Chemistry of Heterocyclic Compounds, Vol. 34, No. 5, 1998

SYNTHESIS OF NITRO DERIVATIVES OF 2-ALKYLAMINO-4-NITROPICOLINES AND THEIR N-OXIDES

J. Lorenc and A. Puszko

2-Alkylamino-4-nitro-3- or -5-methylpyridines, 2-alkylnitramino-4-nitro-3- or -5-methylpyridines, and their N-oxides were synthesized in good yields. Some properties of the products are reported.

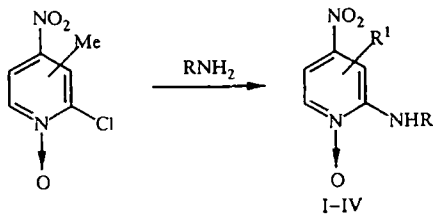
Pyridine N-oxides show a considerable physiological activity and they can find various applications (e.g., as germicides, fungicides, insecticides, additives to detergents and soaps, additives to novel paints, as anticorrosive agents [1, 2]). Pyridine N-oxides form complexes with various metals, which play an important role as catalysts for transacylation [3] and nucleophilic substitution [4]. In addition, it should be mentioned that these compounds with high molecular hyperpolarizability β possess a high electron-donor (push) and electron-acceptor (pull) group in such position that there occurs an intramolecular charge-transfer. Among plenty of organic molecules, 2-N-substituted amino-5-nitropyridine N-oxides attract attention [7] because of their promising nonlinear optical properties in the crystalline state.

Wide applications of pyridine N-oxide derivatives prompted us to study 2-N-substituted 4-nitropicoline N-oxides. The most probable reaction of these compounds is the nucleophilic replacement of the nitro group, since this group is very susceptible to attack by nucleophilic reagents. If any reaction of this type plays a dominant role in fungicidal action, the order of antifungal activity must be parallel with the reactivity index of the attached position [8]. Okabayashi's experiment showed that the nitro group of 4-nitropyridine N-oxide was easily substituted by the SH group of cysteine and the substituted compounds lost their antifungal activity [8]. Bearing this fact in mind, together with theoretical results obtained by the present authors, it may be possible to correlate the ease of nucleophilic substitution at the carbon atom, to which the nitro group is attached, with the antifungal activity of nitro-substituted pyridine N-oxides. It is known that the nitro group situated in pyridine ring gives antifungal properties to the compounds [9]. The compounds studied are also interesting with regard to accumulation and mutual interaction of nitro substituents in a molecule.

Within the extensive investigations on the reactivity and structure of pyridine N-oxides performed in our Department, it was interesting to examine the spectroscopic properties of the studied compounds and to compare them with previous results [2, 7, 9-18]. The present paper deals with the synthesis of the above-mentioned compounds and with determination of their chemical structure.

The halogen atom in 2- and 4-halopyridine N-oxides can be displaced by amines to give the corresponding amino-substituted N-oxides [19]. A route to 2-alkylamino-4-nitropicoline N-oxides is illustrated by transformations of 2-chloro-4-nitropicoline N-oxides, which were prepared [20], from 2-chloropicolines. 2-Chloro-4-nitropicoline N-oxides react with primary amines (molar ratio 1:2) under reflux in methanol to give the 2-alkylamino derivatives (I-IV, Table 1) in good yields.

N-Deoxygenation can be performed by phosphorous trichloride in chloroform and occurs on brief heating to give 2-alkylamino-4-nitropicolines (V-VIII).

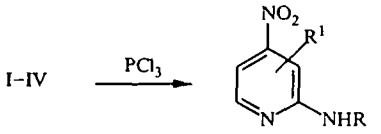


I–IV

I, III R = Me; II, IV R = Et; I, II R^1 = 3-Me; III, IV R^1 = 5-Me

Department of Organic Chemistry, University of Economics, PL-53-342 Wroclaw, Poland. Published in Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 652-656, May, 1998. Original article submitted August 26, 1997.

