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REACTION OF 9-AMINO(PHENYLAMINO)METHYLENE- AND 9-α-AMINOBENZYLIDENE-4-AZAFLUORENES WITH SOME ELECTROPHILIC REAGENTS

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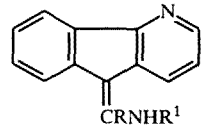
It was shown that initial protonation of 9-aminomethylene-4-azafluorene takes place at the pyridine nitrogen atom. In nitrosation of this azafluorene, 4-azafluorenone oxime is formed, and in reaction with dichlorocarbene, 1'-amino-2',2'-dichlorospiro[4-azafluorene-9,3'-cyclopropane] is formed. Acylation yields mono- or diacyl derivatives as a function of the acylating agent and reaction conditions.

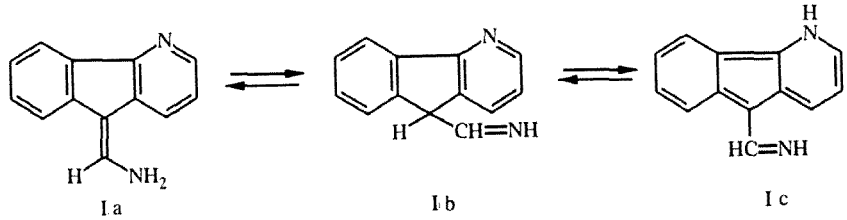
We previously synthesized 9-amino (I) [phenylamino (II)]methylene- and 9-α-aminobenzylidene (III)-4-azafluorenes [1]



I, II R = H; III R = C_6H_5; I, III R = H; II R = C_6H_5

Protonation and nitrosation of compound I, its reaction with dichlorocarbene, and acylation of compounds I-III were investigated to establish the structure and study the chemical properties of aminomethylene-substituted 4-azafluorenes and to obtain their derivatives — potentially biologically active compounds.

The existence of 9-aminomethylene-4-azafluorene (I) in the form of tautomers can be hypothesized: enamine Ia, imine Ib, and imine-4H Ic.



Ia Ib Ic

The analysis of the IR and UV spectra and quantum chemical calculations (PPP method) unambiguously show that compound I has the structure of enamine Ia. The calculated heat of atomization ΔH_{at} for form Ia is higher than for form Ic (Table 1).

The IR spectrum of compound I contains an intense band of $\nu_{C=C}$, δ_{NH_2} in the 1652 cm^{-1} region. Stretching vibrations of the amino group, ν_{NH_2}, appear as a broad multicomponent band in the 3500-2500 region, and there are pronounced maxima at 3460 and 3400 ($\nu_{NH_2}^{as}$) and 3320 and 3280 cm^{-1} ($\nu_{NH_2}^{s}$) against this background. The two $\nu_{NH_2}^{as}$ maxima and two $\nu_{NH_2}^{s}$ maxima are probably due to the existence of compound I in the form of a mixture of *Z*- and *E*-isomers [1]. The character of

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the ν_{NH_2} band suggests the participation of an amino group in formation of stable hydrogen bonds of the N–H-Nsp^2 type. The large difference between the experimental values of $\nu_{NH_2}{}^s$ and the values calculated with Eqs. 1 and 2 (Δ = 56 cm^{-1}) and $\Delta\nu = \nu_{NH_2}{}^{as} - \Delta_{NH_2}{}^s$ (Δ = 140 cm^{-1}) are in agreement with this [2, 3].

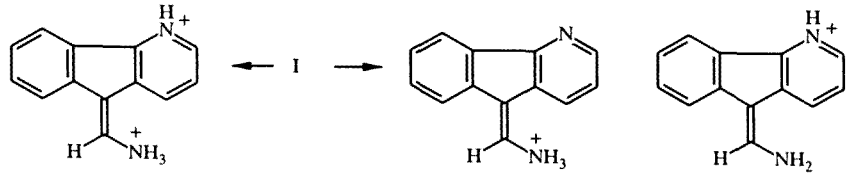
$$\nu^s = 345{,}53 + 0{,}876\,\nu^{as} \quad (1)$$

