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Ozonization of Thio- and Azauracils

Masaki MATSUI,* Kazusaki KAMIYA, Shigeo KAWAMURA,
Katsuyoshi SHIBATA, and Hiroshige MURAMATSU
Department of Chemistry, Faculty of Engineering, Gifu University, 1-1 Yanagido, Gifu 501-11
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The reactions of 2-thiouracils and azauracils with ozone have been examined. 2-Thiouracils were ozonized to give the corresponding 4(3*H*)-pyrimidinones and uracils. Ozone attacks the thiocarbonyl moiety and the desulfurization process to give 4(3*H*)-pyrimidinones competes with the oxidation process to give uracils. 5-Azauracil was stable for ozone, while 6-azauracil readily reacted with ozone to give parabanic acid.

The ozonization of the C=S moiety has been reported to give the corresponding C=O and/or C=S=O moieties.[1] Interestingly, in our study on the ozonization of pyrimidine bases, 2-thiouracils were found to give 4(3*H*)-pyrimidinones as the main products. This is the first report on the transformation of C=S into the C–H moiety by ozone. The reaction of azauracils with ozone was also investigated.

Experimental

Instruments. Ozone was generated with a Nihon Ozon 0-1-2 ozonizer. Melting points were measured by a Yanagimoto micro melting point apparatus and uncorrected. NMR and mass spectra were recorded on JEOL JNM-GX 270 FT NMR and Shimadzu QP-1000 mass spectrometers, respectively. High-performance liquid chromatography was performed on a Jasco Familic 100N liquid chromatograph.

Materials. Uracil (**1a**) and azauracils (**11** and **12**) were purchased from Tokyo Kasei Kogyo Co., Ltd. and used without further purification. Thiouracils (**3a—g** and **5**), dithiouracil (**6**) and 2-methylthio-4(3*H*)-pyrimidinone (**7**) were synthesized as described in the literature. Their melting points and spectral data are as follows:

2-Thiouracil (**3a**): mp >300 °C (lit,[2] 340 °C); ^{1}H NMR (DMSO-d_6) δ=5.81 (d, J=7 Hz, 1H), 7.40 (d, J=7 Hz, 1H), 12.37 (br. s, 2H); MS (70 eV) m/z (rel intensity) 128 (M^+, 100).

5-Methyl-2-thiouracil (**3b**): mp 265—267 °C (lit,[3] 265—267 °C); ^{1}H NMR (DMSO-d_6) δ=1.77 (s, 3H), 7.31 (s, 1H), and 12.29 (br. s, 2H); MS(70 eV) m/z (rel intensity) 142 (M^+, 80) and 55 (100).

5-Ethyl-2-thiouracil (**3c**): mp 191—192 °C (lit,[4] 190—192 °C); ^{1}H NMR (DMSO-d_6) δ=1.01 (t, J=7 Hz, 3H), 2.21 (q, J=7 Hz, 2H), 7.21 (s, 1H), and 12.35 (br. s, 1H); MS (70 eV) m/z (rel intensity) 156 (M^+, 100).

6-Methyl-2-thiouracil (**3d**): mp >300 °C (lit,[4] >300 °C); ^{1}H NMR (DMSO-d_6) δ=2.06 (s, 3H), 5.68 (s, 1H), and 12.27 (br. s, 2H); MS (70 eV) m/z (rel intensity) 142 (96) and 44 (100).

3-Methyl-2-thiouracil (**3e**): mp 272—273 °C; ^{1}H NMR (DMSO-d_6) δ=3.52 (s, 3H), 5.94 (d, J=8 Hz, 1H), 7.44 (d, J=8 Hz, 1H), and 12.60 (br. s, 1H); MS (70 eV) m/z (rel intensity) 142 (M^+, 100).

