A GENERAL SYNTHESIS OF 7,9-DIALKYLADENINIUM SALTS

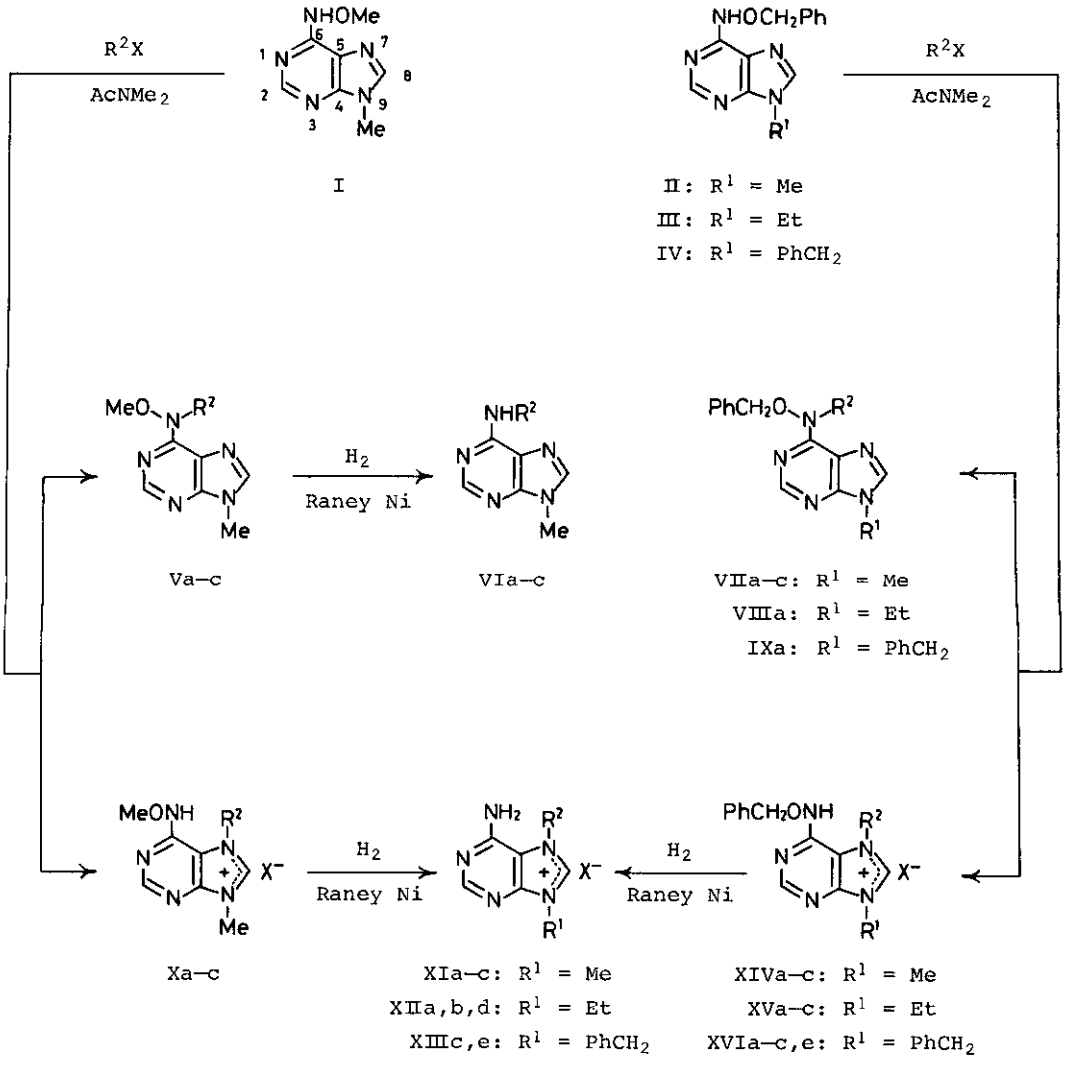
Tozo Fujii,* Tohru Saito, Teruyo Sakuma, Masako Minami, and Isao Inoue

Faculty of Pharmaceutical Sciences, Kanazawa University, Takara-machi, Kanazawa 920, Japan

Abstract —— Alkylations of N^6-methoxy-9-methyladenine (I) and 9-alkyl-N^6-benzyloxyadenines (II–IV) with MeI, EtI, and $PhCH_2Br$ in N,N-dimethylacetamide yielded the corresponding 7-alkylated derivatives (X, XIV–XVI), together with small amounts of the N^6-alkylated isomers (V, VII–IX). Hydrogenolysis of the former compounds with hydrogen and Raney Ni produced 7,9-dialkyladenines (XI–XIII).

