Synthesis and Properties of Some Hydrazo- and Oxamido-bridged Purine Nucleosides

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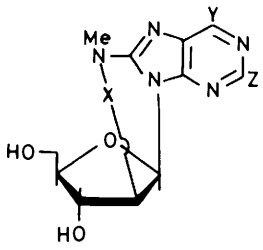
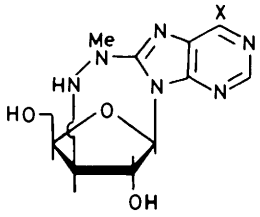
In a search for further long-bridged purine cyclonucleosides suceptible to further chemical transformations, 8,2′-hydrazo-9-(2′-deoxy-β-D-arabinofuranosyl)adenine (**8a**), and its hypoxanthine (**8b**) and guanosine analogues (**8c**) have been synthesized from 8-bromo-2′-*O*-tosyladenosine and other analogous precursors with an excess of hydrazine. Compound (**8a**, **b**) were oxidized to the corresponding 2′,N^{8}-didehydrocyclonucleosides (**9a**, **b**). Sodium methoxide catalysed aerial oxidation of (**8a**) and (**8b**) [or or (**9**)] gave the triazinopurines (**10a**) and (**10b**). To elucidate the mechanism of the conversion of (**8**) into (**10**), the 5′-*O*-trityl analogues (**12**) and (**13**) were also synthesized. 8,3′-Aminoimino-(**16**) and 8,2′-oxamido-adenine cyclonucleosides (**19**) have also been synthesized.

Recent reports from this laboratory have described the synthesis of some purine cyclonucleosides having a methylhydrazo or methyloxamido bridge between C-8 and C-2′ [(**1**)—(**4**), Scheme 1][1] and analogous 8,3′-methylhydrazocyclonucleosides (**5a**, **b**)[2] as part of our program to expand the range of model conformations of cyclonucleosides. Interestingly, a novel tricyclic system represented by compounds (**6a**, **b**) was also formed in the search for compounds (**5**),[2] and all these compounds were transformed in a variety of ways.

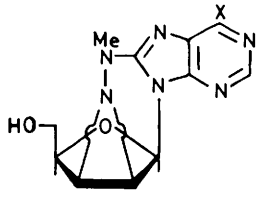
In view of the known oxidative nitrogen release from carbocycles containing a naked hydrazo group during various radical reactions,[3] we were particularly intrigued by the unequivocal synthesis of cyclonucleosides having a hydrazo bridge.



(**1**) X = NH; Y = NH_2; Z = H
(**2**) X = NH; Y = OH; Z = H
(**3**) X = NH; Y = OH; Z = NH_2
(**4**) X = O; Y = NH_2; Z = H



(**5**)
a; X = NH_2
b; X = OH



(**6**)
a; X = NH_2
b; X = OH

Scheme 1.

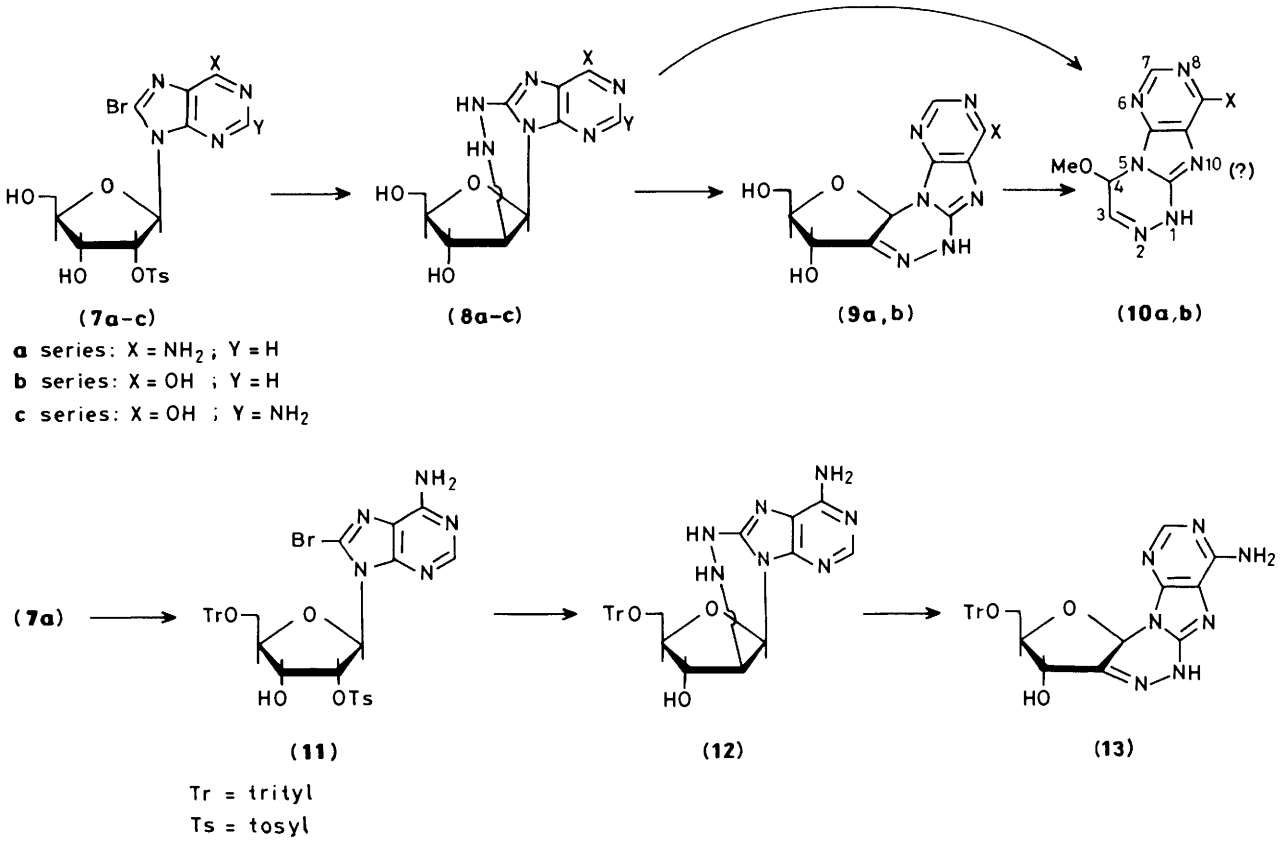
Table 1. U.v. absorptions of (**1**)—(**3**), (**8a**—**c**), (**9a**, **b**), (**10a**, **b**), (**12**), (**13**), (**16**), (**18**), and (**19**) in methanol

