Systematic General Synthesis of Purine 8,5'-Imino and Substituted Imino Cyclonucleosides

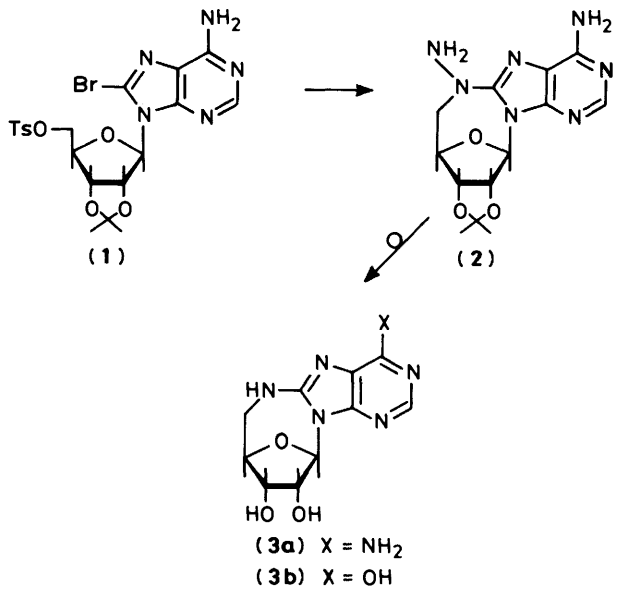
Katsumaro Minamoto,* Yasumi Fujiki, Niro Shiomi, Yoriaki Uda, and Tadashi Sasaki
Institute of Applied Organic Chemistry, Faculty of Engineering, Nagoya University, Furo-cho, Chikusa-ku, Nagoya, Japan

2',3'-*O*-Isopropylidene-8-methylaminoadenosine (**7a**), its hypoxanthine analogue (**7b**), 2',3'-*O*-isopropylidene-8-benzylaminoadenosine (**7c**), its hypoxanthine analogue (**7d**), 2',3'-*O*-isopropylidene-8-allylaminoadenosine (**7e**), its hypoxanthine analogue (**7f**), 8-benzylamino-2',3'-*O*-isopropylideneguanosine (**7g**), its 2-dimethylaminomethyleneamino derivative (**7h**), 8-allylamino-2',3'-*O*-isopropylideneguanosine (**7i**) and its 2-dimethylaminomethyleneamino derivative (**7j**) have been synthesized. Compounds (**7a**—**f**), (**7h**), and (**7j**) have been converted into the corresponding 8,5'-substituted imino cyclonucleosides (**8a**—**f**), (**8g**), and (**8i**), utilizing diphenyl carbonate–triethylamine (Method A), *N,N'*-carbonyldi-imidazole (CDI) (Method B), and the Mitsunobu reaction (Method C). 5',8-Carbamoyloxycyclonucleosides (**9a,b**) were also isolated in the cyclization reactions of (**7h**) and (**7j**).

Although the chemistry of pyrimidine and purine cyclonucleosides has generated a considerable literature,[1] there is a dearth of information on nitrogen-bridged cyclonucleosides,[2] compounds which have recently generated much interest.[3] In 1978 we described the synthesis of 8,5'-imino-9-(5'-deoxy-β-D-ribofuranosyl)adenine (**3a**) and its hypoxanthine analogue (**3b**) as the first 8,5'-iminocyclonucleosides prepared *via* 8,5'-amino-imino-9-(5'-deoxy-β-D-ribofuranosyl)adenine (**2**).[3b] The 8,5'-aminoimino bridge was realized by treating 2',3'-*O*-isopropylidene-5'-*O*-tosyl-8-bromoadenosine (**1**)[4] with strongly nucleophilic hydrazine as a nitrogen source at room temperature, thus circumventing the formidable intramolecular quaternization at N-3 by the 5'-carbon in (**1**). The *N*-amino group in (**2**) was, luckily, very easily removed, by an unknown mechanism, upon oxidation with iodine pentaoxide or nitrous acid to provide compounds (**3a,b**) in high yields: no products stemming from homolytic N,5'- or N,C(8)-bond fission were observed. Analogous 8,5'-cyclization by the use of hydrazine was also achieved in the guanosine series,[3c] although the target molecule in fully deprotected form was not realized. As a result of claims for the biological activity of 8-amino and 8-substituted amino purine nucleosides,[5] coupled with the interest generated by the compounds prepared earlier, we have again initiated further studies in this area and describe here three further syntheses of purine 8,5'-*N*-cyclonucleosides.

Since bromine at the C-8 of purine bases can be easily replaced by alkyl or aralkyl amines[5d,e] but not by ammonia,[5a,e] we chose to apply the common dehydration methods to purine nucleosides substituted with an alkylamine or protected amines (benzylamine and allylamine).

Substrate Synthesis.—8-Methylamino- (**5a**) and 8-benzylamino-adenosine (**5c**) can be obtained from 8-bromoadenosine (**4a**) as described[5e] earlier (Scheme 1). 8-Methylaminoinosine (**5b**) was similarly obtained from 8-bromoinosine (**4b**) as an amorphous solid (glass) (see Experimental section). Compounds (**5a**) and (**5b**) were acetonated to give 2',3'-*O*-isopropylidene-8-methylaminoadenosine (**7a**) (67%) (Method A) and 2',3'-*O*-isopropylidene-8-methylaminoinosine (**7b**) (72%). The former can be obtained from 8-bromo-2',3'-*O*-isopropylideneadenosine (**6a**) more economically (Method B, 71%). 8-Benzylamino-2',3'-*O*-isopropylideneadenosine (**7c**) and its inosine analogue (**7d**) were similarly obtained from crude (**5c**) and (**5d**) in 76 and 55% yield, respectively (Method A), but more economically from (**6a**) and 2',3'-*O*-isopropylidene-8-bromoinosine (**6b**) obtainable from (**6a**)[6] (Method B) in over 90% yields. Analogously, the 8-allylamino compounds (**7e**) and (**7f**) were also obtained from (**6a**) and (**6b**) in over 90% yields.



Scheme 1.

Amination experiments in the guanosine series were less successful: thus amination of 8-bromoguanosine or 8-bromo-2',3'-*O*-isopropylideneguanosine (**6c**) with methylamine and of the former compound with allylamine occurred extremely slowly as compared with the adenosine series, and to only a limited extent. The products generally had a very strong propensity for solvation with alcoholic solvents or with mixed solvents, which excluded their separation, despite the described synthesis of 8-methylaminoguanosine.[5d] Nevertheless, 8-benzylamino-2',3'-*O*-isopropylideneguanosine (**7g**) and its allylamino analogue (**7i**), prepared from (**6c**), could be isolated as foams which were convertible into the crystalline compounds 8-benzyl-2-dimethylaminomethyleneamino-2',3'-*O*-isopropylidene-guanosine (**7h**) and its allylamino analogue (**7j**); these

Table 1. The yields of cyclonucleosides (**8**) and the solvent systems used for preparative t.l.c.

Compound (**8**)[a]				Solvent systems for preparative t.l.c.	Yields (%)[b]		
	X	Y	R		Method A	Method B	Method C
a	NH_2	H	Me	$CHCl_3$–MeOH (9:1)	42.8	50.8	64.4
b	OH	H	Me		25	24	*c*
c	NH_2	H	Bn		40.6	28.4	55.3
d	OH	H	Bn		24.4	28.7	48.1
e	NH_2	H	Al		44.5	51.6	37.4
f	OH	H	Al		16.7	27.3	28.8
g	OH	DMAMA	Bn		29.1	39.2	55.1
i	OH	NH_2	Al	$CHCl_3$–MeOH (85:15)	*d*	*d*	52.2[e]

[a] Me = methyl; Bn = benzyl; Al = allyl; DMAMA = dimethylaminomethyleneamino. [b] Method A: $(PhO)_2CO$ (1.5 equiv.)/Et_3N (1.5 equiv.)/DMF, 135 °C, 2 h; Method B: *N,N'*-Carbonyldi-imidazole (1.5 equiv.)/DMF, 125 °C, 2 h; Method C: Diethyl azodicarboxylate (1.5 equiv.)/Ph_3P (1.5 equiv.)/THF, room temp., 10 h. [c] Not conducted. [d] Only the cyclic carbamate ester (**9b**) was isolated. [e] Deprotected during the isolation procedure.

