Nucleic acid related compounds. 37. Convenient and high-yield syntheses of *N*-[(2-hydroxyethoxy)methyl] heterocycles as "acyclic nucleoside" analogues[1]

MORRIS J. ROBINS AND PETER W. HATFIELD[2]

Department of Chemistry, The University of Alberta, Edmonton, Alta., Canada T6G 2G2

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Treatment of 1,3-dioxolane with acetyl bromide gave (2-acetoxyethoxy)methyl bromide (**2***a*) in 88% yield. A number of pyrimidines and three chloropurines were trimethylsilylated and coupled with **2***a*. The respective *N*-1 and *N*-9 alkylated products (obtained in 79–89% yields) were deacetylated to give *N*-[(2-hydroxyethoxy)methyl] heterocycles. The 6-amino or 6-chloro substituent of the 2-amino-6-substituted-purine derivatives was hydrolyzed smoothly with adenosine deaminase to give 9-[(2-hydroxyethoxy)methyl]guanine (acycloguanosine), the potent antiviral agent.

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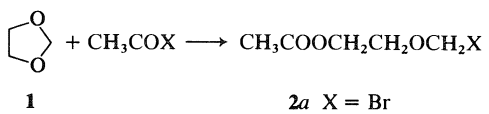
Le dioxolanne-1,3 réagit avec le bromure d'acétyle en donnant le bromure de (acétoxy-2 éthoxy)méthyle (**2***a*) avec un rendement de 88%. On a couplé ce produit **2***a* avec un certain nombre de pyrimidines et trois chloropurines sur lesquelles on a fixé un groupement triméthylsilyle. Les produits alkyles respectivement *N*-1 et *N*-9 (obtenus avec des rendements allant de 79 à 89%), soumis à une désacétylation conduisent à des hétérocycles substitués par des groupes *N*-[(hydroxy-2 éthoxy)méthyle]. On a hydrolysé, dans des conditions douces en utilisant la désaminase d'adénosine, les substituants amino-6 ou chloro-6 des dérivés de l'amino-2 purine substitué en position 6 pour obtenir la [(hydroxy-2 éthoxy)méthyl]-9 guanine (acylguanosine), un agent antiviral puissant.

[Traduit par le journal]

A surge of interest in the application of nucleosides and acyclic nucleoside analogues as antiviral agents is underway. The well known 5-iodo-2′-deoxyuridine has been in clinical use for over a decade and 5-trifluoromethyl-2′-deoxyuridine has been employed. Approval of 9-(β-D-arabinofuranosyl)adenine (araA) for treatment of human herpes encephalitis has been given. Potent antiviral activity has been reported for 1-(β-D-ribofuranosyl)-1,2,-4-triazole-3-carboxamide (ribavirin), (*E*)-5-(2-bromovinyl)-2′-deoxyuridine, and 1-(2-fluoro-2-deoxy-β-D-arabinofuranosyl)-5-iodocytosine (FIAC) (2). Schaeffer and co-workers had prepared 9-(hydroxyalkyl)adenine derivatives as putative inhibitors of adenosine deaminase and found that 9-[(2-hydroxyethoxy)methyl]adenine was a substrate of the enzyme (3). They later reported the synthesis and potent antiviral activity of the acycloguanosine analogue, 9-[(2-hydroxyethoxy)-methyl]guanine (4). This agent has been carried into clinical trials (5). Other types of "acyclic nucleoside" analogues have been reported by De Clercq and Holý (6), Barrio and co-workers (7), Ogilvie and Gillen (8), McCormick and McElhinney (9), and ourselves (10).

Schaeffer employed alkylation of 6-chloropurine with (2-benzyloxyethoxy)methyl chloride to give the *N*-9 product in 44% yield. Ammonolysis and hydrogenolytic debenzylation gave 9-[(2-hydroxyethoxy)methyl]adenine (3). A similar sequence using 2,6-dichloropurine and (2-benzoyloxyethoxy)methyl chloride (41% yield) gave acycloguanosine (4). Barrio and co-workers studied reactions of chloro- and methylthio-substituted purines with (2-trimethylsilyloxyethoxy)methyl iodide (**7***a*). Alkylations proceeded in 50–80% yields at −63°C with this reagent (**7***a*,*c*). Two very recent abstracts noted work on related pyrimidine acyclonucleosides (11, 12).[3]

