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AZAINDOLE DERIVATIVES

LII.* SYNTHESIS OF 2-SUBSTITUTED 6-AZAINDOLES

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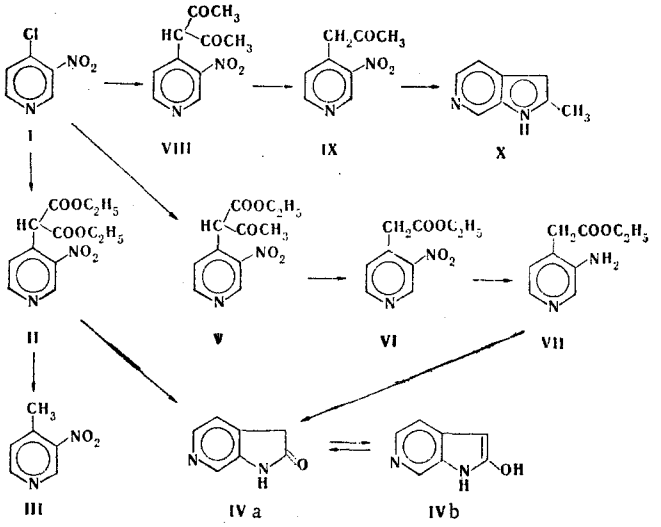
UDC 547.75'821.07

Condensation products, which were converted to 2-substituted (2-hydroxy- and 2-methyl)-6-azaindoles by reductive cyclization, were obtained in high yields from 3-nitro-4-chloropyridine by reaction with malonic and acetoacetic esters and acetylacetone in the presence of sodium hydride in dimethylformamide at room temperature.

Until now a small number of 2-monosubstituted 6-azaindoles have been described [2-4]; most of these compounds were synthesized in low yields by the high-temperature Madelung reaction. In the case of 2-hydroxy-6-azaindole (6-azahydroxyindole) (IV) and 2-methyl-6-azaindole (X) we studied a different method for the preparation of 2-substituted 6-azaindoles on the basis of the accessible 3-nitro-4-chloropyridine (I) [2].



The previously described [2, 5] condensation of I with malonic ester in the presence of sodium alkoxides leads to II in 37-55% yields. Equally low yields were also obtained in the analogous reaction with cyanoacetic ester [6]. According to our data, the low yields are associated with the side reaction to give 3-nitro-4-alkoxypyridines, which are readily saponified on subsequent workup of the reaction mixture. When the reaction was carried out in dimethylformamide (DMF) in the presence of sodium hydride, it was possible to obtain II in practically quantitative yield in 30 min at room temperature. Subsequent saponification and decarboxylation of

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II by heating for 3 h with 18% hydrochloric acid ensured the production in 86% yield of 3-nitro-4-methylpyridine (III) – the intermediate in our recently described two-step synthesis of unsubstituted 6-azaindole [7]. Diester II is converted to 2-hydroxy-6-azaindole (IV) through the corresponding 3-ethoxycarbonyl derivative in 82% overall yield [8]. As one should have expected, the condensation of I with acetoacetic ester under the influence of sodium hydride in DMF at room temperature proceeded somewhat more slowly than the reaction with malonic ester, and, according to the results of thin-layer chromatography (TLC), the process is still not complete after 30 min. It was necessary to allow the mixture to stand at 20 deg C for 1 h to complete the reaction. The (3-nitro-4-pyridyl)acetoacetic ester (V), which was isolated in 96% yield, undergoes partial deacetylation with cleavage of the C–C bond when it is converted to the hydrochloride under the influence of an alcohol solution of hydrogen chloride. The process is driven to completion by treatment of keto ester V with hydrogen chloride at room temperature for 12 h. The reduction of the nitro group in the resulting (3-nitro-4-pyridyl)acetic ester (VI) in the presence of a palladium catalyst made it possible to obtain (3-amino-4-pyridyl)-acetic ester (VII) in 88% yield; the latter was converted to 2-hydroxy-6-azaindole (IV) in 89% yield by heating in a sublimation apparatus at 180 deg C for 1 h and subsequent vacuum sublimation of the reaction product.

The condensation of acetylacetone and I proceeds even more slowly than the reaction with malonic and acetoacetic esters: according to the results of TLC and preparative isolation of the reaction products, after 3 h at 20 deg C the degree of reaction is 25%, as compared with 66% after 21 h. Heating to 70 deg C accelerates the process (VIII is obtained in 64% yield after 2 h), but the reaction under these conditions is accompanied by resinification, which hinders the isolation and purification of diketone VIII. As in the case of keto ester V, treatment of diketone VIII with hydrogen chloride at room temperature leads to ketone cleavage. (3-Nitro-4-pyridyl)acetone (IX) is obtained in 96% yield, and its catalytic reduction with palladium makes it possible to obtain 2-methyl-6-azaindole (X) in 81% yield.

