

N-1 OXIDATION OF ADENINE SUBSTITUTED AT N-9 BY AN OLEFINIC CHAIN

René Beugelmans*, André Lechevallier, Rachid Benhida, Tawfik Gharbaoui, and Angela Morris

Institut de Chimie des Substances Naturelles, C.N.R.S., 91198 Gif-sur-Yvette, France

Abstract-The oxidation of 9-vinyladenine derivatives (**1a-c**) with *m*-chloroperoxybenzoic acid (MCPBA) leads selectively to the corresponding *N*-1 oxides (**2a-c**) and when the 6-amino group is protected, the oxidation occurs on the double bond of the olefinic chain to give the epoxides (**6a, b**) selectively.

There is a permanent interest for purine *N*-oxides, mostly because of potential therapeutic interest.¹ These compounds have been prepared by total synthesis,¹⁻³ by functional group transformation of purine *N*-oxide precursors⁴⁻⁶ and, whenever chemoselectivity made it possible, by direct oxidation of purine derivatives.⁷ For adenine^{8a,b} and its *N*-7 or *N*-9 substituted derivatives^{3,9} the direct oxidation was known to give preferentially *N*-1-oxides while it was recently reported¹⁰ that oxidation of 3-benzyladenine unequivocally occurred at *N*-7. The oxidation of adenine carrying an unsaturated side chain at *N*-9 was unambiguously demonstrated¹¹ to take place at *N*-1 when the chain is *allylic*. To our knowledge, nothing was reported in the literature about the behavior of 9-vinyl adenine, and it appeared of interest to investigate oxidation of this little documented class of compounds which became available from nucleophilic radical chain (SRN1) reactions.¹²

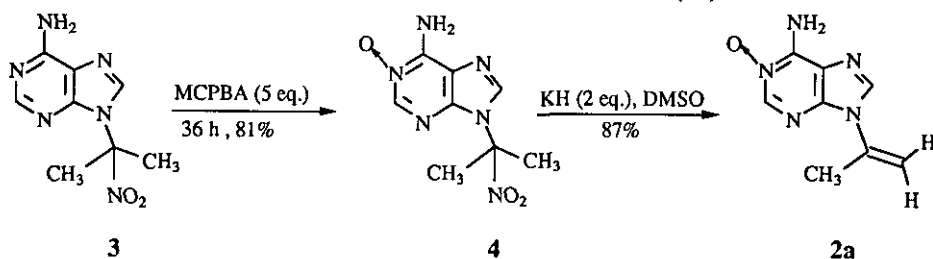
Treatment of 9-vinyl adenine derivatives (**1a-c**) with *m*-chloroperoxybenzoic acid (MCPBA) at room temperature selectively led to the corresponding *N*-1-oxide derivatives (**2a-c**) in high yields (Table 1). The reactions times were in a range of 14 to 48 h, but no clear relationship between the rate of oxidation at *N*-1 and the structure of the *N*-9 olefinic substituent emerged.

Table 1. Selective *N*-1 oxidation of adenine substituted at *N*-9 by an olefin chain.

	R₁	R₂	R₃	Time (h)	Recovered starting material %	N₁-Oxide %
1a	CH ₃	H	H	14	15	2a 72 ^a (85) ^b
1b	CH ₃	CH ₃	CH ₃	48	33	2b 62 ^a (92) ^b
1c	CH ₃	-CH ₂ OCH(Ph)OCH ₂ -		24	25	2c 60 ^a (80) ^b

a) Pure isolated products; *b)* Yield calculated upon the converted starting material.