We have developed methods for the convenient and high-yield syntheses of *N*-[(2-hydroxyethoxy)-methyl] heterocycles. Acetolysis of 1,3-dioxolane (**1**) (see Scheme 1) gave (2-acetoxyethoxy)methyl acetate (**2***c*) as reported (13). However, treatment of trimethylsilylated pyrimidines with **2***c* in the presence of tin(IV) chloride according to the glycosylation procedure of Vorbrüggen (14) gave ~ 50% yields of *N*-1 products. Similar results have been noted recently (12). We repeated the cleavage



1

2*a* X = Br
b X = Cl
c X = $OCOCH_3$

SCHEME 1

[1]For the previous paper in this series see ref. 1.

[2]Alberta Heritage Foundation for Medical Research Graduate Studentship Awardee 1980 to present.

[3]Note added in proof: publications by these authors (19, 20) have appeared since submission of the present work.

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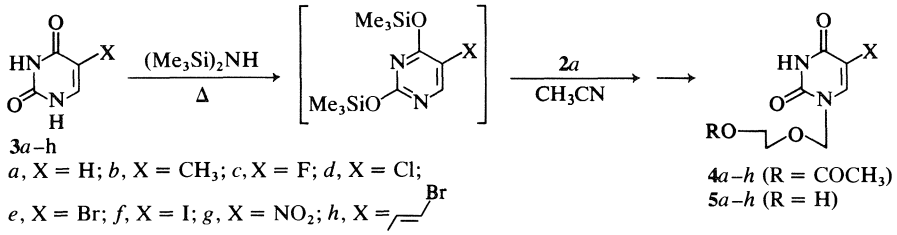


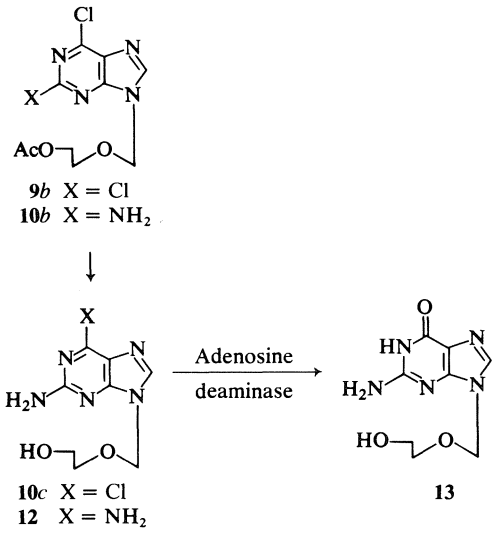
SCHEME 2

of **1** with trimethylsilyl iodide at −78°C (*7a*). However, this preparation was sensitive to moisture and temperature. The failure to isolate an alkylating agent (*7b*) necessitated repetitious *in situ* generation, and attempted use of this preparation with the sodium salt of adenine was not successful. Treatment of **1** with acetyl chloride in the presence of sulfuric acid gave (2-acetoxyethoxy)methyl chloride (**2***b*) contaminated with a tenacious by-product. Coupling yields using this preparation were depressed.

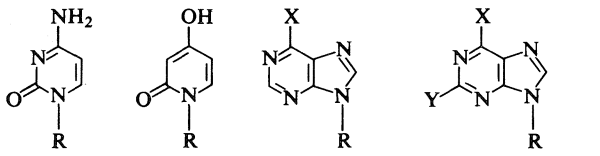
Treatment of **1** with neat acetyl bromide gave pure (2-acetoxyethoxy)methyl bromide (**2***a*) in 88% yield as a readily distilled colorless oil. Storage of **2***a* in a refrigerator for several months with frequent use resulted in no apparent decomposition. Trimethylsilylation of a series of uracils (**3***a–h*) (see Scheme 2), whose nucleosides are of biological interest (2), and *in situ* coupling with **2***a* in dry acetonitrile proceeded without difficulty. The same procedure was applied successfully to cytosine (**6***a*) and 3-deazauracil (4-hydroxy-2-pyridinone) (**7***a*) (see Fig. 1). The *N*-1 derivatives (**4***a–h*, **6***b*, **7***b*) were obtained regiospecifically in yields of 79–88% after recrystallization.

