THE DIMROTH REARRANGEMENT IN THE ADENINE SERIES: A REVIEW UPDATED

Tozo Fujii* and Taisuke Itaya

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

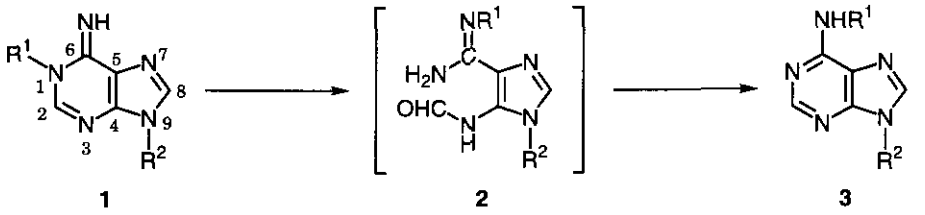
Abstract—Advances in the Dimroth rearrangement in the adenine series are reviewed with 212 reference citations.

CONTENTS

I. INTRODUCTION

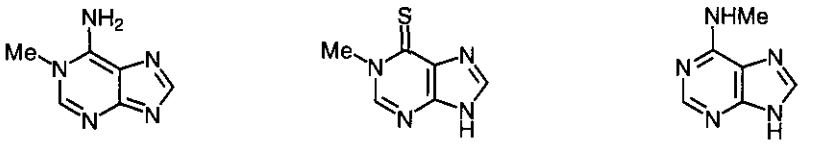
The ring system isomerization process that involves ring fission and subsequent recyclization, whereby a heterocyclic nitrogen and its attached substituent exchange places with an α-amino or α-imino group, is commonly known as the Dimroth rearrangement;[1] a term that was coined by Brown and Harper[2] in 1963 for the "amidine rearrangement".[1a,3] Since the first observation (with no explanation) of Rathke in 1888 on a triazine derivative,[4] followed by that (with an eventually correct mechanistic interpretation) of Dimroth in 1909 on a triazole derivative,[5] this type of rearrangement has been found to occur in many heterocyclic systems;[1] and perhaps the most intensively studied examples were those in the pyrimidine series.[1]

In the adenine series, N(1)-substituted derivatives [*e. g.*, type **1** (where R^2 can be H)] commonly undergo Dimroth rearrangement under basic conditions, accommodating the N(1)-substituent on the exocyclic nitrogen (N^6) (type **3**) (Scheme 1).[1,6] This has often been the basis for synthesis of N^6-substituted adenines. However, no ring-opened inter-



1 2 3

Scheme 1



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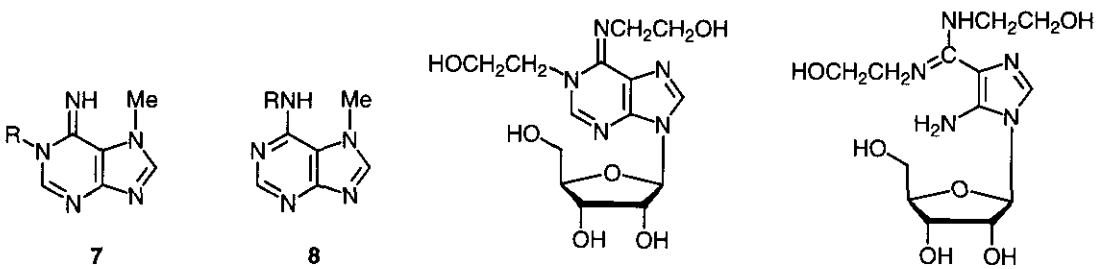
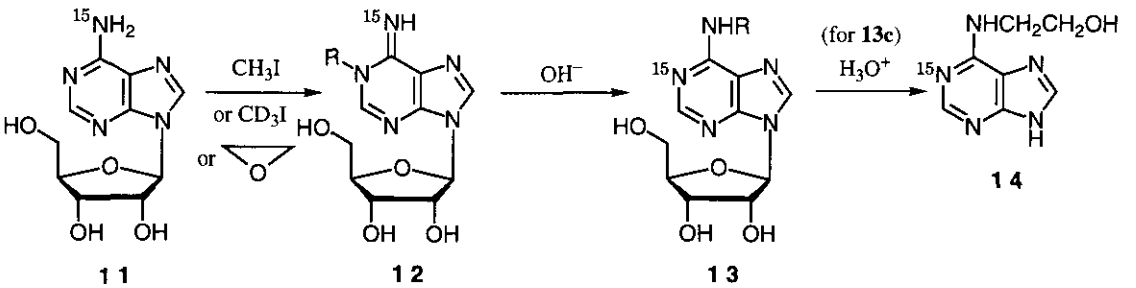


7 8 9 10



11 12 13 14

a: R = CH_3 **b**: R = CD_3 **c**: R = $HOCH_2CH_2$

Scheme 2

mediates (type **2**) have been directly detected.[1a,7,8] Earlier work on such rearrangements of the adenine lineage was included in two reviews[1] that appeared in the period 1968–1969. Since that time, special phases of the subject have been summarized in several forms.[6,9] The present review article aims at supplementing the previous ones[1,6,9] by updating the literature through mid-1997.

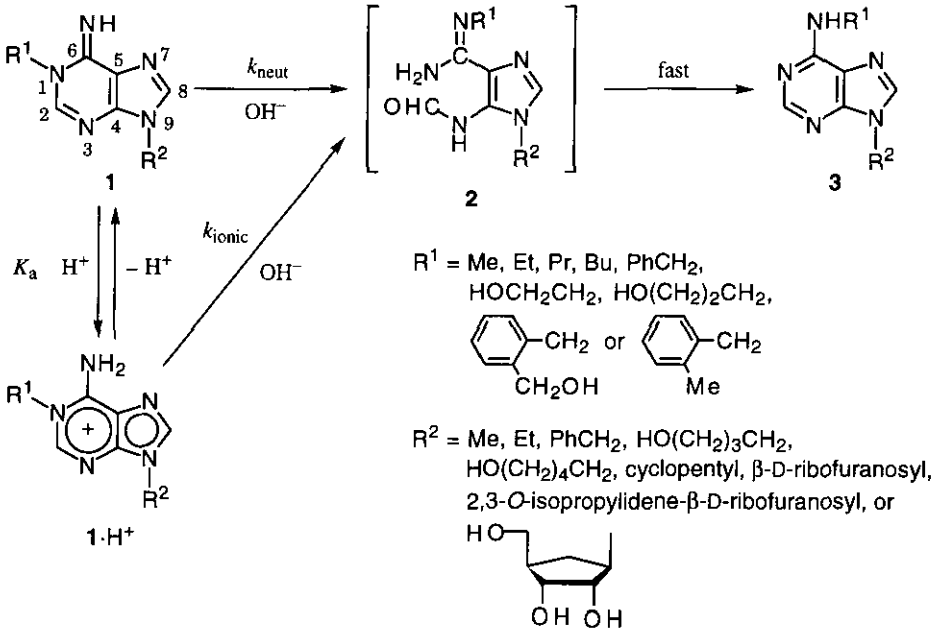
II. MECHANISM OF THE DIMROTH REARRANGEMENT

