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SYNTHESIS OF 4-AZAFLUORENE DERIVATIVES BASED ON 9-(3,6-DIPHENYLPYRIDAZIN-4-YL)-4-AZAFLUORENE

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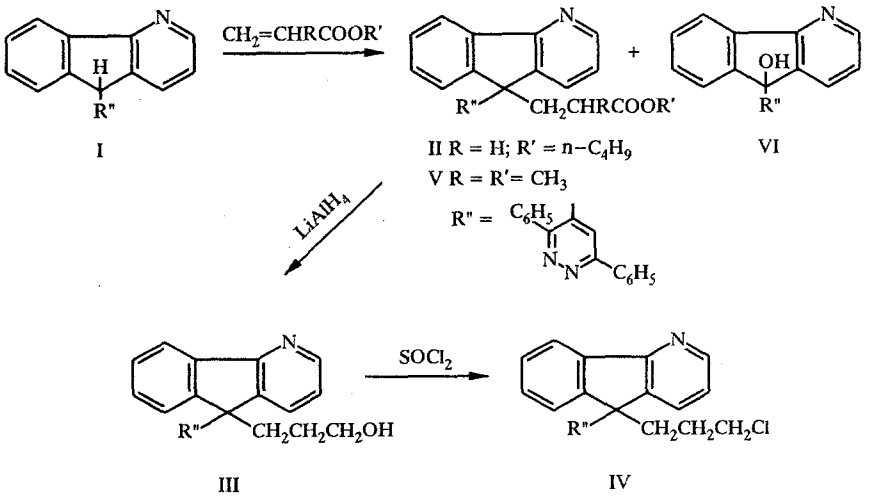
The reaction of 9-(3,6-diphenylpyridazin-4-yl)-4-azafluorene with n-butyl acrylate under conditions of the Michael reaction affords the product of the condensation at the methine group. When sterically hindered esters of methacrylic, crotonic, and cinnamic acid are utilized, the condensation does not occur, and the main reaction product under these conditions is 9-hydroxy-(3,6-diphenylpyridazin-4-yl)-4-azafluorene. The supposition concerning the existence of its conformers (rotamers) with different orientation of the diphenylpyridazinyl ring in relation to the azafluorene fragment was expressed.

Using several examples, reactions of 9-(3,6-diphenylpyridazin-4-yl)-4-azafluorene (I) [1] as CH-acids were studied in Michael condensations. Its condensation with n-butyl acrylate in the presence of dimethylphenylammonium ethoxide (the catalyst of V. M. Rodionov) proceeds with the formation of 9-(β-n-butoxycarbonylethyl)-4-(3,6-diphenylpyridazin-4-yl)-4-azafluorene (II). The ester (II) was reduced by lithium aluminum hydride to 9-(γ-hydroxypropyl)-9-(3,6-diphenylpyridazin-4-yl)-4-azafluorene (III), which is converted by thionyl chloride to 9-(γ-chloropropyl)-9-(3,6-diphenylpyridazin-4-yl)-4-azafluorene (IV). The sterically hindered olefins methyl methacrylate and ethyl crotonate, as well as ethyl cinnamate, were also subjected to the reaction with the CH-acid (I). Catalysts utilized were the catalyst of Rodionov and metallic potassium. The formation of 9-(2-methoxycarbonyl-1-propyl)-9-(3,6-diphenylpyridazin-4-yl)-4-azafluorene (IV) could only be detected mass spectrometrically in the case of the reaction of the compound (I) with methyl methacrylate in the presence of the catalyst of Rodionov. A crystalline substance, which corresponds to 9-hydroxy-9-(3,6-diphenylpyridazin-4-yl)-4-azafluorene (VI) according to the data of the elemental analysis, the IR and mass spectra, and the PMR spectrum, was isolated chromatographically from the reaction products [1]. The hydroxy derivative (VI) was isolated with the yield of 83% by the condensation of the compound (I) with methyl methacrylate in the presence of potassium.



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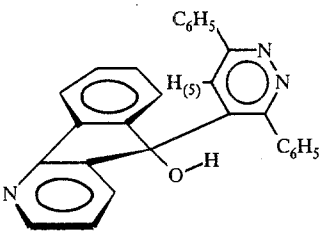
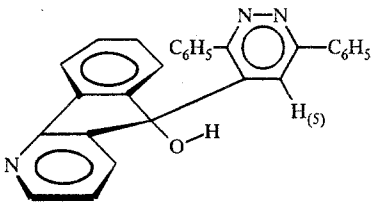
Analogous results were obtained in the condensation of the pyridazinyl-substituted azafluorene (I) with ethyl crotonate and ethyl cinnamate both in the presence of the catalyst of Rodionov, and potassium. Consequently, the oxidation of compound (I) proceeds with the formation of the alcohol (VI) instead of the condensation by the Michael reaction. We established previously that the substitution reaction competes with the oxidation reaction for the 2- and 4-azafluorenes in the presence of the catalyst of Rodionov [2]. In that case, when methyl methacrylate, ethyl crotonate, and ethyl cinnamate were taken into the reaction, the condensation reaction does not occur probably due to steric factors, and the hydroxy derivative (VI) is formed exclusively. It should be noted that the samples of the alcohol isolated in different experiments have different melting temperatures, but they do not give a depression of the temperature in the mixed test with the known sample of the alcohol (VI) [1], obtained by the oxidation of compound (I) with potassium permanganate. Moreover, there are some differences in the PMR spectrum of the hydroxy derivative (VI), described in the work [1], and the spectra of the alcohols isolated from the reaction products. Thus, the signal of the 5-H proton of the pyridazine ring is shifted to lower field. This is probably associated with the occurrence of the hydroxy derivative (VI) in the form of the rotamers (conformers) A and B.



