3-METHYL-9-BENZYLIDENE-2-AZAFLUORENE AND ITS ANALOGS

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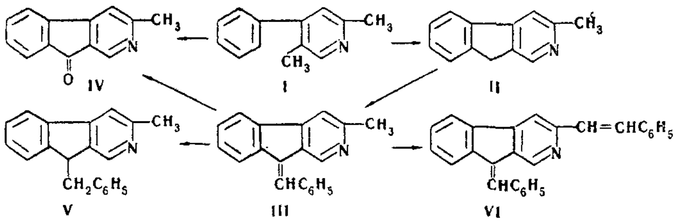
The possibility of obtaining 3-methyl-2-azafluorene by dehydrocyclization of 2,5-dimethyl-4-phenylpyridine at 500-750° in the absence of a catalyst was examined. This azafluorene was condensed with aromatic aldehydes. Several transformations of the geometrical isomers of 3-methyl-9-benzylidene-2-azafluorene and its analogs were studied.

The synthesis of 3-methyl-2-azafluorene (II) and its analogs by the catalytic dehydrocyclization of 2,5-dimethyl-4-phenylpyridine (I) was described in previous communications [1,2]. In connection with the accumulation of facts necessary for the study of the mechanism of this reaction, we turned to an elucidation of the possibility of carrying out the dehydrocyclization of I in the absence of a catalyst. We carried out a series of experiments in which the temperature ranged from 500 to 750° and quartz was used as the packing. The thermal dehydrocyclization of I proceeds only above 600° to give low yields of II: at 750° the yield of II is about 9% (based on the amount of I converted). Destructive processes accompanied by the formation of gaseous products occur to a considerable degree.

Considering that dehydrogenation processes are initiated by iodine [3], we carried out a number of similar experiments with the addition of iodine. In this case, 3-methyl-2-azafluorenone (IV) rather than II is isolated after appropriate workup of the reaction products. At high temperatures, II is apparently iodinated at the methylene group to form a geminal dihalo derivative, from which IV is obtained during alkaline workup. The addition of iodine has a considerable effect on the dehydrocyclization of I. While only traces of II are detected when iodine is absent, the yield of IV is 30% at the same temperature when an equimolecular amount of iodine is added.



Continuing our research involving a study of various derivatives of azafluorene systems, we turned our attention to the condensation of II with benzaldehyde and to a study of the geometrical isomers of 3-methyl-9-benzylidene-2-azafluorene (III) that are formed in the process. The condensation was carried out in the presence of potassium ethoxide. Compound III is a bright-yellow, crystalline substance. One proof of the structure of III is its oxidation to IV and benzoic acid. A band of medium intensity at 1632 cm^{-1} in the IR spectrum of III is caused by stretching vibrations of the $C=C$ bond of the conjugated ring and the benzylidene grouping. The band at 935 cm^{-1} is affiliated with the out-of-plane stretching vibrations of the hydrogen atom of the ethylene bond.

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Reduction of III with lithium aluminum hydride in tetrahydrofuran yielded 3-methyl-9-benzyl-2-azafluorene (V) as a colorless, crystalline substance. Only one intense band at 1614 cm^{-1}, caused by vibrations of the aromatic rings, is present in the IR spectrum of V in the region of the C=C stretching vibrations. The signal at δ 2.62 ppm in the NMR spectrum of V (in CCl$_4$) corresponds to the protons of the CH$_3$ group. The doublet at 3.09 and 3.17 ppm is related to protons of the CH$_2$ group (this doublet is absent in the NMR spectrum of III), the triplet at 4.20, 4.27, and 4.34 ppm is caused by the proton attached to C$_{(9)}$, and the singlet at 8.17 ppm is affiliated with the proton in the α position relative to the nitrogen atom.

The condensation of III with benzaldehyde at the methyl group, as a result of which 9-benzylidene-3-(β-styryl)-2-azafluorene (VI) is formed, was carried out in acetic acid and acetic anhydride. The condensation product (VI) is bright yellow. The oxidation of VI at the benzylidene and styryl groups led to 2-azafluorenone-3-carboxylic acid (VII).

3-Methyl-9-benzylidene-2-azafluorene (III) is formed as a mixture of geometrical isomers, which were isolated by means of adsorption chromatography on aluminum oxide (mp 115-116.5° and 129-130.5°).

