[Chem. Pharm. Bull. 18(7)1446—1456(1970)]

UDC 547.857.04

N→N Alkyl and Glycosyl Migration of Purines and Pyrimidines. III.[1] N→N Alkyl and Glycosyl Migration of Purine Derivatives[2]

Michiko Miyaki and Bunji Shimizu

Central Research Laboratories, Sankyo Co., Ltd.[3]

(Received February 13, 1970)

Alkyl and glycosyl migration reactions of N-1, N-3, N-7 and N-9 substituted derivatives of adenine, N^6,N^6-dimethyladenine, N^2-acetylguanine and purine were demonstrated. In addition, the chemical shifts of these derivatives in nuclear magnetic resonance (NMR) were determined and the frontier π-electron densities of nitrogens in purine ring were calculated by simple LCAOMO method.

These results provided the order of thermodynamical stability and kinetical favour of the derivatives on the alkylation reaction.

Although various kinds of N-substituted derivatives of N^6,N^6-dimethyladenine, N^2-acetylguanine and purine have been synthesized and their properties have been investigated, the conversion reaction from one to another has never been described. The N-3→N-9 migration described in the previous papers was extended to the derivatives of purine bases other than N^6-acyladenine and other N→N migrations were also investigated. We wish to discuss relative reactivity of nitrogen in purine ring and thermodynamic stability of various N-substituted derivatives based on the results of migration reactions, nuclear magnetic resonance (NMR) spectra and molecular orbital calculation.

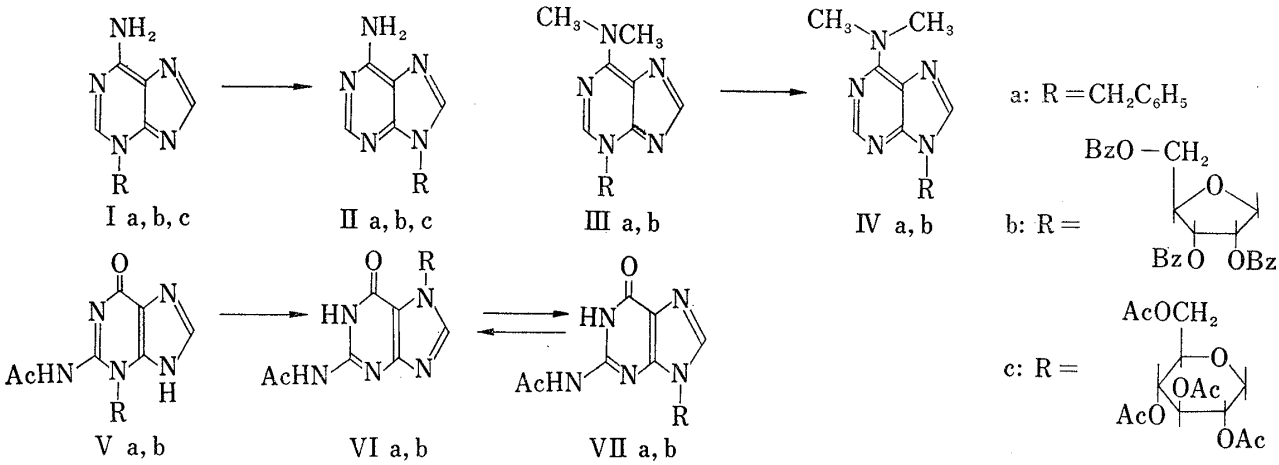


Chart 1

N-3→N-9 Migration of Alkyl and Glycosyl Adenines

Both the alkylation and glycosylation of adenine gave the 3- and 9-substituted derivatives, but the ratio of yields of 3-derivatives to that of 9-isomers (ratio 3-R/9-R) varied depending on the nature of alkyl and glycosyl halides used, for example, the ratio in benzylation was 14 and that in glycosylation was 1.3. The difference in the ratio (3-R/9-R) seemed to be

1) Part II: M. Miyaki and B. Shimizu, *Chem. Pharm. Bull.* (Tokyo) **18**, 732 (1970).
2) A part of this paper was presented in *Chem. Pharm. Bull.* (Tokyo), **15**, 1066 (1967) as a preliminary communication.
3) Location: *2–58, 1-chome, Hiromachi, Shinagawa-ku, Tokyo.*

due to the difference in the rate of N-3→N-9 migration reaction between alkyl and glycosyl groups.

3-Benzyladenine (Ia) hydrobromide was not entirely changed under the conditions (heating at 110° for 38 hr) under which the migration of 3-benzyl-N^6-benzoyladenine hydrobromide occurred, as described previously. When Ia –HBr was heated at a higher temperature, 170—180° for 44 hr, the N-3→N-9 migration occurred to give 9-benzyladenine (IIa) in 30% yield. When 3-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)adenine (Ib) was heated with mercuric bromide in a mixture of xylene and DMA (5:1) under reflux, N-3→N-9 ribosyl migration was also observed. This migration took 75 min for completion, although that of a N^6-acyladenine derivative was complete in only 5 min. Debenzoylation of 9-(2,3,5-tri-O-benzoyl-D-ribofuranosyl)adenine (IIb) thus produced gave β-adenosine (20% yield based on Ib) and α-adenosine (0.8%). 3-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)adenine also underwent glucosyl migration when heated with mercuric bromide and 9-β-D-glucopyranosyladenine was obtained in 18% yield after deacetylation of the migration product.

N-3→N-9 Migration of Alkyl and Glycosyl N^6,N^6-Dimethyladenines

The glycosylation of chloromercuri-N^6,N^6-dimethyladenine with various glycosyl halides has been reported to give "7"-glycosides, a mixture of "7"- and 9-glycosides or 9-glycosides alone.[4] (Later, the "7"-glycosides were reassigned as the 3-glycosides.[5]) The variety of the products from this glycosylation has been assumed to be due to the nature of glycosyl halide, however, no satisfactory explanation has been given. On the other hand, the reaction of N^6,N^6-dimethyladenine and 2,3,5-tri-O-benzoyl-D-ribofuranosyl bromide at 60—65° for 18 hr was found to give 3-(2,3,5-tri-O-benzoyl-D-ribofuranosyl)-N^6,N^6-dimethyladenine (IIIb, 36%) and the 9-riboside (IVb, 11%) in contrast with the analogous reaction which gave only the 9-riboside.[4b] Difference in the products between the above two ribosylation reactions was assumed to reflect the change in reaction temperature, and the N-3→N-9 migration was expected to occur at rather a high temperature such as at boiling point of xylene (about 140°).