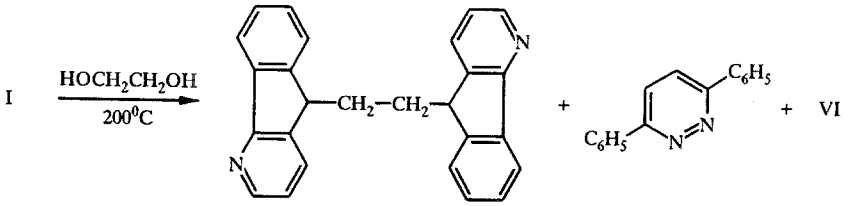
A



B

In the rotamer A, when the 5-H hydrogen atom occurs in the shielding zone of the azafluorene ring, the proton signal is shifted to low field (9.00 ppm); it is not subjected to the influence of the azafluorene fragment in the rotamer B, and gives the resonance signal at higher field (from 7.02 to 8.5 ppm). The observed difference in the melting temperatures of the hydroxy derivative (VI) isolated from different experiments is probably also explained by the rotamers.

The heating of compound (I) with sodium in ethylene glycol led to the isolation of 3,6-diphenylpyridazine (VII) [3], 1,2-di(4-azafluoren-9-yl)ethane (VIII) (20%), and the mixture of the pyridazine (VII) and the hydroxy derivative (VI). The di(azafluorenyl)ethane (VIII) was previously obtained from 4-azafluorene and ethylene glycol in the presence of sodium [4]. The data of the mass spectrum and the PMR spectrum confirm the structure of the compound (VIII) which we isolated.



VIII VII

EXPERIMENTAL

The mass spectra were obtained on the Hewlett Packard HP 597IA instrument. The IR spectra were obtained on the UR-20 instrument using tablets with KBr. The PMR spectra of 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 with the 2:3 mixture of heptane–ethyl acetate as the eluent; development was effected using iodine vapor.

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

9-(β-n-Butoxycarbonylethyl)-4-(3,6-diphenylpyridazin-4-yl)-4-azafluorene (II) ($C_{35}H_{31}N_3O_2$). To the solution of 0.93 g (2.34 mmoles) of compound (I) in 30 ml of benzene is added 0.3 ml of the freshly prepared catalyst of Rodionov. The

reaction mixture acquires a raspberry color. Then, 9.9 g (1 ml, 7.1 mmoles) of n-butyl acrylate are added. The reaction mixture becomes brown; it is boiled for 7 h. The benzene is distilled off, and diethyl ether is added to the residue. The residue is filtered off and washed with ether. The residue (0.83 g) is a white powder, which is chromatographed on a column of Al_2O_3, h = 50 cm, d = 0.5 cm, with the eluent of heptane, and then the 3:1 and 1:1 mixtures of heptane–ethyl acetate. The ester (II) is isolated with the yield of 0.14 g (11.4%); it has the mp 180-183°C, the R_f 0.2, and the M^+ 525. The IR spectrum is characterized at 1735 cm^{-1} (C=O). The PMR spectrum is as follows: 0.8-1.79 ppm (9H, m, aliphatic protons), 2.88 ppm (2H, t, CH_2CO), 3.88 ppm (2H, t, CH_2O), 8.50 ppm (1H, s, 5-H), and 5.98-8.45 ppm (17H, m, aromatic protons). Also isolated is 0.51 g of the mixture of the compounds (I) and (II), with the R_f values of 0.08 and 0.2, and the M^+ values of 397 and 525, correspondingly. The elution with chloroform leads to the isolation of 0.15 g (15.5%) of a white crystalline substance with the mp 286-290°C and the R_f 0.0, namely, 9-hydroxy-9-(3,6-diphenylpyridazin-4-yl)-4-azafluorene (VI) [1]. The mp obtained in the mixed test with the known sample is 268-274°C. The literature mp is 245-247°C.

