1,4-Di(7-aza-3-oxo-1,2,3,10b-tetrahydrofluoranthen-10b-yl)butane (VIII). A mixture of 1 g (1.88 mmole) of diacid VII and 64 g of polyphosphoric acid are allowed to stand for 2 h at 160°C. The reaction mixture is poured onto ice (150 g) and neutralized by ammonia. The mixture is extracted by chloroform, and the extract is dried over potassium carbonate. After the distillation of chloroform, the residue is chromatographed, using ethyl acetate as eluent. Yield, 0.21 g (23%) of compound VIII, light-yellow crystals, mp 304-305°C (from a 1:2 benzene–hexane mixture). IR spectrum: 2944, 2875 (C_{al}–H), 1690 cm^{-1} (CO). UV spectrum, λ_{max} (log ε): 207 (4.69); 262 (4.48); 284 (4.14); 294 (4.25); 326 nm (4.19). Found, %: C 82.1; H 5.8; N 5.3; M^+ 496. $C_{34}H_{28}N_2O_2$. Calculated, %: C 82.2; H 5.6; N 5.6; M 496.

1,2,3-Tri(4-azafluoren-9-yl)propane (IX). A 0.14 g portion (6 mmoles) of sodium is dissolved in 3 g (32 mmoles) of glycerin, 1 g (5.9 mmoles) of azafluorene I are added, and the mixture is heated for 24 hours at 230°C. When cool, 20 ml of water are added, and the mixture is extracted by chloroform. After distillation of chloroform, the residue is chromatographed, using ether as eluent. Yield of compound IX 15%, mp 277-278°C (from a 2:1 hexane–benzene mixture). IR spectrum: 3050 (C_{ar}–H), 2910, 2860 (C_{al}–H), 1580 m, 1570 m, 1560 m, 1500 w (C=C, skeleton), 1450, 1410 cm^{-1} (C_{al}–H), 740 cm^{-1} (C_{ar}–H). UV spectrum, λ_{max} (log ε): 200 (4.93); 255 (4.55); 282 (4.4); 288 (4.57); 314 nm (4.76). Found, %: C 86.5; H 5.4; N 7.9; M^+ 539. $C_{39}H_{29}N_3$. Calculated, %: C 86.3; H 5.3; N 7.7; M 539.

LITERATURE CITED

1. N. S. Prostakov, V. P. Shalimov, and Galo B. Montenegro Cordova, Khim. Geterotsikl. Soedin., No. 11, 1525 (1984).

SYNTHESIS STARTING FROM 3-METHYL-2-PHENYL-5-(3-METHYL-2-PHENYL-3,4-DEHYDROPIPERIDYL-6)PYRIDINE. 2-PHENYLDINICOTINIC AND 4-AZAFLUORENONE-2-CARBOXYLIC ACIDS

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N-Methyl (ethyl, benzoyl, trifluoroacetyl)-substituted 3-methyl-2-phenyl-5-(3'-methyl-2'-phenyl-3',4'-dehydropiperidyl-6')pyridines and di(N-oxide) of the correspondingly substituted α,β-dipyridyl were prepared. A method for synthesizing 2-phenyldinicotinic acid was developed. Cyclodehydration of this acid gave 4-azafluorenone-2-carboxylic acid. Transformations of this acid were carried out with respect to two functional groups.

We used the structural analog of anabasine, 3-methyl-2-phenyl-5-(3'-methyl-2'-phenyl-3',4'-dehydropiperidyl-6')pyridine (I), in the syntheses of its derivatives, potentially physiologically active compounds, for the preparation of 2-phenyldinicotinic acid, and also for developing a new path for building up of a 4-azafluorene system.

The syntheses which we carried out served as an additional proof of the structure of α-dehydropiperidyl-β-pyridine I, described in [1]; its N-alkyl substituted derivatives were obtained by two paths. 3-Methyl-2-phenyl-5-(1',3'-dimethyl-2'-phenyl-3',4'-dehydropiperidyl-6') pyridine (II) was synthesized by the Leuckart method. The N-ethyl-substituted derivative III was obtained by reducing the analogous N-acetyl-substituted derivative IV with lithium aluminum hydride [1].

