Convenient Preparations of 9-β-D-Arabinofuranosylguanine, 9-β-D-Arabinofuranosylhypoxanthine and Derivatives

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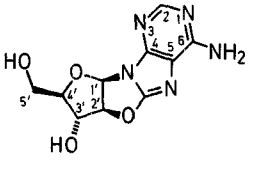
9-β-D-Arabinofuranosyladenine (ara-A, **2a**) has been shown to have both anti-tumour[1] and anti-viral[2] activity. Several other purine arabinosides have also shown promise as antiviral agents[3] but it is unlikely that a full evaluation of the biological activity of these compounds will be possible until they become more readily accessible. We recently reported[4] that ara-A (**2a**) and certain derivatives of 8-amino-ara-A (**2b**) can easily be prepared in high yields from the readily accessible 8,2′-*O*-cycloadenosine (**1**). Related work on the aminolysis of **1** has since appeared in the Japanese literature[5].



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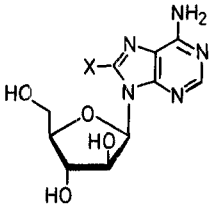


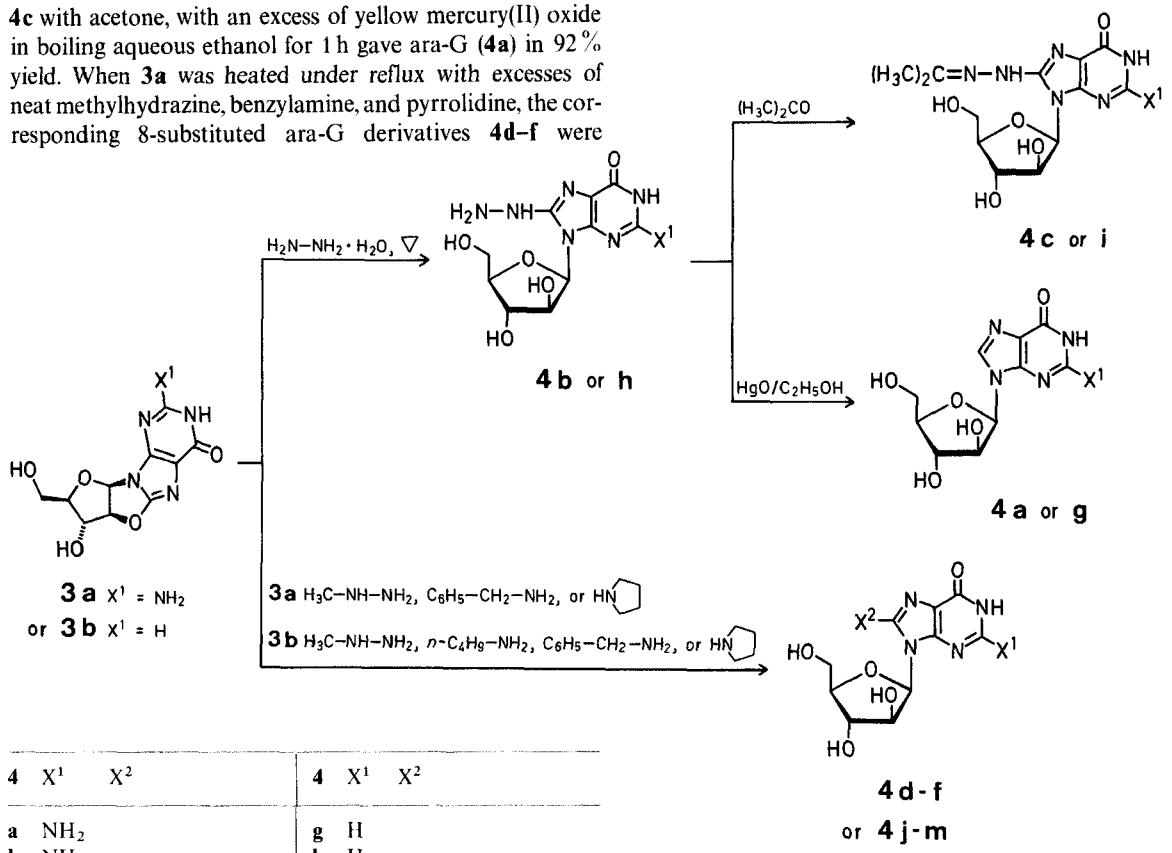
2a X = H
b X = NH_2

We now report that 9-β-D-arabinofuranosylguanine (ara-G, **4a**), 9-β-D-arabinofuranosylhypoxanthine (ara-Hx, **4g**) and their corresponding derivatives can, in the same way, be prepared from the equally readily accessible 8,2′-*O*-cyclonucleosides (**3a** and **3b**, respectively).

