9-α-NITRO(HYDROXY, AMINO)BENZYLIDENE- AND 9-HYDROXY(AMINO)METHYLENE-4-AZAFLUORENES

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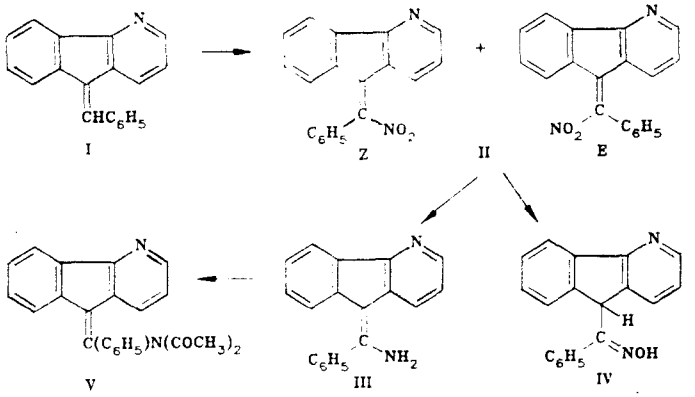
Nitration of 9-benzylidene-4-azafluorene with acetyl nitrate leads to the formation of its 9-α-nitrobenzylidene derivative; reduction of the latter gives the corresponding enamine and oxime. Reaction of 4-azafluorene with ethyl benzoate and ethyl formate gives the hydroxybenzylidene and hydroxymethylene derivatives, which upon condensation with amines generate the corresponding enamines. Reduction of 9-formylazafluorene oxime gives 9-aminomethyleneazafluorene. All of the newly synthesized compounds were isolated in the form of mixtures of their Z- and E-isomers, and their structures were established using PMR spectroscopy.

9-Alkylidene(arylidene)azafluorenes are of interest as potential physiologically active compounds, as well as sythons for the synthesis of more complex heterocyclic compounds [1, 2]. There have been only limited reports in the literature concerning compounds in this series containing functional groups attached to the exocyclic double bond in the 9-position: in [3] the synthesis and reactions of 3-methyl-9-acyl(aroyl)-2-azafluorenes were reported.

In the present paper we have carried out the synthesis of 4-azafluorene derivatives containing hydroxy, nitro, and amino groups attached to the double bond in the designated position. The nitration of 9-benzylidene-4-azafluorene (I) by acetyl nitrate was investigated in glacial acetic acid solution. It is known [4] that alkenes react with acetyl nitrate at −70 to 0°C to form β-nitroacetoxy compounds, as well as β-nitronitrates and β-nitroalkenes.

Nitration of benzylideneazafluorene I takes place only at temperatures above 50°C, and the reaction mixture turns brown from the formation of nitrogen oxides. Substitution of the hydrogen atom in the benzylidene group by a nitro group occurs under these reaction conditions. 9-(α-Nitrobenzylidene)-4-azafluorene (II) is formed in quantitative yield.



The nitration experiment was carried out on a mixture of Z- and E-isomers of compound I. The nitro derivative II also consisted of a mixture of geometric isomers, from which the individual pure Z- and E-isomers could be isolated by chromatography. The configuration of each isomer was established based on the chemical shift values for the 1-H and 8-H protons in their PMR spectra (Table 1). Using two-dimensional spectroscopy of the Nuclear Overhauser Effect (NOESY), it was found [5] that in the Z- and E-isomers of compound I the 1-H proton has characteristic CS values of 7.76 and 7.98 ppm, while the CS of the 8-H proton is 7.83 and 7.62 ppm in the two isomers, respectively. Based on these values we cannot explain the observed anomalous upfield shifts of the 1-H proton in the high-melting isomer II (6.78 ppm) and of the 8-H proton in the other isomer (6.56 ppm) in terms

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TABLE 1. PMR Spectra of 4-Azafluorenes II-V, VII-XIV*

