965, 925, 900, 885, 865, 855, 825, 805, 765, 730, 700. Anal. Calcd for $C_{19}H_{22}NO_6$: C, 62.80; H, 6.93; N, 3.85. Found: C, 62.92; H, 6.85; N, 3.85.

3-*tert*-Butyl-4-bromo-3aα,4β,5,6,7,7aα-hexahydrobenzoxazolin-2-one (20). Treatment of the sodium salt of **1** with *tert*-butyl isothiocyanate, then iodomethane as in the preparation of **2**, gave *O*-3-cyclohexenyl *S*-methyl *N*-*tert*-butylthiocarbonimadate in quantitative yield: NMR 1.25 (s, 9 H), 1.4-2.2 (m, 6 H), 2.35 (s, 3 H), 4.95-5.4 (m, 1 H), 5.9 (app s, 2 H); IR (film) 3025, 2965, 2930, 2860, 2825, 1640, 1470, 1450, 1435, 1385, 1360, 1335, 1315, 1305, 1235, 1220, 1135, 1055, 1025, 1010, 965, 925, 915, 860, 840, 815, 800, 720. A 1 M solution of bromine in dichloromethane (11.75 mL, 11.75 mmol) was added dropwise to a suspension of silver(I) bis(collidine) perchlorate (5.5 g, 12 mmol) in 20 mL of dichloromethane. The bromine color was discharged and silver bromide precipitated during the addition. The reaction mixture was filtered and solvent removed to give white, crystalline bromonium bis(collidine) perchlorate, which was redissolved in 25 mL of dichloromethane. A solution of 2.27 g (10 mmol) of the carbonimidothioate in 5 mL of dichloromethane was added, and the reaction was stirred for 30 min. The reaction was quenched with saturated aqueous sodium carbonate, stirred for 15 h to complete the hydrolysis, and then filtered through Celite with dichloromethane rinse (2 × 10 mL). The aqueous layer was back extracted with dichloromethane (2 × 10 mL), and the combined organic extract was washed with 5% aqueous hydrochloric acid (2 × 10 mL) and saturated aqueous sodium bicarbonate (20 mL), dried, and concentrated. Chromatography with 4:1 petroleum ether-ethyl ether as eluant gave 2.374 g (86% yield) of **20**. A sample crystallized from petroleum ether-ethyl ether had mp 100-101 °C: NMR 1.50 (s, 9 H), 1.6-2.4 (m, 6 H), 3.9-4.34 (m, 2 H), 4.34-4.7 (m, 1 H); IR (KBr) 2965, 2915, 2875, 1730, 1660, 1525, 1480, 1460, 1445, 1395, 1365, 1340, 1310, 1290, 1270, 1230, 1205, 1175, 1155, 1140, 1100, 1050, 1025, 955, 890, 865, 825, 800, 760, 670, 655. Anal. Calcd for $C_{11}H_{18}BrNO_2$: C, 47.84; H, 6.57; Br, 28.93; N, 5.07. Found: C, 47.93; H, 6.60; Br, 28.94; N, 4.98.

4-Bromo-3aα,4β,5,6,7,7aα-hexahydrobenzoxazolin-2-(3*H*)-one (21). A solution of 276 mg (1 mmol) of **20** in 4 mL of trifluoroacetic acid was allowed to stand at 25 °C for 24 h. Removal of solvent and passage through a small silica column with 1:1 petroleum ether-ethyl ether as eluant gave acid-free **21**: 218 mg (99%); mp 125-126 °C (petroleum ether-ethyl ether); NMR 1.2-2.6 (m, 6 H), 3.6-4.2 (m, 2 H), 4.5-4.9 (m, 1 H), 5.87-6.4 (br s, 1 H); IR (KBr) 3250, 3125, 2950, 2940, 2860, 1750, 1640, 1545, 1445, 1420, 1385, 1365, 1350, 1320, 1285, 1250, 1235, 1205, 1175, 1115, 1075, 1040, 985, 965, 950, 880, 820, 765, 720, 700, 680, 640. Anal. Calcd for $C_7H_{10}BrNO_2$: C, 38.21; H, 4.58; Br, 36.31; N, 6.37. Found: C, 38.38; H, 4.57; Br, 36.50; N, 6.46.

4-Hydroxy-3aα,4β,5,6,7,7aα-hexahydrobenzoxazolin-2-(3*H*)-one (19a). A solution of 220 mg (1 mmol) of **21** in 5 mL of nitromethane was treated with 331.5 mg (1.5 mmol) of silver(I) trifluoroacetate and 16 μL (0.9 mmol) of water and then heated at reflux for 8 h. The reaction mixture was cooled, diluted with 5 mL of ether, and filtered through Celite with ether rinse (3 × 5 mL). The organic extract was dried, concentrated, and chromatographed with 1:1 then 1:4 petroleum ether-ethyl ether as eluant to give in order of elution the alkene (9.3 mg, 7%) and the alcohol **19a** (140 mg, 89%). **19a** was conveniently characterized as its acetate derivative **19b** (163 mg, 82% overall yield): mp 149-151 °C; NMR 1.1-2.47 (m, 6 H), 2.08 (s, 3 H), 3.58 (app t, J = 7, 1 H), 4.43-5.03 (m, 2 H), 6.63 (br s, 1 H); IR (KBr) 3260, 2935, 1740, 1720, 1440, 1415, 1375, 1360, 1300, 1235, 1220, 1170, 1100, 1075, 1060, 1040, 995, 915, 870, 840, 815, 770, 745, 710. Anal. Calcd for $C_9H_{13}NO_4$: C, 54.27; H, 6.58; N, 7.03. Found: C, 53.92; H, 6.75; N, 6.98.