Table 2. M.p.s and analysis data of (**8**)

Compound (**8**)[a]				M.p. °C		Analysis values (%)					
						Found			Calc.		
	X	Y	R	(Recryst. solvent)	Formula	C	H	N	C	H	N
a	NH_2	H	Me	267.5—268 (MeOH)	$C_{14}H_{18}N_6O_3$	53.05	5.7	26.55	52.82	5.70	26.40
b	OH	H	Me	>300 (MeOH)	$C_{14}H_{17}N_5O_4 \cdot 0.5CH_3OH$	52.15	5.55	20.85	51.93	5.71	20.89
c	NH_2	H	Bn	247—249 (MeOH)	$C_{20}H_{22}N_6O_3$	60.95	5.5	21.25	60.90	5.62	21.31
d	OH	H	Bn	>300 (MeOH)	$C_{20}H_{21}N_5O_4$	60.5	5.55	17.45	60.75	5.35	17.71
e	NH_2	H	Al	215.5—217 (MeOH)	$C_{16}H_{20}N_6O_3$	55.75	5.8	24.5	55.80	5.85	24.41
f	OH	H	Al	>300 (MeOH)	$C_{16}H_{19}N_5O_4$	55.65	5.65	20.2	55.64	5.55	20.28
g	OH	DMAMA	Bn	298—299 (EtOH)	$C_{23}H_{27}N_7O_4$	59.3	6.05	20.9	59.34	5.85	21.06
i	OH	NH_2	Al	241—243[b]	$C_{16}H_{20}N_6O_4 \cdot 0.33CH_3COCH_3$	53.75	5.75	22.25	53.77	5.84	22.13

[a] Me = methyl; Bn = benzyl; Al = allyl; DMAMA = dimethylaminomethyleneamino. [b] Amorphous glass.

proved to be more suitable than (**7g**) and (**7i**) for cyclization after some preliminary experimentation.

It is noteworthy that t.l.c. monitoring of the amination experiments showed the absence of any other products or intermediates and, accordingly, it is likely that the aminations occurred by direct displacement of bromine without intermediacy of 8,5'-anhydronucleosides. The electronic absorptions of these new intermediates are given in Table 3 together with those of the cyclonucleosides.

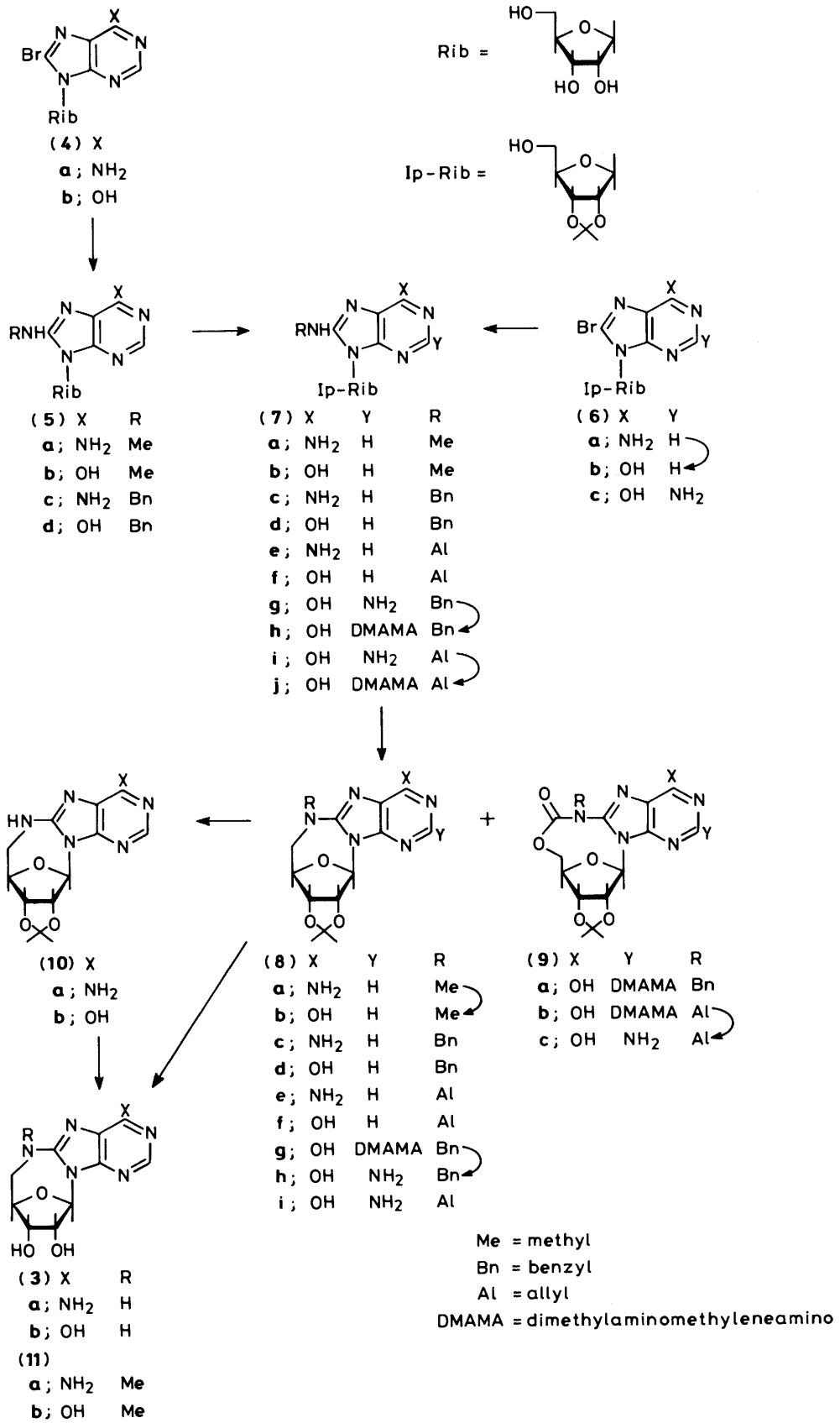
Cyclonucleoside Synthesis.—Cyclizations were conducted in three ways, using diphenyl carbonate (Method A), *N,N'*-carbonyldi-imidazole (CDI) (Method B), and the Mitsunobu reaction[7] (Method C). Thus, (**7a**) with 1.5 equiv. of diphenyl carbonate in the presence of triethylamine (Method A) gave two products, one of which was isolated as crystals in *ca.* 43% yield and characterized as 8,5'-methylimino-9-(5'-deoxy-2',3'-*O*-isopropylidene-β-D-ribofuranosyl)adenine (**8a**) (see Table 1). Analogous cyclonucleosides (**8b**—**g**) were obtained as crystals from the corresponding precursors (**7b**—**f**) and (**7h**) in the yields shown in Table 1. These compounds were also synthesized using the same substrates (**7**) and CDI (Method B) by a similar process. The general synthetic procedures for these cyclonucleosides are described in the Experimental section with some selected examples of experimentation; the structural assignments are consistent with the u.v. and ^1H n.m.r. spectroscopic results (Tables 3 and 4).*

* All the 200 MHz ^1H n.m.r. spectra were recorded in the laboratory of the Daiichi Pharmaceutical Co., Ltd. The assignments of the sugar protons are based upon extensive spin-decoupling experiments.

It is interesting to note that in the reaction of (**7h**) with diphenyl carbonate a new type of compound, 8,5'-(*N*-benzylcarbamoyloxy)-2-dimethylaminomethyleneamino-9-(2',3'-*O*-isopropylidene-β-D-ribofuranosyl)guanine (**9a**) was isolated as the least polar, crystalline product in 14.2% yield. Similarly, (**7j**) with diphenyl carbonate or CDI gave 8,5'-(*N*-allylcarbamoyloxy)-2-dimethylaminomethyleneamino-9-(2',3'-*O*-isopropylidene-β-D-ribofuranosyl)guanine (**9b**) in 27—30% isolated yields. In these particular reactions with (**7j**), the desired 8,5'-allyliminocyclonucleoside was not isolated but the more economical Method C was used. Structures (**9a**) and (**9b**) followed from microanalytical results, the i.r. absorption at 1 735 and 1 745 cm^{-1}, respectively, characteristic of a carbamate ester partial structure, and from the ^1H n.m.r. 5'-methylene signal at a field (3.98—3.99 p.p.m.) substantially lower than that for the corresponding signal of an 8,5'-iminocyclonucleoside (2.95—3.20 p.p.m.) (Table 4). The carbamate ester function in (**9b**) was unaffected by the weakly acidic conditions used to remove the dimethylaminomethylene function,[8] and 8,5'-(*N*-allylcarbamoyloxy)-9-(2',3'-*O*-isopropylidene-β-D-ribofuranosyl)guanine (**9c**) was obtained in nearly 90% yield.

