11-Hydroxy-6a,11a,11b-trihydro-5,7,8-trimethoxy-3,6a,10,11b-tetramethyldiindeno[7,1-*bc*:2,1-*e*]pyran (8). Compound 8 was isolated as a coproduct with 7 in the reduction and subsequent dehydration of **3c**. This product was isolated from the slower moving zone in the preparative thin-layer chromatographic separation: 16 mg (oil); ^{1}H NMR δ 6.77 (1 H, olefinic, J = 6 Hz), 6.54 (1 H, aromatic), 6.52 (1 H, olefinic), 6.38 (1 H, aromatic), 4.02 (3 H, methoxyl), 3.78 (3 H, methoxyl), 3.68 [1 H, C(11) methine d, J = 6 Hz], 3.63 (3 H, methoxyl), 2.82 [1 H, C(11a) methine d, J = 6 Hz], 2.29 (3 H, aromatic methyl), 2.22 (3 H, aromatic methyl), 2.10 [3 H, methyl at C(11b)], 1.46 [3 H, methyl at C(6a)].

Acknowledgment. We thank William K. Rohwedder for the mass spectral analyses.

Registry No. 1a, 39994-32-6; **1b**, 78018-35-6; **1c**, 39994-33-7; **2**, 78004-33-8; **3a**, 78004-34-9; **3b**, 78004-35-0; **3c**, 78004-36-1; **3d**, 78004-37-2; **3e**, 78004-38-3; **3f**, 78018-36-7; **4**, 78004-39-4; **5a**, 78018-37-8; **5b**, 78018-38-9; **6**, 78004-40-7; **7**, 78004-41-8; **8**, 78004-42-9; **9b**, 77028-56-9; **9c**, 77028-54-7; propyl gallate, 121-79-9.

Nucleosides. 120. Syntheses of 2′-Deoxy-ψ-isocytidine and 2′-Deoxy-1-methyl-ψ-uridine from ψ-Uridine[1]

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2′-Deoxy-ψ-isocytidine (**9**, R = H) and 2′-deoxy-1-methyl-ψ-uridine (**6**), *C*-nucleoside isosteres of deoxycytidine and thymidine, were synthesized by two different procedures. Treatment of ψ-uridine (**1**) with α-acetoxyisobutyryl chloride gave a mixture containing the 2′-chloro-2′-deoxyribosyl (**2**) and 3′-chloro-3′-deoxyxylosyl (**3**) *C*-nucleosides. After hydrodehalogenation of the mixture with n-Bu_3SnH, a mixture was obtained from which 2′-deoxy-ψ-uridine (**4**) and its 3′-deoxy isomer **5** were isolated. Compound **4** was converted into 2′-deoxy-1-methyl-ψ-uridine (**6**) by trimethylsilylation followed by treatment with methyl iodide. The mixture containing **4** and **5** was directly treated with DMF dimethyl acetal. 2′-Deoxy-1,3-dimethyl-ψ-uridine (**7**) and the 3′-deoxy analogue (**8**) were obtained from the mixture. Treatment of **7** with guanidine gave an α,β mixture of 2′-deoxy-ψ-isocytidine from which the β isomer (**9**, R = H) was isolated in low yield. Compound **8** was converted into 3′-deoxy-ψ-isocytidine (**10**) by treatment with guanidine. In the second procedure, **1** was converted into 1-methyl-ψ-uridine (**11**) which was tritylated to **12** and then thiocarbonylated to give the cyclic thionocarbonate **13**. Upon treatment of **13** with n-Bu_3SnH, three products, the 2′,3′-olefinic nucleoside **14**, 2′-deoxy-1-methyl-5′-*O*-trityl-ψ-uridine (**15**), and the 3′-deoxy *C*-nucleoside **16**, were obtained in 18%, 45%, and 25% yields, respectively. De-O-tritylation of **15** and **16** afforded the 2′-deoxy (**6**) and 3′-deoxy (**17**) analogues of 1-methyl-ψ-uridine, respectively, in good yield. Compound **15** was further methylated to 2′-deoxy-1,3-dimethyl-5′-*O*-trityl-ψ-uridine (**18**), and subsequent treatment with guanidine afforded an α,β mixture of the 2′-deoxy-ψ-isocytidine derivatives. The components were readily separated into pure isomers by chromatography. 2′-Deoxy-ψ-isocytidine (**9**, R = H) was obtained in high yield after de-O-tritylation of the β isomer **9** (R = Tr).

ψ-Isocytidine[2,3] was shown to have marked activity against several mouse leukemias that are sensitive or resistant to arabinofuranosylcytosine in vivo as well as in vitro.[4] This *C*-nucleoside is converted into the triphosphate in mouse, P815, and liver cells and incorporated into RNA.[5,6] The radioactivity of ψ-isocytidine-2-^{14}C was also found to be incorporated into the DNA of P815 or of mouse liver cells but to a much lesser extent.[5,6] Phase I clinical studies at this Center, however, showed[7] that ψ-isocytidine caused severe hepatotoxicity in humans.

Recently, we reported[8] the synthesis of the 2′-deoxy analogue of ψ-isocytidine from ψ-uridine. In preliminary tissue culture experiments, this analogue showed growth inhibitory activity against P815 cells. Whereas the growth inhibitory activity of ψ-isocytidine is reversed by cytidine (not by deoxycytidine), the activity of 2′-deoxy-ψ-isocytidine is reversed by deoxycytidine but not by cytidine. In this report, we describe details of our original syntheses of 2′-deoxy-ψ-isocytidine (a 2′-deoxy analogue of antileukemic ψ-isocytidine and also a *C*-nucleoside isostere of deoxycytidine) and 2′-deoxy-1-methyl-ψ-uridine (a *C*-nucleoside analogue of thymidine). We also report herein an alternate and more practical synthesis of these 2′-deoxy-*C*-nucleosides.

ψ-Uridine (**1**, Scheme I) was treated with α-acetoxyisobutyryl chloride[9] or acetylsalicyloyl chloride.[10] An intractable mixture containing the 2′-chloro (**2**) and 3′-chloro (**3**) derivatives was obtained which, without purification, was treated with tri-n-butyltin hydride and 2,2′-azobis(2-methylpropionitrile)[11] in boiling dimethoxyethane. Two products were isolated in crystalline form from the reaction mixture. One of these products (mp 216–217 °C) gave a

(1) This investigation was supported in part by funds from the National Cancer Institute, U.S. Department of Health and Human Services, Grants No. CA-08748 and CA-24634.

