(td, J = 12.8, 5.1 Hz, 2 H, exo H) 1.37 (s, 2 H, bridge), 1.25 (dd, J = 12.8, 5.5 Hz, 2 H, endo H); $^{13}C\{^1H\}$ NMR ($CDCl_3$), assignments aided by INEPT experiment, δ 139.1 (d, J_{CP} = 12 Hz, ipso), 133.0, 128.3 (ortho and meta), 125.1 (para), 42.1 (d, J_{CP} = 9 Hz, *C*H bridgehead), 41.5 (s, CH_2 bridge), 37.5 (d, J_{CP} = 13 Hz, *C*H β to P), 31.0 (d, J_{CP} = 13 Hz, CH_2P), 29.6 (d, J_{CP} = 7 Hz, C3 and C6); $^{31}P\{^1H\}$ NMR ($CDCl_3$) δ −17.81 (s); HRMS Calcd for $C_{33}H_{34}P_2$ 492.2136, found 492.2193.

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Ozonolysis of Substituted Uracils

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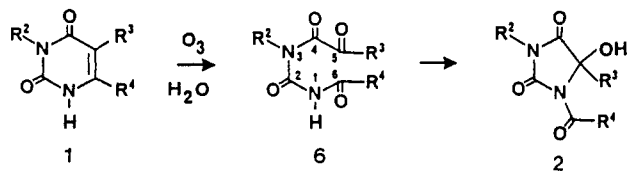
The reactions of cellular substances with ozone is one of the most important subjects in ozone chemistry. Although the ozonization reactions of DNA and RNA are of interest in connection with damage to biological systems, these reactions have received only limited attention.[1,2] With pyrimidine nucleotides, ozone preferentially attacks the base moieties.[3] Recently, the ozonolysis of uracils to give 1-acyl-5-hydroxyhydantoins has been reported.[4] Since some hydantoins have been used as anticonvulsants, their synthesis is also of interest for medicinal applications. Hydantoins are generally prepared by heating carbonyl compounds with potassium cyanide and ammonium carbonate.[5] However, little is known concerning the synthesis of 1-acyl-5-hydroxyhydantoins.[6] In order to obtain new substituted 1-acyl-5-hydroxyhydantoins, substituent effects on the ozonolysis of uracils were examined.

Table I summarizes the results of the ozonolyses of uracils. Ozonolysis of uracil (**1a**) gave 1-formyl-5-hydroxyhydantoin (**2a**) in 29% yield. This compound has previously been obtained by the radiolysis of uracil.[6] Ozonolysis of 3-methyluracil (**1b**) gave 1-formyl-5-hydroxy-3-methylhydantoin (**2b**) in 59% yield. 5-Alkyluracils **1c,d** gave the corresponding 5-alkyl-1-formyl-5-hydroxyhydantoins **2c,d** in low yields. While that of 5-phenyluracil (**1e**) did not give the 1-acyl derivative. 5-(Trifluoromethyl)uracil (**1f**), bearing a strongly electron attracting substituent, did not readily react with ozone and gave 5-hydroxy-5-(trifluoromethyl)hydantoin (**3**) in 98% yield. The ozonolyses of 5,6-dialkyl- and 6-alkyluracils **1g–j** gave the corresponding 1-acyl-5-hydroxyhydantoins **2g–j** in 32, 50, 20, and 23% yields, respectively, while 6-(trifluoromethyl)uracil (**1k**) afforded 5-hydroxyhydantoin (**4**) in 85% yield. The ozonolyses of 6-aryluracils **1l,m** gave the corresponding 1-aroyl-5-hydroxyhydantoins **2l,m**, accompanied by the formation of *N*-aroylureas. 1-Substituted uracils **1n,o** gave small amounts of parabanic acids. 5-Halouracils **1p,q** gave parabanic acid (**5**) quantitatively.

