

5,5'-Biindole

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Abstract: Synthesis of 5,5'-biindole was carried out by the Madelung indole reaction. Under strong basic conditions and high temperatures (350 °C), *N,N'*-bis-formyl-*o*-tolidine underwent cyclization to produce high amounts of the dimeric indole. Full and unambiguous assignments of all ¹H- and ¹³C-NMR resonances of indole and 5,5'-biindole in DMSO-*d*₆ are also reported.

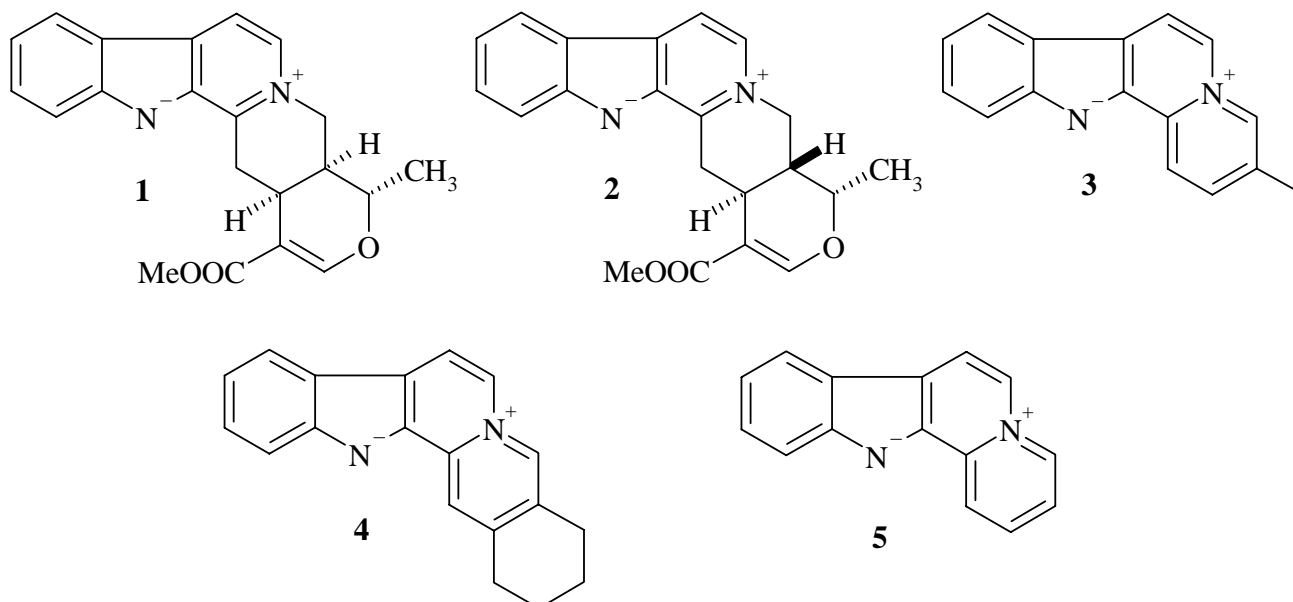
Keywords: Indoloquinolizine, Antitumor activity, Teuber's reaction, Indole synthesis, ¹H-NMR, ¹³C-NMR.

Introduction

Indoles are one of the most widely distributed heterocyclic compounds in nature [1-3]. The indole ring appears in tryptophan [4], an essential amino acid, and metabolites of tryptophan are important in the biological chemistry of both plants and animals. In plants, indole alkaloids, including indole-3-acetic acid and its secondary metabolites, are known as plant growth hormones [5]; in animals, serotonin (5-hydroxytryptamine) is a crucial neurotransmitter in the central nervous system [6]. The potent physiological properties of these indole derivatives led to vast research of their use as medicines in the field of pharmaceutical chemistry. Furthermore, indomethacin [7], a non-steroidal anti-inflammatory agent, and pindolol [8], a β -adrenergic blocker, are clinically proven indole compounds. Several naturally-occurring indoles are also of clinical relevance; vincristine, a dimeric indole alkaloid, and related compounds, were the first of the antimitotic class of chemotherapeutic agents for cancer [9]. The mitomycins [10] and derivatives of ellipticine [11] are other examples of compounds having antitumor activity. Extensive research on reactivity and synthesis of indoles has been done and there is increased interest for the development of new strategies to produce indole skeletons [12].