Compound	Chemical shifts, δ, ppm								
	1-H	2-H	3-H	5-H	6-H	7-H	8-H	9-H	substituents on $C_{(10)}$
Z-II	6,78	6,87	8,48	8,03	7,54	7,42	7,59	—	7,59 ... 7,68 (C_6H_5)
E-II	7,76	7,20	8,59	7,99	7,41	7,07	6,56	—	7,59 ... 7,69 (C_6H_5)
Z-III	8,10	7,26	8,53	8,14	7,19	6,99	6,34	—	5,11 (NH_2) | 7,52 ... 7,63
E-III	6,46	6,79	8,34	8,29	7,42	7,51	7,89	—	5,25 (NH_2) / (C_6H_5)
IV	7,77	7,17	8,65	8,24	7,51	7,39	7,54	6,26	6,88 ... 7,14 (C_6H_5); 10,05 (OH)
Z-V	7,77	7,20	8,57	8,02	7,39	7,09	7,02	—	2,44 (CH_3); 7,49 ... 7,67 (C_6H_5)
E-V	7,14	6,89	8,47	8,09	7,50	7,43	7,61	—	2,45 (CH_3)
Z-VII	8,35	7,32	8,45	8,00	7,36 ... 7,45		7,96	—	7,30 (10-H)
E-VII	8,22	7,25	8,41	8,16			7,90	—	7,32 (10-H)
VIII	7,81	7,18	8,65	8,19	7,31 ... 7,81			5,66	7,31 ... 7,81 (C_6H_5)
Z-IX	8,51	7,22	8,41	7,97	7,22 ... 7,33		7,80	—	8,97 (NH); 7,93 (10-H) | 6,96 ... 7,33
E-IX	8,21	7,13	8,36	8,03	7,22 ... 7,44		7,95	—	8,92 (NH); 7,88 (10-H) / (C_6H_5)
Z-X	7,85	7,17	8,49	8,21	7,39	7,40	7,57	—	7,32 (10-H) | 3,55 и 3,87
E-X	7,78	7,22	8,51	8,14	7,39	7,39	7,66	—	7,43 (10-H) / (CH_2)$_2$
Z-XI	8,32	7,24	8,42	8,07	7,34	7,19	7,70	—	7,65 (10-H) | 3,54 и 3,75
E-XI	7,94	7,18	8,36	8,16	7,30	7,45	7,99	—	7,59 (10-H) / (CH_2)$_2$; 6,83 (NH)
Z-XII	8,0	7,20	8,54	8,11	7,36	7,43	7,81	—	8,35 (10-H); 7,56 (NH) | 6,90 ... 8,34
E-XII	8,01	7,23	8,51	8,22	7,44	7,50	7,79	—	8,33 (10-H); 7,68 (NH) / (Py)
Z-XIII	7,77	7,28	8,67	8,19	7,48	7,54	7,67	5,79	6,65 (10-H); 10,24 (OH)
E-XIII	7,88	7,26	8,69	8,19	7,48	7,53	7,61	4,81	7,27 (10-H); 9,60 (OH)
Z-XIV	7,85	7,23	8,53	8,14	7,32	7,39	7,62	—	7,53 (10-H); 4,91 (NH_2)
E-XIV	7,82	7,17	8,48	8,25	7,41	7,49	7,63	—	7,44 (10-H); 5,02 (NH_2)

*The PMR spectra of compounds VII and XI were recorded for DMSO-D_6 solutions; the other spectra were taken in $CDCl_3$.

of an anisotropic effect of the phenyl substituent. The observed phenomenon must be due to magnetic anisotropy of the nitro group [6]. Because of the nonplanar conformation of the nitro group in the cis-orientation, the 1-H proton is located in its shielding cone or radius. For this reason, we have assigned the high-melting isomer of compound with mp 191-193°C, which exhibits the more upfield 1-H proton signal, the Z-configuration, while the isomer with mp 179-181°C, which exhibits the more upfield 8-H proton signal, is thus assigned the E-configuration. The Z- to E-isomer ratio in the reaction mixture was determined using PMR spectroscopy and was found to be equal to 1:2.5. An isomeric mixture having the same composition was also obtained upon nitration of the Z-isomer of compound I by concentrated HNO_3 in acetic acid. Under these conditions the E-isomer of the nitro derivative II is partially converted to its Z-isomer. The nitration process thus results in an equilibrium between the Z- and E-isomers of compound II, with the E-isomer representing the thermodynamically more stable isomer.

