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PYRROLOINDOLES. 2.* SOME ELECTROPHILIC SUBSTITUTION REACTIONS IN THE 1H,6H-PYRROLO[2,3-e]INDOLE SERIES

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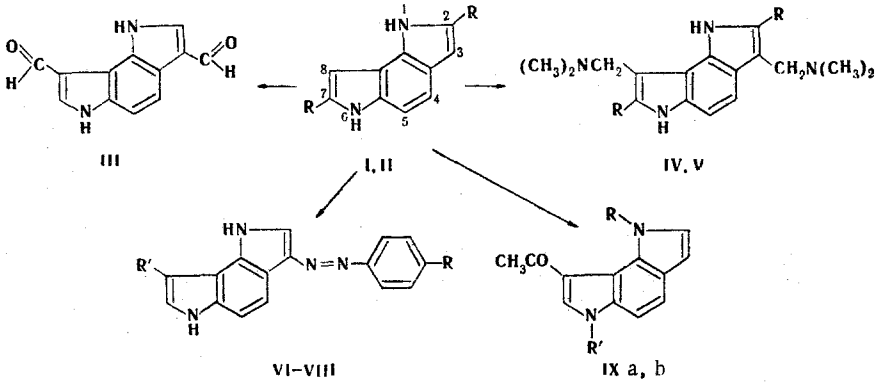
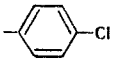
UDC 547.759.3.5

As expected, the 3 and 8 positions are the reaction centers of 1H,6H-pyrrolo-[2,3-e]indole in the Vilsmeier—Haack and Mannich reactions. Diazo coupling takes place primarily in the 3 position and leads primarily to monosubstitution products. 6,8-Diacetyl-1H,6H-pyrrolo[2,3-e]indole and 1,8-diacetyl-1H,6H-pyrrolo-[2,3-e]indole were isolated from the acetylation products.

The present communication is devoted to a study of some electrophilic substitution reactions in the case of the previously obtained [1] 1H,6H-pyrrolo[2,3-e]indole (I). We accomplished Vilsmeier—Haack formylation, the Mannich reaction, diazo coupling, and acetylation at the nitrogen atoms and the carbon atom of the pyrrole ring (see the scheme presented below).



I, IV IX b R = H, II, V R = $CO_2C_2H_5$; VI, VII R = Cl; VIII R = R′ = H; IX a R = $COCH_3$;

VI R′ = N=N–  –Cl; VII, IX a R′ = H; IX b R′ = $COCH_3$

As expected, the 3 and 8 positions (the corresponding β position of indole, benzindoles, pyrroloquinolines, and other indole-containing condensed systems) are the reaction centers of pyrroloindole I in the Vilsmeier—Haack and Mannich reactions.

Formylation gives 3,8-diformyl-1H,6H-pyrrolo[2,3-e]indole (III) in high yield.

*See [1] for communication 1.

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The dimethylaminomethylation of I with a freshly prepared Mannich reagent (formalin, dimethylamine, and acetic acid) [2] gives, in addition to the chief reaction product, viz., 3,8-bis(dimethylaminomethyl)-1H,6H-pyrrolo[2,3-e]indole (IV), a compound that is insoluble in most organic solvents, the formation of which is not observed in the reaction of I with the crystalline reagent prepared by the method in [3]; from this it may be assumed that the side product is formed as a result of condensation of pyrroloindole I with formalin, as in the formation of 3,3'-diindolylmethane from indole and formaldehyde [4, 5].

The Mannich reaction with II gives 3,8-bis(dimethylaminomethyl)-2,7-dicarbethoxy-1H,6H-pyrrolo[2,3-e]indole (V) in high yield. The need for a high temperature and a tenfold excess of the Mannich base for the reaction can probably be explained by the electron-acceptor and steric effects of the 2,7-dicarbethoxy groups on the adjacent reaction centers.

Diazo coupling takes place primarily at the 3 position of pyrroloindole I and leads primarily to monosubstituted products. Coupling was carried out in aqueous dioxane at pH 7-8 as with indole [6].

