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PYRROLOINDOLES.

11.* ELECTROPHILIC SUBSTITUTION IN THE 1H,7H-PYRROLO[3,2-f]INDOLE SERIES

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543.422.25'4'6

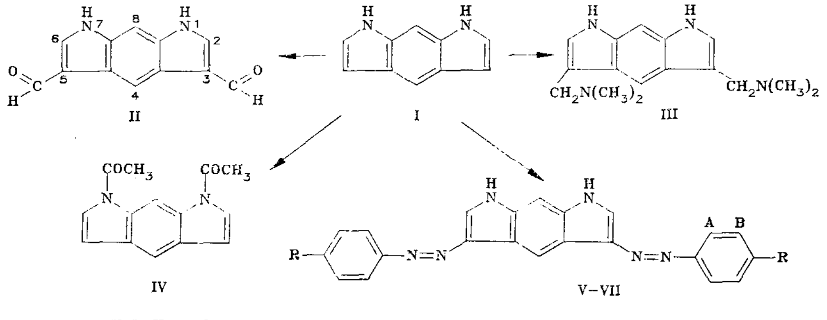
It has been shown with the aid of quantum-chemical calculation by the CNDO/2 method that the reaction centers of electrophilic attack in the molecule of 1H,7H-pyrrolo[3,2-f]indole are positions 3 and 5. These results are in agreement with those of studies of electrophilic substitution reactions.

Electrophilic substitution reactions of the 1H,7H-pyrrolo[3,2-f]indole (I) which we synthesized previously [2] have been investigated. The Vilsmeier, Mannich, azo-coupling, and acetylation reactions have been performed.

In order to determine the main reaction centers in electrophilic substitution reactions in the heterocycle (I), a quantum-chemical calculation of its molecule has been made by the SCF MO method in the CNDO/2 approximation [3] for a planar structure and the geometric parameters of the indole ring [4]. The results of the quantum-chemical calculations are presented in Fig. 1 in the form of a molecular diagram (the total electron densities are shown with the π-electron densities in parentheses).

It can be seen from the molecular diagram of the pyrroloindole (I) that the nature of the electron density distribution of the indole ring is retained in its molecule. The greatest electron densities, both the total ($\sigma + \pi$) and the π-electron densities, are concentrated in the β positions of the pyrrole nuclei. Consequently, in electrophilic substitution the process should take place at positions 3 and 5.

The formylation of the pyrroloindole (I) using the Vilsmeier complex [5] in a ratio of 1:3 led to 3,5-diformyl-1H,7H-pyrrolo[3,2-f]indole (II). When compound (I) was aminomethylated in acetonitrile with the crystalline Mannich reagent at room temperature, 3,5-bisdimethyl-



V R=H; VI R=Cl; VII R=NO_2

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*For communication 10, see [1].

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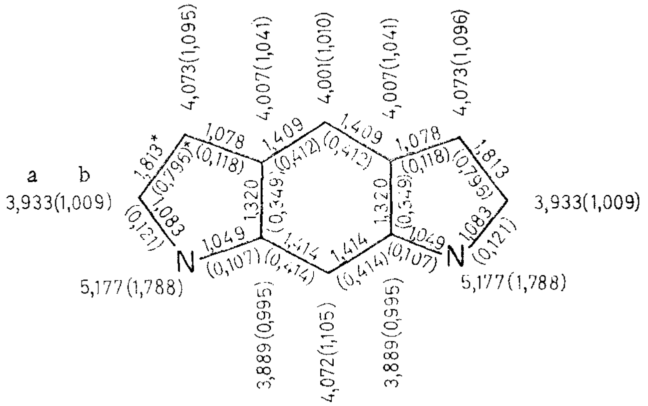

Fig. 1. Molecular diagram of 1H,7H-pyrrolo[3,2-f]indole: a) total (σ + π) charges; b) π-electron densities; an asterisk denotes the electron densities on the bonds in the form of the Wiberg indices.

aminomethyl-1H,7H-pyrrolo[3,2-f]indole (III) was formed. The acetylation [7] of the pyrroloindole (I) with acetic anhydride in glacial acetic acid led to the formation of 1,7-diacetyl-1H,7H-pyrrolo[3,2-f]indole. The azo-coupling of the pyrroloindole (I) with benzenediazonium, p-chlorobenzenediazonium, and p-nitrobenzenediazonium chlorides in aqueous dioxane solution at pH 6-7 [8] with a ratio of the reactants of 1:3 led to the 3,5-disubstitution products (V-VII).

