9-ACETYL-(p-TOLYLCARBAMOYL)AMINOAZAFLUORENES

N. S. Prostakov, Hanna Bu Habib,
L. M. Kirillova, O. I. Sorokin,
and A. V. Varlamov

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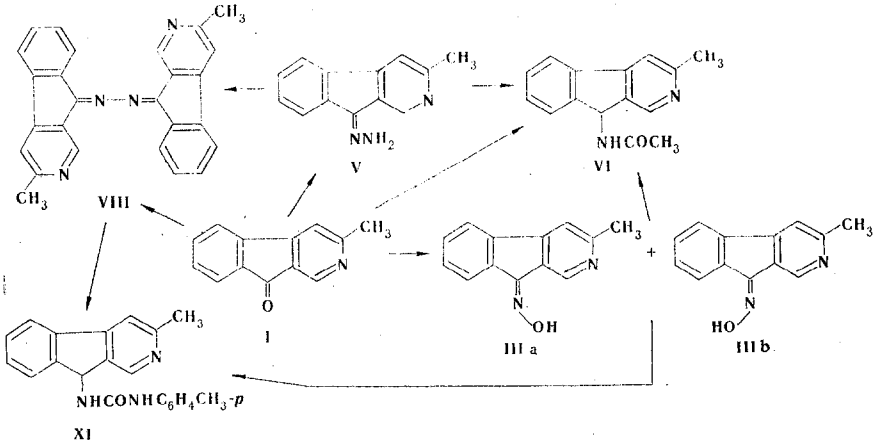
In the case of 9-amino-3-methyl-2-azafluorene and 9-amino-4-azafluorene, which are formed in the reduction of the hydrazones and oximes of the corresponding azafluorenones with hydrazine hydrate in the presence of pyrophoric nickel, it was confirmed that 9-aminoazafluorenes are unstable. N-Acetyl and N-carbamoyl derivatives of the indicated 9-aminoazafluorenes were obtained. According to the PMR spectral data, 3-methyl-2-azafluorenone oxime is produced in the form of a mixture of Z and E isomers. Ketazines corresponding to 3-methyl-2-azafluorenone and 4-azafluorenone were synthesized.

Information regarding 9-aminoazafluorenes is limited to the description of 9-acetamido-1,3-dimethyl-2-azafluorene, which is a derivative of the unstable 9-amino-1,3-dimethyl-2-azafluorene, which is a derivative of the unstable 9-amino-1,3-dimethyl-2-azafluorene [1]. The latter has rather strong basic properties and vigorously absorbs carbon dioxide from the air.

We undertook a study of aminoazafluorenes obtained on the basis of 3-methyl-2-azafluorenone (I) and 4-azafluorenone (II) in order to investigate their physiological activity. The precursors of 9-aminoazafluorenes, viz., the oximes and hydrazones of azafluorenones, are also of interest in this respect. It has been reported [2-4] that the isomeric (with respect to the position of the acetamido group) fluorenes display carcinogenic activity.

3-Methyl-2-azafluorenone oxime (III) and 4-azafluorenone oxime (IV) were obtained in quantitative yields from ketones I and II and hydroxylamine in pyridine. It follows from the data from the PMR spectrum of oxime III that it is produced in the form of a mixture of Z and E isomers (IIIa,b) with significant preponderance of the E isomer. The ratio of the Z and E isomers (1:2.5, respectively) was found from an evaluation of the integral intensities of the protons attached to $C_{(1)}$. In the PMR spectrum of the mixture of these isomers the proton in the $C_{(1)}$ position at δ 8.6 ppm is related to the E isomer, whereas the proton at δ 9.19 ppm is related to the Z isomer (the assignment was made as described in [5]).*



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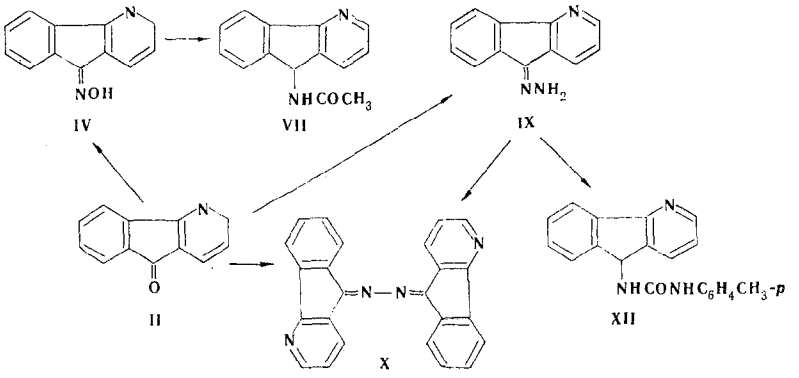
3-Methyl-2-azafluorenone hydrazone (V) and 4-azafluorenone hydrazone (IX) are formed very readily in yields greater than 75%. Up to 5% 4-azafluorene ketazine (X) is formed as a side product in the synthesis of hydrazone IX.

