THE PHENYLATION OF β-PICOLINE. ISOLATION AND ESTABLISHMENT OF THE STRUCTURE OF β-PYRIDYL-α-DEHYDROPIPERIDINE

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It was established that the side product that is formed in substantial amounts in the phenylation of β-picoline by phenyllithium is 3-methyl-2-phenyl-5-(3-methyl-2-phenyl-3,4-dehydropiperidyl-6)pyridine — a structural analog of anabasine. Its structure was demonstrated by spectral methods and by chemical conversions.

Nucleophilic substitution of β-picoline using phenyllithium is a preparative method for the production of 3-methyl-2-phenylpyridine. In a study of this reaction it was established that under optimum conditions 3-methyl-2-phenylpyridine and 5-methyl-2-phenylpyridine are formed with a yield of up to 42% (content in the mixture 95 and 5%, respectively) [1-3].

A shortcoming of this method is the comparatively moderate yield of the end product and the formation of a substantial amount of side products. In [1] an attempt was undertaken to establish the nature of the side products. Despite a large and careful experiment, this problem could not be solved, and further investigations along this line were stopped. In [3] it was suggested that one of the pathways of the reaction of β-picoline with phenyllithium is conversion of an intermediate — methylphenyl-substituted dihydropyridyllithium, which is formed at the first step of the reaction — to side products. It was assumed that the main direction of such conversions is polymerization, due to the presence of a cis-butadiene-like system in its molecule. Thus, the question of the nature of the indicated side products of this reaction remained open.

Reproducing experiments on the phenylation of β-picoline with phenyllithium in ether, we established that 3-methyl-2-phenylpyridine is formed with a yield of ~32%, while the side product has a yield of ~17%. We isolated the latter in the form of colorless crystals, which melt in the range of 137-140°C after crystallization from hexane and appear chromatographically as an individual substance. The mass spectrum contains the peak of the molecular ion M^+ 340.

To obtain information on the structure of this compound we investigated its NMR spectrum in ultrastrong fields (250 MHz for protons and 90.5 MHz for ^{13}C) in various solvents in the range of temperatures from 25 to 100°C. In the assignment of the signals, experiments on double resonance were conducted, and the proton-coupled spectra of ^{13}C were recorded. On the basis of these data (Table 1) it was established that the molecule of the compound contains: a 2,3,5-trisubstituted pyridine ring (the characteristic signals of the protons 4-H and 6-H and the carbons 2-C, 4-C, and 6-C of the pyridine ring were observed), the fragment $CHCH_2CH{=}C(CH_3)$ in the cyclic system with predominantly axial orientation of the methine proton at the sp^3-carbon (in addition to the characteristic chemical shifts of ^1H and ^{13}C, SSIC of protons specific for such a fragment were observed; see Table 1), and a secondary amino group (broad signal of 1H at 1.99 ppm in $CDCl_3$, which disappeared when D_2O was added).

On the basis of the NMR data we suggested that this compound is a substituted β-pyridyl-α-dehydropiperidine, and it is obtained as follows. The intermediate — N-lithium-5-methyl-6-phenyl-1,6-dihydropyridine, formed at the first step of the reaction — is an enamine, in which the α,β-unsaturated bond is polarized to a substantial degree under the influence of the

*Here and henceforth, values of m/z are given for the peaks of the ions.

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TABLE 1. NMR Data of 3-Methyl-2-phenyl-5-(3-methyl-2-phenyl-3,4-dehydropiperidyl-6)pyridine (I)

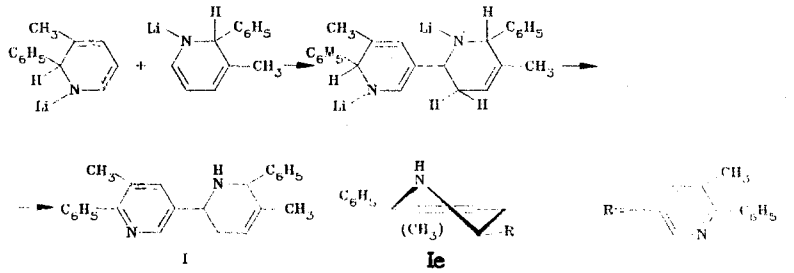
	piperidine ring							pyridine ring			
	NH	2′-H	4′-H	5′-H_a	5′-H_e	6′-H_a	3′-CH_3	4-H	6-H	3-CH_3	phenyl
Chemical shifts of ^1H, ppm DMSO D_6, 250 MHz, 50°C*											
δ	3,33	4,40	5,31	2,23	2,39	3,90	1,55	7,58	8,33	2,24	10H: 7,2—7,3
J_{HH}, Hz	(3′-CH_3, 4′-H) 1,4; (4′-H, 5′-H_e) 4,5; (4′-H, 5′-H_a) 3,0; (4H, 6H) 2,0; (5′-H_a, 5′-H_e) −17,0; (5′-H_a, 6′-H_a) 9,5; (5′-H_e, 6′-H_a) 4,5										

