

A GENERAL SYNTHESIS OF 7,9-DIALKYLADENINIUM SALTS

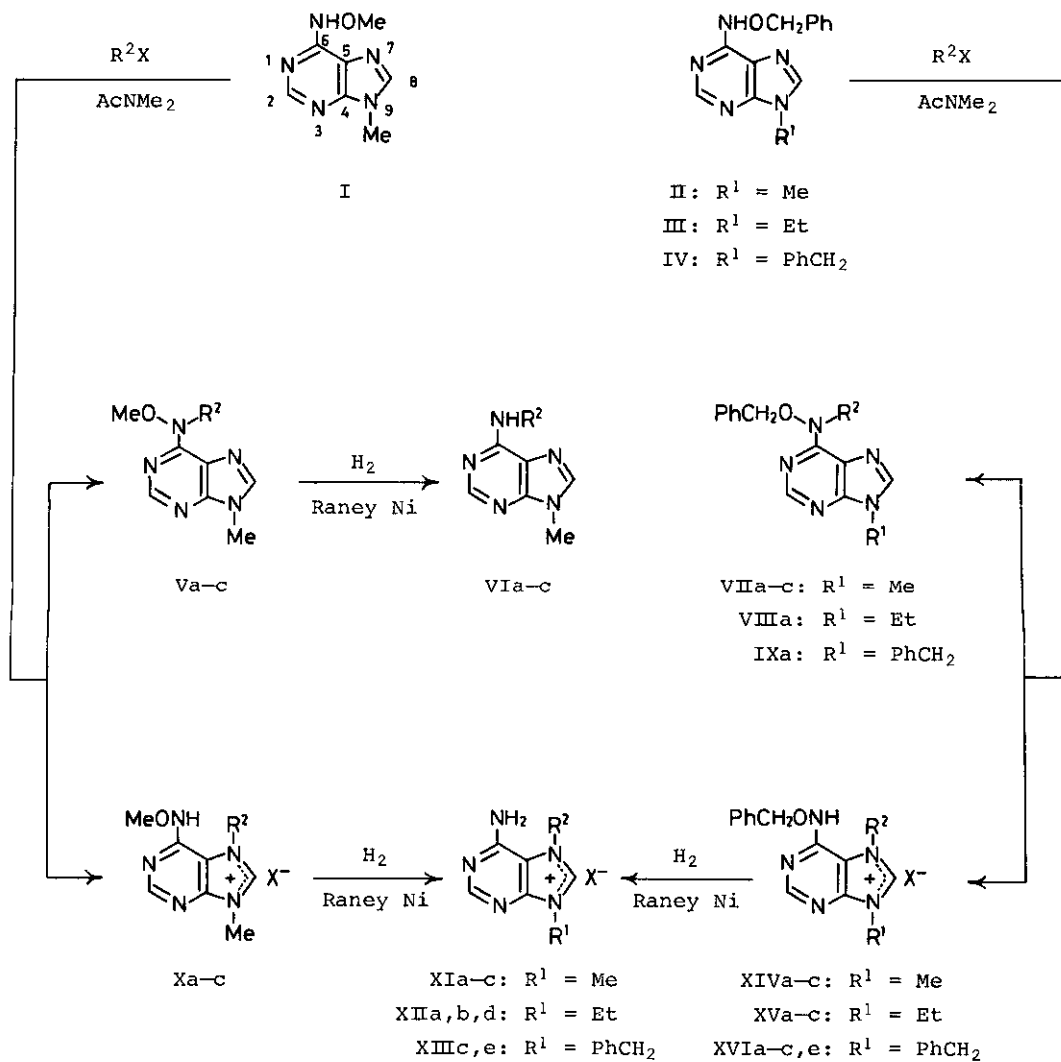
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Abstract — Alkylations of N⁶-methoxy-9-methyladenine (I) and 9-alkyl-N⁶-benzyloxyadenines (II-IV) with MeI, EtI, and PhCH₂Br in N,N-dimethylacetamide yielded the corresponding 7-alkylated derivatives (X, XIV-XVI), together with small amounts of the N⁶-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 synthesis¹ of 7,9-dimethyladeninium perchlorate (type XIa, ClO₄ for X) or 7-methyladenosine sulfate from N⁶-methoxy-9-methyladenine (I) or N⁶-methoxyadenosine. The synthesis consisted of the methylation of the 9-substituted N⁶-methoxyadenine (type I) with MeI to give the 7-methylated derivative (type Xa) [together with the N⁶-methylated derivative (type Va)] and hydrogenolysis of the N⁶-methoxy group with hydrogen and Pd-C. Cullen and Devlin² 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 PhCH₂Br in AcNMe₂ furnished the corresponding 7-alkylated 9-methyladenine derivative (Xb or Xc) as well as the N⁶-alkylated product (Vb or Vc). With a view to studying the effect of the N⁶-benzyloxy group on regioselectivity in such alkylations, we also allowed N⁶-benzyloxy-9-methyladenine (II)⁵ to react with MeI, EtI, and PhCH₂Br under similar conditions. Table 1 summarizes the results of these alkylation studies. Characterization of all the major products⁶ as



