CYANOETHYLATION OF AZAFLUORENES AND SYNTHESES OF ALCOHOLS CONTAINING AN AZAFLUORENE FRAGMENT

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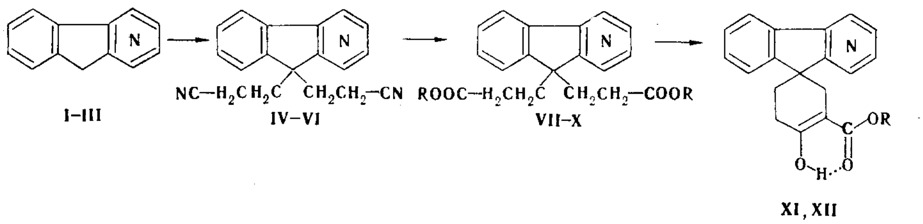
Isomeric (with respect to the position of the nitrogen atom) azafluorenes were cyanoethylated. The resulting 9,9-bis(β-cyanoethyl) derivatives were converted to the corresponding dibasic acids and their diesters. The latter were subjected to the Dieckmann reaction to obtain spiro compounds with azafluorene and cyclohexene fragments. The analogous spirans with 1,3-dioxalane and 1,3-dioxane rings were obtained from 3-methyl-2-azafluorenone.

The cyanoethylation of 3-methyl-2-azafluorene and the conversion of the resulting 3-methyl-9,9-bis(β-cyanoethyl)-2-azafluorene to 3-methyl-4-hydroxy-3-carbethoxyspiro(2-azafluorene-1,1'-cyclohex-3'-ene) were described in [1]. In connection with the study of the properties (including the physiological action) of such heterocyclic compounds it seemed of interest to obtain similar compounds from other isomeric (with respect to the position of the nitrogen atom) azafluorenes.

The development of a method for the preparation of 1-azafluorene (I) and 4-azafluorene (III) by catalytic dehydrocyclization of, respectively, 2-methyl-3-phenylpyridine [2] and 3-methyl-2-phenylpyridine [3] made it possible to carry out such syntheses in part. In repeating the experiments on the cyanoethylation of 3-methyl-2-azafluorene, in addition to the above-indicated 3-methyl-9,9-bis(β-cyanoethyl)-2-azafluorene, we isolated its dimethylated analog by chromatography. Consequently, in the catalytic dehydrocyclization of 2,5-dimethyl-4-phenylpyridine, in addition to the principal substance, viz., 3-methyl-2-azafluorene, 2-azafluorene (II), which had not been previously detected in the dehydrocyclization products [4], is also formed as a result of hydrogenolysis.



I, IV, VII — 1-aza; II, V, VIII, XI — 2-aza; III, VI, IX, X, XII — 4-aza; VII, IX R=H; VIII, XI R=C_2H_5; X, XII R=CH_3

The condensation of azafluorenes I-III with acrylonitrile was carried out in the presence of trimethylphenylammonium ethoxide [the Rodionov catalyst (RC)]. Dibasic acids, viz., 9,9-bis(β-carboxyethyl)-1-aza- and -4-azafluorenes (VII and IX), were obtained in the alkaline hydrolysis of 9,9-bis(β-cyanoethyl)-1-aza- and -4-azafluorenes (IV and VI). Diethyl ester XI was obtained from acid IX. 9,9-Bis(β-cyanoethyl)-2-azafluorene (V) was converted directly to diethyl ester VIII, Dieckmann condensation of which gave 4'-hydroxy-3'-carbethoxyspiro-[2-azafluorene-9,1'-cyclohex-3'ene] (IX) (isolated in the form of the picrate). The IR spectrum of this compound does not contain the band of the ester group (1730 cm^{-1}) of starting ester VIII, and the bands at 1600-1660 cm^{-1} indicate that it has a chelate form.