Acetate **19b** was also prepared from **4a** as follows. A solution of 247 mg (1 mmol) of **4a** in 6 mL of ammonia was stirred at -33 °C. Freshly cut lithium metal (17 mg, 2.43 mmol) was added in two portions. The blue solution was stirred at -33 °C for 15 min, then excess solid ammonium chloride was added, and the ammonia was allowed to evaporate at 25 °C. The residue was triturated with dichloromethane (3 × 10 mL) with the aid of a sonicator, and the organic extract was concentrated to give 164 mg (96%) of crude **19a**. Acetylation and chromatography produced the acetate **19b** (87% overall yield from **21**), which was identical with that prepared previously according to melting point, NMR, IR, and TLC.

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Cyclonucleoside Formation and Ring Cleavage in the Reaction of 2',3'-*O*-Isopropylideneadenosine with Benzoyl Chloride and Its Substituted Derivatives

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Reaction conditions suitable for the formation of 8,5'-*O*-cycloadenosine derivatives in the reaction of 2',3'-*O*-isopropylideneadenosine (**1**) with benzoyl chloride and substituted benzoyl chlorides were investigated. Thus, reaction of **1** with *p*-toluyl chloride in a CH_2Cl_2-Et_3N mixture afforded 8,5'-*O*-cyclonucleosides **7** (34%) and **20** (11%), a noncyclized acylate **6** (30%), and a ring-cleaved imidazole compound **21** (12%). The structures of these compounds were determined by LSPD ^{13}C NMR.

The discovery that 2',3'-*O*-isopropylideneadenosine (**1**) (Chart I) was converted to its 8,5'-*O*-cyclonucleoside derivative **2**[1] prompted us to investigate the acylation of **1** using benzoyl chloride and substituted benzoyl chlorides with the aim of synthesizing the corresponding 8,5'-*O*-cyclonucleoside derivatives (Chart II).

In a reinvestigation of the preparation of **2**[2] 2',3'-*O*-isopropylideneadenosine was treated with phenyl chloroformate in pyridine following the method reported by Lyon and Reese[3] for the preparation of N^6,N^6-bis(phenoxycarbonyl)-2',3',5'-tri-*O*-acetyladenosine. 8,5'-*O*-cyclo-

(1) Anzai, K.; Hunt, J. B.; Zon, G.; Egan, W. *J. Org. Chem.* **1982**, *47*, 4281.

(2) The yield of the triacylated product **2** was low (6%) and the corresponding N^6,7-diacylate was predominant (29%) if the reaction was carried out in DMF-pyridine.[1]

(3) Lyon, P. A.; Reese, C. B. *J. Chem. Soc., Perkin Trans. 1* **1978**, 131.

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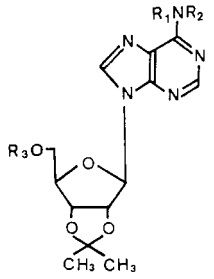
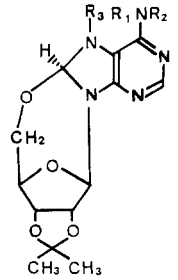
Chart I



1, $R_1 = R_2 = R_3 = H$
3, $R_1 = R_2 = R_3 = C_6H_5OCO$
4, $R_1 = H$; $R_2 = NH_2CO$; $R_3 = H$
6, $R_1 = R_2 = R_3 = p\text{-}CH_3C_6H_4CO$
8, $R_1 = R_2 = R_3 = C_6H_5CO$
10, $R_1 = R_2 = R_3 = p\text{-}CH_3OC_6H_4CO$
11, $R_1 = H$; $R_2 = R_3 = p\text{-}CH_3OC_6H_4CO$
13, $R_1 = R_2 = R_3 = p\text{-}NCC_6H_4CO$
15, $R_1 = H$; $R_2 = R_3 = C_6H_5CO$
16, $R_1 = R_2 = H$; $R_3 = C_6H_5CO$
18, $R_1 = H$, R_3,$R_3 = p\text{-}CH_3C_6H_4CO$
19, $R_1 = R_2 = H$; $R_3 = p\text{-}CH_3C_6H_4CO$

Chart II



2, $R_1 = R_2 = R_3 = C_6H_5OCO$
5, $R_1 = H$; $R_2 = NH_2CO$; $R_3 = CH_3OCO$
7, $R_1 = R_2 = R_3 = p\text{-}CH_3C_6H_4CO$
9, $R_1 = R_2 = R_3 = C_6H_5CO$
12, $R_1 = H$; R_2,$R_3 = p\text{-}CH_3OC_6H_4CO$
14, $R_1 = R_2 = R_3 = p\text{-}NCC_6H_4CO$
17, $R_1 = H$; $R_2 = R_3 = C_6H_5CO$
20, $R_1 = H$; $R_2 = R_3 = p\text{-}CH_3C_6H_4CO$

nucleoside **2**, the major product (60%), was accompanied by 13% of noncyclized compound **3**. In aqueous alkaline solutions (0.1 N NaOH in H_2O–PrOH, room temperature, 1 h) **2** was converted to **1**, but, on exposure to MeOH–NH_4OH for a short period, N^6-carbamoyl-2',3'-O-isopropylideneadenosine (**4**) was obtained accompanied by methoxycarbonyl compound **5**.