In an attempt to prepare 1-methyladenine (**4**) by heating 1,6-dihydro-1-methyl-6-thiopurine (**5**) with ethanolic NH_3 at 155°C for 24 h, Elion[10] obtained N^6-methyladenine (**6**) and explained its formation in terms of rearrangement (under these conditions) of **4** once formed.[10b] This view was based on the work of Brookes and Lawley,[11] who found that **4** rearranged to **6** in over 80% yield by heating at 100°C in concd aqueous NH_3 for 18 h. Elion[10b] further explained that this rearrangement appeared to involve opening of the N(1)–C(2) bond and subsequent reclosure as shown in Scheme 1 (R^1 = Me; R^2 = H). A similar mechanism was considered by Taylor and Loeffler[12] for the rearrangement of 1-substituted 7-methyladenines (**7**: R = Me, Bu, or D-1-sorbityl) in boiling H_2O to give N^6-substituted 7-methyladenines (**8**: R = Me, Bu, or D-1-sorbityl). A large probability of the initial ring opening in the Dimroth rearrangement in this series was indirectly demonstrated by Windmueller and Kaplan,[13] who found that N^6,1-bis(2-hydroxyethyl)adenosine (**9**) could not rearrange in dilute alkali, but an intermediate ring-opened product was deformylated to form a diazotizable aminoimidazole (**10**).

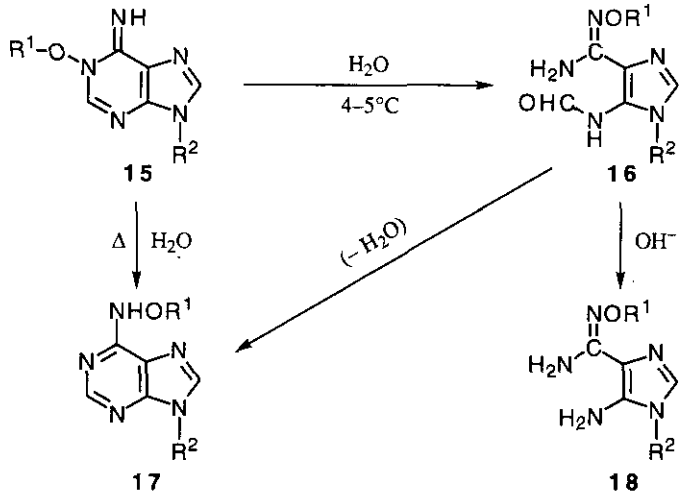
Place exchange between the ring and exocyclic nitrogens in the Dimroth rearrangement has been confirmed by experiments using [6-^{15}N]-labeled adenosine (**11**) (Scheme 2). Wilson and McCloskey[14] separately alkylated **11** with CH_3I and CD_3I to obtain **12a** and **12b**, respectively. The N(1)-alkylated derivatives (**12a** and **12b**) were then treated under Dimroth rearrangement conditions, and the correctness of the [1-^{15}N]-labeled structures of the products (**13a** and **13b**) was supported by comparison of their MS data. Engel[15] also obtained **13a** from **11** through **12a** in a similar manner and established the [1-^{15}N]-labeled structure of **13a** by means of NMR spectroscopy. Later on, Grenner and Schmidt[16] obtained **14** from **11** through **12c** and **13c** and confirmed the [1-^{15}N]-labeled structure of **14** by means of MS.

In a kinetic approach to the mechanistic problem, Fujii's group has found that the rearrangement of 9-substituted 1-alkyladenines (**1**) to the N^6-alkyl isomers (**3**) at 40°C proceeds by a mechanism involving a rate-determining initial ring opening, caused by attack of hydroxide ion on both the protonated (**1**·H^+) and the neutral species (**1**) at the 2-position, and a subsequent fast ring closure of the putative monocyclic intermediates (**2**) (Scheme 3).[8,9d,17] This is in general agreement with the mechanism which Macon and Wolfenden[7] proposed for the Dimroth rearrangement of 1-methyladenosine (**1**: R^1 = Me; R^2 = β-D-ribofuranosyl) to produce N^6-methyladenosine (**3**: R^1 = Me; R^2 = β-D-

ribofuranosyl) at 25°C. The hydroxide attack on the protonated species is much faster than that on the neutral species (by a factor of 90–1100),[7,8,9d,17] and the former is influenced by the electronic effect of a substituent at the 1-position, whereas the latter is influenced by the steric effect.[17a,c] Interestingly, the electron-withdrawing β-D-ribofuranosyl group at the 9-position accelerates the ring opening of both the protonated and the neutral species.[17a,b]

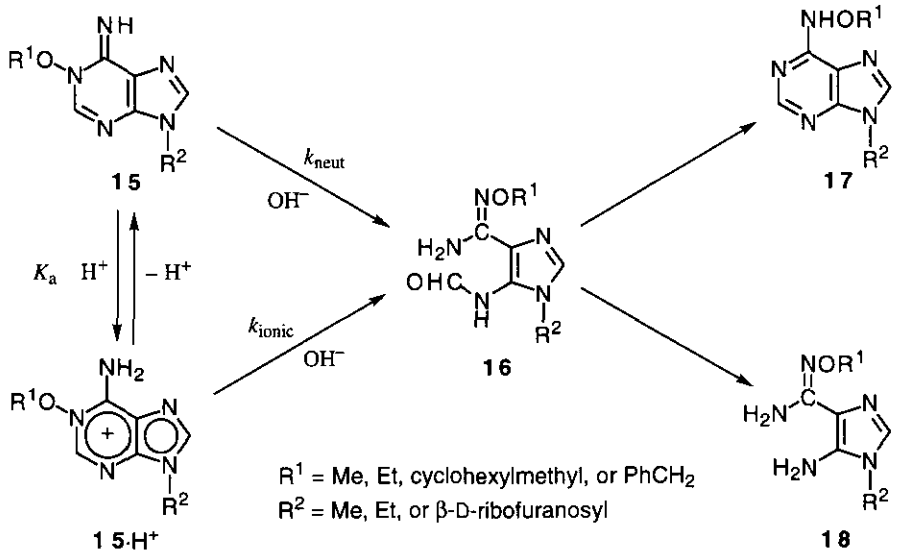


Scheme 3



Scheme 4

The first isolation of a Dimroth intermediate in the adenine series was realized by Fujii and co-workers in the case of 1-alkoxyadenine derivatives (type **15**):[18] On treatment with H_2O at 4–5°C, the free base (**15**) underwent ring opening to give the monocycle (**16**), which recyclized to the rearranged product (**17**) when heated in H_2O (Scheme 4). Treatment of **15** with boiling H_2O completed this rearrangement to **17** in a one-step manner.[18] The reaction of **15** or **16** with hot aqueous alkali gave the deformylated monocycle (**18**) as the main product.[18b] The process **15**→**16**→**17** represents itself to be a genuine Dimroth rearrangement, and a positive answer to the age-old question as to the intermediacy of the ring-opened derivative (type **16**) was further given from the kinetic study of this process, as described below.