Compound	$\lambda_{max.}$/nm (ε)
(**1**)[a]	278 (18 800)
(**2**)[a]	266 (12 200), 293 (7 900)[b]
(**3**)[a]	262 (10 100), 293 (5 700)
(**8a**)	275 (15 400)
(**8b**)	288 (8 480)
(**8c**)	259 (7 000), 292 (4 700)
(**9a**)	253 (6 050), 300 (20 400)
(**9b**)	249 (2 300), 296 (12 300)
(**10a**)	249 (3 100), 293 (17 100)
(**10b**)	246 (2 970), 292 (13 020)
(**12**)	271 (23 900)
(**13**)	253 (4 700), 299 (15 600)
(**16**)	279 (26 600)
(**18**)	273 (15 400)
(**19**)	272 (18 400)

[a] Cited from the Table in ref. 1. [b] Shoulder.

In 1978, Chattopadhyaya and Reese[4] reported that 8-hydrazino-2′-*O*-tosyladenosine, obtained from 8-bromo-2′-*O*-tosyladenosine (**7a**) and hydrazine, when heated under reflux in ethanol gave 8,2′-hydrazo-9-(2′-deoxy-β-D-arabinofuranosyl)-adenine (**8a**) contaminated with its oxidation product, 2′,N^{8}-didehydro-8,2′-hydrazino-9-(2′-deoxy-β-D-arabinofuranosyl)-adenine (**9a**) (*ca.* 15%) (Scheme 2). A repeat of this reaction using a procedure avoiding aerial oxidation as far as possible gave (**8a**) in 77% yield. In a similar way 8-bromo-2′-*O*-tosylinosine (**7b**) and the guanosine analogue (**7c**) gave, respectively, 8,2′-hydrazo-9-(2′-deoxy-β-D-arabinofuranosyl)-hypoxanthine (**8b**) and 8,2′-hydrazo-9-(2′-deoxy-β-D-arabinofuranosyl)guanine (**8c**) in similar yields. The structures of these compounds were characterized unequivocally by their u.v.† results (Table 1) and extensive n.m.r. spin decoupling experiments (Table 2). Since these compounds are susceptible to aerial oxidation, they are partially convertible into the corresponding

† The absorption of (**8b**) at 288 nm is rather different from the absorption pattern of (**2**) (266 and 293 nm).[1] Repeated measurements in degassed methanol gave the same absorption. The other spectral and analysis data are consistent with this structure, and therefore we postulate at present at least partial participation by zwitterionic molecules, formed by dissociation of the lactam group by the hydrazo bridge, for this particular compound.



Scheme 2.

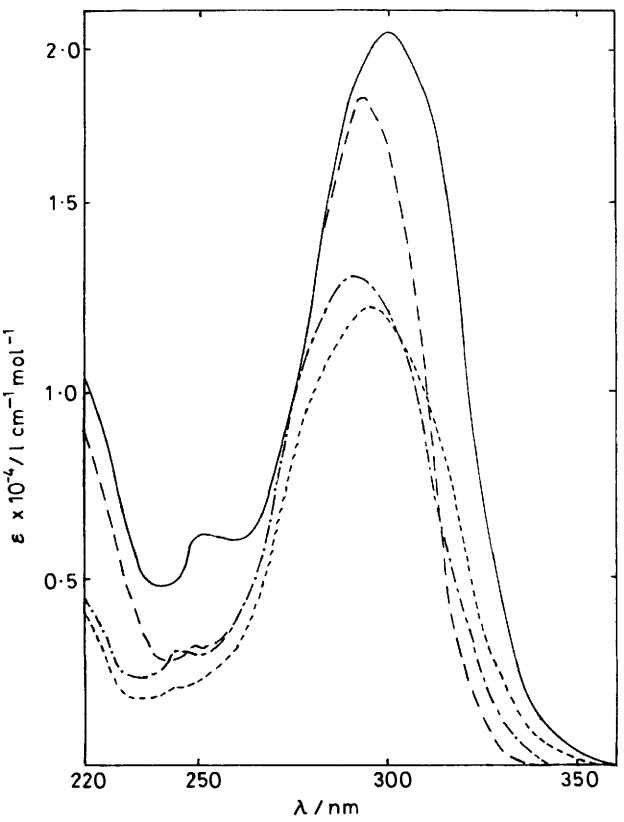


Figure. U.v. spectra of (**9a**) (——), (**10a**) (— — —), (**9b**) (- - - -), and (**10b**) (— · — · —) in methanol

