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9-(2',5'-DIMETHYL-4'-PYRIDYL)FLUORENE IN SYNTHESES OF FLUOROSPIRODIHYDROFUROPYRIDINE AND PYRIDOFLUORANTHENE

N. S. Prostakov, Ishmael Rafael Vaskes,
N. M. Mikhailova, V. P. Zvolinskii,
V. F. Zakharov, and M. A. Galiullin

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1,2,5-Trimethyl-4-(9'-fluorenylidene)piperidine, which is formed by condensation of fluorene with 1,2,5-trimethyl-4-piperidone, is converted catalytically to 9-(2',5'-dimethyl-4'-pyridyl)fluorene, from which 2-methylpyrido[4,5-a]fluoranthene and its demethylated analog were obtained by catalytic dehydrocyclization. Oxidation of 9-(2',5'-dimethyl-4'-pyridyl)fluorene gave 9-(2',5'-dimethyl-4'-pyridyl)-9-fluorenol and fluorene-9-spiro-4'-(6'-oxo-2'-carboxypyrido[4',5'-c]-4'-6'-dihydrofuran). 6-Methyl-2-phenyl-7-(9'-fluorenyl)indolizine was synthesized by the Chichibabin method.

Many relatively simple fluorene derivatives have a broad spectrum of physiological activity, and some of them have already found extensive practical application [1]. In this connection, further research for the development of new methods for the synthesis of substituted fluorenes and their study is expedient. Pyridyl-substituted fluorenes, which are interesting per se as starting materials for the synthesis of polynuclear systems in which the fluorene fragment is bonded to indolizine or dihydrofuropyridine rings or is incorporated in the pyridofluoranthene system, remain virtually unknown in this respect.

Catalytic dehydrogenation and N-demethylation of substituted piperidines, which comprise a method that has been previously used extensively in the synthesis of substituted pyridine bases [2], were used for the synthesis of a pyridyl-substituted fluorene. 9-(2',5'-Dimethyl-4'-pyridyl)fluorene (III) was obtained from the accessible 1,2,5-trimethyl-4-piperidone (I). Condensation of piperidone I with fluorene in the presence of potassium hydroxide, as a result of which 1,2,5-trimethyl-4-(9'-fluorenylidene)piperidine (II) is formed, was accomplished in the first step. However, we were unable to isolate it quantitatively from the complex mixture of substances either by distillation or by means of chromatography. It was obtained in small amounts as reddish crystals with mp 93-95°C and was characterized by derivatives. The conversion of II to pyridine base III was accomplished with the crude product on a K-16 catalyst as described in [2]. Fluorenyl-substituted pyridine III, which was used in the synthesis of polynuclear heterocyclic systems, including previously unknown systems, was obtained from II in quantitative yield as a result of dehydrogenation, N-demethylation, and hydrogenation of the exocyclic double bond.

