## Notes

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# Oxidation of 5-Nitrosopyrimidines by Nitrous Acid. A Synthesis of 5-Nitropyrimidines

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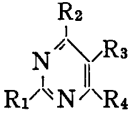
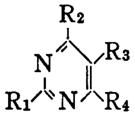
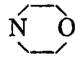
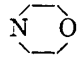
The use of oxidizing agents for the oxidation of 5-nitroso- to 5-nitropyrimidines is well documentated and pertrifluoroacetic acid seems to be a reagent of choice.[2] In connection with other studies, it was found that the oxidation of 5-nitrosopyrimidines can be effected with sodium nitrite in concentrated sulfuric acid. We describe here preliminary work on the preparation of some 5-nitropyrimidines by this method.

Treatment of 4-hydroxy-6-morpholino-2-phenylpyrimidine with sodium nitrite in about 70% sulfuric acid at room temperature afforded the corresponding 5-nitropyrimidine in quantitative yield. This nitration proceeds without doubt *via* nitrosation, because the initial intensely colored solution includes only the intermediate 5-nitrosopyrimidine. Futhermore, treatment

TABLE I. Preparations of Some 5-Nitropyrimidines

| No. | Starting material  R1 | R2 | R3 | R4 | Product  R1 | R2 | R3 | R4 | Yield (%) | mp (°C) |
|---|---|---|---|---|---|---|---|---|---|---|
| I | Ph | OH | H |  | Ph | OH | $NO_2$ |  | 100.0 | >300 |
| II | Ph | $NH_2$ | H |  | Ph | $NH_2$ | $NO_2$ |  | 41.6 | 240 |
| III | Ph | OH | H | $NH_2$ | Ph | OH | $NO_2$ | $NH_2$ | 65.2 | 280 |
| IV | $NH_2$ | OH | NO | $NH_2$ | $NH_2$ | OH | $NO_2$ | OH | 82.4 | >320[a] |
| V | Ph | OH | NO | $NH_2$ | Ph | OH | $NO_2$ | $NH_2$ | 70.1 | 280 (decomp.) |

| No. | Recrystn. Solvt. | Appearance | Formula | Analysis (%) Calcd. C | H | N | Found C | H | N |
|---|---|---|---|---|---|---|---|---|---|
| I | DMF | yellow prisms | $C_{14}H_{14}O_4N_4$ | 55.62 | 4.67 | 18.54 | 55.39 | 4.55 | 18.32 |
| II | EtOH | yellow needles | $C_{15}H_{17}O_2N_5$ | 60.19 | 5.72 | 23.40 | 59.93 | 5.77 | 23.19 |
| III | DMF–EtOH | colorless powder | $C_{10}H_8O_3N_4$ | 51.72 | 3.47 | 24.13 | 51.64 | 3.41 | 24.09 |
| IV | DMF–$H_2O$ | colorless powder | $C_4H_5O_3N_5$ | 28.07 | 2.95 | 40.93 | 27.99 | 3.10 | 40.55 |
| V | DMF–EtOH | colorless powder | $C_{10}H_8O_3N_4$ | 51.72 | 3.47 | 24.13 | 51.77 | 3.27 | 23.89 |

*a*) lit.[7] mp >350°

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[1] Location: *35, Shinanomachi, Shinjuku-ku, Tokyo.*

[2] E.C. Taylor and A. McKillop, *J. Org. Chem.*, **30**, 3153 (1965).

of an isolated 5-nitrosopyrimidine with the same reagent under the same conditions gave also the corresponding 5-nitropyrimidine. When the reaction was done in a dilute acid such as diluted sulfuric or hydrochloric acid and in acetic acid under the same conditions, the product was the nitrosopyrimidine. These facts point out that nitrite in concentrated sulfuric acid[3] is a considerable strong oxidizing agent.

Some examples of this oxidation are summarized in Table I. The structures of the products have been established by elemental analysis, by the presence of the nitro stretching absorption bands in infrared (IR) spectra, by molecular weight determination by.mass spectrometry, and by comparison with authentic samples where available. It will be noted that 2,4-diamino-6-hydroxy-5-nitrosopyrimidine[6] was converted to 2-amino-4,6-dihydroxy-5-nitropyrimidine[7] under these conditions. 4,6-Dipiperidino-2-phenylpyrimidine did not react under any conditions because of its presumable steric hindrance recovering the starting material.

