9-AMINO DERIVATIVES OF 4-AZAFLUORENE

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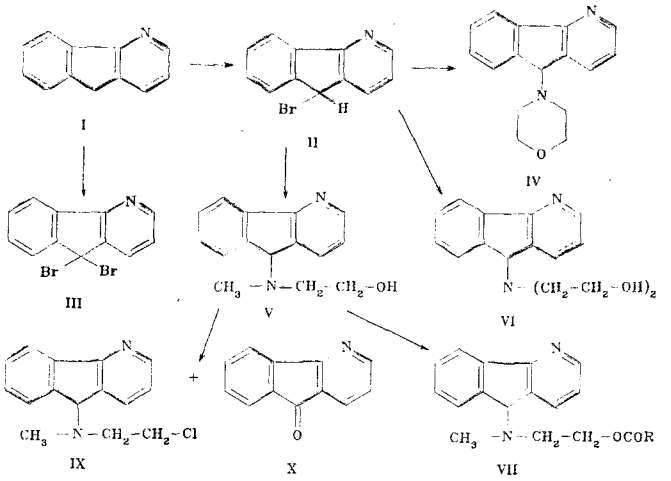
For the purpose of finding physiologically active compounds among the amino derivatives of azafluorenes, 9-amino derivatives containing N-β-hydroxyethyl and N-β-chloroethyl radicals have been obtained from 9-bromo-4-azafluorene and the corresponding amines. The conversion of 9-phenylamino-4-azafluorene into 9-phenylimino-4-azafluorene discovered is a new method for obtaining Schiff bases in the azafluorene series.

The development of a method for the synthesis of 4-azafluorene by the catalytic dehydrocyclization of 3-methyl-2-phenylpyridine [1] has made it possible to expand the investigations of the synthesis of derivatives of this heterocyclic system. Taking into account the fairly large amount of information on the broad spectrum of the physiological activity of various derivatives of fluorene, we turned to the synthesis of 9-amino derivatives of 4-azafluorene. The main intermediate compound in the syntheses carried out is 9-bromo-4-azafluorene (II), which is obtained with a quantitative yield by reacting 4-azafluorene (I) with N-bromosuccinimide in carbon tetrachloride. When this reaction is carried out with more than a twofold amount of N-bromosuccinimide and prolonged heating, 9,9-dibromo-4-azafluorene (III) forms.

The reactions of bromide II with morpholine, methyl(β-hydroxyethyl)amine, and diethanolamine were carried out in dimethylformamide at room temperature. Azafluorenes IV-VI were obtained in this manner.

For the purpose of synthesizing substances with possible biological activity, we obtained 9-[N-methyl-N-(β-chloroethyl)amino]-4-azafluorene (IX) from V.



VII R = C_6H_5, VIII R = $NHC_6H_4CH_3$-*p*

The replacement of the hydroxyl groups in alcohol V and glycol VI was carried out by treating them at room temperature with thionyl chloride. In the case of alcohol V, 4-azafluorenone (XI) was obtained as a secondary product with 36% yield. Similar conversions of 9-amino derivatives into azafluorenone were previously established by us in the example cases of amino derivatives which are isomeric with respect to the position of the nitrogen atom in the azafluorenes.

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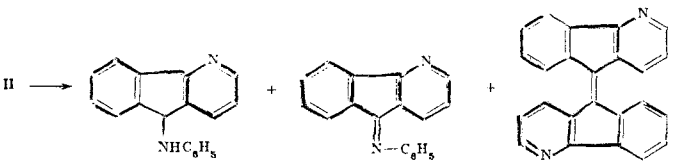
Aniline and β-phenylethylamine served as the secondary amines, which were reacted with bromide II under similar conditions. In the first case, the following were recovered from the complex mixture of reaction products by chromatography: 9-(N-phenylamino)-4-azafluorene (XI), 9-(N-phenylimino)-4-azafluorene (XII) [2], and, with a small yield, di(4-azafluorylidene) (XIII) [3].

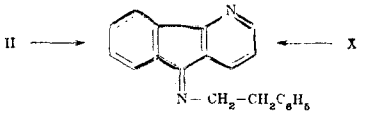


XI XII XIII

The first step in this reaction is the formation of amine XI, which is then converted into Schiff base XII. This hypothesis is supported by the quantitative conversion of amine XI into imine XII when it is heated in DMFA, as well as by the varying quantitative ratio between amine XI and azomethine XII as a function of the conditions under which the reaction is carried out. For example, at room temperature (19 h) amine XI was obtained with a 58% yield, and azomethine XII was obtained with a 15% yield, whereas at 50-60°C (6 h) the yields are 12 and 48%, respectively.

