1,5-NAPHTHYRIDINES AND THEIR N-OXIDES

II.* SYNTHESIS OF SOME 2-CARBONYL DERIVATIVES OF 1,5-NAPHTHYRIDINE AND THEIR N-OXIDES

R. M. Titkova and A. S. Elina

UDC 547.834.2:542.943:543.422.4.25

The oxidation of 2-methyl-1,5-naphthyridine and its di-N-oxide has yielded 1,5-naphthyridine-1-carboxylic acid and its di-N-oxide, and the di-N-oxide of 1,5-naphthyridine-2-carbaldehyde, some derivatives of which have been obtained.

The object of the present investigation was to study the oxidation reactions of 2-methyl-1,5-naphthyridine (I) and its di-N-oxide (II) in order to obtain 1,5-naphthyridine derivatives containing a carbaldehyde or carboxy group in position 2. These compounds could be of interest for biological study.

It was found that when (I) was heated with selenium dioxide in various solvents (toluene, dimethylformamide, pyridine, etc.) the methyl group was oxidized to a carboxy group, but the reaction was accompanied by considerable resinification and the yield of 1,5-naphthyridine-2-carboxylic acid (III) was only 16%; only traces of 1,5-naphthyridine-2-carbaldehyde were found in the reaction mixture. Similar results have been obtained previously in the oxidation of 2-methylpyridine with SeO_2 [2].

When compound (I) was oxidized with $KMnO_4$, one ring was destroyed with the formation of 3-acetylaminopyridine-2-carboxylic acid (IV).

Satisfactory results were obtained in the oxidation of 2-styryl-1,5-naphthyridine (V) with potassium permanganate in acetone; under these conditions, (III) was formed with a yield of 62%.

To obtain (II) we used the N-oxidation of the initial base with perhydrol in the presence of sodium vanadate, which we have used previously with success for the synthesis of the N-oxides of 2-amino- and 2-hydroxy-1,5-naphthyridines [1].

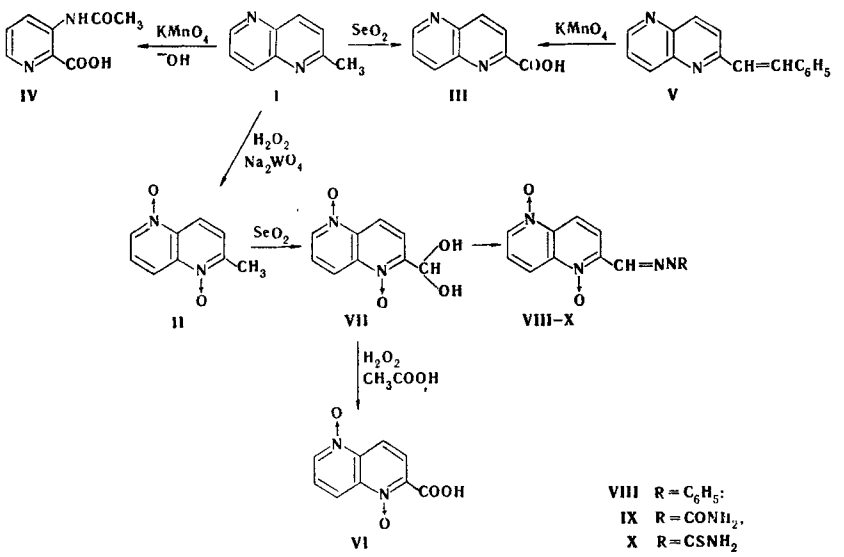
In the reaction of (II) with SeO_2, the CH_3 group was oxidized to a carbaldehyde group. Traces of the di-N-oxide of 1,5-naphthyridine-2-carboxylic acid (VI) were detected in the reaction mixture only chromatographically. The use of dimethylformamide as solvent permitted this reaction to be performed under mild conditions (20-40°C) with the production of the di-N-oxide of 1,5-naphthyridine-2-carbaldehyde in fairly high yield (68%). The aldehyde obtained was characterized by appropriate derivatives (VIII, IX, and X); the IR spectrum of this compound (in the crystalline state) had a strong broad band of associated hydroxyls and a very weak band in the region of the stretching vibrations of the HC=O group. The PMR spectra had a signal corresponding to the methine proton of a $CH(OH)_2$ group (δ 6.5 ppm) and a weak signal (δ 10.5 ppm) which could correspond to the proton of the CH=O group. On the basis of these results, it was concluded that the aldehyde existed predominantly in the hydrated form (VII).