1-Methyl-2-thiouracil (**3f**): mp 229 °C (lit,[5] 228 °C); ^{1}H NMR (DMSO-d_6) δ=3.56 (s, 3H), 5.91 (d, J=8 Hz, 1H), 7.83 (d, J=8 Hz, 1H), and 12.58 (br. s, 1H); MS (70 eV) m/z (rel intensity) 142 (M^+, 72) and 42 (100).

1,3-Dimethyl-2-thiouracil (**3g**): mp 104 °C (lit,[6] 103 °C); ^{1}H NMR (DMSO-d_6) δ=3.56 (s, 3H), 3.65 (s, 3H), 6.05 (d, J=8 Hz, 1H), and 7.97 (d, J=8 Hz, 1H); MS (70 eV) m/z (rel intensity) 156 (M^+, 72) and 42 (100).

4-Thiouracil (**5**): mp >300 °C (lit,[7] 317—321 °C); ^{1}H NMR (DMSO-d_6) δ=5.74 (d, J=8 Hz, 1H), 7.38 (d, J=8 Hz, 1H), and 12.20 (br. s, 2H); MS (70 eV) m/z (rel intensity) 128 (M^+, 100).

2,4-Dithiouracil (**6**): mp 267—273 °C (lit,[8] 265—275 °C); ^{1}H NMR (DMSO-d_6) δ=6.50 (d, J=7 Hz, 1H), 7.26 (d, J=7 Hz, 1H), 12.87 (br. s, 1H), and 13.62 (br. s, 1H); MS (70 eV) m/z (rel intensity) 144 (M^+, 100).

2-Methylthio-4(3*H*)-pyrimidinone (**7**): mp 190—192 °C (lit,[9] 198—199 °C); ^{1}H NMR (DMSO-d_6) δ=2.54 (s, 3H), 6.12 (d, J=7 Hz, 1H), and 7.89 (d, J=7 Hz, 1H); MS (70 eV) m/z (rel intensity) 142 (M^+, 100).

The purity of used materials was checked by TLC (SiO_2, AcOEt:Me_2CHOH:H_2O=75:16:9).

Ozonization Reaction. Ozonization was carried out with an ozone-oxygen mixture (O_3: 0.22 mmol min^{-1}, O_2: 200 ml min^{-1}) on 2 mmol of substrate in 100 ml of acetic acid at room temperature. The end point of the reaction was monitored by TLC (SiO_2, AcOEt:Me_2CHOH:H_2O=75:16:9). In order to remove the dissolved ozone, nitrogen gas (100 ml min^{-1}, 10 min) was bubbled into the solution, which was allowed to stand overnight. The disappearance of peroxide activity was checked by a KI test. The solution was concentrated on a rotary evaporator and chromatographed on preparative TLC (SiO_2, AcOEt:Me_2CHOH:H_2O=75:16:9). The isolated products were identified on the basis of their spectral data shown below: 5-Methyluracil (**1b**): mp >300 °C (lit,[10] 313—314 °C); ^{1}H NMR (DMSO-d_6) δ=1.71 (s, 3H), 7.24 (s, 1H), 10.57 (br. s, 1H), and 10.99 (br. s, 1H); MS (70 eV) m/z (rel intensity) 126 (M^+, 39) and 55 (100).

5-Ethyluracil (**1c**): mp 290 °C (lit,[11] 300—303 °C); ^{1}H NMR (DMSO-d_6) δ=0.99 (t, J=7 Hz, 3H), 2.16 (q, J=7 Hz, 2H), 7.16 (d, J=7 Hz, 1H), 10.61 (br. s, 1H), and 10.97 (br. s, 1H); MS (70 eV) m/z (rel intensity) 140 (M^+, 100).

6-Methyluracil (**1d**): mp >300 °C (lit,[12] 340 °C); ^{1}H NMR (DMSO-d_6) δ=2.00 (s, 3H), 5.31 (s, 1H), and 10.82 (br. s, 2H); MS (70 eV) m/z (rel intensity) 126 (M^+, 29) and 42 (100).

