DI- AND TRIMETHYL-SUBSTITUTED 2-AZAFLUORENES AND DIBASIC ACIDS OF 2-AZAFLUORENONE

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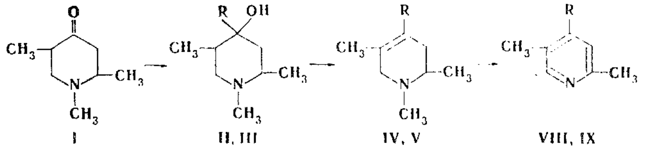
Dehydrocyclization of the corresponding 2,5-dimethyl-4-arylpyridines gave 3,5- and 3,8-dimethyl- and 3,5,7- and 3,5,8-trimethyl-2-azafluorenones. Dibasic acids of 2-azafluorenone were obtained from γ-carboxyarylcinchomeronic acid.

Substituted azafluorenes and their partially hydrogenated analogs are of interest as physiologically active substances [1,2]. 2-Azafluorenes can be obtained by cyclization of substituted pyridinecarboxylic acids [2] and by catalytic dehydrocyclization of γ-aryl-substituted pyridine bases containing a methyl group in the β position [3].

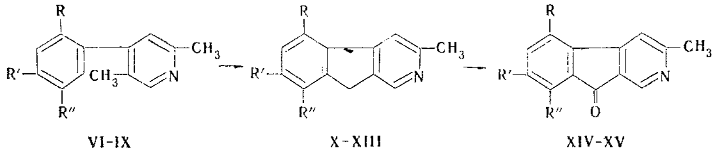
In the present communication we describe the dehydrocyclization of 2,5-dimethyl-4-[o-tolyl, m-tolyl, 2,4-xylyl, and 2,5-xylyl]pyridines (VI [4], VII [5], VIII, and IX, respectively). Pyridine bases VIII and IX were obtained for the first time from 1,2,5-trimethyl-4-piperidone (I) via the scheme in [6].



II, IV, VIII $R = C_6H_3(CH_3)_2$-2,4; III, V, IX $R = C_6H_3(CH_3)_2$-2,5

1,2,5-Trimethyl-4-(2,4-xylyl)- and -(2,5-xylyl)-4-piperidols (II and III), which are formed in the reaction of I with the appropriate dimethylphenyllithium, were each isolated in the form of only one isomer. The dehydrogenation and N-demethylation of piperideines IV and V were accomplished catalytically. The specificity of the synthesis and the spectral data confirm the order of substitution of the benzene rings of VIII and IX. Absorption bands at 828 and 880 cm^{-1} and at 827 and 880 cm^{-1}, respectively, are observed in the IR spectra of VIII and IX in the region of the CH deformation vibrations of 1,2,4-trisubstituted benzenes.

The dehydrocyclization of VI-IX was carried out on a K-16 industrial dehydrogenating catalyst. 3,5- and 3,8-Dimethyl- and 3,5,7- and 3,5,8-trimethyl-2-azafluorenes (X, XI, XII, and XIII) were obtained in 14-34% yields.



VI, X, XIV $R = CH_3$, $R' = R'' = H$; VII, XI, XV $R = R' = H$, $R'' = CH_3$;
VIII, XII $R = R' = CH_3$, $R'' = H$; IX, XIII $R = R'' = CH_3$, $R' = H$

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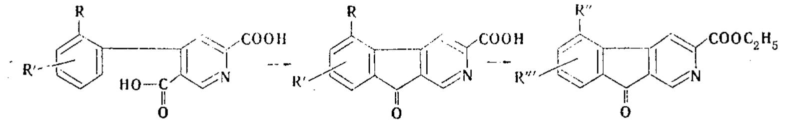
The dehydrocyclization of VI, VIII, and IX should proceed unambiguously to give X, XII, and XIII, respectively. The dehydrocyclization of VI, VIII, and IX to 2-azaphenanthrenes does not occur under the selected conditions. The formation of 3,8- (XI) or 3,6-dimethyl-2-azafluorene is possible in the dehydrocyclization of VII. The conclusion regarding the position of the methyl group in the benzene ring of XI was made on the basis of spectral data. The IR spectra of X and XI at 750-810 cm^{-1} contain bands corresponding to the vibrations of three adjacent C−H bonds of the benzene ring. Consequently, XI is isomeric to X with respect to the position of the methyl group. Bands corresponding to the out-of-plane vibrations of two adjacent C−H bonds of the benzene ring, as observed in the spectrum of 3,7-dimethyl-2-azafluorene [7,8], should be present in the IR spectrum of the possible 3,6-dimethyl-2-azafluorene at 800-860 and 860-900 cm^{-1}. However, no such bands are present in the spectrum of XI.

