

BISINDOLES.

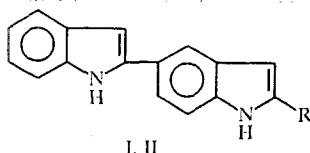
29.* ELECTROPHILIC SUBSTITUTION REACTIONS IN THE

2,5'-BIS-1H-INDOLE SERIES

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Quantum-chemical calculations and NMR spectroscopic data have been used to determine electron density distribution in the 2,5'-bis-1H-indole molecule. Several electrophilic substitution reactions have been carried out for 2,5'-bis-1H-indole and its 2'-ethoxycarbonyl derivative. It has been shown that only the β -position of one pyrrole ring is involved in selective electrophilic substitution.

We have previously reported [2, 3] on the synthesis of new unsymmetrical bisindole systems of 2,5'-bis-1H-indole (I) having two nonequivalent free β -positions on the pyrrole rings.



I R=H; II R=COOEt

With the object of predicting the preferred point of electrophilic attack together with the probable mutual arrangement of the indole rings, a quantum-chemical calculation was carried out on the 2,5'-bis-1H-indole (I) molecule using the MINDO/3 method [4] with rotation around the C_2-C_5 bond (Table 1, Fig. 1).

From the minimum value of the total energy and the heat of formation one can postulate that the angle between the indole fragments in the 2,5'-bis-1H-indole molecule amounts to 80° . It has been established that in terms of the nature of the distribution of the electron density, independently of the angle of rotation of the indole fragments, 2,5'-bis-1H-indole (I) is not, in principle, different from indole. The highest electron density is concentrated on the C_3 and $C_{3'}$ atoms with C_3 predominant. Consequently the primary electrophilic attack must be directed at just these positions, and first of all at position 3.

According to the PMR spectrum of bisindole (I) (Table 2), the signal of the 3-H proton appears downfield (6.74 ppm) relative to that of 3'-H (6.48 ppm) which probably indicates a lower electron density on the C_3 atom compared to $C_{3'}$. However, a qualitative picture obtained in a study of the kinetics of protonation (deuteration by means of CD_3O) of positions 3 and 3' showed that the rate of deuteration in the first ring (3-H \rightarrow 3-D) exceeds that for the second ring (3'-H \rightarrow 3'-D) by a factor of approximately 5. From this one can form an assessment of the greater electron density at position 3.

*For communication 28, see [1].

TABLE 1. Energy and Electronic Indexes for 2,5'-Bisindole with Rotation Around the C₂-C₅ Bond

φ , °	Total energy E, kcal/mole	Heat of formation H, kcal/mole	Charge density, C(3), electron, units	Charge density, C(3'), electron, units
0	-59555,5	217,7	-0,1528	-0,1412
20	-59556,3	216,9	-0,1520	-0,1409
40	-59557,6	215,6	-0,1514	-0,1406
60	-59558,5	214,8	-0,1519	-0,1409
80	-59559,0	214,2	-0,1531	-0,1412
100	-59558,8	214,4	-0,1542	-0,1415
120	-59558,3	214,9	-0,1552	-0,1420
140	-59557,2	216,0	-0,1560	-0,1423
160	-59555,9	217,4	-0,1568	-0,1427
180	-59554,9	218,3	-0,1573	-0,1426

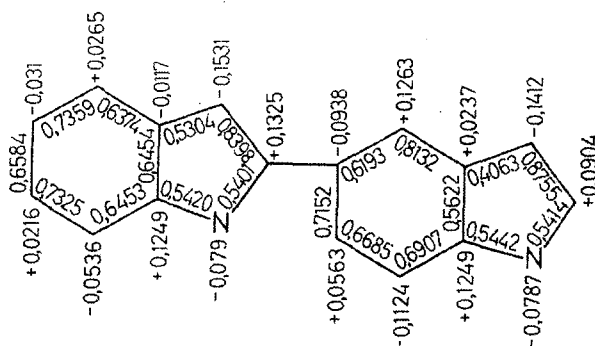


Fig. 1. Electron density and Wyberg indexes in the 2,5'-bis-1H-indole (I) molecule with rotation angle 80°.

