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Some Specific Features of Acid Nitration of 2-Substituted 4,6-Dihydroxypyrimidines. Nucleophilic Cleavage of the Nitration Products

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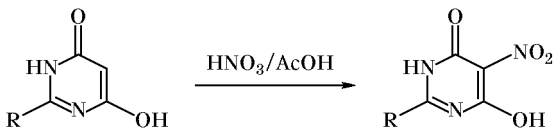
Abstract—The nitration of 2-substituted 4,6-dihydroxypyrimidines in concentrated sulfuric acid yields the corresponding 5,5-dinitro derivatives. When the substituent in position *2* is an alkyl group, the nitration occurs both at position *5* and at the α-carbon atom of the side chain. Hydrolysis of 2-substituted 4,6-dihydroxy-5,5-dinitropyrimidines leads to formation of 1,1-diamino-2-R-2-nitroethylene derivatives. 1,1-Diamino-2,2-dinitroethylene was obtained by nitration of 4,6-dihydroxy-2-methylpyrimidine and subsequent hydrolysis of 4,6-dihydroxy-5,5-dinitro-2-(dinitromethylene)-2,5-dihydropyrimidine.

Acid nitration of heterocyclic compounds often takes different pathways due to concomitant prototropic transformations. The ambident character of heterocycles also strongly affects the reaction course. In particular, diazines, despite their sufficiently high basicity, are fairly weak nucleophiles in electrophilic substitution reactions. It is even more difficult to interpret their reactivity when the molecule contains a substituent capable of prototropic isomerization. Unlike unsubstituted pyrimidine, its 4,6-dihydroxy derivative is readily nitrated with nitric acid in acetic acid at 20°C, yielding 5-nitro-4,6-dihydroxypyrimidine [1–6]. Under the same conditions 4,6-dihydroxy-2-methylpyrimidine gives rise to 4,6-dihydroxy-2-methyl-5-nitropyrimidine which is formed in high yield [7] (Scheme 1). However, there are no published data on nitration of such substrates in media with high acidity and high nitrating power.

Scheme 1.



R = H, CH_3.

† Deceased.

While studying the nitration of 2-substituted 4,6-dihydroxypyrimidines in concentrated sulfuric acid, we have found that only the corresponding 5,5-dinitro derivatives are formed. Unlike nitration in acetic acid which provides relatively weak acidity of the medium, the nitration in concentrated sulfuric acid does not give 5-mononitropyrimidines. 5,5-Dinitro derivative is the only reaction product even when the amount of nitric acid is clearly insufficient. At the same time, the nitration of 2-substituted 4,6-dihydroxypyrimidines with aqueous nitric acid yields only mononitro derivatives even with a large excess of HNO_3.

In most cases, the formation of 5,5-dinitropyrimidines was judged by the formation of geminal dinitroacetamide derivatives. By nitration of 2-amino-4,6-dihydroxypyrimidine in sulfuric acid and subsequent treatment of the reaction mixture with water we isolated *N*-diaminomethylene-2,2-dinitroacetamide (**I**) whose structure was established on the basis of its elemental composition and IR and ^{13}C NMR spectra (Scheme 2). The formation of nitroguanidine and dinitromethane on treatment of **I** with concentrated nitric acid provides an additional support to the proposed structure.

Figure 1 shows the UV spectra of aqueous solutions of compound **I** at different pH values. It is seen that compound **I** is a weak acid (pK_a ~6.6); the absorption of the conjugate anion is located in the

