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Synthesis of Azinoazole Structural Isomers by Photocyclization

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Abstract—Irradiation of 2-chloro-*N*-(pyridin-2-yl)pyridin-3-amine and *N*-(2-chloropyridin-3-yl)-4,6-dimethylpyrimidin-2-amine in aqueous–alcoholic solution gave new azinoazole derivatives, 6-chlorodipyrido[1,2-*a*:5',4'-*d*]imidazole and 1,3-dimethylpyrido[3',2':4,5]imidazo[1,2-*a*]pyrimidine, respectively.

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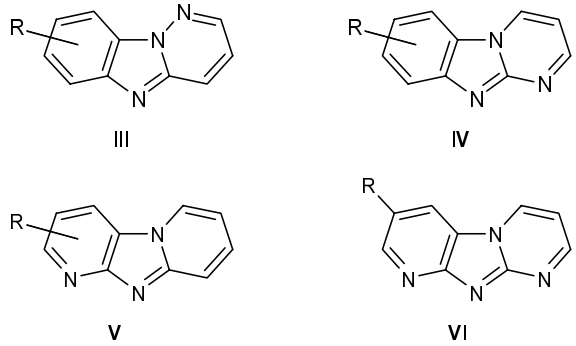
It is known [1] that photolysis of binuclear tetrahalo-substituted pyridine derivatives promotes their intermolecular arylation. For example, irradiation of 2,3,5,6-tetrachloro-4-(pyridin-2-ylsulfanyl)pyridine leads to the formation of 1,3,4-trichlorodipyrido[2,3-*b*:3',4'-*d*]thiophene. The regioselectivity in this process (the reaction occurs at the carbon atom in the heteroring) differs from that observed in the heteroatom photocyclization (at the nitrogen atom) of structurally related compounds like 3,5-dichloro-*N*-(pyridin-2-yl)pyridin-2-amine, which gives rise to tricyclic azinoazoles [2].

Photochemical dehalogenation, arylation, and intramolecular arylation of perchloropyridine, 4-bromotetrachloropyridine, and perchloro-4-(phenylsulfanyl)pyridine involve halogen atom in the β-position with respect to the pyridine nitrogen atom [1]. Judging by the composition of the reaction products, an analogous tendency is typical of heteroatom photocyclization of halogen derivatives of *N*-pyridylpyridinamine [2] and *N*-pyridylpyrimidinamine [3].

In continuation of our studies on the synthesis of new heterocyclic systems, the present communication reports on the composition of products obtained by heteroatom photocyclization of 2-chloro-*N*-(pyridin-2-yl)pyridin-3-amine (**I**) and *N*-(2-chloropyridin-3-yl)-4,6-dimethylpyrimidin-2-amine (**II**) with a view to elucidate the effect of structural factors on the direction of heterocyclization. As shown previously, heteroatom photocyclization of haloarylhetareneamines provides a convenient method for the synthesis of fused polycyclic azinoazoles containing pyridine-type nitrogen atoms in different positions of the azinoazole system, e.g., pyridazino[1,2-*a*]benzimidazole (**III**) [2], pyrimidino[1,2-*a*]benzimidazole (**IV**) [3, 4], dipyrido[1,2-*a*:2',3'-*d*]imidazole (**V**) [2], and pyrido[2',3':4,5]imidazo[1,2-*a*]pyrimidine (**VI**) derivatives [3].



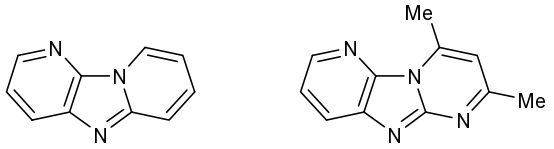
Compounds **I** and **II** were synthesized by a conventional procedure (by analogy with 2,2'-dipyridylamine derivatives [5]) via arylation of 2-chloropyridin-3-amine with 2-bromopyridine and 2-chloro-4,6-dimethylpyrimidine, respectively, in the absence of BaO. The formation of amines **I** and **II** was accompanied by intramolecular cyclization leading to dipyrido[1,2-*a*:3',2'-*d*]imidazole (**VII**) or pyridoimidazopyrimidine **VIII**. In the arylation with 2-bromopyridine, the major product was dipyridoimidazole **VII**. If a stronger arylating agent was used, chlorodimethylpyrimidine, the reaction gave mainly the chlorine replacement product, *N*-pyridylpyrimidineamine **II**. The yield of intramolecular cyclization product **VIII** did not exceed 2.5%.

