N_7-ALKYLATION AND RING-TRANSFORMATION OF N^6-ACYL-9-SUBSTITUTED ADENINES

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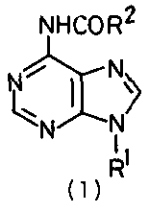
Abstract --- An N^6-acyl group in 9-substituted adenines shows the prominent substituent effect in the alkylation with alkyl halides; In a sharp contrast to 9-substituted adenines, alkylation of their N^6-acyl derivatives occurred at N_7-nitrogen rather than N_1-nitrogen. The N^6-acyl-7-alkyl-9-substituted adeninium halogenides thus prepared were converted into 7-substituted adenine and pteridine derivatives.

Among possible N,N-disubstituted adenines, 7,9-disubstituted adenines have not been generally well-known.[1] Although alkylation of 9-substituted adenines has been known to occur preferentially at N_1-nitrogen,[2] Fujii and his co-workers[3] have demonstrated that introduction of the methoxy group at N^6-nitrogen results in the alkylation at N_7-nitrogen. This result was utilized in the first preparation of 7,9-disubstituted adenines.

We wish to report that simple and common N^6-acyl substitution of 9-substituted adenines also causes almost exclusive alkylation at N_7-nitrogen rather than N_1-nitrogen. This intriguing observation was successfully applied to the novel ring-transformation of 9-substituted adenines to 7-substituted adenine and pteridine derivatives.

Our previous work[4] has shown that N^6-benzoyl-9-benzyladenine (1a) is easily reduced with sodium borohydride in acetic acid to give unexpectedly 7,8-dihydro derivative. The nmr spectroscopic study[5] has also suggested that contrary to 9-benzyladenine, protonation of (1a) occurs at N_7-nitrogen in preference. These observations point the remarkable substituent effect of the N^6-acyl group in the 9-substituted adenines. Thus, alkylation of the N^6-acyl-9-substituted adenines

(1a-c) with alkyl halides was examined.

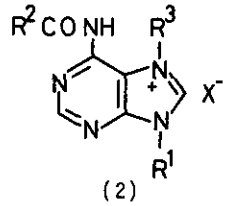


(1)

a: R^1= CH_2Ph, R^2= Ph

b: R^1= CH_2Ph, R^2= Me

c: R^1=  , R^2= Ph



(2)

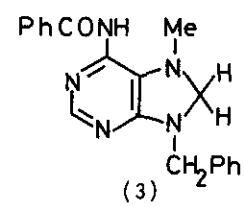
a: R^1= CH_2Ph, R^2= Ph, R^3= Me

b: R^1= CH_2Ph, R^2= Ph, R^3= Et

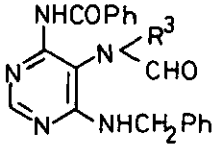
c: R^1= CH_2Ph, R^2= Me, R^3= Me

d: R^1=  , R^2= Ph, R^3= Me

e: R^1= CH_2Ph, R^2= Ph, R^3= CH_2COPh



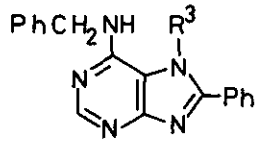
(3)



(4)

a: R^3= Me

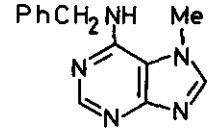
b: R^3= CH_2COPh



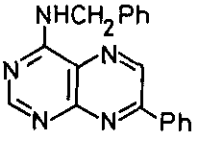
(5)

a: R^3= Me

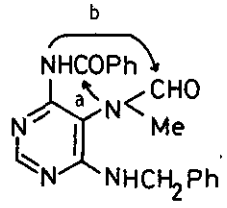
b: R^3= CH_2COPh



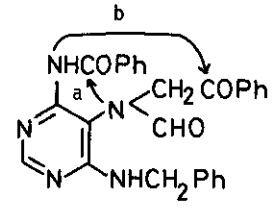
(6)



(7)



A



B

The N^6-benzoyl derivative (1a) was allowed to react with methyl iodide in dimethylacetamide at 80° for several h. After evaporation of the solvent, the solid residue was recrystallized from water to give N^6-benzoyl-7-methyl-9-benzyladeninium

iodide (2a) in 70% yield [mp 209°: uv (0.1N-HCl) 283nm (ε21300); uv (H_2O) 280nm (ε14400), 320nm (sh, ε3000); nmr (DMSO-$\underline{d}_6$) δ4.18 (3H, s, N-Me), 5.75 (2H, s, $NC\underline{H}_2$-Ph), 7.30-7.80 (8H, m, ArH), 8.00-8.30 (2H, m, ArH), 9.04 (1H, s, C_2-H), 10.18 (1H, s, C_8-H), 12.35 (1H, br, NH)]. Isolation of detectable amounts of other methylated adenines from the reaction mixture was unsuccessful.

Reduction of (2a) with sodium borohydride in methanol gave N^6-benzoyl-7-methyl-9-benzyl-7,8-dihydroadenine (3), mp 159°, quantitatively [uv (MeOH) 320nm (ε11000)].