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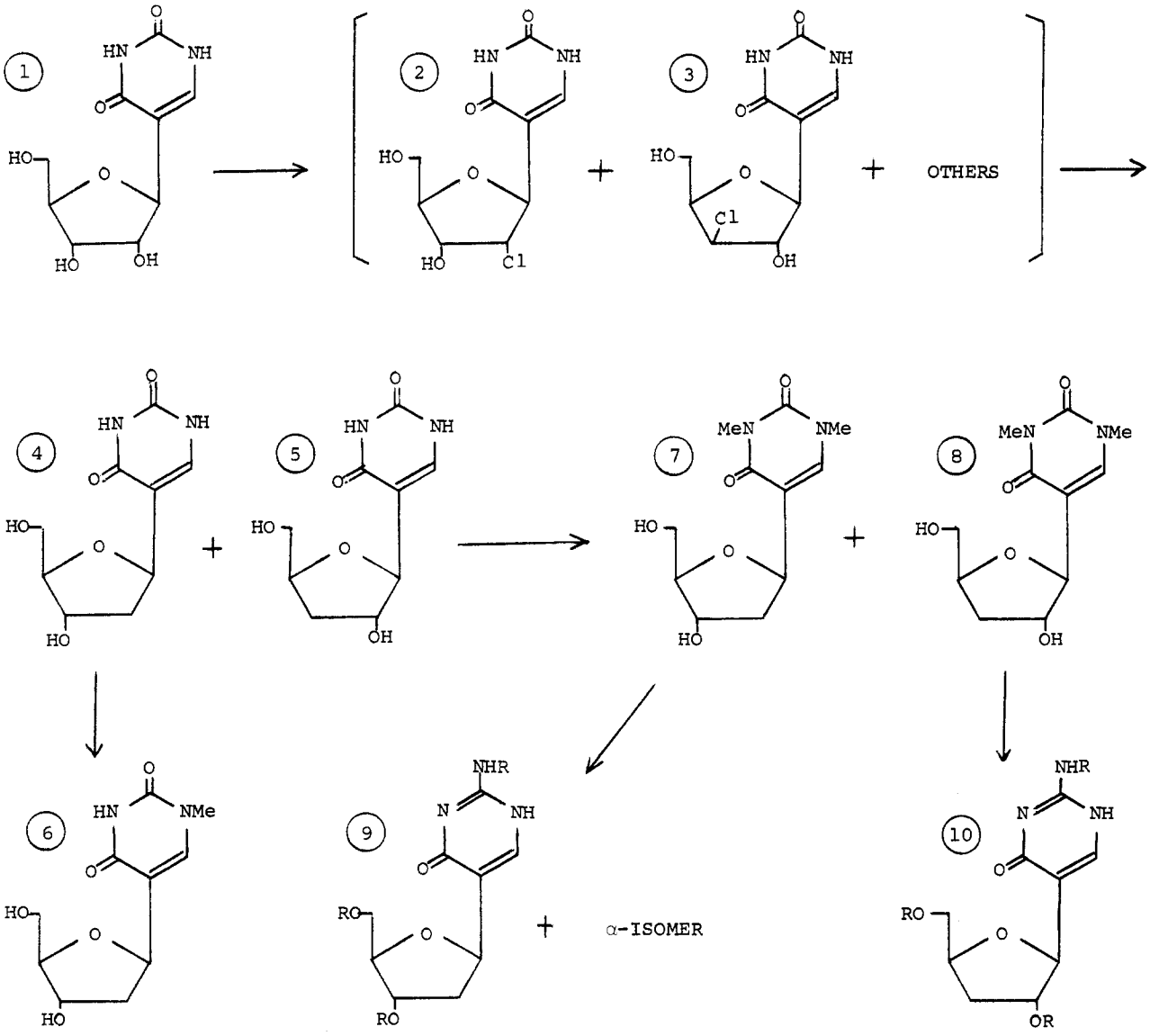
0022-3263/81/1946-3603$01.25/0

Scheme I



^{1}H NMR spectral pattern akin to that of 3′-deoxycytidine and was assigned a 3′-deoxy-ψ-uridine structure (**5**).[12] The other product (mp 221–223 °C) was the desired β isomer of 2′-deoxy-ψ-uridine (**4**).[13]

Compound **4** was converted into the thymidine analogue **6** by trimethylsilylation followed by treatment with methyl iodide. This procedure was developed in our laboratory for the synthesis of 1-methyl-ψ-uridine,[14] a natural *C*-nucleoside elaborated by *Streptomyces platensis*.[15]

For the synthesis of 2′-deoxy-ψ-isocytidine, a crude mixture containing **2** and **3** was treated with (dimethoxymethyl)dimethylamine (DMF dimethyl acetal), and the products were purified by column chromatography. The 3′-deoxy-1,3-dimethyl-ψ-uridine (**8**)[16] was eluted first, followed by the desired β isomer of 2′-deoxy-1,3-dimethyl-ψ-uridine (**7**).

Treatment of **7** with guanidine[3] afforded an α,β mixture of 2′-deoxy-ψ-isocytidine. The β isomer **9** (R = H) was obtained in 16% yield as a pure powder from the upper part of an elongated band on a thick-layer plate coated with silica gel GF_{254}. The triacetate **9** (R = Ac) was obtained in crystalline form. When the 3′-deoxy-1,3-dimethyl-ψ-uridine (**8**) was treated with guanidine, only the β isomer of 3′-deoxy-ψ-isocytidine **10** (R = H) was obtained. The triacetate **10** (R = Ac) was obtained as colorless crystals.

In the above synthesis of 2′-deoxy-ψ-isocytidine (**9**, R = H) and 2′-deoxy-1-methyl-ψ-uridine (**6**), the unavoidable formation of undesirable isomers occurred during several steps in the reaction sequence. The presence of a dissociable proton on N-1 should facilitate α,β-epimerization according to Scheme II,[17] and it is reasonable to assume that substitution of the N-1 proton by a methyl group might prevent this isomerization. Therefore, 1-methyl-ψ-uridine (**11**, Scheme III)[14] was tritylated with excess trityl chloride in pyridine, and the desired 5′-*O*-trityl product **12** was obtained in 96% yield after 5 days of reaction. Compound **12** was then treated with (thiocarbonyl)diimidazole in dry dimethylformamide at room temperature.