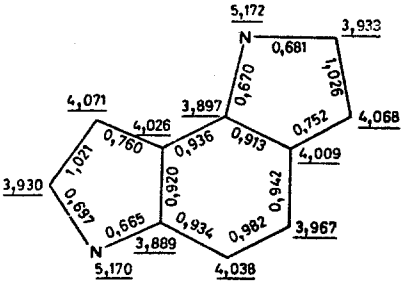
3,8-Bis(p-chlorophenylazo)-1H,6H-pyrrolo[2,3-e]indole (VI) and 3-(p-chlorophenylazo)-1H,6H-pyrrolo[2,3-e]indole (VII) in a ratio of 1:3 were isolated in the coupling of I with p-chlorobenzenediazonium chloride. The principal product in the coupling of I with benzenediazonium chloride is 3-phenylazo-1H,6H-pyrrolo[2,3-e]indole (VIII). We were unable to isolate the disubstitution product even in the case of a threefold excess of the diazo component; this is associated with the lower activity of the latter.

The acetylation of I was carried out with acetic anhydride in the presence of acetic acid with refluxing for 24 h. 1,8-Diacetyl-1H,6H-pyrrolo[2,3-e]indole (IXa) and 6,8-diacetyl-1H,6H-pyrrolo[2,3-e]indole (IXb, the principal product) were isolated in very small amounts from the reaction mixture, which contained several components (according to chromatography on Silufol).

According to our study, the reactivity of 1H,6H-pyrrolo[2,3-e]indole is in agreement with quantum-chemical calculations of the electron densities of this heterocycle that were performed by the MO CNDO (complete neglect of differential overlap) method with the program of Maslov [7]. The calculations were made with a BÉSM-6 computer in the Institute of Applied Mathematics of Tbilisi State University.

Substitution takes place in the 3 and 8 positions in the reaction of 1H,6H-pyrrolo[2,3-e]indole with weak electrophiles (in the Vilsmeier and Mannich reactions); this is in agreement with the results of the quantum-chemical calculation: The highest electron density of the skeleton of the molecule is concentrated on the C_3 and C_8 atoms. The bond orders and overall ($\sigma + \pi$) charges on each atom are also presented in the molecular diagram given below.

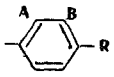
The increased reactivity of the 3 position of pyrroloindole I as compared with the 8 position is displayed distinctly in diazo coupling. Since the difference between the electron densities (0.003) is slight (see the diagram), the reason for the reduced reactivity of the 8 position is probably the steric effect of the second pyrrole ring on the course of the reaction. One must also take into account the high selectivity of the arenediazonium cation due to its weak electrophilicity as compared with the other electrophiles that we used.



The structures of the compounds obtained were established from the data from the PMR, IR, UV, and mass spectra and the results of elementary analysis.

An unambiguous assignment of the lines in the PMR spectra was made owing to the observation of the long-range spin–spin coupling constants (SSCC) of the transoid type through five bonds (^5J) and the different rates of deuteration of the asymmetrically substituted

TABLE 1. Chemical Shifts (ppm) and Spin–Spin Coupling Constants (J, Hz) in the PMR Spectra of I-IXb (in Deuteroacetone)