Although IIIb was unchanged at 100° for 1.5 hr in the presence of mercuric bromide, it underwent migration when heated at 130—140° for 2 hr giving the 9-riboside (IVb) in 36% yield. This N-3→N-9 migration reaction can be used to explain the variety of products from glycosylation as follows: The ribosylation of chloromercuri-N^6,N^6-dimethyladenine in refluxing xylene gave only the 9-riboside because the rapid N-3→N-9 ribosyl migration of initially formed 3-riboside was complete during the ribosylation reaction, whereas the glucosylation of the same salt gave only the 3-glucoside because the N-3→N-9 glucosyl migration hardly took place at the same temperature. Benzylation of N^6,N^6-dimethyladenine with benzyl bromide at 110° for 7 hr afforded mainly 3-benzyl-N^6,N^6-dimethyladenine (IIIa, 66%) accompanied by the 9-isomer (IVa, 5%). The former was converted into the latter (22% yield) when heated at 150° for 40 hr in the presence of hydrogen bromide.

N-3→N-9(N-7) and N-7→N-9 Migrations of Alkyl and Glycosyl N^2-Acetylguanines

Glycosylation of chloromercuri-N^2-acetylguanine or N^2,9(7)-diacetylguanine have afforded the 7- and 9-glycosides.[6] In the present investigation, coupling of N^2-acetylguanine and 2,3,5-tri-O-benzoyl-D-ribofuranosyl bromide in DMA at 60—65° for 40 hr gave 7-(2,3,5-tri-

4) *a*) B.R. Baker, J.P. Joseph, R.E. Shaub and J.H. Williams, *J. Org. Chem.*, **19**, 1780 (1954); *b*) H.M. Kissmann, C. Pidacks and B.R. Baker, *J. Am. Chem. Soc.*, **77**, 18 (1955); *c*) B.R. Baker and R.E. Shaub, *ibid.*, **77**, 5900 (1955); *d*) B.R. Baker, J.P. Joseph and R.E. Schaub, *ibid.*, **77**, 5905 (1955); *e*) G.M. Blackburn and A.W. Johnson, *J. Chem. Soc.*, **1960**, 4347.

5) L.B. Townsend, R.K. Robins, R. Leoppky and N.J. Leonard, *J. Am. Chem.Soc.*, **86**, 5320 (1964).

6) *a*) Z.A. Shabarova, Z.P. Polyakova and M.A. Prokofev, *Zh. Obsch. Khim.*, **29**, 215 (1959); S.R. Jenkins, F.W. Holly and E. Walton, *J. Org. Chem*, **30**, 285 (1965); K. Imai, A. Nohara and M. Honjo, *Chem. Pharm. Bull.* (Tokyo), **14**, 1377 (1966).

O-benzoyl-β-D-ribofuranosyl)-N^2-acetylguanine (VIb, 21%) and the 9-isomer (VIIb, 19%). Condensation of N^2-acetylguanine with benzyl bromide at 90° for 7 hr gave mainly 7-benzyl- (VIa, 22%) and 9-benzyl-(VIIa, 16%) N^2-acetylguanine and a trace of the 3-benzylisomer (Va, 0.2%). Formation of only a trace amount of 3-benzyl derivative in the benzylation suggested that if the 3-benzyl derivative was produced, it would rapidly be converted into the 7- and 9-benzyl derivatives under the benzylation conditions employed. To confirm this conversion, previously unreported 3-benzyl-N^2-acetylguanine (Va) was synthesized. 3-Benzyl-2-mercaptopurine-6-one, prepared from 5,6-diamino-1-benzyl-4-hydroxypyrimidine-2(*H*)-thione,[7] was S-methylated with dimethyl sulfate to give 3-benzyl-2-methylthiopurine-6-one. This methylthiopurine was heated in formamide under reflux in a similar manner as described for 3-methylguanine.[8a] Acetylation of the crude product with acetic anhydride gave 3-benzyl-N^2-acetylguanine (Va) which was purified by chromatography on silica gel (43% yield based on the methylthiopurine). Benzyl migration was found to occur when the hydrobromide of Va was heated in DMF at 100—110° for 24 hr giving VIa and VIIa, in 10—28% and 10—30% yields respectively. The migration proceeded more rapidly than in the case of N^6-benzoyladenine derivative. This indicated the effect of oxy group at 6 position in addition to the acetyl group at N^2 on the benzyl migration. The intermolecular nature of this benzyl migration was suggested by the following result. When a solution of equimolar amounts of Va-HBr and N^2-acetylguanine-8-^{14}C in DMA at 130° for 20 hr, the labeled VIa and VIIa formed had 53% and 56%, respectively, of the specific activity of initial N^2-acetylguanine-8-^{14}C. The radioactivity of the recovered N^2-acetylguanine was reduced to 46%.

Furthermore, reversible conversion of the 7-substituted- to the 9-substituted-N^2-acetylguanine was observed. The mixture of VIa and VIIa was obtained when either VIa-HBr or VIIa-HBr was heated at 140—160° for 70—80 hr. The ratio of VI to VII in the resulting mixture was about 1:2 in both cases, which indicated that the 9-isomer is thermodynamically more stable than the 7-isomer. A similar result was obtained in the case of the ribosyl derivatives, VIb and VIIb.

NMR Spectra of Substituted Purines

A purine ring can be assumed to be derived by fusion of a pyrimidine and an imidazole ring, the former being π-electron-defficient system and the latter, π-electron-excess system. In NMR spectra, the chemical shifts of the aromatic protons seem to partially reflect the electron distribution in the pyrimidine and imidazole moieties of purine, respectively. The difference in the chemical shifts between the signal for 2- and 8-aromatic protons of the 3-substituted purines was 0.51—0.88 ppm, whereas that of the 9-isomer was only 0.00—0.30 ppm (probably, the 2-protons were at a lower field than the 8-protons[9]) as shown in Table I.

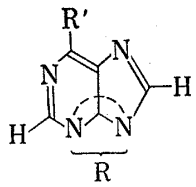
Such as difference in NMR spectra seems to suggest that purine rings in the 3-substituted derivatives are more polarized than those in the 9-isomers, namely, the positive charge in the pyrimidine moiety and the negative charge in the imidazole ring of 3-isomer are larger than those of the 9-isomers. On the other hand, the protons in N-substituents in the 3-isomer were found to be less shielded than the corresponding protons in the 9-isomer by 0.12—0.32 ppm as listed in Table II.

Influence of a Substitution at Carbon in Pyrimidine Ring on the Rate of Migration Reaction

The ribosyl migration of N^6-benzoyladenine derivative was complete in only 0.1—0.5 hr at 90—130°, whereas that of N^6,N^6-dimethyladenine derivative was complete in 2 hr at 130—

7) J.A. Montgomery and H.J. Thomas, *J. Org. Chem.*, **28**, 2304 (1963).
8) *a*) G.B. Elion, *J. Org. Chem.*, **27**, 2478 (1962); *b*) L.B. Townsend and R.K. Robins, *J. Am. Chem. Soc.*, **84**, 3008 (1962).
9) *a*) S. Matsuura and T. Goto, *Tetrahedron Letters*, **1963**, 1499; *b*) M.P.Schweizer, S.I. Chan, G.K. Helmkamp and P.O. Ts'o, *J. Am. Chem. Soc.*, **86**, 696 (1964); *c*) W.C. Coburn, M.C. Thorpe, J.A. Montgomery and K. Hewson, *J. Org. Chem.*, **30**, 1114 (1965); *d*) R.J. Pugmire, D.M. Grant, R.K. Robins and G.W. Rhodes, *J. Am. Chem. Soc.*, **87**, 2225 (1965).