Analogous trimethylsilylation of 6-chloro- (**8***a*), 2,6-dichloro- (**9***a*), and 2-amino-6-chloropurine (**10***a*) and treatment with **2***a* in the presence of mercury(II) cyanide resulted in *N*-9 coupling to give **8***b*, **9***b*, and **10***b* (83–89% conversions). Use of this silylation/mercuric cyanide procedure (15) enhanced yields and effectively eliminated the *N*-7 isomers normally found in alkylations of purine sodium salts (*7c*). However, this method did not give high yields with adenine (**11***a*). Alkylation of the adenine anion with **2***a* in purified DMF gave 75% of 9-[(2-acetoxyethoxy)methyl]adenine (**11***b*). The coupling results and characterization data are summarized in Table 1 and spectral data in Table 2. Deacetylation of these compounds with methanolic ammonia or sodium methoxide occurred readily. Data for the deprotected acyclonucleosides (**5***a–h*, **6***c*, **7***c*, **10***c*, **11***c*) are summarized in Tables 3 and 4.

High-temperature ammonolysis of the 2-chloro group was required previously to prepare acycloguanosine (4, *7c*). Analogous ammonolysis of **9***b* at 150°C gave 2,6-diamino-9-[(2-hydroxyethoxy)-methyl]purine (**12**) (see Scheme 3). Adenosine deaminase was known to effect hydrolytic deamination and dechlorination at C-6 of related purine nucleosides (16) and 6-amino-9-[(2-hydroxyethoxy)methyl]purine (**11***c*) (3). Treatment of **12** with this enzyme effected clean conversion to 9-[(2-hydroxyethoxy)methyl]guanine (**13**). A route to this antiviral drug then was developed that employed convenient ambient temperature and pressure conditions. Mild deprotection of **10***b* followed by enzymatic dechlorination of **10***c* gave



SCHEME 3



Series: *a*, R = H; *b*, R = $CH_2OCH_2CH_2OCOCH_3$;
c, R = $CH_2OCH_2CH_2OH$

FIG. 1

acycloguanosine (**13**) in 76% yield overall for the 3-step sequence (**10***a* → **10***b* → **10***c* → **13**).

This study has provided convenient procedures for the high-yield syntheses of *N*-[(2-hydroxyethoxy)methyl] heterocycles. The facile preparation of (2-acetoxyethoxy)methyl bromide from 1,3-dioxolane provided a stable alkylating bromomethyl ether. Coupling of a number of silylated bases with this agent proceeded smoothly. Adenosine deaminase effected hydrolytic deamination or dechlorination at C-6 of the purine acyclonucleosides to give a mild synthetic route to the antiviral guanine compound (17).

Experimental

General

Melting points were determined on a Reichert microstage block and are uncorrected. Ultraviolet (uv) spectra were recorded on a Cary 15 spectrophotometer. The high-field nmr laboratory of this department obtained ^{1}H spectra on Varian 100, Bruker WH-200, and WH-400 spectrometers. The ^{13}C nmr spectra were measured at 22.6 MHz with proton decoupling on a Bruker HFX-90 instrument. Tetramethylsilane was used as internal standard for all nmr data. The mass spectra (ms) laboratory of this department measured EI spectra on an AEI MS-50 instrument with coupled computer analysis at 70 eV using direct probe sample introduction. Compounds that failed to give a molecular ion peak were examined by chemical ionization (ammonia gas) with an AEI MS-12 instrument at 70 eV. Elemental analyses were determined by the microanalytical laboratory of this department.

Evaporations were effected at room temperature with a Buchler rotary evaporator equipped with a Dewar "Dry-Ice" condenser under water tap or mechanical oil pump vacuum. Reagent grade acetonitrile and *N*,*N*-dimethylformamide (DMF) were refluxed with and then distilled from P_2O_5 into oven-dried flasks. Adenosine deaminase (adenosine aminohydrolase, E. C. 3.5.4.4) was purchased from Sigma Chemical Co. (crude, Type II). Silica gel for column chromatography was J. T. Baker 5-3405 and thin-layer chromatography was performed on small glass plates coated with E. Merck silica gel PF-254 for tlc using solvent systems (A) 10% MeOH in $CHCl_3$ or (B) EtOAc/*n*-PrOH/H_2O (4:1:2) upper phase.

