ISOHARMINE REVISITED: THERMAL REARRANGEMENT OF A 3-CYANOMETHYL-2-VINYLINDOLE

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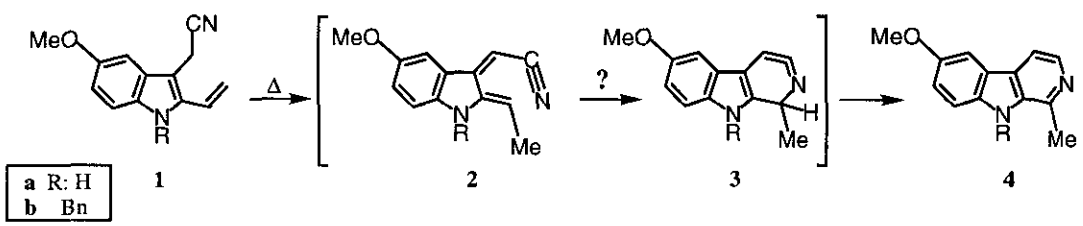
Abstract - Thermolysis of 2-vinylindole derivative (**1**) led to indolylacrylonitrile (**6**) instead of β-carboline alkaloid isoharmine (**4**). Latter was prepared by following the conventional method and was fully characterized.

Thermal electrocyclic ring closure of 1-azahexatriene proved to be a versatile method for the construction of fused pyridine ring systems. Hibino,[1] Gilchrist[2] and Bergman[3] have successfully used this reaction for the synthesis of functionalized γ- and β-carbolines, respectively.

In continuation of our interest in the chemistry of 2-vinylindoles, we have recently found that 1-benzyl-3-cyanomethyl-2-vinylindole (**1b**) could thermally rearrange *via* [1,5] H shift into the corresponding indole-2,3-quinodimethane (**2b**) trapped by dienophiles to afford functionalized tetrahydrocarbazoles.[4]

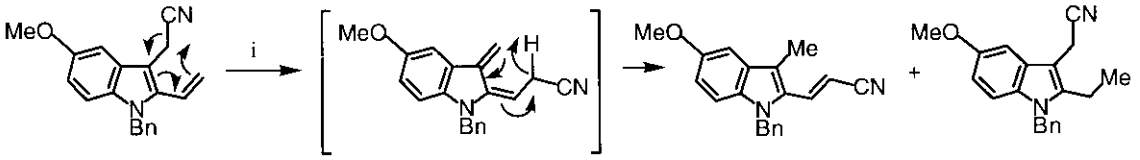


Scheme 1

On the basis of these findings, we hoped that in the absence of dienophile *in situ* formed indolo-2,3-quinodimethane would give β-carboline derivative (**4b**) through the transient aza-allene (**3b**) followed by [1,3] H shift. Debenzylation of latter (**4b**) could afford isoharmine (**4a**), recently isolated from the seeds of *Peganum harmala*.[5]

Attempted thermal electrocyclization of 1b

1-Benzyl-3-cyanomethyl-5-methoxy-2-vinylindole (**1b**), prepared according to the described procedure,[6] was subjected to thermolysis in a sealed tube at 170°C for 72 h to afford, after column chromatographic purification, a yellowish crystalline product (mp 132°C) (**6b**) (18 %), along with 2-ethyl derivative (**7b**) (29 %), some recovered starting material (11 %) and tar.



1b **5b** **6b** **7b**

i: toluene, sealed tube, 170°C, 72 h.

Scheme 2

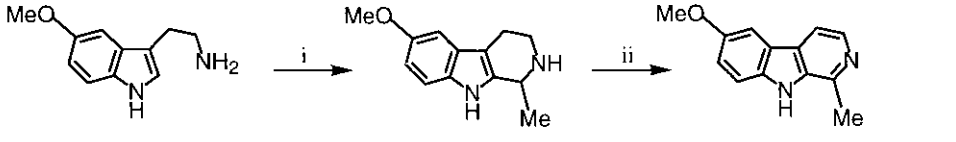
Despite the presence of the molecular ion in MS spectrum (M^+ 302.14159 for $C_{20}H_{18}N_2O$) other spectroscopic data of **6b** were in discordance with a β-carboline skeleton. Thus, UV maxima at 215, 246, 260 and 352 nm, an IR absorption at 2210 cm^{-1} (CN) suggested rather a cyano group conjugated 2-vinylindole chromophore. Apart from the signals of the *N*-benzylindole core, ^{1}H-NMR spectrum displayed a deshielded methyl singlet (δ=2.47 ppm) and two *trans* olefin protons at δ=5.51 and 7.39 ppm (J=17 Hz). Location of the methyl group on the C-3 carbon and the acrylonitrile moiety on C-2 of indole was deduced from HETCOR and HMBC experiments.

Formation of **6b** might be rationalized by two successive sigmatropic shifts as depicted in Scheme 2. However, an ionic mechanism cannot be discarted (elimination-addition of CN^-), since addition of KCN during the thermolysis improved the yield (39 %) of **6b**. 2-Ethyl derivative (**7b**) was formed probably by thermal disproportion of **1b**.