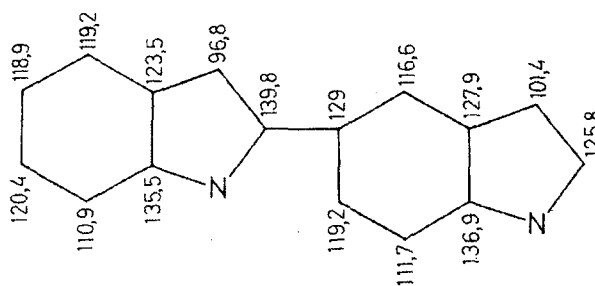


Fig. 2. Chemical shifts (δ ppm) of carbon atom signals in the ¹³C NMR spectrum of 2,5-bis-1H-indole (I).

The numerically greater chemical shift of the 3-H proton (6.74 ppm) can be explained in terms of an anisotropic effect of the second indole ring. Assuming the geometry of indole is normal and taking into account that the minimum of the total energy of the bisindole (I) corresponds to a mutual rotation of the planes of the indole fragments by approximately 80°, the contribution to the shielding constant of the 3-H proton from the anisotropy of the ring current of the benzene part of the second indole ring was calculated. From the data of Johnson and Bovey [5], for the indicated angle of rotation (calculated rotation barrier 3.5 to 4.0 kcal/mole) this contribution amounts to more than 0.3 ppm which is greater than the experimental difference between the chemical shifts of these protons (0.26 ppm). Consequently, allowing for anisotropy, the 3-H proton signal must be stronger, which is in accord with a greater electron density at the C₃ atom. This also supports the reduced value of the chemical shift of the C₃ signals in the uncoupled ¹³C NMR spectrum of bisindole (I) (Fig. 2).

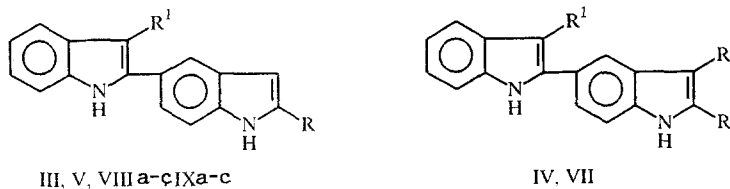
The experimental results support the calculated and spectroscopic data as regards the greater reactivity of position 3 compared with position 3'. Thus, Vilsmeier formulation and Mannich aminomethylation take place at positions 3 and 3' of

