AZAINDOLE DERIVATIVES.

LV.* SYNTHESIS OF 3-SUBSTITUTED 6-AZAINDOLES

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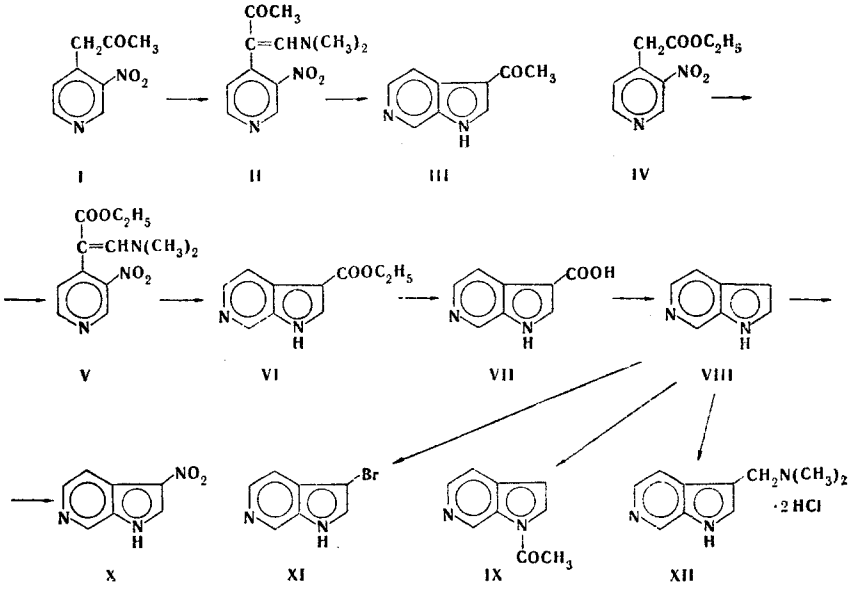
UDC 547.75'821.07

The preparation of 3-substituted 6-azaindoles by the formation of an azaindole ring on the basis of compounds that already contain the necessary substituent (3-acetyl-6-azaindole and 6-azaindole-3-carboxylic acid and its ethyl ester) and by introduction of substituents in the 6-azaindole molecule by means of electrophilic reagents (3-nitro-, 3-bromo-, and 3-dimethylaminomethyl-6-azaindoles) is described.

We have previously described new methods for the preparation of 6-azaindole and its 2-substituted and 2,3-disubstituted derivatives [1-3]. The present communication is devoted to the synthesis of 3-substituted derivatives of 6-azaindole and completes the section of the research involving the construction of 6-azaindole structures containing substituents attached to the carbon atoms of the pyrrole portion of the molecule.

Two possible methods of synthesis — the formation of an azaindole ring on the basis of compounds that already contain the necessary substituent, and introduction of substituents into the 6-azaindole molecule by means of electrophilic substitution reactions — were used for the preparation of 3-substituted 6-azaindoles.

The first method was used for the preparation of 3-acetyl-6-azaindole (III) and 6-azaindole-3-carboxylic acid (VII) and its ethyl ester (VI), and the second method was used for the synthesis of 3-nitro- (X), 3-bromo- (XI), and 3-dimethylaminomethyl-6-azaindole (XII):



The previously described [2] intermediates in the synthesis of 2-substituted 6-azaindoles — (3-nitro-4-pyridyl)acetone (I) and (3-nitro-4-pyridyl)acetic ester (IV) — were used as the starting compounds in the first method; in analogy with the synthesis of unsubstituted 6-azaindole [3], I and IV were subjected to condensation with dimethylformamide diethylacetal (XIII). In contrast to 3-nitro-4-methylpyridine, for which condensation with acetal XIII proceeds almost quantitatively at 80-90°C in 30 min [3], the analogous reaction with I and IV

*See [1] for communication LIV.