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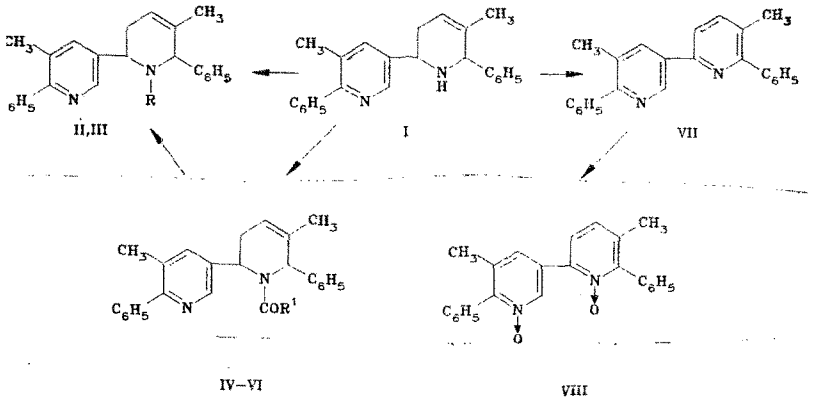
TABLE 1. IR Spectra of N-Acyl-α-dehydropiperidyl-β- pyridine

Compound	R¹	Frequency of main bands, cm^{-1}			
		C–H arom	C–H aliph	C=O	C–F stretching vibrations (polysubst.)
IV	CH_3	3065, 3035	3000—2870	1643	
V	C_6H_5	3063, 3032	2990—2850	1643	
VI	CF_3	3072, 3040	3000—2850	1683—1702 (split.)	1210—1226 (split.) 1150



II R=CH_3; III R=C_2H_5; IV R^1=CH_3; V R^1=C_6H_5; VI R^1=CF_3

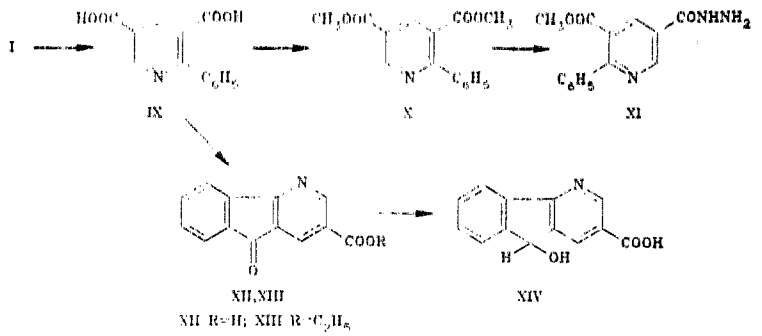
In the benzoylation of compound I according to Schotten-Baumann, 3-methyl-2-phenyl-5-(3'-methyl-2'-phenyl-1'-benzoyl-3',4'-dehydropiperidyl-6')pyridine (V) is formed, and when treated with trifluoroacetanhydride, N-trifluoroacetyl-substituted pyridine VI is obtained. The IR spectra of compounds V and VI are similar to the IR spectrum of the N-acetyl derivative IV, already obtained in [1] (Table 1). The presence of split bands in the IR spectrum of derivative VI indicates the presence of two rotation isomers, as revealed by means of a PMR spectrum for compound IV [1]. For the trifluoro-substituted amide VI, the carbonyl group band is shifted by 40-50 cm^{-1}, compared to the shift of an analogous band of amides IV and V, which is characteristic of these compounds [2].

As N-oxides of 2-alkylpyridines have different pesticidal activity [3], we synthesized the di(N-oxide) VIII from 3-methyl-2-phenyl-5-(3'-methyl-2'-phenylpyridyl-6')pyridine (VII), already obtained from the compound I in [1]. It is a high melting compound, which is practically insoluble in organic solvents.

From compound I, the previously unknown 2-phenyldinicotinic acid IX was obtained. Derivatives of this acid, being analogs of nicotinic acid, may be of a pharmacological interest, while the acid itself can be used as a starting compound in the synthesis of substituted 4-azafluorene.