Analogous borohydride reduction of the C_8-deuterated salt (2a-$\underline{d}$) prepared by methylation of the C_8-deuterated N^6-benzoyladenine (1a-$\underline{d}$) gave the corresponding deuterated dihydroadenine (3-$\underline{d}$). The nmr spectrum of (3-$\underline{d}$) clearly showed a singlet methylene signal (δ4.78) which is reduced approximately to 1H. Above results unequivocally established that the alkylation site of (1a) is N_7-nitrogen.

Similarly, N_7-alkyl-9-substituted adeninium iodides [(2b), mp 211°; (2c), mp 202°; (2d), mp 164° (unpurified)] were prepared from the corresponding N^6-acyl-9-substituted adenines (1a-c) in moderate to high yields, respectively. When phenacyl bromide was employed as an alkylating reagent for (1a), N_7-phenacyl-9-substituted adeninium bromide (2e) was obtained in 65% yield.

Mild alkaline hydrolysis of (2a) with 0.05N ethanolic sodium hydroxide at room temperature for 0.5 h occurred smoothly to give the ring-opening product (4a), mp 177°, in 68% yield. The structural proof of (4a) rests upon its nmr spectrum; The benzyl methylene protons appeared at δ4.65 as a doublet signal which coalesces to a sharp singlet by addition of deuterium oxide.

Acid treatment of the ring-opening product (4a) with 10% hydrochloric acid at 100° for 2 h resulted in the cyclization of N^6-benzyl-7-methyl-8-phenyladenine (5a), mp 244°, in 54% yield [nmr δ4.75 (2H, d, $NHC\underline{H}_2Ph$)]. Hplc of the reaction mixture showed the presence of a small amount of N^6-benzyl-7-methyladenine (6) (yield: about 7%). Alkaline treatment of (4a) with boiling 0.1N ethanolic sodium hydroxide for 2 h, however, gave preferentially the 7-substituted adenine (6), mp 234°, in 71% yield [nmr δ4.75 (2H, d, $NHC\underline{H}_2Ph$)]. In this case, the formation of (5a) was observed only as a minor process (yield: about 8%, by hplc).

It should be noted that the recyclization of (4a) to 7-substituted adenines (5a and 6) depends upon the reaction conditions employed (see path a or b in formula A).

Analogous alkaline hydrolysis of (2e) (0.05N ethanolic sodium hydroxide at room temperature for 0.5 h) gave the ring-opening product (4b), mp 206°, in 60% yield

[nmr δ4.70 (2H, d, $NHCH_2Ph$)].

Recyclization of (4b) was also destined by the employed conditions (see path a and b in formula B); While acid treatment of (4b) (10% HCl, 2 h) gave N^6-benzyl-7-phenacyl-8-phenyladenine (5b), mp 100°, in 15% yield[6] [nmr δ4.65 (2H, d, $NHCH_2Ph$)], alkaline treatment of (4b) (0.1N ethanolic NaOH, 2 h) led to the formation of 4-benzylamino-7-phenylpteridine (7), mp 231°, in 60% yield[7] [nmr δ4.75 (2H, d, $NHCH_2Ph$), 7.30 (5H, s, ArH), 7.45-7.70 (5H, m, ArH), 8.55 and 9.35 (each 1H, s, C_2-H and C_8-H)].

The ring-transformations of 9-substituted adenines to 7-substituted adenines and pteridines have been unprecedented.[8]

Further extension of the present results is now in progress and will appear in the forthcoming papers.

ACKNOWLEDGMENT We thank the Ministry of Education, Science and Culture, Japan for a Grant-in-Aid for Special Project Research " Nitrogen Organic Resources ".

REFERENCES AND FOOTNOTES

1. Recently, quaternary 7,9-disubstituted adenines have been found in nature (E. Cullen and J. P. Devlin, Can. J. Chem., 1975, 53, 1690).
2. N. J. Leonard and T. Fujii, Proc. Natl. Acad. Sci. U. S., 1964, 51, 73.
3. T. Fujii, F. Tanaka, K. Mohri, T. Itaya and T. Saito, Tetrahedron Letters, 1973, 4873.
4. Y. Maki, M. Suzuki and K. Ozeki, Tetrahedron Letters, 1976, 1199.
5. Y. Maki, M. Suzuki, K. Ozeki and K. Kameyama, 5th Symposium on Progress in Organic Reactions and Syntheses, Abstracts of Papers, Shizuoka, Japan, 1978, p. 163.
6. We did not attempt to optimize the reaction conditions. Hplc of the reaction mixture showed the presence of the starting material and a small amount of 4-benzylamino-7-phenylpteridine (7) in addition to (5b).
7. (7) was obtained directly from (2e) with boiling 0.1N ethanolic sodium hydroxide in 41% yield.
8. Ring-transformation of guanines to pteridines has been studied in view of the biomimetic interest (K. Eistetter and W. Pfleiderer, Chem. Ber., 1973, 106, 1389).

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