(12) This compound was originally assigned as the α isomer of **2**. Later this compound was synthesized and assigned as **3** by M. J. Robins and W. H. Muhs, *J. Chem. Soc., Chem. Commun.*, 677 (1978).
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(16) This compound was originally assigned as the α isomer of **7**.
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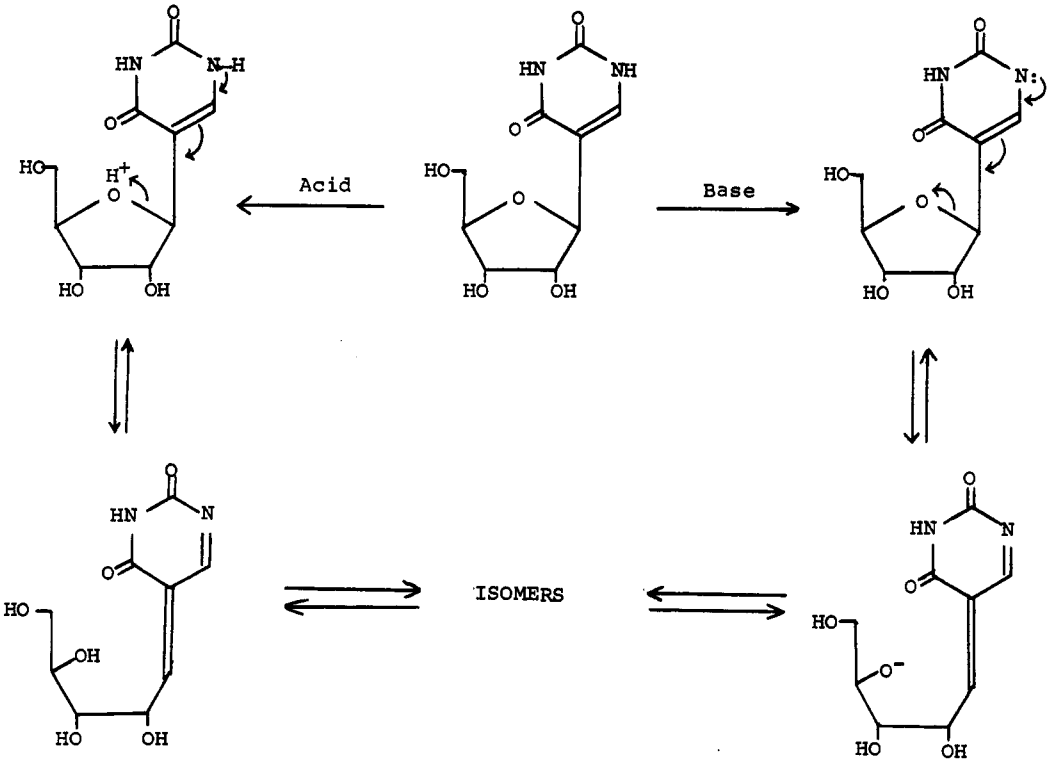
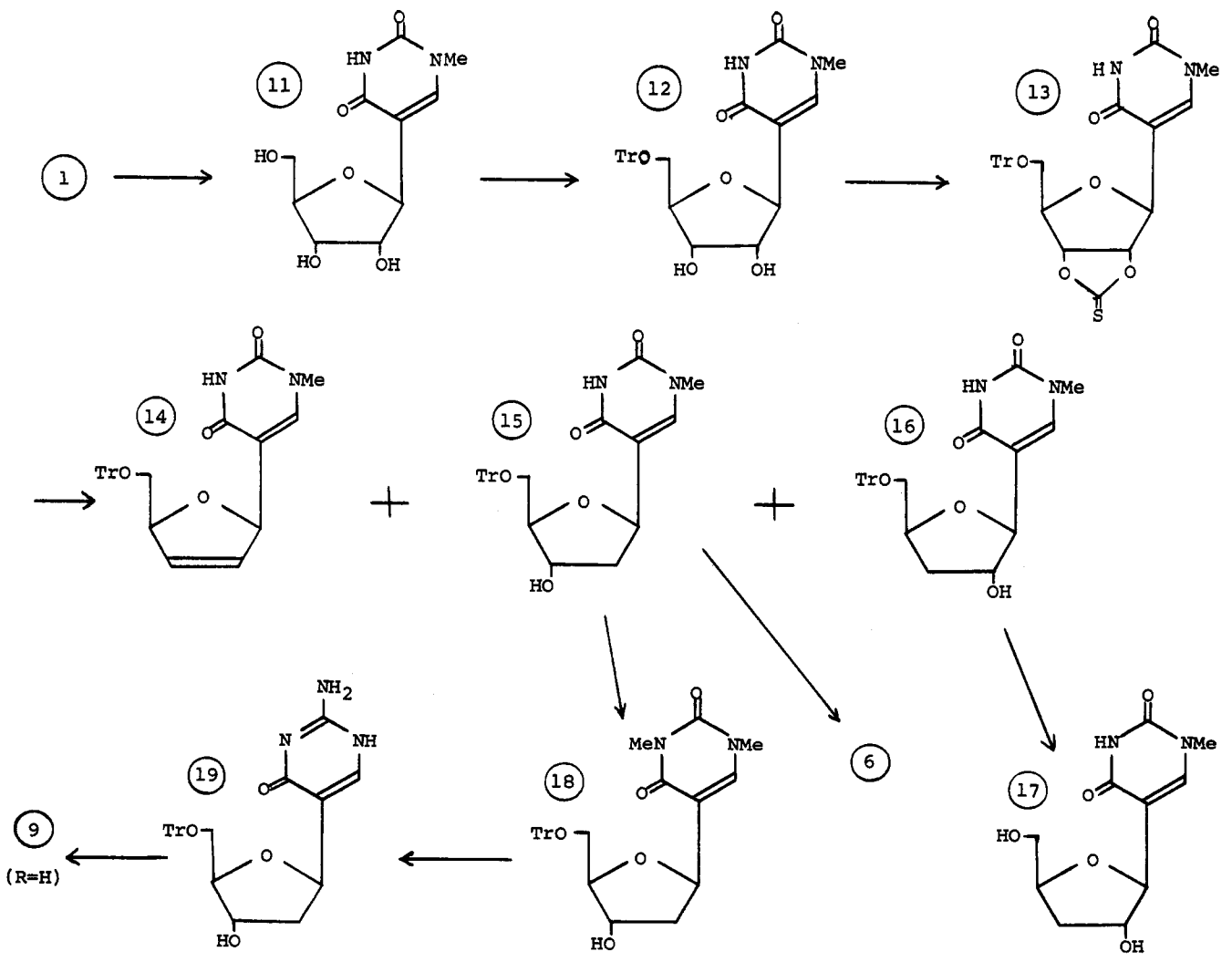
Scheme II. Mechanism of Isomerization[17]