The Mitsunobu reaction was then applied to (**7a**), (**7c**—**f**), (**7h**), and (**7j**) under standard reaction conditions; selected examples are given in the Experimental section. The yields were generally better than those in the two methods described earlier. In the reaction of (**7j**), the product was isolated in a deprotected form, *i.e.* 8,5'-allylimino-9-(5'-deoxy-2',3'-*O*-isopropylidene-β-D-ribofuranosyl)guanine (**8i**), which resisted crystallization but permitted thorough characterization. Compound (**8a**) was convertible into (**8b**) and (**8g**) into (**8h**) in good yields.

Deprotection of compound (**8**) was then examined. Deaceton-


Rib =
Ip-Rib =
(4) X
a; NH2
b; OH
(5) X R
a; NH2 Me
b; OH Me
c; NH2 Bn
d; OH Bn
(7) X Y R
a; NH2 H Me
b; OH H Me
c; NH2 H Bn
d; OH H Bn
e; NH2 H Al
f; OH H Al
g; OH NH2 Bn
h; OH DMAMA Bn
i; OH NH2 Al
j; OH DMAMA Al
(6) X Y
a; NH2 H
b; OH H
c; OH NH2
(10) X
a; NH2
b; OH
(8) X Y R
a; NH2 H Me
b; OH H Me
c; NH2 H Bn
d; OH H Bn
e; NH2 H Al
f; OH H Al
g; OH DMAMA Bn
h; OH NH2 Bn
i; OH NH2 Al
(9) X Y R
a; OH DMAMA Bn
b; OH DMAMA Al
c; OH NH2 Al
(3) X R
a; NH2 H
b; OH H
(11)
a; NH2 Me
b; OH Me
Me = methyl
Bn = benzyl
Al = allyl
DMAMA = dimethylaminomethyleneamino

Scheme 2.

Table 3. U.v. absorption of (**5b**), (**7a**—**j**), (**8a**—**i**), (**9a**—**c**), and (**11a,b**), (**12**), and (**13**) in methanol

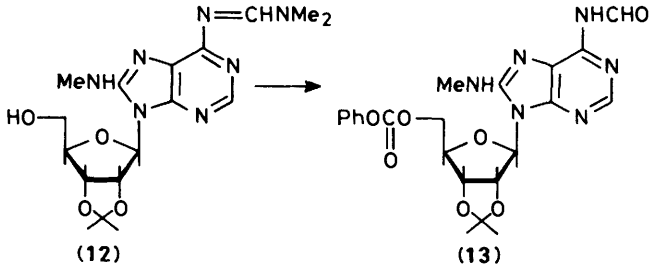
Compound	$\lambda_{max.}$/nm (ε)
(**5b**)	265 (16 900)
(**7a**)	275 (15 800)
(**7b**)	263 (12 400)
(**7c**)	275 (27 000)
(**7d**)	265 (15 000), 292 (7 100)[a]
(**7e**)	276 (18 500)
(**7f**)	266.5 (16 900), 292 (7 700)[a]
(**7g**)	258 (15 500), 292 (7 000)[a]
(**7h**)	240 (19 800), 292 (15 800),[a] 323 (19 800)
(**7i**)	263 (15 800), 290 (7 800)
(**7j**)	241 (18 200), 294 (14 500),[a] 323 (17 600)
(**8a**)	273 (20 200)
(**8b**)	264 (17 200)
(**8c**)	275 (30 600)
(**8d**)	264 (16 900), 289 (8 000)[a]
(**8e**)	277 (21 300)
(**8f**)	263 (18 000), 291 (7 500)[a]
(**8g**)	239 (16 400), 289 (15 000),[a] 316 (18 600)
(**8h**)	262 (22 500), 284 (12 500)[a]
(**8i**)	263 (15 600), 288 (7 500)[a]
(**9a**)	237 (14 500), 296 (18 100),[a] 308 (23 500)
(**9b**)	238 (14 500), 287 (17 700),[a] 308 (23 500)
(**9c**)	269 (25 900)
(**11a**)	274 (16 900)
(**11b**)	264 (14 100)
(**12**)	250 (21 400), 323 (24 900)
(**13**)	226 (22 900), 267 (9 200),[a] 299 (16 900)

[a] Shoulder.

ation of (**8a**) and (**8b**) with 90% trifluoroacetic acid was straightforward and provided 8,5′-methylimino-9-(5′-deoxy-β-D-ribofuranosyl)adenine (**11a**) and its hypoxanthine analogue (**11b**), respectively. Debenzylation of (**8c**) with sodium naphthalenide[9] also proceeded smoothly to afford a 55% yield of 8,5′-imino-9-(5′-deoxy-2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)adenine (**10a**)[3b] (Method A), which was also obtainable from (**8e**) by the standardized procedure involving alkali-catalysed isomerization of the allyl to the isopropenyl group followed by potassium permanganate oxidation[10] (Method B). The somewhat low yields in both cases are due to loss during the isolation procedures: the deprotection itself proceeded nearly quantitatively as judged by t.l.c. in each case. Similarly, the hypoxanthine analogue (**10b**)[3b] was obtained from (**8d**) in 55% yield and also from (**8f**) in a low yield.* Conversion of (**10a,b**) into (**3a,b**) has already been recorded.[3b]

In contrast to the above work, in the guanosine series problems were encountered at the deprotection step, principally as a result of the sparing solubilities and gelatinizing nature of the *N*-deprotected crude products. Thus, debenzylation of (**8h**) with sodium naphthalenide gave, after difficult processing, a very small amount of a gummy product, which on the basis of u.v.-absorption at 235 nm and its elemental analysis seemed to be a perhydro compound.

In the light of the above results, the following comments on the mechanism of cyclization of (**7**) to (**8**) may be made. First, use of methods A and B usually gave side products less polar than the cyclonucleosides (**8**). Since a prolonged reaction time appeared not to change the product distribution sufficient for its detection by t.l.c., it is unlikely that these less polar substances were cyclization intermediates. Moreover, a carbamate ester such as (**9**) is unlikely to be an intermediate for cyclization, since (**9a**) and (**9b**) were unchanged when heated in DMF to 180 °C. Accordingly, we attempted an independent synthesis of a derivative of (**7a**) carrying a phenoxycarbonyl group on either the 5′-oxygen or 8-nitrogen, compounds of this type being considered as likely intermediates for 8,5′-imimo- or 8,5′-carbamoyloxy-cyclonucleosides. Compound (**7a**) was first protected by



(**12**) (**13**)

conversion into 2′,3′-*O*-isopropylidene-6-dimethylaminomethyleneamino-8-methylaminoadenosine (**12**), and this upon treatment with phenyl chloroformate gave, unexpectedly, 9-(2′,3′-*O*-isopropylidene-5′-phenoxycarbonyl-β-D-ribofuranosyl)-6-formamido-8-methylaminopurine (**13**) as a major product. The ^{1}H n.m.r. spectrum of this showed split signals for the 8-NHMe group at δ 2.98 and 7.68 as well as for the 6-NHCHO group at δ 9.83 and 10.81. This compound, most likely formed by hydrolytic cleavage of the dimethylamino group during chromatography,† discouragingly was recovered unchanged after a prolonged period of heating at 135—140 °C in DMF containing triethylamine.

Thus, despite the mechanistic ambiguity and problematic deprotection of the guanosine derivatives described above, direct cyclizations offer promising syntheses of 8,5′-imino-nucleosides, in as much as the relative difficulties encountered depend largely upon the critical choice of a protecting method. Furthermore, the application of Methods A and B giving rise, apparently, to dehydrative N–C bond formation offer further examples of this rather rare reaction.‡§ Finally, the formation of compounds (**9a,b**) suggests the possibility of spanning nucleoside molecules with new types of bridge.

Experimental¶

8-Methylaminoinosine (**5b**).—A mixture of 8-bromoinosine (700 mg, 2.02 mmol), methylamine hydrochloride (1.36 g, 20.2 mmol), triethylamine (2.83 ml, 20.2 mmol), and methanol (20 ml) in a pressure tube was heated at 115—120 °C for 11 h under argon. After cooling and evaporation of the solvent, the residue was heated to reflux in chloroform (30 ml) and then cooled to room temperature. The insoluble solid was collected, digested with ice–water (3 ml), and the sparingly soluble precipitate collected by suction. After drying *in vacuo* at 50—60 °C, the crude product was dissolved in a large amount of hot methanol, treated with Norit and the solvent evaporated to give a foam, which was extracted with hot acetone. The acetone extract was concentrated to give amorphous (**5b**) (326 mg, 54.5%) after drying under high vacuum at 90 °C. Attempted crystallization

* The description of this experiment is omitted from the Experimental section, because we could not repeat it for optimization of the yield owing to shortage of material.

