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SYNTHESIS OF 4-AZAFLUORENES SUBSTITUTED AT THE POSITION 9 BASED ON 9,9-DIPHENACYL(PHENACYLIDENE)-4-AZAFLUORENE

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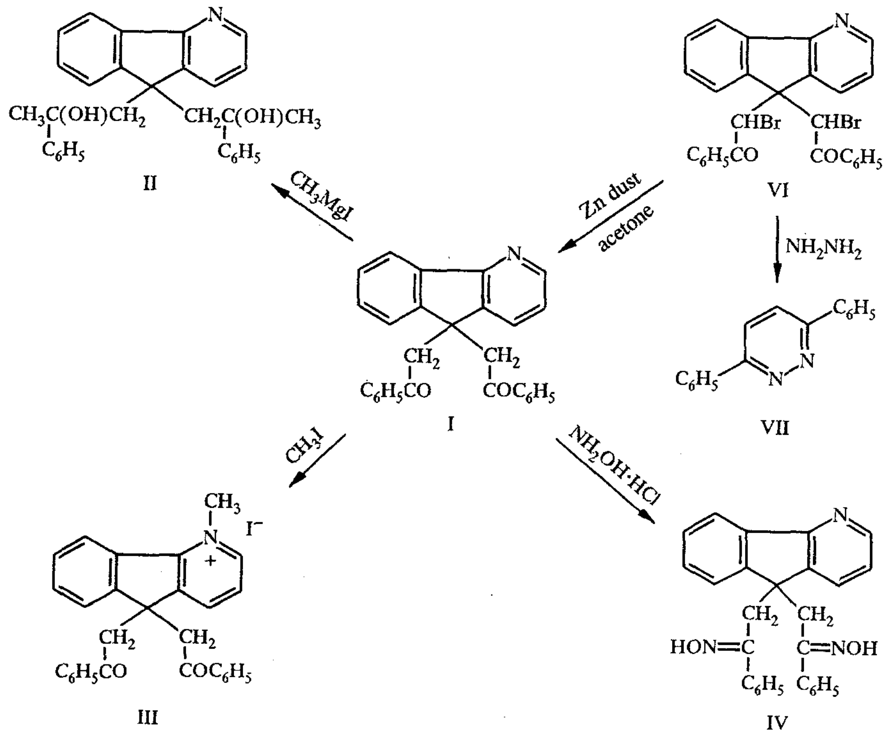
Functionally substituted 4-azafluorenes were synthesized by the modification of the carbonyl groups of 9,9-diphenacyl-4-azafluorene. The usual reductive cleavage of 9,9-di(α-bromophenacyl)-4-azafluorene by hydrazine, leading to the formation of diphenylpyridazine, was found. A method for the oxidation of methiodides of 9-substituted 4-azafluorenes to the corresponding indenopyridones was developed.

We utilized the previously isolated 9,9-diphenacyl-4-azafluorene (I) [1] for the synthesis of functionally substituted azafluorenes. The 9,9-di(2-hydroxy-2-phenylpropyl)-4-azafluorene (II) was obtained with a low yield from the ketone (I) and methylmagnesium iodide. For the characterization of the compound (I), it was converted to the methiodide (III), the dioxime (IV), and the dioxime trimethiodide (V). An attempt, based on 9,9-di(α-bromophenacyl)-4-azafluorene (VI) [2], was made to accomplish the synthesis of spiro compounds with the cyclopropane, pyrazolidine, and 4-azafluorene fragments. The formation of the cyclopropane ring does not occur when the compound (VI) is heated with zinc dust in acetone. As a result of the reduction, the dibromide (VI) is converted to the diphenacyl derivative (I) with the yield of 45%.



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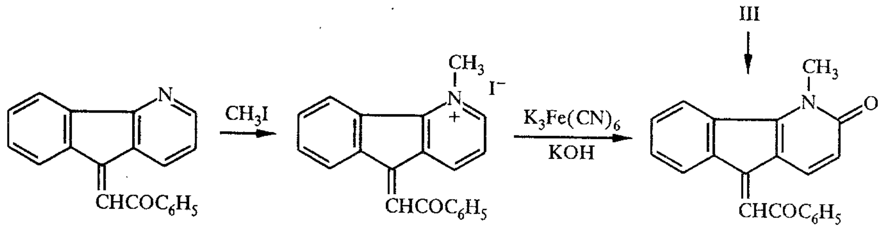
The reaction of the dibromide (VI) with hydrazine proceeds unusually. The prolonged heating in ethanol led to the isolation of 3,6-diphenylpyridazine (VII) with the yield of 48%. The reductive cleavage of the compound (VI) probably occurs on the exposure to hydrazine. Bromophenacyl radicals, the recombination of which leads to di(α-bromophenacyl), are thereby formed. The last is reduced by hydrazine to 1-bromo-1,2-dibenzoylethane; its condensation with hydrazine should lead to 4-bromo-3,6-diphenyl-4,6-dihydropyridazine, and the subsequent aromatization (dehydrobromination) gives 3,6-diphenylpyridazine (VII). It should be noted that the first syntheses of this substituted pyridazine utilized condensation reactions of γ-bromo(chloro)diphenacyl with hydrazine [3].

