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

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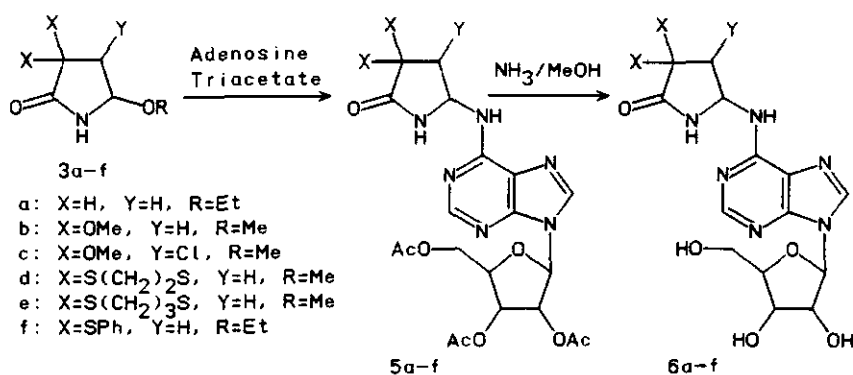
Abstract —— A convenient method for introducing a pyrrolidinyl moiety into adenosine N^6-position by utilizing the acyliminium activity of ω-alkoxylactams is described. Condensation of 5-alkoxy-2-pyrrolidinones (3a-f) and adenosine triacetate followed by deacetylation gave N^6-(2-oxopyrrolidin-5-yl)adenosines (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.
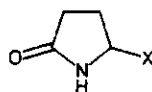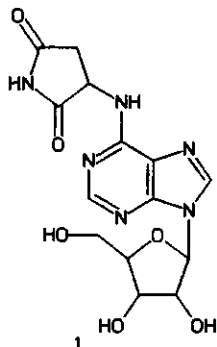
2: X=NH$_2$
3a: X=OEt
4: X=OAc

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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 in vacuo, 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.

3a-f
a: X=H, Y=H, R=Et
b: X=OMe, Y=H, R=Me
c: X=OMe, Y=Cl, R=Me
d: X=S(CH$_2$)$_2$S, Y=H, R=Me
e: X=S(CH$_2$)$_3$S, Y=H, R=Me
f: X=SPh, Y=H, R=Et

5a-f   6a-f

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}; ^{1}H-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}; ^{1}H-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), 1610(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

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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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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.