PECULIARITIES OF THE NITRATION OF 2-METHYL-4-METHOXYMETHYL-5-CYANO-6-PYRIDONE IN A MIXTURE OF HNO_3 AND H_2SO_4

N. A. Shul'ga, M. V. Balyakina, and V. I. Gunar

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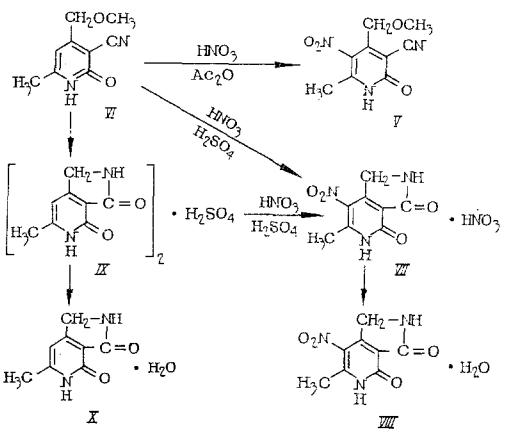
A mixture of nitric and sulfuric acids is successfully used for the production of nitro derivatives of 2- and 4-pyridones [1, 2]. Actually, in the case of nitration of 2-methoxymethyl-4-methyl-5-cyano-6-pyridone (I) and 2,4-dimethyl-5-cyano-6-pyridone (II) with a mixture of HNO_3 and H_2SO_4, we isolated 2-methoxymethyl-3-nitro-4-methyl-5-cyano-6-pyridone (III) and 2,4-dimethyl-3-nitro-5-cyano-6-pyridone (IV) with yields of 56 and 65%, respectively.

In one of the well-known syntheses of vitamin B_6, the main intermediate product, 2-methyl-3-nitro-4-methoxymethyl-5-cyano-6-pyridone (V) is produced by nitration of 2-methyl-4-methoxymethyl-5-cyano-6-pyridone (VI) with nitric acid in acetic anhydride [3]. To replace acetic anhydride by H_2SO_4 for the production of V, we conducted the nitration of VI with a mixture of HNO_3 and H_2SO_4. In this case, instead of the expected V, the nitrate of 6-methyl-7-nitro-1H-pyrrolo[3,4-c]pyridine-3,4(2H, 5H)-dione (VII) was obtained; its neutralization with a solution of sodium hydroxide or sodium bicarbonate leads to 6-methyl-7-nitro-1H-pyrrolo[3, 4-c]pyridine-3,4(2H, 5H)-dione, which was isolated in the form of its hydrate (VIII).



We established that under the action of sulfuric acid on compound VI, the sulfate of bis[6-methyl-1H-pyrrolo[3,4-c]pyridine-3,4(2H, 5H)-dione] (IX) is formed; 6-methyl-1H-pyrrolo-[3,4-c]pyridine-3,4(2H, 5H)-dione was obtained from it in the form of its hydrate (X) by neutralization with a solution of sodium bicarbonate.

In the nitration of IX with a mixture of HNO_3 and H_2SO_4, we isolated compound VII, while V in this mixture could not be converted to VII. Probably the formation of VII begins not with nitration of compound VI at the 3-position but with an interaction of the 5-methoxymethyl and 5-cyano groups with H_2SO_4.

It was shown in the literature [4] on the example of 2-ethoxymethyl-4-methyl-5-cyano-6-pyridone that the activity of the alkoxymethyl and cyano groups depends on the temperature and the H_2SO_4 concentration. Concentrated H_2SO_4 at 5-10°C converts the ethoxymethyl group to a hydroxymethyl group without affecting the cyano group; when the temperature is raised to 100°C there is a hydration of the cyano group with the formation of 2-hydroxymethyl-4-methyl-5-carbamoyl-6-pyridone. When 2-ethoxymethyl-4-methyl-5-cyano-6-pyridone is boiled in dilute H_2SO_4 there is a conversion of both groups; the cyano group is hydrolyzed to a carboxyl group. These conclusions were confirmed in [5, 7], and the possibility of using concentrated HCl instead of dilute H_2SO_4 was demonstrated.