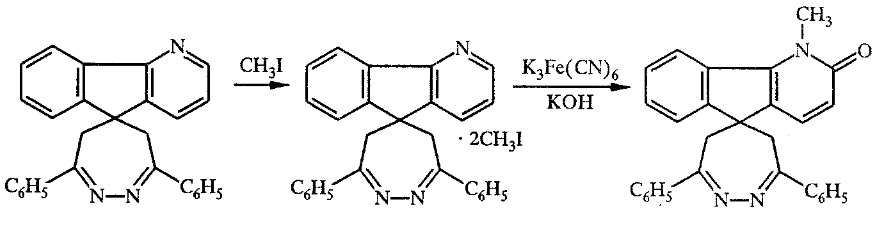
We obtained previously unknown compounds containing the condensed system of indene and α-pyridone on the basis of 4-azafluorene [4]. The synthesis of analogous compounds from derivatives of 4-azafluorene — the diphenacyl derivative (I), 9-phenacyliden-4-azafluorene (VIII) [5], and 3,7-diphenylspiro[4-azafluorene-9,5-(5H-4,6-dihydro-1,2-diazepine)] (IX) — is a development of this route [2].



VIII X XI

The 4-methyl-9-phenacyliden-4-azafluorenium iodide (X) was obtained in quantitative yield from the base (VIII), and was oxidized by potassium hexacyanoferrate in aqueous potassium hydroxide solution. The 4-methyl-3-oxo-9-phenacylidene-3,4-dihydro-4-azafluorene (XI) was obtained in a moderate yield in the form of dark red crystals. The same compound (XI) was obtained with the yield of 58% under analogous conditions from the quaternary salt (III). The formation of compound (XI) from the salt of the diphenacyl derivative (III) probably proceeds as a result of the "reverse" Michael reaction. In the synthesis of compound (XI) from the phenacylidene derivative (VIII), the mixture of its E- and Z-isomers was utilized. The 4-methyl-3-oxo-9-phenacylidene-3,4-dihydro-4-azafluorene (XI), isolated in both experiments, has the Z-configuration. In its PMR spectrum, the signal of the proton at the position 1 is noticeably shifted to low field: 8.45 ppm, $J_{1,2}$ = 9.5 Hz. This is determined by the deshielding influence of the benzoyl group situated in the Z-position relative to the pyridone ring. The high spin–spin coupling constant is most probably associated with the neighboring carbonyl group at the position 3. The signal at 6.50 ppm ($J_{2,1}$ = 9.5 Hz) pertains to the 2-H proton, and the signal at 4.05 ppm pertains to protons of the $N-CH_3$ group.

The heating of compound (IX) with excess methyl iodide in chloroform gave its quaternary salt both at the nitrogen of the azafluorene ring, and at the nitrogen of the dihydrodiazepine fragment — 1,4-dimethyl-3,7-diphenylspiro[4-azafluorenium-9,5-(5H-4,6-dihydro-1,2-diazepinium)]diiodide (XII). The treatment of the salt (XII) with potassium hexacyanoferrate afforded a low yield of 1-methyl-2-oxo-3,7-diphenylspiro[indeno[2,3-e]pyridine-5,5-(5H-4,6-dihydro-1,2-diazepine)] (XIII).



IX XII XIII

In the PMR spectrum of compound (XIII), the multiplicity and position of the signals of the α-pyridone fragment are analogous to those in the spectrum of compound (XI). The methylene protons of the diazepine ring appear in the form of a wide singlet at 3.00 ppm. The mass spectrum of the spiran (XIII) contains the peak of the molecular ion with 429,* corresponding to its molecular mass. The main direction of decomposition is associated with the cleavage of the diazepine ring. The release of the nitrogen molecule leads to the fragment ion 401. The peak of the ion 209, which probably has the structure of the cation-radical of 1-methyl-2-oxo-5-methylenindenopyridine, has the maximal intensity. Further, this ion loses CO and hydrogen sequentially with the formation of the ions 181 and 180 correspondingly. Compound (XIII) is also characterized by the elimination of a molecule of benzonitrile with the formation of the $[M-C_6H_5C\equiv N]^+$ ion 326, the intensity of which equals the intensity of the M^+ ion.