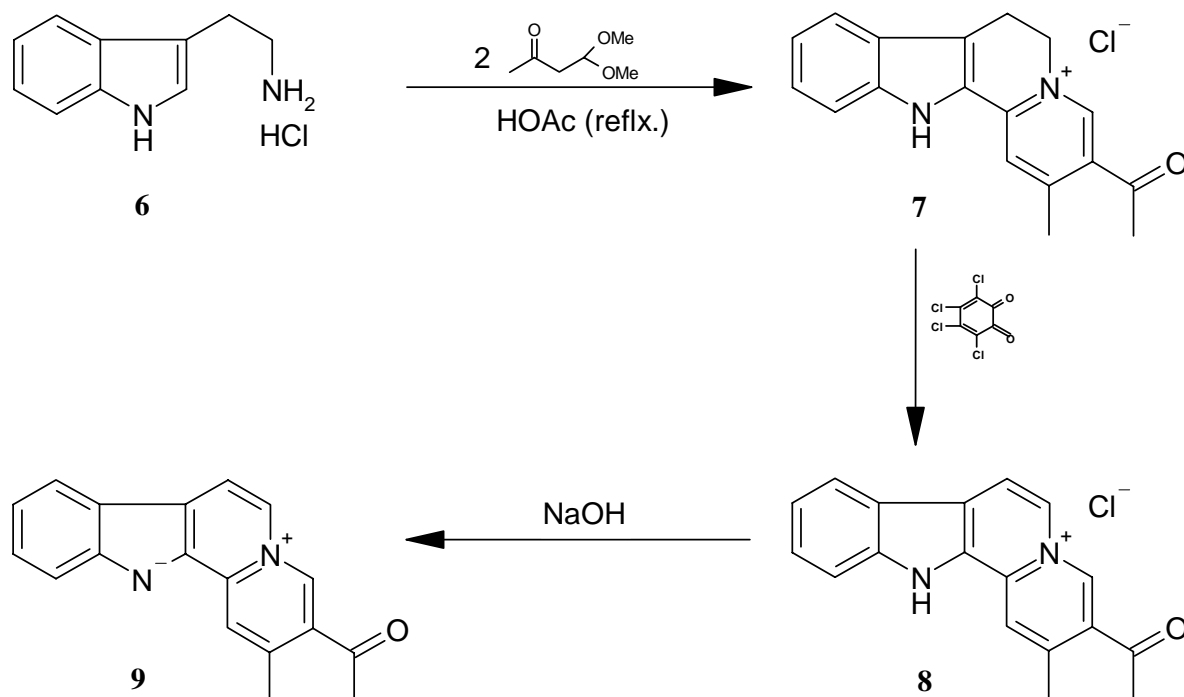
Indoloquinolizines [13] are a small group of indole alkaloids-related natural products, commonly found in plants of the genus *Rauwolfia* as zwitterionic compounds (e.g. alstonine **1**, serpentine **2**, flavopereirine **3** and sempervirine **4**). Indoloquinolizines contain at least one tetracyclic ring with a β -carboline unit, like the indolopyridocoline **5** from *Gonioma kamassi* (Scheme 1) [3].

Scheme 1. Naturally-occurring indoloquinolizines.