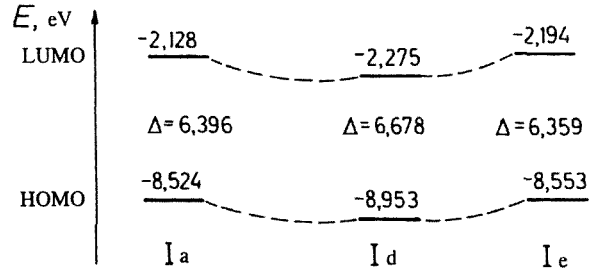
$$\Delta\nu = \nu^{as} - \nu^s = 0{,}4219\,\nu^s - 1348{,}2 \quad (2)$$

The electronic absorption spectrum calculated for compound Ia is in agreement with the experimental spectrum (Table 1). According to the calculation, the long-wave band at 342.5 nm is 81% due to the electronic transition from HOMO to LUMO. The atoms in the enamine fragment, =C=CH–NH_2, make the basic contribution to HOMO (22, 14, and 18%). The analysis of the values of the π charges in the ground and first excited states shows that the long-wave electronic transition is primarily due to electron transfer from the =C=CH–NH_2 exocyclic group (ΔQ = 0.188 e$^-$) to the pyridine fragment (ΔQ = –113 e). This allows using the position of the long-wave band for comparing the nucleophilicity of the nitrogen atoms in compound I. Protonation of an amine (sp^3-hybridized) nitrogen atom ejects its electron pair from the π system, resulting in a decrease in E_{HOMO}, and has little effect on E_{LUMO}, where the contribution of this nitrogen atom is much smaller (7%). As a result of an increase in $\Delta E = E_{LUMO} - E_{HOMO}$, a hypsochromic shift in the long-wave band will be observed. On the other hand, protonation of the pyridine nitrogen atom will increase its electron-acceptor properties, resulting in a decrease in ΔE, since in this case E_{LUMO} decrease more than E_{HOMO}. As a result, a bathochromic shift in the long-wave band should be observed in the electronic absorption spectrum. The results of the quantum chemical calculations of compound I and its protonated forms Id-f are reported in Table 1 and Fig. 1.

The experimental data obtained are in good agreement with the results of the calculation. A bathochromic shift of the long-wave band by ~6 cm^{-1} indicative of protonation of the pyridine nitrogen atom is observed in the electronic absorption spectrum under the effect of HCl on compound I. The bands at 251 and 256 nm are hypsochromically shifted to 246 nm. A hypsochromic shift of the long-wave band (by 8 nm) indicating formation of dianion If is only observed in concentrated sulfuric acid.

Nitrosation of compound I with nitrous acid was conducted in hydrochloric or acetic acid medium. In both cases, 4-azafluorenone oxime was obtained with a yield of 79%.





9-Hydroxymethylene-4-azafluorene (IV) is probably formed initially and nitrosated in the oxo form with formation of 9-nitroso-9-formyl-4-azafluorene. Oxidation of the aldehyde group, decarboxylation and isomerization of 9-nitroso-4-azafluorene into oxime V the take place. This hypothesis was confirmed by conversion of 9-formyl-substituted 4-azafluorene IV [1] into oxime V under the effect of nitrous acid. The reaction of compound I with dichlorocarbene was conducted in chloroform in

TABLE 1. Calculated and Experimental Data on Protonation of Aminomethyleneazafluorene I

Compound	ΔH_{AT}^0, eV	M_{solv}	UV spectrum	
			calculated λ, nm (f)	experimental λ, nm (log ε)
Ia	128,87	0,575	342,5 (0,44); 313,2 (0,66); 300 (0,32)	334 (4,08); 316 (4,12); 271 (4,03); 256 (4,04); 251 (4,03); 231 (sh) (4,26); 226 (4,30); 204 (3,84)
Ic	127,91	2,324	636 (0,06); 382 (0,19); 335,4 (0,553)	—
Id	132,03	0,298	328,7 (0,26); 313 (0,11); 292 (0,10)	—
Ie	133,52	1,304	350,1 (0,35); 321,6 (0,10); 314,9 (0,47)	340 (4,29); 272 (4,16); 246 (4,04); 224 (4,18)*
If	136,69	1,037	335,1 (0,30); 319,3 (0,14); 299 (0,25)	326 (4,16); 251 (3,70); 243 (3,70); 210 (4,01)*2

*Spectrum recorded with HCl.