Scheme I



1 6 2

a: $R^2=R^3=R^4=H$
b: $R^2=Me$, $R^3=R^4=H$
c: $R^2=H$, $R^3=Me$, $R^4=H$
d: $R^2=H$, $R^3=Et$, $R^4=H$
g: $R^2=H$, $R^3=Me$, $R^4=Me$
h: $R^2=H$, $R^3=H$, $R^4=Me$
i: $R^2=H$, $R^3=H$, $R^4=CH_2Cl$
j: $R^2=H$, $R^3=H$, $R^4=CH_2OMe$
l: $R^2=H$, $R^3=H$, $R^4=Ph$
m: $R^2=H$, $R^3=H$, $R^4=$ *p*-$MeOC_6H_4$

Scheme I presents a reasonable reaction path for the formation of 1-acyl-5-hydroxyhydantoins. The ozonolyses of the 5–6 bond of uracils **1** gives the key intermediates **6**, followed by intramolecular cyclization to afford 1-acyl-5-hydroxyhydantoins **2**. In the ozonolyses of 5-substituted uracils, the reaction time to ozonize the substrate completely varied drastically with substituent, and increased in the following order: H < Br, F < CF_3. This reactivity order suggests an electrophilic ozone attack. The yield of **2** increased in the following order based on substituent: Ph < Et < Me < H. These results indicate that a bulky 5-substituent depresses the cyclization of **6**. The substituent at the 5-position affects the reaction time with ozone much more so than does one at the 6-position. The steric bulk of the 6-substituent does not affect the cyclization of **6**. An electron-releasing methyl group increases the electron density at the N-1 position of **6**, accelerating the cyclization. 1-Acyl-5-hydroxyhydantoins thus obtained showed no optical activity. It is well known that amides are easily hydrolyzed to give amines. Among simple amides, hydrolysis stability is substituent dependent, increasing in the order HCO < Ac < Bz. The lability of the haloacetyl derivatives to mild acid hydrolysis increases in the order Ac < $ClCH_2CO$ < Cl_2CHCO < Cl_3CCO < F_3C-CO.[7] Since a small amount of water is contained in acetic acid, it is likely that amides are easily hydrolyzed to give amines during the ozonolysis reaction. Other hydrolysis processes of N-1–C-2, C-2–N-3, and N-3–C-4 bonds of the key intermediates **6** to form urea derivatives also compete with the cyclization process.

In the ozonolyses of 1-methyluracils **1n,o**, parabanic acids can be produced by the mechanism proposed in the literature.[2]

Scheme II shows a probable mechanism in the ozonolyses of 5-halouracils **1p,q**. Key intermediates **6** can be converted into parabanic acid (**5**) by way of three processes: (a) a hydrolysis of the N-1–C-6 bond of **6** to give **7**, which in turn undergoes an intramolecular cyclization to give **8**, followed by the elimination of hydrogen halide to afford

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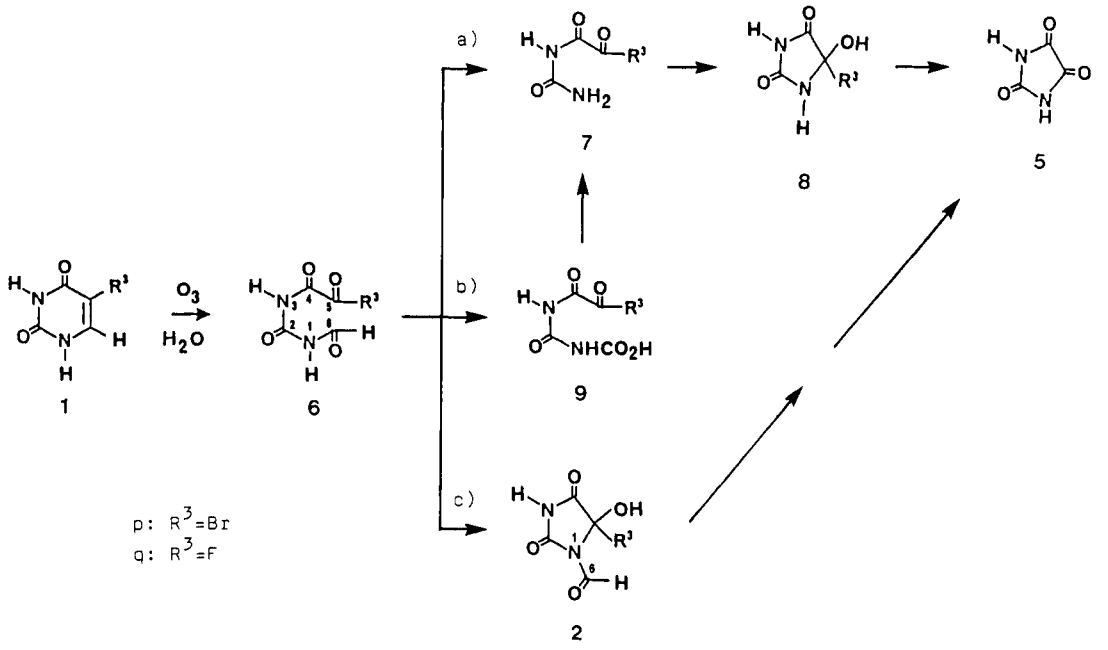
Table I. Ozonolysis of Uracils