† In a separate experiment, we observed that the initial major product completely transformed to a slightly less polar substance (**13**) after second preparative t.l.c.

‡ We are unaware of any example other than the case of an 8,5′-methylhydrazocyclonucleoside (**13**) in ref. 3*g*.

§ See ref. 7, p. 5.

¶ The general methods used are similar to those described earlier.[3e]

Table 4. ^{1}H N.m.r. resonances of (**8a**—**i**), (**9a**—**c**), (**10a,b**), (**11a,b**), and (**3a,b**) in $(CD_3)_2SO$[a,b]

Compd.	5′-H	4′-H	3′-H	2′-H	1′-H	2-H	1-H	2-NH_2	Others
(**8a**)	3.20 (dd, J_{gem} 14.4, $J_{5'a,4'}$ 4.4, 5′a-H), 3.49 (dd, J_{gem} 14.4, $J_{5'b,4'}$ 3.6, 5′b-H)	4.65 (dd, $J_{4',5'a}$ 4.4, $J_{4',5'b}$ 3.6)	4.61 (d, $J_{3',2'}$ 6.0)	4.95 (d, $J_{2',3'}$ 6.0)	6.15 (s)	8.05 (s)			1.27 (3 H, s, Ip)[c] 1.46 (3 H, s, Ip) 3.03 (3 H, s, N–CH_3 bridge) 6.83 (2 H, s, C_6-NH_2)
(**8b**)	3.15 (d, J_{gem} 13.2, 5′a-H), 3.46 (dd, J_{gem} 13.2, $J_{5'b,4'}$ 4.0, 5′b-H)	4.64 (2 H, m, $J_{4',5'b}$ 4.0, $J_{3',2'}$ 6.0, 4′-H, and 3′-H)		4.95 (d, $J_{2',3'}$ 6.0)	6.09 (s)	7.98 (s)	12.28 (s)		1.27 (3 H, s, Ip) 1.44 (3 H, s, Ip) 2.97 (3 H, s, N–CH_3 bridge)
(**8c**)	3.12 (d, J_{gem} 14.0, 5′a-H), 3.32 (dd, J_{gem} 14.0, $J_{5'b,4'}$ 2.4, 5′b-H)	4.59 (d, $J_{4',5'b}$ 2.4)	4.48 (d, $J_{3',2'}$ 6.0)	4.74 (d, $J_{2',3'}$ 6.0)	6.16 (s)	8.07 (s)			1.23 (3 H, s, Ip) 1.42 (3 H, s, Ip) 4.37 (d, J_{gem} 14.4, $PhCH_a$) 5.02 (d. J_{gem} 14.4, $PhCH_b$) 6.89 (2 H, s, 6-NH_2) 7.32—7.45 (5 H, m, Ph)
(**8d**)	3.07 (d, J_{gem} 14.0, 5′a-H), 3.30 (dd, J_{gem} 14.0, $J_{5'b,4'}$ 2.8 5′b-H)	4.59 (d, $J_{4',5'b}$ 2.8)	4.53 (d, $J_{3',2'}$ 6.0)	4.76 (d, $J_{2',3'}$ 6.0)	6.11 (s)	8.01 (s)	12.36 (s)		1.24 (3 H, s, Ip) 1.42 (3 H, s, Ip) 4.37 (d, J_{gem} 14.4, $PhCH_a$) 4.90 (d, J_{gem} 14.4, $PhCH_b$) 7.28—7.58 (5 H, m, Ph)
(**8e**)	3.15 (d, J_{gem} 14.0, 5′a-H), 3.45 (dd, J_{gem} 14.0, $J_{5'b,4'}$ 2.6, 5′b-H)	4.68 (d, $J_{4',5'b}$ 2.6)	4.62 (d, $J_{3',2'}$ 5.4)	4.85 (d, $J_{2',3'}$ 5.4)	6.16 (s)	8.06 (s)		6.84 (s)	1.28 (3 H, s, Ip) 1.46 (3 H, s, Ip) Allyl signal[d]
(**8f**)	3.12 (d, J_{gem} 14.4, 5′a-H), 3.44 (dd, J_{gem} 14.4, $J_{5'b,4'}$ 3.2, 5′b-H)	4.69 (d, $J_{4',5'b}$ 3.2)	4.67 (d, $J_{3',2'}$ 6.4)	4.87 (d, $J_{2',3'}$ 6.4)	6.13 (s)	8.02 (s)	12.33 (s)		1.29 (3 H, s, Ip) 1.47 (3 H, s, Ip) Allyl signal[e]
(**8g**)	3.03 (d, J_{gem} 14.0, 5′a-H), 3.22 (dd, J_{gem} 14.0, $J_{5'b,4'}$ 3.2, 5′b-H)	4.55 (d, $J_{4',5'b}$ 3.2)	4.50 (d, $J_{3',2'}$ 6.0)	4.75 (d, $J_{2',3'}$ 6.0)	6.15 (s)		11.30 (s)		1.25 (3 H, s, Ip) 1.42 (3 H, s, Ip) 3.06 (3 H, s, DMAN's methyl)[c] 3.18 (3 H, s, DMAM's methyl) 4.26 (d, J_{gem} 14.5, $PhCH_a$) 4.89 (d, J_{gem} 14.5, $PhCH_b$) 7.28—7.57 (5 H, m, Ph) 8.68 (s, N=C*H*NMe_2)
(**8h**)	2.95 (d, J_{gem} 13.0, 5′a-H), 3.19 (dd, J_{gem} 13.0, $J_{5'b,4'}$ 3.0, 5′b-H)	4.51 (d, $J_{4',5'b}$ 3.0)	4.49 (d, $J_{3',2'}$ 6.0)	4.76 (d, $J_{2',3'}$ 6.0)	5.95 (s)		10.59(s)	6.44 (s)	1.25 (3 H, s, Ip) 1.41 (3 H, s, Ip) 4.21 (d, J_{gem} 13.5, $PhCH_a$) 4.83 (d, J_{gem} 13.5, $PhCH_b$) 7.25—7.59 (5 H, m, Ph)
(**8i**)	2.97 (d, J_{gem} 14.4, 5′a-H), 3.34 (dd, J_{gem} 14.4, $J_{5'b,4'}$ 3.0, 5′b-H)	4.61 (d, $J_{5'b,4'}$ 3.0)	4.63 (d, $J_{3',2'}$ 6.0)	4.84 (d, $J_{2',3'}$ 6.0)	5.95 (s)		No scan	6.57 (s)	1.28 (3 H, s, Ip)[c] 1.43 (3 H, s, Ip) Allyl signal[f]

Table 4 (*continued*)

