of anion-radicals **A** due to aromatization of a similar kind.



In conclusion, it should be noted that **5** is the first representative of a new heterocyclic system, pyrido[3′,2′: 4,5]pyrrolo[1,2–*a*]indole. Up to now only one paper on the synthesis of compounds of this type has been published, namely on the synthesis of isomeric system derivatives, pyrido[2′,3′: 4,5]pyrrolo[1,2–*a*]indole.[4]

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[‡] For **3**: IR ν/cm^{-1} 2200, 1700, 1600; ^{1}H NMR (CDCl$_3$) δ 1.39 (tr., 3H,CH$_2$*CH$_3$*), 4.37 (qu., 2H,*CH$_2$*CH$_3$), 4.23 (s., 3H,OMe), 7.15–7.70 (m., 4H,arom.protons), 8.16 (s., 1H, 1–CH) and 8.42 (s., 1H,2^1–CH); MS *m*/*z* 322 (M$^{+\cdot}$).

[¶] Spectroscopic data for **5**: IR ν/cm^{-1} 3500, 3420, 3300, 3160, 2200, 1690, 1660, 1630; ^{1}H NMR ([^{2}H$_6$]Me$_2$SO) δ 6.97 (br. s, 2H,NH$_2$), 7.20–7.94 (m., 4H,arom.protons), 8.17 (s., 1H,1–CH), 12.40 (br.s, 1H,NH); ^{13}C NMR ([^{2}H$_6$]Me$_2$SO) δ 139.9 (d, 1–C), 86.3 (s, 1a–C), 157.3 (s, 2–C), 109.2 (t, 3–C), 119.9 (s, CN), 137.4 (s, 4–C), 147.2 (d, 5a–C), 134.1 (m, 6a–C), 113.3, 122.6, 123.9, 130.8 (d, 7,8,9,10–C), 126.9 (m, 10a–C), 161.2 (d, 11–C), 112.4 (s, 11a–C); MS *m*/*z* 276 (M$^{+\cdot}$).