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PREPARATION OF α - AND γ -(α -FURYL)PYRIDINES

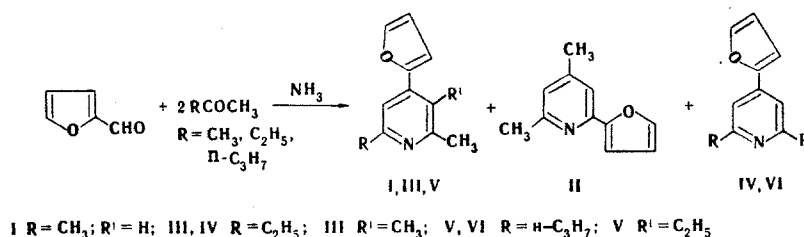
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UDC 547.727'828

Mixtures of isomeric alkyl-substituted (in the pyridine ring) α - and γ -(α -furyl)-pyridines were obtained in up to ~40% yields by condensation of furfural and ammonia with several aliphatic ketones and aldehydes (at 370-380°C with a cadmium calcium phosphate catalyst). The dependence of the yields and structures of the corresponding isomers on the structure of the starting carbonyl compound was examined. Data from the PMR and mass spectra were used to prove the structures of the pyridine bases obtained.

In series of heteroaryl-substituted pyridine bases furylpyridines remain relatively little-studied and difficult-to-obtain compounds; this is due to the limitations involved in the methods for their synthesis [1, 2]. The interest in furylpyridines is due to the fact that substances that have high and diverse biological activity are found among them [2, 3]. Continuing our research on the chemistry of pyridine bases we turned to the synthesis of α - and γ -(α -furyl)pyridines by the Chichibabin method [4] by condensation of furfural and ammonia with ketones (acetone, methyl ethyl ketone, and methyl n-propyl ketone) and aldehydes (acetaldehyde, propionaldehyde, butyraldehyde, and crotonaldehyde). The condensation was carried out in the vapor phase at 370-380°C in the presence of a cadmium calcium phosphate catalyst.

Mixtures of primarily two isomers of furyl-substituted pyridines in overall yields up to 40% with various isomer ratios are formed in the condensation of furfural and ammonia with these carbonyl compounds. The structures of the isomers and their quantitative ratios depend on the structure of the starting carbonyl compound.



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TABLE 1. PMR Spectra of α - and γ -(α -Furyl)pyridines I-III, V-X, and XII

Com- pound	Chemical shifts, δ , ppm											SSCC, J, Hz
	2-H	3-H	4-H	5-H	6-H	3'-H	4'-H	5'-H	CH ₃	CH ₂		
I	—	7.03 c	—	7.03 s	—	6.64 d	6.35 dd	7.38 d	2.45 s	—		$J_{3',4'}=3.5; J_{4',5'}=1.8$
II	—	6.63 br.s	—	7.18 br.s	—	6.91 dd	6.33 dd	7.03 d	2.26s 2.39s	—		$J_{3',4'}=3.6; J_{3',5'}=0.7; J_{4',5'}=1.8$
III	—	—	—	7.04 s	—	6.48 d	6.36 dd	7.40 d	1.25t 2.29s	2.66 q		$J_{3',4'}=3.5; J_{4',5'}=1.8$
V	—	—	—	7.01 s	—	6.47 d	6.33 dd	7.38 d	2.45 s	1.73 m 2.44 m		$J_{3',4'}=3.5; J_{4',5'}=1.8$
VI	—	7.07 s	—	7.07 s	—	6.67 d	6.36 d	7.38 d	0.96t 1.20t	2.88 m		$J_{3',4'}=3.5; J_{4',5'}=1.8$
VII	8.41dd	7.46 dd	—	7.46 dd	8.41 dd	6.97 dd	6.46 dd	7.58 dd	0.99t	1.78 sext.		$J_{3',4'}=3.5; J_{3',5'}=0.8; J_{4',5'}=1.8; J_{2,3}=5.5; J_{2,5}=1.5$
VIII	—	7.41dd	7.30 dd	7.00—	8.36 m	7.00—	6.33 dd	7.48 d	—	—		$J_{3',4'}=3.5; J_{3',5'}=0.8; J_{4',5'}=1.8; J_{2,3}=5.5; J_{2,5}=1.5$
IX	8.16br.s	—	—	6.85 m	8.16 br.s	6.85 m	6.42 m	7.37 d	—	—		$J_{3',4'}=3.8; J_{4',5'}=1.9; J_{6,5}=5.0; J_{6,3}=1.0; J_{6,4}=1.5$
X	—	—	7.40 d	—	8.06 br.s	6.82 d	6.32 d	7.10 br.s	2.18 s 2.45 s	—		$J_{3',4'}=3.7; J_{4',5'}=1.9$
XII	—	—	7.27 d	—	8.29 d	7.00 dd	6.47 dd	7.13 dd	1.18 t	2.60 q		$J_{3',4'}=3.6; J_{4',5'}=1.8$
										2.91 q		$J_{3',4'}=3.6; J_{4',5'}=1.8$