Compd.	5′-H	4′-H	3′-H	2′-H	1′-H	2-H	1-H	2-NH_2	Others
(**9a**)	3.98 (dd, J_{gem} 12.0, $J_{5'a,4'}$ 4.0, 5′a-H), 4.81 (d, J_{gem} 12.0, 5′b-H)	4.55 (d, $J_{4',5'a}$ 4.0)	4.64 (d, $J_{3',2'}$ 6.4)	4.90 (d, $J_{2',3'}$ 6.4)	6.27 (s)		11.58 (s)		1.11 (3 H, s, Ip) 1.42 (3 H, s, Ip) 3.05 (3 H, s, DMAM's methyl)[c] 3.19 (3 H, s, DMAM's methyl) 4.99 (d, J_{gem}15.6, $PhCH_a$) 5.05 (d, J_{gem} 15.6, $PhCH_b$) 8.62 [s, $N{=}CHN(CH_3)_2$]
(**9b**)	3.99 (dd, J_{gem} 12.0, $J_{5'a,4'}$ 3.6, 5′a-H), 4.80 (d, J_{gem} 12.0, 5′b-H)	4.59 (d, $J_{4',5'a}$ 3.6)	5.01 (d, $J_{3',2'}$ 6.0)	5.33 (d, $J_{2',3'}$ 6.0)	6.39 (s)		11.52 (s)		1.29 (3 H, s, Ip) 1.50 (3 H, s, Ip) 3.05 (3 H, s, DMAM's methyl) 3.19 (3 H, s, DMAM'S methyl) Allyl signal[g] 8.63 (s, $N{=}CHNMe_2$)
(**9c**)	3.99 (dd, J_{gem} 12.0, $J_{5'a,4'}$ 4.0, 5′a-H), 4.80 (d, J_{gem} 12.0, 5′b-H)	4.58 (d, $J_{4',5'a}$ 4.0)	5.00 (d, $J_{3',2'}$ 6.0)	5.33 (d, $J_{2',3'}$ 6.0)	6.28 (s)		10.78 (s)	6.69 (s)	1.31 (3 H, s, Ip) 1.49 (3 H, s, Ip) Allyl signal[h]
(**10a**)[b]	3.08—3.51 (2 H, m)	4.63 (m)	4.56 (d, $J_{3',2'}$ 6.0)	4.87 (d, $J_{2',3'}$ 6.0)	6.11 (s)	8.01 (s)			1.28 (3 H, s, Ip) 1.47 (3 H, s, Ip) 6.64 (2 H, br. s. 6-NH_2) 6.96 (br d, *J* 4.0, NH bridge)
(**10b**)[b]	3.00—3.46 (2 H, m)	4.65 (s)	4.59 (d, $J_{3',2'}$ 6.0)	4.85 (d, $J_{2',3'}$ 6.0)	6.03 (s)	7.87 (s)	12.16 (br s)		1.28 (3 H, s, Ip) 1.46 (3 H, s, Ip) 6.97 (br d, *J* 5.0, NH bridge)
(**11a**)	3.21 (dd, J_{gem} 13.6, $J_{5'a,4'}$ 4.4, 5′a-H), 3.43 (dd, J_{gem} 13.6, $J_{5'b,4'}$ 3.2, 5′b-H)	4.48 (dd, $J_{4',5'a}$ 4.4, $J_{4',5'b}$ 3.2)	4.28 (dd, $J_{3',2'}$ 6.8, $J_{3',3'OH}$ 6.8)	3.99 (dd, $J_{2',3'}$ 6.8, $J_{2',2'OH}$ 6.8)	6.08 (s)	8.04 (s)			3.04 (3 H, s, N-CH_3 bridge) 5.22 (d, *J* 6.8, 3′-OH) 5.50 (d, *J* 6.8, 2′-OH) 6.79 (2 H, s, 6-NH_2)
(**11b**)	3.13 (d, J_{gem} 14.0, 5′a-H), 3.40 (d, J_{gem} 14.0, 5′b-H)	4.48 (s)	4.27 (dd, $J_{3',2'}$ 5.5, $J_{3',3'OH}$ 5.5)	4.03 (dd, $J_{3',2'}$ 5.5, $J_{2',2'OH}$ 6.5)	6.02 (s)	7.96 (s)	No scan		2.99 (3 H, s, NCH_3 bridge) 5.25 (d, *J* 5.5, 3′-OH) 5.49 (d, *J* 6.5, 2′-OH)
(**3a**)[b]	3.06—3.46 (2 H, m)	*i*	4.27 (1 H, t $J_{2',3'} = J_{2',2'OH} = J_{3',3'OH}$ 6.0) 3.99 (1 H, t $J_{2',3'} = J_{2',2'OH} = J_{3',3'OH}$ 6.0) Collapsed to d on addition D_2O		6.06 (s)	8.03 (s)			5.22 (br d, *J* 6.0 2′ or 3′-OH) 5.44 (br d, *J* 6.0 2′, 3′-OH) 6.62 (2 H, br, s, 6-NH_2) 6.94 (br d, *J* 4.0, NH bridge)
(**3b**)[b]	3.02—3.42 (2 H, m)	4.47 br s)	4.00 (d, $J_{2',3'}$ 6.0, 2′-H 3′-H) 4.24 (d, $J_{2',3'}$ 6.0, 2′-H 3′-H)		5.98 (s)	7.88 (s)	No scan		5.30 (2 H, br s, 2′-OH and 3′-OH) 6.96 (br d, *J* 4.0, NH bridge)

[a] s = Singlet, d = doublet, dd = doublet of doublets, t = triplet, dt = doublet of triplets, m = multiplets. Chemical shifts are given in p.p.m. and *J* values in Hz. [b] The spectra of (**10a**,**b**) and (**11c**,**d**) were measured at 100 MHz, the others at 200 MHz, and most of the sugar proton resonances are recorded from spin-decoupling experiments after D_2O addition [the spectra of (**10**) and (**3**) are cited from ref. 3*b*]. [c] Ip = isopropylidenemethyl, DMAM = dimethylaminomethylene. [d] 3.98 (dd, J_{gem} 13.0, *J* 6.6, N-CH_a-CH=CH_2), 4.24 (dd, J_{gem} 13.0, *J* 6.4, N-CH_bCH=CH_2), 5.31 (dd, J_{gem} 6.8, *J* 9.6, N-$CH_2CH{=}CH_a$), 5.38 (dd, J_{gem} 6.8, *J* 13.2, N-$CH_2CH{=}CH_b$), 5.98—6.22 (m, $NCH_2CH{=}CH_2$). [e] 3.96 (dd, J_{gem} 15.2, *J* 6.0, $NCH_aCH{=}CH_2$), 4.15 (dd, J_{gem} 15.2, *J* 6.8, NCH_b-CH=CH_2), 5.31 (dd, J_{gem} 6.8, *J* 9.6, $NCH_2CH{=}CH_a$), 5.39 (dd, J_{gem} 6.8, *J* 13.2, $NCH_2CH{=}CH_b$), 5.98—6.21 (m, $NCH_2CH{=}CH_2$). [f] 3.83 (dd, J_{gem} 14, *J* 6, $NCH_aCH{=}CH_2$), 4.07 (dd, J_{gem} 14, *J* 6, $NCH_bCH{=}CH_2$), 5.30 (2 H, m, $NCH_2CH{=}CH_2$), 6.06 (m, $NCH_2CH{=}CH_2$). [g] 4.40 (2 H, m, $NCH_2CH{=}CH_2$), 5.35 (2 H, m, $NCH_2CH{=}CH_2$), 6.08 (m, $NCH_2CH{=}CH_2$). [h] 4.40 (2 H, m, $NCH_2CH{=}CH_2$), 5.30 (2 m, $NCH_2CH{=}CH_2$), 6.06 (m, $NCH_2CH{=}CH_2$). [i] Did not appear clearly.

from methanol or ethanol was unsuccessful owing to strong gelatination (Found: C, 44.3; H, 5.35; N, 23.4. $C_{11}H_{15}N_5O_5$ requires C, 44.44; H, 5.09; N, 23.56%).

2′,3′-O-*Isopropylidene*-8-*methylaminoadenosine* (**7a**).—*Method A*. A mixture of (**5a**) (1.73 g, 5.84 mmol), 2,2-dimethoxypropane (2.86 ml, 23.3 mmol), acetone (8.1 ml, 0.11 mol), and methanesulphonic acid (0.69 ml, 10.6 mmol) in DMF (20 ml) was stirred at room temperature overnight in a closed vessel. The solution was then neutralized by vigorous stirring with an excess of solid sodium hydrogencarbonate and the inorganic salt removed by filtration. The filtrate was evaporated, the residue taken into ethyl acetate (50 ml), and the EtOAc solution washed with water (2 × 20 ml). The separated and dried organic phase gave, after evaporation, a paste, which was recrystallized from a small volume of acetone to yield (**7a**) (1.32 g, 67.1%), m.p. 263—265 °C (Found: C, 50.0; H, 6.0; N, 25.2. $C_{14}H_{20}N_6O_4$ requires C, 44.99; H, 5.99; N, 24.99%).

Method B. A mixture of 8-bromo-2′,3′-*O*-isopropylideneadenosine (**6a**) (800 mg, 2.07 mmol) and 40% aqueous methylamine (1.68 ml, 9 × 2.07 mmol) in methanol (16 ml) was heated in a pressure tube at 90—100 °C for 40 h under argon. After having removed the solvent, the residue was partitioned between ethyl acetate (40 ml) and water (10 ml). The separated organic layer was dried (Na_2SO_4) and evaporated to give (**7a**) (495 mg, 71.1%) after one recrystallization from acetone, identical with the product in Method A.