In the oxidation of α-dehydropiperidyl-β-pyridine I by potassium permanganate in water at 100°C, acid IX is formed in a yield of less than 2%. Under these conditions, according to TLC data, about 20% of the initial compound I converts into dipyridyl VII, while a considerable part of the starting compound remains unchanged.

By oxidizing compound I under the same conditions and by adding a catalytic amount of acetone (∿0.6% of the volume of water), acid IX was isolated in a yield of 74%, in the form of high-melting crystals, which are insoluble in ether, ethyl acetate, chloroform, but are readily soluble in alcohol and acetone.



The dibasic acid IX was identified by its hydrochloride and dimethyl ester X. In the reaction of the latter with hydrazine hydrate, according to the data of elemental analysis and mass-spectrometric analysis, the reaction proceeds at one ester group. Because of steric hindrances by the phenyl substituent at the 2-position, it can be assumed that the reaction proceeds at the ester group at the 5-position, and the compound obtained is a hydrazide of 2-phenyl-3-methoxycarbonyl-5-pyridinecarboxylic acid (XI).

The structure of 2-phenyldinicotonic acid IX predetermines the possible synthesis of 4-azafluorenone-2-carboxylic acid (XII). It is important that a functionally substituted 4-azafluorene can be obtained by this path.

Azafluorenonecarboxylic acid XII is formed in a ~50% yield in the cyclodehydration of acid IX, when the latter is heated with polyphosphoric acid. Acid XII was isolated in the form of high-melting yellow crystals, which are practically insoluble in organic solvents, a characteristic property for these acids [4]. Esterification of acid XII gave its ethyl ester XIII.

The first representative of the hydroxy acids in the 4-azafluorene series, 9-hydroxy-2-carboxy-4-azafluorene (XIV), is obtained by reducing compound XII by sodium borohydride. Hydroxy acid XIV is readily oxidized in an aqueous medium in air into the initial keto acid XII.

Thus, two paths of transition from β-picoline to compounds with a 4-azafluorene structure have been developed. In the phenylation of β-picoline two main compounds are formed, 3-methyl-2-phenylpyridine [5] and 3-methyl-2-phenyl-5-(3'-methyl-2'-phenyl-3',4'-dehydropiperidyl-6')-pyridine (I) [1]. We converted the first of these compounds by catalytic dehydrocyclization into 4-azafluorene [6], which was then oxidized to 4-azafluorenone. The second path for building up the azafluorene system, i.e., the oxidation of compound I to acid IX and its intramolecular cyclodehydration to azafluorenonecarboxylic acid has been described above.

EXPERIMENTAL

The IR spectra of compounds IV-VI, VIII, IX, and XIV were run on a Specord UR-75 spectrophotometer in KBr tablets. The PMR spectra of compounds II, III, and XIII were recorded on a Bruker WP-80 spectrometer (80 MHz) in $CDCl_3$, and of compound X on a Tesla BS-487C spectrometer (60 MHz) in CCl_4. The mass spectra were obtained on a MX-1303 mass spectrometer with a direct introduction of the sample into the ionic source at a ionization voltage of 70 V.

3-Methyl-2-phenyl-5-(1',3'-dimethyl-3',4'-dehydropiperidyl-6')pyridine (II). A solution of 1 g (3 mmoles) of compound I and 4 ml of 40% formalin in 15 ml of formic acid is boiled for 1 h (the end of the reaction is controlled according to TLC and cessation of gas evolution). The reaction mixture is evaporated in vacuo to dryness. The residue (1 g) is pruified on a chromatographic column with aluminum oxide, using ether as eluent. Ether is distilled off, and the oily residue is crystallized in 5 ml hexane. After prolonged standing at −5°C, 0.48 g (45%) of compound II separate, mp 127-128°C. PMR spectrum: 1.36 (3H, s, 3'-CH_3), 1.93 (3H, s, N-CH_3), 2.36 (3H, s, 3-CH_3), 2.38 (2H, m, 5'-CH_2), 3.47 (1H, d.d, 6'-CHC_5H_4N), 3.66 (1H, s, 2'-CH-(C_6H_5)-), 5.61 (1H, s, 4'-CH=), 7.63 (1H, d, 4-H), 8.48 (1H, d,6-H), 7.3-7.5 ppm (10 H, m, aromatic protons). Found, %: C 84.5; H 7.2; N 7.7; M^+ 354. $C_{25}H_{26}N_2$. Calculated, %: C 84.7; H 7.3; N 7.9; M 354.