EXPERIMENTAL

The course of the reactions was followed and the purity of the compounds was checked by the TLC method on Silufol UV-254 plates. The preparative chromatography of the compounds was carried out on SiO_2 with particle dimensions of 100-250 µ. IR spectra were taken on a UR-20 instrument in paraffin oil, UV spectra on a Specord spectrophotometer in ethanol, and PMR spectra on a Varian CFT-20 spectrometer with TMS as internal standard. The accuracy of measurement of the chemical shifts was ±0.2 ppm and of the SSCCs ±0.1 Hz. Mass spectra were taken on a MKh-1303 instrument with direct introduction of the sample into the ion source with an energy of the ionizing electrons of 50 eV.

3,5-Diformyl-1H,7H-pyrrolo[3,2-f]indole (II). Dropwise, 0.59 g (3.8 mmole) of freshly distilled $POCl_3$ was added to 1.1 g (15.3 mmole) of redistilled DMFA that had been cooled to −5°C, and the mixture was stirred at room temperature for 40 min. Then it was again cooled to −5°C and a solution of 0.2 g (1.3 mmole) of compound (I) and 2 ml of DMFA was slowly added so that the temperature did not exceed 0°C. The resulting mixture was stirred at room temperature for 1.5 h. A yellow precipitate deposited. This was treated with 30 ml of ice water and the mixture was made alkaline with 10% aqueous NaOH. The resulting precipitate was filtered off, washed with water to neutrality, and dried. Yield 0.2 g (74%). It was recrystallized from dimethylformaide—water and then had mp 360°C (decomp.); R_f 0.21 [benzene—acetone (1:1)]. IR spectrum, cm^{-1}, 3160-3200 (NH), 1630 (CO). UV spectrum, λ_{max}, nm: 208.5, 230, 292, 335. Found, %: C 69.0, H 4.1, N 13.0. M^+ 212. $C_{12}H_8N_2O_2$. Calculated, %: C 67.9, H 3.8, N 13.2%; mol. wt. 212.

3,5-Bis(dimethylaminomethyl)-1H,7H-pyrrolo[3,2-f]indole (III). A solution of 0.2 g (1.3 mmole) of compound (I) in 15 ml of dry acetonitrile was added dropwise to a solution of 0.4 g of crystalline Mannich reagent in 20 ml of dry acetonitrile. The mixture was stirred at room temperature for 2 h. The solvent was decanted off, the precipitate was dissolved in 25 ml of water, and the solution was alkalinized to pH 11 with 10% aqueous NaOH. The resulting precipitate was filtered off, washed with water, and dried. Yield 0.27 g (77%), mp 129-130°C, R_f 0.71 [isopropanol—33% aqueous ammonia (3:1)]. IR spectrum: 3175-3220 cm^{-1} (NH). UV spectrum, λ_{max}, nm (log ε): 206 sh (4.37), 229.8 (4.64), 304 (4.13), 322 sh (4.05), 333 sh (3.94). Found, %: N 20.4. $C_{16}H_{22}N_4$. Calculated, %: N 20.7.

1,7-Diacetyl-1H,7H-pyrrolo[3,2-f]indole (IV). A mixture of 0.2 g (1.3 mmole) of pyrrolo[3,2-f]indole (I), 5 ml of freshly distilled acetic anhydride, and 0.4 ml of glacial acetic acid was boiled for 30 h. Then the reaction mixture was poured into water, the precipitate

TABLE 1. PMR Spectra of Compounds (II-V) (DMSO-D_6) and (VI) and (VII) (acetone-D_6)

Compound	Chemical shifts, δ, ppm									SSCCs, J, Hz
	1-H	2-H	3-H	4-H	5-H	6-H	7-H	8-H	A—H, B—H	
II[a]	11,8; br.s	8,19; s	—	8,85; d	—	8,19; s	11,8; br.s	7,54; d	—	$J_{48}=0,5$
IIIb	10,1; br.s	6,99; d	—	7,17; m	—	6,99; d	10,1; br.s	7,62; d	—	$J_{12}=J_{67}=2,2$; $J_{14}=J_{74}=0,9$; $J_{48}=0,6$
IV[c]	—	7,76; d	6,75; d.d	7,71; d	6,75; d.d	7,76; d	—	9,40; m	—	$J_{23}=J_{56}=4,0$; $J_{38}=J_{48}=J_{58}=0,9$
V	11,8; br.s	8,27; d	—	9,50; d	—	8,27; d	11,8; br.s	7,50; d	7,34—7,88	$J_{12}=J_{67}=2,9$; $J_{48}=0,9$
VI	11,0; br.s	8,24; d	—	9,72; m	—	8,24; d	11,0; br.s	7,59; br.s	7,83 d (A); 7,55 d (B)	$J_{12}=J_{67}=3,0$; $J_{AB}=8,8$; $J_{14}=J_{74}=J_{48}==0,7$
VII	11,0; br.s	8,44; d	—	9,75; m	—	8,44; d	11,0; br.s	7,67; br.s	8,09 d (A); 8,43 d (B)	$J_{12}=J_{67}=3,0$; $J_{AB}=9,3$; $J_{14}=J_{74}=J_{48}==0,6$