*The PMR spectra of II and VIII were recorded with D₂O as the external standard, while the spectrum of VII was recorded in d₆-acetone.

The isomeric 2,6-dimethyl-4-(2-furyl)pyridine (I) and 2,4-dimethyl-6-(2-furyl)pyridine (II) with a significant (8:1) preponderance of the former are formed in the condensation of furfural and acetone with ammonia.

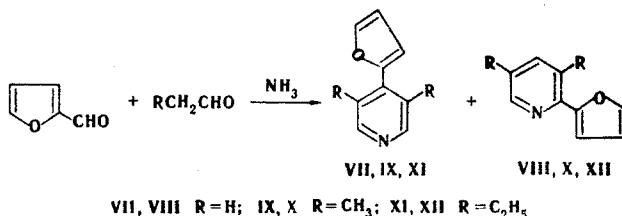
Data from the PMR spectra (Table 1) confirm the structures of I and II. In the spectrum of pyridine base I the lone singlet signal of two methyl groups (6H) corresponds to their symmetrical orientation relative to the nitrogen atom.

Virtually only γ -(α -furyl)-substituted pyridines (in up to 20% overall yields), which are isomeric with respect to the mutual orientation of the alkyl substituents in the pyridine ring, are formed in the case of the condensation of furfural and ammonia with methyl ketone and with methyl n-propyl ketone. 2,3-Dimethyl-6-ethyl-4-(2-furyl)pyridine (III) and 2,6-diethyl-4-(2-furyl)pyridine (IV) are formed in a ratio of 4:1 in the first case. 2-Methyl-3-ethyl-6-n-propyl-4-(2-furyl)pyridine (V) and 2,6-di-n-propyl-4-(2-furyl)pyridine (VI) are formed in a ratio of 0.8:1 (in 12.5% overall yield) when methyl n-propyl ketone is used.

The structures of III, V, and VI were confirmed by data from their PMR spectra, while the structure of IV was confirmed by chromatographic mass spectrometry from the molecular ion peak (M^+), which has the maximum intensity and an m/e value that corresponds to the molecular mass of the substance. It should be noted that the peaks of $[M-H]^+$ and $[M-C_2H_4]^+$ ions that are characteristic for α -ethylpyridine [5] are absent in the mass spectrum of IV, whereas an intense (54%) peak of $[M-29]^+$ ions due to the elimination of a CHO radical from the furan ring [5] is observed; this constitutes evidence for the lower stability of the furan ring as compared with the pyridine ring.

The amounts of γ -(α -furyl)-substituted pyridines I, III, and V relative to their isomers II, IV, and VI, respectively, in this series decrease considerably. This is evidently associated with the fact that the steric hindrance due to the alkyl group of methyl ethyl ketone to crotonic condensation of furfural with ketones at their α -methylene group increases on passing from acetone to methyl ethyl ketone and then to methyl n-propyl ketone.

