Dehydrohalogenation of Some 3',5'-Dichloro-2',3',5'-trideoxynucleosides[1]

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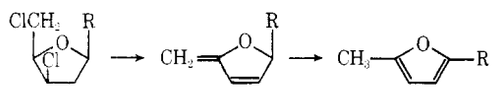
The 3',5'-dichloro-2',3',5'-trideoxynucleosides prepared from the parent 2'-deoxyribonucleosides with thionyl chloride in hexamethylphosphoramide were dehydrochlorinated to their corresponding diolefinic nucleosides. Treatment of 9-(3,5-dichloro-2,3,5-trideoxy-β-D-*threo*-pentofuranosyl)adenine (**1**) with dilute sodium hydroxide in ethanol gave the endocyclic diolefinic nucleoside 9-[2-(5-methylfuryl)]adenine (**11**). In contrast, similar treatment of 1-(3,5-dichloro-2,3,5-trideoxy-β-D-*threo*-pentofuranosyl)thymine (**3**) and the corresponding uracil derivative (**4**) afforded the exocyclic diolefinic nucleosides 2-methylene-5(*R*)-(thymin-1-yl)-2,5-dihydrofuran (**8**) and 2-methylene-5(*R*)-(uracil-1-yl)-2,5-dihydrofuran (**9**). Dehydrochlorination of 9-(3,5-dichloro-2,3,5-trideoxy-β-D-*threo*-pentofuranosyl)hypoxanthine (**2**) and 1-(3,5-dichloro-2,3,5-trideoxy-β-D-*threo*-pentofuranosyl)cytosine (**5**) gave under the same conditions a mixture of the exo- and endocyclic diolefinic nucleosides. On the other hand, treatment of all 3',5'-dichloro-2',3',5'-trideoxynucleosides with strong base, such as potassium *tert*-butoxide in dimethyl sulfoxide, gave exclusively the endocyclic diolefinic nucleosides.

Various synthetic approaches have been used to introduce endo- and exocyclic unsaturation into the sugar moiety of both purine and pyrimidine nucleosides.[2] For instance, Robins and co-workers[3,4] recently reported the preparation of the three possible endocylic unsaturated nucleosides derived from adenosine as well as the 2',3' and 3',4' olefinic nucleosides derived from tubercidin. The syntheses of the exocyclic 4',5'-unsaturated nucleosides derived from adenosine and from the pyrimidine nucleosides have been described by Moffatt and colleagues.[5,6] The endocyclic diolefinic nucleosides 1-[2-(5-methylfuryl)]thymine (**13**) and 9-[2-(5-methylfuryl)]adenine (**11**) have been prepared by Horwitz et al.[7] and McCarthy and co-workers[8] from 3',5'-di-*O*-mesylthymidine and 5'-*S*-ethyl-3'-*O*-tosyl-5'-thio-2',5'-dideoxyadenosine, respectively, via base-catalyzed double-elimination reactions. On the other hand, dehydrohalogenation of 3',5'-dideoxy-3',5'-diiodothymidine with silver fluoride in pyridine or of 1-(2,3,5-trideoxy-5-iodo-β-D-*glycero*-pent-2-enofuranosyl)-thymine with 1,5-diazabicyclo[4.3.0]non-4-ene in acetonitrile yielded the exocyclic diolefinic nucleoside 2-methylene-5(*R*)-(thymin-1-yl)-2,5-dihydrofuran (**8**). Our earlier observation[9] that 9-(3,5-dichloro-2,3,5-trideoxy-β-D-*threo*-pentofuranosyl)adenine (**1**) is readily converted to **11** in weak alkali prompted us to investigate the dehydrohalogenation of several base analogues of **1**. The conversion of **1** to **11** involves the intermediacy of the exocyclic diolefinic nucleoside 2-methyl-5(*R*)-(adenin-9-yl)-2,5-dihydrofuran (**6**), which readily isomerizes to the stable endocyclic nucleoside. In contrast, treatment of the corresponding dichlorotrideoxy derivatives of thymine (**3**) and uracil (**4**) with ethanolic sodium hydroxide under identical conditions gave exclusively the exocyclic biolefinic nucleosides **8** and **9**. However, when **3** or **4** are treated with a strong base such as potassium *tert*-butoxide in dimethyl sulfoxide the endocyclic dienes 1-[2-(5-methylfuryl)]thymine (**13**) and 1-[2-(5-methylfuryl)]uracil (**14**) are the only nucleoside products. Apparently the two exocyclic pyrimidine nucleosides **8** and **9** do not isomerize in weak alkali because under these conditions the thymine (pK_a = 9.8) and uracil (pK_a = 9.2) moieties carry a negative charge, thus rendering the anomeric proton less acidic. Indeed, dehydrochlorination of 1-(3,5-dichloro-2,3,5-trideoxy-β-D-*threo*-pentofuranosyl)cytosine which is only partially ionized (pK_a = 12.3) in weak alkali yields a mixture of the exocyclic and endocyclic nucleosides **10** and **15**. Similarily dehydrohalogenation of 9-(3,5-dichloro-2,3,5-trideoxy-β-D-*threo*-pentofuranosyl)hypoxanthine (**2**) (pK_a = 8.9) in dilute sodium hydroxide yields a mixture of the exocyclic and endocyclic hypoxanthine derivatives **7** and **12**. It would thus appear that the anomeric proton of the hypoxanthine moiety is of intermediate acidity probably because the negative charge on the purine ring is diffuse. Attempts to isolate the exocyclic diolefinic nucleosides **7** and **10** as homogeneous preparations have been unsuccessful; during the workup both nucleosides convert to the more stable endocyclic derivatives **12** and **15**. Irradiation of all the UV-quenching exocyclic biolefinic nucleosides **6–10** on paper chromatograms with UV light causes isomerization to the fluorescent endocyclic nucleosides.