In order to determine the relative stability of the Z- and E-isomers in compound II, we have carried out quantum mechanical calculations for both isomers using MNDO, a semiempirical valence bonding approximation. All the bond lengths and bonding angles in the 4-azafluorene fragment were optimized during the calculations process. The following standard or normal bond-length values were used for the phenyl fragment and the nitro group: C—C 1.397, C—H 1.09, C—NO_2 1.42, N—O 1.32 Å; the phenyl fragment was rotated by 60°. The calculations revealed that the E-isomer is more stable than the Z-isomer by 4.3 kcal/mole. The dipole moment of the E-isomer (4.5 D) is also greater than that of the Z-isomer (2.6 D), which suggests that additional stabilization of the former is possible in polar solvents.

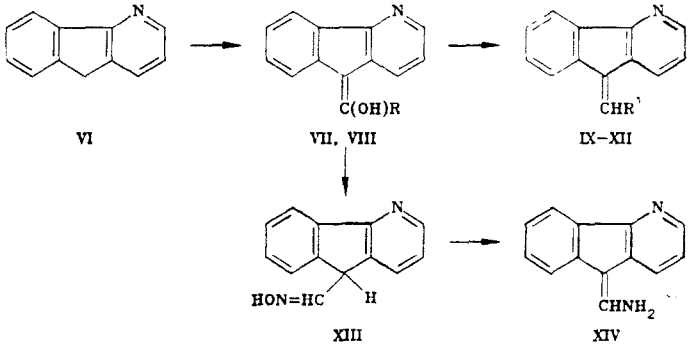
The reduction of the mixture of isomers II was examined using a series of different reducing agents. Reduction with zinc dust in alcohol ammonia medium gave 9-(α-aminobenzylidene)-4-azafluorene (III) in high yield in the form of a mixture of Z- and E-isomers in a 1:2.6 ratio, based on its PMR spectral data. Reduction with sodium borohydride in a mixture of chloroform and isopropyl alcohol led to the formation of 9-(α-hydroxyimino-

benzylidene)-4-azafluorene (IV), which exists as a pure isomer based on its PMR data. Reduction of compound II with lithium aluminum hydride gave a mixture of compounds III and IV.

Signal assignments for the Z- and E-isomers in the PMR spectrum of compound III were made using difference NOE spectroscopy. Upon alternating irradiation of the 8-H (7.89 ppm) and 1-H (6.46 ppm) protons in the predominant isomer the NOE for the NH_2 group signal was 4.5 and 0%, respectively, indicating that the 8-H and NH_2 protons are in proximity to one another, i.e., the predominant isomer has the E-configuration. This result is also supported by the configuration assignment deduced above for the geometric isomers in the nitro derivative II. Retention of the Z- to E-isomer ratio leads us to conclude that reduction of the nitro group in compound II occurs with retention of configuration. The anomalous upfield shifts of the 1-H proton in the E-isomer and the 8-H proton in the Z-isomer of the amino derivative III must be due to anisotropy of the phenyl group. Molecular mechanics calculations [7] carried out with geometry optimization have shown that in compound III the phenyl group is rotated by 77° relative to the azafluorene fragment; in compound II the angle of rotation is 62°. Thus, in the Z- and E-isomers the 8-H and 1-H protons, respectively, are oriented near the symmetry axis of the phenyl ring, resulting in the observed upfield shifts of these protons.

Acetylation of enamine III with acetic anhydride gave 9-(α-diacetylaminobenzylidene)-4-azafluorene (V).

The condensation of 4-azafluorene (VI) was attempted with both ethyl formate and ethyl benzoate in the presence of sodium. The formyl and benzoyl derivatives were isolated in the form of high-melting yellow and red crystals, respectively. According to their IR and PMR spectral data, the compounds exist in their enol structures.