Although spectroscopic data excluded a β-carboline structure for the newly formed product, formal comparison of **6b** to isoharmine (**4a**) needed a debenzylation. Since debenzylation of **6b** by catalytic hydrogenation failed, we decided to prepare isoharmine (**4a**) and then to benzylate it. Otherwise, a short synthesis of isoharmine was justified by the fact that comparison of some physical data of natural isoharmine from *P. harmala* to those of different origin revealed some discrepancies (mp 200°C[5] *vs.* 266°C[7] or 273°C[8]).

Preparation of 5-methoxy-1-methyl-β-carboline (4a)

Our short approach was based on the well-known Pictet-Spengler cyclization followed by dehydrogenation of the corresponding tetrahydro-β-carboline moiety.



8 **9** R: H isoharmine (**4a**) Bn **4b**

i: MeCHO, rt, phosphate buffer; ii: DDQ, toluene, reflux; iii: BnBr, 35% NaOH, CH_2Cl_2.

Scheme 3

Treatment of 5-methoxytryptamine (**8**) with freshly distilled acetaldehyde in aqueous phosphate buffer at room temperature led smoothly to the expected tetrahydro-β-carboline derivative (**9**). Aromatization of **9**

was carried out by DDQ assisted oxidation in boiling toluene to afford **4a** in 53 % yield. Melting point (mp 267°C) and UV maxima (λ=215, 231, 245, 256, 287, 295, 360 nm) of our synthetic product (**4a**) were comparable rather to those of described by Cassady[8] than to isoharmine recently isolated.[5] Similarly, ^{1}H-NMR data of synthetic **4a** were in good accordance with those of the 5-trimethylsilyloxy derivative.[9] ^{13}C-NMR data of **4a** have been described for the first time.

Finally, comparison of spectral data of **6b** to those of N_a-benzylisoharmine (**4b**), obtained by a classical two-phase alkylation method (CH_2Cl_2/NaOH aq), unequivocally excluded any structural relationship.

EXPERIMENTAL

Melting points, determined on a Reichert hot plate apparatus, are uncorrected. IR spectra were recorded on a BOMEM FTIR apparatus with COSMIC interferometer. UV spectra (in MeOH) were recorded on a Unicam 8700 spectrometer. ^{1}H- and ^{13}C-NMR spectra were measured on a Bruker AC 300 apparatus at 300 and 75 MHz, respectively. MS spectra were obtained on a VG Autospec (Fisons) spectrometer.

General extraction protocol: After evaporation, the residue was made alkaline with 10% Na_2CO_3, then extracted with CH_2Cl_2 (3x10 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated to dryness.

Thermolysis of 1b

A solution of **1b** (300 mg, 0.99 mmol) in dry toluene (10 mL) was heated in a sealed tube at 170°C for 72 h. After evaporation, the reaction mixure was purified by column chromatography (silica gel, eluent: CH_2Cl_2) to give **6b** (53 mg, 18%), 2-ethyl derivative (**7b**) (90 mg, 29 %), and recovered starting material (33 mg, 11%).

3-(1-Benzyl-3-methyl-5-methoxyindol-2-yl)acrylonitrile (6b) : mp 132°C (ether). UV 215, 246, 260, 352 nm. IR (KBr) 2210, 1605 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 7.40 (1H, d, J=17 Hz, C<u>H</u>=CH-CN), 7.37-7.25 (2H, m, aromatic), 7.15 (1H, d, J=9 Hz, H-7), 7.03 (1H, d, J=2.3 Hz, H-4), 6.98-6.92 (4H, m, aromatic), 5.51 (1H, d, J=17 Hz, CH=CH), 5.36 (2H, s, C<u>H</u>$_2$Ph), 3.88 (3H, s, OCH_3), 2.45 (3H, s, CH_3). ^{13}C-NMR ($CDCl_3$) δ 154.6 (C-5), 138.0 (<u>C</u>H=CH-CN), 137.0, 134.2 (C-7a), 130.6 (C-2), 129.0, 128.2 (C-3a), 127.7, 125.6, 119.0 (CN), 116.9 (C-6), 116.4 (C-3), 110.7 (C-7), 100.6 (C-4), 94.9 (CH=<u>C</u>H-CN), 55.8 (CH_3O) 47.4 (<u>C</u>H$_2$Ph), 10.6 (CH_3). MS *m/z* 302 (M^+), 262 (100), 229, 211, 168. HREIMS Calcd for $C_{20}H_{18}N_2O$ *m/z* 302.14191. Found 302.14159.

1-Benzyl-3-cyanomethyl-2-ethyl-5-methoxyindole (7b): amorphous. UV 208, 256, 280, 297, 311. IR (film) 3374, 2218 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 7.37-7.82 (8H, m, aromatic), 5.26 (2H, s, C<u>H</u>$_2$Ph), 3.90 (3H, s, OCH_3), 3.75 (2H, s, CH_2CN), 2.83 (2H, q, J=7.5 Hz, C<u>H</u>$_2$-CH_3), 1.15 (3H, t, J=7.5 Hz, CH_2C<u>H</u>$_3$). MS *m/z* 304 (M^+), 278, 275, 262.