*2 Spectrum recorded with conc. H_2SO_4.

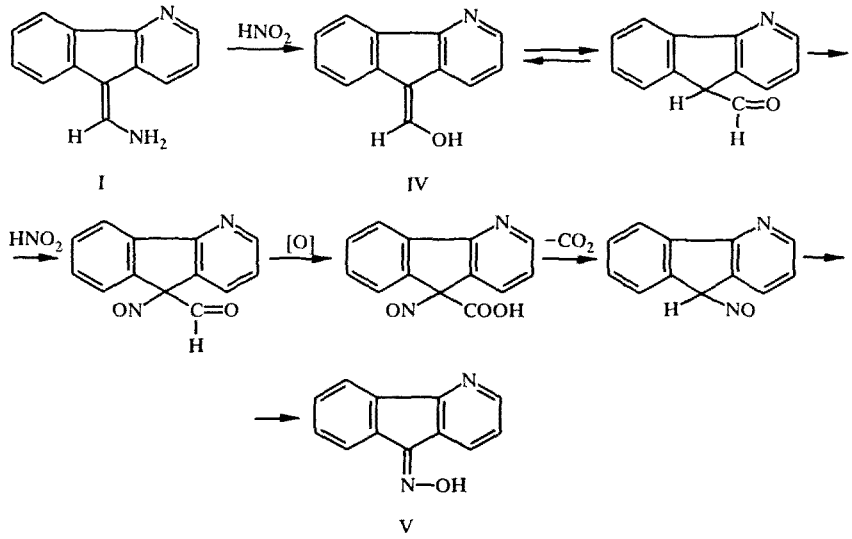
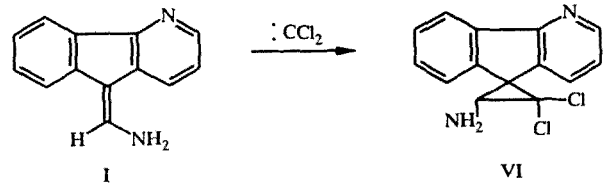


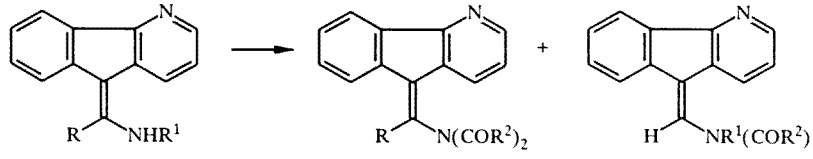
Fig. 1. Calculated LUMO and HOMO energies of aminomethyleneazafluorene I and its protonated forms Id, Ie.

the presence of 18-crown-6 and dichlorocarbene was generated with sodium hydroxide solution. 1′-Amino-2′,2′-dichlorospiro[4-azafluorene-9,3′-cyclopropane] (VI) was chromatographically separated from the reaction mixture with a low yield.



Spiro compound VI was an oily yellow substance which rapidly darkened in air. According to the TLC data, it is a mixture of two geometric isomers. There is no molecular ion peak in its mass spectrum, which is characteristic of decomposition of gem-dichloro-substituted cyclopropanes [4]. The presence of the fragmentary ions $[M-Cl]^+$ 241/243 (85*) and $[MnHCl]^+$ 240/242 (27*) in the mass spectrum† confirms the structure of compound VI.

Acylation of compounds I-III was conducted with acetic and trifluoroacetic anhydrides, benzoyl chloride, and chloroacetyl chloride. In the reaction of compound I with two moles of benzoyl chloride, 9-(benzoylaminomethylene)-4-azafluorene (VII) was basically formed (74% yield). Dibenzoyl derivative VIII was separated with a yield of 5%. When a four-fold molar excess of benzoyl chloride was used in the reaction, compound VIII was formed with a quantitative yield.