Solvent systems for recrystallization were: A, chloroform with diffusion of diethyl ether; B, methanol with diffusion of ether; C, 2-propanol with diffusion of ether; D, dichloromethane with diffusion of ether; E, methanol; F, methanol–water; G, 95% ethanol; H, acetone with diffusion of *n*-pentane; I, 2-propanol; J, ethanol–water. "Diffusion crystallization" is described in ref. 18.

*(2-Acetoxyethoxy)methyl bromide (***2***a)*

Freshly distilled acetyl bromide (13.0 g, 106 mmol) was stirred magnetically with cooling in an ice bath while 7.4 g (100 mmol) of 1,3-dioxolane (**1**) was added slowly. A rapid exothermic reaction occurred giving quantitative conversion to **2***a* (as judged by ^{1}H nmr). Vacuum distillation of this material gave 17.4 g (88%) of **2***a*, bp 58–60°C/0.1 Torr; ^{1}H nmr ($CDCl_3$) δ: 2.10 (s, 3, $COCH_3$), 3.88 (A_2B_2m, 2, $AcOCH_2CH_2$), 4.27 (A_2B_2m, 2, $AcOCH_2CH_2$), 5.72 (s, 2, OCH_2Br); ^{13}C nmr ($CDCl_3$) δ: 20.80 (CH_3CO), 62.14 ($AcOCH_2CH_2$), 69.22 ($AcOCH_2CH_2$), 75.60 (OCH_2Br), 170.69 (CH_3CO); ms (CI) *m*/*z*: 214, 216 (M^+ + 18 [^{79}Br, ^{81}Br]). *Anal.* calcd. for $C_5H_9BrO_3$: C 30.48, H 4.60, Br 40.55; found: C 30.55, H 4.59, Br 40.72.

TABLE 1. Synthetic and characterization data for preparation of acetylated products

Starting material				Product												
					Yield		Melting		Calculated				Found			Molecular ion
Compound	X	mg	Method[a]	Compound	mg	%	point °C	Solvent[a]	C	H	N	C	H	N	Calculated	Found
3*a*	H	168	A	**4***a*	181	79	77–78	A	47.38	5.30	12.28	47.10	5.39	12.16	228.0742	228.0747
b	CH_3	189	A	*b*	203	84	123–125	A	49.59	5.83	11.57	49.32	5.72	11.57	242.0903	242.0903
c	F	195	A	*c*	207	84	148–149	A	43.91	4.50	11.38	43.68	4.63	11.20	246.0652	246.0652
d	Cl	220	A	*d*	228	87	119–120	A	41.16	4.22	10.67	41.10	4.06	10.66	262.0357[b]	262.0359[b]
e	Br	287	A	*e*	264	86	131–132	A	35.20	3.61	9.12	35.04	3.66	8.99		324[c,d]
f	I	357	A	*f*	280	79	121–123	A	30.53	3.13	7.91	30.53	3.18	7.60	353.9713	353.9727
g	NO_2	236	A	*g*	236	86	134–135	B	39.57	4.06	15.38	39.31	4.03	15.22		291[d]
h	≈Br	326	A	*h*	289	87	109–110	A	39.66	3.93	8.41	39.53	4.02	8.31		350[c,d]
6*a*		167	A	**6***b*	193	85	184–186	B	47.58	5.77	18.49	47.43	5.71	18.42	227.0907	227.0907
7*a*		122	A	**7***b*	200	88	123–124	C	52.87	5.77	6.17	52.87	5.76	6.15	227.0794	227.0795
8*a*		170	B	**8***b*	224	83	96–97	D	44.38	4.10	20.70	44.02	4.04	20.78		271[b,d]
9*a*		208	B	**9***b*	270	88	96–97	A	39.37	3.30	18.36	39.18	3.44	18.22	304.0130[b]	304.0124[b]
10*a*		187	B	**10***b*	239	84	132–133	A	42.04	4.23	24.52	41.81	4.21	24.56	285.0628[b]	285.0633[b]
11*a*		149	C	**11***b*	188	75	156–158	A	47.81	5.22	27.88	47.51	5.05	28.01	251.1019	251.1020

[a]See the Experimental for coupling methods A–C and recrystallization solvent systems A–D.
[b]For ions containing ^{35}Cl.
[c]For ions containing ^{79}Br.
[d]Chemical ionization (NH_3) molecular ion plus ammonium (M^+ + 18). No M^+ was observed at 70 eV EI.