We assigned the cis and trans configurations, respectively, to the isomers of III with respect to formal characteristics (the position of the phenyl ring and o-phenylene group of the azafluorene system relative to the double bond). The assumption regarding the structure of these isomers was made on the basis of a comparison of some of their properties. The cis isomer (IIIa) has lower chromatographic mobility than the trans isomer (IIIb) (Table 1). This can be explained by the fact that the nitrogen of the pyridine ring in the trans isomer is shielded by the phenyl group, as a consequence of which its interaction with the adsorbent is weakened. In addition to steric factors, one must take into account the interaction of the electron pair of the nitrogen atom with the conjugated system of π electrons of the neighboring benzene ring, which, as follows from an examination of the molecular model, is in a plane almost perpendicular to the plane of the azafluorene system. This sort of interaction will apparently be more distinctly displayed in the analogous geometric isomer of the 1-azafluorene derivative. The different solubilities of the isomers of III in nonpolar solvents and the observed (chromatographically) difference in the rate of interconversions of the isomers on heating can be explained by this interaction. Isomer IIIa is more soluble in hexane, ligroin, decalin, and ether than IIIb. When the individual isomers of III are heated to 140° in decalin, they undergo interconversions but at different rates. Isomer IIIa is converted to IIIb more rapidly than IIIb is converted to IIIa. The trans configuration of IIIb is probably stabilized to a certain degree through interaction of the electron pair on the nitrogen atom with the benzene ring.

The IR spectra of carbon tetrachloride solutions of isomers III are identical, but there are certain differences in the spectra of mineral oil pastes of the isomers. In this case, the IR spectrum of IIIa contains a band of medium intensity at 1708 cm^{-1}, which is absent in the spectrum of IIIb. A greater number of bands than for IIIa are observed in the IR spectrum of IIIb in the region of the out-of-plane deformation vibrations of the C–H bonds. These differences are more distinctly seen in the IR spectra of KBr pellets of the isomers of III. Bands at 1707 cm^{-1}, a shoulder on the band at 1461 cm^{-1}, and a weak band at 1410 cm^{-1} are observed for IIIa. These bands are absent in the spectrum of IIIb. A greater number of bands are observed in the IR spectrum of IIIa in the LiF prism region.

In the crystalline state, the isomers of III differ considerably in color. Isomer IIIa has a more intense color (bright-yellow crystals) than IIIb. However, the UV spectra of the isomers of III are practically identical. The NMR spectra of CDCl$_3$ solutions of the isomers of III are completely identical. They contain signals from protons of a CH$_3$ group at 2.61 ppm and aromatic protons at 7.30-7.74 ppm.

As in the case of III, 3-methyl-9-(p-dimethylaminobenzylidene)-2-azafluorene (VIII) was obtained as two isomers by the condensation of II with p-dimethylaminobenzaldehyde. These isomers differ considerably with respect to melting points and coloration: the cis isomer (VIIIa) was obtained as orange crystals, while the trans isomer (VIIIb) was obtained as bright-yellow crystals. Their properties are similar to those of the isomers of III. When II was condensed under the same conditions with benzophenone, diphenyl-(3-methyl-2-aza-9-fluorenylidene)methane (IX) was obtained as high-melting, light-orange crystals.

2-Azafluorene (XIV) was used in order to obtain an analog of III that does not contain a methyl group in the azafluorene ring. We realized the scheme for its synthesis as follows:

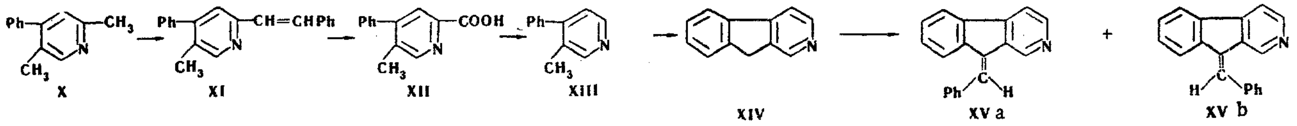

TABLE 1. Chromatographic Mobility of 9-Benzylidene Derivatives of 2-Azafluorene

Compound	II	IIIa	IIIb	VIIIa	VIIIb	XIV	XVa	XVb
R_f	0,55	0,64	0,81	0,34	0,64	0,39	0,40	0,65

*On activity II Al_2O_3 in ether.