The ^1H NMR spectrum of **5** was similar to that of **2**, a 8,5'-O-cyclonucleoside structure of **5** being shown by the chemical shift at H-8 (δ 6.44) as in the case of **2** (δ 6.76). However, all the protons in **5** were detected as singlets[4] (see Experimental Section) and information about the position of methoxy and carbamoyl group was given by long-range selective proton-decoupled (LSPD) ^{13}C NMR spectrometry[5] as follows. The broad signal of a carbonyl group at δ 153.6 was converted to a quartet (J_{CH_3CO} = 4.0 Hz) by irradiating at the fequency of H-8 (δ 6.44), thus giving proof for the presence of partial structure, HC(8)–N(7)–C(O)–OCH_3. The broad signal of another carbonyl group at δ 154.5 was altered to a siglet on addition of D_2O.

Reaction of **1** with *p*-toluyl chloride in pyridine furnished two products (TLC), the main product (70%) being 2',3'-O-isoproylidene-N^6,N^6,5'-O-tri-*p*-toluyladenosine (**6**).[6] The ^1H NMR spectrum of the minor product (6%) showed that it was 8,5'-O-cyclonucleoside **7**, because of the upfield shift of H-8 from δ 8.10 in **1** to δ 6.04, which suggested that an sp_2 carbon in the base portion of **1** was changed to an sp_3 carbon. The width of the signals of *p*-toluyl groups in **7** indicated crowding within the molecule, which was also reflected in the ^{13}C NMR spectrum showing collapse of the signals of two *p*-toluyl groups at room temperature and appearance of the signals of three *p*-toluyl groups at −25 °C (see Experimental Section).

Similarly, reaction of **1** with benzoyl chloride and substituted benzoyl chlorides in pyridine (Table I, entries 1–4) afforded, in all instances, the noncyclized acylates as the main products accompanied by a small amount of 8,5'-O-cyclonucleoside derivatives of adenosine, the ^1H NMR spectra data being shown in Table II.

Reaction of **1** with benzoic anhydride in a mixture of *p*-dioxane and pyridine did not result in cyclization. However, in the absence of pyridine, **1** was partially converted to cyclonucleoside **17** (Table I, entries 5–8).

Table I. Reaction Products of 2',3'-O-Isopropylideneadenosine with Benzoyl Chloride and Its Substituted Derivatives

entry	acylating reagents	reaction conditions[a]	products (yield, %) noncyclized products	cyclized products
1	C_6H_5COCl	A	**8** (76)	**9** (6)
2	$p\text{-}CH_3C_6H_4COCl$	A	**6** (70)	**7** (6)
3	$p\text{-}CH_3OC_6H_4COCl$	A	**10** (64) **11** (16)	**12** (5)
4	$p\text{-}NCC_6H_4COCl$	A	**13** (85)	**14** (7)
5	$(C_6H_5CO)_2O$	B	**8** (34) **15** (58)	
6	$(C_6H_5CO)_2O$	C	**8** (0.5) **15** (10) **16** (62)	**17** (21)
7	$(C_6H_5CO)_2O$	D	**8** (4) **15** (35) **16** (35)	**17** (16)
8	$(p\text{-}CH_3C_6H_4CO)_2O$	D	**6** (2) **18** (26) **19** (37)	**20** (20)
9	$p\text{-}CH_3C_6H_4COCl$	E	**6** (30) **21** (12)	**7** (34) **20** (11)

[a] Reaction conditions: (A) pyridine, room temperature, 24 h; (B) *p*-dioxane–pyridine, reflux, 24 h; (C) *p*-dioxane, reflux, 6 h; (D) *p*-dioxane, reflux, 24 h; (E) CH_2Cl_2–Et_3N, room temperature, 24 h.

Table II. ^1H NMR Chemical Shifts (δ)[a] of 8,5'-O-Cycloadenosine Derivatives

no.	H-2[b]	H-8[b]	H-1'[b]	H-5'a[c]	H-5'b[c]
2	8.52	6.76	5.90	4.00	4.00
5	8.22	6.44	5.80	3.92	3.92
7	8.18	6.04	5.80	3.92	3.36
9	8.20	6.08	5.82	3.92	3.34
12	8.54	6.08	5.84	3.96	3.50
14	8.16	6.08	5.82	3.94	3.30
17	8.56	6.02	5.82	3.90	3.34
20	8.56	6.02	5.82	3.92	3.40

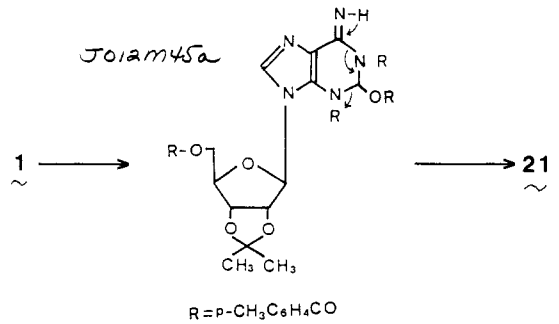
[a] 100 MHz, $CDCl_3$ (Me_4Si). [b] All of the proton signals at H-2, H-8, and H-1' are singlets. [c] J_{gem} = 14 Hz, $J_{H\text{-}4',H\text{-}5'a}$ = 0, $J_{H\text{-}4',H\text{-}5'b}$ = 3 Hz (except **2** and **5**).

(4) (a) All ^1H NMR spectra reported here were taken in $CDCl_3$ (Me_4Si) at 100 MHz. (b) The assignment was confirmed by ^{13}C [^1H] selective decoupling.

(5) (a) Uzawa, J.; Uramoto, M. *Org. Magn. Reson.* **1979**, *12*, 612 and references therein. (b) ^{13}C NMR spectra were recorded on a JEOL FX-100 FT NMR spectrometer at 25 MHz. Experimental conditions: repitition, 1.8 s × 9000; data points, 16K; spectral width, 4 kHz; power level for ^1H irradiation ($\gamma H_2/2\pi$), 20 Hz; concentration, 100 mg in 0.4 mL $(CD_3)_2CO$ + $CDCl_3$.