3-Methyluracil (**1e**): mp 169 °C (lit,[13] 174—175 °C); ^{1}H NMR (DMSO-d_6) δ=3.12 (s, 3H), 5.57 (d, J=7 Hz, 1H), 7.39 (dd, J=7 and 6 Hz, 1H), and 10.97 (br. s, 1H); MS (70 eV) m/z (rel intensity) 126 (M^+, 90) and 69 (100).

1-Methyluracil (**1f**): mp 178—182 °C (lit,[14] 232 °C); ^{1}H NMR (DMSO-d_6) δ=3.23 (s, 3H), 5.50 (dd, J=8 and 2 Hz, 1H), 7.58 (d, J=8 Hz, 1H), and 11.07 (br. s, 1H); MS (70 eV) m/z (rel intensity) 126 (M^+, 52) and 42 (100).

1,3-Dimethyluracil (**1g**): mp 122—123 °C (lit,[15] 122—124 °C); ^{1}H NMR (DMSO-d_6) δ=3.14 (s, 3H), 3.29 (s, 3H),

5.65 (d, J=8 Hz, 1H), and 7.65 (d, J=8 Hz, 1H); MS (70 eV) m/z (rel intensity) 140 (M^+, 91) and 42 (100).

1-Formyl-5-hydroxyhydantoin (**2**): mp 153—155 °C; ^{1}H NMR (DMSO-d_6) δ=5.47 (d, J=8 Hz, 1H), 7.56 (d, J=8 Hz, 1H, exchanges with D_2O), 8.95 (s, 1H), and 11.70 (br. s, 1H, exchanges with D_2O); ^{13}C NMR (DMSO-d_6) δ=75.8 (d), 154.2 (s), 158.9 (d), and 171.1 (s); MS (70 eV) m/z (rel intensity) 144 (M^+, 5), 116 (54), and 88 (100); MS (CI, 200 eV, isobutane) m/z 145 (MH^+, 100%); Found: m/z 144.0175. Calcd for $C_4H_4N_2O_4$: M^+, 144.0171.

4(3*H*)-Pyrimidinone (**4a**): mp 160—163 °C (lit,[16] 163—164 °C); ^{1}H NMR (DMSO-d_6) δ=6.31 (d, J=7 Hz, 1H), 7.89 (d, J=7 Hz, 1H), 8.16 (s, 1H), and 12.54 (br. s, 1H); ^{13}C NMR (DMSO-d_6) δ=115.9 (d), 150.5 (d), and 161.3 (s); MS (70 eV) m/z (rel intensity) 96 (M^+, 100).

5-Methyl-4(3*H*)-pyrimidinone (**4b**): mp 145—147 °C (lit,[17] 153—154 °C); ^{1}H NMR (DMSO-d_6) δ=2.13 (s, 3H), 7.89 (s, 1H), and 8.18 (s, 1H); ^{13}C NMR (DMSO-d_6) δ=13.7 (q), 126.7 (s), 148.8 (d), 152.1 (d), and 163.3 (s); MS (70 eV) m/z (rel intensity) 110 (M^+, 100).

5-Ethyl-4(3*H*)-pyrimidinone (**4c**): mp 88—90 °C; ^{1}H NMR (DMSO-d_6) δ=1.22 (t, J=7 Hz, 3H), 2.53 (q, J=7 Hz, 2H), 7.90 (s, 1H), 8.27 (s, 1H), and 9.39 (s, 1H); ^{13}C NMR (DMSO-d_6) δ=12.4 (q), 20.8 (t), 131.1 (s), 147.0 (d), 150.0 (d), and 164.0 (s); MS (70 eV) m/z (rel intensity) 124 (M^+, 100).