TABLE 2. Ultraviolet and ^{1}H nmr spectral data for acetylated products

Compound	X	Ultraviolet data: 0.1 *N* HCl max nm (ε)	Ultraviolet data: 0.1 *N* HCl min nm (ε)	Ultraviolet data: 0.1 *N* NaOH max nm (ε)	Ultraviolet data: 0.1 *N* NaOH min nm (ε)	^{1}H nmr data: δ ppm from Me_4Si internal in Me_2SO-d_6 solution[a]: CH_3COO[b]	$AcOCH_2CH_2$[c]	$AcOCH_2CH_2$[c]	OCH_2-Base[b]	Base
4*a*[a]	H	259(9800)	228(2300)	259(6800)	243(5700)	2.07	3.81	4.23	5.21	5.80 (d, J = 8 Hz, H-5), 7.33 (H-6)
b	CH_3	264(9600)	233(2500)	265(7000)	246(4800)	2.01	3.70	4.11	5.08	1.78 (s, CH_3), 7.56 (s, H-6)
c	F	266(8600)	232(2000)	265(6200)	248(5000)	1.98	3.74	4.13	5.04	8.10 (d, J = 6.6 Hz, H-6)
d	Cl	274(8700)	238(1500)	271(5900)	249(3600)	2.01	3.73	4.11	5.11	8.20 (s, H-6)
e	Br	277(8600)	241(1100)	274(5900)	250(3300)	2.00	3.73	4.10	5.10	8.26 (s, H-6)
f	I	285(7000)	246(2000)	276(5000)	252(3300)	1.99	3.70	4.09	5.08	8.25 (s, H-6)
g	NO_2	296(9900) 234(8000)	257(3200)	323(13 000)	264(2700)	1.99	3.79	4.11	5.27	9.29 (s, H-6)
h		289(11 300) 249(16 400)	270(8900) 214(8300)	280(9800)[d] 251(16 500)	230(14 000)	1.99	3.72	4.10	5.12	6.85 (d, J = 13.5 Hz, ), 7.28 (d, ), 8.00 (s, H-6)
6*b*		275(12 000)	240(1600)	266(7700)	249(6200)	1.98	3.66	4.06	5.06	5.68 (d, J = 7.5 Hz, H-5), 7.15 (br, NH_2), 7.58 (d, H-6)
7*b*		280(4600)	247(700)	256(6800)	232(3700)	2.00	3.66	4.08	5.21	5.59 (d, J = 2.4 Hz, H-3), 5.90 (dd, H-5), 7.54 (d, J = 7.6 Hz, H-6)
8*b*		263(9100) 250(6300)[d]	222(2100)	263(8800) 250(6300)	230(3300)	1.91	3.76	4.06	5.74	8.84, 8.86 (s, s, H-2, H-8)
9*b*		273(9400) 250(4800)[d]	228(2400)	274(8900) 250(4800)[d]	233(2800)	2.03	3.80	4.20	5.68	8.27 (s, H-8)
10*b*[a]		309(7800) 246(6900)	262(700) 232(5000)	309(7800) 246(6900)	262(700) 232(5000)	2.03	3.75	4.18	5.52	5.28 (br, NH_2), 7.92 (s, H-8)
11*b*		256(16 600)	225(2400)	260(16 900)	227(3300)	1.92	3.72	4.06	5.56	7.23 (br, NH_2), 8.16 (s, H-2), 8.26 (s, H-8)

[a] ^{1}H nmr spectra of **4***a* and **10***b* were determined in $CDCl_3$.
[b] Singlet.
[c] A_2B_2 multiplet.
[d] Shoulder.

Coupling Method A

*1-[(2-Acetoxyethoxy)methyl]uracil (**4**a)*

To a suspension of 168 mg (1.5 mmol) of uracil (**3***a*) in 5 mL of hexamethyldisilazane was added a drop of chlorotrimethylsilane and the stirred mixture was heated at reflux with exclusion of moisture until a clear solution was obtained. Excess silylating reagent was removed *in vacuo* with protection against moisture. The residual clear oil was dissolved in 15 mL of dry acetonitrile and cooled to 0°C. A solution of 197 mg (1 mmol) of (2-acetoxyethoxy)methyl bromide (**2***a*) in 5 mL of dry acetonitrile was added slowly with stirring. The solution was allowed to stir for 2 h while warming to room temperature at which time tlc(A) indicated complete reaction. Volatile materials were evaporated *in vacuo*. The resulting yellow oil was chromatographed on a column (3 cm diameter) of 20 g of silica gel using 2% MeOH/$CHCl_3$ for elution. Fractions containing **4***a* were combined and evaporated. The residue was crystallized from $CHCl_3$ with diffusion of Et_2O to give 181 mg (79%) of pure **4***a* with the physical and analytical data recorded in Tables 1 and 2.