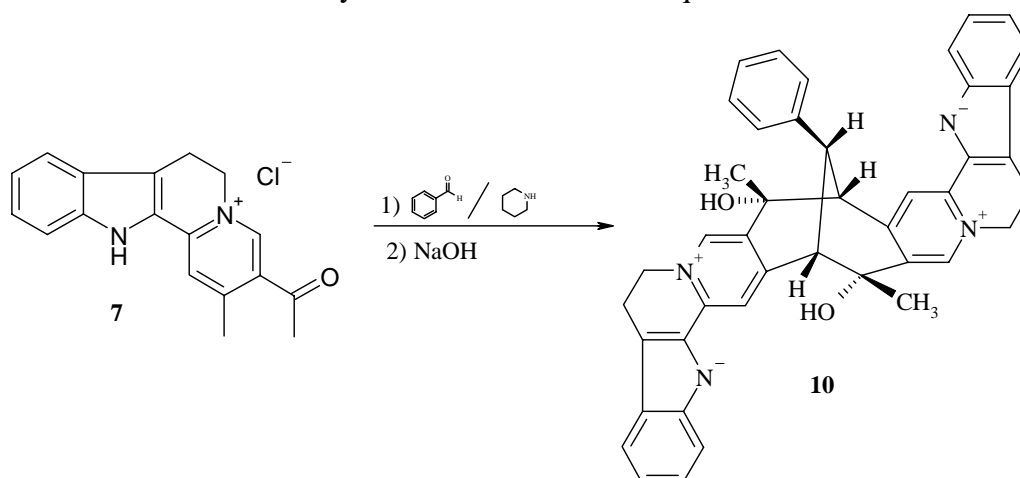


Natural indoloquinolizines have been reported to inhibit DNA synthesis in cancer cell lines [14-16]. In this regard, alstonine **1**, serpentine **2** and sempervirine **4** (Scheme 1), were shown to protect BALB/c and Swiss mice from cancer induced by YC8 lymphoma and Ehrlich carcinoma cells, respectively [15]. In addition, it was reported that synthetic derivatives of the natural product javacarboline showed potent antitumor activities against P-388 murine leukemia cells and PC-6 human lung carcinoma cells [16].

Since there are few and complex strategies available to obtain the indoloquinolizine basic tetracyclic structure [17], we are developing Teuber's reaction [18] as a useful and easy method for obtaining synthetic indoloquinolizines, as new antitumor agents, from tryptamines and β -dicarbonyl compounds. Thus, starting with tryptamine hydrochloride **6** and acetylacetaldehyde dimethyl acetal, Teuber *et al.* obtained 3-acetyl-7,12-dihydro-2-methyl-6*H*-indolo[2,3-*a*]quinolizinium chloride **7**, which after oxidation with *o*-chloranyl yielded the compound **8** with ring C of the tetracyclic system completely aromatized; treatment of **8** with base yielded the corresponding indoloquinolizine **9** (Scheme 2) [19, 20].

Scheme 2. Teuber's reaction for synthesis of indoloquinolizines.

