Reaction Between 8-Bromoadenosine and Amines. Chemistry of 8-Hydrazinoadenosine

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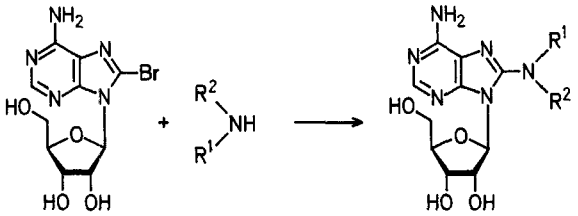
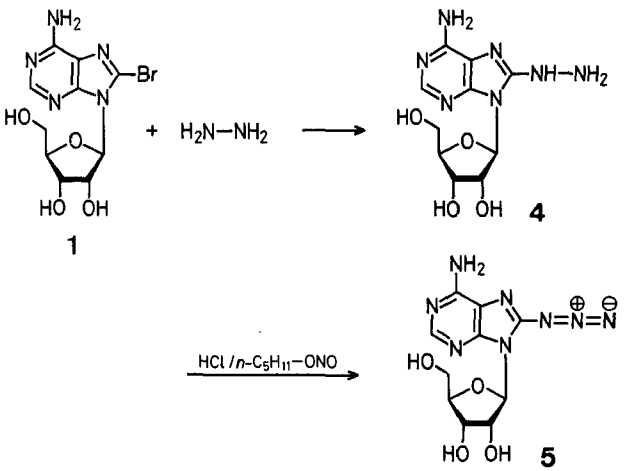
It has been reported[1] that 8-bromoadenosine[2] (**1**) does not react with ammonia to give **3a** either in aqueous or in alcoholic solution below 120°. In contrast, when **1** is stirred with an excess of aqueous methylamine at 20° for 16 h, 8-methylaminoadenosine (**3b**) is obtained as the sole product and may be isolated crystalline in over 90% yield.



1 **2** **3b-f**

3	R^1	R^2
a	H	H
b	H	CH_3
c	H	$C_6H_5CH_2$
d	H	n-C_4H_9
e	—(CH$_2$)$_4$—	
f	—(CH$_2$)$_5$	

8-Aminoadenosine[1] (**3a**) has been shown[3] to have anti-tumour activity. In the hope that related 8-substituted adenosine derivatives might also be biologically active we have examined the reaction between 8-bromoadenosine (**1**) and other primary and secondary amines **2**. The experimental conditions (see below) for the reaction between **1** and benzylamine are typical: the reaction is complete in boiling ethanol solution in 24 h and the yield of isolated 8-benzylaminoadenosine (**3c**) is high. The reactions between **1** and n-butylamine, pyrrolidine, and piperidine occur under the same conditions to give the corresponding 8-aminoadenosine derivatives (**3d**, **3e** and **3f**, respectively) in high yields. The actual yields and other data relating to the aminolysis products are given in Table 1. Details of the ^{1}H-N.M.R. spectra of these compounds are given in Table 2.



1 **4** **5**

We have confirmed that 8-bromoadenosine (**1**) also reacts with hydrazine in boiling ethanol solution to give 8-hydra-

zinoadenosine (**4**) but have obtained a much higher yield than that reported[1] previously. The latter compound **4**, which readily forms hydrazone and 3,5-dimethylpyrazole derivatives on treatment with acetone and pentane-2,4-dione, respectively, may be converted into adenosine in very high yield by heating it in boiling ethanol solution with an excess of yellow mercury(II) oxide. Alternatively, this transformation may be effected by stirring **4** with sodium methoxide in methanol solution at 20°. We have previously prepared[4] 9-β-D-arabinofuranosyladenine (ara-A) from its 8-hydrazino derivative under the same conditions but are unaware of other reports in the literature relating to the oxidative removal of hydrazino groups in nucleoside chemistry. Treatment of **4** with bromine water at 20° rapidly gives 8-bromoadenosine (**1**) in high yield. When **4** is stirred with hydrochloric acid and an excess of pentyl nitrite at 20°, 8-azidoadenosine[1] (**5**), a convenient precursor of 8-aminoadenosine (**3a**), is obtained in high yield. On the basis of these preliminary studies, we believe that hydrazino derivatives such as **4** will prove to be valuable synthetic intermediates in nucleoside chemistry.

8-Methylaminoadenosine (3b):
8-Bromoadenosine[2] (1.50 g, 4.3 mmol) and aqueous methylamine (100 ml; ~30% w/v) are stirred together at 20°. After several h, a deep blue homogeneous solution is obtained; after 16 h, the products are concentrated under reduced pressure and the residue crystallized from water; yield: 1.17 g (93%); m.p. 227–228° (dec.).

$C_{11}H_{16}N_6O_4$	calc.	C 44.59	H 5.44	N 28.37
(296.3)	found	44.7	5.4	28.2

8-Benzylaminoadenosine (3c):
8-Bromoadenosine[2] (1.50 g, 4.3 mmol), benzylamine (1.33 g, 13.0 mmol), and ethanol (150 ml) are heated together, under reflux, for 24 h. The cooled products are concentrated under reduced pressure and the residue crystallized from aqueous ethanol; yield: 1.35 g (87%); m.p. 201–202°.