I VIII VII, IX–XI

VII R^1 = H, R^2 = C_6H_5; VIII R = H, R^2 = C_6H_5; IX R^1 = H, R^2 = CF_3;
X R^1 = H, R^2 = $ClCH_2$; XI R^1 = R^2 = C_6H_5

Acylation of compound I with a four-fold molar excess of trifluoroacetic anhydride yielded monotrifluoroacetyl derivative IX. In chloroacetylation of compound I in benzene in the presence of triethylamine, a complex mixture of substances was formed, and chloroacetyl derivative X was separated from them with a low yield. 9-(N-Phenyl-N-benzoylaminomethylene)-4-azafluorene (XI) was obtained in benzoylation of compound II.

It was previously shown in [1] that 9-(α-diacetylaminobenzylidene)-4-azafluorene is formed when 9-(α-aminobenzylidene)-4-azafluorene III is boiled in acetic anhydride.

The structure of acylamino-substituted methylene- and benzylideneazafluorenes VII-XI was demonstrated with IR, PMR (Table 2), and mass spectroscopy.

Molecular ion peaks corresponding to their empirical formulas are observed in the mass spectra of compounds VII-XI. Bands of stretching vibrations of an exocyclic C=C$^-$ bond are present in the 1632-674 cm^{-1} region in their IR spectra. The band of stretching vibrations of an amide group C=O bond is observed in the 1704-1763 cm^{-1} region. Since the starting aminomethylene- and benzylidene-substituted azafluorenes were mixtures of geometric isomers, the products of acylation VII-XI were also mixtures of *Z*- and *E*-isomers. The configuration of these isomers was established with the values of the chemical shifts of 1-H and 8-H protons in their PMR spectra. In the case of compounds VII-XI, the isomer with the weaker pole signal of the 1-H proton was assigned to the *Z* configuration, and the isomer with the weaker 8-H proton signal was assigned to the *E* configuration. In the case of compound XI, in consideration of the shielding effect of the phenyl substituent at the nitrogen atom, the *Z* configuration was assigned to the isomer with the stronger 1-H signal and the *E* configuration was assigned to the isomer with the strong 8-H proton signal.

The number of acyl groups involved in acylation at the exocyclic nitrogen is thus a function of the structure and amount of acylation reagent entering into the reaction and the structure of the substrate.

EXPERIMENTAL

The IR spectra were recorded on UR-20 and Specord 75-IR spectrometers in KBr pellets. The UV spectra were recorded on a Specord M-40V in 96% ethanol, and the mass spectra were recorded on a MX-1303 with direct sample introduction into the ion source and ionizing voltage of 760 eV. The PMR spectra were made on a Bruker WM-400 in $CDCl_3$,

*The values of *m/z* (intensity) are reported here and below.

†Intensity for ^{35}Cl isotope.

TABLE 2. Proton Chemical Shifts in the PMR Spectra of Acylated 9-Aminomethylene-4-azafluorenes (VII-XI) in $CDCl_3$

Compound		Characteristic shifts, δ, ppm										Z:E isomer ratio
		1-H	2-H	3-H	5-H	6-H	7-H	8-H	10-H	N—H	Side chain substituents	
VII	Z	8,01	7,28	8,58	8,06	7,42	7,45	7,60...7,70	8,28	8,70	7,60...7,70 (3H, C_6H_5), 8,95...8,99 (2H, C_6H_5)	1 : 1
	E	7,86	7,23	8,55	8,19	7,50	7,54	7,82	8,21	8,80	7,60...7,70 (3H, C_6H_5), 8,95...8,99 (2H, C_6H_5)	
VIII	Z	8,93	7,30	8,57	8,01	7,41	7,31	7,64	8,05	—	8,31 (O—H), 7,50...7,77 (C_6H_5)	1 : 1,5
	E	7,82	7,09	8,51	8,04	7,54	7,54	8,78	7,96	—	8,31 (O—H), 7,50...7,77 (C_6H_5)	
IX	Z	7,96	7,78	8,60	8,04	7,44...7,48		7,54	7,86	8,23	—	1 : 1
	E	7,79	7,25	8,58	8,15	7,52...7,56		7,74	7,80	8,34	—	
X	Z	7,93	7,20	8,54	8,16	7,48...7,52		7,64	7,86	9,30	4,34 CH_2Cl	1 : 1,7
	E	7,84	7,24	8,57	8,05	7,40...7,44		7,74	7,94	9,14	4,34 CH_2Cl	
XI	Z	7,29	6,92	8,44	8,00	7,35	7,47	7,71	7,64	—	7,59 (O—H); 7,20...7,35 (C_6H_5)	2 : 1
	E	7,89	7,17	8,53	8,00	7,35	7,47	7,25	7,64	—	7,59 (O—H); 7,20...7,35 (C_6H_5)	