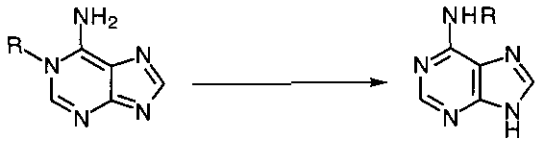


Scheme 5

Fujii's group[19] found that the initial ring opening of the 1-alkoxyadenine derivatives (**15**) is also caused by two modes of hydroxide attack (Scheme 5), as in the case of the 1-alkyladenine derivatives (**1**), and that the rate (k_{ionic}) of attack of hydroxide ion on the protonated species (**15**·H^+) is faster than that (k_{neut}) of hydroxide attack on the neutral species (**15**) by a factor of 560–1200. However, both rates are faster than those observed for the corresponding 1-alkyladenine derivatives (**1**) by a factor of 6–38, respectively.[17a,19] At pH 7.80 and above, the rates of recyclization of **16** to **17** and of the hydrolysis of **16** to **18** were comparable to each other, and the sum of them did not exceed one eighth of the rate of the ring opening of **15**, presenting a striking contrast to the feature of the Dimroth rearrangement of the 1-alkyl analogues (**1**) (Scheme 3).[8,19] Thus, the acceleration of the ring opening step and retardation of the recyclization step observed for the 1-alkoxy analogues (**15**) could be attributed directly to the electron-withdrawing nature of the N(1)-alkoxy group.

III. EXAMPLES IN 1-MONOSUBSTITUTED ADENINES

Good examples of Dimroth rearrangement under this category (**19**→**20**) (Scheme 6) are listed in Table I.[11,20–29]



19 **20**

Scheme 6

TABLE I. Rearrangement of 1-Monosubstituted Adenines (**19**) to the N^6-Isomers (**20**)

19 → **20**	Reaction conditions			Yield of **20** (%)	Literature (ref. No.)
R	Solvent	Temp. (°C)	Time (h)		
Me	concd NH_4OH	100	18	>80	(11)
Me	H_2O (pH 7.2)	100	18	96	(20)
Me	0.2 N NaOH	95–100	4	65	(21)
Et	0.2 N NaOH	100	7	91	(22)
$Me_2C{=}CHCH_2$					(23)
$H_2C{=}CHCH(OH)CH_2$	H_2O (pH 7.5)[a]	70	12		(24)
$PhCH_2$					(23)
2-Azidobenzyl	0.1 N NaOH	—[b]	1.5		(25)
4-Azidobenzyl	0.1 N NaOH	—[b]	1.5		(25)
Ph	4 N NaOH	60	24		(26)
a sugar group[c]	Nil	230			(27)
$HO_2CCH_2CH_2$	H_2O (pH 7.2)	100	18	74	(20)
GS–CH_2CH_2[d]	H_2O (pH 10)	37	5 d	50	(28)
MeO	H_2O	reflux	4	59	(29)
$PhCH_2O$	H_2O/$AcNMe_2$	reflux	10	*ca.* 10	(29)

a) In phosphate buffer. *b*) Heated on a steam bath. *c*) In the form of 5-substituted methyl 5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranoside, a "reversed" nucleoside. *d*) The abbreviation GSH stands for glutathione.

When carried out in 0.2 N aqueous NaOH at 100°C for 7 h, the rearrangement of 1-ethyladenine (**19**: R = Et) to give N^6-ethyladenine (**20**: R = Et) (91% yield) was accompanied by unusual hydrolytic deaminations to produce hypoxanthine (2%) and 1-ethylhypoxanthine (2%).[22] Comparison of the reaction rates in the Dimroth rearrangements of **19** (R = Et) and 1-ethyl-9-methyladenine (**1**: R^1 = Et; R^2 = Me) in H_2O at pH 6.92 and

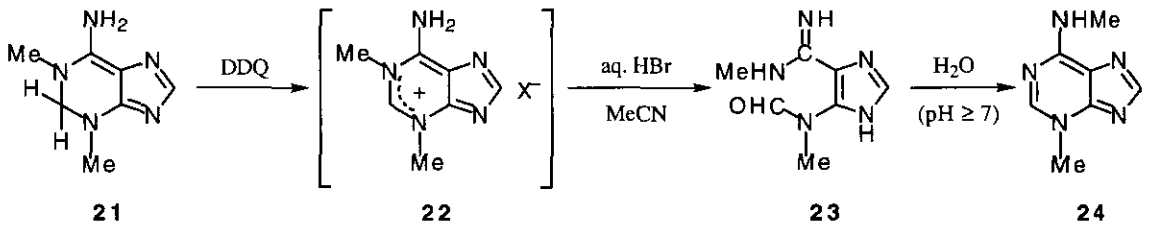
8.70 at 70°C has revealed that nonsubstitution at the 9-position decreases the rearrangement rate by a factor of 4–30 under these conditions.[22] A similar kinetic relation has been reported to hold between the Dimroth rearrangement of 1-(3-methyl-2-butenyl)adenine (**19**: R = $Me_2C{=}CHCH_2$) and that of the corresponding 9-riboside (**1**: R^1 = $Me_2C{=}CHCH_2$; R^2 = β-D-ribofuranosyl).[23d,e]

Reaction of 1-benzyloxyadenine (**19**: R = $PhCH_2O$) in 50% aqueous $AcNMe_2$ at reflux for 10 h was found to give the ring-opened intermediate (**16**: R^1 = $PhCH_2$; R^2 = H) as the major product (39–50% yield) and the N^6-isomer (**20**: R = $PhCH_2O$) as the minor product (*ca.* 10%).[29] Cyclization of the former to the latter was effected by treating with boiling H_2O for 11 h.[29]

Plna *et al.*[30] reported the rearrangement of a compound presumed to be 1-(3-allyloxy-2-hydroxypropyl)adenine to the N^6-isomer, which occurred on incubation overnight at pH 13 and rt.

