Photochemical Synthesis of *P*,5′-Anhydroadenosine-8-phosphonic Acid[1,2]

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Photoirradiation of diethyl 8-bromo-2′,3′-*O*-isopropylideneadenosine 5′-phosphite (**2**) provided ethyl hydrogen *P*,5′-anhydro-2′,3′-*O*-isopropylideneadenosine-8-phosphonates (**3a** and **3b**). The two isomers were subjected to deacetonation with trifluoroacetic acid to give ethyl hydrogen *P*,5′-anhydroadenosine-8-phosphonates (**4a** and **4b**). Treatment of either **4a** or **4b** with ammonium hydroxide afforded *P*,5′-anhydroadenosine-8-phosphonic acid (**5**). The steric configurations of **3a** and **3b** were determined by ^{1}H NMR spectroscopy, and the CD spectra of **4a** and **4b** were also discussed.

Cyclonucleosides are not only useful intermediates for the synthesis of nucleoside analogues but are also important tools for studies of nucleoside conformations. A number of cyclonucleosides have already been reported that bear oxygen, nitrogen, sulfur, or carbon bridges between their base and sugar moieties.[3] As a part of our studies directed toward the synthesis of cyclonucleosides, this paper deals with the synthesis of adenosine-8,5′-phosphonic acid[2] by photoirradiation.

Synthesis. Treatment of **1** with diethyl chlorophosphite in the presence of triethylamine afforded diethyl 5′-phosphite **2** in 48% yield. The structure of **2** was determined on the basis of its UV absorption and mass and proton nuclear magnetic resonance (^{1}H NMR) spectra as well as elemental analysis. Photoirradiation[4] of **2** in acetonitrile under argon gas with a low-pressure mercury lamp provided, by the repeated silica gel chromatography, two products whose isolated yields were 24% and 15%, respectively. These products were found to be diastereoisomers and were assigned the ethyl hydrogen *P*,5′-anhydro-2′,3′-*O*-isopropylideneadenosine-8-phosphonate structures (**3a** and **3b**) based on the following data: Their UV absorption maxima were similar to that of diethyl adenosine-8-phosphonate.[5] The mass spectra exhibited the same molecular ion peaks at m/z 397 with high intensity. The ^{1}H NMR spectra revealed that each two C-5′ protons were shifted downfield compared with those of **2** and could be analyzed as the spin system due to the coupling with C-4′ proton and phosphorus.[6] Their formulas, $C_{15}H_{20}N_5O_6P$, were confirmed by the elemental analyses.

The photocyclization may be explained by an intramolecular attack of the adeninyl-8-radical of **2** on the phosphite group with the formation of an 8,5′-diethoxyphosphoranyl radical.[7] The phosphoranyl radical would then decompose to **3** and an ethyl radical, which would disproportionate to **3a** and **3b** (see Scheme I).

Photoirradiation is necessary for the formation of **3** from **2**, because no irradiation resulted in recovery of **2**.

Deacetonation of **3a** or **3b** with 80% trifluoroacetic acid afforded trifluoroacetic salts of **4a** or **4b**, respectively, whose structures were established by the elemental analyses and the UV, ^{1}H NMR, and ^{31}P NMR spectra. Treatment of either **4a** or **4b** with concentrated ammonia at 50 °C overnight resulted in release of the ethoxy group to yield the ammonium salt of *P*,5′-anhydroadenosine-8-phosphonic acid (**5**). The structure of **5** was established by the elemental analysis, the UV, ^{1}H NMR, and fast atom bombardment (FAB) mass spectra. This compound is the first example of a novel type of cyclonucleoside bridged with a phosphorus atom between the base and the sugar moieties (Scheme I).

