Chemistry of Heterocyclic Compounds, Vol. 40, No. 3, 2004

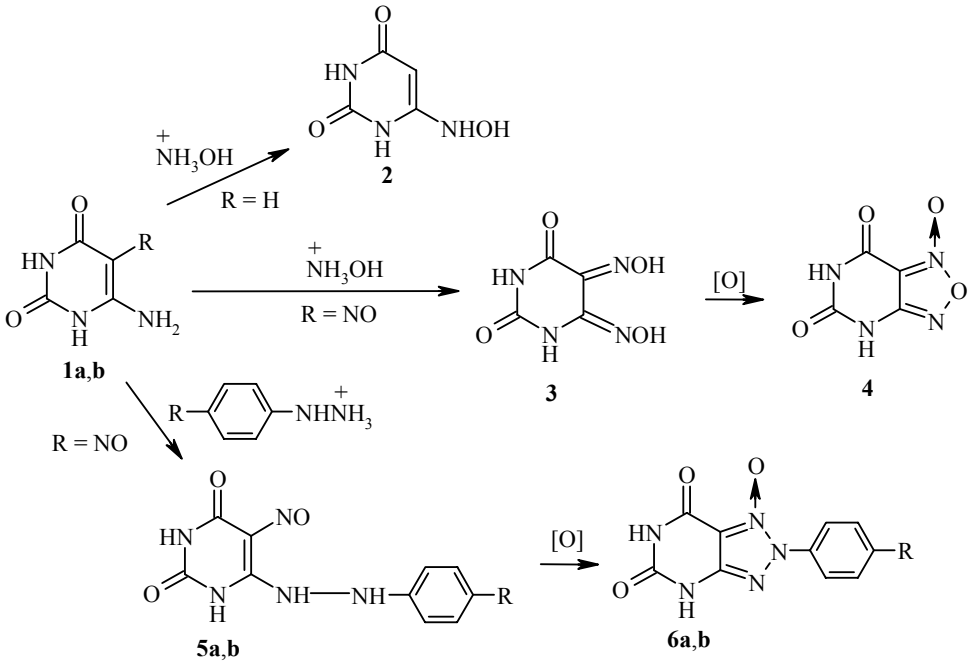
CONVERSION OF AMINO GROUP IN POSITION 6 OF URACIL

A. A. Yavolovskii and E. I. Ivanov

The possibility of substituting amino groups in position 6 of 5-R-uracils (R = H, NO) by hydroxylamine and phenylhydrazine has been demonstrated. The products of substitution – 6-hydroxyaminouracil, 5,6-dihydroxydiiminouracil, and 5-nitroso-6-phenylhydrazinouracil – are readily oxidized into 1,2,5-oxadiazolo- and 1,2,3-triazolo[3,4-d]pyrimidine N-oxides respectively.

Keywords: 5,6-dihydroxydiiminouracil, 6-hydroxyaminouracil, 5-nitroso-6-phenylhydrazinouracil, 1,2,5-oxadiazolo- and 1,2,3-triazolo[3,4-*d*]pyrimidine N-oxides, nucleophilic substitution, oxidation.

The most widely used method for the preparation of pyrimidines with nitrogen-containing functional groups in positions 2,4 (or 6) is the nucleophilic substitution on chloropyrimidines [1-3]. Transamination [4, 5] has received considerably less attention although in some cases aminopyrimidines are much more available than the corresponding 4(6)-chloro derivatives.



1 a R = H, **b** R = NO; **5 a** R = H, **b** R = *t*-Bu; **6 a** R = H, **b** R = *t*-Bu

A. V. Bogatsky Physico-Chemical Institute, Ukraine National Academy of Sciences, Odessa 65080, Ukraine; e-mail: ivanov.u@paco.net. Translated from Khimiya Geterotsiklicheskikh Soedinenii, pp. 443-446, March, 2004. Original article submitted July 27, 2001.