TABLE 2. PMR Spectra of Compounds I-IX a-c*

Compound	Chemical shift, δ ppm	Spin-spin coupling, Hz
I	10.05 (1H, s); 10.03 (1'H, s); 7.3 (2'H, d, d); 6.73 (3H, d, d); 6.48 (3'H, m); 8.00 (4'H, d, d); 6.9...7.04 (5H, 6H, m); 7.6 (6'H, d, d); 7.37 (7H, d); 7.43 (7'H, d, d)	$J_{13} = 2$; $J_{2'3'} = 3.1$; $J_{1'2'} = 2.5$; $J_{37} = 0.5$; $J_{46} = 2.2$; $J_{45} = -J_{67} = J_{6'7'} = J_{56} = 8.5$
II	11.4 (1H, s); 11.9 (1H, s); 6.97 (3H, d, d); 7.16 (3H, d, d); 7.48 (4H, d, d); 8.09 (4H, d); 6.9...7.0 (5H, 6H, m); 7.76 (6H, d, d); 7.37 (7H, d, d); 4.34 (CH ₂ , d); 1.36 (CH ₃ , t)	$J_{13} = 1.6$; $J_{1'3'} = 2.2$; $J_{37} = 0.8$; $J_{46} = 1.2$; $J_{\text{CH}_2\text{-CH}_3} = 7.0$; $J_{45} = -J_{56} = J_{67} = 9.1$
III	12.0 (1H, s); 11.9 (1'H, s); 7.24 (3'H, d); 8.1 (4H, m); 7.62 (4'-H, d); 7.2...7.6 (5H, 6H, 6'-H, 7H, 7'-H, m); 4.36 (CH ₂ , q); 1.36 (CH ₃ , t); 9.97 (CHO, s)	$J_{46} = 1.9$; $J_{\text{CH}_2\text{-CH}_3} = 6.9$; $J_{1'3'} = 1.7$
IV	12.44 (1H, br. s); 12.4 (1'H, br. s); 8.48 (2'H, d); 8.23 (4H, br. s); 8.48 (4'H, d); 7.25...7.53 (5H, 6H, 7H, m); 7.70 (6'H, d); 7.76 (7'H, d); 10.03 (3-CHO, s); 10.01 (3'-CHO, s)	$J_{1'2'} = 2.4$; $J_{4'6'} = 3.0$; $J_{45} = -J_{56} = J_{67} = 7.7$
V	11.96 (1H, s); 11.38 (1'H, s); 7.2 (2'H, m); 6.57 (3'-H, br. s); 8.43 (4H, d, d); 7.81 (4'H, d, d); 7.2...7.67 (5H, 6H, 7H, m); 7.3 (6'H, d, d); 7.31 (7'H, d); 2.02 (CH ₃ , s)	$J_{4'6'} = 1.65$; $J_{6'7'} = 8.3$; $J_{45} = -J_{56} = J_{67} = 8.4$
VI	11.1 (1H, s); 11.7 (1'H, s); 7.15 (3'H, br. s); 8.61 (4H, d, d); 8.07 (4H, d, d); 6.9...7.3 (5H, 6H, 7H, m); 7.74 (6'-H, d, d); 7.51 (7'-H, d, d); 4.35 (CH ₂ , q); 1.36 (CH ₃ , t); 2.25 (NCH ₃ , s); 3.64 (NCH ₃ , s)	$J_{46} = 1.3$; $J_{47} = 0.7$; $J_{4'6'} = 1.4$; $J_{\text{CH}_2\text{-CH}_3} = 7.1$; $J_{45} = -J_{56} = J_{67} = 9.0$
VII	10.04 (1H, br. s); 11.86 (1'H, br. s); 7.6 (2'H, d); 7.62 (4H, br. s); 8.17 (4'H, br. s); 6.9...7.59 (5H, 6H, 7H, m); 7.7 (7H, m); 2.25 (3-NCH ₃ , s); 2.19 (3'-NCH ₂ , s); 3.59 (3-NCH ₂ , s); 3.55 (3'-NCH ₂ , s)	$J_{46} = 1.4$; $J_{47} = 0.9$; $J_{1'2'} = 2.2$; $J_{45} = -J_{56} = J_{67} = 8.9$
VIIIa	12.3 (1H, br. s); 11.9 (1'H, br. s); 7.25 (3'H, br. s); 7.82 (4H, m); 8.41 (4'H, m); 7.25...7.8 (5H, 6H, 7H, m); 8.09 (6'H, d, d); 7.44 (7'H, d); 4.37 (CH ₂ , q); 1.37 (CH ₃ , t); 7.25...7.8 (Ph, m)	$J_{46} = 1.3$; $J_{47} = 1.0$; $J_{6'7'} = 8.6$
VIIIb	12.3 (1H, s); 11.9 (1'H, br. s); 7.3 (3'H, br. s); 7.3...7.7 (4H, 5H, 6H, 7H, m); 8.46 (4'H, br. s); 8.09 (6'H, m); 7.65 (7'H, d); 4.38 (CH ₂ , q); 1.38 (CH ₃ , t); 7.89 (A-H, d); 8.31 (B-H, d)	$J_{6'7'} = -J_{AB} = 9.2$; $J_{\text{CH}_2\text{-CH}_3} = 7.1$
VIIIc	12.1 (1H, s); 11.9 (1'H, s); 7.27 (3'H, br. s); 8.40 (4H, d); 8.41 (4'-H, d); 7.3...7.5 (5H, 6H, 7H, m); 8.04 (6'H, d, d); 7.75 (7'H, d); 4.31 (CH ₂ , q); 1.31 (CH ₃ , t); 7.5 (A-H, d); 7.77 (B-H, d)	$J_{\text{CH}_2\text{-CH}_3} = 7.1$; $J_{AB} = J_{6'7'} = 9.2$
IXa	11.27 (1H, s); 10.54 (1'H, br. s); 7.3 (2'H, m); 6.65 (3'-H, m); 8.65 (4H, m); 8.46 (4H, br. s); 7.2...7.94 (5H, 6H, 7H, m); 8.07 (6'H, d, d); 7.64 (7'H, d); 7.92 (A-H, d); 7.4...7.6 (B-H, B-11m)	$J_{1'3'} = 2.2$; $J_{2'3'} = 3.0$; $J_{4'6'} = 1.5$; $J_{ABC} = J_{67} = 8.8$
IXb	11.55 (1H, s); 10.6 (1H, br. s); 7.48 (2'H, d, d); 6.68 (3'H, d, d); 8.65 (4H, m); 8.47 br. s) 7.3...7.5 (5H, 6H, 7H, m); 8.04 (6'H, d, d); 7.66 (7'H, d); 8.05 (A-H, d); 8.39 (B-H, d)	$J_{1'2'} = 2.2$; $J_{1'3'} = 2.0$; $J_{2'3'} = 3.0$; $J_{4'6'} = 2.4$; $J_{6'7'} = J_{A5} = 8.8$
IXc	6.57 (3'H, d); 8.42 (4H, m); 8.37 (4'H, m); 7.2...7.4 (5H, 6H, 7H, m); 7.92 (6'-H, d); 7.5 (7'H, d); 7.47 (A-H, d); 7.74 (B-H, d)	$J_{1'2'} = 2.6$; $J_{1'3'} = 2.1$; $J_{2'3'} = 3.0$; $J_{AB} = J_{6'7'} = 8.6$

