SYNTHESIS OF UNSATURATED DERIVATIVES OF 2,5-DIMETHYL-4-PHENYLPYRIDINE AND 3-METHYL-2-AZAFLUORENE

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A substituted butadiene – 1-phenyl-4-(5-methyl-4-phenyl-2-pyridyl)buta-1,3-diene with a trans, trans configuration – was obtained by condensation of 2,5-dimethyl-4-phenylpyridine with cinnamaldehyde. Two 3-methyl-9-cinnamylidene-2-azafluorene isomers are formed as a result of condensation of the same aldehyde with 3-methyl-2-azafluorene. Data from the PMR and IR spectra were used to prove the configuration of the compounds obtained. It was established that the condensation of 3-methyl-2-azafluorene with salicylaldehyde gives 3-methyl-9-(2-hydroxybenzylidene)-2-azafluorene, which has a zwitterionic structure, and 1,2-bis(3-methyl-2-aza-9-fluorenylidene)ethane. Ideas regarding the chemical mechanism of the formation of the latter are presented. The preparation of an unsaturated alcohol – 3-methyl-9-allyl-2-aza-9-fluorenol – is described.

Conjugated dienes with heterocyclic substituents are of interest as compounds with several different reaction centers – a fact that is important from the point of view of synthesis. New problems arise during the study of the three-dimensional structures of such systems in connection with the presence of a heterocyclic fragment in them.

In the present research we used 2,5-dimethyl-4-phenylpyridine (I) [1] for the synthesis of a pyridine derivative containing an unsaturated substituent. 1-Phenyl-4-(5-methyl-4-phenyl-2-pyridine)buta-1,3-diene (II) was obtained by condensation of I with cinnamaldehyde in the presence of acetic anhydride. To establish the configuration of II we obtained the PMR spectra with the application of the paramagnetic shift reagent (PSR) $Eu(DPM)_3$. The assignment of the signals of the protons was confirmed by the double-resonance spectra (Fig. 1, spectra a and b). The spin-spin coupling constants (SSCC) of the protons attached to the double bonds (^3J = 15 Hz) provide evidence for a trans orientation of the protons attached to C_1, C_2, and C_3, C_4. This conclusion is also confirmed by the data from the IR spectrum, in which the intense absorption band at 995 cm^{-1} is related to the out-of-plane deformation vibrations of the CH bonds of the trans-divinyl fragment.

We used 3-methyl-2-azafluorene (III) [2] for the synthesis of unsaturated systems in the azafluorene series. The condensation of azafluorene III with cinnamaldehyde was carried out in the presence of potassium ethoxide. If one takes into account the fact that the s-trans conformation of the diene fragment should be stable for the product of this condensation – 3-methyl-9-cinnamylidene-2-azafluorene (IV) – one must expect the formation of two geometrical isomers of substituted azafluorene IV. Both isomers (IVa and IVb) were isolated.

Low-melting isomer IVb is converted to the more stable high-melting isomer IVa when it is heated in acetone. The different chromatographic mobilities of these isomers are evidently explained by the degree of shielding of the heteroring nitrogen atom, which should be greater for isomer IVb. This is possible when the styryl fragment of the divinylphenyl group is located on the same side as the pyridine ring of the azafluorene system. Isomer IVa can be assigned a configuration with a divinylphenyl group in the opposite position. (See scheme on following page).

The α proton of the pyridine ring in isomer IVb is located in the plane of the double bond of the styryl fragment. Because of this, its PMR signal appears at weaker field (9.00 ppm) than the signal of the same proton in the spectra of starting III and isomer IVa (at 8.46 and 8.65 ppm, respectively). A signal of the protons of the unbonded shift reagent is observed in the PMR spectra of a mixture of isomer IVb and small amounts of the PSR; this indicates incomplete coordination. This is evidently a consequence of shielding of the nitrogen