TABLE 1 . Spectral Characteristics of the Compounds Synthesized

Com-pound	Mass spectrum, *m/z* (I_{rel}, %)	IR spectrum, ν, cm^{-1}
2	143(83), 100(100), 68(12), 58(39), 57(14)	3400, 3230-3000, 1730, 1710, 1680, 1660
3	154(39), 111(12), 70(10), 68(15), 58(8), 54(10), 53(13), 43(100)	3320-3000, 1720, 1680, 1600
4	170(100), 154(10), 140(76), 97(10), 70(15), 69(31), 68(7), 67(59), 54(22), 53(14)	3510, 3480, 3300-3000, 1750, 1700, 1680, 1660, 1590, 1540, 1520
5a	247(20), 245(8), 231(18), 229(33), 213(8), 202(8), 200(6), 186(18), 105(24), 92(13), 91(14), 77(100)	3250-3000, 1710, 1700, 1680, 1660, 1645, 1590, 1570, 1550, 1530
5b	303(15), 301(8), 287(59), 285(25), 272(45), 270(95), 149(61), 132(71), 133(100), 119(53), 117(31), 110(30), 105(35), 103(15), 93(20), 91(78), 77(41)	3250-3000, 1730, 1720, 1700, 1690, 1670, 1650, 1600, 1570, 1630, 1510, 15000
6a	245(28), 229(4), 139(9), 105(27), 96(6), 77(100), 51(19)	3200-3000, 1720, 1705, 1695, 1690, 1670, 1600, 1560
6b	301(51), 285(12), 270(35), 230(5), 222(6), 207(11), 161(13), 133(100), 117(16), 105(25), 91(37), 77(21)	3240-3000, 1715, 1680, 1590, 1560

We have established that 6-aminouracil (**1a**) and its 5-nitroso derivative (**1b)** readily undergo acid catalyzed substitutions with hydroxylamine and phenylhydrazine. Use of the free bases or their salts with weak acids does not always lead to the satisfactory results which were achieved by using a mixture of acetate and hydrochloride salts as the nucleophile. We obtained 6-hydroxyaminouracil (**2**) by refluxing 6-aminouracil (**1a**) [6,7] for a short time with an excess of a mixture of hydroxylaminium acetate and chloride in water. Substitution of the amino group in 6-amino-5-nitrosouracil **1b** by hydroxylamine at 65-75°C was completed in 1.5-2 h to give 5,6-dihydroxydiiminopyrimidin-2,4-dione (**3**). Dioxime **3** is a colorless compound, which dissolves poorly in organic solvents and water, but well in aqueous solutions of amines and alkalis.

The molecular ion is absent from the mass spectrum of oxime **3**. The heaviest ion in the mass spectrum of **3** corresponds to the loss of water from the molecular ion $[M - 18]^+$. Dioxime **3** is converted to 1,2,5-oxadiazolo[3,4-*d*]pyrimidin-5(4H),7(6H)-dione (**4**) by oxidation with concentrated nitric acid. The accessibility of the starting materials and the high yields of this synthesis for furoxanopyrimidine **4** is more effective than methods published previously [8-10]. It should be noted that the dioximes are not formed on nitrosation of 1-R-6-hydroxyamino-3-methyluracils [8,9] but instead the products of oxidative cyclization, furoxanopyrimidines, the mass spectra of which contain intense peaks at $[M + 2]^+$. The authors attributed the presence of these peaks to the addition of two hydrogen atoms as a result of adsorption of water under the spectrometric conditions. In our case the intensity of the $[M + 2]^+$ peaks corresponded to the isotopic composition of **4** which is apparently connected with the low stability of the hydrogenated form **3**. In reaction conditions similar to those with hydroxylamine, the substitution of the amino group in **1b** by phenylhydrazine gave 5-nitrosophenylhydrazones **5a** and **5b**. Subsequent oxidation under mild conditions with $K_3[Fe(CN)_6]$ in alkaline media gave the 1,2,3-triazolopyrimidine N-oxides **6a** and **6b**. Although the N-oxides **6a** and **6b** appeared to be stable with respect to 30% hydrogen peroxide, use of H_2O_2 to oxidize the nitrosohydrazines **5a** and **5b** was accompanied by side reactions and consequently gave impure **6a** and **6b** as final products.

EXPERIMENTAL

Purity of compounds was monitored by TLC on Silufol UV-254 strips. Mass spectra were recorded on a Varian MAT-112 with an ionizing voltage of 70 eV and a chamber temperature of 220°C. IR spectra of nujol mulls were recorded with Specord-80 instrument

6-Hydroxyaminopyrimidin-2,4-(1H,3H)-dione (2). A mixture of 6-aminouracil **1a** (1.0 g, 8 mmol), hydroxylamine hydrochloride (2 g, 30 mmol), and sodium acetate (1.6 g, 20 mmol) was boiled in water (75 ml) until it dissolved. The mixture was slowly evaporated under normal conditions until crystallization began. The precipitate was separated and recrystallized from water. Yield 0.9 g (80%); mp 320°C (dec.). Found, %: C 33.62; H 3.48; N 29.11. $C_4H_5N_3O_3$. Calculated, %: C 33.57; H 3.50; N 29.37.

