BISINDOLES.

14.* ELECTROPHILIC SUBSTITUTION REACTIONS IN THE DI(5-INDOLYL) OXIDE SERIES

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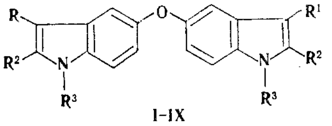
Some electrophilic substitution reactions in the di(5-indolyl) oxide series were studied. The Vilsmeier and Mannich reactions and diazo coupling and N-alkylation were realized. The di(5-indolyl) oxide molecule was subjected to quantum-chemical calculation.

We have previously [4] synthesized di(5-indolyl) oxide (II). In the present paper we describe some electrophilic substitution reactions in this compound and its 2,2'-bis(ethoxycarbonyl) derivatives (I).



I-IX

I $R=R^1=R^3=H$, $R^2=COOC_2H_5$; II $R=R^1=R^2=R^3=H$; III $R=R^1=CHO$, $R^2=COOC_2H_5$, $R^3=H$; IV $R=R^1=-CH_2N(CH_3)_2$, $R^2=COOC_2H_5$, $R^3=H$; V $R=R^1=CHO$, $R^2=R^3=H$;
a b

VI $R=R^1=-CH_2N(CH_3)_2$, $R^2=R^3=H$; VII $R=R^2=R^3=H$, $R^1=-N=N$NO_2;
VIII $R=R^2=R^3=H$, $R^1=-N=N-C_6H_5$; IX $R=R^1=R^2=H$, $R^3=CH_3$

It is known that in the case of indole the Vilsmeier and Mannich reactions and diazo coupling give products of substitution in the 3 position, whereas products of substitution in the 3 and 3' positions are obtained in the case of the previously synthesized bisindoles [1, 3, 5].

In order to determine the primary reaction centers in di(5-indolyl) oxide in electrophilic substitution reactions we subjected its molecule to quantum-chemical calculation by the self-consistent field (SCF) MO method within the CNDO/2 (complete neglect of differential overlap) approximation [6] for a planar structure and the geometrical parameters of the indole ring [7]. The results of the quantum-chemical calculations are presented in the form of a molecular diagram (the total electron densities are indicated, and the π-electron densities are given in parentheses) (Fig. 1).

It is apparent from the diagram that the character of the electron-density distribution of the indole ring is retained in the di(5-indolyl) oxide molecule. The greatest electron density, both total and π-electron, is concentrated in the 3 and 3' positions. Consequently, electrophilic substitution reactions should take place in the 3 and 3' positions.

The Vilsmeier reaction with the utilization of the complex obtained from phosphorus oxychloride and dimethylformamide proceeds under conditions similar to those used for indole [8] to give disubstitution products III and V.

We carried out the aminomethylation of di(5-indolyl) oxide and its 2,2'-bis(ethoxycarbonyl) derivative by means of N,N-dimethylaminomethyleneimmonium chloride [9] in dimethylformamide. Bisgramines IV and VI were obtained in high yields.

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*See [1-3] for communications 11-13.

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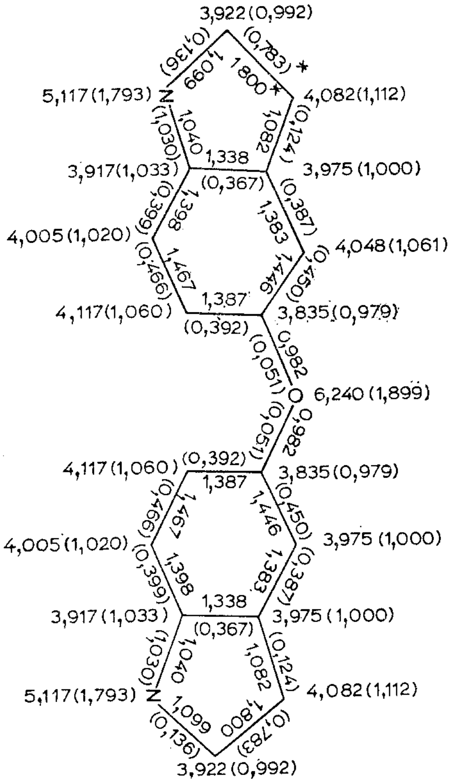

Fig. 1. Molecular diagram of di-(5-indolyl) oxide.

