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AZAINDOLE DERIVATIVES.

61.* ELECTROPHILIC SUBSTITUTION REACTIONS IN 1-BENZYL-6-METHOXY-7-CYANO-5-AZAINDOLE AND 6-OXO-5-AZAINDOLINE

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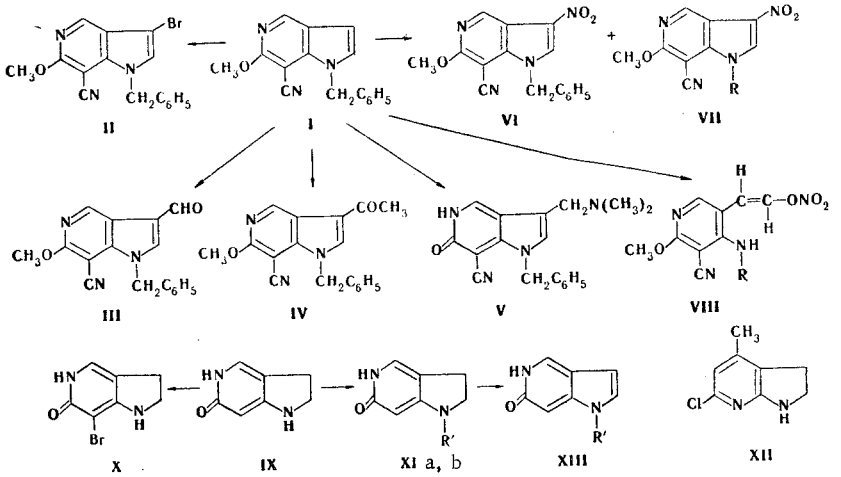
The electrophilic substitution reactions (nitration, bromination, acylation, and the Mannich and Vilsmeier reactions) of 1-benzyl-6-methoxy-7-cyano-5-azaindole and the nitration and Vilsmeier reaction of 6-hydroxy-5-azaindoline were studied.

Some of the efficient methods for the synthesis of polysubstituted 5-azaindoles, which are of interest for biological study, are the conversion of N-benzyl-2-pyrrolidone to 1,6,7-tri- or 1,4,6,7-tetrasubstituted 5-azaindolines [2, 3], their oxidation to the corresponding azaindoles [3], and the introduction of additional groups in the 3 position by means of electrophilic substitution reactions. We have previously shown [4] that despite the literature data [5], electrophilic substitution in the 3 position of 5-azaindoles is realized readily; however, the presence of electron-acceptor substituents may hinder these reactions.

In the present communication we examine the peculiarities of electrophilic substitution processes in 1-benzyl-6-methoxy-7-cyano-5-azaindole (I).



XIa $R'=NO_2$; b $R'=CHO$; VII $R=CH_2C_6H_4NO_2$-p; VIII $R=CH_2C_6H_4NO_2$

The process takes place most smoothly with a strong electrophilic reagent such as bromine. Azaindole I reacts with bromine in chloroform at 0°C to give 1-benzyl-3-bromo-6-methoxy-7-cyano-5-azaindole (II) in

*See [1] for Communication 60.

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97% yield. The reaction proceeds with greater difficulty with milder electrophilic agents, viz., the Vilsmeier complex and a mixture of acetyl chloride with aluminum chloride: 1-benzyl-3-formyl (III) and 1-benzyl-3-acetyl-6-methoxy-7-cyano-5-azaindole (IV) are obtained in 52 and 48% yields, respectively. The deactivating effect of the electron-acceptor nitrile residue in the 7 position of the azaindole molecule is evidently substantial in these cases. A similar effect of the nitrile group is also observed in the Mannich reaction. In this case the process is additionally complicated by hydrolysis of the methoxy group. In contrast to 1-benzyl-6-methoxy-7-cyano-5-azaindoline, in which the methoxy group is hydrolyzed only under sufficiently severe conditions, viz., in the case of prolonged refluxing in alcohols with the continuous passage of hydrogen chloride into the mixture, this process takes place by refluxing in butanol with dimethylamine hydrochloride in the case of the corresponding 5-azaindole derivative I. The final reaction product, viz., 1-benzyl-3-dimethylaminomethyl-6-hydroxy-7-cyano-5-azaindole (V), which was isolated in 42% yield, exists primarily in the oxo form, according to the IR, UV, and PMR spectroscopic data.