EXPERIMENTAL

The mass spectra were obtained on the HP 5972 A Hewlett Packard instrument. The IR spectra were obtained on the UR-20 instrument using KBr tablets. The PMR spectra of the solutions in $CDCl_3$ (the internal standard TMS) were obtained on the Bruker WP-80 spectrometer of the firm Varian at 80 MHz. The course of the reactions and the purity of the compounds obtained were monitored by the method of TLC on plates of Silufol UV-254; the eluent was the 1:2 mixture of heptane–ethyl acetate, and development was effected with iodine vapor.

The data of the elemental analysis for C, H, and N correspond with the calculated data.

9,9-Di(2-hydroxy-2-phenylpropyl)-4-azafluorene (II) ($C_{30}H_{29}NO_2$). To methylmagnesium iodide, obtained from 0.96 g (40 mmoles) of magnesium and 2.4 ml (39 mmoles) of methyl iodide in 15 ml of ether, is added the solution of 0.9 g (2.23 mmoles) of the diketone (I) in 50 ml of THF. The mixture is boiled with stirring for 2 h. Water (50 ml) is added. The mixture is extracted with ether and dried with magnesium sulfate. The ether is evaporated prior to the chromatography on Al_2O_3 using the 2:1 mixture of ethyl acetate–heptane as the eluent. The diol (II) is isolated with the yield of 0.1 g (10%) as pale yellow crystals having the mp 128-130°C (the 2:1 mixture of ethyl acetate–heptane). The IR spectrum is characterized at 3450 cm^{-1} (OH). The M^+ 435.

4-Methyl-9,9-diphenacyl-4-azafluorenium Iodide (III) ($C_{29}H_{24}INO_2$). To the solution of 3 g (7.4 mmoles) of compound (I) in 70 ml of chloroform are added 10 ml (4.3 g, 0.03 mmole) of methyl iodide. The reaction mixture is boiled for 20 h. The precipitated yellow crystals are filtered off and washed with ether and then acetone. The yield of 3.09 g (76%) of the salt (III), having the mp 224-226°C, is obtained.

9,9-Di(2-hydroximino-2-phenylethyl)-4-azafluorene (IV) ($C_{28}H_{23}N_3O_2$). The solution of 0.5 g (1.24 mmoles) of compound (I) and 0.5 g (7.2 mmoles) of hydroxylamine hydrochloride in 5 ml of the 1:1 mixture of pyridine and abs. ether is boiled for 3 h. The solvents are then distilled off, and water is added to the residue. The precipitated residue is filtered off, washed with distilled water, and dried over phosphorus oxide. The yield of 0.36 g (67%) of the dioxime (IV), which has white crystals with the mp 178-180°C (from ethanol), is obtained. The IR spectrum is as follows: 3280 cm^{-1} (OH), 1640 cm^{-1} (C=N), and 955 and 935 cm^{-1} (N–O). The M^+ is 433.

9,9-Diphenacyl-4-azafluorene Dioxime Trimethiodide (V) ($C_{31}H_{32}I_3N_3O_2$). To the solution of 0.23 g (0.53 mmole) of the dioxime (IV) in 5 ml of dry acetone is added 1 ml of methyl iodide. The reaction mixture is left at room temperature for 20 h, and is then boiled for 3 h. The precipitated crystals are filtered off and washed with abs. ether. The yield of 0.27 g (63%) of the trimethiodide (V), as yellow crystals with the mp 200-203°C, is obtained.

3,6-Diphenylpyridazine (VII) ($C_{16}H_{12}N_2$). To the solution of 0.5 g (0.89 mmole) of the dibromide (VI) in 60 ml of abs. ethanol are added 6 ml of hydrazine. The mixture is heated for 10 h at 55°C. The alcohol is distilled off to ~2/3 of the volume. The precipitated white crystals are filtered off and washed with hexane and ethyl acetate. Compound (VII) is obtained with the yield of 0.1 g (48%); it has the mp 215-218°C. According to the literature data [3], the mp is 221-222°C. The IR spectrum is as follows: 3070 cm^{-1} (CH), 1550 and 1560 cm^{-1} (C=C), 750 cm^{-1}, 740 cm^{-1}, and 690 cm^{-1} (CH arom.). The PMR spectrum is as follows: 7.45-8.25 ppm (m, arom. protons). The mass spectrum, given as the m/z (intensity in %), is as follows: 232 (60.5) M^+, 204 (14) $[M-N_2]^+$, and 102 (100) $[C_6H_5C\equiv CH]^+$.