The 7,9-disubstituted adenine structure has first been shown to exist by our previous synthesis[1] of 7,9-dimethyladeninium perchlorate (type XIa, ClO_4 for X) or 7-methyladenosine sulfate from N^6-methoxy-9-methyladenine (I) or N^6-methoxyadenosine. The synthesis consisted of the methylation of the 9-substituted N^6-methoxyadenine (type I) with MeI to give the 7-methylated derivative (type Xa) [together with the N^6-methylated derivative (type Va)] and hydrogenolysis of the N^6-methoxy group with hydrogen and Pd-C. Cullen and Devlin[2] later on disclosed evidence of the natural occurrence of such a 7,9-disubstituted adenine structure in the form of agelasine, a major constituent of the sponge Agelas dispar. This finding has renewed our interest in investigating the synthesis and properties of 7,9-dialkyladenines. We now report the extension of the 7-methylation of 9-substituted adenine derivatives to other 7-alkylations, which has established a general synthetic route to 7,9-dialkyladeninium salts.

Treatment of I[3,4] with EtI or $PhCH_2Br$ in $AcNMe_2$ furnished the corresponding 7-alkylated 9-methyladenine derivative (Xb or Xc) as well as the N^6-alkylated product (Vb or Vc). With a view to studying the effect of the N^6-benzyloxy group on regioselectivity in such alkylations, we also allowed N^6-benzyloxy-9-methyladenine (II)[5] to react with MeI, EtI, and $PhCH_2Br$ under similar conditions. Table 1 summarizes the results of these alkylation studies. Characterization of all the major products[6] as



a: R^2 = Me; X = I
b: R^2 = Et; X = I
c: R^2 = $PhCH_2$; X = Br
d: R^2 = $PhCH_2$; X = ClO_4
e: R^2 = Et; X = ClO_4

Chart 1[4]

TABLE 1. Alkylation of N^6-Alkoxy-9-alkyladenines

Starting material	Alkylating agent	Reaction conditions		Product			
		Temp. (°C)	Time (h)	Compound number	M.p.[a] (°C)	Yield (%)	N^7- /N^6-Alkylation[b]
I	MeI	30	7	Xa	250–251	59[c]	2.5 (2.1)[d]
				Va·HI	170.5–171.5	24[c]	
I	EtI	50	28	Xb	250.5–251.5	66	2.9 (2.6)[e]
				Vb·HCl[f]	182–183.5	23	
I	$PhCH_2Br$	30	30	Xc[f]	236.5–237.5	54	4.5
				Vc	191–192	12	
II	MeI	30	4	XIVa	232.5–233.5	58	3.2 (3.3)[d]
				VIIa	115–116.5	18	
II	EtI	50	24	XIVb	224.5–226	77	6.4 (4.9)[e]
				VIIb·HCl[g]	188–189	12	
II	$PhCH_2Br$	30	24	XIVc[g]	224–225	63	5.7
				VIIc·$HClO_4$	141.5–143	11	
III	MeI	30	5	XVa	225.5–227.5	71	7.1
				VIIIa	75–76.5[h]	10	
III	EtI	50	24	XVb[i]	216.5–219.5	66	
III	$PhCH_2Br$	30	22	XVc[i]	202–203.5	65	
IV	EtI	50	27	XVIb[i]	190–191.5	46	
IV	$PhCH_2Br$	30	23	XVIc[i]	218–219	67	

