AZAINDOLE DERIVATIVES.

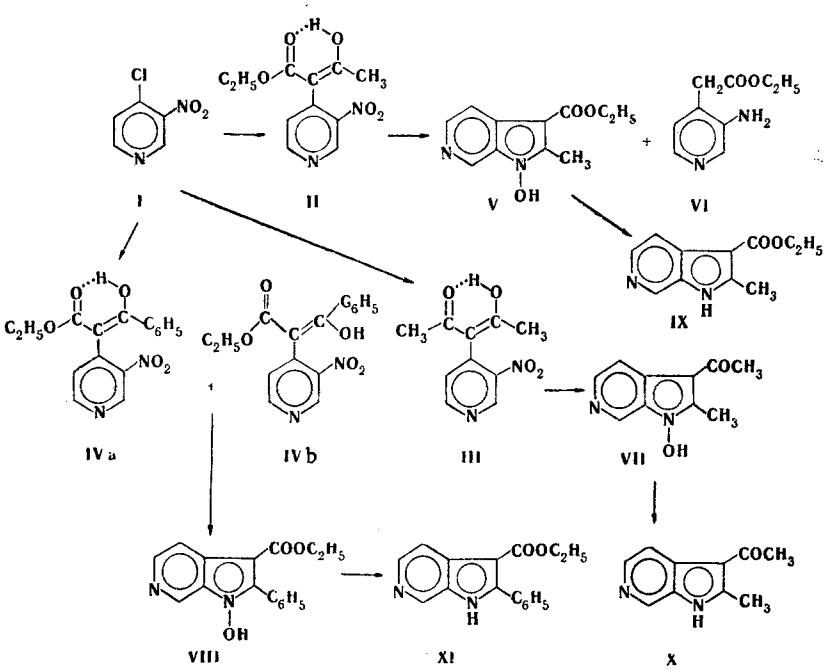
LIV.* SYNTHESIS OF 2,3-DISUBSTITUTED 6-AZAINDOLES

A. A. Prokopov, L. F. Linberg, T. F. Vlasova,
Yu. N. Sheinker, and L. N. Yakhontov

UDC 547.75'821.07

1-Hydroxy derivatives of 2,3-disubstituted 6-azaindoles, which were converted to the corresponding 2,3-disubstituted 6-azaindoles, were obtained from the products of condensation of 3-nitro-4-chloropyridine with acetoacetic and benzoylacetic esters and acetylacetone.

In an earlier communication [2] we described a new method for the synthesis of 2-substituted 6-azaindoles from the accessible 3-nitro-4-chloropyridine (I) through the corresponding products of condensation of I with dicarbonyl compounds. In the present research we used a similar method for the preparation of 2,3-disubstituted 6-azaindoles.



Analysis of the PMR spectrum of ester II, which was obtained in 96% yield by condensation of I with acetoacetic ester [2], shows that II exists in CCl_4 solution in the cis-enol form rather than in the ketone form. The PMR spectrum does not contain a signal corresponding to the 4α proton in the alternative keto structure but does contain a signal of a hydroxyl proton at 13.5 ppm, which participates in an intramolecular hydrogen bond with the ester group. The formation of a sufficiently stable six-membered cyclic structure in this case is possible only for a cis orientation of the methyl group and the nitropyridine ring.

The PMR spectrum of III (in $CDCl_3$), in which a signal of the proton of an enol hydroxyl group is also observed at 13.5 ppm, is also similar. A six-membered cyclic structure with a cis orientation of the methyl group and the nitropyridine residue is probably also formed in this case.

*See [1] for communication LIII.

S. Ordzhonikidze All-Union Scientific-Research Pharmaceutical-Chemistry Institute, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 492-495, April, 1978. Original article submitted April 12, 1977.

