AZAINDOLE DERIVATIVES

XLI.* SYNTHESIS OF 3-SUBSTITUTED 5-AZAINDOLES

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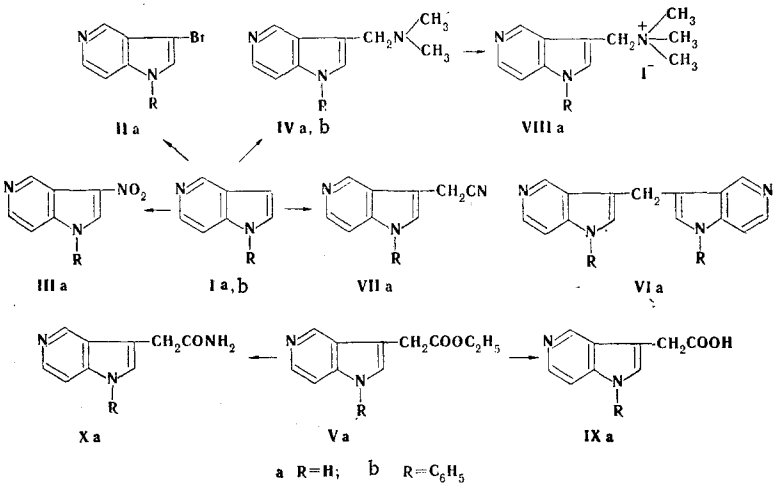
Electrophilic substitution reactions – cyanomethylation, bromination, nitration, and the Mannich reaction – in the 5-azaindole series were studied. It is shown that, despite the literature data, 5-azaindole behaves like the isomeric 4- and 7-azaindoles in these reactions. Conditions that make it possible to synthesize various 3-substituted 5-azaindoles in high yields were found.

Electrophilic substitution reactions that lead to various functional derivatives with respect to the 3 position of the pyrrole ring have been well studied for the isomeric 7- and 4-azaindoles [2-4]. According to the literature [5], similar reactions in the 5-azaindole series have not given positive results; this was ascribed to the high basicity of 5-azaindole, which readily forms a protonated form in which the electron density on C_3 is reduced [6].

In the present paper we have studied various electrophilic substitution reactions – cyanomethylation, bromination, nitration, and the Mannich reaction – in 5-azaindoles, and we have shown that, despite the literature data, 5-azaindole (Ia) is similar in reactivity to the isomeric 4- and 7-azaindoles [7].

Selection of the experimental conditions made it possible to accomplish the indicated reactions in high yields and to develop preparative methods for the synthesis of the previously undescribed 3-substituted 5-azaindoles. It should be noted that, as in the case of the isomeric 4- and 7-azaindoles, the introduction of an electron-acceptor residue into the 1 position of 5-azaindole hinders electrophilic substitution processes. Thus, for example, 1-phenyl-5-azaindole (Ib) forms the corresponding azagramine (IVb) in 10-13% yield.



*See [1] for communication XL.

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It is known that cyanomethylation is the most sensitive of the reactions under consideration to the magnitude of the electron density in the molecule undergoing attack. In this connection, the decrease in electron density of the pyrrole ring due to the electron-acceptor effect of the pyridine ring, which is characteristic for all of the pyrrolopyridines, shows up most strongly in precisely this reaction.

In the case of 5-azaindole, the yield of ethyl 5-aza-3-indolylacetate (Va) after treatment of the cyanomethylation products with alcoholic hydrogen chloride solution was 37%. Moreover, Ia (25%) and bis(5-aza-3-indolyl)methane (VIa) (23%) were also isolated along with Va. The corresponding cyanomethyl derivative (VIa) was obtained from 5-azagramine (IVa) through its methiodide (VIIIa) with subsequent treatment with potassium cyanide. The use of a 10-fold excess of potassium cyanide made it possible to obtain VIIa in 61.3% yield. 5-Azaheteroauxin (5-aza-3-indolylacetic acid) (IXa) was synthesized by saponification of ester Va, while 5-aza-3-indolylacetamide (Xa) was synthesized by the reaction of Va with liquid ammonia.