R			
adenin-9-yl	1	6	11
hypoxanthin-9-yl	2	7	12
thymin-1-yl	3	8	13
uracil-1-yl	4	9	14
cytidin-1-yl	5	10	15

While reaction of 2'-deoxycytidine with thionyl chloride in hexamethylphosphoramide yields 1-(3,4-dichloro-2,3,5-trideoxy-β-D-*threo*-pentofuranosyl)cytosine (**5**) in good yield, similar treatment of 2'-deoxyinosine gave only dark intractable mixtures. Furthermore, deamination of 3',5'-dichloro-2',3',5'-trideoxyadenosine (**1**) with sodium nitrite in acetic acid as described by MacNutt[10] did not yield the desired inosine derivative **2**. However, smooth deamination of **1** was effected using nitrosyl chloride in dimethylformamide at 0 °C.

The ^1H NMR and ^{13}C NMR spectra of all the nucleosides are consistent with the assigned structures (Tables I and II). Robins and co-workers[11] have recently shown that the 2'-*pro-R* proton of the pyrimidine 2'-deoxynucleosides resonates at lower field than 2'-H_S while in the case of the purine 2'-deoxynucleosides the reverse is the case. As pointed out before[12] chlorination of 2'-deoxyribonucleosides at C-3' occurs with inversion of configuration to yield the threo isomer. Thus the chlorine atom causes shielding of 2'-H_S while 2'-H_R is no longer shielded by the hydroxyl group. As a result the 2'-protons of **5** show markedly different chemical shifts (2'-H_S at higher field) while compared to the parent deoxyribonucleoside, 2'-deoxyinosine, the order of the 2'-methylene protons of **2** is reversed (2'-H_S also at higher field). Furthermore, the anomeric proton of both **2** and **5** appears as a quartet because the coupling constants between H-1' and the two C-2' protons are quite distinct. The ^{13}C NMR spectra of **2** and **5** also demonstrate chlorination of C-3' and C-5'; the replacement of the hydroxyl group at both carbons by a chloro group is accompanied by a large unfield shift of both carbon resonances. The ^1H NMR spectra of the endocyclic biolefinic nucleosides show the expected proton signals for the methylfuryl moiety. While H-2' appears as a doublet, the small long-range coupling between the methyl protons and H-3' produces a doublet at high field corresponding to the methyl