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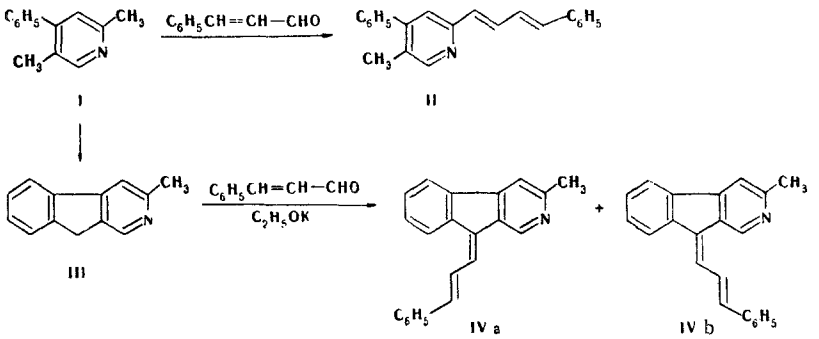
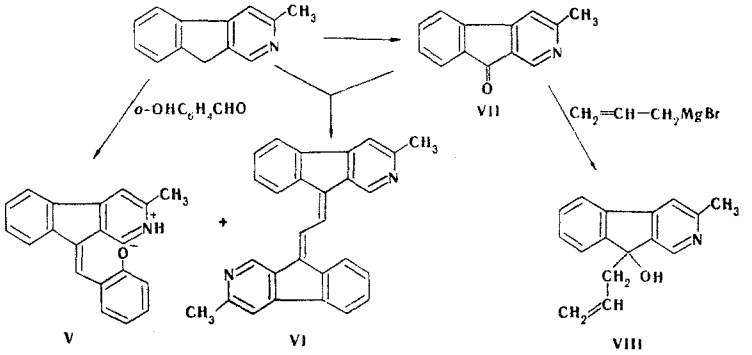


atom by the divinylphenyl fragment. Thus the data presented above confirm the structures of isomers IVa and IVb. Data from the PMR spectra ($^3J = 15$ Hz) and IR spectra (intense absorption bands of out-of-plane vibrations of the CH bonds of the diene fragment at 965 cm^{-1}) provide evidence for the trans orientation of the hydrogen atoms attached to the double bonds of isomers IVa and IVb. The UV absorption spectra of IVa and IVb are similar to the UV spectrum of s-trans-cinnamylidenefluorene [3].

Two substances were obtained in the condensation of azafluorene III with salicylaldehyde in the presence of potassium ethoxide. One of the substances is the normal condensation product – 3-methyl-9-(2-hydroxybenzylidene)-2-azafluorene (V). The relatively high melting point (262-264°C) of this product can be explained by its saltlike structure, which is formed as a result of interaction of the acidic proton of the phenolic hydroxyl group with the pyridine ring nitrogen atom. This apparently determines the configuration of V, which was isolated in the form of a single geometrical isomer. The IR spectrum of V does not contain the absorption band of a free hydroxyl group. At the same time, it does contain intense absorption bands at 2564 and 2339 cm^{-1}, which evidently can be assigned to the quaternized nitrogen atom. The second substance is 1,2-bis(3-methyl-2-azafluorenylidene)ethane (VI), which was obtained as red high-melting crystals (mp 321.5-323°C). The UV spectrum of VI is similar to the UV spectrum of 1,6-bis(diphenylyl)hexatriene [3]. The formation of substituted butadiene VI evidently takes place in several steps. 3-Methyl-2-azafluorene (VII) [2] is formed relatively easily from azafluorene III in a medium unprotected from oxygen in the presence of strong bases; we demonstrated this in the case of the direct oxidation of azafluorene III. It was shown in [4, 5] that in the alkylation of fluorene with alcohols in the presence of alkoxides the reaction mixture always contains an aldehyde (acetaldehyde in the case of ethanol). Aldol condensation of azafluorenone VII with acetaldehyde gives 3-methyl-2-azafluorenylideneacetaldehyde, which then condenses with azafluorene III. To a certain extent this scheme for the formation of VI is confirmed by its synthesis from azafluorenone VII and azafluorene III in an alcohol solution of potassium ethoxide.



The mass spectrometric data confirm the empirical formula of VI. The ion with m/e 369 (M – 15) indicates elimination of a methyl group from the molecular ion. The ion with m/e 357 corresponds to elimination of hydrocyanic acid, and the intense ion with m/e 343 indicates elimination of acetonitrile; this confirms the position of the methyl group in the pyridine ring. An unsaturated alcohol of the azafluorene series – 3-methyl-9-allyl-2-aza-9-fluorenol (VIII) was obtained from azafluorenone VII and allylmagnesium bromide.

EXPERIMENTAL

The PMR spectra of $CDCl_3$ solutions of the compounds were recorded with a Tesla BS-487C spectrometer with hexamethyldisiloxane as the internal standard. The IR spectra of KBr pellets of the compounds were