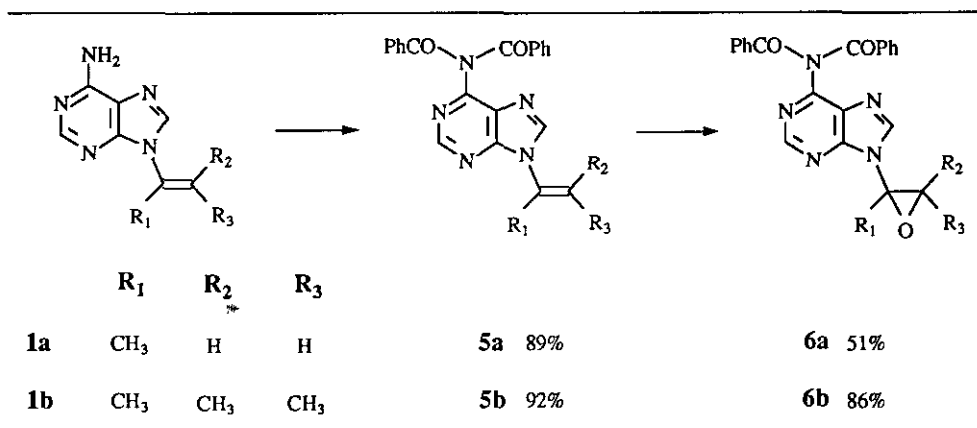
That oxidation of **1a** gave the *N*-1-oxide (**2a**) was shown by an alternative synthesis of this compound (Scheme 1). Consistently with oxidation of *N*-9 *alkyl* substituted adenine derivatives known to lead selectively to the corresponding to *N*-1 oxides.⁹ MCPBA treatment of the *N*-9 *alkyl* derivative (**3**)¹³ thus led to the *N*-1-oxide (**4**). Elimination of HNO₂ from **4** was performed by means of KH^{12,13} to give **2a**, identical (mp, nmr) with the compound obtained by direct oxidation of **1a**.

Scheme 1. Alternative access to *N*-1-oxide (**2a**)

Thus, adenine derivatives substituted at *N*-9 by a vinylic chain (**1a-c**), or by an alkyl chain (**3**) are oxidized at *N*-1 due to the strong electron releasing 6-NH₂ group. It was therefore felt of interest to know if deactivation of this group might divert oxidation to another site available on the adenine skeleton. On treatment with MCPBA, the *N*-6 dibenzoyl derivatives (**5a, b**) were found to give the corresponding epoxy derivatives (**6a, b**)

with no trace of other *N*-oxide derivatives (Scheme 2). Thus the decrease of electron density, together with possible hindrance of *N*-1 by the closely located 6-*N,N*-dibenzoyl group prevent oxidation to take place on the purine ring, and facilitate oxidation of the vinyl bond.

Scheme 2. Preparation and oxidation of *N*-6 protected adenine derivatives (**5a,b**)



In this study, we have shown that 6-*NH*₂ unprotected adenine compounds substituted at *N*-9 by a *vinyl*ic chain are selectively oxidized at *N*-1 and that the *vinyl*ic double bond can be selectively epoxidized when the amino group is protected.

EXPERIMENTAL

General procedure for oxidation: The oxidation was performed on compounds (**1a-c**, **3** and **5a,b**) (1 mmol) using MCPBA (5mmol) in methylene chloride (20 ml). The organic phase was washed with aq. NaHCO₃, dried over sodium sulfate and concentrated. Column chromatography on silica gel (methylene chloride, methanol 5%) gave the oxides.

9-(Propen-2-yl)adenine 1-oxide (**2a**):

-from (**1a**)

mp 178-180°C, 70% aq. EtOH; ¹H nmr (CDCl₃ + CD₃OD, 250 MHz) δ: 2.40 (s, 3H, CH₃), 5.23 and 5.70 (s, 1H each, CH₂=C), 8.15 and 8.57 (s, 1H each, H₂-H₈ adenine); ms (CI)*m/z*: 192 (MH)⁺, 176 (MH⁺ - (O) + H),

136 (adenine + H)⁺; uv λ_{max} (95% aq. EtOH) 236 nm (ϵ 13500), 261 (9500). Anal. Calcd for C₈H₉N₅O: C 50.26; H 4.71; N 36.65. Found: C 59.96; H 4.8; N 36.18.