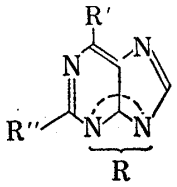
TABLE I. Difference in the Chemical Shift for 2- and 8-Protons

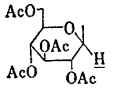


R′	R	3-R			9-R		
		H_2,H_8		Δ	H_2,H_8		Δ
$NHCOCH_3$	benzyl	8.97	8.13	0.84	8.62	8.52	0.10
$NHCOC_6H_5$	H				8.42	8.29	0.13
	allyl	8.68	8.17	0.51	8.69	8.42	0.27
	γ,γ-dimethylallyl	8.70	8.12	0.58	8.70	8.40	0.30
	α,α-dimethylallyl				8.80	8.51	0.29
	benzyl	9.05	8.30	0.75	8.82	8.69	0.13
NH_2	allyl	8.32	7.77	0.55	8.12	8.06	0.06
	γ,γ-dimethylallyl	8.33	7.80	0.53	8.17	8.08	0.09
	α,α-dimethylallyl				8.22	8.13	0.09
	benzyl	8.49	7.77	0.72	8.28	8.18	0.05
	ribofuranosyl	8.59	7.80	0.79	8.25	8.06	0.19
	tetra-O-acetyl-glucopyranosyl	8.64	7.76	0.88	8.36	8.16	0.20
$N(CH_3)_2$	H				8.20	8.07	0.13
	benzyl	8.53	7.77	0.76	8.20	8.20	0.00
	ribofuranosyl	8.60	7.76	0.84	8.29	8.18	0.11
OH	benzyl	8.53	8.12	0.41			
	ribofuranosyl				8.30	8.05	0.25

The NMR spectra were taken in DMSO-d_6 at 60 Mcps, and chemical shifts are given in ppm with TMS as an internal standard. Solute concentration is about 0.25M.

TABLE II. Chemical Shift of the Protons in N-Alkyl Group

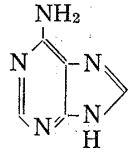


R′	R″	N-R	N-3-R	N-9-R
$NHCOCH_3$	H	$-C\underline{H}_2-C_6H_5$	5.72	5.47
$NHCOC_6H_5$	H	$-C\underline{H}_2-CH=C\langle^{CH_3}_{CH_3}$	5.18	4.86
		$-C\underline{H}_2-C_6H_5$	5.75	5.56
NH_2	H	$-C\underline{H}_2-CH=C\langle^{CH_3}_{CH_3}$	4.95	4.74
		$-C\underline{H}_2-C_6H_5$	5.52	5.40
			6.40	6.17
$N(CH_3)_2$	H	$-C\underline{H}_2-C_6H_5$	5.53	5.37
OH	$NHCOCH_3$	$-C\underline{H}_2-C_6H_5$	5.48	5.36

The NMR spectra were taken under the same conditions as in Table I.

140°. The benzyl migration of N^2-acetylguanine derivative was complete in 24 hr at 100—110° and that of N^6-benzoyladenine derivative being in 70 hr at the same temperature, while that of 3-benzyladenine or 3-benzyl-N^6,N^6-dimethyladenine proceeded with difficulty at 150—180°. These facts indicate that N-3→N-9 (or N-7) migration of the purines bearing a weak electron-donating group at 2 or 6 position proceeded more easily than that of purines

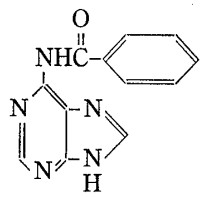
Table III. (a) Frontier and Total π-Electron Density of Nitrogens in Purines



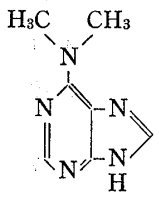
N	9–H		9–H	
	F	T	F*	T**
1	0.1407	1.3016	0	1.3966
3	0.1674	1.2969	0.2764	1.3913
7	0.0330	1.3477	0.1602	1.3267
9	0.0138	1.5035	0.0032	1.7220

N	7–H		3–H	
	F	T	F	T
1	0.1401	1.3025	0.1276	1.2968
3	0.1659	1.2979	0.1396	1.4371
7	0.0281	1.4947	0.0339	1.3727
9	0.0131	1.3645	0.0093	1.3867

N	1–H	
	F	T
1	0.1135	1.4371
3	0.1499	1.2852
7	0.0392	1.3708
9	0.0123	1.3852



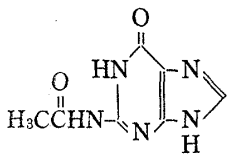
N	9–H	
	F	T
1	0.1069	1.2882
3	0.2771	1.2790
7	0.2535	1.3470
9	0.0811	1.5031



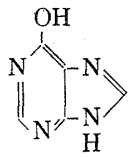
N	9–H		7–H	
	F	T	F	T
1	0.2414	1.3722	0.2433	1.3737
3	0.2547	1.3580	0.2565	1.3602
7	0.0202	1.3459	0.0207	1.4900
9	0.0120	1.5047	0.0133	1.3656

N	3–H		1–H	
	F	T	F	T
1	0.2149	1.3555	0.1986	1.5055
3	0.2182	1.4929	0.2224	1.3357
7	0.0216	1.3716	0.0241	1.3700
9	0.0067	1.3869	0.0084	1.3861

Table III. (b)



N	9-H		7-H	
	F	T	F	T
1	0.0562	1.5376	0.0585	1.5743
3	0.4400	1.4251	0.4655	1.4282
7	0.1120	1.3272	0.1058	1.4833
9	0.3942	1.5066	0.0425	1.3684



N	9-H		7-H	
	F	T	F	T
1	0.1543	1.3058	0.1623	1.3065
3	0.2233	1.2974	0.2297	1.2990
7	0.0801	1.3491	0.0681	1.4938
9	0.0277	1.5042	0.0288	1.3643

N	3-H		1-H	
	F	T	F	T
1	0.1407	1.3008	0.1180	1.4402
3	0.1852	1.4364	0.2023	1.2854
7	0.0944	1.3733	0.1047	1.3711
9	0.0250	1.3870	0.0329	1.3854

F: frontier electron density, T: total electron density π-Electron densities were calculated by the simple LCAO MO method. (*, ** by Pariser-Parr-SCF method by C. Nagata, A. Imamura, *et al.*)[15]
Parameters are as follows: coulomb integral $\alpha_X=\alpha+a\beta$
resonance integral $\beta_{C\text{-}X}=1\beta$

X	a	l
=N−	0.6	1
>N−	1	1
CH_3 / CH_3>N−	0.9	1
$-NH_2$	0.4	0.6
$-CH_3$	3	1
−OH	0.6	0.7
=O	2	$\sqrt{2}$ (benzoyladenine)
=O	0.8	$\sqrt{2}$ (acetylguanine)

bearing a strong electron-donating group. The order of the substituents which accelerate the migration is as follows:

$$N^3HCOCH_3 + 6\text{-}C{=}O > N^6COC_6H_5 > N^6H_2 \geqq N^6(CH_3)_2$$

This order is also found in the yield of alkylation or glycosylation products of purines (the ratio of 9-isomer to 3-isomer). For example, the relative yield of 9-benzyl-N^6-benzoyladenine(9-benzyl/3-benzyl=0.39) was larger than that of 9-benzyladenine (9-benzyl/3-benzyl =0.07) in benzylation reactions at 100° for 3 hr.