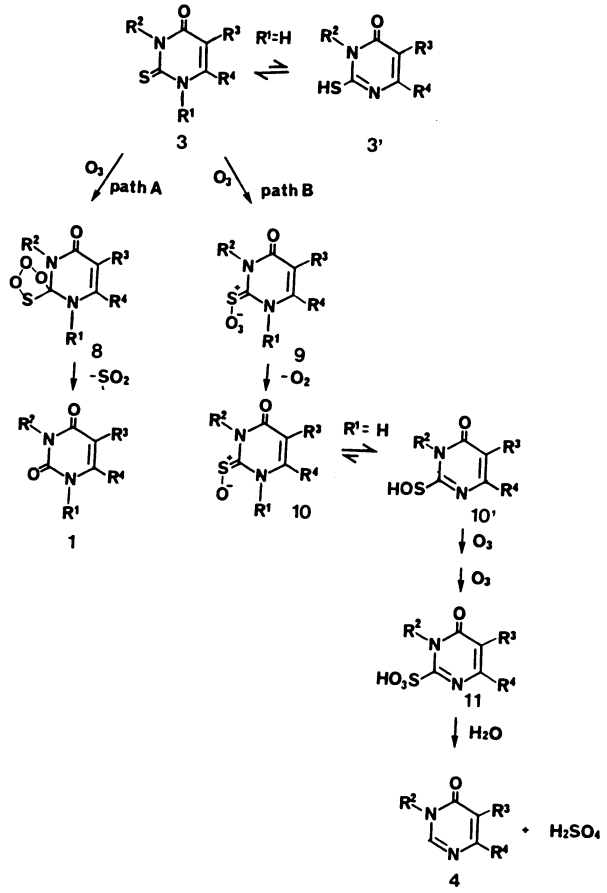
6-Methyl-4(3*H*)-pyrimidinone (**4d**): mp 145—147 °C (lit,[18] 149—150 °C); ^{1}H NMR (DMSO-d_6) δ=2.17 (s, 3H), 6.16 (s, 1H), and 8.08 (s, 1H); ^{13}C NMR (DMSO-d_6) δ=23.0 (q), 112.6 (d), 149.2 (d), 160.8 (d), and 164.3 (s); MS (70 eV) m/z (rel intensity) 110 (M^+, 100).

3-Methyl-4(3*H*)-pyrimidinone (**4e**): mp 118—120 °C (lit,[19] 121—122 °C); ^{1}H NMR (DMSO-d_6) δ=3.32 (s, 3H), 6.49 (d, J=7 Hz, 1H), 7.90 (d, J=7 Hz, 1H), and 8.21 (s, 1H); MS (70 eV) m/z (rel intensity) 110 (M^+, 42) and 42 (100).

Parabanic acid (**13**): mp 236—240 °C (lit,[20] 238—244 °C); ^{1}H NMR (DMSO-d_6) δ=11.75 (br. s, 2H); MS (70 eV) m/z (rel intensity) 114 (M^+, 72), 86 (64), and 43 (100). The purity of all products was checked by TLC (SiO_2, AcOEt:Me_2CHOH:H_2O=75:16:9). Analysis of products was carried out by HPLC (SS-10, AcOEt:Me_2CHOH:H_2O=75:16:9, 254 nm).

Results and Discussion

The ozonization reactions of uracil (**1a**), 2-thiouracils (**3a—d**), 4-thiouracil (**5**), and 2,4-dithiouracil (**6**) are summarized in Table 1. The reaction of uracil (**1a**) gave 1-formyl-5-hydroxyhydantoin (**2**) in a 29% yield (Run 1). Interestingly, the reaction of 1-unsubstituted 2-thiouracils **3a—e** under the same conditions gave the corresponding uracils **1a—e** and 4(3*H*)-pyrimidinones **4a—e** in 7—37 and 48—72% yields, respectively (Runs 2—6). The reaction of 1-methyl-2-thiouracils **3f,g** preferentially gave 1-methyluracils **1** in 19 and 47% yields, respectively (Runs 7 and 8). The ozonization of 4-thiouracil (**5**) gave only uracil (**1a**) in a 41% yield (Run 9). In the case of insoluble

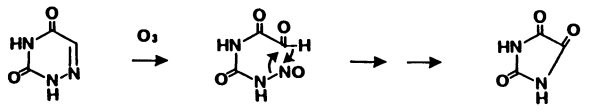


Scheme 1.

