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# 9-(β-PYRIDYLMETHYLENE)-4-AZAFLUORENE SYNTHESIS OF THE Z- AND E-ISOMERS OF ITS METHIODIDES AND REDUCTION OF THE Z-ISOMER

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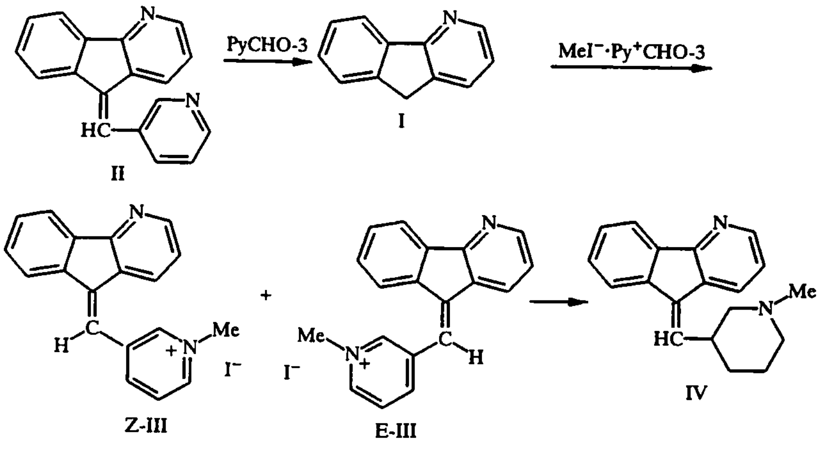
*The 9-(β-pyridylmethylene)-4-azafluorene was obtained as the mixture of the Z- and E-isomers. Condensation of 4-azafluorene with methiodides of 3-formylpyridine afforded the methiodides of these isomers which were isolated in discrete form. Their configuration was established. It was established using the example of the reduction of the methiodide of the Z-isomer by sodium borohydride that the β-pyridinium portion of this quaternary salt is completely reduced to the piperidyl.*

In the continuation of work into the synthesis and the study of the structure [1-3] and chemical conversions [4] of 9-hetarylmethylenazafluorenes, we obtained 9-(β-pyridylmethylene)-4-azafluorene (II) with the yield of 70% by the condensation of 4-azafluorene (I) with 3-formylpyridine. According to the data of the PMR spectrum, it is formed with the 1:1 ratio of the Z- and E-isomers. However, the isolation of the individual isomers by crystallization or chromatographically was not managed. They show practically no difference in the chromatographic mobility on silica and alumina.



In connection with the impossibility of the separation of the Z- and E-isomers of compound (I) as the free bases, we carried out the condensation of 4-azafluorene with β-pyridinaldehyde methiodide (acetic anhydride, 50°C) with the object of isolating the geometrical isomers in the form of the quaternary salts (III) by the method of crystallization. It was found that, in this case, the mixture of the Z- and E-isomers of (III), with the Z−E ratio of 1:4 according to the data of the PMR spectrum, readily passes over into the solid phase when the liquid reaction mixture is cooled, whereby the Z-isomer forms a light yellow amorphous powder, and the E-isomer crystallizes in the form of stable prisms of dark yellow color. That allowed the separation of the individual isomers mechanically by the "Pasteur method." The Z-isomer was thereby obtained with the yield of 57% (the mp 235-237°C), and the E-isomer was thereby obtained with the yield of 3% (the mp 216-217°C).

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TABLE 1. Physicochemical Characteristics of the Compounds (II)-(IV)

| Compound | Empirical formula | mp, °C | Found, % / Calculated, % | | | | Ratio* | Yield, % | |
|---|---|---|---|---|---|---|---|---|---|
| | | | C | H | N | Cl | | total | after separation |
| *E,Z*-II | $C_{18}H_{12}N_2$ | 95...96 | 84,0<br>84,4 | 4,4<br>4,7 | 10,2<br>10,9 | | 1 : 1 | 70 | — |
| *E*-III | $C_{19}H_{15}IN_2$ | 216...217 (decomp.) | 43,2<br>43,4 | 3,0<br>2,9 | 7,1<br>7,0 | | 1 : 4 | 60 | 3 |
| *Z*-III | $C_{19}H_{15}IN_2$ | 235...237 (decomp.) | 43,5<br>43,4 | 2,9<br>2,9 | 6,9<br>7,0 | | | | 57 |
| IV | $C_{19}H_{20}IN_2$ | | 82,9<br>82,6 | 7,2<br>7,3 | 9,6<br>10,1 | | | | 99 |
| *Z*- IV · 2HCl | $C_{19}H_{22}Cl_2N_2$ | 155...157 | | | 8,6<br>9,0 | 20,3<br>20,0 | | | Quantitative |
| III-$Br_2$ | $C_{19}H_{15}Br_2IN_2$ | 192...194 | 40,4<br>40,9 | 2,7<br>2,7 | 4,8<br>5,0 | | | | 67 |

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*The ratio of the E- and Z-isomers in the reaction mixture.