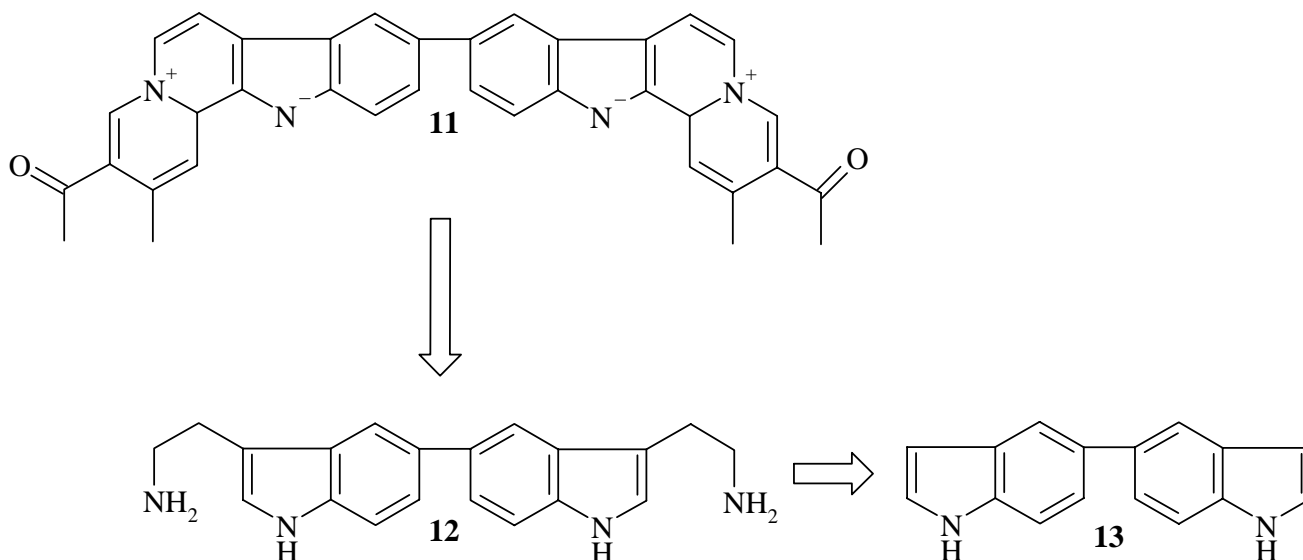
Recently, Solís-Maldonado *et al.* [21] demonstrated that compounds **7-9** possessed differential effects on *in vitro* rat lymphocyte and macrophage functions; proliferation of thymic lymphocytes was significantly ($p < 0.05$) increased (up to 30% increase) by compound **7** at concentrations ranging from 10^{-11} to 10^{-5} M, compared with untreated control. In addition, tumor necrosis factor- α and nitric acid production by peritoneal macrophages was significantly ($p < 0.05$) increased (up to 30% increase) by compounds **8** and **9** (Scheme 2) at concentrations of 10^{-11} to 10^{-5} M, and 10^{-5} M, respectively. The dimeric indoloquinolizine **10** (Scheme 3), obtained by reaction of dihydroindoloquinolizine **7** (Scheme 2) with benzaldehyde under piperidine catalysis [20], showed higher effects (up to 40% increase) on lymphocytes proliferation than the monomeric ones [21].

Scheme 3. Synthesis of dimeric indoloquinolizine **10**.

These synthetic indoloquinolizines, particularly the dimeric compounds, could serve then as immunotherapeutic agents by selectively increasing the pool of activated T lymphocytes or stimulating macrophage functions, with potential use in treatment of infectious diseases and cancer.

In order to be able to continue our research on this subject, we want to synthesize the dimeric indoloquinolizine **11** according to the retrosynthesis of Scheme 4. Using Teuber's reaction, compound **11** can be obtained from the dimeric tryptamine **12** by first synthesizing 5,5'-biindole **13**.

Scheme 4. Retrosynthesis of dimeric indoloquinolizine **11**.



In this paper we describe an efficient synthesis of 5,5'-biindole **13** using the Madelung synthesis of indoles. As we have noted a lack of accurate ^1H - and ^{13}C -NMR data for indole in $\text{DMSO}-d_6$ in the literature, we also report here a detailed ^{13}C - and ^1H -NMR study for both compounds.

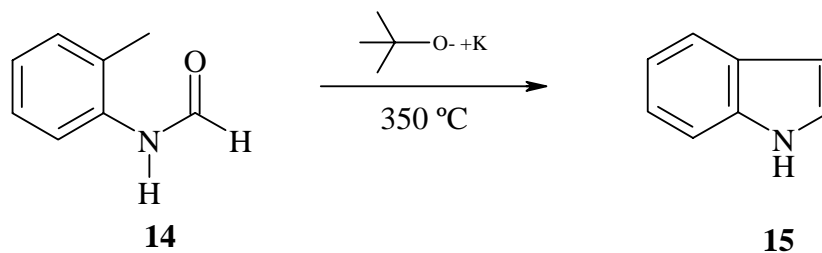
Results and Discussion

Since the first indole synthesis in 1866 [22], a number of synthetic methods for the construction of the indole nucleus have been devised, the most common or "classical" are the Fischer, Bischler, Reissert, Nenitzescu and Madelung ones [1, 23-25]. The availability of the starting material and compatibility with the reaction conditions determine the choice of the appropriate synthesis method for a target molecule containing this type of nucleus [2, 26, 27]. Therefore, a large number of new original syntheses or modifications and applications of known methods continue to be reported [28-30].

