CHEMISTRY OF HETEROCYCLIC N-OXIDES AND RELATED COMPOUNDS

I. SYNTHESIS OF ANABASINE AND ISONICOTEINE N-OXIDES

Yu. V. Kurbatov, Sh. V. Abdullaev,
A. S. Kurbatova, O. S. Otroshchenko,
and A. S. Sadykov

UDC 547.828 07:543.422.4.6

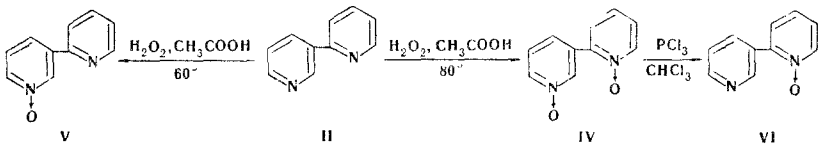
Isonicoteine N-oxide and N'-oxide were synthesized. A preparative method for the synthesis of anabasine Py-N-oxide is proposed.

It is known [1] that the introduction of an N-oxide group into the molecules of nitrogen heterocycles increases the reactivities of the latter. Moreover, a possibility opens up for the directed synthesis of physiologically active substances. The usefulness of such syntheses also consists in the fact that some N-oxides [2] prove to be less toxic than the corresponding bases.

In the present research we have obtained the N-oxides of the alkaloids anabasine (I) and isonicoteine (2,3'-dipyridyl) (II) for use as starting materials for the synthesis of new pharmacologically active substances and for the study of their chemical properties. Anabasine Py-N-oxide (III) cannot be obtained by a direct path [3, 4]. When I is oxidized, the piperidine ring opens to form δ-oximino-δ-(3-pyridyl)valeric acid or its N-oxide. It was later reported [5] that III had been synthesized by prior protection of the piperidine ring of anabasine with a benzoyl group.

In the present study we also noted the fundamental possibility of the synthesis of III through an N-acyl derivative. We used this reaction for the development of a preparative method for the synthesis of anabasine Py-N-oxides. The structure of III was confirmed by reductive elimination of the N-oxide oxygen by means of zinc dust and acetic acid.

The N-oxides of isonicoteine were synthesized by a combination of oxidative and reductive methods. Isonicoteine N,N'-dioxide (IV) was obtained by prolonged oxidation in the presence of a large excess of oxidizing agent at 80°C [6]. Isonicoteine N'-oxide was obtained by a similar method but under milder conditions (brief heating at 60° with a small excess of oxidizing agent). The isomeric isonicoteine N-oxide (VI) was synthesized by selective reduction of IV with phosphorus trichloride:



V II IV VI

The structures of V and VI were proved on the basis of the UV, IR, and PMR spectra. The character of the electronic spectra (Fig. 1) indicates the presence of the isonicoteine skeleton in V and VI [7]. The IR spectra of the investigated N-oxides contain absorption bands at 1255-1300 cm^{-1} (1310 cm^{-1} for V and 1250 cm^{-1} for VI), which characterize the stretching vibrations of the N→O bond [8]. The position of the signals of the protons of the β-substituted ring has changed in the PMR spectrum (Table 1) of 2,3'-dipyridyl N'-oxide (V) as compared with the spectrum of 2,3'-dipyridyl, while the shifts of the protons of the α-sub-

A. Navoi Samarkand State University. V. I. Lenin Tashkent State University. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 378-380, March, 1973. Original article submitted January 5, 1972.

TABLE 1. Parameters of the PMR Spectra of 2,3'-Dipyridyl N-Oxides

Compound	δ, ppm								J, Hz					
	3-H	4-H	5-H	6-H	2'-H	4'-H	5'-H	6'-H	$J_{6,4}$	$J_{6,5}$	$J_{2',4'}$	$J_{4',5'}$	$J_{4',6'}$	$J_{5',6'}$
V	7,9—7,7	7,92	7,46	8,70	8,82	7,9—7,7	7,45	8,21	1,6	4,9	1,5	—	1,2	6,2
VI	7,6	—	7,3	8,29	8,95	8,22	7,6—7,3	8,74	1,4	4,0	1,9	2,5	1,3	5,1