Scheme III



The cyclic thionocarbonate **13** was obtained in quantitative yield. Unlike 5′-*O*-trityluridine, which, upon treatment with (thiocarbonyl)diimidazole, gave the corresponding 2,2′-anhydronucleoside in good yield,[18] no 4,2′-anhydro-*C*-nucleoside was detected in the reaction of **12** with this reagent. The Barton reduction[19] of the 2′,3′-cyclic thionocarbonate **13** afforded three products which could be separated easily by column chromatography. The least polar product isolated in crystalline form in 18% yield was 2′,3′-didehydro-2′,3′-dideoxy-1-methyl-5′-*O*-trityl-ψ-uridine (**14**). The β configuration was established by ^{1}H NMR analysis of the 1,4 couplings. Since the 2,3-unsaturated furanoid ring is planar and rather inflexible, the sugar ring protons in the unsaturated β-nucleoside **14** should exhibit ^{1}H NMR characteristics similar to those of the β anomer of methyl 5-*O*-benzoyl-2,3-didehydro-2,3-dideoxy-D-*glycero*-pento-2-enofuranoside ($J_{1,4}$ = 1.2 Hz) but not to those of the α anomer which exhibits a large long-range coupling ($J_{1,4}$ = 4.4 Hz).[20] The $J_{1,4}$ value for **14** is ~1.5 Hz which establishes its β configuration.

The second product obtained in 25% yield was 3′-deoxy-1-methyl-5′-*O*-trityl-ψ-uridine (**16**). After detritylation of **16** with 88% formic acid, 3′-deoxy-1-methyl-ψ-uridine (**17**) was obtained in 70% yield. The ^{1}H NMR spectrum of **17** was very similar to that of the β-*C*-nucleoside **5**. The third and major product, which was most polar, was the desired 2′-deoxy-1-methyl-5′-*O*-trityl-ψ-uridine (**15**), obtained in crystalline form in 45% yield. Detritylation of **15** with 88% formic acid gave the thymidine analogue **6** in 90% yield. It should be noted that during the conversion of ψ-uridine (**1**) into the deoxy-*C*-nucleosides, little α,β-epimerization took place, due probably to the protection of N-1 with a methyl group.

Treatment of compound **15** with DMF dimethyl acetal afforded 2′-deoxy-1,3-dimethyl-5′-*O*-trityl-ψ-uridine (**18**) in quantitative yield. Without purification, **18** was treated with guanidine, and from the reaction mixture the α and β isomers of 2′-deoxy-5′-*O*-trityl-ψ-isocytidine (**19**) were isolated in 42% and 38% yields, respectively. Detritylation of **19** with formic acid gave 2′-deoxy-ψ-isocytidine (**9**, R = H) in almost quantitative yield. The ^{1}H NMR spectrum of the product was identical with that of **9** (R = H) obtained previously by the alternate route described above.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. TLC was performed on Uniplates purchased from Analtech Co. and column chromatography on silica gel G60 (70–230 mesh, ASTM, Merck). Elemental analyses were performed by Galbraith Laboratories, Inc., or by Spang Microanalytical Laboratory. ^{1}H NMR spectra (Table I) were recorded on a JEOL PFT-100 spectrometer, and Me_4Si was the internal standard for organic solvents and DSS for deuterium oxide; chemical shifts are reported in parts per million (δ). Values given for coupling constants are first order.

2′-Deoxy-ψ-uridine (4) and 3′-Deoxy-ψ-uridine (5). A mixture of ψ-uridine (**1**, 10.0 g) and α-acetoxyisobutyryl chloride (15.0 g) in dry acetonitrile (500 mL, dried over 4-Å molecular sieves) was refluxed gently for 2 h and the solvent evaporated in vacuo. The residual syrup was dissolved in methanol (30 mL) and the solution diluted with 500 mL of ether. The syrup that precipitated was collected by decantation of the solvent. The crude syrup was dissolved in 1,2-dimethoxyethane (30 mL), and the solution was refluxed with tri-*n*-butyltin hydride (10 g) and 2,2′-azobis(2-methylpropionitrile) (1.0 g) for 48 h. The solvent was removed by evaporation in vacuo, and the residue was suspended in concentrated ammonium hydroxide (50 mL). The mixture was stirred at room temperature for 24 h and then evaporated to a syrup in vacuo. The residue was triturated with ethanol whereupon an ~1:1 mixture (4.6 g) of two products crystallized. Two recrystallizations of the solid from ethanol gave pure 2′-deoxy-ψ-uridine (**4**): 1.15 g (12.3%); mp 221–223 °C; UV (H_2O) λ_{max} 263 nm (ε 7800), λ_{min} 233 (2000).

Anal. Calcd for $C_9H_{12}N_2O_5$: C, 47.37; H, 5.30; N, 12.27. Found: C, 47.17; H, 5.44; N, 12.45.

The mother liquors of both crystallizations were placed on a column of silica gel G60 (500 g) and eluted with a mixture of chloroform and methanol (8:2). Fractions were monitored by TLC ($CHCl_3$–MeOH, 8:2). 3′-Deoxy-ψ-uridine (**5**, 1.07 g, 11.5%) was eluted first: mp 216–217 °C (after crystallization from ethanol); UV (H_2O) λ_{max} 263 nm (ε 7800), λ_{min} 233 (2000).

Anal. Calcd for $C_9H_{12}N_2O_5$: C, 47.37; H, 5.30; N, 12.27. Found: C, 47.52; H, 5.42; N, 12.01.