Compound	1H	2H	3H	4H	5H	6H	7H	8H		CH_2—N	CH_3—N	CH_2—Et	CH_3—Et		$COCH_3$	J, Hz
I	10,3 br s	7,10 dd	6,46 dd	7,30 dd	7,12 dd	10,1 br s	7,18 dd	6,66 m	—	—	—	—	—	—	—	$J_{1,2}=2,4$; $J_{1,3}=2,1$; $J_{1,4}=0,8$; $J_{2,3}=3,0$; $J_{4,5}=8,6$; $J_{5,8}=0,7$; $J_{6,7}=2,5$; $J_{6,8}=2,2$; $J_{7,8}=3,0$
II*	11,1 br s	—	7,25 d	7,54 dd	7,31 dd	11,0 br s	—	7,62 d	—	—	—	4,35 q	1,37 t	—	—	$J_{1,3}=2,0$; $J_{1,4}=0,8$ $J_{4,5}=8,3$; $J_{5,8}=0,8$; $J_{6,8}=1,8$
III	11,6 brs	8,17 d	—	8,18 dd	7,45 d	11,2 br s	8,28 d	—	10,10 s 9,99 s	—	—	—	—	—	—	$J_{1,2}=3,1$; $J_{1,4}=0,9$; $J_{4,5}=8,7$; $J_{6,7}=3,2$
IV	10,5 br s 10,6 brs†	7,01 dt	—	7,42 dd	7,06 d	9,9 br s (8,1† br s)	7,07 dt	—	—	3,68 d 3,58 d	2,32 s 2,20 s	—	—	—	—	$J_{1,2}\approx J_{6,7}\approx 2$; $J_{1,4}=0,8$; $J_{4,5}=8,7$; $J_{CH_3,7H}\approx J_{CH_2,2H}\approx 0,7$
V	12,0 s (12,2† brs)	—	—	7,77 dd	7,20 d	10,9 s (9,0† br s)	—	—	—	4,20 s 4,01 s	2,44 s 2,25 s	4,38 q 4,36 q	1,43 t 1,39 t			$J_{4,5}=8,9$
VI*	11,5 br s	‡	—	7,50 d	7,37 d	11,4 br s	‡	—	—	—	—	—	—	7,51 d (A), 7,36 d (B), R=Cl	—	$J_{4,5}=8,7$ $J_{A,B}=9,3$
VII*	10,9 br s	7,29 d	—	7,36 dd	7,15 dd	10,4 br s	7,17 dd	6,84 m	—	—	—	—	—	7,78 d (A), 7,44 d (B), R=Cl		$J_{1,2}=2,0$; $J_{1,4}<0,7$; $J_{4,5}=8,7$; $J_{5,8}=0,7$; $J_{6,8}=1,8$; $J_{6,7}=2,2$; $J_{7,8}=2,9$; $J_{A,B}=8,8$
VIII	11,1 br s	‡	—	7,42 dd	7,22 dd	10,5 br s	‡	6,92 m	—	—	—	—	—	7,3—7,9, R=H	—	$J_{4,5}=8,8$; $J_{5,8}=0,7$; $J_{6,8}=1,7$; $J_{7,8}=2,6$
IXa	—	7,74 d	6,79 d	7,53 d	8,55 d	10,9 br s	7,69 d	—	—	—	—	—	—	—	2,75 s 2,71 s	$J_{2,3}=3,8$; $J_{4,5}=8,8$; $J_{6,7}=2,0$
IXb	10,9 br s (10,8† brs)	7,40 dd	6,60 dd	7,60 dd	8,18 d	—	8,63 s	—	—	—	—	—	—	—	2,65 s 2,82 s	$J_{1,2}=2,4$; $J_{1,3}=2,3$; $J_{1,4}\approx 0,5$; $J_{2,3}=3,0$; $J_{4,5}=8,9$

*At 45°C.
†In $CDCl_3$.
‡Located in the region of the shifts of aromatic protons.

compounds in deuterated solvents. The rapid rate (comparable to the recording time) of this process for compounds that contain strong electron-acceptor substituents often makes it impossible to observe small $^5J_{NH,CH}$ values ($^5J_{ND,CH} \approx 0$). However, this "negative" result as compared with the data from the PMR spectra for other compounds nevertheless was of aid in the correct interpretation of the spectra.

It follows from the PMR spectral data that the introduction of electron-acceptor substituents decreases the electron density primarily on the closest carbon atoms, which is in agreement with the weak-field chemical shift of the corresponding protons.

Compound III displays a somewhat greater difference in the chemical shifts of the protons of the two NH groups (δ_H) than the 3-unsubstituted compounds, and this makes it possible to assume that the 1-H proton participates in an intramolecular hydrogen bond with the carbonyl group in the 8 position. We were unable to verify this in an inert solvent because of the low solubility of the substance; however, the IR spectrum of III in chloroform gives two absorption bands of an NH group (at 3455 and 3360 cm^{-1}), in contrast to unsubstituted analog I, in the spectrum of which one band of an NH group at 3485 cm^{-1} is observed.

