SYNTHESIS AND SOME PROPERTIES OF SUBSTITUTED 4-AZAFLUORENES

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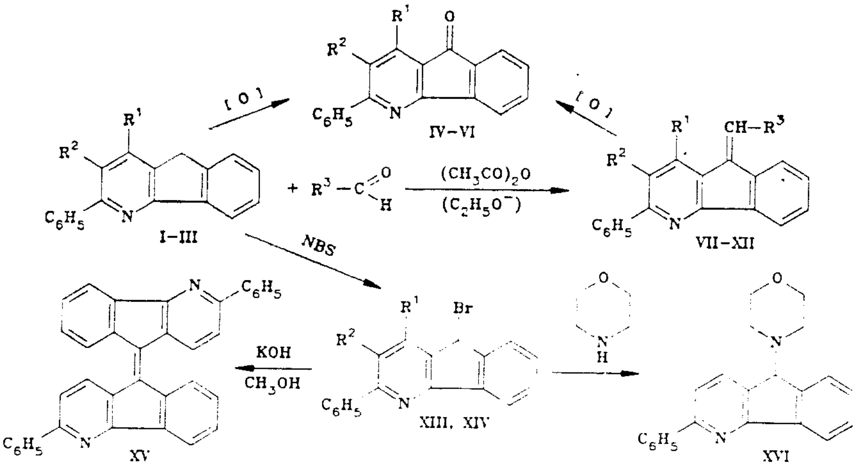
Some chemical properties – the oxidation, condensation with aromatic aldehydes, bromination, dimerization, and amination – of 4-azafluorenes derived from α-methylene-1,5-diketones are studied.

Azafluorenes and their derivatives possess a broad spectrum of biological activity [1]. It was shown previously [2, 3] that α-methylene-1,5-diketones are convenient starting compounds for the synthesis of azafluorenes, and compounds I and II were prepared from them.

We have prepared azafluorene III by a route analogous to the preparation of I and II [2, 3]. The structures of azafluorene III and the intermediates compounds in its synthesis were confirmed by IR and PMR spectroscopy and mass spectrometry.

To characterize the properties of the azafluorenes obtained, and to obtain new kinds of biologically active compounds, we carried out oxidations. Previously, azafluorene I was subjected to oxidation and the phenyl analog of the alkaloid onyquine, IV, was isolated [3]. We have carried out the oxidation of azafluorenes II and III under these same conditions with the formation of corresponding 4-azafluorenones V and VI. In the IR spectra of resultant compounds V and VI, strong, carbonyl absorption bands at 1710-1716 cm^{-1}, respectively, appear and are characteristic of compounds of similar structure [3, 4].

We have also studied the condensation of azafluorenes I-III with the aromatic aldehydes benzaldehyde and p-nitrobenzaldehyde.



I, IV, XIII $R^1=CH_3$, $R^2=H$; II, V, XIV $R^1=R^2=H$; III, VI $R^1=H$, $R^2=CH_3$; VII $R^1=CH_3$, $R^2=H$, $R^3=C_6H_5$; VIII $R^1=CH_3$, $R^2=H$, $R^3=p\text{-}C_6H_4NO_2$; IX $R^1=R^2=H$, $R^3=C_6H_5$; X $R^1=R^2=H$, $R^3=p\text{-}C_6H_4NO_2$; XI $R^1=H$, $R^2=CH_3$, $R^3=C_6H_5$; XII $R^1=H$, $R^2=CH_3$, $R^3=p\text{-}C_6H_4NO_2$

On condensation of azafluorenes I-III with *p*-nitrobenzaldehyde in acetic anhydride and with benzaldehyde under the influence of potassium ethoxide, the corresponding 9-(p-nitrobenzylidene)-4-azafluorenes VIII, X, and XII and 9-benzylidene-4-azafluorenes VII, IX, and XI were obtained. In the IR spectra of compounds VIII, X, and XII, a weak absorption at 1670-1675 cm^{-1}, which corresponds to a trisubstituted double bond [5], and strong nitro group absorption bands at 1520 and 1347 cm^{-1} were found. In the IR spectra of benzylidene derivatives VII, IX, and XI, a weak band was found at 1630-1640 cm^{-1}, corresponding to the absorption of a C=C bond.