The products of the condensation of furfural and aldehydes with ammonia are γ - and α -furylpyridines. Their ratios also vary as a function of the size of the alkyl group of the aldehyde. Mixtures of the following pyridine bases, respectively, were obtained in the condensation of furfural, ammonia, and acetaldehyde, propionaldehyde, and butyraldehyde: 4-(2-furyl)pyridine (VII) and 2-(2-furyl)pyridine (VIII) (VII:VIII \cong 1:0.8) 3,5-dimethyl-4-(2-furyl)pyridine (IX) and 3,5-dimethyl-2-(2-furyl)pyridine (X) [6] (IX:X \cong 1:1), and 3,5-diethyl-4-(2-furyl)pyridine (XI) and 3,5-dimethyl-2-(2-furyl)pyridine (XII) (XI:XII \cong 1:2.5).



The structures of pyridine bases VII-X and XII were confirmed by data from their PMR spectra (Table 1), while the structure of XI was confirmed by chromatographic mass spectrometry. In addition to the maximally intense M^+ peak (201)* peaks of $[M-15]^+$ ions (60%), which are formed as a result of the characteristic (for β -ethylpyridine) elimination of a methyl group from the ethyl substituent as a consequence of β cleavage [5], $[M-29]^+$ ions (66%), which are due to ejection of CHO \cdot from the furan ring, and of fragments with m/e 158 ($[M-CH_3, -C_2H_4]^+$, 40%) and m/e 143 ($[M-CHO, -C_2H_4]^+$, 30%) are observed in its mass spectrum. Peaks of the same ions are present in the mass spectrum of XII.

The amounts of γ -(α -furyl)-substituted pyridines VII, IX, and XI decrease as compared with their α isomers VIII, X, and XII, respectively, in this series; this is also apparently due to steric factors, viz., the ortho effect of bulky alkyl groups attached to the C₃ and C₅ atoms of the pyridine ring.

If paraldehyde is used in place of acetaldehyde in the condensation, the overall yield of pyridine bases VII and VIII increases (from 11% to 36%), and their ratio changes signifi-

*Here and subsequently, the numbers that characterize the ions are the mass-to-charge ratios.

cantly (VII:VIII \cong 1:2.3). This is evidently explained by the fact that under the conditions of the Chichibabin reaction paraldehyde is readily converted to crotonaldehyde, the subsequent condensation of which should yield mainly α -furyl-substituted pyridine VIII. This assumption is confirmed to a certain extent by the fact that 2-(2-furyl)pyridine (VIII) was obtained in 30% yield in the condensation of furfural and crotonaldehyde with ammonia. Isomer VII is formed in very small amounts (VII:VIII \cong 1:20).

5-Ethyl-2-(2-furyl)pyridine (XIII) (\sim 1% yield) and 2-methyl-5-(α -furylmethyl)pyridine (XIV) (\sim 2% yield) were identified among the products of condensation of furfural and acetaldehyde (paraldehyde) by means of chromatographic mass spectroscopy. The M^+ peaks (m/e 173) in the mass spectra of these compounds have the maximum intensity, while the rather intense (18 and 22%, respectively) $[M-CH_3]^+$ ion peaks confirm the presence of an ethyl group in the β position.

It seemed of interest to compare the ratio of γ - and α -furylpyridines XI:XII (1:2.5) with the ratio of the corresponding 3,5-diethyl-4- and -2-phenylpyridines (1:8), which we obtained in [7] by similar condensation of benzaldehyde with butyraldehyde.