π-Electron Densities at Nitrogens in Purine Ring as calculated by Simple LCAO MO Method

Occurrence of the N-3→N-9(N-7) migration, and comparison of the NMR spectra indicated the instability of the 3-substituted purines as compared with the corresponding 9-(or 7) substituted isomers. In spite of such a stability relationship, 3-substitution is pre-

ferred under the general alkylation condition which are milder than the migration conditions, such as benzylation at 60—100° for several hours. Allylation,[10] 3-methyl-2-butenylation[11] and ethylation[12] of adenine have also given 3-alkyladenines in the highest yields. In contrast to these fact, N-3 has been theoretically predicted to be less reactive by the use of calculated basisity of various nitrogens in the purine ring.[13]

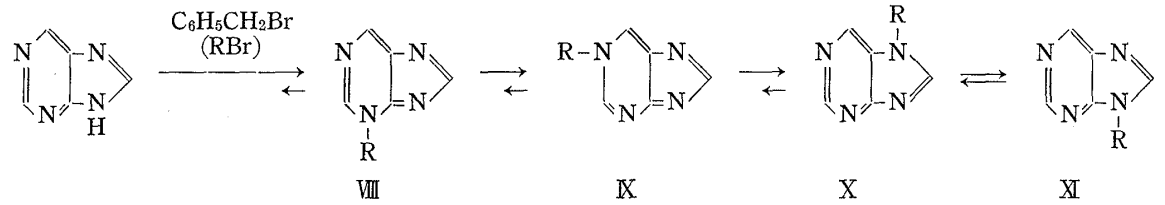
An attempt was made to compare the products in alkylation of purines with the π-electron densities of nitrogens calculated by the simple LCAO MO method. However, no correlation was observed between the total π-electron densities and the reactivity indicated by the experimental data. The frontier (highest occupied level) electron densities have been taken as the indices for electrophilic attack.[14] As shown in Table III, the frontier electron density was the highest at N–3 in every purine base and this fact seems to support the experimental results indicating the highest reactivity of N–3, although applicability of correlation of reactivity with π–electron densiry is limited to the highest values. These facts can lead to the conclusion that the reactivity of nitrogens in various purines bases is the greatest at N–3, and hence the alkylation or glycosylation of purines would initially give the 3-substitued derivatives which then undergo a rapid or slow migration giving rise to the thermodynamically more stable 9-substituted isomers at a high temperature or by prolonged reactien times.

Various N→N Migration of Alkyl Purines

An although the order of nitrogen at 3, 7 and 9 positions which were substituted by alkyl or glycosyl group was became clear by the facts described above, purine has still more one nitrogen, N-1. To elucidate relationship between all nitrogens in purine ring, we finally investigated the alkylation of purine itself which lacks substituents on the aromatic carbons. Glycosylation of purine has been reported to give the 9- and 7-glycosides.[16] Under milder alkylation conditions, however, the 3-substituted purine was expected to be formed analogously as in the case of other purine derivatives,.

Reaction of purine with benzyl bromide at 80° for 2 hr gave 1-benzyl (IX, 45% yield) and 3-benzyl- (VIII, 14%) purines accompanied by a small amounts of the 7- (X, 1%) and 9- (XI, 3%) isomers in contrast to the reaction at 140° for 48 hr which afforded only X (15%) and XI (33%). On heating at 140° for 48 hr in the presence of hydrogen bromide 3-benzylpurine (VIII) was converted into IX, X and XI, IX disappeared during prolonged heating, and finally X (7%) and XI (17%) were isolated. Benzyl migration of 1-benzylpurine (IX) also occurred under similar conditions to the case of 3-benzylpurine to give X (7%) and XI (17%).

These results suggested the formation of the 1- and 3- substituted derivatives by kinetic control, and the 7- and 9- substituted isomers by thermodynamic control. It was concluded



Ⅷ Ⅸ X Ⅺ

Chart 2

10) N.J. Leonard and T. Fujii, *J. Am. Chem. Soc.*, **85**, 3719 (1963).
11) N.J. Leonard and J.A. Deyrup, *J. Am. Chem. Soc.*, **84**, 2148 (1962).
12) B.C.Pal, *Biochemistry*, **1**, 558 (1962).
13) *a*) B. Pullmann and T. Nakajima, *Bull. Soc. Chim. France*, **1958**, 1502; *b*) B. Pullmann, *J. Chem. Soc.*, **1959**, 1621.
14) *a*) K. Fukui, T. Yonezawa, C. Nagata and H. Shingu, *J. Chem. Phys.*, **22**, 1433 (1954); R.L. Miller, P.C. Lykos and H.N. Schmeising, *J. Am. Chem. Soc.*, **84**, 4623 (1962).
15) C. Nagata and A. Imamura, private communication.
16) T. Hashizume and H. Iwamura, *Tetrahedron Letters*, **1966**, 643.

that the order of thermodynamic stabilty of these N-substituted purines was as follows:

$$9 > 7 > 1 > 3$$

Experimental

Benzylation of Adenine——A mixture of adenine (20 g), benzyl bromide (50.6 g) and DMF (100 ml) was stirred at 100° for 3 hr and the reaction mixture was evaporated to dryness *in vacuo*. The residue was dissolved in hot EtOH (150 ml) and the solution was cooled to 0°. Recrystallization of the crystals appeared gave Ia–HBr (37.9 g, 83.8%), mp 273—275.5°, UV $\lambda_{max}^{H_2O}$ mμ: pH 1, 274.5; pH 7, 272; pH 13, 272. *Anal.* Calcd. for $C_{12}H_{11}N_5 \cdot HBr$: C, 47.06; H, 3.92; N, 22.89. Found: C, 47.44; H, 4.07; N, 23.39. To the mother liquor was added NH_4OH at 0° and the solvent was removed. Chromatography on the residue of silica gel gave Ia (1.2 g, 2.7%), IIa (2.6 g, 5.7%) [mp 230°, UV $\lambda_{max}^{H_2O}$ mμ: pH 1, 259; pH 7. 261; pH 13, 261], and 1,9-dibenzyladenine (0.2 g, 0.36%), mp 170—172°. UV $\lambda_{max}^{H_2O}$ mμ(ε): pH 1, 267 (21500); pH 7, 270 (22000); pH 13, 270.5 (21500). *Anal.* Calcd. for $C_{19}H_{17}N_5$: C, 72.36; H, 5.43; N, 22.21. Found: C, 71.92; H, 5.52; N, 22.35.