6-Methoxy-1-methyl-1,2,3,4-tetrahydro-β-carboline (9)

To a solution of 5-methoxytryptamine HCl salt (**8**) (226 mg, 1.0 mmol) in 5 mL of phosphate buffer (pH=4.1) freshly distilled acetaldehyde (220 mg, 5.0 mmol) was added, and the reaction mixture was stirred at rt for 24 h. The residue resulting from the general extraction protocol was purified by column chromatography (silica gel, eluent: CH_2Cl_2:MeOH 95:5) followed by crystallization to give **9** (170 mg, 79 %), mp 150-151°C (EtOAc). UV 218, 275, 296, 308 nm. IR (KBr) 3352, 1611 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 7.88 (1H, s, indole NH), 7.19 (1H, d, J=8 Hz, H-8), 6.95, (1H, d, J=1.8 Hz, H-5), 6.81 (1H, dd, J_1=8, J_2=1.8 Hz, H-7), 4.18 (1H, q, J=8 Hz, H-1), 3.85 (3H, s, OCH_3), 3.37 and 3.08 (2H, m, H-3), 2.73 (2H, m, H-4), 1.71 (1H, s, NH), 1.45 (3H, d, J=8 Hz, CH_3). ^{13}C-NMR

($CDCl_3$) δ 153.5 (C-6), 136.1 (C-8a), 130.9 (C-9a), 127.0 (C-4b), 111.5 (C-5), 111.0 (C-7), 106.7 (C-4a), 100.1 (C-8), 55.7 (OCH_3), 48.2 (C-1), 42.0 (C-3), 21.4 (C-4), 20.0 (CH_3). MS *m/z* 216 (M^+), 201 (100), 187, 172. Anal. Calcd for $C_{13}H_{16}N_2O$: C 72.19, H 7.46, N 12.95. Found: C 72.36, H 7.77, N 13.21.

6-Methoxy-1-methyl-β-carboline (4a) (isoharmine)

A solution of **9** (90 mg, 0.42 mmol) and DDQ (200 mg, 0.88 mmol) in toluene (10 mL) was refluxed under N_2 for 3 h. After evaporation of the solvent, the residue resulting from the general extraction protocol was purified by preparativ TLC (silica gel, eluent: CH_2Cl_2:MeOH:NH_4OH 100:90:0.1) to afford **4a** (36 mg, 40 %) along with some starting material (**9**) (16 mg, 17 %). **4a**: mp 267°C (EtOH). UV 215, 231, 245, 256, 287, 295, 360 nm. IR (KBr) 3348, 1608 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 11.41 (1H, s, indole NH), 8.18 (1H, d, J=5.3 Hz, H-3), 7.91 (1H, d, J=5.3 Hz, H-4), 7.74 (1H, d, J=2.2 Hz, H-5), 7.53 (1H, d, J=8.8 Hz, H-8), 7.20 (1H, dd, J_1=8.8, J_2=2.2 Hz, H-7), 3.89 (3H, s, OCH_3), 2.78 (3H, s, CH_3). ^{13}C-NMR (DMSO-d_6) δ 153.4 (C-6), 142.3 (C-1), 137.0 (C-3), 135.4 (C-8a), 135.2 (C-9a), 126.6 (C-4b), 121.5 (C-4a), 117.9 (C-4), 112.9 (C-5), 112.8 (C-7), 103.7 (C-8), 55.7 (OCH_3), 20.6 (CH_3). MS *m/z* 212 (M^+), 197 (100), 169. Anal. Calcd for $C_{13}H_{12}N_2O$: C 73.56, H 5.70, N 13.20. Found: C 73.36, H 6.03, N 13.01.

9-Benzyl-6-methoxy-1-methyl-β-carboline (4b)

A solution of **4a** (30 mg, 0.14 mmol), $Bu_4N^+HSO_4^-$ (4 mg, 0.01 mmol), 35% NaOH (0.3 mL), and benzyl bromide (51 mg, 0.30 mmol) in CH_2Cl_2 (3 mL) was stirred at rt until the disappearance of the starting material. After separation and extraction of the aqueous phase with CH_2Cl_2, the combined organic layer was treated according to the general protocol. The residue was purified by chromatography (silica gel, eluent: CH_2Cl_2) to give **4b** (29 mg, 68%) as an amorphous solid. UV 203, 218, 232, 247, 260, 268, 286, 297, 366 nm. IR (film) 2917, 2850, 1489, 1425 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 8.30 (1H, d, J=5 Hz, H-3), 7.91 (1H, d, J=5 Hz, H-4), 7.67 (1H, d, J=1.5 Hz, H-5), 7.37-7.21 (5H, m, aromatic), 6.98 (2H, d, J=7 Hz, aromatic), 5.65 (2H, s, CH_2Ph), 3.95 (3H, s, OCH_3), 2.95 (3H, s, CH_3). MS *m/z* 302 (M^+, 100), 287, 259. HREIMS Calcd for $C_{20}H_{18}N_2O$ *m/z* 302.14191. Found 302.14178.

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