The γ -furyl-substituted pyridine is formed in relatively larger amounts than the γ -phenyl-substituted compound. The more favorable relative orientation of the intermediate condensation product will be that in which interaction of the free electron pairs of the oxygen atoms of the aliphatic aldehyde (or the nitrogen atom of the aldimine) and the furan ring is absent. An electron repulsion effect is evidently realized in the unstable intermediate state at the instant of formation of the α -furyl-substituted pyridines, and this leads to a decrease in their relative yields.

A change in the ratios of the γ - and α -arylpyridines was also noted in [7] on passing to the synthesis of 3,5-diethyl-4- and -2-(*p*-methoxyphenyl)pyridines (1:5).

We thank A. A. Fomichev for his discussion of the PMR spectra of II, VII, and VIII.

EXPERIMENTAL

The PMR spectra of solutions of the compounds in CCl_4 were recorded with Tesla BS-487C and Bruker WP-80 spectrometers (80 MHz) with tetramethylsilane as the internal standard. The preparative isolation of the furylpyridines was carried out by means of column chromatography on aluminum oxide [elution with ether-heptane (1:1)]. The individuality of the compounds was monitored by thin-layer chromatography (TLC) and gas-liquid chromatography (GLC) with an LKhM-7A chromatograph with a 1.8 m by 3 mm column (5% XE-60 on Chromaton) at 140-160°C, a thermal conductivity detector, and helium as the carrier gas (75 ml/min). Chromatographic mass-spectrometric analysis was performed with an LKB -2091 apparatus with a 1 m by 3 mm column (5% SE-30 on Chromosorb W) at an ionization energy of 70 eV.

Condensation of Furfural and Acetone (Methyl Ethyl Ketone, Methyl *n*-Propyl Ketone, Acetaldehyde, Propionaldehyde, and Butyraldehyde) with Ammonia. A mixture of furfural with the carbonyl compound and ammonia (in a molar ratio of 1:3-4:7) was passed at a constant volume rate (\sim 2 ml/h) through a reactor of the flow type filled with 100 ml of industrial cadmium calcium phosphate catalyst (CdO 10:13, CaO 41:45, and P_2O_5 41:45 wt.%). The temperature in the catalyst zone was 370-380°C. The condensate was acidified with respect to Congo with 18% hydrochloric acid, and the neutral substances were extracted with ether. The aqueous solution was treated with sodium hydroxide, and the pyridine bases were extracted with ether. The individual furylpyridines were isolated by fractional distillation, crystallization of the picrates, and chromatography. The condensation of furfural and paraldehyde with ammonia was carried out similarly. Furylpyridines I-III, V-X, and XII were isolated in the form of analytically and chromatographically pure samples. Furfuralacetone was isolated in 15% yield in the condensation of furfural and acetone with ammonia. The yields of the pyridine bases were calculated from GLC data.

The PMR spectra of the α - and γ -(α -furyl)pyridines obtained are presented in Table 1. The molecular masses of I-XIV determined by mass spectrometry were in agreement with their empirical formulas. We were unable to isolate IV, XI, XIII, and XIV in pure form; they were characterized by chromatographic mass spectrometry. Data from a mass-spectrometric study of furylpyridines I-XIV will be presented in our next communication.

2,6-Dimethyl-4-(2-furyl)pyridine (I). This compound, with mp 37-38°C (from ether) [mp

41°C (from petroleum ether) [8], was obtained in 8% yield. The picrate had mp 243-245°C (from acetone). Found: N 13.9%. $C_{11}H_{11}NO \cdot C_6H_3N_3O_7$. Calculated: N 13.9%.

2,4-Dimethyl-6-(2-furyl)pyridine (II). This compound, with bp 111-115°C (2 mm), was obtained in 1% yield. Found: C 76.2; H 6.4; N 8.0%; M^+ 173. $C_{11}H_{11}NO$. Calculated: C 76.3; H 6.4; N 8.1%; M 173.