We were unable to isolate and characterize in the free form 9-amino-3-methyl-2-azafluorene and 9-amino-4-azafluorene, which are formed in the reduction of oximes III and IV. They are unstable and change rapidly in the air, ultimately undergoing conversion to the corresponding azafluorenones. These amines were therefore isolated in the form of the N-acetyl derivatives, which are the subjects of pharmacological study.



9-Acetamido-3-methyl-2-azafluorene (VI) was obtained by reduction of oxime III or hydrazone V with hydrazine hydrate in the presence of Raney nickel and also by the direct reaction of ketone I with hydrazine hydrate in the presence of the same catalyst with subsequent treatment of the resulting amine with acetic anhydride in each case.

9-Acetamido-4-azafluorene (VII) was obtained by the reduction of oxime IV with hydrazine hydrate in the presence of pyrophoric nickel with subsequent treatment of the reaction products with acetic anhydride.

3-Methyl-2-azafluorene ketazine (VIII) and 4-azafluoro ketazine (X), respectively, were obtained in quantitative yields by the reaction of azafluorenones I and II with a threefold to fivefold excess of hydrazine hydrate with subsequent treatment of the reaction mixtures with potassium hydroxide. Azafluorene ketazines VIII and X were also obtained from hydrazones V and IX upon contact of alcohol solutons of the latter with air in the presence of potassium hydroxide. The corresponding hydrazones, which were then oxidized in the presence of alkali by air oxygen to the azines [6], are initially formed in experiments in which ketones I and II were used as the starting compounds. The synthesized ketazines are colored crystalline substances with high melting points.

3-Methyl-9-(p-tolylcarbamoylamino)-2-azafluorene (XI) was obtained in the reduction of ketazine VIII with hydrazine hydrate in the presence of Raney nickel with subsequent treatment of the resulting amine with p-tolyl isocyanate. This compound was obtained via a similar pathway from oxime III. Hydrazone IX was used in the synthesis of 9-(p-tolylcarbamoylamino)-4-azafluorene (XII).

Thus the formation of 9-aminoazafluorenes was also established by means of N-carbamoyl derivatives. The instability of the 9-aminoazafluorenes is evidently due to the fact that the basic amino group in them is attached to the CH acid center of the azafluorene system. Just like their fluorene analogs, the amino derivatives of azafluorenes with different positions of the **anion** group are stable compounds.

EXPERIMENTAL

The IR spectra of III and V-VII were recorded with a Specord IR-75 spectrometer, whereas the IR spectra of IV, XI, and XII were recorded with a UR-20 spectrometer. The PMR spectrum of a solution of III in CD_3OD was recorded with a Tesla BS-487C spectrometer (60 MHz), whereas the PMR spectra of solutions of XI and XII in DMSO were recorded with a Tesla BS-497 spectrometer (100 MHz) (the internal standard was tetramethylsilane). The mass spectra were obtained with an MKh-1303 spectrometer with direct introduction of the samples into the ion source at an ionizing voltage of 70 V.

3-Methyl-2-azafluorenone Oxime (III) and 4-Azafluorenone Oxime (IV). These compounds were obtained by refluxing azafluorenones I and II, respectively, for 10 h with hydroxylamine hydrochloride (in a molar ratio of 1:6) in pyridine. The reaction mixtures were then poured into water, and the crystals of the oximes were removed by filtration.

Oxime III was obtained in 98% yield and had mp 240-240.5°C (dec., from ethanol). PMR spectrum: 13.0 ppm (1H, OH). IR spectrum (in mineral oil): 3200 cm^{-1} (OH with a hydrogen bond). Found: C 74.2; H 5.1; N 13.0%; M^+ 210. $C_{13}H_{10}N_2O$. Calculated: C 74.3; H 4.8; N 13.3%. M 210.