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 0009-3122/78/1404-0406$07.50

with acetal XIII requires more severe conditions, evidently because of steric hindrance, and in the case of IV, for example, proceeds at 90-95°C only after 11 h, according to the results of gas–liquid chromatography (GLC). In addition, the presence of additional functional groups increases the thermal lability of condensation products II and V and hinders their isolation and purification. In this connection, V was obtained in only 81% yield and II was obtained in only 32% yield. As in the case of 3-nitro-4-dimethylaminovinylpyridine, the reductive cyclization of dimethylaminovinyl derivatives II and V proceeds smoothly and gives, respectively, 3-acetyl- (III) and 3-ethoxycarbonyl-6-azaindole (VI) in high yields. 6-Azaindole-3-carboxylic acid (VII) was obtained by alkaline hydrolysis of ester VI. Brief heating of carboxylic acid VII at ~200°C leads to decarboxylation and the formation of unsubstituted 6-azaindole (VIII) in high yield. A limitation in the use of the first method for the synthesis of 3-substituted 6-azaindoles is the impossibility of its application for the cyclization of compounds with substituents that readily undergo reduction (halo and nitro groups). To prepare 3-nitro- (X) and 3-bromo-6-azaindole (XI) we therefore used electrophilic substitution reactions, which proceed quite smoothly in the 3 position of other isomeric azaindoles [4]. As expected, the nitration of 6-azaindole VIII proceeds virtually quantitatively at 0°C, and the bromination of VII with dioxane dibromide proceeds smoothly at room temperature. These processes are realized with greater difficulty with weaker electrophilic reagents. 6-Azaindole undergoes acetylation only in the 1 position to give 1-acetyl-6-azaindole (IX) even under the conditions for which a 3-acetylindole derivative can be obtained from unsubstituted indole [5]. The reaction of 6-azaindole with paraformaldehyde and dimethylamine hydrochloride in butanol by the method used for other isomeric azaindoles [4] made it possible to obtain 6-azagramine hydrochloride (XII) in less than 20% yield, and only the use of methylenedimethylamine chloride in acetonitrile made it possible to increase the yield of azagramine dihydrochloride (XII) to 46%.

Thus the results of the present research are in good agreement with the earlier conclusion [4] regarding the mutual effect of π-electron-surplus and π-electron-deficient rings in condensed systems, one of the consequences of which is a decrease in the reactivities of azaindoles as compared with indoles in electrophilic substitution processes involving the carbon atoms of the pyrrole ring.

EXPERIMENTAL

The PMR spectra of the compounds were recorded with a JNM-4H-100 spectrometer (100 MHz) on the δ scale with tetramethylsilane as the internal standard. The IR spectra of mineral oil suspensions of the compounds were recorded with a Perkin–Elmer 457 spectrometer. The mass spectra were obtained with a Varian MAT-112 mass spectrometer at an ionizing-electron energy of 70 eV and an emission current of 1.5 μA. Chromatographic monitoring was accomplished with a Pye–Unicam 104 gas–liquid chromatograph with a catharometer and a 2.1 mm by 4 mm column filled with 10% SE-30 silicone elastomer on silanized diatomaceous earth (100-120 mesh); the helium flow rate was 29 ml/min, and the temperature was 200°C.

3-Nitro-4-(α-acetyl-β-dimethylaminovinyl)pyridine (II). A 1.5-ml (8.7 mmole) sample of dimethylformamide diethylacetal (XIII) was added to a solution of 0.9 g (5 mmole) of (3-nitro-4-pyridiyl)acetone (I) in 5 ml of anhydrous DMF, and the mixture was heated in a stream of nitrogen for 5 h at a bath temperature of 85-90°C. The end of the reaction was monitored by GLC from the disappearance of the peak of I (the retention time of I was 2.8 min, and the retention time of II was 18.5 min). The reaction mixture was vacuum evaporated in a stream of nitrogen, and the residue was extracted with boiling heptane. The extract was allowed to stand at room temperature for 24 h, after which it was filtered to give 0.38 g (32%) of yellow-brown crystals with mp 141-142°C (from ethyl acetate). The product was only slightly soluble in heptane, hexane, cyclohexane, and water but quite soluble in ether, benzene, acetone, alcohols, ethyl acetate, and chloroform. IR spectrum: 1600, 1580 ($COCH_3$, C=C and C=N); 1520 cm^{-1} (NO_2). PMR spectrum ($CDCl_3$): 903 s (2-H), 7.52 s (β-H), 2.81 s [$N(CH_3)_2$], 2.15 s ($COCH_3$), 8.68 d (6-H), and 7.10 d (5-H). Found: C 56.4; H 5.4; N 18.1%. $C_{11}H_{13}N_3O_3$. Calculated: C 56.2; H 5.5; N 17.9%.