3-Methyl-2-phenyl-5-(3-methyl-1-ethyl-2-phenyl-3,4-dehydropiperidyl-6)pyridine (III). Lithium aluminum hydride (1 g, 28.6 mmoles) is added in portions in the course of 5 h to a boiling solution of 1 g (2.6 mmoles) of acetyl derivative IV [1] in 40 ml of absolute

tetrahydrofuran. A 50 ml portion of water is added, and the mixture is filtered. The mother liquor is extracted by three 20 ml portions of chloroform. After the distillation of chloroform, the residue is dissolved in ether and passed through a chromatographic column with aluminum oxide. The eluent is distilled off and the oily residue is crystallized from 5 ml of hexane. After standing for 12 h at −5°C, 0.4 g (42%) of compound III separate, mp 97-99°C. PMR spectrum: 0.77 (3H, t, N−CH_2−CH_3), 2.47 (2H, q, N−CH_2−CH_3), 1.39 (3H, s, 3'-CH_3), 2.37 (3H, s, 3-CH_3), 2.42 (2H, m, 5'-CH_2), 3.86 (1H, d.d, 6'-CHC_5CH_4N), 4.19 (1H, s, 2'-$CH(C_6H_5)$-), 5.57 (1H, s, 4'-CH=), 7.65 (1H, d, 4-H), 8.52 (1H, d, 6-H), 7.3-7.6 ppm (10H, m, aromatic protons). Found, %: N 7.5%; M^+ 368. $C_{26}H_{28}N_2$. Calculated, %: N 7.6; M 368.

3-Methyl-2-phenyl-5-(3-methyl-2-phenyl-1-benzoyl-3,4-dehydropiperidyl-6)pyridine (V). A 6 g portion (4.1 mmoles) of benzoyl chloride and 100 ml of a 10% solution of potassium hydroxide are added with stirring to a solution of 2 g (5.9 mmoles) of compound I in 80 ml of dry benzene. The mixture is stirred for 2 h, the benzene layer is separated, and benzene is distilled off. The residue dissolved in a minimal amount of chloroform is deposited on aluminum oxide (H 15 cm, d 4 cm) and eluted with a 1:1 hexane–ether mixture. The eluent is distilled off and the residue is crystallized from heptane. Yield, 1.7 g (65.4%) of colorless crystals of compound V, mp 139.5-140°C. Found, %: C 83.8; H 6.4; N 6.2. $C_{31}H_{28}N_2O$. Calculated, %: C 83.8; H 6.3; N 6.3.

3-Methyl-2-phenyl-5-(3-methyl-2-phenyl-1-trifluoroacetyl-3,4-dehydropiperidyl-6)pyridine (VI). A mixture of 1 g (2.94 mmoles) of compound I and 0.82 ml (6 mmoles) of trifluoroacetic anhydride is boiled for 2 h. The excess anhydride is distilled off in vacuo at room temperature. The residue is dissolved in a mixture of acetone with chloroform, and the solution is deposited on a chromatographic column with aluminum oxide (H 20 cm, d 1 cm). The elution is carried out with chloroform. After the distillation of the eluent, the residue is crystallized from heptane. Yield, 0.75 g (62.5%) of colorless crystals of compound VI, mp 133-134°C. Found, %: C 71.5; H 5.5; N 6.4. $C_{26}H_{23}F_3N_2O$. Calculated, %: C 71.6; H 5.3; N 6.4.

3-Methyl-2-phenyl-5-(3-methyl-2-phenylpyridyl-6)pyridine Di(N-oxide) (VIII). A solution of 1.3 g (3.9 mmoles) of dipyridyl VII [1] and 3 ml of 27% hydrogen peroxide in 45 ml of glacial acetic acid is held at 90°C for 10 h. A 100 ml portion of water is added and the mixture is left to stand for another 12 h. The precipitate is filtered to yield 1.02 g (73%) of di(N-oxide) VIII, light cream-colored crystals, mp 327°C (from a 1:2 acetic acid–water mixture). IR spectrum: 1283 cm^{-1} (N→O). Found, %: N 7.3; M^+ 368. $C_{24}H_{20}N_2O_2$. Calculated, %: N 7.6; M 368.

