A New Method for the Preparation of 7,9-Disubstituted 8-Oxoadenines

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The present communication deals with a convenient method for the synthesis of 7,9-disubstituted 8-oxoadenines which are of interest from a physiological standpoint. A previously reported method[1] for the synthesis of 7-methyl-8-oxoadenosine involves bromination of adenosine at the 8-position and subsequent hydroxylation followed by methylation. In our view, this method is not satisfactory with respect to the total yield and versatility.

It has been demonstrated that introduction of electron-withdrawing acyl groups into the amino group of 9-substituted adenines causes regiospecific alkylation at the 7-position[2]. The present method for the synthesis of 7,9-disubstituted 8-oxoadenines involves hydrogen peroxide (Method A) or photochemical (Method B) oxidation at the 8-position of the easily available N^6-benzoyl-7,9-disubstituted adeninium salts **1a-c**[2]. These novel oxidative reactions proceed in high yields under mild conditions.

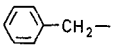
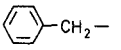
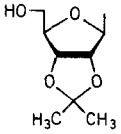
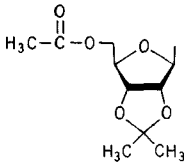
N^6-Benzoyl-7-alkyl-9-benzyl(or 9-ethyl)-adeninium iodides **(1a-c)** were prepared by the reaction of N^6-benzoyl-9-benzyl(or 9-ethyl)-adenines with alkyl iodides in dimethylacetamide in high yields[2]. The 7-methyl or ethyl derivatives **1a-c** were oxidized in acetic acid by 30% hydrogen peroxide at room temperature affording the corresponding 8-oxo derivatives **2a-c** in high yields. Deprotection of the N^6-benzoyl group of the 8-oxo derivatives **2a-c** was performed quantitatively using sodium methoxide to afford 7-alkyl-9-benzyl(or 9-ethyl)-8-oxoadenines **(3a-c).** The structures of the 8-oxo derivatives **3a-c** were supported by microanalytical and spectral data.

Oxidation of **1a-c** to **2a-c** was also achieved with high yields by ultraviolet irradiation (100W high-pressure mercury lamp, pyrex filter) in absolute methanol in a stream of oxygen.

N^6-Benzoyl-7-methyl-9-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-adeninium iodide **(4)** was readily prepared by the reaction of the corresponding protected adenosine with methyl iodide[2]. When **4** was oxidized with 30% hydrogen peroxide in acetic acid as described above, the corresponding 8-oxo derivative **5** and its 5′-*O*-acetyl derivative **6** were isolated from the reaction mixture by silica gel chromatography in 70% and 26% yields, respectively. The structures of **5** and **6** were supported by microanalytical and spectral data. For example, the ^{1}H-N.M.R. spectrum of 5′-*O*-acetyl derivative **6** in $CDCl_3$ shows characteristic signals at $\delta = 2.05$ and 4.34 ppm ($H_3CCOOCH_2$—). Photochemical oxidation of **4** produced **5** in only 40% yield together with other products.

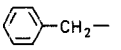
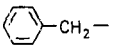
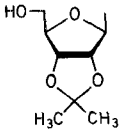
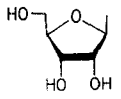
7-Methyl-8-oxoadenosine **(8)** was obtained by treatment of a mixture of **5** and **6** with sodium methoxide followed by 10% acidic acid. The identity of **8** was proved by comparison with an authentic specimen[1].