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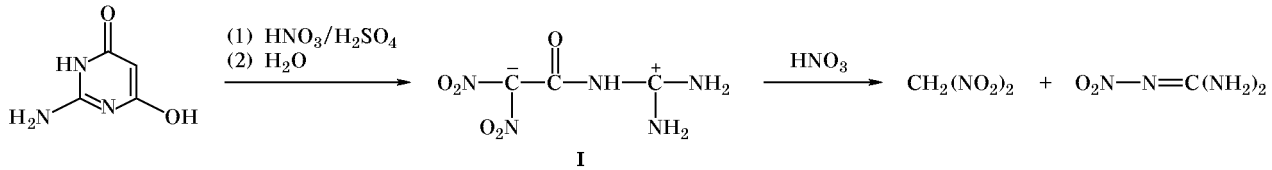
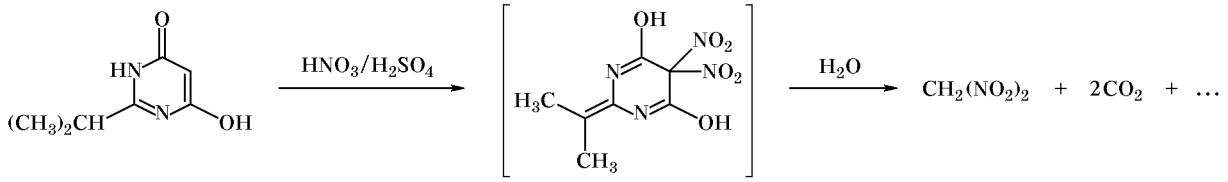
Scheme 2.



I

Scheme 3.



II

region typical for most anions derived from geminal dinitroalkanes [8] and α,α-dinitroacetamides [9]. Taking into account the results of nitration of 2-substituted 4,6-dihydroxypyrimidines in weakly and strongly acidic media, we presumed that 5-mononitro derivative formed in the first stage is low reactive; therefore, it does not undergo further nitration. When the acidity is high, 5-nitropyrimidine can undergo protonation to give a reactive intermediate which is nitrated to 5,5-dinitro derivative. The structure of this intermediate was not studied, but it was firmly established that its nitration leads to formation of a double bond between C^2 and the substituent. In the ^{1}H NMR spectrum of a solution of 4,6-dihydroxy-2-isopropylpyrimidine in concentrated sulfuric acid we observed a doublet signal from the methyl group and a septet from the CH proton, i.e., signals typical of an isopropyl group. On addition to the solution of nitric acid (as potassium nitrate) the doublet and septet are converted into a singlet due to formation of 5,5-dinitro derivative (Fig. 2). This means that the nitration product has a quinoid structure (Scheme 3).

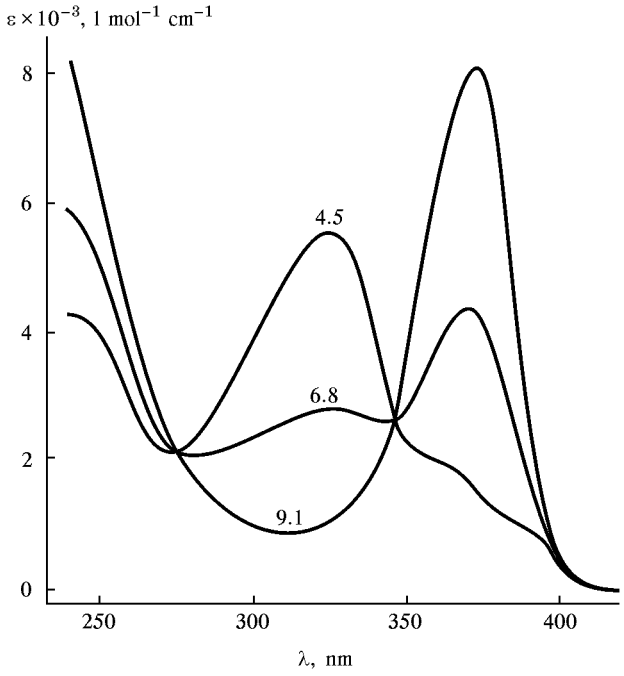
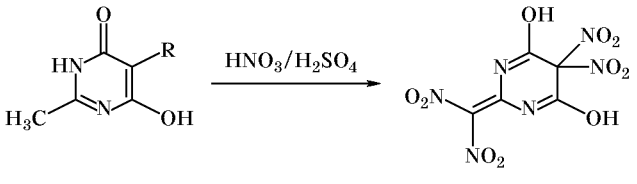


Fig. 1. UV spectra of aqueous solutions of 1-diaminomethyleneamino-2,2-dinitrovinyl alcohol (**I**). The numbers on the curves denote the pH values.