Benzyl Migration of Ia——Ia-HBr (180 mg) was heated in DMA (2 ml) at 110° for 38 hr and additionally at 170—180° for 44 hr. The reaction mixture was neutralized with NH_4OH, the solvent was evaporated, and the $CHCl_3$–MeOH solution of the residue was chromatographed on silica gel (4 g). The fraction eluted with $CHCl_3$–MeOH (98:2) on recrystallization from EtOH gave IIa (40 mg, 30%), mp 230°, which was identified with the authentic sample[17] in infrared spectrum (IR) and ultraviolet spectrum (UV).

Ribosyl Migration of Ib——Ib (58 mg) was heated with $HgBr_2$ (36 mg) in a mixture of xylene (0.5 ml) and DMA (0.1 ml) under reflux for 75 min, and the solvent was evaporated *in vacuo*. The residue was extracted with $CHCl_3$ and the solution was washed with 30% KI and H_2O, dried and evaporated to dryness. The crude product was heated in 0.05N NaOMe/MeOH under reflux for 30 min and the solvent was evaporated. After washed with ether, the residue was dissolved in H_2O and the solution was neutralized by addition of IRC 50 (H^+) resin which was then removed by filtration. The filtrate was chromatographed on Dowex-1 (OH^-) (5 ml). The first fraction eluted with H_2O–MeOH (70:30, 80—160 ml) gave a small amount (0.8%) of a substance (UV $\lambda_{max}^{H_2O}$: 260 mμ), and the second fraction (180—400 ml) gave β-adenosine (total $OD_{260}=290$, 20%).

Glucosyl Migration of Ic——Ic (93 mg) was heated with $HgBr_2$ (72 mg) in a mixture of xylene (1 ml), DMA (0.1 ml) and nitrobenzene (0.1 ml) at 150° for 90 min. After removal of the solvent, the residue was post-treated as described above and deacetylated in 0.05N NaOMe/MeOH (2 ml). H_2O solution of the deacetylated derivative was applied to Dowex-50 (H^+) column (2 ml) and the column was eluted with 1N NH_4OH. UV-absorbing fraction was evaporated to dryness and chromatographed on Dowex-1 (OH^-) (10 ml). The fraction eluted with H_2O–MeOH (70:30, 70—340 ml) gave 9-β-D-glucopyranosyladenine (11 mg, 18%) which was confirmed by undepression of the mixed melting point with an authentic sample.[18]

Ribosylation of N^6,N^6-Dimethyladenine——A mixture of N^6,N^6-dimethyladenine (490 mg) and 2,3,5-tri-O-benzoylribofuranosyl bromide[19] (prepared from 1.51 g of the acetate and 9 ml of HBr/AcOH) in CH_3CN (7 ml) was heated at 60—65° for 18 hr. The reaction mixture was treated with NH_4OH and the solvent was evaporated. $CHCl_3$ solution of the residue was chromatographed on silica gel (22 g). The first fraction eluted with $CHCl_3$–MeOH (99:1) on evaporation of the solvent gave IVb (200 mg, 11%), amorph, UV λ_{max}^{EtOH}: 230 and 275 mμ which was debenzoylated with 0.05N NaOMe/MeOH to give 9-β-D-ribofuranosyl-N^6,N^6-dimethyladenine,[5] mp 184°. UV $\lambda_{max}^{H_2O}$ mμ: pH 1, 269; pH 7, 275; pH 13, 275. $pK_{a'}$: 3.83. The second fraction eluted with $CHCl_3$–MeOH (99:1) gave IIIb (630 mg. 36,4%), amorph. UV λ_{max}^{EtOH}: 231 and 305 mμ; $\lambda_{max}^{HCl/EtOH}$: 231 and 295 mμ. *Anal.* Calcd. for $C_{33}H_{29}O_7N_5$: C, 65.23; H, 4.81; N, 11.53. Found: C, 64.95; H, 4.86; N, 11.55. Debenzoylation of IIIb (200 mg) with 0.05N NaOMe/MeOH (10 ml) gave 3-β-D-ribofuranosyl-N^6,N^6-dimethyladenine[5] (45 mg, 46%), mp 204°. UV $\lambda_{max}^{H_2O}$ mμ(ε): pH1, 230 (9050, sh) and 292 (24200); pH 7, 225 (14800) and 297 (19100); pH 13, 228 (13100) and 297.5 (19100). NMR: $H_1'=5.89$ ppm ($J_{1'-2'}=6$ cps) from TMS in DMSO-d_6. pKa': 5.65. *Anal.* Calcd. for $C_{12}H_{17}O_4N_5$: C, 48.80; H, 5.80; N, 23.72. Found: C, 48.70; H, 5.86; N, 23.45. The fraction eluted with $CHCl_3$–MeOH (95:5) from silica gel column gave a unknown substance (100 mg), mp 196—198°. UV λ_{max}^{EtOH}: 230 and 302 mμ, $\lambda_{max}^{HCl/EtOH}$: 231 and 295 mμ. *Anal.* Found: C, 64.98; H, 4.96; N, 11.84. Debenzoylated derivative of this compound exhibited the UV spectra of 9-ribosyl-N^6,N^6-dimethyladenine.

Ribosyl Migration of IIIb——IIIb (304 mg) was heated with $HgBr_2$ (180 mg) in a mixture of xylene (2 ml) and DMA (0.2 ml) at 100° for 1.5 hr and additionally at 130—140° for 2 hr, and the reaction mixture was evaporated to dryness. The $CHCl_3$ solution of the residue was washed with 30% KI and H_2O, dried and chromatographed on silica gel (10 g). The fraction eluted with $CHCl_3$ gave IVb (110 mg, 36%) which was

17) Part 1: B. Shimizu and M, Miyaki, *Chem. Pharm. Bull.* (Tokyo), **18**, 570 (1970).
18) T. Nishimura, B. Shimizu and I. Iwai, *Chem. Pharm. Bull.* (Tokyo), **12**, 1471 (1964).
19) J.D. Stevens, R.K. Ness and H.G. Fletcher, Jr., *J. Org. Chem.*, **33**, 1806 (1968).

debenzoylated with NaOMe. Recrystallization of the debenzoylated product from acetone gave 9-β-D-ribofuranosyl-N^6,N^6-dimethyladenine (78%),[5] mp 183—184.5°. UV $\lambda_{max}^{H_2O}$ mμ (ε): pH 1, 268.5 (20200); pH 7, 275 (20600); pH 13, 275 (20800). NMR: H_1'=5.9 ppm ($J_{1'-2'}$=6 cps) from TMS in DMSO-d_6. *Anal.* Calcd. for $C_{12}H_{17}O_4N_5$: C, 48.80; H, 5.80; N, 23.72. Found: C, 48.52; H, 5.98; N, 23.47.