2,3-Dimethyl-6-ethyl-4-(2-furyl)pyridine (III). This compound was obtained in 16% yield and had mp 35-36°C (from ether). Found: C 77.5; H 7.6; N 6.8%; M^+ 201. $C_{13}H_{15}NO$. Calculated: C 77.6; H 7.5; N 6.9%; M 201. The picrate had mp 215-216°C (from ethanol). Found: N 12.9%. $C_{13}H_{15}NO \cdot C_6H_3N_3O_7$. Calculated: N 13.0%.

2,6-Diethyl-4-(2-furyl)pyridine (IV). This compound was obtained in 4% yield. The structure was established by chromatographic mass spectrometry. Found: M^+ 201. $C_{13}H_{15}NO$. Calculated: M 201.

2-Methyl-3-ethyl-6-n-propyl-4-(2-furyl)pyridine (V). This compound was obtained in 5.5% yield. Found: C 78.4; H 8.5; N 6.0%; M 229. $C_{15}H_{19}NO$. Calculated: C 78.6; H 8.3; N 6.1%. The methiodide had mp 125-126°C (from ethanol). Found: C 51.6; H 6.3; N 3.5%. $C_{15}H_{19}NO \cdot CH_3I$. Calculated: C 51.8; H 6.0; N 3.8%.

2,6-Di-n-propyl-4-(2-furyl)pyridine (VI). This compound was obtained in 7% yield. Found: C 78.3; H 8.4; N 5.9%; M 229. $C_{15}H_{19}NO$. Calculated: C 78.6; H 8.3; N 6.1%; M 229. The methiodide had mp 253-255°C (from ethanol). Found: C 51.5; H 6.1; N 3.6%; $C_{15}H_{19}NO \cdot CH_3I$. Calculated: C 51.8; H 6.0; N 3.8%.

4-(2-Furyl)pyridine (VII). This compound was obtained in 6% yield (from acetaldehyde), 11% yield (from paraldehyde), and 1.5% yield (from crotonaldehyde) and had mp 65-67°C (from ether) (mp 69°C [9]). Found: M^+ 145. C_9H_7NO . Calculated: M 145. The methiodide had mp 176-177°C (from acetone) [mp 179°C (from ethanol) [9]].

2-(2-Furyl)pyridine (VIII). This compound was obtained in 5% yield (from acetaldehyde), 25% yield (from paraldehyde), and 30% yield (from crotonaldehyde). Found: M^+ 145. C_9H_7NO . Calculated: M 145. The methiodide had mp 156-157°C (from acetone) [mp 158°C (from ethanol) [9]].

3,5-Dimethyl-4-(2-furyl)pyridine (IX). This compound was obtained in 17% yield. Found: C 76.1; H 6.6; N 7.8%; M 173. $C_{11}H_{11}NO$. Calculated: C 76.3; H 6.4; N 8.1%; M 173. The methiodide had mp 209-211°C (from ethanol). Found: N 4.1%. $C_{11}H_{11}NO \cdot CH_3I$. Calculated: N 4.4%.

3,5-Dimethyl-2-(2-furyl)pyridine (X). This compound was obtained in 17% yield and had bp 97-98°C (2 mm). Found: C 76.4; H 6.4; N 7.9%; M 173. $C_{11}H_{11}NO$. Calculated: C 76.3; H 6.4; N 8.1%; M 173. The picrate had mp 177-179°C (from ethanol). Found: N 13.7%. $C_{11}H_{11}NO \cdot C_6H_3N_3O_7$. Calculated: N 14.0%.

3,5-Diethyl-4-(2-furyl)pyridine (XI). This compound was obtained in 4.5%. Mass spectrum, m/e (percent of the maximum peak): M^+ 201 (100), 186 (60), 172 (66), 158 (40), 143 (30). $C_{13}H_{15}NO$. Calculated: M 201.