2′-Deoxy-1-methyl-ψ-uridine (6). A mixture of **4** (200 mg) and ammonium sulfate (~5 mg) in hexamethyldisilazane (10 mL) was heated at reflux for 2 h. The excess reagent was evaporated in vacuo to a syrup which was dissolved in acetonitrile (10 mL). Methyl iodide (2 mL) was added to the solution and the mixture stirred at room temperature for 72 h. After removal of the solvent in vacuo, the residual syrup was treated with saturated methanolic ammonia (10 mL). The mixture was filtered through a Celite pad, and the Celite was washed with methanol. The combined filtrate and washings were concentrated to dryness in vacuo. The syrupy residue was dissolved in a 9:1 mixture of chloroform and methanol and chromatographed over a column of silica gel (30 × 3 cm) by using the same solvent system as the eluent. Fractions were monitored by TLC and the product fractions were collected and evaporated to dryness. The residue was crystallized from ethanol to afford 120 mg (56.5%) of 2′-deoxy-1-methyl-ψ-uridine (**6**): mp 158–160 °C; UV (H_2O) λ_{max} 271 nm (ε 9000), λ_{min} 236 (1600).

Anal. Calcd for $C_{10}H_{14}N_2O_5$: C, 49.59; H, 5.79; N, 11.57. Found: C, 49.74; H, 5.96; N, 11.48.

2′-Deoxy-1,3-dimethyl-ψ-uridine (7) and 3′-Deoxy-1,3-dimethyl-ψ-uridine (8). A crude mixture of **4** and **5** (~1:1, 1.2 g) was treated with dimethylformamide dimethyl acetal (15 mL) at reflux temperature for 1.5 h, and then the solvent was removed by evaporation in vacuo to a syrup which was dissolved in 5 mL of a mixture of chloroform and methanol (12:1). The solution was placed on a column of silica gel G60 (30 × 3 cm) and eluted with the same solvent mixture. Two UV-absorbing fractions were obtained (R_f values of 0.5 and 0.45 in $CHCl_3$–MeOH, 9:1, on TLC). Each fraction was concentrated in vacuo to dryness, and the residue was crystallized from ethanol. 3′-Deoxy-1,3-dimethyl-ψ-uridine (**8**) was obtained from the first fraction: 300 mg (22%); mp 171–172 °C.

Anal. Calcd for $C_{11}H_{16}N_2O_5$: C, 51.56; H, 6.29; N, 10.93. Found: C, 51.42; H, 6.34; N, 10.99.

2′-Deoxy-1,3-dimethyl-ψ-uridine (**7**) was obtained from the second fraction: 300 mg (22%); mp 136–137 °C; UV (H_2O) λ_{max} 269 nm (ε 8100), λ_{min} 237 (1800).

Anal. Calcd for $C_{11}H_{16}N_2O_5$: C, 51.56; H, 6.29; N, 10.93. Found: C, 51.26; H, 6.39; H, 10.90.

2′-Deoxy-ψ-isocytidine (9, R = H). Guanidine hydrochloride (2.5 g, 0.04 mol) was added to 4 M ethanolic sodium ethoxide (20 mL), stirred at room temperature for 10 min, and filtered from sodium chloride. The filtrate was evaporated to dryness in vacuo below 35 °C. To the residue was added compound **7** (300 mg), and the mixture was heated to 90–100 °C for 70 min. After cooling, water (20 mL) was added to the mixture. Insoluble impurities were removed by filtration, the filtrate passed through a column of Amberlite IRC-50 (H^+) (30 × 3 cm), and the column washed with water. UV-absorbing fractions were combined and evaporated to give a white solid (300 mg). Of this solid residue, 150 mg was dissolved in water (5 mL) and the solution added to a column of Dowex 1 (OH^-) (100–200 mesh, 30 × 3 cm). The column was eluted with water. Fractions containing UV-absorbing material were combined and evaporated to dryness in vacuo to give an α,β mixture of 2′-deoxy-ψ-isocytidine (115 mg, 43%).

The mixture (50 mg) was separated on a thin-layer plate (coated with silica gel GF_{254}, 20 × 10 cm) after three developments in a 2-propanol–ethyl acetate–water (2:2:1) system. The upper band was extracted with water. The extracts were evaporated to dryness

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Table I. ^{1}H NMR Parameters[a] for *C*-Nucleosides

compd	chemical shifts, δ										approx coupling constants, Hz								
	H-1′	H-2′	H-2″	H-3′	H-3″	H-4′	H-5′	H-5″	H-6	others	$J_{1',2'}$	$J_{1',2''}$	$J_{2',2''}$	$J_{2',3'}$	$J_{3',4'}$	$J_{4',5'}$	$J_{4',5''}$	$J_{5',5''}$	solvent
4	4.97 t	2.05–2.19 m		4.35 m		3.97 m	3.64 m (2 H)		7.57 s		7.2	8.5							D_2O
5	4.66 d	4.32 m		1.87–1.99 m[b]		4.32 m	3.61 dd	3.82 dd	7.58 s		2.7					3.4	5.2	12.5	D_2O
6	4.81 dd	1.73–2.11 m		4.13 m		3.70 m	3.44 d (2 H)		7.61 s		4.6	6.1							Me_2SO-d_6
7	5.04 dd	2.08–2.30 m		4.39 m		4.01 m	3.70 m (2 H)		7.72 s	3.30 s (3 H, 1-Me), 3.42 s (3 H, 3-Me)	6.0	6.4							D_2O
8	4.74 d	4.40 m		1.91–2.04 m		4.40 m	3.69 dd	3.90 dd	7.73 s	3.30 s (3 H, 1-Me), 3.42 s (3 H, 3-Me)	2.4					3.3	5.2	12.5	D_2O
9 (R = Ac)	5.11 dd	2.00–2.64 m		5.27 d		4.25–4.45 m (3 H)			7.92 s	2.11 s (3 H), 2.14 s (3 H) 2.27 s (3 H) 3 × Ac	4.9	6.1							D_2O
9 (R = H)	4.83 t	1.89 m (2 H)		4.13 m		3.70 m	3.40 d (2 H)		7.59 s		7.6	8.2							Me_2SO-d_6
10 (R = Ac)	4.75 s	5.18 brs		2.05[c]		4.18–4.32 m (3 H)			7.80 s	2.05 brs (7 H, 2Ac, H-3′), 2.15 s (4 H, Ac, H-3″)									Me_2SO-d_6
10 (R = H)	4.71 d	4.39 m		1.91–2.03 m		4.39 m	3.65 dd	3.86 dd	7.69 s		2.4					3.5	5.5	12.5	D_2O
12	4.81 d	4.25–4.10 m (3 H)					3.25 dd	3.41 dd		3.16 s (3 H, Me), 7.24–7.49 m (16 H, Tr, H-6)	5.8					2.8	3.4	10.4	$CDCl_3$
13	4.86 d	5.55 d		5.38 dd		4.26 dd	3.39 d (2 H)			3.30 s (3 H, Me), 7.23–7.48 m (16 H, Tr, H-6)	3.1			7.6	4.6	8.7			$CDCl_3$
14	5.81 q	6.07 dt		5.90 dq		5.04 m	3.32 d (2 H)			2.75 s (3 H, Me), 7.24–7.43 m (16 H, Tr, H-6)	1.5			6.1	1.3	2.8			$CDCl_3$
15	5.10 dd	1.94 m	2.46 m	4.42 m		4.04 dd	3.29 d			3.13 s (3 H, Me), 7.24–7.49 m (16 H, Tr, H-6)	6.4	8.6	14.6	2.8	7.3	4.3			$CDCl_3$
16	4.79 brs	4.54 m		1.97–2.20 m		4.38 m	3.22 dd	3.47 dd		2.95 s (3 H, Me), 7.25–7.52 m (16 H, Tr, H-6)						0.5	3.7	10.1	$CDCl_3$
17	4.46 d	4.10 m		1.54–1.98 m		4.10 m	3.56 m		7.69 s		0.5								Me_2SO-d_6
18	5.12 dd	1.94 m	2.47 m	4.43 brs		4.03 dd	3.30 d			3.17 s (3 H, 1-Me), 3.34 s (3 H, Me), 7.24–7.49 m (16 H, Tr, H-6)	6.3	8.5	13.3	3.2[d]	7.6	4.3			$CDCl_3$
19	4.92 dd	1.85–2.00 m		4.04 brs		3.82 m	3.05 d		7.64 s		6.1	9.2				4.9			Me_2SO-d_6

