CYANOETHYLATION OF 3-METHYL-2-AZAFLUORENE

N. S. Prostakov, V. P. Shalimov,
and V. P. Zvolinskii

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3-Methyl-9,9-di(β-cyanoethyl)-2-azafluorene was obtained from 3-methyl-2-azafluorene via the Michael reaction and was converted to the dibasic acid and its diester. Dieckmann condensation of the latter and subsequent hydrolysis gave 3-methyl-4'-oxospiro(2-azafluorene-9,1'-cyclohexane).

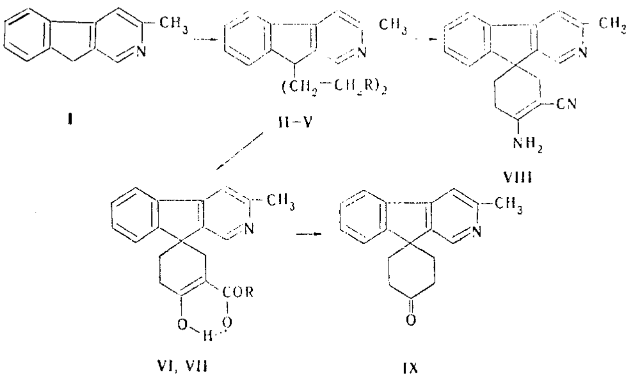
Up until now, compounds of the spiro(azafluorene-9,1'-cyclohexane) type have not been obtained. The analogous compounds of the fluorene series have been synthesized and subjected to pharmacological study [1-3]. In this connection, we thought it would be expedient to accomplish the synthesis of 3-methyl-4-oxo-spiro(2-azafluorene-9,1'-cyclohexane) (IX) – the first representative of compounds of this type in the azafluorene series.

3-Methyl-2-azafluorene (I), the method for the preparation of which was developed in [4], was used as the starting substance.

The first step in the synthesis was cyanoethylation of I via the Michael reaction. The condensation of I with acrylonitrile was carried out in the presence of an alcohol solution of an ethoxytrimethylphenylammonium salt (the Rodionov catalyst) [5]. 3-Methyl-9,9-di(β-cyanoethyl)-2-azafluorene (II) was obtained in quantitative yield. The formation of a monocyanoethyl derivative under these conditions was not established.

Subsequent hydrolysis of II gave 3-methyl-9,9-di(β-carboxyethyl)-2-azafluorene (III). The esters (IV and V) of this dibasic acid were obtained both by esterification of III and by treatment of II with the appropriate alcohol in the presence of sulfuric acid.

The cyclization of II in the presence of sodium and potassium gave 3-methyl-3'-cyano-4'-aminospiro-(2-azafluorene-9,1'-cyclohex-3-ene) (VIII). Intense bands at 3455 (ν_{as} NH_2), 3365 (ν_s NH_2), 4652 (δ NH_2), and 2178 (ν $C \equiv N$) cm^{-1} are observed in its IR spectrum; this indicates that this compound exists in the enamine nitrile form [6].



II R=CN; III R=COOH; IV R=COOCH$_3$; V R=COOC$_2$H$_5$; VI R=CH$_3$; VII R=C$_2$H$_5$

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Dieckmann cyclization of diesters IV and V gave VI and VII, to which the 3-methyl-4'-hydroxy-3'-carbomethoxy- and -3'-carbethoxyspiro(2-azafluorene-9,1'-cyclohex-3-ene) structures, respectively, were assigned on the basis of the IR spectra.*

Subsequent hydrolysis of VI and decarboxylation of the resulting β-keto acid gave 3-methyl-4'-oxospiro(2-azafluorene-9,1'-cyclohexane) (IX), which was characterized by analysis, spectroscopy, and derivatives.

All of the spectral characteristics of the compounds obtained are in agreement with the literature data on the analogous fluorene derivatives [3].

EXPERIMENTAL

3-Methyl-9,9-di(β-cyanoethyl)-2-azafluorene (II). A 2.3-g (0.43 mole) sample of acrylonitrile was added at 40° in the course of 20 min to a solution of 2 g (0.011 mole) of I in 20 ml of benzene and 0.2 ml of a freshly prepared alcohol solution of the Rodionov catalyst, and the mixture was stirred at 50° for 2 h. Water (50 ml) was added, the benzene layer was washed with water and dried with magnesium sulfate. Removal of the benzene by distillation gave 2.54 g (81%) of colorless crystals of II with mp 159-160.5° (from alcohol). Found,%: C 79.6; H 6.1; N 14.3. $C_{19}H_{17}N_3$. Calculated,%: C 79.4; H 5.9; N 14.6. IR spectrum: 2253 cm^{-1} ($C\equiv N$). The PMR spectrum of II in CF_3COOH demonstrated the presence of two CH_2CH_2CN groups at δ 2.54 and 1.53 ppm. The molecular weight of II, measured with an MKh-1303 spectrometer, was 287. The picrate of II had mp 216.5-217.5° (from alcohol–acetone). Found,%: N 16.0. $C_{19}H_{17}N_3 \cdot C_6H_3N_3O_7$. Calculated,%: N 16.3.

3-Methyl-9,9-di(β-carboxyethyl)-2-azafluorene (III). A mixture of 1.5 g (5 mmole) of II, 50 ml of 20% potassium hydroxide, and 15 ml of alcohol was refluxed for 15 h and neutralized with 70% sulfuric acid to give 1.36 g (80%) of colorless crystals of III with mp 242-243° (from aqueous alcohol). Found,%: C 69.7; H 5.6; N 4.2. $C_{19}H_{19}NO_4$. Calculated,%: C 70.0; H 5.8; N 4.3. IR spectrum, cm^{-1}: 2530 (bonded OH), 1725 (carbonyl group).

