AZAINDOLE DERIVATIVES

XXIX. Synthesis of 1-Substituted 7-Azatryptamines*

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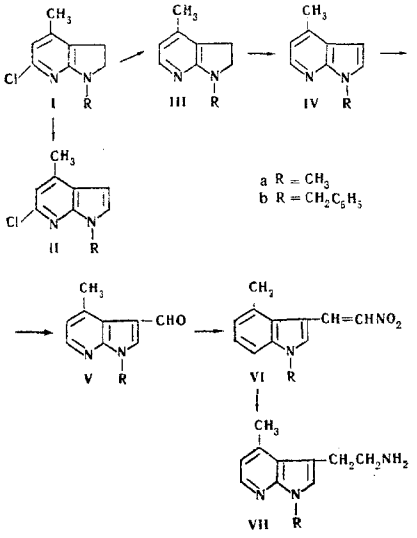
The synthesis of 1-substituted 7-azatryptamines having aliphatic and aliphatic-aromatic groups as substituents on the pyrrole nitrogen has been effected. The features of the reaction of the 7-azaindoline derivatives with quinones have been considered in connection with the nature of the substituents in position 1 and the presence or absence of a chlorine atom in position 6 of the azaindoline molecule.

A general method for the synthesis of azatryptamines has been described previously [2–5] which starts from the corresponding 7-azaindoles and passes through the 3-formyl and 3-β-nitrovinyl derivatives and which, with a number of azaindoles, has given better results than other methods of introducing the 3-β-aminoethyl chain, for example via the nitriles or amides of azaindol-3-ylacetic acids [2, 3].

This paper is devoted to the synthesis of 7-azatryptamines containing aliphatic and aliphatic-aromatic groups on the pyrrole nitrogen ring.



To obtain 1,4-dimethyl-7-azatryptamine (VIIa) we started from 6-chloro-1,4-dimethyl-7-azaindoline (Ia) [7], the dehalogenation of which in the presence of a palladium catalyst took place smoothly and led to 1,4-dimethyl-7-azaindoline (IIIa). The latter, on treatment with chloranil was converted into 1,4-dimethyl-7-azaindole (IVa). In contrast to 1-phenyl- and 1-butyl-7-azaindolines [8, 9], in the case of the 1-methyl derivatives, dehydrogenation with chloranil also takes place for compounds containing a halogen atom in position 6, e.g., 6-chloro-1,4-dimethyl-7-azaindoline (Ia). The corresponding 6-chloro-1,4-dimethyl-7-azaindole (IIa) was obtained with a yield of 45.4% by boiling Ia with chloranil in xylene for 3 hr. A similar dehydrogenation of the 6-chloro derivative of 7-azaindoline is observed [10] in the case of 6-chloro-4-methyl-7-azaindoline, which is unsubstituted on the nitrogen, while the oxidation of 1-butyl-6-chloro-4-methyl- and of 6-chloro-4-methyl-1-phenyl-7-azaindolines took place only under the action of a stronger oxidizing agent, dichlorodicyanobenzoquinone [9].

It has been mentioned previously [11] that the treatment of 1-benzyl-6-chloro-4-methyl-7-azaindoline (Ib) with chloranil leads not only to dehydrogenation but also to N-debenzylation, and the reaction product is 6-chloro-4-methyl-7-azaindole. Experiments on the reaction with the same dehydrogenating agent of the corresponding dehalogenated compound, 1-benzyl-4-methyl-7-azaindoline (IIIb) showed that in this case the oxidation of the pyrroline ring is not accompanied by the elimination of the N-benzyl group. In the reaction of IIIb with chloranil in boiling benzene, the yield of 1-benzyl-4-methyl-7-azaindole (IVb) was 51%. The use of a higher-boiling solvent (xylene) decreased the amount of IVb formed to 20.7% through the resinification of the reaction mixture, while lowering the reaction temperature to 60° C ensured the production of IVb with a yield of 61.2%.

In the formulation of IVa and IVb by the Vilsmeier reaction the best results were obtained in the case of the 1-benzyl derivative. At the same time, for the subsequent reactions of Va and Vb with nitromethane and the reduction of the nitrovinyl derivatives formed (VIa and VIb), substituents of different types on the pyrrole nitrogen had no substantial influence on the course of the reactions. The yields of the reaction products scarcely changed on passing from the 1-methyl to the 1-benzyl derivative.

