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SYNTHESIS AND TRANSFORMATIONS OF 1-METHYL-4-AZAFLUORENE

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By means of catalytic dehydrocyclization of dimethyl-substituted 2-phenylpyridines in a pyridine ring to 1(2,3)methyl-4-azafluorenes with subsequent oxidation, synthesis of alkaloid onychine — 1-methyl-4-azafluorene — several of its isomers were achieved. Using 1-methyl-4-azafluorene, we obtained a C_9 furfurylidene product, substituted tetrahydroindine[1,2-b]pyridine and NH-indine[1,2-b]-pyridine. We obtained 7-nitro-1-methyl-4azafluorene by nitration of onychine and oxidation of nitro-substituted azafluorene; this indicates an identical orientation of 4-azafluoren(one) and fluoren(one) during nitration.

1-Methyl-4-azafluorenone — the alkaloid isolated from *Onychopetalum amazonicum* [1] — has been called onychine. Several reports have been devoted to the establishment of its structure and synthesis [2-4]. Continuing our research on azafluorenes, we addressed ourselves to the development of a new method for the synthesis of onychine and its analogs and to a study of some transformations of 1-methyl-4-azafluorene, the heterocyclic system of which is the foundation of this alkaloid.

As the starting compound in the synthesis of onychine we used 3,4-dimethyl-4-phenylpyridine (I), which was obtained by the Chichibabin method [5, 6] by condensation of crotonaldehyde with propiophenone and ammonia in the vapor phase on a cadmium calcium phosphate catalyst. 3,6-Dimethyl-2-phenylpyridine (II) is also formed in this condensation. The overall yield of isomeric pyridine bases I and II (in a ratio of 3.4:1) was ~50%. For the conversion of these pyridine bases to methyl-substituted 4-azafluorenes the mixture of them was subjected to catalytic dehydrocyclization, as described in [7]. 1-Methyl-4-azafluorene (III), 3-methyl-4-azafluorene (IV), and a very small amount of demethylation product, viz., 4-azafluorene, were isolated from the catalyzate by crystallization and chromatography. 2-Methyl-4-azafluorene (V) was similarly obtained from 3,5-dimethyl-2-phenylpyridine [6].

1-Methyl-4-azafluorenone (VI) (onychine) was obtained in high yield by the liquid-phase oxidation of III with oxygen in dimethyl sulfoxide (DMSO) in the presence of a catalytic amount of sodium hydroxide [8], while isomers of this alkaloid with respect to the position of the methyl group in the pyridine ring, viz., 3-methyl- (VII) and 2-methyl-4-azafluorenone (VIII), respectively, were obtained in the oxidation of azafluorenes IV and V.

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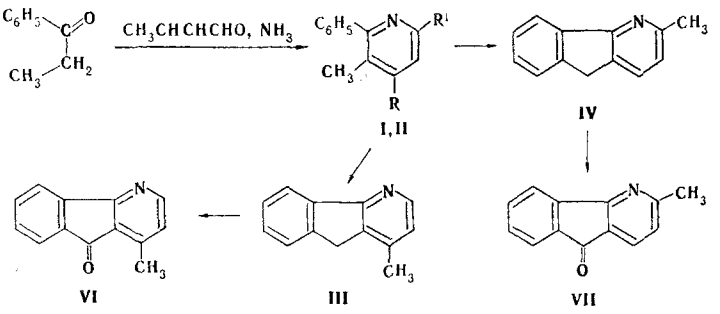
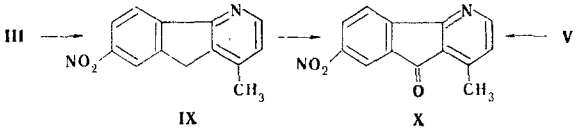
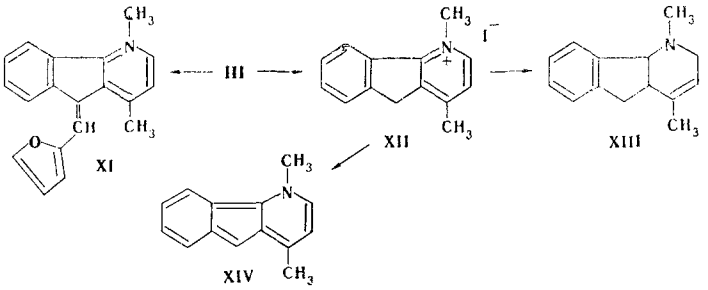


I R=CH_3, R^1=H; II R=H, R^1=CH_3

Nitro-substituted onychine was obtained by two methods. The nitration of azafluorene III gave 7-nitro-1-methyl-4-azafluorene (IX) (in 60% yield), which was oxidized to 7-nitro-1-methyl-4-azafluorenone (X). The latter was also synthesized in 85% yield by direct nitration of onychine.