We failed to isolate 4,6-dihydroxy-2-isopropylidene-5,5-dinitropyrimidine (**II**) from the reaction mixture because of its high solubility in concentrated sulfuric acid. Nevertheless, the amount of dinitromethane determined in the solution (after decomposition of the reaction mixture with water) indicated that compound **II** was formed in 85% yield. The final product of the nitration of 4,6-dihydroxy-2-methylpyrimidine was 4,6-dihydroxy-5,5-dinitro-2-dinitromethylene-2,5-dihydropyrimidine (**III**) (Scheme 4). The same product was also isolated from the reaction mixture obtained by nitration of 4,6-dihydroxy-2-methyl-5-nitropyrimidine.

Scheme 4.

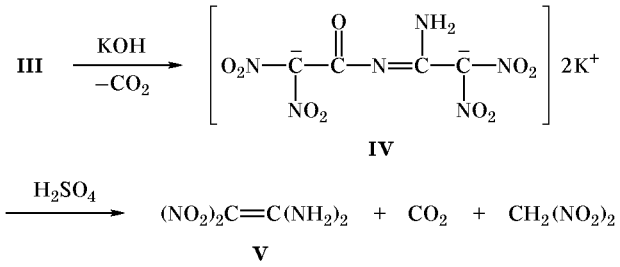


III

R = H, NO_2.

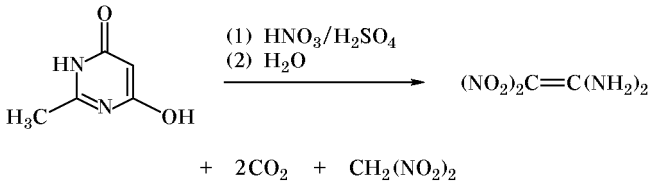
Compound **III** is unstable. It decomposed within several hours, but we succeeded in proving its structure by elemental analysis and reactions with nucleophiles. The hydrolysis of **III** in water occurs instantaneously. The reaction on strong dilution (more than 500 : 1), pH 7, results in evolution of 1 mol of CO_2. An analogous reaction occurs in alkaline medium. In this case 2-amino-1,1,5,5-tetranitro-4-oxo-3-aza-2-pentene dipotassium salt (**IV**) is formed. Our attempt to isolate the free tetranitro derivative by acidification of a solution containing salt **IV** resulted in instantaneous hydrolysis with liberation of one more equivalent of CO_2 and 1 equiv. of dinitromethane and formation of a light yellow solid which was assigned the structure of 1,1-diamino-2,2-dinitroethylene (**V**) (Scheme 5).

Scheme 5.



The structure of compound **V** was determined from its elemental composition and IR and ^{13}C NMR spectra. The ^{13}C NMR spectrum of **V** contained only two signals at δ_C 158.2 and 128.4 ppm. These data are consistent with those reported for 1,1-bis(dimethylamino)-2,2-dinitroethylene [10] which also showed in the spectrum two carbon signals at δ_C 162.3 and 128.2 ppm. The formation of compound **V** with liberation of 2 equiv of CO_2 and 1 equiv of dinitromethane was also observed on mixing pyrimidine **III** with 5–7 parts of water (pH < 3) and on dilution with water of the reaction mixture obtained in the nitration of 4,6-dihydroxy-2-methylpyrimidine with a mixture of sulfuric and nitric acids (Scheme 6). In such a way we can obtain 1,1-diamino-2,2-dinitroethylene in more than 80% yield by nitration of 4,6-dihydroxy-2-methylpyrimidine withouth isolation of intermediate tetranitro derivative **III**.