$C_{17}H_{20}N_6O_4 \cdot 0.5H_2O$				
(381.4)	calc.	C 53.54	H 5.29	N 22.04
	found	53.3	5.35	22.25

Conversion of 8-Hydrazinoadenosine (4) into Adenosine:
8-Hydrazinoadenosine (1.0 g, 3.36 mmol; prepared by the method of Holmes and Robins[1] but isolated in 85% yield), yellow mercury(II) oxide (3.0 g, 13.9 mmol) and ethanol (200 ml) are heated together, under reflux, for 1 h. The cooled products are filtered and concentrated under reduced pressure. Recrystallization of the residue from methanol gives adenosine; yield: 0.832 g (93%); m.p. 233–234°; identical to authentic material.

Conversion of 8-Hydrazinoadenosine (4) into 8-Bromoadenosine (1):
Saturated bromine water (4 ml; ~0.9 mmol) is added dropwise to a stirred solution of 8-hydrazinoadenosine (0.50 g, 1.68 mmol) in ethanol (50 ml) at 20°. The consumption of bromine, as indicated by the discharge of its colour, is accompanied by effervescence. When the addition of bromine water is completed, its colour persists. The products are then concentrated under reduced pressure and the residue treated with 10% aqueous sodium hydrogen sulphite (20 ml) to give crude 8-bromoadenosine[2]; yield: 0.513 g (88%). Recrystallization of this material from aqueous methanol gives colourless crystals which are identical (U.V. and N.M.R. spectra; T.L.C. in several systems) to authentic 8-bromoadenosine.

8-Azidoadenosine (5):
8-Hydrazinoadenosine (0.50 g, 1.68 mmol), pentyl nitrite (1.50 g, 10.9 mmol), and 1 molar hydrochloric acid (1.5 ml) are stirred together at 20° for ~30 min until a homogeneous solution is obtained. Ethanol (20 ml) is added and the resultant mixture is carefully neutralized with methanolic sodium methoxide. The resultant clear solution is concentrated under reduced pressure and the residue crystallized from water; yield: 0.43 g (83%); m.p. 227–229° (dec.), Lit.[1] 226–229° (dec.).

I.R. (nujol): ν_{max}: 2167 cm^{-1}.

$C_{10}H_{12}N_8O_4 \cdot 2.2H_2O$				
(347.9)	calc.	C 34.53	H 4.17	N 32.21
	found	34.4	4.2	32.3

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[2] R. E. Holmes, R. K. Robins, *J. Am. Chem. Soc.* **86**, 1242 (1964).
[3] A. Bloch, E. Mihich, C. A. Nichol, R. K. Robins, R. H. Whistler, *Proc. Amer. Assoc. Cancer Res.* **7**, 7 (1966).
[4] J. B. Chattopadhyaya, C. B. Reese, *J. Chem. Soc. Chem. Commun.* **1977**, 860.

Table 1. Data Relating to Aminolysis Products of 8-Bromoadenosine (**1**)

Product	Yield [%]	m.p.	$[\alpha]_D^{22}$	Ultraviolet Absorption Spectrum pH 1 λ_{max}	pH 1 λ_{min}	pH 7 λ_{max}	pH 7 λ_{min} [nm]
3b	93	227–228°	−50° (c = 0.45, C_2H_5OH)	279	243	279	240
3c	87	201–202°	−33° (c = 0.4, C_2H_5OH)	284	245	282	240
3d	87	199–200°	+39° (c = 0.38, C_2H_5OH)	283	245	283	240
3e	89	143°	−29° (c = 0.5, C_2H_5OH)	285	245	283	245
3f	81	204.5–205°	+47° (c = 0.43, C_2H_5OH)	287	247	280	243
4	86	202–203° (dec.)	+21° (c = 0.28, CH_3OH)	270	237	276	240

Table 2. ^{1}H-N.M.R. Spectra[a] of 8-Substituted Adenosine Derivatives

Compound	H-2	H-1′ ($J_{1',2'}$ Hz)	H-2′	H-3′	H-4′	H-5′	Other Signals
3b	7.91 s	5.88 d (6)	4.69 dd	4.15 dd	3.97 m	3.67 m	2.94 s (3 H)
3c	7.92 s	5.98 d (7)	4.74 dd	4.16 dd	4.00 m	3.66 m	4.60 s (2 H), 7.34 m (5 H)
3d	7.91 s	5.93 d (6)	4.66 dd	4.14 dd	4.00 m	3.68 m	0.91 t (3 H), 1.28 m (4 H), 3.35 m (2 H)
3e	7.95 s	5.79 d (6)	5.12 m	4.23 m	3.94 m	3.66 m	1.91 m (4 H), 3.66 m (4 H)
3f	8.05 s	5.72 d (6)	5.11 dd	4.25 dd	4.02 m	3.68 m	1.63 m (4 H), 3.24 m (4 H)
4	7.99 s	5.93 d (7)	4.68 dd	4.20 m	4.02 m	3.70 m	

[a] N.M.R. spectra were measured at 90 MHz in DMSO-d_6/CD_3OD solution. Chemical shifts are given in ppm on the δ scale.