SYNTHESIS AND REACTIONS OF 9-HYDROXY-(α-ALKOXYCARBONYLALKYL)-4-AZAFLUORENES

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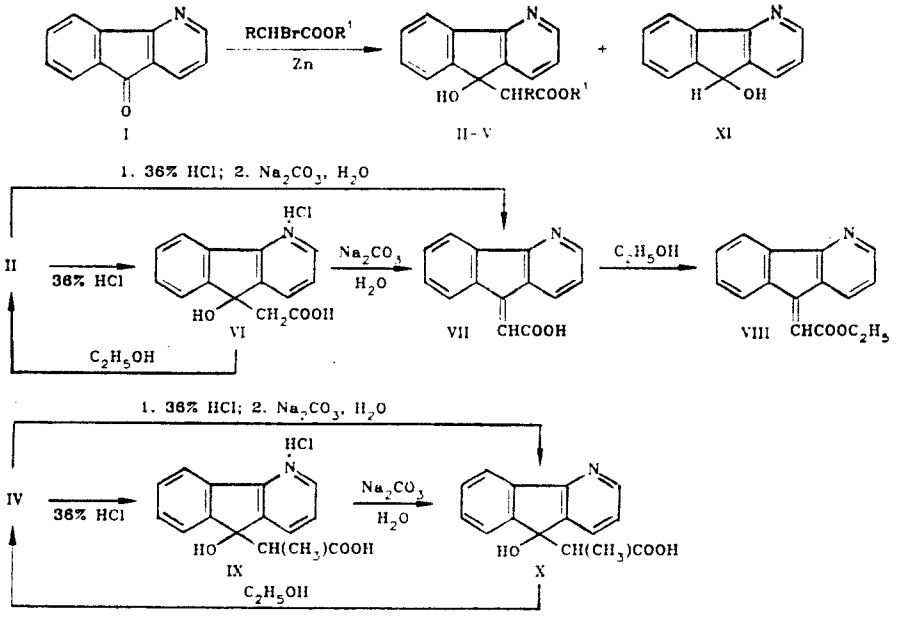
The Reformatsky reaction with 4-azafluorenone has given 9-hydroxy-9-(α-alkoxycarbonylalkyl)-4-azafluorenes. The course of this reaction with respect to the α-haloester used, and the conversion of these hydroxyesters into hydroxy- and αβ-unsaturated acids have been examined.

The Reformatsky reaction of 4-azafluorene (I) with esters of the appropriate α-brominated carboxylic acids has given 9-hydroxy-9-ethoxycarbonylmethyl-, α-methoxycarbonylethyl-, α-ethoxycarbonylethyl-, and α-ethoxycarbonylpropyl-4-azafluorenes (II-V) (Table 1). Dehydration of these β-hydroxyesters, such as frequently occurs during the synthesis of similar compounds, was not observed. This could be due to stabilization by intermolecular and intramolecular hydrogen bonding, the presence of which was confirmed by IR spectroscopy.

Hydrolysis of the esters (II) and (IV) with 36% HCl afforded the crystalline hydrochlorides of 9-hydroxy-9-carboxymethyl- and 9-hydroxy-9-α-carboxyethyl-4-azafluorene (VI and (IX). The conversion of these compounds into the free bases proceeded differently. Treatment of the hydrochloride (VI) with sodium carbonate to pH 7 gave a quantitative yield of 4-azafluorenylidene-9-acetic acid (VII). This acid was also obtained on hydrolysis of the ester (II) followed by treatment of the reaction products with base to the same pH. In the course of these reactions, 9-hydroxy-9-carboxymethyl-4-azafluorene (II) was formed in small amounts, as shown by PMR and mass spectroscopy of the reaction mixtures. Esterification of (VI) gave the ester (II), confirming that the β-hydroxyester grouping had been retained in the original hydrochloride (VI), while the acid (VII) gave ethyl 4-azafluorenylidene-9-acetate (VIII).



