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PERMANGANATE OXIDATION OF N^6,N^6,8-TRISUBSTITUTED-2',3',5'-TRI-O-ACETYLADENOSINES

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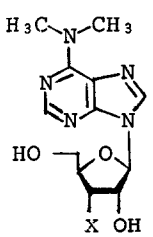
Summary: Oxidation of 2',3',5'-tri-O-acetyl derivatives of N^6,N^6-dialkyladenosines(3a-g) with $KMnO_4$ in 50% AcOH gave both the mono(5a-g) and didealkyl derivatives(6a-c) ; it was conclusively proved that one and two methylene groups of the title nucleosides(1a-g) in the α position to the exocyclic nitrogen atom were simultaneously oxidized.

N^6,N^6-Dimethyladenosine(1a) is found as the component of RNA[1] or as antibiotic puromycin(1b)[2]. The nucleoside(1a) occurs as a part of 16s and 18s ribosomal RNA which is believed to be responsible for the binding of antibiotic Kasugamycin[3]. Very recently, one of authors has reported the synthesis of such a " reduced " analogue of puromycin, compound(1c)[4]. Continuously, we attempted to synthesized 8-substituted-N^6,N^6-dimethyladenosines, because it is of interest to know the structure-activity relationships between 3' and 8-substituted derivatives.



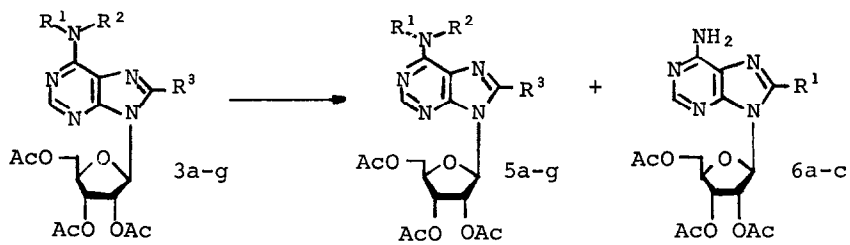
1a) X = OH
1b) X = NHCOCHCH$_2$(NH$_2$)-C$_6$H$_4$-OCH$_3$
1c) X = NHCH$_2$CHCH$_2$(NH$_2$)-C$_6$H$_5$
1d) X = NH$_2$

In general, 8-bromo-N^6,N^6-dimethyladenosine(2)[5] is useful intermediate for the preparation of 8-halo, 8-amino, and 8-thio-N^6,N^6-dimethyladenosine. Attempts to displace the 8-bromo group with inactive nucleophiles such as secondary amines or amino acids have been unsuccessful. A methylsulfonyl group is known to be a good leaving group in the reaction with nucleophiles in nucleosides[6]. Thus, we attempted to synthesize 8-methylsulfonyl-N^6,N^6-dimethyl-2',3',5'-tri-O-acetyladenosine(4) from 8-methylthio-N^6,N^6-dimethyl-2',3',5'-tri-O-acetyladenosine(3g)[7] by oxidation.

We found the mono and didemethylation of N^6,N^6-dimethyl group under the condition of $KMnO_4$- 50% AcOH, and 3g was converted to N^6-methyl-8-methylsulfonyl-2',3',5'-tri-O-acetyladenosine(5g) and 8-methylsulfonyl-2',3',5'-tri-O-acetyladenosine(6c)[6]. Puromycin(1b) is converted in vivo to the highly nephrotoxic aminonucleoside(1d), which is then selectively monodemethylated and phosphorylated to the corresponding 5'-phosphate[8]. Recently, Žemlička,et.al.,[9] have reported a selective N^6-monodealkylation sequence with RuO_4 as a nonenzymatic model.

We now wish to report the result of the oxidation of a series of N^6,N^6,8-trisubstituted-2',3',5'-tri-O-acetyladenosines(3a-g) with $KMnO_4$ in a polar solvent (50% AcOH), and the difference in the reactivities between $KMnO_4$ and RuO_4 as a oxidizing reagent.

Table I. The results of oxidation of N^6,N^6,8-trisubstituted-2',3',5'-tri-O-acetyladenosines(3a-g) with $KMnO_4$ under various conditions[10]



Starting Material				Amount of $KMnO_4$ (equ.)	Temp (°C)	Time (hr)	Products				Yield (%)
No.	R^1	R^2	R^3				No.	R^1	R^2	R^3	
3a	CH_3	CH_3	H	1	r.t.	1.5	5a	CH_3	H	H	26.3
3a	CH_3	CH_3	H	3	40	1	5a	CH_3	H	H	32.3
3b	C_2H_5	C_2H_5	H	3	r.t.	0.5	5b	C_2H_5	$COCH_3$	H	42.5
3b	C_2H_5	C_2H_5	H	3	r.t.	1	5b	C_2H_5	$COCH_3$	H	38.9
5b	C_2H_5	$COCH_3$	H	3	r.t.	0.5					
3c	CH_2-Ph	CH_2-Ph	H	3	r.t.	0.67	5c	CH_2-Ph	H	H	23.3
3d	$(CH_2)_4$		H	3	40	1	5d	$(CH_2)_3CO$		H	48.2
3e	$(CH_2)_5$		H	3	r.t.	0.17	5e	$(CH_2)_4COOH$		H	31.1
3f	CH_3	CH_3	Br	3	40	0.17	5f	CH_3	H	Br	36.0
3g	CH_3	CH_3	SCH_3	3	4	1.5	5g	CH_3	H	$SOCH_3$	52.3