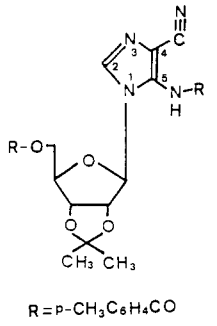
(6) (a) Anzai, K.; Matsui, M. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 3228. (b) Lyon, P. A.; Reese, C. B. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2645.

Scheme I



The 8*R* configuration was assigned to the di-*p*-toluyl-8,5′-*O*-cycloadenosine derivative **20** based on the NOE difference spectra,[7] which showed the proximity of H-8 to one of H-5′ and H-1′. The observed NOE enhancement was H-8[H-5′b] 23%, H-8[H-1′] 1.4%, H-1′[H-8] 2.2%.[8] The absence of any observable NOE between H-2′ and H-8 as well as between H-3′ and H-8 also seemed to support this assignment.[9]

Cyclonucleoside formation was realized as the main reaction path when **1** was treated with *p*-toluyl chloride in a CH_2Cl_2–Et_3N mixture, though, even in this case, the reaction partially proceeded without cyclization (yield 34% **7**, 11% **20**, 30% **6**). An additional compound, formed quite unexpectedly in 12% yield, had the molecular formula $C_{28}H_{28}O_6N_4$ and its ^{13}C NMR and ^1H NMR spectra were found to lack the C2 and H2 signals. The structural assignment of this ring-cleaved product as the imidazole compound **21** ($\nu_{C\equiv N}$ 2250 cm^{-1}) was supported by LSPD



21

^{13}C NMR spectrometry (Table III). A larger value of $^3J_{C,NH}$ compared to $^2J_{C,NH}$ was also observed in N^6-acylated adenosine derivatives ($^3J_{C5,NH}$ = ~2 Hz, $^2J_{C6,NH}$ = ~0 Hz),[10] giving the basis to determine the position of the acylamino group in **21**. The chemical shifts and the vicinal coupling constants between carbon and hydrogen of the noncyclized acylate **18** and the cyclonucleoside derivative **20** are shown in Table III for comparison.

The formation of **21** can be explained in terms of a possible reaction path which starts with acylation at N1 and N3 and is followed by ring cleavage, as shown in Scheme I.

In conclusion, the reaction of 2′,3′-*O*-isopropylideneadenosine with benzoyl chloride and substituted benzoyl chlorides seems to proceed through various reaction paths which include acylation of N^6 and 5′-*O* as well as 8,5′-*O*-cyclonucleoside formation and decomposition of the adenine nucleus, the ratio of these paths depending upon the reaction conditions.

Table III. ^{13}C NMR Chemical Shifts of Compounds 18, 20, and 21

C[a]	18	20	21
	$^1J_{C,H}$		
2	152.2 (206.6)	154.6 (205.1)	
4	150.8	156.6	133.4
5	123.4	111.0	109.5
6	149.6	142.1	113.7
8	141.7 (212.5)	99.1 (186.1)	133.7 (216.1)
$NHC(O)C_6H_4CH_3$	164.5	164.1	166.5
$OC(O)C_6H_4CH_3$	165.6	170.2[b]	166.0
1′	91.3 (170.0)	91.9 (172.9)	92.5 (171.4)
2′	83.8 (161.1)	84.6 (161.2)	85.1 (159.7)
3′	81.2 (158.3)	82.0 (158.3)	81.1 (158.3)
4′	84.7 (155.3)	88.2 (152.4)	84.0 (153.9)
5′	63.7 (149.5)	69.1 (146.5)	63.7 (150.0)
$C(CH_3)_2$	114.3	112.7	114.7
isopropylidene methyl	26.9	25.9	26.8
isopropylidene methyl	25.0	24.3	25.0
two toluyl methyl[c]	21.2	21.2	21.4

C[a]	H	18	20	21[d]
		$^3J_{C,H}$		
4	2	11.7	10.3	
	8	4.4	4.4	4.4
	1′	3.9	≃0	1.0
5	8	11.7	4.3	11.7
6	2	11.7	11.7	
8	1′	2.4	6.1	2.9
	5′		9.8	
	5′		2.4	

[a] Numbering, based on adenosine, in these tables, preserved in **21** for the benefit of readers in comparing these structurally related compounds: i.e., C4, C5, C6, and C8 in **21** are, in fact, C5, C4, C≡N, and C2. [b] >$NC(O)C_6H_5$. [c] The chemical shifts of two toluyl methyls are the same in the ^{13}C NMR spectrum, though different in the ^1H NMR spectrum. [d] $^3J_{C,NH}$ = ~2 Hz, $^2J_{C,NH}$ = 0.

Experimental Section

Reaction of 2′,3′-*O*-Isopropylideneadenosine with Phenyl Chloroformate. To a stirred solution of **1** (3.07 g, 10 mmol) in pyridine (50 mL) was added phenyl chloroformate (6.26 g, 40 mmol) at once, and the mixture was stirred at room temperature for 24 h. During this time the reagent gradually came into solution. The pyridine was removed by evaporation and, after the reagent was quenched with aqueous $NaHCO_3$, the products were extracted with $CHCl_3$. TLC showed the presence of one major product accompanied by a minor one, and they were separated by silica gel chromatography. Elution with 4:1 C_6H_6–EtOAc afforded **7,8-dihydro-2′,3′-*O*-isopropylidene-N^6,N^6,7-tris(phenoxycarbonyl)-8,5′-*O*-cycloadenosine (2)**: yield 4.0 g (60%); mp 121–3 °C (MeOH); for ^1H NMR data, see Table II.