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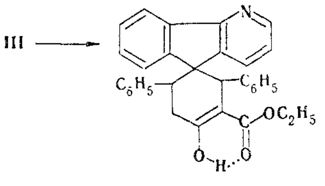
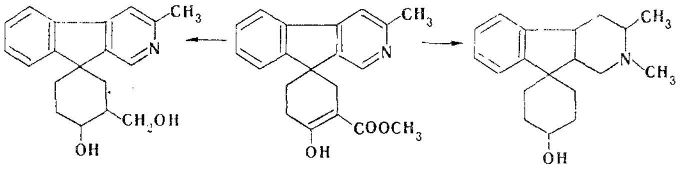
As a result of a similar condensation, we obtained 4'-hydroxy-3-carbomethoxyspiro[4-azafluorene-9,1'-cyclohex-3'-ene] (XII) from diester XI. The data from the IR spectrum of XII [1668 (CO), 1623 (C=C), and 3030 cm^{-1} (associated OH)] and from the PMR spectrum (weak-field singlet at 12.31 ppm with an intensity corresponding to one proton unit) confirm its chelate structure.

As a result of condensation of azafluorene III with ethyl cinnamate in dimethyl sulfoxide (DMSO) in the presence of potassium we obtained 4'-hydroxy-2',6'-diphenyl-3'-carbethoxyspiro[4-azafluorene-9,1'-cyclohex-3'-ene] (XIII). Its spectral characteristics are the same as those from the analogous spiran obtained from 3-methyl-2-azafluorene, the chelate structure of which has been confirmed [5].



XIII

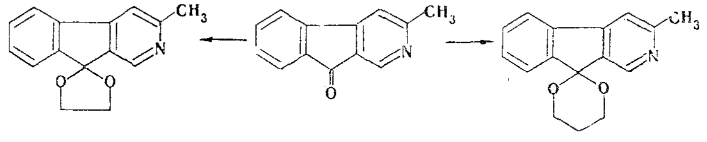
In order to obtain hydroxy derivatives of the investigated spirans we carried out the reduction of our previously obtained [1] 3-methyl-4'-hydroxy-3'-carbethoxyspiro[2-azafluorene-9,1'-cyclohex-3'-ene] (XIV) with lithium aluminum hydride, as well as catalytic hydrogenation of this compound in methanol in the presence of rhenium heptasulfide. In the first case we isolated 3-methyl-4'-hydroxy-3'-hydroxymethylspiro[2-azafluorene-9,1'-cyclohexane] (XV) from the reaction products. The bands at 2600-3630 cm^{-1} in its IR spectrum correspond to associated hydroxy groups. The signal at 5.16 ppm (2H, m, C_3'—CH_2) in the PMR spectrum corresponds to the protons of the hydroxymethyl group, while the signal at 5.25 ppm (1H, m, C_4'—H) corresponds to a proton that is geminal with respect to the hydroxy group.



XV XIV XVI

The hydrogenation of compounds that contain pyridine and benzene rings on rhenium heptasulfide proceeds selectively – only the pyridine ring is hydrogenated [6]. In the hydrogenation of spiran XIV (at 136 atm and 250°C) we isolated 1,2,3,4,4a,9a-hexahydro-2,3-dimethyl-4'-hydroxyspiro(2-azafluorene-9,1'-cyclohexane) (XVI) from the reaction products. In this case hydrogenation is accompanied by removal of the carbomethoxy group and N-methylation. The band at 3170 cm^{-1} in the IR spectrum of XVI corresponds to a hydroxy group with an intermolecular hydrogen bond. The presence in the PMR spectrum of a strong-field signal at 1.11 ppm (3H, d, 3-CH_3) and a doublet at 2.56 ppm (the signal of N-methyl protons) and the absence of a 1-H signal at weak field serve as evidence that the pyridine ring is completely hydrogenated.

3-Methylspiro[2-azafluorene-9,2'-(1',3'-dioxolane)] (XVIII), which is the first representative of this spiro heterocyclic system, was obtained from 3-methyl-2-azafluorene (XVII) [4] and ethylene glycol by three methods. Bands that are characteristic for cyclic ketals (1172, 1155, 1060, and 1043 cm^{-1}) are present in the IR spectrum of XVIII. The presence in the PMR spectrum of a four-proton multiplet at relatively weak fields at 4.4 ppm constitutes evidence for the presence of two methylene groups bonded to a electronegative element.