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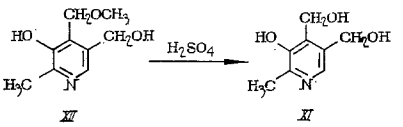
In the nitration of VI with a mixture of HNO_3 and H_2SO_4 we varied the mole ratio of VI to HNO_3, the reaction temperature (from −20°C to 60°C), and the HNO_3 concentration (98 and 57%). However, in all cases only one product was isolated, i.e., compound VII. The optimum conditions for the synthesis of VII were determined: mole ratio of VI to HNO_3 1:5, reaction temperature 18-24°C using fuming NHO_3 and 40-45°C for 57% HNO_3.

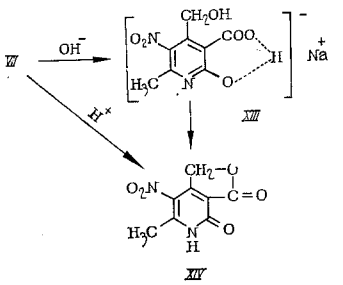
Thus, under the conditions of nitration of I, II, and VI that we are considering, inertness of the 4-methoxymethyl and 5-cyano groups of I and II and a high reactivity of these groups in compound VI are observed: The formation of VII occurs even at −20°C. Therefore, it is quite probable to assume that the lability of the cyano group in compound VI is associated with the presence of a methoxymethyl group in the 4-position of the pyridine ring.

We confirmed the conversion of the 4-methoxymethyl group to a hydroxymethyl group in compound VI in sulfuric acid medium by producing pyridoxine (XI) from its 4'-methyl ester (XII).



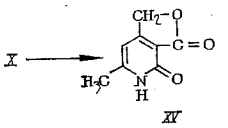
XII XI

It should be noted that the heating of compound VII in alkaline medium leads to opening of the γ-lactam ring. Thus, when VII is boiled in 0.1 N sodium hydroxide, the sodium salt of 2-methyl-3-nitro-4-hydroxymethyl-6-hydroxypyridine-5-carboxylic acid (XIII) is formed but when VII is heated, for example, in water or hydrochloric acid or compounds VIII and XIII in dilute sulfuric acid, 6-methyl-7-nitro-1H-furano[3,4-c]pyridine-3,4-(5H)-dione (XIV) was obtained.



VII XIII XIV

6-Methyl-1H-furano[3,4-c]pyridine-3,4(5H)-dione (XV) was produced analogously from compound X.



X XV

The structures of compounds VII, VIII, IX, X, XIII, XIV, and XV was confirmed by the data of elementary analysis, PMR, IR, and mass spectra.

The mass spectra of compounds VII, VIII, IX, and X are characterized by the presence of a peak of the molecular ion, as well as a number of ions characteristic of fragments of lactams under the action of electron impact [8].

In the PMR spectra of compounds of VII-X and XIII-XV, the signal of the protons of the methylene group is substantially shifted in the weak field direction (6.3-5.2 ppm) in comparison with its position in compound VI (4.5 ppm). Such a shift is evidently due to the formation of γ-lactam (for VII-X) or γ-lactone (for XIV and XV) rings, as well as the influence of the nitro group (for VII and VIII).

In the IR spectra of compounds VIII-X the absorption band of the stretching vibrations of the CO group of the γ-lactam ring lies in the region of 1690 cm^{-1}, characteristic of other lactams (1600-1700 cm^{-1}) [9] and is somewhat shifted in the short-wave direction (1725 cm^{-1}) for VII. The stretching vibrations of the CO group of the γ-lactone ring in compounds XIV and XV induce absorption in the region of 1770 and 1765 cm^{-1}. The broad absorption band

in the region of 2500-3700 cm^{-1} for compounds VII-X is evidence of the presence of associated NH and OH groups. For compounds VII, VIII, and XIV a substantial shift of the absorption band of the antisymmetrical stretching vibrations of the NO_2 group is observed in the region of higher values (1585, 1575, 1583 cm^{-1}) in comparison with its position in compound V (1535 cm^{-1}).