a) With decomposition. *b*) Ratio of the 7-alkylated product to the N^6-alkylated product isolated. The ratio in parentheses was obtained by high-performance liquid chromatographic analysis [Bondapak C_{18}/Porasil B, MeOH–0.02 M KH_2PO_4 (92 : 8, v/v), 350–400 p.s.i.] of the reaction mixture. *c*) From ref. 1. *d*) Determined on an 8-hour reaction mixture. *e*) Determined on a 30-hour reaction mixture. *f*) As a monohydrate. *g*) Found to contain 1/3 equivalent mole of H_2O of crystallization. *h*) Melted without apparent decomposition. *i*) No attempts were made for isolation of the N^6-alkylated product.

7-alkylated derivatives was readily achieved by their uv spectra [e. g., Xb: λ_{max} (95% EtOH) 291 nm (ε 7900); $\lambda_{max}^{H_2O}$ (pH 1) 226 (20000), 283 (9200); $\lambda_{max}^{H_2O}$ (pH 7) 226 (20000), 283 (9200); $\lambda_{max}^{H_2O}$ (pH 13) unstable] similar to those reported previously[1] for N^6-methoxy-7,9-dimethyladeninium hydriodide (Xa). The minor products were characterized as N^6-alkylated isomers on the basis of their uv spectra [e. g., Vb·HCl:

TABLE 2. Conversion of N^6-Alkoxy-7,9-dialkyladeninium Salts into 7,9-Dialkyladeninium Salts

Starting material	Reaction conditions		Product		
	Solvent	Time (h)	Compound number	M.p. (°C)[a]	Yield (%)
Xa	H_2O	18	XIa	267–268	80
Xb	H_2O	45	XIb	238–239.5	81
Xc[b]	H_2O	52	XIc[b]	225–226	51
XIVa	H_2O	13	XIa	267–268	72
XIVb	H_2O	40	XIb	238–239	83
XIVc[c]	H_2O	43	XIc[b]	225–226	60
XVa	50% aq. MeOH	25	XIIa	264–267	65
XVb	50% aq. MeOH	30	XIIb	254–257.5	70
XVc	50% aq. MeOH	40	XIId[d]	201–202	57
XVIe	85% aq. MeOH	34	XIIIe	255–256	22
XVIc	85% aq. MeOH	40	XIIIc	193–195	22

a) *With decomposition.*

b) As a monohydrate.

c) A sample containing 1/3 equivalent mole of H_2O of crystallization was used.

d) Isolated as the perchlorate.

$\lambda_{max}^{95\%\ EtOH}$ 277 nm (ε 18300); $\lambda_{max}^{H_2O}$ (pH 1) 277 (17500); $\lambda_{max}^{H_2O}$ (pH 7) 277 (18400); $\lambda_{max}^{H_2O}$ (pH 13) 276 (18500)] similar to those[1] of N^6-methoxy-N^6,9-dimethyladenine hydriodide (Va·*HI*) and hydrogenolysis (Raney *Ni*/H_2, EtOH, 1 atm, 50°C, 6–8 h) of Vb,c leading to N^6-ethyl-9-methyladenine (VIb)[7] (92% yield) and N^6-benzyl-9-methyladenine (VIc)[8] (71% yield).

It may be seen from Table 1 that in all cases the reaction proceeds smoothly and an N^6-alkoxy group orients the alkylation to both the 7- and the N^6-position but with an advantage to the former position. The N^6-benzyloxy group causes the extent of the 7-alkylation to increase and that of the N^6-alkylation to decrease. This change *in regioselectivity may be due to a reduction in the nucleophilicity of the* N^6 *atom*, which is caused by the replacement of the N^6-methoxy group by the more strongly electron-withdrawing[5,8] benzyloxy group. Since the above finding suggested the use of the N^6-benzyloxy group for an efficient 7-alkylation of the adenine ring, we next

carried out the reactions of N^6-benzyloxy-9-ethyladenine (III) [mp 187.5–188.5°C,[9] newly synthesized in 69% yield by treating 1-benzyloxy-9-ethyladenine perchlorate with boiling 0.5 M phosphate buffer (pH 6.5) for 2 h] and 9-benzyl-N^6-benzyloxyadenine (IV)[3] with MeI, EtI, and $PhCH_2Br$ in $AcNMe_2$. The results are also included in Table 1. In the case of the methylation of IV with MeI, the progress of the reaction was certainly fast. However, we failed in isolating XVIa and/or IXa in a pure form.