When 8,2′-*O*-cycloguanosine[6] (**3a**), which may be prepared from 8-bromoguanosine[7] in 67% overall yield, was heated under reflux with a large excess of hydrazine hydrate for 25 min, 8-hydrazino-ara-G (**4b**) was obtained in 88% yield. Treatment of **4b**, which readily formed a hydrazone

0039–7881/78/1232–0908 $ 03.00

4c with acetone, with an excess of yellow mercury(II) oxide in boiling aqueous ethanol for 1 h gave ara-G (**4a**) in 92% yield. When **3a** was heated under reflux with excesses of neat methylhydrazine, benzylamine, and pyrrolidine, the corresponding 8-substituted ara-G derivatives **4d–f** were



4	X^1	X^2	4	X^1	X^2
a	NH_2		g	H	
b	NH_2		h	H	
c	NH_2		i	H	
d	NH_2	$H_2N—N(CH_3)$	j	H	$H_2N—N(CH_3)$
e	NH_2	$C_6H_5—CH_2—NH$	k	H	$n\text{-}C_4H_9—NH$
f	NH_2		l	H	$C_6H_5—CH_2—NH$
			m	H	

obtained and isolated in 81, 76, and 67% yields, respectively. These reactions went to completion within 2, 1 and 6 h, respectively.

8,2′-*O*-Cycloinosine[8] (**3b**) was isolated in 84% yield from the products of the reaction between 8,2′-*O*-cycloadenosine (**1**) and sodium nitrite in acetic acid at 20°; when **3b** was heated, under reflux, with an excess of hydrazine hydrate for 4 min, 8-hydrazino-ara-Hx (**4h**) was obtained in 94% yield. Treatment of **4h**, which like **4b** readily formed an acetone hydrazone, with an excess of yellow mercury(II) oxide in boiling aqueous ethanol under the above conditions gave ara-Hx (**4g**) in 82% yield. The latter compound **4g** was also obtained in 91% yield by treating ara-A (**2a**) with sodium nitrite in acetic acid. When **3b** was heated, under reflux, with excesses of methylhydrazine, *n*-butylamine, benzylamine, and pyrrolidine, the corresponding 8-substituted ara-Hx derivatives **4j–m** were obtained and isolated in 71, 78, 68, and 77% yields, respectively.

We feel justified in concluding that the hydrazinolysis of 8,2′-*O*-cyclonucleosides, followed by oxidative removal of the 8-hydrazino group, represents the best general method so far available for the synthesis of purine arabinosides, unsubstituted at the 8-position.

9-β-D-Arabinofuranosylguanine (ara-G, 4a):
8,2′-*O*-Cycloguanosine (0.50 g, 1.78 mmol) and hydrazine hydrate (5.0 ml, 0.103 mol) are heated together, under reflux, for 25 min. The cooled products are concentrated under reduced pressure and the residual glass is triturated with methanol to give 8-hydrazino-ara-G (**4b**; 0.49 g, 88%).

Yellow mercury(II) oxide (0.80 g, 3.7 mmol) is added to a solution of the latter compound (**4b**; 0.30 g, 0.96 mmol) in boiling water (100 ml) and ethanol (100 ml). The resultant suspension is heated under reflux for 1 h and then concentrated under reduced pressure. The pale yellow residue obtained is crystallized from aqueous methanol; yield: 0.249 g (92%); m.p. 223–225° (dec.).

$C_{10}H_{13}N_5O_5 \cdot 0.7H_2O$	calc.	C 40.59	H 4.90	N 23.67
(295.9)	found	40.7	4.6	23.6

8-Benzylamino-ara-G (4e):
A magnetically-stirred suspension of 8,2′-*O*-cycloguanosine (0.50 g, 1.78 mmol) in redistilled benzylamine (6.0 g, 56 mmol) is heated under reflux with stirring for 1 h. The cooled products are concentrated under reduced pressure. The residue obtained is triturated with ether and then crystallized from water; yield: 0.523 g (76%); m.p. >260°.