Anal. Calcd for $C_{34}H_{29}O_{10}N_5$: C, 61.16; H, 4.38; N, 10.49. Found: C, 61.00; H, 4.34; N, 10.49.

2′,3′-*O*-Isopropylidene-N^6,N^6,5′-*O*-tris(phenoxycarbonyl)adenosine (3) was eluted with 2:1 C_6H_6–EtOAc: yield 900 mg (13%); glassy solid from C_6H_6–ligroin; ^1H NMR δ 6.28 (d, 1 H, H-1′, $J_{1',2'}$ = 3 Hz), 8.37 (s, 1 H, H-8), 9.02 (s, 1 H, H-2).

Anal. Calcd for $C_{34}H_{29}O_{10}N_5$: C, 61.16; H, 4.38; N, 10.49. Found: C, 61.23; H, 4.34; N, 10.28.

Ammonolysis of 2 in CH_3OH. A solution of **2** (216 mg, 0.33 mmol) in a mixture of MeOH (20 mL) and concentrated NH_4OH (10 mL) was left at room temperature for 10 min, and, after the MeOH was removed by evaporation, the products were extracted with $CHCl_3$. Elution from a silica gel column using 9:1 EtOAc–MeOH afforded **N^6-carbamoyl-7,8-dihydro-2′,3′-*O*-isopropylidene-7-(methoxycarbonyl)-8,5′-*O*-cycloadenosine (5)**: yield 90 mg (44%); mp 209–11 °C (BuOAc); mass spectrum, *m/e* 408 (M^+), 365 ($M^+ - H_2NCO + 1$), 350 ($M^+ - CH_3OCO + 1$); ^1H NMR δ 1.32 and 1.54 (2 s, 6 H, two isopropylidene methyls), 3.92

(7) NOE difference spectra were recorded on a JEOL GX-400 FT NMR spectrometer at 400 MHz.

(8) Reliability of these values is shown by other NOE data: H-1′[H-4′] 2.0%, H-5′a[H-4′] 3.1%, H-5′b[H-5′a] 13%.

(9) Dreiding model construction shows that, in either case of *R* or *S* configuration at C-8, the N(9)-C(1′)-*O*(4′)-C(4′)-C(5′)-O(5′)-C(8) seven membered ring can take the pseudochair or pseudoboat conformer, the latter being unlikely because of unfavorable dipole orientation of the oxygen atoms, and the NOE data can only be explicable based on the pseudochair conformer having *R* configuration at C8.

(10) Unpublished data of the present authors.

(s, 5 H, H-5′ and CH_3O), 4.66 (s, 3 H, H-2′, H-3′, and H-4′), 5.80 (s, 1 H, H-1′), 6.44 (s, 1 H, H-8), 8.22 (s, 1 H, H-2).

Anal. Calcd for $C_{16}H_{20}O_7N_6$: C, 47.05; H, 4.94; N, 20.58. Found: C, 47.01; H, 4.92; N, 20.33.

N^6-Carbamoyl-2′,3′-O-isopropylideneadenosine (4) was eluted following **5** by using the same solvent: yield 70 mg (39%); mp 182–4 °C (BuOAc); ^{1}H NMR δ 6.02 (d, 1 H, H-1′, $J_{1',2'}$ = 3 Hz), 8.38 (s, 1 H, H-8), 8.54 (s, 1 H, H-2).

Anal. Calcd for $C_{14}H_{18}O_5N_6 \cdot 0.5H_2O$: C, 46.79; H, 5.32; N, 23.39. Found: C, 46.86; H, 5.06; N, 23.35.

General Procedure for Reaction of 2′,3′-O-Isopropylideneadenosine with Aroyl Chlorides in Pyridine. To a stirred and ice-cooled solution of 1 was added, portionwise, an aroyl chloride with an amount of 4–5 molar excess, and the solution was stirred at room temperature overnight. The reagent was quenched with an ice-cooled solution of $NaHCO_3$ and the products were extracted with $CHCl_3$. The organic layer, after washing with water, was condensed with the pyridine was removed by coevaporation with toluene. The residue was applied to a silica gel chromatography column developing with benzene, thus a large amount of the acid anhydride being removed. The acylated derivatives of 1 were obtained by eluting with a mixture of benzene and ethyl acetate, gradually increasing the latter content (19:1 to 1:1 C_6H_6–EtOAc). Further chromatography was needed to obtain an analytically pure sample of the 8,5′-O-cycloadenosine derivative because of the close R_f value to that of the noncyclized acylate, and the cyclization product was always found to move faster on a silica gel column than the noncyclized isomer, making isolation of the former possible in spite of the low yield. The size of a silica gel column was 2 × 100 cm for 3–5 mmol of the starting material 1.

Note: the experiment numbers mentioned below correspond to entry numbers in Table I.

(1) Reaction of 1 (1.0 g, 3.26 mmol) with benzoyl chloride (1.8 g, 12.8 mmol) in pyridine (20 mL) gave, after silica gel chromatography (4:1 to 2:1 C_6H_6–EtOAc), **7,8-dihydro-2′,3′-O-isopropylidene-N^6,N^6,7-O-tribenzoyl-8,5′-O-cycloadenosine (9)** as the minor product: yield 120 mg (6%); glassy solid from toluene–hexane; for ^{1}H NMR data, see Table II.

Anal. Calcd for $C_{34}H_{29}O_7N_5$: C, 65.90; H, 4.72; N, 11.30. Found: C, 65.78; H, 4.68; N, 11.22.