 0009-3122/78/1404-0402$07.50

As noted in [2], prolonged reaction is necessary for the preparation of the products of condensation of I with acetylacetone and benzoylacetic ester in sufficiently high yields. Thus, an increase in the reaction time for the condensation of I with acetylacetone from 3 to 36 h makes it possible to raise the yield of III from 25% to 76%, and the yield of III reaches 80% after 60 h under the same conditions. When the condensation of I with benzoylacetic ester in dimethylformamide (DMF) under the influence of sodium hydride is carried out at 20°C, (3-nitro-4-pyridyl)benzoylacetic ester (IV) is obtained in 46% yield after 17 h, 76% yield after 36 h, 92% yield after 48 h, and 93% yield after 60 h. In contrast to II and III, IV in various solvents exists in the form of an equilibrium mixture of cis (IVa) and trans (IVb) forms. Two sets of signals of protons of a carbethoxy group and phenyl and nitropyridine rings are observed in all cases in the PMR spectra of IV in CCl_4, $CDCl_3$, and d_6-DMSO, and the signal corresponding to the 4α proton that is characteristic for the corresponding keto form is absent. Signals of hydroxyl protons amounting to one proton unit and related to the cis and trans forms of enol structures IVa and IVb are present in the PMR spectrum at 13.5 and 6.5 ppm; as in the case of II and III, the weak-field signal is probably the signal of the proton of a hydroxyl group that forms an intramolecular hydrogen bond with the ester group; this is possible for IV only in the case of a cis orientation of the nitropyridine and phenyl rings. According to the PMR data, the ratio of the cis and trans forms is 5:1 in CCl_4, 3.5:1 in $CDCl_3$, and 1:1 in DMSO.

The reduction of 3-nitro-4-pyridyl dicarbonyl compounds II, III, and IV in the presence of a palladium catalyst does not proceed in the same way as the analogous reaction [2] of 3-nitro-4-pyridyl monocarbonyl derivatives, which under these conditions are smoothly converted to amino derivatives, which undergo cyclization to 2-substituted 6-azaindoles. However, the reduction of 3-nitro-4-pyridyl dicarbonyl compounds II-IV in the presence of palladium stops with the formation of the corresponding two-ring hydroxylamino derivatives — 2,3-disubstituted 1-hydroxy-6-azaindoles (V, VII, and VIII). In the case of III and IV, reductive cyclization gives 1-hydroxyazaindoles in 89-91% yields. In the case of ester II, where, as noted in [2], deacetylation with cleavage of a C—C bond is realized very easily at room temperature, two competitive processes — conversion of II to (3-nitro-4-pyridyl)acetic ester and subsequent reduction to (3-amino-4-pyridyl)acetic ester (VI), and reductive cyclization of II to 1-hydroxy-2-methyl-3-ethoxycarbonyl-6-azaindole (V) — occur. The ratio of products V and VI in this case is 3:5. The further reduction of 1-hydroxy-6-azaindoles V, VII, and VIII to the corresponding 1-deoxy compounds IX-XI in the presence of a palladium catalyst cannot be realized even in the case of repeated addition of fresh portions of palladium and reaction for many hours. A stronger reducing agent — zinc in acetic acid — was required to accomplish this reaction. Reduction with zinc takes place when the reaction mixture is refluxed briefly (for 60 min) and makes it possible to obtain 6-azaindoles IX-XI in 72-78% yields. The structure of V and VII-XI are in good agreement with the results of PMR and mass spectral studies, which are presented in the experimental section. A general characteristic feature of the fragmentation of V and VII-XI under electron impact is elimination of CH_3, CH_2CO, and CH_3CO fragments corresponding to the substituents and, when an ethoxycarbonyl group is present, the loss of C_2H_4, C_2H_5, OC_2H_5, $COOC_2H_4$, and $COOC_2H_5$ fragments. An intense peak of an M — 16 ion, which is formed as a result of the loss of an oxygen atom, is observed in the mass spectra of 1-hydroxyazaindole derivatives (V, VII, and VIII); this is specific for the N—OH bond of heterocyclic systems [3].

EXPERIMENTAL

The PMR spectra of solutions of the compounds in d_6-DMSO* were recorded with a JNM-4H-100 spectrometer with tetramethylsilane as the internal standard. The IR spectra of mineral oil pastes of the compounds were recorded with a Perkin—Elmer 457 spectrometer. The mass spectra were recorded with a Varian MAT-112 spectrometer at an ionizing-electron energy of 70 eV and an emission current of 1.5 μA. The relative intensities of the peaks are given in parentheses.

