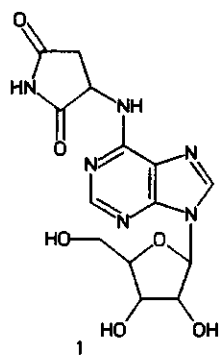
# SYNTHESIS OF $N^6$-(2-OXOPYRROLIDIN-5-YL)ADENOSINE DERIVATIVES

Yoshiyuki Kosugi*, Tatsuo Nagasaka, Fumiko Hamaguchi, and Sadao Ohki

Tokyo College of Pharmacy, Horinouchi 1432-1, Hachioji, Tokyo 192-03, Japan

Abstract —— A convenient method for introducing a pyrrolidinyl moiety into adenosine $N^6$-position by utilizing the acyliminium activity of ω-alkoxylactams is described. Condensation of 5-alkoxy-2-pyrrolidinones (**3a-f**) and adenosine triacetate followed by deacetylation gave $N^6$-(2-oxopyrrolidin-5-yl)adenosines (**6a-f**) in good yields.

During our investigation for the pharmacological activities of 2-pyrrolidinones, it was observed that $N^6$-(2,5-dioxopyrrolidin-3-yl)adenosine (1) possessed anti-hypertensive activity against the circulating systems in rats and dogs, while non-substituted adenosine was less active. In order to examine the bioactivity of its analogues, a series of $N^6$-substituted adenosine derivatives has been prepared from 6-chloropurine riboside by nucleophilic substitution with the appropriate amines. However, our preliminary experiments suggested that this usual method[1] was troublesome when 5-amino-2-pyrrolidinone (2) was used as a nucleophile.[2] This paper describes an alternative method for introducing a 2-pyrrolidinone moiety into adenosine $N^6$-position by utilizing the acyliminium activity of ω-alkoxylactams.



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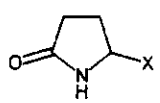
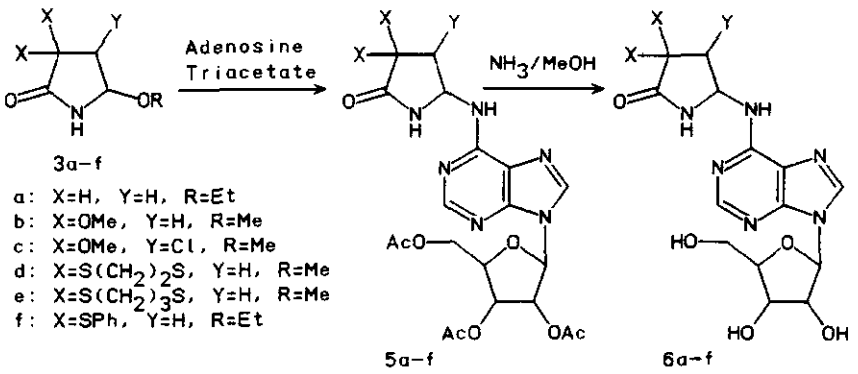


**2**: X=$NH_2$
**3a**: X=OEt
**4**: X=OAc

As we have previously reported that the reaction of 5-ethoxy- (**3a**) or 5-acetoxy-2-pyrrolidinone (**4**) with nucleophiles such as carbamates, amides and amines afforded 5-amino-2-pyrrolidinones in moderate to high yields,[3] the amino group in nucleosides was expected to have a sufficient nucleophilicity toward the acyliminium ions derived from the alkoxylactams. Thus, the reaction of 5-alkoxy-2-pyrrolidinones (**3a-f**), prepared by $NaBH_4$ reduction of succinimide[4] or by ring conversion of 2-furanones,[5] with adenosine and its triacetate was studied.

The mixture of adenosine triacetate (2.0 g, 5.1 mmol) and **3a** (1.20 g, 9.3 mmol) dissolved in DMF was refluxed for 12 h and the solution was evaporated <u>in vacuo</u>, and then the residue was column chromatographed on silica gel (hexane-acetone) to give a new adenosine derivative, $N^6$-(2-oxopyrrolidin-5-yl)adenosine triacetate (**5a**), as a syrupy oil in 91 % yield (2.20 g, 4.6 mmol). Deprotection could be accomplished by using a standard procedure,[6] namely by treatment with ammonia in methanol (0°C, overnight), followed by chromatographical purification ($SiO_2$, $CHCl_3$-MeOH) to afford the corresponding $N^6$-substituted adenosine (**6a**) as a white powder in 68 % yield. Although the reaction of **3a** with adenosine was tried to obtain the compound (**6a**) directly, only poor yield (16%) of the desired compound was obtained by refluxing the mixture in DMF for 12 h followed by chromatographical separation.




