3-AZAFLUORENES WITH NITROGEN-CONTAINING SUBSTITUENTS IN THE C_9 POSITION

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In the case of the reaction of 9-bromo-4-azafluorene with 2,5-dimethyl-4-piperidone and p-anisidine it was confirmed that the reactions of this bromide with secondary aliphatic and primary aromatic amines proceed via different mechanisms. Propionyl and phenylcarbamoyl derivatives of 9-bis(β-hydroxy-ethyl)amino-4-azafluorene were synthesized. Spectral data on the pseudoazulenes formed from 9-morpholino-4-azafluorene mono- and dimethiodide were obtained.

4-Azafluorene derivatives with various tertiary amine functions, which were synthesized in our laboratory, have proved to be of promise within the framework of the search among them of compounds with various types of physiological activity, particularly inhibitors of the peroxide oxidation of lipids [1].

9-Bromo-4-azafluorene (II) [2], which is the starting compound in the syntheses of 4-azafluorene derivatives with nitrogen-containing substituents in the C_9 position, is formed in quantitative yield when 4-azafluorene (I) is treated with N-bromosuccinimide (NBS).

A fundamental difference in the mechanisms of the reactions was demonstrated in the case of the reactions of bromide II with secondary aliphatic and primary aromatic amines. Nucleophilic substitution, which leads to the formation of a tertiary amine, occurs in the first case, whereas an azomethine is formed in the second case [2]. The analogous reaction of 2,7-dinitro-9-bromofluorene with aniline [the preparation of N-(2,7-dinitro-9-fluorenylidene)aniline] is explained by the formation in the first step of an intramolecular charge-transfer complex [3].

In the present paper we present two examples that confirm the common character of these reactions. The reaction of bromide II with the secondary amine 2,5-dimethyl-4-piperidone gave 9-(4'-2',5'-dimethyl-1'-piperidyl)-4-azafluorene (III), which is of independent interest.

p-Anisidine was introduced as the primary aromatic amine in the reaction with bromide II. An azomethine, viz., N-(4-aza-9-fluorenylidene)-p-anisidine (IV), was isolated from the reaction products.

In order to study the physiological activity of new 4-azafluorene derivatives with a tertiary amine function in the C_9 position, starting from the previously described 9-bis(β-hydroxyethyl)amino-4-azafluorene (V) [2] we obtained 9-bis(propionyloxyethyl)-amino-4-azafluorene (VI) by propionylation and 9-bis(β-phenyl-carbamoyloxyethyl)amino-4-azafluorene (VII) by reaction with phenyl isocyanate.

4-Azafluorenes with a tertiary amino group in the C_9 position are interesting subjects for the study of the possibility of their conversion to amino-substituted pseudoazulenes, which have been unknown up until now.

With this end in mind, as the starting compound we used the accessible 9-morpholino-4-azafluorene (VIII) [2], from which we obtained monomethiodide IX and dimethiodide X. The development of an intense dark-blue coloration that is characteristic for pseudoazulenes is observed when these methiodides are treated with an aqueous solution of sodium hydroxide. However, the resulting NH-indenopyridines are extremely unstable and change very rapidly. The color of the solution vanishes after a few seconds.

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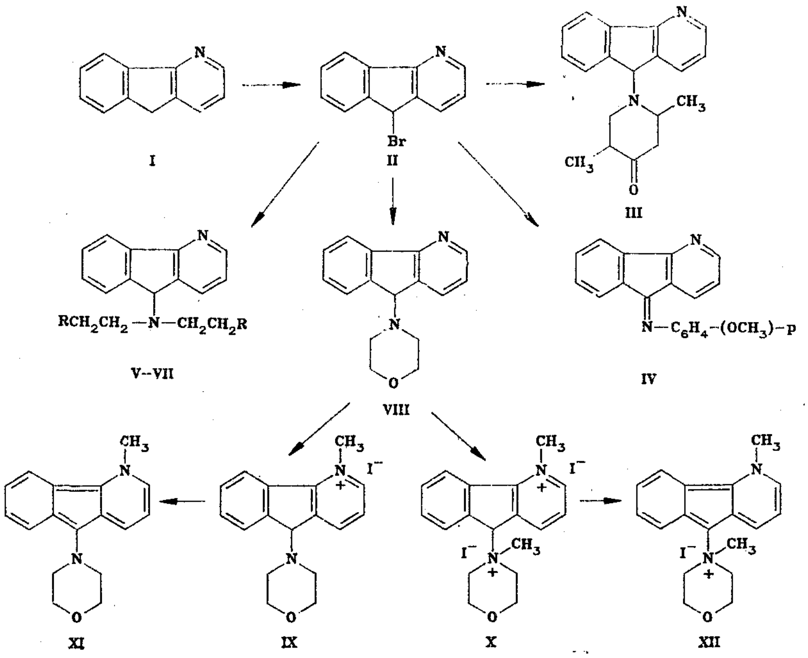

V R=OH; VI R=$OCOC_2H_5$; VII R=$OCONHC_6H_5$

The formation of pseudoazulenes XI and XII was determined from the UV spectral data. Absorption bands with the following λ_{max} values (log ε) appear in the visible region of the spectrum at the instant of alkalization of a solution ($3 \cdot 10^{-4}$ mole/liter) of monomethiodide IX: 508 (2.98), 422 (3.10), 384 (3.50), 372 (3.48), and 355 nm (3.44). The development of these absorption bands in the UV spectra is characteristic for pseudoazulene structures [4]; this may serve as evidence for the formation of pseudoazulenes XI. The bands in the spectrum are shifted somewhat to the short-wave region as a consequence of the stabilizing effect of the substituent in the C_9 position.