TMS internal standard. The quantum chemical calculations were performed with the PPP method with optimization of interatomic distances based on the minimum of the heats of atomization [5]. Silufol UV-254 and Alufol plates were used for thin-layer chromatography, and silica gel 40/100 and aluminum oxide with Brockmann degree II activity were used for column chromatography. The developer was iodine vapors.

The data from elemental analysis for C, H, N, and Cl were in agreement with the calculated data.

Reaction of 9-Aminomethylene-4-azafluorene with Nitrous Acid. A. A solution of 0.7 g (10.25 mmole) of sodium nitrite in 5 ml of water was added to a solution of 1 g (5.1 mmole) of compound I in 20 ml of dilute (1:1) hydrochloric acid at 0°C over 0.5 h while stirring. It was mixed for 1 h at 0°C and alkalized with an aqueous solution of soda at pH 9-10. It was extracted with ether (3 × 100 ml) and dried with magnesium sulfate. The residue after distillation of the ether was crystallized from ethyl acetate, yielding 0.79 g (79%) of 4-azafluorenone-9-oxime (V), pale yellow crystals with mp = 247°C. A sample mixed with a reference sample [6] melted without temperature depression. Mass spectrum: M^+ 196.

B. Analogously, 0.75 g (75%) of oxime V, mp = 247-248°C (from ethyl acetate) was obtained in diazotization of 1 g (5.1 mmole) of compound I in 20 ml of glacial acetic acid.

In the reaction of 9-hydroxymethylene-4-azafluorene with nitrous acid according to method A, 0.84 g (84%) of oxime V, mp = 247°C, was obtained from 1 g (5.1 mmole) of 9-hydroxymethylene-4-azafluorene.

1′-Amino-2′,2′-dichlorospiro[4-azafluorene-9,3′-cyclopropane] (VI, $C_{14}H_{10}N_2Cl_2$). A catalytic quantity of 18-crown-6 and 5 ml of 50% aqueous solution of sodium hydroxide were added to a solution of 1 g (5.1 mmole) of compound I in 50 ml of chloroform at 20°C. It was stirred for 1 h at 20°C and 1 h at 50°C. Then 10 ml of water was added. The organic layer was separated, and the aqueous layer was extracted with chloroform (3 × 25 ml) and dried with magnesium sulfate. The residue after elimination of the chloroform was chromatographed in a column with silica gel (60 × 1.7 cm) with ethyl acetate–hexane, 1:10, as eluent. Then 0.19 g (14%) of compound VI, a yellow oil, R_f = 0.54 and 0.58 (Silufol, ethyl acetate–hexane, 1:1) was obtained.