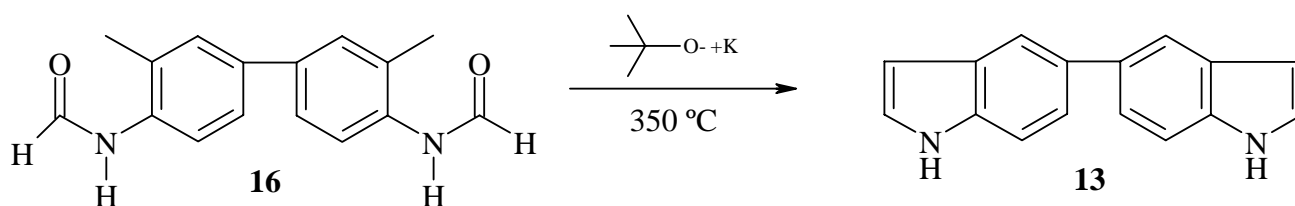
The Madelung indole synthesis is a method for producing indoles from a base-catalyzed thermal cyclization of *N*-acyl-*o*-toluidides [31, 32], and is one of the few known reactions by which the simple indole compound **15** (Scheme 5) can be obtained [33-35].

The most usual conditions previously reported by others include sodium or potassium alkoxide at temperatures of 200-400 °C; thus, indole **15** (79% yield) can be obtained from *N*-formyl-*o*-toluidine **14** (Scheme 5) [36-38]. This yield is calculated on the assumption that 2 moles of *N*-formyl-*o*-toluidine **14** are required for the production of 1 mole of indole [33], although the mechanism of Madelung's reaction has not been completely elucidated [32].

Scheme 5. Madelung's indole reaction.



Therefore we decided to use the Madelung's indole reaction to synthesize 5,5'-biindole **13** starting from *N,N'*-bis-formyl-*o*-tolidine **16** (Scheme 6) [36].

Scheme 6. Synthesis of 5,5'-biindole **13**.

After work-up, we obtained a brown oil which crystallized on cooling. The yield was 1.9 g (88%). Purification by recrystallization in chloroform led to a light-brown solid with a melting point of $195\text{ }^\circ\text{C}$. The ESMS showed a molecular ion at 233 Daltons ($[\text{M}+\text{H}]^+$), in agreement with the molecular formula $\text{C}_{16}\text{H}_{12}\text{N}_2$. There are no accurate ^1H - and ^{13}C -NMR available reports for indole in $\text{DMSO-}d_6$ [39-43] to be compared with those of 5,5'-biindole, therefore we used commercially available indole to acquire this spectroscopic information.

^1H - ^1H -COSY, HMQC and HMBC experiments established geminal and vicinal hydrogen interactions, as well as direct ($^1J_{\text{CH}}$) and two and three bond correlations between carbon and hydrogen in the structure of both indole **15** and 5,5'-biindole **13**. The definite assignment of the chemical shifts of protons and carbons are shown in Tables 1 and 2.

Table 1. ^1H (400 MHz) and ^{13}C (100MHz) NMR spectral data for indole **15** in $\text{DMSO-}d_6$, including results obtained by heteronuclear 2D shift-correlated HMQC ($^1J_{\text{CH}}$) and HMBC ($^nJ_{\text{CH}}$, $n=2$ and 3). Chemical shifts (δ , ppm) and coupling constants (J , Hz, in parenthesis).^a

