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Practical Syntheses of Hexahydroazepino[4,5-*b*]- and Hexahydroazocino[4,5-*b*]indoles

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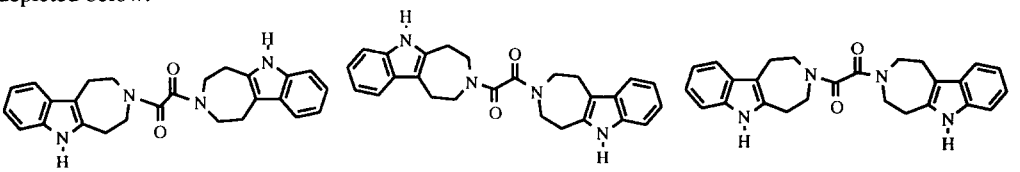
Abstract: *Catalytic hydrogenation (Pd•C) of 2-(2-benzylaminoethyl)-3-cyanomethyl indoles gave hexahydroazepino[4,5-b]indoles in good yields. 2-(2-Benzylaminoethyl)-3 cyanoethyl indoles were cyclized to hexahydroazocino[4,5-b]indoles under identical conditions.*

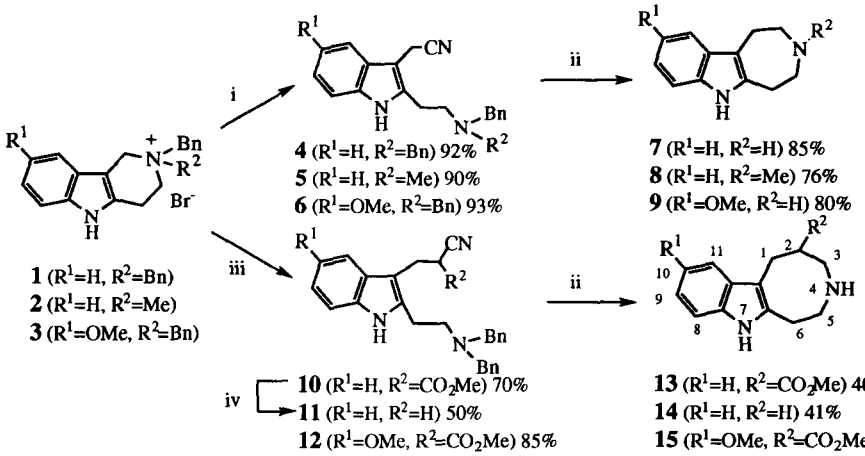
During a study aimed at the synthesis of macrocyclic bis-indole derivatives, 2-(2-dibenzylaminoethyl)-3-cyanomethylindole **4** (scheme) was submitted to catalytic hydrogenation (Pd•C[1], AcOH) and further acylated with oxalyl chloride without isolation of the expected bis-2,3-(2-aminoethyl)indole[2]. The MS of the product that was isolated in 54 % yield, ($M^{+\cdot}$= 426), the occurence of three spots on tlc and NMR spectra showing three interconvertible conformers (1:2:1) strongly suggested the bis(hexahydroazepino[4,5-*b*]indolyl)oxalamide structure, in the form of the three possible conformers depicted below.



Characterisation[3] of the hydrogenation product of **4** as hexahydroazepino[4,5-*b*]indole **7**[4] rapidly confirmed the deduction. Catalytic hydrogenation had thus performed in a fairly good yield hydrogenolysis of the two benzyl groups, reduction of the nitrile to the imine oxidation level, intramolecular attack of the protonated imine by the free amino group, elimination of ammonia, and final hydrogenation of the resulting imine. Formation of C-N bonds during catalytic hydrogenation of aminonitriles is well precedented[5], although it had not been shown until now that the relative rates of reduction of the nitrile *vs* N-benzyl hydrogenolysis are compatible with the process.

Extension of the reaction to azepinoindoles **8**, **9**, and to azocinoindoles **13**-**15**[6] was straighforward (scheme). The starting materials were obtained through the application[7] of gramine chemistry to the readily obtainable[7,8] tetrahydro-γ-carbolinium salts **1**-**3**: treatment with KCN gave the 3-cyanomethylindoles **4**-**6**; compounds **10** and **12** resulted from treatment with methyl cyanoacetate; compound **11** was obtained from **10** under the conditions described by Krapcho[9].

The yields ranged around 80% in the azepino- and around 40% in the azocino- series. No example of such hexahydroazocino[4,5-*b*]indoles could be found in literature. The lower yield in this last series, which illustrates the more difficult formation of eight-membered cycles, is balanced by the ready access to these original compounds with potential pharmacochemical developments.



Reagents: i, THF-H_2O (7:1), KCN, 3eq, reflux 2h; ii, H_2,Pd•C,AcOH, 48 h; iii, $NCCH_2CO_2Me$, NaH, THF; iv, LiCl, H_2O, DMF.

Scheme

Although numerous elaborate methods for the construction of annelated nitrogenous heterocycles are on hand nowadays, a more frequent use of the formation of C-N bonds through reduction of aminonitriles should be of interest in the obtention of various heterocyclic systems. Intramolecular cyclizations in the course of catalytic hydrogenation of nitriles were otherwise applied in this Laboratory to the synthesis of tetrahydro-β-carbolines[10].