Scheme 6.



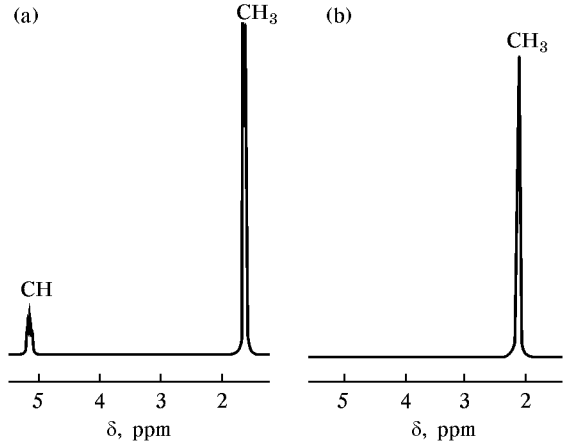
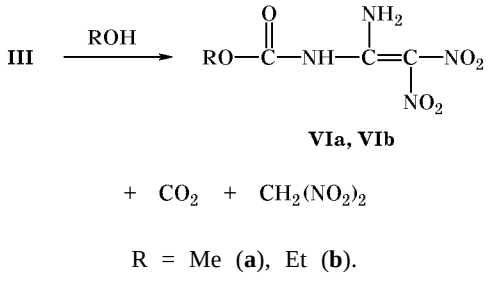


Fig. 2. Fragments of the ^1H NMR spectra of a solution of 4,6-dihydroxy-2-isopropylpyrimidine in concentrated sulfuric acid (a) before and (b) after addition of potassium nitrate.

Heating of compound **III** with anhydrous ethanol or methanol gave the corresponding *N*-(1-amino-2,2-dinitrovinyl)carbamate, 1 equiv of CO_2, and 1 equiv of dinitromethane (Scheme 7).

Scheme 7.

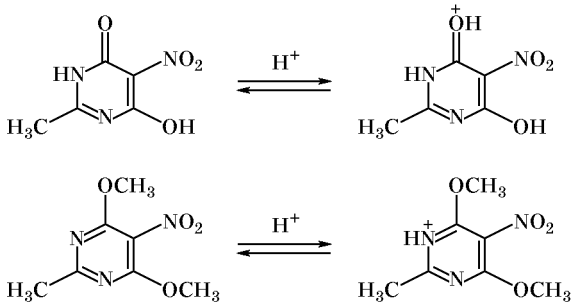


The formation of esters **VIa** and **VIb** indicates that cleavage of 4,6-dihydroxy-5,5-dinitro-2-(dinitromethylene)-2,5-dihydropyrimidine begins with attack by nucleophilic species on C^4 of the pyrimidine ring.

It is interesting that 4,6-dihydroxy-2-methyl-5-nitropyrimidine is readily nitrated to the corresponding 5,5-dinitro derivative, whereas introduction of the second nitro group into 4,6-dimethoxy-2-methyl-5-nitropyrimidine is impossible. Our attempts to accomplish this transformation by varying the reaction conditions (such as temperature, composition of the nitrating mixture, and reaction time) were unsuccessful. As a result, either the initial compound was recovered from the reaction mixture or profound decomposition products were isolated. In order to elucidate the reason for the different reactivities of 4,6-dihydroxy-2-methyl-5-nitropyrimidine and its

4,6-dimethoxy analog, we examined the ^{1}H NMR spectra of these compounds in sulfuric acid solutions with different concentrations. Judging by the position of the methyl proton signal, the ionization of 4,6-dihydroxy-2-methyl-5-nitropyrimidine is well described by the acidity function H_a corresponding to protonation of amides at the carbonyl oxygen atom [11]: pK_{BH^+} –4.25. 4,6-Dimethoxy-2-methyl-5-nitropyrimidine is a Hammett base with pK_{BH^+} –2.2 (in terms of H_0 units) [12]. These values suggest different mechanisms of protonation: 4,6-dimethoxy-2-methyl-5-nitropyrimidine is protonated at the ring nitrogen atom, and its dihydroxy analog, at the exocyclic oxygen atom (Scheme 8).