EXPERIMENTAL

3-Bromo-5-azaindole (IIa). A solution of 0.2 g (1.6 mmole) of Ia in 7 ml of dioxane was added dropwise at room temperature with stirring in the course of 10 min to a solution of 0.35 g (2.2 mmole) of bromine in 7 ml of dioxane. Stirring was continued for another 10 min, after which the precipitated yellow crystals were removed by filtration and washed with dioxane, acetone, and ether to give 0.42 g of the hydrobromide of IIa. The overall yield of product with mp 260-261° (from isopropyl alcohol) was 0.47 g (100%). The product was only slightly soluble in ethyl acetate, acetone, dioxane, and chloroform but soluble in dimethylformamide, ethanol, and hot isopropyl alcohol. Found, %: Br 57.3; N 10.0. $C_7H_5BrN_2 \cdot HBr$. Calculated, %: Br 57.6; N 10.1. Base IIa was obtained as yellow crystals with mp 184-185° (from benzene). The base was quite soluble in ether and hot benzene, slightly soluble in ethyl acetate, alcohols, chloroform, and acetone, and insoluble in water and petroleum ether. Found, %: C 42.5; H 2.36; Br 40.5; N 14.4. $C_7H_5BrN_2$. Calculated, %: C 42.6; H 2.5; Br 40.6; N 14.2.

3-Nitro-5-azaindole (IIIa). A 0.2-g (1.6 mmole) sample of Ia was added in portions in the course of 10 min to 2 ml (3.2 mmole) of cooled (to 0°) fuming nitric acid (sp. gr. 1.52), after which the mixture was held at 0° for 1 h and poured over 20 g of ice. The light-yellow precipitate was removed by filtration, washed with ice water, and dissolved in 20 ml of boiling water. The solution was made alkaline to pH 9 with 25% ammonium hydroxide, and IIIa was removed by filtration to give 0.27 g (100%) of a product with mp 296-297° [from water–dimethylformamide (10:1)]. The light-yellow crystals were only slightly soluble in ordinary organic solvents but soluble in dimethylformamide. Found, %: C 51.3; H 3.1; N 25.9. $C_7H_5N_3O_2$. Calculated, %: C 51.5; H 3.1; N 25.8.

5-Azagramine (IVa). A mixture of 1 g (8.5 mmole) of Ia, 2.07 g (25.4 mmole) of dimethylamine hydrochloride, 0.29 g (10 mmole) of paraformaldehyde, and 16 ml of butanol was refluxed for 15 min and vacuum evaporated to dryness. The residue was dissolved in 15 ml of 10% hydrochloric acid, and the nonbasic impurities were extracted with four 25-ml portions of ether. The aqueous layer was made alkaline with 50% potassium carbonate solution and extracted with chloroform. The chloroform was removed by distillation, and the residue (1.48 g) was dissolved in 5 ml of anhydrous benzene and acidified with alcoholic hydrogen chloride to pH 1. The colorless crystals of the dihydrochloride of IVa were removed by filtration and washed with alcohol and ether to give 1.95 g (92%) of a product with mp 236-237° (from benzene–alcohol). The product was quite soluble in water but only slightly soluble in ordinary organic solvents. Found, %: C 48.0; H 6.3; Cl 28.8; N 17.2. $C_{10}H_{13}N_3 \cdot 2HCl$. Calculated, %: C 48.4; H 6.0; Cl 28.6; N 16.9.

The methiodide of IVa (VIIIa) was obtained as colorless crystals with mp 100° (dec.). Found, %: I 40.5; N 13.6. $C_{11}H_{16}IN_3$. Calculated, %: I 40.1; N 13.3.

1-Phenyl-5-azagramine (IVb). A mixture of 0.5 g (2.6 mmole) of Ib, 2.1 g (26 mmole) of dimethylamine hydrochloride, and 0.39 g (13 mmole) of paraformaldehyde was refluxed for 30 min in 10 ml of diethylene glycol. The solution was then vacuum evaporated (200°/5 mm), and the residue was made alkaline with 10 ml of 25% potassium carbonate solution and extracted with benzene. Compound IVb was extracted from the benzene extract with phosphate–citrate buffer solution [evaporation of the residual benzene extract gave 0.28 g (56%) of Ib]. The buffer solution was made alkaline with 50% potassium carbonate solution, and IVb was extracted with ether and converted to the dihydrochloride by treatment with an alcoholic hydrogen chloride solution to give 0.11 g (13.1%) of a product with mp 273-274°. Found: C 59.2; H 6.2; Cl 22.2; N 13.2. $C_{16}H_{17}N_3 \cdot 2HCl$. Calculated, %: C 59.2; H 5.9; Cl 21.9; N 13.0.