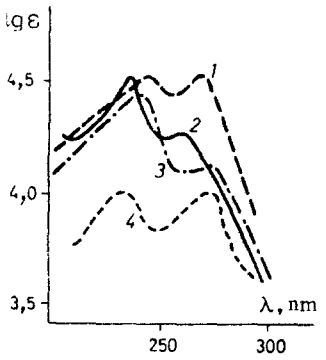


Fig. 1. UV spectra (in ethanol): 1) 2,3'-dipyridyl N'-oxide; 2) 2,3'-dipyridyl N,N'-dioxide; 3) 2,3'-dipyridyl N-oxide; 4) 2,3'-dipyridyl.

stituted ring are practically unchanged; this indicates that the N-oxide oxygen is in the β ring. The positions of the signals of the protons of the α ring are changed in the spectrum of 2,3'-dipyridyl N-oxide (VI); except for the ortho protons [2-4], the signals of the protons of the β ring remain practically unshifted; this indicates that the N-oxide group is in the α-substituted ring.

EXPERIMENTAL

The UV spectra were recorded with an SF-4A spectrometer. The IR spectra were recorded with a UR-10 spectrophotometer. The PMR spectra of acetonitrile solutions were recorded with a Hitachi H-60' spectrometer. The course of the reactions was monitored by paper chromatography with a butanol—acetic acid—water system (50:7:14) (system A) and by means of thin-layer chromatography (TLC) on activity-II aluminum oxide with a benzene—acetone system (3:2) (system B).

N-Acetylanabasine Py-N-Oxide. A mixture of 56 g (0.28 mole) of freshly distilled N-acetylanabasine [9], 160 ml of glacial acetic acid, and 45 ml (0.4 mole) of 30% hydrogen peroxide was heated at 80-84° for 10 h, after which the same amount of hydrogen peroxide and acetic acid were added, and the mixture was heated for another 15 h. The excess reagents were removed by vacuum distillation at 15-16 mm, and water was added to the residue and then removed by vacuum distillation. The residual mixture was dissolved in 50 ml of water, and the solution was made slightly alkaline with potassium carbonate and extracted initially with benzene to remove the unchanged N-acetylanabasine and then with chloroform. The solvent was removed by distillation, and absolute alcohol (twice, with 30-ml portions) was added to the residue and then removed by vacuum distillation. N-Acetylanabasine N-oxide [44.1 g (73%)] was obtained as a slightly colored uncrystallizable vitreous mass. The Py-N-oxide of N-acetylanabasine was hygroscopic and quite soluble in water, alcohols, acetone, and dioxane and had R_f 0.72 (system A).

Anabasine Py-N-Oxide Dihydrochloride. A mixture of 30 g (0.14 mole) of N-acetylanabasine Py-N-oxide and 400 ml of hydrochloric acid (sp. gr. 1.17) was refluxed for 17 h, after which the excess hydrochloric acid was removed by distillation, and the residue was treated with water (five 50-ml portions) with subsequent removal of the water each time by vacuum distillation. The dihydrochloride was then washed with acetone to give 34 g (~100%) of a product with mp 197-200° (dec.) [5] and R_f 0.26 (system A).

Anabasine Py-N-Oxide (III). A solution of 19.8 g (0.075 mole) of anabasine Py-N-oxide dihydrochloride in the minimum amount of water was made alkaline with sodium carbonate and evaporated to dryness. The residue was extracted with absolute benzene to give 10.1-11.0 g (71-77%) of hygroscopic crystals with mp 130-131° (from benzene) (mp 115-117° [5]) and R_f 0.32 (system A).

Reduction of Anabasine Py-N-Oxide. Equivalent amounts of III, zinc dust, and excess glacial acetic acid were refluxed until the zinc dissolved. The mixture was then made alkaline with sodium hydroxide, and the precipitated zinc hydroxide was removed by filtration. The filtrate was extracted with ether, and the ether was removed by distillation to give anabasine with R_f 0.54 (system A). The picrate had mp 203-205° (from water). No melting point depression was observed for a mixture of this picrate with the picrate of anabasine.