run	substrate	R^1	R^2	R^3	R^4	time, min	yield of 2,[a] %	others (yield, %)
1	**1a**	H	H	H	H	20	29	
2	**1b**	H	Me	H	H	20	59	
3	**1c**	H	H	Me	H	20	9	
4	**1d**	H	H	Et	H	25	5[b]	
5	**1e**	H	H	Ph	H	45	0	
6	**1f**	H	H	CF_3	H	135	0	5-hydroxy-5-(trifluoromethyl)hydantoin (98)
7	**1g**	H	H	Me	Me	25	32	
8	**1h**	H	H	H	Me	20	50	
9	**1i**	H	H	H	CH_2Cl	20	20	chloroacetic acid (6) 5-hydroxyhydantoin (6)
10	**1j**	H	H	H	CH_2OMe	20	23	
11	**1k**	H	H	H	CF_3	25	0	5-hydroxyhydantoin (85)
12	**1l**	H	H	H	Ph	30	67	*N*-benzoylurea (15) *N*-formylbenzamide (trace)
13	**1m**	H	H	H	*p*-$MeOC_6H_4$	25	28	
14	**1n**	Me	H	H	H	30	–	1-methylparabanic acid (trace)
15	**1o**	Me	Me	H	H	30	–	1,3-dimethylparabanic acid (19)
16	**1p**	H	H	Br	H	45	0	parabanic acid (97)
17	**1q**	H	H	F	H	45	0	parabanic acid (98)

[a] Isolated yield. [b] Impure, determined by ^1H NMR spectroscopy.

Scheme II



5; (b) an oxidation of the formyl group at the C-6 position of **6** to give **7** via **9** as previously proposed in the literature;[2] and (c) an intramolecular cyclization of **6** to give **2** followed by the elimination of hydrogen halide and hydrolysis of the N-1–C-6 bond or the oxidation of the formyl group and decarboxylation to afford **5**.

Scheme III shows a reasonable mechanism in the ozonolyses of (trifluoromethyl)uracils (**1f,k**). In the case of 5-(trifluoromethyl)uracil (**1f**), three processes are possible for the formation of 5-hydroxy-5-(trifluoromethyl)hydantoin (**3**): (a) a hydrolysis of the N-1–C-6 bond of **6** to give **7**, which is cyclized to afford **3**; (b) an oxidation of the formyl group at the C-6 position of **6** to give carboxylic acid **9**, followed by the elimination of carbon dioxide to afford **7**, a precursor of **3**; and (c) an intramolecular cyclization of **6** to give **2**, which is in turn easily hydrolyzed and/or oxidized to afford **3**. In the ozonolysis of 6-(trifluoromethyl)uracil (**1k**), 5-hydroxyhydantoin (**4**) can be obtained by two processes: (a) a hydrolysis of the N-1–C-6 bond of **6** to give **7** followed by the cyclization and (b) an intramolecular cyclization of **6** to give **2** followed by hydrolysis of the N-1–C-6 bond to afford **4**.

Experimental Section

Instruments. Ozone was generated by a Nihon Ozon 0-1-2 ozonizer. Mass spectra were recorded on Shimadzu QP-1000 and 9020-DF spectrometers. NMR spectra were obtained by using a JEOL JNM-GX 270 FT NMR spectrometer. Melting points were measured with a Yanagimoto micro-melting point apparatus. Gas chromatography was performed on a Shimadzu 4C-PF gas chromatograph.

Starting Materials. Commercially available uracil (**1a**, Tokyo Kasei Kogyo Co., Ltd.), 5-methyluracil (**1c**, Wako Pure Chemical Industries, Ltd.), 5,6-dimethyluracil (**1g**, Nakalai Tesque, Inc.), 6-methyluracil (**1h**, Nakalai Tesque, Inc.), 6-(chloromethyl)uracil (**1i**, Tokyo Kasei Kogyo Co., Ltd.), 1,3-dimethyluracil (**1o**, Nakalai Tesque, Inc.), 5-bromouracil (**1p**, Tokyo Kasei Kogyo Co., Ltd.), and 5-fluorouracil (**1q**, Tokyo Kasei Kogyo Co., Ltd.) were used without furhter purification. The other uracils were synthesized as described in the literature. Their melting points and spectral data are given below.

