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

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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. Diazoc 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).

As expected, the 3 and 8 positions (the corresponding 8 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.

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 benzene-diazonium 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 BESM-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 C₃ and C₈ atoms. The bond orders and overall (σ + π) 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