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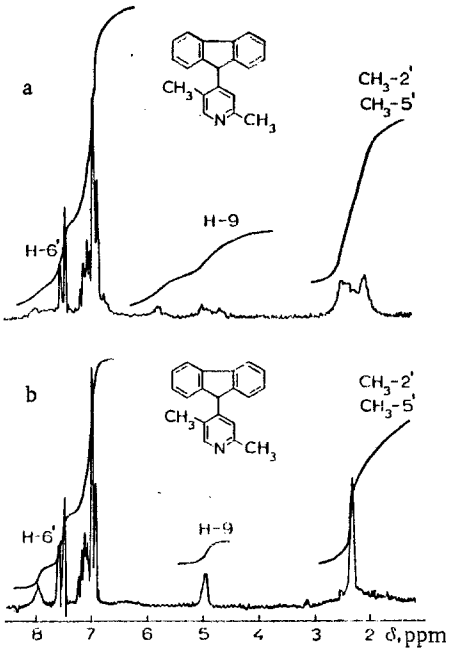
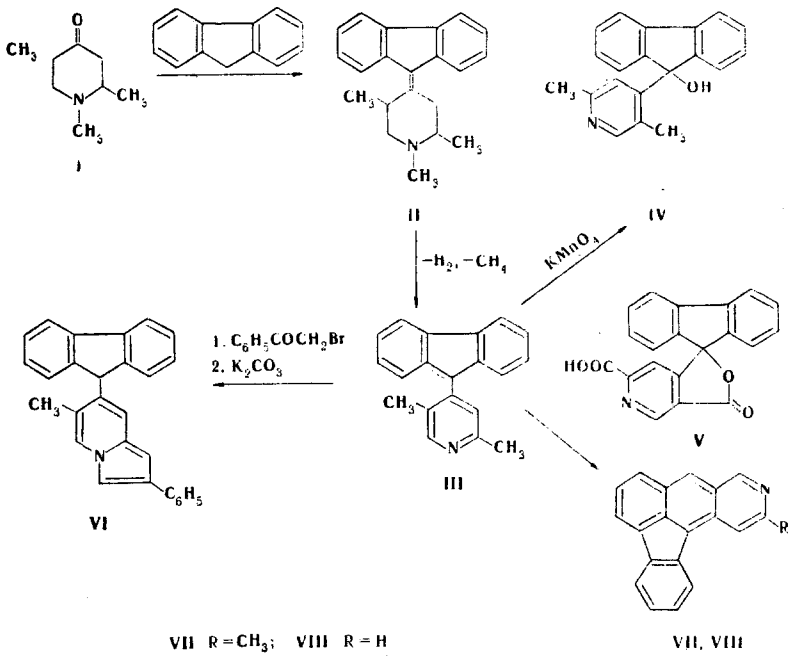


Fig. 1. PMR spectra of 9-(2',5'-dimethyl-4'-pyridyl)fluorene: a) at 25°C; b) at 60°C in CCl_4.

Because of steric factors created by the methyl group attached to C'_5, rotation of the pyridine ring in pyridyl-substituted fluorene III should be restricted [3, 4]. One might therefore have expected the existence of rotational isomers of this compound with different orientations of the methyl groups attached to C'_2 and C'_5 relative to the hydrogen atom attached to C_9. In fact, in the PMR spectrum of III, which was recorded at 25°C (Fig. 1, spectrum *a*), the 6'-H, 9-H, 2'-CH_3, and 5'-CH_3 signals are markedly broadened; this evidently constitutes evidence for the presence of conformers. However, both the signal of the proton attached to C_9 and the signals of the protons of both methyl groups appear distinctly in the PMR spectrum recorded at 60°C (Fig. 1, spectrum b). It must be assumed that free rotation of the pyridine ring occurs at this temperature.



VII R = CH_3; VIII R = H

Oxidation of substituted pyridine base III gave the product of its partial oxidation [9-(2',5'-dimethyl-4'-pyridyl)-9-fluorenol (IV)] and a lactone [fluorene-9-spiro-4'-(6'-oxo-2'-carboxypyrido[4',5'-c]-4',6'-dihydrofuran) (V)] which is formed from the product of

complete oxidation – 4-(9'-hydroxy-9'-fluorenyl)isocinchomeronic acid. An absorption band at 3080-3300 cm^{-1} is observed in the IR spectrum of fluorenol IV and an absorption band at 1785 cm^{-1} is observed in the spectrum of lactone V; these bands are characteristic, respectively, for the hydroxyl group of fluorenol and the carbonyl group of the lactone fragment.