*Spectra of compounds I, IXa, IXc run in acetone D₆, of II-VIIIa-c, IXb, in DMSO-D₆

bisindole I whereas the more selective reactions – Vilsmeier acetylation and azocoupling – occur only at position 3 (compounds V, IXa-c).



III R = COOEt, R¹ = CHO; IV R = H, R¹ = CHO; V R = H, R¹ = COMe; VI R = COOEt, R¹ = CH₂NMe₂; VII R = H, R¹ = CH₂NMe₂; VIIIa—c R = COOEt; IXa—c R = H; VIII, IXa R¹ = N=N-C₆H₅, b R¹ = N=N-C₆H₄-NO₂, c R¹ = N=N-C₆H₄Cl

Formulation of compounds I and II by means of Vilsmeier's reagent takes place under conditions similar to those for indole [6]. Substitution into the bisindole I leads to the formation of the 3,3'-diformyl derivative IV. In bisindole II the formyl group is introduced only in position 3, forming compound III. Further formulation does not occur even under more rigorous conditions (100°C, 2-3 h). Evidently the 2'-ethoxycarbonyl group prevents the introduction of a second formyl group in position 3', although the acceptor effect of the formyl group already introduced cannot be excluded (compound III).

Dimethylaminomethylation of compounds I and II is carried out under conditions similar to those for indole [7] yielding bisgramine VII and the monosubstitution product VI. We were not able to introduce a substituent into position 3' of compound II even at 90-100°C and a hundred times excess of the Mannich base.

2,5'-Bis-1H-indole (I) and its derivative II entered into an azo-coupling reaction with phenyldiazonium salts only at position 3, forming azo-compounds VIIIa-c and IXa-c in high yields.

EXPERIMENTAL

Monitoring of the progress of the reactions and the purity of the reagents, together with determination of R_f values, was carried out on Silufol UV-254 plates. Silica gel with particle size 100-200 μm was used as a sorbent. The UV spectra were run on a Specord spectrophotometer in ethanol, IR spectra on a UR-20 instrument as mulls in mineral oil. The ¹H and ¹³C NMR spectra were recorded on a Varian CFT-20 at a working frequency of 80 MHz and on a WP-200SY; TMS was used as internal standard and chemical shifts were measured with an accuracy of 0.01 ppm, coupling constants to 0.1 Hz.