*The electron densities on the bonds in the form of Weiberg indexes.

The diazo coupling of di(5-indolyl) oxide was carried out with benzenediazonium and p-nitrobenzenediazonium chlorides. We were able to isolate 3-nitrophenylazodi(5-indolyl) oxide (VII), 3-phenylazodi(5-indolyl) oxide (VIII), and unchanged starting bisindole II from the reaction products. The formation of monosubstitution products can be explained by the weak electrophilicity of the diazo components.

N-alkylation of di(5-indolyl) oxide was carried out with methyl iodide in the presence of trimethylbenzylammonium chloride [10]. The structures of IV-IX were confirmed by data from the IR, UV, and PMR spectra.

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 ethanol solutions were recorded with a Specord spectrophotometer. The PMR spectra of solutions in d_6-DMSO 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.

2,2'-Bis(ethoxycarbonyl)-3,3'-diformyldi(5-indolyl) Oxide (III). A solution of 0.59 g (1.5 mmole) of I in DMF was added dropwise at –5°C to the complex prepared from 2.62 g (36.0 mmole) of DMF and 1.3 g (9.0 mmole) of $POCl_3$, after which the mixture was heated to 70°C for 1.5 h. It was then cooled and poured with stirring into a mixture of water and ice, and the aqueous mixture was made alkaline to pH 10. The precipitate was removed by filtration, washed with water, and dried to give 0.6 g (89%) of crude product. Recrystallization from DMF gave 0.47 g (70%) of a product with mp 223-224°C. IR spectrum: 1655, 1710 (C=O); 3330 cm^{-1} (NH). PMR spectrum: 12.1 (1-H, s), 7.72 (4-H, d), 7.12 (6-H, q), 7.56 (7-H, d), 4.44 (CH_2CH_3, q), 1.39 (CH_3CH_2, t), and 10.48 ppm (CHO, s); J_{46} = 2.3, J_{67} = 8.8, and $J_{CH_2CH_3}$ = 7.3 Hz. Found, %: C 64.7; H 5.0; N 6.3. $C_{24}H_{20}N_2O_7$. Calculated, %: C 64.3; H 4.5; N 6.3.

2,2'Bis(ethoxycarbonyl)-3,3'-bis(dimethylaminomethyl)di(5-indolyl) Oxide (IV). A 5.6-g (60.0 mmole) sample of $[CH_2=\overset{+}{N}(CH_3)_2]Cl^-$ was added to a solution of 2.36 g (6.0 mmole) of I in 40 ml of DMF, and the mixture was stirred at 90°C for 1 h. It was then poured into 0.5 liter of cold water, and the aqueous mixture was made alkaline to pH 10. The resulting precipitate was removed by filtration, washed with water, and dried to give 2.8 g (90%) of a product with mp 138-140°C. IR spectrum: 1710 (C=O) and 3360 cm^{-1} (NH). UV spectru, λ_{max}: 218 (shoulder), 230, and 305 nm. PMR spectrum: 11.3 (1-H, s), 7.31 (4-H, d), 6.93 (6-H, dd), 7.38 (7-H, d), 4.32 (CH_2CH_3, q), 1.39 (CH_3CH_2, t), 2.11 (NCH_3, s), and 3.79 ppm (NCH_2, s); J_{46} = 2.4, J_{67} = 8.8, and JCH_2CH_3 = 7.0 Hz. Found, %: C 66.2; H 6.9; N 10.4. $C_{28}H_{34}N_4O_5$. Calculated, %: C 66.4; H 6.7; N 11.0.