This procedure was used to couple 1.5 mmol samples of **3***b–h* and **6***a*, and 1.1 mmol of **7***a* with 1 mmol of **2***a* to give **4***b–h*, **6***b*, and **7***b* as indicated in Tables 1 and 2. In the case of **3***f* → **4***f*, rigorous removal of the coupling by-product Me_3SiBr was necessary in order to avoid deiodination of **4***f* to given contaminating **4***a* during processing and recrystallization.

Coupling Method B

*9-[(2-Acetoxyethoxy)methyl]-2-amino-6-chloropurine (**10**b)*

A stirred mixture of 187 mg (1.1 mmol) of 2-amino-6-chloropurine (**10***a*), 45 mg of $(NH_4)_2SO_4$, and 5 mL of hexamethyldisilazane was heated at reflux for 3 h with exclusion of moisture. Volatile materials were evaporated *in vacuo* with protection against moisture. The residue was stirred with 15 mL of dry benzene and 344 mg of $Hg(CN)_2$ was added. This mixture was stirred at reflux under a dry nitrogen atmosphere for 30 min. A solution of 197 mg (1 mmol) of (2-acetoxyethoxy)methyl bromide (**2***a*) in 5 mL of benzene was added and reflux was continued for 2 h. The mixture was cooled, 150 mL of $CHCl_3$ was added, and the organic phase was washed with 30 mL of saturated $NaHCO_3/H_2O$ followed by 30 mL of 1 *M* KI/H_2O. The organic solution was dried over Na_2SO_4, filtered, and evaporated to give 239 mg (84%) of an oil that was homogeneous by tlc(A). This product was crystallized from $CHCl_3$ with diffusion of Et_2O to give pure **10***b* with the physical and analytical data given in Tables 1 and 2.

This procedure was used to couple 1.1 mmol samples of **8***a* and **9***a* to give **8***b* and **9***b* as indicated in Tables 1 and 2.

Coupling Method C

*9-[(2-Acetoxyethoxy)methyl]adenine (**11**b)*

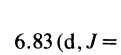
To a stirred solution of 149 mg (1.1 mmol) of adenine (**11***a*) in 25 mL of dry (and *amine-free*) DMF was added 29 mg (1.2 mmol) of NaH. After evolution of hydrogen had ceased, the mixture was cooled to −63°C and a solution of 197 mg (1 mmol) of (2-acetoxyethoxy)methyl bromide (**2***a*) in 5 mL of DMF was added slowly. The stirred mixture was allowed to warm slowly to room temperature over a period of 2 h, 0.5 mL of 1 *M* $NaHCO_3/H_2O$ was added, and volatile materials were evaporated *in vacuo*. The residue was chromatographed on a column (30 g) of silica gel using 5% MeOH/$CHCl_3$ for elution. Appropriate fractions were combined and evaporated to give 188 mg (75%) of an oily product. This material was crystallized from $CHCl_3$ with diffusion of Et_2O to give pure **11***b* with physical and analytical data as indicated in Tables 1 and 2.

TABLE 3. Synthetic and characterization data for preparation of deprotected acyclonucleosides