2′,N^{B}-didehydro derivatives (**9**) when heated under reflux in methanol for a prolonged period.[4] Rapid manipulation on a small scale is, therefore, desirable for purification. Oxidation of (**8a, b**) with hypobromous acid generated *in situ*[1] gave (**9a**)[4] and its hypoxanthine analogue (**9b**) (this oxidation was quantitative in terms of t.l.c.). The structures of (**9a, b**) were evident from the spectral data and from spectral comparison with the N^{α}-methyl analogue.[1] Similar oxidation of (**8c**) was abandoned owing to its very limited solubility in most organic solvents and water. All the trial experiments to generate a diradical from (**8a**) using other oxidants invariably resulted in the formation of (**9a**) or intractable mixtures contaminated to some extent with (**9a**). On the other hand, when (**8a**) was subjected to sodium methoxide catalysed aerial oxidation in methanol, a crystalline compound corresponding to the molecular formula, $C_8H_9N_7O$ (mass *m/z* 219, M^+), was isolated in a low yield from a complex mixture of unstable products. Its structure was tentatively assigned as (**10a**) on the basis of the following evidence. The u.v. absorption pattern of (**10a**) parallels that of (**9a**) (see Figure and Table 1). Its ^{1}H n.m.r. spectrum displayed a doublet peak at δ 6.31 interacting with a 1 H proton signal at δ 7.07 (*J* 3.0 Hz) (see Experimental section). The chemical shift of 6.31 p.p.m. is in the range at which the general anomeric protons of nucleosides resonate, while the δ 7.07 signal corresponds to those of imine or hydrazone methine protons.[5] Furthermore, the resonance of 6-H at δ 11.80 is in good accord with the δ 11.74 signal of α-H in (**9a**) (Table 2). Moreover, rearrangement of the purine base under such mild reaction conditions is unlikely. Similar oxidation of (**8b**) afforded an analogous product (**10b**) in a similar yield (for spectral data see Experimental section). It should be noted that this reaction failed to proceed in methanol deoxygenated by supersonification during the passage of argon. Several attempts to isolate the other unstable (probably kinetic)

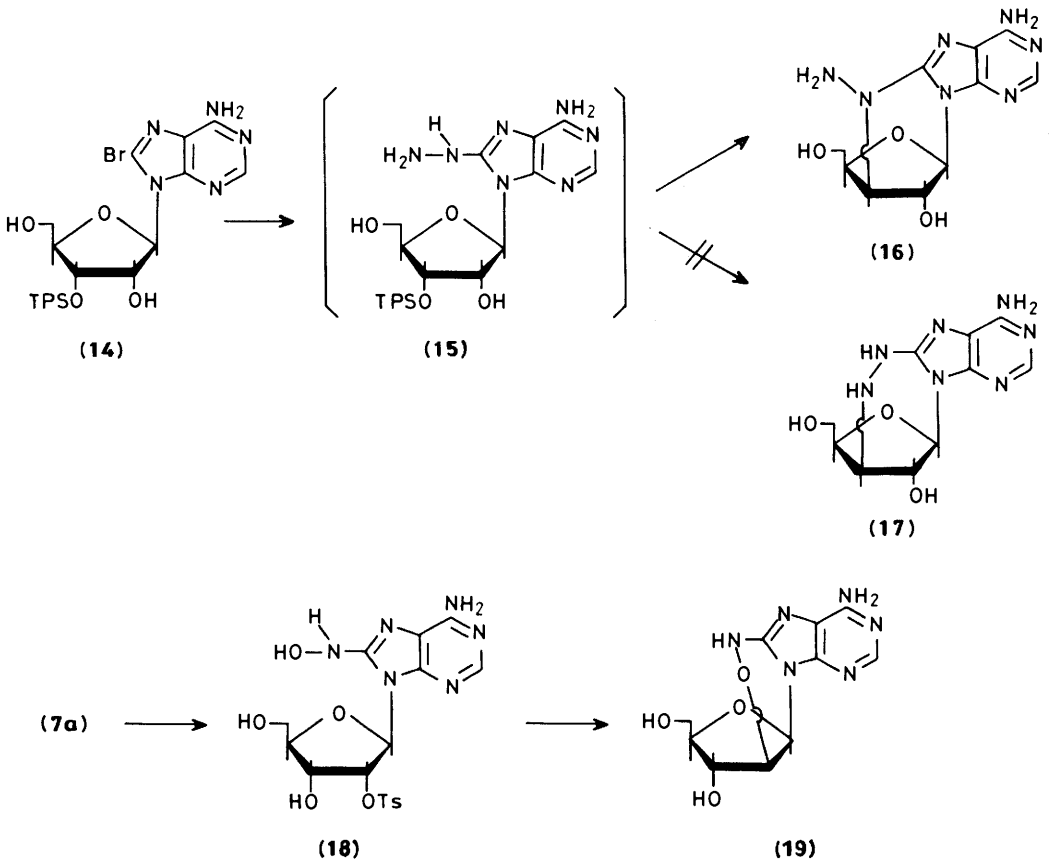
Table 2. ^{1}H N.m.r. resonances of (**8a**—**c**), (**9a**, **b**), (**13**), (**16**), (**18**), and (**19**) in $(CD_3)_2SO$[a,b]