[a] Signals are quoted as s (singlet), d (doublet), t (triplet), q (quartet), dd (double doublet), dt (double triplet), dq (double quartet), m (multiplet), brs (broad singlet). [b] Five lines. [c] Overlapped with Ac signals. [d] $J_{2'',3'} = 5.3$ Hz.

to a syrup which was coevaporated several times with ethanol until a colorless powder was obtained: 8 mg (16%); UV (H_2O) λ_{max} 289 nm (ϵ 4700), λ_{min} 249 (2400).

Anal. Calcd for $C_9H_{13}N_3O_4 \cdot H_2O$: C, 44.08; H, 6.17; N, 17.13. Found: C, 44.32; H, 6.26; N, 16.98.

$N,O^{3'},O^{5'}$-Triacetyl-2'-deoxy-ψ-isocytidine (9, R = Ac). Guanidine hydrochloride (2.5 g) was added to ethanolic sodium ethoxide (freshly prepared by dissolving 550 mg of metallic sodium in 25 mL of ethanol), and the mixture was stirred for 10 min. The precipitated sodium chloride was removed by filtration and the filtrate concentrated in vacuo to a syrup. Compound **7** (460 mg) was mixed with the syrup, and the mixture was heated at 95 °C for 40 h. After the reaction mixture was cooled to room temperature, pyridine (3 mL) and acetic anhydride (3 mL) were added, and the mixture was stirred for 15 h. Insoluble crystals were removed by filtration, and the filtrate was diluted with ethanol (10 mL) and then evaporated in vacuo to a syrup, which was dissolved in a 12:1 mixture of chloroform and methanol and chromatographed on a silica gel column (30 × 3 cm) with the same solvent mixture as the eluant. The nucleoside fractions were collected and evaporated in vacuo. The residue was crystallized from ethanol to give 340 mg of an α,β mixture. The mother liquor was evaporated and the residue recrystallized from ethanol to give pure **9** (R = Ac): 100 mg, (16%); mp 194–197 °C.

Anal. Calcd for $C_{15}H_{19}N_3O_7$: C, 50.99; H, 5.38; N, 11.89. Found: C, 50.93; H, 5.40; N, 11.90.

3'-Deoxy-ψ-isocytidine (10, R = H). Compound **8** (500 mg) was treated with guanidine as in the synthesis of **9**. After heating at 95 °C for 1 h, the mixture was cooled to room temperature and dissolved in water (25 mL), and the solution was passed through a column of Amberlite IRC-50 (H^+) (18 × 3 cm). The column was washed with water. The UV-absorbing fractions were collected and evaporated in vacuo to a hygroscopic white powder (1.0 g) which was dissolved in ethanol and then precipitated with acetone to give 360 mg of solid. This product was further purified by paper chromatography (Whatman No. 1 paper, 46 × 57 cm) with 2:2:1 mixture of 2-propanol–ethyl acetate–water as the solvent. The UV-absorbing band was extracted with water, and the extracts were evaporated in vacuo. The residue was coevaporated several times with ethanol until colorless powder was obtained; 70 mg (16%).

Anal. Calcd for $C_9H_{13}N_3O_4 \cdot H_2O$: C, 44.08; H, 6.17; N, 17.13. Found: C, 44.18; H, 5.83; N, 17.04.

$N,O^{2'},O^{5'}$-Triacetyl-3'-deoxy-ψ-isocytidine (10, R = Ac). A mixture of **10** (R = H, 220 mg), acetic anhydride (2 mL), and pyridine (4 mL) was stirred overnight at room temperature. Insoluble materials were removed by filtration, and the filtrate was diluted with ethanol (10 mL) and then evaporated in vacuo. The solid residue was recrystallized from ethanol to give 95 mg (28%) of **10** (R = Ac), mp 254–256 °C.

Anal. Calcd for $C_{15}H_{19}N_3O_7$: C, 50.99; H, 5.38; N, 11.89. Found: C, 51.09; H, 5.50; N, 11.92.