Table 1. Ozonization of Thiouracils[a]

Run	Substrate	Substituent				Time	Conv.	Yield/%		
		R^1	R^2	R^3	R^4	min	%	**1**	**2**	**4**
1	**1**					20	99	—	29	—
2	**3a**	H	H	H	H	15	97	18	0	68
3	**3b**	H	H	Me	H	10	98	7	0	58
4	**3c**	H	H	Et	H	12	92	7	0	48
5	**3d**	H	H	H	Me	9	97	37	0	56
6	**3e**	H	Me	H	H	6	97	25	0	72
7	**3f**	Me	H	H	H	6	92	19	0	0
8	**3g**	Me	Me	H	H	5	93	47	0	0
9	**5**					8	87	41	Trace	0
10	**6**					50[b]	98	4	0	4

a) Ozonization was carried out with an ozone-oxygen mixture (O_3: 0.22 mmol min^{-1}, O_2: 200 ml min^{-1}) on 2 mmol of substrate in 100 ml of acetic acid at room temperature. b) 2,4-Dithiouracil (**6**) is insoluble in acetic acid under the conditions.



12 14 13

Scheme 2.

2,4-dithiouracil (**6**) in acetic acid, the reaction gave small amounts of uracil (**1a**) and 4(3*H*)-pyrimidinone (**4a**) (Run 10).

A proposed path for the formation of uracils **1** and 4(3*H*)-pyrimidinones **4** is shown in Scheme 1. It is clear that ozone preferentially attacks the thiocarbonyl moiety of 2-thiouracils **3** rather than the olefinic 5–6 bond. 2-Thiouracils **3** can be in equilibrium with the thiol form **3′** in solution. It has been reported that the thione form **3** is predominant under acidic conditions.[21] Besides the ozonization of 2-methylthio-4(3*H*)-pyrimidinone (**7**), which exists in thiol form, was complicated and gave neither uracil nor 4(3*H*)-pyrimidinone. Therefore, it is concluded that ozone reacts with the thione form **3**. In the ozonization of thiocarbonyl moiety, both 1,3-dipolar cycloaddition and electrophilic attack of ozone have been proposed.[1] In the cases of 1-unsubstituted 2-thiouracils **3a—e**, the former to give uracils **1a—e** competes with the latter to afford 4(3*H*)-pyrimidinones **4a—e**. 1,3-Dipolar cycloaddition of ozone to the C=S moiety gives the ozone-adduct **8** followed by the elimination of sulfur dioxide to give uracils **1** (path A). Electrophilic ozone attack on the S-atom gives the ozone-adduct **9** followed by deoxygenation to give sulfine **10**, which is in equilibrium with sulfenic acid **10′** (path B). This intermediate **10′** is further oxidized to give sulfonic acid **11**. Since a small amount of water is contained in the solvent, the sulfonic acid **11** is desulfurized to give 4(3*H*)-pyrimidinones **4a—e**. After the ozonization of 2-thiouracil (**3a**), the pH value of the solution was 1.5 and a sulfate ion was detected by the barium chromate–diphenylcarbonohydrazide method.[22] In the cases of 1-substituted 2-thiouracils **3f,g**, uracils **1f,g** are preferentially obtained via path A, because no equilibrium between sulfine **10** and sulfenic acid **10′** exists and the sulfines **10f,g** are further ozonized to give unidentified products. In the case of **3f**, 1-methyl-4(1*H*)-pyrimidinone was not detected.