IV. EXAMPLES IN 1,3-DISUBSTITUTED ADENINES

Among the 11 possible N^x,N^y-disubstituted adenines, 1,3-disubstituted adenine (type **22**) is now the only isomer that remains unknown.[11,31,32] With the aim of synthesizing a genuine 1,3-dimethyladenine structure (**22**), Fujii *et al.*[32] treated the 1,2-dihydro derivative (**21**) with DDQ in $CHCl_3$ at rt and obtained a dark brown solid presumed to be **22** (X = 2,3-dichloro-5,6-dicyano-4-hydroxyphenolate) (Scheme 7). Since the solid was unstable and difficult to purify by recrystallization, conversion into the bromide salt (**22**: X = Br) was attempted by treating it with concd aqueous HBr in MeCN under ice-cooling. However, the product isolated was not the desired salt but the hydrobromide of the ring-opened derivative (**23**). The HBr salt of **23** was also found to be unstable in H_2O at rt at pH 7 or above: It quickly underwent recyclization to give N^6,3-dimethyladenine (**24**) in 53% overall yield (from **21**). The sequence **22**→**23**→**24** thus concluded a Dimroth rearrangement.

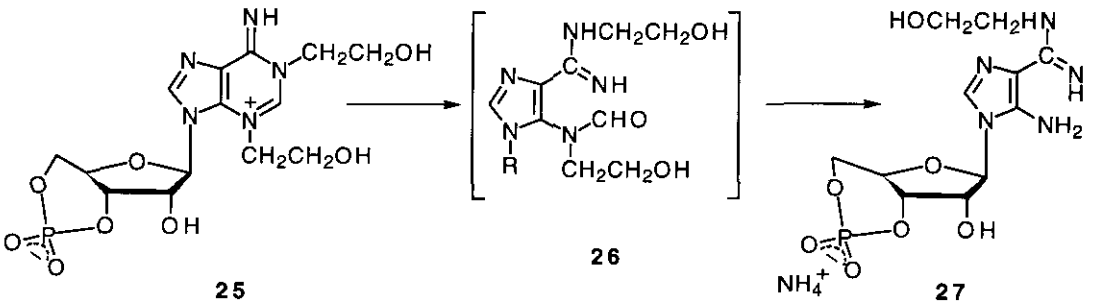


21 **22** **23** **24**

Scheme 7

Schweizer and co-workers[33] reported that treatment of 1,3-bis(2-hydroxyethyl)adenosine 3',5'-phosphate (**25**) with 1 N aqueous NaOH at rt for 2 d failed to undergo the expected Dimroth rearrangement to form the N^6,3-bis(2-hydroxyethyl) isomer. It pro-

duced the aminoimidazole derivative (**27**) (Scheme 8), presumably resulted from ring opening of the pyrimidine moiety to form **26** followed by loss of ethylene oxide and formate. Interestingly, the ready ring opening of **25** appears to be a reflection of its coexistent unstable 3,9-disubstituted adenine structure or that of the expected rearranged structure (the N^6,3,9-trisubstituted isomer), as demonstrated by Fujii and coworkers.[34]

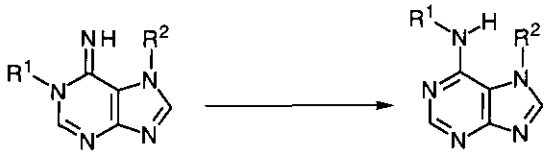


25 **26** **27**

Scheme 8

V. EXAMPLES IN 1,7-DISUBSTITUTED ADENINES

The chemical behavior of 1,7-disubstituted adenines (**28**) may be characterized primarily by the susceptibility to Dimroth rearrangement to furnish isomeric N^6,7-disubstituted adenines (**29**) (Scheme 9). Table II lists actual examples.[12,35–38]



28 **29**

Scheme 9

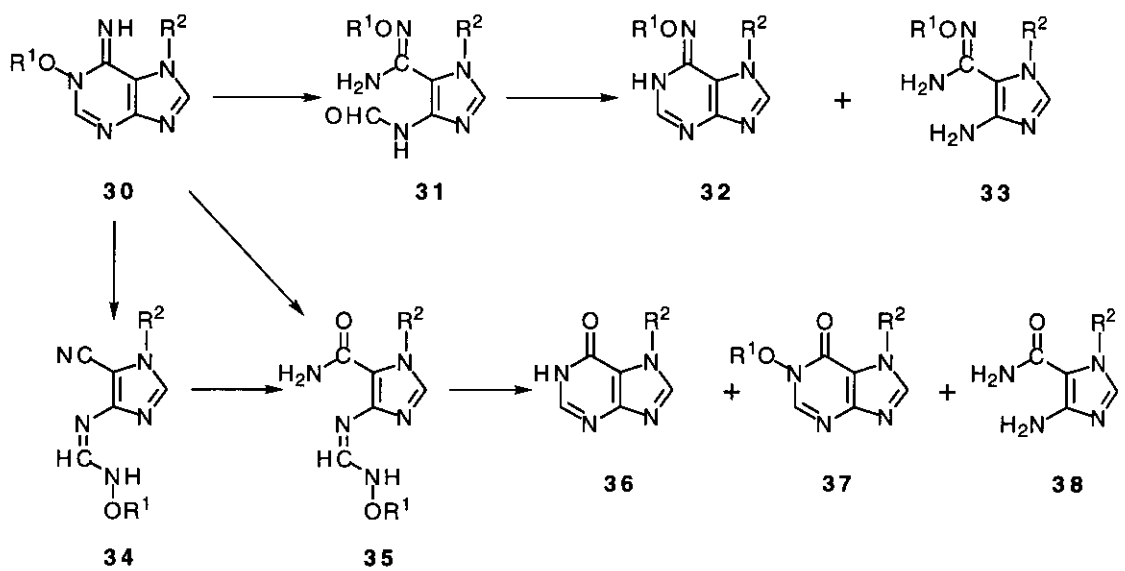
In the case of 1-butyl-7-methyladenine (**28**: R^1 = Bu; R^2 = Me) (Table II), Taylor and Loeffler[12] observed the concomitant formation of a minor amount of 7-methylhypoxanthine (**36**: R^2 = Me), a deaminated product. Fujii's group[35] found that the rearrangement of 7-alkyl-1-methyladenines (**28**: R^1 = Me; R^2 = Me, Et, or $PhCH_2$) to produce 7-alkyl-N^6-methyladenines (**29**: R^1 = Me; R^2 = Me, Et, or $PhCH_2$) (63–72% yields) was accompanied by unusual hydrolytic deaminations to give 7-alkyl-1-methylhypoxanthines (1–3.5%) and/or 7-alkylhypoxanthines (**36**) (12–22%), when effected in boiling H_2O for 4–70 h.