The other analogues (**3b-f**)[5,7] bearing substituents at the 3-position also underwent nucleophilic substitution to afford the expected $N^6$-substituted adenosine derivatives (**5b-f**) in good yields by heating the reactant mixtures at 120-170 °C with or without solvent (Table I). In the absence of solvent, the reactions were accelerated and completed within 1-2 h. Subsequent deacetylation afforded the $N^6$-substituted adenosines (**6b-f**), respectively (Table II). The structures of these compounds obtained here were confirmed by spectrometrical analyses.[8]

Table I. Synthesis of $N^6$-(2-Oxopyrrolidin-5-yl)adenosine Triacetates (5a-f).

| 2-Pyrrolidinones (Reaction Conditions) | Products (Yields) | Spectral Data [ir (KBr) $cm^{-1}$; $^1H$-nmr ($CDCl_3$) δ] |
|---|---|---|
| **3a** X=H, Y=H, R=Et (DMF, reflux, 12 h) | **5a** (91 %) | ir 3370 and 3250(NH), 1750(C=O), 1700(C=O), 1620(purine); nmr 8.35 and 7.95(2H,s×2,purine), 7.8 and 7.3(2H,br d×2,NH), 6.15-5.55 (4H,m, OCHN, CHOAc and NCHN), 4.40(3H,s,CHCH$_2$OAc), 2.6-2.1(4H,m, CH$_2$), 2.13, 2.10, and 2.09(9H,s×3,OAc). |
| **3b** X=OMe, Y=H, R=Me (neat, 160°C, 2 h) | **5b** (77 %) | ir 3330(NH), 1740(C=O), 1715(sh,C=O), 1610(purine); nmr 8.33 and 7.93(2H,s×2,purine), 7.5 and 6.8(2H,br d×2,NH), 6.25-5.6(4H,m,OCHN, CHOAc and NCHN), 4.43(3H,s,CHCH$_2$OAc), 3.45(6H,s,OMe×2), 2.9-2.4 (2H,m,CH$_2$), 2.22, 2.18, and 2.15(9H,s×3,OAc). |
| **3c** X=OMe, Y=Cl, R=Me (neat, 170°C, 1 h) | **5c** (63 %) | ir 3350(NH), 1750(C=O), 1725(sh,C=O), 1615(purine); nmr 8.32 and 7.93(2H,s×2,purine), 7.45 and 6.7(2H,br d×2,NH), 6.2-5.55(4H,m, OCHN, CHOAc and NCHN), 4.38(3H,s,CHCH$_2$OAc), 4.28(1H,d,CHCl), 3.48 and 3.45(6H,s×2,OMe), 2.12, 2.09, and 2.07(9H,s×3,OAc). |
| **3d** X=S(CH$_2$)$_2$S, Y=H, R=Me (neat, 150°C, 2 h) | **5d** (97 %) | ir 3300(NH), 1750(C=O), 1685(C=O), 1620(purine); nmr 8.33 and 7.95(2H,s×2,purine), 7.5 and 6.9(2H,br×2,NH), 6.2-5.6(4H,m,OCHN, CHOAc and NCHN), 4.42(3H,s,CHCH$_2$OAc), 3.8-3.3(4H,m,SCH$_2$CH$_2$S), 3.1 and 2.7(2H,AB of ABX,CH$_2$), 2.15, 2.10, and 2.08(9H,s×3,OAc). |
| **3e** X=S(CH$_2$)$_3$S, Y=H, R=Me (neat, 150°C, 2 h) | **5e** (85 %) | ir 3250(NH), 1750(C=O), 1675(C=O), 1630(purine); nmr 8.35 and 7.93(2H,s×2,purine), 7.4 and 7.0(2H,br d×2,NH), 6.2-5.6(4H,m,OCHN, CHOAc and NCHN), 4.38(3H,s,CHCH$_2$OAc), 3.85(2H,m,SCH), 2.8-1.75(6H, m,CH$_2$), 2.10, 2.08, and 2.06(9H,s×3,OAc). |
| **3f** X=SPh, Y=H, R=Et (Toluene, reflux, 28 h) | **5f** (96 %) | ir 3200(NH), 1750(C=O), 1720(C=O), 1620(purine); nmr 8.41 and 7.99(2H,s×2,purine), 7.75 and 7.45(10H,m×2,SPh), 6.75(1H,br s,NH), 6.25-5.6(4H,m, OCHN, CHOAc and NCHN), 4.43(3H,s,CHCH$_2$OAc), 2.85 and 2.35(2H,AB of ABX,CH$_2$), 2.15, 2.12, and 2.07(9H,s×3,OAc). |

Table II. $N^6$-(2-Oxopyrrolidin-5-yl)adenosines (6a-f).