5-Azauracil (**11**) was very stable for ozone under the same conditions, while 6-azauracil (**12**) readily reacted with ozone to give parabanic acid (**13**) in a 34% yield. Similarly, 5-azacytosine was stable for ozone, while 6-azacytosine readily reacted with ozone to give unidentified several compounds in low yields. A mechanism for the ozonization of 6-azauracil (**12**) is proposed in Scheme 2. The reaction of C=N bond with ozone gives the corresponding carbonyl and nitroso compounds.[23] The ozonization of 5–6 bond of 6-azauracil (**12**) may give the intermediate **14**, followed by the elimination of HNO (or HNO_2) to give parabanic acid (**13**). Nitrite and/or nitrate ions were detected by a sulfuric acid–iron(II) sulfate method.[24]

References

1) B. Zwanenburg and W. A. Janssen, *Synthesis*, **1973**, 617; N. H. Nilsson and A. Senning, *Angew. Chem., Int. Ed. Engl.*, **11**, 295 (1972).

2) H. L. Wheeler and L. M. Liddle, *Am. Chem. J.*, **40**, 547 (1908).

3) H. Vorbruggen and P. Strehlke, *Chem. Ber.*, **106**, 3039 (1973).

4) G. W. Anderson, I. F. Halverstadt, W. H. Miller, and R. O. Roblin, *J. Am. Chem. Soc.*, **67**, 2197 (1945).

5) G. Shaw and R. N. Warrener, *J. Chem. Soc.*, **1958**, 153.

6) K. Hirota, K. A. Watanabe, and J. J. Fox, *J. Org. Chem.*, **43**, 1193 (1978).

7) D. J. Brown and K. Shinozuka, *Aust. J. Chem.*, **33**, 1147 (1980).

8) D. J. Brown, *J. Soc. Chem. Ind.*, **69**, 353 (1950).

9) H. L. Wheeler and H. F. Merriam, *Am. Chem. J.*, **29**, 478 (1903).

10) H. W. Scherp, *J. Am. Chem. Soc.*, **68**, 912 (1946).

11) J. H. Burckhalter and H. C. Scarborugh, *J. Am. Pharm. Assoc.*, **44**, 545 (1955).

12) M. M. Endicott and T. B. Johnson, *J. Am. Chem. Soc.*, **63**, 1286 (1941).

13) T. B. Johnson and F. W. Heyl, *Am. Chem. J.*, **37**, 628 (1907).

14) H. L. Wheeler and T. B. Johnson, *Am. Chem. J.*, **37**, 30 (1907).

15) K. J. Kolonko, R. H. Shapiro, R. M. Barkley, and R. E. Sievers, *J. Org. Chem.*, **44**, 3769 (1979).

16) L. Bauer, G. E. Wright, B. A. Mikrut, and C. L. Bell, *J. Heterocycl. Chem.*, **2**, 447 (1965).

17) D. J. Brown, *Aust. J. Chem.*, **21**, 243 (1968).

18) H. M. Foster and H. R. Sbyder, *Org. Synth.*, **35**, 80 (1955).

19) J. P. Jonak, G. C. Hopkins, H. J. Minnemeyer, and H. Tieckelmann, *J. Org. Chem.*, **35**, 2512 (1970).

20) T. B. Johnson and R. B. Flint, *J. Am. Chem. Soc.*, **53**, 1082 (1931).

21) G. B. Elion, W. S. Ide, and G. H. Hitchings, *J. Am. Chem. Soc.*, **68**, 2137 (1946); D. Shugar and J. J. Fox, *Bull. Soc. Chim. Belg.*, **61**, 293 (1952).

22) I. Ishizaki, S. Utsumi, K. Hagino, T. Tarutani, and T. Ozawa, *Bull. Chem. Soc. Jpn.*, **30**, 847 (1957).

23) A. H. Liebel, R. E. Erickson, C. J. Abshire, and P. S. Bailey, *J. Am. Chem. Soc.*, **82**, 1801 (1960).

24) "Bunsekikagakubinran," Maruzen, Tokyo (1961), p. 223.