EXPERIMENTAL

1,4-Dimethyl-7-azaindoline (IIIa). A solution of 26 g of palladous chloride in 200 ml of boiling 18% HCl was added to a solution of 26 g (142 mM) of Ia in 300 ml of ethanol. Hydrogenation was carried out at room temperature with an overpressure of 15–20 cm of water. The catalyst was filtered off and the filtrate was evaporated in vacuum. The residue was converted into the base by treatment with 25% aqueous potassium carbonate solution and the base was extracted with ether. The ethereal extract was dried with potassium carbonate and distilled. A fraction with bp 89–91° C (3 mm) was collected, representing 18.6 g (87.7%) of IIIa. Colorless crystals, mp 38–39° C (from heptane). The substance is soluble in ether, benzene,

*For part XXVIII, see [1].

acetone, and chloroform, and insoluble in water. Found, %: C 73.24; H 8.05; N 18.97. Calculated for $C_9H_{12}N_2$, %: C 72.97; H 8.10; N 18.92.

6-Chloro-1,4-dimethyl-7-azaindole (IIa). A mixture of 0.9 g (4.9 mM) of Ia and 1.2 g (4.9 mM) of chloranil was boiled in 50 ml of xylene for 3 hr. The xylene solution was poured off from the solid residue, washed with 10% aqueous caustic potash solution, and dried over potassium carbonate. The solvent was driven off and the residue was distilled, giving 0.4 g (54.4%) of IIa with bp 130–132° C (1 mm). Bright red crystals, mp 41–42° C (from heptane). The substance is soluble in benzene, acetone, chloroform, and alcohols, and insoluble in water and petroleum ether. Found, %: C 59.82; H 4.79; Cl 19.91; N 15.74. Calculated for $C_9H_9ClN_2$, %: C 59.84; H 4.98; Cl 19.66; N 15.51.

1,4-Dimethyl-7-azaindole (IVa). With stirring, 14.5 g (59 mM) of IIIa and 23.2 g (59 mM) of chloranil were heated at 95° C in 200 ml of toluene for 2 hr. The toluene solution was poured off from the solid matter, and the latter was boiled for 15 min with 50 ml of benzene and 50 ml of 10% caustic potash solution, filtered off, and again washed by being boiled for 15 min with 50 ml of benzene and 50 ml of 10% caustic potash solution. The benzene–toluene solutions were separated off, washed with 10% aqueous caustic potash solution and then with water, and were dried over potassium carbonate. After the solvents had been driven off, the residue was distilled in vacuum. This gave 8 g (55.9%) of IVa with bp 100–101° C (5 mm). Colorless crystals, mp 34–35° C (from petroleum ether). Substance IVa is soluble in the usual organic solvents, and insoluble in water. Found, %: C 73.95; H 6.95; N 18.93. Calculated for $C_9H_{10}N_2$, %: C 73.97; H 6.85; N 19.17.

3-Formyl-1,4-dimethyl-7-azaindole (Va). To 10 ml of dimethylformamide cooled to 10° C were added in drops first 5 ml of phosphorus oxychloride and then a solution of 5 g (34 mM) of IVa in 10 ml of dimethylformamide. The reaction mixture, which had become dark, was heated at 40° C for 1 hr and was then poured onto ice. The mixture was made alkaline to phenolphthalein with 40% caustic soda solution and was heated to the boil. After cooling it was extracted with ether, and the extract was dried with magnesium sulfate and distilled. Two fractions were collected: 1) bp 100–101° C (5 mm), the initial IVa, 3.1 g; and 2) bp 150–152° C (5mm), Va, 1.1 g (16.6%). Colorless crystals, mp 89–90° C (from heptane). The substance is readily soluble in the usual organic solvents, and insoluble in water. IR spectrum*: 1670 cm^{-1} (CHO). Found, %: C 68.56; H 5.80; N 16.20. Calculated for $C_{10}H_{10}N_2O$, %: C 68.96; H 5.75; N 16.09.

1,4-Dimethyl-3-(β-nitrovinyl)-7-azaindole (VIa). A mixture of 0.3 g (1.7 mM) of Va 0.15 g (1.9 mM) of ammonium acetate, and 2 ml of nitromethane was boiled for 1 hr, whereupon VIa separated out in the form of crystals. The precipitate was filtered off and washed with ether, giving 0.2 g (54%) of VIa in the form of yellow crystals, mp 196–197° C (from ethanol). The substance dissolves readily in acetone and chloroform and sparingly in alcohols, and is insoluble in water, ether, and petroleum ether. UV spectrum*: λ_{max}, nm (log ε): 226 (4.34); 285 (4.04); 395 (4.19). Found, %: C 60.59; H 4.88; N 19.54. Calculated for $C_{11}H_{11}N_3O_2$, %: C 60.83; H 5.06; N 19.35.