Similar spectral data were obtained when dimethiodide X was treated with alkali (the formation of pseudoazulene XII). In this case the detachment of a proton is sterically hindered. The specific coloration of the solution and the appearance of the corresponding absorption bands are therefore observed when the concentration of the solution is increased by an order of magnitude ($3 \cdot 10^{-3}$ mole/liter). In this case of conversion of methiodide X to the anhydro base one might have expected splitting out of an iodide anion from the morpholine fragment. However, it follows from the virtually identical UV spectral data that an aromatic NH-indenopyridine system is formed from both quaternary salts.

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were obtained with a UR-20 spectrometer. The UV spectra of solutions in ethanol were recorded with a Specord UV-vis recording spectrophotometer. The PMR spectra were obtained with a Tesla BS-497 spectrometer (100 MHz) with tetramethylsilane (TMS) as the internal standard. The molecular masses were determined with an MKh-1303 mass spectrometer. Column chromatography and thin-layer chromatography (TLC) were carried out on activity II aluminum oxide in an ether–hexane system (3:1).

9-(4'-Oxo-2',5'-dimethyl-1'-piperidyl)-4-azafluorene (III). A solution of 1 g (4 mmole) of bromide II and 2 g (15 mmole) of 2,5-dimethyl-4-piperidone in 15 ml of dimethylformamide (DMF) was maintained at 60°C for 24 h in a steady stream of nitrogen, after which the DMF was removed by distillation, 20 ml of water was added, and the mixture was made alkaline to pH 9 with sodium carbonate. The reaction products were extracted with ether, and the extract was dried with potassium carbonate. The ether was removed by distillation, and the residue was chromatographed by elution with ether–hexane (3:1) to give, successively, 0.17 g (8.5%) of the bromide and 0.74 g (62%) of III with mp 120-121°C (from hexane). IR spectrum: 1718 (CO): 2970, 2934, 2900, and 2815 cm^{-1} (CH_2 and CH_3 of the piperidine fragment). PMR spectrum: 0.5 (3H, 5-CH_3), 1.02 (3H, 2-CH_3), 2.25 (1H, 3-H), 4.78 (1H, 9-H), 8.58 (1H, 3-H), 8.26 (1H, 1-H), and 6.64 ppm (1H, 2-H). Found: C 77.8; H 7.0; N 9.3%. M^+ 292. $C_{19}H_{18}N_2O$. Calculated: C 78; H 6.8; N 9.6; M 292.

N-(4-Aza-9-fluorenylidene)-p-anisidine (IV). This compound was similarly obtained from 0.5 g (2 mmole) of bromide II, 0.75 g (6 mmole) of p-anisidine, and 15 ml of DMF. The yield of azomethine IV, with mp 164-165°C (from hexane–benzene), was 0.44 g (76%). IR spectrum: 1650 (C=N) and 1240 cm^{-1} (CO). Found: C 79.4; H 4.6; N 9.7%; M^+ 286. $C_{19}H_{14}N_2O$. Calculated: C 79.7; H 4.8; N 9.7%; M 286.

9-Bis(β-propionyloxyethyl)amino-4-azafluorene (VI). The esterification of 0.4 g (1.4 mmole) of amino glycol V with 5.3 g (57 mmole) of propionyl chloride in toluene (70°C, 10 h) gave 0.24 g (42%) of diester VI (isolated by chromatography) in the form of a green oily substance. IR spectrum: 1734 (C=O) and 1200 cm^{-1} (C–O–). PMR spectrum: 1.1 (3H, CH_3), 2.3 (2H, CH_2), 2.8 (2H, CH_2), 3.0 (CH_2–O–C), and 5.48 ppm (1H, 9-H). Found: N 7.2%: M^+ 382. $C_{22}H_{26}N_2O_4$. Calculated: N 7.31%; M 382.

9-Bis(β-phenylcarbamoyloxyethyl)amino-4-azafluorene (VII). A solution of 0.4 g (1.4 mmole) of V and 0.55 g (4.6 mmole) of phenyl isocyanate in 20 ml of benzene was maintained at 70°C for 12 h, after which 20 ml of water was added. Workup of the benzene solution gave 0.42 g (56%) of VII with mp 169-170°C (from hexane–benzene) and R_f 0.14. IR spectrum: 1732 and 1717 (C=O); 3420, 3208, and 3055 cm^{-1} (free and associated NH). PMR spectrum: 2.88 (2H, –N–CH_2), 4.17 (2H, CH_2OCO), 4.89 (1H, 9-H), 7.76 (1H, 2-H), 7.94 (1H, 1-H), 8.08 (1H, 5-H), and 8.62 ppm (1H, 3-H). Found: C 71.1; H 5.6; N 10.8%; M^+ 508. $C_{30}H_{28}N_4O_4$. Calculated: C 70.8; H 5.6; N 11.0%; M 508.

9-Morpholino-4-azafluorene Methiodide and Dimethiodide (IX, X). A) A solution of 0.24 g (0.9 mmole) of VIII and 4.66 g (32 mmole) of methyl iodide in 15 ml of acetone was allowed to stand for 48 h, after which the precipitate was washed with ether to give 0.23 g (61%) of dark-brown crystals of methiodide IX with mp 154-155°C. Found: N 7.0%. $C_{16}H_{16}N_2O \cdot CH_3I$. Calculated: N 7.1%.

B) A solution of 0.24 g (0.9 mmole) of VII and 0.32 g (65 mmole) of methyl iodide in 15 ml of ethanol was refluxed for 3 h to give 0.21 g (41%) of dimethiodide X in the form of black crystals that decomposed at 182°C. Found: N 5.2%. $C_{16}H_{16}N_2O \cdot 2CH_3I$. Calculated: N 5.2%.

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