Steric Configuration of 3a and 3b. Compounds **3** may have four stereoisomers: The two conformers based on the conformation of O-5′ (endo and exo) and the two enantiomers based on the asymmetry of phosphorus (*R* and *S*). In the ^{1}H NMR spectrum of **3a**, the coupling constants of H-5′ and H-4′ were $J_{5'a,4'}$ = 2.46 Hz and $J_{5'b,4'}$ = 0 Hz. A Dreiding model of **3** showed that in the O-5′ endo conformation, the dihedral angles between the H-(5′a)–C(5′)–C(4′) and C(5′)–C(4′)–H(4′) planes, and the H(5′b)–C(5′)–C(4′) and C(5′)–C(4′)–H(4′) planes were ca. 45° and 75°, respectively, whereas in the O-5′ exo conformation, the corresponding angles were ca. 120° and 0°, respectively. In the endo form, the vicinal coupling constants of $J_{5'a,4'}$ = 4.3 Hz and $J_{5'b,4'}$ = 0.3 Hz were calculated, based on the Karplus equation, while in the exo form, the respective constants were 2.04 and 9.0 Hz. The observed coupling constants of **3a** are closer to those calculated for the endo form, which is consistent with **3a** in the O-5′ endo conformation. The observed coupling constants of **3b** were $J_{5'a,4'}$ = 2.06 Hz and $J_{5'b,4'}$ = 0 Hz, which suggests that **3b** is also the O-5′ endo conformer.

A great difference was observed in the chemical shifts of methylene protons in the ethoxy group bound to phosphorus of **3a** and **3b**: The proton signal appeared at 4.48 ppm in **3a**, while it was split at 4.44 and 4.28 ppm in **3b**. A CPK model of **3** adopting the O-5′ endo form disclosed that in the *S* configuration of phosphorus the ethoxy group has a small steric hindrance, whereas in the *R* configuration of phosphorus, the ethoxy group has more steric hindrance. If the above-described nonequivalence of the methylene proton signals could be attributable in part to the steric hindrance of the ethoxy groups, the phosphorus of **3b** would adopt the *R*-configuration. The absolute steric configuration of **3b** was determined by X-ray crystallography,[8] which supports correctness of the assumption based on the ^{1}H NMR spectrum (see Table I).

CD Spectra of 4a, 4b, and 5. The CD spectra of **4a** and **4b** reversed their signs near the UV absorption maxima but did not show an overall symmetry (Figure 1). This result may be attributable to the additivity of the spectral contribution of the asymmetric phosphorus atom

(1) Part of this work was presented at the 13th Symposium on Nucleic Acids Chemistry, Osaka, Nov 1985.

(2) This compound is tentatively named adenosine-8,5′-phosphonic acid.

(3) For a recent review on cyclonucleosides, see: Mizuno, Y. *The Organic Chemistry of Nucleic Acid*; Elsevier: Amsterdam, 1986; pp 113, 133.

(4) Photochemical cyclization of 2′,3′-*O*-isopropylidene-8-(phenylthio)adenosine to the 8,5′ (*R* and *S*)-cycloadenosines has been reported by Matsuda, A.; Tezuka, M.; Ueda, T. *Tetrahedron* **1978**, *34*, 2449.

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(8) Yamagata, Y.; Tomita, K.; Maruyama, T.; Honjo, M., submitted for publication in *Nucleosides Nucleotides*.