1-Methylpseudouridine (11). A suspension of pseudouridine (28 g, 115 mmol) and ammonium sulfate (50 mg) in hexamethyldisilazane (300 mL) was heated at reflux until a clear solution was obtained (about 2 h). The solvent was removed by evaporation in vacuo and the residue dissolved in a mixture of acetonitrile (500 mL, dried over 4-Å molecular sieves) and methyl iodide (200 mL). The mixture was protected from moisture, stirred for 65 h, and then evaporated to a syrup in vacuo. A mixture of water (150 mL), methanol (50 mL), and Amberlite IR-45 (OH^- form, 700 mL) was added to the residue with shaking. The whole mixture was placed on a column (5 × 40 cm) which was eluted with a 1:4 mixture of ethanol and water (1.5 L) and then with ethanol until the last of the UV-absorbing material was eluted from the column. The combined eluates were evaporated in vacuo, and the residue was crystallized from hot ethanol to afford 27.3 g (92%) of **11**, mp 180–181 °C (lit.[14] mp 181–182 °C). The ^1H NMR spectrum of this sample was identical with that of an authentic sample.[14]

1-Methyl-5'-*O*-tritylpseudouridine (12). A solution of **11** (5.16 g, 20 mmol) and trityl chloride (6.67 g, 24 mmol) in dry pyridine (100 mL) was stirred at room temperature. Additional trityl chloride was added at 24 and 48 h (2.0 g each), and the mixture was stirred 3 more days. The solvent was removed in vacuo below 40 °C and the residue partitioned between chloroform (500 mL) and water (100 mL). The organic layer was separated, washed with water (3 × 100 mL), dried over sodium sulfate, and then purified by chromatography on a column of silica gel (5 × 25 cm) with 8% ethanol in chloroform as the eluant. The main UV-absorbing fractions were combined and evaporated in vacuo, and the residue was crystallized from benzene–*n*-hexane to give 9.65 g (96%) of **12**, mp 114–116 °C, mp 121–122 °C (after resolidification).

Anal. Calcd for $C_{29}H_{28}N_2O_6$: C, 69.59; H, 5.64; N, 5.60. Found: C, 69.39; H, 5.73; N, 5.56.

1-Methyl-2',3'-*O*-(thionocarbonyl)-5'-*O*-tritylpseudouridine (13). A mixture of **12** (5.0 g, 10 mmol) and (thiocarbonyl)diimidazole (2.77 g, 1.4 equiv) in dry dimethylformamide (20 mL, dried over 4-Å molecular sieves) was stirred overnight at room temperature and then directly partitioned between ethyl acetate (350 mL) and water (100 mL). The organic layer was washed with water (3 × 100 mL), dried over sodium sulfate, and evaporated in vacuo, and the residue was crystallized from ethanol to give 5.4 g (quantitative yield) of **13**, mp 140–143 °C, mp 155–158 °C dec (after resolidification).

Anal. Calcd for $C_{30}H_{26}N_2O_6S$: C, 66.41; H, 4.83; N, 5.16; S, 5.91. Found: C, 66.22; H, 5.08; N, 5.12; S, 5.70.

Reduction of 13 with Tri-*n*-butyltin Hydride. A refluxing solution of **13** (10.4 g, 19.2 mmol) in dry toluene (150 mL, dried over 4-Å molecular sieves) was treated with a mixture of 2,2'-azobis(methylpropionitrile) (2 g) and tri-*n*-butyltin hydride (20 g, 69 mmol) in dry toluene (150 mL) added dropwise over 2 h. The mixture was heated at reflux for an additional 3 h. The solvent was removed in vacuo, the residue dissolved in acetonitrile (150 mL), and the solution extracted with petroleum ether (3 × 50 mL) to remove most of the tri-*n*-butyltin derivatives. The acetonitrile solution was evaporated in vacuo, and the residue was dissolved in chloroform (50 mL) and then applied on a column of silica gel G60 (5 × 35 cm). The column was washed with chloroform (2 L) to remove residual tri-*n*-butyltin derivatives. The products were then eluted with 1% ethanol in chloroform, and the fractions were monitored by thin-layer chromatography (19:1 chloroform–ethanol). 2',3'-Didehydro-2',3'-dideoxy-1-methyl-5'-*O*-tritylpseudouridine (**14**; 1.65 g, 18%) was eluted first from the column (crystallization from hot ethanol, mp 191–192 °C) followed by 3'-deoxy-1-methyl-5'-*O*-tritylpseudoridine (**16**; 2.32 g, 25%; crystallized from methanol, mp 149–150 °C). The desired product, 2'-deoxy-1-methyl-5'-*O*-tritylpseudouridine (**15**), was eluted with 2% ethanol in chloroform: yield 4.2 g (45%); mp 174–175 °C (crystallized from acetone–ether).

Anal. Calcd for $C_{29}H_{26}N_2O_4$ (**14**): C, 74.66; H, 5.62; N, 6.00. Found: C, 74.41; H, 5.69; N, 5.78. Calcd for $C_{29}H_{28}N_2O_5$ (**15** and **16**): C, 71.89; H, 5.82; N, 5.78. Found for **16**: C, 71.73; H, 6.00; N, 5.69. Found for **15**: C, 72.00; H, 6.01; N, 5.75.

3'-Deoxy-1-methylpseudouridine (17). A suspension of **16** (885 mg, 1.8 mmol) in 88% formic acid (15 mL) was vigorously shaken for 3 min at room temperature and then quickly frozen in a dry ice–acetone bath. The formic acid was removed by lyophilization, the residue was dissolved in water (15 mL), and the insoluble materials were removed by filtration. The filtrate was evaporated in vacuo and the residue crystallized from ethanol to give 310 mg (70%) of **17**, mp 80 °C. After resolidification it melts at 174–175 °C.

Anal. Calcd for $C_{10}H_{14}N_2O_5$: C, 49.59; H, 5.83; N, 11.56. Found: C, 49.24; H, 5.93; N, 11.63.

2'-Deoxy-1-methylpseudouridine (6). A mixture of **15** (1.12 g, 2.3 mmol) in 88% formic acid (20 mL) was shaken vigorously for 3 min at room temperature and then quickly frozen in a dry ice–acetone bath. The formic acid was removed by lyophilization and the residue suspended in water (20 mL). The insoluble triphenylcarbinol was removed by filtration, the filtrate evaporated in vacuo, and the residue crystallized from ether: yield of **6**, 504 mg (90%); mp 158–159 °C (lit.[14] mp 158–160 °C). The ^1H NMR spectrum of this product was identical with that of an authentic sample.

1,3-Dimethyl-2'-deoxy-5'-*O*-tritylpseudouridine (18). A suspension of compound **15** (2.9 g, 6 mmol) in dimethylformamide dimethyl acetal (20 mL) was heated at 95–100 °C for 2 h. The solution was concentrated in vacuo to a syrup which was dissolved in chloroform, and the solution was passed through a short column of silica gel to remove traces of dimethylformamide and di-

methylformamide dimethyl acetal. The column was washed with chloroform. The combined filtrate and washings were evaporated in vacuo to a foam (2.96 g, quantitative yield) which was used directly in the next step.