Compd.	5′-H	4′-H	3′-H	2′-H	1′-H	2-H	α-H	β-H	Others
(**8a**)	3.48 (dd, J_{gem} 13.2, $J_{5'a,4'}$ 3.8, 5′a-H), 3.58 (dd, J_{gem} 13.2, $J_{5'b,4'}$ 3.8, 5′b-H)	3.97 (dt, $J_{4',5'a}$ = $J_{4',5'b}$ = $J_{4',3'}$ = 3.8)	3.79 (dd, $J_{3',4'}$ 3.6, $J_{3',2'}$ 2.0)	3.35 (dd, $J_{2',3'}$ 2.0, $J_{2',1'}$ 3.5)	5.82 (d, $J_{2',1'}$ 3.5)	7.97 (s)	8.68 (br s)	5.17 (br s)	5.12 (t, *J* 6.0, 5′-OH), 5.61 (d, *J* 5.0, 3′-OH), 6.62 (br s, NH_2)
(**8b**)	3.46 (dd, J_{gem} 13.0, $J_{5'a,4'}$ 3.8, 5′a-H), 3.58 (dd, J_{gem} 13.0, $J_{5'b,4'}$ 3.5, 5′b-H),	3.98 (dt, $J_{4',5'a}$ = $J_{4',5'b}$ = $J_{4',3'}$ = 3.6)	3.78 (dd, $J_{3',4'}$ 3.6, $J_{3',2'}$ 2.5)	3.37 (dd, $J_{2',3'}$ 2.5, $J_{2',1'}$ 3.5)	5.84 (d, $J_{2',1'}$ 3.5)	7.90 (s)	8.60 (br s)	5.10—5.14 (m) [overlapped on 5′-OH signal]	5.61 (d, *J* 5.0, 3′-OH), 12.22 (br s, lactam NH)
(**8c**)	3.33 (dd, J_{gem} 13.0, $J_{5',a,4'}$ 3.8, 5′a-H), 3.53 (dd, J_{gem} 13.0, $J_{5',b4'}$ 3.8, 5′b-H)	3.90 (dt, $J_{4',5'a}$ 3.6, $J_{4',3'}$ 3.8)	3.69 (dd, $J_{3',4'}$ 3.8, $J_{3',2'}$ 2.0)	3.15 (dd, $J_{2',3'}$ 2.0, $J_{2',1'}$ 3.5)	5.59 (d, $J_{1',2'}$ 3.5)		8.11 (br s)	4.83 (br s)	5.01 (t, *J* 5.0, 5′-OH), 5.53 (d, *J* 3.0, 3′-OH), 6.42 (br s, NH_2), 10.50 (br s, lactam NH)
(**9a**)	3.24 (dd, J_{gem} 12.5, $J_{5'a,4'}$ 4.8, 5′a-H), 3.46 (dd, J_{gem} 12.5, $J_{5'b,4'}$ 4.8, 5′b-H)	4.09 (t, $J_{4',5'a}$ = $J_{4',5'b}$ = 4.8)	4.52 (s)		6.25 (s)	8.07 (s)	11.74 (s)		4.97 (t, *J* 4.4, 5′-OH), 6.04 (d, *J* 4.0, 3′-OH), 6.87 (br s, NH_2)
(**9b**)	3.20 (dd, J_{gem} 12.5, $J_{5',a4'}$ 4.8, 5′a-H), 3.30 (dd, J_{gem} 12.5, $J_{5'b,4'}$ 4.8, 5′b-H)	3.95 (t, $J_{4',5'a}$ = $J_{4',5'b}$ = $J_{4',3'}$ = 4.8)	4.48 (s)		6.26 (s)	7.93 (s)	11.68 (s)		4.94 (t, *J* 4.4, 5′-OH), 5.97 (d, *J* 4.0, 3′-OH), 12.10 (br s, lactam NH)
(**13**)	2.87 (dd, J_{gem} 11.6, $J_{5'a,4'}$ 4.0, 5′a-H), 3.15 (dd, J_{gem} 11.60, $J_{5'b,4'}$ 4.0, 5′b-H)	4.31 (br s)	4.55 (br s)		6.41 (s)	8.16 (s)	11.81(s)		6.08 (s, 3′-OH), 6.87 (s, NH_2), 7.23 (m, Aryl-H)
(**16**)	3.50 (dd, J_{gem} 15.2, $J_{5'a,4'}$ 4.8, 5′a-H), 3.65 (dd, J_{gem} 15.2, $J_{5'b,4'}$ 4.8, 5′b-H)	4.43 (dt, $J_{4',5'a}$ = $J_{4',5'b}$ = 4.8, $J_{4',3'}$ 3.0)	3.87 (d, $J_{3',4'}$ 3.0)	4.66 (s)	5.66 (s)	7.95 (s)			4.93 (br s, =N–NH_2), 4.96 (t, *J* 6.0, 5′-OH), 6.15 (d, *J* 3.2, 2′-OH), 6.65 (br s, 6-NH_2)
(**18**)	3.60 (2 H, m)	4.03 (s)	4.33 (d, $J_{3',2'}$ 4.0)	5.56 (dd, $J_{2',3'}$ 4.0, $J_{2',1'}$ 6.4)	6.05 (d, $J_{1',2'}$ 6.4)	7.75 (s)	6.53 (8-NH)		1.05 (t, CH_3CH_2OH), 3.47 (q, CH_3CH_2OH), 6.00 (m, –NH–O*H* and 3′-OH), 6.61(s, NH_2)
(**19**)	3.18 (2 H, m)	4.02 (t, $J_{4',5'}$ 7.6)	4.21 (s)	4.64 (d, $J_{2',1'}$ 6.4)	6.40 (d, $J_{1',2'}$ 6.4)	7.93 (s)	7.89 (br s)		4.84 (t, *J* 4.4, 5′-OH), 5.61 (d, *J* 3.6, 3′-OH), 6.53 (s, NH_2)
(**5a**)[c]	3.87 (d, $J_{5',4'}$ 5.3)	4.47 (dd, $J_{4',3'}$ 5.0, $J_{4',5'}$ 5.3)	3.50 (d, $J_{3',4'}$ 5.0)	4.20 (d, *J* 3.3)	6.04 (s)	8.03 (s)		5.59 (br s)	4.70 (t, *J* 5.0, 5′-OH), 5.87 (d, 2′-OH), 6.48 (br s, NH_2)