$C_{17}H_{20}N_6O_5 \cdot 0.5H_2O$	calc.	C 51.38	H 5.33	N 21.15
(397.4)	found	51.0	5.1	21.5

8,2′-*O*-Cycloinosine (3b):
Sodium nitrite (1.0 g, 14.5 mmol) is added in small portions over a period of 90 min to a stirred solution of 8,2′-*O*-cycloadenosine (1.0 g, 3.8 mmol) in glacial acetic acid (60 ml) at 20°. After a further period of 4 h, the products are concentrated under reduced pressure (bath temperature: 35–40°) and a colourless precipitate is obtained. The latter material (0.61 g) is collected by filtration. Concentration of the mother liquors and crystallization of the product from water gives a second crop (0.237 g) of product; total yield: 0.847 g (84%); m.p. >260°.

$C_{10}H_{10}N_4O_5 \cdot 0.2H_2O$	calc.	C 44.51	H 3.89	N 20.77
(269.8)	found	44.7	3.9	20.7

9-β-D-Arabinofuranosylhypoxanthine (ara-Hx, 4g):
Method A: 8,2′-*O*-Cycloinosine (0.50 g, 1.88 mmol) and hydrazine hydrate (0.5 ml, 10.0 mmol) are heated together under reflux for 4 min. The cooled products are concentrated under reduced pressure and the residue is triturated several times with ether. Crystalli-

Table 1. Data Relating to Purine Arabinosides **4**

Compound	Yield[a] [%]	m.p.	Molecular formula[b]	U.V. (95% C_2H_5OH)[c] λ_{max} [nm]	^{13}C-N.M.R. (DMSO-d_6)[d] δ [ppm] C-5′	C-2′,3′	C-1′,4′
4a	81	223–225° (dec.)	$C_{10}H_{13}N_5O_5 \cdot 0.7H_2O$ (295.9)	260, 272 (infl.)	60.9	75.3	83.3, 84.1
4b	88	>260°	—	268, 293 (infl.)	59.7	75.0, 76.7	82.7, 83.7
4c	77	>260°	$C_{13}H_{19}N_7O_5 \cdot 1.5H_2O$ (380.3)	282	61.5	76.3, 76.9	84.6
4d	81	245° (dec.)	$C_{11}H_{17}N_7O_5 \cdot 0.5H_2O$ (336.3)	254	61.4	75.5, 76.9	82.6, 84.8
4e	76	>260°	$C_{17}H_{20}N_6O_5 \cdot 0.5H_2O$ (397.4)	265, 300 (infl.)	59.7	75.2, 76.8	82.9, 84.3
4f	67	219–221° (dec.)	$C_{14}H_{20}N_6O_5$ (352.4)	266, 300 (infl.)	61.6	75.5, 77.0	82.6, 83.7
4g	77	234–235°	$C_{10}H_{12}N_4O_5$ (268.2)	252	60.6	74.7, 75.5	83.9, 84.1
4h	94	163–164° (dec.)	$C_{10}H_{14}N_6O_5 \cdot 1.5H_2O$ (325.2)	265, 290 (infl.)	59.3	74.6, 76.8	82.4, 84.1
4i	86	219–221°	$C_{13}H_{18}N_6O_5 \cdot H_2O$ (356.3)	280	61.3	76.2, 77.0	84.6, 85.3
4j	71	222° (dec.)	$C_{11}H_{16}N_6O_4 \cdot 0.5H_2O$ (321.3)	264, 292 (infl.)	61.1	74.9, 76.9	82.5, 85.4
4k	68.5	233–234° (dec.)	$C_{14}H_{21}N_2O_5 \cdot 0.1H_2O$ (341.2)	272	59.5	75.1, 77.0	82.9, 84.8
4l	78	213–214°	$C_{17}H_{19}N_5O_5 \cdot 0.5H_2O$ (382.4)	270, 290 (infl.)	59.2	74.7, 76.9	82.5, 84.5
4m	77	203–204°	$C_{14}H_{19}N_5O_5$ (337.3)	269, 295 (infl.)	61.5	75.0, 76.6	82.4, 84.1

[a] Overall yield based on 8,2′-cyclonucleoside precursor (**3a** or **3b**).
[b] All products except **4b** gave satisfactory microanalyses (C ±0.3, H ±0.4, N ±0.4).
[c] Measured with a Perkin-Elmer 402 spectrophotometer.
[d] Measured at 22.63 MHz with a Bruker HFX 90 spectrometer.

