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BISINDOLES.

11.* ELECTROPHILIC SUBSTITUTION REACTIONS IN THE BIS(5-INDOLYL) SULFONE SERIES AND DATA ON THE REACTIVITY INDEXES OF SOME BISINDOLES

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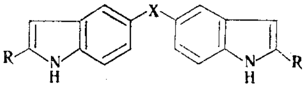
The principles of the electron density distribution in 5,5'-bis-1H-indole, bis(5-indolyl)methane, and bis(5-indolyl) sulfone were determined on the basis of quantum-chemical calculations. Several electrophilic substitution reactions in the bis(5-indolyl) sulfone series were realized.

We have previously reported [2-4] the synthesis of a number of new bisindole systems that each have two pyrrole rings with unsubstituted β positions, viz., 5,5'-bis-1H-indole (I), bis(5-indolyl)methane (II), bis(5-indolyl) sulfones (III), and their 2,2'-bis(ethoxycarbonyl) derivatives (IV-VI):



I-VI

I X=—, R=H; II X=CH$_2$, R=H; III X=SO$_2$, R=H; IV X=—, R=COOC$_2$H$_5$; V X=CH$_2$, R=COOC$_2$H$_5$; VI X=SO$_2$, R=COOC$_2$H$_5$

In order to theoretically examine the potential reaction centers in the electrophilic substitution reactions of bisindoles I-III we subjected their molecules and, for comparison, the indole molecule to quantum-chemical calculations by the CNDO (complete neglect of differential overlap) MO method [5].† As in the case of 3,5'-bis-1H-indole, a planar structure was selected for 5,5'-bis-1H-indole (I) [7]. A tetrahedral structure of the central bonding atoms was taken into account for bisindoles II and III. To simplify the calculations the indole fragments were situated in the same plane. The angles and bond lengths of the indole ring [8] were used in all cases.

The results of the quantum-chemical calculations are presented in the form of molecular diagrams in Fig. 1 (the overall electron charges are given; the π-electron densities are indicated in parentheses).

It is apparent from the diagrams presented below that the character of the electron density distribution of the indole ring is retained in bisindoles I-III. The highest electron density, both the overall and the π-electron density, is concentrated in the 3 and 3' positions of the bisindoles; consequently, initial attack should be directed to these positions in electrophilic substitution reactions.

We have previously reported [9] some electrophilic substitution reactions of bis(5-indolyl)methane (II). It was shown that in the Vilsmeier, Mannich, and diazo coupling reactions bis(5-indolyl)methane (II) undergoes reaction in the 3 and 3' positions to give disubstitution products, which is in good agreement with the data for its molecular diagram.

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*See [1] for Communication 10.

†The calculations were performed by means of the program of V. G. Maslov [6] with a BÉSM-6 computer in the Institute of Applied Mathematics of Tbilisi State University.

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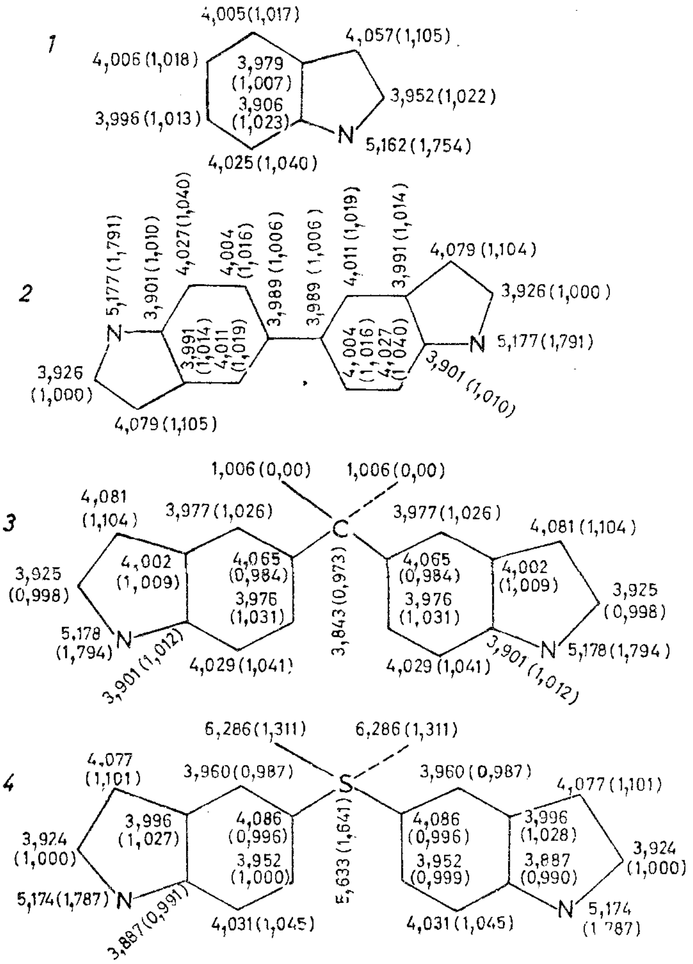
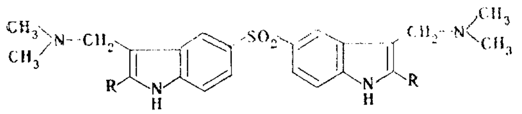
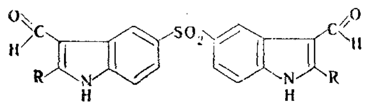