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Table I. ^{1}H NMR Spectral Data of Nucleosides[a]

compd	registry no.	H-1′	H-2′	H-3′	H-4′	H-5′	Other
2	66792-18-5	6.36 (q, 1) $J_{1',2'H_S}$ = 3.1 $J_{1',2'H_R}$ = 7.5	2.78 (o, 1) H_S 3.24 (o, 1) H_R $J_{2'H_S,2'H_R}$ = −14.4 $J_{2'H_S,3'}$ = 1.9 $J_{2'H_R,3'}$ = 5.6	4.93 (o, 1) $J_{3',4'}$ = 3.8	4.48 (sext, 1) $J_{4',5'}$ = 6.3	3.94 (d, 2)	12.42 (s, 1) C_6OH 8.24 (s, 1) C_8H 8.08 (s, 1) C_2H
12	66792-19-6		6.58 (d, 1) $J_{2',3'}$ = 3.2	6.30 (o, 1) $J_{3',5'}$ = 0.8		2.34 (d, 3)	12.57 (s, 1) C_6OH 8.32 (s, 1) C_8H 8.09 (s, 1) C_2H
5	64710-39-0	6.00 (q, 1) $J_{1',2'H_S}$ = 2.2 $J_{1',2'H_R}$ = 7.5	2.42 (o, 1) H_S 3.13 (o, 1) H_R $J_{2'H_S,2'H_R}$ = −15.5 $J_{2'H_S,3'} \sim 1$ $J_{2'H_R,3'}$ = 5.8	4.84 (o, 1) $J_{3',4'}$ = 3.4	4.50 (sext, 1) $J_{4',5'}$ = 6.5	3.98 (d, 2)	9.83; 8.78 (s) NH 8.09 (d, 1) C_6H 6.22 (d, 1) C_5H $J_{5,6}$ = 7.9
8	52523-38-3	7.11 (t, 1) $J_{1',2'}$ = 1.8 $J_{1',3'}$ = 1.7	6.77 (q, 1) $J_{2',3'}$ = 5.8	6.42 (2 sextets, 1) $J_{3',5'H_Z}$ = 1.6 $J_{3',5'H_E}$ = 0.9		4.40 (q, 1) H_Z 4.27 (m, 1) H_E $J_{5'H_Z,5'H_E}$ = −3.4	11.50 (5, 1) NH 6.97 (d, 1) C_6H 1.75 (d, 3) C_5Me $J_{6,5Me}$ = 1.3
13	5983-11-9		6.36 (d, 1) $J_{2',3'}$ = 3.1	6.19 (o, 1) $J_{3',5'}$ = 0.8		2.27 (d, 3)	11.58 (s, 1) NH 7.57 (s, 1) C_6H 1.80 (d, 3) C_5Me $J_{6,5Me}$ = 1.3
9	66792-20-9	7.11 (t, 1) $J_{1',2'}$ = 1.7 $J_{1',3'}$ = 1.5	6.79 (q, 1) $J_{2',3'}$ = 5.7	6.42 (2 sextets, 1) $J_{3',5'H_Z}$ = 1.5 $J_{3',5'H_E}$ = 0.9		4.42 (q, 1) H_Z 4.27 (m, 1) H_E $J_{5'H_Z,5'H_E}$ = −3.3	11.48 (s, 1) NH 7.12 (d, 1) C_6H 5.64 (q, 1) C_5H $J_{5,6}$ = 8.0 $J_{5,NH}$ = 2.1
14	66792-21-0		6.38 (d, 1) $J_{2',3'}$ = 3.2	6.19 (o, 1) $J_{3',5'}$ = 0.9		2.27 (d, 3)	11.51 (s, 1) NH 7.67 (d, 1) C_6H 5.69 (d, 1) C_6H $J_{5,6}$ = 8.0
15	6679-22-1		6.18 (d, 1) $J_{2',3'}$ = 3.2	6.15 (o, 1) $J_{3',5'}$ = 0.6		2.26 (d, 3)	7.61 (d, 1) C_6H 7.40 (s, 2) NH_2 5.84 (d, 1) C_5H $J_{5,6}$ = 7.4

[a] All spectra were determined at 80 MHz in Me_2SO-d_6; chemical shifts are in ppm downfield from external Me_4Si. Coupling constants were estimated from the peak positions determined by computer examination of the final Fourier-transformed spectrum.