3-Methyl-9,9-di(β-carbomethoxyethyl)- and -di(β-carbethoxyethyl)-2-azafluorenes (IV and V, respectively). A. A mixture of 2 g (7 mmole) of II, 10 ml of methanol, and 2 ml of concentrated sulfuric acid was refluxed for 12 h, after which 30 ml of water was added, and the mixture was treated with sodium carbonate. The reaction products were extracted with ether to give 1.92 g (78%) of IV. Esterification of III with methanol gave IV in 37% yield as colorless crystals with mp 98-99.5° (from heptane). Found,%: N 4.2. $C_{21}H_{23}NO_4$. Calculated,%: N 4.0.

B. Ester V was similarly obtained from II in 66% yield, while esterification of III gave the same product in 76% yield with mp 64-65.5° (from hexane). Found,%: C 72.6; H 7.4; N 3.7. $C_{23}H_{27}NO_4$. Calculated,%: C 72.3; H 7.4; N 3.7. IR spectra: 1747 (IV) and 1743 (V) cm^{-1} (ester $C=O$), 1180 (IV), and 1187 cm^{-1} (ester $C-O-C$).

3-Methyl-4'-hydroxy-3'-carbomethoxy- and -3'-carbethoxyspiro(2-azafluorene-9,1'-cyclohex-3-enes) (VI and VII, respectively). A. The experiment was carried out under nitrogen. A solution of 1.8 g (5.1 mmole) of IV in 20 ml of toluene and 0.01 g (1.7 mmole) of sodium methoxide were vigorously stirred at 100° for 2 h, after which 25 ml of water and 5 ml of acetic acid were added. The toluene layer was washed with 20% sodium carbonate solution and water and dried with calcium chloride to give 1.25 g (85%) of colorless crystals of VI with mp 120-121.5° (from heptane). Found,%: C 75.0; H 5.6; N 4.5. $C_{20}H_{18}NO_3$. Calculated,%: C 74.8; H 5.9; N 4.4. The picrate of VI had mp 206-209° (from alcohol–acetone). Found,%: N 10.0. $C_{20}H_{18}NO_3 \cdot C_6H_3N_3O_7$. Calculated,%: N 10.0. The signals at δ 3.66 ppm in the PMR spectrum of VI in CCl_4 are related to the methoxy group, while the two multiplets at 2.63 and 1.92 ppm are due to the spin–spin coupling of the cyclohexane ring. The two multiplets at 3.01 and 2.17 ppm in the PMR spectrum of VI in CF_3COOH also correspond to this coupling. Ester VI gives a characteristic violet color with aqueous ferric chloride solution.

B. Compound VII was similarly obtained from V in 56.5% yield. It was characterized as the picrate with mp 199-200° (from alcohol–acetone). Found,%: N 10.1. $C_{21}H_{20}NO_3 \cdot C_6H_3N_3O_7$. Calculated,%: N 10.0.

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*The intense bands at 1657 and 1623 cm^{-1} are related to the chelate structure, which contains conjugated $C=O$ and $C=C$ bonds.

3-Methyl-3'-cyano-4'-aminospiro(2-azafluorene-9,1'-cyclohex-3-ene) (VIII). A solution of 1 g (3.5 mmole) of II in 10 ml of toluene was added with stirring at 80° to a suspension of 0.1 g of sodium and 0.01 g of potassium in 5 ml of toluene, and the mixture was held at 95° for 5 h, after which 10 ml of alcohol and 40 ml of water were added. The reaction products were extracted with ether to give 0.4 g (40%) of light-yellow crystals of VIII with mp 216-219° (from hexane–benzene). Found,%: C 79.5; H 6.0; N 14.7. $C_{19}H_{17}N_3$. Calculated,%: C 79.5; H 6.0; N 14.6.

3-Methyl-4'-oxospiro(2-azafluorene-9,1'-cyclohexane) (IX). A mixture of 0.5 g (1.16 mmole) of VI, 3 ml of acetic acid, 3 ml of concentrated hydrochloric acid, and 0.5 ml of water was refluxed for 6 h, after which it was neutralized with 20% sodium hydroxide, and the organic bases were extracted with benzene. The benzene was removed from the extract by distillation, and the residue was converted to the hydrochloride, from which the free base was isolated with a column (under pressure, with activity II Al_2O_3 and elution with chloroform) to give 0.2 g (54%) of IX with mp 210-212° (from heptane–ethyl acetate). Found,%: C 81.7; H 6.9; N 5.3. $C_{18}H_{17}NO$. Calculated,%: C 82.0; H 6.5; N 5.4. The picrate of IX had mp 230° (dec., from alcohol–acetone). Found,%: N 11.3. $C_{18}H_{17}NO \cdot C_6H_3N_3O_7$. Calculated,%: N 11.4. The oxime of IX had mp 166-176° (from aqueous alcohol). Found,%: N 10.0. $C_{18}H_{18}N_2O$. Calculated,%: N 10.0. IR spectra of IX: intense band at 1730 cm^{-1}, which was somewhat higher than the frequency of the $C=O$ bond in a six-membered saturated ring. PMR spectrum of IX: two multiplets at 3.01 and 2.17 ppm, probably caused by spin–spin coupling of the protons of the cyclohexane ring.

The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrophotometer at 400-3300 cm^{-1} with LiF, NaCl, and KBr prisms. The PMR spectra were obtained with a Varian HA-100 D spectrometer with tetramethylsilane as the internal standard.

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