Benzylation of N^6,N^6-Dimethyladenine——A mixture of N^6,N^6-dimethyladenine (490 mg) and benzyl bromide (520 mg) in DMA (5 ml) was heated at 110° for 7 hr. After addition of NH_4OH, the solvent was evaporated and the $CHCl_3$ solution of the residue was chromatographed on silica gel (15 g). The fraction eluted with $CHCl_3$–MeOH (99:1) on recrystallization gave IVa (38 mg, 5%), mp 126°. UV $\lambda_{max}^{H_2O}$ mμ: pH 1, 268.5; pH 7, 277; pH 13, 277. *Anal.* Calcd. for $C_{14}H_{15}N_5$: C, 66.38; H, 5.97; N, 27.65. Found: C, 66.53; H, 5.90; N, 27.47. The fraction eluted with $CHCl_3$–MeOH (98:2) on recrystallization gave IIIa (554 mg, 66%), mp 142°. UV $\lambda_{max}^{H_2O}$ mμ (ε): pH 1, 291 (21000); pH 7, 295 (16400); pH 13, 295 (15800).

Benzyl Migration of IIIa——IIIa–HBr (360 mg) was heated in DMF (2 ml) at 150° for 40 hr. After addition of NH_4OH, the solvent was evaporated to dryness. The $CHCl_3$ extract of the residue was chromatographed on silica gel (6 g). The fraction eluted with benzene–$CHCl_3$ (50:50) and $CHCl_3$ on recrystallization gave IVa (60 mg, 22%), mp 128—129°. UV $\lambda_{max}^{H_2O}$ mμ (ε): pH 1, 268.5 (21200); pH 7, 277 (18900); pH 13, 277 (19500). *Anal.* Calcd. for $C_{14}H_{15}N_5$: C, 66.38; H, 5.97; N, 27.65. Found: C, 66.27; H, 6.09; N, 28.04.

Ribosylation of N^2-Acetylguanine——A mixture of N^2-acetylguanine (4.45 g) and 2,3,5-tri-O-benzoyl-D-ribofuranosyl bromide (prepared from 11.6 g of the acetate) in DMA (180 ml) was stirred at 60—65° for 40 hr. After addition of NH_4OH, the reaction mixture was evaporated to dryness. The $CHCl_3$ extract of the residue was chromatographed on silica gel (150 g). The first fraction eluted with $CHCl_3$–MeOH (98:2) on evaporation of the solvent gave VIIb (592 mg, 4.0%), amorph. UV λ_{max}^{EtOH} mμ (ε): 231 (46500), 252 (20600), 260 (19400), 275 (15100) and 282 (14700). *Anal.* Calcd. for $C_{33}H_{27}O_9N_5$: C, 62.16; H, 4.24; N, 10.99. Found: C, 61.80; H, 4.46; N, 10.69. 250 mg of VIIb was heated in 0.1N NaOMe/MeOH (12 ml) under reflux for 30 min and the solvent was removed. After washing with ether, the residue was dissolved in H_2O (3 ml) and the solution was neutralized with 2N AcOH. Recrystallization of the precipitate appeared gave 9-β-D-ribofuranosylguanine (82 mg, 72%), mp 237° (decomp.). UV $\lambda_{max}^{H_2O}$ mμ (ε): pH 1, 254.5 (12000) and 278 (8150, sh); pH 7, 252.5 (14100) and 272 (9700, sh); pH 13, 257 (12300) and 265 (12400). pK_a': 2.11 and 9.23. NMR: H_1'=5.73 ppm ($J_{1'-2'}$=5.8 cps) from TMS in DMSO-d_6. *Anal.* Calcd. for $C_{10}H_{13}O_5N_5 \cdot 1/2\ H_2O$: C, 41.10; H, 4.79; N, 23.97. Found: C, 41.64; H, 4.94; N, 23.96. These values were similar to those of the authentic sample of guanosine.

The second fraction eluted with $CHCl_3$–MeOH (98:2) from silica gel column was rechromatographed on alumina. The first fraction eluted with acetone–MeOH (99:1–95:5) gave VIIb (2.2 g, 15%). The second fraction gave VIb (3.1 g, 21%), amorph. UV λ_{max}^{EtOH} mμ (ε): 225.5 (52400), 265.5 (16500), 275 (15300, sh) and 283 (13300, sh). *Anal.* Calcd. for $C_{33}H_{27}O_9N_5$: C, 62.16; H, 4.24; N, 10.99. Found: C, 61.61; H, 4.48; N, 10.69. 404 mg of VIb was deacetylated and recrystallized from H_2O to give 7-β-D-ribofuranosylguanine (156 mg, 87%), mp 250° (decomp.). UV $\lambda_{max}^{H_2O}$ mμ (ε): pH 1, 249.5 (10300) and 271 (7200, sh); pH 7, 244 (6700) and 286 (7900); pH 13, 240 (7600, sh) and 282 (6900). pK_a': 2.89 and 9.16. NMR: H_1'=6.04 ppm ($J_{1'-2'}$=5.3 cps) from TMS in DMSO-d_6. $[\alpha]_D^{20}$: −17° (c=1.0 in 0.1N NaOH). *Anal.* Calcd. for $C_{10}H_{13}O_5N_5$: C, 42.40; H, 4.63; N, 24.73. Found: C, 42.67; H, 4.93; N, 24.61.

The fraction eluted with $CHCl_3$–MeOH (97:3) from silica gel column gave a substance (500 mg, 3.4%) (UV λ_{max}^{EtOH}: 229, 266.5, 275 (sh) and 283 (sh) mμ) which was assumed to be the α-anomer of VIb. The another fraction eluted with $CHCl_3$–MeOH (97:3) gave a substance (480 mg, 3.3%) (UV λ_{max}^{EtOH}: 230, 254, 262, 275 and 282 mμ) which was assumed to be the α-anomer of VIIb. These compounds, however, were not investigated further.

Benzylation of N^2-Acetylguanine——A mixture of N^2-acetylguanine (975 mg) and benzyl bromide (865 mg) in DMA (32 ml) was heated at 90° for 7 hr with stirring. After addition of NH_4OH, the solvent was evaporated *in vacuo*. The residue was extracted with a mixture of $CHCl_3$ and acetone and the extract was chromatographed on silica gel (30 g). The first fraction eluted with $CHCl_3$–MeOH (98:2) gave Va (3 mg, 0.2%). UV $\lambda_{max}^{H_2O}$ mμ: pH 1, 265; pH 7, 227 and 270; pH 13, 229 and 276.5. The *Rf* value of thin-layer chromatography (TLC) was similar to that of an authentic sample described below. The second fraction eluted with the same solvent gave VIa (320 mg, 22.4%), mp 239—241°. UV $\lambda_{max}^{H_2O}$ mμ (ε): pH 1, 263.5 (19500); pH 7, 222 (21800) and 265 (15900); pH 13, 222.5 (26800) and 269 (11700). *Anal.* Calcd. for $C_{14}H_{13}O_2N_5$: C, 59.35; H, 4.63; N, 24.72. Found: C, 59.40; H, 4.91; N, 24.44. The fraction eluted with $CHCl_3$–MeOH (96:4) gave VIIa (235 mg, 16.4%), mp 227—229°. UV $\lambda_{max}^{H_2O}$ mμ (ε): pH 1, 263 (20800); pH 7, 257 (18700, sh), 261 (19100) and 283 (11700, sh); pH 13, 264 (14200). *Anal.* Found: C, 59.04; H, 4.66; N, 24.63.