Oxime IV was obtained in 86% yield and had mp 247-247.5°C (from ethanol). IR spectrum (KBr pellet): 2650 (OH), 1670 (C=N), and 970 cm^{-1} (N–O). Found: C 73.7; H 4.2; N 14.7%. $C_{12}H_8N_2O$. Calculated: C 73.4; H 4.1; N 14.3%.

3-Methyl-2-azafluorenone Hydrazone (V) and 4-Azafluorenone Hydrazone (IX). These compounds were obtained by refluxing azafluorenones I and II, respectively, in alcohol for 15 min with a fourfold to fivefold excess of hydrazine hydrate. The resulting precipitates were crystallized. Hydrazone IX was contaminated with a small amount (up to 5%) of ketazine X (mp 266-267°C).

Hydrazone V was obtained in 77.5% yield and had mp 192-193°C [from ethanol–chloroform (3:1)] and R_f 0.31 (activity II Al_2O_3, ethyl acetate). IR spectrum (in chloroform): 3430 and 3330 cm^{-1} (NH_2). Found: C 74.4; H 5.5; N 20.3%; M^+ 209. $C_{13}H_{11}N_3$. Calculated: C 74.6; H 5.3; N 20.1%; M 209.

Hydrazone IX was obtained in 96% yield and had mp 158-159°C (from ethanol) and R_f 0.5 (Silufol UV-254, ethyl acetate). IR spectrum (in chloroform): 3430 and 3330 cm^{-1} (NH_2). Found: C 73.7; H 4.4; N 21.9%; M^+ 195. $C_{12}H_9N_3$. Calculated: C 73.8; H 4.6; N 21.5%; M 195.

3-Methyl-9-acetamido-2-azafluorene (VI) and 9-Acetamido-4-azafluorene (VII). A) A 6-g (0.12 mole) sample of hydrazine hydrate and 0.5 g of Raney nickel were added to a suspension of 3 g (0.014 mole) of oxime III in 100 ml of ethanol, and the mixture was stirred for 5 h, during which two 2-g (0.04 mole) portions of hydrazine hydrate were added. The catalyst was removed by filtration, and the alcohol was removed by distillation. Acetic anhydride (50 ml) was added to the residue, and the mixture was heated at 80°C for 1 h. The acetic anhydride was removed by distillation, and the residue was crystallized from benzene to give 2.1 g (62%) of amide VI with mp 218-219°C. IR spectrum (in mineral oil): 3260 (–NH), 1650 (C=O), and 1545 cm^{-1} (NH deformation band). Found: C 75.6; H 5.5; N 11.8%; M^+ 238. $C_{15}H_{13}N_2O$. Calculated: C 75.6; H 5.5; N 11.8%; M 238.

B) A solution of 0.5 g (0.025 mole) of azafluorenone I and 2 g (0.04 mole) of hydrazine hydrate in 5 ml of ethanol was heated at 60°C for 5 min, after which 1 g of Raney nickel was added, and stirring at room temperature was continued for 3 h. The catalyst was removed by filtration, the alcohol was removed by distillation, and the residue was heated with 5 ml of acetic anhydride at 50°C for 15 min. The acetic anhydride was removed by distillation, and the residue (0.6 g) was crystallized from benzene to give 0.4 g (65.5%) of VI with mp 218-219°C.

C) A mixture of 0.06 g (0.03 mmole) of 3-methyl-2-azafluorenone hydrazone (V), 3 g (0.06 mole) of hydrazine hydrate, and 0.3 g of Raney nickel in 10 ml of ethanol was heated at 40°C for 20 min. The subsequent acetylation and isolation of the product were carried out as in method A to give 0.04 g (68.3%) of amide VI with mp 218-219°C.

Amide VII, with mp 218-219°C [from heptane–ethyl acetate (20:1)], was obtained in 54.3% yield from oxime IV by method A. IR spectrum (in chloroform); 3420 (–NH) and 1680 cm^{-1} (C=O). Found: N 12.1%. $C_{14}H_{12}N_2O$. Calculated: N 12.5%.