TABLE 2. PMR Spectral Parameters, δ, ppm*

| Compound | 1-H | 2-H | 3-H | 5-H | 8-H | 10-H | 2'-H | 3'-H | 4'-H | 5'-H | 6'-H | $CH_3$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (*E*-II)*2 | *3 | 7,23 | 8,59 | 8,04 | *3 | 7,68 | 8,83 | | *3 | *3 | 8,66 | 8,66 |
| (*Z*-II) | *3 | 6,96 | 8,51 | 8,04 | *3 | 7,66 | 8,83 | | *3 | *3 | | |
| *E*-III | 7,94 | 7,16 | 8,55 | 8,14 | 7,44 | 8,0 | 9,33 | | 8,78 | 8,31 | 9,09 | 4,45 |
| *Z*-III | 8,39 | 7,6 | 8,63 | 8,03 | *3 | 7,89 | 9,3 | | 8,8 | 8,3 | 9,08 | 4,45 |
| IV | 7,92 | 7,25 | 8,5 | 7,92 | *3 | 7,48 | 4,15 (1H) | 5,45 | 2,0...3,2 (7H) | | | 2,2 |
| IV · 2HCl | 8,7 | 8,55 | 8,3...7,4 | | | 7,8 | 4,15...4,55 | 5,6 | 2,6...2,9 | | 3,3...3,9 | 4,06 |
| III-$Br_2$ | 8,39 | 7,6 | 8,63 | 8,03 | *3 | 7,89 | 9,3 | | 8,8 | 8,3 | 9,08 | 4,45 |

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*The spin–spin coupling constants of the pyridine portions (J, Hz) are as follows: $J\alpha\beta = 4.8\text{-}5.0$, $J\alpha\gamma = 1.6$, and $J\beta\gamma = 8.0$.

*2Compound (II) was characterized as the mixture of the E- and Z-isomers.

*3The chemical shifts of these protons, as well as those of the protons 6-H and 7-H, were not determined due to the superposition on signals of other protons.

In the PMR spectra of the compounds (III), the signals corresponding to the protons of the $CH_3$ and 6'-, 4'-, and 2'-H groups have the same chemical shifts for both isomers. However, the close disposition of the pyridinium nucleus to the pyridine portion of azafluorene for the Z-isomer of (III) leads to a low-field shift ($\Delta\delta \sim 0.1\text{-}0.4$ ppm) of the signals of the 1-, 2-, and 3-H protons by comparison with the E-isomer of (III).

The partially reduced derivatives of pyridylmethylenazafluorenes may present interest in the study of their pharmacological action. For this purpose, the isomer Z-(III) was reduced by sodium borohydride. Instead of the expected tetrahydro derivative, 9-(1-methylpiperidyl-3-methylene)-4-azafluorene (IV) was isolated with a quantitative yield [5]. The mass spectrum of compound (IV) contains the peak of the molecular ion $M^+$ with the m/z 276 (5%) as well as peaks of the $[M-H]^{+\cdot}$ (2.5%) and $[CH{=}C_5H_9NCH_3]^{+\cdot}$ ions with maximum intensity. Data of the PMR spectrum serve as confirmation of the complete reduction of the pyridinium nucleus whereby the 10-H proton (the exocyclic double bond of the fulvene portion) resonates as a doublet at 7.78 ppm with the SSCC 6.0 Hz. The methine proton at the $C_{(3)}$ of the piperidine portion appears in the form of a broad multiplet at 5.45 ppm. The remaining cyclic piperidine protons give complex imposed multiplets at 2.0-3.2 ppm with the integral intensity 7H, and one triplet signal with the intensity of one proton unit at 4.15 ppm (2-H); the protons of the $N-CH_3$ group resonate at 2.2 ppm as a singlet.

It is known [5, 6] that the pyridinium nucleus is generally reduced by sodium borohydride to 3-piperidines. In the given case, the formation of the hexahydro derivative probably occurs owing to the isomerization of 3-piperidine to 2-piperidine, which leads to an energetically more favorable dienamine system. Protonation of the last in an alcoholic medium facilitates the nucleophilic attack by the hydride ion.

