

Ozonization of Thio- and Azauracils

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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); ¹H 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); ¹H 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); ¹H 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); ¹H 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; ¹H 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); ¹H 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);

¹H 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); ¹H 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); ¹H 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); ¹H 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 (SiO₂, AcOEt:Me₂CHOH:H₂O=75:16:9).

Ozonization Reaction. Ozonization was carried out with an ozone-oxygen mixture (O₃: 0.22 mmol min⁻¹, O₂: 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 (SiO₂, AcOEt:Me₂CHOH:H₂O=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 (SiO₂, AcOEt:Me₂CHOH:H₂O=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); ¹H 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); ¹H 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); ¹H 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); ¹H 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); ¹H 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); ¹H 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; ^1H NMR (DMSO- d_6) $\delta=5.47$ (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) $\delta=75.8$ (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 ($M\text{H}^+$, 100%); Found: m/z 144.0175. Calcd for $\text{C}_4\text{H}_4\text{N}_2\text{O}_4$: M^+ , 144.0171.

4(3H)-Pyrimidinone (**4a**): mp 160–163 °C (lit.¹⁶) 163–164 °C; ^1H NMR (DMSO- d_6) $\delta=6.31$ (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) $\delta=115.9$ (d), 150.5 (d), and 161.3 (s); MS (70 eV) m/z (rel intensity) 96 (M^+ , 100).

5-Methyl-4(3H)-pyrimidinone (**4b**): mp 145–147 °C (lit.¹⁷) 153–154 °C; ^1H NMR (DMSO- d_6) $\delta=2.13$ (s, 3H), 7.89 (s, 1H), and 8.18 (s, 1H); ^{13}C NMR (DMSO- d_6) $\delta=13.7$ (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(3H)-pyrimidinone (**4c**): mp 88–90 °C; ^1H NMR (DMSO- d_6) $\delta=1.22$ (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) $\delta=12.4$ (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(3H)-pyrimidinone (**4d**): mp 145–147 °C (lit.¹⁸) 149–150 °C; ^1H NMR (DMSO- d_6) $\delta=2.17$ (s, 3H), 6.16 (s, 1H), and 8.08 (s, 1H); ^{13}C NMR (DMSO- d_6) $\delta=23.0$ (q), 112.6 (d), 149.2 (d), 160.8 (d), and 164.3 (s); MS (70 eV) m/z (rel intensity) 110 (M^+ , 100).

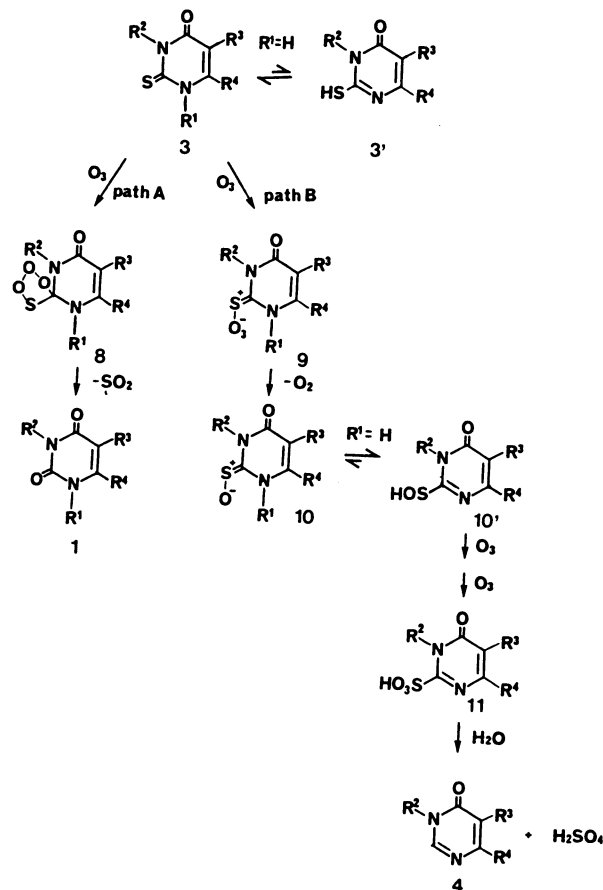
3-Methyl-4(3H)-pyrimidinone (**4e**): mp 118–120 °C (lit.¹⁹) 121–122 °C; ^1H NMR (DMSO- d_6) $\delta=3.32$ (s, 3H), 6.49 (d, $J=7$ Hz, 1H), 7.90 (d, $J=7$ Hz, 1H), and 8.21 (s, 1H); MS (70 eV) m/z (rel intensity) 110 (M^+ , 42) and 42 (100).

Parabanic acid (**13**): mp 236–240 °C (lit.²⁰) 238–244 °C; ^1H NMR (DMSO- d_6) $\delta=11.75$ (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 , $\text{AcOEt}:\text{Me}_2\text{CHOH}:\text{H}_2\text{O}=75:16:9$). Analysis of products was carried out by HPLC ($\text{SS}-10$, $\text{AcOEt}:\text{Me}_2\text{CHOH}:\text{H}_2\text{O}=75:16:9$, 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(3H)-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

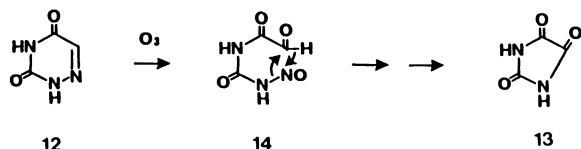


Scheme 1.

Table 1. Ozonization of Thioracils^{a)}

Run	Substrate	Substituent				Time min	Conv. %	Yield/%		
		R ¹	R ²	R ³	R ⁴			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.



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 HNO₂) to give parabanic acid (**13**). Nitrite and/or nitrate ions were detected by a sulfuric acid–iron(II) sulfate method.²⁴

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