The formation of azomethine XII as a result of the reaction of bromide II with aniline is the basis of a new method for the synthesis of Schiff bases in the azafluorene series and is apparently due to the special properties of the 9-amino derivatives of azafluorenes. We found that 9-aminoazafluorenes are extremely unstable and can be isolated only in the form of acyl derivatives.

The compound 9-(N-β-phenylethylamino)-4-azafluorene (XIV) was isolated from the products of the reaction of bromide II with β-phenylethylamine.



XIV

Azomethine XIV was also obtained upon the condensation of 4-azafluorenone (X) with β-phenylethylamine according to a known method [2].

EXPERIMENTAL

The IR spectra were recorded on a UR-20 instrument in tablets with KBr, and the PMR spectra were recorded on a Tesla BS-497 spectrometer with a working frequency of 100 MHz and tetramethylsilane as the internal reference. The mass spectra were obtained on an MKh-1303 instrument.

The column chromatography and TLC were carried out on aluminum oxide in a 3:1 ether–hexane system.

9-Bromo-4-azafluorene (II). A mixture of 2 g (12 mmole) of 4-azafluorene I and 2.5 g (14 mmole) of N-bromosuccinimide in 45 ml of CCl_4 is heated for 4 h at 50°C. The precipitate is filtered out, and the filtrate is passed through a column. The residue remaining after distillation of the solvents is crystallized from hexane. This gives 2.84 g (96%) of bromide II, light yellow needles, mp 101-102°C, R_f 0.69. PMR spectrum: 7.25 (1-H), 7.20 (2-H), 8.56 (3-H), 7.99 (5-H), 7.49 (6-H), 7.45 (7-H), 7.68 (8-H), 6.0 ppm (9-H). The chemical shifts of the aromatic protons were obtained as a result of the computer analysis of complex ABC and ABCD spectra. Mass spectrum:* M^+ 245 and 247 (67), 166 (100). Found: C, 58.4; H, 3.2; Br, 32.3; N, 5.6%. Calculated for $C_{12}H_8BrN$: C, 58.5; H, 3.3; Br, 32.5; N, 5.7%.

9,9-Dibromo-4-azafluorene (III). First, 2 g (12 mmole) of 4-azafluorene (I), 4.7 g (26 mmole) of N-bromosuccinimide, and 90 ml of CCl_4 are taken for the reaction. The mixture is boiled for 10 h. The isolation of the reaction product is carried out in analogy to the

*Here and in the following, the values of the ratio m/z are presented, and the relative intensities are given in % in parentheses.

case of compound II. This gives 2.84 g (73%) of dibromide III, light yellow crystals, mp 180-181°C (from heptane), R_f 0.74. The PMR spectrum does not show signals of protons in position 9. Found: N, 4.4%; M^+ 325. Calculated for $C_{12}H_7Br_2N$: N, 4.3%; M 325.

9-Morpholino-4-azafluorene (IV). A solution of 1 g (4 mmole) of bromide II in 10 ml of DMFA is given a gradual addition of a solution of 1.5 g (17 mmole) of morpholine in 5 ml of DMFA. The mixture is stirred at room temperature for 4 h in a stream of nitrogen. After the DMFA has been distilled off, 10 ml of water are added to the residue, and then the pH is adjusted to 8 with sodium carbonate. The reaction products are extracted with ether and dried with potassium carbonate. The residue remaining after the removal of the ether by distillation is crystallized from heptane. This gives 0.69 g (67%) of IV, yellow crystals, mp 118-119°C. PMR spectrum: 2.59 (4H, N—CH_2); 3.56 (4H, O—CH_2); 4.79 ppm (1H, C_9—H). IR spectrum: 1012 (C—N); 1115 cm^{-1} (C—O—C). Found: C, 76.2; H, 6.3; N, 11.04%; M^+ 252. Calculated for $C_{16}H_{16}N_2O$: C, 76.2; N, 6.3; N, 11.1%; M 252.