3,3'-Diformyldi(5-indolyl) Oxide (V). This compound was obtained from 0.5 g (2.0 mmole) of di(5-indolyl) oxide I at 45°C by a method similar to that used to prepare III. Recrystallization from DMF gave 0.45 g (75%) of a product with mp 305-306°C. IR spectrum: 1655 (C=O) and 3360 cm^{-1} (NH). PMR spectrum: 11.8 (1-H, s), 8.12 (2-H, d), 7.59 (4-H, dd), 6.97 (6-H, dd), 7.45 (7-H, dd), and 9.81 ppm (CHO, s); J_{2CHO} = 0.7, J_{47} = 0.6, J_{46} = 2.2, and J_{67} = 8.9 Hz. Found, %: C 70.8; H 4.1; N 9.6. $C_{22}H_{20}N_2O_5$. Calculated, %: C 71.0; H 4.0; N 9.2.

3,3-Bis(dimethylaminomethyl)di(5-indolyl) Oxide (VI). This compound was obtained from 2.48 g (10.0 mmole) of di(5-indolyl) oxide and 4.7 g (50.0 mmole) of $[CH_2=\overset{+}{N}(CH_3)_2]Cl^-$ at room temperature by a method similar to that used to prepare IV. This compound undergoes rapid oligomerization in air, and it was therefore converted immediately to the dimethosulfate. The yield of product with mp 175-176°C was 5 g (79%). UV spectrum, λ_{max}: 220 and 276 nm. PMR spectrum (in D_2O): 7.80 (2-H, s), 7.39 (4-H, d), 6.95 (6-H, dd), 7.57 (7-H, d), 3.12 (NCH_3, s), and 3.88 ppm (NCH_2, s); J_{46} = 2.2 and J_{67} = 8.8 Hz. Found, %: C 51.2; H 6.6; N 9.8. $C_{32}H_{46}N_4O_{13}S_2$. Calculated, %: C 50.8; H 6.2; N 9.1.

3-(p-Nitrophenylazo)di(5-indolyl) Oxide (VII). Water (10 ml) was added to a solution of 0.5 g (2.0 mmole) of II in 20 ml of DMF, the mixture was cooled to 0°C, and a solution obtained by diazotization of 0.56 g (4.0 mmole) of p-nitroaniline was added dropwise. The mixture was stirred at a temperature below 5°C for 3 h at pH 5-6, after which it was diluted with cold water and extracted with ether. The extract was washed with 10% NaOH solution and water until the wash water was neutral and dried over Na_2SO_4. The ether was evaporated, and the residual oil was purified with a column by elution with chloroform. The fraction with R_f 0.24 [benzene–acetone (5:1)] was evaporated to give 0.3 g (38%) of a product with mp 192-193°C. IR spectrum: 3400 (NH) and 1460 cm^{-1} (N=N). UV spectrum, λ_{max}: 225 and 282 nm. PMR spectrum: 12.1 (1-H, s), 10.80 (1'H, s), 8.37 (2-H, s), 6.33 (3'-H, m), 7.95 (4-H, d), 7.11 (4'H, d), 6.8-7.5 (2'-H, 6-H, 7-H, 6'-H, 7'-H, m), 7.75 (aH, d), 8.23 ppm (bH, d). $J_{1'3'}$ = 2.2; $J_{2'3'}$=3.5; J_{ab} = 9.2 Hz, Found, %: C 66.2; H 3.5; N 17.3. $C_{22}H_{15}N_5O_3$. Calculated, % C 66.5; H 3.8; N 17.6.