[a] Chemical shifts are given in p.p.m. and *J* values in Hz. [b] All the spectra were measured at 200 MHz and the sugar proton resonances are recorded from spin-decoupling experiments after D_2O addition. [c] Cited from the Table in ref. 2.

products for mechanistic inspection failed.* In order to obtain some clue as to the mechanisms for these strange reactions from more readily isolated products, we decided to synthesize the 5′-*O*-trityl analogues of (**8a**) and (**9a**), and utilize them as models. After our initial attempts to tritylate (**9a**) selectively had failed, tritylation of (**7a**) was examined. In 1970, Pfleiderer and co-workers reported a tritylation study with adenosine and its derivatives under rather drastic conditions.[6] In our repeat experiments, successive addition of trityl chloride (TrCl) at a milder temperature allowed the synthesis of 8-bromo-2′-*O*-tosyl-5′-*O*-trityladenosine (**11**) in over 60% yields. Treatment of (**11**) with an excess of hydrazine provided a 65% yield of 8,2′-hydrazo-9-(2′-deoxy-5′-*O*-trityl-β-D-arabinofuranosyl)adenine

* In small-scale experiments similar to the conversion of (**8a**) into (**10a**), using (**9a**) and sodium methoxide, t.l.c. showed that (**10a**) was formed with two other products, one of which was a yellow substance of the same mobility as that formed in the reaction of (**8a**). Therefore, (**10**) must have formed *via* (**9**), although standardization of the base-catalysed oxidation of (**9**) was abandoned because of their limited solubility in methanol. It should be noted that the N^9-methyl analogue of (**9a**) is unchanged under similar reaction conditions.



Scheme 3. TPS = 2,4,6-tri-isopropylbenzenesulphonyl

(12), which was quantitatively converted into 2′,N^6-didehydro-8,2′-hydrazo-9-(2′-deoxy-5′-O-trityl-β-D-arabinofuranosyl)-adenine (13) using, this time, sodium metaperiodate as a neutral oxidant. The structures of (12) and (13) are evident from the spectral data. However, the results of the analogous base-catalysed aerial-oxidation of (13) followed by two chemical transformations are, at present, not sufficiently conclusive for mechanistic arguments and have, therefore, been omitted from this paper.

We then attempted the construction of a hydrazo bridge between the C-8 and C-3′ of adenosine. On the basis of our previous experience,[2] our initial efforts were directed towards the isolation of 8-hydrazino-3′-*O*-[(2,4,6-tri-isopropyl)benzenesulphonyl]adenosine (15) after the reaction of 8-bromo-3′-*O*-[(2,4,6-tri-isopropyl)phenylsulphonyl]adenosine (14)[7] with an excess of hydrazine. The reaction proceeded quantitatively, but the intermediate (15) obtained (the ^{1}H n.m.r. spectrum of a crude sample showed the presence of the TPS group) was resistant to crystallization and decomposed during attempted purification (probably through aerial oxidation). Hence, the crude intermediate (15) was used directly for cyclization at a higher temperature to provide, instead of the desired hydrazo cyclonucleoside (17), 8,3′-aminoimino-9-(3′-deoxy-β-D-xylofuranosyl)adenine (16) in low yield. Creation of a 6-membered rather than a 7-membered ring seems to be energetically favoured in such bicyclic systems. In the ^{1}H n.m.r. spectrum of (16), the signal of the *N*-amino group appeared at δ 4.93 as a broad singlet in contrast with the distinctly separated signals for N^{α}-H and N^{β}-H in compounds (8a—c) (Table 2). It is seen that 3′-H and 2′-H in (16) resonate at a field notably lower than that for the corresponding protons in (5a).[2] This, and other differences support the skeletal differences between compounds (16) and (5a).

Next, we attempted to synthesize purine 8,2′-cyclonucleosides having an unsubstituted oxamido bridge, since this class of compounds seemed to be interesting as biological models of 8-hydroxyaminopurine nucleosides[8] or as precursors for 8-aminopurine arabinosides. Rather unexpectedly, reaction of (7a) with a 15-fold excess of hydroxylamine under conditions similar to those for (4)[1] or (8a) gave the 8-hydroxyamino intermediate (18) instead of cyclized product, probably as a result of the reduced nucleophilicity of the hydroxylamino group. The intermediate (18) when treated with triethylamine under forcing conditions similar to those for the formation of (5) and (6) gave a resinous mixture, from which 8,2′-oxamido-9-(2′-deoxy-β-D-arabinofuranosyl)adenine (19) was isolated as methanol solvate (39%). The presence of an 8,2′-oxamido instead of an 8,2′-hydroximino bridge in (19) was substantiated by the u.v. and especially the ^{1}H n.m.r. spectral results. It is seen from Table 2 that 3′-H and 2′-H in (19) resonates at δ 4.21 and 4.64, respectively, in good agreement with the corresponding δ 4.18 and 4.70 signals for compound (4),[1] while the protons on the *N*-substituted C-2′ positions of (8a—c) generally resonate at a distinctly higher field. Similar experiments with (7b, c) failed as a result of the far less reactive nature of the 8-bromo substituent in these compounds and the difficulty in purifying the complex mixtures.