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Scheme I

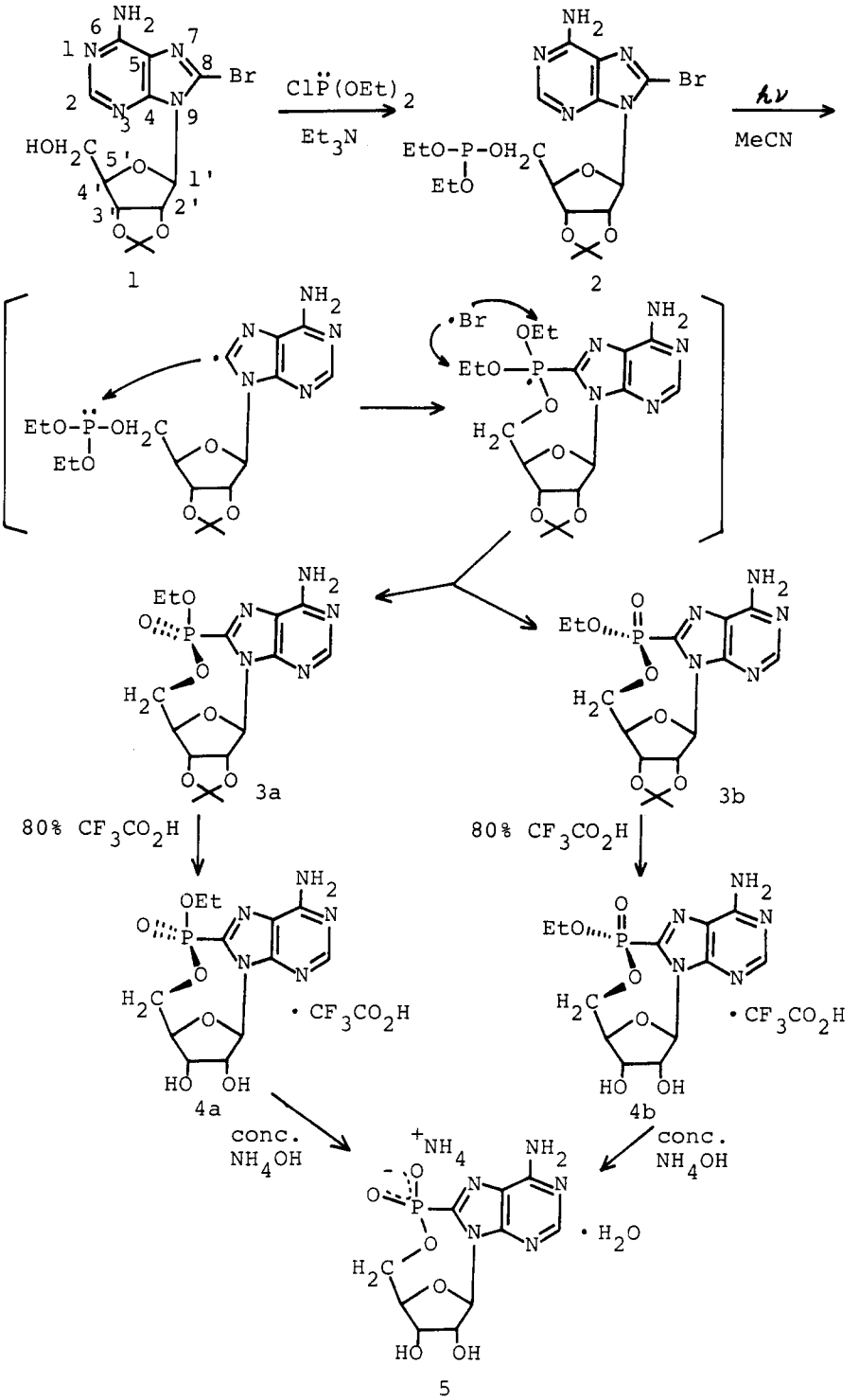

Table I. 400-MHz Proton Chemical Shifts (ppm) of *P*,5′-Anhydroadenosine-8-phosphonic Acid and Its Derivatives in $CDCl_3$ (x), DMSO-d_6 (y), or D_2O (z)

compd	H-2	NH_2	H-1′	H-2′	H-3′	H-4′	H-5′a	H-5′b	CH_2	CH_3	$C(CH_3)_2$
3a (x)	8.43 (s)	6.43 (br s)	6.73 (d)	4.80 (q)	4.98 (d)	4.74 (s-like)	5.02 (sextet)	4.32 (q)	4.48 (m)	1.47 (t)	1.67 (s), 1.38 (s)
3b (x)	8.44 (s)	6.36 (br s)	6.77 (d)	4.85 (q)	5.02 (d)	4.71 (s-like)	4.82 (octet)	4.40 (q)	4.44 (m), 4.28 (m)	1.36 (t)	1.67 (s), 1.37 (s)
4a (y)	8.39 (s)	8.5 (br s)	6.14 (d)	4.33 (q)	4.23 (t)	4.37 (s-like)	4.74 (octet)	4.23 (q)	4.32 (m)	1.37 (t)	
4b (y)	8.37 (s)	8.3 (br s), 8.5 (br s)	6.20 (d)	4.38 (m)	4.26 (t)	4.38 (s-like)	4.66 (octet)	4.44 (q)	4.22 (m), 4.14 (m)	1.24 (t)	
5 (z)	8.21 (s)		6.32 (d)	4.64 (q)	4.49 (d)	4.47 (s-like)	4.66 (octet)	4.24 (q)			

and furanose moiety in each compound. The spectra of **4a** and **4b** due to their furanose moieties and that of **5** should be similar each other, because these three compounds adopt the similar O-5′ endo furanose conformations and **5** has no asymmetric phosphorus atom. Thus, the spectra of **4a** and **4b** due to the asymmetric phosphorus