Removal of the alkoxyl group from the 7-alkylated derivatives Xa–c, XIVa–c, XVa–c, XVIc, and XVIe (derived from XVIb) was then accomplished by catalytic hydrogenolysis (Raney Ni/H_2, H_2O or aq. MeOH, 1 atm, room temp.) under conditions similar to those[9,10] employed for our recent hydrogenolytic cleavage of N'-alkoxy group in an imidazolecarboxamidine system. As shown in Table 2, the hydrogenolyses produced the corresponding 7,9-dialkyladeninium salts in acceptable yields (except for the last two cases). The correctness of the structures of the salts thus obtained were supported by their uv spectra [e. g., XIb: $\lambda_{max}^{95\%\ EtOH}$ 273 nm (ε 11600); $\lambda_{max}^{H_2O}$ (pH 1) 269 (11900); $\lambda_{max}^{H_2O}$ (pH 7) 270.5 (11900); $\lambda_{max}^{H_2O}$ (pH 13) unstable] essentially identical with those reported[1] for 7,9-dimethyladeninium perchlorate (type XIa, ClO_4 for X) and by their nmr spectra [e. g., XIb (in Me_2SO-d_6): δ 1.49 (3H, t, J = 7 Hz, CH_2CH_3), 4.61 (2H, q, J = 7 Hz, CH_2CH_3), 3.90 (3H, s, N(9)-CH_3), 7.94 (2H, NH_2), 8.44 (1H, s, C(2)-H), 9.69 (1H, s, C(8)-H)].

In conclusion, it has been well known that a 9-substituent of adenine orients alkylation to the 1-position.[11,12] The present results confirm that such a directing effect is altered quite differently by the N^6-methoxy group as well as the N^6-benzyloxy group. They have also established a general synthetic route to 7,9-dialkyladeninium salts, and will facilitate further studies on the chemical behavior of these unique structures.

ACKNOWLEDGMENT This work was supported in part by a Grant-in-Aid for Special Project Research [to Professor Y. Ban (Sapporo)] from the Ministry of Education, Science and Culture, Japan.

REFERENCES

1. T. Fujii, F. Tanaka, K. Mohri, T. Itaya, and T. Saito, Tetrahedron Lett., 1973, 4873.
2. E. Cullen and J. P. Devlin, Can. J. Chem., 1975, 53, 1690.

3. T. Fujii, T. Itaya, C. C. Wu, and F. Tanaka, Tetrahedron, 1971, 27, 2415.
4. We prefer not to commit ourselves as to tautomeric forms by the designations of structure employed for compounds I–IV, X, and XIV–XVI, since there has been certain spectroscopic evidence in support of the 6-imino-1*H*-purine structure. The details will be published elsewhere at a later date.
5. T. Itaya, T. Saito, S. Kawakatsu, and T. Fujii, Chem. Pharm. Bull., 1975, 23, 2643.
6. Routine C, H, N analyses agreed with calculated values within ±0.3% for all compounds reported herein.
7. T. Itaya, F. Tanaka, and T. Fujii, Tetrahedron, 1972, 28, 535.
8. T. Fujii, T. Itaya, and T. Saito, Chem. Pharm. Bull., 1975, 23, 54.
9. T. Fujii, T. Itaya, T. Saito, and M. Kawanishi, Chem. Pharm. Bull., 1978, 26, 1929.
10. T. Fujii, T. Saito, and M. Kawanishi, Tetrahedron Lett., 1978, 5007.
11. J. W. Jones and R. K. Robins, J. Am. Chem. Soc., 1963, 85, 193.
12. N. J. Leonard and T. Fujii, Proc. Natl. Acad. Sci. U. S. A., 1964, 51, 73.

Received, 3rd October, 1980