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TABLE 1. Melting Points and Yields of Compounds Synthesized

Compound	Empirical formula	mp, °C*	Yield, %
V	$C_{18}H_{11}NO$	148...150	44
VI	$C_{19}H_{13}NO$	186...188	36
VII	$C_{26}H_{19}N$	203...205	77
VIII	$C_{26}H_{18}N_2O_2$	253...255	35
IX	$C_{25}H_{17}N$	142...144	79
X	$C_{25}H_{16}N_2O_2$	260...262	70
XI	$C_{26}H_{19}N$	198...200	61
XII	$C_{26}H_{18}N_2O_2$	198...200	53
XIII	$C_{19}H_{14}BrN$	110...112	31
XIV	$C_{18}B_{12}BrN$	136...138	31
XV	$C_{36}H_{22}N_2$	300	57
XVI	$C_{22}H_{20}N_2O$	140...142	85

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*Compounds V and VI were recrystallized from propanol; VII, IX, and XVI from ethanol; VIII and X from DMF; XI from isopropanol; XII from methanol; XIII and XIV from petroleum ether; and XV from a 2:1 ethanol/benzene mixture.

Further confirmation of the presence of a benzylidene group in compound IX was its destructive oxidation to azafluorenone V. The identity of the oxidation product and the formation of V was shown by IR spectroscopy and thin-layer chromatography as well as by the fact that the melting point of a mixed sample was not depressed.

The PMR spectrum showed that the condensation of azafluorene I with p-nitrobenzaldehyde in acetic anhydride takes place at the methylene group of the indole ring in I and does not affect the methyl group in the γ-position of the pyridine ring. In the PMR spectrum of reaction product VIII there was, besides the signal from aromatic protons in the 8.33-7.12 ppm region and the signal from a vinyl proton in the same region [6], a singlet from a methyl group at 2.72 ppm. The signal from the methylene group of azafluorene I at 3.78 ppm [3] was absent.

On oxidation of the resultant substances, VII and VIII, with potassium permanganate in acetone, 1-methyl-3-phenyl-4-azafluorenone (IV) [3] was evolved. A comparison of the IR spectra and the mixed melting point of the samples confirmed their identity.

Azafluorenes I and II are easily brominated at the 9-CH_2 group by N-bromosuccinimide. Strong absorption bands were found in the IR spectra of compounds XIII and XIV at 700 cm^{-1} due to the C–Br bond.

9-Bromo-3-phenyl-4-azafluorene XIV in methanolic KOH solution at room temperature is converted to di(3-phenyl-4-azafluorenylidene-9) (XV) in good yield.

On treating compound XIV with morpholine in dimethylformamide, the corresponding 3-phenyl-9-morpholino-4-azafluorene (XVI) was obtained. In the IR spectrum of the resultant amine XVI, a strong band was found at 1112 cm^{-1}, corresponding to the absorption of the C–O–C ether bond of the morpholine fragment, and a band at 1007 cm^{-1} from the C–N bond.

The IR spectra of all of the compounds obtained showed peaks of molecular ions appearing at values corresponding to the calculated molecular masses of these compounds.

EXPERIMENTAL

The IR spectra were taken in chloroform on a Specord IR-75 instrument. The PMR spectra in deuterochloroform were taken on a Bruker HX-90E (90 MHz) instrument with TMS as an internal standard. The course of the reactions and the individuality of the new compounds were checked by means of TLC on Silufol UV-254 plates (1:1 petroleum ether/ethyl acetate).

The syntheses of 4-azafluorenes I and II, as well as of the intermediate compounds (*a*, b, c) in the synthesis for the first time of 4-azafluorene III, were effected by known procedures [3, 7, 8]. 4-Azafluorenones V and VI were prepared by the procedure in [3].

The characteristics of the newly prepared compounds are shown in Table 1. The elementary analyses for C, H, and N correspond to the calculated values.

1-Dimethylamino-2,4-dibenzoyl-4-methylbutane (*a*, $C_{21}H_{25}NO_2$). Yield 32%. A colorless liquid that decomposed on distillation, n_D^{20} 1.5455. IR spectrum: 2830, 2780 [$N(CH_3)_2$], 1682 cm^{-1} (C=O). Picrate ($C_{21}H_{25}NO_2 \cdot C_6H_3N_3O_7$), yellow crystals, T_{mp} 159-160°C (ethanol). Iodomethylate, colorless crystals, T_{mp} 217-218°C (ethanol).