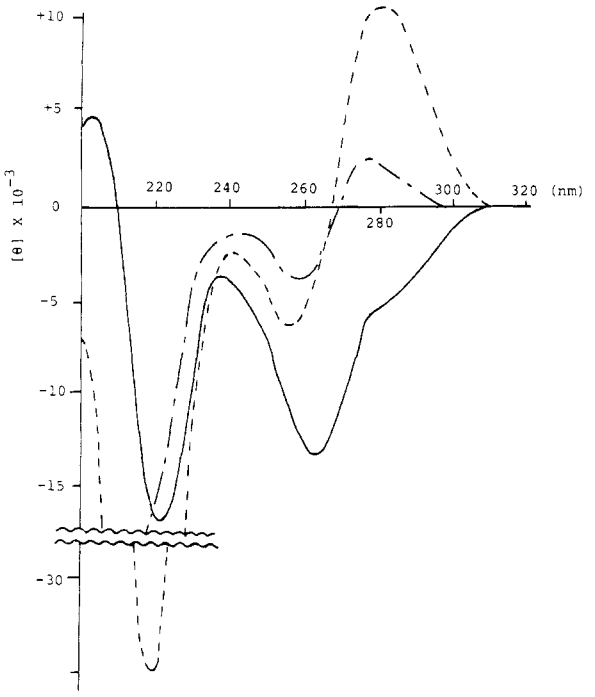

Figure 1. CD spectra of **4a** (—), **4b** (- - -), and **5** (- — -).

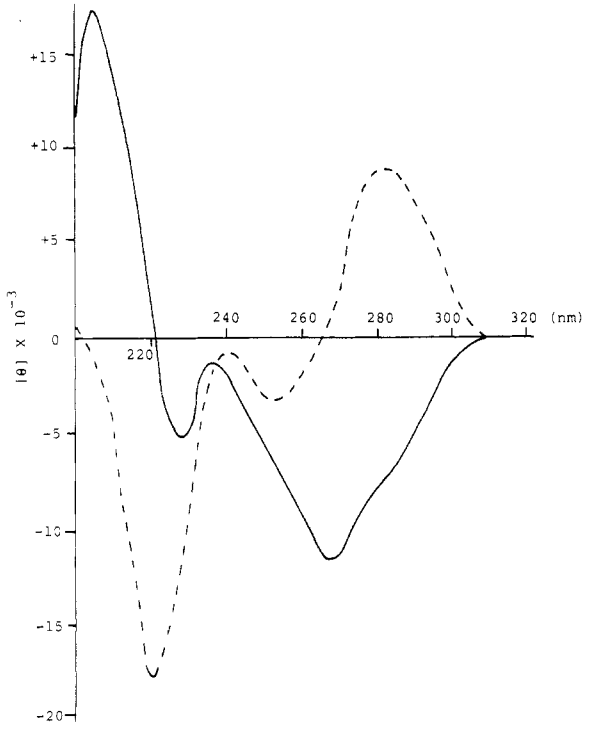

Figure 2. Calculated CD spectra of **4a** (—) and **4b** (- -) due to their P atoms.

atoms may be obtained by subtracting the spectrum of **5** from the spectra of **4a** and **4b**. These spectra are then shown to be nearly symmetrical between the upper and lower sides (Figure 2).

Experimental Section

All melting points were determined on a Yanagimoto micro-melting point apparatus (hot stage type) and are uncorrected. The UV spectra were recorded with a Shimadzu UV-190 digital spectrometer. The ^1H NMR spectra were recorded with a JEOL GX-400 (400 MHz) spectrometer in $CDCl_3$ (or DMSO-d_6) with a tetramethylsilane and in D_2O with sodium 3-(trimethylsilyl)-propionate-d_4 as an internal standard, respectively. Circular dichroism (CD) spectra were recorded with JASCO J500C spectropolarometer at 25 °C. Photoreactions were performed with low-pressure Hg lamp (a quartz filter) at a light intensity of 30 W under argon gas. Thin-layer chromatography (TLC) was carried out on plates (2 × 10 cm) coated with Wakogel B-5 including fluorescent indicator F_{254} (Merck).