	2-C	4-C	6-C	2′-C	4′-C	5′-C	6′-C	3-CH_3	3′-CH_3
Chemical shifts of ^{13}C, δ, ppm and SSIC $^1J_{CH}$, Hz,† CD_3OD, 90.5 MHz, 25°C									
δ	159,1	139,0	146,4	62,2	123,8	34,0	49,8	21,1	19,6
$^1J_{CH}$	—	160	176	130	156	144	130	123	125

*The SSIC of J_{HH}, like δ_H, exhibited a dependence on the solvent and temperature.
†In the ^{13}C NMR spectrum, in contrast to the protons, not all the signals were assigned; the authors are grateful to N. I. Golovtsov for aid in the interpretation of these spectra.

charge on the nitrogen atom. In the interaction of two molecules of the intermediat, one of which reacts like an enamine, while the other acts as an electrophile, there is a dimerization accompanied by proton transfer.

In the subsequent conversion of the adduct, the ring containing the diene fragment is converted to a pyridine ring (elimination of lithium hydride), while the tetrahydropyridine ring is preserved (hydrolysis at the N—Li bond).



I Ie

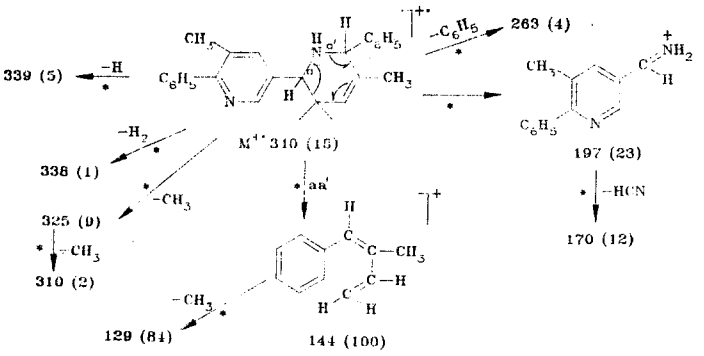
The analytical and spectral data for 3-methyl-2-phenyl-5-(3-methyl-2-phenyl-3,4-dihydropiperidyl-6)pyridine (I) and the compounds obtained in its chemical conversions confirm its β-pyridyl-α-dehydropiperidine structure.

According to the ^1H and ^{13}C NMR data (Table 1), the compound I isolated is one of the possible geometrical isomers. Moreover, the conformer Ie with an equatorial orientation of the pyridine radical predominates (vicinal SSIC or the proton 6′*-H 9.5 and 4.5 Hz). Considering the information on the three-dimensional structure of analogously substituted cyclohexenes [4], we believe that the phenyl radical at $C_{(2)}$ of the hydrogenated ring is also equatorial. Consequently, compound I is a cis-isomer.

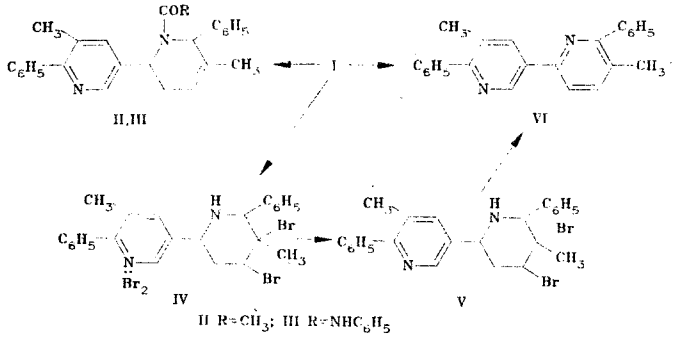
The structure of compound I is also confirmed by the data of the mass spectrum. The stability of the molecule to electron impact (W_M = 3.6%) and the formation of a medium-intensity peak of the molecular ion (18%) are characteristic of the decomposition of diazabicyclic compounds with incompletely conjugated bonds [5]. In the region of the molecular ion the peaks $(M - H)^+$, $(M - 2)^+$, $(M - 3)^+$ and $(M - 4)^+$ are noted, which indicates the presence of a phenyl group in the molecule, bonded to the aromatic ring [6].