The 1-H protons of IV and V also form a rather strong intramolecular hydrogen bond with the unshared pair of electrons of the nitrogen atom of the dimethylamino group; this follows from the fact of the independence of the chemical shift of the 1-H proton ($\Delta\delta_{1\text{-}H}$ = 0.1-0.2 ppm) on the nature of the solvent (compare with $\Delta\nu_{6\text{-}H}$ = 1.8-1.9 ppm for the free NH group). The H chelate formed in this case is an unconjugated seven-membered ring; generally speaking, this is unfavorable for an intramolecular hydrogen bond, although this bond has been observed for unconjugated six-membered rings [8]. However, the geometry of the ring evidently favors pronounced overlapping of the orbitals of the 1-H atom and the unshared pair of electrons of the nitrogen atom. The introduction of the electron-acceptor $COOC_2H_5$ group in the 2 position of the pyrrole rings (V), which primarily affects the acidity of the 1-H atom, increases the energy of the intramolecular hydrogen bond and makes it comparable to the energy for the intramolecular hydrogen bond of the NH...N type in six-membered conjugated rings [9].

Compound IXb also displays an intramolecular hydrogen bond of the 1-H proton with the C=O group of the acetyl substituent, which evidently also stabilizes the indicated structure: of all of the acetylation products, IXb is formed in highest yield.

The data from the PMR spectra serve as evidence for the site of substitution in diazo coupling reactions. It is apparent from Table 1 that the signals of the protons in the 2 and 7 positions in the spectrum of 3,8-diazo compound VI are not observed because of the superimposition of other spectral lines; however, the $^5J_{5,8}$ constant is absent. As regards monosubstituted VII and VIII, a low $^5J_{5,8}$ value of 0.7 Hz, which is absent for the protons of the other pyrrole ring, is observed in their PMR spectra.

EXPERIMENTAL

The course of the reactions was monitored on Silufol UV-254, and the purity of the compounds and their R_f values were established on the same adsorbent. The UV spectra of solutions of the compounds in ethanol were recorded with a Specord spectrophotometer. The IR spectra were recorded with a UR-20 spectrometer with NaCl and LiF prisms. The mass spectrum of VI was recorded at 60-125°C with a Varian MAT-311A spectrometer at an ionizing-electron energy of 70 eV. The mass spectra of III-V and VII-IXb were recorded with an MKh-1303 spectrometer with a modified system for introduction of the samples (direct introduction of the samples into the ion source) and a system for recording of the spectra at an ionizing-electron energy of 50 eV. The PMR spectra were recorded with a Varian CFT-20 spectrometer (f_0 = 80 MHz) with tetramethylsilane as the internal standard; the accuracy in the measurement of the chemical shifts did not exceed 0.01 ppm, while the accuracy in the measurement of the SSCC did not exceed 0.1 Hz. Chromatography of the compounds was carried out on SiO_2.

3,8-Diformyl-1H,6H-pyrrolo[2,3-e]indole (III). This compound was obtained from 0.47 g (3 mmole) of I and a mixture of 2.62 g (36 mmole) of dimethylformamide (DMF) with 1.38 g (9 mmole) of $POCl_3$ at room temperature in analogy with the method described in [10]. Workup gave 0.58 g (91%) of light-colored crystals with mp 260.5-262°C (from ethanol) and R_f 0.55 (ethyl acetate). UV spectrum, λ_{max} (log ε): 204 (4.26) sh, 216 (4.47), 234 (4.06) sh, and 292 nm (4.38). IR spectrum (in $CHCl_3$): 3455, 3360 (NH); 1630-1660 cm^{-1} (C=O;. Found:

C 68.0; H 4.0; N 12.8%. $C_{12}H_8N_2O_2$. Calculated: C 67.9; H 3.8; N 13.2%. M^+ 212 (from the mass spectrum), M 212.