Complications associated with the effect of substituents in 5-azaindole molecule I were also observed in the case of nitration. When we used sulfuric acid with concentrated nitric acid at low temperatures (−15°C), in addition to simultaneous electrophilic substitution in the 3 position of azaindole I, which leads to 1-benzyl-3-nitro-6-methoxy-7-cyano-5-azaindole (VI), we observed nitration in the para position of the phenyl ring of the benzyl substituent to give 1-(p-nitrobenzyl)-3-nitro-6-methoxy-7-cyano-5-azaindole (VII). According to the PMR spectroscopic data, the ratio of VI and VII in the reaction products was 2.5 : 1; some of the starting azaindole I remained unchanged in the process. Nitration of azaindole I with fuming nitric acid led to opening of the pyrrole ring and the formation of 2-methoxy-3-cyano-4-(p-nitrobenzylamino)-5-β-nitrooxyvinyl)pyridine (VIII) in 81% yield. We also previously observed similar cleavage of the pyrrole ring during a study of the Chichibabin reaction in the 5-azaindole series [6].

The mass spectrum of VIII contains a molecular-ion peak with m/z 371 and peaks of fragments with m/z 326 ($M-NO_2$), 310 ($M-NO_3$), and 284 ($M-C_2H_2NO_3$). The following characteristic signals are present in the PMR spectrum of pyridine VIII (in $CDCl_3$ + CF_3COOH): 4.1 (d, 2H, $C_6H_4CH_2$), 4.32 (s, 3H, CH_3O), 5.20 (d, 1H, α-H of the pyridine ring), 5.60 (d, 1H, $=CH-CNO_2$; J = 20 Hz), 6.20 (s, 1H, CH=), 7660 (d, 2H, 2-H and 6-H in the phenyl ring), and 7.40 ppm (d, 2H, 3-H, and 5-H in the phenyl ring, J = 8 Hz).

It has been previously shown [7] that, depending on the character of the reagent and the reaction conditions, electrophilic substitution reactions in 4-methyl-6-chloro-7-azaindoline (XII) take place in the 5 position of the pyridine fragment of the molecule or at the nitrogen atom of the pyrroline ring. We also uncovered similar principles of electrophilic reactions in the case of 6-oxo-5-azaindoline (IX). During a study of the PMR spectra of IX we observed that the 7-H proton of this substance is readily exchanged by deuterium when the compound is dissolved in deuteroacetic acid at 20°C. As in the case of 7-azaindoline derivative XII [7], the bromination of IX takes place quite smoothly at the carbon atom of the pyridine ring. 6-Oxo-7-bromo-5-azaindoline (X) is obtained in 74% yield [1]. Just as in the case of XII [7], the chlorination of IX does not stop with the monochloro derivatives but readily proceeds further to give products of more profound chlorination. It has been previously noted that a mixture of N_1- and C_5-nitro derivatives is obtained in the nitration of 7-azaindoline compound XII; N→C migration of the nitro group proves to be hindered [7]. In the case of 6-oxo-5-azaindoline (IX) nitration under various conditions (at 0 and −15°C) leads to the formation of only the N_1-nitro derivative (XIa). Attempts to realize N→C migration of the nitro group did not give positive results: Redox processes take place when XIa is treated with sulfuric acid at 20°C, and 1-nitro-6-oxo-5-azaindole (XIIIa) is formed (according to the PMR spectroscopic data). The following signals are observed in the PMR spectrum of a mixture of XIa and XIII recorded in $CDCl_3$ with added CH_3COOH: 3.30 (t, 2H, 3-H, XIa), 4.60 (t, 2H, 2-H, XIa), 7.0 (s, 1H, 7-H, XIa), 7.80 (s, 1H, 7-H, XIII), 7.83 (s, 1H, 4-H, XIa), 8.52 (s, 1H, 2-H, XIII), and 9.35 ppm (s, 1H, 4-H, XIII). The reaction is accompanied by pronounced resinification, which hinders separation of XIa and XIII, the ratio of which in the reaction mixture is 1 : 5, according to the PMR spectroscopic data.

