(9-(PYRIDAZINYL-4)-4-AZAFLUORENES AND SPIRO COMPOUNDS WITH 4-AZAFLUORENE AND INDENO[1,2-*c*]PYRIDAZINE (4H-5,6-DIHYDRO-1,2-DIAZEPINE) FRAGMENTS

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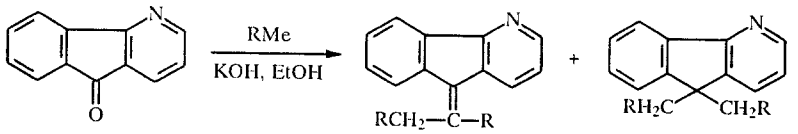
9-(3,6-Diphenylpyridazinyl-4)-4-azafluorene has been synthesized, and its conversions at the C^9 position have been studied. From its C^9-hydroxy derivative, 3'-phenylspiro-[4-azafluorene-9,5'-indeno[1,2-c]pyridazine] has been obtained. From 9-(1,2-dibenzoylethylidene-4-azafluorene, 3,7-diphenylspiro-[4H-5,6-dihydro-1,2-diazepine-5,9'-4'-azafluorene] has been synthesized.

Previously, by the condensation of 4-azafluorenone (I) with acetophenone, we had obtained 9,9-diphenacyl-4-azafluorene (II) and 9-(1,2-dibenzoylethylidene)-4-azafluorene (III) in approximately equal quantities with a total yield of 70% [1].



I II III

II, III R = COPh

We used the diketones II and III in syntheses of previously unknown heterocyclic compounds containing the 4-azafluorene and pyridazine fragments. Upon interaction of compound II with hydrazine, we obtained a quantitative yield of 9-(3,6-diphenylpyridazinyl-4)-azafluorene (IV). Initially formed, apparently, is the cyclic azine 9-[3,6-diphenylpyridazylidene-4(5H)]-4-azafluorene, which is isomerized to compound IV with an aromatic pyridazine ring. From an examination of the Dreiding molecular model of the substituted azafluorene IV, it follows that the pyridazine ring deviates from the plane of the azafluorene fragment and that free rotation around the C^9—$C^{4'}$ bond is hindered, by the phenyl substituent in the C^3 position [2]. This is confirmed by the PMR spectrum of compound IV: At room temperature, the signal of the 5'-H proton (singlet, 7.02 ppm) is broadened. When the temperature is increased to 65°C, this signal is narrowed as a result of lowering of the barrier to rotation and elimination of the retardation of the pyridazine ring rotation.

In the mass spectrum of the pyridazinyl-substituted azafluorene IV, the maximum-intensity peak is that of the molecular ion with *m/z* 397 (100%). Also present are peaks of fragment ions corresponding to the pyridazine part of the molecule with *m/z* 231 (4.8%) and to the azafluorene part with *m/z* 166 (14.5%).

The molecule of the azafluorene IV contains two heterocyclic fragments, i.e., the pyridine fragment and the pyridazine fragment; an attempt was made to obtain the quaternary salts of this heterocyclic base, it being considered that diquaternary salts of pyridazine are not formed [3]. Upon the interaction of compound IV with excess methyl iodide, the monoiodomethylate V was obtained in the form of a dark-yellow, high-melting crystalline substance. Its PMR spectrum contained signals from protons of two methyl groups at 4.00 and 4.37 ppm, equal in intensity. Quite probably, in DMSO solution, an equilibrium