-from (4)

Potassium hydride (0.120 g, 3 mmol) obtained from a 35% oil suspension placed in a 50 ml flask and washed under argon atmosphere with *n*-pentane was added with DMSO (15 ml). The mixture was stirred for 15 min, then the nitroalkane (4) (0.357 g, 1.5 mmol) in DMSO (1 ml) was added by syringe. Reaction progress was monitored by *TLC* and after consumption of the substrate, the reaction medium was poured into iced water (50 ml), neutralized with 5% HCl and extracted with methylene chloride (3x30 ml). The organic phase was dried and concentrated. Purification of the residual oil by column chromatography on silica gel (methylene chloride, methanol 5%) gave 2a (0.249, 87%) identical (mp; nmr) with the compound obtained from 1a.

9-(3-Methyl-2-buten-2-yl)adenine 1-oxide (2b):

mp 124-142°C (amorphous solid); ¹H nmr (CDCl₃ + CD₃OD, 200 MHz) δ : 1.50 (s, 3H, CH₃), 1.90 (s, 3H, CH₃), 2.13 (s, 3H, CH₃), 7.89 and 8.73 (s, 1H each, H₂-H₈ adenine); ms (CI) m/z : 220 (MH)⁺, 204 (MH⁺ - (O)), 136 (adenine + H)⁺; uv λ_{max} (95% aq. EtOH) 236 nm (ϵ 16500), 261 (11000). Anal. Calcd for C₁₀H₁₃N₅O: C 54.79; H 5.93; N 31.96. Found: C 55.10; H 6.28; N 31.61.

9-[1-Methyl-2-(2-phenyl-1,3-dioxane)-ethen-1-yl]adenine 1-Oxide (2c):

mp 192-194°C, 70% aq. EtOH; ¹H nmr (CDCl₃ + CD₃OD, 200 MHz) δ : 1.88 (s, 3H, CH₃), 4.22, 4.47, 4.76 and 4.98 (d, 1H each, J = 12 Hz, CH₂O dioxane), 5.53 (s, 1H, OCH(Ph)O), 7.21-7.53 (m, 5H, C₆H₅), 7.99 and 8.63 (s, 1H each, H₂-H₈ adenine); ms (CI) m/z : 340 (MH)⁺, 324 (MH⁺ - (O)), 136 (adenine + H)⁺. Anal. Calcd for C₁₇H₁₇N₅O₃: C 60.17; H 4.26; N 17.54. Found: C 60.24; H 3.98; N 17.21.

9-[2-Nitropropan-2-yl]adenine 1-oxide (4):

mp 110-128°C (amorphous solid); ¹H nmr (CDCl₃ + CD₃OD, 200 MHz) δ : 2.45 (s, 6H, (CH₃)₂), 8.53 and 8.63 (s, 1H each, H₂-H₈ adenine); ¹³C nmr (Me₂SO-*d*₆, 50 MHz) δ : 150.68 (C6), 145.59 (C2), 145.35 (C4), 143.96 (C8), 121.00 (C5), 98.45 ((CH₃)C(NO₂)), 26.04 (CH₃); ms (CI) m/z : 239 (MH)⁺, 223 (MH⁺ - (O)), 192 (MH⁺ - (HNO₂)), 136 (adenine + H)⁺. Anal. Calcd for C₈H₁₀N₆O₃: C 40.33; H 4.20; N 35.29. Found: C 40.08; H 4.48; N 34.92.

General procedure for dibenzoylation: The benzoilation was carried out on compounds (1a-b) (1mmol) which were treated in THF (5 ml) with sodium hydride (0.100 g, 2.5 mmol) obtained from a 60% oil suspension washed with *n*-pentane and then with benzoyl chloride (0.295 g, 2.1 mmol). Addition of water (30 ml) containing HCl (5%) and extraction with methylene chloride gave the crude compounds which were crystallized.