Like other α-alkyl-substituted pyridine bases, III was converted by the Chichibabin method through its quaternary salt with bromoacetophenone to the previously unknown 6-methyl-2-phenyl-7-(9'-fluorenyl)indolizine (VI), which is a stable compound with a high melting point. From the data from the PMR spectrum of indolizine VI it may be concluded that it exists in two forms that differ with respect to the orientation of the 9'-H proton and the CH_3 group on the same or different sides of the fluorene fragment [3]. In the first case the protons of the methyl group are situated in the plane of the fluorene ring and give resonance signals at 2.56 ppm, i.e., in the region characteristic for the protons of methyl groups in aromatic compounds. In the second case the methyl group is located above the plane of the fluorene ring and, because of the anisotropic effect of the latter, absorbs at stronger field (δ 0.87 ppm). The ratio of the intensities of the signals under consideration is 1:2, which constitutes evidence in favor of the above assignment, since the first form is energetically less favorable because of mutual repulsion of the 9'-H proton and the protons of the methyl group. The 9'-H proton, which experiences the anisotropic effect of the indolizine fragment, also gives two signals (6.62 and 4.85 ppm); the aromatic protons give signals at 7.08-7.80 ppm.

It seemed of interest to realize the dehydrocyclization of pyridine base III; this reaction should proceed via splitting out of hydrogen from the β-methyl group of the pyridine ring and of the hydrogen attached to the C_1 atom of the fluorene fragment. The reaction was carried out on the same catalyst at 540-560°C. 2-Methylpyrido[4,5-a]fluoranthene (VII) (a yellow crystalline substance with mp 166-167°C) and its demethylated analog (VIII) were obtained in low yields. These compounds were isolated by means of column chromatography. The UV spectrum of VII [λ_{max} (log ε): 424 (4.25), 380 (3.77), 365 (4.05), 345 (3.82), 305 (4.42), and 270 nm (5.14)] is similar to the UV spectrum of 2,3-benzofluoranthene [5]. According to preliminary data, compound VII has growth-regulating activity.

EXPERIMENTAL

The PMR spectra of solutions of the compounds in $CDCl_3$ and CCl_4 were measured with Tesla BS-487C and Varian XL-100 spectrometers with hexamethyldisiloxane as the internal standard. The IR spectra of KBr pellets of the compounds were measured with a UR-20 spectrometer. The UV spectra of $CHCl_3$ solutions of the compounds were recorded with a Hitachi spectrophotometer. The mass spectra were measured with an MKh-1303 mass spectrometer.

9-(2',5'-Dimethyl-4'-pyridyl)fluorene (III). A mixture of 300 ml of toluene, 50 g (0.35 mole) of piperidone I, 59 g (0.35 mole) of fluorene, 20 g (0.35 mole) of powdered potassium hydroxide, and 0.3 ml of piperidine was refluxed for 16 h, during which 2.5 ml of water was liberated. The mixture was then treated successively with 75 ml of water and 200 ml of 18% hydrochloric acid. Workup of the toluene layer gave 36 g (61%) of fluorene. The aqueous layer was saturated with potassium hydroxide and extracted with ether. Vacuum distillation of the extract yielded 6 g (12%) of the starting piperidone. The pot residue (60 g) was an uncrystallizable, dark-red, viscous mass. Heated (130°C) steam was passed through a 0.5-g sample of this residue, and the aqueous suspension was allowed to stand. It was then worked up to give 0.5 g of crystals of condensation product II with mp 93-95°C (dec.). Found: N 5.1%; M^+ 289. $C_{21}H_{23}N$. Calculated: N 4.8%; M 289. Derivatives of II were obtained from the residual oily substance. The picrate had mp 180-182°C (from alcohol). Found: N 11.0%. $C_{21}H_{23}N \cdot C_6H_2(NO_2)_3OH$. Calculated: N 10.8%. The methiodide had mp 215-217°C (from alcohol). Found: N 3.1%. $C_{21}H_{23}NCH_3I$. Calculated: N 3.2%. Compound II was obtained in 80% yield (calculated with respect to the methiodide).

A solution of 70 g of the crude product of condensation of fluorene with piperidone I (the pot residue) in 450 ml of benzene was passed at a constant rate in the course of 7 h through a contact tube filled with K-16 catalyst (30 ml). The temperature in the catalyst zone was 400-410°C. A total of 6.5 liters of gas (61% C_nH_{2n+2}, 8% C_nH_{2n}, and 29% H_2 at 22°C and 752 mm) was collected. The catalysate was treated with 200 ml of 18% hydrochloric acid. Workup of the benzene layer gave 2 g of fluorene. The aqueous layer was saturated with potassium hydroxide and extracted with ether to give 18.5 (18%) of pyridine base III with mp 134-135°C (from acetone). Found: C 88.7; H 6.3; N 5.2%; M^+ 271. $C_{20}H_{17}N$. Calculated: C 88.6; H 6.3; N 5.1%; M 271.