3-Phenylazodi(5-indolyl) Oxide (VIII). This compound was obtained from 0.5 g (2.0 mmole) of compound II and 0.37 g (8.0 mmole) aniline by a method similar to that used to prepare VII. The fraction with R_f 0.38 [benzene–acetone (3:1)] was evaporated to give 0.28 g (40%) of a product with mp 146-147°. IR spectrum: 3430 (NH), 1420 cm^{-1} (N=N). UV spectrum, λ_{max}: 225 and 285 nm. PMR spectrum: 11.8 (1-H, s), 10.8 (1'-H, s), 8.18 (2-H, d), 6.32 (3'-H, m), 7.93 (4-H, s), 7.10 (4'-H, s), 6.8-7.5 (2'-H, 6-H, 7-H, 6'-H, 7'-H, m), 7.5-7.95 ppm (Ph, m). J_{12} = 2.3; $J_{1'2'}$ = 2.0; $J_{2'3'}$ = 3.5 Hz. Found, %: C 74.8; H 4.3; N 14.8. $C_{22}H_{16}N_4O$. Calculated, %: C 75.0; H 4.6; N 15.0.

N,N'-Dimethyldi(5-indolyl) Oxide (IX). A 0.5-g (2.0 mmole) sample of II and 8 ml of 50% NaOH were added to a mixture of 7.1 g (50.0 mmole) of methyl iodide and 0.2 g of trimethylbenzylammonium chloride, and the mixture was stirred at 40-50°C for 3 h, after which it was diluted with 50 ml of water and extracted with ether. The extract was washed with water and dried over $MgSO_4$, after which the ether was removed by distillation to give 0.44 g (80%) of IX with mp 124-125°C (from alcohol). UV spectrum, λ_{max}: 229 and 279 nm. PMR spectrum: 7.19 (2-H, d), 6.27 (3-H, dd), 7.04 (4-H, d), 6.82 (6-H, dd), 7.32 (7-H, d), and 3.73 ppm (NCH_3, s); $J_{3,7}$ = 0.3, $J_{4,6}$ = 2.2, $J_{2,3}$ = 3.2, and $J_{6,7}$ = 8.7 Hz. Found, %: C 78.0; H 5.6; N 10.3. $C_{18}H_{16}N_2O$. Calculated, %: C 78.3; H 5.8; N 10.1.

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AZAINDOLE DERIVATIVES.

63.* EFFECT OF THE SOLVATING CAPACITIES OF SOLVENTS ON THE PATHWAYS OF REACTIONS UNDER THE CONDITIONS OF THE HOFMANN REARRANGEMENT

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It is shown that 1-benzyl-6-chloro-7-carbamoyl-5-azaindoline undergoes primarily normal skeletal rearrangement to give 1-benzyl-6-chloro-7-methoxycarbonylamino-5-azaindoline under the conditions of the Hofmann reaction in the presence of pyridine, whereas the primary process in aqueous methanol is splitting out of an isocyanate anion to give 1-benzyl-6-chloro-7-bromo-5-azaindoline. Under the same conditions 1-benzyl-6-chloro-7-carbamoyl-5-azaindole is converted to a mixture of 1-benzyl-6-chloro-7-methoxycarbonylamine-5-azaindole and products of electrophilic substitution of the hydrogen in the 3 position of the starting compound and the final reaction products by bromine, whereas 1-benzyl-7-carbamoyl-5-azaindoline forms 1-benzyl-7-methoxy-carbonylamino-5-azaindoline in ∿50% yield.

In a continuation of our earlier research [1] on the synthesis and biological activity of 6,7-disubstituted 5-azaindolines we studied the Hofmann reaction for 1-benzyl-6-chloro-7-carbamoyl-5-azaindoline (I) [2]. As a consequence of the low solubility of amide I in water, the process was carried out under anhydrous conditions with bromine and sodium methoxide. However, when refluxing methanol was used as the solvent, considerable amounts of starting I were recovered unchanged. The addition of pyridine made it possible to raise the boiling point of the mixture and led to the production of the normal rearrangement product, viz., 1-benzyl-6-chloro-7-methoxycarbonylamino-5-azaindoline (II).

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*See [1] for communication 62.

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