Table II. ^{13}C NMR Chemical Shifts of Nucleosides[a]

compd	registry no.	C-2	C-4	C-5	C-6	C-8	C-1′	C-2′	C-3′	C-4′	C-5′	C_5-Me
1	63162-55-0	152.68	149.06	118.74	155.91	138.41	82.36	41.04	59.02	81.86	43.07	
2		146.14	147.98	124.31	156.65	137.97	82.83	41.22	58.88	82.19	42.85	
12		147.09	150.17	124.23	156.71	139.15	148.37	107.86	103.42	138.57	13.22	
3	34627-68-4	150.29	163.56	109.45	135.47		83.47	40.43	59.18	81.40	41.28	12.47
8		150.49	163.60	110.62	134.99		89.22	130.68; 130.82		161.94	84.40	12.14
13		149.84	164.07	110.00	139.92		149.59	107.52	105.14	142.14	13.21	11.63
4	64032-44-6	150.44	163.19	101.67	140.11		84.06	41.50	59.02	81.88	42.56	
9		150.39	162.84	102.86	139.81		89.27	130.63; 130.72		161.77	84.60	
14		149.82	163.34	102.33	144.51		149.82	107.56	105.43	141.93	13.21	
5		143.25	159.48	93.39	146.68		86.09	40.45	58.88	83.52	41.93	
15		148.42	165.93	94.75	144.27		153.82	107.30	103.18	144.50	13.15	

[a] Chemical shifts are given relative to Me_4Si at 25.2 MHz, Me_2SO-d_6 (39.53 ppm) was used as the solvent.

group and a set of quartets at lower field corresponding to H-3′. The ^{13}C NMR spectra confirm the assigned structures; all carbon resonances of the ribofuranosyl moiety have undergone drastic changes on dehydrochlorination. The resonance due to C-5′ is shifted upfield while the other four carbon resonances have undergone large downfield shifts. The NMR spectra of the exocyclic biolefinic nucleosides **8** and **9** also are in accord with the 2,5-dihydrofuran structure. The signal for C_4′H is missing and the two magnetically nonequivalent exocyclic 5′-protons appear as well separated multiplets at 4.40 and 4.20 ppm. The 5′-proton cis to the ring oxygen (H_Z) was assigned to the downfield quartet because in vinyl ethers the vinylic proton cis to the oxygen is usually found 0.2–0.3 ppm downfield from the vinylic proton trans to the oxygen.[13] The ^{13}C NMR spectra show that the resonances due to carbons 2′, 3′, 4′, and 5′ have undergone large downfield shifts on dehydrochlorination while the C-1′ resonance is much less affected. These spectral properties would be expected from a 2′,3′ and

4′,5′ unsaturated system. The IR spectra of **8** and **9** also show the C=CH_2 asymmetric stretching (3100, 3080 cm^{-1}) and the wagging vibration (830 cm^{-1}) for the vinyl ether.

Experimental Section

Materials. Nucleosides were purchased from Sigma Chemical Co. or P-L Biochemicals and nitrosyl chloride from Matheson Co. The dichlorotrideoxynucleosides were prepared as described before.[12]

General Procedures. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Melting points were measured on a hot stage equipped with a microscope and are not corrected. Pulse proton nuclear magnetic resonance spectra (^1H NMR) were recorded on a Varian CFT-20 spectrometer; pulse carbon-13 nuclear magnetic resonance spectra (^{13}C NMR) were obtained using a Varian XL-100-15 spectrometer; chemical shifts are recorded in ppm downfield from an external standard of tetramethylsilane. Ultraviolet (UV) spectra were recorded with a Cary Model 15 spectrometer. Other absorbance measurements were made with a Zeiss PMQ II spectrophotometer. Optical rotation measurements were made in a 2 dm tube with a Schmidt–Haensch polarimeter. Descending chromatography on Whatman No. 1 paper was conducted with the following solvent systems: solvent I, 10:3:7 1-butanol–ethanol–water; II 25:18:7 *sec*-butyl alcohol–water–ammonium hydroxide; III 4:1:5 1-butanol–acetic acid–water. Nucleosides on paper chromatograms were detected by their absorption of ultraviolet light or by their fluorescence under ultraviolet light.