3-Acetyl-6-azaindole (III). A solution of 0.58 g (2.5 mmole) of II in 150 ml of ethanol was hydrogenated in the presence of 0.5 g of 6% palladium oxide on charcoal at room temperature and an excess hydrogen pressure of 20-30 cm (water column). The catalyst was separated, the alcoholic filtrate was vacuum evaporated, and the residue was triturated with a small amount of acetone to give 0.24 g of azaindole III. The acetone solution was evaporated, and

the residue was recrystallized from ethyl acetate to give an additional 0.08 g of 3-acetyl-6-azaindole (III) for an overall yield of 0.32 g (80%) of III as colorless crystals with mp 231-232°C (from ethyl acetate). The product was insoluble in ether, heptane, and benzene, only slightly soluble in acetone, ethyl acetate, water, and chloroform, and quite soluble in alcohols. IR spectrum: 1640 ($COCH_3$); 1610 and 1570 cm^{-1} (C=C and C=N). PMR spectrum (CD_3OD), ppm: 8.79 s (7-H), 8.42 s (2-H), 2.61 s (CH_3), and 8.24 m (5-H and 4-H). Found: C 67.3; H 5.2; N 17.5%; M^+ (by mass spectrometry) 160. $C_9H_8N_2O$. Calculated: C 67.5; H 5.0; N 17.5; M 160.

Ethyl α-(3-Nitro-4-pyridyl)-β-dimethylaminoacrylate (V). A solution of 1.3 ml (7.5 mmole) of dimethylformamide diethylacetal (XIII) in 5 ml of anhydrous DMF was added to a solution of 1 g (4.8 mmole) of ester IV in 5 ml of anhydrous DMF, and the mixture was heated for 11 h in a stream of nitrogen at a bath temperature of 90-95°C. The end of the reaction was monitored by GLC from the disappearance of the peak of ester IV (the retention time of ester IV was 1.2 min, and the retention time of V was 19 min). The reaction mixture was vacuum evaporated in a stream of nitrogen, and the residue was extracted repeatedly with boiling heptane. The extract was allowed to stand at room temperature for 24 h, after which it filtered to give 1.02 g (81%) of dark-red crystals of V with mp 92-93°C (from heptane). The product was only slightly soluble in heptane, hexane, cyclohexane, and water but was quite soluble in ether, benzene, acetone, alcohols, ethyl acetate, and chloroform. IR spectrum: 1680 ($COOC_2H_5$) and 1590 cm^{-1} (C=C and C=N). PMR spectrum ($CDCl_3$), ppm: 9.05 s (2-H), 7.71 s (β-H), 2.82 s [$N(CH_3)_2$], 8.65 d (6-H), 7.07 d (5-H), 1.14 t (CH_2CH_2), 4.07 q (CH_2). Found: C 54.3; H 5.8; N 15.7%. $C_{12}H_{15}N_3O_4$. Calculated: C 54.3; H 5.7; N 15.8%.

3-Ethoxycarbonyl-6-azaindole (VI). A solution of 0.5 g (1.9 mmole) of V in 150 ml of ethanol was hydrogenated in the presence of 0.3 g of 6% palladium on carbon at room temperature and an excess hydrogen pressure of 20-30 cm (water column). The catalyst was separated, and the alcoholic filtrate was evaporated to give 0.33 g (92%) of 3-ethoxycarbonyl-6-azaindole (VI) as colorless crystals with mp 173-174°C (from benzene). The product was insoluble in petroleum ether and heptane, only slightly soluble in ether, benzene, and water, and quite soluble in acetone, alcohols, ethyl acetate, and chloroform. IR spectrum: 3100 (NH), 1690 ($COOC_2H_5$), and 1620 cm^{-1} (C=C and C=N). PMR spectrum ($CDCl_3$):, ppm: 8.82 s (7-H), 8.18 s (2-H), 8.38 d (5-H), 8.12 d (4-H), 1.43 t (CH_3), and 4.41 q (CH_2). Found: C 62.9; H 5.4; N 14.7%. $C_{10}H_{10}N_2O_2$. Calculated: C 63.2; H 5.3; N 14.7%.