References and Notes

1. Purchased from Aldrich, batch nr 66966-024.
2. This compound was obtained from **4** through stepwise LAH reduction and further hydrogenolysis.
3. All compounds were characterized by their MS, IR,UV, ^1H and ^{13}C NMR spectra.
   A reference sample of **7** was prepared by unambiguous synthesis from **4**: i, methanolysis to the ester (92%); ii; hydrogenolysis to the free amine (75%); iii, lactamisation (LiOH, 75%); iv, LAH reduction (64%); overall yield = 33%.
4. Hester, J. B.; Tang, A. H.; Keasling, H. H.; Veldkamp, W. *J. Med. Chem.* **1968**, *11*, 101-106.
5. Rylander, P. *Catalytic Hydrogenation in Organic Syntheses*; Academic Press: New York, 1979; pp. 138-152 and references cited therein.
6. Selected data: **13** MS: 258 ($M^{+\cdot}$, 72), 216 (47), 184 (92), 169 (44), 156 (25), 144 (100); HRMS calcd for $C_{15}H_{18}N_2O_2$: 258.1364 found: 258.1368; UV (MeOH, nm) 291, 282, 225; IR (KBr, film, cm^{-1}), 3393, 2949, 1724, 1452; ^1H NMR δ(300 MHz, $CDCl_3$) 2.53 (dd, J=4.5, 15.7 Hz, 1H), 2.63 (s, NH, 1H), 2.7-2.96 (m, 4H), 3.1 (m, 2H), 3.22 (d, J=6.7 Hz, 2H), 3.7 (s, CO_2Me, 3H), 7.1 (m, 2H), 7.28 (dd, J=9, 2.2 Hz, 1H), 7.49 (dd, J=9, 2.2 Hz, 1H), 8.17 (s, NH, 1H); ^{13}C NMR δ(75 MHz, $CDCl_3$) 22.7, 29.6, 46.9, 48.4, 50.5, 51.7, 109.2, 110.6, 117.7, 119.2, 121.0, 128.2, 135.0, 135.3, 175.5.
   14 MS: 200 ($M^{+\cdot}$, 95), 171 (28), 158 (62), 144 (100); HRMS calcd for $C_{13}H_{16}N_2$: 200.1310 found: 200.1313; UV (MeOH, nm) 290, 282, 223; IR (KBr, film, cm^{-1}) 3400, 2930, 1464; ^1H NMR δ(300 MHz, $CDCl_3$) 1.6 (s, NH, 1H), 1.8 (m, 2H), 2.7 (t, J=6.7 Hz, 2H), 2.83 (t, J=6.7 Hz, 2H), 2.88-3.0 (m, 4H), 7.1 (m, 2H), 7.23 (dd, J=9, 2.2 Hz, 1H), 7.5 (dd, J=9, 2.2 Hz, 1H), 7.98 (s, NH, 1H); ^{13}C NMR δ(75 MHz, $CDCl_3$) 20.9, 29.3, 31.7, 47.8, 49.8, 110.4, 112.3, 117.6, 119.0, 120.8, 128.3, 133.9, 135.0.
   15 MS: 289 (M+1, 79), 247 (48), 214 (84), 174 (100), 167 (68), 158 (39); HRMS calcd for $C_{16}H_{20}N_2O_3$: 288.1463 found: 288.1473; UV (MeOH, nm) 290, 288, 220; IR (KBr, film, cm^{-1}) 3390, 2950, 1726, 1454; ^1H NMR δ($CDCl_3$, 300 MHz) 2.59 (dd, J=4.5, 15.7 Hz, 1H), 2.7-2.93 (m, 5H), 3.08-3.2 (m, 4H), 3.7 (s, CO_2Me, 3H), 3.86 (s, OMe, 3H), 6.77 (dd, J=2.5, 9 Hz, 1H), 6.93 (d, J= 2.5 Hz, 1H), 7.15 (d, J=9 Hz, 1H), 8.16 (s, NH, 1H); ^{13}C NMR δ(75 MHz, $CDCl_3$) 22.8, 29.2, 46.5, 48.2, 50.2, 51.7, 55.8, 99.9, 108.9, 110.8, 111.3, 128.5, 130.1, 136.1, 153.9, 175.1.
7. a. Zinnes, H.; Schwartz, M. L. *U.S.Pat.* 3 931 230 (1976); (*Chem. Abstr.* **1976**, *84*, 150497r). b. Sapi, J.; Grébille, Y.; Laronze, J. Y.; Lévy, J. *Synthesis.* **1992**, 383-386.
8. Kuehne, M. E.; Matsko, T. H.; Bohnert, J. C.; Kirkemo, C. L. *J. Org. Chem.* **1979**, *44*, 1063-1068.
9. Krapcho, A. P. *Synthesis.* **1982**, 893-914.
10. Diker, K.; Döé de Maindreville, M.; Lévy, J. *Tetrahedron Lett.* **1995**, in press.

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