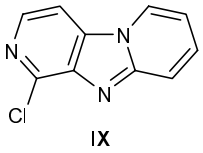
Saint-Ruf et al. [6] reported on the synthesis of azinoazoles like **VII** by cyclization of imidazo[1,2-*a*]pyridin-3-amine in the presence of glycerol and sulfuric acid or by dehydrazination of the corresponding hydrazino derivatives [6].

Compound **I** has four reaction centers capable of being involved in cyclization. Irradiation of amine **I** in

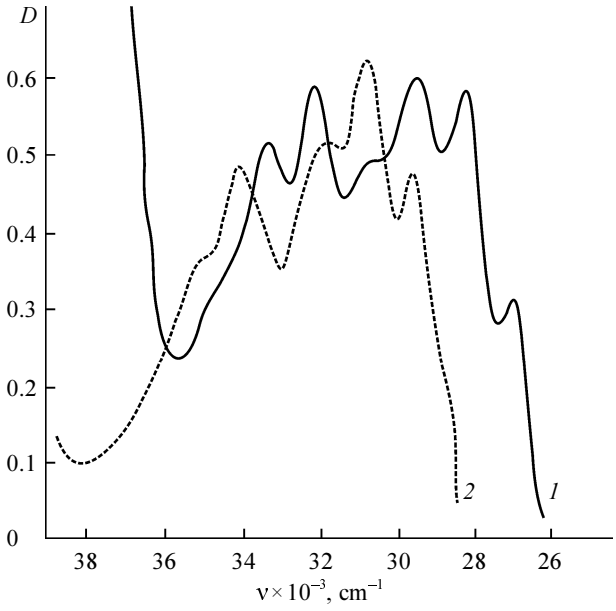
aqueous *tert*-butyl alcohol promoted regioselective process at the heterocyclic nitrogen atom with formation of only one product whose properties differed from those of azinoazole **VII** and regioisomeric triazafluorenes like 1,5,9-triaza-9*H*-fluorene. On the basis of spectral data, the product was assigned the structure of 6-chlorodipyrido[1,2-*a*:5',4'-*d*]imidazole (**IX**).

Photochemical heterocyclization of compound **II** was also regioselective, and it gave the expected product, 1,3-dimethylpyrido[3',2':4,5]imidazo[1,2-*a*]pyrimidine (**VIII**).





The IR spectra of compounds **VII**–**IX** contained a set of absorption bands at 1590–1400 (C=C) and 1640 cm^{-1} (C=N), which are typical of an azinobenzimidazole system [7]. Unlike compounds **V**, no absorption at 1610 cm^{-1} was observed in the IR spectra of **VII** and **IX**. The IR spectra of the latter compounds are similar: the differences include a slight shift and intensity redistribution of the absorption bands; also, additional absorption bands appear in the region 1100–1150 cm^{-1} (ring vibrations) and at 819 and 700 cm^{-1}. The band at 819 cm^{-1} is likely to belong to stretching vibrations of the C–Cl bond in **IX**.



Electronic absorption spectra of dipyrido[1,2-*a*:3',2'-*d*]imidazole in (*1*) 50% aqueous ethanol and (*2*) 1.5 N hydrochloric acid.

The electronic absorption spectra of compounds **VII** and **IX** resemble that described for dipyridoimidazole **V** [2, 8] in the number of bands, their vibrational structure, energies, and absorption coefficients. The effect of the pyridine nitrogen atom on the transitions energies and absorption coefficients is more appreciable for compound **V**. The energy of the low-frequency band changes as follows ($\nu\times10^{-3}$, cm^{-1}): 27.0 (**VII**), 26.6 (**IX**), 26.0 (**V**). The molar absorption coefficient at the low-frequency maximum is ~6000–7000 $l\times mol^{-1}\,cm^{-1}$ for compounds **VII** and **IX** and ~10000 for dipyridoimidazole **V**. Probably, these differences originate from increased contribution of a state with charge transfer from the dihydropyridine fragment to the pyridine ring in **V**, as compared to compounds **VII** and **IX**.

Analogous relations are typical of the UV spectra of isomeric pyridoimidazopyrimidines **VI** and **VIII**. Slight differences are observed in the energies and molar absorption coefficients for the transition to the second singlet state (see [3] and Experimental).