EXPERIMENTAL

The PMR spectra of $CDCl_3$ solutions of the compounds were recorded with a JNM-4H-100 spectrometer with tetramethylsilane as the internal standard. The IR spectra of mineral oil suspensions of the compounds were obtained with a Perkin–Elmer 457 spectrometer. The mass spectra were obtained with an MKh-1303 mass spectrometer at an ionizing voltage of 50 eV. Thin-layer chromatography was carried out on Silufol in an acetone–ethanol system (1 : 1); chlorotolidine was used to detect the spots.

Condensation of 3-Nitro-4-chloropyridine (I) with Malonic Ester under the Influence of Sodium Ethoxide. A 31-g (0.19 mole) sample of malonic ester was added to sodium ethoxide, obtained from 11.1 g (0.48 mole) of sodium in 200 ml of absolute alcohol, and the mixture was stirred at 20 deg C for 30 min. A 31.4-g (0.16 mole) sample of the hydrochloride of I was added, and the resulting dark-red solution was allowed to stand at 20 deg C for 1 h. It was then diluted with 400 ml of ether, and the mixture was extracted twice with 500-ml portions of 4% aqueous sodium hydroxide solution. The ether layer was separated, dried with magnesium sulfate, and saturated with gaseous hydrogen chloride. The mixture was filtered to give 17.5 g (53%) of 3-nitro-4-ethoxy-pyridine hydrochloride as shiny crystals with mp 270-271 deg C [9]. The aqueous alkaline solution was acidified carefully with concentrated HCl until its color changed from red to yellow, after which it was extracted with ether. The ether extract was dried with magnesium sulfate and vacuum evaporated to give 16.8 g (37%) of (3-nitro-4-pyridyl)malonic ester (II). The hydrochloride [8] had mp 125-126 deg C.

(3-Nitro-4-pyridyl)malonic Ester (II). A 53-ml (0.47 mole) sample of malonic ester was added gradually with vigorous stirring in a stream of argon to a suspension of 11.3 g (0.47 mole) of sodium hydride in 50 ml of dry DMF, during which the temperature was not allowed to rise above 50 deg C. When hydrogen evolution ceased, the mixture was allowed to stand for 10 min, after which 25 g (0.13 mole) of the hydrochloride of I was added in portions while the temperature was held at no higher than 70 deg C by cooling. The mixture was then stirred for 30 min, after which it was vacuum evaporated, and the residue was dissolved in 50 ml of water. The aqueous solution was neutralized with acetic acid, and II was extracted with ether. Workup of the extract gave 35.1 g (97%) of II. The hydrochloride [8] had mp 125-126 deg C.

3-Nitro-4-methylpyridine (III). A solution of 32.3 g of II in 150 ml of 18% hydrochloric acid was heated at 100 deg for 3 h, after which it was evaporated, and the residue was triturated with acetone to give 15.2 g (86%) of the hydrochloride of III with mp 177-178 deg C [5]. No melting-point depression was observed for a mixture of a sample of the product with an authentic sample.

(3-Nitro-4-pyridyl)acetoacetic Ester (V). The method used to prepare II was employed to obtain this compound from 2.3 g (96 mmole) of sodium hydride, 12.5 ml (93 mmole) of acetoacetic ester, and 5.2 g (26.7

mmole) of the hydrochloride of I in 20 ml of DMF by reaction for 1 h. Workup of the reaction mixture gave 6.4 g (96%) of V as an oily yellow-brown substance that was insoluble in water but quite soluble in ordinary organic solvents and had n_D^{20} 1.5440. IR spectrum: 1740 ($COOC_2H_5$); 1650 ($COCH_3$); 1600 (C=C, C=N); 1320, 1350 cm^{-1} (NO_2). Mass spectrum: M^+ 252. Found: C 52.4; H 4.9; N 11.3%. $C_{11}H_{12}N_2O_5$. Calculated: C 52.4; H 4.8; N 11.1%.