VI VII, VIII IX–XII XIII XIV

VII, IX–XI R=H, VIII R=C_6H_5; IX R^1=NHC_6H_5; X R^1=morpholino; XI R^1= =$NH(CH_2)_2OH$; XII R^1=NH (α-Py)

The fact that the PMR spectrum of compound VII contains two signals for each of the 1-H, 8-H, and 10-H protons suggests that the compound exists in DMSO solution in the form of a 1:1 mixture of Z- and E-isomers. Upon dissolving the hydroxybenzylidene derivative VIII in chloroform the red color dissipates and a colorless solution is formed, corresponding to the keto form of compound VIII, as inferred from the appearance of an intense carbonyl group stretching band at 1678 cm^{-1} in its IR spectrum.

Condensation of compound VII with aniline, morpholine, ethanolamine, and α-aminopyridine in the presence of boron trifluoride etherate gave the corresponding 9-aminomethylene-4-azafluorene derivatives IX-XII in greater than 70% yield each. Their PMR spectra exhibit singlets for the 10-H proton in the 7.32-7.93 ppm region. The presence of two signals for each of the 1-H and 8-H protons in their spectra is due to the existence of enamines IX-XII in the form of mixtures of geometric isomers. The isomer with the more downfield 1-H proton signal in each case is assigned the Z-configuration, the isomer with the more downfield 8-H proton signal the E-configuration.

Compound VII reacts with hydroxylamine in pyridine in its oxo form. The structure of the resulting product 9-(hydroxyiminomethyl)-4-azafluorene (XIII) was established based on the presence in its PMR spectrum of coupled 9-H and 10-H proton signals with J = 8 Hz. The appearance of two signals for each of the 1-H, 8-H, 9-H, 10-H, and N—OH protons is again due to the existence of oxime XIII in the form of a 1:1 mixture of Z- and E-isomers relative to the C=N bond. In analogy with earlier research [5, 8], the isomer with the more downfield 9-H proton signal is assigned the Z-configuration.

Oxime XIII was reduced to enamine XIV, also in the form of a mixture of geometric isomers. During the process of recrystallization of enamine XIV the isomer ratio in the crystals was altered. Assignment of the Z- and E-isomers for enamine XIV was derived based on the results of two-dimensional NOESY spectroscopy, which exhibited cross peaks for the 1-H—NH_2 proton pair in the Z-isomer, and for the 8-H—NH_2 proton pair in the E-isomer.

EXPERIMENTAL

IR spectra were recorded on a UR-20 spectrophotometer using KBr pellets. PMR spectra were obtained on a Bruker WM-400 spectrometer using solutions in $CDCl_3$ and DMSO-D_6 versus TMS as internal standard. Mass spectra were measured on an MX-1303 mass spectrometer at an ionizing electron energy of 70 eV.

Column chromatography was carried out using L 40/100 silica gel with 1:1 heptane—ethyl acetate as eluent. TLC analyses were performed using Silufol UV-254 plates with the same solvent mixture. The product extracts were dried over $MgSO_4$.

The results of C, H, N elemental analysis agreed with calculations.

9-(α-Nitrobenzylidene)-4-azafluorene (II, $C_{19}H_{12}N_2O_2$). A. To a mixture of 0.5 g (1.9 mmoles) of the benzylideneazafluorene isomeric mixture I in 15 ml glacial acetic acid at 20°C was added 1.5 ml of concentrated HNO_3. The mixture was heated 3 h at 75-80°C (as the reaction course was followed by TLC). The mixture was cooled, poured into 100 ml water, and neutralized with saturated sodium hydroxide solution. The reaction products were extracted with ether (3 × 75 ml). The residue (0.49 g) remaining from the extract (after evaporation) was subjected to column chromatography (40 × 5 cm). Yield 0.33 g (60%) of the E-isomer of compound II, yellow crystals, mp 179-181°C (from ethyl acetate—heptane), R_f 0.57. M^+ 300. Further elution gave 0.13 g (24%) of the Z-isomer of compound II, yellow crystals, mp 191-193°C (from ethyl acetate—heptane), R_f 0.2. M^+ 300.

B. Upon heating in an analogous manner, 0.25 g (0.95 mmoles) of the Z-isomer of compound I (mp 96-98°C) gave 0.22 g (73%) of nitro derivative II as a mixture of Z- and E-isomers.