Dihydrochloride of 1,4-dimethyl-7-azatryptamine (VIIa). 1.2 g (5 mM) of VIa in 50 ml of tetrahydrofuran was added to 1.17 g (30 mM) of lithium aluminum hydride in 30 ml of tetrahydrofuran. Reduction was carried out with the reaction mixture at the boil for 6 hr with stirring. The product was worked up in the usual manner. The dihydrochloride was precipitated from an ethereal solution of the base VIIa by the addition of an ethanolic solution of hydrogen chloride. The yield of VIIa was 1.05 g (75%). Colorless crystals, mp 219–220° C (decomp., from a mixture of ethanol and acetone). The substance is readily soluble in ethanol and water, and insoluble in ether, acetone, benzene, and chloroform. Found, %: C 50.27; H 6.80; Cl 26.70; N 15.99. Calculated for $C_{11}H_{15}N_3 \cdot 2HCl$, %: C 50.39; H 6.48; Cl 27.09; N 16.03.

1-Benzyl-4-methyl-7-azaindole (IVb). A mixture of 1.5 g (6.7 mM) of IIIb [10] and 1.7 g (6.9 mM) of chloranil was heated in 20 ml of benzene at 60° C* for 3 hr with stirring. The benzene solution was separated off, and the resinous residue was washed with benzene and 10% caustic soda solution and then with water, and it was dried over potassium carbonate. Vacuum distillation yielded 0.9 g (61.2%) of IVb with bp 154–156° C (1 mm). Colorless crystals, mp 63–64° C (from petroleum ether). The substance is readily soluble in ether, benzene, chloroform, ethyl acetate, and acetone, and less readily in ethanol, and is insoluble in methanol and water. Found, %: C 80.68; H 6.35; N 12.39. Calculated for $C_{15}H_{14}N_2$, %: C 81.08; H 6.30; N 12.61.

1-Benzyl-3-formyl-4-methyl-7-azaindole (Vb) was synthesized from 2.1 g (9.4 mM) of IVb, with 1.5 ml of phosphorus oxychloride and 8 ml of dimethylformamide, in a similar manner to Va. When the reaction products were distilled, two fractions were collected: 1) bp 154–156° C (1 mm), the initial IVb, 0.8 g; 2) bp 188–190° C (1 mm), Vb, 0.8 g (34%). Colorless crystals, mp 81–83° C (from methanol). The substance is readily soluble in benzene, acetone, chloroform, and ethanol, and less readily in methanol, and is insoluble in petroleum ether and water. IR spectrum: 1670 cm^{-1} (CHO). Found, %: C 76.86; H 5.66; N 10.97. Calculated for $C_{16}H_{15}N_2O$, %: C 76.80; H 5.60; N 11.20.

1-Benzyl-4-methyl-3-(β-nitrovinyl)-7-azaindole (VIb) was obtained from 0.4 g (1.6 mM) of Vb with 0.18 g (2.3 mM) of ammonium acetate and 2 ml of nitromethane in a similar manner to VIa. The yield of VIb was 0.25 g (53.1%). Yellow crystals, mp 160–161° C. The substance is soluble in benzene, acetone, chloroform, and alcohols, and insoluble in ether, petroleum ether, and water. Found, %: C 69.25; H 5.17; N 13.98. Calculated for $C_{17}H_{15}N_3O_2$, %: C 69.62; H 5.12; N 14.33.

1-Benzyl-4-methyl-7-azatryptamine (VIIb) was obtained in a similar manner to VIIa by the reduction of 0.2 g (0.7 mM) of VIb with 0.15 g (3.9 mM) of lithium aluminum hydride in boiling tetrahydrofuran. The yield of the base VIIb was 0.13 g (72.2%). The dihydrochloride of VIIb was isolated in the form of the stable dihydrate with mp 186–188° C (from a mixture of ethanol and acetone). The substance is soluble in alcohols and water, and insoluble in ether, benzene, and acetone. Found, %: C 54.41; H 6.62; Cl 18.56; N 11.45. Calculated for $C_{17}H_{19}N_3 \cdot 2HCl \cdot 2H_2O$, %: C 54.54; H 6.68; Cl 18.98; N 11.23.

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*All the IR spectra were taken on a UR-10 spectrometer in paraffin oil, and the UV spectra on an EPS-3 spectrophotometer in ethanol.

*When this reaction was carried out at room temperature with stirring, the initial IIIb was recovered quantitatively.

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