(3-Nitro-4-pyridyl)acetic Ester (VI). A solution of 3.0 g (11.9 mmole) of keto ester V in 40 ml of anhydrous ether was acidified with an alcohol solution of hydrogen chloride to pH 3, after which the mixture was allowed to stand overnight at 20 deg C. The hydrochloride of VI was removed by filtration to give 2.5 g (86%) of colorless crystals with mp 145-146 deg C (from acetone). The product was quite soluble in water and alcohols, less soluble in chloroform and acetone, and insoluble in other ordinary organic solvents. IR spectrum: 1720 ($COOC_2H_5$), 1640 (C=C, C=N), 1590 cm^{-1} (NO_2). PMR spectrum (CF_3COOH): 4.64 s ($PyCH_2$), 9.78 s (2-H), 8.38 d (5-H), 9.33 d (6-H), 1.39 t (CH_3), and 4.41 q (CH_2). Found: C 43.7; H 4.5; Cl 14.4; N 11.4%. $C_9H_{10}N_2O_4 \cdot HCl$. Calculated: C 43.8; H 4.5; Cl 14.4; N 11.4 %.

(3-Amino-4-pyridyl)acetic Ester (VII). A solution of 5.8 g (23.5 mmole) of VI·hydrochloride in 150 ml of ethanol was hydrogenated in the presence of 1 g of 6% palladium oxide on carbon at room temperature and an excess hydrogen pressure of 20-30 cm (water column). Workup of the mixture gave 4.5 g (88%) of the hydrochloride of VII as white crystals with mp 171-172 deg C (dec., from alcohol). The product was quite soluble in water and alcohols but insoluble in ether, benzene, acetone, and chloroform. IR spectrum: 3320, 3160 (NH^+), 1720 ($COOC_2H_5$), 1650 cm^{-1} (C=C, C=N). Found: C 50.0; H 6.0; Cl 16.1; N 13.2%. $C_9H_{12}N_2O_2 \cdot HCl$. Calculated C 49.9; H 6.0; Cl 16.4; N 12.9%. Base VII was obtained as colorless crystals with mp 59-60 deg C (from heptane). The base was quite soluble in ordinary organic solvents, less soluble in heptane, and insoluble in water. IR spectrum: 3360, 3200 (NH_2), 1720 ($COOC_2H_5$), 1650 (C=C, C=N), 1600 cm^{-1} (NH_2). PMR spectrum: 3.55 s ($PyCH_2$), 8.09 (2-H), 6.97 d (5-H), 8.03 d (6-H), 1.22 t (CH_3), 4.11 q (CH_2), and broadening in the region of the signal at 4.11 ppm (NH_2). Found: C 59.9; H 6.8; N 15.8%. $C_9H_{12}N_2O_2$. Calculated: C 60.0; H 6.7; N 15.6%.

2-Hydroxy-6-azaindole (6-Azahydroxyindole) (IV). A) A solution of 13.4 g (47.5 mmole) of II in 400 ml of ethanol was hydrogenated in the presence of a palladium catalyst, as described in the preparation of VII. The catalyst was separated, and the solution was vacuum evaporated to dryness. The residue was triturated with alcohol, and the resulting 3-ethoxycarbonyl-6-azahydroxyindole (9.73 g) [8], with mp 299-300 deg C, was dissolved in 100 ml of 18% hydrochloric acid. The solution was refluxed for 5 h, after which it was vacuum evaporated to dryness. A solution of 3.47 g of sodium bicarbonate in 30 ml of water was added to the residue, and the mixture was extracted with butanol. The butanol solution was dried with magnesium sulfate and evaporated to dryness to give 5.47 g (83%) of azaindole IV as colorless slightly yellowing crystals with mp 231-232 deg C (dec., from alcohol) [8]. The product was soluble in alcohols, water, and DMF but insoluble in ether, benzene, chloroform, acetone, and ethyl acetate. According to the IR and PMR spectral data, IV exists in the form of a mixture of comparable amounts of the oxo (IVa) and hydroxy (IVb) forms. IR spectrum: 1660 cm^{-1} (CO). PMR spectrum (two sets of signals): 6.67 d, 7.30, 7.35, 8.15 (4-H and 5-H), 7.37 s and 8.10 (7-H), 10.15 and 10.59 (NH), 5.02 s ppm. The picrate was obtained as yellow crystals with mp 201-202 deg C (from water). Found: C 42.5; H 2.6; N 19.1%. $C_7H_6N_2O \cdot C_6H_3N_3O_7$. Calculated: C 42.9; H 2.5; N 19.3%.

B) A 0.15-g (0.83 mmole) sample of VII was placed in a sublimation apparatus and heated at 180 deg C (bath temperature) for 1 h, after which it was sublimed at a residual pressure of 0.3 mm to give 0.1 g (89.3%) of azaindole IV with mp 231-232 deg C. No melting-point depression was observed for a mixture of a sample of this product with a sample of IV obtained by method A, and the IR spectra of the two samples were identical.