(3-Nitro-4-pyridyl)acetoacetic Ester (II) [2]. PMR spectrum (CCl_4): 13.5 (1H, s, OH), 9.09 (1H, s, 2-H), 8.69 (1H, d, 6-H), 7.19 (1H, d, 5-H), 4.10 (2H, q, CH_2), 1.93 (3H, s, CH_3—Ac), and 1.14 ppm (3H, t, CH_3—Et).

(3-Nitro-4-pyridyl)acetylacetone (III) [2]. PMR spectrum ($CDCl_3$): 13.5 (1H, s, OH), 9.19 (1H, s, 2-H), 8.85 (1H, d, 6-H), 7.33 (1H, d, 5-H), and 1.85 ppm (6H, s, CH_3—C—C=C—CH_3).

*The use of other solvents is specially stipulated in the text.

1-Hydroxy-2-methyl-3-ethoxycarbonyl-6-azaindole (V). A solution of 5.7 g (22.6 mmole) of keto ester II [2] in 300 ml of ethanol was hydrogenated in the presence of 5.0 g of 6% palladium oxide on carbon at room temperature and an excess hydrogen pressure of 20-30 cm (water column). The catalyst was separated and washed with boiling alcohol, and the combined alcohol solutions were vacuum evaporated. The residue was triturated twice with ether to give 1.8 g (36%) of yellowish crystals of azaindole V with mp 260-261°C (dec., from alcohol). The product was only slightly soluble in alcohols and water and insoluble in ether, heptane, benzene, acetone, ethyl acetate, and chloroform. IR spectrum: 1700 ($COOC_2H_5$) and 1620 cm^{-1} (C=C and C=N). PMR spectrum: 8.71 (1H, s, 7-h), 8.17 (1H, d, 5-H), 7.77 (1H, d, 4-H), 4.29 (2H, q, CH_2), 2.69 (3H, s, CH_3—Ar), 1.43 ppm (3H, t, CH_3—Et). Mass spectrum: m/e 220 (100) M; 204 (27.5) M − O; 203 (8.5) M − OH; 192 (23.5) M − C_2H_4; 191 (12.0) M − C_2H_5; 175 (90) M − OC_2H_5; 159 (81.5) M − O − OC_2H_5. Found: C 59.8; H 5.5; N 12.8%. $C_{11}H_{12}N_2O_3$. Calculated: C 60.0; H 5.5; N 12.7%.

The ether solution obtained after washing the hydrogenation products was evaporated to give 2.45 g (60%) of (3-amino-4-pyridyl)acetic ester (VI) with mp 59-60°C. No melting-point depression was observed for a mixture of this product with an authentic sample of VI, and the IR spectra of the two substances were identical.

2-Methyl-3-ethoxycarbonyl-6-azaindole (IX). A 0.75-g (11.5 mmole) sample of zinc dust was added in small portions to a refluxing solution of 0.25 g (1.2 mmole) of hydroxyazaindole V in 15 ml of acetic acid, and the mixture was refluxed for 1 h. It was filtered, and the filtrate was allowed to stand for 12 h at room temperature. The resulting precipitate was separated, and the solution was vacuum evaporated. The residue was triturated with boiling water, and the mixture was filtered to give 0.18 g (78%) of yellowish crystals of IX with mp 209-210°C (dec., from acetone). The product was quite soluble in alcohols and chloroform, only slightly soluble in benzene, acetone, and ethyl acetate, and insoluble in ether, heptane, and water. IR spectrum: 3200 (NH), 1700 ($COOC_2H_5$), and 1660 cm^{-1} (C=C and C=N). PMR spectrum: 8.72 (1H, s, 7-H), 8.14 (1H, d, 5-H), 7.85 (1H, d, 4-H), 4.28 (2H, q, CH_2), 1.89 (3H, s, 2-CH_3), and 1.37 ppm (3H, t, CH_3—Et). Mass spectrum: m/e 204 (92) M; 176 (23.5) M − C_2H_4; 175 (13.1) M − C_2H_5; 159 (100) M − OC_2H_5; 132 (23.4) M − $CO_2C_2H_4$; 131 (13.8) M − CO_2-C_2H_5. Found: C 64.8; H 5.8; N 13.7%. $C_{11}H_{12}N_2O_2$. Calculated: C 64.7; H 5.9; N 13.7%.