Scheme 8.



Izomerization of the *O*-protonated form leads to a reactive intermediate which readily undergoes further nitration to 5,5-dinitro derivative. Presumably, the rate of nitration of this intermediate is much higher than the rate of nitration of the initial substrate. Therefore, we observed no accumulation of 4,6-dihydroxy-2-methyl-5-nitropyrimidine in concentrated sulfuric acid even when the amount of nitric acid was insufficient. The failure to nitrate 4,6-dimethoxy-2-methyl-5-nitropyrimidine in concentrated sulfuric acid suggests that isomerization of its N-protonated form does not give a reactive intermediate.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-300 spectrometer (300 MHz for ^{1}H); DMSO-d_6 was used as solvent, and tetramethylsilane, as internal reference. The UV spectra were measured on a Specord M40 spectrophotometer. The elemental compositions were determined on a Hewlett–Packard 185B CHN-analyzer. The basicity of 4,6-dihydroxy-2-methyl-5-nitropyrimidine was determined by spectrophotometry at λ 320 nm (ε_B 7260, ε_{BH^+} 6670 l × mol^{-1} cm^{-1}); for 4,6-dimethoxy-2-methyl-5-nitropyrimidine, λ 280 nm (ε_B 5980, ε_{BH^+} 7200 l mol^{-1} cm^{-1}). The pK_{BH^+} values were calculated as described in [13] using the dependence of the ionization ratio logarithm log I on the acidity function. The slopes of the linear plots log I—H_0 for 4,6-dimethoxy-2-methyl-5-nitropyrimidine and log I—H_a for 4,6-dihydroxy-2-methyl-5-nitropyrimidine were –0.95 and –0.98, respectively.

4,6-Dihydroxy-2-methyl-5-nitropyrimidine. 4,6-Dihydroxy-2-methylpyrimidine, 9 g (0.05 mol), was added in portions to 21 ml of 98% HNO_3 under vigorous stirring and cooling (15–20°C). The mixture was stirred for 2–3 h at 15–20°C, cooled below 5°C, and diluted with 30 ml of ice water. The mixture was left to stand for 2–3 h, and the precipitate was filtered off, washed with cold water, and dried in air. Yield of the crude product 10 g. After recrystallization from water, we obtained 9.1 g (75%) of the product with mp 287–288°C (decomp.) [7].

N-Diaminomethylene-2,2-dinitroacetamide (I). 2-Amino-4,6-dihydroxypyrimidine, 12.6 g (0.07 mol), was added in portions to 50 ml of concentrated sulfuric acid, vigorously stirred at 15–20°C. To the resulting mixture 22 g of 98% HNO_3 was added, maintaining the temperature at 15–20°C. After 1 h, the mixture was poured into 700–800 ml of ice water and was left to stand for 2–3 h. The precipitate was filtered off, washed with water, and recrystallized from 100 ml of aqueous DMF (1:4). Yield 9.4 g (50%). mp 167.5°C (decomp.). ^{1}H NMR spectrum, δ, ppm: 8.1 s (NH_2), 8.8 s (NH_2). ^{13}C NMR spectrum, δ_C, ppm: 156.83 [$C(NO_2)_2$], 156.09 (C=O), 134.64 [$C(NH_2)_2$]. Found, %: C 18.69; H 1.47; N 36.48. $C_3H_3N_5O_5$. Calculated, %: C 18.83; H 1.56; N 36.63.