The rearrangement of 1-alkoxy-7-alkyladenine (**30**) to N^6-alkoxy-7-alkyladenine (**32**) was found to proceed through the imidazole-5-carboxamidine (**31**) more slowly than that

TABLE II. Rearrangement of 1,7-Disubstituted Adenines (**28**) to N^6,7-Disubstituted Adenines (**29**)

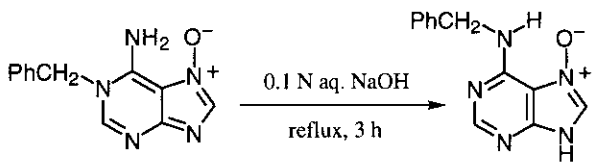
28 → **29**		Reaction conditions			Yield of **29** (%)	Literature (ref. No.)
R^1	R^2	Solvent[a]	Temp. (°C)	Time (h)		
Me	Me	A	reflux	20	*ca.* 100	(12)
Me	Me	A	reflux	9.5	63	(35)
Me	Et	A	reflux	70	67	(35)
Me	$PhCH_2$	A	reflux	4	72	(35)
Bu	Me	A	reflux	20	*ca.* 100	(12)
THMB[b]	β-D-Gf[c]	B	100	1	very low[d]	(36)
THMB[b]	β-D-Gp[e]	—	(*in vacuo*) 100	1	58[d]	(36)
$PhCH_2$	$PhCH_2$	C	reflux	1	56	(37)
$PhCH_2$	$PhCH_2$	D	reflux	30 d	75	(37)
$PhCH_2$	β-D-Gf[c]	E	reflux	2	6[d]	(36)
$PhCH_2$	β-D-Gp[e]	—[f]	100	1	80[d]	(36)
D-SBT[g]	Me	A	reflux	20	*ca.* 100	(12)
MeO	Me	F	reflux	30 min	82	(38)
EtO	Et	F	reflux	20 min	86	(38)
EtO	$PhCH_2$	F	reflux	30 min	83	(38)
$PhCH_2O$	Et	F	reflux	30 min	80	(38)

a) A = H_2O; B = aqueous NaOH (pH 9); C = 2 N aqueous NaOH/EtOH; D = 50% aqueous EtOH; E = benzylammonium acetate/MeOH; F = 0.1 N aqueous NaOH. *b*) THMB = (*E*)-$HOCH_2(Me)C{=}CHCH_2$. *c*) β-D-Gf = β-D-glucofuranosyl. *d*) Overall yield from the imidazole precursor of **28**. *e*) β-D-Gp = β-D-glucopyranosyl. *f*) In the presence of benzylammonium acetate. *g*) D-SBT = D-1-sorbityl.



Scheme 10

of the 9-alkyl analogues (**15**) at pH 7 and above, being accompanied by hydrolysis to give the deformylated product (**33**) and by deamination through **35** leading to 7-alkylhypoxanthine (**36**), 1-alkoxy-7-alkylhypoxanthine (**37**), and 1-alkyl-4-aminoimidazole-5-carboxamide (**38**) (Scheme 10).[38] Interestingly, the N(1)–C(6) bond fission product (**34**: R^1 = R^2 = Me) was obtained from **30** (R^1 = R^2 = Me) by treatment with 0.01 N aqueous NaOH at 4°C for 35 d, but in only 2% yield.[38]



39 **40**

Scheme 11

The conversion of 1-benzyladenine 7-oxide (**39**) into N^6-benzyladenine 7-oxide (**40**) in 77% yield under basic conditions (Scheme 11)[39] may also deserve a niche in Section V.

VI. EXAMPLES IN 1,9-DISUBSTITUTED ADENINES

The Dimroth rearrangement of 1,9-disubstituted adenines (type **1** or **15**) to N^6,9-disubstituted adenines (type **3** or **17**) is the one that has been most extensively studied in the adenine series. Tables III–VI, given on the next four consecutive pages, summarize a number of examples under this category.[7,8,11,13–20,23c–e,31,40–105]

The following Dimroth rearrangements have also been reported: 1-methylaristeromycin to N^6-methylaristeromycin (in boiling H_2O, 4 h, 25% yield);[17b] 1-methyl(or alkyl or aralkyl)griseolic acid to the N^6-methyl(or alkyl or aralkyl) isomer [boiling H_2O (pH 7), 5 h];[106] 1-(arylmethyl)adenosine-5'-*N*-alkyluronamides to the corresponding N^6-(arylmethyl) isomers (concd NH_4OH/MeOH, 90°C, 45 min, 14–67%);[107] 1-(3-allyloxy-2-hydroxypropyl)-2'-deoxyadenosine and its 3'- and 5'-phosphates to the corresponding N^6-isomers;[30] 1-(2-hydroxybenzyl)adenosine 5'-*S*-methyl phosphorothiolate to the N^6-(2-hydroxybenzyl) isomer;[108] 9-substituted 1-(arylmethyl)adenines to the corresponding N^6-isomers;[109] 1-(2-carboxyethyl)-2'-deoxyadenosine and its 5'-phosphate and 5'-(2-carboxyethyl) phosphate to the corresponding N^6-(2-carboxyethyl) isomers (at various pH's and temperatures);[20] 1-(2-carboxyethyl)-2'-deoxyadenosine to N^6-(2-carboxyethyl)-2'-deoxyadenosine [in phosphate buffer (pH 7.0) at 37°C for 3 h; then at pH 6.3 and 23–25°C for 18 h] [and a postulate in regard to the pathway for formation of N^6-(2-carboxy-2-hydroxyethyl)-2'-deoxyadenosine from its N(1)-isomer];[110] 1-(carboxymethyl)adenosylcobalamin to N^6-(carboxymethyl)adenosylcobalamin [in buffer (pH 11) at 70–72°C for 1 h, 22%];[111] 1-methyl- and 1-ethyladenosylcobalamins to N^6-methyl- and N^6-ethyladenosylcobalamins, respectively [H_2O (pH 11.0), 70°C, 30 min];[112] 1-methyladenosine to N^6-

TABLE III. Rearrangement of 9-Substituted 1-Methyladenines (**1**: R^1 = Me) to 9-Substituted N^6-Methyladenines (**3**: R^1 = Me)