TABLE 2

Expt.	Temp., °C	I/I_2, mole/mole	Overall conv. of I, %	Yield of polycyclic compounds, % *	Yield of gas components, mole/100 mole of I		
					H_2	C_nH_{2n+2}	C_nH_{2n}
1	500	—	8	0(0)	0,9	15,9	1,1
2	600	—	20	traces (traces)	5,2	18,5	3,0
3	700	—	26	3(7)	38,2	53,3	8,5
4	750	—	31	4(9)	48,4	59,5	8,4
5	500	2	34	4(6)	0,7	32,0	2,9
6	550	1	57	10(14)	1,5	30,6	3,5
7	600	1	76	23(30)	3,4	35,5	5,7

*In experiments 1-4, II was isolated as a polycyclic compound, while IV was isolated in experiments 5-7. The direct yield with respect to the I passed through is presented; the figure in parentheses is the yield based on the amount of I converted.

5-Methyl-4-phenyl-2-(β-styryl)pyridine (XI) [4], which is formed by the condensation of 2,5-dimethyl-4-phenylpyridine (X) with benzaldehyde, is oxidized to 5-methyl-4-phenylpyridine-2-carboxylic acid (XII). The latter is subjected to decarboxylation, and the resulting 3-methyl-4-phenylpyridine (XIII) is converted to 2-azafluorene (XIV) [5] by dehydrocyclization on a K-16 catalyst. The condensation of XIV with benzaldehyde yields the cis and trans isomers of 9-benzylidene-2-azafluorene (XVa and XVb), which are similar in properties to the isomers of III.

The isolation of the isomeric 9-benzylidene derivatives of azafluorene was successfully accomplished by means of adsorption chromatography on aluminum oxide. In all of the examples considered, the substituted azafluorenes with more shielded nitrogen atoms have higher chromatographic mobilities (Table 1).

EXPERIMENTAL

Dehydrocyclization of 2,5-Dimethyl-4-phenylpyridine. The experiments were carried out with an apparatus of the flow type (a quartz tube, *l* 50 cm, d 3.5 cm, quartz packing). A 10-g (0.055 mole) sample of I and 14 g (0.055 mole) of iodine in 100 ml of benzene was subjected to prior vaporization and passed through a scrubber containing 10% sodium hydroxide solution, and the liquid reaction products were treated with alkali. The catalyzate remaining after distillation was analyzed by chromatography (activity II aluminum oxide). The gases were analyzed with a modified KhT-2M chromatograph. The experimental results are presented in Table 2.

3-Methyl-9-benzylidene-2-azafluorene (III). A mixture of 1 g (5 mmole) of II, 0.7 g (7 mmole) of benzaldehyde, and 10 ml of 10% potassium ethoxide in 75 ml of alcohol was refluxed with stirring for 6 h. Water (20 ml) was added, the alcohol was removed by distillation, and the excess benzaldehyde was removed by steam distillation. The organic bases were extracted with ether. The residue (1.4 g) after removal of the ether by distillation was separated chromatographically with a column filled with activity II aluminum oxide to give initially 0.57 g of the trans isomer of III (IIIb) with mp 129-130.5° (from ligroin) as pale-yellow crystals. Found: C 89.0; H 5.5; N 5.2%. $C_{20}H_{15}N$. Calculated: C 89.2; H 5.5; N 5.2%. UV spectrum, λ_{max}, nm (log ε): 228 (4.56), 258 (4.41), ~332 (4.24). The picrate of IIIb melted at 257-258° (from alcohol). The next compound eluted was 0.55 g of the cis isomer of III (IIIa) with mp 115-116.5° (from ligroin) as bright-yellow crystals. Found: C 89.2; H 5.7; N 5.3%. $C_{20}H_{15}N$. Calculated: C 89.2; H 5.5; N 5.2%. UV spectrum, λ_{max}, nm (log ε): 226 (4.64), 258 (4.56), ~330 (4.34). The picrate of IIIa melted at 239-240° (from alcohol). The yield of III was 75%.

Isomer IIIa is converted to IIIb (about 50%) and IIIb is converted to IIIa (30%) (according to thin-layer chromatography) 45 min after refluxing IIIa and IIIb in decalin.