2,4-Dibenzoyl-4-methylbutene-1 (b, $C_{19}H_{18}O_2$). Yield 70%. Bright yellow liquid, R_f 0.45, decomposes on distillation. IR spectrum: 1682, 1652 (C=O), 1624 cm^{-1} (C=C).

2-(3-Oxo-2-methyl-3-phenylpropyl)-1-indanone (c, $C_{19}H_{18}O_2$). Yield 67% of a mixture of stereoisomers with R_f 0.32 and 0.35 on threefold chromatographing in a 10:1 petroleum ether/ethyl acetate system. After thin layer chromatography on silica gel, the individual compound with R_f 0.35 is obtained as a colorless liquid that decomposes on distillation. IR spectrum: 1682, 1706 cm^{-1} (C=O).

2-Methyl-3-phenyl-4-azafluorene (III, $C_{19}H_{15}N$). Yield 77%. Colorless crystals, mp 148-150°C (methanol). PMR spectrum: 2.4 (3H, s, CH_3), 3.9 ppm (2H, s, CH_2). Picrate ($C_{19}H_{15}N \cdot C_6H_3N_3O_7$), lemon-yellow needles, mp 204-206°C (ethanol).

Condensation of Azafluorenes I-III with p-Nitrobenzaldehyde. A solution of 2 mmoles of azafluorenes I-III and 2.1 mmoles of p-nitrobenzaldehyde in 5 ml of acetic anhydride is boiled for 5-7 h. The deposit of arylidene derivative VIII, X, or XII that precipitates when the reaction mixture is cooled is filtered, washed with acetic anhydride and water, dried, and purified by crystallization.

Condensation of Azafluorenes I-III with Benzaldehyde. A solution of 4 mmoles of azafluorenes I-III and 5.7 mmoles of benzaldehyde in 20-30 ml of ethanol with an addition of 10 ml of 10% alcohol solution of potassium ethoxide is boiled for 2-5 h. The deposit of the benzaldehyde derivative that precipitates is filtered, washed with ethanol, dried, and purified by crystallization.

Oxidation of 3-Phenyl-9-benzylidene-4-azafluorene (IX), 1-Methyl-3-phenyl-9-benzylidene-4-azafluorene (XI), and 1-Methyl-3-phenyl-9-p-nitrobenzylidene-4-azafluorene (XII). At 0°C and with continuous stirring, 2.9 g (18 mmoles) of potassium permanganate is added in portions over 20 min to a solution of 1 g (3 mmoles) of azafluorene IX, XI, or XII in 120 ml of acetone. Afterwards, the mixture is stirred for an additional 10 min at 0°C and then for an hour and a half at room temperature. Excess permanganate is decomposed by adding a 30% aqueous solution of hydrogen peroxide. The precipitate of manganese dioxide is filtered off and washed several times with acetone. After the acetone is distilled off, the residue is dried and contains compounds V or IV in a yield of 55 or 71-79%.

3-Phenyl-9-bromo-4-azafluorene (XIV). A solution of 1 g (4.1 mmole) of azafluorene II and 0.85 g (4.8 mmoles) of N-bromosuccinimide in 20 ml of carbon tetrachloride is boiled for 4 h 30 min. After cooling, the mixture is filtered, the precipitate washed with carbon tetrachloride, and the combined filtrate evaporated under vacuum. The residue is purified by crystallization.

In analogous fashion, **1-methyl-3-phenyl-9-bromo-4-azafluorene** (XIII) is obtained from azafluorene I.

Di(3-phenyl-4-azafluorenylidene-9) (XV). A solution of 0.28 g (5 mmoles) of KOH in 3 ml of methanol is added in portions over 1 h with stirring to a solution of 0.7 g (2.2 mmoles) of compound XIV in 25 ml of methanol. In 5 min a red precipitate begins to form. The reaction mixture is then diluted, with stirring, with 10 ml of water, the precipitate filtered off, dried, and purified by crystallization.

3-Phenyl-9-morpholino-4-azafluorene (XIII). A solution of 1.7 g (19 mmoles) of morpholine in 6 ml of DMF is added in portions over 1 h with stirring at room temperature to a solution of 1.5 g (5 mmoles) of compound XIV in 15 ml of DMF. The stirring is carried out in a stream of argon for 3 h 30 min. The DMF is distilled off under vacuum, the residue diluted with water and made basic with a solution of soda. The residue is filtered off, washed with water, dried, and purified by crystallization.

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