3,8-Bis(dimethylaminomethyl)-1H,6H-pyrrolo[2,3-e]indole (IV). A Mannich reagent prepared from 1.23 g (9 mmole) of a 33% solution of dimethylamine, 0.68 g (9 mmole) of 40% formalin, and 1.2 g of acetic acid by the method in [2] was added to a solution of 0.47 g (3 mmole) of I in 11 ml of acetic acid, and the mixture was stirred at room temperature for 3 h. It was then diluted with 200 ml of water, and the aqueous mixture was made alkaline to pH 11 with a 10% solution of NaOH. The precipitate was removed by filtration, washed with water, and dried to give 0.38 g of product. The product was extracted with ether, and the extract was dried over Na_2SO_4. The solvent was removed by evaporation to give 0.40 g (49.4%) of IV as colorless crystals with mp 130-131°C (dec.) and R_f 0.48 (33% aqueous ammonium hydroxide). UV spectrum, λ_{max} (log ε): 205.7 (4.33) sh, 238 (4.56), 270 (4.01) sh, 281.7 (4.12), 296 (3.92) sh, and 307.7 nm (3.71) sh. IR spectrum (in mineral oil): 3050 (NH) and 1530 cm^{-1} (C–N$\langle$). Found: N 20.4%. $C_{16}H_{22}N_4$. Calculated: N 20.7%, M^+ 270 (from the mass spectrum), M 270.

3,8-Bis(dimethylaminomethyl)-2,7-dicarbethoxy-1H,6H-pyrrolo[2,3-e]indole (V). This compound was obtained from 0.75 g (2.5 mmole) of II and a Mannich reagent prepared from 3.75 g (50 mmole) of 40% formalin, 6.8 g (50 mmole) of a 33% solution of dimethylamine, and 6.8 g of acetic acid [2]. The reaction mixture was stirred at 95°C for 1 h, after which it was diluted with 500 ml of water. The aqueous mixture was filtered, and the filtrate was made alkaline to pH 11 with 10% NaOH solution. The precipitate was removed by filtration, washed with water, and dried to give 0.73 g (71%) of colorless crystals with mp 167-168.5°C (from benzene) and R_f 0.56 [acetone–33% ammonium hydroxide (300:1)]. UV spectrum, λ_{max} (log ε): 208.5 (4.38), 293, (4.56), 331 (4.05) sh, and 348 nm (3.82) sh. IR spectrum (in chloroform): 3460 (NH); 1680, 1690 (C=O); 1545 cm^{-1} (C–N$\langle$). Found: 63.9; H 7.6; N 13.7%. $C_{22}H_{30}N_4O_4$. Calculated: C 63.8; H 7.2; N 13.5%. M^+ 414 (from the mass spectrum), M 414.

The dihydrochloride (colorless crystals) had mp 182-184°C. IR spectrum (in KBr): 3450 (NH); 1680, 1690 (C=O); 2700 cm^{-1} ($R_3\overset{+}{N}H$). Found: C 53.8; H 6.6; N 11.5; Cl 14.2%. $C_{22}H_{30}N_4O_4 \cdot 2HCl$. Calculated: C 54.2; H 6.6; N 11.5; Cl 14.6%.

3,8-Bis(p-chlorophenylazo)-1H,6H-pyrrolo[2,3-e]indole (VI) and 3-(p-Chlorophenylazo)-1H,6H-pyrrolo[2,3-e]indole (VII). A solution of 9 mmole of p-chlorobenzenediazonium chloride was added dropwise at 0°C to a solution of 0.47 g (3 mmole) of I in 45 ml of dioxane and 30 ml of water while maintaining the pH of the solution at six to seven by the addition of sodium acetate. The mixture was then stirred for 3 h, after which it was extracted with ether. The extract was washed successively with a 10% solution of NaOH and with water until the wash waters were neutral, after which it was dried over Na_2SO_4, and the solvent was removed by evaporation to give 1 g of product. The latter was purified with a column by elution with hexane–ether (200:15). Two substances were isolated. Workup of the eluate with R_f 0.79 [benzene–ether (5:1)] gave 60 mg of yellow crystals of VI with mp 121-122°C. Found: N 19.1%. $C_{22}H_{14}N_6Cl_2$. Calculated: N 19.4%. The mass spectrum did not change as a function of the temperature of the input system; an M^+ peak was absent, but peaks of fragment ions with masses 265(2), 237(10), 139(73), 127(46), 111(100), and 77(11), which do not contradict the proposed structure, were observed. UV spectrum, λ_{max}: 240, 298, and 363 nm. IR spectrum (in chloroform): 3330 (NH) and 1610 cm^{-1} (–N=N–).

