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Unusual formation of β-carboline dimers under Bischler–Napieralski reaction conditions: an old reaction with a new direction

Bikash Pal,[a] Parasuraman Jaisankar,[a] Venkatachalam Sesha Giri,[a,*] Swastik Mondal[b] and Monika Mukherjee[b]

[a]*Department of Medicinal Chemistry, Indian Institute of Chemical Biology, 4, Raja S.C. Mullick Road, Jadavpur, Calcutta 700 032, India*

[b]*Department of Solid State Physics, Indian Association for the Cultivation of Science, Jadavpur, Calcutta 700 032, India*

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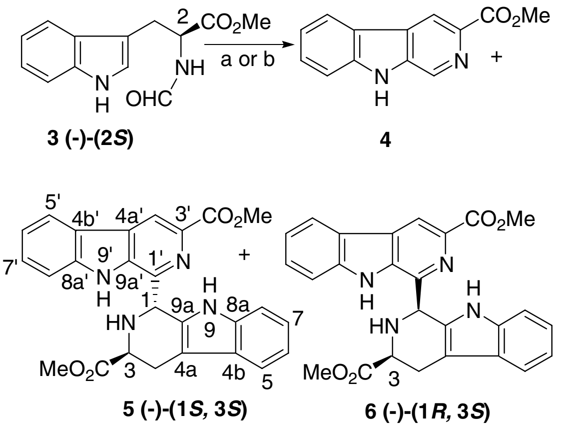
Abstract—L-*N*-Formyl tryptophan methyl ester (**3**) underwent a Bischler–Napieralski reaction with $POCl_3$ at room temperature or under microwave irradiation, resulting in the unusual formation of β-carboline dimers **5** and **6**. Most importantly, acetylation using Ac_2O of each of the dimers **5** and **6** separately afforded 1-[3′-carbomethoxy-β-carbolinyl]-3-carbomethoxy-9-acetyl-β-carboline (**7**) as the only product, the structure of which was confirmed by X-ray crystallography studies.

The use of chemotherapeutic agents in cancer has advanced from the treatment of late diseases to the early use of effective agents in patients with relatively small tumors. Among the various chemotherapeutic agents, 1-substituted-β-carboline derivatives,[1] including the recently synthesized dimeric β-carboline alkaloid bengacarboline,[2] have attracted the attention of organic chemists because of their potential anti-tumor activity. In our endeavor to obtain 1-substituted β-carbolines of physiological importance, the β-carbolines **2** were synthesized from the corresponding tryptamine derivatives **1** using the microwave assisted Bischler–Napieralski reaction. The Bischler–Napieralski reaction[3] is one of the most widely used reactions in the synthesis of β-carboline derivatives. Many indole alkaloids have been synthesized with the help of this reaction.

Treatment of *N*-formyl tryptamine **1** (R = H) and *N*-acetyl tryptamine **1** (R = Me) with $POCl_3$ under microwave irradiation or at room temperature gave 3,4-dihydro-β-carboline **2** (R = H) and 1-methyl-3,4-dihydro-β-carboline **2** (R = Me) in very good yields. Surprisingly, reaction of L-*N*-formyl tryptophan methyl ester **3** with $POCl_3$ under microwave irradiation resulted in the dimeric β-carbolines **5** (30%) and **6** (10%) together with the expected β-carboline derivative **4** (50%) as the major product (Scheme 1). The same reaction when performed[4] with $POCl_3$ at room temperature for 30 min



Scheme 1. Reaction conditions: (a) $POCl_3$, microwave irradiation, 600 W, 10 min; (b) $POCl_3$, 28 °C, 30 min.

Keywords: Bischler–Napieralski; Chiral β-carboline dimers; Tryptophan methyl esters; $POCl_3$; Microwave.