Starting material				Product											
					Yield		Melting		Calculated			Found			Molecular ion
Compound	X	mg	Method[a]	Compound	mg	%	point °C	Solvent[a]	C	H	N	C	H	N	Calculated	Found
4*a*	H	228	A	**5***a*	169	91	147–148	E	45.17	5.41	15.05	44.93	5.33	15.06	186.0641	186.0640
b	CH_3	4000	B	*b*	3077	93	150.5–152	E	48.00	6.04	13.99	48.00	5.95	13.95	200.0797	200.0801
c	F	1476	B	*c*	1175	96	154–156	F	41.19	4.44	13.72	41.12	4.56	13.63	204.0546	204.0541
d	Cl	200	A	*d*	164	98	167–168	G	38.11	4.11	12.70	37.88	3.96	12.42	220.0251[b]	220.0248[b]
e	Br	307	A	*e*	206	78	152–153	G	31.72	3.42	10.57	31.91	3.52	10.46	263.9746[c]	263.9746[c]
f	I	708	B	*f*	576	92	175–176	A	26.94	2.91	8.98	27.02	3.00	8.84	311.9607	311.9612
g	NO_2	180	B	*g*	140	92	173–175	B	36.38	3.92	18.18	36.24	3.88	18.21	231.0491	231.0487
h	≷Br	500	A	*h*	398	91	130–133	H	37.14	3.81	9.62	37.04	3.87	9.51		308[c,d]
6*b*		2905	B	**6***c*[e]	2220	94	170–171	C	45.41	5.99	22.69	45.37	6.10	22.66	185.0800	185.0803
7*b*		250	B	**7***c*	169	83	137–139	C	51.90	5.99	7.56	51.80	6.00	7.53	185.0688	185.0689
10*b*		226	A	**10***c*	168	87	204–205	I	39.44	4.14	28.74	39.25	4.12	28.54	243.0523[b]	243.0520[b]
11*b*		830	B	**11***c*[f]	648	94	204–206	E	45.93	5.30	33.48	45.69	5.29	33.24	209.0913	209.0910
10*c*		110	*g*	**13**	88	87	265–266	J	42.67	4.92	31.10	42.45	4.93	30.95	225.0862	225.0863

[a]See the Experimental for deprotection methods A and B and recrystallization solvent systems A–J.
[b]For ions containing ^{35}Cl.
[c]For ions containing ^{79}Br.
[d]Chemical ionization (NH_3) molecular ion plus ammonium ($M^+ + 18$). No M^+ was observed at 70 eV EI.
[e]See ref. 7*c* for prior synthesis and data.
[f]See refs. 3, 7*c* for prior synthesis and data.
[g]See the Experimental.

TABLE 4. Ultraviolet and ^{1}H nmr spectral data for deprotected acyclonucleosides

		Ultraviolet data				^{1}H nmr data			
		0.1 *N* HCl		0.1 *N* NaOH		δ ppm from Me_4Si internal in Me_2SO-d_6 solution			
Compound	X	max nm (ε)	min nm (ε)	max nm (ε)	min nm (ε)	OCH_2CH_2O[a]	OH[b]	OCH_2-Base[a]	Base
5*a*[a]	H	259(9700)	229(2500)	260(6700)	243(5400)	3.48	4.64	5.08	5.60 (d, J = 8 Hz, H-5), 7.67 (d, H-6)
b	CH_3	265(9000)	234(2200)	264(6500)	245(4400)	3.50	4.65	5.06	1.78 (s, CH_3), 7.55 (s, H-6)
c	F	266(8200)	232(1800)	265(6100)	248(4700)	3.48	4.61	5.05	8.10 (d, J = 6.6 Hz, H-6)
d	Cl	274(8500)	238(1500)	272(5800)	249(3500)	3.50	4.62	5.08	8.16 (s, H-6)
e	Br	276(8600)	241(1700)	274(5700)	251(3300)	3.51	4.65	5.10	8.25 (s, H-6)
f	I	286(7100)	245(2000)	277(5000)	251(3100)	3.50	4.65	5.08	8.20 (s, H-6)
g	NO_2	297(9900) 232(7700)	257(3100) 209(4800)	323(13 300)	263(2800)	3.58[c]	5.70[d]	5.28	9.30 (s, H-6)
h		290(10 300) 249(14 900)	270(7900) 213(6600)	280(8900)[e] 253(15 300)	230(12 500)	3.50	4.60	5.10	6.83 (d, J = 14 Hz, ), 7.28 (d,), 7.97 (s, H-6)
6*c*		276(12 000)	240(1700)	267(7900)	250(6400)	3.46	4.60	5.06	5.72 (d, J = 7.5 Hz, H-5), 7.2 (br, NH_2), 7.60 (d, H-6)
7*c*		280(4600)	247(800)	256(6900)	232(3700)	3.46	4.55	5.18	5.56 (d, J = 2.5 Hz, H-3), 5.87 (dd, H-5), 7.52 (d, J = 7.5 Hz, H-6)
10*c*		307(7600) 246(7200)	264(1000) 232(5300)	307(7600) 246(7200)	265(1100) 232(5400)	3.50	4.66	5.47	6.99 (br, NH_2), 8.28 (s, H-8)
11*c*		256(14 200)	225(2300)	259(14 500)	227(3200)	3.50	4.65	5.56	7.24 (br, NH_2), 8.17 (s, H-2), 8.26 (s, H-8)
13		271(8800)[e] 252(13 000)	224(2800)	260(11 400)	229(4700)	3.34[c]	4.56	5.34	6.49 (br, NH_2), 7.81 (s, H-8)