1-Hydroxy-2-methyl-3-acetyl-6-azaindole (VII). A solution of 2.0 g (9 mmole) of III [2] in 200 ml of ethanol was hydrogenated in the presence of 1.0 g of 6% palladium oxide on carbon at room temperature and an excess hydrogen pressure of 20-30 cm (water column). The mixture was worked up as in the synthesis of hydroxyazaindole V to give 1.55 g (91%) of yellowish crystals of azaindole VII with mp 267-268°C (dec., from alcohol). The product was soluble in alcohols and water but insoluble in ether, heptane, benzene, acetone, ethyl acetate, and chloroform. IR spectrum: 1630 ($COCH_3$) and 1460 cm^{-1} (C=C and C=N). PMR spectrum: 8.72 (1H, s, 7-H), 8.25 (1H, d, 5-h), 7.88 (1H, d, 4-H), 2.71 (3H, s, CH_3—Ar), and 2.55 ppm (3H, s, CH_3—Ac). Mass spectrum: m/e 190 (100) M; 175 (85.6) M − CH_3; 174 (23.8) M − O; 173 (14.3) M − OH; 159 (58.1) M − CH_3 − O; 148 (41.0) M − CH_2CO; 147 (14.8) M − CH_3CO. Found: C 62.9; H 5.0; N 14.7%. $C_{10}H_{10}N_2O_2$. Calculated: C 63.2; H 5.3; N 14.7%.

2-Methyl-3-acetyl-6-azaindole (X). A 0.85-g (13 mmole) sample of zinc dust was added in small portions to a refluxing solution of 0.25 g (1.3 mmole) of hydroxyazaindole VII in 15 ml of acetic acid, and the mixture was refluxed for 1 h. It was then cooled to room temperature, and the unchanged zinc and partially precipitated zinc acetate were removed by filtration. The filtrate was vacuum evaporated, and the residue was triturated with boiling water to give 0.18 g (78%) of azaindole X as white crystals with mp 248-249°C (dec., from alcohol). The product was quite soluble in alcohols, only slightly soluble in benzene, acetone, ethyl acetate, and chloroform, and insoluble in ether, heptane, and water. IR spectrum: 1640 ($COCH_3$) and 1610 cm^{-1} (C=C and C=N). PMR spectrum: 8.65 (1H, s, 7-H), 8.18 (1H, d, 5-H), 7.82 (1H, d, 4-H), 2.54 (3H, s, 2-CH_3), and 1.90 ppm (3H, s, $COCH_3$). Mass spectrum: m/e 174 (51.0) M; 159 (100) M − CH_3; 131 (7.9) M − $COCH_3$. Found: C 68.7; H 5.7; N 16.0%. $C_{10}H_{10}N_2O$. Calculated: C 69.0; H 5.7; N 16.1%.

(3-Nitro-4-pyridyl)benzoylacetic Ester (IV). A 19.5-g (0.1 mole) sample of benzoylacetic ester was added gradually with vigorous stirring in a stream of nitrogen to a suspension of 2.4 g (0.1 mole) of sodium hydride in 25 ml of anhydrous DMF, during which the temperature was not allowed to rise above 50°C. When hydrogen evolution was complete, the mixture was maintained under the same conditions for another 20 min, after which 5.4 g (0.028 mole) of the hydrochloride of nitrochloropyridine I was added in portions, and the mixture