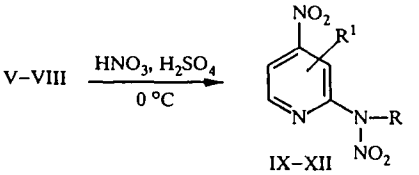
0009-3122/98/3405-0575$20.00



V–VIII

V, VII R = Me; VI, VIII R = Et; V, VI R^1 = 3-Me; VII, VIII R^1 = 5-Me

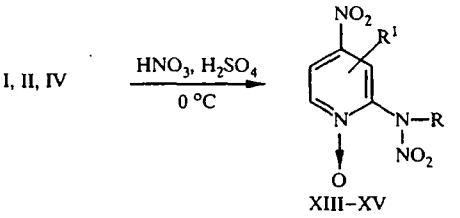
When 2-alkylamino-4-nitropicolines V-VIII react with a mixture of nitric and sulfuric acid nitramino derivatives (IX-XII) are formed.



IX–XII

IX,XI R = Me; X, XII R = Et; IX, X R^1 = 3-Me; XI, XII R^1 = 5-Me

The 2-alkylamino-4-nitropicoline N-oxides I, II, IV behave on nitration in the same way and give nitramines XIII-XV. 2-Methylnitramino-5-methyl-4-nitropyridine N-oxide could not be isolated in analytically pure state.



XIII–XV

XIII R = Me; XIV, XV R = Et; XIII, XIV R^1 = 3-Me; XV R^1 = 5-Me

The IR spectra of pyridine N-oxide are characterized by two strong absorption bands within the region 1200-1300 cm^{-1} (1265 cm^{-1} in CS_2). The position and nature of a substituent in the pyridine ring influence the stretching frequency of the N-oxide group. In 2- and 4-picoline N-oxides the frequency of stretching vibration of the N → O group is 5 cm^{-1} lower than in pyridine N-oxide, which results from the electron-releasing properties of the methyl group [19]. The IR spectra of monosubstituted pyridine N-oxides were discussed earlier by Katritzky and Lagowski [20]. The N → O stretching absorption of pyridine N-oxides occurs at a higher frequency than that in aliphatic N-oxides, which has been attributed to back donation of the N-oxide group. The electron-acceptor substituents in position 4 favor the backdonating effect of N → O function. The ν_{NO} values of 2,4-dihalopicoline N-oxides and 2-halo-4-nitropicoline N-oxides were reported previously [11]. The frequency of stretching vibrations of the N-oxide group is lower in 2,4-dihalopicoline N-oxides than in 2-halo-4-nitropicoline N-oxides and increases together with the increase of electron-withdrawing properties of substituents. The displacement of chlorine by methylamino group in position 2 results in absorption shift toward longer wavelengths (1291 → 1220 cm^{-1}) in the case of 3-methyl derivative. The IR spectra of 2-alkylamino-5-methyl-4-nitropyridine N-oxides are characterized by the longer stretching frequency ν_{NO} (1300 cm^{-1}) in comparison to 3-methyl analogs. This fact can be explained by the complementary interaction (resonance effect) between the 2-alkylamino group and the 5-methyl group and the effect of hyperconjugation. The introduction of the nitro group instead of a hydrogen atom causes an increase in the stretching frequency of the N-oxide group due to electron-acceptor ability of the nitramino group, and shifts the stretching frequency of $N-CH_3$ and $N-NO_2$ towards lower values (Table 1). This supports the partial double-bond character of the N–O bond. The N-oxide function can play the double role of π-donor and π-electron acceptor, which results in an enhanced effect of both electron-withdrawing and -donating substituents on the electronic structure [13-18] and spectroscopic properties, and therefore linear free energy correlations must take into account this dual mesomeric effect [1].

TABLE 1. Properties, Analysis, and IR Spectra of 2-Alkylamino-4-nitropicolines, 2-Alkylnitramino-4-nitropicolines, and Their N-Oxides

