BISINDOLES.

18.* SOME ELECTROPHILIC SUBSTITUTION REACTIONS IN

THE 1,2-DI(INDOL-5-YL)ETHANE SERIES

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A quantum-chemical calculation has been made and the laws of the electron-density distribution in the molecule of 1,2-di(indol-5-y1)ethane have been determined. The electrophilic substitution reactions most characteristic for it have been studied.

The present paper is devoted to a study of the electrophilic substitution reactions of 1,2-di(indo1-5-y1)ethane (I) and its 2,2'-diethoxycarbonyl derivative (II), which have been synthesized previously [4]. The reactions most characteristic for indole were selected: azo coupling, the Vilsmeier and Mannich reactions, and acetylation.

In order to establish the potential reaction centers in electrophilic substitution reactions, we performed a quantum-chemical calculation of the 1,2-di(indole-5-yl)ethane molecule (I) by the CNDO MO method [5].†





The results of the calculations are given in the form of a molecular diagram which shows the total populations of the atomic orbitals (AOs) (in parentheses - the ρ_{π} populations of the AOs) (Fig. 1).

*For communications 15-17, see [1-3].

†The calculations were performed by means of a program due to V. G. Maslov [6] by Dzh. A. Kereselidze on the BESM-6 computer in the Institute of Applied Mathematics of the Tbilisi State University.

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Fig. 1. Molecular diagram of the 1,2-di(indol-5yl)ethane molecule.

TABLE 1. Parameters of the PMR Spectra of Compounds (III-VI, VIII, and IX)

	Chemical shifts, ppm								
-un							3R		SSCC, J, Hz
о g	1-H	2-H	4-H	6-H	7-H	(CH ₂) ₂	a	b	
ш	11,7 (br.s)	8,13	8,22	7,11	7,30	3,07	7,3 : 7,7		$J_{12}=2,4; J_{46}=0,9;$
IV	11,8 (br.s)	(d) 8,18 (d)	(d) 8,18 (d)	(d.d) 7,10 (d.d)	(d.) 7,31 (d.)	(s) 3,10 (s)	7,70 (d)	m) 7,44 (d)	$J_{67} \sim 8$ $J_{12} = 2,6; J_{46} = 1,0;$ $J_{57} = 8,0; J_{ab} = 8,7$
v	12,0 (br.s)	8,20 (d)	8,29 (d)	7,16 (d.d.)	7,38 (d)	3,10 (s)	8,25 (d)	7,82 (d)	$J_{12} = 2.5; J_{46} = 1.7; J_{67} = 8.3; J_{ab} = 9.0$
VI	11,7 (br.s)	8,04 (d)	7,29 (d)	7,08 (d.d)	7,34 (d)	3,01 (s)	9,86 (CHO;s)		$J_{12} = 3,1; J_{46} = 1,2; J_{67} = 8,5$
VIII*	11,1 (br.s)	_	7,49 (.d)	7,07 (d.d)	7,29 (d)	2,97 (s)	3,81 (CH ₂ , s)	2,11 (CH ₃ , s)	$J_{46} = 1,4; J_{67} = 8,5; JCH_3CH_2 = 7,0$
IX	2,60 (COCH ₃ , s)	7,68 (d)	7,37 (d)	7,13 (d.d)	8,13 (d)	2,98 (^{\$})	6,58 (3H, d)		$J_{23} = 3,7; J_{46} = 1,7; J_{67} = 8,2$

 $*2R = COOC_2H_5$: 1.34 (t CH₃); 4.31 ppm (q, CH₂).

It can be seen from the diagram that the greatest electron density is concentrated in the 3 and 3' positions. Thus, the molecule of the bisindole (I) retains the nature of the electron-density distribution of the indole ring.

The diindolylethane (I) takes part in the electrophilic substitution reactions under conditions similar to those of indole. The azo coupling reaction takes place in aqueous dioxane at pH 5-6. In this pH interval, azo coupling takes place without appreciable complications by side-reactions in the indole and bisindole series [7, 8]. In the investigations of the azo coupling reaction, as the diazo components we chose benzenediazonium and p-chloro- and p-nitrobenzenediazonium chlorides. The reactions led to the formation of the disubstituted compounds (III-V).