2′,3′-*Isopropylidene*-8-*methylaminoinosine* (**7b**).—A mixture of (**5b**) (297 mg, 1.0 mmol), acetone (1.4 ml, 19 mmol), 2,2-dimethoxypropane (0.49 ml, 4 mmol), and methanesulphonic acid (0.12 ml, 1.8 mmol) in DMF (3.5 ml) was stirred at room temperature overnight. The mixture was neutralized with triethylamine, evaporated, and the residue digested with ice–water. The sparingly soluble solid was collected and dried under high vacuum. The product gave a gelatine in a rather small volume of methanol, and hence a solution of the product in hot methanol (100 ml) was treated with Norit and the solvent again evaporated off. Digestion of the residue with a small volume of chloroform gave (**7b**) as amorphous powder (244 mg, 72.3%), m.p. 253—254 °C (Found: C, 49.95; H, 5.9; N, 20.45. $C_{14}H_{19}N_5O_5$ requires C, 49.84; H, 5.68; N, 20.76%).

8-*Benzylamino*-2′,3′-O-*isopropylideneadenosine* (**7c**).—*Method A*. A mixture of (**4a**) (300 mg, 0.867 mmol), benzylamine (1.82 ml, 20 × 0.867 mmol), and ethanol (30 ml) in a pressure tube was stirred at 90—100 °C for 15 h. After evaporation of the solvent, the residue was repeatedly digested with ether to remove excess of the benzylamine. The sparingly soluble precipitate was fractionated by preparative t.l.c. [silica, 20 × 20 cm, 2 mm-thick, 2 sheets; $CHCl_3$–MeOH (85:15), developed three times] and the appropriate fractions were eluted with methanol to give a glass, which was dried *in vacuo* at 80 °C. A mixture of this product, DMF (3.0 ml), acetone (1.2 ml, 16.4 mmol), 2,2-dimethoxypropane (0.42 ml, 3.4 mmol), and methanesulphonic acid (0.1 ml, 1.54 mmol) was stirred at room temperature overnight. The solution was neutralized with solid sodium hydrogencarbonate and the inorganic salt filtered off. The filtrate was evaporated and the residue digested with ice–water to give a solid product, which was collected, dried, and recrystallized from acetone to afford (**7c**) [76% yield on the basis of the used (**4a**)], which decomposed above 204 °C and did not melt up to 300 °C (Found: C, 58.45; H, 5.95; N, 19.3. $C_{20}H_{24}N_6O_4 \cdot 0.5CH_3COCH_3$ requires C, 58.49; H, 6.16; N, 19.04%).

Method B. A mixture of (**6a**) (1.88 g, 4.87 mmol), benzylamine (5.11 ml, 10 × 4.87 mmol), and methanol (30 ml) in a pressure tube was stirred at 90—100 °C for 10 h under an argon atmosphere. The complete consumption of the starting material was confirmed by t.l.c. After having removed the solvent, the residue was thoroughly triturated with ether to remove excess of benzylamine and the resulting paste was subjected to preparative t.l.c. [silica, 20 × 20 cm, 4 sheets; $CHCl_3$–MeOH (85:15), twice developed]. The combined major bands were eluted with MeOH to give a crystalline fraction, which was recrystallized from acetone to afford 1.93 g (90%) of (**7c**), identical with the aforementioned product in terms of i.r. spectroscopy.

8-*Benzylamino*-2′,3′-O-*isopropylideneinosine* (**7d**).—*Method A*. A mixture of (**4b**) (300 mg, 0.864 mmol), benzylamine (1.82 ml, 20 × 0.864 mmol), and ethanol (30 ml) in a pressure tube was stirred at 115 °C for 35 h. The mixture was evaporated, the residue thoroughly washed with ether to remove excess of benzylamine, and then fractionated by preparative t.l.c. [silica, 20 × 20 cm, 2 sheets; $CHCl_3$–MeOH (85:15), developed 3 times]. The major bands were eluted with MeOH and the finally obtained glass was dried *in vacuo* at 90—100 °C. To this crude product was added DMF (3.0 ml), acetone (1.2 ml, 16.4 mmol), 2,2-dimethoxypropane (0.42 ml, 3.4 mmol), and methanesulphonic acid (0.1 ml, 1.54 mmol) and the mixture stirred at room temperature overnight with exclusion of moisture. After neutralization of this solution with solid sodium hydrogencarbonate and filtration, the filtrate was evaporated. Digestion of the residue with a small volume of ice–water gave a solid precipitate, which was collected, dried, and recrystallized from acetone to give (**7d**) as crystals [198 mg, 55.4% on the basis of (**4b**)], m.p. 226—227 °C (Found: C, 58.1; H, 5.8; N, 16.75. $C_{20}H_{23}N_5O_5$ requires C, 58.10; H, 5.61; N, 16.94%).

Method B. Compound (**6b**) (1.0 g, 2.58 mmol), methanol (20 ml), and benzylamine (5.42 ml, 20 × 2.58 mmol) were combined in a pressure tube and the mixture was stirred at 90—100 °C for 35 h under an argon atmosphere. The solvent was evaporated off and the excess of benzylamine was removed by repeated digestion of the residue with ether and decantation. The pasty residue was then fractionated using 4 sheets of 20 × 20 cm plates of silica gel [$CHCl_3$–MeOH (85:15), twice developed] and the finally obtained solid recrystallized from acetone to give (**7d**) (1.01 g, 95%) identical with the above obtained product.

8-*Allylamino*-2′,3′-O-*isopropylideneadenosine* (**7e**).—Compound (**6a**) (1.0 g, 2.59 mmol) was treated with allylamine (1.94 ml, 10 × 2.59 mmol) in methanol (10 ml) at 90—95 °C for 11 h in a pressure tube. After evaporation and ether washing as above, the residue in ethyl acetate (50 ml) was washed with water (2 × 20 ml), dried, and the solvent evaporated off. Preparative t.l.c. using 2 sheets of silica plates (20 × 20 cm) and $CHCl_3$–MeOH (85:15) (twice developed) gave a foam which resisted crystallization. Hence, the total was dissolved in MeOH, treated with Norit and again thoroughly evaporated to give (**7e**) as a homogeneous foam (after drying at 80—90 °C under high vacuum) (882 mg, 90%) (Found: C, 52.6; H, 6.1; N, 22.25. $C_{16}H_{22}N_6O_4 \cdot 0.5CH_3OH$ requires C, 52.37; H, 6.39; N, 22.21%).

8-*Allylamino*-2′,3′-O-*isopropylideneinosine* (**7f**).—Compound (**6b**) (500 mg, 1.29 mmol) was treated with allylamine (1.94 ml, 20 × 1.29 mmol), and triethylamine (0.18 ml, 1.29 mmol) in methanol at 90—100 °C for 50 h as above. The mixture was evaporated and the residue partitioned between ethyl acetate (30 ml) and water (10 ml). The separated EtOAc layer was again washed with water (10 ml), dried, and evaporated. Crystallization and recrystallization of the residue from methanol gave (**7f**) (447 mg, 93%), m.p. 199—201 °C (Found: C, 52.4; H, 5.85; N, 18.55. $C_{16}H_{23}N_5O_5 \cdot 0.5CH_3OH$ requires C, 52.23; H, 6.12; N, 18.46%).

8-*Benzylamino*-2',3'-O-*isopropylideneguanosine* (**7g**).—A suspension of (**6c**) (1.0 g, 2.48 mmol) and benzylamine (5.2 ml, 20 × 2.48 mmol) in ethanol was heated in a pressure tube at 115—120 °C for 75 h, by which time the starting material was completely consumed. The mixture was evaporated, the residue washed with ether and then subjected to preparative t.l.c. [silica, 20 × 20 cm 4 sheets; $CHCl_3$–MeOH (85:15), twice developed] and the major bands eluted with MeOH. The combined amorphous product was again dissolved in methanol and the solution treated with Norit and evaporated to a foam (**7g**), which was thoroughly dried *in vacuo* at 90—100 °C (it resisted crystallization) and had m.p. 266—268 °C; yield, quantitative (Found: C, 56.3; H, 5.55; N, 19.35. $C_{20}H_{24}N_6O_5$ requires C, 56.07; H, 5.65; N, 19.61%).

8-*Benzyl*-2-*dimethylaminomethyleneamino*-2',3'-O-*isopropylideneguanosine* (**7h**).—A mixture of (**7g**) (603 mg, 1.41 mmol), and *N*,*N*-dimethylformamide dimethylacetal (DMF–acetal) (0.94 ml, 5 × 1.41 mmol) in DMF (9 ml) was stirred at room temperature for 3 h and then evaporated. On treatment with a small volume of methanol, the residue gave crystals, which were recrystallized from methanol to afford (**7h**) (511 mg, 75%), m.p. 268—270 °C (Found: C, 57.0; H, 5.95; N, 20.5. $C_{23}H_{29}N_7O_5$ requires C, 57.13; H, 6.05; N, 20.28%).