Table 1. N^6-Benzoyl-7,9-disubstituted 8-Oxoadenines **2a–c**, **5**, and **6**

Product No.	R^1	R^2	Yield [%] by Method A	B	m.p. [°C] (solvent)	Molecular formula[a]	
2a	H_3C		78	89	219–220° (C_2H_5OH)	$C_{20}H_{17}N_5O_2$	(359.4)
2b	C_2H_5		75	85	161–162° (C_2H_5OH)	$C_{21}H_{19}N_5O_2$	(373.4)
2c	H_3C	C_2H_5	72	82	200–201° (H_2O)	$C_{15}H_{15}N_5O_2$	(297.3)
5	H_3C		70	40	188–189° (C_2H_5OAc)	$C_{21}H_{23}N_5O_6$	(441.4)
6[b]	H_3C		26	—	181–182° (C_2H_5OH)	$C_{23}H_{25}N_5O_7$	(483.5)

[a] Satisfactory microanalyses obtained: C ±0.11, H ±0.13, N ±0.20. [b] By-product from the hydrogen peroxide oxidation of **4**.

Table 2. 7,9-Disubstituted 8-Oxoadenines **3a–c**, **7**, and **8**

Product No.	R^1	R^2	Yield [%]	m.p. [°C] (solvent)	Molecular formula[a]		I.R. (KBr) $\nu_{C=O}$ [cm^{-1}]
3a	H_3C		90[b]	176–177° (C_2H_5OH)	$C_{13}H_{13}N_5O$	(255.3)	1710
3b	C_2H_5		91[b]	222–224° (C_2H_5OH)	$C_{14}H_{15}N_5O$	(269.3)	1715
3c	H_3C	C_2H_5	85[b]	174–175° (C_6H_6)	$C_8H_{11}N_5O$	(193.2)	1690
7	H_3C		90[c]	199–200° (ether)	$C_{14}H_{19}N_5O_5$	(337.3)	1710
8	H_3C		90[d]	268–269° (CH_3OH)	m.p. 266–267°[1]		1715

[a] Satisfactory microanalyses obtained: C ±0.20, H ±0.12, N ±0.25.
[b] Based on **2**.
[c] Based on **5** + **6**.
[d] Based on **7**.

N^6-Benzoyl-7,9-disubstituted 8-oxoadenines 2a–c, 5 and 6; General Procedure:

Method A: To a solution of **1a–c** or **4** (2 mmol) in acetic acid (50 ml) is added 30% hydrogen peroxide (0.86 ml, 10 mmol) and the mixture is stirred at room temperature overnight. After decomposition of excess hydrogen peroxide by 5% palladium on carbon, the solvent is evaporated under reduced pressure. The residue is recrystallized from aqueous ethanol to give an analytically pure sample. In the case of **4**, the resulting mixture of the 8-oxo derivative **5** and its 5′-*O*-acetyl derivative **6** can be separated by silica gel column chromatography (ethyl acetate/benzene, 7:3) (Table 1).

Method B: A suspension of **1a–c** or **4** (1 mmol) in absolute methanol (250 ml) is irradiated with 100W high-pressure mercury lamp (pyrex filter) in a stream of oxygen for 8 h. The solvent is removed under reduced pressure, and the residue is recrystallized from an appropriate solvent to give **2a–c**. In the case of **4**, the residue is subjected to silica gel chromatography (ethyl acetate/benzene, 7:3) to give the 8-oxo derivative **5** (Table 1).

7,9-Disubstituted 8-oxoadenines 3a–c and 7; General Procedure:

To a solution of **2a–c** or the mixture of **5** and **6** (2 mmol) in methanol (30 ml) is added sodium methoxide (1.62 g, 30 mmol) and the mixture is refluxed for 24 h. An excess Amberlite IR-120 ion exchange resin (pyridinium form; 5.0 g) is then added to remove sodium ions. After removal of the resin by filtration, the solvent is evaporated under reduced pressure. The residue is recrystallized from an appropriate solvent to give an analytically pure sample (Table 2).

7-Methyl-8-oxoadenosine (8):

A solution of **7** (337 mg, 1.0 mmol) in 10% acetic acid (20 ml) is heated under reflux for 1.5 h. The solvent is removed under reduced pressure and the residue is recrystallized from methanol to give **8** quantitatively (Table 2).

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