9-α-CARBETHOXY(CARBOXY)ALKYL-4-AZAFLUORENES

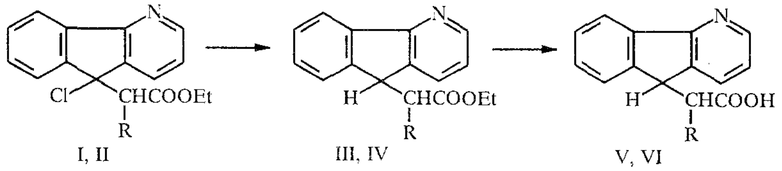
N. S. Prostakov, E. V. Kruglyak, and V. P. Shalimov

9-Carbethoxymethyl- and 9-(α-carbethoxyethyl)-4-azafluorenes were obtained by the reduction of 9-chloro-9-α-carbethoxyalkyl-4-azafluorenes, and the corresponding acids were obtained from them. Some information regarding the transformations of 9-hydroxy-9-α-carboxyethyl-4-azafluorene under the influence of polyphosphoric acid (PPA) with heating was obtained.

According to the data obtained in the laboratory of pharmacology of Russian International-Friendship University (T. A. Ventslavskaya), 9-hydroxy-9-α-carbethoxyalkyl-4-azafluorenes have cardiotropic activity [1]. Continuing our search for substances with similar physiological activity among azafluorene derivatives, we turned to the synthesis of 9-α-carbethoxyalkyl-4-azafluorenes and the acids corresponding to them.

The reduction of 9-chloro-9-carbethoxymethyl-4-azafluorene (I) and 9-chloro-9-α-carbethoxyethyl-4-azafluorene (II) with zinc in ethanol gave 9-carbethoxymethyl-4-azafluorene (III) and 9-α-carbethoxyethyl-4-azafluorene (IV) in quantitative yields. Considering the weakly acidic properties of the proton attached to the $C_{(9)}$ atom, one might assume that these esters exist in the form of five-membered chelates with an intramolecular hydrogen bond with the participation of the carbonyl oxygen atom of the carbethoxy group.

The hydrolysis of esters III and IV was carried out in concentrated hydrochloric acid. 9-Carboxymethyl-4-azafluorene (V) and 9-α-carboxyethyl-4-azafluorene (VI) were isolated in the form of colorless relatively high-melting crystals. The presence in the IR spectrum of V of the intense band with a maximum at 2500 cm^{-1} that is characteristic for a protonated pyridine nitrogen atom constitutes evidence that it exists in the form of intermolecular associates. Data from the UV spectra of V and VI serve as a confirmation of this assumption. As compared with 4-azafluorene (λ_{max}^{DPP} = 300 nm), the long-wave absorption band of their azafluorene fragment is shifted to 310 nm and is broadened; this is characteristic for the $N^{+}H$ cation of 4-azafluorene [3].



I, III, V R=H; II, IV, VI R=Me

The conversion of 9-hydroxy-9-carboxymethyl-4-azafluorene, as well as 9-carboxymethylidene-4-azafluorene, to spirobis(4-azafluorene)-9-1′,3′-cyclobutane by the action of polyphosphoric acid (PPA) with heating has been previously described [2]. To obtain additional information regarding the transformations that take place in this process we carried out a similar reaction with 9-hydroxy-9-α-carboxyethyl-4-azafluorene (VII) [2]. Its heating with PPA was carried out at 180°C. From the reaction products we isolated a mixture of 9-ethylidene-4-azafluorene (VIII) and its dimer — 2′,4′-dimethylspirobis(4-azafluorene)-9-1′,3′-cyclobutane (IX). A molecular-ion peak with m/z 193 (100%), which corresponds to the empirical formula of VIII, and a molecular-ion peak with m/z 386 (45%), which is related to spiro compound IX, are observed in the mass spectrum of the mixture. The principal product of this reaction (56%) is polymer X — a colorless substance with mp 206-

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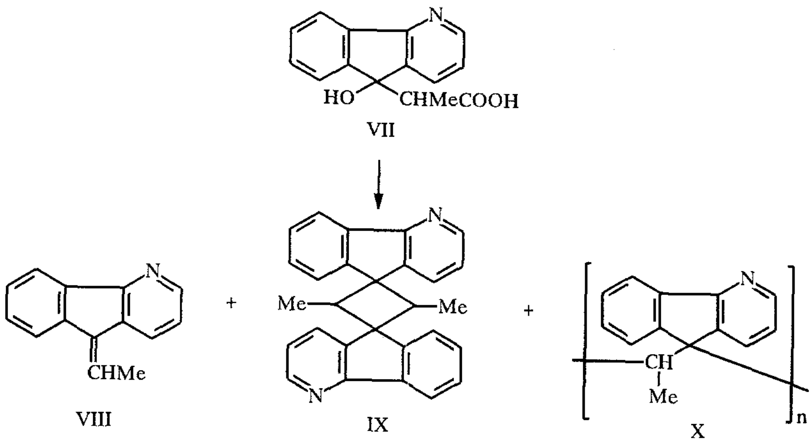
208°C that is insoluble in acetone. The molecular peak of a monomer — 9-ethylidene-4-azafluorene (VIII), the formation of which possibly takes place through the depolymerization of X, was recorded in its mass spectrum recorded at 190°C. The 9-methylene(ethylidene)fluorenes are unstable and are polymerized readily [4]. If it is assumed that linear polymerization occurs in this case, the structure depicted by formula X can be assigned to the polymer obtained from VII.



