AZAINDOLE DERIVATIVES

XXXI. The Synthesis of 3-Substituted 4-Azaindoles*

L. N. Yakhontov and V. A. Azimov

Khimiya Geterotsiklicheskikh Soedinenii, Vol. 6, No. 1, pp. 32–36, 1970

UDC 547.741'821.07:542.944'958

Electrophilic substitution reactions (cyanomethylation, bromination, nitration, Mannich reaction) are investigated in some 4-azaindoles. The effect on reactivity of the presence of an acyl group in the 1-position is examined. Conditions have been found for the synthesis in high yield of various 3-substituted 4-azaindoles.

Previous communications in this series [1] have described the synthesis and chemical properties of derivatives of 5- and 7-azaindoles. This paper is devoted to another type of aza analog of indole compounds, the 4-azaindoles.

The chemical properties of this type of pyrrolopyridine have hardly been investigated at all. If unsuccessful attempts to decarboxylate 4-azaindole-3-carboxylic acid [2] are disregarded, there is only one reference in the literature dealing with the chemical behavior of 4-azaindoles [3]. The authors [3] described the N-acylation of 2, 5-dimethyl-4-azaindole and its reactions with bromine in acetic acid, benzaldehyde, benzenediazonium chloride, and chloroform and alcoholic alkali. They also described the deacylation, oxidative degradation, bromination, and nitration of 1-benzoyl-2, 5-dimethyl-4-azaindole. There is no information in the literature concerning the introduction of functional groups into unsubstituted 4-azaindole.

We have examined some electrophilic substitution reactions of 4-azaindole (cyanomethylation, bromination, nitration, and the Mannich reaction), and we have found conditions affording various 3-substituted 4-azaindoles in high yields. The starting material for these reactions was unsubstituted 4-azaindole (I) [4].

Investigation of the Mannich reaction, which had not previously been carried out in the 4-azaindole series, showed that I reacted more vigorously than the corresponding 7-aza isomer. Under the same conditions which gave a 28% yield of the corresponding gramine from 4-methyl-7-azaindole [5], the yield of 4-azagramine reached 43%. An increase in the reaction time from 15 min to 1 hr resulted in a drop in yield of II to 28%, while the amount of bis(4-aza-3-indolyl)methane (III) formed increased from a trace to 20%. Formation of III was also favored by raising the reaction temperature. When the reaction was carried out in boiling ethylene glycol, the main product (isolated in 94% yield) was III. The highest yield of II (98.4%) was obtained by using an excess of paraformaldehyde and dimethylamine hydrochloride, and (see scheme at top of next page) carrying out the reaction for 15 min in boiling butanol.

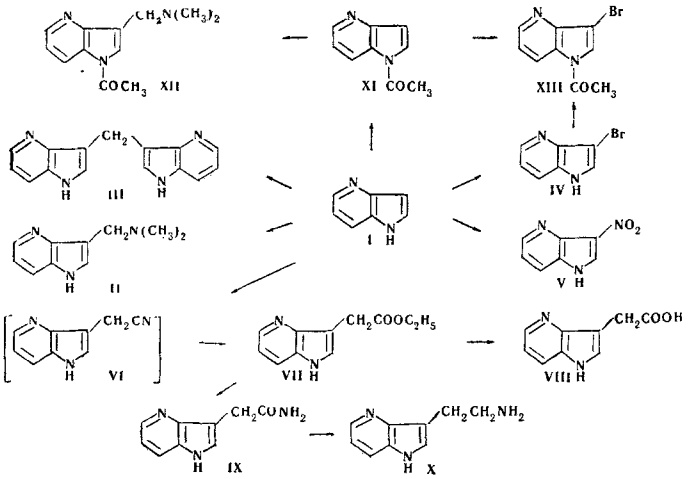
Bromination of I with dioxane dibromide, and nitration with nitric acid at −5° proceeded smoothly to give the 3-bromo- and 3-nitro-4-azaindoles (IV and V) in yields of 88.6 and 99%, respectively.

Cyanomethylation, carried out for the first time in the 4-azaindole series, was shown to be accompanied by the formation of substantial amounts of III (up to 45% of the amount of I used). This is in agreement with the ease of formation of III noted above under the conditions of the Mannich reaction.