C. A solution of 0.3 g (1 mmole) of the E-isomer of nitro derivative II in 0.5 ml concentrated HNO_3 and 5 ml acetic acid was heated at 80°C for 2 h. The reaction products were isolated as described above. Yield 0.25 g (83%) of a mixture of Z- and E-isomers of compound II (based on TLC analysis).

9-(α-Aminobenzylidene)-4-azafluorene (III, $C_{19}H_{14}N_2$). A mixture of 0.5 g (1.6 mmoles) nitro compound II (isomeric mixture), 0.2 g (3.2 mmoles) zinc dust, and 0.24 g (3.2 mmoles) ammonium acetate in 100 ml ethanol and 100 ml 25% aqueous ammonia was refluxed for 10 h. The alcohol was distilled, and the solution was then extracted with chloroform, and the residue remaining from the extract was purified by column chromatography (35 × 2 cm). Yield 0.33 g (74%) of enamine III, yellow crystals, mp 160-161°C (from ethyl acetate—heptane), R_f 0.47 (2:1 ethyl acetate—heptane). IR spectrum: 3460, 3380 (NH_2), 1622 cm^{-1} (exocyclic C=C). M^+ 270.

9-(α-Hydroxyiminobenzyl)-4-azafluorene (IV, $C_{19}H_{14}N_2O$). A. A solution of 0.5 g (1.6 mmoles) nitrocompound II and 0.13 g (3.2 mmoles) lithium aluminum hydride was refluxed for 4 h in 300 ml absolute ether. Ethyl acetate (5 ml) was added, followed by a solution of 20% potassium hydroxide until a solid precipitate formed. The reaction products were extracted with ether. The residue remaining from the extract was subjected to column chromatography (45 × 1.5 cm). Yield 0.15 g (33%) of oxime IV as colorless crystals, mp 181-183°C (from heptane—ethyl acetate). IR spectrum: 3100 cm^{-1} (OH). M^+ 286.

This was followed by the elution of 70 mg (15%) enamine III, mp 145-147°C.

B. To a solution of 0.3 g (1 mmole) nitro compound II in 15 ml chloroform and 2 ml isopropyl alcohol was added 0.16 g (4.2 mmoles) sodium borohydride in portions over a 45-min period. The mixture was refluxed for 10 h, 30 ml water was added, and the chloroform layer was separated. The reaction products were extracted from the aqueous layer with ether (2 × 20 ml). The residue remaining from the combined extracts was subjected to column chromatography (40 × 2 cm). Yield 0.14 g (50%) of oxime IV, mp 181-183°C.

9-(α-Diacetylaminobenzylidene)-4-azafluorene (V, $C_{23}H_{16}N_2O_2$). A solution of 0.3 g (1.1 mmoles) enamine III in 15 ml acetic anhydride was refluxed for 4 h, poured into 150 ml water, and extracted with ether; the residue after evaporation of the ether solvent was recrystallized from a mixture of ethyl acetate—heptane. Yield 0.28 g (81%) of compound V as colorless crystals, mp 149-151°C, R_f 0.48. IR spectrum: 1720 and 1704 (CO); 1632 cm^{-1} ($C{=}C_{exocyclic}$). M^+ 354.

9-Hydroxymethylene-4-azafluorene (VII, $C_{13}H_9NO$). To a solution of 1 g (5.9 mmoles) 4-azafluorene (VI) in 1.46 g (19.7 mmoles) ethyl formate was added 0.28 g (12 mmoles) finely shaved sodium, and the mixture was stirred for 1 h at 20°C. Absolute ether (20 ml) was added, and the mixture was refluxed for 1 h. The solution was then treated sequentially with 15 ml alcohol and 35 ml 15% aqueous acetic acid solution. The precipitate was removed by filtration and washed successively with water, acetone, and ether, and then crystallized from ethyl alcohol. Yield 1.03 g (89%) of compound VII as yellow crystals, mp 230-232°C, R_f 0.31 (ethyl acetate—hexane, 10:1). IR spectrum: 2480 (OH); 1670 cm^{-1} ($C{=}C_{exocyclic}$). M^+ 195.