* Corresponding author. Fax: +91-33-24735197; e-mail: vsgiri@iicb.res.in

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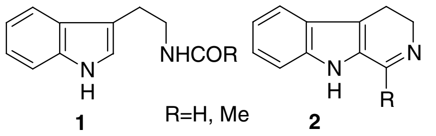
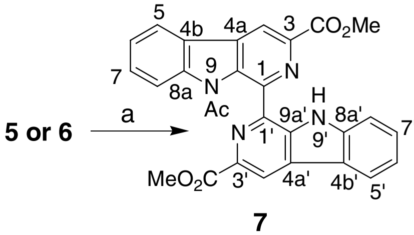


Figure 1.

afforded the dimeric β-carbolines **5**[5] and **6**[6] in 70% and 12% yields, respectively, together with 3-carbomethoxy-β-carboline **4** in 8% yield. This is the first report on the formation of such chiral dimeric β-carbolines under the well-known Bischler–Napieralski reaction conditions. The above reaction when performed under an oxygen-free nitrogen atmosphere gave the same dimeric β-carbolines **5** and **6** in 50% and 15% yields, respectively. Also, the reaction when performed using an equimolar mixture of **3** (246mg; 1mmol) and **4** (226mg; 1mmol) afforded **4** (235mg), **5** (165mg), and **6** (26mg) in the molar ratio 1.04:0.36:0.05, respectively. Therefore, it appears that the dimeric b-carbolines **5** and **6** are probably formed due to the presence of the acidic a-proton of the COOMe group, which is involved in amine–imine tautomerism facilitating addition to another molecule of an imine followed by ring closure. No dimeric product was formed with *N*-formyl tryptamine under the same reaction conditions (Fig. 1).



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Scheme 2. Acetylation of chiral β-carbolines **5** or **6**. Reaction conditions: (a) Ac$_2$O–Py, 80°C, 4h.

Cook et al.[7] have previously shown that the stereochemistry at the C-1 and C-3 positions in 1,3-disubstituted 1,2,3,4-tetrahydro-β-carbolines can be assigned from the chemical shifts of the carbons at C-1 and C-3 in their ^{13}C NMR spectra. The signals for the C-1 and C-3 carbons of the *cis* diastereoisomers are clearly distinct from those of the analogous signals for the *trans* diastereoisomers. The reason for the higher yield of the *trans* isomer **5** compared to the *cis* isomer **6** is due to the absence of the 1,4-gauche effect in the *trans* isomer. It should be mentioned that Bailey et al.[8] have shown that by employing the kinetically controlled Pictet–Spengler reaction, the *cis* 1,3-disubstitued tetrahydro-b-carbolines are the favored products. As expected, the Bischler–Napieralski reaction when performed using D-*N*-formyl tryptophan methyl ester with POCl$_3$ afforded the *trans* isomer (+)-(*1R*,*3R*)-1-(3-carbomethoxy-1,2,3,4-tetrahydro-b-carbolinyl)-3-carbo-methoxy-b-carboline, [9] and the *cis* isomer (+)-(*1S*,*3R*)-1-(3-carbomethoxy-1,2,3,4-tetra-hydro-b-carbolinyl)-3-carbomethoxy-b-carboline[10] along with **4** in the same proportion as was obtained from **3**.

Surprisingly and most importantly, acetylation[11] of both the isomers **5** and **6** separately using Ac$_2$O in pyridine at 80°C for 4h afforded a single compound **7**[12] in near quantitative yield, wherein acetylation had occurred at the indole N*H* (H-9′) of the dimer rather than the secondary amino group (H-2) of the tetrahydro-β-carbolinyl moiety (Scheme 2). As anticipated, acetylation of the corresponding *trans* and *cis* isomers obtained from