As is also the case in the 7-azaindoles [5], the cyanomethyl derivative VI was hydrolyzed during the course of the reaction, and the final reaction product from VI, ethyl (4-aza-3-indolyl)acetate (VII), was isolated in 51.4% yield. The ester VII was hydrolyzed to (4-aza-3-indolyl)acetic acid (VIII), which is the 4-aza analog of the known plant growth regulator heteroauxin. The acid VIII undergoes esterification with great ease. Formation of VII takes place even on recrystallization of the hydrochloride of VIII from anhydrous ethanol.

(4-Aza-3-indolyl)acetamide (IX) was obtained by reaction of VII with ammonia in an autoclave at 100° C. A series

*For part XXX, see [1].



of experiments showed that it was necessary to use a quantity of liquid ammonia which permitted complete conversion to the gas phase on heating to 100° C. The yield of IX under these conditions attained 76%. Use of a larger excess of liquid ammonia (28 mole, i. e., a threefold excess over the saturated free volume) resulted, even when the reaction time was doubled, in the bulk of the starting material VII (70%) being recovered. Treatment of VII with alcoholic ammonia at room temperature, or in a tube at 60° C (for 6 hr) resulted in practically no reaction. Traces of IX were only detected by chromatography and IR spectroscopy.

Reduction of IX with lithium aluminum hydride in boiling tetrahydrofuran proceeded smoothly to give 4-azatryptamine (X) in 84.6% yield.

Introduction of acyl groups into the 1-position of 4-azaindole (I), since they are strong electron acceptors, results in reduction of the high reactivity of I toward electrophilic substitution, as was to be expected. For example, 1-acetyl-4-azaindole (XI) gives a yield of only 28% in the Mannich reaction, and 27% on bromination, under the same conditions in which I, unsubstituted in the 1-position, gives yields of 98.4 and 88.6% respectively.

EXPERIMENTAL

4-Azagramine (II). To a solution of 3.17 g (26.8 mM) of 4-azaindole I in 85 ml of butanol was added 0.92 g (30.7 mA) of paraformaldehyde and 6.8 g (83.4 mM) of dimethylamine hydrochloride. The reaction mixture was boiled for 15 min, the butanol removed in vacuo, and to the residue was added 60 ml of 5% HCl and nonbasic impurities removed by extraction with ether. The aqueous layer was basified with 50% aqueous potassium carbonate, the free base II extracted with ether, dried over potassium carbonate and evaporated in vacuo. There was obtained 4.62 g (98.4%) of II as colorless crystals, mp 127–128.5° C (from benzene), readily soluble in chloroform, acetone, and alcohols, less so in benzene, ethyl acetate, ether, and water, and insoluble in heptane. Found, %: C 68.7; H 7.5; N 23.8. Calculated for $C_{10}H_{13}N_3$, %: C 68.5; H 7.5; N 24.0.

In a series of experiments to examine the effect of temperature, time, and proportions of reagents on the course of the Mannich reaction, the reaction was carried out as above, with changes in the appropriate parameters, and the mixtures of I, II, and III were separated quantitatively on alumina columns. Ether eluted first I, then II, and III was finally eluted with methanol. The course of the separation was checked by descending paper chromatography in the system butanol–acetic acid–water (4 : 1 : 5). Detection was by the blue fluorescence under UV irradiation, and by the formation of a red complex with Dragendorff's reagent. R_f of I, 0.52, and of II, 0.34.

3-Bromo-4-azaindole (IV). Two grams (17 mM) of I was dissolved in 25 ml of dioxane, and 3.12 g (19.5 mM) of bromine in 50 ml of dioxane added dropwise with stirring during 1 hr, the temperature of the reaction mixture being kept at 15° C. The precipitated IV **hydrobromide** was filtered off and washed with acetone, giving 4.0 g (81%) of colorless crystals, mp 243.5–244.5° C. The substance was readily soluble in water, methanol, and ethanol, but less so in propan-2-ol and dioxane, and insoluble in heptane, ether, and chloroform. Found, %: C 30.2; H 2.4; Br 57.5; N 10.0. Calculated for $C_7H_5BrN_2 \cdot HBr$, %: C 30.2; H 2.2; Br 57.5; N 10.1.