Workup of the eluate with R_f 0.54 gave 181 mg (20.5%) of yellow crystals of VII [benzene–ether (5:1)] with mp 192.5-193°C (dec.). UV spectrum, λ_{max}, (log ε): 206.5 (4.32), 222 (4.28), 256 (4.14) sh, 268.5 (4.21), and 454 nm (3.50). IR spectrum (in mineral oil): 3375, 3455 (NH); 1640 cm^{-1} (–N=N–). Found: Cl 11.5; N 18.6%. $C_{16}H_{11}N_4Cl$. Calculated: Cl 12.1; N 19.0%; M^+ 294-296, doublet (from the mass spectrum), M 294.5.

3-Phenylazo-1H,6H-pyrrolo[2,3-e]indole (VIII). This compound was obtained as in the preceding experiment by the reaction of 0.47 g (3 mmole) of I with a solution of 9 mmole of benzenediazonium chloride. The crude product [0.7 g (90%)] was purified with a column by elution with hexane–ether (100:15) to give 77 mg of yellow needles with mp 197-197.5°C and R_f 0.61 [benzene–ether (5:1)]. UV spectrum, λ_{max} (log ε): 204.5 (4.21), 227 (4.18), 268.5 (4.14), and 444 nm (4.52). IR spectrum (in mineral oil): 3385, 3460 (NH); 1640 cm^{-1} (–N=N–). Found: N 21.5%. $C_{16}H_{12}N_4$. Calculated: N 21.5%; M^+ 260 (from the mass spectrum), M 260.

1,8-Diacetyl-1H,6H-pyrrolo[2,3-e]indole (IXa) and 6,8-Diacetyl-1H,6H-pyrrolo[2,3-e]-indole (IXb). A mixture of 0.47 g (3 mmole) of I, 11.02 g (250 mmole) of freshly distilled acetic anhydride, and 1.02 ml of glacial acetic acid was refluxed for 24 h, after which the solvent was removed by evaporation, and the residual mixture was poured into water. The aqueous mixture was extracted with ethyl acetate, and the extract was washed with water until the wash waters were neutral. It was then dried, and the solvent was removed by evaporation. The residue was purified with a column by elution with benzene–acetone (30:1). Two substances were isolated. Workup of the eluate with R_f 0.67 gave 10 mg of IXa [benzene–acetone (4:1)] as colorless crystals with mp 192-194°C. UV spectrum, λ_{max}: 227 sh, 237, 283.5, and 325 nm. IR spectrum: 1670, 1730 cm^{-1} (C=O). Found: C 69.7; H 4.9; N 11.3%. $C_{14}H_{12}N_2O_2$. Calculated: C 70.0; H 5.0; N 11.7%. M^+ 240 (from the mass spectrum), M 240.

Workup of the eluate with R_f 0.62 gave 96 mg of IXb [benzene–acetone (3:1)] as colorless crystals with mp 220-225°C (dec.). UV spectrum, λ_{max}: 212.7, 240, 284, and 330 nm. IR spectrum (in mineral oil): 3385 (NH); 1660, 1725 cm^{-1} (C=O). Found: C 70.2; H 5.6; N 11.7%. $C_{14}H_{12}N_2O_2$. Calculated: C 70.0; H 5.0; N 11.7%. M^+ 240 (from the mass spectrum), M 240.

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