6-(*N,N*-Dibenzoyl)-9-(propen-2-yl)adenine (5a):

mp 173-175°C, Methylene chloride; ^1H nmr (CDCl_3 , 200 MHz) δ : 2.35 (s, 3H, CH_3), 5.12 and 5.66 (s, 1H each, $\text{CH}_2=\text{C}$), 7.11-7.51 and 7.65-7.90 (m, 10H, 2x C_6H_5), 8.10 and 8.61 (s, 1H each, $\text{H}_2\text{-H}_8$ purine); ^{13}C nmr (CDCl_3 , 50 MHz) δ : 172.38 (C=O amide), 152.97, 152.49, 152.18, 143.27, 137.20, 134.20, 133.08, 129.57, 128.80, 128.14, 109.17, 20.96 (CH_3); ms (IE) m/z : 383 (M^+), 355 ($\text{M}^+ - \text{CO}$), 278 ($\text{M}^+ - \text{C}_6\text{H}_5\text{CO}$), 122, 105 ($\text{C}_6\text{H}_5\text{CO}$), 77 ($\text{C}_6\text{H}_5\text{CO} - \text{CO}$). Anal. Calcd for $\text{C}_{22}\text{H}_{17}\text{N}_5\text{O}_2$: C 68.93; H 4.38; N 18.27. Found: C 69.11; H 4.24; N 17.92.

6-(*N,N*-Dibenzoyl)-9-(3-methyl-2-buten-2-yl)adenine (5b):

mp 178-179°C, Methylene chloride; ^1H nmr (CDCl_3 , 200 MHz) δ : 1.48, 1.95 and 2.17 (s, 3H each, 3x CH_3), 7.17-7.71 and 7.79-8.17 (m, 10H, 2x C_6H_5), 8.07 and 8.70 (s, 1H each, $\text{H}_2\text{-H}_8$ purine); ^{13}C nmr (CDCl_3 , 50 MHz) δ : 172.35 (C=O amide), 152.85, 152.47, 151.85, 145.44, 131.21, 133.63, 133.32, 132.98, 130.21, 129.48, 128.69, 128.35, 126.68, 122.53, 20.13, 19.98 and 18.65 (CH_3); ms (FAB) m/z : 412 (MH^+), 308 ($\text{MH}^+ - \text{C}_6\text{H}_5\text{CO} + \text{H}$), 105, 91, 77. Anal. Calcd for $\text{C}_{24}\text{H}_{21}\text{N}_5\text{O}_3$: C 70.07; H 5.1; N 17.03. Found: C 69.72; H 5.42; N 16.71.

6-(*N,N*-Dibenzoyl)-9-(2-methyloxiran-2-yl)adenine (6a):

mp 96-120°C (amorphous solid); ^1H nmr (CDCl_3 , 250 MHz) δ : 2.03 (s, 3H, CH_3), 3.17 and 3.38 (d, 1H each, $\text{Jab} = 4.5$ Hz, CH_2O epoxide), 7.13-7.60 and 7.68-8.01 (m, 10H, 2x C_6H_5), 8.23 and 8.83 (s, 1H each, $\text{H}_2\text{-H}_8$ adenine); ^{13}C nmr (CDCl_3 , 50 MHz) δ : 172.39 (C=O amide), 152.95, 152.49, 152.17, 142.61, 134.16, 133.15, 129.57, 128.84, 127.63, 65.66 and 53.95 (oxiranic carbons); 21.39 (CH_3); ms (FAB) m/z : 422 (MNa^+), 400 (MH^+), 386 ($\text{MH}^+ - \text{CH}_3 + \text{H}$), 344 ($\text{MH}^+ - \text{CH}_2\text{OC}(\text{CH}_3) + \text{H}$), 296 ($\text{MH}^+ - \text{C}_6\text{H}_5\text{CO} + \text{H}$), 240 ($344 - \text{C}_6\text{H}_5\text{CO} + \text{H}$), 105 (C_6H_5); uv λ_{max} (95% aq. EtOH) 236 nm (ϵ 11000), 261 (5000). Anal. Calcd for $\text{C}_{22}\text{H}_{17}\text{N}_5\text{O}_3$: C 66.16; H 4.26; N 17.54. Found: C 66.29; H 4.51; N 17.12.