3.5 g of IV hydrobromide was dissolved in 75 ml of water and basified with sodium bicarbonate. The free base IV which separated was filtered off, washed with 35 ml of water, and dried in a desiccator to constant weight, giving 2.48 g of IV as colorless crystals, mp 228° C (from alcohol). The substance was sparingly soluble in water, ether, benzene, and heptane, and more soluble in ethyl acetate, dioxane, chloroform, alcohols, and acetone. Found, %: C 42.9; H 2.6; Br 40.8; N 14.5. Calculated for $C_7H_5BrN_2$, %: C 42.7; H 2.6; Br 40.6; N 14.2. The dioxane mother liquors after isolation of the hydrobromide of IV were evaporated to dryness in vacuo. The residue was treated with the aqueous-alkaline solution obtained as in the above-mentioned description of the isolation of the free base IV and its hydrobromide. The mixture was extracted with chloroform, and the residue after removal of the chloroform was recrystallized from ethyl acetate to give a further 0.29 g of IV. The overall yield of IV was 2.97 g (88.6%).

3-Nitro-4-azaindole (V). Two grams (17 mM) of I was added in small portions with stirring during 50 min to 20 ml of nitric acid (d 1.52), keeping the temperature of the reaction mixture at −5° C. Stirring was then continued for 1 hr at 0° C, and the reaction mixture was poured on to 400 g of ice and neutralized with 50% potassium carbonate solution (68 ml). The light yellow precipitate of V which separated was filtered off, washed carefully with water and dried in vacuo, giving 2.73 g (99%) of V, mp 348° C (decomp.). The mp was unchanged after recrystallization from a large volume of dimethylformamide. The compound was poorly soluble in water and the usual organic solvents. Found, %: C 5.15; H 3.4; N 25.6. Calculated for $C_7H_5N_3O_2$, %: C 51.5; H 3.1; N 25.8.

Cyanomethylation of I. A mixture of 6.33 g (53.7 mM) of I, 5.45 g (80.2 mM) of 96% potassium cyanide, 4.46 g (59.5 mm) of 40% formalin, 1.49 g (15.2 mM) of potassium acetate, 1.75 g of alumina, and 40 ml of 85% alcohol was heated with stirring in a 500 ml stainless steel autoclave for 4 hr at 120° C and at an initial pressure of 10 atm of nitrogen. The reaction mixture was diluted with 100 ml of water and basified with 50% aqueous potassium carbonate after the alcohol had been removed in vacuo. The precipitate was filtered off and washed with 200 ml of water. In order to remove inorganic materials, the precipitate was dissolved in boiling methanol; the solution was filtered and evaporated in vacuo. The residue was washed with a small quantity of acetone, giving 3 g (45%) of **bis(4-aza-3-indolyl)methane (III)**, colorless crystals, mp 292–293° C (from dimethylformamide), sparingly soluble in heptane, benzene, acetone, and chloroform, and more soluble in alcohols and in dimethylformamide. Found, %: C 72.5; H 5.2; N 22.6. Calculated for $C_{15}H_{12}N_4$, %: C 72.6; H 4.9; N 22.6.

The aqueous-alkaline solution after removal of III and inorganic material was extracted with ether (3 × 150 ml). The ether extracts were separated, dried over potassium carbonate, and evaporated in vacuo. The IR spectrum of the residue (0.32 g) showed only traces of compounds containing CN and $CONH_2$ groups, and it did not seem worthy of further investigation. The aqueous layer from the ether extraction was evaporated to dryness and the residue dried in vacuo over phosphorus pentoxide and boiled for 6 hr with 100 ml of alcoholic hydrogen chloride. The reaction mixture was evaporated in vacuo, and the residue dissolved in 50 ml of water, basified with 50% aqueous potassium carbonate, and extracted with ether. Evaporation of the ethereal solution in vacuo gave 5.2 g (51.4%) of ethyl (4-aza-3-indolyl)acetate (VII), colorless crystals, mp 142–144° C (from benzene). The compound was readily soluble in alcohols, acetone, ethyl acetate, and chloroform, but less so in ether, benzene, and water, and sparingly soluble in heptane. IR spectrum: 1729 cm^{-1} ($-CH_2COOC_2H_5$) (All IR spectra were taken on a UR-10 recording spectrometer as pastes in vaseline oil. We thank Yu. N. Sheinker and Yu. I. Pomerantsev for their help in carrying out the spectral investigations) Found, %: C 64.7; H 5.9; N 13.8. Calculated for $C_{11}H_{12}N_2O_2$, %: C 64.7; H 5.9; N 13.7.