II R=H; III, IV R=CH_3, V R=C_2H_5; II, IV, V R¹=C_2H_5, III R¹=CH_3

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TABLE 1. Properties of Compounds Obtained (II-VI)

Compound	Mp, °C	IR spectrum, cm^{-1}	Yield, %
II	97...98	3130, 3110, 3100 (OH-assoc.);1745, 1720 (C=O); 1300, 1271 (CO)	81
III	118...120	3460, 3345, 3180 (OH-assoc.);1744, 1732 (C=O); 1225, 1190 (CO)	54
IV	100...102	3470, 3400, 3178, 3080 (OH-assoc.);1735, 1710 (C=O); 1198, 1172 (CO)	85
V	140...142	3550, 3350, 3270 (OH-assoc.);1740, 1730 (C=O); 1200, 1174 (CO)	67
VI	234,5...236	3190...2980, 2480 (OH-assoc., N+H); 1690, 1632 (C=O); 1089 (CO)	64

Conversion of the hydrochloride (IX) into the free base in the same way, and also acid hydrolysis of the ester (IV) followed by treatment with base, gave 9-hydroxy-9-(α-carboxyethyl)-4-azafluorene, from which the ester (IV) was obtained.

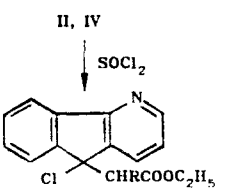
These experimental findings do not support the view that β-hydroxyacids with a tertiary carbon atom undergo dehydration more readily than the analogous compounds with secondary carbon atoms. Some understanding of this anomaly may be obtained by a study of the spatial structure of the hydroxyacids corresponding to the esters (II) and (IV) using Drieding models. When the hydrochlorides of these compounds are converted into the free bases, quaternary salts may be formed by intermolecular reaction of the carboxylate anion of the hydroxyacid with the nitrogen atom of the pyridine ring in the azafluorene fragment. In the case of β-hydroxyacids corresponding to the ester (II), there is no steric hindrance to the formation of such a salt, and it possesses the most favorable configuration, with the transoid disposition of the hydroxyl group and the hydrogen atoms of the methylene group, for dehydration to occur.

It appears that in the hydroxyacid (X) the methyl group in the α-position is the steric factor which prevents the formation of a similar salt. Bearing in mind the increased CH-acidity in (IX) and the relatively weak basic nature of the pyridine nitrogen, it may be assumed that the hydroxyacid (X) exists preferentially as a six-membered chelate with an intramolecular hydrogen bond.

The reactions of 4-azafluorenone (I) with zinc and methyl chloracetate, and diethyl bromomalonate, are anomalous. In both cases quantitative yields of 4-azafluoren-9-ol (XI) were obtained. Mass spectrometry showed that the expected Reformatsky products, 9-hydroxy-9-methoxycarbonylmethyl- and 9-hydroxy-9-di(ethoxycarbonyl)methyl-4-azafluorene, were present in the reaction mixtures in insignificant amounts. The same spectral method showed that the reaction mixtures obtained in the Reformatsky synthesis of esters (II-V) also contained the azafluorenol (XI) as an impurity. Reduction of the ketone (I) with zinc to the alcohol (XI) takes place in the presence of a proton donor (α-haloester). Reaction of the hydroxyesters (II) and (IV) with thionyl chloride afforded 9-chloro-9-ethoxycarbonylmethyl- and α-ethoxycarbonylethyl-4-azafluorene (XII, XIII).

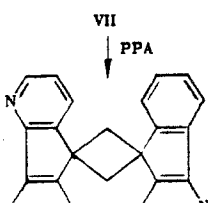
The compounds described above were obtained with a view to examining their cardiotropic activity, on which some preliminary information has been reported [1].

Attempts were made to effect the cyclodehydration of the acid (VII) with PPA. The main reaction product was, however, spirobis(4-azafluorene)-9-1',3'-cyclobutane (XIV). This is the dimerization product of 9-methylene-4-azafluorene, formed by decarboxylation of the α,β-unsaturated acid (VII). Compound (XIV) had previously been obtained in 10% yield by dehydration of 9-methyl-4-azafluoren-9-ol with phosphorus pentoxide in boiling xylene [2].



