SYNTHESIS OF PHENYL(BENZYL)-SUBSTITUTED (IN THE PYRIDINE RING) AZAFLUORENES

N. S. Prostakov, A. V. Varlamov,
G. A. Vasil'ev, O. G. Kesarev,
and G. A. Urbina

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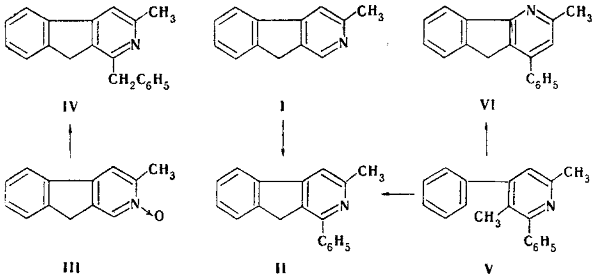
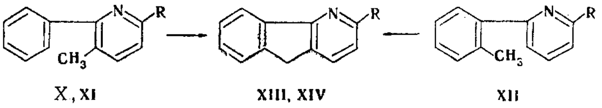
Phenyl and benzyl groups were introduced in the 1 position of 3-methyl-2-azafluorene by treatment of it or its N-oxide with organometallic compounds. 1-Phenyl-substituted 2-azafluorene was also obtained by catalytic dehydrocyclization of 2,5-dimethyl-4,6-diphenylpyridine, during which the simultaneous formation of the isomeric 4-azafluorene was established.

Nucleophilic substitution in the pyridine ring of 3-methyl-2-azafluorene (I) proceeds in a manner similar to substitution of the α position of the pyridine bases. In the present paper we report the phenylation of azafluorene I with phenyllithium, as a result of which we obtained 3-methyl-1-phenyl-2-azafluorene (II). 3-Methyl-2-azafluorene N-oxide (III), which is formed by oxidation of azafluorene I with hydrogen peroxide, was also used for the synthesis of II. 1-Benzyl-3-methyl-2-azafluorene (IV) is formed in the reaction of oxide III with benzylmagnesium chloride.



Azafluorene II was also synthesized by catalytic dehydrocyclization of 2,5-dimethyl-4,6-diphenylpyridine (V) [1]. Dehydrocyclization of V may occur both through the phenyl ring attached to C_4 and the phenyl ring attached to C_6. In fact, azafluorene II and the isomeric 3-methyl-1-phenyl-4-azafluorene (VI), as well as 2-methyl-4,6-diphenylpyridine (VII), formed as a result of detachment of the methyl group attached to C_5 of starting V, were isolated from the complex mixture of substances obtained as a result of the catalytic transformations. Azafluorenes II and VI were oxidized to the corresponding azafluorenones VIII and IX.

Catalytic dehydrocyclization was found to be convenient for the synthesis of various substituted 4-azafluorenes, concerning which little was known up until now: Only the preparation of 1,3-diphenyl-4-azafluorene from 2-benzylidene-1-indanone and phenacylpyridinium bromide has been described [2]. 3-Methyl-2-phenylpyridine (X), 3-methyl-2,6-diphenylpyridine (XI), and 2-(o-tolyl)pyridine (XII) were subjected to catalytic dehydrocyclization.



X, XII, XIII R = H; XI, XIV R = C_6H_5

The yields of the 4-azafluorenes are almost identical, regardless of whether cyclization is realized with respect to the phenyl ring or the pyridine ring.

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EXPERIMENTAL

The IR spectra of the compounds were recorded with a UR-20 spectrometer. The electronic spectra of alcohol solutions of the compounds were measured with SF-4a and EPS-3T spectrophotometers. The PMR spectra of the compounds were recorded with Varian HA-100D and T-60 spectrometers. Thin-layer chromatography (TLC) and separation of the reaction products by means of column chromatography were carried out with activity II Al_2O_3.

3-Methyl-2-azafluorene N-Oxide (III). A 6-ml sample of 30% hydrogen peroxide was added gradually to a solution of 6 g (33 mmole) of azafluorene I in 40 ml of glacial acetic acid, and the mixture was then stirred at 80-85° for 36 h with the addition of another three 6-ml portions of hydrogen peroxide every 10 h. The solution was then diluted with an equal volume of water and vacuum evaporated. The residue was dissolved in 100 ml of water, and the aqueous solution was made alkaline to pH 8 with sodium carbonate. The reaction products were extracted successively with ether and chloroform. Workup of the ether extract yielded 2 g of starting azafluorene I, and workup of the chloroform extract yielded 3.15 g (72% based on converted azafluorene I) of N-oxide III as light-yellow crystals with mp 178-180° (from acetone) and R_f 0.33 (chloroform); the product was soluble in water and chloroform. IR spectrum: 1280, 1270, and 1250 cm^{-1}. Found: N 7.1%. $C_{13}H_{11}NO$. Calculated: N 7.1%.