N	Compound	M. p., °C	Found, % / Calculated, %			Formula	IR, cm^{-1}	Yield, % Cryst. from*
			C	H	N			
I	2-Methylamino-3-methyl-4-nitropyridine N-oxide	100	46,17 / 45,90	4,79 / 4,95	23,21 / 22,94	$C_7H_9N_3O_3$	1080 N–CH3; 1380, 1440 CH_3 ring; 1340, 1540 NO_2; 1220 NO; 3280 NH	71 W
II	2-Ethylamino-3-methyl-4-nitropyridine N-oxide	99	49,06 / 48,73	5,41 / 5,62	21,53 / 21,31	$C_8H_{11}N_3O_3$	1125 N–C_2H_5; 1380, 1420 CH_3 ring; 1340, 1535 NO_2; 1220 NO; 3240 NH	67 W
III	2-Methylamino-5-methyl-4-nitropyridine N-oxide	177	45,78 / 45,90	4,81 / 4,95	23,17 / 22,94	$C_7H_9N_3O_3$	1070 N–CH_3; 1370, 1450 CH_3; 1320, 1500 NO_2; 1300 NO; 3260 NH	76 W
IV	2-Ethylamino-5-methyl-4-nitropyridine N-oxide	105	48,91 / 48,73	5,75 / 5,62	21,42 / 21,31	$C_8H_{11}N_3O_3$	1045 N–CH3; 1370, 1440 CH_3 ring; 1350, 1500 NO_2; 1300 NO; 3340 NH	72 W
V	2-Methylamino-3-methyl-4-nitropyridine	80	50,71 / 50,30	5,38 / 5,43	25,29 / 25,14	$C_7H_9N_3O_2$	1030 N–CH_3; 1360, 1380 d NO_2; 1520 NO_2; 1430, 1470 CH_3 ring; 3440 NH	65 W
VI	2-Ethylamino-3-methyl-4-nitropyridine	—	53,38 / 53,03	6,31 / 6,12	23,04 / 23,19	$C_8H_{11}N_3O_2$	1035 N–C_2H_5; 1350, 1370 d NO_2; 1530, 1580 d NO_2; 3460 NH	71
VII	2-Methylamino-5-methyl-4-nitropyridine	102	50,06 / 50,30	5,26 / 5,43	25,15 / 25,14	$C_7H_9N_3O_2$	1090 N–CH_3; 1240 NH; 1350, 1430 CH_3 ring; 1380, 1390 d NO_2; 1520, 1550 d NO_2; 3262 NH	68 W + A
VIII	2-Ethylamino-5-methyl-4-nitropyridine	84	53,13 / 53,03	6,10 / 6,12	22,97 / 23,19	$C_8H_{11}N_3O_2$	1005 N–C_2H_5; 1235 NH; 1355, 1375 d NO_2; 1520, 1550 d NO_2; 1410, 1460 CH_3 ring; 3269 NH	91 W + A
IX	2-Methylnitramino-3-methyl-4-nitropyridine	43	39,32 / 39,63	3,64 / 3,81	26,05 / 26,41	$C_7H_8N_4O_4$	1030 N–CH_3; 1280, 1500 NO_2; 1280 NO_2(N–NO_2); 1400, 1430 CH_3 ring	63 A + W
X	2-Ethylnitramino-3-methyl-4-nitropyridine	—	42,23 / 42,48	4,38 / 4,45	24,95 / 24,77	$C_8H_{10}N_4O_4$	1040 N–$C2H_5$; 1265, 1540 NO_2; 1290 NO_2(NNO_2); 1445, 1385 CH_3; 1390, 1430 CH_3(NC_2H_5)	50
XI	2-Methylnitramino-5-methyl-4-nitropyridine	46	39,81 / 39,63	3,90 / 3,81	26,24 / 26,41	$C_7H_8N_4O_4$	1070 N–CH_3; 1285, 1540 NO_2; 1420, 1440 CH_3 ring; 1385, 1480 CH_3(N–CH_3)	95 A + W
XII	2-Ethylnitramino-5-methyl-4-nitropyridine	—	42,34 / 42,48	4,41 / 4,45	24,81 / 24,77	$C_8H_{10}N_4O_4$	995 N–C_2H_5; 1380, 1475 CH_3 ring; 1270, 1575 NO_2 ring; 1360, 1540 NO_2(NNO_2)	92
XIII	2-Methylnitramino-3-methyl-4-nitropyridine N-oxide	144	36,68 / 36,85	3,42 / 3,54	24,33 / 24,56	$C_7H_8N_4O_5$	1015 N–CH_3; 1360, 1525 NO_2(NNO_2); 1320, 1560 NO_2 ring; 1390, 1430 CH_3 ring; 1290 N→O	57 A + W
XIV	2-Ethylnitramino-3-methyl-4-nitropyridine N-oxide	90	39,47 / 39,67	4,06 / 4,16	22,84 / 23,13	$C_8H_{10}N_4O_5$	1020 N–CH_3; 1280, 1555 NO_2 ring; 1350, 1515 NO_2(NNO_2); 1430, 1470 CH_3 ring; 1255, 1470 CH_3(N–CH_3); 1280 N→O	71 A + W
XV	2-Ethylnitramino-5-methyl-4-nitropyridine N-oxide	89	39,71 / 39,67	3,95 / 4,16	22,98 / 23,13	$C_8H_{10}N_4O_5$	1020 N–CH3; 1350, 1515 NO_2(NNO_2); 1300, 1555 NO_2 ring; 1390, 1430 CH_3 ring; 1440, 1480CH_3(N– CH_3); 1280 N→O	28 A + W

