Ring Transformations in Reactions of Heterocyclic Compounds with Nucleophiles (XX) (1). Conversion of 5-Nitropyrimidine into 3,5-Dinitropyridine. A Novel Ring Transformation (2)

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Received August 2, 1977

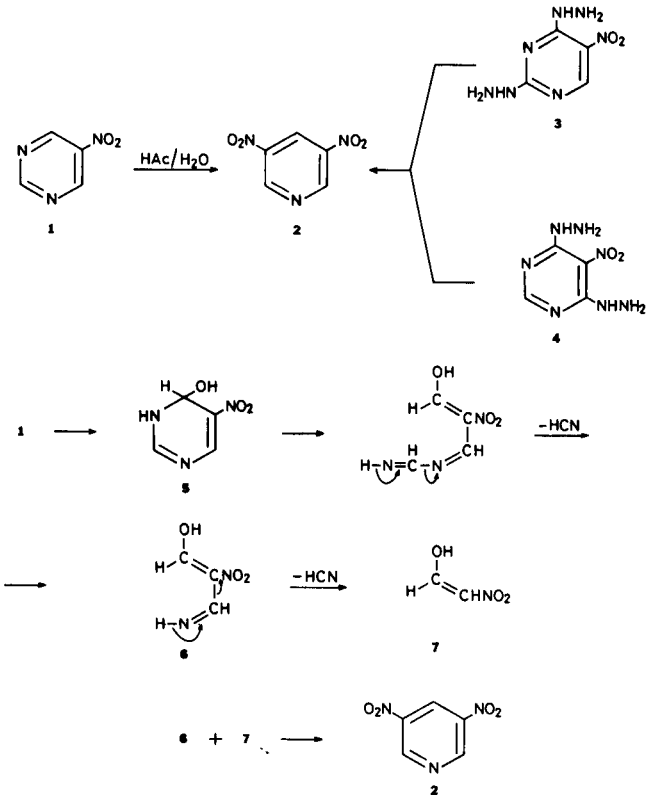
Heating of 5-nitropyrimidine with acetic acid in water leads to the formation of 3,5-dinitropyridine. The mechanism proposed for this novel ring transformation involves a fragmentation of the pyrimidine ring, leading to the formation of a *two*-atom and a *four*-atom moiety, which on condensation gives the pyridine ring. With hydrazine hydrate, 5-nitropyrimidine undergoes ring contraction into 4-nitropyrazole.

J. Heterocyclic Chem., **15**, 485 (1978)

Much of our work on ring transformations of heterocycles has been concerned with the study of the occurrence of ring interconversions in reactions of diazines with strong nucleophilic reagents [amide ions (3) and carbanions (4)] and weak nitrogen-containing nucleophiles [ammonia (5,6), hydrazine (7), hydroxylamine (8)]. So far only one ring transformation has been reported to occur with the nucleophile water (7b). We wish to report in this communication an acid-catalysed ring transformation of a pyrimidine into a pyridine on treatment with water.

5-Nitropyrimidine (**1**) was prepared in high yield by oxidation of 4,6-dihydrazino-5-nitropyrimidine (**4**) with silver acetate in the solvent water. This method was found to be a better procedure than the one using silver oxide as the oxidizing agent and methanol as the solvent (9). Although it has been reported that **1** is quite stable in acid (9), we found that the heating of **1** with acetic acid in water gave a compound (m.p. 102-104°) to which the structure of 3,5-dinitropyridine (**2**) could be assigned (yield 45-50%). This assignment was based on the microanalysis, nmr and ir data and the observation of no melting point depression if the compound was mixed with an authentic specimen of 3,5-dinitropyridine. The above-mentioned ring transformation has never been observed before and can be explained by a fragmentation of the pyrimidine ring, partly into the two-carbon C_4-$C_5(NO_2)$ moiety and partly into the carbon-nitrogen C_4-$C_5(NO_2)$-C_6-N_1 fragment, which both recombine into a new heterocyclic ring. This fragmentation occurred *via* an initial hydration of **1** into the 1,6-dihydro-6-hydroxy-5-nitropyrimidine (**5**) (10) which undergoes a carbon-carbon bond fission (see Scheme).

Fragmentation of the pyrimidine ring into a *two*-carbon fragment is not unprecedented. ^{14}C-labelling studies on the conversion of pyrimidines into 5-ethyl-2-methylpyridine (6) by treatment with methylamine have unequivocally shown that this fragmentation can indeed occur. Also the fragmentation of the pyrimidine ring into a *four*-atom C-C-C-N fragment has been observed before as exemplified in the conversion of 4-hydrazinopyrimidines into 3-aminopyrazoles (11,7b). The interesting, new



feature of the ring transformation of **1** → **2** is that under the applied reaction conditions, the pyrimidine ring is able to provide a *two*-atom as well as a *four*-atom fragment, *i.e.*, the nitroacetaldehyde (**7**) and the "imine of nitromalonaldehyde" (**6**), which on condensation gave **2**. The formation of a pyridine ring by condensation of a three-carbon moiety with a two-carbon fragment is well established for synthesizing pyridines (12). It was expected and indeed established that when 4,6-dihydrazino-5-nitropyrimidine (**4**) or 2,4-dihydrazino-5-nitropyrimidine (**3**) was heated with silver acetate in water, compound **2** was also formed. However, the yield was found to be considerably lower (20-25%) than in the reaction of **1** with acid. This may be due to the fact that the silver ions form with the nitro-containing fragments **6** and/or **7** a silver salt (13), which possibly prevents an effective condensation.