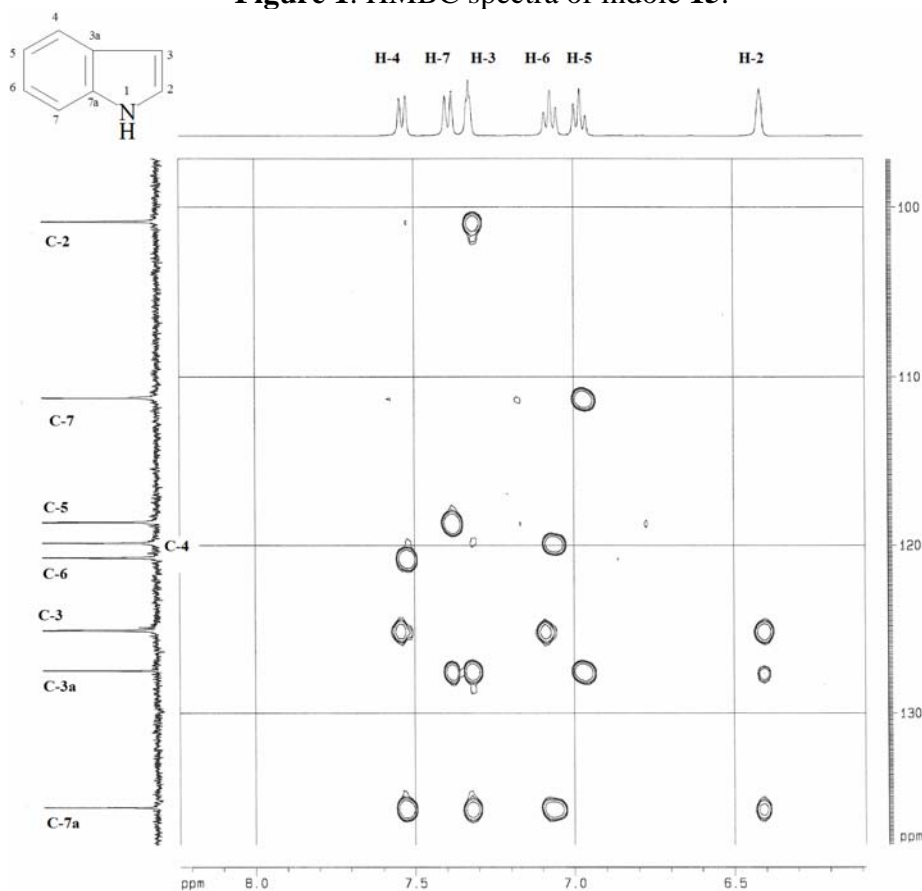
POSITION	δ_{H}	δ_{C}	^b DEPT 135	COSY ^1H - ^1H Correlations	^c HMQC	^c HMBC (12Hz)	
					$^1J_{\text{CH}}$	$^2J_{\text{CH}}$	$^3J_{\text{CH}}$
1 (N-H)	11.08 (s)			H-2			
2	7.33 (t, 2.65)	125.07	(+) CH	N-H, H-3	H-2	H-3	
3	6.42 (d, 2.65)	100.84	(+) CH	H-2, H-4	H-3	H-2	
3a		127.47	(0) C_q			H-3	H-2, H-5, H-7
4	7.53 (d, 7.82)	119.87	(+) CH	H-5	H-4		H-6

Table 1. Cont.

5	6.98 (t, 7.37)	118.64	(+) CH	H-4	H-5		H-7
6	7.07 (t, 7.52)	120.75	(+) CH	H-7	H-6		H-4
7	7.39 (d, 8.06)	111.26	(+) CH	H-6	H-7		H-5
7a		135.71	(0) C _q				H-2, H-3, H-4, H-6

- a) Number of hydrogens bound to carbon atoms deduced by comparative analysis of DEPT 135-¹³C-NMR spectra. Chemical shifts and coupling constants (*J*) obtained of 1D ¹H-NMR spectrum
- b) DEPT shows CH, CH₂, CH₃, C_q
- c) Correlation from C to the indicated hydrogens

Figure 1. HMBC spectra of indole 15.