Fig. 1. Molecular diagrams: 1) indole; 2) 5,5'-bis-1H-indole (I); 3) bis(5-indolyl)methane (II); 4) bis(5-indolyl) sulfone (III).

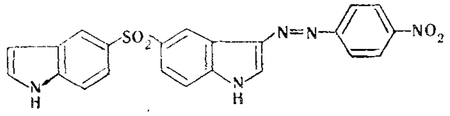
In the present research we studied the electrophilic substitution reactions of bis(5-indolyl) sulfone (III) and its 2,2'-bis(ethoxycarbonyl) derivative (VI) and accomplished the Vilsmeier, Mannich, and diazo coupling reactions. It seemed of interest to ascertain in a qualitative respect the effect of the electron-acceptor SO_2 and $COOC_2H_5$ groups on the course of these reactions.



VII, VIII



IX, X



XI

VII, IX R=H; VIII, X R=$COOC_2H_5$

Despite the electron-acceptor effect of the SO_2 group, the aminomethylation of unsubstituted bis(5-indolyl) sulfone (III) with a freshly prepared complex (dimethylamine, formaldehyde, and acetic acid [10]) proceeds under conditions similar to those used in indole [10] and bis(5-indolyl)methane [9]. However, in addition to the expected 3,3'-bis(dimethylaminomethyl)bis(5-indolyl) sulfone (VII), we also isolated side products (in 20% yield). These were found to be a mixture of slightly soluble products (probably oligomers), which are evidently formed as a result of reaction of starting heterocycle III and formaldehyde, as in the condensation of indole with formaldehyde [11, 12].

When N,N-dimethylmethyleneimmonium chloride [13] in absolute dimethylformamide (DMF) is used, the reaction proceeds unambiguously and leads to the formation of a bisgramine (VII) in high yield.

The formylation of bis(5-indolyl) sulfone (III) with the Vilsmeier complex based on phosphorus oxychloride and DMF also proceeds under conditions similar to those used with indole [14] and bis(5-indolyl)methane [9] to give a disubstitution product, viz., 3,3'-diformylbis(5-indolyl) sulfone (IX).

Virtually no diazo coupling is observed in the reaction of III with benzenediazonium and p-chlorobenzenediazonium chlorides; in the case of p-nitrobenzenediazonium chloride 3-(p-nitrophenylazo)bis(5-indolyl) sulfone (XI) (39%) and starting sulfone III (45%) were isolated from the reaction products.

In our opinion, the formation of monosubstitution product XI and the recovery of unchanged sulfone III can be explained by the low electrophilicities of the diazo components, which are not capable of surmounting the additional energy barrier created by the effect of the electron-acceptor SO_2 group. It is evident that this effect is intensified in XI due to the substituent in the 3 position.

The formylation and aminomethylation of 2,2'-bis(ethoxycarbonyl)bis(5-indolyl) sulfone (VI) proceed, respectively, at 80 and 95°C. This is due to the electron-acceptor and steric effect of the o-ethoxycarbonyl groups. The same factors apparently promote suppression of the competitive reaction in the aminomethylation of VI; 2,2'-bis(ethoxycarbonyl)-3,3'-bis(dimethylaminomethyl)bis(5-indolyl) sulfone (VIII) is formed in 92% yield.