Thus, the synthesis and chemical manipulation of purine cyclonucleosides having an unsubstituted hydrazo or oxamido bridge proved to be difficult and, accordingly, further work along these lines was abandoned. Interestingly, the reactivities of these cyclic hydrazo as well as dehydro-hydrazo compounds

are characterized by stabilization through enhanced aromatization in the present oxidation reactions as they commonly are in heterocyclic chemistry.

Experimental *

8,2′-*Hydrazo*-9-(2′-*deoxy*-β-D-*arabinofuranosyl*)*adenine* (**8a**).—A mixture of (**7a**) (3.0 g, 6 mmol) and hydrazine hydrate (6 ml, 30 mmol) in methanol (59 ml) in a pressure tube was heated at 90—100 °C for 48 h under argon. After cooling, the mixture was evaporated and then repeatedly co-evaporated with methanol. The residue was digested with a small volume of methanol to give a t.l.c. pure solid precipitate, which was quickly collected, washed with a small volume of methanol, and dried (1.3 g, 77%). For analysis, a part was recrystallized from methanol at room temperature, using vacuum concentration; it had m.p. 182—184 °C (Found: C, 40.4; H, 5.1; N, 33.0. $C_{10}H_{13}N_7O_3 \cdot H_2O$ requires C, 40.54; H, 4.88; N, 33.05%).

8,2′-*Hydrazo*-9-(2′-*deoxy*-β-D-*arabinofuranosyl*]*hypoxanthine* (**8b**).—A mixture of (**7b**) (1.5 g, 3 mmol) and hydrazine hydrate (3 ml, 15 mmol) in methanol (30 ml) in a pressure tube was heated at 90—100 °C for 24 h under argon after which it was worked up as in the case of (**8a**); yield 647 mg (77%). A part was recrystallized from methanol for analysis, heating being avoided as far as possible, m.p. 260—261 °C (Found: C, 40.55; H, 4.7; N, 31.6. $C_{10}H_{12}N_7O_4$ requires C, 40.52; H, 4.80; N, 31.50%).

8,2′-*Hydrazo*-9-(2′-*deoxy*-β-D-*arabinofuranosyl*)*guanine* (**8c**).—A mixture of (**7c**) (500 mg, 1 mmol) and hydrazine hydrate (1 ml, 5 mmol) in methanol (10 ml) was heated in a pressure tube at 100 °C overnight under argon, and the mixture worked up as above to give t.l.c.-pure (**8c**) as powdery crystals (230 mg, 78%). For analysis, a part was recrystallized from a large volume of methanol at room temperature to give again powdery crystals, which became brown at *ca.* 250 °C but did not melt <300 °C (Found: C, 40.55; H, 4.7; N, 31.6. $C_{10}H_{13}N_7O_4 \cdot 0.5CH_3OH$ requires C, 40.52; H, 4.86; N, 31.50%).

2′,N^6-*Didehydro*-8,2′-*hydrazo*-9-(2′-*deoxy*-β-D-*arabinofuranosyl*)*adenine* (**9a**).—*N*-Bromoacetamide (NBA) (138 mg, 1 mmol) was added to a solution of (**8a**) (279 mg, 1 mmol) in methanol–water (9:1; 150 ml). After being stirred at room temperature for 20 min, the mixture was neutralized with triethylamine and concentrated under reduced pressure to *ca.* 30 ml to give a t.l.c. pure powdery solid, which was collected and dried *in vacuo* at 60 °C (200 mg, 70%). An analysis sample recrystallized from a large volume of warm methanol began to decompose at 241 °C but did not melt <300 °C (Found: C, 43.5; H, 4.0; N, 35.15. $C_{10}H_{11}N_7O_3$ requires C, 43.32; H, 4.00; N, 35.37%).

2′,N^6-*Didehydro*-8,2′-*hydrazo*-9-(2′-*deoxy*-β-D-*arabinofuranosyl*)*hypoxanthine* (**9b**).—A solution of (**8b**) (280 mg, 1 mmol) in methanol–water (9:1; 150 ml) was treated with NBA (138 mg, 1 mmol) at room temperature for 40 min after which the mixture was worked up as for (**9a**) to give t.l.c.-pure (**9b**) as powder (245 mg, 88%). An analysis specimen recrystallized from methanol became brown >192 °C but did not melt <300 °C (Found: C, 42.8; H, 4.0; N, 28.75. $C_{10}H_{10}N_6O_4 \cdot 0.5CH_3OH$ requires C, 42.86; H, 4.11; N, 28.57%).