XII, XIII

XII R=H; XIII R=CH_3



XIV

The PMR spectra of (II-V) and (VIII) are shown in Table 2. The chemical shifts and coupling constants for the protons of the azafluorene moiety lie in the range characteristic of 4-azafluorenes. Compounds (III-V) were isolated as mixtures of

TABLE 2. PMR Spectra of Hydroxyesters (II-V) and Ester (VIII) ($CDCl_3$, TMS)

Compound, proton	Chemical shifts, δ, ppm (J, Hz)					
	1-H	2-H	3-H	CH—CH_3	OCH_2CH_3	OH
II	7,83	7,07	8,30	AB type spectrum 2,90 and 3,06 (CH_2) (J=−15,7)	4,12 q and 1,15 t (J=7,1)	5,24
IIIa	7,90	7,10	8,40	3,31 q and 0,70 d (J=7,3)	3,79 (OCH_3, s)	4,75
IIIb	7,74	7,11	8,42	3,20 q and 0,87 d (J=7,5)	3,72 (OCH_3, s)	4,85
IVa	7,94	7,09	8,41	3,26 q and 0,74 d (J=7,1)	4,24 q and 1,28 t (J=6,95)	4,72
IVb	7,75	7,22	8,43	3,17 q and 0,93 d (J=7,3)	4,16 q and 1,20 t (J=6,95)	4,85
Va*	8,12	7,00	8,37	3,1 m (CH)	4,25 q and 1,27 t (J=7,0)	4,2
Vb	7,85	7,01	8,39		4,10 q and 1,10 t (J=7,0)	br.s
Z-VIII	9,15	7,20	8,50		4,35 q and 1,38 t (J=7,0)	
E-VIII**		7,20	8,50		4,37 q and 1,33 t (J=7,0)	

*(Va, b) 0.6-1.6 ppm (m, CH_2–CH_3).

**The signal for the 1-H proton together with the remaining protons of the azafluorene ring gave a multiplet at 7.3-8.5 ppm, and the 8-H proton signal gave a multiplet at 8.9 ppm.

two diastereoisomers (a and b), for which the greatest differences in chemical shifts were seen for the 1-H protons (0.2 ppm), the protons of the methyl group in the fragment $CH(CH_3)COOR$, and the hydroxyl protons (0.1-0.15 ppm), which are seen in the spectrum as separated, broadened signals at 4.75-4.85 ppm.

According to their PMR spectra, (IX) and (X) were isolated as a mixture of diastereoisomers in a ratio of ~1:2. 4-Azafluorenylidene-9-acetate (VIII) was obtained as the Z- and E-isomers in a ratio of 5:1. Assignment of the isomers was made on the basis of the low-field shift of the signals for the 1-H (Z) and 8-H (E) protons (δ 9.15 and 8.90 ppm, respectively), which are in the cis-position to the ethoxycarbonyl group.

EXPERIMENTAL

IR spectra were obtained on a UR-20 spectrophotometer in KBr disks. PMR spectra were recorded on Tesla BS-467 (60 MHz) and Bruker WP-80 (80 MHz) instruments, internal standard TMS. Molecular masses were determined by mass spectrometry on an MX-1303 mass spectrometer, ionizing electron energy 70 eV.

The progress of the reactions was followed and the purity of the products checked by TLC on grade II alumina, eluent a mixture of ether and hexane (3:1). The reaction products were isolated by column chromatography on grade IV alumina, eluent a mixture of ether and hexane (1:1).

The elemental analysis of (II-XIV) for C, H, and N were in agreement with the calculated values.

