A FORMAL SYNTHESIS OF NAUCLÉFINE

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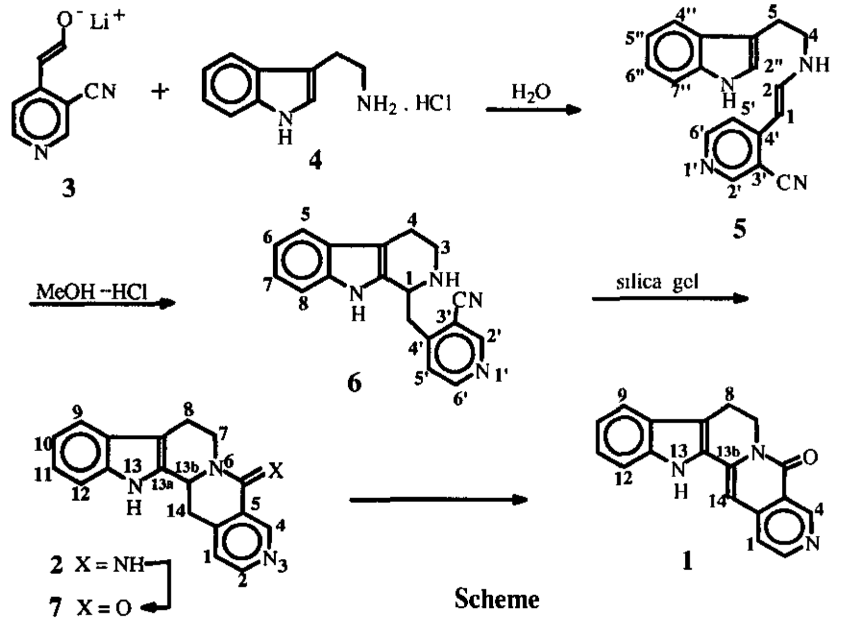
Abstract - The amidine (**2**) has been prepared in three steps from the enolate of (3-cyanopyridin-4-yl)acetaldehyde and tryptamine hydrochloride by way of the enamine (**5**) and the 1,2,3,4-tetrahydro-ß-carboline (**6**). The conversion of **2** into nauclėfine has been previously reported.

Nauclėfine (**1**) *(8,13-dihydroindolo[2′, 3′: 3,4]pyrido[1, 2 - b][2, 7]naphthyridin-5[7H]-one)* was isolated first from *Nauclea latifolia*[1] and has been found since then in other *Nauclea* species.[2a-c] A number of synthetic routes to **1** have been developed that differ from one another in the nature of the starting materials and in the order of ring-formation. Several syntheses began with harmalan and nicotinoyl chloride and proceeded through an enamide intermediate;[3a-c] another used harmalan and isonicotinoyl chloride and involved a spirodihydropyridine intermediate.[4] The same order of ring-formation but different bond-forming steps pertained in a recently reported synthesis[5] that used 3,4-dihydro-ß-carboline and lithiated 3-cyano-4-methylpyridine as starting materials. A key intermediate in this synthesis was the amidine (**2**) (8,13,13b,14-tetrahydroindolo[2′,3′:3,4]pyrido[1,2–*b*][2,7]naphthyridin-5[7*H*]-imine), that, on hydrolysis and oxidation, afforded **1**. Other approaches to **1** involving a different order of ring-formation have been reported.[6,7] We present here a formal synthesis of **1** that affords amidine (**2**) in 3 steps from the enolate (**3**) of (3-cyanopyridin-4-yl)acetaldehyde and tryptamine hydrochloride (**4**) (Scheme).



Scheme

The enolate (3) was prepared by treatment of a solution of the lithium derivative[5] of 3-cyano-4-methylpyridine[8] in THF with ethyl formate (1.60 eq.) at -20°C. The mixture was stirred for 20 min, warmed to 20°C, and stirred for 2 h. An aqueous solution of **4** (1.15 eq.) was added dropwise and the heterogeneous mixture was stirred for 12 h. The extract was purified by radial chromatography on silica gel [Merck 60 PF_{254}, EtOAc-C_6H_{14} (1/1: v/v)] to afford the enamine (**5**) as a yellow oil (64%). Enamine (**5**) has been assigned the (*E*)-configuration on the basis of the coupling constant between the vinylic protons, J = 13.5 Hz. Treatment of **5** with a saturated solution of hydrogen chloride in methanol, first at 0°C for 1 h, and then at 20°C for 2 h, gave, after processing, compound (**6**) (89%) as a crystalline solid, mp 168-169°C (EtOAc). The characteristic enamine absorption present in the ^{1}H nmr spectrum of **5** is absent in the spectrum of **6**; however, a signal at δ 4.34 (1H, dd, J = 9.8 and 3.3 Hz) is characteristic of H-1 in 1-substituted 1,2,3,4-tetrahydro-β-carbolines. When **6** was adsorbed on silica gel (Merck 60, PF_{254}) and the plate eluted with EtOAc–MeOH (2/1: v/v), the amidine (**2**) was obtained (87%); none of **6** was detected. The ir spectrum of **2** had an absorption at 1613 cm^{-1} (amidine) but the nitrile absorption observed in the spectra of **5** and **6** was absent. Moreover, in its ^{13}C nmr spectrum, **2** exhibited a signal at δ 157.79 attributed to C-5, the carbon atom of the amidine function (see ref. 9 for spectroscopic data).