[a]Singlet.
[b]Broad singlet.
[c]Multiplet.
[d]Triplet.
[e]Shoulder.

Deprotection Method A

*2-Amino-6-chloro-9-[(2-hydroxyethoxy)methyl]purine (**10**c)*

A 226 mg (0.79 mmol) sample of **10***b* was added to 40 mL of MeOH saturated with NH_3 at −10°C. The flask was stoppered tightly and the solution was stirred for 5 h at room temperature. Thin-layer chromatography(A) indicated that complete deprotection of **10***b* had occurred. Volatile materials were evaporated and the resulting solid was recrystallized from 2-propanol to give 168 mg (87%) of pure **10***c* with physical and analytical data as indicated in Tables 3 and 4.

Deprotection Method B

*5-Fluoro-1-[(2-hydroxyethoxy)methyl]uracil (5*c*)*

To 60 mL of dry MeOH was added 0.23 g (10 mmol) of sodium metal. After hydrogen evolution was complete, 1.476 g (6 mmol) of **4***c* was added and stirring was continued for 2 h at room temperature. Thin-layer chromatography(A) indicated that complete deprotection of **4***c* had occurred. Amberlite IR-120 (H^+) resin was added until the solution was neutral to moist pH paper. The mixture was filtered, the resin washed with MeOH, and the combined filtrate evaporated. The colorless residual powder was recrystallized from MeOH–H_2O to give 1.175 g (96%) of pure **5***c* with physical and analytical data as indicated in Tables 3 and 4.

*9-[(2-Hydroxyethoxy)methyl]guanine (acycloguanosine) (**13**) (4, 7c)*

A. *From 2-amino-6-chloro-9-[(2-hydroxyethoxy)methyl]-purine (10*c*)*

To a solution of 110 mg (0.45 mmol) of **10***c* in 25 mL of aqueous phosphate buffer (0.05 *M*, pH 7.5) was added 30 mg of adenosine deaminase. The reaction mixture was stirred magnetically at room temperature and monitored by tlc(B) until complete hydrolytic dechlorination had occurred. The crude product could be obtained directly by crystallization from the concentrated reaction mixture. However, a convenient purification procedure employed adsorption of the product from the aqueous medium on a carbon column (18), washing the column with water, and elution of **13** with 35% CH_3CN/H_2O. Evaporation of the appropriately pooled fractions, recrystallization of the solid from EtOH–H_2O, and thorough drying of the product *in vacuo* over P_2O_5 gave 88 mg (87%) of pure **13** with physical and analytical data as indicated in Tables 3 and 4.

B. *From 9-[(2-acetoxyethoxy)methyl]-2,6-dichloropurine (**9**b)*

A solution of 510 mg (1.67 mmol) of **9***b* in 15 mL of liquid ammonia was sealed in a Parr steel bomb and heated at 150°C for 3 days. After cooling, the bomb was vented and tlc(B) indicated complete conversion to the 2,6-diamino product (**12**) (none of the 6-amino-2-chloropurine analogue was detected). The residue was purified on a column of silica gel using 10% MeOH/$CHCl_3$ for elution to give 350 mg (93%) of oily **12**. This material was treated with adenosine deaminase as described above (A. **10***c* → **13**) to give 312 mg (89%) of pure **13**.

C. *Overall from 2-amino-6-chloropurine (**10**a)*

A 187 mg (1.1 mmol) sample of **10***a* was coupled with 197 mg (1 mmol) of **2***a* as described under Coupling Method B. The oily **10***b* obtained was treated by Deprotection Method A to give a crude solid, **10***c*, that was subjected directly to adenosine deaminase as described above (A. **10***c* → **13**). The resulting carbon column-purified product was recrystallized and dried to give 172 mg (76% overall from **2***a*) of pure **13**.

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