XVIII XVII XIX

A similar compound, viz., 3-methylspiro[2-azafluorene-9,2'-(1',3'-dioxane)] (XIX), was obtained from azafluorenone XVII and 1,3-propanediol. The bands in the IR spectrum of XIX (1165, 1110, and 1065 cm^{-1}) are related to the C—O bonds of cyclic ketals. In addition to signals of the protons of the azafluorene ring, signals of six protons of the methylene groups of the dioxane ring (4.32 ppm) are present in its PMR spectrum.

EXPERIMENTAL

The PMR spectra of solutions of the compounds in $CDCl_3$ were recorded with a Tesla BS-487C spectrometer with hexamethyldisiloxane as the internal standard. The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer. The mass spectra were obtained with an MKh-1303 mass spectrometer.

9,9-Bis(β-cyanoethyl)-1-azafluorene (IV). A solution of 0.9 g (5 mmole) of 1-azafluorene, 0.9 g (0.017 mole) of acrylonitrile, and 0.15 ml of an alcohol solution of the Rodionov catalyst (RC) in 15 ml of benzene was stirred at 50°C for 2 h, after which 4 ml of water was added, and the mixture was neutralized with hydrochloric acid. The benzene solution was dried with potassium carbonate, the benzene was removed by distillation, and the residue (1.2 g) was crystallized from alcohol to give 0.5 g (32%) of IV with mp 150-151°C and R_f 0.08 [ether—hexane (3:1)]. Found: C 78.9; H 5.6; N 15.4%; M^+ 273. $C_{18}H_{15}N_3$. Calculated: C 79.1 H 5.5; N 15.4%; M 273.

3-Methyl-9,9-bis(β-cyanoethyl)-2-azafluorene and 9,9-Bis(β-cyanoethyl)-2-azafluorene (V). For this reaction we used 10 g of the product of catalytic dehydrocyclization of 2,5-dimethyl-4-phenylpyridine, 11.5 g of acrylonitrile, 1 ml of the Rodionov catalyst, and 100 ml of benzene. The reaction was carried out similarly. Chromatographic separation of the reaction products [elution with ethyl acetate—hexane (1:2)] gave initially 0.5 g of V with mp 126-128°C [from heptane—ethyl acetate (1:1)] and R_f 0.7. Found: C 79.1; H 5.5; N 14.9%. $C_{18}H_{15}N_3$. Calculated: C 79.1; H 5.5; N 15.4%. Subsequent elution gave 12.7 g of 3-methyl-9,9-bis(β-cyanoethyl)-2-azafluorene with mp 159-160°C (from alcohol) and R_f 0.7 [1].

9,9-Bis(β-cyanoethyl)-4-azafluorene (VI). This compound was similarly obtained in 58% yield from 4-azafluorene. The colorless crystals had mp 132-133°C (from ether) and R_f 0.4 (ether). Found: C 79.2; H 5.4; N 15.5%. $C_{18}H_{15}N_3$. Calculated: C 79.1; H 5.5; N 15.4%.

9,9-Bis(β-carboxyethyl)-1-azafluorene (VII). A solution of 7.3 g (0.023 mole) of dinitrile IV in 100 ml of an 18% alcohol solution of potassium hydroxide was refluxed for 20 h, after which the alcohol was removed by distillation, and the residue was treated with 70% sulfuric acid until it had pH 7. Workup gave 6 g (63.8%) of acid VII with mp 212-213°C (from alcohol). Found: C 69.6; H 5.6; N 4.5%; M^+ 311. $C_{18}H_{17}NO_4$. Calculated: C 69.5; H 5.5; N 4.5%; M 311.

