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# 1,1'-Bi-9*H*-pyrido[3,4-*b*]indolyl, a New Dimeric β-Carboline

**Franz Bracher and Dirk Hildebrand**

Braunschweig, Institut für Pharmazeutische Chemie der Technischen Universität

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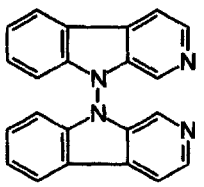
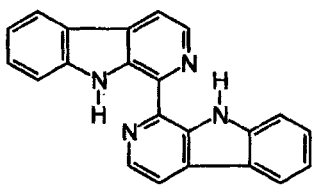
β-Carboline alkaloids represent a large group of biologically active tryptophan-derived natural products and have been found in plants, microorganisms and animals [1]. Very recently, Kearns et al. described the isolation of the symmetric norharman dehydro-dimer **1** containing a $N_9$,$N_{9'}$-linkage from the tunicate *Didemnum* sp. [2]. The authors noted that the extract of this tunicate contains further, unidentified β-carboline dimers. This prompted us to report the accidental synthesis of the isomeric 1,1'-dimer **2**.



**1**

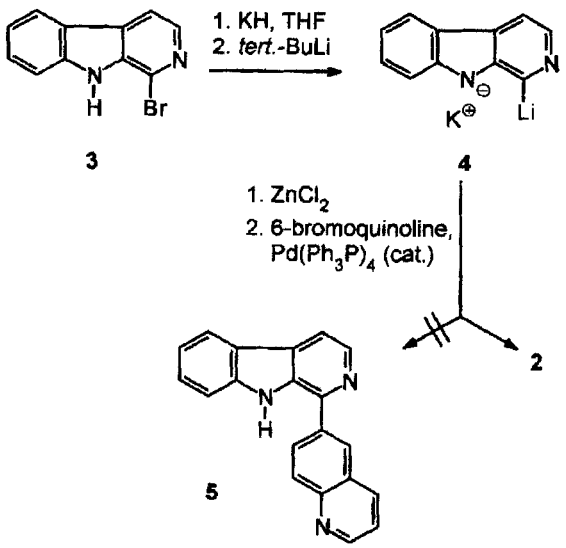


**2**

**Scheme 1**

Earlier we described [3] the preparation of 1-substituted β-carbolines starting from 1-bromo-β-carboline (**3**) *via* the dimetalated compound **4** prepared by *N*-deprotonation with potassium hydride and subsequent bromo–lithium exchange with *tert*-butyllithium. Intermediate **4** can either be trapped by electrophiles (aldehydes, DMF) or be transmetalated with zinc chloride and then subjected to a palladium-catalyzed cross-coupling reaction with 2-chloroquinoline to give the alkaloid nitramarine (1-(2-quinolinyl)-β-carboline). As an extension of this work we examined an analogous cross-coupling reaction of the zinc-species derived from **4** with 6-bromoquinoline [4] aimed to obtain the alkaloid komarovinine **5** [5]. Surprisingly, we did not obtain the desired alkaloid **5**, but isolated the symmetric biaryl **2** in 59% yield. The formation of **2** was neither observed in the reactions of **4** with electrophiles, nor with $ZnCl_2$/2-chloroquinoline [3].

The structure of **2** was unambiguously determined by spectroscopic methods. The mass spectrum ($m/z = 334$, 100%, $M^+$) showed that a norharman dehydro-dimer had been formed. The position of the linkage was determined by $^1H$ and $^{13}C$ NMR spectroscopy. Only a single set of resonances was obtained




**Scheme 2**

indicating a symmetric structure of the dimer. Compared to norharman, the resonance of 1-H was missing in the $^1H$ NMR spectrum [6] and in the $^{13}C$ NMR spectrum [7] C-1 was found to be a quaternary carbon atom. These results can only be explained by a 1,1'-linkage of the two β-carboline rings.

We can only speculate about the mechanism of the formation of the dimer **2**. Probably a partial metal-bromo exchange of **4** or the organozinc species derived thereof with 6-bromoquinoline occured. The resulting *N*-metalated 1-bromo-β-carboline could undergo palladium-catalyzed cross-coupling with remaining organozinc species to give the symmetric biaryl **2**. This proposed mechanism is supported by the fact that quinoline, probably arising from the hydrolysis of a 6-metalated quinoline formed by the halogen-metal exchange, was identified as a by-product.