9-*Amino*-4-*methoxy*-1H-*triazino*[3,4-e]*purine* (**10a**).—To a suspension of compound (**8a**) (200 mg, 0.72 mmol) in methanol (24 ml) was added sodium methoxide (19.4 mg, 0.36 mmol). Within 20 min the mixture became orange-coloured. [In preliminary experiments, t.l.c. (silica gel, $CHCl_3$–MeOH, 8:2) at this stage showed no starting material and two major faster-moving u.v.-absorbing spots. The polar, yellow substance (A) proved to be extremely unstable]. The mixture was neutralized with solid CO_2 and evaporated. When the mixture was left in a small volume of methanol at room temperature overnight, it became a deep red with formation of a small amount of tarry precipitate, which was filtered off. T.l.c. at this stage showed the presence of the initial less-polar product (B) and disappearance of compound A with formation of two other products. Preparative t.l.c. (silica gel, $CHCl_3$–MeOH, 8:2) gave (**10a**) (16 mg, 10%) after recrystallization of the least-polar fraction from methanol. This sample began to decompose in the range 245—250 °C but did not melt <300 °C; *m/z* 219 (M^+); δ[$(CD_3)_2SO$] 3.32 (3 H, s, OMe), 6.31 (1 H, d, $J_{9,8}$ 3.0 Hz, 4-H), 6.92 (2 H, br s, D_2O-exchangeable, 9-NH_2), 7.07 (1 H, d, $J_{3,4}$ 3.0 Hz, 3-H), 8.09 (1 H, s, 7-H), and 11.80 (1 H, s, D_2O-exchangeable, 1-H) (Found: C, 44.15; H, 4.2; N, 4.35. $C_8H_9N_7O$ requires C, 43.83; H, 4.14; N, 44.73%).

The other two products underwent considerable decomposition during preparative t.l.c.

9-*Hydroxy*-4-*methoxy*-1H-*triazino*[3,4-e]*purine* (**10b**).—To a suspension of (**8b**) (280 mg, 1 mmol) in methanol (20 ml) was added sodium methoxide (63 mg, 1.2 mmol). After 3 h, the resulting solution, t.l.c. of which indicated the presence of three products, was neutralized with solid CO_2, concentrated, and filtered. The filtrate was subjected to preparative t.l.c. (silica, $CHCl_3$–MeOH, 8:2) to give from the fastest-moving band (**10b**) as powder (11 mg, 8%), m.p. 244—246 °C (decomp.); δ[$(CD_3)_2SO$] 2.96 (3 H, s, OMe), 6.32 (1 H, d, $J_{3,4}$ 3.0 Hz, 4-H), 7.00 (1 H, d, $J_{3,4}$ 3.0 Hz, 3-H), 7.96 (1 H, s, 7-H), 9.90 (1 H, s, D_2O-exchangeable, 8-H, lactam), and 11.88 (1 H, s, D_2O-exchangeable, 1-H) (Found: C, 43.5; H, 3.8; N, 36.9. $C_8H_8N_6O_2$ requires C, 43.43; H, 3.98; N, 36.83%). The other two compounds decomposed after the appropriate bands had been eluted with methanol and hence were discarded.

8-*Bromo*-2′-O-*tosyl*-5′-O-*trityladenosine* (**11**).—A mixture of (**7a**) (1 g, 2 mmol), trityl chloride (613.3 mg, 2.2 mmol), DMF (2 ml), and pyridine (6 ml) was stirred at 40 °C for 20 h. Further trityl chloride (TrCl) (110 mg, 0.4 mmol) was added and the mixture was stirred at this temperature for 24 h. Further TrCl (100 mg, 0.34 mmol; total 2.95 mmol) was added and heating continued at the same temperature for a further 30 h. Subsequently the mixture was treated with water (2 ml) for 30 min at room temperature and then evaporated. The residue was dissolved in methanol (30 ml) and poured into ice–water (350 ml) with vigorous stirring. The precipitate, collected by suction, was dissolved in chloroform and the solution dried (Na_2SO_4) and evaporated. The resulting residue was fractionated by preparative t.l.c. [silica, 20 × 20 cm, two sheets; $CHCl_3$–EtOAc (1:1), twice developed] to give from the major band 920 mg (62%) of a t.l.c-pure foam (**11**), which was directly used for the next step.

8,2′-*Hydrazo*-9-(2′-*deoxy*-5′-O-*trityl*-β-D-*arabinofuranosyl*)-*adenine* (**12**).—A mixture of compound (**11**) (1.26 g, 1.7 mmol) and hydrazine hydrate (1.7 ml, 34 mmol) in methanol (14 ml) in a pressure tube was stirred at 85—89 °C for 25 h under an argon atmosphere. T.l.c. at this stage [silica, $CHCl_3$–MeOH (85:15)] showed a single polar product. The mixture was cooled and the crystalline precipitate collected by suction. The filtrate was evaporated and the residue partitioned between ethyl acetate and water. Work-up of the organic phase gave no second crop. Recrystallization of the filter-cake afforded (**12**) (566 mg,

* The general methods are similar to those described earlier.[9]

64.7%), m.p. 247 °C (Found: C, 66.75; H, 5.5; N, 18.55. $C_{29}H_{27}N_7O_3$ requires C, 66.78; H, 5.22; N, 18.80%).

2′,N⁶-*Didehydro*-8,2′-*hydrazo*-9-(2′-*deoxy*-5′-O-*trityl*-β-D-*arabinofuranosyl*)*adenine* (**13**).—To a solution of (**12**) (823 mg, 1.58 mmol) in DMF (27 ml) was added sodium metaperiodiate (438.5 mg, 1.3 × 1.58 mmol) and the mixture was stirred at room temperature for 4.5 h; t.l.c. showed the formation of a single less-polar product. Evaporation of the mixture gave a residue which was digested with ice–water and this provided an insoluble product which was collected by suction, air-dried, and washed with a small volume of hot acetone to give (**13**) as a t.l.c.-homogeneous powder (764 mg, 93%). For analysis, a part was dissolved in warm methanol and the solution treated with Norit and concentrated under reduced pressure to give powdery crystals, which gradually decomposed >220 °C but did not melt <290 °C (Found: C, 67.07; H, 4.91; N, 18.78. $C_{29}H_{25}N_7O_3$ requires C, 67.04; H, 4.85; N, 18.87%).