9,9-Bis(β-carbethoxyethyl)-2-azafluorene (VIII). Hydrogen chloride was bubbled through a refluxing solution of 0.73 g (2.67 mmole) of dinitrile V in 25 ml of absolute alcohol for 7 h, after which 10 ml of water was added, and the mixture was made alkaline with sodium carbonate and extracted with ether. The ether was removed by distillation, and the residue was purified with a column filled with aluminum oxide to give 0.7 g (71.4%) of diester VIII with mp 104.5-195.5°C (from ether) and R_f 0.1 (ether). Found: C 72.1; H 6.5; N 3.9%. $C_{20}H_{25}NO_4$. Found: C 71.9; H 6.4; N 3.8%.

9,9-Bis(β-carboxyethyl)-4-azafluorene (IX). The hydrolysis of dinitrile VI was carried out in the same way as the hydrolysis of IV. Diacid IX was obtained in 64% yield. The colorless crystals had mp 215-216°C (from alcohol). Found: C 69.7; H 5.6; N 4.5%; M^+ 311. $C_{18}H_{17}NO_4$. Calculated: C 69.5; H 5.5; N 4.5%; M 311.

9,9-Bis(β-carbomethoxyethyl)-4-azafluorene (X). A solution of 1.5 g (4.8 mmole) of acid IX and 2 ml of sulfuric acid in 30 ml of methanol was refluxed by distillation. The residue was neutralized to pH 9 with sodium carbonate, and the reaction products were extracted with ether. The ether was removed by distillation, and the residue was crystallized from ether to give 0.6 g (40%) of diester X with mp 104-105°C and R_f 0.5 (ether). Found: C 70.5; H 6.6; N 4.3%. $C_{20}H_{21}NO_4$. Calculated: C 70.8; H 6.2; N 4.1%.

4'-Hydroxy-3'-carbethoxyspiro(2-azafluorene-1,1'-cyclohex-3'-ene) (XI). A solution of 0.3 g (10.8 mmole) of diester VIII in 10 ml of toluene was stirred with 0.1 g (1.8 mmole) of sodium methoxide at 100°C for 3 h, after which 10 ml of water and 10 ml of acetic acid were added, and the toluene solution was dried with sodium sulfate. The toluene was removed by distillation, and the oily residue was chromatographed with a column filled with 5/40μ silica gel to give 0.14 g (30.5%) of XI, which was converted to the picrate with mp 196-197°C (from alcohol). Found: N 10.3%. $C_{20}H_{19}NO_3 \cdot C_6H_2(OH)(NO_3)_3$. Calculated: N 10.2%.

4'-Hydroxy-3'-carbomethoxyspiro(4-azafluorene-9,1'-cyclohex-3'-ene) (XII). This compound was similarly obtained in 11.5% yield from diester X. The colorless crystals had mp 172-175°C (from ether) and R_f 0.1 [ether—hexane (2:1)]. Found: N 4.3%. $C_{19}H_{17}NO_3$. Calculated: N 4.6%.

4-Hydroxy-2',6'-diphenyl-3'-carbethoxyspiro(4-azafluorene-9,1-cyclohex-3'-ene) (XIII). A 1.76-g (44 mmole) sample of finely cut potassium was added to a solution of 4 g (24 mmole) of 4-azafluorene (III) in 60 ml of benzene. After 30 min, 5 ml of DMSO was added. A solution of 11.2 g (64 mmole) of ethyl cinnamate in 20 ml of benzene was then added with stirring to the red reaction mass, and the mixture was stirred at 60°C for 2 h. It was then cooled and treated with 60 ml of water, and the mixture was extracted with ether. The ether—benzene extract was dried with magnesium sulfate, the solvents were removed, and the residue was purified with a chromatographic column filled with silica gel. Crystallization of the product from ether gave 2.03 g (18%) of colorless crystals of spiro compound XIII with mp 197-199°C and R_f 0.8 (Silufol, chloroform). Found: C 81.0; H 5.7; N 2.9%. $C_{32}H_{27}NO_3$. Calculated: C 81.2; H 5.7; N 2.9%.