3-Methyl-2-azafluorene Ketazine (VIII) and 4-Azafluorene Ketazine (X). A) A 0.4-g (2 mmole) sample of ketone I and 2 g (0.04 mole) of hydrazine hydrate were refluxed in 10 ml of ethanol for 15 min, after which 1 ml of 15% alcoholic potassium hydroxide solution was added, and the mixture was stirred vigorously at room temperature for 1 h. The resulting precipitate was removed by filtration to give 0.37 g (98%) of ketazine VIII in the form of brick-red crystals with mp 260-261°C [from alcohol–chloroform (1:2)]. Found: C 80.6; H 4.8; N 14.3%; M^+ 386. $C_{26}H_{18}N_4$. Calculated: C 80.8; H 4.6; N 14.5%; M 386.

B) Red crystals of ketazine X, with mp 266-267°C (from n-butanol), were similarly obtained in 70% yield from azafluorenone II. Found: C 80.4; H 4.2; N 15.5%; M^+ 358. $C_{24}H_{14}N_4$. Calculated: C 80.5; H 3.9; N 15.6%; M 358.

C) A 0.5-1 g sample of solid potassium hydroxide was added to a solution of 0.1 g of hydrazones V and IX, respectively, in 5-10 ml of ethanol, and the mixture was stirred vigorously at 45-50°C for 0.5-1 h. Ketazines VIII and X were isolated in yields greater than 90%. Ketazine VIII had mp 260-262°C, while ketazine X had mp 266-267°C.

3-Methyl-9-(p-tolylcarbamoylamino)-2-azafluorene (XI) and 9-(p-Tolylcarbamoylamino)-4-azafluorene (XII). A) A mixture of 0.6 g (2.9 mmole) of oxime III, 1 g (0.02 mole) of hydrazine hydrate, 0.3 g of Raney nickel, and 20 ml of ethanol was stirred for 1 h, after which the catalyst was removed by filtration, and the alcohol was removed by distillation. The residue was dissolved in 10 ml of benzene, 0.5 g (3 mmole) of p-tolyl isocyanate was added, and the resulting precipitate was removed by filtration and washed with ether to give 0.65 g (68.4%) of XI in the form of colorless crystals with mp 262-263°C [from benzene–ethanol (2:1)]. PMR spectrum: 2.23 (3H, s, tolyl CH_3), 2.54 (3H, s, 3-CH_3), 5.96 (1H, d, J_{HCNH} = 8.5 Hz, 9-H), 6.74 (1H, d, J_{HCNH}=8.5 Hz, –NH–C(=O)–), 7.66 (1H, m, 8-H), 7.72 (1H, s, 4-H), 7.93 (1H, m, 5-H), 8.37 (1H, s, –C(=O)–NH–Ar), and 8.64 ppm (1H, s, 1-H). IR spectrum (KBr pellet): 3325, 3293 (–NH); 1640 (C=O); 1575 cm^{-1} (NH deformation band). Found: N 12.8%; M^+ 329. $C_{21}H_{19}N_3O$. Calculated: N 12.7%; M 329.

B) The similar reaction of 1 g (2.6 mmole) of ketazine VIII, 2 g (0.04 mole) of hydrazine hydrate, 0.2 g of Raney nickel, and 0.7 g (5.26 mmole) of p-tolyl isocyanate gave 1.27 g (75%) of XI.

For the preparation of XII we used 0.5 g (2.5 mmole) of hydrazone IX, 1 g (0.02 mole) of hydrazine hydrate, 0.2 g of Raney nickel, 0.5 g (3.7 mmole) of p-tolyl isocyanate, and 25 ml of ethanol. The reaction and isolation of the product were carried out by method A to give 0.88 g (45%) of XII with mp 258-260°C [with sublimation, from benzene–ethanol (3:1)]. PMR spectrum: 2.23 (3H, s, CH_3), 5.91 (1H, d, J_{HCNH} = 8.5 Hz, 9-H, 6.78 (1H, d, J_{HCNH} = 8.5 Hz, –NH–C(=O)–), 7.02-7.53 (H, m, azafluorene and benzene ring protons), 7.67 (1H, m, 8-H), 7.94 (2H, m, 1-H and 5-H), 8.41 (1H, s, –C(=O)–NH–Ar), and 8.55 ppm (1H, q, J_{23} = 5 Hz, J_{31} = 1.5 Hz, 3-H). IR spectrum (KBr pellet): 3320, 3283 (–NH); 1640 (C=O); 1580 cm^{-1} (NH deformation band). Found: N 13.6%; M^+ 315. $C_{20}H_{17}N_3O$. Calculated: N 13.3%; M 315.

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