AZAINDOLE DERIVATIVES

XLIII.* SYNTHESIS OF 1-ACETYL-4-METHYL-7-AZATRYPTAMINE

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It is shown that it is possible to synthesize 1-acyl-4-methyl-7-azatryptamines from ethyl (4-methyl-7-aza-3-indolyl)acetate through 3-(β-chloroethyl)-4-methyl-7-azaindole with subsequent acylation by replacement of halogen by a nitro group and reduction. The N-acetyl group is cleaved in the reaction of 1-acetyl-3-(β-chloroethyl)-4-methyl-7-azaindole with ammonia, bis(dimethylmethoxysilyl)amide potassium salt, and potassium phthalimide (with subsequent removal of the phthalimide protective group).

The 7-aza analog of the natural biogenic amine tryptamine was first synthesized by Robison in 1956 [2]. Subsequent investigations led to the preparation of various substituted (in the 1 position and side chain) 7-azatryptamines [3]. The synthesis of 2-methyl-7-azatryptamine was recently described by Grandberg and Yaryshev [4].

A pharmacological study of substituted 7-azatryptamines showed that introduction of electron-acceptor groups into the pyrrole nitrogen atom intensifies the psychotropic activity. In this connection, we made a search for methods for the synthesis of 1-acyl-7-azatryptamines.

The task of obtaining this type of compound is not a trivial one, since the known methods for the synthesis of azatryptamines through 3-cyanomethyl [2] or 3-nitrovinyl [3] derivatives have not made it possible to retain the acyl group attached to the pyrrole nitrogen atom. However, the selective acylation of tryptamines or their aza analogs only at the cyclic nitrogen atom has not been described.

To obtain 1-acetyl-4-methyl-7-azatryptamine (I), we selected a scheme based on the reduction of ethyl (4-methyl-7-aza-3-indolyl)acetate (II) [5] to the corresponding azatryptophol (III), replacement of the hydroxyl group by chlorine, acetylation of chloro derivative IV, and subsequent replacement of the chlorine atom by an amino group.

No difficulties were encountered in the synthesis of chloro derivative V. The ester group of II was readily reduced with lithium aluminum hydride in refluxing ether, the hydroxyl group in III was replaced by chlorine with thionyl chloride at room temperature, and acetylation of IV proceeded quite completely on heating with acetic anhydride. The chlorine atom in V proved to be quite labile and was practically quantitatively replaced by a phthalimide residue with potassium phthalimide in dimethylformamide at 100°C this made it possible to pass to 4-methyl-7-azatryptamine (VII) by subsequent removal of the phthalide protective group (the acetyl group is also simultaneously saponified). In the course of work with V, we encountered not only the high reactivity of the chlorine atom with respect to nucleophilic agents but also the considerable lability of the acetyl residue bonded to the cyclic nitrogen atom. In contrast to the selective replacement of the chlorine atom by a primary amino group as described in [6], this sort of reaction could not be carried out in the case of V. Reaction of V under mild conditions (1.5 h at room temperature in tetrahydrofuran) with bis(dimethylmethoxysilyl)amide potassium salt and subsequent methanolysis at room temperature gave VIII. The yield of product of the intermolecular alkylation of VIII was 51%, and I was not detected in the reaction products by gas–liquid chromatography (GLC). Partial or com-

*See [1] for communication XLII.

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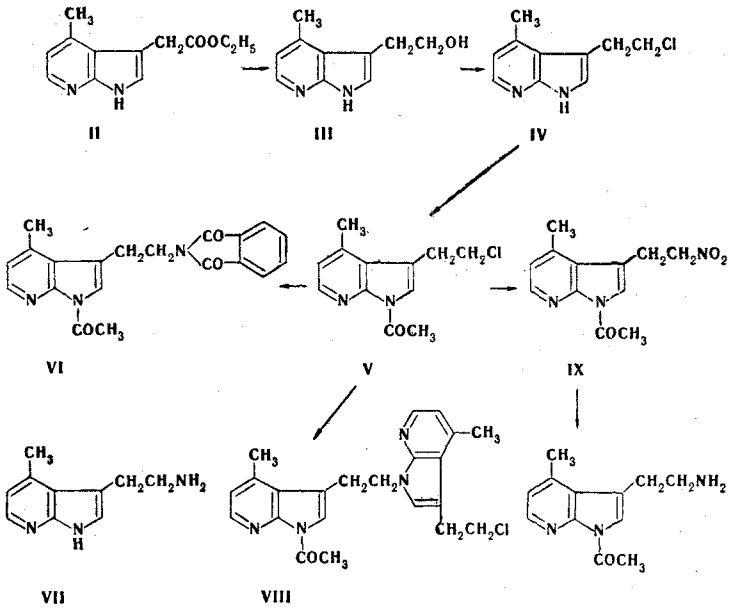

plete removal of the N-acetyl group was also observed in the replacement of the chlorine atom in V by ammonia under various conditions.