VII

VIII IX X

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer. The PMR spectra were obtained with Tesla BS-467 (60 MHz) and Bruker WP-80 (80 MHz) spectrometers with tetramethylsilane (TMS) as the internal standard. The molecular masses were determined by mass spectrometry with an MKh-1303 mass spectrometer at an ionizing-electron energy of 70 eV.

The progress of the reactions and the individuality of the compounds obtained were monitored by TLC on activity II Al_2O_3 with elution by ether—hexane (3:1). The reaction products were isolated by column chromatography on activity IV Al_2O_3 with elution by ether—hexane (1:1).

The results of elementary analysis of III-VI for C, H, and N were in agreement with the calculated values.

9-Carbethoxymethyl-4-azafluorene (III, $C_{16}H_{15}NO_2$) and 9-α-Carbethoxyethyl-4-azafluorene (IV, $C_{17}H_{17}NO_2$). **A.** A 15-g (5.24 mmole) sample of I was refluxed with excess activated zinc dust in 50 ml of ethanol for 8 h, after which the reaction mixture was filtered. The alcohol was removed from the filtrate by distillation, 25 ml of water was added to the residue, and the aqueous mixture was neutralized with sodium carbonate to pH 9 and extracted with ether (3 × 30 ml). The extract was dried with potassium carbonate and worked up to give 0.77 g (58%) of III in the form of an oily substance. IR spectrum: 1730 (C=O), 1160-1260 (CO), 3600 cm^{-1} (OH_{ass}). Mass spectrum: M^+ 253.

B. Similarly, ester IV was obtained as an oily substance in 96% yield from chloride II. PMR spectrum ($CDCl_3$) of a mixture of the racemates: 0.62 and 0.75 (1H, dd, J = 7.1 Hz, $CH—CH_3$); 1.18 and 1.30 (2H, dd, J = 7.0 Hz, $CH_2—CH_3$; 3.22 (3H, m, $CH—CH_3$); 4.16 and 4.21 (3H, qq, J = 4 Hz, $CH_2—CH_3$); 4.35 and 4.45 (1H, dd, J = 5 Hz, H_9); 7.2-8.6 ppm (7H, m, H_{arom}). Mass spectrum: M^+ 267.

9-Carboxymethyl-4-azafluorene (V, $C_{14}H_{11}NO_2$) and 9-α-Carboxyethyl-4-azafluorene (VI, $C_{15}H_{13}NO_2$). **A.** A 1.5-g (5.9 mmole) sample of ester III was refluxed for 17 h in 20 ml of concentrated HCl, after which the mixture was evaporated to half its original volume and neutralized with dry sodium carbonate to pH 7 to give 0.53 g (40%) of acid V in the form of colorless crystals with mp 205-207°C (from aqueous ethanol). IR spectrum: 2200-3100 (OH, N^+H), 1740 cm^{-1} (CO). PMR spectrum (DMSO): 7.2-8.6 (7H, m, H_{arom}), 4.3 (1H, d, J = 7 Hz, H_α), 2.8 ppm (1H, d, J = 7 Hz, CH_2). Mass spectrum: M^+ 225.

B. Acid VI was similarly obtained in 85% yield in the form of colorless crystals with mp 186-187°C (from aqueous ethanol). PMR spectrum ($CDCl_3$): 0.8-0.9 (3H, dd, J = 7.0 Hz, CH_3), 3.3-3.6 (1H, m, $CH—CH_3$), 4.8 (1H, m, H_α), 12.2 (1H, broad s, COOH), 7.1-8.8 ppm (7H, m, H_{arom}).

9-Ethylidene-4-azafluorene (VIII, $C_{14}H_{11}N$), 2′,4′-Dimethylspirobis(4-azafluorene)-9-1′,3′-cyclobutane (IX, $C_{28}H_{22}N_2$), and Polymer X [$(C_{14}H_{11}N)_n$]. A mixture of 2 g (7.8 mmole) of acid VII and PPA (16 g of 85% orthophosphoric acid and 16 g of phosphorus pentoxide) was heated for 4.5 h at 180°C, after which it was poured over 50 g of ice, and the aqueous mixture was neutralized with sodium carbonate solution. The reaction products were extracted with chloroform (3

× 30 ml), and the extract was worked up to give 1.1 g of a mixture of substances, from which 0.84 g (56%) of polymer X in the form of colorless crystals with mp 206-207°C (dec.) was isolated by trituration in 30 ml of acetone. Workup of the acetone extract gave 0.25 g (17%) of a mixture of VIII and IX. Mass spectrum: M^+ 183 and 386, respectively.

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