*Here and henceforth, the protons and carbon atoms of the hydrogenated ring are marked by primes.

The presence of a phenyl and two methyl groups in compound I is also responsible for the formation of the peaks 263, 325, and 410, respectively, in the mass spectrum (scheme).



The maximum-intensity peak of the ion 144 is due to retrodiene decomposition of the tetrahydropyridine ring with synchronous cleavage of the $C_{(2)}$—$N_{(1)}$ and $C_{(6')}$—$C_{(5')}$ bonds. In this case the positive charge is localized on the carbon fragment, which is confirmed by a measurement of the exact mass 144 (meas. 144.0930, calc. 144.0930, $C_{11}H_{12}$) and 129 (meas. 129.0700, calc. 129.0704, $C_{10}H_9$). The occurrence of a Diels—Alder retrodecompsition in the molecular ion also leads to the formation of an intense peak of the ion 197 (meas. 197.1068, calc. 197.1079, $C_{13}H_{13}N_2$). In this case there is a migration of the hydrogen atom to the heterocyclic fragment with localization of a positive charge on the latter.



In the acetylation of compound I, 3-methyl-2-phenyl-5-(3-methyl-2-phenyl-1-acetyl-3,4-dehydropiperidyl-6)pyridine (II) was obtained. Effects associated with inhibited rotation around the amide bond are observed in its PMR spectrum. The PMR spectrum (250 MHz) is deuterochloroform at room temperature is extremely complex, substantially broadened, and is evidence of the presence of two rotamers: two broadened signals of approximately the same intensity, from the α-proton of the pyridine ring (8.40 and 8.56 ppm) are observed. In the case of heating in DMSO-D_6 there is a further broadening and merging of the signals: the α-proton 8.2 ppm, $COCH_3$ 1.80 ppm (at 100°C).

The N-phenylcarbamoyl derivative III was produced from compound I and phenyl isocyanate.

In the braodening of compound I in glacial acetic acid, we obtained perbromide-3-methyl-2-phenyl-5-(3,4-dibromo-3-methyl-2-phenylpiperidyl-6)pyridine (IV), a yellow crystalline substance that decomposes upon melting, which is characteristic of compounds of this type. After the perbromide IV was heated in acetone (removal of bromine bound to the nitrogen atom of the pyridine ring) and the dibromide V formed in this case was passed through a layer of aluminum oxide, a substantial portion of the dibromide underwent dehydrobromination (aromatization of the second nitrogen-containing ring). Evidently the influence of the presence of two basic nitrogen atoms in the β-pyridyl-α-piperidine molecule, as well as the ability of aluminum oxide to decompose salts of pyridine bases, on the dehydrobromination reaction must be taken into consideration.

In conducting this experiment we isolated the dibromide V and 3-methyl-2-phenyl-5-(3-methyl-2-phenylpyridyl-6)pyridine (VI). The dipyridyl (VI) was also produced directly from compound I by its treatment with chloranil.

An analysis of the PMR spectrum of the dibromide V at 250 MHz using double resonance showed that the piperidine ring in it has a "chair" conformation with an axial orientation

of the bromine atoms and an equatorial orientation of the remaining substitutents. Thus, the dibromide V is 3-methyl-2-phenyl-5-(3a,4a-dibromo-3e-methyl-2e-phenylpiperidyl-6e)pyridine (V). The structure of the dipyridyl VI was also confirmed by the data of an analysis of its PMR spectrum.

EXPERIMENTAL

The PMR spectra of 5-10% solutions of the compounds I-III, V, and VI in DMSO-D_6, C_6D_6, and deuterochloroform were obtained on a Fourier spectrometer with WM-250 superconducting solenoid (250 MHz). The ^{13}C NMR spectra of a solution of compound I in deuteromethanol were recorded on a WH-360 spectrometer at the frequency 90.5 MHz. For an assignment of the signals in the spectra we used the methods of double resonance and the data of the proton-acoupled ^{13}C NMR spectra. The chemical shifts were measured relative to TMS as the internal standard. The mass spectra were recorded on an LKB-9000 mass spectrometer with direct introduction of the sample into the source. The ionizing voltage was 70 V, temperature of admission 35-40°C. The precise masses were determined on an MS-30 instrument. Chromatographic isolation of the substance was performed on aluminum oxide of II degree of activity.