9-Hydroxy-9-ethoxycarbonylmethyl- (II, $C_{16}H_{15}NO_3$), α-Methoxycarbonylethyl- (III, $C_{16}H_{15}NO_3$), α-Ethoxycarbonylethyl- (IV, $C_{17}H_{17}NO_3$), and α-Ethoxycarbonylpropyl-4-azafluorene (V, $C_{18}H_{19}NO_3$). To a solution of 10 mmoles of the azafluorenone (I) in 35 ml of toluene was added 14.6 mmoles of zinc dust, and a catalytic amount of tartaric acid. The bromoester (30 mmoles) was added at 70°C, then the mixture was boiled for 2.5 h. After cooling, the mixture was poured into 18 ml of 10% HCl, the aqueous layer separated and treated with sodium carbonate solution to pH 8. The mixture was then extracted with ether (3 × 50 ml), the extracts dried over calcined potassium carbonate, and the residue from the ether extract chromatographed. The product obtained was crystallized from heptane.

9-Hydroxy-9-carboxymethyl-4-azafluorene Hydrochloride (VI, $C_{14}H_{11}NO_3 \cdot HCl$) and 4-Azafluorenylidene-9-acetic Acid (VII, $C_{14}H_9NO_2$). A. A solution of 2.2 g (8.2 mmoles) of the ester (II) in 25 ml of 36% HCl was boiled for 15 h. The solid which separated on cooling was filtered off and washed with 36% HCl to give 1.45 g (64%) of the hydrochloride (VI) as cream-colored crystals, mp 234.5-236°C (decomp.). IR spectrum: 3190-2980, 12480 (assoc. OH, N^+H), 1690, 1632 (C=O), 1089 cm^{-1} (CO). PMR spectrum (DMSO-D_6): 3.25, 3.42 (2H, AB spectrum, J = −15.0 Hz, CH_2), 7.4-7.9 and 8.2-8.8 (7H, m, H_{arom}), 6-8 ppm (br.s –COOH and water from DMSO). $[M–HCl]^+$ 241.

B. The reactants in the same amounts were boiled for 15 h, then neutralized with sodium carbonate to pH 7 and concentrated to half the volume. The solid which separated on cooling was filtered off and washed with water to give 1.1 g (62%) of

the acid (VII) as light reddish-brown crystals, mp 256-257°C. IR spectrum: 2600-2380 (OH and N^+H), 1720 (C=O), 1650 cm^{-1} (C=C). M^+ 223.

C. To a solution of 1 g (3.6 mmoles) of the hydrochloride (VI) in 10 ml of water was added gradually a solution of sodium carbonate to pH 7. The solid was filtered off to give 0.7 g (87%) of the acid (VII).

Esterification of 0.3 g (1.3 mmoles) of the acid (VII) in 5 ml of ethanol and 0.3 ml of sulfuric acid (boiled for 5.5 h) followed by removal of the alcohol, neutralization with sodium carbonate, and extraction with ether gave 0.27 g (80%) of the ester (VIII) as yellow crystals, mp 71-72°C. IR spectrum: 1710 (C=O), 1652 cm^{-1} (C=C). M^+ 251.

9-Hydroxy-9-(α-carboxyethyl)-4-azafluorene Hydrochloride (IX, $C_{15}H_{13}NO_3 \cdot HCl$) and 9-Hydroxy-9-(α-carboxyethyl)-4-azafluorene (X, $C_{15}H_{13}NO_3$). A. A Solution of 2.27 g (8 mmoles) of the ester (IV) was boiled in concentrated HCl (30 ml) for 15 h. The mixture was worked up as for (VI), to give 2.1 g (90%) of the hydrochloride (IX) as yellow crystals, mp 244.5-245.6°C (decomp.). IR spectrum: 3300-3110, 2700 (assoc. OH, N^+H), 1750, 1650 cm^{-1} (C=O). PMR spectrum (DMSO-D_6) of the mixed isomers (1:2): 0.85 and 1.15 (3H, two d, J = 7.0 Hz, CH_3), 3.35 (1H, q, J = 7.0 Hz, CH), 8.0-8.8 (3H, m, 1-H, 2-H, 3-H), 7.4-7.9 (4H, m, 5-H-8H), 3.5-4.5 ppm (br.s, COOH and water from DMSO). $[M-HCl]^+$ 255.