- a: R² = Me; X = I
 b: R² = Et; X = I
 c: R² = PhCH₂; X = Br
 d: R² = PhCH₂; X = ClO₄
 e: R² = Et; X = ClO₄

Chart 1⁴

TABLE 1. Alkylation of N⁶-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 ^{e)}	2.5 (2.1) ^{d)}
				Va·HI	170.5-171.5	24 ^{e)}	
I	EtI	50	28	Xb	250.5-251.5	66	2.9 (2.6) ^{e)}
				Vb·HCl ^{f)}	182-183.5	23	
I	PhCH ₂ Br	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 ₂ Br	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 ₂ Br	30	22	XVc ⁱ⁾	202-203.5	65	
IV	EtI	50	27	XVIb ⁱ⁾	190-191.5	46	
IV	PhCH ₂ Br	30	23	XVIc ⁱ⁾	218-219	67	

a) With decomposition. b) Ratio of the 7-alkylated product to the N⁶-alkylated product isolated. The ratio in parentheses was obtained by high-performance liquid chromatographic analysis [Bondapak C₁₈/Porasil B, MeOH-0.02 M KH₂PO₄ (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 H₂O of crystallization. h) Melted without apparent decomposition. i) No attempts were made for isolation of the N⁶-alkylated product.

7-alkylated derivatives was readily achieved by their uv spectra [e. g., Xb: λ_{\max} (95% EtOH) 291 nm (ϵ 7900); $\lambda_{\max}^{\text{H}_2\text{O}}$ (pH 1) 226 (20000), 283 (9200); $\lambda_{\max}^{\text{H}_2\text{O}}$ (pH 7) 226 (20000), 283 (9200); $\lambda_{\max}^{\text{H}_2\text{O}}$ (pH 13) unstable] similar to those reported previously¹ for N⁶-methoxy-7,9-dimethyladeninium hydriodide (Xa). The minor products were characterized as N⁶-alkylated isomers on the basis of their uv spectra [e. g., Vb·HCl:

TABLE 2. Conversion of N⁶-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 ₂ O	18	XIa	267-268	80
Xb	H ₂ O	45	XIb	238-239.5	81
Xc ^{b)}	H ₂ O	52	XIc ^{b)}	225-226	51
XIVa	H ₂ O	13	XIa	267-268	72
XIVb	H ₂ O	40	XIb	238-239	83
XIVc ^{e)}	H ₂ O	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	XIIc ^{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 H₂O of crystallization was used.

d) Isolated as the perchlorate.

$\lambda_{\max}^{95\% \text{ EtOH}}$ 277 nm (ϵ 18300); $\lambda_{\max}^{\text{H}_2\text{O}}$ (pH 1) 277 (17500); $\lambda_{\max}^{\text{H}_2\text{O}}$ (pH 7) 277 (18400); $\lambda_{\max}^{\text{H}_2\text{O}}$ (pH 13) 276 (18500)] similar to those¹ of N⁶-methoxy-N⁶,9-dimethyladenine hydriodide (Va-HI) and hydrogenolysis (Raney Ni/H₂, EtOH, 1 atm, 50°C, 6-8 h) of Vb,c leading to N⁶-ethyl-9-methyladenine (VIb)⁷ (92% yield) and N⁶-benzyl-9-methyladenine (VIc)⁸ (71% yield).

It may be seen from Table 1 that in all cases the reaction proceeds smoothly and an N⁶-alkoxy group orients the alkylation to both the 7- and the N⁶-position but with an advantage to the former position. The N⁶-benzyloxy group causes the extent of the 7-alkylation to increase and that of the N⁶-alkylation to decrease. This change in regioselectivity may be due to a reduction in the nucleophilicity of the N⁶ atom, which is caused by the replacement of the N⁶-methoxy group by the more strongly electron-withdrawing^{5,8} benzyloxy group. Since the above finding suggested the use of the N⁶-benzyloxy group for an efficient 7-alkylation of the adenine ring, we next

carried out the reactions of N⁶-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-N⁶-benzyloxyadenine (IV)³ with MeI, EtI, and PhCH₂Br in AcNMe₂. 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 XVIIe (derived from XVIIb) was then accomplished by catalytic hydrogenolysis (Raney Ni/H₂, H₂O 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: $\lambda_{\max}^{95\% \text{ EtOH}}$ 273 nm (ϵ 11600); $\lambda_{\max}^{\text{H}_2\text{O}}$ (pH 1) 269 (11900); $\lambda_{\max}^{\text{H}_2\text{O}}$ (pH 7) 270.5 (11900); $\lambda_{\max}^{\text{H}_2\text{O}}$ (pH 13) unstable] essentially identical with those reported¹ for 7,9-dimethyladeninium perchlorate (type XIa, ClO₄ for X) and by their nmr spectra [e. g., XIb (in Me₂SO-d₆): δ 1.49 (3H, t, $J = 7$ Hz, CH₂CH₃), 4.61 (2H, q, $J = 7$ Hz, CH₂CH₃), 3.90 (3H, s, N(9)-CH₃), 7.94 (2H, NH₂), 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 N⁶-methoxy group as well as the N⁶-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.

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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-1H-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 $\pm 0.3\%$ 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.

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