The IR spectra of compounds (III-V) contained, in addition to an intense absorption band of the NH groups $(3380-3350 \text{ cm}^{-1})$ a narrow strong absorption band in the 1410 cm⁻¹ region due to the stretching vibrations of the azo groups [9].

The UV spectra, taken in ethanol, showed a similarity of the structures of compounds (III-V). They contain strong absorption maxima in the long-wave region (for compounds (III-V) at 473, 465, and 437 nm, respectively).

In each of the PMR spectra of compounds (IV) and (V) (see Table 1) there are two signals in the form of a doublet with a spin-spin coupling constant $J_{ab} \sim 9$ Hz, which can be assigned to the protons of a phenylazo group. In compound (III), these two signals appear in the 7.3-7.7 ppm interval in the form of a multiplet, which likewise does not contradict the structure of this compound.

The molecular masses of compounds (III-V), determined mass-spectrometrically, correspond to the calculated figures, and the nature of the further fragmentation does not contradict the proposed structures.

III M⁺ 468 (18) *
$$\xrightarrow{-CH_2Ind-N=N-Ar} 234 (32) \xrightarrow{-N=N-Ar} 130 (17)$$

 $\downarrow -Ar$
 $391 (2)$ $157 (8)$

The fragmentation of compounds (IV) and (V) has an analogous nature.

The formylation of compounds (I) and (II) gave the aldehydes (VI) and (VII), respectively. The PMR spectra of compound (VI) lacked the signal characteristic for the 3-H and 3'-H protons (Table 1) [4]. The molecular mass of compound (VI) was determined mass-spectrometrically and corresponded to the calculated value:

$$\begin{array}{c} -\text{OH } 299 \ (20) \\ \xrightarrow{} & -\text{CO} \\ \text{VI } \text{M}^{+} 316 \\ \xrightarrow{} & -\text{CH}_{2}^{-} \text{CH}_{2}^{-} \text{Ind} \\ \downarrow -\text{CH}_{2}^{-} \text{CH}_{2}^{-} \text{Ind} \\ \hline & -\text{CH}_{2}^{-} \text{CHO}^{-} \text{Ind}^{-} \text{CHO}_{2} \\ \hline & 158 \ (91) \\ \hline & -\text{CO} \\ 158 \ (100)^{-} - \text{Ind}^{-} \text{CO} \\ \hline & 130 \ (100)^{-} - \text{Ind}^{-} \text{O} \\ \hline & 103 \ (86) \end{array}$$

In the IR spectrum of compound (VII), in addition to two absorption bands characteristic for the NH groups (3320, 3150 cm⁻¹), there are three absorption bands of CO groups in the 1720, 1710, and 1700 cm⁻¹ regions. The PMR spectrum of compound (VII) has the signals of the 3'-H proton (in the 6.95 ppm region) and lacks a signal characteristic for the 3-H proton.

The aminomethylation of 1,2-di-(2-ethoxycarbonylindol-5-yl)ethane (II) was carried out by the action of formaldehyde in an aqueous solution of dimethylamine. The PMR spectrum of compound (VIII) confirmed that the dimethylamino groups were present on carbon atoms 3 of the indole rings: The signal of NH protons was observed in the 11.1 ppm region and the signals of the 3-H atoms of the indole rings were absent (Table 1). In the IR spectrum of compound (VIII), the absorption bands of the NH and CO groups (3320 and 1680 cm⁻¹, respectively) were retained, and an absorption band appeared at 1360 cm⁻¹ probably due to the vibrations of a C-N < bond.

The reaction of acetic anhydride with compound (I) gave a mixture of compounds from which it was possible to isolate two: 1,2-di-(1-acetylindo1-5-yl)ethane (IX) and 1,1',3-triacetyl-<math>1,2-di-indo1-5-yl)ethane (X). The IR spectra of compounds (IX) and (X) lacked the characteristic absorption band of an NH group. Furthermore, in the spectrum of compound (IX) there was one absorption band characteristic for a CO group in the 1720 cm^{-1} region, while in compound (X) there were three of them (1730, 1705, and 1660 cm⁻¹). The PMR spectrum confirmed that in compound (IX) the acyl groups were present on the pyrrole nitrogen atoms, while in the PMR spectrum of compound (X) there was no signal characteristic for the 3-H proton, which corresponds to the suggested structure of this compound.