B. The reaction was carried out with 2 g (7.1 mmoles) of the ester (IV) and 30 ml of 36% HCl. After boiling for 15 h, sodium carbonate solution was added to pH 10. Neutral material was extracted with ether, and to the aqueous solution was added slowly 70% sulfuric acid to pH 7. There separated 1.28 g (71%) of the hydroxyacid (X) as cream-colored crystals, mp 181-182.5°C (decomp.). IR spectrum: 3410-3200 (assoc. OH), 1730 cm^{-1} (C=O). PMR spectrum ($CDCl_3$): 0.70 and 0.85 (3H, two d, J = 7 Hz, CH_3); 3.20 and 3.30 (2H, two d, J = 7 Hz, CH), 8.4 (1H, br.s, 3-H), 7.0-8.1 ppm (6H, m, H_{arom} and COOH). When the temperature was raised to 323 K, the signal for the labile protons was seen as a broadened singlet at 6.9 ppm. M^+ 255.

C. From 0.3 g (1 mmole) of the hydrochloride (IX) there was obtained 0.23 g of the acid (X) by slowly adding a solution of sodium carbonate to an aqueous solution of the hydrochloride to pH 7. Esterification of the acid (X) with ethanol gave the ester (IV) in 58% yield.

4-Azafluoren-9-ol (XI, $C_{12}H_9NO$). A. The reaction was carried out as for compounds (II-V), using 1 g (5.5 mmoles) of the azafluorenone (I), 25 ml of toluene, 0.5 g (7.7 mmoles) of zinc dust, 1.8 g (17 mmoles) of methyl chloroacetate, and a catalytic amount of tartaric acid. There was obtained 0.43 g (43%) of the alcohol (XI) as colorless crystals, mp 152-153°C.

B. The reaction was carried out with the same amounts of starting materials and 4 g (16.7 mmoles) of diethyl bromomalonate. The mixture was boiled for 8 h, to give 0.9 g (90%) of the azafluorenol (XI), mp 151-152°C, M^+ 183.

9-Chloro-9-ethoxycarbonylmethyl- (XII, $C_{16}H_{13}ClNO_2$) and α-Ethoxycarbonylethyl-4-azafluorene (XIII, $C_{17}H_{16}NO_2$). A. A solution of 0.3 g (1.12 mmoles) of the hydroxyester (II) in 5 ml of thionyl chloride was boiled for 4 h. The thionyl chloride was then removed, and 10 ml of water added followed by sodium carbonate solution to pH 9. The residue from the ether extracts was chromatographed, eluent ether and hexane, 2:1, to give 0.2 g (63%) of (XII) as an oil. IR spectrum: 1745 cm^{-1} (CO), M^+ 286/288.

B. A solution of 1.5 g (5.3 mmoles) of the hydroxyester (IV) in a mixture of 20 ml of dry ether and 5 ml of thionyl chloride was kept for 2 h. The ether and thionyl chloride were removed, and 10 ml of water added, followed by sodium carbonate solution to pH 9, then extracted with ether. The ether was removed, and from the oily residue (1.3 g) there was obtained the hydrochloride of (XIII), mp 124-125°C (from absolute ethanol). IR spectrum: 1740 cm^{-1} (C=O). PMR spectrum ($CDCl_3$) of the mixed isomers (1:2): 0.88 (3H, t, J = 7 Hz, CH_3CH_2), 1.5 (3H, d, J = 7 Hz, CH_3), 3.8 (2H, q, J = 7 Hz, OCH_2), 3.65 and 4.20 (1H, two q, J = 7 Hz, CH), 7.4-8.9 ppm (7H, m, H_{arom}). M^+ 301/303.

Spirobis(4-azafluorene)-9,1',3'-cyclobutane (XIV, $C_{26}H_8N_2$). A mixture of 0.55 g (25 mmoles) of the acid (VII) and PPA (6 g of 85% orthophosphoric acid and 10 g of phosphorus pentoxide) was heated for 2 h at 150-160°C. The mixture was then poured onto ice, neutralized with sodium carbonate and the reaction products extracted with chloroform. There was obtained 0.24 g (54%) of the spiro-compound (XIV) as yellow crystals, mp 195-197°C (from heptane), M^+ 358 [2].

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