Azafluorenes X and XI were oxidized under conditions in which the methyl group is not involved to give 3,5- and 3,8-dimethyl-2-azafluorenones (XIV and XV, respectively).

Similar 2-azafluorene structures were obtained by cyclization of 4-(o-carboxyphenyl)- and 4-(m-carboxyphenyl)pyridine-2,5-dicarboxylic acids (XVI, XIX). Tribasic acids − XVI in the oxidation of VI [4], and XIX in the oxidation of VII [5] − were obtained. The cyclization was accomplished by means of oleum at 100°.



XVI, XIX XVII, XX a,b XVIII, XXI a,b

XVI, XVII R = COOH, R′ = H; XVIII R″ = $COOC_2H_5$, R‴ = H; XIX R = H, R′ = 3-COOH; XXa,b R = H, R′ = 6-COOH ; 8-COOH; XXI a,b R″ = H, R‴ = 6-$COOC_2H_5$; 8-$COOC_2H_5$

2-Azafluorenone-3,5-dicarboxylic acid (XVII) was obtained from XVI, and the diester (XVIII) was then obtained from the acid. As expected, the cyclodehydration of XIX gives a mixture of 2-azafluorenone-3,6- and -3,8-dicarboxylic acids (XX a,b), which could not be separated. The individual diethyl esters (XXIa,b) of these acids were isolated by esterification.

Up until now, dibasic 2-azafluorenecarboxylic acids were unknown. Considerable experimental difficulties are encountered during their isolation and in investigating them. The acids are practically insoluble in known solvents and have indistinct melting points above 250°. They are isolated from the reaction mixtures as yellow and pale green crystals that become dark blue at 200°. On the basis of the analytical data, it can be assumed that they crystallize in a solvated form. The esters of these acids, however, crystallize satisfactorily and have sharp melting points.

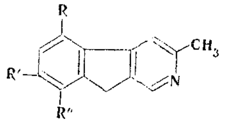
EXPERIMENTAL

The dehydrogenation and N-demethylation of piperideines IV and V and the dehydrocyclization of pyridine bases VI-IX were carried out on 100 ml of K-16 industrial catalyst in a flow system. The contact tube and the packing were made of quartz. The catalyst was activated at 600° for 2 h in a gentle stream of air.

1,2,5-Trimethyl-4-(2,4-xylyl)- and -(2,5-xylyl)-4-piperidols (II, III). A 0.28-mole sample of I was added gradually at 0° to xylyllithium [obtained from 0.25 mole of the corresponding 1-bromo-2,4(2,5)-dimethylbenzene and 0.5 g-atom of lithium in 200 ml of ether], and 100 ml of water, 8 ml of 18% hydrochloric acid, and 20 ml of 36% hydrochloric acid were added successively at 0°. The mixture was treated with sodium hydroxide, and the organic bases were extracted from the aqueous layer with ether. The extract was dried with magnesium sulfate and distilled to give 0.046 mole of I and, respectively, II and III. Compound II [0.12 mole (51%, based on the converted I)] had bp 146-149° (1 mm), mp 124-125° (from hexane), and R_f 0.4 [activity IV Al_2O_3, ethyl acetate−heptane (1 :1)]. Found,%: C 78.0; H 9.9; N 5.7. $C_{16}H_{25}NO$. Calculated,%: C 77.7; H 10.1; N 5.7. Compound III [0.19 mole (81%)] had bp 180-182° (2 mm), mp 89-91° (from hexane), and R_f 0.25 (activity III Al_2O_3). Found,%: C 78.0; H 10.3; N 5.8. $C_{16}H_{25}NO$. Calculated,%: C 77.7; H 10.1; N 5.7.

IR spectrum: OH 3170 (II), 3190 cm^{-1} (III).