(4-Aza-3-indolyl)acetic acid (VIII). 2.5 g (12.2 mM) of VII was boiled for 6 hr with 30 ml of 17% HCl. The reaction mixture was evaporated to dryness in vacuo, and the residue washed with acetone and dried in vacuo at 100° over sodium hydroxide, giving 2.34 g (90%) of VIII hydrochloride. Colorless crystals, mp 207–208° C (decomp.), were readily soluble in water and alcohol, but sparingly so in ether and acetone. IR spectrum: 1731, 2500–2700 cm^{-1} (COOH). Found, %: C 50.6; H 4.2; Cl 16.9; N 13.4. Calculated for $C_9H_8N_2O_2 \cdot HCl$, %: C 50.8; H 4.3; Cl 16.7; N 13.2.

(4-Aza-3-indolyl)acetamide (IX). Two grams (9.8 mM) of VII and 3 g (176 mM) of liquid ammonia were placed in a stainless-steel autoclave of 55 ml capacity, and heated for 5 hr in a boiling water bath. The conversion of VII into IX was followed by thin-layer chromatography of the reaction products on silica gel, using 1 : 3 methanol–benzene as the mobile phase and iodine vapor as detector. Under the conditions described above, only traces of VII (R_f 0.44) were found, almost all the compound being converted into IX (R_f 0.25). The reaction products were washed out of the autoclave with methanol, and the methanol removed in vacuo to give 1.3 g (76%) of IX as colorless crystals, mp 209–211° C (from propan-2-ol). The compound was readily soluble in alcohols and water, but only sparingly in benzene, dioxane, ethyl acetate, and ether. IR spectrum: 1643, 3200 cm^{-1} ($CONH_2$, NH). Found, %: C 62.0; H 5.3; N 24.4. Calculated for $C_9H_9N_3O$, %: C 61.7; H 5.2; N 24.0.

4-Azatryptamine (X). To a boiling suspension of 1.57 g (41.4 mM) of lithium aluminum hydride in 100 ml of tetrahydrofuran was added a solution of 1.34 g (7.6 mM) of **IX.** The reaction mixture was boiled for a further 6 hr, then 3 ml of water was added. The precipitated lithium and aluminum hydroxides were filtered off and washed with 300 ml of ether. The combined solutions of **X** in tetrahydrofuran and ether were dried over potassium carbonate and evaporated in vacuo. The residue (1.3 g) was dissolved in anhydrous alcohol, and alcoholic hydrogen chloride added to precipitate crystals of the **hydrochloride of X,** 1.45 g (84.6%). Colorless crystals, mp 257-258° C, were readily soluble in water but less so in alcohols, and insoluble in ether, benzene, and acetone. Found, %: C 46.5; H 5.9; Cl 30.4; N 17.8. Calculated for $C_9H_{11}N_3 \cdot 2HCl$, %: C 46.2; H 5.6; Cl 30.3; N 18.0.

1-Acetyl-4-azaindole (XI). Eight grams (67.7 mM) of I was mixed with 50 ml of acetic anhydride. The reaction mixture heated up spontaneously and the solid I dissolved. After standing overnight, coarse crystals of the acetate salt of **XI** separated. The solid was filtered off, washed with a small amount of acetic anhydride and then with heptane, giving 4.04 g of the **acetate of XI** as colorless crystals, mp 77–78° C. The substance was readily soluble in water, alcohol, and chloroform, but less so in benzene and heptane. Found, %: C 60.4; H 5.5; N 12.5, Calculated for $C_9H_8N_2O \cdot C_2H_4O_2$, %: C 60.0; H 5.5; N 12.7. The mother liquors after the separation of **XI** acetate were concentrated to a small volume in vacuo to give a further 4.7 g of the acetate, mp 75–76° C. The mother liquors were again evaporated in vacuo, this time to dryness, and the residue sublimed at 128° C under a pressure of 10 mm. This gave 3.48 g of the free base **XI.** Total yield (calculated as free base) 9.78 g (90%). Colorless crystals, mp 77–78° C. A mixed mp with the acetate of **XI** gave mp 55–58° C, but with a sample of material obtained by treating the acetate of **XI** with 50% aqueous potassium carbonate and extraction with chloroform it gave no depression of the mp. The compound was readily soluble in water, alcohols, and chloroform, but less so in benzene and heptane. Found, %: C 67.3; H 4.9; N 17.6. Calculated for $C_9H_8N_2O$, %: C 67.5; H 5.0; N 17.5.