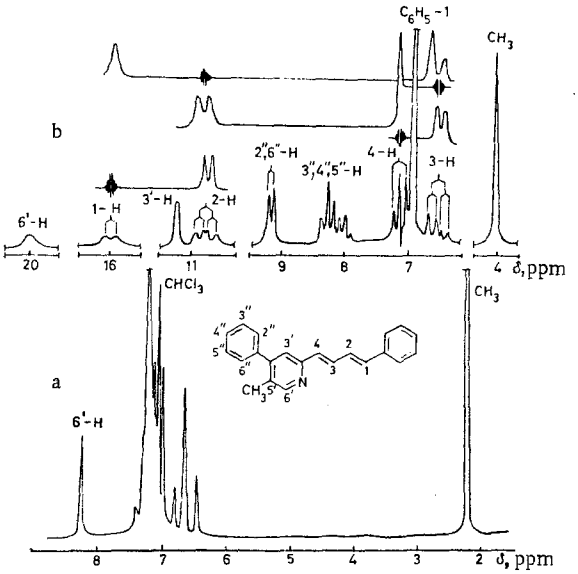


Fig. 1. Double-resonance PMR spectra of II: a) monoresonance spectrum; b) spectrum of II containing Eu(DPM)$_3$ [[Eu(DPM)$_3$]/[substrate] = 0.66].

obtained with a UR-20 spectrometer. The UV spectra of ethanol solutions of the compounds were recorded with a Hitachi spectrophotometer. The mass spectra were obtained with an MKh-1303 mass spectrometer. Chromatography was carried out on activity II Al_2O_3.

1-Phenyl-4-(5-methyl-4-phenyl-2-pyridyl)buta-1,3-diene (II). A solution of 5.1 g (28 mmole) of pyridine base I, 8 g (61 mmole) of cinnamaldehyde, 3 ml of acetic anhydride, and 2 ml of glacial acetic acid was refluxed for 10 h, after which it was made alkaline to pH 10 with 40% sodium hydroxide solution. The reaction product was extracted with ether, and the extract was dried with magnesium sulfate. Dry hydrogen chloride was passed into the ether solution, and the precipitated hydrochloride was dissolved in 20 ml of alcohol. The alcohol solution was passed through a layer of aluminum oxide, and the residue isolated from the eluate was crystallized repeatedly from hexane to give 0.4 g (5%) of yellow crystals of substituted butadiene II with mp 116.5-118°C. PMR spectrum ($CDCl_3$): 8.26 (1H, s, α-H) and 6.45-7.40 ppm (15H, m, aromatic and divinyl protons). IR spectrum: 1620 (ν = CH−CH = CH−C_6H_5) and 995 cm^{-1} (δ_{CH} band of the trans-divinyl fragment). UV spectrum, λ_{max} (log ε): 205 (4.64), 240 (4.41), 316 (4.52), and 342 nm (4.74). Found: C 88.9; H 6.4; N 4.6%. $C_{22}H_{19}N$. Calculated: C 88.9; H 6.4; N 4.7%. The picrate was obtained as red crystals with mp 238-239°C (from acetone). Found: N 10.5%. $C_{22}H_{19}N \cdot C_6H_3N_3O_7$. Calculated: N 10.6%.

3-Methyl-9-cinnamylidene-2-azafluorene (IV). A solution of 1 g (5.5 mmole) of azafluorene III, 0.94 g (7.1 mmole) of cinnamaldehyde, and 10 ml of 10% potassium ethoxide in 75 ml of absolute ethanol was refluxed for 6 h, after which it was cooled and worked up to give 0.24 g (14.8%) of isomer IVa as bright-yellow crystals with mp 213-214°C (from alcohol) and R_f 0.7. PMR spectrum ($CDCl_3$): 6.80-8.08 ppm (13H, aromatic and divinyl protons). IR spectrum: 1622 ($\nu_{C=C}$) and 966 cm^{-1} (δ_{C-H} in the =CH−CH=CH−C_6H_5 fragment). UV spectrum, λ_{max} (log ε): 209 (4.70), 240 (4.94), 264 (4.64), 275 (4.50). and 389 (4.99). Found: C 89.4; H 5.9; N 4.6%; M 295 by mass spectrometry. $C_{22}H_{17}N$. Calculated: C 89.5; H 5.8; N 4.7%; M 295.

Water (20 ml) was added to the alcohol mother liquor, and the mixture was evaporated to 40 ml and worked up to give 0.6 g of a mixture of isomers IVa and IVb (R_f 0.9 and 0.7), from which 0.1 g (6.2%) of yellow crystals of isomer IVb with mp 159-161°C and R_f 0.9 was isolated by chromatography (elution with ether). PMR spectrum ($CDCl_3$): 6.78-8.00 ppm (13 H, m, aromatic and divinyl protons). IR spectrum: 1623 ($\nu_{C=C}$) and 966 cm^{-1} (δ_{C-H} in the =CH−CH=CH−C_6H_5 fragment). UV spectrum, λ_{max} (log ε): 208 (4.29), 215 (4.26), 244 (4.53), 264 (4.28), 275 (4.09), and 388 nm (4.58). Found: C 89.4; H 5.9; N 4.6%; M 295 by mass spectrometry. $C_{22}H_{17}N$. Calculated: C 89.5; H 5.8; N 4.7%; M 295. When isomer IVb (mp 159-161°C) was refluxed in acetone, it was converted to isomer IVa (mp 213-214°C). A mixture of both isomers (established by chromatography) was formed when isomer IVa was heated in toluene in the presence of iodine.