An MKh-1303 instrument with direct introduction of the sample into the ionizing chamber, and a Nermag R 10-10 chromatograph-mass spectrometer were used to obtain mass spectra, with ionizing energy 50 eV.

The results of elemental analysis of the compounds prepared were in agreement with calculations.

2'-Ethoxycarbonyl-3-formyl-2,5'-bis-1H-indole (III). To 3.6 g (49 mmole) freshly distilled DMF, cooled to -5°C, was added, dropwise, 1.89 g (12 mmole) phosphoryl chloride; this was stirred at room temperature for 1 h, cooled to -5°C and a solution of 0.3 g (1 mmole) bisindole II added, maintaining the temperature below 0°C. The mixture was stirred 2 h at room temperature, poured onto 100 g crushed iced, and the pH adjusted to 10. The precipitate which formed was filtered off, washed with water until the washings were neutral, and dried. Yield 0.31 g.

3,3'-Diformyl-2,5'-bis-1H-indole (IV). Prepared in a similar manner, from 0.23 g (1 mmole) bisindole I. Yield 0.28 g.

3-Acetyl-2,5'-bis-1H-indole (V). To 2.4 ml (27.4 mmole) dimethylacetamide, cooled to 0°C, was added, dropwise, 0.93 ml (11.4 mmole) phosphoryl chloride; the mixture was stirred at room temperature for 30 min, cooled to 0°C and a solution of 0.3 g (1 mmole) bisindole II in 2 ml dimethylacetamide added slowly, maintaining the temperature below 0°C. It was then stirred for 3 h at 40°C, cooled, and poured into 20 ml ice/water and the pH adjusted to 10. The precipitate which formed was filtered off, washed with water until the washings were neutral, and dried. Yield 0.25 g.

3-Dimethylamino-2'-ethoxycarbonyl-2,5'-bis-1H-indole (VI). A. To a solution of 0.3 g (1 mmole) bisindole II in 5 ml dry DMF was added 0.46 g (5 mmole) CH₂=N⁺(CH₃)₂Cl⁻ and the mixture stirred 2 h at 0°C. The solution so obtained was poured into 50 ml cold water and the pH adjusted to 10. The precipitate which formed was filtered off, washed with water until the washings were neutral, and dried. Yield 0.35 g.

TABLE 3. Characteristics of Compounds Prepared

Com- pound	Empirical formula	mp, °C	IR spectrum, ν cm^{-1}	UV spectrum, λ nm (log ϵ)	k_f	M^+ , m/z	Yield %
III	$\text{C}_{20}\text{H}_{16}\text{N}_2\text{O}_3$	244...246	1640, 1700 (C=O), 3330 (NH)	228 (4,3), 263 (4,7), 303 (4,4)	0,45*	232	95
IV	$\text{C}_{18}\text{H}_{12}\text{N}_2\text{O}_3$	267...268	1635, 1650 (C=O), 3200, 3300 (NH)	215 (4,3), 230 (4,2), 308 (4,8)	0,4 ether	288	99
V	$\text{C}_{18}\text{H}_{14}\text{N}_2\text{O}$	160	1620, 1630 (C=O), 3180...3270 (NH)	213 (4,8), 224 (4,4), 256 (4,8)	0,22*	—	98
VI	$\text{C}_{22}\text{H}_{23}\text{N}_3\text{O}_2$	159...161	1710 (C=O), 3340, 3390 (NH)	214 (4,5), 247 (4,7), 299 (4,6)	0,8**	361	98
VII	$\text{C}_{22}\text{H}_{26}\text{N}_4$	137...137,5	3405 (NH)	215 (4,6), 243 (4,4), 253 (4,6), 300 (4,1)	0,45**	346	98
VIII a	$\text{C}_{25}\text{H}_{26}\text{N}_4\text{O}_2$	223...224	1425 (N=N), 1705 (C=O), 3325 (NH)	214 (4,2), 255 (4,4), 298 (4,5)	0,5***	408	60
VIII b	$\text{C}_{25}\text{H}_{19}\text{N}_5\text{O}_4$	280...281	1420 (N=N), 1315, 1525 (NO_2), 1700 (C=O), 3360 (NH)	214 (4,2), 239 (4,3), 253 (4,3), 291 (4,5), 481 (4,2)	0,44***	453	50
VIII c	$\text{C}_{25}\text{H}_{19}\text{ClN}_4\text{O}_2$	246...247	1420 (N=N), 1715 (C=O), 3330 (NH)	215 (4,6), 253 (4,7), 296 (4,8)	0,53***	442	82
IX a	$\text{C}_{22}\text{H}_{16}\text{N}_4$	77...79	1440 (N=N), 3400, 3445 (NH)	202 (4,5), 250 (4,5), 307 (4,3)	0,5***	—	74
IX b	$\text{C}_{22}\text{H}_{15}\text{N}_5\text{O}_2$	285...286	1325, 1510 (NO_2), 1420 (N=N), 3380, 3420 (NH)	204 (4,4), 244 (4,6), 307 (4,0), 495 (4,3)	0,36***	—	94
IX c	$\text{C}_{22}\text{H}_{15}\text{ClN}_4$	96...98	1410 (N=N), 3290, 3400 (NH)	218 (4,4), 250 (4,9), 316 (4,3)	0,5***	—	95