9-(2',5'-Dimethyl-4'-pyridyl)-9-fluorenol (IV) and Fluorene-9-spiro-4'-(6'-oxo-2'-carboxypyrido[4',5'-c]-4',6'-dihydrofuran) (V). A solution of 10 g (0.036 mole) of III in 650 ml of water was heated to the boiling point, and 15.5 g (0.098 mole) of potassium permanganate was added in portions with stirring in the course of 40 h. The precipitated manganese dioxide was removed by filtration and washed with hot water, and the filtrate was extracted with ether. The aqueous filtrate was evaporated to 50 ml and acidified with 15 ml of 50% sulfuric acid, and the precipitate was removed by filtration to give 1.45 g (12%) of lactone V with mp 229-230°C (from methanol). Found: C 72.3; H 3.5; N 4.1%; M^+ 329. $C_{20}H_{11}NO_4$. Calculated: C 72.9; H 3.3; N 4.1%; M 329. The manganese dioxide was washed with hot water and refluxed with acetone, after which it was removed by filtration. This operation was removed by filtration. This operation was repeated three times. The acetone filtrate and the ether extract were combined, and the solvents were removed by distillation to give 5.2 g (49%) of fluorenol IV with mp 263-265°C (from chloroform). Found: C 83.3; H 5.7; N 4.5%; M^+ 287. $C_{20}H_{17}NO$. Calculated: C 83.6; H 5.9; N 4.9%; M 287.

6-Methyl-2-phenyl-7-(9'-fluorenyl)indolizine (VI). A quaternary salt was obtained in 76% yield from pyridine base III and bromoacetophenone in acetone and had mp 254-255°C (from alcohol). IR spectrum: 1685 cm^{-1} (CO). Found: C 71.0; H 5.2; N 3.1%; M^+ 371. $C_{28}H_{24}BrNO$. Calculated: C 71.4; H 5.1; N 3.0%; M 470. A mixture of 3 g (0.006 mole) of the salt and 10 ml of 40% aqueous potassium carbonate solution was refluxed for 4 h, and the resulting precipitate was washed to neutrality with hot water to give 2.5 g (93%) of substituted indolizine VI with mp 229-230°C (from benzene). Found: C 90.0; H 5.9; N 3.9%; M^+ 371. $C_{28}H_{21}N$. Calculated: C 90.0; H 5.7; N 3.8%; M 371.

2-Methylpyrido[4,5-a]fluoranthene (VII). A solution of 20 g (0.073 mole) of pyridine base III in 150 ml of benzene was passed at a constant rate in the course of 3.5 h over K-16 catalyst (50 ml). A total of 4 liters of gas was collected (at 22°C and 759 mm). The benzene was removed from the catalysate by distillation, 30 ml of hexane was added to the residue, and the mixture was refluxed with charcoal. It was then cooled and worked up to give 1.75 g of yellow crystals, which were chromatographed [on activity II Al_2O_3, elution with hexane–ether (1:2)] to give 0.94 g of starting III and 0.16 g (1%) of pyridofluoranthene VII as yellow crystals with mp 166-167°C and R_f 0.44 (in the same system). PMR spectrum: δ 2.72 (3H, s, CH), 9.26 (1H, s, 4-H), 8.22 (1H, s, 5-H), and 7.24-804 ppm (aromatic protons). Found: N 5.4%; M^+ 267. $C_{20}H_{13}N$. Calculated: N 5.1%; M 267. At the end of the chromatographic procedure, 0.01 g of yellow crystals of VIII, with mp 169-170°C and R_f 0.33, was isolated. Found: M^+ 253. $C_{19}H_{11}N$. Calculated: M 253.

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