3-Methyluracil (1b): mp 169 °C (lit.[8] mp 174–175 °C); ^1H NMR (270 MHz, DMSO-d_6) δ 3.12 (3 H, s), 5.57 (1 H, d, J = 7 Hz), 7.39 (1 H, dd, J = 7 and 6 Hz), 10.97 (1 H, br s); EIMS m/z

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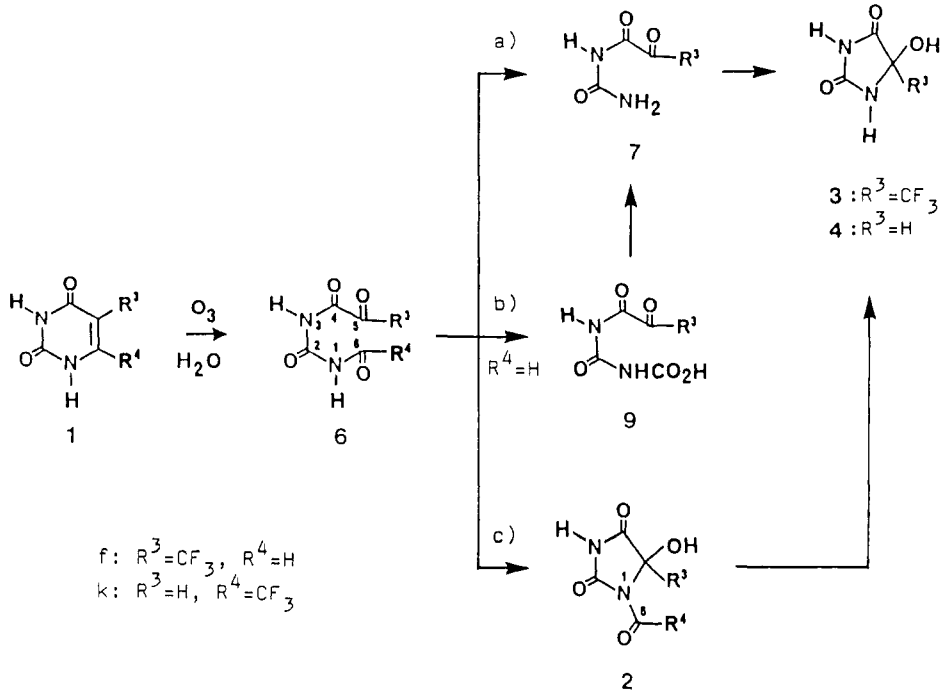
Scheme III



(rel intensity) 126 (M^+, 90), 69 (100), 68 (17), 42 (60), 41 (34).

5-Ethyluracil (1d): mp 290 °C (lit.[9] mp 300–303 °C); ^{1}H NMR (270 MHz, DMSO-d_6) δ 0.99 (3 H, t), 2.16 (2 H, q), 7.16 (1 H, d, J = 6 Hz), 10.61 (1 H, br s), 10.97 (1 H, br s); EIMS m/z (rel intensity) 140 (M^+, 100), 125 (99), 96 (13), 82 (96), 69 (59).

5-Phenyluracil (1e): mp >300 °C (lit.[9] mp >350 °C); ^{1}H NMR (270 MHz, DMSO-d_6) δ 7.25–7.53 (5 H, m), 7.61 (1 H, s), 11.12 (1 H, s), 11.24 (1 H, s); EIMS m/z (rel intensity) 188 (M^+, 100), 145 (18), 144 (38), 117 (19).

5-(Trifluoromethyl)uracil (1f): mp 245–249 °C (lit.[10] mp 247–249 °C); ^{1}H NMR (270 MHz, DMSO-d_6) δ 8.01 (1 H, s), 11.58 (2 H, br s); EIMS m/z (rel intensity) 180 (M^+, 100), 137 (53), 136 (7), 110 (41), 109 (16), 108 (8), 91 (22).

6-(Methoxymethyl)uracil (1j) was prepared by treating 6-(chloromethyl)uracil with sodium methoxide: mp 203–205 °C; ^{1}H NMR (270 MHz, DMSO-d_6) δ 3.30 (3 H, s), 4.10 (2 H, s), 5.43 (1 H, s), 10.94 (1 H, br s), 10.98 (1 H, br s); EIMS m/z (rel intensity) 156 (M^+, 18), 126 (53), 83 (24), 68 (100).

