Pyrimidines VIII. Direct Nitration of Mono-oxopyrimidines (1)

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Until recently, it has been assumed (2) that successful synthesis of 5-nitropyrimidine derivatives by direct nitration required the presence of at least two electron-releasing groups in the molecule. It has since been demonstrated (3), however, that 2-oxopyrimidine (I) can be nitrated in good yield in a hot nitric acid-sulfuric acid mixture to its 5-nitro derivative (II). Attempts to apply this nitration procedure to 4-oxopyrimidine (III) were unsatisfactory. We wish to report a general method for the *direct* nitration of mono-oxopyrimidines to 5-nitro-mono-oxopyrimidines (II and IV) by use of a modified nitrating medium.

In this procedure, potassium nitrate (instead of fuming nitric acid) is used as the nitrating reagent. This procedure offers the advantage of ease of handling and, more importantly, results in smooth isolation of the product. Initially, compound II was obtained from ethanol, without excessive drying, as a stable ethanol-adduct, as proved by analysis and nmr spectroscopy. The free 5-nitro-2-oxopyrimidine was obtained only after rigorous drying in high vacuum.

The nmr spectrum of free 5-nitro-2-oxopyrimidine in dimethylsulfoxide-d_6 shows only one proton signal (δ = 9.15) which can be attributed to rapid exchange of the

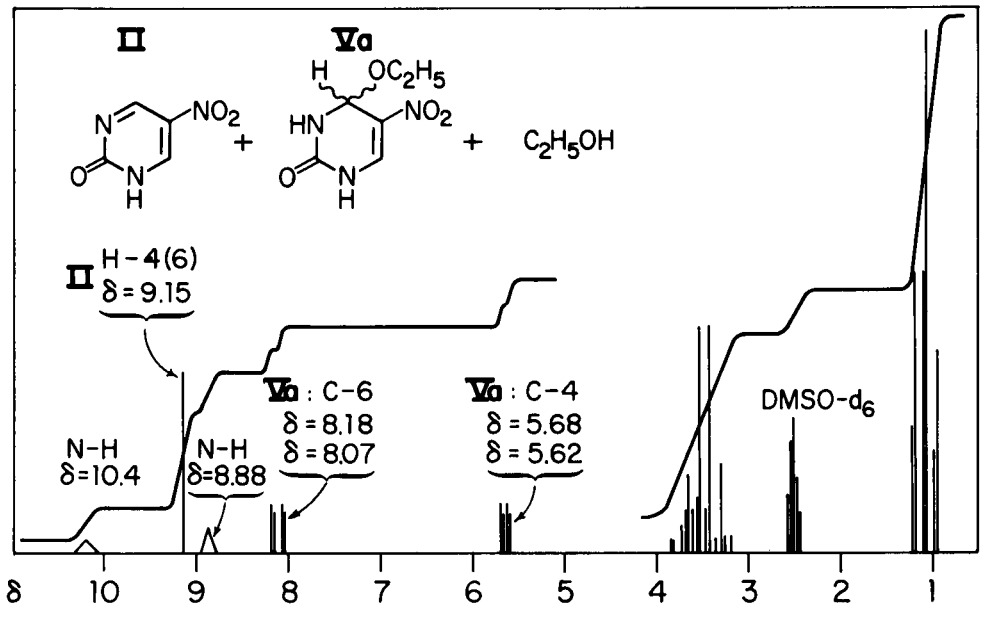
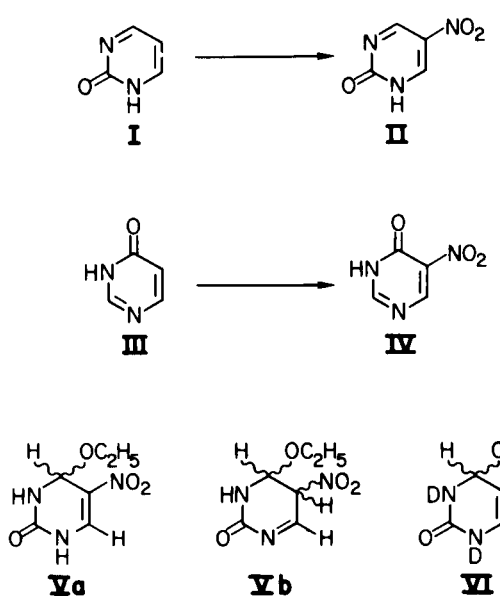


Figure I. Schematic representation of the nmr spectrum of the ethanol adduct of 2-oxo-5-nitropyrimidine in dimethylsulfoxide-d_6. The spectrum represents a mixture of II and Va, together with ethanol (see text). The exchangeable protons do not all appear, probably because of some exchange effects even in dimethylsulfoxide-d_6. The multiplets centered at δ = 3.5 and δ = 1.1 belong to the ethyl groups of both forms of Va and of ethanol.



hydrogen between N-1 and N-3 resulting in equivalence of the positions C-4 and C-6.