TABLE 1. Di- and Trimethyl-Substituted 2-Azafluorenes



Compound	Starting pyridine	Temp. in the catalyst zone, °C	Mp, °C	Empirical formula	Found, %			Calc., %			Yield, based on conv. pyridine, %	Mp, °C (from alcohol)	
						H	N	C	H	N		picrate	hydrochloride
X	VI	500—515	75—76	$C_{14}H_{13}N$	86,1	6,6	7,1	86,1	6,7	7,2	18*	218—219	304—306
XI	VII	510—520	114	$C_{14}H_{13}N$	86,1	6,4	7,2	86,1	6,7	7,2	34	216—217	
XII	VIII	580—600	100—101,5	$C_{15}H_{15}N$	85,9	7,4	6,4	86,1	7,2	6,7	15		
XIII	IX	580—600	151,5——153	$C_{15}H_{15}N$	86,3	7,2	6,9	86,1	7,2	6,7	14	187	

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*Compound X was isolated by chromatography on Al_2O_3 [ethyl acetate–hexane (1 : 20)].

1,2,5-Trimethyl-4-(2,4-xylyl)- and -(2,5-xylyl)piperideines (IV, V). A mixture of 0.13 mole of piperidol and 120 ml of 36% hydrochloric acid was refluxed for 8 h. The acid was then removed by vacuum distillation, 80 ml of water and 50 ml of saturated sodium carbonate solution were added to the residue, and the mixture was refluxed for 2 h. The organic bases were extracted with ether, and the extract was dried with magnesium sulfate and distilled to give piperideines in 76.5% yield. Compound IV had bp 163-164.5° (3 mm), n_D^{20} 1.5308 and d_4^{20} 0.9389. Found,%: C 84.0; H 10.0; N 5.8; MR_D 75.4. $C_{16}H_{23}N$. Calculated,%: C 83.8; H 10.0; N 6.1; MR_D 74.9. The picrate of IV had mp 168-169.5° (from alcohol). Found,%: N 12.0. $C_{16}H_{23}N \cdot C_6H_3N_3O_7$. Calculated,%: N 12.2. Compound V had bp 108-109° (1 mm) and n_D^{20} 1.5329. Found,%: C 83.5; H 10.1; N 6.2. $C_{16}H_{23}N$. Calculated,%: C 83.8; H 10.0; N 6.1. The hydrochloride of V had mp 192-194° (from acetone). Found,%: Cl 13.0. $C_{16}H_{23}N \cdot HCl$. Calculated,%: Cl 13.4.

2,5-Dimethyl-4-(2,4-xylyl)- and -(2,5-xylyl)pyridines (VIII, IX). A. A solution of 57 g (0.25 mole) of IV in 115 ml of benzene was passed at a constant rate in the course of 6 h through a contact tube (the temperature in the catalyst zone was 400-410°). A total of 13.5 liters of gas was collected. The catalyzate was dried with potassium hydroxide and distilled to give 43 g (81.5%) of VIII with bp 166-168° (2 mm) and n_D^{20} 1.5660. Found,%: C 85.4; H 7.9; N 6.4. $C_{15}H_{17}N$. Calculated,%: C 85.3; H 8.1; N 6.6. The picrate of VIII had mp 154-156° (from alcohol). Found,%: N 12.5. $C_{15}H_{17}N \cdot C_6H_3N_3O_7$. Calculated,%: N 12.7.

B. A 66-g (0.3 mole) sample of V was used in the reaction, and 15.2 liters of gas was collected. The catalyzate yielded 43.8 g (72.6%) of IX with bp 163-165° (2 mm) and mp 82.5-84° (from hexane). Found,%: C 85.6; H 8.0; N 6.1. $C_{15}H_{17}N$. Calculated,%: C 85.3; H 8.1; N 6.6.

3,5- and 3,8-Dimethyl- and 3,5,7- and 3,5,8-Trimethyl-2-azafluorenes (X, XI, XII, and XIII, respectively). To dehydrocyclize pyridine bases VI-IX, solutions of them in benzene were passed at a constant rate through a contact tube. The catalyzate was vacuum distilled to separate the starting material, and crystallization of the residue from hexane gave X-XIII. The results of the experiments are presented in Table 1.