The structure of VII-XI were confirmed by data from IR, UV and, PMR spectra.

In the PMR spectrum of 3-(p-nitrophenylazo)bis(5-indolyl) sulfone (XI) the signals of the protons in the 2' and 3' positions show up in the form of doublets ($J_{2,3}$ = 3.1 Hz) at 7.44 and 6.60 ppm, and the signal of the 2-H proton appears in the form of a doublet ($J_{1,2}$ = 1.2 Hz) at 8.78 ppm. The signals of the remaining protons appear at 7.54-8.40 ppm. Because of the complex superimposition upon one another, it is impossible to unambiguously assign them.

EXPERIMENTAL

The course of the reactions and the purity of the compounds were monitored on Silufol UV-254. Silica gel (100-250 μ) was used for column chromatography. The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-20 spectrometer. The UV spectra of solutions in ethanol were recorded with a Specord spectrophotometer. The PMR spectra of solutions in d_6-dimethyl sulfoxide were recorded with a Varian CFT-20 spectrometer (80 MHz) with tetramethylsilane as the internal standard; the accuracies in the measurement of the chemical shifts and spin–spin coupling constants were ±0.01 ppm and ±0.1 Hz, respectively.

3,3'-Bis(dimethylaminomethyl)bis(5-indolyl) Sulfone (VII). A 4.7-g (0.05 mole) sample of $[(CH_3)_2\overset{+}{N}{=}CH_2]Cl^-$ [13] was added to a solution of 2.96 g (0.01 mole) of bis(5-indolyl) sulfone (III) in 40 ml of absolute DMF, and the mixture was stirred at 20°C for 2 h. It was then diluted with 0.5 liter of cold water and made alkaline to pH 10, and the resulting precipitate was removed by filtration, washed with water until the washings had pH 7, and dried *in vacuo* over KOH to give 3.8 g (93%) of a product with mp 182-184°C. IR spectrum: 3340 (NH) and 1140 cm^{-1} (SO_2). UV spectrum, λ_{max}: 240, 249, and 281 nm. PMR spectrum: 11.17 (NH, s), 7.33 (2H, s), 8.23 (4H, s), 7.54 (6H, dd), 7.47 (7H, d), 3.56 ($N{-}CH_2$, s), and 2.48 ppm ($N{-}CH_3$, s) $J_{4,6}$ = 1.6, $J_{6,7}$ = 8.8 Hz. Found: C 64.7; H 5.9; N 14.0; S 7.5%. $C_{22}H_{26}N_4O_2S$. Calculated: C 64.4; H 6.3; N 13.7; S 7.8%.

2,2'-Bis(ethoxycarbonyl)-3,3'-bis(dimethylaminomethyl)bis(5-indolyl) Sulfone (VIII). A. This compound was similarly obtained from 4.4 g (0.01 mole) of VI and 4.7 g (0.05 mole) of $[CH_2{=}\overset{+}{N}(CH_3)_2]Cl^-$) at 90-95°C. The yield was 5.2 g (94%).

B. Glacial acetic acid (30 ml) was added slowly at 0°C to 28 ml of 33% aqueous dimethylamine, and 18 ml of 40% formalin was added to this mixture after 1-2 min. The resulting solution was added immediately to a suspension of 4.4 g of 2,2'-bis(ethoxycarbonyl)bis(5-indolyl) sulfone (VI) in 20 ml of glacial acetic acid, and the mixture was heated to 90-95°C and stirred for 2 h. The resulting soltion was cooled, diluted with 0.8 liter of cold water, and made alkaline to pH 10. The precipitate was removed by filtration, washed with water until the washings had pH 7, and dried *in vacuo* over KOH to give 5.1 g (92%) of a product with mp

169-170°C. IR spectrum: 3340 (NH); 1730, 1695 (C=O); 1145 cm^{-1} (SO_2). UV spectrum, λ_{max} (log ε): 260 (4.58) and 312 nm (4.27). PMR spectrum: 11.48 (NH, s), 8.44 (4H, s), 7.67 (6H, d), 7.51 (7H, d), 4.34 (CH_2—CH_3, q), 1.34 (CH_3—CH_2, t), 3.92 (N—CH_2, s), and 2.17 ppm (N—CH_3, s); $J_{6,7}$ = 8.8 Hz. Found: C 60.9; H 6.2; N 9.8; S 6.0%. $C_{28}H_{34}N_4O_6S$. Calculated: C 60.6; H 6.1; N 10.1; S 5.8%.