1 → **3**		Reaction conditions				
R^1	R^2 [a]	Solvent	Temp. (°C)	Time (h)	Yield of **3** (%)	Literature (ref. No.)
Me	Me	0.1 N NaOH	—	5 min	—	(31)
Me	Me	H_2O	reflux	3	54	(8)
Me	Me	buffer (various pH's)	40	(a rate study)		(8, 17a)
Me	Me	H_2O (pH 9.5–10)	37	24	3	(40)
Me	Me	$H_2NNH_2 \cdot H_2O$/MeOH	rt	36	16	(41)
Me	Me [b]	0.2 N NaOH	reflux	15 min	72	(42)
Me	Et	0.2 N NaOH	reflux	20 min	95	(17b)
Me	$HOCH_2CH_2$	0.3 N NaOH	100	3	83	(43)
Me	$HO(CH_2)_4$	H_2O	reflux	4	70	(17b)
Me	$HO(CH_2)_5$	0.2 N NaOH	reflux	15 min	97	(17b)
Me	cyclopentyl	buffer (various pH's)	40	(a rate study)		(17b)
Me	$PhCH_2$	0.2 N NaOH	reflux	15 min	82	(17b)
Me	2-F-$C_6H_4CH_2$	10% NaOH/MeOH	rt	2.5 d	83	(44)
Me	2-Cl-6-F-$C_6H_3CH_2$	10% NaOH/MeOH	rt	3.2 d	72	(45)
C_{1-6} alkyl	2-Cl-6-F-$C_6H_3CH_2$	NaOH	—	—	—	(46)
Me	$PhCH_2CH_2$	alkaline conditions	—	—	—	(47)
Me	Rib	0.25 N NaOH	—[c]	75 min	—	(48)
Me	Rib	H_2O	reflux	3	51	(17a)
Me	Rib	buffer (various pH's)	22–40	(rate studies)		(7, 17a, 49, 50)
Me	Rib	Me_3SeOH/DMF	25	2	100	(51)
Me	Rib	raw milk	115–150	—	—	(52)
Me	Rib [d]	H_2O (pH 11)	100	2	—	(14, 15)
CD_3	Rib [d]	H_2O (pH 7 or 11)	100	2	—	(14)
Me	Rib(>CMe_2) [e]	H_2O	reflux	3	46	(17b)
Me	5-phospho-Rib	H_2O (pH 11.7)	37	—	—	(11)
Me	5-phospho-Rib	H_2O (various pH's)	37	(a rate study)		(53)
Me	5-phospho-Rib	H_2O (pH 11–12)	45	24	71	(54)
Me	5-phospho-Rib	H_2O or D_2O	rt	—	—	(55)
Me	3,5-phospho-Rib	H_2O (pH 10)	60	12	—	(56)
Me	3,5-phospho-Rib	H_2O (pH 10)	rt	3 d	47	(57)
Me	dRib	H_2O (pH 10.4)	37	18	—	(58)
Me	dRib	0.2 N NaOH	—[c]	30 min	—	(48a, 59)
Me	dRib	D_2O (pD 8.6)	rt	—	—	(60)
Me	5-phospho-dRib	H_2O (various pH's)		(a rate study)		(53)
Me	5-phospho-dRib	H_2O (pH 7)	60	24	—	(61)
Me	3-deoxy-Rib [f]	0.25 N NaOH	100	1	80	(62)

a) dRib = 2-deoxy-β-D-ribofuranosyl; Rib = β-D-ribofuranosyl. *b*) As the 2-deuterated species. *c*) Heated on a steam bath. *d*) Started from **1** with or without isotopic labeling at N^6. *e*) As the derivative of 2',3'-*O*-isopropylideneadenosine. *f*) As the derivative of cordycepin.

TABLE IV. Rearrangement of 1,9-Disubstituted Adenines (**1**: $R^1 = C_{2-4}$ unit) to N^6,9-Disubstituted Adenines (**3**: $R^1 = C_{2-4}$ unit)

1 → **3**		Reaction conditions				
R^1	$R^{2a)}$	Solvent	Temp. (°C)	Time (h)	Yield of **3** (%)	Literature (ref. No.)
Et	Me	H_2O	reflux	3	51	(8)
Et	Me	buffer (various pH's)	40	(a rate study)		(17a)
Et	Et	0.2 N NaOH	95	10 min	94	(63)
Et	Et	$(EtO)_3P$/DMF	reflux	20 min	13	(64)
Et	Et	buffer (various pH's)	40	(a rate study)		(17c)
Et	Rib	H_2O (pH 12.5)	22–37	(a rate study)		(50)
Et	3,5-phospho-Rib	——	——	——	——	(56)
Et	dRib	H_2O (pH 12.5)	22–37	(a rate study)		(50)
Et	5-phospho-dRib	H_2O (pH 7)	37	(a rate study)		(53)
$H_2N(CH_2)_2$	Rib	H_2O (pH 8)	50	8	11.7	(65)
$H_2N(CH_2)_2$	5-phospho-Rib	H_2O (pH 11)	60	7	98	(66)
$H_2N(CH_2)_2NH(CH_2)_2$	Rib$^{b)}$	H_2O (pH 7.0)	50	22	100	(65)
$HO(CH_2)_2$	Et	0.2 N NaOH	reflux	15 min	94	(17c)
$HO(CH_2)_2$	Et	NaOEt/EtOH	reflux	3.5	95	(67)
$HO(CH_2)_2$	Rib	H_2O (pH 11)	60	24	83–93	(13,17c)
$HO(CH_2)_2$	Rib$^{b)}$	H_2O (pH 11)	80	5	100	(16)
$HO(CH_2)_2$	3,5-phospho-Rib	D_2O (pD 10)	50	24	——	(68)
$EtS(CH_2)_2$	dRib	H_2O (pH 6.0)	25	1	——	(69)
HO_2CCH_2	Me	0.1 N NaOH	100	45 min	100	(70)
HO_2CCH_2	5-phospho-Rib	H_2O (pH 8.5)	90	1.5	——	(71)
Pr	Me	0.2 N NaOH	95–100	10 min	94	(8)
Pr	Me	buffer (various pH's)	40	(a rate study)		(17a)
Pr	Et	0.2 N NaOH	100	25 min	93	(17c)
allyl	allyl	Aliquat®336/KOH	80	2	72	(72)
allyl	$H_2C=CH(CH_2)_2$	Aliquat®336/KOH	80	2	78	(72)
allyl	5-phospho-Rib	concd NH_4OH	60	3	28	(73)
allyl	3,5-phospho-Rib	H_2O (pH 9–11)	——$^{c)}$	1–2	——	(74)
$HO(CH_2)_3$	Et	0.2 N NaOH	100	25 min	90	(17c)
$HO_2C(CH_2)_2$	dRib	H_2O (pH 11.7)	37	18	100	(20)
$HO_2C(CH_2)_2$	dRib	H_2O (pH 7.0)	37	40 d	80	(75, 76)
$HO_2C(CH_2)_2$	5-phospho-dRib	H_2O (pH 11.7)	37	18	100	(20)
$^-O_3S(CH_2)_3$	Rib	H_2O (pH 11.5)	70	1	46	(77)
Bu	Et	0.2 N NaOH	reflux	15 min	——	(17c)
Bu	3,5-phospho-Rib	——	——	——	——	(56)
$MeCH=CHCH_2$	3,5-phospho-Rib	1 N NaOH	75	2	——	(78)
$H_2C=CH(CH_2)_2$	allyl	Aliquat®336/KOH	80	2	54	(72)
$H_2C=CHCH(OH)CH_2$	Rib	H_2O (pH 7.4)	80	1	——	(79)
$H_2C=CHCH(CH_2OH)$	Rib	H_2O (pH 7.4)	80	1	——	(79)