2′,3′-O-Isopropylidene-N^6,N^6,5′-O-tribenzoyladenosine (8) was the main product: yield 1.4 g (76%); glassy solid from benzene–hexane; ^{1}H NMR δ 6.14 (d, 1 H, H-1′, $J_{1',2'}$ = 3 Hz), 8.16 (s, 1 H, H-8), 8.57 (s, 1 H, H-2).

Anal. Calcd for $C_{34}H_{29}O_7N_5$: C, 65.90; H, 4.72; N, 11.30. Found: C, 65.98; H, 4.74; N, 11.25.

(2) Reaction of 1 (1.0 g, 3.26 mmol) with *p*-toluyl chloride (2.0 g, 12.9 mmol) in pyridine gave, after silica gel chromatography (4:1 to 2:1 C_6H_6–EtOAc), **7,8-dihydro-2′,3′-O-isopropylidene-N^6,N^6,7-tri-p-toluyl-8,5′-O-cycloadenosine (7)** as the minor product: yield 140 mg (6%); mp 182–5 °C (toluene–hexane); mass spectrum, *m/e* 661 (M^+); ^{1}H NMR δ 1.36 and 1.56 (2 s, 6 H, two isopropylidene methyls), 2.35 (br s, 6 H, two toluyl methyls), 2.41 (s, 3 H, one toluyl methyl); for other ^{1}H NMR data see Table II; ^{13}C NMR (−25 °C) δ 172.1, 169.2, and 168.2 (three carbonyl carbons of toluyl group), 144.0, 142.8, and 142.2 (three aromatic carbons of toluyl group ajacent to methyl); ^{13}C NMR (25 °C) δ 169.0 (one carbonyl carbon of toluyl group), 142.7 (one aromatic carbon of toluyl group ajacent to methyl).

Anal. Calcd for $C_{37}H_{35}O_7N_5$: C, 67.16; H, 5.33; N, 10.59. Found: C, 66.89; H, 5.24; N, 10.47.

2′,3′-O-Isopropylidene-N^6,N^6,5′-O-tri-p-toluyladenosine (6) was eluted later: yield 1.5 g (70%); mp 189–90 °C (MeOH); mass spectrum, *m/e* 661 (M^+); ^{1}H NMR δ 1.40 and 1.62 (2 s, 6 H, two isopropylidene methyls), 2.32 (s, 6 H, two toluyl methyls), 2.40 (s, 3 H, one toluyl methyl) 4.56 (br s, 3 H, H-4″ and H-5′), 5.12 (dd, 1 H, H-3′), 5.50 (dd, 1 H, H-2′), 6.14 (d, 1 H, H-1′), 8.16 (s, 1 H, H-8), 8.60 (s, 1 H, H-2), $J_{1',2'}$ = 2 Hz, $J_{2',3'}$ = 7 Hz, $J_{3',4'}$ = 3 Hz.

Anal. Calcd for $C_{37}H_{35}O_7N_5$: C, 67.16; H, 5.33; N, 10.59. Found: C, 66.96; H, 5.32; N, 10.58.

(3) The reaction products from 1 (1.0 g, 3.26 mmol) and *p*-methoxybenzoyl chloride (2.3 g, 13.5 mmol) were separated by silica gel chromatography. The least polar product, **2′,3′-O-isopropylidene-N^6,N^6,5′-O-tris(p-methoxybenzoyl)adenosine (10)**, was eluted with 2:1 C_6H_6–EtOAc: yield 1.48 g (64%); glassy solid from EtOAc–ligroin; ^{1}H NMR δ 3.80 (s, 6 H, 2 CH_3O), 3.84 (s, 3 H, CH_3O), 6.16 (d, 1 H, H-1′, $J_{1',2'}$ = 2 Hz), 8.16 (s, 1 H, H-8), 8.62 (s, 1 H, H-2).

Anal. Calcd for $C_{37}H_{35}O_{10}N_5$: C, 62.61; H, 4.97; N, 9.87. Found: C, 62.57; H, 5.12; N, 9.66.

7,8-Dihydro-N^6,7-bis(p-methoxybenzoyl)-2′,3′-O-isopropylidene-8,5′-O-cycloadenosine (12) was eluted from a silica gel column with EtOAc: yield 200 mg (11%); glassy solid from toluene–ligroin; for ^{1}H NMR data, see Table II.

Anal. Calcd for $C_{29}H_{29}O_8N_5$: C, 60.51; H, 5.08; N, 12.17. Found: C, 60.25; H, 5.09; N, 11.84.

N^6,5′-O-Bis(p-methoxybenzoyl)-2′,3′-O-isopropylideneadenosine (11), the most polar product, was eluted with 9:1 EtOAc–MeOH: yield 90 mg (5%); glassy solid from toluene–ligroin; ^{1}H NMR δ 3.84 (s, 3 H, CH_3O), 3.92 (s, 3 H, CH_3O), 6.20 (d, 1 H, H-1′, $H_{1',2'}$ = 2 Hz), 8.10 (s, 1 H, H-8), 8.80 (s, 1 H, H-2).

Anal. Calcd for $C_{29}H_{29}O_8N_5$: C, 60.51; H, 5.08; N, 12.17. Found: C, 60.33; H, 5.08; N, 12.06.

(4) A reaction mixture of 1 (1.0 g, 3.26 mmol) and *p*-cyanobenzoyl chloride (2.2 g, 13.3 mmol) in pyridine (20 mL) was concentrated and the products were distributed between aqueous $NaHCO_3$ and $CHCl_3$. The organic layer was, after washing with water, concentrated to dryness, and the residue was taken in hot DMF–BuOAc, thus giving **2′,3′-O-isopropylidene-N^6,N^6,5′-O-tris(p-cyanobenzoyl)adenosine (13)**: yield 1.95 g (85%); mp 246 °C (DMF–BuOAc); ^{1}H NMR δ 6.36 (d, 1 H, H-1′, $J_{1',2'}$ = 2 Hz), 8.68 and 8.72 (2 s, H-8 and H-2).