3-Methyl-4'-hydroxy-3'-hydroxymethylspiro(2-azafluorene-9,1'-cyclohexane) (XV). A solution of 0.85 g (2.65 mmole) of spiro compound XIV in 20 ml of benzene was added slowly dropwise to a solution of 1 g (26 mmole) of lithium aluminum hydride in 40 ml of absolute ether, and the mixture was refluxed with stirring for 3 h. Water (20 ml) was then added, and the organic layer was washed with water and dried with sodium sulfate. The solvents were removed by distillation, and the residue was recrystallized to give 0.14 g (16%) of XV with mp 130-132°C [from benzene—hexane (1:3)]. Found: N 4.4%. $C_{19}H_{21}NO_2$. Calculated: N 4.7%.

1,2,3,4a,9a-Hexahydro-2,3-dimethyl-4'-hydrospiro(2-azafluorene-9,1'-cyclohexane) (XVI). A 250-ml rotating autoclave was charged with 0.98 g (3.05 mmole) of XIV, 26 ml of methanol, and 0.1 g of Re_2S_7. Hydrogenation was carried out at 250°C for 5 h at an initial hydrogen pressure of 136 atm. At total of 7 liters of hydrogen was absorbed. The catalyst was separated, the methanol was removed by distillation, and the residue (0.83 g) was separated with a chromatographic column filled with aluminum oxide to give 0.15 g (10%) of XVI with mp 230-232.5°C [from hexane—benzene (1:1)] and R_f 0.8 [ethyl acetate—alcohol (3:1)]. Found: N 4.6%. $C_{10}H_{27}NO$. Calculated: N 5.0%.

3-Methylspiro[2-azafluorene-9,2'-(1',3'-dioxolane)] (XVIII). A) A 2.3-g (16 mmole) sample of boron trifluoride etherate was added to a solution of 1.7 g (8.7 mmole) of ketone XVII and 0.89 g (14 mmole) of ethylene glycol in 9 ml of acetonitrile, and the mixture was refluxed with stirring for 1 h. It was then poured into ice water saturated with sodium carbonate, and the mixture was extracted with ether. The solvents were removed from the extract, and the residue was separated with a chromatographic column filled with aluminum oxide to give 0.2 g (13%) of spiro compound XVIII with mp 101.5-102.5°C and R_f 0.3 (ether). Found: C 75.2; H 5.4; N 5.7%. $C_{15}H_{13}NO_2$. Calculated: C 75.3; H 5.5; N 5.9%.

B) A mixture of 3.2 g (164 mmole) of ketone XVII, 1.0 g (16 mmole) of ethylene glycol and 3.4 g (20 mmole) of p-toluenesulfonic acid in 100 ml of benzene was refluxed with stirring with a Dean—Stark trap for 20 h. Workup gave 0.4 g (10%) of XVIII with mp 101.5-102°C.

C) A mixture of 3.2 g (13.8 mmole) of 3-methyl-2-azafluorenone hydrochloride and 3.34 g (41 mmole) of ethylene glycol in 100 ml of benzene was refluxed with a Dean—Stark trap for 12 h, during which 0.13 ml of water separated. The mixture was poured into ice water saturated with sodium carbonate, and the benzene layer was separated. Removal of the benzene by distillation gave 0.4 g (10%) of XVIII with mp 101.5-102.5°C. No melting-point depression was noted for mixtures of all of the samples of spiro compound XVIII with the genuine compound.

3-Methylspiro[2-azafluorene-9,2'-(1',3'-dioxane)] (XIX). A mixture of 4 g (20 mmole) of ketone XVII, 2.11 g (28 mmole) of 1,3-propanediol, and 6 g (34.9 mmole) of p-toluenesulfonic acid in 150 ml of benzene was refluxed for 18 h, during which 0.6 ml of water separated. The reaction mixture was poured over ice with sodium carbonate, and the benzene layer was separated. The products were extracted from the aqueous layer with ether. The solvents were removed by distillation, and the residue was chromatographed to give 0.6 g (11.5%) of XIX with mp 110-112.5°C (from heptane) and R_f 0.3 (ether). Found: N 5.6%. $C_{16}H_{15}NO_2$. Calculated: N 5.5%.