The di-N-oxide of 1,5-naphthyridine-2-carboxylic acid was obtained by oxidizing (VII) with perhydrol in acetic acid (see scheme on following page).

Compounds (V), (VII), and (VIII) possessed weak activity in vitro in relation to the tubercle bacillus and the causative agents of dermatomycosis.

*For Communication I, see [1].

S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow.
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1279-1281, September, 1973. Original article submitted July 31, 1972.



EXPERIMENTAL

Chromatography was performed on paper: for compounds (II) and (VII) in the isoamyl alcohol–6% acetic acid (1 : 1) system, and for the others in the butanol–25% ammonia (1 : 1) system. The spots were revealed in UV light.

The PMR spectra were taken on a JNM-4H-100 instrument at a working frequency of 100 MHz with tert-butanol as internal standard.

1,5-Di-N-oxide of 2-Methyl-1,5-naphthyridine (II). A mixture of 4.5 g (31.2 mmoles) of (I), 24 ml of 30% H_2O_2, and 0.33 g of $Na_2WO_4 \cdot 2H_2O$ was stirred at 40-45°C for 75 h, and then 30 ml of water was added and it was evaporated in vacuum to one-half of its initial volume. The operation was repeated until the unchanged hydrogen peroxide had been decomposed completely, and then the solution was evaporated to dryness. The residue in the flask was triturated with methanol, giving 3.9 g (71%) of (II) with mp 180-181.5°C (decomp.), R_f 0.2 (dark green spot). Found, %: C 61.2; H 4.5; N 16.0. $C_9H_8N_2O_2$. Calculated, %: C 61.3; H 4.6; N 15.9.

1,5-Naphthyridine-2-carboxylic Acid (III). A. As the oxidation proceeded, a solution of 1.4 g (8.87 mmoles) of $KMnO_4$ in 50 ml of acetone was added to a solution of 0.7 g (3 mmoles) of (V) (obtained by the method of Rapoport and Batcho [3]) in 15 ml of acetone at 20-25°C, and then the mixture was stirred for 15 min. The precipitate of MnO_2 was treated with boiling water. The aqueous solution was evaporated in vacuum to a volume of about 6 ml and was acidified with hydrochloric acid to pH 3. The resulting precipitate was extracted with ether to eliminate benzoic acid and was crystallized from acetic acid. This gave 0.32 g (62%) of (III), mp 248-249°C. R_f 0.24 (dark spot). Found, %: C 61.9; H 3.2; N 16.4. $C_9H_6N_2O_2$. Calculated, %: C 62.1; H 3.5; N 16.1. The methyl ester of (III) was obtained by stirring (III) (20-25°C, 48 h) in anhydrous methanol containing 6% of H_2SO_4; mp 144-144.5°C, R_f 0.7 (dark violet spot). Found, %: C 64.0; H 4.3; N 14.8. $C_{10}H_8N_2O_2$. Calculated, %: C 63.8; H 4.3; N 14.9.

B. To 15 ml of boiling pyridine were added 0.5 g (3.47 mmoles) of (I) and 0.4 g (3.6 mmoles) of SeO_2. The reaction mixture was stirred at the boil for 6 h 30 min and was cooled to 20°C. The precipitate that deposited was filtered off, washed with ether, treated with $NaHCO_3$ solution, and filtered from the deposit of Se. The filtrate was acifidied with hydrochloric acid to pH 3, giving 0.1 g (0.575 mmole; 16%) of (III), mp 246-248°C. A mixture with the (III) obtained by method A gave no depression of the melting point.