9-(α-Hydroxybenzylidene)-4-azafluorene (VIII, $C_{19}H_{13}NO$). A mixture of 1 g (5.9 mmoles) azafluorene VI, 2.7 g (18 mmoles) ethyl benzoate, and 0.28 g (0.12 mmoles) sodium was stirred for 12 h at 20°C and 2 h at 70°C.

After addition of ethanol and acetic acid the mixture was extracted with ether. The residue remaining after ether evaporation was purified by column chromatography (50 × 1.7 cm); elution with 1:1 hexane—ethyl acetate gave 0.8 g (40%) compound VIII as red crystals, mp 155-157°C (from ethyl acetate—heptane), R_f 0.35. IR spectrum: 2500 (OH); 1658 cm^{-1} ($C{=}C_{exocyclic}$). M^+ 271.

9-Phenylamino(IX) [Morpholino (X), β-Hydroxyethylamino (XI), α-Pyridylamino (XIII)]methylene-4-azafluorene. A solution of equimolar amounts of compound VII and the appropriate amine in 100 ml absolute alcohol was refluxed for 5 h with a catalytic amount of boron trifluoride etherate. The residue after evaporation of the alcohol solvent was crystallized from a mixture of ethyl acetate—heptane (compound IX), or heptane—alcohol (compounds X-XIII). Compound IX, $C_{19}H_{14}N_2$, yellow crystals, mp 170-172°C, R_f 0.35. IR spectrum: 3300 (NH); 1672 ($C{=}C_{exocyclic}$); 1618 cm^{-1} (δ_{NH}). M^+ 217. Yield 86%. Compound X, $C_{17}H_{16}NO$, yellow crystals, mp 150-152°C, 78%, R_f 0.25. IR spectrum: 1622 cm^{-1} ($C{=}C_{exocyclic}$). M^+ 264. Yield 78%. Compound XI, $C_{15}H_{14}N_2O$, yellow crystals, mp 166-168°C, R_f 0.4. IR spectrum: 3342 (NH); 3120 (OH); 1642 cm^{-1} ($C{=}C_{exocyclic}$). M^+ 238. Yield 78%. Compound XII, $C_{18}H_{13}N_3$, yellow crystals, mp 183-185°C, R_f 0.51, 0.65 (alufol, ethyl acetate—heptane, 4:1). IR spectrum: 3300 (NH), 1647 cm^{-1} ($C{=}C_{exocyclic}$). M^+ 271. Yield 80%.

9-Hydroxyiminomethyl)-4-azafluorene (XIII, $C_{13}H_{10}N_2O$). A solution of 1 g (5.12 mmoles) compound VII and 0.82 g (12.4 mmoles) hydroxylamine hydrochloride in 35 ml absolute pyridine was refluxed for 2 h. The pyridine was distilled off. To the residue was added 100 ml water and the reaction products were extracted with ether (3 × 50 ml). The residue remaining after ether evaporation was crystallized from heptane—ethyl acetate. Yield 1.03 g (96%) of oxime XIII, colorless crystals, mp 151-153°C, R_f 0.37 (ethyl acetate—heptane, 2:1). IR spectrum: 3182 cm^{-1} (OH). M^+ 210.

9-Aminomethylene-4-azafluorene (XIV, $C_{13}H_{10}N_2$). A mixture of 1 g (4.76 mmoles) oxime XIII, 1 g (15 mmoles) zinc dust, 10 ml ethanol, and 1 g ammonium acetate in 100 ml 25% aqueous ammonia was refluxed for 5 h. The reaction products were extracted with chloroform (4 × 50 ml). The residue remaining from the extract was crystallized from a mixture of heptane with ethyl acetate. Yield 0.78 g (85%) of enamine XIV as yellow crystals, mp 180-182°C, R_f 0.30 (from ethyl acetate—hexane, 3:1). IR spectrum: 3480, 3300, 3170 (NH_2); 1667 ($C{=}C_{exocyclic}$); 1625 cm^{-1} (δ_{NH}). M^+ 194.

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