6-Azaindole-3-carboxylic Acid (VII). A solution of 0.11 g (1.9 mmole) of potassium hydroxide in 5 ml of water was added to 0.3 g (1.6 mmole) of ester VI, and the mixture was heated on a boiling-water bath for 1 h, after which it was acidified to pH 6 with acetic acid and allowed to stand at 5°C for several hours. The precipitated 6-azaindole-3-carboxylic acid hydrate was separated, and the aqueous mother liquor was evaporated to one-third of its original volume and again allowed to stand in a refrigerator. Both batches of crystals were combined and dried for 10 h *in vacuo* over P_2O_5 at 100°C to give 0.18 g (69%) of acid VII as shiny crystals with mp 194-195°C (dec., from water) [6]. The product was only slightly soluble in water and ethanol and insoluble in ether, heptane, benzene, ethyl acetate, and chloroform. IR spectrum: 1640 (C=O) and 1630 cm^{-1} (C=C and C=N). PMR spectrum [$(CD_3)_2SO$], ppm: 9.28 s (7-H), 8.75 s (2-H), and 8.42 m (5-H and 4-H). Found: C 59.3; H 3.7; N 17.2%. $C_8H_6N_2O_2$. Calculated: C 59.3; H 3.7; N 17.3%.

6-Azaindole (VIII). A 0.03-g (0.19 mmole) sample of acid VII was heated in an open sublimation apparatus at a bath temperature of 195-198°C for 15 min, after which the apparatus was cooled and sealed, and the substrate was sublimed at a bath temperature of 110-120°C and a residual pressure of 0.5 mm to give 0.02 g (91%) of 6-azaindole VIII with mp 140-141°C. No melting-point depression was observed for a mixture of this product with an authentic sample of VIII synthesized by the method in [3], and the IR spectra of the two substances were identical.

1-Acetyl-6-azaindole (IX). A solution of 0.5 g (4.2 mmole) of 6-azaindole (VIII) and 0.3 ml of styrene in 7.0 ml of distilled acetic anhydride was refluxed for 1 h, after which the mixture was vacuum evaporated, and the residue was dissolved in 15 ml of ethanol. The solution was refluxed with activated charcoal for 5 min, after which it was filtered, and the alcoholic filtrate was evaporated to give 0.56 g (82%) of colorless crystals of IX with mp 124-125°C (from heptane). The product was only slightly soluble in heptane, but quite soluble in other ordinary organic solvents and water. IR spectrum: 1710 ($COCH_3$) and 1590 cm^{-1} (C=C and (C=N). PMR spectrum [$(CD_3)_2SO$], ppm: 9.52 s (7-H), 2.70 s (CH_3), 8.36 d (5-H),

8.07 d (2-H), 7.62 d (4-H), and 6.78 d (3-H). Found: C 67.3; H 4.9; N 17.4%; M^+ (by mass spectrometry) 160. $C_9H_8N_2O$. Calculated: C 67.5; H 5.0; N 17.5%; M 160.