EXPERIMENTAL

The IR spectra were taken on a Perkin-Elmer 180 spectrophotometer (Sweden) the PMR spectra on a Hitachi R-20A instrument (Japan) (60 MHz) with TMS as an internal standard. The mass spectra were obtained on a JMC-OJ instrument at an ionizing voltage of 75 eV. The course of the reaction and purity of the compounds obtained were monitored by thin-layer chromatography on Silufol UV-254 plates in the systems: acetone–dioxane–25% aqueous ammonia, 9:9:2 (A), n-butanol–acetic acid–water, 3:1:1 (B), methanol–benzene–25% aqueous ammonia, 5:5:1 (C), and methanol–benzene, 2:5 (D).

2-Methyl-4-methoxymethyl-5-cyano-6-pyridone (VI). Compound VI was produced by the method of [10], mp 243-244°C.

2-Methoxymethyl-4-methyl-5-cyano-6-pyridone (I). This was isolated from a mixture of the isomers VI and I, produced by the method of [10], by successive recrystallization from solutions of alcohol and acetone (1:1, 3:1) and 15% aqueous alcohol. mp 169-170°C. According to the literature data [11], mp 152°C.

2,4-Dimethyl-5-cyano-6-pyridone (II). This was produced by the method of [12], mp 293-294°C.

2-Methoxymethyl-3-nitro-4-methyl-5-cyano-6-pyridone (III). Compound I (1 g) was dissolved in 5 ml of concentrated H_2SO_4, and 2 ml of fuming HNO_3 in 3 ml of concentrated H_2SO_4 was added at temperatures from −1 to −3°C, mixed for 1.5 h at 18-24°C, and poured out onto finely crushed ice. The precipitate was filtered off, washed with cold water, and dried. Yield 0.7 g (56%), mp 191-192°C (from methanol). According to the literature data [13], mp 191-192°C.

2-4-Dimethyl-3-nitro-5-cyano-6-pyridone (IV). Compound II (2 g) was dissolved in 10 ml of concentrated H_2SO_4, and 4 ml of fuming HNO_3 in 6 ml of concentrated H_2SO_4 was added at temperatures from −1 to −3°C, mixed for 1 h at 18-24°C, poured out onto finely crushed ice, washed with cold water, and dried. Yield 1.7 g (65%), mp 270-272°C (from acetic acid). According to the literature data [12], mp 272-272.6°C.

Nitrate of 6-Methyl-7-nitro-1H-pyrrolo[3,4-c]pyridine-3,4(2H, 5H)-dione (VII). A. To a solution of 2 g compound VI in 10 ml of concentrated H_2SO_4, at temperatures from −1 to −3°C, we added 2.4 ml of fuming HNO_3 in 3.5 ml concentrated H_2SO_4 and mixed for 30 min at 18-24°C. The reaction mixture was poured out into finely crushed ice, the precipitate filtered off, washed with cold water, and dried. Yield 2.15 g (70.5%), mp > 350°C (from methanol), R_f 0.35 (system A); gives a blue color with diphenylamine. PMR spectrum (CF_3COOH), δ, ppm: 3.08 (s, CH_3), 6.30 (s, CH_2), 9.12 and 9.46 (broadened s, 2NH, 34°C). IR spectrum (KBr), ν, cm^{-1}: 1585 (antisymmetrical vibration of NO_2), 1610 (pyridine ring), 1725 (C=O), 2500-3700 (associated NH, OH). Mass spectrum, m/z (relative intensity, %): M^+ 209 (100), 192 (9.5), 167 (11.6), 150 (8.7), 135 (6.3), 81 (7.3), 57 (5.6). Found, %: C 35.21; H 3.04; N 20.39, $C_8H_7N_3O_4 \cdot HNO_3$. Calculated, %: 35.29; H 2.96; N 20.59; M 272.