3-Methyl-1-phenyl-2-azafluorene (II). A) A solution of phenyllithium, obtained from 0.7 g (0.1 g-atom) of lithium and 7.6 g (48 mmole) of bromobenzene in 100 ml of ether, was added gradually with vigorous stirring to a solution of 3 g (16 mmole) of azafluorene I in 15 ml of absolute ether, after which the mixture was refluxed for 1 h. It was then treated with 25 ml of toluene, and the ether was removed by distillation. The toluene solution was refluxed for 10 h, after which it was cooled and treated with 15 ml of water. The toluene layer was separated, and the aqueous layer was extracted with ether. The combined extract and toluene layer was dried with magnesium sulfate, the solvents were evaporated, and the residue was subjected to column chromatography [elution with chloroform–petroleum ether (1 : 10)] to give 0.6 g (14%) of colorless crystals of II with mp 123.5-124° (from hexane). IR spectrum: 1560 (pyridine ring) and 695 cm^{-1} (monosubstituted benzene ring C–H). PMR spectrum, δ: 2.57 ($3-CH_3$, s, 3H) and 3.83 ppm ($9-CH_2$, s, 2H). The product had R_f 0.46 [chloroform–petroleum ether (3 : 1)]. Found: C 88.5; H 6.2; N 5.2%. $C_{19}H_{15}N$. Calculated: C 88.7; H 5.9; N 5.4%. The hydrochloride had mp 265-266° (from alcohol). Found: Cl 12.3; N 4.6%. $C_{19}H_{15}N \cdot HCl$. Calculated: Cl 12.1; N 4.8%.

B) A solution of phenylmagnesium bromide [from 3 g (0.13 g-atom) of magnesium and 9.6 g (61 mmole) of bromobenzene] in 40 ml of absolute tetrahydrofuran (THF) was added with vigorous stirring to a solution of 2 g (0.01 mole) of N-oxide III in 10 ml of THF, and the mixture was heated at 70° for 14 h. It was then cooled and treated with 20 ml of water, and the reaction products were extracted repeatedly with ether. The extract was dried with magnesium sulfate and evaporated, and the residue was separated with a chromatographic column [elution with chloroform–petroleum ether (1 : 10)] to give 0.7 g (27%) of II with mp 123.5-124°.

1-Benzyl-3-methyl-2-azafluorene (IV). A solution of benzylmagnesium chloride, obtained from 2.8 g (0.12 g-atom) of magnesium and 7.4 g (58.5 mmole) of benzyl chloride in 36 ml of THF, was added at 0° with stirring to a solution of 1.9 g (9.6 mmole) of N-oxide III in 30 ml of THF, and the mixture was stirred at 20° for 1 h, after which it was refluxed for 15 h. Water (20 ml) was added, the organic layer was separated, and the aqueous layer was extracted repeatedly with chloroform. The combined extract and organic layer was dried with magnesium sulfate, the solvents were removed by distillation, and the residue was dissolved in 100 ml of absolute ether. An ether solution of hydrogen chloride was added, and the resulting precipitate was subjected to column chromatography [elution with hexane-ether (1 : 5)] to give 0.6 g (23%) of light-yellow crystals of IV with mp 94-95° (from petroleum ether). IR spectrum: 1570 (pyridine ring) and 700 cm^{-1} (monosubstituted benzene ring C–H). PMR spectrum, δ: 2.50 ($3-CH_3$, s, 3H), 3.5 ($1-CH_2$, s, 2H), and 4.06 ppm ($9-CH_2$, s, 2H). UV spectrum, λ_{max} (log ε): 265 (4.37), 286 (4.24), and 296 nm (4.20). The product had R_f 0.64 (chloroform). Found: C 88.4; H 5.9; N 5.4%. $C_{20}H_{17}N$. Calculated: C 88.6; H 6.2; N 5.2%. The hydrochloride had mp 263-265° (from alcohol–acetone). Found: Cl 12.0%. $C_{20}H_{17}N \cdot HCl$. Calculated: Cl 11.5%. The methiodide had mp 306-307° (from methanol). Found: N 3.3%. $C_{20}H_{17}N \cdot CH_3I$. Calculated: N 3.4%.