6-(*N,N*-Dibenzoyl)-9-(2,3,3-trimethyloxiran-2-yl)adenine (6b):

mp 203-205°C, AcOEt; ^1H nmr (CDCl_3 , 250 MHz) δ : 1.01, 1.59 and 1.97 (s, 3H each, 3x CH_3), 7.02-7.69 and 7.72-8.22 (m, 10H, 2x C_6H_5), 8.37 and 8.74 (s, 1H each, H_2 - H_8 purine); ^{13}C nmr (CDCl_3 , 50 MHz) δ : 170.77 ($\text{C}=\text{O}$); 152.60, 143.45, 134.84, 134.39, 133.87, 133.11, 131.39, 130.38, 129.90, 129.62, 128.78 and 128.42, 74.13 and 61.28 (oxiranic carbons), 20.34, 19.62 and 19.01 (CH_3); ms (FAB) m/z : 450 (MNa^+), 428 (MH^+), 344 ($\text{MH}^+ - (\text{CH}_3)_2\text{COC}(\text{CH}_3) + \text{H}$), 324 ($\text{MH}^+ - \text{C}_6\text{H}_5\text{CO} + \text{H}$), 240 ($324 - (\text{CH}_3)_2\text{COC}(\text{CH}_3) + \text{H}$ or $344 - \text{C}_6\text{H}_5\text{CO} + \text{H}$), 222, 105 ($\text{C}_6\text{H}_5\text{CO}^+$); uv λ_{max} (95% aq. EtOH) 236 nm (ϵ 14400), 261 (4800). Anal. Calcd for $\text{C}_{24}\text{H}_{21}\text{N}_5\text{O}_3$: C 67.44; H 4.91; N 16.39. Found: C 67.63; H 4.71; N 16.01.

REFERENCES

1. F. Nohara, M. Nishii, K. Ogawa, K. Isono, M. Ubukata, T. Fujii, T. Itaya, and T. Saito, *Tetrahedron Lett.*, 1987, **28**, 1287 and references therein.
2. K. Ogawa, T. Saito, F. Nohara, M. Nishii, T. Itaya, and T. Fujii, *Heterocycles*, 1988, **27**, 885.
3. For a very recent report dealing with studies of oxidation and alkylation at *N*-1 or *N*-3 substituted adenine compounds, see: K. Ogawa, T. Saito, T. Itaya, and T. Fujii, *Heterocycles*, 1994, **38**, 253 and references therein.
4. J. C. Parham, J. Fissekis, and G. B. Brown, *J. Org. Chem.*, 1966, **31**, 966.
5. I. Scheinfeld, J. C. Parham, S. Murphy, and G. B. Brown, *J. Org. Chem.*, 1969, **34**, 2153.
6. A. Giner-Sorolla, C. Gryte, A. Bendich, and G. B. Brown, *ibid.*, 1969, **34**, 2157.
7. H. Kawashima and I. Kumashiro, *Bull. Chem. Soc. Jpn.*, 1969, **42**, 750.
8. a) M. A. Stevens, D. I. Magrath, H. W. Smith, and G. B. Brown, *J. Am. Chem. Soc.*, 1958, **80**, 2755. b) M. A. Stevens and G. B. Brown, *ibid.*, 1958, **80**, 2759.
9. T. Fujii, C. C. Wu, and T. Itaya, *Chem. Pharm. Bull.*, 1971, **19**, 1368.
10. T. Fujii, K. Ogawa, T. Saito, K. Kobayashi, and T. Itaya, *Heterocycles*, 1994, **38**, 477.
11. T. Fujii, I. Inoue, T. Itaya, and T. Saito, *Chem. Pharm. Bull.*, 1980, **28**, 3443.
12. R. Beugelmans, A. Lechevallier, T. Frinault, T. Gharbaoui, and R. Benhida, *Synlett*, in press.
13. T. Gharbaoui, R. Benhida, J. Chastanet, A. Lechevallier, P. Maillos, and R. Beugelmans, *Bull. Soc. Chim. Fr.*, 1994, in press.

Received, 9th May, 1994