Table II. First-Order Coupling Constants of P,5′-Anhydroadenosine-8-phosphonic Acid and Its Derivatives (Hz)

compd	$J_{1',2'}$	$J_{2',3'}$	$J_{3',4'}$	$J_{4',5'a}$	$J_{4',5'b}$	$J_{5'a,5'b}$	$J_{5'a,p}$	$J_{5'b,p}$
3a	1.71	5.86	*a*	2.46	0	11.97	11.66	15.87
3b	1.83	5.86	0	2.06	0	11.88	9.57	15.15
4a	2.59	4.86	4.32	2.59	0	11.89	7.46	13.40
4b	4.03	*a*	*a*	2.50	0	11.89	7.68	19.78
5	2.93	4.43	0	2.85	0	12.46	9.15	18.31

[a] Unsolved.

Diethyl 8-Bromo-2′,3′-*O*-isopropylideneadenosine 5′-Phosphite (2). Diethyl chlorophosphite (1.80 g, 11.52 mmol) and triethylamine (1.8 mL, 12.91 mmol) were added with stirring to an ice-cooled suspension of 8-bromo-2′,3′-*O*-isopropylideneadenosine (1) (4.00 g, 10.36 mmol) in dry THF (40 mL). The mixture was stirred at 0 °C for 1 h, and after further addition of triethylamine (1.8 mL), the solution was partitioned between ice–water (50 mL) and benzene (100 mL). The organic layer was washed twice with ice–water (50 mL), dried over $MgSO_4$, and evaporated to a small volume, which was chromatographed over a column of alumina (Woelm N-super 1, ϕ 3.0 × 25 cm) with a gradient (2 L) of 0–5% MeOH in AcOEt. The first fraction was evaporated to dryness to afford a caramel (**2**) (2.51 g, 48%): UV (0.1 N HCl) λ_{max} 263 nm (ϵ 16 300); UV (MeOH) λ_{max} 264 nm (ϵ 13 900); UV (0.1 N NaOH) λ_{max} 264 nm (ϵ 14 300); MS, *m/z* 507, 509 (M^+), 213, 215 (8-bromoadenine); ^1H NMR ($CDCl_3$) δ 8.15 (1 H, s, H-2), 6.10 (1 H, d, H-1′), 5.73 (2 H, br s, NH_2), 5.58 (1 H, m, H-2′), 5.09 (1 H, m, H-3′), 4.2 (1 H, m, H-4′), 3.75 (6 H, q-like, H-5′, $POCH_2CH_3$), 1.55 and 1.32 (each 3 H, s, $>C(CH_3)_2$), 1.11 (6 H, sextet, $POCH_2CH_3$). Anal. Calcd for $C_{17}H_{25}BrN_5O_6P$: C, 40.33; H, 4.98; N, 13.83. Found: C, 39.96; H, 5.18; N, 13.42.

From the second fraction, **1** was recovered (674 mg, 17%).

Ethyl Hydrogen P,5′-Anhydro-2′,3′-*O*-isopropylideneadenosine-8-phosphonate (3). A stirred solution of **2** (1.20 g, 2.37 mmol) in acetonitrile (100 mL) was irradiated at 0 °C for 2 days. After evaporation of the solvent, the residue was dissolved in a small amount of $CHCl_3$, and the solution was chromatographed over a column of silica gel G (ϕ 3.0 × 75 cm) by using a gradient (2 L) of 2–6.3% EtOH in $CHCl_3$ to remove all unknown byproducts. The main fractions were combined and evaporated to give a diastereomeric mixture of **4**, which was separated on a column of silica gel G (ϕ 2.0 × 40 cm) with a gradient (1.5 L) of 2–5% EtOH in AcOEt. The first fraction was evaporated to afford a caramel (**3a**) (229 mg, 22%): UV (0.1 N HCl) λ_{max} 272 nm (ϵ 16 800); UV (MeOH) λ_{max} 282 nm (ϵ 12 400); UV (0.1 N NaOH) λ_{max} 276 nm (ϵ 12 600); MS, *m/z* (relative intensity) 397 (M^+, 82.6), 382 (M^+–CH_3, 24.7), 354 ($M^+ - C_2H_3O$, 13.5); CD $[\theta]^{25}$ (nm) −8590 (280) (negative shoulder), −13 200 (265) (negative maximum), +3620 (228) (positive maximum); for ^1H NMR parameters, see Tables I and II. Anal. Calcd for $C_{15}H_{20}N_5O_6P \cdot {}^3/_4C_2H_5OH$: C, 45.89; H, 5.72; N, 16.22. Found: C, 45.45; H, 5.48; N, 15.84.