a) dRib = 2-deoxy-β-D-ribofuranosyl; Rib = β-D-ribofuranosyl. *b*) Started from **1** with isotopic labeling at N^6. *c*) Heated on a steam bath.

TABLE V. Rearrangement of 1,9-Disubstituted Adenines (**1**: $R^1 \geq C_5$ unit) to N^6,9-Disubstituted Adenines (**3**: $R^1 \geq C_5$ unit)

1 → **3**		Reaction conditions				
R^1	R^2 [a]	Solvent	Temp. (°C)	Time (h)	Yield of **3** (%)	Literature (ref. No.)
$Me(CH_2)_4$	Rib	H_2O (pH 12)	90–95	3	30	(80)
$Me_2C{=}CHCH_2$	Rib	H_2O (pH 7.5)	—— [b]	1.5–2.5	38	(23c,d, 81)
$Me_2C{=}CHCH_2$	Rib	Me_2NH/MeOH/DMF	20	12	47	(23e)
$Me_2C{=}CHCH_2$	Rib	Me_2NH/MeOH	rt	2	74	(82)
$Me_2C{=}CHCH_2$	Rib [c]	Me_2NH/aq. EtOH	rt	2 d	——	(83)
$Me_2C{=}CHCH_2$	a modified Rib [d]	H_2O (pH 12)	50	3	20	(84)
$Me_2C{=}CHCH_2$	5-phospho-Rib [e]	H_2O (pH 7.5)	—— [b]	2.5	19	(23d)
$Me_2C{=}CHCH_2$	dRib	Me_2NH/MeOH	rt	2	23	(82)
$Me_2C{=}CHCH_2$	Ara	NH_4OH	reflux	——	54	(82)
$Me(CH_2)_5$	Rib	H_2O (pH 12)	90–95	3	24	(80)
$PhCH_2$	Me	0.2 N NaOH	reflux	10 min	99	(17a)
$PhCH_2$	t-$BuCO_2CH_2$ [f]	0.2 N NaOH	reflux	1	77	(85)
$PhCH_2$	cyclopentyl	aq. EtOH	reflux	24	87	(86)
$PhCH_2$	$PhCH_2$	2 N NaOH/EtOH	reflux	1	98	(37)
$PhCH_2$	$PhCH_2$	K_2CO_3/$AcNMe_2$	110	9	——	(87)
$PhCH_2$	Rib	0.1 N NaOH	37	(a rate study)		(88)
$PhCH_2$	Rib	H_2O (pH 12)	90–95	3	50.6	(80)
$PhCH_2$	Rib	Me_2NH/MeOH	rt	4	67	(82)
$PhCH_2$	Rib	H_2O	reflux	3	51	(17a)
$PhCH_2$	Rib	solvents (pH 6.8–7.4)	25	——	——	(89)
$PhCH_2$	Rib	NH_3/MeOH	80	2 d	——	(86)
$PhCH_2$	Rib(>CMe_2) [g]	Me_2NH/MeOH	rt	3	82.5	(90)
$PhCH_2$	5-phospho-Rib	concd NH_4OH	60	3.5	28	(73)
$PhCH_2$	3,5-phospho-Rib	——	——	——	——	(56)
$PhCH_2$	dRib	Me_2NH/MeOH	rt	4	42	(82)
$PhCH_2$	dRib [h]	Me_2NH/MeOH	——	——	89	(91)
$PhCH_2$	3-deoxy-Rib [i]	Me_2NH/MeOH	rt	4	65	(82)
$PhCH_2$	3-deoxy-Rib [i]	0.25 N NaOH	100	1.5	70	(92)
$PhCH_2$	Ara	Me_2NH/MeOH	rt	4	69	(82)
2-$MeC_6H_4CH_2$	Et	0.2 N NaOH/MeOH	reflux	30 min	97	(17c)
2-$MeC_6H_4CH_2$	3-deoxy-Rib [i]	——	——	——	——	(92)
2-$(HOCH_2)C_6H_4CH_2$	Et	0.2 N NaOH/MeOH	reflux	20 min	82	(17c)
4-$MeC_6H_4CH_2$	3,5-phospho-Rib	——	——	——	——	(56)
$PhO(CH_2)_2$	Rib	H_2O (pH 12)	80–90	2	11	(80)
$PhOCH_2CH(OH)CH_2$	dRib	buffer (pH 7)	37	(a rate study)		(93)
benzo[*a*]pyrenyl-6-CH_2	Rib	concd NH_4OH	100	1	——	(94)
benzo[*a*]pyrenyl-6-CH_2	Rib	NaOH/50% MeOH	50	24	——	(94)

a) Ara = β-D-arabinofuranosyl; dRib = 2-deoxy-β-D-ribofuranosyl; Rib = β-D-ribofuranosyl. *b*) Heated on a steam bath. *c*) As the [8-^{14}C]-labeled adenosine derivative. *d*) As the derivative of 2',3'-*O*-(*R*)-(3-carboxy-1-methylpropylidene)adenosine. *e*) Or as the derivative of adenosine 5'-β-cyanoethyl phosphate. *f*) Started from **1** with or without isotopic labeling at N^6, and the rearranged product was isolated as the 9-deprotected derivative (**3**: R^2 = H). *g*) Started from the derivative of [6-^{15}N]-labeled 2',3'-*O*-isopropylideneadenosine. *h*) Started from **1** with isotopic labeling at N^6. *i*) As the derivative of cordycepin.