was stirred at 20°C for 60 h. Water (25 ml) was then added, and the aqueous mixture was extracted with ether. The aqueous alkaline solution was separated, acidified to pH 8 with acetic acid, and extracted with ether. The ether extract was dried with magnesium sulfate and evaporated to give 8.1 g (93%) of yellow crystals of IV with mp 114-115°C (from cyclohexane). The product was quite soluble in ordinary organic solvents and insoluble in water. IR spectrum: 1640 ($COOC_2H_5$); 1600, 1580, and 1560 (C=C and C=N); 1520 cm^{-1} (NO_2). PMR spectrum: 9.25 and 9.10 (1H, s, 2-H); 8.85 and 8.49 (1H, d, 6-H); 8.02, 7.49, and 7.29 (5H, m, Ph); 7.29 and 7.02 (1H, d, 5-H); 1.18 (2H, q, CH_2); 13.8 and 6.59 (1H, s, OH); 1.18 ppm (3H, t, CH_3). Found: C 61.0; H 4.6; N 8.7%. $C_{16}H_{14}N_2O_5$. Calculated: C 61.1; H 4.5; N 8.9%.

1-Hydroxy-2-phenyl-3-ethoxycarbonyl-6-azaindole (VIII). A solution of 1.5 g (4.8 mmole) of IV in 150 ml of ethanol was hydrogenated in the presence of 1.0 g of 6% palladium oxide on carbon at room temperature and an excess hydrogen pressure of 20-30 cm (water column). Workup as in the synthesis of V gave 1.2 g (89%) of yellowish crystals of VIII with mp 192-193°C (dec., from alcohol). The product was quite soluble in alcohols, only slightly soluble in water, and insoluble in chloroform, ether, acetone, and toluene. IR spectrum: 1710 ($COOC_2H_5$) and 1610 cm^{-1} (C=C and C=N). PMR spectrum: 8.73 (1H, s, 7-H), 8.60 (1H, d, 5-H), 8.10 (1H, d, 4-H), 7.53 (5H, m, Ph), 4.15 (2H, q, CH_2), and 1.20 ppm (3H, t, CH_3). Mass spectrum: m/e 282 (55.3) M; 266 (54.5) M − O; 237 (42.8) M − OC_2H_5; 221 (100) M − O − OC_2H_5; 209 (17.9) M − $CO_2C_2H_5$. Found: C 67.9; H 5.0; N 9.9%. $C_{16}H_{14}N_2O_3$. Calculated: C 68.1; H 5.0; N 9.9%.

2-Phenyl-3-ethoxycarbonyl-6-azaindole (XI). A 1.2-g (18 mmole) sample of zinc dust was added in small portions to a refluxing solution of 0.5 g (1.8 mmole) of hydroxyazaindole VIII in 30 ml of acetic acid, and the mixture was refluxed for 1 h. The zinc was removed by filtration and washed with boiling chloroform. The solutions were combined and evaporated *in vacuo*, and the residue was triturated with boiling water. The mixture was filtered to give 0.34 g (72%) of white crystals of azaindole XI with mp 254-255°C (dec., from alcohol). The product was quite soluble in alcohols and chloroform, only slightly soluble in benzene, acetone, and ethyl acetate, and insoluble in ether, heptane, and water. IR spectrum: 1700 ($COOC_2H_5$) and 1610 cm^{-1} (C=C and C=N). PMR spectrum: 12.9 (1H, s, NH), 8.78 (1H, s, 7-H), 8.28 (1H, d, 5-H), 7.92 (1H, d, 4-H), 7.71 and 7.51 (5H, m, Ph), 4.22 (2H, q, CH_2), and 1.26 ppm, (3H, t, CH_3). Mass spectrum: m/e 266 (52.5) M; 238 (14.0) M − C_2H_4; 237 (7.6) M − C_2H_5; 221 (100) M − OC_2H_5; 194 (52.0) M − $CO_2C_2H_4$; 193 (11.5) M − $CO_2C_2H_5$. Found: C 71.8; H 5.4; N 10.6%. $C_{16}H_{14}N_2O_2$. Calculated: C 72.2; H 5.3; N 10.5%.

LITERATURE CITED

1. V. A. Azimov, V. G. Granik, R. G. Glushkov, and L. N. Yakhontov, Khim. Geterotsikl. Soedin., No. 3, 355 (1978).
2. A. A. Prokopov and L. N. Yakhontov, Khim. Geterotsikl. Soedin., No. 11, 1531 (1977).
3. R. T. Coutts and K. W. Hindmarsh, Org. Mass Spectr., 3, 108 (1970).