4-Methyl-9-phenacyliden-4-azafluorenium Iodide (X) ($C_{21}H_{16}INO$). To the solution of 0.78 g (2.76 mmoles) of compound (VIII) in 30 ml of chloroform are added 4 ml (0.57 mmole) of methyl iodide. The mixture is boiled for 4 h. The

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*Here and subsequently, the m/z values are presented for the ion peaks.

solvent is then distilled off to 2/3 of the volume. The precipitated crystals are filtered off and washed with ether. The yield of 0.86 g (72%) of the salt (X), with the mp 203-206°C, is obtained.

4-Methyl-3-oxo-9-phenacylidene-3,4-dihydro-4-azafluorene (XI) ($C_{21}H_{15}NO_2$). A. To the suspension of 0.48 g (1.13 mmoles) of the salt (X) in 3 ml of water is added, gradually and with stirring, the solution of 2.8 g (2.26 mmoles) of potassium hexacyanoferrate and 0.6 g (10.7 mmoles) of potassium hydroxide in 65 ml of water. The mixture is stirred for 20 h at room temperature. It is extracted with chloroform. The chloroform is distilled off, and the residue is recrystallized from the 1:5 mixture of ethyl acetate–hexane. Compound (XI) is obtained with the yield of 0.08 g (23%) as dark red crystals with the mp 173-178°C and the M^+ 313. The PMR spectrum is as follows: 4.05 ppm (3H, s, NCH_3), 6.50 ppm (1H, d, $J_{2,1}$ = 9.5 Hz), 8.45 ppm (1H, d, $J_{1,2}$ = 9.5 Hz), and 7.40-8.15 ppm (10H, m, remaining protons).

B. The mixture of 0.6 g (1.1 mmoles) of the salt (III), 2 g (35.7 mmoles) of potassium hydroxide, and 6 g (18.2 mmoles) of potassium hexacyanoferrate in 120 ml of water is stirred for 11 h at room temperature. The color of the reaction mass changes from orange to dark red. The product is recovered by the repeated extraction with ether. After the distillation of the ether, compound (XI) is obtained with the yield of 0.2 g (58%) as dark red crystals having the mp 169-171°C. In the mixed test with the sample obtained by the method A, the mp is 171-175°C. The IR spectrum is characterized at 1655 cm^{-1} (CO). The M^+ is 313. The PMR spectrum is identical to the spectrum of the sample of compound (XI) obtained by the method A.

1,4-Dimethyl-3,7-diphenylspiro[4-azafluorenium-9,5-(5H-4,6-dihydro-1,2-diazepinium)diiode] (XII) ($C_{30}H_{27}I_2N_3$). This is obtained by the boiling of 0.91 g (2.28 mmoles) of the diazepine (IX) and 8 ml of methyl iodide in 50 ml of chloroform for 15 h. The salt (XII) is isolated with the yield of 1.2 g (78%); it has the mp 140-144°C.

1-Methyl-2-oxo-3,7-diphenylspiroindeno[2,3-e]-1,2 -dihydropyridine-5,5-(5H-4,6-dihydro-1,2-diazepine) (XIII) ($C_{29}H_{23}N_3O$). The mixture of 0.5 g (0.75 mmole) of the salt (XII), 3 g (10 mmoles) of potassium hexacyanoferrate, and 0.75 g (14 mmoles) of potassium hydroxide in 50 ml of water is stirred for 3 days at room temperature. The reaction products are extracted with ether and chloroform. The extract is dried. After the evaporation to 1/3 of the volume, the precipitated crystals are filtered off. The spiro compound (XIII) is isolated with the yield of 0.02 g (6.7%); it has the mp 229-231°C. The PMR spectrum is as follows: 3.00 ppm (4H, br.s, 2 × CH_2), 4.08 ppm (3H, s, $N-CH_3$), 6.38 ppm (1H, d, 3-H, $J_{3,4}$ = 9.0 Hz), and 7.10-8.00 ppm (15H, m). The mass spectrum, given as the m/z (relative intensity in %), is as follows: 429 (93.2), 401 (13.6), 326 (93.2), 311 (22.7), 298 (29.5), 232 (18.2), 233 (27.3), 223 (65.9), 209 (100), 191 (27.3), 181 (54.5), 180 (36.4), 102 (54.5), and 77 (52.3).

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