(3-Nitro-4-pyridyl)acetylacetone (VIII). The procedure used for the preparation of II was employed to prepare this compound from 2.1 g (87 mmole) of sodium hydride, 9 ml (87 mmole) of acetylacetone, and 4.6 g (24 mmole) of the hydrochloride of I in 20 ml of DMF at 20 deg C for 21 h. The yield of diketone VIII was 3.45 g (66%). The light-yellow crystals had mp 102-103 deg C (from cyclohexane). The product was soluble in ordinary organic solvents and in hot water but only slightly soluble in cold water and cyclohexane. IR spectrum: 1600 (CO) and 1510 cm^{-1} (NO_2). Found: C 54.1; H 4.6; N 12.6%. $C_{10}H_{10}N_2O_4$. Calculated: C 54.1; H 4.5; N 12.6%.

(3-Nitro-4-pyridyl)acetone (IX). An alcohol solution of hydrogen chloride was added to a solution of 2 g (9.0 mmole) of diketone VIII in 40 ml of anhydrous ether until the mixture was acidic with respect to Congo Red, after which it was allowed to stand overnight at room temperature. The resulting precipitate of the hydrochloride of IX was removed by filtration to give 1.88 g (96.4%) of a white crystalline substance with mp 178-179 deg C (dec., from alcohol). The product was soluble in water and alcohols but only slightly soluble in other

ordinary organic solvents. IR spectrum: 1710 (CO), 1640 (C=C), and 1530 cm^{-1} (NO_2). Found: C 44.4; H 4.1; Cl 16.4; N 12.9%. $C_8H_8N_2O_3 \cdot HCl$. Calculated: C 44.3; H 4.1; Cl 16.4; N 12.9%. Base IX was obtained as light-yellow crystals with mp 74-75 deg C (from heptane). The product was soluble in ordinary organic solvents but insoluble in water. IR spectrum: 1710 (CO), 1600 (C=C, C=N), and 1510 cm^{-1} (NO_2). PMR spectrum: 9.21 s (2-H), 4.18 s ($PyCH_2$), 2.32 s (CH_3), 8.67 d (6-H), and 4.35 d ppm (5-H). Mass spectrum: M^+ 180. Found: C 53.2; H 4.4; N 15.5%. $C_8H_8N_2O_3$. Calculated: C 53.3; H 4.4; N 15.5%.

2-Methyl-6-azaindole (X). A solution of 0.6 g (2.8 mmole) of the hydrochloride of IX in 100 ml of ethanol was hydrogenated in the presence of 0.4 g of 6% palladium oxide on carbon at room temperature and an excess hydrogen pressure of 20-30 cm (water column), after which the catalyst was separated, and the filtrate was vacuum evaporated to dryness. The residue (0.47 g) was recrystallized from absolute ethanol to give 0.38 g (81%) of the hydrochloride of X with mp 231-232 deg C. The white crystals were soluble in water and alcohols but insoluble in other ordinary organic solvents. Found: C 57.1; H 5.2; Cl 21.0; N 16.7%. $C_8H_8N_2 \cdot HCl$. Calculated: C 57.0; H 5.3; Cl 21.1; N 16.6%. Base X [5] had mp 183-183.5 deg C. PMR spectrum: 6.13 s (3-H), 11.21 s (NH), 2.44 s (CH_3), 8.56 d (7-H, J=1 Hz), and 7.30 d ppm (4-H, J=5.5 Hz).

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CHEMISTRY OF HETEROCYCLIC N-OXIDES AND RELATED COMPOUNDS

VIII.* DEHYDROGENATION OF PIPERIDINES BY PYRIDINE N-IMINE DERIVATIVES

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The dehydrogenation of anabasine, piperidine, and isoanabasine N-imine hydrochlorides by pyridine N-imine hydrochloride and the dehydrogenation of anabasine pyridinia-p-toluenesulfonamidate were studied. The corresponding pyridines and products of reductive deimination were obtained.

We have demonstrated the possibility of the application of pyridine N-imine hydrochlorides as homogeneous dehydrogenating agents for the dehydrogenation of the completely saturated heterocyclic ring of anabasine [2]. In the present research we extended the limits of applicability of the method by studying the thermal transformation of anabasine N-imine hydrochloride (I), the dehydrogenation of piperidine (II) and isoanabasine (III) hydrochlorides by pyridine N-imine hydrochloride (IV), and the dehydrogenation of anabasine (V) by pyridinia-p-toluenesulfonamidate (VI).

*See [1] for communication VII.

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