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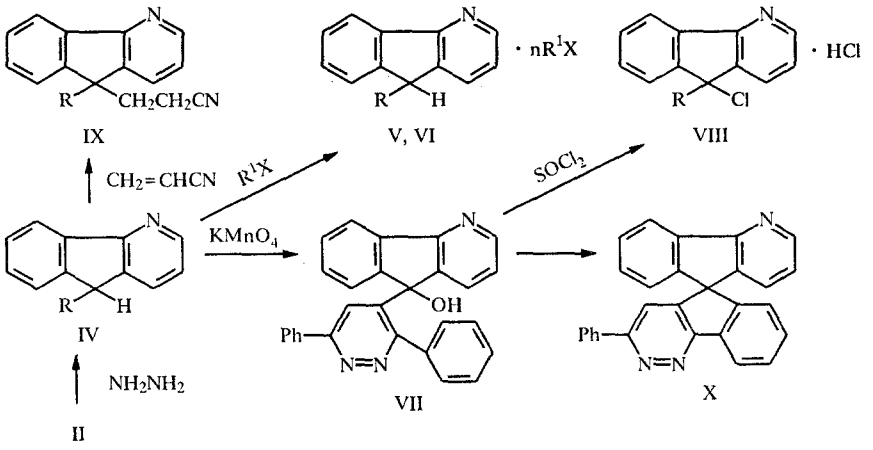
is established between the salt in which the nitrogen atom of the azafluorene fragment is quaternized and the salt with the quaternary nitrogen atom of the pyridazine ring. Upon interaction of compound IV with the more active halogen derivative bromacetophenone, we obtained the diquaternary salt VI.

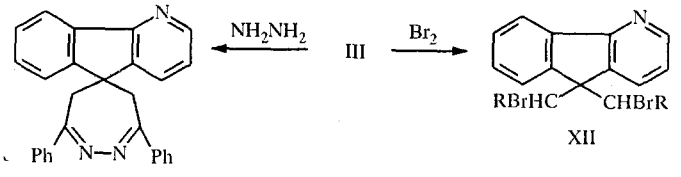


IV – VI,VIII,IX R= 3,6-diphenylpyridazinyl-4; V) n=1, R^1X=MeI; VI) n=2, R^1X=$PhCOCH_2Br$

Upon oxidation of compound IV by potassium permanganate in acetone, we obtained a 65% yield of 9-hydroxy-9-(3,6-diphenylpyridazinyl-4)-4-azafluorene (VII) — a crystalline substance. In its IR spectrum (in chloroform), the stretching vibrations in the 3675 cm^{-1} region correspond to free hydroxyl groups, and those in the 3400—3590 cm^{-1} region, to associated hydroxyl groups. In the PMR spectrum of the alcohol VII, the signal of the proton of the OH group is manifested at 3.75 ppm in the form of a broadened singlet. In the mass spectrum of compound VII, the most intense peak is that of the molecular ion with *m/z* 413. Treatment of the alcohol VII with thionyl chloride gave the hydrochloride of 9-chloro-9-(3,6-diphenylpyridazinyl-4)-4-azafluorene.

Availability of the hydroxyazafluorene VII enabled us to synthesize a polynuclear condensed system with the spirane structure. By intramolecular cyclocondensation under the influence of polyphosphoric acid at 200°C, we obtained from compound VII with a 65% yield 3′-phenylspiro-[4-azafluorene-9,5′-indeno[1,2-*c*]pyridazine] (X). Its mass spectrum contains a peak of the molecular ion with *m/z* 395. In the PMR spectrum we observe signals of only aromatic protons at 6.79-8.65 ppm; in the ^{13}C NMR spectrum, the signal of the C^9 carbon atom is found at 61.57 ppm. Upon cyanoethylation of compound IV in the presence of Rodionov catalyst (dimethylethylphenylammonium ethoxide), we obtained a quantitative yield of 9-(β-cyanoethyl)-9-(3,6-diphenylpyridazinyl-4′)-4-azafluorene (IX). The PMR and mass spectra confirm the structure shown for compound IX (see Experimental).

We used the diketone III, which was formed by the condensation of 4-azafluorene (I) with acetophenone, in the synthesis of a new spiroheterocyclic system with an azafluorene fragment and a partially hydrogenated diazepine fragment:



By interaction of the diketone III with hydrazine, we obtained a 58% yield of 3,6-diphenylspiro-[4H-5,6-dihydro-1,2-diazepine-5,9′-4′-azafluorene] (XI). Its PMR spectrum contains a signal of methylene groups at 3.05 ppm in the form of a broad singlet, related to the presence of conformers of the seven-membered ring; when the temperature is raised to 60°C, the signal of the CH_2 group protons becomes narrower. In the high-resolution PMR spectrum (400 MHz), the signals of the CH_2 group protons appear in the form of two broadened singlets at 2.65 and 3.31 ppm, with a 2H intensity each. In the ^{13}C PMR spectrum, the signal of the carbon atom in position 9 is located at 61.83 ppm. The mass spectrum of the spiro compound XI contains a peak of the molecular ion with *m/z* 399.