EXPERIMENTAL

The course of the reactions was followed, the purity of the compounds was checked, and the R_f values were determined on Silufol UV-254 plates. IR spectra were taken on UR-20 instrument in paraffin oil, and UV spectra on a Specord spectrophotometer in ethanol. The mass spectra of all the compounds apart from (VI) were taken on a Varian Mat-311A mass spectrometer with the direct introduction of the substance into the ion source at an energy of the ionizing electron of 70 eV. The mass spectrum of compound (VI) was taken on an MKh-1303 mass spectrometer by the direct introduction of the sample into the ion source at an energy of the ionizing electrons of 50 eV. The PMR spectra were recorded on a Varian CFT-20 spectrometer (80 MHz) in DMSO-d₆. The error of measurement of the chemical shifts does not exceed ± 0.01 ppm and of the SSCC ± 0.1 Hz. TMS was used as internal standard. The preparative chromatographic separation of the compound obtained was carried out on silica gel with particle dimensions of 100-250 μ m.

1,2-Di-(3-phenylazoindol-5-yl) ethane (III). A solution of 0.26 g (1 mmole) of compound (I) in 30 ml of dioxane was treated with 10 ml of water and cooled to 0°C, and then a solution obtained by diazotizing 0.29 g (3 mmole) of aniline was added dropwise, the pH being maintained at 5-6 by the addition of sodium acetate. The reaction mixture was stirred at 0-5°C for 3 h and 100 ml of water was added. The resulting precipitate was filtered off, washed with water

^{*}Here and below are given the m/z values, and, in parentheses, the intensities of the ion peaks as percentages of the maximum peak.

to neutrality, and dried over CaCl₂. Compound (III) was purified chromatographically on a column with elution by chloroform. Yield 0.25 g (53%), mp 220-221°C. R_f 0.45 (chloroform-acetone (10:1)). IR spectrum, cm⁻¹: 3380 (NH); 1410 (N=N). UV spectrum, λ_{max} (nm, log ε): 227 (4.65), 232 (4.60), 281 (4.47), 473 (4.67). Found: C 76.8; H 5.2; N 18.0%; M⁺ 468. C₃₀H₂₄N₆. Calculated: C 76.9; H 5.1; N 17.9%; mol. wt. 468.

 $\frac{1,2-\text{Di}-(3-\text{p-chlorophenylazoindol}-5-\text{yl})\text{ethane (IV)}.$ This was obtained in a similar manner to compound (III). Yield 0.35 g (61%), mp 115-116°C. Rf 0.6 (ether-benzene (3:1)). IR spectrum, cm⁻¹: 3350 (NH), 1410 (N=N). UV spectrum, λ_{max} (nm, log ε): 222 (3.42), 285 (3.99), 465 (3.45). Found: C 67.1; H 4.1; Cl 13.1; N 15.5%; M⁺ 537. C₂₀H₂₂Cl₂N₆. Calculated: C 67.0; H 4.1; Cl 13.2; N 15.6%; mol. wt. 537.

 $\frac{1,2-\text{Di}-(3-\text{p-nitrophenylazoindol}-5-\text{yl})\text{ethane (V)}.$ This was obtained in a similar manner to compound (III). Yield 0.42 g (72%), mp 226-227°C. Rf 0.45 (ether-benzene (3:1)). IR spectrum, cm⁻¹: 3350 (NH); 1520, 1330 (NO₂); 1410 (N=N). UV spectrum, λ_{max} : 229.8; 289.8; 436.8. Found: C 64.6; H 3.9; N 20.0%; M⁺ 558. C₂₀H₂₂N₈O₄. Calculated: C 64.5; H 3.9; N 20.1%; mol. wt. 558.