Anal. Calcd for $C_{37}H_{26}O_7N_8 \cdot 0.5H_2O$: C, 63.15; H, 3.87; N, 15.93. Found: C, 63.08; H, 3.80; N, 15.92.

After collecting **13**, the filtrate was applied to a silica gel chromatography column (2:1 C_6H_6–EtOAc), giving **7,8-dihydro-2′,3′-O-isopropylidene-N^6,N^6,7-tris(p-cyanobenzoyl)-8,5′-O-cycloadenosine (14)**: yield 150 mg (7%); mp 194–7 °C (toluene–ligroin); for ^{1}H NMR data, see Table II.

Anal. Calcd for $C_{37}H_{26}O_7N_8 \cdot 0.5H_2O$: C, 63.15; H, 3.87; N, 15.93. Found: C, 63.11; H, 3.78; N, 15.67.

Reaction of 2′,3′-O-Isopropylideneadenosine with Benzoic Anhydride or p-Toluic Anhydride in Refluxing p-Dioxane. (5) A solution of **1** (921 mg, 3 mmol) and benzoic anhydride (4.8 g, 21.2 mmol) in a mixture of *p*-dioxane (50 mL) and pyridine (50 mL) was refluxed for 24 h. The solution was concentrated to dryness and the residue was distributed between $CHCl_3$ and aqueous $NaHCO_3$. The organic layer was, after washing with water, subjected to silica gel chromatography. The tribenzoate **8** was eluted with 2:1 C_6H_6–EtOAc; yield 630 mg (34%).

N^6,5′-O-Dibenzoyl-2′,3′-O-isopropylideneadenosine (15) was eluted with EtOAc: yield 900 mg (58%); glassy solid from toluene and ligroin; ^{1}H NMR δ 6.18 (d, 1 H, H-1′, $J_{1',2'}$ = 2 Hz), 8.13 (s, 1 H, H-8), 8.79 (s, 1 H, H-2).

Anal. Calcd for $C_{27}H_{25}O_6N_5$: C, 62.90; H, 4.89; N, 13.59. Found: C, 62.71; H, 4.88; N, 13.49.

(6) A solution of **1** (921 mg, 3 mmol) and benzoic anhydride (2.4 g, 10.6 mmol) in *p*-dioxane (50 mL) was refluxed for 6 h, and the reaction mixture was treated as described in (5). Thus, silica gel chromatography (4:1 C_6H_6–EtOAc) afforded **8** as the least polar product, yield 10 mg (0.5%).

N^6,7-Dibenzoyl-7,8-dihydro-2′,3′-O-isopropylidene-8,5′-O-cycloadenosine (17) was eluted from a silica gel column with 1:1 C_6H_6–EtOAc: yield 320 mg (21%); mp 138–40 °C (EtOAc–ligroin); mass spectrum, *m/e* 515 (M^+); for ^{1}H NMR, see Table II.

Anal. Calcd for $C_{27}H_{25}O_6N_5$: C, 62.90; H, 4.89; N, 13.59. Found: C, 62.85; H, 4.96; N, 13.48.

After elution of **15** using EtOAc (yield 150 mg, 10%), the most polar product, **5′-O-benzoyl-2′,3′-O-isopropylideneadenosine (16)**, was eluted from a silica gel column using 9:1 EtOAc–MeOH: yield 800 mg (62%); mp 131 °C (toluene); ^{1}H NMR δ 5.98 (d, 1 H, H-1′, $J_{1',2'}$ = 3 Hz) 8.12 (s, 1 H, H-8), 8.72 (s, 1 H, H-2).

Anal. Calcd for $C_{20}H_{21}O_5N_5$: C, 58.38; H, 5.15; N, 17.02. Found: C, 58.00; H, 5.10; N, 16.87.

(7) The same experiment was carried out as described in (6) except that the time for reflux was 24 h. The following products were isolated by silica gel chromatography: **8** (yield 80 mg, 4%), **17** (yield 250 mg, 16%), **15** (yield 540 mg, 35%), **16** (yield 430 mg, 35%).

(8) A solution of **1** (921 mg, 3 mmol) and *p*-toluic anhydride (2.54 g, 10 mmol) in *p*-dioxane (50 mL) was refluxed for 24 h, and the reaction mixture was treated as described in (5), (6), and (7). From a silica gel column (4:1 C_6H_6–EtOAc) **6** was eluted first; yield 40 mg (2%).

7,8-Dihydro-N^6,7-di-*p*-toluyl-2′,3′-*O*-isopropylidene-8-5′-*O*-cycloadenosine (20) was eluted with 1:1 benzene–EtOAc: yield 320 mg (20%); mp 229–30 °C (C_6H_6); for ^1H NMR and ^{13}C NMR data, see Tables II and III.

Anal. Calcd for $C_{29}H_{29}O_6N_5$: C, 64.08; H, 5.38; N, 12.89. Found: C, 64.35; H, 5.37; N, 12.75.

N^6,5′-*O*-Di-*p*-toluyl-2′,3′-*O*-ispropylideneadenosine (18) was eluted from a silica gel column with EtOAc: yield 430 mg (26%); glassy solid from toluene–ligroin; ^1H NMR δ 2.35 and 2.41 (2 s, 6 H, two toluyl methyls), 6.10 (d, 1 H, H-1′, $J_{1',2'}$ = 2 Hz), 8.13 (s, 1 H, H-8), 8.75 (s, 1 H, H-2); for ^{13}C NMR, see Table III.