Upon bromination of the diphenacyl derivative III, we obtained 9,9-bis(α-bromophenacyl)-4-azafluorene (XII). The signals of methine protons in the PMR spectrum of compound XII at 6.58 and 6.74 ppm indicate that this compound, which contains two asymmetric carbon atoms, exists in the form of two racemates.

EXPERIMENTAL

The mass spectra were obtained in MKh-1303 and Kratos MS 25 RF-DS 90 instruments. The UV spectrum was taken in a Specord UV-Vis instrument (in ethanol). The IR spectra were taken in a Specord IR-75 instrument (in chloroform solution) and a UR-20 instrument (in tablets with KBr). The ^1H and ^{13}C NMR spectra of solutions in $CDCl_3$ or DMSO-d_6 (internal standard TMS) were obtained in Bruker WP-80 and Varian VSP-400 spectrometers, respectively, for the protons at 80 and 400 MHz and for the ^{13}C atoms at 20 and 100 MHz. If necessary, the spectra were taken at elevated temperatures; the course of the reaction and the purity of the compounds that were obtained were monitored by TLC on Silufol UV-254 plates, eluent heptane—ethyl acetate 1:2, development by iodine vapor.

Elemental analyses for C, H, and N were in agreement with the calculated values.

9-(3,6-Diphenylpyridazinyl-4-4-(azafluorene (IV, $C_{28}H_{19}N_3$). To a solution of 0.2 g (0.5 mmole) of compound II in 45 ml of absolute ethanol, 2 ml of hydrazine was added. The yellow color of the solution rapidly turned to a raspberry color, and then in 10 min again to yellow. The mixture was heated for 1.5 h at 55°C, and about 30 ml of the alcohol was driven off. The yellow crystals that precipitated were filtered off and washed with alcohol and then with ether. Obtained 0.19 g (99%) of compound IV, mp 230-232°C. UV spectrum, λ_{max} (log ε): 216 (5.08); 264 (4.74); 314 (444). PMR spectrum ($CDCl_3$), δ, ppm: 8.62 (3-H, ddd, J_{32} = 4.9 Hz, J_{31} = 1.6 Hz, J_{39} = 0.8 Hz); 7.14 (2-H, dd, J_{23} = 4.9 Hz, J_{21} = 7.7 Hz); 8.11 (5-H, m), 7.89 (8-H, m), 7.02 (5′-H, brs); 5.5 (9-H, brs).

From the hydrochloride of compound II and hydrazine hydrate, compound IV was obtained analogously with a 44% yield.

Iodomethylate of V ($C_{29}H_{22}IN_3$) and Diphenacylbromide of 9-(3,6-Diphenylpyridazinyl-4)-4-azafluorene VI ($C_{44}H_{33}Br_2N_3O_2$). The salts of V and VI were obtained with respective yields of 90% and 45% from compound IV and a fivefold excess of the halogen derivative in acetone, by holding the reaction mass for 3 days or 1 day, respectively. The salts of V and VI are colorless crystals, mp 220-222°C and 203-205°C, respectively. PMR spectrum (DMSO-d_6), δ, ppm: 4.00 (CH_3); 4.37 (CH_3); 6.23 (9-H).

9-Hydroxy-9-(3,6-diphenylpyridazinyl-4)-4-azafluorene (VII, $C_{28}H_{19}N_3O$). To a boiling solution of 0.2 g (0.5 mmole) of compound IV in acetone, 0.053 g (0.33 mmole) of potassium permanganate was added in portions over the course of 2.5 h. The precipitated magnesium dioxide was filtered off and washed repeatedly with hot acetone. After distilling off the acetone from the filtrate and washings, the residue was crystallized in benzene. Obtained 0.13 g (65%) of compound VII, colorless crystals, mp 244-247°C. Mass spectrum, *m/z*, %: 413 (M^+, 100), 395 (46), 367 (15), 366 (23), 182 (67), 153 (23), 102 (79.3).