The second fraction was evaporated to dryness, and the solid was recrystallized from AcOEt (2 mL) to give colorless prisms (**3b**) (144 mg, 15%): mp 213–217 °C; UV (0.1 N HCl) λ_{max} 273 nm (ϵ 17 200); UV (MeOH) λ_{max} 284 nm (ϵ 12 600); UV (0.1 N NaOH) λ_{max} 268–276 nm (ϵ 12 800); MS, *m/z* (relative intensity) 397 (M^+, 89.3), 382 ($M^+ - CH_3$, 68.6), 354 ($M^+ - C_2H_3O$, 81.5); CD $[\theta]^{25}$ (nm) +9550 (281.5) (positive maximum), −1910 (258) (negative maximum), −23 500 (217) (negative maximum); for ^1H NMR parameters, see Tables I and II. Anal. Calcd for $C_{15}H_{20}N_5O_6P \cdot {}^1/_2H_2O$: C, 44.34; H, 5.21; N, 17.24. Found: C, 44.41; H, 5.20; N, 16.88.

Ethyl Hydrogen P(*S*),5′-Anhydroadenosine-8-phosphonate Trifluoroacetic Salt (4a). A solution of **3a** (220 mg, 0.51 mmol) in 80% CF_3CO_2H (2 mL) was kept at room temperature for 30 min, and the solvent was evaporated. The residue was evaporated azeotropically with water (3 mL) and triturated with EtOH (2 mL) to give white needles (168 mg, 70%):

mp >300 °C; UV (0.1 N HCl) λ_{max} 271 nm (ε 18 400); UV (H_2O) λ_{max} 280 nm (ε 14 500); UV (0.1 N NaOH) λ_{max} 279 nm (ε 14 400); ^{31}P NMR (DMSO-d_6 + D_2O) δ 1.66 (P-8); CD $[\theta]^{25}$ (nm) −5460 (280) (negative shoulder), −13 400 (263) (negative maximum), −17 080 (221) (negative maximum); for ^1H NMR parameters, see Tables I and II. Anal. Calcd for $C_{12}H_{16}N_5O_6P{\cdot}CF_3CO_2H$: C, 35.68; H, 3.64; N, 14.86. Found: C, 35.78; H, 3.87; N, 14.72.

Ethyl Hydrogen *P*(*R*),5′-Anhydroadenosine-8-phosphonate Trifluoroacetic Salt (4b). A solution of **3b** (160 mg, 0.40 mmol) in 80% CF_3CO_2H (2 mL) was kept at room temperature for 30 min. After evaporation of the solvent, the residue was triturated with a small amount of water to afford white needles (120 mg, 62%): mp >300 °C; UV (0.1 N HCl) λ_{max} 272 nm (ε 17 600); UV (H_2O) λ_{max} 281.5 nm (ε 13 600); UV (0.1 N NaOH) λ_{max} 279 nm (ε 13 500); ^{31}P NMR (DMSO-d_6 + D_2O) δ −1.50 (P-8); CD $[\theta]^{25}$ (nm) +11 370 (280) (positive maximum), −6520 (257) (negative maximum), −34 800 (220) (negative maximum); for ^1H NMR parameters, see Tables I and II. Anal. Calcd for $C_{12}H_{16}N_5O_6P{\cdot}{}^4/_5CF_3COOH{\cdot}2H_2O$: C, 33.71; H, 4.33; N, 14.45. Found: C, 33.68; H, 4.48; N, 14.74.