2-Phenyldinicotinic Acid (IX). In the reaction 5 g (15 mmoles) of compound I, 750 ml of water and 5 ml of acetone are used. The mixture is heated to boiling, and 47 g (300 mmoles) of potassium permanganate are added in portions of 3-5 g in the course of 15 h, with vigorous stirring. The last portion of the oxidizing agent decolorizes after 5 h. Manganese dioxide is filtered and washed with 100 ml of water. The aqueous solution is evaporated to a volume of 150 ml. To the residual solution, 40 ml of chloroform are added, and then, with vigorous stirring, 18% hydrochloric acid to pH 3. The precipitate that separates is filtered and dried. Yield, 2.1 g of acid IX. By concentration of the mother liquor, an additional 0.54 g of compound is isolated (overall yield 74%). Acid IX — colorless crystals, mp 269-273°C (from water). IR spectrum: 2540 (br.), 1910 (br.), 1720, 1302-1264 cm^{-1} (split). Found, %: C 63.8; H 4.1; M^+ 243. $C_{13}H_9NO_4$. Calculated, %: C 64.2; H 3.7; M 243.

Hydrochloride of acid IX — colorless crystals, mp 266-268°C (from alcohol). Found, %: Cl 12.5; N 4.8. $C_{13}H_9NO_4 \cdot HCl$. Calculated, %: Cl 12.7; N 5.0.

After evaporation of the chloroform mother liquid, 1.15 g of benzoic acid are isolated, mp 118-122°C (from water).

2-Phenyl-3,5-di(methoxycarbonyl)pyridine (X). In the reaction 3.0 g (12.3 mmoles) of acid IX, 20 ml of absolute methanol and 3 ml of sulfuric acid are used. The mixture is boiled for 15 h, and after adding 50 ml of water, is neutralized by sodium carbonate to pH ∿9 and extracted by ether. After distillation of ether, the residue is chromatographed on aluminum oxide, using ether as eluent. From 3.5 g of an oily substance remaining after the distillation of the eluent, after crystallization in 5 ml of hexane and prolonged standing at −5°C, 2.68 g (80.2%) of diester X are obtained, colorless crystals, mp 50-50.5°C (from hexane). PMR spectrum: 3.7 (3H, s, CH_3), 3.98 (3H, s, CH_3), 8.55 (1H, d, J_{31} = 3 Hz, 4-H), 9.28 (1H, d, J_{13} = 3 Hz, 6-H), 7.26-7.66 ppm (5H, m, aromatic protons). Found, %: C 66.2; H 4.6; N 4.9; M^+ 271. $C_{15}H_{13}NO_4$. Calculated, %: C 66.4; H 4.8; N 5.2; M 271.

2-Phenyl-3-methoxycarbonyl-5-pyridinecarboxylic Acid Hydrazide (XI). A solution of 0.05 g (0.18 mmole) of diester X and 0.5 ml of hydrazine hydrate in 10 ml of ethanol is boiled for 1 h. A 10 ml portion of water is added. The mixture is allowed to stand for 3 days at −5°C to yield 0.024 g (48%) of compound XI, pale-yellow crystals, mp 144-146°C (from 50% aqueous ethanol). Found, %: N 15.4; M^+ 271. $C_{14}H_{13}N_3O_3$. Calculated, %: N 15.5; M 271.

4-Azafluorenone-2-carboxylic Acid (XII). A mixture of 1 g (4.1 mmoles) of diacid IX and 10 ml of polyphosphoric acid is gradually heated to 100°C. The homogeneous mixture is then held for 10 h at 210-250°C. When cool, the mixture is poured into 100 ml of water. The precipitate (1.1 g) is crystallized in 400 ml of 80% alcohol. Yield 0.44 g (47.8%) of compound XII, greenish-yellow needle-like crystals, mp 305°C. IR spectrum: 2500 (br.), 1910 (br.), 1732-1720 (split.), 1265 cm^{-1}. Found, %: C 69.1; H 3.3; N 5.9; M^+ 225. $C_{13}H_7NO_3$. Calculated, %: C 69.3; H 3.1; N 6.2; M 225.