6-(Trifluoromethyl)uracil (1k): mp 242–243 °C (lit.[11] mp 220–222 °C); ^{1}H NMR (270 MHz, DMSO-d_6) δ 6.05 (1 H, s), 11.53 (1 H, br s), 12.06 (1 H, br s); EIMS m/z (rel intensity) 180 (M^+, 55), 137 (29), 68 (100).

6-Phenyluracil (1l): mp 266–270 °C (lit.[12] mp 270 °C); ^{1}H NMR (270 MHz, DMSO-d_6) δ 5.82 (1 H, s), 7.49–7.74 (5 H, m), 11.15 (1 H, br s), 11.16 (1 H, br s); EIMS m/z (rel intensity) 188 (M^+, 100), 145 (37), 117 (7), 104 (26).

6-Anisyluracil (1m) was prepared according to the same procedure as the synthesis of 6-phenyluracil,[12] i.e., 6-(*p*-methoxyphenyl)-2-thiouracil was treated with chloroacetic acid: mp 288 °C; ^{1}H NMR (270 MHz, DMSO-d_6) δ 3.82 (3 H, s), 5.74 (1 H, s), 7.03 (2 H, d, J = 9 Hz), 7.70 (2 H, d, J = 9 Hz), 10.88 (1 H, s), 10.92 (1 H, s); EIMS m/z (rel intensity) 218 (M^+, 100), 176 (14), 175 (16), 147 (3), 134 (14).

1-Methyluracil (1n): mp 178–182 °C (lit.[13] mp 232 °C); ^{1}H NMR (270 MHz, DMSO-d_6) δ 3.23 (3 H, s), 5.50 (1 H, dd, J = 8 and 2 Hz), 7.58 (1 H, d, J = 8 Hz), 11.07 (1 H, br s); EIMS m/z (rel intensity) 126 (M^+, 52), 83 (30), 82 (18), 55 (32), 42 (100).

The purity of all starting materials was checked by TLC (SiO_2; EtOAc–Me_2CHOH–H_2O, 75:16:9).

General Procedure for the Ozonolysis of Uracils. To uracils (2 mmol) dissolved in acetic acid (100 mL), an O_3–O_2 mixture (O_3, 0.22 mmol min^{-1}; O_2, 200 mL min^{-1}) was bubbled through at 20 °C. The end point of the reaction was monitored by TLC (SiO_2; EtOAc–Me_2CHOH–H_2O, 75:16:9). After the reaction, in order to remove the dissolved ozone, nitrogen gas (200 mL min^{-1}) was bubbled through the solution for 5 min. The solution was allowed to stand overnight. The disappearance of peroxide activity was checked by a KI test. The products were concentrated using a rotary evaporator and isolated by column chromatography (SiO_2, EtOAc–Me_2CHOH–H_2O, 75:16:9). In all cases except **1f,k,p,q**, unidentified products which were not eluted by the mixed solvent were produced. The physical and spectral data of the isolated products are shown below.

1-Formyl-5-hydroxyhydantoin (2a): mp 153–155 °C; ^{1}H NMR (270 MHz, DMSO-d_6) δ 5.47 (1 H, d, J = 8 Hz), 7.56 (1 H, d, J = 8 Hz, exchanges with D_2O), 8.95 (1 H, s), 11.70 (1 H, br, exchanges with D_2O); ^{13}C NMR (70 MHz, DMSO-d_6) δ 75.8 (d), 154.2 (s), 158.9 (d), 171.1 (s); EIMS m/z (rel intensity) 144 (M^+, 5), 116 (54), 88 (100), 73 (51); CIMS (C_4H_{10}) m/z (rel intensity) 145 (MH^+, 100); HRMS m/z calcd for $C_4H_4N_2O_4$ 144.0171, found 144.0175. Anal. Calcd for $C_4H_4N_2O_4$: C, 33.34; H, 2.80; N, 19.44. Found: C, 33.11; H, 2.95; N, 19.25.