The conversion of **2** into 13b,14-dihydronauclėfine (**7**) has been reported to proceed in 89% yield[5,10] and of **7** into **1** in 91% yield.[5] Thus, the preparation of **2** reported herein constitutes a formal synthesis of **7** and of **1**. This method of synthesis of amidine (**2**) compares favourably in terms of yield and convenience, only 3 steps are required, with that previously reported[5] and it has the advantage that protection of the indole nitrogen is not required at any stage in the syntheses. Moreover, if one dispenses with the purification of the enamine, the overall yield of **2** is improved.

This method of preparation of 1-substituted 1,2,3,4-tetrahydro-ß-carbolines has been reported previously[11 a-c] but seems to have been used sparingly. We have applied this methodology also to the synthesis of other 1,2,3,4-tetrahydro-1-pyridinylmethyl-ß-carbolines using both tryptophans and tryptamines as amine components and other pyridines as enolate precursors. Details of the latter research will appear in a subsequent publication.

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9. **5**. Ir (KBr): 2217 (CN), 1628 (enamine), 1584 (Ar) cm^{-1}; ^{1}H nmr (200 MHz, CDCl$_3$)δ: 3.09 (2H, t, J = 6.6 Hz, H - 5), 3.42 (2H, m, H - 4), 4.90 (1H, br s, N^{b}H), 5.51 (1H, d, J = 13.5 Hz, H - 1), 7.04 (2H, m, H - 2", H - 5′), 7.23 (3H, m, H - 2, H - 5", H - 6"), 7.38 (1H, d, J = 7.3 Hz, H - 7"), 7.60 (1H, d, J = 7.3 Hz, H - 4"), 8.18 (1H, d, J = 5.8 Hz, H - 6′), 8.44 (1H, s, H - 2′), 8.77 (1H, br s, N^{a}H); ms m/z (CI-NH$_3$): 289 [M + H]$^+$ (100), 183 (8), 144 (15). Exact mass (hrms) calcd for C$_{18}$H$_{16}$N$_4$: 288.1374; found: 288.1355. **6**. Ir (KBr): 2229 cm^{-1} (CN); ^{1}H nmr (200 MHz, CDCl$_3$)δ: 2.69 - 3.41 (7H, m, 2H - 3, 2H - 4, 2H -7, N^{b}H), 4.34 (1H, dd, J = 9.8 and 3.3 Hz, H - 1), 7.05 - 7.53 (5H, m, H - 5, H - 6, H - 7, H - 8, H - 5′), 8.13 (1H, br s, N^{a}H), 8.70 (1H, d, J = 5.2 Hz, H - 6′), 8.86 (1H, s, H - 2′); ms m/z (CI-NH$_3$): 289 [M + H]$^+$ (100), 288 (68), 171 (41), 169 (36), 119 (57). Exact mass (hrms) calcd for C$_{18}$H$_{16}$N$_4$: 288.1374; found: 288.1369. **2**: Ir (KBr): 1613 cm^{-1} (C=N); ^{1}H nmr (200 MHz, DMSO-d$_6$)δ: 2.75 - 3.01 (4H, m, 2H - 8, H - 7$_{ax}$, H - 14$_{ax}$), 3.10 - 3.65 (1H, br s, N^{a}H), 3.48 - 3.60 (1H, dd, J = 16.2 and 3.3 Hz, H - 14$_{eq}$), 4.77 (1H, dd, J = 12.2 and 3.3 Hz, H - 13b), 4.93 (1H, apparent d, J = 12.2 Hz, H - 7$_{eq}$), 6.97 - 7.10 (2H, m, H - 10, H - 11), 7.32 - 7.39 (2H, m, H - 1, H - 12), 7.47 (1H, d, J = 7.2 Hz, H - 9), 8.57 (1H, d, J = 5.0 Hz, H - 2), 9.27 (1H, s, H - 4), 10.56 (1H, br s, N^{a}H); ms m/z (CI - NH$_3$): 289 [M+H]$^+$ (100), 287 (36), 171 (10), 119 (9). Exact mass (hrms) calcd for C$_{18}$H$_{16}$N$_4$: 288.1374; found: 288.1383. A sample of compound (**2**) was hydrolysed to 13b,14-dihydronauclėfine (**7**) and compared with a sample of 7[5] provided by Dr. Jahangir. The two samples were identical: mp, mixed mp, tlc, ms, and ^{1}H nmr. A reference sample of **2** was not available.

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