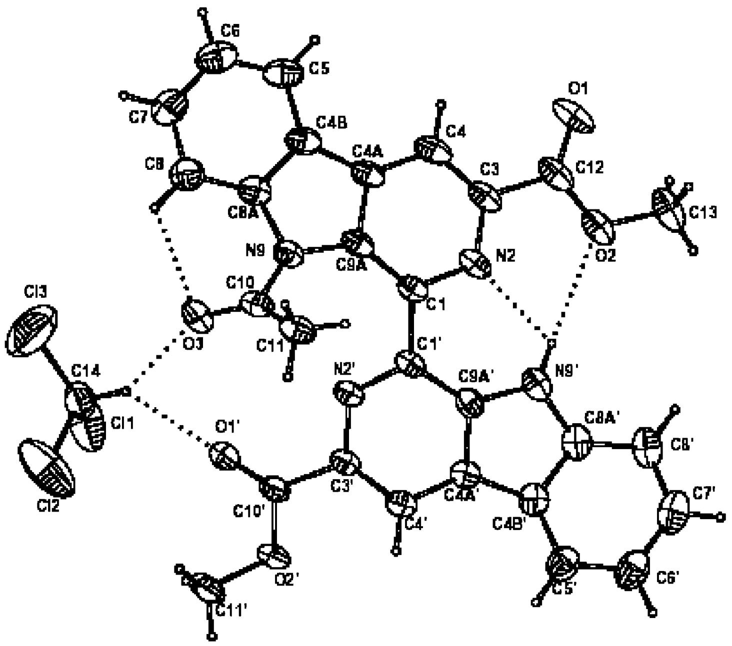

Figure 2. X-ray crystal structure 1-[3′-carbomethoxy-β-carbolinyl]-3-carbomethoxy-9-acetyl-β-carboline (**7**) with an entrapped CHCl$_3$ in the single crystal.

D-*N*-formyl tryptophan methyl ester gave **7** in similar yield. The acetylation reaction, when performed under an oxygen-free nitrogen atmosphere with or without a base (pyridine), afforded the same product **7**. This could plausibly have arisen by initial acetylation of the secondary N*H* (H-2) followed by transacetylation due to the close proximity of the indole N*H* (H-9′) and subsequent aromatization. The structure of compound **7** has been confirmed by X-ray crystallographic studies[13] (Fig. 2). All new compounds have been characterized from their spectral data, particularly NMR (including COSY and HMBC).

In summary, the present observation is the first report of the formation of dimeric β-carbolines using the well-known Bischler–Napieralski reaction from *N*-formyl tryptophan methyl esters. Moreover the formation of the fully aromatized system **7** from the chiral dimers **5** or **6** is interesting due to the unusual acetylation as well as the consequent aromatization.