As in the case of nitration, formylation of IX by means of the Vilsmeier complex, which leads to the formation of 1-formyl-6-oxo-5-azaindoline (XIb), takes place selectively at the N_1 atom.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with a Perkin-Elmer-467 spectrometer. The UV spectra of solutions of the compounds in ethanol were recorded with a Perkin-Elmer-402 spectrophotometer. The PMR spectra of solutions of the compounds in $CDCl_3$, except where specially indicated otherwise in the text, were recorded with a JNM-4H-100 spectrometer with tetramethylsilane as the

internal standard. The chromatographic mass spectra were recorded with a Varian Matt III chromatographic mass spectrometer at 70 eV with helium as the carrier gas.* The synthesis of 6-oxo-7-bromo-5-azaindoline (Xa) was described in [1].

1-Benzyl-3-bromo-6-methoxy-7-cyano-5-azaindole (II). A 2.49-g (16 mmole) sample of bromine was added dropwise at 0°C to a solution of 1.57 g (6 mmole) of 1-benzyl-6-methoxy-7-cyano-5-azaindole (I) in 15 ml of chloroform, after which the mixture was stirred at the same temperature for 4 h. The precipitate was removed by filtration and washed with acetone to give 2.4 g of the hydrobromide of II, which was dissolved in 50 ml of water. The solution was made alkaline with 50% aqueous potassium carbonate solution, and the resulting precipitate was removed by filtration to give 2 g (97%) of yellow crystals with mp 274-275°C (from methanol). The product was quite soluble in chloroform, alcohols, acetone, and dimethylformamide (DMF), only slightly soluble in ethyl acetate, and insoluble in ether, hexane, and water. IR spectrum: 1575 (C=C), 1600 (C=N), and 2220 cm^{-1} (C≡N). UV spectrum, λ_{max} (log ε): 208 (4.40), 238 (4.58), 295 (3.60), and 335 nm (3.64). PMR spectrum: 4.10 (s, 3H, CH_3O), 5.55 (s, 2H, $CH_2C_6H_5$), 7.00 (s, 1H, 2-H), 7.10-7.40 (m, 5H, C_6H_5), and 8.50 ppm (s, 1H, 4-H). Found: C 56.4; H 3.7; Br 23.2; N 12.4%; M^+ 342. $C_{16}H_{12}BrN_3O$. Calculated %: C 56.2; H 3.5; Br 23.4; N 12.3%; M 342.

1-Benzyl-3-formyl-6-methoxy-7-cyano-5-azaindole (III). A 0.23-g (9 mmole) sample of azaindole I was added to the Vilsmeier reagent prepared from 10 ml of DMF and 1 ml (10 mmole) of phosphorus oxychloride, after which the mixture was stirred at 70°C for 2 h. It was then poured over ice, 20 ml of a 20% aqueous solution of sodium hydroxide was added, and the mixture was heated to the boiling point. The resulting precipitate was removed by filtration and washed with water to give 0.13 g (52%) of formylazindole III as colorless crystals with mp 189-190°C. The product was quite soluble in methanol and chloroform, only slightly soluble in ethyl acetate and benzene, and insoluble in ether, heptane, and water. IR spectrum : 1580 (C=C); 1615 (C=N); 1680 (C=O); 2220 (C≡N); 2750, 2820 cm^{-1} (CHO). PMR spectrum: 4.10 (s, 3H, CH_3O), 5.65 (s, 2H, $CH_2C_6H_5$), 7.20-7.35 (m, 5H, C_6H_5), 7.60 (s, 1H, 2-CH), 9.24 (s, 1H, 4-CH), and 9.94 (s, 1H, CHO). Found: C 69.8; H 4.8; N N 14.3%; M^+ 291. $C_{17}H_{13}N_3O_2$. Calculated %: C 70.1; H 4.5; N 14.4%; M 291.