B. To a solution of 3 g of compound VI in 8.9 ml of concentrated H_2SO_4 at temperatures from −1 to −2°C we added 6.8 ml of 57% HNO_3 in 5.2 ml of concentrated H_2SO_4 then heated at 40-45°C for 3.5 h. The reaction mixture was treated analogously to experiment A. Yield 2.8 g (61%).

C. The reaction was conducted according to experiment A, with the difference that the mixture of acids was added at temperatures from −18 to −20°C and mixed at this temperature for 5 h. Yield 0.8 g (26%).

D. The reaction was conducted according to experiment A with the difference that the reaction mixture was heated for 30 min at 60°C. Yield 0.6 g (20%).

E. The reaction was conducted according to experiment A with the difference that compound IX was used in the reaction instead of VI. Yield 69%.

Hydrate of 6-Methyl-7-nitro-1H-pyrrolo-[3,4-c]pyridine-3,4(2H, 5H)-dione (VIII). A solution of 0.7 g of compound VII in 55 ml of 0.1 N NaOH or $NaHCO_3$ was neutralized with 6% H_2SO_4 to pH 5.0-6.0; the precipitate formed was filtered off, washed with cold water, and dried. Yield 0.4 g (63.5%), mp > 350°C, R_f 0.24 (system B). PMR spectrum (CF_3COOH), δ, ppm: 2.95 (s, CH_3), 6.0 (s, CH_2). IR spectrum (liquid petrolatum), ν, cm^{-1}: 1575 (antisymmetrical vibrations of NO_2), 1645 (C=O), 1692 (C=O), 2500-3680 (associated NH, OH). Mass spectrum, m/z (relative intensity, %): $(M + 1)^+$ 210 (18.7), 193 (36.2), 167 (12.8), 139 (71.5), 81 (31.2), 57 (9.8), 44 (100). Found, %: C 42.63; H 3.95; N 18.44. $C_8H_7N_3O_4 \cdot H_2O$. Calculated, %: C 42.29; H 3.96; N 18.5. M 227.

Sulfate of Bis-[6-methyl-1H-pyrrolo[3,4-c]pyridine-3,4(2H, 5H)-dione (IX). A solution of 2 g of compound VI and 20 ml of concentrated H_2SO_4 was exposed for 48-72 h at 18-20°C, then poured out with cooling into 100 ml of absolute ethanol, and a colorless precipitate formed. Yield 2.6 g (53%), mp 210-211°C (from 20% aqueous acetone), R_f 0.84 (system C). PMR spectrum (CF_3COOH), δ, ppm: 2.57 (s, CH_3), 5.7 (s, CH_2), 6.5 (s, H-3), 8.5 and 8.64 (broad s, 2NH, 34°C). IR spectrum (liquid petrolatum), ν, cm^{-1}: 1560, 1605 (pyridone ring), 1670 (shoulder, C=O, 1695 (C=O), 2200-3300 (associated NH, OH). Mass spectrum, m/z (relative intensity, %): M+ 164 (61.7); 136 (16.8); 109 (28.0); 81 (5.0); 64 (100); 57 (3.9). Found, %: C 45.29; H 4.50; N 13.12; S 7.50. $(C_8H_8N_2O_2)_2 \cdot H_2SO_4$. Calculated, %: C 45.05; H 4.25; N 13.14; S 7.50. M 426.17.

Hydrate of 6-Methyl-1H-pyrrolo[3,4-c]pyridine-3,4(2H, 5H)-dione (X). An aqueous solution of 1 g of compound IX was neutralized with a solution of $NaHCO_3$, the colorless precipitate formed was filtered off, washed with water and dried. Yield 0.66 g (86%), mp > 350°C, R_f 0.84 (system C). PMR spectrum (CF_3COOH), ppm: 2.7 (s, CH_3), 5.95 (s, CH_2), 6.8 (s, H-3), 8.8 and 9.1 (broad s, 2NH, 34°C). IR spectrum (liquid petrolatum), ν, cm^{-1}: 1560, 1615 (pyridine ring), 1640 (C=O), 1695 (C=O), 3110, 3300, 3430 (NH, OH). Mass spectrum, m/z (relative intensity, %): M^+ 164 (100), 136 (5.9), 135 (11.4), 109 (37.1), 107 (10.0), 81 (6.8), 57 (7.1). Found, %: C 52.72; H 5.49; N 15.38. $C_8H_8N_2O_2 \cdot H_2O$. Calculated, %: C 52.83; H 5.41; N 14.78. M 182.