Acknowledgements

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4. A solution of 3.0 mmol of L-*N*-formyl tryptophan methyl ester **3** and 2.0 mL of $POCl_3$ was stirred at room temperature for 30 min. After completion, excess $POCl_3$ was decomposed by the addition of ice at 0–5 °C and the reaction mixture neutralized with satd $NaHCO_3$ solution and extracted with $CHCl_3$ (3×15 mL). The organic layer was washed with H_2O (2×15 mL), dried (Na_2SO_4), and the solvent removed under vacuum to afford a mixture of β-carbolines **4**–**6**. Fractional crystallization of the mixture obtained using MeOH yielded the *trans* isomer **5** (60%). The filtrate obtained from the above mixture was chromatographed over silica-gel using initially $CHCl_3$ and then a mixture of $CHCl_3$–MeOH, to afford **4** (8%), **5** (10%) and **6** (12%), respectively.
5. (−)-(*1S,3S*)-1-(3-Carbomethoxy-1,2,3,4-tetrahydro-β-carbolinyl)-3-carbomethoxy-β-carboline (**5**): mp 310–312 °C; $[\alpha]_D^{28}$ −13.7 (*c* 0.165, $CHCl_3$); IR (KBr): 3378, 3320, 1738, 1723, 1346, 1262 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 3.12 (br dd, *J* = 15.2 Hz, 3.0 Hz, 2H, H-4), 3.67 (s, 3H, $-CO_2C\mathit{H}_3$), 3.84 (br s, 1H, N*H*), 3.90 (s, 3H, $-CO_2C\mathit{H}_3$), 4.39 (br s, 1H, H-3), 6.01 (br s, 1H, H-1), 6.92–7.01 (m, 2H, H-6, H-7), 7.15 (d, *J* = 6.5 Hz, 1H, H-8), 7.29 (t, *J* = 7.5 Hz, 1H, H-6′), 7.48 (d, *J* = 6.9 Hz, 1H, H-5), 7.57 (t, *J* = 7.5 Hz, 1H, H-7′), 7.74 (d, *J* = 8.1 Hz, 1H, H-8′), 8.38 (d, *J* = 7.5 Hz, 1H, H-5′), 8.89 (s, 1H, H-4′), 10.27 (s, 1H, N*H*), 11.39 (s, 1H, N*H*); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 24.79 (C-4), 52.57 ($-CO_2\mathit{C}H_3$), 52.84 ($-CO_2\mathit{C}H_3$), 53.95 (C-3), 55.42 (C-1), 107.24 (C-4a), 112.09 (C-8), 113.75 (C-8′), 117.91 (C-5), 118.55 (C-5′), 119.22 (C-6′), 121.06 (C-6), 121.67 (C-7), 121.82 (C-4b′), 122.65 (C-4′), 127.46 (C-4b), 129.39 (C-7′), 129.44 (C-4a′), 133.47 (C-9a), 135.97 (C-9a′), 136.57 (C-8a), 137.15 (C-8a′), 141.57 (C-3′), 146.21 (C-1′), 166.92 ($-\mathit{C}O_2CH_3$), 175.11 ($-\mathit{C}O_2CH_3$); EIMS: *m*/*z*: 454 (M^+, 100%), 450 (40), 390 (24), 366 (40), 307 (30), 229 (25), 169 (70).
6. (−)-(*1R,3S*)-1-(3-Carbomethoxy-1,2,3,4-tetrahydro-β-carbolinyl)-3-carbomethoxy-β-carboline (**6**): mp 320-322 °C; $[\alpha]_D^{28}$ −13.2 (*c* 0.155, $CHCl_3$); IR (KBr): 3379, 3319, 1740, 1724, 1346, 1262 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 3.12 (br dd, *J* = 14.8 Hz, 3.0 Hz, 2H, H-4), 3.67 (s, 3H, $-CO_2C\mathit{H}_3$), 3.84 (br s, 1H, N*H*), 3.91 (s, 3H, $-CO_2C\mathit{H}_3$), 4.39 (br d, *J* = 4.9 Hz, 1H, H-3), 6.01 (br s, 1H, H-1), 6.92–6.99 (m, 2H, H-6, H-7), 7.01–7.19 (m, 1H, H-8), 7.26–7.34 (m, 1H, H-6′), 7.44–7.52 (m, 1H, H-5), 7.53–7.62 (m, 1H, H-7′), 7.75 (d, *J* = 8.2 Hz, 1H, H-8′), 8.37 (d, *J* = 7.8 Hz, 1H, H-5′), 8.89 (s, 1H, H-4′), 10.27 (s, 1H, N*H*), 11.38 (s, 