5,6-Dihydroxydiiminopyridin-2,4-(1H,3H)-dione (3). A mixture of 6-amino-5-nitrosouracil (1.4 g, 9 mmol), hydroxylamine hydrochloride (2 g, 30 mmol), and sodium acetate (1.6 g, 20 mmol) in water (50 ml) was heated to 65-70°C with intense stirring to give a colorless solution. The precipitate was filtered off, washed with cold water, and dried in the air. Yield 1.4 g (91%); mp >250°C. Found, %: C 30.12; H 2.36; N 32.40. $C_4H_4N_4O_4$. Calculated, %: C 27.90; H 2.33; N 32.56.

1,2,5-Oxadiazolo[3,4-*d*]pyrimidin-5,7-(4H,6H)dione N-Oxide (4). A solution of compound **3** (1.7 g, 100 mmol) in nitric acid (10 ml) and sulfuric acid (1 ml) was cautiously heated at 40-50°C until solution occurred. The reaction mixture was cooled diluted with twice as much water, and neutralized with cold ammonia solution. The precipitate was filtered off, washed with water, and dried in a desiccators over P_2O_5. Yield 1.48 g (87%); mp 260°C. Found, %: C 28.12; H 1.22; N 32.99. $C_4H_2N_4O_4$. Calculated, %: C 28.24; H 1.18; N 32.94.

6-[2-(4-R-Phenylhydrazino)pyrimidin-2,4-(1H,3H)-diones, (5a,b). A mixture of 6-amino-5-nitrosouracil **1b** , phenylhydrazine hydrochloride (20 mmol), and sodium acetate (15 mmol) in water (150 ml) was heated for 2 h at 70°C with intense stirring. The precipitate was filtered off, washed twice with hot water , dried in the air, and washed with toluene until the washing were no longer colored. It was dried in air again to give a yield of 1.98 g (80%) of chromatographically pure **5a**; mp 250°C. Found, %: C 48.50; H 3.66; N 28.37. $C_{10}H_9N_5O_3$. Calculated, %: C 48.58; H 3.64; N 28.34. Yield of compound **5b**, 2.33 g (77%); mp 232-238°C. Found, %: C 55.43; H 5.63; N 23.09. $C_{14}H_{17}N_5O_3$. Calculated, %: C 55.45; H 5.61; N 23.10.

1-Oxides of 2-(4-R-Phenyl)-1,2,3-triazolo[4,5-*d*]pyrimidin-5,7-(4H,6H)diones (6a,b). Compound **5a** (10 mmol) and small portions of a saturated aqueous solution of sodium hydroxide (60 mmol) were added with stirring to a solution of $K_3[Fe(CN)_6]$ (60 mmol) in water (100 ml). Stirring was continued until the color of the initial solution had disappeared. The solution was then neutralized with acetic acid. The precipitate was filtered off, washed with water, and recrystallized from ethanol to give compound **6a** (1.84 g, 75%); mp >300°C. Found, %: C 48.95; H 2.8; N 28.56. $C_{10}H_7N_5O$. Calculated, %: C 48.98; H 2.86; N 28.57. Yield of compound **6b**, 1.8 g (60%); mp 250-255°C. Found, %: C 55.80; H 4.95; N 23.27. $C_{14}H_{15}N_3O_3$. Calculated, % : C 55.81; H 4.98; N 23.25.

REFERENCES

1. A. V. Ivashenko and O. N. Garicheva, *Khim. Geterotsikl. Soedin*., *579 (1982).*
2. W. Pfleiderer and K. H. Schundehutte, *Liebig Ann. Chem.,* **612**, 158 (1958).
3. F. Yoneda and T. Nagamatsu, *Synthesis,* 177 (1975).
4. G. W. Whitehead and J. J. Traverso, *J. Am. Chem. Soc.,* **82**, 3971 (1960).
5. H. Sun, Ch. Zhi, G. E. Wright, D. Ubiali, M. Pregnolato, A. Verri, F. Focher, and S. Spadari, *J. Med. Chem.,* **42**, 2344 (1999).
6. W. Traube, *Ber.,* 3035 (1900).
7. K. Burger, *Talanta,* **8**, 77 (1961).
8. F. Yoneda, Y. Sakuma, and M. Ueno, *J. Heterocycl. Chem.,* **10**, 415 (1973).
9. F. Yoneda, and Y. Sakuma, *J. Heterocycl. Chem.,* **10**, 993 (1973).
10. C. Temple, C. L. Kussner, and J. A. Montgomery, *J. Org. Chem.,* **10**, 2086 (1967).