The position of the nitro group in IX and X was confirmed by data from the experimental and calculated PMR spectra of substituted azafluorenes III, VI, IX, and X (Figs. 1 and 2). The presence of only one pair of protons with a spin–spin coupling constant (SSCC) of 8 Hz in the calculated ABC spectrum of the phenylene protons of IX and X excludes the location of the nitro group at C_5 or C_8. If the nitro group had entered the C_6 position in the nitration of III and VI, one should have expected a significant shift (0.98 ppm [9]) of the proton attached to C_5 to the ~9 ppm region. In fact, the signal of this proton is observed at 7.91-8.17 ppm in the spectrum of both starting azafluorenes III and VI and their nitro derivatives IX and X, and this constitutes evidence for location of the nitro group at C_7. Consequently, the orientation in the nitration of the alkaloid onychine and its precursor III is the same as in the nitration of fluorene and fluorenone.



We used the intermediate in the synthesis of onychine, viz., 1-methyl-4-azafluorene (III), also for the preparation of 1-methyl-9-furfurylidene-4-azafluorene (XI) (a compound with possible antibacterial activity), and we used its methiodide XII in the synthesis of 1,4-dimethyl-1,2,4a,9b-tetrahydroindeno[1,2-b]pyridine (XIII) (with respect to its structure a potentially antihistaminic preparation) and a new pseudoazulene, viz., 1H-1,4-dimethylindeno[1,2-b]pyridine (XIV).

Furfurylidene derivative XI was obtained by condensation of azafluorene III with furfural in the presence of sodium ethoxide. It was isolated only in the form of a single E isomer; this is not unexpected if one takes into account the presence of a methyl group attached to C_1. The significant weak-field shift of the signal of the proton attached to C_8 in the PMR spectrum of this compound, which is due to the magnetic anisotropy of the furan ring, confirms the cis orientation of the furan and phenylene rings.

Compound XIII was obtained by reduction of methiodide XII with sodium borohydride. On the basis of the PMR spectral data it may be assumed that it exists in the form of two conformations of a distorted half chair of the nitrogen-containing ring with cis fusion of the

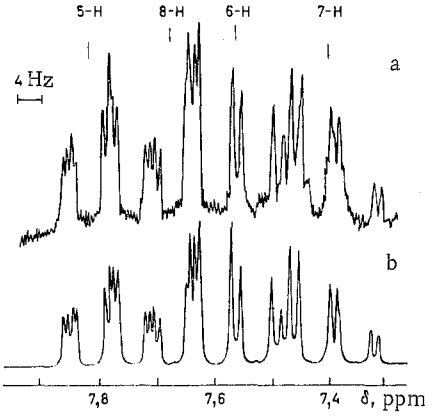


Fig. 1. Iteration analysis of the PMR spectrum of VI: a) experimental spectrum; b) theoretical spectrum.

latter with the five-membered ring. A broad signal of a methyl group attached to C_4 is observed at 1.80 ppm, whereas two broad signals of a vinyl proton appear at 5.85 and 5.56 ppm. The ratio of the integral intensities of these signals is 1:2 with an overall integral intensity of one proton unit. A doublet that evidently is related to the proton attached to C_{9b} is observed at strong field at 3.60 ppm. Pseudoazulene XIV was obtained as crystals with a characteristic dark-blue color and absorption at 553 nm in the UV spectrum by treatment of salt XII with sodium hydroxide. 1H-7-Nitro-1,4-dimethylindeno[1,2-b]pyridine (XVI) was similarly obtained from methiodide XV.

EXPERIMENTAL

The PMR spectra of the compounds were recorded with BS-467 and 497C (60 and 100 MHz) and Brucker WP-80 (80 MHz) spectrometers with tetramethylsilane as the internal standard. The calculated PMR spectra were obtained with a BNC-28 computer by means of the ITRCAL iteration program. The mass spectra were recorded with an MKh-1303 spectrometer at an ionizing-electron energy of 70 eV.