The nmr spectrum of the ethanol-adduct of II, a chromatographically homogeneous compound, shows part of the ethanol to be covalently bound. The spectrum in dimethylsulfoxide-d_6 (see Figure I) indicates the presence of two different ethanol-adducts together with the free 5-nitro-2-oxopyrimidine. Each of the doublets at δ = 8.18 and δ = 8.07 is coupled to one of the doublets at δ = 5.68 and δ = 5.62; the coupling constant, J, in each case is about 1.3 to 1.4 hz. Since both of the doublets at $\delta \cong 8.1$ or at $\delta \cong 5.6$ were affected simultaneously during the decoupling experiments, it was not possible to determine which were coupled. The best interpretation of the nmr spectrum in dimethylsulfoxide-d_6 is the assumption that this mixture contains about 50% of II together with about 25% of each of the two stereoisomers of Va which has an asymmetric carbon at C-4. The two doublets at $\delta \cong 8.1$ then belong to H-6 of the two stereoisomers of Va and the two doublets at $\delta \cong 5.6$ to H-4. Contributions from Vb, a tautomeric form of Va, with one of the exchangeable protons bound to C-5 are considered unlikely since in structure Vb the coupling (H-4 - H-6) would not occur.

Addition of deuterium oxide to a solution of the free 5-nitro-2-oxopyrimidine in dimethylsulfoxide-d_6 gives a solution containing about 90% of a covalent deuterium oxide-adduct to which we assign structure VI. This adduct is an analog of Va but in this case the two stereoisomers have fortuitously the same chemical shift. The most plausible interpretation for this difference between the two adducts VI and Va is that the former is more nearly planar. H-4 (δ = 5.69) and H-6 (δ = 7.98) in VI are coupled, J = 1.3 Hz.

The nmr spectrum of 5-nitro-4-oxopyrimidine (IV) in dimethylsulfoxide-d_6, on the other hand, gives no indication of adduct formation when either deuterium oxide or deuterium chloride is added to the solution. Signals for H-2 and H-6 are observed at δ = 8.13 and δ = 8.9. Addition of sodium deuteroxide results in a new type of spectrum with two strong C-H signals at δ = 8.35 and δ = 9.75. The downfield signal indicates a C-formyl group and suggests that ring-opening of IV at C-6 has occurred.

Decomposition of 5-nitro-4-oxopyrimidine in aqueous solution with probable ring opening is also observed by ultraviolet spectroscopy. Irreversible spectral shifts with time are noted even in neutral solutions of IV. These spectral changes are much more rapid in alkaline solutions. A spectrophotometric determination of the pK_a value of IV was found not to be possible. By contrast, though 5-nitro-2-oxopyrimidine was also unstable in alkali, a spectrophotometric determination of its pK_a (6.05) has been carried out (3).

EXPERIMENTAL

5-Nitro-4-oxopyrimidine (IV).

To a solution of 4-oxopyrimidine (III, 4.08 g., 0.043 mole) in 40 ml. of concentrated sulfuric acid was added 8.6 g. (0.086 mole) of finely divided potassium nitrate and the reaction mixture was heated in a bath at 90-95° for *ca.* 20 hours. The progress of the reaction was monitored spectrophotometrically as follows: a small aliquot of solution was triturated with portions of anhydrous ether until acid-free, then taken up in 0.1 *N* sodium hydroxide and the ultraviolet absorption spectrum was recorded immediately. The ratio of the optical density readings at 337 and 265 mμ is *ca.* 2.7 for completely nitrated product. The solution was cooled and was dropped slowly into 1500 ml. of anhydrous ether with vigorous stirring. A sticky semi-solid precipitated. The ether was decanted, fresh ether was added and stirring was continued. The decantation and addition of fresh ether was repeated until the syrup was transformed into an amorphous solid. The white solid was filtered and washed with ether. The precipitate was treated with absolute ethanol, the insoluble salts were removed by filtration, and the ethanol filtrate was evaporated *in vacuo*. The crystalline product, 2.3 g. (38%) was recrystallized from hot ethanol to yield shining prisms, m.p. 190-192° (Lit. (4) reports 192°); ultraviolet absorption data: (1 *N* hydrochloric acid) maxima at 233 (ϵ, 6,110) and 312 mμ (4,775); minimum at 257 mμ (ϵ, 1,660); (1 *N* sodium hydroxide), maximum at 337 (ϵ, 6,285), minimum at 267 mμ (ϵ, 740). The instability of compound II in aqueous solution made determination of the pK_a by spectrophotometric methods impossible.

Anal. Calcd. for $C_4H_3N_3O_3$: C, 34.05; H, 2.14; N, 29.78. Found: C, 34.10; H, 2.13; N, 29.57.

5-Nitro-2-oxopyrimidine (II).

2-Oxopyrimidine hydrochloride (III, 5.28 g., 0.04 mole) was added portionwise to 40 ml. of concentrated sulfuric acid. To the clear solution was added 8 g. (0.08 mole) of finely divided potassium nitrate and the reaction mixture was heated at 95° for 3 days. The degree of nitration was checked by the same procedure

outlined in previous preparation. Completely nitrated product has an optical density ratio 327/292 ≅ 1.9. The reaction mixture was cooled and treated with ether exactly as in the preceding example. The crude solid was extracted with hot ethanol, the combined extracts were evaporated *in vacuo* and the residue was crystallized from ethanol. The light yellow product, 3.64 g. (49%) ethanol-adduct m.p. 203-203.5° was identical with an authentic sample (3) when compared by ultraviolet absorption properties and by thin layer chromatography.

Anal. Calcd. for $C_6H_9N_3O_4$: C, 38.50; H, 4.85; N, 22.45. Found: C, 38.29; H, 5.00; N, 22.80.

A sample of the adduct was dried over phosphorous pentoxide under high vacuum at 140° for 3 days. Pure 5-nitro-2-oxopyrimidine (m.p. 202-203°) was obtained.

Anal. Calcd. for $C_4H_3N_3O_3$: C, 34.05; H, 2.14; N, 29.78. Found: C, 34.08; H, 2.06; N, 29.80.

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