3-Methyl-9-(2-hydroxybenzylidene)-2-azafluorene (V) and 1,2-Bis(3-methyl2-azafluorenylidene)ethane (VI). A) A 2.2-g (18 mmole) sample of salicylaldehyde and 20 ml of 10% potassium hydroxide in 40 ml of ethanol were added to a solution of 2 g (11 mmole) of azafluorene III in 90 ml of absolute ethanol, and the mix-

ture was refluxed for 7 h. The mixture was evaporated to 50 ml and worked up to give 0.2 g (6.4%) of red crystals of VI with mp 321.5-323°C (from chloroform). UV spectrum, λ_{max} (log ε): 216 (4.58), 240 (4.64), 267 (4.45), 401 (4.57), 420 (4.63), and 448 nm (4.62). Found: N 6.4%; M 3.84 (by mass spectrometry). $C_{28}H_{20}N_2$. Calculated: N 7.3%; M 3.84. Water (120 ml) was added to the alcohol mother liquor, and the mixture was evaporated to 100 ml and extracted with chloroform. The extract was dried with magnesium sulfate and worked up to give 1.2 g (38.3%) of yellow crystals of V with mp 262-264°C (from chloroform). IR spectrum: 2700, 2564, 2339 ($\nu_{>N^+-H}$), and 1633 cm^{-1} ($\nu_{C=C}$). UV spectrum λ_{max} (log ε): 210 (4.74), 223 (4.78), 246 (4.56), 290 (4.08), and 340 nm (4.36). Found: C 84.3; H 6.7; N 4.1%; M 285 (by mass spectrometry). $C_{20}H_{15}NO$. Calculated: C 84.2; H 5.43; N 5.0%; M 285.

B) A mixture of 40 ml of ethanol, 10 ml of 10% potassium ethoxide solution, 1 g (5.5 mmole) of azafluorene III, and 1.17 g (6 mmole) of azafluorene was refluxed for 8 h, and the resulting precipitate was removed by filtration, washed with alcohol, and crystallized from chloroform to give 0.2 g (5%) of red crystals of VI with mp 303.5-304.5°C, which differs from the melting point of the sample described above. IR spectrum: 1660 cm^{-1} ($\nu_{C=C}$). Found: N 7.6%; M 384 (by mass spectrometry). $C_{28}H_{20}N_2$. Calculated: N 7.3%; M 384. The mass spectra of the two samples of VI were identical.

3-Methyl-2-azafluorene (VII). Oxygen was passed through a solution of 0.5 g (2.7 mmole) of azafluorene III and 2 ml of the Rodinov catalyst in 40 ml of pyridine with stirring at 45°C for 40 min, after which the pyridine was removed by distillation, and the residue was purified with a column filled with aluminum oxide (elution with chloroform) to give 0.47 g (90%) of azafluorene VII with mp 143-144°C [2].

3-Methyl-9-allyl-2-aza-9-fluorenol (VIII). A solution of 1 g (5 mmole) of azafluorene VII in 75 ml of absolute benzene was added to allylmagnesium bromide, obtained from 6 g (50 mmole) of allyl bromide and 1.2 g (50 mmole) of magnesium in 40 ml of ether, and the mixture was refluxed for 4 h. Water (40 ml) and 80 ml of a saturated solution of ammonium chloride were added, and the benzene layer was separated and dried with magnesium sulfate. The benzene was removed from the extract, and the residue was crystallized from heptane to give 0.2 g (16.5%) of colorless crystals of azafluorenol VIII with mp 145-146°C. PMR spectrum ($CDCl_3$): 7.98 (1H, s, α-H), 5.01-5.65 (1H, m, 2-H), 4.81 (1H, d, J = 11 Hz, cis-3-H), 4.77 (1H, d, J = 17 Hz, trans-3-H), 3.88 (1H, broad s, O−H), and 2.72 ppm (2H, d, J = 7 Hz, $-CH_2-$). IR spectrum: 3080 (associated OH), 1640 ($\nu_{C=C}$), and 1070 cm^{-1} (ν_{C-OH}). Found: N 6.1%. $C_{16}H_{15}NO$. Calculated: N 5.9%.

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