1-Benzyl-3-acetyl-6-methoxy-7-cyano-5-azaindole (IV). A 5-ml (70 mmole) sample of acetyl chloride was added to a solution of 5.2 g (39 mmole) of aluminum chloride in 20 ml of dichloroethane, and the mixture was stirred for 15 min. A solution of 0.5 g (2 mmole) of azaindole I in 20 ml of dichloroethane was added, and the mixture was stirred at 20°C for 2 h. It was then poured into a solution of 20.3 g of potassium sodium tartate in 100 ml of water, and the mixture was extracted with two 100-ml portions of n-butyl alcohol. The combined butanol extracts were dried with magnesium sulfate and evaporated, and the residue (0.6 g) was recrystallized from benzene to give 0.28 g (48.3%) of acetylazaindole IV as colorless crystals with mp 152-153°C. The product was quite soluble in ethyl acetate, chloroform, alcohols, and DMF, only slightly soluble in ether and benzene, and insoluble in hexane and water. IR spectrum (in $(CHCl_3)$): 1580 (C=C), 1615 (C=N), 1675 (C=O), 2220 cm^{-1} (C≡N). UV spectrum, λ_{max} (log ε): 206 (4.44), 228 (4.46), 270 (3.87), 292 (3.95), and 325 nm (4.36). PMR spectrum: 2.45 (s, 3H, CH_3CO), 4.10 (s, 3H, CH_3O), 5.62 (s, 2H, $CH_2C_6H_5$), 7.25-7.40 (m, 5H, C_6H_5), 7.56 (s, 1H, 2-H), and 9.32 ppm (s, 1H, 4-H). Found: C 70.6; H 5.0; N 14.1%; M^+ 305. $C_{18}H_{15}N_3O_2$. Calculated %: C 70.9; H 5.0; N 13.8%; M 305.

1-Benzyl-3-dimethylaminomethyl-6-hydroxy-7-cyano-5-azaindole (V). A 0.33-g (4 mmole) sample of dimethylamine hydrochloride and 0.12 g (4 mmole) of paraformaldehyde were added to a solution of 0.5 g (2 mmole) of azaindole I in 20 ml of n-butyl alcohol, and the mixture was refluxed for 5 h. It was then evaporated to dryness, 50 ml of 1 N hydrochloric acid was added, and the nonbasic impurities were extracted with ether. The aqueous layer was neutralized with ammonia and extracted with two 100-ml portions of n-butyl alcohol. The combined butanol extracts were dried with magnesium sulfate and evaporated, and the residue (0.43 g) was treated with an alcohol solution of hydrogen chloride. The precipitate was recrystallized from isopropyl alcohol to give 0.29 g (42.6%) of azaindole V hydrate hydrochloride as colorless crystals with mp 150-151°C. The product was quite soluble in water, methanol, and DMF, only slightly soluble in isopropyl alcohol and acetone, and insoluble in ether and hexane. Found: C 60.2; H 5.6; Cl 9.9; N 15.7%. $C_{18}H_{18}N_4O \cdot HCl \cdot H_2O$. Calculated: C 59.9; H 5.9; Cl 9.8; N 15.6%. Base V was obtained as colorless crystals with mp 290-291°C. The base was quite soluble in isopropyl alcohol, methylene chloride, and DMF, only slightly soluble in acetone, and insoluble in ether, hexane, and ethyl acetate. IR spectrum: 1580 (C=C); 1620 (C=N); 1670 (C=O); 2200 (C≡N); 3100, 3260 cm^{-1} (NH). Found: C 70.7; H 5.5; N 18.5%; M^+ 306. $C_{18}H_{18}N_4O$. Calculated: C 70.6; H 5.9; N18.3%; M306.

*The spectral studies were made by K. F. Turchin, O. S. Anisimova, and E. M. Peresleni and co-workers in the Laboratory of Physicochemical Methods of Investigation of the S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry under the direction of Professor Yu. N. Sheinker.

1-Benzyl-3-nitro-6-methoxy-7-cyano-5-azaindole (VI) and 1-(p-Nitrobenzyl)-3-nitro-6-methoxy-7-cyano-5-azaindole (VII). A 0.2-ml sample of concentrated HNO_3 was added to a cooled (to −10°C) solution of 0.5 g (21 mmole) of azaindole I in 10 ml of concentrated H_2SO_4, and the mixture was stirred at −10°C for 30 min. It was then poured over a mixture of ice with concentrated ammonium hydroxide, and the aqueous mixture was extracted with methylene chloride (two 200-ml portions). The solvent was removed by distillation to give 0.47 g of yellow crystals with mp 190-192°C. The product was quite soluble in chloroform, ethyl acetate, and DMF, only slightly soluble in benzene, and insoluble in water and ether. Three molecular ions are present in the mass spectrum: M^+ 308 and 353 (VI and VII, respectively) and 263 (I). PMR spectrum (in $CF_3COOD + CDCl_3$): 4.37 (VII, s, 3H, CH_3O), 4.45 (VI, s, 3H, CH_3O). 5.75 (VI, s, 2H, $CH_2C_6H_5$), 5.95 (VII, s, 2H, $CH_2C_6H_5$), 7.00-7.50 (m, VI, 2H, 2-H + VII, 5H, C_6H_5), 8.21 (m, VII, 2H, 2-H, 6-H, $C_6H_4NO_2$ + VII, 2H, 2-H), 8.81 (m, VII, 2H, 3-H, 5-H, $C_6H_4NO_2$ + VI, 2H, 4-H), and 9.42 (VII, s, 1H, 4-H). The ratio of VI to VII was 2.5 : 1.