Reaction of 18 with Guanidine. Guanidine hydrochloride (9.0 g, 94 mmol) was added to ethanolic sodium ethoxide (prepared by dissolving 1.6 g of metallic sodium in 100 mL of ethanol) and the mixture stirred for 5 min. Sodium chloride which precipitated was removed by filtration and the filtrate concentrated in vacuo. A solution of 18 (2.96 g, 5.94 mmol) in ethanol (10 mL) was added to the residue, and the mixture was refluxed for 4 h. After cooling to room temperature, the mixture was poured onto ice–water (600 mL) with stirring. The suspension was neutralized with acetic acid to pH ~6. The precipitate was collected by filtration, washed with water (200 mL), and redissolved in ethanol, and the solution was concentrated to dryness in vacuo. The residue was dissolved in methanol. Silica gel G60 (100 mL) was added to the solution, and the suspension was concentrated to dryness in vacuo. The residue was placed on a silica gel column (34 × 3.5 cm), and the column was washed successively with 200 mL each of chloroform, 1% ethanol in chloroform, 2% ethanol in chloroform, and 4% ethanol in chloroform. 5′-*O*-Trityl-2′-deoxy-α-ψ-isocytidine (the α isomer of **19**) was then eluted from the column with 8% ethanol in chloroform (1.5 L). Evaporation of the eluent afforded a foam (1.17 g, 42%).

Anal. Calcd for $C_{28}H_{27}N_3O_4 \cdot 0.5H_2O$: C, 70.28; H, 5.90; N, 8.78. Found: C, 69.97; H, 5.84; N, 8.53.

5′-*O*-Trityl-2′-deoxy-ψ-isocytidine (**19**) was eluted with 16% ethanol in chloroform (1.5 L). Evaporation of the solvent and recrystallization of the semicrystalline residue from ethanol afforded 1.06 g (38%) of **19**, mp 198–201 °C dec.

Anal. Calcd for $C_{28}H_{27}N_3O_4$: C, 71.62; H, 5.80; N, 8.95. Found: C, 71.36; H, 6.00; N, 8.88.

2′-Deoxy-ψ-isocytidine (9, R = H) from 19. Compound **19** (375 mg, 0.8 mmol) suspended in 88% formic acid (10 mL) was vigorously stirred for 3 min at room temperature. The mixture was quickly frozen in a dry ice–acetone bath and then lyophilized. The residue was suspended in water (10 mL), insoluble triphenylcarbinol removed by filtration, and the filtrate lyophilized. The residue was crystallized from ethanol to afford 152 mg (84%) of **9** (R = H), mp 165–167 °C. The ^{1}H NMR spectrum of this sample was identical with that of an authentic sample previously obtained by the alternate procedure.

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Registry No. 1, 1445-07-4; 4, 39967-60-7; 5, 69265-05-0; 6, 65358-15-8; 7, 65358-16-9; 8, 78064-58-1; 9 (R = H), 65358-18-1; (R = H) (α isomer), 65358-19-2; 9 (R = Ac), 65449-72-1; 10 (R = H), 78064-59-2; 10 (R = Ac), 78064-60-5; 11, 13860-38-3; 12, 78064-61-6; 13, 78064-62-7; 14, 78064-63-8; 15, 78064-64-9; 16, 78109-46-3; 17, 78064-65-0; 18, 78064-66-1; 19, 78064-67-2; 19 (α isomer), 78064-68-3; guanidine·HCl, 50-01-1; trityl chloride, 76-83-5; (thiocarbonyl)diimidazole, 6160-65-2.

Photochemistry of Alkenes. 7. $E \rightleftarrows Z$ Isomerization of Alkenes Sensitized with Benzene and Derivatives

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Contrary to numerous previous reports placing the $(E/Z)_{pss}$ ratios from benzene-sensitized isomerization of various alkenes at unity, the $(E/Z)_{pss}$ ratios for alkenes 1–4 (Table I) have been found to (a) differ from unity, with the less highly strained isomer predominating, (b) vary depending on the structure of the alkene, and (c) bear an apparently linear relationship with the triplet excitation energy of the sensitizer. The results are tentatively interpreted in terms of "nonvertical" energy transfer, with transfer occurring more efficiently to the thermodynamically less stable isomer. Possible difficulties with the quantitative aspects of this interpretation are discussed. Of several sensitizers evaluated for efficiency in effecting $E \rightleftarrows Z$ isomerization of 3,4-dimethyl-2-pentene (**2**) (Table III), *p*-xylene and phenol were found to be superior. The latter has the added advantage of being easily separated from the alkene by extraction with base.

It is generally accepted that the lowest lying triplet excited state of ethene and its simple alkyl derivatives is π,π^*.[1] Except for highly constrained cycloalkenes, the principal chemical property of this state is to undergo rotation about the double bond, with the resulting formation of a mixture of the *E* and *Z* isomers of the alkene.[2] Previous reports have indicated that high-energy triplet sensitizers, such as benzene, afford *E*/*Z* photostationary state ratios $[(E/Z)_{pss}]$ of unity.[3,4] Such a result was reasonable in light of the then-accepted value of ≤82 kcal/mol for the vertical triplet excitation energy (E_T) of alkenes but is questionable in view of recent reports placing the value considerably higher.[5] We report here that benzene and its simple derivatives in fact afford $(E/Z)_{pss}$ ratios which (a) differ from unity, with the less highly strained isomer predominating, (b) vary depending on the structure of the alkene, and (c) bear an apparently linear relationship with the triplet excitation energy (E_T) of the sensitizer.

Results

The data obtained from *E*/*Z* isomerization of alkenes

(1) For a review of the excited states of alkenes see A. J. Merer and R. S. Mulliken, *Chem. Rev.*, **69**, 639 (1969).

(2) For a review of the photobehavior of alkenes in solution see P. J. Kropp, *Org. Photochem.*, **4**, 1 (1979).

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(4) By contrast low-energy sensitizers, usually carbonyl compounds, afford $(E/Z)_{pss}$ ratios approaching thermodynamic values because of competing isomerization via a Schenck-type mechanism; see N. C. Yang, J. I. Cohen, and A. Shani, *J. Am. Chem. Soc.*, **90**, 3264 (1968), and J. Saltiel, K. R. Neuberger, and M. Wrighton, *ibid.*, **91**, 3658 (1969).

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