3-Methyl-2-phenylpyridine and 3-Methyl-2-phenyl-5-(3-methyl-2-phenyl-3,4-dehydropiperidyl-6)pyridine (I). To phenyllithium obtained from 110 g (0.7 mole) bromobenzene and 10 g (1.43 mmoles) lithium in 350 ml of absolute ether at 8-10°C, 65 g (0.7 mole) of β-picoline was added dropwise over a period of 1 h. The reaction mixture was mixed vigorously at room temperature for 3 h and then boiled for 30 min. Then 350 ml of water was gradually added with mixing. The ether layer was removed, and the aqueous layer extracted with three 100-ml portions of ether. The organic layer and the ether extracts were combined and dried with magnesium sulfate. After the ether was distilled off, the residue was redistilled under vacuum: fraction 1: bp 45-60°C (10 mm), 11 g, n_D^{18} 1.5110 — β-picoline; fraction 2: bp 131.5-133°C (10 mm), 31 g, n_D^{18} 1.5781 — 3-methyl-2-phenylpyridine.

From the still residue (72 g), by crystallization from acetone and then from a mixture of heptane with chloroform (5:1) we isolated: 17 g (17%) of compound I, colorless crystals, mp 137-140°C (from heptane). Found: C 84.9; H 6.9; N 7.8%; M^+ 340. $C_{21}H_{24}N_2$. Calculated: C 84.7; H 7.1; N 8.2%; M 340.

Dihydrochloride of the base I: mp 174-176°C (from acetone). Found: N 6.1; Cl 16.8%. $C_{24}H_{24}N_2 \cdot 2HCl$. Calculated: N 6.7; Cl 17.1%.

3-Methyl-2-phenyl-5-(3-methyl-2-phenyl-1-acetyl-3,4-dehydropiperidyl-6)pyridine (II). A solution of 0.4 g (1.17 mmoles) of compound I and 2 ml of acetic anhydride in 10 ml of benzene was boiled for 15 min. After the benzene and excess anhydride were distilled off, the residue was dissolved in a mixture of 10 ml of benzene and 20 ml of hexane, and exposed for 12 h. The precipitate formed was filtered off and washed on the filter with a mixture of the same solvents. Yield 0.41 g (92%) of the acetyl derivative II, colorless crystals, mp 181-182°C (from a benzene—hexane mixture, 1:2). Found: C 81.4; H 6.8; N 7.5%; M^+ 382. $C_{26}H_{26}N_2O$. Calculated: C 81.7; H 6.8; N 7.3%; M 382.

3-Methyl-2-phenyl-5-(3-methyl-2-phenyl-1-phenylcarbamoyl-3,4-dehydropiperidyl-6)pyridine (III). To a solution of 1.8 g (5.29 mmoles) of compound I in 40 ml of benzene, a solution of 3 g (25.3 mmoles) of phenylisocyanate in 10 ml of dry ether was added at 60°C, and the reaction mixture was exposed at this temperature for 5 min. The residue after the solvents were distilled off was recrystallized from a benzene—heptane mixture, 1:4. Yield 2.4 g (99%) of the carbamoyl derivative III, colorless crystals, mp 190-192°C. Found: C 81.0; H 6.4; N 9.1%. $C_{31}H_{29}N_3O$. Calculated: C 81.0; H 6.3; N 9.1%.

Perbromide of 3-Methyl-2-phenyl-5-(3,4-dibromo-3-methyl-2-phenylpiperidyl-6)pyridine (IV). To a solution of 1.5 g (4.4 mmoles) of compound I in 20 ml of glacial acetic acid, a solution of 1 g (12.5 mmoles) of bromine and 10 ml of acetic acid was added gradually with mixing. The yellow precipitate formed was filtered off, washed on the filter with glacial acetic acid, and exposed over phosphorus pentoxide under vacuum of 2 mm. Yield 22.2 g (77%) of the perbromide IV, mp 85-90°C (with dec.). Found: N 4.4%. $C_{24}H_{24}Br_4N_2$. Calculated: N 4.2%.