9-(3,5-Dichloro-2,3,5-trideoxy-β-D-*threo*-pentofuranosyl)-hypoxanthine (2). Nitrosyl chloride was introduced into a stirred solution of 3′,5′-dichloro-2′,3′,5′-trideoxyadenosine (**1**) (2.0 g, 6.94 mmol) in dry dimethylformamide (45 mL) at 0 °C for 1.5 h. The orange colored solution was then warmed to room temperature, cooled again, added to cold water (40 mL), and neutralized with solid sodium bicarbonate. The resulting solution was applied to a column (2 × 60 cm) of Dowex 1-X2 (CO_3^{2-}) (100–200 mesh). The column was washed with water and then eluted with 2 M ammonium carbonate. The fractions containing the desired product were combined and evaporated to dryness. The residue was triturated with cold water and crystallized from aqueous ethanol to yield 1.36 g (65%) of **2**: mp 121–123 °C; UV (H_2O, pH 7) 249 nm (ε 14.12 × 10^3). Anal. Calcd for $C_{10}H_{10}Cl_2N_4O_2 \cdot 0.75H_2O$ (302.63): C, 39.68; H, 3.83; Cl, 23.43; N, 18.51. Found: C, 39.38; H, 3.77; Cl, 23.39; N, 18.45.

1-(3,5-Dichloro-2,3,5-trideoxy-β-D-*threo*-pentofuranosyl)-cytosine (5). To a solution of thionyl chloride (5 mL) in hexamethylphosphoramide (25 mL) was added 2′-deoxycytidine hydrochloride (3.0 g, 11.4 mmol), and the mixture was stirred, with exclusion moisture, for 12 h at room temperature. To the reaction mixture was then added 1 M K_2HPO_4 (60 mL) and the solution was applied to a column (4 × 8 cm) of Dowex 50-X2 (H^+) (200–400 mesh). The column was washed with water and then eluted with 1 M ammonium hydroxide–methanol (1:1). The eluate was evaporated to dryness and the residue was crystallized from aqueous ethanol with the aid of charcoal: yield 2.14 g (62%); mp 162–164.5 °C; UV (H_2O, pH 7) 271 nm (ε 9.59 × 10^3). Anal. Calcd for $C_9H_{11}Cl_2N_3O_2 \cdot HCl$ (300.57): C, 35.96; H, 4.02; Cl, 35.39; N, 13.98. Found: C, 35.98; H, 4.01; Cl, 35.36; N, 13.88.

2-Methylene-5(*R*)-(thymin-1-yl)-2,5-dihydrofuran (8). A solution of 3′,5′-dichloro-3′,5′-dideoxythymidine (**3**) (600 mg, 2.14 mmol) in 6 N sodium hydroxide (1.2 mL, 7.2 mmol) and ethanol (6 mL) was stirred at 70 °C for 1.5 h. Ice cold water (10 mL) was then added and the solution was adjusted to pH 9 with 10% acetic acid in ethanol and concentrated to slight turbidity under reduced pressure. The concentrated solution was kept overnight at 4 °C. The product (**8**) was collected by filtration, washed with cold water, and recrystallized from ethanol: yield 299 mg (68%); mp ~150 °C[14] (lit.[6] mp 163–165 °C); UV (H_2O, pH 7) 264 nm (ε 12.19 × 10^3); $[\alpha]D^{20}$ 168.0° (*c* 0.20, ethanol).

2-Methylene-5(*R*)-(uracil-1-yl)-2,5-dihydrofuran (9). 3′,5′-Dichloro-2′,3′,5′-trideoxyuridine (500 mg, 1.89 mmol) was dehydrohalogenated as described for compound **8**. The crude product was recrystallized from ethanol–water: yield 270 mg (74%); mp 163–165 °C; UV (H_2O, pH 7) 259 nm (ε 13.01 × 10^3); $[\alpha]D^{20}$ 133.9° (*c* 0.20, ethanol). Anal. Calcd for $C_9H_8N_2O_3$ (192.18): C, 56.25; H, 4.20; N, 14.58. Found: C, 56.04; H, 4.03; N, 14.30.