8-*Allylamino*-2',3'-O-*isopropylideneguanosine* (**7i**).—A mixture of (**6c**) (1.0 g, 2.50 mmol), allylamine (7.75 ml, 45 × 2.50 mmol), and EtOH (25 ml) in a pressure tube was heated at 120—125 °C for 191 h under argon. After evaporation, the residue was fractionated by preparative t.l.c. [silica, 20 × 20 cm; 4 sheets; $CHCl_3$–MeOH (85:15), developed 3 times] and the major bands were eluted with MeOH. The product resisted crystallization, and hence it was dissolved again in methanol, the solution treated with Norit, and the solvent evaporated off under reduced pressure followed by suction under high vacuum at 90 °C to afford (**7i**) as a foam (705 mg, 75%), m.p. 246—248 °C (Found: C, 50.9; H, 5.8; N, 22.15. $C_{16}H_{22}N_6O_5$ requires C, 50.74; H, 5.85; N, 22.28%).

8-*Allylamino*-2-*dimethylaminomethyleneamino*-2',3'-O-*isopropylideneguanosine* (**7j**).—A mixture of (**7i**) (200 mg, 0.528 mmol) and DMF–acetal (0.105 ml, 1.5 × 0.528 mmol) in DMF (4 ml) was stirred at room temperature for 5 h and then evaporated. The residue was digested with a small volume of ice–water, after which the insoluble solid was collected and dried *in vacuo*. Recrystallization from methanol gave (**7j**) (208 mg, 91%), m.p. 225.5—227 °C (Found: C, 52.75; H, 6.25; N, 22.5. $C_{19}H_{27}N_7O_5$ requires C, 52.60; H, 6.27; N, 22.69%).

General Procedures for Cyclizing (**7a—f,h,j**)

Method A.—A mixture of each of the compounds (**7**) and 1.5 mol equiv. of diphenyl carbonate and triethylamine in DMF (6—6.5 mol per mmol of the starting material) was stirred at 135 °C for 2 h. T.l.c. (silica gel) at this stage generally showed the presence of one major faster-moving product (**8**) with one or two more faster-running side products and, in some cases, starting material. After evaporation of the solvent at *ca.* 40 °C under reduced pressure the residue was fractionated by thick-layer chromatography (silica, 2 mm-thick), using $CHCl_3$–MeOH (9:1, v/v) as a developer. The major fraction was eluted with MeOH and recrystallized from MeOH or EtOH (see Table 1).

8,5'-*Benzylimino*-2-*dimethylaminomethyleneamino*-9-(5'-*deoxy*-2',3'-O-*isopropylidene*-β-D-*ribofuranosyl* (**8g**) *and* 8,5'-(N-*benzylcarbamoyloxy*)-2-*dimethylaminomethyleneamino*-9-(2',3'-O-*isopropylidene*-β-D-*ribofuranosyl*)*guanine* (**9a**). A mixture of (**7h**) (300 mg, 0.62 mmol), diphenyl carbonate (200 mg, 1.5 × 0.62 mmol), and Et_3N (0.13 ml, 1.5 × 0.62 mmol) in DMF (4 ml) was stirred at 135 °C for 2 h in a pressure tube. T.l.c. at this stage exhibited the presence of a small amount of the starting material and of three faster-running products. After the solvent had been evaporated off, the residue was applied to two sheets of silica plates of 20 × 20 cm and developed three times with the above mentioned solvent system. Work-up with the fraction of intermediate mobility gave (**8g**) in 29.1% isolated yield (84 mg) (see Tables 1 and 2).

On the other hand, elution of the fastest-running fraction with MeOH gave (**9a**) as crystals (45 mg, 14.2%), m.p. 254—256 °C (from MeOH); ν(C=O) (KBr) 1 735 cm^{-1} (Found: C, 56.55; H, 5.35; N, 19.3. $C_{24}H_{27}N_7O_6$ requires C, 56.57; H, 5.34; N, 19.24%).

The most polar, minor product was not isolated.

8,5'-(N-*Allylcarbamoyloxy*)-2-*dimethylaminomethyleneamino*-9-(2',3'-O-*isopropylidene*-β-D-*ribofuranosyl*)*guanine* (**9b**).—A mixture of (**7j**) (100 mg, 0.23 mmol), diphenyl carbonate (74 mg, 1.5 × 0.23 mmol), and Et_3N (0.05 ml, 1.5 × 0.23 mmol) in DMF (1.5 ml) was heated at 135 °C for 2 h as above. Consumption of the starting material and formation of three less polar substances were indicated by t.l.c. This reaction mixture was worked up as above to give, from the most mobile band, (**9b**) as crystals (32 mg, 30.3%), m.p. >300 °C; ν(C=O) (KBr) 1 745 cm^{-1} (Found: C, 52.45; H, 5.5; N, 21.15. $C_{20}H_{25}N_7O_6$ requires C, 52.33; H, 5.48; N, 21.41%). The other products were not isolated owing a to a paucity of material.

Method B.—A mixture of each of the compounds (**7**) and 1.5 mol equiv. of *N*,*N'*-carbonyldi-imidazole (CDI) and DMF (6—6.5 ml per mmol of the starting material) was stirred at 125 °C for 2 h in an argon-filled pressure tube. After evaporation, the residue was directly fractionated by thick-layer chromatography (2 mm-thick) using $CHCl_3$–MeOH (9:1) as a developer. The t.l.c. patterns of the reaction mixtures were generally quite similar to those obtained by Method A and each isolation procedure followed the corresponding case in Method A. Identities of the products with the authentic samples were confirmed by i.r. spectroscopy or/and mixed m.p. determinations.

Method C.—To a solution of each of the compounds (**7**) in THF [16—20 ml per mmol of (**7**), depending on the solubilities of the substrates] was added 1.5 mol equiv. of diethyl azodicarboxylate (DEAD) and Ph_3P, and the mixture was stirred at room temperature for 10 h in a closed vessel. After evaporation, the residue was directly fractionated by preparative t.l.c. using the same thick plates and developer as above except that $CHCl_3$–MeOH (85:15) was used for isolating (**8i**). The identities of the products were confirmed by comparison with the authentic samples or by independent analysis (**8i**).

Conversion of (**8a**) *into* (**8b**).—To a stirred solution of (**8a**) (93 mg, 0.292 mmol) in 80% acetic acid (5.7 ml) was added at 0 °C sodium nitrite (201.5 mg, 10 × 0.292 mmol). After being stirred for 30 min, the mixture was left at 0 °C for 30 h. It was then evaporated, repeatedly co-evaporated with MeOH, and the residue digested with a small volume of ice–water to give a solid precipitate, which was collected and dried. Recrystallization from MeOH gave (**8b**) (73 mg, 78.3%), identical with an authentic sample obtained by cyclizing (**7b**) (Method A or B).

8,5'-*Benzylimino*-9-(5'-*deoxy*-2',3'-O-*isopropylidene*-β-D-*ribofuranosyl*)*guanine* (**8h**).—Compound (**8g**) (300 mg, 0.644 mmol) in concentrated ammonia–MeOH (1:3) (60 ml) was stirred at room temperature for 3 h. The mixture was evaporated, repeatedly co-evaporated with MeOH, and the residual solid recrystallized from ethanol to give (**8h**) (192 mg, 72.6%), m.p. >300 °C (Found: C, 58.7; H, 5.55; N, 20.2. $C_{20}H_{22}N_6O_4$ requires C, 58.53; H, 5.40; N, 20.48%).

Conversion of (**9b**) *into* (**9c**).—A suspension of (**9b**) (300 mg, 0.652 mmol) in a mixture of DMF (2 ml), acetic acid (1 ml), and water (1 ml) was stirred at room temperature for 1 h, and then at 70 °C for 4 h to give a solution. After cooling, the mixture was evaporated to leave a glass, which crystallized on addition of a little MeOH. Recrystallization from MeOH gave (**9c**) (233 mg, 88.3%), m.p. >300 °C (Found: C, 50.5; H, 4.95; N, 20.9. $C_{17}H_{20}N_6O_6$ requires C, 50.49; H, 4.98; N, 20.78%).