1-Formyl-5-hydroxy-3-methylhydantoin (2b): mp 142–146 °C; ^{1}H NMR (270 MHz, DMSO-d_6) δ 2.92 (3 H, s), 5.54 (1 H, s), 7.60 (1 H, br, exchanges with D_2O), 9.01 (1 H, s); ^{13}C NMR (70 MHz, DMSO-d_6) δ 24.4 (q), 75.2 (d), 158.9 (d), 159.4 (s), 169.8 (s); EIMS m/z (rel intensity) 158 (M^+, 3), 130 (27), 128 (24), 102 (9), 100 (22), 74 (19), 72 (34), 70 (18), 58 (100); HRMS m/z calcd for $C_5H_6N_2O_4$ 158.0328, found 158.0301. Anal. Calcd for $C_5H_6N_2O_4$: C, 37.98, H, 3.83; N, 17.72. Found: C, 37.75; H, 4.05; N, 17.57.

1-Formyl-5-hydroxy-5-methylhydantoin (2c): mp 182–184 °C; ^{1}H NMR (270 MHz, DMSO-d_6) δ 1.67 (3 H, s), 7.30 (1 H, s, exchanges with D_2O), 8.94 (1 H, s), 11.80 (1 H, br, exchanges with D_2O); ^{13}C NMR (70 MHz, DMSO-d_6) δ 20.4 (q), 84.4 (s), 153.8 (s), 158.7 (d), 173.1 (s); EIMS (rel intensity) 158 (M^+, 1), 130 (13), 115 (42), 112 (96), 102 (24), 87 (38), 59 (47), 43 (100); HRMS m/z calcd for $C_5H_6N_2O_4$ 158.0328, found 158.0343. Anal. Calcd for $C_5H_6N_2O_4$: C, 37.98; H, 3.83; N, 17.72. Found: C, 37.71; H, 3.95; N, 17.65.

1-Acetyl-5-hydroxy-5-methylhydantoin (2g): mp 179–182 °C; ^{1}H NMR (270 MHz, DMSO-d_6) δ 1.68 (3 H, s), 2.39 (3 H, s), 7.18 (1 H, s, exchanges with D_2O), 11.63 (1 H, br, exchanges with D_2O; ^{13}C NMR (70 MHz, acetone-d_6) δ 21.6 (q), 25.9 (q), 87.6 (s),

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153.5 (s), 170.2 (s), 172.3 (s); EIMS m/z (rel intensity) 172 (M^+, 5), 130 (46), 129 (43), 102 (39), 87 (29), 86 (69), 59 (18), 43 (100); HRMS m/z calcd for $C_6H_8N_2O_4$ 172.0484, found m/z 172.0478. Anal. Calcd for $C_6H_8N_2O_4$: C, 41.86; H, 4.68; N, 16.27. Found: C, 41.52; H, 4.73; N, 15.94.

1-Acetyl-5-hydroxyhydantoin (2h): mp 139–143 °C; ^1H NMR (270 MHz, DMSO-d_6) δ 2.62 (3 H, s), 5.61 (1 H, d, J = 8 Hz), 7.53 (1 H, d, J = 8 Hz, exchanges with D_2O), 11.65 (1 H, br, exchanges with D_2O); ^{13}C NMR (70 MHz, DMSO-d_6) δ 24.7 (q), 77.5 (d), 153.4 (s), 168.7 (s), 170.7 (s); EIMS m/z (rel intensity) 158 (M^+, 6), 130 (9), 116 (36), 115 (45), 88 (15), 87 (23), 72 (34), 43 (100); HRMS m/z calcd for $C_5H_6N_2O_4$ 158.0328, found 158.0293. Anal. Calcd for $C_5H_6N_2O_4$: C, 37.98; H, 3.83; N, 17.72. Found: C, 37.75; H, 3.96; N, 17.51.

1-(Chloroacetyl)-5-hydroxyhydantoin (2i): mp 138–143 °C; ^1H NMR (270 MHz, DMSO-d_6) δ 4.75 (1 H, d, J = 16 Hz), 4.86 (1 H, d, J = 16 Hz), 5.55 (1 H, d, J = 8 Hz), 7.64 (1 H, d, J = 8 Hz, exchanges with D_2O), 11.72 (1 H, br, exchanges with D_2O); ^{13}C NMR (70 MHz, DMSO-d_6) δ 44.8 (t), 78.0 (d), 153.2 (s), 165.0 (s), 170.5 (s); EIMS m/z (rel intensity) 174 ($M^+ - H_2O$, 10), 143 (27), 115 (62), 72 (99), 44 (100); CIMS (C_4H_{10}) m/z (rel intensity) 193 (MH^+, 100). Anal. Calcd for $C_5H_5N_2O_4Cl$: C, 31.19; H, 2.62; N, 14.55. Found: C, 31.16; H, 2.45; N, 15.12.