<u>1,2-Di-(3-formylindol-5-yl)ethane</u> (VI). With stirring, 0.69 g (4.5 mmole) of phosphorus oxychloride was added to 1.31 g (18 mmole) of freshly distilled dimethylformamide cooled to -5°C. The complex formed was stirred at room temperature for 1 h 30 min. Then it was again cooled to -5°C, and a solution of 0.39 g (1.5 mmole) of 1,2-di-(indol-5-yl)ethane (I) in 2 ml of dimethylformamide was added dropwise. The orange suspension formed was stirred at 70°C for 3 h. Then it was cooled and 50 ml of cold water was added. The solution was made alkaline to pH 10. The precipitate that deposited was filtered off, washed with water to pH 7, and dried. Yield 0.4 g (85%), mp 310-311°C (from dimethylformamide). IR spectrum, cm⁻¹: 3280 (NH), 1630 (C=0). UV spectrum, λ_{max}, nm: 217, 250, 303. Found: C 75.8; H 4.9; N 9.0%; M⁺ 316. C₂₀H₁₆N₂O₂. Calculated: C 75.9; H 5.0; N 8.9%; mol. wt. 316.

<u>3-Formyl-1,2-di-(2-ethoxycarbonylindol-5-yl)ethane (VII).</u> With stirring, 0.69 g (4.5 mmole) of phosphorus oxychloride was added dropwise to 1.31 g (18 mmole) of freshly distilled dimethylformamide cooled to -5° C. The complex formed was stirred at room temperature for 1 h. Then it was cooled to -5° C, and a solution of 0.6 g (1.5 mmole) of compound (II) in 3 ml of dimethylformamide was added dropwise. The reaction mixture was stirred at 60-65°C for 2 h and was poured onto ice (70 g). Then the mixture was made alkaline to pH 7-8 with 10% NaOH solution and it was stirred at 20°C for 1 h. The precipitate that deposited was filtered off, washed with water to pH 7, and dried. It was chromatographed on a column using benzene-ether (5:1) as eluent. Yield 0.48 g (75%), mp 238-239°C. Rf 0.25 (benzene-acetone (5:1)). IR spectrum, cm⁻¹: 3320, 3150 (NH), 1720, 1700 (C=0). UV spectrum, λ_{max} (nm, log ε): 235 (3.68), sh 259.7 (3.52), 303 (3.61); sh 322 (3.50). PMR spectrum (ppm): 12.6 (br.s, 1-H); 8.05 (d, 4-H), 2.99 (s, CH₂CH₂); 10.52 (s, CH0); 4.43 (q, α -CH₂); 1.40 (t, β -CH₃); 11.6 (br.s, 1'-H); 6.95 (d, 3'-H); 7.4-7.1 (4'-H, 6'-H, 7'-H, 6-H, 7-H); 4.30 (q, α' -CH₂); 1.33 (t, β' -CH₃). J_{$\alpha\beta$} = 7.2, J_{$\alpha'\beta'$} = 7.1, J_{1'3'} = 1.9, J₄₆ = 0.7 Hz. Found: C 69.4; H 5.5; N 6.6%; M⁺ 432. C₂₅H₂₄N₂O₅. Calculated: C 69.4; H 5.5; N 6.6%; mol. wt. 432.

 $\frac{1,2-\text{Di}-(2-\text{ethoxycarbonyl}-3-\text{dimethylaminomethylindol}-5-\text{yl})\text{ethane (VIII)}. To 0.4 g (9 mmole)}{33\%}$ aqueous solution of dimethylamine cooled to 0°C were slowly added 6 ml of glacial acetic acid, 0.23 g (8 mmole) of 40% formalin, and 0.42 g (1 mmole) of 1,2-di-(2-ethoxycarbonylin-dol-5-yl)ethane (II). The reaction mixture was stirred at 75-80°C for 3 h. Then 10 ml of water was added and it was filtered. The filtrate was made alkaline to pH 9 with 10% NaOH solution. The precipitate that deposited was filtered off, washed with water, and dried over KOH. Yield 0.4 g (80%), mp 180-181°C. IR spectrum, cm⁻¹: 3320 (NH), 1680 (C=0), 1360 (C-N). UV spectrum, λ_{max} , nm: 215, 235, 303. Found: C 69.4; H 7.3; N 10.9%; M⁺ 518. C₃₀H₃₈N₄O₄. Calculated: C 69.5; H 7.3; N 10.8%; mol. wt. 518.