a) 9.91 ppm (CHO, s). b) 3.53 ppm (CH_2N, s), and 2.16 ppm (CH_3N, s). c) 2.63 ppm ($COCH_3$, s).

was filtered off, washed with water to neutrality, and dried. It was purified on a column with elution by benzene—ether (10:1). This gave 0.1 g (22%) of product with mp 215-216°C, Rf 0.36 [benzene—ether (3:1)]. IR spectrum: 1700 cm^{-1} (CO). UV spectrum, λ_{max}, nm (log ε): 204 (3.76), 228 (4.05), 265 (4.53), 289.8 sh (3.99), 308 (3.78), 322 (3.78). Found, %: C 70.5, H 5.0, N 11.6. M^+ 240. $C_{13}H_{12}N_2O_2$. Calculated, %: C 70.0, H 5.0, N 11.7; mol. wt. 240.

3,5-Di(phenylazo)-1H,7H-pyrrolo[3,2-f]indole (V). A solution of 3.9 g of benzenediazonium chloride was added dropwise at −5°C to solution of 0.2 g (1.3 mmole) of compound (I) in 20 ml of dioxane and 10 ml of water, the pH being kept at 6-7 by the addition of sodium acetate. The mixture was stirred for 3 h. The resulting precipitate was filtered off, giving 0.35 g (76%) of product. The substance was purified on a column with elution with petroleum ether—ethyl acetate (2:3); mp 150-152°C (decomp.); R_f 0.21 [petroleum ether—ethyl acetate (2:3)]. IR spectrum, cm^{-1}: 3330 (NH), 1390 (N=N). UV spectrum, nm, λ_{max}: 208, 225 sh, 236 sh, 263, 294, 305.9. Found, %: N 22.7, M^+ 364. $C_{22}H_{16}N_6$. Calculated, %; N 23.1; mol. wt. 364.

3,5-Di(p-chlorophenylazo)-1H,7H-pyrrolo[3,2-f]indole (VI). This was obtained in a similar manner to compound (V) by the reaction of 0.2 g (1.3 mmole) of the pyrroloindole (I) with a solution of 3.9 mmole of p-chlorobenzenediazonium chloride. Yield 0.5 g (89%). The reaction product was purified on a column with elution by petroleum ether—ethyl acetate (1:1), mp 240-242°C (decomp.). R_f 0.29 [petroleum ether—ethyl acetate (1:1)]. IR spectrum, 3280 (NH), 1410 (N=N). UV spectrum, λ_{max}, nm (log ε): 204.5 (3.37), 208.5 (3.34), 224 (2.38), 225 (3.44), 238 sh (3.18), 256 (3.15), 303 (3.28), 355 (3.32). Found, %: N 19.3. M^+ 4.33. $C_{22}H_{14}Cl_2N_2$. Calculated, %: N 19.4; mol. wt. 433.

3,5-Di(p-nitrophenylazo)-1H,7H-pyrrolo[3,2-f]indole (VII). This was obtained in a similar manner to compound (V) by the reaction of 0.2 g (1.3 mmole) of compound (I) with a solution of 3.9 mmole of p-nitrobenzenediazonium chloride. Yield 0.5 g (86%). The reaction product was purified on a column with elution by benzene—acetone (3:1). mp 240-242°C (decomp.), R_f 0.29 [benzene—acetone (3:1)]. IR spectrum, cm^{-1}: 3330 (NH), 1420 (N=N), 1520 (NO_2). UV spectrum, λ_{max}, nm (log ε): 206 (4.44), 228 (4.37), 234 (4.34), 295 (4.24), 333 (4.25). Found, %: N 24.1. M^+ 454. $C_{22}H_{14}N_8O_4$. Calculated, %: N 24.6; mol. wt. 454.

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