We were able to accomplish the transition from V to 1-acetyl-4-methyl-7-azatryptamine (I) only by replacement of the chlorine atom in V with a nitro group with subsequent reduction of 1-acetyl-3-(β-nitroethyl)-4-methyl-7-azaindole (IX) over a palladium catalyst. In contrast to 3-(β-acetamidoalkyl)-7-azaindoles with an acetyl group in the side chain, which are characterized in the IR spectra by a carbonyl band at 1656-1680 cm^{-1} [7], V and IX, which have an acetyl group attached to the pyrrole nitrogen atom, have a carbonyl band at 1705-1735 cm^{-1}.

EXPERIMENTAL

The IR spectra of mineral oil pastes were recorded with a UR-10 spectrometer.

3-(β-Hydroxyethyl)-4-methyl-7-azaindole (III). A solution of 3.5 g (16 mmole) of II in 30 ml of ether was added to a suspension of 3 g (80 mmole) of lithium aluminum hydride in 100 ml of refluxing ether, after which the mixture was refluxed for 6 h and worked up in the usual manner. Compound III was extracted from the mixture of lithium and aluminum hydroxides, initially with ether and then with chloroform. The combined extracts were dried with magnesium sulfate and vacuum evaporated to give 1.65 g (58.5%) of III as white crystals with mp 171-172° (from acetone). The product was only slightly soluble in ether and benzene but more soluble in alcohol, acetone, chloroform, and water. Found,%: C 67.9; H 6.6; N 16.2. $C_{10}H_{12}N_2O$. Calculated,%: C 68.2; H 6.8; N 15.9. The hydrochloride was obtained as a white crystalline substance with mp 210-211° (from acetone). The hydrochloride was soluble in water and alcohol but insoluble in acetone. IR spectrum: broad band at 3000-3500 cm^{-1} (associated OH and NH groups). Found,%: C 56.3; H 6.0; Cl 16.6; N 12.9. $C_{10}H_{12}N_2O \cdot HCl$. Calculated,%: C 56.5; H 6.1; Cl 16.7; N 13.2.

3-(β-Chloroethyl)-4-methyl-7-azaindole (IV). A 3-ml sample of thionyl chloride was added dropwise to a suspension of 1.2 g (7 mmole) of the hydrochloride of III in 15 ml of anhydrous chloroform, after which the reaction mixture was allowed to stand at 20° for 10 h. The solvent was vacuum evaporated, and the residual thionyl chloride was removed by distillation with benzene to give 1.05 g (80.6%) of the hydrochloride of IV as a white crystalline substance with mp 216-217° [from alcohol–acetone (1:1)]. The product was quite soluble in water but less soluble in alcohol, acetone, and ethyl acetate. Found,%: C 52.2; H 5.4; Cl 30.8; Cl' 15.2; N 12.4. $C_{10}H_{11}ClN_2 \cdot HCl$. Calculated,%: C 52.0; H 5.2; Cl 30.7; Cl' 15.4; N 12.1.

1-Acetyl-3-(β-chloroethyl)-4-methyl-7-azaindole (V). A solution of 0.7 g (3 mmole) of the hydrochloride of IV in 5 ml of acetic anhydride was heated for 1 h on a boiling-water bath, after which it was evaporated to dryness in vacuo. The residue was extracted with boiling petroleum ether to give 0.45 g (63%) of colorless crystals with mp 90° (from petroleum ether). The product was quite soluble in ether, benzene, chloroform, and acetone but less soluble in alcohol, water, and petroleum ether. IR spectrum: 1705 cm^{-1} (CON⟨). Found,%: C 61.1; H 5.7; Cl 15.0; N 11.9. $C_{12}H_{12}N_2O \cdot HCl$. Calculated,%: C 61.0; H 6.5; Cl 15.0; N 11.6.

1-Acetyl-3-(β-N-phthalimidoethyl)-4-methyl-7-azaindole (VI). A 0.1-g (0.53 mmole) sample of potassium phthalimide was added to a solution of 0.1 g (0.42 mmole) of V in 5 ml of dimethylformamide, after which the mixture was heated at 100° for 6 h and then poured into 50 ml of water. The aqueous mixture was extracted with chloroform, and the extract was washed successively with 2 N sodium hydroxide and water, dried with magnesium sulfate, and vacuum evaporated to give 0.14 g (93%) of colorless crystals of VI with mp 198-199° (from alcohol). The product was soluble in benzene, acetone, and alcohol but insoluble in ether and water. IR spectrum: broad intense band at 1690-1720 cm^{-1} (CON⟨); no absorption at 3200-3600 cm^{-1}. Found,%: C 68.8; H 4.9; N 11.9. $C_{20}H_{17}N_3O_3$. Calculated,%: C 69.1; H 4.9; N 12.1.