1-(Methoxyacetyl)-5-hydroxyhydantoin (2j): mp 171–172 °C; ^1H NMR (270 MHz, DMSO-d_6) δ 3.34 (3 H, s), 4.40 (1 H, d), 4.49 (1 H, d), 5.52 (1 H, s), 11.62 (1 H, br, exchanges with D_2O); ^{13}C NMR (70 MHz, DMSO-d_6) δ 58.6 (q), 72.0 (t), 77.6 (d), 153.3 (s), 169.1 (s), 171.0 (s); EIMS m/z (rel intensity) 72 (26), 45 (100); CIMS (C_4H_{10}) m/z (rel intensity) 189 (MH^+, 100). Anal. Calcd for $C_6H_8N_2O_5$: C, 38.30; H, 4.28; N, 14.89. Found: C, 37.72; H, 4.05; N, 14.30.

1-Benzoyl-5-hydroxyhydantoin (2l): mp 102–104 °C; ^1H NMR (270 MHz, DMSO-d_6) δ 5.80 (1 H, s), 7.5–7.7 (5 H, m), 11.52 (1 H, br, exchanges with D_2O); ^{13}C NMR (70 MHz, DMSO-d_6) δ 78.3 (d), 128.2 (d), 129.0 (d), 132.5 (d), 134.6 (s), 152.5 (s), 168.2 (s), 171.0 (s); EIMS m/z (rel intensity) 220 (M^+, 6), 105 (100), 77 (11); HRMS m/z calcd for $C_{10}H_8N_2O_4$ 220.0484, found m/z 220.0491. Anal. Calcd for $C_{10}H_8N_2O_4$: C, 54.55; H, 3.66; N, 12.72. Found: C, 54.73; H, 3.81; N, 12.51.

1-Anisoyl-5-hydroxyhydantoin (2m): mp 158–161 °C; ^1H NMR (270 MHz, DMSO-d_6) δ 3.39 (3 H, s), 5.83 (1 H, d, J = 8 Hz), 7.00 (2 H, d, J = 9 Hz), 7.49 (1 H, d, J = 8 Hz, exchanges with D_2O), 7.68 (2 H, d, J = 9 Hz), 11.46 (1 H, br, exchanges with D_2O); ^{13}C NMR (70 MHz, DMSO-d_6) δ 55.5 (q), 78.1 (d), 113.2 (d), 126.2 (s), 131.6 (d), 152.5 (s), 162.7 (s), 167.0 (s), 171.0 (s); EIMS m/z (rel intensity) 250 (M^+, 11), 177 (4), 152 (4), 151 (5), 136 (12), 135 (100), 107 (4); HRMS m/z calcd for $C_{11}H_{10}N_2O_5$ 250.0589, found 250.0586. Anal. Calcd for $C_{11}H_{10}N_2O_5$: C, 52.80; H, 4.03; N, 11.20. Found: C, 52.56; H, 4.24; N, 11.48.

5-Hydroxy-5-(trifluoromethyl)hydantoin (3): mp 181–182 °C; ^1H NMR (270 MHz, DMSO-d_6) δ 8.33 (1 H, s, exchanges with D_2O), 9.34 (1 H, s, exchanges with D_2O), 11.34 (1 H, br, exchanges with D_2O); ^{13}C NMR (70 MHz, DMSO-d_6) δ 82.8 (q, J = 33 Hz), 121.7 (q, J = 285 Hz), 155.7 (s), 169.1 (q, J = 3 Hz); EIMS m/z (rel intensity) 115 ($M^+ - CF_3$, 24), 87 (3), 44 (100); CIMS (C_4H_{10}) m/z (rel intensity) 185 (MH^+, 100). Anal. Calcd for $C_4H_3N_2O_3F_3$: C, 26.10; H, 1.64; N, 15.22. Found: C, 26.40; H, 1.72; N, 15.49.

5-Hydroxyhydantoin (4): mp 153–156 °C (lit.[14] mp 157–158 °C; ^1H NMR (270 MHz, DMSO-d_6) δ 5.09 (1 H, d, J = 8 Hz), 6.68 (1 H, d, J = 8 Hz, exchanges with D_2O), 8.28 (1 H, s, exchanges with D_2O), 10.59 (1 H, br s, exchanges with D_2O); ^{13}C NMR (70 MHz, DMSO-d_6) δ 77.3 (d), 157.3 (s), 174.9 (s); EIMS m/z (rel intensity) 116 (M^+, 3), 88 (100), 60 (23), 59 (55), 45 (62).