4,6-Dihydroxy-5,5-dinitro-2-(dinitromethylene)-2,5-dihydropyrimidine (III). 4,6-Dihydroxy-2-methylpyrimidine, 12.6 g (0.07 mol), was added in portions under vigorous stirring to 38 ml of concentrated sulfuric acid, maintaining the temperature at 15–20°C. The mixture was cooled to 5–10°C, and 85 g of 98% HNO_3 was added. After 1 h, the mixture was cooled to 0–5°C, and the precipitate was filtered off, immediately washed with 20 ml of trifluoroacetic anhydride and 20 ml of trifluoroacetic acid, and dried. Yield 16.9 g (75%). The product had no definite melting point. Found, %: C 19.58; H 0.03; N 27.38. $C_5H_2N_6O_{10}$. Calculated, %: C 19.60; H 0.06; N 27.44.

2-Amino-1,1,5,5-tetranitro-4-oxo-3-aza-2-pentene dipotassium salt (IV). Freshly prepared compound **III**, 5 g (0.016 mol), was added with stirring at 15–20°C to a solution of 2 g (0.035 mol) of potassium hydroxide in 15 ml of water. The solution was evaporated in air, and the residue was recrystallized from 10 ml of methanol. Yield 2.6 g (45%). mp 105°C (decomp.). Found, %: C 13.50; H 0.78; N 23.46.

$C_4H_2K_2N_6O_9$. Calculated, %: C 13.43; H 0.83; N 23.50.

1,1-Diamino-2,2-dinitroethylene (V). *a.* 4,6-Dihydroxy-2-methylpyrimidine, 12.6 g (0.07 mol), was nitrated as described above for the synthesis of compound **III**. The reaction mixture was cooled to 0–5°C and poured into 600–700 ml of water. After 10–12 h, the precipitate was filtered off and recrystallized from DMF. Yield 8.1 g (75%). mp 220°C (decomp.). ^{1}H NMR spectrum, δ, ppm: 8.77 s (NH_2). ^{13}C NMR spectrum, δ_C, ppm: 158.83 [$C(NO_2)_2$], 128.56 [$C(NH_2)_2$]. Found, %: C 16.22; H 2.72; N 37.84. $C_2H_4N_4O_4$. Calculated, %: C 16.11; H 2.62; N 37.68.

b. Freshly prepared compound **III**, 10 g (0.03 mol), was added at 15–20°C to 70 ml water under vigorous stirring. If necessary, the mixture was acidified with dilute sulfuric acid to pH 2 and was stirred for 1–2 h at 18–20°C. The yellow crystalline product was filtered off, washed with water, and dried in air. Yield 4.4 g (90%).

Methyl and ethyl *N*-(1-amino-2,2-dinitrovinyl)-carbamates VIa and VIb. Freshly prepared compound **III**, 10 g (0.03 mol), was added at 18–20°C to 50 ml of anhydrous methanol or ethanol. The mixture was kept for 1 h at that temperature and was then refluxed for 30 min. The solvent was removed under reduced pressure (water-jet pump), and the residue was recrystallized from aqueous DMF (1 : 4).

Ester **VIa**. Yield 3.4 g (45%). mp 151°C (decomp.). ^{1}H NMR spectrum, δ, ppm: 8.77 s (NH_2), 3.8 s (CH_3). ^{13}C NMR spectrum, δ_C, ppm: 159.77 [$C(NO_2)_2$], 156.73 (C=O), 144.5 ($NHCNH_2$), 51.37 (OCH_3). Found, %: C 23.3; H 3.01; N 27.2. $C_4H_6N_4O_6$. Calculated, %: C 23.28; H 2.91; N 27.14.

Ester **VIb**. Yield 3.2 g (45%). mp 141°C (decomp.). ^{1}H NMR spectrum, δ, ppm: 8.77 s (NH_2), 3.9 q (CH_2), 1.9 t (CH_3). ^{13}C NMR spectrum, δ_C, ppm: 159.73 [$C(NO_2)_2$], 155.56 (C=O), 144.5 ($NHCNH_2$), 61.37 (OCH_2), 14.47 (CH_3). Found, %: C 27.24; H 3.59; N 25.40. $C_5H_8N_4O_6$. Calculated, %: C 27.25; H 3.63; N 25.4.

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