1H, N*H*); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 26.15 (C-4), 52.74 ($-CO_2\mathit{C}H_3$), 52.82 ($-CO_2\mathit{C}H_3$), 55.41 (C-3), 57.74 (C-1), 107.90 (C-4a), 112.10 (C-8), 113.76 (C-8′), 117.91 (C-5), 118.17 (C-5′), 119.19 (C-6′), 121.04 (C-6), 121.64 (C-7), 121.84 (C-4b′), 122.83 (C-4′), 127.47 (C-4b), 129.45 (C-7′), 129.65 (C-4a′), 133.51 (C-9a), 135.98 (C-9a′), 136.59 (C-8a), 137.16 (C-8a′), 141.82 (C-3′), 146.22 (C-1′), 166.91 ($-\mathit{C}O_2CH_3$), 173.91 ($-\mathit{C}O_2CH_3$); LCMS (ES^+) *m*/*z*: 477 (M+Na).
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9. (+)-(*1R,3R*)-1-(3-Carbomethoxy-1,2,3,4-tetrahydro-β-carbolinyl)-3-carbomethoxy-β-carboline: mp 312–314 °C; $[\alpha]_D^{28}$ +13.4 (*c* 0.156, $CHCl_3$).
10. (+)-(*1S,3R*)-*1*-(3-Carbomethoxy-1,2,3,4-tetrahydro-β-carbolinyl)-3-carbomethoxy-β-carboline: mp 318–320 °C; $[\alpha]_D^{28}$ +11.48 (*c* 0.155, $CHCl_3$).
11. To a solution of 2 mmol (908 mg) of chiral β-carboline dimer **5** in pyridine (2 mL) was added dry acetic anhydride (2 mL) and this reaction mixture was warmed on a water bath at 80 °C for 4 h. After completion of the reaction [monitored by TLC; EtOAc–benzene (1:9)], the excess acetic anhydride was decomposed by the addition of ice-cold water and the reaction neutralized with satd $NaHCO_3$ solution and then extracted with $CHCl_3$ (3×20 mL). The organic layer was washed with water (2×20 mL), dried (Na_2SO_4) and then the solvent was removed. The residue was purified by column chromatography over silica gel using $CHCl_3$ to yield **7** (865 mg; 88%). The same procedure was followed to obtain compound **7** from each of the other stereoisomers.
12. *1*-(3′-Carbomethoxy-β-carbolinyl)-3-carbomethoxy-9-acetyl-β-carboline (**7**): mp 210–212 °C; IR (KBr): 3312, 3029, 1740, 1724, 1619, 1265 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.32 (s, 3H, $-COC\mathit{H}_3$), 4.14 (s, 3H, $-CO_2C\mathit{H}_3$), 4.22 (s, 3H, $-CO_2C\mathit{H}_3$), 7.40 (t, *J* = 7.4 Hz, 1H, H-6), 7.51 (t, *J* = 7.3 Hz, 1H, H-7′), 7.60–7.80 (m, 3H, H-6′, H-7, H-8), 8.19 (d, *J* = 7.7 Hz, 1H, H-8′), 8.26 (d, *J* = 7.8 Hz, 1H, H-5), 8.33 (d, *J* = 8.4 Hz, 1H, H-5′), 8.83 (s, 1H, H-4), 8.98 (s, 1H, H-4′), 12.38 (s, 1H, N*H*); ^{13}C NMR ($CDCl_3$, 75 MHz): 28.17 ($-CO\mathit{C}H_3$), 52.79 ($-CO_2\mathit{C}H_3$), 58.38 ($-CO_2\mathit{C}H_3$), 112.88 (C-8), 115.64 (C-5′), 116.50 (C-4),

119.16 (C-4′), 121.46 (2×C, C-6, C-8′), 121.93 (C-4b), 122.30 (C-5), 122.84 (C-4b′), 124.12 (C-7′), 129.64 (C-6′), 131.08 (C-7), 131.54 (C-4a′), 134.28 (C-4a), 136.32 (C-9a), 136.48 (C-9a′), 137.15 (C-1), 137.84 (C-1′), 139.21 (C-8a), 141.74 (C-8a′), 142.13 (C-3), 144.23 (C-3′), 165.86 (–CO_2CH_3), 166.83 (–CO_2CH_3), 171.41 (–$COCH_3$); EIMS *m*/*z* 492 (M^+, 20%), 450 (100), 390 (60), 330 (50).

13. CCDC-241575 contains the supplementary crystallographic data for this paper. This data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44-1223-336033.