EXPERIMENTAL

2-Alkylamino-3- or -5-methyl-4-nitropyridine N-oxides (I-IV). A sample of 5 g of 2-chloro-3-methyl-4-nitropyridine N-oxide and 20 ml of 30% methylamine solution in methanol was refluxed for 5 h. Then reaction mixture was evaporated to dryness. After distilling off methanol and adding water, the precipitate was filtered off and recrystallized from water to give 2-methylamino-3-methyl-4-nitropyridine N-oxide (I). Compounds II-IV were obtained analogously. Their characteristics are given in Table 1.

2-Alkylamino-3- or -5-methyl-4-nitropyridines (V-VIII). A sample of 4 g of 2-methylamino-3-methyl-4-nitropyridine N-oxide was dissolved in 40 ml of chloroform, 8 ml PCl_3, was added, and the mixture was refluxed for 1 h. Then the reaction mixture was evaporated to dryness. After distilling off the chloroform, adding ice, and neutralization with potassium carbonate, the residue was extracted with chloroform. The extract was dried with anhydrous magnesium sulfate, the chloroform was removed, and the residue recrystallized from water to give compound V. Compounds VI-VIII were prepared similarly but the liquid product VI was chromatographed on alumina to give the desired pure product. The characteristics of compounds V-VIII are shown in Table 1.

2-Alkylnitramino-3- or -5-methyl-4-nitropyridines and Their N-oxides (IX-XV). Sulfuric acid (5 g) was added to 2 g of fuming nitric acid (d = 1.52) and then 2 g of 2-alkylamino-3- or -5-methyl-4-nitropyridine was added dropwise, maintaining the temperature at 0°C. After addition of 2-alkylamino-3- or -5-methyl-4-nitropyridine, the reaction mixture was kept at 0°C for one hour and then poured onto 50 g crushed ice and filtered to yield the desired product. The liquid 2-ethyl derivative was extracted with ether. The extract was dried with anhydrous magnesium sulfate, and ether was removed. The product was added on top of an aluminum oxide column; elution with methanol yielded the pure product. The N-oxide derivatives were prepared analogously. All the compounds IX-XV are characterized in Table 1.

REFERENCES

1. A. Albini and S. Pietra, Heterocyclic N-Oxides, CRC Press, Inc. (1991), p. 273.
2. A. Puszko and Z. Talik, Polish J. Chem., **65**, 377 (1991).
3. S. Rubinsztajn and M. Zeldin, Macromolecules, **23**, 4026 (1990).
4. E. Delancy, L. E. Wood, and J. M. Klotz, J. Am. Chem. Soc., **104**, 799 (1982).
5. T. Kondo, F. Akase, M. Kumogin, and R. Ito, Opt. Rev., **2**, 128 (1995).
6. R. W. Munn and S. P. B. Smith, Adv. Mat. Opt. Electron., **1**, 65 (1995).
7. A. Puszko, L. Wasylina, and Z. Pawelka, Monatsh. Chem., **127**, 601 (1996).
8. T. Okabayashi, J. Ferment. Tech., **31**, 373 (1953).
9. A. Puszko, J. Mol. Struct., **344**, 1 (1995).
10. A. Puszko, Magn. Reson. Chem., **30**, 271 (1992).
11. A. Puszko, Pol. J. Chem., **66**, 1615 (1992).
12. A. Puszko, Pol. J. Chem., **66**, 1979 (1992).
13. A. Puszko, J. Crystallogr. Spectrosc. Res., **23**, No. 1, 23 (1993).
14. A. Puszko, Pol. J. Chem., **67**, 2005 (1993).
15. A. Puszko, Pol. J. Chem., **67**, 837 (1993).
16. A. Puszko, Pol. J. Chem., **68**, 657 (1995).
17. A. Puszko, Chem. Pap., **49**, No. 4, 182 (1995).
18. H. Ciurla and A. Puszko, Chem. Heterocycl. Comp., **32**, 1173 (1996).
19. A. R. Katritzky and J. M. Lagowski, Chemistry of the Heterocyclic N-Oxides (Organic Chemistry, A Series of Monographs), Academic Press, New York (1971), p. 599.
20. A. Puszko and Z. Talik, Roczn. Chem., **50**, 2209 (1976).