3-Methyl-2-azafluorenone (IV). Potassium permanganate [6.2 g (39.3 mmole)] was added gradually to a solution of 2 g (6.4 mmole) of III in 100 ml of acetone at 0°, and the mixture was stirred at room temperature until it was completely decolorized. The manganese dioxide was removed by filtration and washed twice with acetone and then with hot water. The acetone solution yielded 1.4 g (91%) of IV with mp 140-141° (from ligroin). Found: C 79.8; H 4.5; N 7.1%. $C_{13}H_9NO$. Calculated: C 80.0; H 4.6; N 7.1%. The picrate of IV melted at 217-218° (from alcohol). Found: N 13.4%. $C_{13}H_9NO \cdot C_6H_3N_3O_7$. Calculated: N 13.2%. After neutralization with 50% sulfuric acid, the aqueous solution yielded 0.7 g (94%) of benzoic acid.

3-Methyl-9-benzyl-2-azafluorene (V). A solution of 1.9 g (6 mmole) of III in 50 ml of tetrahydrofuran was added gradually to 0.28 g (7.4 mmole) of lithium aluminum hydride in 100 ml of tetrahydrofuran. The mixture was refluxed for 6 h and then treated with moist ether, 20 ml of 10% sulfuric acid, and 50 ml of 40% sodium hydroxide. The ether extract yielded 1.9 g (100%) of colorless crystals of V with mp 118-119° (from ligroin); a mixture of IIIa and V melted at 88-94°. Found: C 88.6; H 6.5; N 4.8%. $C_{20}H_{17}N$. Calculated: C 88.5; H 6.2; N 5.1%. The picrate of V melted at 197-198.5° (from acetone–alcohol). Found: N 10.7%. $C_{20}H_{17}N \cdot C_6H_3N_3O_7$. Calculated: N 11.2%.

9-Benzylidene-3-(β-styryl)-2-azafluorene (VI). A mixture of 2 g (6.4 mmole) of III, 0.95 g (9 mmole) of benzaldehyde, 0.8 g of acetic anhydride, and 0.5 g of acetic acid was refluxed for 16 h. The unchanged benzaldehyde was removed by steam distillation, and 20 ml of 40% sodium hydroxide was added to the residue. The organic bases were extracted with ether. The ether extract yielded 2.46 g of VI, which was purified with a chromatographic column filled with aluminum oxide to give dark-yellow crystals of VI with mp 147-148.5° (from ligroin). Found: C 90.7; H 5.3; N 3.9%. $C_{27}H_{19}N$. Calculated: C 90.7; H 5.3; N 3.9%. The hydrochloride of VI had mp 253-254° (precipitated with ether). Found: N 3.4%. $C_{27}H_{19}N \cdot HCl$. Calculated: N 3.5%.

2-Azafluorenone-3-carboxylic Acid (VII). Potassium permanganate [16.5 g (0.015 mole)] was added gradually at 0° to a solution of 4.4 g (0.011 mole) of VI in 250 ml of acetone, and the mixture was stirred at room temperature until it was completely decolorized. The manganese dioxide was removed by filtration and washed twice with hot water. The aqueous solution was partially evaporated and then neutralized with 50% sulfuric acid. The precipitate was removed by filtration and washed with ether. The ether yielded 2.55 g (88%) of benzoic acid. The ether-insoluble residue [0.95 g (34%)] was yellow crystals of VII with mp 211-212° (from alcohol). Found: C 69.5; H 3.4; N 6.2%. $C_{13}H_7NO_3$. Calculated: C 69.3; H 3.3; N 6.2%.

3-Methyl-9-(p-dimethylaminobenzylidene)-2-azafluorene (VIII). A mixture of 2 g (0.011 mole) of II, 2.2 g (0.014 mole) of p-dimethylaminobenzaldehyde, and 20 ml of 10% potassium ethoxide in 120 ml of alcohol was refluxed with stirring for 8 h. Water (20 ml) was added, and the alcohol was removed by distillation. The organic bases were extracted with benzene. The residue (3 g) after removal of the benzene by distillation was dissolved in 30 ml of benzene, and the solution was introduced into a chromatographic column filled with aluminum oxide and eluted with ether to give initially 1.48 g of the trans isomer of VIII (VIIIb) as bright-yellow crystals with mp 182-184° (from ether–petroleum ether). Found: C 84.4; H 6.7; N 9.2%. $C_{22}H_{20}N_2$. Calculated: C 84.6; H 6.4; N 8.9%. The picrate of VIIIb melted at 241-243°. The next substance isolated was 1 g of orange crystals of the cis isomer of VIII (VIIIa) with mp 149-150° (from ether–petroleum ether). Found: C 84.5; H 6.5; N 9.1%. $C_{22}H_{20}N_2$. Calculated: C 84.6; H 6.4; N 8.9%.