Hydrochloride of 9-Chloro-9-(3,6-diphenylpyridazinyl-4)azafluorene (VIII, $C_{28}H_{18}ClN_3 \cdot HCl$). To a solution of 0.57 g (1.4 mmole) of compound VII in 40 ml of benzene, 4 ml (34 mmoles) of thionyl chloride was added gradually. The residue after vacuum-evaporating the benzene and thionyl chloride (without heating) was washed with ether. Obtained 0.33 g (58%) of compound VIII, colorless crystals, mp 263-265°C. Mass spectrum, *m/z*, %: 431 (M^+ 42/12), 395 (80), 394 (76).

9-(β-Cyanoethyl-9-(3,6-diphenylpyridazinyl-4)-4-azafluorene (IX, $C_{31}H_{22}N_4$). To a solution of 0.8 g (2 mmoles) of compound IV in 10 ml of benzene, 0.8 g (15 mmoles) of acrylonitrile and 0.2 ml of a freshly prepared alcohol solution of Rodionov catalyst were added. The color of the solution changed to red. The mixture was heated for 2 h at 50°C. Then 50 ml of water was added, and the benzene layer was separated and dried with magnesium sulfate. Part of the benzene was driven off, and the precipitated crystals were separated. Obtained 0.73 g (80%) of compound IX, mp 260-269°C (decomp.). IR spectrum: 2250 cm^{-1} (CN); PMR spectrum ($CDCl_3$), δ, ppm: 1.37 (2H, t, J = 7 Hz, α-CH_2); 2.90 (2H, t, J = 7 Hz, β-CH_2). M^+ 450.

3′-Phenylspiro-[4-azafluorene-9,5′-indeno[1,2-*c*]pyridazine] (X, $C_{28}H_{17}N_3$). A mixture of 0.4 g (0.97 mmole) of the alcohol VII and 6 g of polyphosphoric acid was heated for 10 h at 200°C. After cooling, 100 ml of water was added. The reaction products were extracted repeatedly with ether and dried with magnesium sulfate. From the ether extract, recovered 0.25 g (63%) of the spiro compound X, mp 260-263°C. PMR spectrum ($CDCl_3$, δ, ppm: 8.65 (3-H); 7.1 (1-H); 7.05 (2-H); J_{23} = 4.6 Hz, J_{31} = 1.8 Hz, J_{12} = 7.7 Hz. M^+ 395.

3,7-Diphenylspiro-[4H-5,6-dihydro-1,2-pyridazine-5,9′-4′-azafluorene] (XI, $C_{28}H_{21}N_3$). A 1-g quantity (2.48 mmoles) of compound III was dissolved in 100 ml of absolute ethanol, after which 10 ml of hydrazine was added. The mixture was refluxed for 3 h and allowed to stand for 12 h at room temperature. The precipitated crystals were filtered off (0.28 g); about 75 ml of the alcohol was distilled from the mother solution, and the crystals were separated (0.3 g). Obtained 0.58 g (58%) of the pyridazine XI, mp 204-207°C (from a 2:1 heptane—ethyl acetate mixture). PMR spectrum ($CDCl_3$), δ, ppm:

8.60 (1H, d, 3′-H); 8.01 (1H, d, 5′-H); 7.01 (1H, d, 2′-H); 3.05 (4H, brs, CH_2); 6.95-8.00 (m, other aromatic protons). M] + 399.

9,9-Bis(α-bromophenacyl)-4-azafluorene (XII, $C_{28}H_{19}Br_2NO_2$). To a colorless solution of 2 g (5 mmoles) of compound III in 50 ml of chloroform, a solution of 3.2 g (20 mmoles) of bromine in 20 ml of chloroform was added over the course of 40 min. The mixture was refluxed for 6 h, after which it was treated with an aqueous ammonia solution (1:1) to an alkaline reaction. The chloroform layer was separated off, and the aqueous layer was extracted with chloroform. The extract was dried with magnesium sulfate. After driving off the chloroform, the residue was chromatographed in a column (silica gel, h = 55 cm, d = 1.2 cm; eluent petroleum ether, then 1:1 chloroform—heptane). Recovered 1.82 g (64%) of compound XII, mp 157-160°C (from heptane). Mass spectrum, *m/z*, %: 559/560/562 ($M^{]+}$ 0.4/0.5/0.4), 479/481 (0.07/0.07), 400 (2), 105 (100), 77 (35).

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