4-Methyl-7-azatryptamine (VII). A 0.22 g (4.3 mmole) sample of hydrazine hydrate was added to a solution of 1.5 g (4.3 mmole) of VI in 40 ml of alcohol, after which the mixture was refluxed for 2 h and vacuum evaporated. The residue was treated with 25 ml of 2 N hydrochloric acid, and the mixture was stirred at 40° for 5 min. The solid material was then removed by filtration, and the acid solution was vacuum evaporated at no higher than 50°. The resulting oily product (0.6 g) was, according to chromatography on Silufol with butanol–acetic acid–water, a mixture of substances containing VII. The solid material obtained by filtration was refluxed for 6 h with concentrated hydrochloric acid, the resulting solution was vacuum evaporated to dryness, and the residue was triturated with anhydrous acetone to give 0.55 g (45%) of the dihydrochloride of the dihydrate of VII with mp 269-270° [from alcohol–acetone (1 : 1)]. The product did not depress the melting point of the dihydrochloride of VII obtained by reduction of 3-(β-nitrovinyl)-4-methyl-7-azaindole [4] with lithium aluminum hydride. The IR spectra of the two substances were identical. Found,%: C 42.6; H 6.6; Cl 25.1; N 14.6. $C_{10}H_{13}N_3 \cdot 2HCl \cdot 2H_2O$. Calculated,%: C 42.2; H 6.7; Cl 25; N 14.8.

1-[β-(1'-Acetyl-4'-methyl-7-aza-3'-indolyl)ethyl]-3-(β-chloroethyl)-4-methyl-7-azaindole (VIII). A solution of 4 g (17 mmole) of V in 100 ml of anhydrous tetrahydrofuran was added under argon to a solution of 4.2 g (18 mmole) of bis(dimethylmethoxysilyl)amide potassium salt in 100 ml of anhydrous tetrahydrofuran, after which the mixture was stirred at 20° for 1.5 h. It was then treated with 50 ml of distilled (over magnesium) absolute methanol, and the mixture was heated to the boiling point and vaccum evaporated to dryness. The residue was extracted with anhydrous ether, and the ether was removed by vacuum distillation to give 3.4 g (51%) of VIII as colorless crystals with mp 201-203° (from alcohol). The product was soluble in alcohol but only slightly soluble in ether, benzene, chloroform, and acetone. IR spectrum: 1680, 1710 cm^{-1} (CON⟨). Found,%: C 66.9; H 5.8; Cl 9.1; N 14.3. M 394 (mass-spectrometry). $C_{22}H_{23}N_4OCl$. Calculated,%: C 66.8; H 5.8; Cl 9.0; N 14.3.

1-Acetyl-3-(β-nitroethyl)-4-methyl-7-azaindole (IX). A 0.2-g (2.5 mmole) sample of sodium nitrite was added to 0.5 g (2.1 mmole) of V in 5 ml of dimethyl sulfoxide, and the mixture was held at 20° for 6 days, after which the markedly darkened solution was vacuum evaporated to dryness. The residue was extracted with boiling ether. The ether was removed from the extract by distillation, and the oily yellow product was extracted with boiling petroleum ether. Removal of the petroleum ether by distillation gave 0.17 g (32.4%) of IX as a white crystalline substance with mp 98-99° (from ether). The product was quite soluble in organic solvents but less soluble in water. Found,%: C 58.7; H 5.5; N 17.2. $C_{12}H_3N_3O_3$. Calculated,%: C 58.3; H 5.3; N 17.0. The picrate was obtained as yellow crystals with mp 208-210° (from alcohol). It was quite soluble in alcohol and acetone but less soluble in water. IR spectrum: 1735 (CON⟨), 3200-3300 (NH_2, OH) cm^{-1}. Found,%: C 45.1; H 3.5; N 17.7. $C_{12}H_{13}N_3O_3 \cdot C_6H_3N_3O_7$. Calculated,%: C 45.4; H 3.4; N 17.6.

1-Acetyl-4-methyl-7-azatryptamine (I). A thoroughly washed (with alcohol) palladium catalyst, obtained by reduction of 0.1 g of palladium chloride, was added to a solution of 0.2 g (0.08 mmole) of IX in 10 ml of alcohol. The reduction was carried out at room temperature and a pressure of 20-25 cm (water column) until hydrogen absorption had ceased. The catalyst was removed by filtration, and the alcohol was vacuum evaporated. The residue was converted to the picrate by addition of a saturated alcohol solution of picric acid to give 0.12 g (33.3%) of the picrate of I as yellow crystals with mp 199-201° (from alcohol). The picrate was soluble in alcohol and acetone but less soluble in water. Found,%: C 48.0; H 4.8; N 18.6. $C_{12}H_{15}N_3O \cdot C_6H_3N_3O_7$. Calculated,%: C 48.4; H 4.0; N 18.8.

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