Dehydrocyclization of 2,5-Dimethyl-4,6-diphenylpyridine (V). The dehydrocyclization was carried out in a flow system using 20 ml of K-16 industrial dehydrogenating catalyst. The temperature in the catalyst zone was 550-560°. A solution of 28.5 g (0.11 mole) of V in 70 ml of benzene was passed at a constant rate through the contact tube for 3 h. The benzene was removed by distillation to give 23.1 g of residue. A solution of 14.2 g of the residue in 150 ml of acetone was treated with a solution of 17 g of picric acid in 150 ml of acetone, and the precipitated picrates (12.5 g) were removed by filtration. Evaporation of the mother liquor yielded 10.8 g of the picrate of starting pyridine V (mp 184°), from which 5 g of the base (mp 68-72°) was obtained by decomposition on aluminum oxide (elution with chloroform). Fractional crystallization of the filtered mixture of picrates from acetone initially yielded 5.8 g (46% based on converted pyridine V) of the picrate of azafluorene II, with mp 214-215°. Found: N 11.3%. $C_{19}H_{15}N \cdot C_6H_3N_3O_7$. Calculated: N 11.5%. Decomposition of the picrate on aluminum oxide gave 2.1 g of azafluorene II with mp 123-124° (from heptane). Subsequent workup yielded 1.52 g (12%) of the picrate of azafluorene VI, with mp 217-218°. Found: N 11.3%. $C_{19}H_{15}N \cdot C_6H_3N_3O_7$. Calculated: N 11.5%. The picrate yielded 0.8 g of azafluorene VI with mp 78-79° (from hexane). Found: C 88.8; H 6.0; N 5.7%. $C_{19}H_{15}N$. Calculated: C 88.7; H 5.9; N 5.4%.

At the end of crystallization, 3.15 g (25%) of the picrate of pyridine base VII, with mp 212-213°, was obtained. It yielded 1.67 g of base VII with mp 72-73° [4].

Oxidation of azafluorene II with potassium permanganate in acetone at 20° gave 3-methyl-1-phenyl-2-azafluorenone (VIII), with mp 130-131° (from heptane), in 57% yield. Found: C 84.2; H 4.8; N 5.5%. $C_{19}H_{13}NO$. Calculated: C 84.1; H 4.8; N 5.2%. Similarly, oxidation of azafluorene VI gave 3-methyl-1-phenyl-4-azafluorenone (IX), with mp 119-120° (from hexane), in 41% yield. Found: C 84.1; H 4.8; N 5.3%. $C_{19}H_{13}NO$. Calculated: C 84.1; H 4.8; N 5.2%. The picrate had mp 189-190° (from alcohol–acetone). Found: N 11.0%. $C_{19}H_{13}NO \cdot C_6H_3N_3O_7$. Calculated: N 11.2%.

4-Azafluorene (XIII). A) A solution of 27.5 g (0.162 mole) of 3-methyl-2-phenylpyridine (X) in 40 ml of benzene was passed through a catalytic tube at 560-570° for 4 h, after which the benzene was removed by distillation, and the residue (23.9 g) was crystallized from heptane to give 4 g of 4-azafluorene (XIII) with mp 92-93° (from heptane). PMR spectrum, δ: 3.55 ppm (CH_2). Found: C 86.2; H 5.4; N 8.0%. $C_{12}H_9N$. Calculated: C 86.3; H 5.4; N 8.4%. The mother liquor remaining after separation of the 4-azafluorene was treated with a solution of 10 g of picric acid in acetone. Workup gave 6 g of the picrate with mp 207-208° (from acetone), decomposition of which on aluminum oxide (elution with chloroform) yielded an additional 2.15 g of 4-azafluorene for an overall yield of 6.15 g (22%).

B) Dehydrocyclization under similar conditions of 33.8 g (0.2 mole) of 2-(o-tolyl)pyridine (XII) yielded 31.4 g of a residue, which was treated with a solution of 50 g of picric acid in 250 ml of acetone. Workup yielded 11 g of the picrate of 4-azafluorene, decomposition of which gave 5.92 g (18%) of base XIII.

3-Phenyl-4-azafluorene (XIV). A 19.4-g (0.08 mole) sample of pyridine XI was subjected to dehydrocyclization. The residue remaining after removal of the benzene by distillation was converted to the picrate. Workup gave 7 g of the picrate of azafluorene XIV with mp 185-188° (from alcohol–acetone). Found: N 11.8%. $C_{18}H_{13}N \cdot C_6H_3N_3O_7$. Calculated: N 11.9%. Decomposition of the picrate yielded 3.5 g (19%) of XIV with mp 125-126° (from heptane). PMR spectrum, δ: 3.77 ppm (CH_2). Found: C 88.9; H 5.7; N 5.4%. $C_{18}H_{13}N$. Calculated: C 88.8; H 5.5; N 5.6%.

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