9-(Benzoylaminomethylene)-4-azafluorene (VII, $C_{20}H_{14}N_2O$). Here 1.43 g (10.2 mmole) of benzoyl chloride in 3 ml of absolute pyridine was added by drops to a solution of 1 g (5.1 mmole) of compound I in 15 ml of absolute pyridine at 20°C. It was stirred for 3 h, 10 ml of water was added, it was extracted with chloroform (3 × 100 ml), and dried with magnesium sulfate. The residue after distillation of the chloroform was chromatographed in a column with silica gel (80 × 1.7 cm) with ethyl acetate–hexane eluent, 1:4. Then 0.1 g (5%) of dibenzoyl-substituted VIII, yellow crystals with mp = 182-184°C (ethyl acetate) and R_f = 0.29 (Silufol, ethyl acetate–hexane, 1:1) was separated. IR spectrum, ν, cm^{-1}: 1670 ($C{=}C_{exocycl}$), 1763 cm^{-1} (CO). Mass spectrum: M^+ 402. Then 1.13 g (74%) of compound VII was eluted, yellow crystals, mp = 222-224°C (from chloroform), R_f = 0.19 (Silufol, ethyl acetate–hexane, 1:1). IR spectrum: 1674 ($C{=}C_{exocycl}$), 1710 (CO), 3485 cm^{-1} (NH). Mass spectrum: M^+ 298.

9-(Dibenzoylaminomethylene)-4-azafluorene (VIII, $C_{27}H_{18}N_2O_2$). With a similar method, 0.83 g (81%) of dibenzoyl-substituted VIII, mp = 182-184°C, was obtained from 0.5 g (2.6 mmole) of compound I and 1.43 g (10.2 mmole) of benzoyl chloride. A sample mixed with the sample obtained above melted without temperature depression.

9-(Trifluoroacetylaminomethylene)-4-azafluorene (IX, $C_{15}H_9F_3N_2O$). Here 4.33 g (0.02 mole) of trifluoroacetic anhydride in 10 ml of absolute benzene was added by drops to a solution of 1 g (5.1 mmole) of compound I in 40 ml of absolute benzene at 20°C. It was boiled for 6 h. The residue after distillation of benzene was neutralized with saturated soda solution, extracted with ether (3 × 100 ml), and dried with magnesium sulfate. The residue after distillation of the ether was chromatographed in a column with silica gel (62 × 1.7 cm) with ethyl acetate–hexane eluent, 1:4, yielding 0.62 g (68%) of compound IX, pale yellow crystals, mp = 168-170°C (from ethyl acetate), R_f = 0.52 (Silufol, ethyl acetate–hexane, 1:1). IR spectrum: 1670 ($C{=}C_{exocycl}$), 1720 (CO), 3338 cm^{-1} (NH). Mass spectrum: M^+ 290.

9-(Chloroacetylaminomethylene)-4-azafluorene (X, $C_{15}H_{11}ClN_2O$). A solution of 0.95 g (8.4 mmole) of chloroacetyl chloride in 10 ml of absolute benzene was added by drops to a solution of 1.5 g (7.7 mmole) of compound I and 0.64 g (8 mmole) of triethylamine in 150 ml of absolute benzene at 20°C. The sediment was filtered off after 5 h. The residue after distillation of benzene from the filtrate was chromatographed in a column (60 × 1.7 cm) with aluminum oxide, ethyl acetate–hexane eluent, 1:15. Then 0.15 g (7.2%) of compound X was separated, pale yellow crystals, mp = 148-150°C (from heptane), R_f = 0.36 (Alufol, ethyl acetate–hexane, 1:1). IR spectrum: 1660 ($C{=}C_{exocycl}$), 1710, 1690 (CO), 3340 cm^{-1} (NH). Mass spectrum: M^+ 271.

9-(N-Phenyl-N-benzoylaminomethylene)-4-azafluorene (XI, $C_{26}H_{18}N_2O$). Here 0.55 g (3.9 mmole) of benzoyl chloride was added to a solution of 0.5 g (1.9 mmole) of compound II in 20 ml of absolute pyridine at 20°C and boiled for 8 h. It was cooled, poured in 100 ml of water, and alkalized with soda solution to pH 8. It was extracted with ether (4 × 50 ml) and dried with magnesium sulfate. The residue after distillation of the ether was chromatographed in a column (60 × 1.7 cm) with silica gel, ethyl acetate–hexane eluent, 1:5, yielding 0.44 g (64%) of compound XI, pale yellow crystals, mp = 167-169°C (from chloroform), R_f = 0.37 (Silufol, ethyl acetate–hexane, 1:1). IR spectrum: 1641 ($C{=}C_{exocycl}$), 1683 cm^{-1} (CO). Mass spectrum: M^+ 374.

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