The attempt to brominate the quaternary salt (III) at the exocyclic double bond (bromine in chloroform, boiling for 3 h) ended in the isolation of a dark brown substance, with the yield of 67% and the mp 192-194°C, from the reaction mixture; its PMR spectrum was found to be identical to that of the initial salt (III). The presence of two atoms of bromine in this compound was confirmed by elemental analysis. These data favor the proposition that a perbromide is formed with the coordination of one bromine molecule at the pyridinium portion.

## EXPERIMENTAL

The PMR spectra were recorded on the Bruker WP-80 instrument in $CDCl_3$ (for the free bases) and in DMSO-$D_6$ (for the quaternary salts) using TMS as the internal standard. The mass spectra were obtained on the MX-1303 spectrometer with the 70 eV energy of the ionizing electrons. The characteristics and PMR spectra of the compounds obtained are presented in the Tables 1 and 2.

**9-(β-Pyridylmethylene)-4-azafluorene (II).** To the solution of 0.28 g (1.7 mmole) of 4-azafluorene (I) in 30 ml of methanol are added 4 mmole of metallic sodium. When it is dissolved, the solution of 0.21 g (2 mmole) of 3-formylpyridine in 20 ml of methanol is added. The mixture is maintained for 24 h at 20°C prior to the addition of 30 ml of water and the distillation of the alcohol. The residue is extracted with ether, and the ether is distilled off prior to purification of the residue on a column with $SiO_2$. The yield of 0.3 g of the mixture of Z- and E-isomers of compound (II), in the form of yellow crystals, is obtained. The separation of the isomers by crystallization from different solvents as well as adsorption chromatography on $SiO_2$ and $Al_2O_3$ was not managed.

**Methiodides of the Z- and E-Isomers of 9-(β-Pyridylmethylene)-4-azafluorene (III).** To the solution of 0.28 g (1.7 mmole) of azafluorene (I) in 5 ml of acetic anhydride is added, with stirring at 50°C, the solution of 0.42 g (1.7 mmole) of 3-formylpyridinium methiodide. The mixture is heated for 30 min more, and cooled to 20°C. The resulting residue is separated and washed with ether. The yield of 0.4 g of a mixture of solid substances is obtained; the mixture consists of two fractions — a light yellow amorphous powder, and fine stable dark yellow prismatic crystals with a reddish hue, which are separated by hand with pincers under a magnifier (by the "Pasteur method"). The yield of 0.38 g of the Z-isomer (in the form of a powder) and 20 mg of the E-isomer (in the form of prisms) is obtained.

**9-(1-Methylpiperid-3-ylmethylene)-4-azafluorene (IV).** To the suspension of 1 g (2.5 mmole) of the salt Z-(III) in 50 ml of ethanol is added, in portions with stirring, 0.63 g (10 mmole) of $NaBH_4$. The mixture is then maintained for 1 h at 30°C, and for 12 h at 20°C. The solvent is evaporated to 1/3 vol. To the residue are added 150 ml of water prior to extraction with chloroform. The extract affords 0.68 g of the hexahydro derivative (IV) as a thick yellow oil. The mass spectrum is as follows: $M^+$ 276 (5), 275 (2.5), 271 (4), 181 (21), 167 (33), 166 (40), and 110 (100).

**Dihydrochloride of (IV).** This presents as dark yellow hygroscopic plates. The IR spectrum is as follows: 3400 $cm^{-1}$ (broad, $^+NH$), 3140 $cm^{-1}$ (arom. C−H), 2920 $cm^{-1}$ ($CH_2$), 2830 $cm^{-1}$ ($CH_3$), 2700 $cm^{-1}$ ($^+N$), 1650 $cm^{-1}$ ($C_{(9)}=C_{(10)}$), 1530 $cm^{-1}$, 1475 $cm^{-1}$, and 1390 $cm^{-1}$ (broad, $CH_3$, $CH_2$).

**Perbromide of Compound (III) (III·$Br_2$).** To the suspension of 0.84 g (2.1 mmole) of the methiodide Z-(III) in 20 ml of $CHCl_3$ is added, with stirring at 60°C, the solution of 0.34 g (2.1 mmole) of bromine in 10 ml of $CHCl_3$. The mixture is boiled for 3 h, and the residue is separated, washed with ether, and dried. The yield of 0.78 g of the perbromide of compound (III), in the form of brown crystals, is obtained.

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