2-Ethoxycarbonyl-4-azafluorenone (XIII). A. A mixture of 0.26 g (1.16 mmole) of acid XII and 1.5 ml of sulfuric acid in 20 ml of absolute ethanol is boiled for 20 h. When cool, the mixture is poured into 40 ml of water to yield 0.19 g of ester XIII. The mother liquid is neutralized with sodium carbonate to pH 7 to yield additional 0.031 g of compound XIII, yellow needle-like crystals, mp 130-131°C (from petroleum ether). Overall yield 76%. PMR spectrum: 1.44 (3H, t, CH_3), 4.45 (2H, q, CH_2), 7.52 (1H, t, 7-H), 7.66 (1H, t, 6-H), 7.78 (1H, d, 8-H), 7.93 (1H, d, 5-H), 8.45 (1H, d, 1-H), 9.25 ppm (1H, d, 3-H). IR spectrum: 1725 (C=O), 1250, 1122-1138 cm^{-1} (split.). Found, %: C 70.9; H 4.4; N 5.3; M^+ 253. $C_{15}H_{11}NO_3$. Calculated, %: C 71.1; H 4.4; N 5.5; M 253.

B. A mixture of 1.6 g (6.6 mmoles) of acid IX and 20 ml of polyphosphoric acid is held for 15 h at 230-250°C. When cool, the mixture is poured into 150 ml of water. The precipitate that forms (2.6 g after drying) and 3 ml of sulfuric acid are boiled for 12 h in 65 ml of absolute ethanol. The reaction mixture is poured into 200 ml of water, neutralized with sodium carbonate to pH 9, and extracted by ether. After distillation of ether, the residue is chromatographed (aluminum oxide, eluent, a 1:1 hexane–ether mixture) to yield 1.1 g (66% based on acid IX used) of ester XIII, mp 130-131°C (from hexane).

9-Hydroxy-2-carboxy-4-azafluorene (XIV). Sodium borohydride (1 g) is added in 0.1 g portions, in the course of 3 h, to a vigorously stirred suspension of 0.14 g (0.6 mmole) of acid XII in 15 ml of water. The mixture is then heated for 30 min at 70-80°C and 18% hydrochloric acid is added to pH 6. The precipitate formed is washed on the filter to neutral reaction with water. Yield, 0.088 g (63%) of hydroxy-acid XIV, pale-cream-colored crystals, mp 235-237°C (from a 3:1 ethyl acetate–hexane mixture). IR spectrum: 3350 (OH), 2500-3080, 1700 (C=O), 1160, 935 cm^{-1}. Found, %: N 5.9; M^+ 227. $C_{13}H_9NO_3$. Calculated, %: N 6.2%; M 227.

LITERATURE CITED

1. N. S. Prostakov, H. Bu Habib, V. A. Rezakov, A. A. Fomichev, L. M. Kirillova, and V. K. Shevtsov, Khim. Geterotsikl. Soedin., No. 8, 1115 (1984).
2. K. Nakanishi, Infrared Spectra and Structure of Organic Compounds [Russian translation], Mir, Moscow (1965), p. 59.
3. G. V. Protopopova, A. F. Pavlenko, V. S. Petrenko, T. I. Cherepenko, G. V. Shurubura, and V. P. Kukhar', All Union Conference on Chemical Plant Protecting Agents. Section I. Summaries of Lectures [in Russian], Ufa (1982), p. 35.
4. N. S. Prostakov, A. A. Obynochnyi, L. A. Gaivoronskaya, L. M. Kirillova, and V. P. Zvolinskii, Khim. Geterotsikl. Soedin., No. 12, 1664 (1972).
5. R. A. Abramovitch, Giam Chao Seng, and A. D. Notation, Canad. J. Chem., 38, 761 (1960).
6. N. S. Prostakov, A. V. Varlamov, G. A. Vasil'ev, O. G. Kesarev, and G. A. Urbina, Khim. Geterotsikl. Soedin., No. 1, 124 (1977).