3,4-Dimethyl-3-phenyl- and 3,6-Dimethyl-2-phenylpyridines (I, II). These compounds were obtained in 37 and 11% yields, respectively, as described in [6, 8] from propiophenone, crotonaldehyde, and ammonia (in a ratio of 1:2:7) at 400°C. PMR spectrum of I (60 MHz, CCl_4): 2.11 (3-CH_3), 2.17 (4-CH_3), 6.79 (d, J = 4.7 Hz, 5-H), and 8.17 ppm (d, J = 4.7 Hz, 6-H). The picrate of base I had mp 173-175°C (from acetone) (174-175°C [10]). PMR spectrum of II (60 MHz, CCl_4): 2.20 (3-CH_3), 2.43 (6-CH_3), and 6.83 ppm (d, J = 7.6 Hz, 5-H). The picrate of II had mp 133-134°C (from acetone) (133-135°C [10]).

1-Methyl- and 3-Methyl-4-azafluorenes (III, IV). A solution of 19.5 g of a mixture of pyridine bases I and II [consisting, according to data from gas–liquid chromatography (GLC), of 15 g (0.082 mole) of pyridine I and 4.4 g (0.024 mole) of II] in 60 ml of benzene was used in the dehydrocyclization reaction, which was carried out as described in [7]. During distillation of the catalyzate we collected the fraction with bp 125-135°C (1 mm), which was crystallized from hexane to give 4.3 g (30%) of 1-methyl-4-azafluorene (III) with mp 97-99°C (98-100°C [4]). PMR spectrum (80 MHz, $CDCl_3$): 2.31 (1-CH_3), 3.62 (9-CH_2), 7.91 (J = 4.8 Hz, 5-H), and 8.28 ppm (J = 4.8 Hz, 3-H). The mother liquor after the isolation of azafluorene III was chromatographed on aluminum oxide by elution with ether–hexane (1:1) to give 0.4 g (9%) of 3-methyl-4-azafluorene (IV) with mp 27-30°C. PMR spectrum (60 MHz, $CDCl_3$): 2.65 (3-CH_3), 3.80 (9-CH_2), 7.03 (J = 7.5 Hz, 2-H), 7.66 (J = 7.5 Hz, 1-H), and 8.12 (5-H). Found: C 86.1; H 6.3; N 7.4%; M^+ 181. $C_{13}H_{11}N$. Calculated: C 86.2; H 6.1; N 7.7%; M 181. Chromatography also gave 0.1 g of 4-azafluorene with mp 93-95°C (95°C [11]).

2-Methyl-4-azafluorene (V). This compound was obtained (in 18% yield) from 3,5-dimethyl-2-phenylpyridine in the same way as III and had mp 104-105°C (from hexane). PMR spectrum (100 MHz, $CDCl_3$): 2.66 (2-CH_3), 3.92 (9-CH_2), 7.40-7.45 (m, 6-H and 7-H), 7.61 (8-H), 7.93 (5-H), 8.37 (s, 1-H), and 8.62 ppm (s, 3-H). Found: C 86.0; H 6.3; N 8.0%; M^+ 181. $C_{13}H_{11}N$. Calculated: C 86.2; H 6.1; N 7.7%; M 181.

1-Methyl-4-azafluorenone (VI). Oxygen was passed through a solution of 3.9 g (0.02 mole) of azafluorene III in 25 ml of DMSO at 30-40°C for 3 h. A drop of a 20% aqueous solution

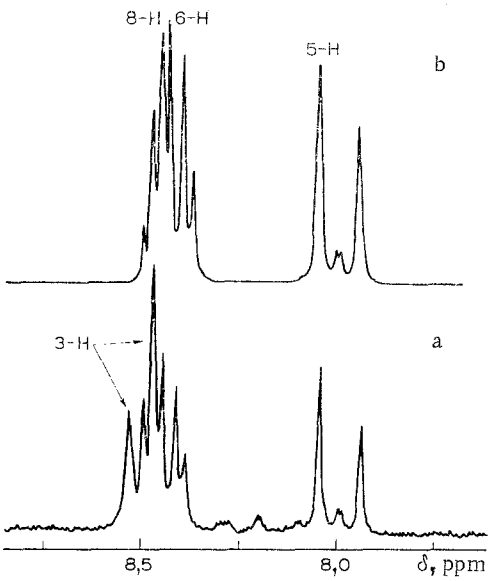


Fig. 2. Iteration analysis of the PMR spectrum of X: a) experimental spectrum; b) theoretical spectrum.

of sodium hydroxide was added at the start of the reaction and every 30 min thereafter. The mixture was poured into 200 ml of water, and the mixture was stirred at 60°C for 1 h. The precipitate was separated and crystallized from acetone to give 3.5 g (81%) of VI with mp 134-135°C (133-135°C [1-3]). PMR spectrum (100 MHz, $CDCl_3$): 2.61 (1-CH_3), 6.94 (J = 5.0 Hz, 2-H), and 8.39 ppm (J = 5.0 Hz, 3-H). The parameters of the complex ABCD spectrum of the phenylene protons were calculated with a computer: 7.95 (5-H), 7.64 (6-H), 7.44 (7-H), and 7.77 ppm (8-H); $J_{5,6}$ = 7.51, $J_{5,7}$ = 1.01, $J_{5,8}$ = 0.66, $J_{6,7}$ = 7.52, $J_{6,8}$ = 1.05, and $J_{7,8}$ = 7.47 Hz.