5-Aza-3-indolylacetonitrile (VIIa). A mixture of 2.5 g (8 mmole) of VIIIa, 4.87 g (75 mmole) of potassium cyanide, and 25 ml of water was heated at 90° for 1 h. It was then cooled to room temperature, and VIIa was extracted repeatedly with ether (about 1 liter), after which it was crystallized from ethyl acetate to give 0.76 g (61.3%) of a product with mp 162-163°. The product was quite soluble in acetone and alcohols but only slightly soluble in ether, benzene, and petroleum ether. Found, %: C 68.5; H 4.2; N 27.0. $C_9H_7N_3$. Calculated, %: C 68.8; H 4.5; N 26.7.

Cyanomethylation of 5-Azaindole (Ia). A mixture of 2.55 g (21.6 mmole) of Ia, 2.2 g (33.7 mmole) of potassium cyanide, 1.76 g (23 mmole) of 40% formalin, 0.78 g (8 mmole) of anhydrous potassium acetate, 0.82 g (8 mmole) of aluminum oxide, and 55 ml of 90% alcohol was heated with stirring under nitrogen at 120° for 4 h in an autoclave. The reaction mass was then vacuum evaporated and treated with 200 ml of 12% aqueous potassium carbonate solution. The precipitate was removed by filtration, dried, and extracted with three 50-ml portions of boiling methanol to give 0.61 g (23%) of VIa with mp 300° (dec.). The product was only very slightly soluble in water and ordinary organic solvents but soluble in dimethylformamide. Found, %: C 72.2; H 5.0; N 22.3. $C_{15}H_{12}N_4$. Calculated, %: C 72.6; H 4.8; N 22.6. The aqueous filtrate from the separation of the precipitated VI was extracted with ten 100-ml portions of chloroform to give 0.65 g (25.5%) of Ia with mp 109.5-110°. The aqueous layer was acidified to pH 1 with concentrated hydrochloric acid and vacuum evaporated to dryness. The residue was dried over P_2O_5 and subjected to two-stage esterification by refluxing with 30% alcoholic hydrogen chloride solution (60 ml each time, refluxing for 3 h with subsequent vacuum distillation). The product was converted to the base by treatment with 50% aqueous potassium carbonate, and the base was extracted with five 100-ml portions of ether to give 1.64 g (37.3%) of Va as colorless crystals with mp 79-80°. The product was quite soluble in benzene, chloroform, ethyl acetate, and alcohols, less soluble in ether, and insoluble in hexane and water. Found, %: C 64.5; H 5.7; N 13.7. $C_{11}H_{12}N_2O_2$. Calculated, %: C 64.7; H 5.9; N 13.7.

5-Aza-3-indolylacetic Acid (IXa). A 0.58-g (2.8 mmole) sample of Va was refluxed for 6 h with 7 ml (35 mmole) of 18% hydrochloric acid. The mixture was vacuum evaporated, and the residual water was removed by distillation as an azeotrope with benzene. The residue was triturated with acetone and dissolved in acetone–water (1:1). The solution was filtered and diluted with acetone until it became turbid, after which it was allowed to stand for 24 h at 0°. The crystals were removed by filtration and dried in a vacuum pistol at 100° to give 0.18 g (31.1%) of the hydrochloride of IXa with mp 212-213°. The product was quite soluble in water but only slightly soluble in acetone and benzene. Found, %: C 50.9; H 4.5; Cl 17.0; N 13.0. $C_9H_8N_2O_2 \cdot HCl$. Calculated, %: C 50.8; H 4.2; Cl 16.7; N 13.2.

5-Aza-3-indolylacetamide (Xa). A 2.8-g (14 mmole) sample of Va in a glass autoclave was drenched with 20 ml (1.2 mole) of liquid ammonia, and the mixture was heated at 100° for 5 h. The ammonia was evaporated, and the residue was dissolved in 30 ml of alcohol. The solution was filtered to remove resinous impurities. The resulting crystals of Xa were separated, washed with absolute alcohol and ether, and treated with a saturated alcohol solution of picric acid to give 1.48 g (27%) of the picrate of Xa with mp 232-234° (from water). Found, %: C 44.5; H 2.9; N 20.4. $C_9H_9N_3O \cdot C_6H_3N_3O_7$. Calculated, %: C 45.5; H 3.0; N 20.8.

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