Bromination of XI. To a solution of 1.55 g (9.67 mM) of **XI** in 20 ml of dioxane was added during 1 hr with stirring at 15° C a solution of 1.7 g (10.6 mM) of bromine in 60 ml of dioxane, and the mixture stirred for a further 10 min, and unreacted bromine decolorized by adding 6 ml of sodium hydrogen sulfite solution. The reaction mixture was evaporated to dryness in vacuo. Chromatography on silica-gel plates (mobile phase chloroform; detector, iodine vapor) revealed the presence of **XI** (R_f 0.20) and **XIII** (R_f 0.42). Since the quantitative separation of the mixture of **XI** and **XIII** obtained was difficult, 50 ml of water was added to the reaction products and the mixture boiled for 15 min. The mixture was basified with 50% aqueous potassium carbonate and the IV which separated was filtered off, washed with water, dried, and shown to be identical with an authentic sample of **IV.** Yield 0.51 g (26.7%). The mother liquors after removal of IV were shaken thoroughly with chloroform, which was evaporated to give 0.67 g (58.7%) of I, which on chromatography on a silica-gel plate (mobile phase 1 : 3 methanol:benzene, detector iodine) was shown not to contain any IV with R_f 0.37. In this system, I had an R_f of 0.49.

1-Acetyl-3-bromo-4-azaindole (XIII). One gram (5.07 mM) of IV was heated to the boil in 5 ml of acetic anhydride. The IV dissolved completely. The mixture was kept overnight, and the resulting precipitate of the **acetate of XIII** was filtered off, giving 1.27 g (83.4%) of colorless crystals, mp 117–118° C. The compound was readily soluble in ether, benzene, chloroform, and alcohols, but sparingly in heptane and water. Found, %: C 44.1; H 3.6; Br 26.9; N 9.3. Calculated for $C_9H_7BrN_2O \cdot C_2H_4O_2$, %: C 44.2; H 3.7; Br 26.7; N 9.4.

XIII free base was obtained as colorless crystals, mp 124–125° C (from benzene), which were readily soluble in alcohols, benzene, acetone, and ether, but sparingly in heptane. Found, %: Br 33.4; N 11.7. Calculated for $C_9H_7BrN_2O$, %: Br 33.2; N 11.9.

Mannich reaction with XI. A mixture of 1.35 g (8.4 mM) of **XI,** 0.3 g (10 mM) of paraformaldehyde, 2.2 g (27 mM) of dimethylamine hydrochloride, and 26 ml of butanol was boiled for 15 min. The reaction mixture was evaporated to dryness, and in view of the difficulty in separating mixtures of **XI** and **XII,** the mixture was de-acetylated by adding 10 ml of 1% HCl and boiling for 15 min. The mixture was basified with 50% aqueous potassium carbonate and extracted with chloroform. Evaporation gave 1.4 g of a mixture of I and II, which were quantitatively separated on an alumina column by the method described above to give 0.71 g (71%) of I and 0.42 g (28%) of II.

REFERENCES

1. L. N. Yakhontov and E. I. Lapan, KhGS [Chemistry of Heterocyclic Compounds], 27, 1970.
2. O. Süs and K. Möller, Ann., **593**, 91, 1955.
3. J. C. Clayton and J. Kenyon, J. Chem. Soc., 2952, 1950.
4. L. N. Yakhontov, V. A. Azimov, and E. I. Lapan, Tetrah. Lett., 1909, 1969.

5. L. N. Yakhontov, M. Ya. Uritskaya, and M. V. Rubtsov, ZhOrKh, 1, 2032, 1965.

28 March 1968

Ordzhonikidze All-Union Scientific-Research Institute of
Pharmaceutical Chemistry, Moscow