9-(5-Methyl-2-furyl)hypoxanthine (12). A. A solution of 3′,5′-dichloro-2′,3′,5′-trideoxyinosine (**2**) (250 mg, 0.86 mmol) in 6 N sodium hydroxide (0.67 mL, 0.40 mmol) and ethanol (3.34 mL) was stirred at 70 °C for 1.5 h. The products were separated by preparative TLC on silica gel ($CHCl_3$–methanol, 9:1). The major fluorescent product (R_f 0.36) was eluted with methanol to give 67% (UV measurement) of the endocyclic biolefinic nucleoside **12**, which was crystallized from ethanol: yield 86 mg (46%); mp 268–271 °C; UV (H_2O, pH 7) 242 nm (ε 23.58 × 10^3). Anal. Calcd for $C_{10}H_8N_4O_2$ (216.20): C, 55.55; H, 3.73; N, 25.91. Found: C, 55.34; H, 3.66; N, 25.78.

The minor UV quenching product (R_f 0.27) was eluted with methanol to give 32% (UV measurement) of the exocyclic biolefinic nucleoside **7**. Evaporation of the solvent gave a clear gum which contained both **7** and **12**.

B. A solution of **2** (125 mg, 0.43 mmol) in dry dimethyl sulfoxide (2.5 mL) containing potassium *tert*-butoxide (148 mg, 1.32 mmol) was stirred at room temperature for 30 min. The reaction mixture was then neutralized with 3 M acetic acid and the precipitate was collected by filtration. Crystallization from ethanol gave 63.7 mg (69%) of **12** identical with the product isolated above.

1-(5-Methyl-2-furyl)thymine (13). A solution of 3′,5′-dichloro-3′,5′-dideoxythymidine (**3**) (500 mg, 1.78 mmol) in dry dimethyl sulfoxide (10 mL) containing potassium *tert*-butoxide (760 mg, 6.77 mmol) was stirred at room temperature for 2.5 h, with exclusion of moisture. The reaction mixture was then treated with ice-cold water (20 mL), neutralized with 10% acetic acid in ethanol, and evaporated to dryness under diminished pressure. The residue was triturated with cold water and crystallized from aqueous ethanol with the aid of charcoal: yield 280 mg (76%); mp 164–166 °C (lit.[7] mp 165–166.5 °C); UV (H_2O, pH 7) 264 (ε 9.28 × 10^3) and 209 nm (ε 13.92 × 10^3).

1-(5-Methyl-2-furyl)uracil (14). 3′,5′-Dichloro-2′,3′,5′-trideoxyuridine (**4**) (250 mg, 0.94 mmol) was dehydrochlorinated as just described for **3** to yield 112 mg (62%) of **14**: mp 188–189 °C; UV (H_2O, pH 7) 255 (ε 8.73 × 10^3) and 210 nm (ε 12.00 × 10^3). Anal. Calcd for $C_9H_8N_2O_3$ (192.18): C, 56.25; H, 4.20; N, 14.58. Found: C, 56.33; H, 4.21; N, 14.53.

1-(5-Methyl-2-furyl)cytosine (15). A. 3′,5′-Dichloro-2′,3′,5′-trideoxycytidine (**5**) (300 mg, 1.14 mmol) was dehydrochlorinated with potassium *tert*-butoxide as described for the preparation of **13** to give 102 mg (47%) of **15**: mp 260–262 °C; UV (H_2O, pH 7) 268 (ε 7.54 × 10^3) and 230 nm (ε 12.19 × 10^3). Anal. Calcd for $C_9H_9N_3O_2$ (191.19): C, 56.54; H, 4.75; N, 21.98. Found: C, 56.44; H, 4.75; N, 22.06.

B. A solution of **5** (250 mg, 0.95 mmol) in 6 N NaOH (0.48 mL) and ethanol (2.4 mL) was heated at 70 °C for 2.5 h. The reaction products were then separated by preparative TLC (silica gel; $CHCl_3$–methanol, 8:2). The major fluorescent product (R_f 0.60) was eluted with ethanol to give 71% (UV measurement) of the endocyclic biolefinic nucleoside, which was crystallized from aqueous ethanol to yield 103 mg (57%) of **15** identical with the product isolated above. The minor UV quenching product (R_f 0.54) was also eluted with ethanol (36%, UV measurement), but evaporation of the solvent yielded a gum which contained both **10** and **15**.

Registry No.—**5**·HCl, 66792-23-2; **7**, 66792-24-3; **10**, 66792-25-4; 2′-deoxycytidine hydrochloride, 25203-63-8.

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(14) It is probable that at this temperature **8** undergoes isomerization to the endocyclic diene **13**.