9-(3-γ-Hydroxypropyl)-9-(3,6-diphenylpyridazin-4-yl)-4-azafluorene (III) ($C_{31}H_{25}N_{30}$). To the solution of 0.2 g (0.38 mmole) of compound (II) in 30 ml of tetrahydrofuran is added 0.2 g of lithium aluminum hydride. The mixture turns dark red; it is boiled for 3 h, and the color disappears. The reaction mixture is decomposed with ethyl acetate, and then water. The upper layer is separated, and the aqueous layer is extracted with tetrahydrofuran and then chloroform. The extracts are combined. The solvents are distilled off, and the residue, a white powder, is chromatographed on Al_2O_3, h = 35 cm and d = 0.5 cm, with the 3:2 mixture of heptane–ethyl acetate as the eluent. Traces of the compound with the R_f 0.21 are isolated. The elution with chloroform leads to the isolation of 0.2 g (61%) of the alcohol (III), which has the mp 245-248°C, the R_f 0.09, and the M^+ 455. The IR spectrum is characterized at 3230-3580 cm^{-1} (OH).

9-(γ-Chloropropyl)-9-(3,6-diphenylpyridazin-4-yl)-4-azafluorene (IV) ($C_{31}H_{26}N_3Cl$). The alcohol (III) (0.11 g, 0.24 mmole) is dissolved with heating in 10 ml of benzene, and 3 ml of thionyl chloride in 5 ml of benzene are added gradually. The mixture is boiled for 3 h. The benzene and the unreacted thionyl chloride are distilled off. To the residue are added 20 ml of water, and the solution is brought to the pH 10 with sodium carbonate prior to the extraction with chloroform. The solvent is evaporated, and the residue is washed with hexane. The chloro derivative is obtained with the yield of 0.07 g (61%) as a white crystalline substance with the mp 220-222°C; it becomes grayish on storage. The mass spectrum, given as the m/z and intensity (%), is as follows: 473/475 (72.7/25), 437 (9.1), 410 (52.3), 396 (59.1), 382 (27.3), 368 (27.3), 266 (100), and 102 (36.4). The PMR spectrum is as follows: 1.00 ppm (2H, m, β-CH_2), 2.63 ppm (2H, t, α-CH_2), 3.30 ppm (2H, t, γ-CH_2), 8.40 ppm (1H, s, 5-H), and 5.95-8.35 ppm (17H, m, remaining protons).

9-Hydroxy-9-(3,6-diphenylpyridazin-4-yl)-4-azafluorene (VI). A. The reactions of the compound (I) with methyl methacrylate and ethyl crotonate, as well as ethyl cinnamate, were conducted under the same conditions as the reaction of compound (I) with n-butyl acrylate. In the case of the reaction with methyl methacrylate, the compound (VI) was isolated with the yield of 43%. The mp is 288-289°C. In the reaction with ethyl crotonate, the yield is 53% and the mp is 276-279°C. In the reaction with ethyl cinnamate, the yield is 45% and the mp is 263-275°C.

B. When the reactions of the compound (I) are performed with the same esters in benzene in the presence of potassium, compound (VI) was obtained with the yield of 83% and the mp 260-264°C in the case of methyl methacrylate, the yield of 52% and the mp 271-272°C with ethyl crotonate, and the yield of 75% and the mp 271-273°C with ethyl cinnamate.

Isolation of 3,6-Diphenylpyridazine (VII) and 1,2-Di(4-azafluoren-9-yl)ethane (VIII). The solution of 0.5 g (1.26 mmoles) of compound (I) in 15 ml of ethylene glycol and 0.15 g of sodium are heated for 20 h at 200°C. The reaction mixture has a dark red color. Water (50 ml) is added. The deep color disappears. The mixture is extracted with chloroform. The chloroform is distilled off, and 10 ml of ethyl acetate are added to the residue. The resulting crystals are filtered off and washed with hot ethyl acetate. The substituted pyridazine (VII) is isolated with the yield of 0.13 g (44.5%) and the mp 215-217°C [3]. The ethyl acetate filtrates are combined and evaporated to dryness. The residue is chromatographed on a column with the 10:1 mixture of aluminum oxide and silica gel; the eluent is the 1:3 mixture of ethyl acetate–petroleum ether (bp 80-100°C). Traces of the substance with the R_f 0.54 and then 0.09 g (20%) of compound (VIII) with the mp 170-172°C [4] and the R_f 0.33 are isolated sequentially. The mass spectrum, given as the m/z and the intensity (%), is as follows: $[M + H]^+$ 361 (100), 180 (50), and 165 (46.5). The PMR spectrum is as follows: 1.62 ppm (4H, br.s., CH_2-CH_2), 3.78 ppm (2H, br.s, 9-H, 9′-H), and 7.13 ppm (14H, m, aromatic protons). Chromatography leads to the isolation of a third fraction (0.02 g) of the substance with the R_f 0.09, of unestablished structure, and then a fraction (0.15 g) of a mixture of substances. According to the data of the mass spectrum, it contains the pyridazine (VII) with the M^+ 232, and the hydroxy derivative (VI) with the M^+ 413.

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