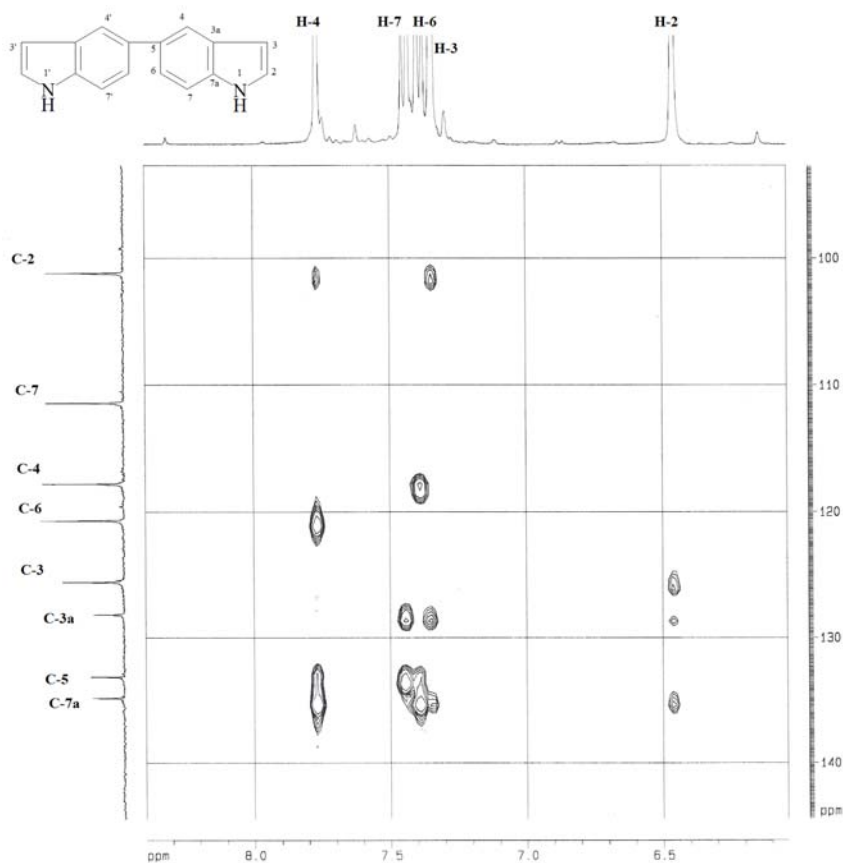
1D NOE difference measurements established the signal of proton 7 of indole in the ¹H-NMR spectrum, since NOEs between the doublet at 7.39 ppm and the singlet at 11.08 ppm (N-H) could be detected. Further NOEs between resonances at 11.08 and 7.33 ppm demonstrated the vicinity of N-H and H-2. In the HMBC spectrum of indole (Figure 1) three bond connectivity between C-7 and H-5 can be observed, whereas in HMBC spectrum of 5,5'-biindole (Figure 2) this is absent, indicating the joint point of the two indole nuclei.

Table 2. ^1H (400 MHz) and ^{13}C (100MHz) NMR spectral data for 5,5'-biindole **13** in $\text{DMSO-}d_6$, including results obtained by heteronuclear 2D shift correlated HMQC ($^1J_{\text{CH}}$) and HMBC ($^nJ_{\text{CH}}$, $n=2$ and 3). Chemical shifts (δ , ppm) and coupling constants (J , Hz, in parenthesis).^a

^b POSITION	δ_{H}	δ_{C}	^c DEPT 135	COSY $^1\text{H-}^1\text{H}$ Correlations	^d HMQC $^1J_{\text{CH}}$	^d HMBC (12Hz) $^2J_{\text{CH}}$ $^3J_{\text{CH}}$	
1 (N-H)	11.06 (s)			H-2, H-3			
2	7.34 (s)	125.59	(+) CH	N-H, H-3	H-2	H-3	
3	6.46 (s)	101.22	(+) CH	H-2	H-3	H-2	H-4
3a		128.18	(0) C _q			H-3	H-2, H-7
4	7.77 (s)	117.81	(+) CH		H-4		H-6
5		133.12	(0) C _q				H-7
6	7.39 (d, 8.42)	120.72	(+) CH	H-7	H-6		H-4
7	7.44 (d, 8.38)	111.45	(+) CH	H-6	H-7		
7a		134.80	(0) C _q				H-2, H-3, H-4, H-6