8,5′-*Imino*-9-(5′-*deoxy*-2′,3′-O-*isopropylidene*-β-D-*ribofuranosyl*)*adenine* (**10a**).[3b]—*Method A*. A solution of sodium naphthalenide in THF (6.3 ml; 2.29 mmol of sodium naphthalenide) [from naphthalene (524 mg, 4.1 mmol) and sodium chips (92 mg, 4.0 mmol) in dry THF (10 ml)] was added, under argon, *via* a syringe to (**8c**) (100 mg, 0.254 mmol) in dry THF (20 ml) under argon. The mixture was stirred at room temperature for 16 h after which time t.l.c. indicated disappearance of (**8c**). The mixture was then left open to the atmosphere until the green colour disappeared after which it was evaporated to dryness. The residue was dissolved in MeOH (4 ml), and the insoluble material (mostly naphthalene) was filtered off and the filtrate fractionated on a silica plate [20 × 20 cm; $CHCl_3$–MeOH (85:15), twice developed]. The appropriate fraction was eluted with MeOH and recrystallized from ethanol to give (**10a**) as a monoethanol solvate (55 mg, 55%), identical with an authentic sample[3b] in terms of mixed m.p. and i.r. spectroscopy (Found: C, 51.6; H, 6.25; N, 24.0. $C_{13}H_{16}N_6O_3 \cdot C_2H_5OH$ requires C, 51.42; H, 6.33; N, 23.98%).

Method B. Potassium t-butoxide (67 mg, 1.5 × 0.398 mmol) was added to a solution of (**8e**) (137 mg, 0.398 mmol) in dry dimethyl sulphoxide (1.5 ml) and the mixture was stirred at 95—100 °C for 30 min; after this time t.l.c. showed disappearance of (**8e**) and appearance of a slightly more polar product [$CHCl_3$–MeOH (9:1)] or EtOH–benzene (2:8)]. The mixture was diluted with water (3 ml), neutralized with solid CO_2, and evaporated to dryness. The residue was extracted with hot acetone and the acetone extract fractionated on a silica gel plate (20 × 20 cm) using EtOH–benzene (2:8) as developer. The desired fraction was eluted with MeOH and the gum obtained was dissolved in 0.5M-NaOH–MeOH (4.8 ml). After addition of 4% $KMnO_4$ solution (1.8 ml, 0.45 mmol), the mixture was stirred at room temperature for 1 h. The precipitate was filtered off and the filtrate subjected to preparative t.l.c. [20 × 20 cm; $CHCl_3$–MeOH (9:1), twice developed] to give (**10a**) as an ethanol solvate (50 mg, 36%) after recrystallization from ethanol, identical with an authentic sample.

8,5′-*Imino*-9-(5′-*deoxy*-2′,3′-O-*isopropylidene*-β-D-*ribofuranosyl*)*hypoxanthine* (**10b**).—A solution of (**8d**) (100 mg, 0.253 mmol) in THF (20 ml) was combined under argon with a solution of sodium naphthalenide (6.3 ml, 2.29 mmol) prepared as described above, and the mixture was then stirred for 2 h; after this time (**8d**) had disappeared. The mixture was worked up as in the case of (**10a**) and the gum so obtained was fractionated on a silica plate [20 × 20 cm; $CHCl_3$–MeOH (9:1), twice developed] to afford (**10b**) (43 mg, 54.3%) after recrystallization from acetone, identical with an authentic specimen[3b] (Found: C, 51.25; H, 5.05; N, 22.9. $C_{13}H_{15}N_5O_4$ requires C, 51.14; H, 4.95; N, 22.94%].

8,5′-*Methylimino*-9-(5′-*deoxy*-β-D-*ribofuranosyl*)*adenine* (**11a**).—A solution of (**8a**) (44 mg, 0.138 mmol) in 90% trifluoroacetic acid (2 ml) was left at room temperature overnight and then evaporated. The residue was repeatedly co-evaporated with MeOH to remove the residual acid. The pasty residue was again dissolved in MeOH (5 ml), neutralized with anion exchange resin IRA-410 (OH-form), and the resin filtered through a small column. After elution of the resin with methanol, the combined eluants were evaporated to give crystals, which were recrystallized from MeOH to afford (**11a**) as a methanol solvate (30.4 mg, 79.1%); this gradually became yellowish above 130 °C and melted at 269—272 °C (Found: C, 46.25; H, 5.7; N, 27.35. $C_{11}H_{14}N_6O_3 \cdot CH_3OH$ reqiures C, 46.44; H, 5.85; N, 27.08%).

8,5′-*Methylimino*-9-(5′-*deoxy*-β-D-*ribofuranosyl*)*hypoxanthine* (**11b**).—Compound (**8b**) (66 mg, 0.2 mmol) in 90% trifluoroacetic acid (4 ml) was stirred at room temperature for 5 h and then evaporated. The residue was worked up in the same way as (**11a**), using this time anion exchange resin IRA-93 (OH-form). Recrystallization of the solid product from MeOH gave (**11b**) (34 mg, 62%), m.p. >300 °C (Found: C, 47.45; H, 4.85; N, 24.9. $C_{11}H_{13}N_5O_4$ requires C, 47.31; H, 4.69; N, 25.08%).

2′,3′-O-*Isopropylidene*-6-*dimethylaminomethyleneamino*-8-*methylaminoadenosine* (**12**).—A mixture of (**7a**) (200 mg, 0.594 mmol) and DMF–acetal (0.79 ml, 5.94 mmol) in DMF (3 ml) was stirred at room temperature overnight and evaporated to give a homogeneous solid, which was recrystallized from acetone to give (**12**) as needles (220 mg, 95%), m.p. 232—233 °C (Found: C, 52.2; H, 6.3; N, 25.2. $C_{17}H_{25}N_7O_4$ requires C, 52.16; H, 6.44; N, 25.05%).

9-(2′,3′-O-*Isopropylidene*-5′-*phenoxycarbonyl*-β-D-*ribofuranosyl*)-6-*formamido*-8-*methylaminopurine* (**13**).—To a stirred ice-cold suspension of (**12**) (300 mg, 0.766 mmol) in a mixture of pyridine (20 ml) and triethylamine (0.13 ml, 0.93 mmol) was added phenyl chloroformate (0.055 ml, 0.44 mmol). After 25 min, more of the reagent (0.055 ml, 0.44 mmol) was added. After being stirred at 0 °C for 1.5 h, the mixture was left at 0 °C overnight and then at room temperature for 1 day. T.l.c. with an aliquot of the reaction indicated that *ca.* 50% of the starting material was converted into a less polar substance, and accordingly further amounts of triethylamine (0.07 ml, 0.5 mmol) as well as phenyl chloroformate (0.06 ml, 0.48 mmol) were added. After being stirred at room temperature for 8 h, the mixture was evaporated to half volume, diluted with MeOH (1 ml), and poured into ice–water (50 ml). The precipitate was collected by suction, dried, and subjected to preparative t.l.c. [20 × 20 cm; $CHCl_3$–EtOAc (1:1), developed three times]. The major fraction was eluted with acetone and recrystallized from a small volume of EtOAc to give (**13**) as woolly crystals (240 mg, 65%), m.p. 125—127 °C; δ[$(CD_3)_2SO$] 1.37 (3 H, s, isopropylidene Me), 1.58 (3 H, s, isopropylidene Me), 2.98 (3 H, d, *J* 4 Hz, s on D_2O-addition, 8-NHC*H*$_3$), 4.32 (2 H, dd, J_{gem} 12 Hz, $J_{4',5'}$ 4 Hz, 5′-CH_2), 4.45 (1 H, ill-resolved dt, $J_{4',5'} = J_{3',4'}$ = 4 Hz, 4′-H), 5.25 (1 H, dd, $J_{3',4'}$ 4 Hz, $J_{3',2'}$ 6 Hz, 3′-H), 5.81 (1 H, dd, $J_{2',3'}$ 6 Hz, $J_{2',1'}$ *ca.* 2 Hz, 2′-H), 6.21 (1 H, d, $J_{1',2'}$ *ca.* 2 Hz, 1′-H), 7.16—7.50 (5 H, m, phenyl), 7.68 (1 H, br q, D_2O-exchangeable, 8-N*H*CH_3), 8.34 (1 H, s, H_2), 9.83 (1 H, d, $J_{NH,CHO}$ 10 Hz, s on D_2O-addition, 6-NHC*H*O), 10.81 (1 H, d, $J_{NH,CHO}$ 10 Hz, D_2O-exchangeable, 6-N*H*CHO).

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