Azinoazoles **VII**–**IX** are fluorophores. The electronic absorption spectra of compounds **V**, **VII**, **IX** and **VI**, **VIII** are similar in neutral medium, but they differ in going to acid solution (see figure); these data may be useful for identification of isomers in the protonated forms. As follows from the absorption spectra in the acidity range from pH ≈ 1 to $H_0 \approx -10$, fused imidazoles **VII** and **IX** give rise to prototropic equilibria like those reported for dipyridoimidazole **V** [9].

The results of this study indicate that photocyclization of chloropyridylhetareneamines having a nucleofugal group in the α-position with respect to the pyridine nitrogen atom is less regioselective than the corresponding reaction of analogous substrates with the same group in the β-position. It should also be noted that heteroatom photocyclization extends the potential in the synthesis of azinoazoles. As applied to the latter, the photochemical procedure can be used to generate fluorophores in solid polymeric solutions [10].

EXPERIMENTAL

The IR spectra were recorded in KBr on a UR-20 spectrophotometer. The UV spectra were measured on an SF-20 spectrophotometer in propan-2-ol. The

^{1}H NMR spectra were obtained on Tesla BS-587 (100 MHz) and Bruker AM-500 (500 MHz) instruments. The melting points were determined in a capillary and were not corrected.

Hetarylation of 2-chloropyridin-3-amine with 2-bromopyridine. A mixture of 0.01 mol of 2-chloropyridin-3-amine and 0.012 mol of 2-bromopyridine was heated for 5 h at 150–160°C. The mixture solidified and was dissolved in water, neutralized with an aqueous solution of sodium carbonate, and extracted with ethyl acetate. The extract was dried over Na_2SO_4 and evaporated, and the residue was subjected to column chromatography on Al_2O_3 using petroleum ether (bp 40–60°C)–chloroform (8 : 2 and 1 : 1) as eluent. Removal of the solvent gave amine **I**. The subsequent elution with chloroform gave a luminescent fraction containing compound **VII**. Amine **I** was purified from an impurity of azinoazole **VII** by recrystallization from petroleum ether.

2-Chloro-*N*-(pyridin-2-yl)pyridin-3-amine (I). Yield 0.4 g (31%), mp 105–107°C (from petroleum ether). IR spectrum, ν, cm^{-1}: 3420, 1620 s, 1520 s, 1495 s, 1430 s, 1350, 1370, 1250, 1160, 1080, 820 s, 770 s, 730 w. UV spectrum, $\nu\times10^{-3}$, cm^{-1} ($\varepsilon\times10^{-3}$, l mol^{-1} cm^{-1}): 36.5 (14.8), 32.8 (11.8). ^{1}H NMR spectrum (CCl_4), δ, ppm: 6.80 m (2H, 4'-H, 5'-H), 7.20 m (2H, 3'-H, 5-H), 7.40 m (2H, 6-H, NH), 8.16 d (1H, 6'-H, J = 5 Hz), 8.80 d (1H, 4-H, J = 8 Hz).

Dipyrido[1,2-*a*:3',2'-*d*]imidazole (VII). mp 129–130°C (from petroleum ether) [6]. Yield 0.6 g (46%). IR spectrum, ν, cm^{-1}: 1640 s, 1580, 1500 s, 1450, 1405 s, 1350, 1280, 1150, 805 s, 760 s, 730 s. UV spectrum, $\nu\times10^{-3}$, cm^{-1} ($\varepsilon\times10^{-3}$, l mol^{-1} cm^{-1}): 42.4 (32.0), 40.8 (16.1), 38.5 (10.8), 37.0 sh, 34.5 sh, 33.3 (5.5), 32.2 (5.8), 30.8 sh, 29.4 (6.6), 28.0 (6.3), 27.0 (4.1).

Hetarylation of 2-chloropyridin-3-amine with 2-chloro-4,6-dimethylpyrimidine. A mixture of 0.01 mol of 2-chloropyridin-3-amine and 0.012 mol of 2-chloro-4,6-dimethylpyrimidine was heated for 4 h at 130–140°C. The mixture was dissolved in water, neutralized with an aqueous solution of sodium carbonate, and cooled, and the precipitate was filtered off. Yield of compound **II** 2 g (85%). According to the TLC data (eluent chloroform–petroleum ether, 1 : 1) and UV spectrum (*i*-PrOH), the product contained 2.5% of compound **VIII**. A 1-g portion of the product was subjected to column chromatography on Al_2O_3 using hexane–chloroform (1 : 1) as eluent. After removal of the solvent, the residue was recrystallized from propan-2-ol. Yield of **II** 0.75 g.