Anal. Calcd for $C_{29}H_{29}O_6N_5$: C, 64.08; H, 5.38; N, 12.89. Found: C, 64.13; H, 5.46; N, 12.67.

2′,3′-*O*-Isopropylidene-5′-*O*-*p*-toluyladenosine (19) was eluted from a silica gel column with 9:1 EtOAc–MeOH: yield 470 mg (37%); mp 165–6 °C (BuOAc); ^1H NMR δ 2.44 (s, 3 H, toluyl), 6.00 (d, 1 H, H-1′, $J_{1',2'}$ = 3 Hz), 8.16 (s, 1 H, H-8), 8.72 (s, 1 H, H-2).

Anal. Calcd for $C_{21}H_{23}O_5N_5$: C, 59.28; H, 5.45; N, 16.46. Found: C, 58.98; N, 5.43; N, 16.23.

Reaction of 2′,3′-*O*-Isopropylideneadenosine with *p*-Toluyl Chloride in CH_2Cl_2–Et_3N. (9) To an ice-cooled and stirred solution of **1** (1.54 g, 5 mmol) in a mixture of CH_2Cl_2 (75 mL) and Et_3N (12 mL) was added *p*-toluyl chloride (5 g, 32 mmol) dropwise, and the solution was left at room temperature overnight with stirring. The reaction mixture, after washing with aqueous $NaHCO_3$ to quench the reagent, was applied to a silica gel chromatography column. The least polar product, **7**, was eluted with 4:1 C_6H_6–EtOAc (yield 1.11 g, 34%), and **6** (yield 1.0 g, 30%) was eluted with 4:1 to 2:1 C_6H_6–EtOAc. Further chromatography was needed to separate **7** and **6** completely.

4-Cyano-1-(2,3-*O*-isopropylidene-5-*O*-*p*-toluyl-β-D-ribofuranosyl)-5-(*p*-toluylamino)imidazole (21) was eluted from a silica gel column with 1:1 C_6H_6–EtOAc: yield 300 mg (12%); mp 95–7 °C (toluene); ^1H NMR δ 2.39 and 2.43 (2 s, 6 H, two toluyl), 5.86 (d, 1 H, H-1′, $J_{1',2'}$ = 3 Hz), 7.64 (s, 1 H, H-2), 8.84 (s, 1 H, NH, collapsed on addition of D_2O); for ^{13}C NMR data, see Table III.

Anal. Calcd for $C_{28}H_{28}O_6N_4$: C, 65.10; H, 5.46; N, 10.85. Found: C, 65.13; H, 5.50; N, 10.77.

Compound **20** was eluted from a silica gel column with 1:1 C_6H_6–EtOAc contaminated by **21**, and complete separation of **20** from **21** was unsuccessful even after additional chromatography. However, **21** was hardly soluble in toluene and, after crystallization of **21** from toluene, the filtrate was condensed and the residue was triturated in benzene to obtain crystals of **20**; yield 300 mg (11%).

Registry No. **1**, 362-75-4; **2**, 93135-57-0; **3**, 93135-58-1; **4**, 93135-59-2; **5**, 93135-60-5; **6**, 51008-69-6; **7**, 93135-61-6; **8**, 93135-62-7; **9**, 93135-63-8; **10**, 93135-64-9; **11**, 93135-65-0; **12**, 93135-66-1; **13**, 93135-67-2; **14**, 93135-68-3; **15**, 93135-69-4; **16**, 93135-70-7; **17**, 93135-71-8; **18**, 93135-72-9; **19**, 93135-73-0; **20**, 93135-74-1; **21**, 93135-75-2; phenyl chloroformate, 1885-14-9; benzoyl chloride, 98-88-4; *p*-toluyl chloride, 874-60-2; *p*-methoxybenzoyl chloride, 100-07-2; *p*-cyanobenzoyl chloride, 6068-72-0; benzoic anhydride, 93-97-0; *p*-toluic anhydride, 13222-85-0.

Stability Constants, Enthalpies, and Entropies for Metal Ion–Lariat Ether Interactions in Methanol Solution[1]

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Log K_n, ΔH_n, and $T\Delta S_n$ values valid in CH_3OH at 25 °C have been determined for the interaction of Na^+, K^+, Cs^+, and Ca^{2+} with 15-crown-5 and several lariat ethers. The lariat ethers studied are based on both 15-crown-5 and 18-crown-6 frameworks and contain various pendant arms extending from either carbon or nitrogen atoms on the crown framework. In comparable cases, enlarging the ring size from 15 to 18 members resulted in increased stability. The inclusion on the aza-15-crown-5 ring of a pendant arm bound to nitrogen and having an oxygen atom in the 3 position increases complex stability about ten-fold for Na^+, K^+, and Ca^{2+} compared to the crown ether with the same ring structure but lacking a heteroatom in the side arm. Generally, little effect on the log K_n value is found either by lengthening the pendant arm (and by including an additional donor atom) on the 18-crown-6 compounds or by appending pendant arms having oxygen atoms on the carbon pivot atom of the 15-crown-5 macrocycles.

Recently, one of us reported the preparation and cation binding properties of a series of compounds named "lariat ethers".[2-4] These compounds (**1–6**) contain a cyclic polyether macroring with an attached, conformationally mobile side chain. The side chains carry heteroatoms (oxygen, nitrogen) which are expected to participate with the macroring in the binding of cations. Thus, these compounds might be expected to be intermediate in their binding and dynamic properties between crown ethers and cryptands.[5-9] Similar molecules having secondary binding arms have been reported by others.[10-16]

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