LITERATURE CITED

1. N. S. Prostakov, V. P. Shalimov, and V. P. Zvolinskii, Khim. Geterotsikl. Soedin., No. 12, 1668 (1972).

2. N. S. Prostakov, A. T. Soldatenkov, and V. O. Fedorov, Khim. Geterotsikl. Soedin., No. 8, 1101 (1979).
3. N. S. Prostakov, A. V. Varlamov, G. A. Vasil'ev. O. G. Kesarev, and G. A. Urbina, Khim. Geterotsikl. Soedin., No. 1, 124 (1977).
4. N. S. Prostakov, K. D. Matthew, and V. A. Kurichev, Khim. Geterotsikl. Soedin., No. 5, 876 (1967).
5. N. S. Prostakov, M. É. Sintra, S. A. Soldatova, V. P. Shalimov, V. P. Zvolinskii, and A. A. Savina, Khim. Geterotsikl. Soedin., No. 9, 1231 (1976).
6. M. A. Ryashentseva, Kh. M. Minachev, V. V. Dorogov, and N. S. Prostakov, Khim. Geterotsikl. Soedin., No. 1, 88 (1972).

QUANTUM-CHEMICAL INTERPRETATION OF RECYCLIZATION REACTIONS.

6.* ISOELECTRONIC ANALOGS OF THE BENZYL CATION. AZA DERIVATIVES

Yu. B. Vysotskii and B. P. Zemskii

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540.14.5:541.621.2:543.51

The scheme, developed within the framework of the π-electron approximation, of the quantum-chemical description of recyclization reactions in the case of the isomerization of benzyl and methylenenaphthyl cations to tropylium ions and their benzo derivatives is extended to rearrangements with ring expansions. The effect of aza substitution on these recrystallizations is examined on the basis of the bonded variant of perturbation theory. The results of the calculations are in good agreement with the mass-spectrometric data.

In the preceding papers of this series we have developed a scheme for the quantum-chemical description of Kost–Sagitullin [1-4], Dimroth [4], and Schmidt [5] rearrangements. A similar approach, but, to be sure, without allowance for interelectronic interaction, has been used together with other reactivity indexes to explain the intramolecular aminolysis of 2-methylamino-N-{1-[3,6-di(2-pyridyl)-4-pyridazinyl]ethylidene}aniline [6, 7] and the conversion of a spiro-fused pyridazine to pyrazole derivatives [7]. Some predictions of this scheme such as the direction of recyclization of 1,2,3-trimethylisoquinolinium iodide [3] have been confirmed experimentally [8]. Experimental verification [9] has also been obtained for the fact that the introduction of an electron-acceptor substituent in the 2 position of 1-methylene-1,2-dihydroisoquinoline substantially hinders its recyclization (see Table 3 in [3]).

At the foundation of the approach under consideration lies the assumption of the possibility of the description of the reactivities of molecules with conjugated bonds in recyclization and cyclization reactions within the framework of the π-electron approximation on the basis of the bonded variant of perturbation theory [1]; the orders of the bonds between the chemically unbonded atoms (the "long-range" or "nonvalent" bond orders) and the bond–bond self-consistent self-polarizabilities of the starting substrate (see [1]) will be the reactivity indexes in these reactions within the approximation of an isolated molecule (a static reactivity model) in this case. Let us note that the residual π-electron charges and atom–atom self-polarizabilities, which are widely used for the interpretation of aromatic substitution reactions, are the reactivity indexes in the similar examination of the latter.

The rearrangements of isoelectronic heteroanalogs of the benzyl cation are examined in the present communication within the framework of the method being developed in this research. A peculiarity of these reactions as compared with the previously described reactions [1-5] is the fact that they generally proceed with ring expansion (for example, see [10-12]).

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*See [1] for Communication 5.

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