When **1** is reacted with hydrazine for 48 hours at room temperature or with hydrazine in water for half an hour at about 100°, a nearly quantitative yield of 4-nitropyrazole is obtained. The initial step is the addition of hydrazine to C_4 in 5-nitropyrimidine; this addition is of course strongly favoured due to the high electron deficiency of this system. The mechanism of the conversion of pyrimidines into pyrazoles has extensively been discussed earlier (7).

EXPERIMENTAL

All melting points are uncorrected. Infrared spectra of solutions in chloroform were taken on a Perkin Elmer model 237 apparatus. The ^{1}H-nmr spectra were recorded on a Jeol JNM C-60 spectrometer, using TMS or DSS as internal standard. Mass spectra were recorded with an AEI-902 mass spectrometer.

Preparation of the Starting Materials.

4,6-Dihydrazino-5-nitropyrimidine (**4**) (14) and 2,4-dihydrazino-5-nitropyrimidine (**3**) (15) were prepared by procedures as described in the literature.

a. 5-Nitropyrimidine (**1**).

A mixture of **4** (1.0 g., 5.4 mmoles) and 4.0 g. of freshly prepared silver acetate in 10 ml. of water was stirred at room temperature for 5 minutes, then 50 ml. of chloroform were added and the stirring was continued for a further 90 minutes. After neutralization with sodium bicarbonate and further stirring for 15 minutes, the chloroform was decanted and the reaction mixture was extracted with chloroform. The combined extracts were dried over anhydrous magnesium sulfate, the solvent evaporated and the residue recrystallized from petroleum ether (b.p. 40-60°). The yield of 5-nitropyrimidine was 0.44 g. (65-70%), m.p. 56-58° (lit. (9) 57-58°). Mixed melting point determination with an authentic specimen (9) gave no depression.

b Reaction of 5-Nitropyrimidine (**1**) with Acetic Acid in Water.

A mixture of 0.5 g. (4 mmoles) of **1** and 2.4 g. (40 mmoles) of acetic acid in 25 ml. of water was heated at 90° for half an hour. After cooling and neutralization with sodium bicarbonate the reaction mixture was extracted with chloroform. The combined extracts were dried over anhydrous magnesium sulfate, the solvent evaporated and the residue subjected to column chromatography through silica gel, using chloroform as an eluent. From the chloroform-eluent 160 mg. (yield 45-50%) of 3,5-dinitropyridine were obtained, m.p. 102-104°; nmr (deuteriochloroform): δ 9.75 (H-2 and H-6, d), δ 9.30 (H-4, t); $J_{2,4} = J_{4,6} = 2.3$ Hz; ir (chloroform) showed the asymmetrical and symmetrical NO_2 stretching vibration at 1540 and 1347 cm^{-1}, respectively; ms: (M^+, 169, M^+-NO_2, 123; M^+-2NO_2, 77). Mixed melting point determination with an authentic specimen (16) gave no depression.

Anal. Calcd. for $C_5H_3N_3O_4$ (169.10): C, 35.51; H, 1.79. Found: C, 35.49; H, 2.14.

c. Reaction of 4,6-Dihydrazino-5-nitropyrimidine (**4**) with Silver Acetate in Water.

A mixture of **4** (1.0 g., 5.4 mmoles) and 4.0 g. of freshly prepared silver acetate in 10 ml. of water was kept at room temperature for 1 hour. Then the reaction mixture was heated at 90° for 1 hour. Nitrogen gas was evolved during the reaction. After neutralization with potassium carbonate, the reaction mixture was extracted with chloroform. These extracts were dried over anhydrous magnesium sulfate. The solvent was evaporated and the residue subjected to column chromatography through silica gel, using chloroform as eluent. From the chloroform eluent 110 mg. of 3,5-dinitropyridine were obtained (yield 25%). For identification see section b.

d. Reaction of 2,4-Dihydrazino-5-nitropyrimidine (**3**) with Silver Acetate in Water.

This reaction was performed in the same way as described in section c. The yield of 3,5-dinitropyridine was 26%.

e. Reaction of 5-Nitropyrimidine (**1**) with Hydrazine Hydrate in Water.

A mixture of 0.1 g. (0.8 mmole) of **1** and 80 mg. (1.6 mmoles) of hydrazine hydrate in 10 ml. of water was stirred at room temperature for half an hour. After acidification with concentrated hydrochloric acid, the reaction mixture was warmed up to 100°, whereby the red solution became nearly colourless. After cooling and neutralization with sodium bicarbonate the reaction mixture was extracted with ether. The ether extracts were dried over anhydrous magnesium sulfate and the solvent evaporated, yielding a solid (0.066 g.) which was purified by sublimation, yield, 85-90% of 4-nitropyrazole, m.p. 156-158° (lit. (17) 157-158°); nmr (acetone-d_6/deuteriochloroform): δ 8.30 (H-3 and H-5, s); ir (chloroform) showed an NH stretching vibration at 3460 cm^{-1}, the asymmetrical and symmetrical NO_2 stretching vibration at 1510 and 1342 cm^{-1}, respectively.

Anal. Calcd. for $C_3H_3N_3O_2$ (118.08): C, 31.86; H, 2.67. Found: C, 32.15; H, 2.70.

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