***P*,5′-Anhydroadenosine-8-phosphonic Acid (5). i.** Compound **4a** (100 mg, 0.21 mmol) was dissolved in concentrated NH_4OH (5 mL), and the mixture was warmed in a steel bomb at 50 °C overnight. After cooling, the solution was concentrated to 1 mL to give white crystals (47.3 mg, 62%): mp >300 °C; FAB-MS (positive), *m/z* 330 (M^+ + H); FAB-MS (negative), *m/z* 328 (M^+ − H); UV (0.1 N HCl) λ_{max} 269.5 nm (ε 19 100), 278 (sh, ε 13 400); UV (H_2O) λ_{max} 269.5 nm (ε 15 400), 275 (sh, ε 15 100), 285 (sh, ε 9700); UV (0.1 N NaOH) λ_{max} 269.5 nm (ε 15 400), 275 (sh, ε 15 000), 285 (sh, ε 9800); for ^1H NMR parameters, see Tables I and II. Anal. Calcd for $C_{10}H_{12}N_5O_6P{\cdot}NH_3{\cdot}H_2O$: C, 32.97; H, 4.70; N, 23.07. Found: C, 33.02; H, 4.47; N, 23.32.

ii. Compound **4b** (50 mg, 0.103 mmol) was treated in a similar manner to that described in section i to give white crystals (19.6 mg, 52%). The product had the same UV and ^1H NMR spectra as those of an authentic sample described above.

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Registry No. 1, 13089-45-7; **2**, 103022-70-4; **3a**, 115794-10-0; **3b**, 115794-11-1; **4a**, 115705-88-9; **4b**, 115794-13-3; **5**, 115705-89-0; $ClP(OEt)_2$, 589-57-1.

Synthesis of Ethylenes with Acyclic Quaternary Carbons by Dehydration of Neopentyl Alcohols. Application of the 2-D INAPT Technique

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Di- and triquaternary ethylenes (**5, 12** and **7, 19**, Scheme I) have been synthesized by dehydration of *sec*- and *tert*-neopentyl alcohols (**4, 11** and **6, 18**) without rearrangement. It is thought that steric factors determine the structures of the products. The intermediate imines **2** and **14**, from the reaction of nitriles **1** and **13** with *t*-C_4H_9Li, may be hydrolyzed only in the first case to ketones (**3**). More highly substituted ketones (**10** and **16**) were obtained by the reaction of *t*-RMgX (**9**) or $(CH_3)_3CMgCl$ with 3,3-dialkyl and 2,3,3-trialkyl acid chlorides (**8** and **15**). Ketones **3** and **10** were reduced by $LiAlH_4$ to secondary carbinols **4** and **11**. The tertiary carbinols **6** were prepared from **3** by treatment with *t*-C_4H_9Li. The more hindered ketones **16** failed to add *t*-C_4H_9Li, but were reduced to secondary alcohols **18**, instead of the desired tertiary alcohols **17**. The carbinols **4, 6, 11**, and **18** were dehydrated by heating with $KHSO_4$. The 2-D INAPT NMR technique was used to establish the stereostructure of **19** by measuring the long-range heteronuclear coupling constants about the ene.

Methods of synthesis of highly hindered olefins have been investigated during the last many years with the goal of obtaining the apparently unknown tetra-*tert*-butylethylene.[1] Bulky 1,2-di- and tri-*tert*-alkylethylenes are known, and several approaches have been developed to obtain them. Among these are the extrusion method of Barton,[2] the McMurry coupling reaction of carbonyls,[3] and others of more limited applicability.[4]

Perhaps the closest approach to tetra-*tert*-butylethylene has afforded the highly strained ethyltri-*tert*-butylethylene.[5] Other crowded molecules such as tetrakis(2-formyl-2-propyl)ethylene,[6] tetrasubstituted ethylenes with "tied-back" structures,[5] tetraisopropylethylene[7] and its cyclic analogues,[8] and tri-*tert*-butylethylene are known.[9] The *tert*-butyl group has been employed most frequently to produce crowding in compounds because of its size, symmetry, and availability. Also, a number of studies of the physical and, to some extent, chemical properties of such strained substances have been carried out.[10] In the present investigation, the availability of procedures and materials for changing the structure of quaternary carbon groups[11] suggested a way of obtaining a series of trialkylethylenes with more structural variability than from the usual three- and four-carbon reagents. 3,3-Dialkyl

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