## Experimental[8]

**4-Hydroxy-6-morpholino-2-phenylpyrimidine**——A mixture of 1.5 g (0.0079 mole) of 4-amino-6-hydroxy-2-phenylpyrimidine,[9] 10 ml of morpholine and 2 ml of conc. HCl was vigorously refluxed for 20 hr. After cooling, the precipitated colorless needles were collected by filtration, washed with EtOH and recrystallized from EtOH to give 1.1 g (48.6%) of the hydrochloride, mp 259—261°. *Anal.* Calcd. for $C_{14}H_{16}O_2N_3Cl$: C, 42.70; H, 4.60; N, 10.67. Found: C, 42.58; H, 4.41; N, 10.37.

**4-Amino-2-phenyl-6-piperidinopyrimidine**——A mixture of 1.71 g (0.01 mole) of 4-amino-6-chloro-2-phenylpyrimidine[10] and 0.85 g (0.01 mole) of piperidine were heated at 190° for 1.5 hr. Recrystallization of the resulted mass from EtOH gave 0.95 g (32.8%) of colorless prisms of the hydrochloride, mp 310° (decomp.). *Anal.* Calcd. for $C_{15}H_{19}N_4Cl$: C, 61.95; H, 6.59; N, 19.27. Found: C, 62.23; H, 6.77; N, 19.24.

**4,6-Dipiperidino-2-phenylpyrimidine**——A mixture of 2.0 g (0.0089 mole) of 4,6-dichloro-2-phenylpyrimidine,[11] 3 ml of piperidine and 2 drops of conc. HCl were heated under reflux for 2.5 hr. After cooling, the reaction mixture was dissolved in EtOH, made alkaline with aq. $NH_3$ and then added with $H_2O$. The white powder which separated were collected by filtration and recrystallized from EtOH to give 1.8 g (68%) of colorless needles, mp 128—130°. *Anal.* Calcd. for $C_{20}H_{26}N_4$: C, 74.49; H, 8.13; N, 17.38. Found: C, 74.55; H, 8.07; N, 17.24.

**4-Amino-6-hydroxy-5-nitroso-2-phenylpyrimidine**——This compound was prepared by means of the method published by E. Bergmann, *et al.*[9]

**Preparation of 5-Nitropyrimidines. General Procedure**——5-Unsubstituted or 5-nitroso pyrimidines were dissolved in a mixture of conc. $H_2SO_4$ and $H_2O$ (5:2), added little by little 4 equivalents of $NaNO_2$ at 5° under stirring. After stirring at room temperature for 7—10 hr, the reaction mixtures were diluted with a large amount of $H_2O$. The precipitated products were filtered off, washed with $H_2O$ and EtOH, and recrystallized from a suitable solvent (Table I).

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[3] It is known that sodium nitrite in aqueous sulfuric acid or perchloric acid is essentially nitrosonium ion above 60—70% acid, and molecular nitrous acid below about 40% acid.[4,5]

[4] K. Singer and P.A. Vamplew, *J. Chem. Soc.*, **1956**, 3971.

[5] N.S. Bayliss and D.W. Watts, *Australian J. Chem.*, **9**, 319 (1956).

[6] P.D. Landauer and H.N. Pydon, *J. Chem. Soc.*, **1953**, 3721.

[7] J.A. Carbon, *J. Org. Chem.*, **26**, 455 (1961).

[8] All melting points were uncorrected.

[9] F. Bergmann, A. Kalmus, H. Ungar-Waron and H. Kwietry-Govrin, *J. Chem. Soc.*, **1963**, **3729.**

[10] E.C. Taylor and J. Weinstock, Brit. Patent 951655 [*C.A.*, **61**, 4387 (1964).].

[11] J.A. Hendry and R.F. Homer, *J. Chem. Soc.*, **1952**, 328.