3-Methyl-4-azafluorenone (VII). Ketone VII was obtained in 40% yield by oxidation of azafluorene IV with potassium permanganate in acetone [8]. The yellow crystals had mp 104-105°C (from heptane). PMR spectrum (100 MHz, $CDCl_3$): 2.60 (3-CH_3), 7.02 (J = 7.5 Hz, 2-H), 7.74 (J = 7.5 Hz, 1-H), 7.39 (6-H), 7.55 (7-H), 7.66 (8-H), and 7.81 ppm (5-H); $J_{5,6} \cong J_{6,7} \cong J_{7,8} \cong$ 7.4 Hz, $J_{5,5} \cong J_{6,8} \cong$ 1.5 Hz, and $J_{5,8}$ = 0.7 Hz. Found: C 79.8; H 4.7; N 7.0%; M^+ 195. $C_{13}H_9NO$. Calculated: C 80.0; H 4.6; N 7.2%; M 195.

2-Methyl-4-azafluorenone (VIII). The oxidation of azafluorene V was carried out in the same way as the oxidation of III. Ketone VIII was obtained in 61% yield as yellow crystals with mp 124-125°C (from acetone). PMR spectrum (80 MHz, $CDCl_3$): 2.35 (2-CH_3), 7.52 (s, 1-H) and 8.25 ppm (s, 3-H). Found: C 79.9; H 4.8; N 6.9%; M^+ 195. $C_{19}H_9NO$. Calculated: C 80.0; H 4.6; N 7.2%; M 195.

7-Nitro-1-methyl-4-azafluorene (IX). A nitrating mixture (from 7 g of sulfuric acid and 3.5 g of nitric acid) was added dropwise at 0°C in the course of 30 min to a solution of 1 g (5.5 mmole) of azafluorene III in 2 ml of sulfuric acid, and the mixture was stirred at 20°C for 10 h. It was then poured over ice, and the aqueous mixture was made alkaline with sodium carbonate solution. The precipitate was washed with water, dried, and crystallized from acetone to give 0.74 g (60%) of IX with mp 182-183°C. PMR spectrum (100 MHz, $CDCl_3$): 2.78 (1-CH_3), 7.14 (J = 5.0 Hz, 2-H), and 8.56 ppm (J = 5.0 Hz, 3-H). The ABC spectrum of the phenylene protons was calculated with a computer: 8.17 (5-H), 8.37 (6-H), and 8.43 ppm (8-H); $J_{5,6}$ = 8.0, $J_{6,8}$ = 2.0, and $J_{5,8} \leqslant 0.6$ Hz. Found: C 62.8; H 4.6; N 12.3%; M^+ 226. $C_{13}H_{10}N_2O_2$. Calculated: C 63.0; H 4.4; N 12.4%; M 226.

7-Nitro-1-methyl-azafluorenone (X). A) A 0.2-g (2 mmole) sample of sodium nitrate was added gradually with stirring at 0°C to a solution of 0.33 g (1.7 mmole) of azafluorenone VI in 3 ml of sulfuric acid, and the mixture was maintained at 20°C for 30 min and at 60°C for 1 h. It was then poured over ice, and the aqueous mixture was made alkaline with 20% sodium hydroxide solution. The precipitate was washed with water, dried, and crystallized from acetone to give 0.3 g (85%) of X as yellow crystals with mp 216-217°C. PMR spectrum (80 MHz, $CDCl_3$): 2.75 (1-CH_3), 7.10 (J = 5.1 Hz, 2-H), and 8.51 ppm (J = 5.1 Hz, 3-H). The ABC spectrum

of the phenylene protons was calculated with a computer: 8.01 (5-H), 8.44 (6-H), and 8.45 ppm (8-H); $J_{5,6}$ = 8.0, $J_{6,8}$ = 2.0, and $J_{5,8} \leqslant 0.6$ Hz. Found: C 66.6; H 3.2; N 11.6%; M^+ 240. $C_{13}H_8N_2O_3$. Calculated: C 65.0; H 3.3; N 11.7%; M 240.