8,3′-*Aminoimino*-9-(3′-*deoxy*-β-D-*xylofuranosyl*)*adenine* (**16**).—A mixture of (**14**) (2.66 g, 4.39 mmol) and hydrazine hydrate (4.4 ml, 5 × 4.39 mmol) in MeOH (50 ml) in a pressure tube was heated at 90—100 °C for 3 h under argon. After cooling, the mixture was evaporated, repeatedly co-evaporated with MeOH to remove the residual hydrazine and the residue dissolved in chloroform (30 ml) and the solution washed with water (30 ml). The separated organic phase was dried (Na_2SO_4) and evaporated. The residue was combined with triethylamine (1.22 ml, 2 × 4.39 mmol) and DMF (30 ml) in a pressure tube and the mixture heated at 135—140 °C for 4 h under argon. The mixture was then thoroughly evaporated and digested with ethanol (10 ml) to give a tarry precipitate which was collected by suction and dissolved in hot methanol (40 ml). The solution was cooled to room temperature and the sparingly soluble resinous fraction filtered off. The filtrate was evaporated to give a red-brown solid mixture (*ca.* 450 mg). T.l.c. (silica; $CHCl_3$–MeOH, 7:3) of an aliquot of this mixture gave a thick immobile spot (a complex mixture of several products as judged by t.l.c. using a more polar solvent mixture) and the presence of a rather more mobile product. The total was fractionated by preparative t.l.c. [silica, 20 × 20 cm, 2 sheets; $CHCl_3$–MeOH (7:3, v/v), developed 3 times]. The combined mobile fractions were thoroughly eluted with methanol and the obtained solid repeatedly recrystallized from methanol to give (**16**) as powdery crystals (139 mg, 10.7%), which began to decompose at 246 °C but did not melt <300 °C (Found: C, 43.0; H, 5.0; N, 33.05. $C_{10}H_{13}N_7O_3 \cdot 0.5CH_3OH$ requires C, 42.71; H, 5.12; N, 33.21%).

8-*Hydroxyamino*-2′-O-*tosyladenosine* (**18**).—Hydroxylamine hydrochloride (1.04 g, 15 mmol) in methanol (8 ml) was neutralized with 4M-KOH–MeOH (3.75 ml). The filtrate separated from the inorganic precipitate was adjusted to pH 8 with the same methanolic alkali and the additional precipitate filtered off. The filtrate (12 ml) and (**7a**) (500.3 mg, 1 mmol) were combined in a pressure tube and heated at 100 °C for 51 h under argon. After cooling, the mixture was evaporated, triturated with a small volume of MeOH, and the resulting u.v.-transparent solid removed by suction. The filtrate was fractionated by preparative t.l.c. [silica, 20 × 20 cm; $CHCl_3$–MeOH (85:15), twice developed] and the main band eluted with methanol. Recrystallization of the product from ethanol containing a small volume of methanol gave (**18**) as an ethanol solvate (193 mg, 39%) which effervesced in the range 97—108 °C, and melted in the range 149—153 °C after drying *in vacuo* at room temperature (Found: C, 45.5; H, 5.55; N, 16.8. $C_{17}H_{20}N_6O_7S$ requires C, 45.78; H, 5.29; N, 16.86%).

8,2′-*Oxamido*-9-(2′-*deoxy*-β-D-*arabinofuranosyl*)*adenine* (**19**).—A mixture of (**18**) (700 mg, 1.4 mmol), triethylamine (0.4 ml, 2.8 mmol), and DMF (14 ml) in a pressure tube was heated at 135—140 °C for 15 h under argon. After removal of the solvent, the tarry residue was digested with warm methanol (15 ml) and the insoluble resinous solid removed by suction. The filtrate was concentrated and subjected to preparative t.l.c. [silica, 20 × 20 cm; $CHCl_3$–MeOH (7:3), twice developed]. The main fraction was eluted with methanol and the obtained solid recrystallized from the same solvent to afford (**19**) as a methanol solvate (170 mg, 39%), which began to shrink >160 °C and gradually melted up to 172 °C after drying *in vacuo* at 60 °C (Found: C, 42.15; H, 5.2; N, 27.05. $C_{10}H_{12}N_6O_4 \cdot CH_3OH$ requires C, 42.31; H, 5.16; N, 26.91%).

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References

1 T. Sasaki, K. Minamoto, S. Yamashita, K. Yamaguchi, and K. Miyake, *J. Org. Chem.*, 1981, **46**, 5176.
2 T. Sasaki, K. Minamoto, S. Yamashita, and Y. Fujiki, *J. Org. Chem.*, 1982, **47**, 4465.
3 S. Patai, 'The Chemistry of the Hydrazo, Azo and Azoxy Group,' John Wiley and Sons, London, 1975, Part 2, p. 861.
4 J. B. Chattopadhyaya and C. B. Reese, *J. Chem. Soc., Chem. Commun.*, 1978, 86.
5 L. M. Jackman and S. Sternhell, 'Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry,' 2nd edn., Pergamon Press, Oxford, 1969, p. 191.
6 H.-U. Blank, D. Frahne, A. Myles, and W. Pfleiderer, *Leibigs Ann. Chem.*, 1970, **742**, 34.
7 M. Ikehara and T. Maruyama, *Tetrahedron*, 1975, **31**, 1369.
8 R. A. Long, R. K. Robins, and L. B. Townsend, *J. Org. Chem.*, 1967, **32**, 2751.
9 T. Sasaki, K. Minamoto, K. Suzuki, and T. Sugiura, *J. Org. Chem.*, 1979, **44**, 1424.

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