*Benzene-ether, 2:1.

**2-Propanol-ammonia, 10:1.

***Benzene-ether, 1:1.

B. To a cooled suspension of 0.3 g (1 mmole) bisindole II in 10 ml glacial acetic acid was added a solution prepared by adding, at 0°C, 0.15 g glacial acetic acid and 0.4 ml (5 mmole) 40 aqueous formaldehyde to 1.4 ml (10 mmole) 33% aqueous dimethylamine. The mixture was stirred 2 h at 90°C, cooled, diluted with 100 ml cold water, and the pH adjusted to 10. The precipitate which formed was filtered off, washed with water until the washings were neutral, and dried. Yield 0.35 g.

3,3'-Di(dimethylaminomethyl)-2,5'-bis-1H-indole (VII) was prepared by a method similar to that for compound VI, method A, using 0.23 g (1 mmole) bisindole I at 50-55°C. Yield 0.33 g.

2'-Ethoxycarbonyl-3-phenylazo-2,5'-bis-1H-indole (VIIIa). To a solution of 0.3 g (1 mmole) bisindole II in 80 ml dioxane was added 20 ml water; this was cooled to 0°C and a solution, prepared by diazotizing 0.37 g (4 mmole) aniline, added dropwise and the mixture stirred 3 h at 0°C, maintaining the pH at 5-6. It was then diluted with 500 ml cold water and extracted with ether. The extract was washed with 10% NaOH and washed with water until neutral and dried over anhyd. Na₂SO₄. The ether was evaporated to yield 0.24 g orange colored crystals.

2'-Ethoxycarbonyl-3-p-nitrophenylazo-2,5'-bis-1H-indole (VIIIb) was prepared by the method described for compound VIIIa from 0.3 g (1 mmole) bisindole II and 0.5 g (3.57 mmole) p-nitroaniline. Yield 0.22 g dark red crystals.

2'-Ethoxycarbonyl-3-p-chlorophenylazo-2,5'-bis-1H-indole (VIIIc) was prepared by the method given for compound VIIIa from 0.3 g (1 mmole) bisindole II and 0.5 g (3.92 mmole) p-chloroaniline. Yield 0.36 g orange crystals.

3-Phenylazo-2,5'-bis-1H-indole (IXa) was prepared by the method described above from 0.23 g (1 mmole) bisindole I and 0.28 g (2.8 mmole) aniline. Yield 0.48 g orange crystals.

3-p-Nitrophenylazo-2,5'-bis-1H-indole (IXb) was prepared by the method described above from 0.23 g (1 mmole) bisindole I and 0.41 g (3 mmole) p-nitroaniline. Yield 0.35 g dark red crystals.

3-p-Chlorophenylazo-2,5'-bis-1H-indole (IXc) was prepared by the method described above from 0.23 g (1 mmole) bisindole I and 0.36 g (3 mmole) p-chloroaniline. Yield 0.35 g orange crystals.

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