Table 2. ^{1}H-N.M.R. Spectra[a] of Purine Arabinosides (**4**)

Compound	H-2(8)	H-1′ ($J_{1',2'}$, Hz)	H-2′,3′	H-4′,5′	Other signals
4a	7.77 (s)	6.04 (d, 3.8)	4.08 (m)	3.76 (m)	—
4b	—	6.00 (d, 5.0)		3.67 (m)	—
4c	—	6.04 (d, 3.5)	4.02 (m)	3.66 (m)	1.93 (s, 3H), 1.82 (s, 3H)
4d	—	6.28 (d, 5.9)	4.28 (m)	3.72 (m)	2.95 (s, 3H)
4e	—	6.10 (d, 4.7)	4.20 (m)	3.72 (m)	4.44 (s, 2H), 7.1–7.4 (m, 5H)
4f	—	5.96 (d, 6.2)	4.15–4.45 (m)	3.68 (m)	—
4g	8.23 (s), 8.09 (s)	6.27 (d, 4.7)	4.20 (m)	3.73 (m)	—
4h	7.82 (s)	6.15 (d, 5.0)	4.15 (m)	3.71 (m)	—
4i	7.86 (s)	6.21 (d, 3.5)	4.10 (m)	3.71 (m)	1.97 (s, 3H), 1.86 (s, 3H)
4j	7.84 (s)	6.50 (d, 5.9)	4.33 (m)	3.75 (m)	3.04 (s, 3H)
4k	7.79 (s)	6.19 (d, 4.7)	4.16 (m)	3.74 (m)	1.1–1.7 (m, 6H), 0.90 (m, 3H)
4l	7.87 (s)	6.28 (d, 5.0)	4.2 (m)	3.72 (m)	4.51 (s, 2H), 7.0–7.5 (m, 5H)
4m	7.89 (s)	6.16 (d, 6.8)	4.49 (m)	3.76 (m)	3.2–3.6 (m, 4H), 1.7–2.1 (m, 4H)

[a] N.M.R. spectra were measured at 90 MHz in DMSO-d_6/D_2O solution with a Bruker HFX 90 spectrometer. Chemical shifts are given in ppm on the δ scale.

zation of the glass so obtained from water gives 8-hydrazino-ara-Hx (**4h**; 0.527 g, 94%); m.p. 163–164° (dec.).

Yellow mercury(II) oxide (0.80 g, 3.7 mmol) is added to a solution of the latter compound (**4h**; 0.50 g, 1.7 mmol) in hot aqueous ethanol (150 ml; 1:1 v/v). The resultant suspension is heated under reflux for 1 h and then concentrated under reduced pressure. The colourless residue obtained is crystallized from water; yield: 0.369 g (82%); m.p. 235–236°.

Method B: Sodium nitrite (0.60 g, 8.7 mmol) is added in small portions over a period of 5 h to a stirred solution of 9-β-D-arabinofuranosyladenine (ara-A; 0.50 g, 1.87 mmol) in glacial acetic acid (25 ml) at 20°. After a further period of 13 h, the resultant crystalline precipitate (0.273 g) is collected by filtration and the mother liquors concentrated under reduced pressure. Crystallization of the residue from water gives a second crop (0.182 g) of product; total yield: 0.455 g (91%); m.p. 234–235°.

$C_{10}H_{12}N_4O_5$	calc.	C 44.78	H 4.51	N 20.89
(268.2)	found	45.2	4.8	21.0

8-Pyrrolidino-ara-Hx (4m):
A suspension of 8,2′-*O*-cycloinosine (0.50 g, 1.88 mmol) in pyrrolidine (1 ml) is heated, under reflux, for 6 h. The cooled products are evaporated under reduced pressure. The residue obtained is triturated several times with ether and then crystallized from water; yield: 0.487 g (77%); m.p. 203–204°.

$C_{14}H_{19}N_5O_5$	calc.	C 49.84	H 5.68	N 20.76
(337.3)	found	49.6	5.6	20.6

We thank the Cancer Research Campaign for generous financial support.

Received: June 19, 1978

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