 $\frac{1,2-\text{Di}-(1-\text{acetylindol}-5-\text{yl})\text{ ethane (IX) and } 1,4',3-\text{Triacetyl}[1,2-\text{di}-(\text{indol}-5-\text{yl})\text{ ethane}] (X)}{\text{A mixture of } 0.52 \text{ g (2 mmole) of compound (I), 3 ml (106 mmole) of freshly distilled acetic anhydride, and 1 ml (170 mmole) of acetic acid was boiled for 45 h. Then it was cooled, poured into 100 ml of water, and extracted with ethyl acetate. The extract was washed with aqueous NaHCO₃ solution and with water and was then concentrated to 30 ml and passed through a column using benzene as the eluent. The yield of compound (IX) was 0.3 g (43%), mp 159-160°C. Rf 0.45 (benzene-acetone (5:1)). IR spectrum, cm⁻¹: 1720 (C=O). UV spectrum, <math>\lambda_{\text{max}}$ (nm; log ε): 204 (4.36), 246.9 (4.65), 274 (4.16), 294 (4.08), 303 (4.11). Found: C 77.5; H 5.8; N 8.0%; M⁺ 344. C₂₂H₂₀N₂O₂. Calculated: C 77.4; H 5,8; N 8.1%; mol. wt. 344.

Compound (X) was eluted by benzene-ether (4:1). Yield 0.2 g (26%), mp 184-185°C. Rf 0.30 (benzene-acetone (5:1)). IR spectrum, cm⁻¹: 1730, 1705 (C=O). UV spectrum, λ_{max} (nm; log ε): 224.7 (4.64), 244 (4.72), 294 (4.27), 303 (4.34). PMR spectrum (ppm): 2,75 (s, α -CH₃); 8.51 (s, 2-H); 2.51 (s, COCH₃); 8.17 (s, 4-H); 7.24 (d, 6-H); 8.23 (d, 7-H); 3.07 (s, CH₂CH₂); 2.61 (s, α' -CH₃); 7.62 (d, 2'-H); 6.56 (d, 3'-H); 7.42 (s, 4'-H); 7.24 (s, 6'-H); 8.23 (d, 7'-H); J₆₇ = 9.1, J_{6'7}' = 9.1, J_{2'3}' = 3.3 Hz. Found: C 74.5; H 5.7; N 7.4%; M⁺ 386. C₂₄H₂₂N₂O₃. Calculated: C 74.6; H 5.7; N 7.3%; mol. wt. 386.

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SYNTHESIS OF HETEROCYCLIC PHTHALIMIDOALKYL KETONES

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We have investigated the 1,3-dipolar cycloaddition of dehydrobenzene, N-phenylmaleimide, and diethyl acetylenedicarboxylate to phthalimidoalkyl diazomethyl ketones, and have obtained phthalimide derivatives of amino ketones of the indazole, pyrazole, and pyrrolo[3,4-d]-2-pyrazoline series.

It is known that amino ketones of the aromatic and heterocyclic series possess a broad spectrum of pharmacological activity, affecting the central and peripheral nervous systems. Phthalimide derivatives of aromatic amino ketones — for example, γ -amino ketones — possess a pronounced saporific and sedative action [1].

At the same time, there is no information in the literature on heterocyclic analogs of the phthalimido ketones. In view of the high activity of diazo ketones in 1,3-dipolar cycloaddition reactions with various dipolarophiles [2-4] we have studied the possibility of synthesizing phthalimide derivatives of heterocyclic amino ketones by means of the 1,3-dipolar cycloaddition reaction to phthalimidoalkyl diazomethyl ketones (Ia-d). For this purpose, as the dipolarophiles we selected dehydrobenzene (II), dimethyl acetylenedicarboxylate (III), and N-phenylmaleimide (IV).

The reactions of the diazo ketones with dihydrobenzene were carried out by boiling a 1,3dipole (Ia-d) with benzenediazonium-2-carboxylate in methylene chloride at a ratio of the reagents of 1:2 [5]. After 1.5-2 h the initial diazo ketone had disappeared from the reaction mixture, and a precipitate of the corresponding phthalimidoalkyl indazol-3-yl ketone (Va-d) had precipitated. The reaction of the diazo ketones (Ia-d) with the dipolarophiles (III) and (IV) took place at room temperature in chloroform during 15-40 days (Table 1). This

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