3-Nitro-6-azaindole (X). A 0.5-g (4.2 mmole) sample of 6-azaindole (VIII) was added in small portions with stirring in the course of 30 min to 5 ml of fuming nitric acid at a reaction mixture temperature of −5°C, after which the mixture was stirred at 0°C for 1 h. It was then poured over 100 g of ice, and the aqueous mixture was neutralized with potassium carbonate solution. The resulting precipitate was removed by filtration, washed with water, and dried *in vacuo* over P_2O_5 at 100°C to give 0.68 g (99%) of azaindole X as fine colorless crystals with mp 309-310°C (dec., from water). The product was insoluble in ordinary organic solvents, only slightly soluble in water, and quite soluble in DMF and acetic acid. IR spectrum: 3140 (NH), 1620 (C=C and C=N), and 1590 cm^{-1} (NO_2). PMR spectrum: (CF_3COOH, protonated form), ppm: 9.09 s (2-H), 9.44 d (7-H), 8.91 d (4-H), and 8.66 t (5-H). Found: C 51.1; H 3.1; N 25.7%; M^+ (by mass spectrometry) 163. $C_7H_5N_3O_2$. Calculated: C 51.5; H 3.1; N 25.9%; M 163.

3-Bromo-6-azaindole (XI). A solution of 0.51 g (3.2 mmole) of bromine in 30 ml of dioxane was added dropwise with stirring at room temperature to a solution of 0.36 g (3 mmole) of 6-azaindole VIII in 30 ml of dioxane, and the precipitate was removed by filtration to give 0.71 g (89%) of hydrobromide of XI. The hydrobromide was dissolved in water, the solution was made alkaline to pH 8 with potassium carbonate solution, and the resulting precipitate was removed by filtration and dried *in vacuo* to give 0.52 g (87%) of shiny crystals of 3-bromo-6-azaindole XI with mp 205-206°C (from benzene). The product was soluble in acetone and alcohols, only slightly soluble in ether, benzene, and chloroform, and insoluble in heptane and water. IR spectrum: 1610 cm^{-1} (C=C and C=N). PMR spectrum: (CD_3OD), ppm: 8.75 s (7-H), 7.67 s (2-H), 8.22 d (5-H), and 7.55 d (5-H). Found: C 42.3; H 2.5; Br 40.4; N 14.3%. $C_7H_5BrN_2$. Calculated: C 42.7; H 2.5; Br 40.6; N 14.2%.

The hydrobromide of 3-bromo-6-azaindole was obtained as yellowish crystals with mp 259-261°C (from alcohol). The product was quite soluble in water, only slightly soluble in acetone, and alcohols, and insoluble in ether, benzene, and chloroform. Found: C 30.4; H 2.1; Br 57.5%. $C_7H_5BrN_2 \cdot HBr$. Calculated: C 30.2; H 2.2; Br 57.5%.

6-Azagramine Dihydrochloride (XII). A) A 0.13-g (4.3 mmole) sample of paraformaldehyde and 1.22 g (15 mmole) of dimethylamine hydrochloride were added to a solution of 0.5 g (4.2 mmole) of azaindole VIII in 15 ml of n-butanol, and the mixture was refluxed for 25 min. It was then vacuum evaporated, and the residue was treated with 10 ml of 5% hydrochloric acid solution. The acidic mixture was extracted twice with ether to remove the nonbasic substances, and the aqueous layer was made alkaline with potassium carbonate and extracted repeatedly with n-butyl alcohol. The extract was dried with $MgSO_4$ and vacuum evaporated, and the residue was dissolved in the minimum amount of ethanol. The ethanol solution was acidified with an alcohol solution of hydrogen chloride, and the mixture was allowed to stand at 0°C for a few hours. The resulting precipitate was removed by filtration to give 0.23 g (19%) of the dihydrate of 6-azagramine dihydrochloride (XII). Found: C 42.3; H 6.6; Cl 25.1; N 15.0%. $C_{10}H_{13}N_3 \cdot 2HCl \cdot 2H_2O$. Calculated: C 42.3; H 6.7; Cl 25.0; N 14.8%. The dihydrate of XII was dried *in vacuo* over P_2O_5 at 100°C for 10 h to give 0.2 g (19%) of dihydrochloride XII as light-yellow crystals with mp 229-230°C (from alcohol). The product was insoluble in heptane, benzene, acetone, and chloroform, slightly soluble in alcohol, and quite soluble in water. IR spectrum: 3340 (NH); 1640 and 1590 cm^{-1} (C=C and C=N). PMR spectrum: (CD_3OD), ppm: 9.24 s (7-H), 8.62 s (2-H), 4.82 s (CH_2), 3.02 s [$N(CH_3)_2$], 8.58 d (5-H), 8.42 d (4-H). Found: C 48.0; H 5.7; Cl 28.3; N 17.3%. $C_{10}H_{13}N_3 \cdot 2HCl$. Calculated: C 48.4; H 6.0; Cl 28.6; N 16.9%.