| Compounds (Yields) | Melting Points (°C) and Spectral Data [ir (KBr) $cm^{-1}$; $^1H$-nmr (DMSO-$d_6$) δ ; uv (EtOH) nm] |
|---|---|
| **6a** (68 %) | mp 164-166; ir 3420(OH), 3240(NH), 1680(C=O), 1670 and 1615(purine); nmr 8.45 and 8.13 (2H,br s×2,NH), 8.42 and 8.25(2H,s×2,purine), 5.95(1H,br,NCHN), 5.90(1H,d,OCHN), 5.5-5.2(3H,m,OH), 4.59 and 4.14(2H,q×2,CHOH), 3.96(1H,q,OCHCH$_2$), 3.66 and 3.56(2H,m, CHCH$_2$OH), 2.42 and 2.10(4H,m×2,CH$_2$); uv 266(ε=1.70×10$^4$). |
| **6b** (82 %) | mp 176-178; ir 3500(OH), 3250(NH), 1700(C=O), 1615(purine); nmr 8.6(1H,br s,NH), 8.48 and 8.32(2H,s×2,purine), 8.15(1H,br d,NH), 6.0(1H,br,NCHN), 5.95(1H,d,OCHN), 5.5-5.1 (3H,m,OH), 4.62 and 4.18(2H,q×2,CHOH), 3.98(1H,q,OCHCH$_2$), 3.65(2H,m,CHCH$_2$OH), 3.33 and 3.31(6H,s×2,OMe), 2.7-2.2(2H,m,CH$_2$); uv 265(ε=1.35×10$^4$). |
| **6c** (90 %) | mp 110-120(dec.); ir 3500-3200(OH and NH), 1720(C=O), 1605(purine); nmr 9.0 and 8.3(2H, br s×2,NH), 8.50 and 8.33(2H,s×2,purine), 5.95(1H,d,OCHN), 5.5-5.2(3H,m,OH), 4.73(1H,d, NCHN), 4.60 and 4.15(3H,m×2,CHOH and CHCl), 3.97(1H,q,OCHCH$_2$), 3.62(2H,m,CHCH$_2$OH), 3.44 and 3.40(6H,s×2,OMe); uv 265(ε=1.94×10$^4$). |
| **6d** (69 %) | mp 215-216; ir 3500(OH), 3300 and 3250(NH), 1695(C=O), 1615(purine); nmr 8.47 and 8.30 (2H,s×2,purine), 8.45 and 8.25(2H,br s×2,NH), 6.15(1H,m,NCHN), 5.95(1H,d,OCHN), 5.5-5.1 (3H,m,OH), 4.63 and 4.17(2H,t×2,CHOH), 4.00(1H,q,OCHCH$_2$), 3.60(2H,m,CHCH$_2$OH), 3.33 (4H,br m,SCH$_2$CH$_2$S), 2.87(2H,m,CH$_2$). |
| **6e** (61 %) | mp 140-147; ir 3500-3100(OH and NH), 1680(C=O), 1630(purine); nmr 8.38 and 8.30(2H,s×2, purine), 8.33(1H,br s,NH), 8.15(1H,br d,NH), 6.2(1H,m,NCHN), 5.95(1H,d,OCHN), 5.6-5.25 (3H,m,OH), 4.66(1H,q,CHOH), 4.25(1H,m,CHOH), 4.1(1H,m,OCHCH$_2$), 3.7(2H,m,CHCH$_2$OH), 3.0-1.7(8H,m,CH$_2$). |
| **6f** (70 %) | mp 131-133; ir 3500-3100(OH and NH), 1705(C=O), 1615(purine); nmr 8.7(1H,br s,NH), 8.48 and 8.30(2H,s×2,purine), 8.2(1H,br d,NH), 7.7 and 7.5(10H,m×2,SPh), 5.95(2H,m,OCHN and NCHN), 5.6-5.1(3H,m,OH), 4.60(1H,q,CHOH), 4.20(1H,m,CHOH), 3.97(1H,q,OCHCH$_2$), 3.65(2H, m,CHCH$_2$OH), 2.9-2.25(2H,m,CH$_2$). |

These results described here demonstrate a convenient method for the synthesis of $N^6$-(2-oxopyrrolidin-5-yl)adenosines and suggest that this procedure may be applicable to the other nucleosides having nucleophilicity on purine or pyrimidine base. The compound (**6a**) was tested for its antihypertensive activity and was found to be about 10 % of the activity of 1. The further studies with biological activities of the compounds described here are in progress.

REFERENCES AND NOTES


1. M. H. Fleysher, J. Med. Chem., 1972, **15**, 187.
2. Only 21 % yield of the condensed product (5a) was obtained, when the mixture of 6-chloropurine triacetylriboside and the amine (2) in DMF was refluxed for 12 h. The lower yield of 5a presumably reflected the instability of 2.[3]
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6. H. M. Kisman and M. J. Weiss, J. Org. Chem., 1956, **21**, 1053.
7. **3d** and **3e** were prepared by the similar method as reported in our previous communication.[5] **3f** was synthesized by the reaction of lithiated 5-ethoxy-1-trimethylsilyl-2-pyrrolidinone with diphenyl disulfide followed by desilylation.
8. IR and UV spectra were recorded on Hitachi 260-10 and Hitachi 200-10 spectrophotometer, respectively. $^1$H-NMR spectra were obtained with Varian EM-390 (90 MHz) spectrometer.


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