3,5-Diethyl-2-(2-furyl)pyridine (XII). This compound was obtained in 12% yield and had bp 145-149°C (2 mm). Found: C 77.2; H 7.4; N 6.6%; M^+ 201. $C_{13}H_{15}NO$. Calculated: C 77.6; H 7.5; N 6.9%; M 201.

3-Ethyl-6-(2-furyl)pyridine (XIII). This compound was obtained in ~1% yield. Mass spectrum, m/e (percent of the maximum peak): M^+ 173 (100), 158 (18), 145 (89), 130 (31), 116 (55). $C_{11}H_{11}NO$. Calculated: M 173.

2-Furyl(2-methyl-5-pyridyl) Methane (XIV). This compound was obtained in ~1% yield. Mass spectrum, m/e (percent of the maximum peak): M^+ 173 (100), 159 (22), 144 (78), 106 (3), 94 (5). $C_{11}H_{11}NO$. Calculated: M 173.

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INVESTIGATION OF PHENANTHRIDONE AND DIOXOTETRAHYDRODIAZAPYRENE.

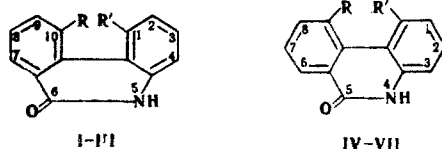
3.* INVESTIGATION OF THE NITRATION OF 5H-PHENANTHRIDIN-6-ONE AND ITS DERIVATIVES

G. I. Magachev, N. G. Grekhova,
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UDC 83:542.958.1

The nitration of 5H-phenanthridin-6-one (I), 5H-phenanthridin-6-one-10-carboxylic (II) and 5H-phenanthridin-6-one-1-carboxylic acids (III), 4H-cyclopenta[k,l,m]-phenanthridine-5,9-dione (IV), 4H-cyclopenta[k,l,m]phenanthridine-5-one (V), 5,10-dioxo-4,5,9,10-tetrahydro-4,9-diazapyrene (VI), and 5,9-dioxo-4,5,9,10-tetrahydro-4,10-diazapyrene (VII) with nitric acid (sp. gr. 1.42-1.51) and a nitrating mixture of 0-120°C was investigated. The orientation and sequence of incorporation of nitro groups in I-VII are determined by the presence of a phenanthridone structure in them. Mono-, di-, tri-, and tetranitro-substituted I-VII were obtained and characterized.

Continuing our study of phenanthridone and dioxotetrahydrodiazapyrene, we investigated the nitration of 5H-phenanthridin-6-one (I) [2], 5H-phenanthridon-6-one-10-carboxylic (II) [3] and 5H-phenanthridin-6-one-1-carboxylic (III) [4] acids, 4H-cyclopenta[k,l,m]phenanthridine-5,9-dione (IV) [5], 4H-cyclopenta[k,l,m]phenanthridine-5-one (V) [6], 5,10-dioxo-4,5,9,10-tetrahydro-4,9-diazapyrene (VI), and 5,9-dioxo-4,5,9,10-tetrahydro-4,10-diazapyrene (VII) [3]. All these compounds contain two benzene rings and one α -pyridone ring, which together form a phenanthridone structure.



I R=R'=H; II R=COOH, R'=H; III R=H, R'=COOH; IV R+R'=CO; V R+R'=CH₂;
VI R+R'=NH-CO; VII R+R'=CO-NH

Little study has been devoted to nitration of the phenanthridone structure [2]. We investigated the reaction of I-VII with HNO₃ (sp. gr. 1.42-1.51) and with a nitrating mixture at 0-120°C. We obtained mono-, di-, and trinitro-substituted derivatives of the heterocyclic systems. The orientation and sequence of incorporation of nitro groups in I-VII are determined by the presence in them of the phenanthridone structure. The presence of substituents or bridged groups in the 1 and 10 positions of the phenanthridone ring has a relatively small effect on them. Nitro-substituted I-VII, the conditions for their preparation, and their characteristics are presented in Table 1.

*See [1] for Communication 2.

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