3-Methyl-2-phenyl-5-(3,4-dibromo-3-methyl-2-phenylpiperidyl-6)pyridine (V) and 3-Methyl-2-phenyl-5-(3-methyl-2-phenylpyridyl-6)pyridine (VI). A. We boiled 2.5 g (3.8 mmoles) of the perbromide IV in 50 ml of acetone for 5 min. The acetone was distilled off, the residue dissolved in 15 ml of ethanol and applied on a chromatographic column with aluminum oxide

(h = 15 cm, d = 3 cm). Substantial spontaneous heating was observed in the zone of contact of the solution with aluminum oxide. It was eluted with a 1:3 mixture of ethyl acetate and hexane. As the solution of the substances advanced along the column, heating of the adsorbent was also observed. From the eluent we isolated 0.48 g (~38%) of the dipyridyl (VI), colorless crystals, mp 110-110.5°C (from heptane). PMR spectrum (C_6D_6, 250 MHz): 8.32 (d, 4-H); 9.35 (d, 6-H); 7.04 (d, 4'-H); 7.0 (d, 5'-H); 2.06 (n.s, 3-CH_3); 2.09 (n.s, 3'-CH_3); 7.1-7.3 ppm; (m, 10H, phenyl protons); J: 2.2 (4-H, 6-H); 8.0 (4'-H, 5'-H); 0.8 (4-H, 3-CH_3); 0.7 Hz (4'-H, 3'-CH_3). Found: C 85.8; H 6.0; N 8.3%; M^+ 336. $C_{24}H_{20}N_2$. Calculated: C 85.7; H 6.0; N 8.3%; M 336.

After isolation of the dipyridyl VI, 0.23 g (12%) of the dibromide V was eluted; colorless crystals, which begin to decompose at 180°C. PMR spectrum ($CDCl_3$, 250 MHz): 1.97 (s, NH); 2.37 (s, 3-CH_3); 1.80 (s, 3'-CH_3); 7.72 (d, 4-H); 8.54 (d, 6-H); 4.23 (n.s, 2'H); 4.93 (t, 4'-H); 4.57 (d.d, 6'-H); 2.55 (m, 5'-H_a); 2.22 ppm (m, 5'-H_e); J: 2.7 (4'-H, 5'-H_e); 3.3 (4'-H, 5'-H_a); 2.7 (5'-H_e, 6'-H); 11.5 (5'-H_a, 6'-H); —14.5 Hz (5'-H_a, 5'-H_e). Found: N 5.3; Br 32.2%. $C_{24}H_{24}Br_2N_2$. Calculated: N 5.6; Br 32.0%.

B. We boiled 3 g (8.82 mmoles) of the piperidylpyridine I and 4.5 g (18.44 mmoles) chloranil in 150 ml of benzene with vigorous mixing for 10 h. Then the benzene was distilled off. 15 ml of chloroform was added to the residue, undissolved crystals were filtered off, the mother liquor applied on a chromatographic column with aluminum oxide, (300 g, h = 25 cm, d = 3 cm), and eluted with ether. After the ether was distilled off, the residue (2.3 g) was recrystallized from heptane, yielding 2.1 g (71%) of compound VI, mp 110-110.5°C.

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MECHANISM OF THE ANTIOXIDANT ACTION OF 2,6-DIMETHYL-3,5-DIMETHOXYCARBONYL-4-(2-NITROPHENYL)1,4-DIHYDROPYRIDINE

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A comparison of data on the kinetics of the accumulation of peroxides and the ESR spectra in the case of inhibition of the autooxidation of methyl oleate by 2,6-dimethyl-3,5-dimethoxycarbonyl-4-(2-nitrophenyl)1,4-dihydropyridine (I) established that the antioxidant action of the latter is exerted by the formation of a nitroxyl radical. This radical is produced analogously to the well-known scheme from 2,6-dimethyl-3,5-dimethoxycarbonyl-4-(2-nitrosophenyl)pyridine, which is generated in the reaction medium from I and methyl oleate.

We found [1] that 4-(2'-nitrophenyl)-1,4-dihydropyridines possess antioxidant activity that significantly exceeds the activity of other dihydropyridines and is specifically characteristic only of the o-nitrophenyl derivatives. Such antioxidant activity of these compounds was rather unexpected, since it is usually considered that it is possessed by compounds with extremely pronounced hydrogen donor or electron donor properties or compounds that are stable radicals. Moreover, up to this time it had been observed that the activity of derivatives of 1,4-dihydropyridine, as a rule, was either substantially decreased or disappeared

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