Isonicoteine N'-Oxide (V). A mixture of 7.8 g (0.05 mole) of isonicoteine [10], 175 ml of glacial acetic acid, and 11 ml (0.095 mole) of 30% hydrogen peroxide was heated at 60° for 4 h. The unchanged hydrogen peroxide and acetic acid were removed by vacuum distillation (15-16 mm). Water was then added to the

residue and removed by distillation. The residue was dried and treated with butyl alcohol. The insoluble material [1.4 g (10%)] was IV with mp 236-238° (from alcohol). The butyl alcohol solution was evaporated to dryness, and the residue was dissolved in water. The solution was made alkaline with sodium carbonate and extracted with ether. The usual workup of the ether solution gave 1.08 g (14%) of unchanged II. The picrate had mp 153-154° (from water).

The aqueous mother liquor was evaporated to dryness and extracted with benzene in a Soxhlet apparatus. The solvent was removed by distillation, and the residue was purified further by extraction with hot absolute ether to give 1.13 g (13%) of white needles of V [mp 52-54° (from ether), R_f 0.09 (system B)] that deliquesced rapidly in air and were soluble in most organic solvents. Found: C 69.6; H 4.3; N 16.0%. $C_{10}H_8N_2O$. Calculated: C 69.8; H 4.6; N 16.2%. The picrate had mp 114-116° (from water).

Isonicoteine N-Oxide (VI). A 0.45-ml (5 mmole) sample of phosphorus trichloride was added with stirring at 0° to a suspension of 1 g (5 mmole) of IV in 25 ml of dry chloroform, and the mixture was allowed to stand at room temperature for 14 h. The solvent was removed by distillation, and the residue was dissolved in 2% hydrochloric acid. The acid solution was made alkaline with potassium carbonate and extracted exhaustively with ether. The ether solution was worked up in the usual manner to give 0.3 g (35%) of isonicoteine. The picrate had mp 153-154° (from water). No melting point depression was observed for a mixture of this picrate and the picrate of II. The mother liquor was evaporated to dryness, and the residue was dried and extracted with hot absolute ether to give 0.21 g (22%) of N-oxide VI as a grayish crystalline powder that was quite soluble in most organic solvents and water and had mp 130-132° (from ether) and R_f 0.1 (system B). Found: C 69.7; H 4.5; N 15.8%. $C_{10}H_8N_2O$. Calculated: C 69.8; H 4.6; N 16.2%.

The residue from the isolation of VI was extracted with hot chloroform to give 0.23 g (23%) of unchanged IV with mp 236-238° (from alcohol).

Isonicoteine (II) from Isonicoteine N,N'-Dioxide (IV). A 1-ml (10 mmole) sample of phosphorus trichloride was added with stirring at room temperature to a suspension of 1 g (5 mmole) of IV in 25 ml of dry chloroform. After 19 h, workup of the reaction mixture by the method described in the preceding experiment gave 0.77 g (92%) of isonicoteine. The picrate had mp 153-154° (from water). No melting point depression was observed for a mixture of this picrate and picrate of II.

The authors thank V. B. Leont'ev for his discussion of the UV, IR, and PMR spectra.

LITERATURE CITED

1. D. V. Ioffe and L. S. Éfros, Usp. Khim., 30, 1325 (1961).
2. G. S. Arutyunyan and M. D. Mashkovskii, Farmakol. i Toksikol., 534 (1961).
3. V. K. Zvorykina, F. D. Alashev, and Ya. L. Gol'dfarb, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk, 788 (1958).
4. Ya. L. Gol'farb, F. D. Alashev, and V. K. Zvorykina, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk, 2209 (1962).
5. Ya. L. Gol'dfarb, F. D. Alashev, and V. K. Zvorykina, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk, 2241 (1964).
6. Yu. V. Kurbatov, O. S. Otroshchenko, A. S. Sadykov, and Sh. V. Abdullaev, Nauchnye Trudy Samarkandsk. Gos. Univ., 1, 167, 43 (1969).
7. P. Krumholz, J. Am. Chem. Soc., 73, 3487 (1951).
8. A. R. Katritzky and A. P. Ambler, in: Physical Methods in Heterocyclic Chemistry, A. R. Katritzky (editor), Academic Press (1963).
9. O. S. Otroshchenko and A. S. Sadykov, Zh. Obshch. Khim., 24, 1884 (1954).
10. A. S. Sadykov, Byul. Akad. Nauk UzbSSR, No. 8 (1946).