3-Benzyl-2-mercaptopurine-6-one——5,6-Diamino-1-benzyl-4-hydroxypyrimidine-(1H)-thione[7] was heated in 98% formic acid under reflux for 2 hr and the reaction mixture was evaporated to dryness. The solution of the residue in formamide was heated at 180° for 2 hr and the solvent was removed. Recrystallization of the residue from EtOH gave 3-benzyl-2-mercaptopurine-6-one, mp 300°. UV $\lambda_{max}^{H_2O}$ mμ (ε): pH 1, 233 (15900) and 287 (20800); pH 7, 234 (15000) and 288 (19800); pH 13, 246.5 (29200) and 297 (17000). *Anal.* Calcd. for $C_{12}H_{10}ON_4S$: C, 55.81; H, 3.88; N, 21.71. Found: C, 55.60; H, 4.01; N, 21.57.

3-Benzyl-2-methylthiopurine-6-one——To a solution of 3-benzyl-2-mercaptopurine-6-one (100 mg) in 2N NaOH (0.39 ml) was added Me_2SO_4 (54 mg) and the mixture was stirred at 25° for 1 hr. The reaction

mixture was neutralized with AcOH and allowed to stand at 0° for 1 hr. The precipitates appeared were collected, washed with H_2O and recrystallized from aqueous EtOH (100 mg, 96%), mp 278°. UV $\lambda_{max}^{H_2O}$ mμ (ε): pH 1, 237 (5300, sh) and 271 (11700); pH 7, 240 (19100) and 279 (13400); pH 13, 237 (21200) and 284 (13500). *Anal.* Calcd. for $C_{13}H_{12}ON_4S$: C, 57.35; H, 4.41; N, 20.59. Found: C, 57.01; H, 4.60; N, 20.44.

3-Benzylguanine and 3-Benzyl-N²-acetylguanine (Va)——3-Benzyl-2-methylthiopurine-6-one (100 mg) was heated in formamide (2.5 ml) under reflux for 2 hr and formamide was evaporated. The residue was heated in acetic anhydride (2 ml) under reflux for 2 hr and acetic anhydride was removed by distillation. The resulting crude product was purified by the use of silica gel column (10 g). The fraction eluted with $CHCl_3$–MeOH (98:2) on recrystallization from acetone gave Va (58 mg, 55%), mp 282—285°. UV $\lambda_{max}^{H_2O}$ mμ (ε): pH 1, 265 (13500); pH 7, 227 (15100) and 270 (14900); pH 13, 229 (15800) and 276.5 (15500). *Anal.* Calcd. for $C_{14}H_{13}O_2N_5$: C, 59.35; H, 4.63; N, 24.72. Found: C, 59.54; H, 4.70; N, 24.77. A solution of Va (52 mg) in 0.1N NaOMe/MeOH (5 ml) was heated under reflux for 80 min. The reaction mixture was neutralized with 2N AcOH and allowed to stand at 0° for 15 hr. The crystals appeared were collected by centrifugation, washed with H_2O and acetone and dried at 100° *in vacuo* to give 3-benzylguanine (41 mg, 92%), mp 340° (decomp). UV $\lambda_{max}^{H_2O}$ mμ (ε): pH 1, 243 (8200, sh) and 263 (12500); pH 7, 326 (11100) and 268.5 (12900); pH 13, 274 (14200). pK_a': 4.00 and 9.70. *Anal.* Calcd. for $C_{12}H_{11}ON_5$: C, 59.74; H, 4.60; N, 29.03. Found: C, 59.65; H, 4.88; N, 28.67.

Benzyl Migration of Va——To the solution of Va (570 mg) in a mixture of $CHCl_3$ and EtOH was added 30% HBr/AcOH (0.5 ml) at 0° and the solvent was evaporated *in vacuo*. The resulting HBr salt was heated in DMF (20 ml) at 100—110° for 24 hr, and the reaction mixture was treated with NH_4OH and evaporated to dryness. The residue was extracted with a mixture of $CHCl_3$ and MeOH, and the extract was chromatographed on silica gel. Va (20 mg, 3.5%) was recovered from the first fraction eluted with $CHCl_3$. The second fraction eluted with $CHCl_3$ gave VIa (60 mg, 10.5%), mp 240—242. UV $\lambda_{max}^{H_2O}$ mμ: pH 1, 264; pH 7, 266; pH 13, 269. *Anal.* Calcd. for $C_{14}H_{13}O_2N_5$: C, 59.35; H, 4.63; N, 24.72. Found: C, 59.93; H, 4.86; N, 24.67. Deacetylation of this compound (50 mg) with 0.1N NaOMe (5 ml) gave 7-benzylguanine (38 mg, 88%), mp >380°. UV $\lambda_{max}^{H_2O}$ mμ (ε): pH 1, 251 (11600) and 275 (7100, sh); pH 7, 248, 6600, sh) and 284.5 (7300); pH 13, 242 (7500, sh) and 281.5 (7400). pK_a': 3.44 and 9.85. *Anal.* Calcd. for $C_{12}H_{11}ON_5$: C, 59.76; H, 4.75; N, 28.71. Found: C, 59.74; H, 4.60; N, 29.03. The third fraction gave VIIa (60 mg, 10.5%), mp 224—228°. UV $\lambda_{max}^{H_2O}$ mμ: pH 1, 264.5; pH 7, 258 (sh), 262 and 284 (sh); pH 13, 266. *Anal.* Found: C, 59.45; H, 4.69; N, 24.08. Deacetylation of VIIa (50 mg) with NaOMe gave 9-benzylguanine (32 mg, 75%), mp 301—304°. UV $\lambda_{max}^{H_2O}$ mμ (ε): pH 1, 255.5 (13300) and 279 (8800); pH 7, 253 (14100) and 272 (10300, sh); pH 13, 258 (10900, sh) and 268.5 (11600). pK_a': 284 and 9.82. *Anal.* Found: C, 59.85; H, 4.78; N, 28.39.

N²-Acetylguanine-8-^{14}C——A mixture of guanine-8-^{14}C (0.1 Ci), cold guanine (1 g) and acetic anhydride (50 ml) was refluxed for 12 hr and allowed to stand at room temperature over night. The crystals appeared was collected by filtration and dissolved in hot H_2O–EtOH together with the cold N²-acetylguanine (2 g). The insoluble material was filtered off and the filtrate was concentrated and cooled to give the crystals which was recrystallized from H_2O–EtOH. Radioactivity: 1.34×10^{10} dpm/mole.