Sodium Salt of 2-Methyl-3-nitro-4-hydroxymethyl-6-hydroxypyridine-5-carboxylic Acid (XIII). A solution of 0.5 g compound VII in 40 ml of 0.1 N NaOH was boiled for 15 min, the precipitate formed filtered off, washed with water, and dried. Yield 0.22 g (49%), mp > 350°C, R_f 0.5 (system D). PMR spectrum (DMSO), δ, ppm: 2.6 (s, CH_3), 5.4 (s, CH_2). IR spectrum (KBr), ν, cm^{-1}: 1575 (antisymmetrical vibration of NO_2), 1595 (pyridone ring), 1742 (C=O), 3180 (associated OH), 3520 (OH). Found, %: C 38.36; H 2.74; N 11.29. $C_8H_7N_2O_6Na$. Calculated, %: C 38.41; H 2.82; N 11.19.

6-Methyl-7-nitro-1H-furano[3,4-c]pyridine-3,4(5H)-dione (XIV). A. A solution of 0.75 g of compound VIII in 8 ml of 6% H_2SO_4 was heated at 50°C for 15 min, cooled, the precipitate formed filtered off, washed with water, and dried. Yield 0.5 g (72.5%), mp 295-296°C (with decomp., from 85% ethanol), R_f 0.6 (system B). PMR spectrum (CF_3COOH), δ, ppm 3.1 (s, CH_3), 5.8 (s, CH_2). IR spectrum (KBr), ν, cm^{-1}: 1590 (antisymmetrical vibrations of NO_2), 1685 (C=O), 1770 (C=O), 3420-3480 (NH). Found, %: C 45.67; H 2.91; N 13.57. M^+ 210. $C_8H_6N_2O_5$. Calculated, %: C 45.71; H 2.85; N 13.33. M 210. According to the literature data [5], mp 279-280°C

B. A solution of 0.5 g of compound VII in 35 ml of concentrated HCl was boiled for 5 h. The reaction mixture was treated as described above. Yield 0.25 g (65%).

C. A suspension of 0.5 g compound VII in 30 ml of water was boiled for 3 h. The reaction mixture was treated as described above. Yield 0.25 g (65%).

D. A solution of 0.18 g of compound XIII in 12% H_2SO_4 was heated at 70°C for 30 min. The reaction mixture was treated as described above. Yield 0.14 g (93%).

6-Methyl-1H-furano-[3, 4-c]pyridine-3,4(5H)-dione (XV). A solution of 1.5 g of compound X in 12% H_2SO_4 was heated at 70°C for 30 min, cooled, the precipitate formed filtered off, washed with water, and dried. Yield 1.1 g (84%), mp 321-322°C (with decomp.), R_f 0.67 (system C). PMR spectrum (CF_3COOH), δ, ppm: 2.7 (s, CH_3), 5.6 (s, CH_2), 6.9 (s, H-3). IR spectrum (liquid petrolatum), ν, cm^{-1}: 1620 (pyridine ring), 1670 (C=O), 1765 (C=O). Found, %: C 58.17; H 4.43; N 8.26. M^+ 165. $C_8H_7NO_3$. Calculated, %: C 58.18; H 4.27; N 8.47; M 165. According to the literature data [5], mp 320°C.

2-Methyl-3-hydroxy-4,5-dihydroxymethylpyridine (XI). A solution of 0.2 g of compound

XII in 1.5 ml of 15% H_2SO_4 was heated in an ampul at 150°C for 12 h. Yield 85.5%, determined by a chromatospectrophotometric method, R_f 0.63 (system A). UV spectrum (in 0.1 N HCl), λ_{max} ($\varepsilon \cdot 10^3$) 290 (8.8).

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