B) A 0.5-g (4.2 mmole) sample of azaindole VIII was added with stirring to a suspension of 0.7 g (8.9 mmole) of methylenedimethylamine chloride [7] in 10 ml of anhydrous acetonitrile, and the mixture was heated at a bath temperature of 60-65°C for 6 h. The resulting solution was decanted from the precipitate (precipitate A) and evaporated, and the residue was dissolved in the minimum amount of absolute ethanol. The solution was diluted to 25 times its original volume with acetone, and the dilute solution was allowed to stand at room temperature for 2-3 h. Workup gave 0.37 g (32%) of colorless acicular crystals, which, according to the IR and PMR spectral data and the results of elementary analysis, were crystals of acetone-solvated 6-azagramine monohydrochloride. The solvate was dried *in vacuo* at 100°C for 12 h with monitoring of the removal of acetone from the disappearance of the carbonyl band at 1700 cm^{-1} in the IR spectrum. This procedure gave 0.28 g of 6-azagramine

monohydrochloride, which was converted quantitatively to dihydrochloride XII by acidification with an alcohol solution of hydrochloric acid; no melting-point depression was observed for a mixture of this product with a sample obtained by method A, and the IR spectra of the two samples were identical.

Precipitate A was dissolved in ethanol, and the solution was acidified with an excess amount of an alcohol solution of hydrogen chloride. The alcohol was vacuum evaporated, and the residue was triturated with a few drops of absolute ethanol at 0°C to give an additional 0.20 g of XII for an overall yield of 0.48 g (46%) of XII.

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CHARACTERISTIC FEATURES OF THE VIBRATIONS OF SUBSTITUTED AROMATIC AZACYCLIC COMPOUNDS.

I. CHARACTERISTIC VIBRATIONS OF MONOSUBSTITUTED PYRIDINES

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UDC 543.422.4:547.822

The characteristic features of the normal vibrations of the aromatic skeleton (C_5H_4XN) of monosubstituted pyridines are analyzed. The general principles in the behavior of the frequencies of the vibrations of monosubstituted pyridines as a function of the position and type of substituent were ascertained on the basis of this analysis.

The quantitative criteria of the characteristic features of vibrations have been worked out [1, 2], and the characteristic features of the normal vibrations of substituted benzenes have been investigated on the basis of these criteria [3-5].

In the present research we analyzed the characteristic features of the normal vibrations of the aromatic skeleton (C_5H_4XN) of monosubstituted pyridines. On the basis of this analysis we ascertained the principles of the behavior of the frequencies of the vibrations of monosubstituted pyridines as a function of the position and type of substituent.

The first step in the solution of the problem of the characteristic features consisted in calculation of the frequencies and forms of the vibrations and the shifts of the atoms in the case of the vibrations of the simplest monosubstituted pyridines (X = F, Cl, Br, I, CH_3, NH_2, and NO_2) [6, 7]. The characteristic and noncharacteristic vibrations of the C_5H_4XN aromatic skeleton of monosubstituted pyridines are presented separately in Table 1 for each type of substitution. The form of the vibrations is denoted by the type of natural coordinates at which the vibration is primarily localized. The types of coordinates are shown (Fig. 1) in the case of γ substitution. In composing the Table we used experimental data on the vibrational spectra of monosubstituted pyridines [8-16].

Characteristic Vibrations

The characteristic vibrations are localized at the group of coordinates of the C_5H_4N aromatic residue and are completely characteristic vibrations (with respect to the frequency,

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Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 501-503, April, 1978. Original article submitted March 4, 1977.

0009-3122/78/1404-0410$07.50