Benzyl Migration of Va in the Presence of N²-Acetylguanine-8-^{14}C——To the solution of Va (100 mg) in a mixture of $CHCl_3$–EtOH was added 35% HBr/AcOH (0.1 ml) and the solvent was evaporated *in vacuo*. After azeotropic distillation of DMA solution of the residue, the resulting Va-HBr was heated with N²-acetylguanine-8-^{14}C (1.34×10^{10} dpm/mole, 68 mg) in DMA (1.8 ml) at 130° for 20 hr. The reaction mixture was treated with NH_4OH and the solvent was removed. The residue was extracted with $CHCl_3$ and the insoluble material was recrystallized from H_2O to give N²-acetylguanine (40 mg, 59% recovery), radioactivity: 6.1×10^9 dpm/mole. The $CHCl_3$ extract was chromatographed on silica gel (20 g). The first fraction eluted with $CHCl_3$–MeOH (97:3) on recrystallization from acetone gave radioactive VIa (28 mg, 28%), mp 240°, radioactivity: 7.1×10^9 dpm/mole. The second fraction on recrystallization from acetone gave radioactive VIIa (30 mg, 30%), mp 225—227°, radioactivity: 7.5×10^9 dpm/mole.

Benzyl Migration of VIa——A mixture of VIa (270 mg) and 30% HBr/AcOH (0.25 ml) was heated in DMA (3 ml) at 140—150° for 80 hr. After addition of NH_4OH, the reaction mixture was evaporated to dryness. The $CHCl_3$-extract of the residue was chromatographed on silica gel (8 g). The fraction eluted with $CHCl_3$–MeOH (98:2) on recrystallization from EtOH gave VIa (65 mg, 24%), mp 236°. *Anal.* Calcd. for $C_{14}H_{13}O_2N_5$: C, 59.35; H, 4.63; N, 24.72. Found: C, 59.53; H, 4.56; N, 25.18. The fraction eluted with $CHCl_3$–MeOH (97:3) on recrystallization from EtOH gave VIIa (114 mg, 42%), mp 225°. *Anal.* Found: C, 59.06; H, 4.72; N, 24.48.

Benzyl Migration of VIIa——A mixture of VIIa (54 mg) and 30% HBr/AcOH (0.05 ml) was heated in DMA at 150° for 72 hr. Treatment of the reaction mixture by the same manner as that described above gave VIa (12 mg, 22%), mp 239° [*Anal.* Found: C, 58.96; H, 4.79; N, 24.50] and VIIa (28 mg, 52%), mp 228° [*Anal.* Found: C, 59.21; H, 4.60; N, 24.52].

Ribosyl Migration of VIb and VIIb——A mixture of VIb (106 mg), $HgBr_2$ (80 mg) and nitrobenzene (0.5 ml) was heated at 160° for 30 min and evaporated to dryness. $CHCl_3$–extract of the residue was washed with 30% KI and H_2O, dried and concentrated. TLC [on silica gel in $CHCl_3$–MeOH (95:5)] of the solution showed two main spots and the *Rf* values were similar to that for the authentic sample of VIb (0.53) and VIIb (0.42),

respectively. When VIIb was heated with $HgBr_2$ the two main spots corresponding to VIb and VIIb were observed on the TLC chromatogram.

Benzylation of Purine——(a) A solution of purine (600 mg) and benzyl bromide (1.025 g) in DMA (5 ml) was heated at 80° for 2 hr. After addition of NH_4OH at 0°, the reaction mixture was evaporated to dryness and the $CHCl_3$–extract of the residue was chromatographed on silica gel (25 g). The fraction eluted with $CHCl_3$–MeOH (99:1) on recrystallization from ether–*n*-hexane gave XI (35 mg, 3%), mp 90—95°. UV $\lambda_{max}^{H_2O}$ mμ (ε): pH 1, 263 (6260); pH 7, 263.5 (7780); pH 13, 263 (8340). *Anal.* Calcd. for $C_{12}H_{10}N_4$: C, 68.55; H, 4.79; N, 26.65. Found: C, 68.31; H, 4.90; N, 26.49. Rechromatography of the fraction eluted with $CHCl_3$–MeOH (98:2) gave X (12 mg, 1%) and VIII (145 mg, 14%). X: mp 144—145° (from ether). UV $\lambda_{max}^{H_2O}$ mμ (ε): pH 1, 258.5 (6490); pH 7, 266 (8180); pH 13, 266.5 (7940). *Anal.* Found: C, 68.30; H, 4.94; N, 26.76. VIII: mp 123—124° (from ether–*n*-hexane). UV $\lambda_{max}^{H_2O}$ mμ (ε): pH 1, 276 (9930); pH 7, 277.5 (7290); pH 11, 278 (7010). *Anal.* Found: C, 68.25; H, 4.62; N, 26.36. The fraction eluted with $CHCl_3$–MeOH (97:3—95:5) on recrystallization from acetone gave IX (470 mg, 45%), mp 206—209°. UV $\lambda_{max}^{H_2O}$ mμ (ε): pH 1, 268 (7900); pH 7, 222 (34500) and 275.5 (7800); pH 11, 222 (34800) and 276 (7700). *Anal.* Found: C, 68.36; H, 4.88; N, 26.48.

(b) A solution of purine (120 mg) and benzyl bromide (171 mg) in DMA (2 ml) was heated at 140° for 48 hr. After addition of NH_4OH at 0°, the reaction mixture was evaporated to dryness and the $CHCl_3$ solution of the residue was chromatographed on silica gel (4 g). The fraction eluted with $CHCl_3$ gave XI (70 mg, 33%) and the fraction eluted with $CHCl_3$–MeOH (99.5:0.5) gave X (31 mg, 15%).

Benzyl Migration of VIII——A mixture of VIII (150 mg) and 30% HBr/AcOH (0.15 ml) in $CHCl_3$ was evaporated to dryness below 40°. The resulting HBr salt heated in DMA (1.5 ml) at 110° for 40 hr. Formation of IX, X, XI were proved by TLC and the spot for IX disappeared after the prolonged heating. To the reaction mixture was added NH_4OH and the solvent was removed. The $CHCl_3$ solution of the residue was chromatographed on silica gel (5 g). The fraction eluted with $CHCl_3$ gave XI (25 mg, 17%) and the fraction eluted with $CHCl_3$–MeOH (99:1) gave X (10 mg, 7%). These derivatives were identified by mixed melting with the authentic samples, respectively.

Benzyl Migration of IX——A mixture of IX (90 mg) and 30% HBr/AcOH (0.15 ml) in $CHCl_3$–EtOH was evaporated to dryness *in vacuo*. The resulting HBr salt was heated at 110° for 40 hr and the reaction mixture was post-treated as described above. Chromatography on silica gel (3 g) of the products gave XI (16 mg, 17%) and X (6 mg, 7%).

Acknowledgement The authors are indebted to Dr. G. Sunagawa, Director of this Laboratories, and Dr. I. Iwai for their encouragement through the course of this work. They are grateful to Dr. T. Nishimura for valuable discussion, and Mr. A. Saito for (his) technical assistance.

Thanks are also due Mr. H. Kuwano for NMR studies, and Dr. K. Okamoto for MO Calculations.