- a) Number of hydrogens bound to carbon atoms deduced by comparative analysis of DEPT 135- ^{13}C -NMR spectra. Chemical shifts and coupling constants (J) obtained of 1D ^1H NMR spectrum
 b) Corresponding also to positions 1'-7a' due to symmetry of the molecule
 c) DEPT shows CH, CH₂, CH₃, C_q
 d) Correlation from C to the indicated hydrogens

Figure 2. HMBC spectra of 5,5'-biindole **13**.



Conclusions

Among several methods available for the synthesis of biindole compounds [44-47], the use of the Madelung's indole reaction was found suitable for the cyclization of *N,N'*-bis-formyl-*o*-tolidine to produce 5,5'-biindole.

Acknowledgments

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Experimental

General

NMR spectra were recorded in DMSO-*d*₆ at 25 °C on a spectrometer Bruker DPX400 operating at 400.13 MHz for ¹H, and 100.61 MHz for ¹³C. Chemical shifts are given in ppm relative to TMS. Thin layer chromatography (TLC) was performed on precoated plates (Aldrich TLC aluminum sheets silica 60 F₂₅₄) with detection by UV light. FTIR spectra were taken on a Perkin-Elmer spectrometer using potassium bromide pellets. Mass spectra were measured with a Varian MAT 311A Spectrometer. Melting points were determined on an Electrothermal 9100 apparatus and are uncorrected. Indole was obtained from Sigma-Aldrich (St. Louis, MO).

5,5'-Biindole (13).

A 500 mL three-necked round-bottomed flask is fitted with a reflux condenser and a gas inlet tube connected to a cylinder of nitrogen. The third opening of the flask is closed by a stopper. The top of the condenser is connected to an air trap which consists of two 250 mL suction flasks connected in series (the first one is empty; the second one contains paraffin oil, and the inlet tube of this flask extends slightly below the surface of the oil). In the reaction flask is placed *tert*-butyl alcohol (150 mL) and the air in the flask is displaced by dry nitrogen gas. Then metallic potassium (4 g, 0.1 mol) is added, in portions, to the alcohol. The mixture is heated gently until all potassium has dissolved, and then *N,N'*-bis-formyl-*o*-tolidine **16** (5 g, 0.019 mol) [36] is added and brought into solution. The condenser is set for distillation with a filter flask as the receiver; this flask is protected from the air by connecting it to the trap used in the initial operation. The reaction flask is surrounded by an electric mantle, and the excess alcohol is removed by distillation. The residue is heated to 350-360 °C for about 30 minutes and then is allowed to cool in a stream of nitrogen. The residue is decomposed by addition of water (100 mL). The mixture is extracted successively with chloroform (100 and 50 mL), and the combined chloroform extracts are shaken with cold dilute 5% hydrochloric acid. The chloroform

extract is washed with water (50 mL) of, followed by 5% sodium carbonate solution (50 mL), and is dried over anhydrous sodium sulfate and the solvent was evaporated. A brown oil was obtained which crystallized on cooling. The yield was 1.9 g (88%). Purification by recrystallization in chloroform led to a light-brown solid with a melting point of 195 °C. TLC: $R_f = 0.6$ (hexane-acetone, 3:2); IR (KBr): ν_{\max} 3406, 1625, 1469, 1406, 1343, 749 cm^{-1} ; ESMS (positive ion mode): m/z 233 ($[\text{M}+\text{H}]^+$, base peak; Calcd. for $\text{C}_{16}\text{H}_{12}\text{N}_2$, 232). $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ see Table 2.

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Sample availability: Available from the author.