Oxidation of 2-Methyl-1,5-naphthyridine (I) with $KMnO_4$. At 68-72°C, 3.25 g (20.6 mmoles) of $KMnO_4$ was gradually added to a solution of 0.5 g (3.47 mmoles) of (I) in 20 ml of water, and the mixture was stirred for 15 min and was filtered hot. The precipitate of MnO_2 was treated with boiling water. The main filtrate and the wash waters were extracted with $CHCl_3$. After evaporation, 0.1 g (0.7 mmole) of (I) was recovered from the chloroform solution. The aqueous solution was evaporated in vacuum to a volume of about 6 ml and was acidified with hydrochloric acid to pH 1. This gave 0.2 g (1.11 mole; 40%) of (IV), mp 220-222°C; R_f 0.4 (gray-blue spot). Found, %: C 53.3; H 4.5; N 15.6. $C_8H_8N_2O_3$. Calculated, %: C 53.3; H 4.5; N 15.5. IR spectrum, cm^{-1}: 1680, 1705 (C=O of amide and carboxyl groups), 2600, 2195 (broad, OH of a carboxyl, associated). The decarboxylation of (IV) in biphenyl at 190-200°C gave 3-acetylaminopyridine, mp 133°C [4].

1,5-Di-N-oxide of 1,5-Naphthyridine-2-aldehyde (VII). A suspension of 2 g (11.36 mmoles) of (II), 2 g (18 mmoles) of SeO_2, and 28 ml of dimethylformamide was stirred at 20-25°C for 6-7 days and then at 40°C for 7 h. The precipitate that deposited was filtered off and treated with boiling water (4 × 20 ml), metallic selenium being separated off each time. The aqueous solutions after decoloration with activated carbon were evaporated to one-half of their initial volume and cooled to 5°C, and the (VII) was filtered off (1.6 g, 7.7 mmoles, 68%); yellow crystals with mp 230-231.5°C (from water), R_f 0.36 (green-blue spot). Found, %: N 13.6. $C_9H_8N_2O_4$. Calculated, %: N 13.5. IR spectrum: 3050-3120 cm^{-1} (OH assoc.). PMR spectrum (D_2O): δ 6.5 ppm [$CH(OH)_2$], δ 10.5 ppm (CH=O). Phenylhydrazone of (VII) (VIII): bright orange crystals with mp 243°C (decomp., from ethanol). Found, %: C 64.0; H 4.4; N 19.9. $C_{15}H_{12}N_4O_2$. Calculated, %: C 64.3; H 4.3; N 20.0. Semicarbazone of (VII) (IX): yellow crystals, mp 283°C (decomp., from water). Found, %: N 28.0. $C_{10}H_9N_5O_3$. Calculated, %: N 28.3. Thiosemicarbazone of (VII) (X): yellow-green crystals, mp 263.5°C (decomp., from CH_3COOH). Found, %: N 23.6; S 10.4. $C_{10}H_9N_5O_2S \cdot \frac{1}{2}CH_3COOH$. Calculated, %: N 23.9; S 10.9.

1,5-Di-N-oxide of 1,5-Naphthyridine-2-carboxylic Acid (VI). A suspension of 0.1 g (0.48 mmole) of (VII), 0.38 ml of 30% H_2O_2, and 1.5 ml of CH_3COOH was stirred at 20-25°C for 3 days and was cooled to 10°C, and 0.06 g (0.29 mmole, 60.7%) of (VI) was filtered off with mp 277-277.5°C (from water). Found, %: C 52.0; H 2.9; N 13.7. $C_9H_6N_2O_4$. Calculated, %: C 52.4; H 2.9; N 13.6. IR spectrum: 3090, 1705 cm^{-1} (carboxyl C=O).

LITERATURE CITED

1. R. M. Titkova and A. S. Elina, Khim. Geterotsikl. Soedin., 1237 (1972).
2. D. Jerchel and H. E. Heck, Ann. Chem., 613, 180 (1958).
3. H. Rapoport and A. D. Batcho, J. Org. Chem., 28, 1753 (1963).
4. R. Camps, Arch. Pharm., 240, 355 (1901).