3,5- and 3,8-Dimethyl-2-azafluorenones (XIV, XV). These compounds were obtained by oxidation of X and XI. A 1.85-g (11.7 mmole) sample of potassium permanganate was added in portions at 60° to a mixture of 1.5 g (7.7 mmole) of azafluorene, 2.31 g of magnesium nitrate (hexahydrate), and 75 ml of water, and the mixture was stirred until it became completely colorless, after which it was heated to 90° and filtered. The manganese dioxide was washed repeatedly with hot water, and the aqueous solution was shaken with ether. The manganese dioxide was then washed with ether and acetone. The solvents were removed by crystallization, and the residue was crystallized from ligroin to give 0.22 g (18%) of XIV and, respectively, 1.43 g (88%) of XV as yellow crystals. Compound XIV had mp 173-175°. Found,%: C 80.2; H 5.5; N 6.5. $C_{14}H_{11}NO$. Calculated,%: C 80.7; H 5.3; N 6.7. The picrate of XIV had mp 223-224° (from alcohol). Found,%: N 12.3. $C_{14}H_{11}NO \cdot C_{16}H_3N_3O_7$. Calculated,%: N 12.8. The hydrochloride of XIV had mp 254-255° (from alcohol. Found,%: Cl 14.8. $C_{14}H_{11}NO \cdot HCl$. Calculated,%: Cl 14.5. Compound XV had mp 151-152°. Found,%: C 80.5; H 5.4; N 6.5. $C_{14}H_{11}NO$. Calculated,%: C 80.7; H 5.3; N 6.7. The picrate of XV had mp 229-230° (from alcohol). Found,%: N 12.7. $C_{14}H_{11}NO \cdot C_6H_3N_3O_7$. Calculated,%: N 12.8.

IR spectrum : CO 1715 (XIV), 1702 cm^{-1} (XV).

2-Azafluorenone-3,5-dicarboxylic Acid (XVII). A mixture of 1.7 g of XVI and 9 ml of 5% oleum was heated at 100° for 4 h, cooled, and poured over ice. Crystallization from alcohol gave 0.95 g (51%) of green crystals of XVII with mp 254-257° (dec.). According to the analytical data, the product was the solvated form of XVII. Found,%: C 60.8; H 4.3; N 4.7. $C_{14}H_7NO_5 \cdot C_2H_5OH$. Calculated,%: C 60.9; H 4.1; N 4.4.

A mixture of 0.4 g (1.4 mmole) of XVII, 10 ml of sulfuric acid, and 25 ml of ethanol was refluxed for 8 h, after which the mixture was cooled and poured over ice. The organic substances were extracted with ether to give 0.47 g (96%) of green crystals of XVIII with mp 147.5-148.5° (from alcohol). Found,%: N 4.2. $C_{18}H_{15}NO_5$. Calculated,%: N 4.3.

Cyclization of 4-(m-Carboxyphenyl)pyridine-2,5-dicarboxylic Acid (XIX). A 2-g (7 mmole) sample of XIX and 10 ml of 5% oleum were used in the reaction. The mixture was heated at 100° for 4 h and was then poured over ice. The solid was dissolved in 1 N sodium hydroxide, and the solution was filtered and treated with 1 N hydrochloric acid to precipitate 1.53 g (81%) of a mixture (XXa,b) of acids as yellow crystals with mp > 270° (dec.). The color of the crystals deepened on slow heating. According to the analytical data, the products were the hydrated forms of acids XXa,b. Found,%: C 58.1; H 3.5; N 5.2. $C_{14}H_7NO_5 \cdot H_2O$. Calculated,%: C 58.5; H 3.1; N 4.9.

A mixture of 0.5 g (1.9 mmole) of XXa,b, 50 ml of ethanol, and 2 ml of sulfuric acid was refluxed for 8 h. The reaction mass was then filtered, and the filtrate was poured into ice water. The aqueous mixture was treated with sodium carbonate until it was alkaline to litmus, and the organic bases were extracted with ether to give 0.38 g (54%) of a mixture of esters XXIa,b as yellow crystals with mp 165-172°. Repeated stepwise crystallization from alcohol and n-hexane gave the individual esters: the n-hexane-soluble ester had mp 110-111°; found,%: C 65.9; H 4.4; the n-hexane-insoluble ester had mp 183-184°; found,%: C 65.9; H 4.3. $C_{18}H_{15}NO_5$. Calculated,%: C 66.5; H 4.6.

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