Diphenyl(3-methyl-aza-9-fluorenylidene)methane (IX). A mixture of 1 g (5 mmole) of II, 1 g (5 mmole) of benzophenone, and 20 ml of 10% potassium ethoxide in 60 ml of ethanol was refluxed with stirring for 11 h. Water (10 ml) was added, and the alcohol and water were removed by distillation. The residue was recrystallized from benzene to give 1.1 g of orange crystals of IX; the crystals darkened above 290° and melted with decomposition. Found: N 4.2%. $C_{26}H_{19}N$. Calculated: N 4.1%.

2-Azafluorene (XIV). A mixture of 60 g (0.328 mole) of X, 40.8 g (0.384 mole) of benzaldehyde, 33.5 g of acetic anhydride, and 19.7 g of acetic acid was refluxed for 40 h. The excess benzaldehyde was removed by steam distillation. A total of 100 ml of 10% sodium hydroxide was added to the residue, and the reaction products were extracted with ether to give 74.55 g of a mixture of XI and starting X (from chromatographic analysis). Potassium permanganate [50 g (0.316 mole)] was added in portions at 0° to a solution of this mixture in 400 ml of acetone, and the mixture was stirred at room temperature for 10 h. The manganese dioxide was removed by filtration. The acetone solution yielded 30.4 g of starting X. The manganese dioxide was washed several times with hot water, and the aqueous solution was partially evaporated and neutralized with 50% sulfuric acid to give 37 g of a mixture of XII and benzoic acid. The mixture was heated with 20 ml of water in an autoclave at 200-210° for 4 h. Sodium hydroxide solution was added, and the mixture was extracted with ether. Distillation of the ether extract yielded 14 g (56% based on converted X) of XIII with bp 120-125° (1 mm). The picrate of XIII had mp 151-153°. A solution of 14 g (0.082 mole) of XIII in 60 ml of benzene was passed over K-16 catalyst at 540-560°. A total of 6.5 liter of gas was sorbed at 20° and 738 mm. The benzene was removed from the catalyzate by distillation to give 7.16 g of substances, which were separated on a chromatographic column (activity II Al_2O_3, ether) to give 4.7 g of XIII and 2.3 g (16%) of XIV with mp 78.5-80° [5].

9-Benzylidene-2-azafluorene (XV). A mixture of 1.1 g (0.006 mole) of XIV, 0.7 g (0.006 mole) of benzaldehyde, and 10 ml of 10% potassium ethoxide in 60 ml of ethanol was refluxed for 7 h. Water (20 ml) was added, and the alcohol was removed by distillation. The benzaldehyde was removed by steam distillation, and the organic bases were extracted with ether to give 1.2 g (71%) of XV, which was subjected to chromatographic separation to give initially 0.66 g of the trans isomer (XVb) as yellow crystals with mp 165-166°. Found: C 89.5; H 5.4; N 5.4%. $C_{19}H_{13}N$. Calculated: C 89.4; H 5.1; N 5.5%. Also isolated subsequently was 0.4 g of the cis isomer (XVa) as yellow crystals with mp 82-83°. Found: C 89.3; H 5.8; N 5.6%. $C_{19}H_{13}N$. Calculated: C 89.4; H 5.1; N 5.5%.

The IR spectra of the compounds were measured with a UR-20 spectrophotometer. The UV spectra of ethanol solutions were measured with an SF-4a spectrophotometer. The NMR spectra of $CDCl_3$ solutions of isomers IIIa and IIIb were obtained with a Varian T-60 spectrometer at 60 MHz. The internal standard was hexamethyldisiloxane. The NMR spectrum of a CCl_4 solution of V was measured with a Varian HA-100 spectrometer at 100 MHz. The internal standard was tetramethylsilane.

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