9-[N-Methyl-N-(β-hydroxyethyl)amino]-4-azafluorene (V). The reaction mixture consists of 2 g (8 mmole) of bromide II, 2 g (25 mmole) of methyl(β-hydroxyethyl)amine, and 20 ml of DMFA. The reaction is carried out precisely as in the preceding experiment. The reaction products are extracted by benzene. This gives 1.25 g (64%) of compound V, mp 103-104°C (from hexane), PMR spectrum: 2.20 (3H, CH_3—N); 2.63 (2H, N—CH_2); 3.60 (2H, CH_2O); 4.83 ppm (1H, C_9—H). IR spectrum: 3300 cm^{-1} (OH). Found: C, 74.8; H, 6.8; N, 11.3%; M^+ 240. Calculated for $C_{15}H_{16}H_2O$: C, 75.0; H, 6.7; N, 11.6%; M 240.

9-[N,N-Di(β-hydroxyethyl)amino]-4-azafluorene (VI). The same method is used to obtain 0.8 g (78%) of compound VI with mp 128-129°C (from heptane) from 0.94 g (4 mmole) of bromide II, 0.6 g (2 mmole) of diethanolamine, and 20 ml of DMFA (extraction of the reaction products by chloroform). PMR spectrum: 2.75 (4H, CH_2—N—CH_2); 3.58 (4H, OCH_2); 4.98 ppm (1H, $C_{(9)}$—H). Mass spectrum: 270 (1), 239 (22.6), 166 (100). IR spectrum: 3490, 3400, 3200 cm^{-1} (hydroxyl groups). Found: C, 71.3; H, 6.8; N, 10.4%, M^+ 270. Calculated for $C_{16}H_{18}N_2O_2$: C, 71.1; H, 6.7; N, 10.4%; M 270.

9-[N-Methyl-N-(β-benzoyloxyethyl)amino]-4-azafluorene (VII). The reaction mixture consists of 0.5 g (2 mmole) of alcohol V, 6.05 g (43 mmole) of benzoyl chloride, and 20 ml of toluene. The reaction is carried out in a similar manner with isolation of the free base. This gives 0.53 g (74%) of ester VII, mp 65-66°C (from hexane), R_f 0.39. PMR spectrum: 2.47 (3H, CH_3—N); 2.80 (2H, —CH_2—N); 4.37 (2H, CH_2—O); 4.88 ppm (1H, $C_{(9)}$—H). IR spectrum: 1280 (C—O—C), 1720 cm^{-1} (C=O). Mass spectrum: M^+ 344 (21), 233 (4), 222 (22), 210 (5.4), 209 (28), 167 (16), 166 (100). Found: C, 76.5; H, 5.6; N, 8.1%. Calculated for $C_{22}H_{20}H_2O_2$: C, 76.7; H, 5.8; N, 8.1%.

β-[Methyl(4-azafluoren-9-yl)amino]ethyl N-p-Tolylcarbamate (VIII). A mixture of 0.37 g (1.5 mmole) of alcohol V and 1 g (7.5 mmole) of p-tolyl isocyanate in 10 ml of benzene is boiled for 30 min. The benzene is distilled off, and the residue is crystallized from a 2:1 mixture of heptane with benzene. This gives 0.34 g (59%) of urethane VIII, mp 148-149°C, R_f 0.26. IR spectrum: 1320, 1070 (C—N), 1720 cm^{-1} (C=O). Mass spectrum: 373 (21), 233 (11), 222 (31), 210 (12), 209 (40), 166 (100), 167 (38), 134 (15), 133 (80). Found: C, 73.7; H, 6.3; N, 10.9%. Calculated for $C_{23}H_{23}N_3O_2$: C, 73.9; H, 6.1; N, 11.3%.

9-[N-Methyl-N-(β-chloroethyl)amino]-4-azafluorene (IX). A solution of 0.92 g (4 mmole) of alcohol V in 10 ml of benzene is given a gradual addition of a solution of 10 ml of thionyl chloride in 10 ml of benzene. The mixture is stirred at room temperature for 1 h. After the benzene and the excess thionyl chloride have been distilled off, 20 ml of water are added, and the pH is adjusted to 8 with sodium carbonate. The reaction products are extracted by ether. The residue remaining after the ether has been distilled off is passed through a chromatographic column (the eluent was ether). Fractional crystallization from hexane gives 0.61 g (61%) of chloride IX in the form of an oily yellowish green substance with R_f 0.59. Found: Cl, 13.5%; M^+ 258. Calculated for $C_{15}H_{15}ClN_2$: Cl, 13.7%; M 258.