Compound **2** was tested for antimicrobial activity, but, in contrast to the monomer norharman, did not show significant antibacterial or antifungal activity.

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## Experimental

NMR (internal standard: TMS, $\delta$ in ppm): Jeol JNM-GX 400 (400 MHz).– MS: Vacuum Generators 7070 H (70 eV). – IR: Nicolet FT-IR Spectrometer 510 P. – Elemental analyses: Carlo Erba C–H–N–O Elemental Analyzer 1106. – KH-suspension and *tert*-butyllithium was purchased from Merck, Darmstadt, $ZnCl_2$-solution and $Pd(Ph_3P)_4$ from Aldrich, Steinheim.

*1,1'-Bi-9H-pyrido[3,4-b]indolyl* (**2**)

KH suspension (35% in mineral oil; 115 mg, 1.0 mmol) was diluted with anhydrous THF (1 ml) under nitrogen atmosphere and cooled to 0 °C. Then a solution of 1-bromo-β-carboline (**3**) [3] (247 mg, 1.0 mmol) in anhydrous THF (4 ml) was added with stirring. The mixture was stirred at 0 °C for 40 min and then cooled to –78 °C. Then a precooled (–78 °C) solution of *tert*-BuLi (1.6 M in pentane; 1.25 ml, 2.0 mmol) was added dropwise. The deep red solution was stirred for additional 20 min at –78 °C. $ZnCl_2$ solution (0.5 M in THF; 4.4 ml, 2.2 mmol) was added and the mixture was stirred at –20 °C for 1 h and then transferred with a steel canula into a stirred solution of 6-bromoquinoline [4] (229 mg, 1.1 mmol) and $Pd(Ph_3P)_4$ (46 mg, 0.04 mmol) in anhydrous THF (4 ml) under a nitrogen atmosphere. The resulting mixture was refluxed for 22 h, then treated with water (50 ml) and extracted with ethyl acetate (2×50 ml). The combined organic layers were dried over $Na_2SO_4$ and evaporated. The residue was recrystallized from THF to give **2** (99 mg, 59%) as pale yellow needles, *m.p.* 364 °C (decomp.). – MS: *m/z* (%) = 334 (100) [$M^+$]; 333 (11); 332 (6); 167 (14). – IR (KBr): $\nu$ ($cm^{-1}$) 3359 (N–H); 1622; 1586; 1488; 1289; 1240; 1117; 938; 743; 521; 429. – $^1$H NMR (DMSO-$d_6$): $\delta$ (ppm) 12.2 (br. s, 2 H, $N_9$–H, $N_{9'}$–H); 8.73 (d, $J$ = 5.2 Hz, 2 H, 3-H, 3'-H); 8.33 (d, $J$ = 7.6 Hz, 2 H, 5-H, 5'-H); 8.29 (d, $J$ = 5.2 Hz, 2 H, 4-H, 4'-H); 7.95 (d, $J$ = 8.2 Hz, 2 H, 8-H, 8'-H); 7.61 (m, 2 H, 7-H, 7'-H); 7.31 (m, 2 H, 6-H, 6'-H). – $^{13}$C NMR (DMSO-$d_6$): $\delta$ (ppm) 140.9 (C-1, C-1'); 140.1 (C-8a, C-8a'); 137.2 (C-3, C-3'); 133.4 (C-9a, C-9a'); 129.3 (C-4a, C-4a'); 128.1 (C-7, C-7'); 121.5 (C-5, C-5'); 120.4 (C-4b, C-4b'); 119.5 (C-6, C-6'); 114.7 (C-4, C-4'); 112.9 (C-8, C-8') [7].

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|---|---|---|---|---|
| $C_{22}H_{14}N_4$ | Calcd.: | C 79.02 | H 4.22 | N 16.76 |
| (334.4) | Found.: | C 78.78 | H 4.19 | N 16.67 |

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Address of correspondence:
Prof. Dr. Franz Bracher
Institut für Pharmazeutische Chemie
Technische Universität Braunschweig
Beethovenstr. 55
D-38106 Braunschweig
e-mail: f.bracher@mac2.ifw.ing.tu-bs.de