2-Methoxy-3-cyano-4-(p-nitrobenzylamino)-5-(β-nitrooxyvinyl)pyridine (VIII). A 1-ml sample of fuming HNO_3 was added to a cooled (to −20°C) 11-ml sample of concentrated H_2SO_4, after which 0.5 g (2 mmole) of azaindole I was sprinkled into the mixture at −15°C, and the mixture was stirred at 1 h. It was then poured over a mixture of ice with concentrated ammonium hydroxide, and the aqueous mixture was extracted with methylene chloride (two 100-ml portions). The extract was dried with magnesium sulfate and evaporated to give 0.58 g (82%) of pyridine VIII as light-yellow crystals with mp 181-182°C (dec.). The product was quite soluble in methanol and DMF, only slightly soluble in ethyl acetate and chloroform, and insoluble in ether and water. IR spectrum: 1580 (C=C), 1610 (C=N), 1645 (ONO_2), 2200 (C≡N), and 3100 cm^{-1} (NH). Found: C 51.6; H 3.2; N 18.9%; M^+ 371. $C_{16}H_{13}N_5O_6$. Calculated: C 51.8; H 3.5; N 18.9%; M 371.

1-Nitro-6-oxo-5-azaindoline (XIa). A 2.5 ml sample of concentrated HNO_3 was added at −15°C to a solution of 5 g (37 mmole) of IX in 60 ml of concentrated H_2SO_4, and the mixture was stirred for 3.5 h. It was then poured over a mixture of ice with concentrated ammonium hydroxide, and the precipitate was removed by filtration to give 6.07 g (91%) of XIa with mp > 300°C (dec.). The yellow crystalline product was soluble in DMF, less soluble in methanol, and insoluble in other organic solvents and water. IR spectrum: 1592 (C=C); 1650 (C=N); 1660 (C=O); 3080, 3100, 3120 cm^{-1} (NH). PMR spectrum (in $CF_3COOD + CDCl_3$): 3.40 (t, 2H, 2-H), 4.68 (t, 2H, 2-H), 7.61 (s, 1H, 4-H), and 7.89 ppm (s, 1-H, 7-H). Found: C 46.4; H 4.1; N 23.1%; M^+ 181. $C_7H_7N_3O_3$. Calculated: C 46.4; H 3.9; N 23.2%; M 181.

1-Formyl-6-oxo-5-azaindoline (XIb). A 0.5-g (4 mmole) sample of IX was added to the Vilsmeier reagent prepared from 20 ml of DMF and 1.68 g (11 mmole) of phosphorus oxychloride, and the mixture was stirred at 50°C for 4 h. It was then cooled and treated with 20 ml of 20% aqueous sodium hydroxide, and the mixture was heated to the boiling point. It was then cooled and extracted with methylene chloride (two 200-ml portions). The extract was dried with magnesium sulfate and evaporated to give 0.05 g (8%) of XIb as shiny yellow plates with mp 305-306°C. The product was quite soluble in methanol, DMF, and water, only slightly soluble in ethyl acetate, and insoluble in benzene, hexane, and ether. IR spectrum: 1620, 1630 (C=N, C=O); 1660 (CHO); 2700 (CHO); 3125, 3320 cm^{-1} (NH). PMR spectrum (d_6-DMSO): 2.76 (t, 2H, 3-H), 3.73 (t, 2H, 2-H), 7.00 (s, 1H, 4-H), 8.70 (s, 1H, 7-H), and 9.30 ppm (s, 1H, CHO). Found: C 58.7; H 4.7; N 17.0%; M^+ 164. $C_8H_8N_2O_2$. Calculated: C 58.5; H 4.9; N 17.1%; M 164. The 0.35 g of substance that precipitated from the aqueous layer was identified (from mass-spectrometric data) as a mixture of 6-chloro-5-azaindoline, 1-formyl-6-chloro-5-azaindoline, and IX.

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