Parabanic acid (5): mp 236–240 °C dec lit.[1] mp 238–244 °C (dec); ^1H NMR (270 MHz, DMSO-d_6) δ 11.75 (2 H, br); EIMS m/z (rel intensity) 114 (M^+, 72), 86 (64), 43 (100).

1-Methylparabanic acid: mp 145–148 °C (lit.[15] mp 155–157 °C); ^1H NMR (270 MHz, DMSO-d_6) δ 2.92 (3 H, s), 12.00 (1 H, br); EIMS m/z (rel intensity) 128 (M^+, 13), 101 (7), 43 (100).

1,3-Dimethylparabanic acid: mp 150 °C (lit.[2] mp 153 °C); ^1H NMR (270 MHz, DMSO-d_6) δ 2.97 (6 H, s); EIMS m/z (rel intensity) 142 (M^+, 100), 114 (10), 70 (19).

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Benzoylurea: mp 215 °C (lit.[16] mp 211–213 °C); ^1H NMR (270 MHz, CD_3OD) δ 5.30 (1 H, br), 7.48–7.87 (5 H, m), 8.38 (2 H, br); EIMS m/z (rel intensity) 164 (M^+, 46), 147 (5), 136 (16), 121 (7), 120 (5), 105 (100), 77 (17).

***N*-Formylbenzamide**: mp 84 °C; ^1H NMR (270 MHz, CD_3OD) δ 7.5–8.0 (5 H, m), 9.31 (1 H, s); EIMS m/z (rel intensity) 149 (M^+, 16), 122 (5), 121 (61), 105 (100), 77 (10).

Chloroacetic acid in the ozonolysis of (**1i**) was identified by comparing the mass spectrum with that of authentic sample and determined by gas chromatography. The conditions were as follows: column, 2% FFAP on Gas Chrom Q (80–100 mesh), 4 mm × 1 m, glass; column temperature, 80–210 °C, programmed at 10 °C min^{-1}; injection temperature, 220 °C; detector temperature, 240 °C; detector, FID.

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Registry No. **1a**, 66-22-8; **1b**, 608-34-4; **1c**, 65-71-4; **1d**, 4212-49-1; **1e**, 15761-83-8; **1f**, 54-20-6; **1g**, 26305-13-5; **1h**, 626-48-2; **1i**, 18592-13-7; **1j**, 124461-06-9; **1k**, 672-45-7; **1l**, 13345-09-0; **1m**, 33166-97-1; **1n**, 615-77-0; **1o**, 874-14-6; **1p**, 51-20-7; **1q**, 51-21-8; **2a**, 43152-24-5; **2b**, 124443-47-6; **2c**, 77719-76-7; **2d**, 124443-48-7; **2g**, 124443-49-8; **2h**, 124443-50-1; **2i**, 124443-51-2; **2j**, 124443-52-3; **2l**, 124443-53-4; **2m**, 124443-54-5; **3**, 105480-41-9; **4**, 29410-13-7; 1-methylparabanic acid, 3659-97-0; 1,3-dimethylparabanic acid, 5176-82-9; parabanic acid, 120-89-8; *N*-benzoylurea, 614-22-2; 6-(*p*-methoxyphenyl)-2-thiouracil, 33166-87-9.

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A Highly Convergent Synthesis of Benzimidazolylpiperidines

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The lithiation of suitably protected imidazoles and benzimidazoles has recently attracted considerable synthetic attention.[1] Of the various groups used to protect the imidazole nitrogen, the benzyl group is generally considered to be unsuitable due to problems of competing benzylic metalation.[2] We have maintained a long-standing interest in the chemistry and pharmacology of 4-aroylpiperidines. In this regard, we wished to prepare some 4-(2-benzimidazolyl)piperidines related to Astemizole (1), a recently marketed nonsedating antihistamine.[3] We now report a convenient synthesis of benzimidazolylpiperidine **2**, which relies on the acylation of 1-(4-fluorobenzyl)-benzimidazole. The 4-fluorobenzyl group in this instance not only serves as a protecting group allowing C_2-deprotonation but also as a part of the desired pharmacophore.

The benzimidazole portion of **2** was synthesized via the alkylation of benzimidazole (**3**) with 4-fluorobenzyl chloride

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