3,3'-Diformylbis(5-indolyl) Sulfone (IX). A solution of 0.89 g (3 mmole) of bis(5-indolyl) sulfone (III) in 3 ml of DMF was added dropwise while maintaining the temperature below 0°C to the Vilsmeier complex prepared by the method in [14] from 2.62 g (0.036 mole) of DMF and 1.38 g (9 mmole) of phosphorus oxychloride, and the mixture was stirred at room temperature for 3 h. It was then cooled and treated with 100 g of ice, and the solution was filtered and made alkaline to pH 10. The resulting precipitate was removed by filtration, washed with water until the washings had pH 7, and dried. Recrystallization from aqueous DMF gave 0.69 g (65%) of a product with mp 324-325°C. IR spectrum: 3250, 3120 (NH); 1660, 1630 (C=O); 1150 cm^{-1} (SO_2). PMR spectrum: 10.76 (NH, s), 8.32 (2H, s), 8.64 (4H, d), 7.74 (6H, dd), 7.61 (7H, dd), and 9.94 ppm (CHO, s); $J_{4,6}$ = 1.6, $J_{4,7}$ = 0.4, and $J_{6,7}$ = 8.6 Hz. Found: C 61.6; H 3.5; N 8.3; S 9.4%. $C_{18}H_{12}N_2O_4S$. Calculated: C 61.4; H 3.4; N 8.0; S 9.1%.

2,2'-Bis(ethoxycarbonyl)-3,3'-diformylbis(5-indolyl) Sulfone (X). This compound was obtained as in the preceding experiment from 1.32 g (3 mmole) of 2,2'-bis(ethoxycarbonyl)bis-(5-indolyl) sulfone (VI) at 80°C. Recrystallization from DMF gave 1 g (68%) of X, which decomposed at 360°C. IR spectrum: 3300, 3150 (NH); 1660, 1705, 1740 (CO); 1140 cm^{-1} (SO_2). PMR spectrum: 12.30 (NH, s), 8.81 (4H, s), 7.85 (6H, dd), 7.68 (7H, d), 4.44 (CH_2—CH_3, q), 1.38 (CH_3—CH_2, t), and 10.54 ppm (CHO, s); $J_{4,6}$ = 1.6, $J_{6,7}$ = 8.8 Hz. Found: C 57.7; H 4.3; N 5.3; S 6.2%. $C_{24}H_{20}N_2O_8S$. Calculated: C 58.1; H 4.0; N 5.6; S 6.5%.

3-(p-Nitrophenylazo)bis(5-indolyl) Sulfone (XI). Water (15 ml) was added to a solution of 0.59 g (2 mmole) of sulfone III in 50 ml of dioxane, the mixture was cooled to 0°C, and a solution obtained by diazotization of 1.39 g (8 mmole) of p-nitroaniline at pH 6 was added dropwise. The mixture was stirred at 0-5°C for 3 h and allowed to stand overnight. Cold water (150 ml) was added, and the aqueous mixture was extracted with ether. The extract was washed twice with 10% NaOH solution and then with water until the washings had pH 7, after which it was dried in Na_2SO_4. The extract was then evaporated, and the residual viscous oil was purified with a column by elution with chloroform—ethyl acetate (1:1). The first fraction contained 0.28 g (44%) of III. Workup of the fraction with R_f 0.23 (ether) gave 0.36 g (39% based on starting III) of XI with mp 297-298°C. IR spectrum: 3400 (NH); 1450 (N=N); 1520, 1340 (NO_2); 1150 cm^{-1} (SO_2). UV spectrum, λ_{max}: 205, 224, 235 (shoulder), 281, and 400 nm. Found: C 59.1; H 3.0; N 16.0; S 7.3%. $C_{22}H_{16}N_5O_4S$. Calculated: C 59.3; H 3.4; N 15.7; S 7.2%.

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