***N*-(2-Chloropyridin-3-yl)-4,6-dimethylpyrimidin-2-amine (II).** mp 103–105°C (from propan-2-ol). IR spectrum, ν, cm^{-1}: 3440, 1610 s, 1550–1580 v.s, 1470 s, 1350 s, 1090, 1060, 860, 815, 780. UV spectrum, $\nu\times10^{-3}$, cm^{-1} ($\varepsilon\times10^{-3}$, l mol^{-1} cm^{-1}): 37.04 (22.4), 34.5 sh (12.7). ^{1}H NMR spectrum (DMF-d_7), δ, ppm: 2.37 s (6H, $2CH_3$), 6.65 s (1H, 5-H), 7.34 d (1H, 5'-H, J = 8 Hz), 7.77 s (1H, NH), 7.96 m (1H, 6'-H), 8.84 d (1H, 4'-H, J = 8 Hz). Found, %: C 53.11; H 4.36; N 22.43. $C_{11}H_{11}N_4Cl\cdot0.5H_2O$. Calculated, %: C 54.21; H 4.52; N 22.99.

Photolysis of compounds I and II. The reactions were carried out in a 0.6-l reactor under irradiation with full spectrum of a DRL-400 mercury lamp (400 W) through a quartz condenser cooled with tap water. A mixture of 0.003 mol of amine **I** or **II** in 500 ml of 80% (by volume) aqueous *tert*-butyl alcohol was irradiated over a period of 5 h under stirring with a stream of nitrogen. When the photolysis was complete, the solvent was distilled off on a rotary evaporator, the aqueous residue was made alkaline (pH 8) and extracted with ethyl acetate, and the extract was dried and evaporated. The residue was subjected to column chromatography on Al_2O_3 using first hexane–chloroform (1 : 1) and then chloroform as eluent. After removal of the solvent, the product was additionally purified by recrystallization.

6-Chlorodipyrido[1,2-*a*:5',4'-*d*]imidazole (IX). Yield 0.4 g (65%), mp 185–187°C (from acetonitrile). IR spectrum, ν, cm^{-1}: 3080, 2920, 1640, 1570 s 1495 s, 1440, 1400, 1350, 1250, 1135, 1115, 1100, 1040, 860, 819 s, 750 s, 730 s, 700 s. UV spectrum, $\nu\times10^{-3}$, cm^{-1} ($\varepsilon\times10^{-3}$, l mol^{-1} cm^{-1}): 41.5 (21.7), 40.2 (20.1), 38.2 (12.0), 36.4 sh, 34.5 sh, 33.0 (5.5), 31.9 (6.2), 30.4 (5.4), 29.2 (6.2), 27.85 (6.7), 26.6 (4.4). ^{1}H NMR spectrum (DMF-d_7), δ, ppm: 7.05 t.d (1H, 2-H, J = 7, 1 Hz), 7.52 d (1H, 9-H, J = 8 Hz), 7.61 m (1H, 3-H), 7.65 m (1H, 4-H), 8.19 d (1H, 8-H, J = 8 Hz), 8.83 d (1H, 1-H, J = 7 Hz). Found, %: C 58.95; H 2.94; N 20.69. $C_{10}H_6N_3Cl$. Calculated, %: C 59.11; H 2.95; N 20.69.

1,3-Dimethylpyrido[3',2':4,5]imidazo[1,2-*a*]-pyrimidine (VIII). Yield 0.45 g (76%), mp 225°C (from acetonitrile). IR spectrum, ν, cm^{-1}: 3080, 2950, 1650 s, 1610 w, 1540 s, 1460 s, 1400 s, 1350 w, 1320 w, 1200, 1120, 1080, 1050, 890, 850, 810, 790 s, 740. UV spectrum, $\nu\times10^{-3}$, cm^{-1} ($\varepsilon\times10^{-3}$, l mol^{-1} cm^{-1}): 41.7 (27.4), 37.7 (10.2), 33.3 (5.5), 32.1 (6.4), 28.6 (4.4). ^{1}H NMR spectrum (DMF-d_7), δ, ppm: 2.63 s (CH_3), 3.18 s (CH_3), 6.82 s (1H, 2-H), 7.51 d (1H, 7-H, J =

8 Hz), 8.14 d (1H, 6-H, J = 8 Hz), 8.40 d (1H, 8-H, J = 5 Hz). Found, %: C 66.40; H 4.70; N 28.50. $C_{11}H_{10}N_4$. Calculated, %: C 66.65; H 5.08; N 28.26.

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