Products		Yield (%)
No.	R^1	
6a	H	none
6a	H	48.1
6a	H	37.3
6a	H	43.7
6a	H	83.2
6a	H	28.4
6a	H	4.3
6a	H	38.2
6b	Br	31.3
6c	SO_2CH_3	6.5

The results of the oxidation of the title series of nucleosides(3a-g) are summarized in Table I. N^6,N^6-Dimethyl-2',3',5'-tri-O-acetyladenosine(3a) was oxidized with 1 equivalent of $KMnO_4$ at room temperature to give the N^6-methyl derivative(5a)[9]. While 3a was oxidized with 3 equivalents of $KMnO_4$ at 40°C to give the didemethylated compound, 2',3',5'-tri-O-acetyladenosine(6a)[11] along with 5a. The properties of 5a and 6a were identical with those of authentic samples by PMR spectra, UV spectra, CD spectra, TLC of silicagel, and PPC. In addition, deacetylation of 5a and 6a with methanolic ammonia gave N^6-methyladenosine[12] and adenosine, respectively, whose properties were in accord with those of an authentic sample.

N^6,N^6-Diethyl-2',3',5'-tri-O-acetyladenosine(3b)[9] afforded the N^6-acetyl-N^6-ethyl derivative(5b)[9] and 6a. Compound(5b) was deacetylated with methanolic ammonia to N^6-ethyladenosine[13], identical with an authentic sample. Further oxidation of 5b did not give the intermediate, $N^6,N^6,2',3',5'$-O-pentaacetyladenosine, but afforded 6a readily. The isolation of 5b suggests the reaction mechanism of 3a to 5a proceeds as follows ; 5b might be formed in some proceeding step , and then, decomposition of the carbinolamine or formylamine intermediate, probably took place.

N^6,N^6-Dibenzyl-2',3',5'-tri-O-acetyladenosine(3c)[9] proved to be less reactive in comparision with 3a and 3b, and N^6-benzyl derivative(5c), and 6a were obtained in 23% and 25% yield, respectively. It seemed that the intermediate, N^6-benzoyl-N^6-benzyl derivative was unstable under the acidic condition, and the phenyl group was rapidly oxidized with $KMnO_4$. The structure of 5c was confirmed by deacetylation with ammonia in methanol to the known N^6-benzyladenosine[14].

As the oxidation of aliphatic amines with $KMnO_4$ was successful, we next examined the oxidation of some purine derivatives substituted at position 6 with a cyclic amine. It was thought that such a reaction would lead to novel 6-substituted purine derivatives which were of interest biologicaly. The pyrrolidino derivative(3d) gave the corresponding lactam(5d) and 6a by the oxidation with $KMnO_4$, under the condition described above. The corroboration of the structure came from the PMR spectrum of 5d similar to the corresponding tribenzoyl derivative[9]. The piperidino derivative(3e) gave on oxidation with $KMnO_4$, N-(2',3',-5'-tri-O-acetyladenosin-6-yl)valeric acid(5e), and 6a. The structure of 5e was comfirmed by deacetylation with ammonia in methanol to N-(adenosin-6-yl)valeric acic which was identical with a sample prepared by alkylation of 6-chloroinosine[15] with 5-amino-*n*-valeric acid in dimethylformamide.

Oxidation of 8-bromo-N^6,N^6-dimethyl-2',3',5'-tri-O-acetyladenosine(3f) gave the similar products, 8-bromo-N^6-methyl(5f), and 8-bromo(6b)[16] derivative , to the above cases. Similary, compound(3g) was converted to 5g and 6c. The PMR spectrum of 5g showed that thiomethyl signal of 3g at δ 2.71 was deshielded to δ 3.41 based on methylsulfonyl group.

Žemlička, et.al.,[9] have reported that selectivity of oxidation of N^6,N^6-

dialkyl-nucleosides with RuO_4 cab be explained in terms of electronic effects of N^6-alkyl group, the pyrimidine portion of the purine ring, and the carbonyl function in the reaction products. We, however, found both the mono and didealkylation of N^6,N^6-dialkyladenosines on oxidation with $KMnO_4$; it was conclusively proved that one and two methylene groups of the title nucleoside in the α position to the exocyclic nitrogen atom were simultaneously oxidized. The fact might be suggested that $KMnO_4$ is more powerful than RuO_4 in the oxidation of the N-alkyl group, and each alkyl group in N^6,N^6-dialkyl derivatives is equivalent.

It will be possible to utilize $KMnO_4$ as a removal of N^6-blocking group under the reaction condition in regard as the studies on cyclonucleosides, nucleotides, and oligonucleotides. Oxidation of N^6-monoalkyl derivatives, and other oxidizing reagents are being currently explored in our laboratory.

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