9-(N-Phenylamino)-4-azafluorene (XI), 9-(N-Phenylimino)azafluorene (XII) and Di(4-azafluorylidene) (XIII). A. A solution of 0.5 g (2 mmole) of bromide II and 1 g (11 mmole) of aniline in 10 ml of DMFA is held at room temperature for 19 h. The DMFA and the excess aniline are distilled off. The residue is given an addition of 10 ml of water, the pH is adjusted to 9 with sodium carbonate, and the reaction products are extracted by ether. Chromatography gives 0.08 g (15%) of azomethine XII, mp 132-133°C, R_f 0.7, as well as 0.3 g (58%) of compound XI, mp 155-156°C (from hexane), R_f 0.6.

B. The reaction mixture consists of 2 g (8 mmole) of bromide II, 3.07 g (33 mmole) of aniline, and 5 ml of DMFA. The mixture is stirred for 6 h at 50-60°C. After similar treatment, the following are isolated chromatographically: 0.98 g (48%) of azomethine XII, 0.25 g (12%) of amino derivative XI, and 0.14 g (5%) of compound XIII (mp 288-289°C).

C. A mixture of 0.5 g (2 mmole) of compound XI in 20 ml of DMFA is heated for 4 h at 160°C 160°C. After the DMFA has been distilled off, and the residue has been cleaned up, 0.38 g (76%) of azomethine XII is isolated in a chromatographic column with mp 132-133°C and R_f 0.7.

9-(N-β-Phenylethylimino)-4-azafluorene (XIV). A. The reaction mixture consists of 2 g (8 mmole) of bromide II, 2.87 g (24 mmole) of β-phenylethylamine, and 40 ml of DMFA. The mixture is stirred for 4 h at 50-60°C in a stream of nitrogen. After similar treatment, 2.2 g (52%) of azomethine XIV with mp 79-80°C (from hexane) and R_f 0.62 are isolated. PMR spectrum: 3.27 (2H, $-CH_2-Ph$); 4.42 ppm (2H, CH_2-N). Mass spectrum: 284 (1), 194 (1.3), 193 (100), 167 (3.8), 166 (1.5). Found: C, 84.3; H, 5.6; N, 9.7%. Calculated for $C_{20}H_{16}N_2$: C, 84.5; H, 5.6; N, 9.7%. Besides azomethine XIV, 0.28 g (10%) of XIII is isolated.

B. A solution of 1.2 g (7 mmole) of 4-azafluorenone (X) and 1.44 g (12 mmole) of β-phenylethylamine in 50 ml of toluene is boiled for 9 h with the removal of water from the reaction mixture. The toluene solution is treated with water and then with sodium carbonate and dried with potassium carbonate. The toluene is distilled off, and the residue is chromatographed. This results in the isolation of 1.46 g (78%) of azomethine XIV, mp 79-80°C, R_f 0.62.

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INVESTIGATIONS IN THE FIELD OF THE CHEMISTRY OF 2-HETARYLBENZIMIDAZOLES.

6.* SYNTHESIS AND PROPERTIES OF 1-METHYL-2-(2'-SELENIENYL)BENZIMIDAZOLE

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2-(2'-Selenienyl)benzimidazole has been synthesized by a Weidenhagen reaction and converted into the N-methylated derivative. Electrophilic-substitution reactions (nitration, sulfonation, bromination, chloromethylation, and acylation) in the selenophene ring have been studied. It has been shown that the substituent enters the α position of the selenophene ring in most cases. The bromination of 1-methyl-2-(2'-selenienyl)benzimidazole in acetic acid produces the 3',5'-dibromo derivative, whereas 1-methyl-5(or 6)-bromo-2-(3',5'-dibromo-2'-selenienyl)benzimidazole is obtained in polyphosphoric acid.

Continuing the study of the conversions of 2-hetarylbenzimidazoles [1, 2], we synthesized 2-(2'-selenienyl)benzimidazole (I) on the basis of 2-formylselenophene and o-phenylenediamine and converted it into the N-methylated derivative II. In comparison to other 2-hetarylbenzimidazoles [hetaryl = 2-furyl- (III) and 2-thienyl- (IV)], 2-(2'-selenienyl)benzimidazole undergoes methylation with difficulty. Compound II can be synthesized with an 81% yield without appreciable formation of the quaternary salt only with the use of a fourfold excess

*For Report 5, see [1].

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