B) A 0.25-g (1.5 mmole) sample of potassium permanganate was added in portions with stirring at 40°C in the course of 5 h to a solution of 0.2 g (0.9 mmole) of azafluorene IX and 0.2 g of magnesium nitrate in 35 ml of acetone, after which the manganese dioxide was separated and washed on the filter with acetone. The acetone was removed by distillation to give 0.1 g (47%) of X with mp 213-215°C. No melting-point depression was observed for a mixture of this product with a sample obtained by method A. The product also had the same mass-spectral and PMR-spectral characteristics as the latter.

1-Methyl-9-furfurylidene-4-azafluorene (XI). A 5-ml sample of 10% sodium methoxide solution was added to a solution of 0.5 g (2.8 mmole) of azafluorene III and 0.57 g (5.9 mmole) of furfural in 10 ml of methanol, and the mixture was refluxed for 2 h. It was then poured into 50 ml of water, the alcohol was removed by vacuum distillation, and the reaction products were extracted with ether. The extract was dried with magnesium sulfate, the ether was removed by distillation, and the residue was chromatographed on aluminum oxide by elution with ether–heptane (1:1) to give 0.15 g (21%) of XI as yellow crystals with mp 123-124°C (from hexane). PMR spectrum (100 MHz, CCl_4): 2.54 (1-CH_3), 6.69 ($J_{3',4'}$ = 3.5 Hz, $J_{3',5'}$ = 0.7 Hz, 3'-H), 6.49 ($J_{3',4'}$ = 3.5 Hz, $J_{4',5'}$ = 1.9 Hz, 4'-H), 7.56 (5'-H), 7.98 (5-H), 8.38 (8-H), and 7.25-7.35 ppm (m, 6-H and 7-H). Found: C 83.5; H 5.9; N 5.1%. $C_{18}H_{13}NO$. Calculated: C 83.4; H 5.0; N 5.4%.

1,4-Dimethyl-1,2,4a,9b-tetrahydroindeno[1,2-b]pyridine (XIII). A 1-g (26 mmole) sample of sodium borohydride was added at 40°C in the course of 30 min to a suspension of 0.4 g (1.2 mmole) of methiodide XII [mp 273-275°C (from acetone)] in 25 ml of methanol, and the mixture was refluxed with stirring for 2 h, after which it was poured into 50 ml of water. The methanol was removed by vacuum distillation, and the reaction products were extracted with ether. The extract was dried with magnesium sulfate, the ether was removed by distillation, and the residue was chromatographed on aluminum oxide by elution with ether–hexane (1:2) to give 0.21 g (91%) of XIII as a light-yellow oily substance that darkened rapidly on standing. PMR spectrum (80 MHz, $CDCl_3$): 1.80 (broad, s, 3H, 4-CH_3), 2.48 (3H, s, 1-CH_3), 3.60 (d, J = 5.2 Hz, 9b-H), and 5.56 and 5.85 ppm (HC=C). Found: C 84.0; H 8.1; N 6.6%; M^+ 199. $C_{14}H_{17}N$. Calculated: C 84.4; H 8.5; N 7.0%; M 199. The hydrochloride of XIII had mp 70-75°C (strongly hydroscopic). Found: N 5.7%. $C_{14}H_{17}N \cdot HCl$. Calculated: N 6.0%.

Pseudoazulenes XIV and XVI. A 3-ml sample of 20% sodium hydroxide solution was added to a solution of 0.5 g (1.5 mmole) of salt XII in 100 ml of water, and the mixture was extracted with benzene. The extract was dried with potassium hydroxide, and the benzene was removed by vacuum distillation to give 0.2 g (67%) of pseudoazulene XIV as dark-blue crystals with mp 139-142°C. Mass spectrum, m/z (%): M^+ 195 (86), 181 (100), 180 (65), 167 (24), 166 (26), 152 (35), M^{++} 97.5 (20). Found: N 6.7%. $C_{14}H_{13}N$. Calculated: N 7.2%; M 195. 1H-7-Nitro-1,4-dimethylindeno[1,2-b]pyridine (XVI) was similarly obtained in 41% yield from salt XV (mp 226-228°C) as black crystals with a green tint with mp >300°C. Mass spectrum, m/z (%): M^+ 240 (26.5), 226 (22.5), 195 (63), 111 (97), 109 (100). Found: N 11.2%. $C_{14}H_{12}N_2O_2$. Calculated: N 11.7%; M 240.

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