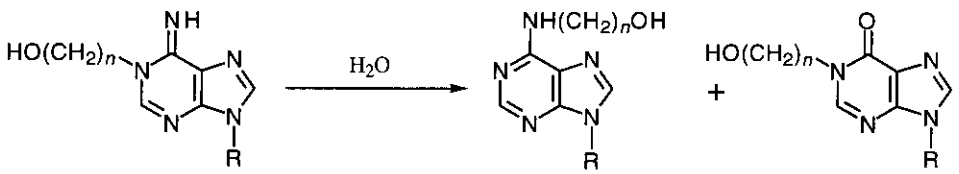
TABLE VI. Rearrangement of 9-Substituted 1-Alkoxydenines (**15**) to the Corresponding N^6-Alkoxy Isomers (**17**)

15 → **17**		Reaction conditions			Yield of **17**	Literature
R^1O	R^2 *a)*	Solvent	Temp. (°C)	Time (h)	(%)	(ref. No.)
MeO	Me	H_2O	reflux	3	74	(18a,b)
MeO	Me	buffer (various pH's)	40	(a rate study)		(8, 19)
MeO	Me *b)*	H_2O	reflux	3	51	(95)
MeO	$PhCH_2$	buffer (pH 6.5)	reflux	4	82	(42)
MeO	$PhCH_2$ *b)*	buffer (pH 6.5)	reflux	4	81	(95)
MeO	Rib	H_2O	80–85	3	66	(18c)
MeO	Rib	H_2O	reflux	3	—	(96)
MeO	Rib *b)*	H_2O	80–85	5	41	(95)
MeO	Rib(>CMe_2) *c)*	EtOH	reflux	2	—	(97)
MeO	Rib(>CMe_2) *c)*	buffer (pH 7)	95–100	8	74	(18c)
MeO	5-phospho-Rib	buffer (pH 8.0)	reflux	2	—	(96)
MeO	3,5-phospho-Rib	aq. $NaHCO_3$	reflux	45 min	53	(98)
MeO	dRib	H_2O (pH 8)	60	5	54.5	(99)
MeO	dRib	H_2O (pH 8.0)	60	12	60	(100)
EtO	Me	H_2O	reflux	3	74	(18b)
EtO	Me	buffer (various pH's)	40	(a rate study)		(8, 19)
EtO	Et	H_2O	reflux	3	77	(18a,b)
EtO	Et	buffer (various pH's)	40	(a rate study)		(8)
EtO	Rib	H_2O	80–85	3	64	(18c)
EtO	Rib(>CMe_2) *c)*	buffer (pH 7)	95–100	5	84	(18c)
EtO	3,5-phospho-Rib	0.67 N NaOH	rt	24	5	(98)
$H_2N(CH_2)_2O$	3,5-phospho-Rib	—	—	—	—	(101)
$PhCH_2O$	Me	buffer (pH 6.5)	reflux	2	66	(19)
$PhCH_2O$	Me	buffer (various pH's)	40	(a rate study)		(19, 102)
$PhCH_2O$	Et	buffer (pH 6.5)	reflux	2	68–69	(103)
$PhCH_2O$	cyclopentyl	aq. EtOH	reflux	8.5	37	(86, 104)
$PhCH_2O$	$PhCH_2$	H_2O (pH 8)	reflux	1.5	86	(18b)
$PhCH_2O$	$PhCH_2$	NaOEt/EtOH	reflux	10.5	61	(105)
$PhCH_2O$	Rib	H_2O	reflux	9	16	(86)
$PhCH_2O$	Rib	H_2O	95–100	3	86	(18c)
$PhCH_2O$	Rib	buffer (various pH's)	40	(a rate study)		(19)
$PhCH_2O$	Rib(>CMe_2) *c)*	buffer (pH 7)	95–100	4	68	(18c)
$PhCH_2O$	3,5-phospho-Rib	aq. $NaHCO_3$	reflux	45 min	10	(98)
4-NO_2-$C_6H_4CH_2O$	Me	buffer (pH 6.7)	reflux	28	59	(102)
4-NO_2-$C_6H_4CH_2O$	Me	buffer (various pH's)	40	(a rate study)		(102)
4-MeO-$C_6H_4CH_2O$	Me	buffer (various pH's)	40	(a rate study)		(102)
cyclohexylmethoxy	Me	H_2O	reflux	5	67	(102)
cyclohexylmethoxy	Me	buffer (various pH's)	40	(a rate study)		(102)

a) dRib = 2-deoxy-β-D-ribofuranosyl; Rib = β-D-ribofuranosyl. *b)* As the 2-deuterated species. *c)* As the derivative of 2',3'-*O*-isopropylideneadenosine.

methyladenosine [during the reaction with aqua(diethylenetriamine) platinum(II) at pH 7.2 and 310 K].[113]

In H_2O at near neutrality, 1-(ω-hydroxyalkyl)adenine derivatives (**41**) have been found to undergo hydrolytic deamination to give the corresponding 1-(ω-hydroxyalkyl)hypoxanthine derivatives (**43**), in competition with the usual Dimroth rearrangement to produce the corresponding N^6-(ω-hydroxyalkyl)adenine derivatives (**42**) (Scheme 12).[17c] The relative rate of deamination with respect to Dimroth rearrangement increased as the pH of the reaction medium was decreased.[17c] The analogous competitive deamination has also been reported for the Dimroth rearrangements of 1-(1-hydroxy-3-buten-2-yl)adenosine[79] and 1-(2-hydroxy-3-buten-1-yl)adenosine[79] and for those of 1-(2-hydroxy-2-phenylethyl)adenosine and 1-(2-hydroxy-1-phenylethyl)adenosine (at neutral pH and 37°C).[114] Interestingly, deamination of the third nucleoside was very slow in comparison to that of the last nucleoside.[114]



41 **42** **43**

a: R = Et; n = 2 **b**: R = Et; n = 3 **c**: R = β-D-ribofuranosyl; n = 2

Scheme 12

Examples at the ADP level include the following rearrangements: 1-methyl-ADP to N^6-methyl-ADP [in H_2O (pH 10–11) at 40°C for 24 h];[54] N(1)-(2-hydroxyethyl)-NADH to N^6-(2-hydroxyethyl)-NADH [H_2O (pH 11.2), 76°C, 1 h];[13] N(1)-(2-aminoethyl)-NAD to N^6-(2-aminoethyl)-NAD [H_2O (pH 6.5), 50°C, 7 h];[115] N(1)-(2-aminoethyl)-NADP to N^6-(2-aminoethyl)-NADP [H_2O (pH 6.0), 50°C, 4 h];[115] 3,4-dimethylpyridine 1-(carboxymethyl)adenine dinucleotide to the N^6-(carboxymethyl) isomer [H_2O (pH 8.5), 37°C, 72 h];[116] N(1)-(carboxymethyl)-ADP to N^6-(carboxymethyl)-ADP [H_2O (pH 8.5), 90°C, 1.5 h];[71] N(1)-(carboxymethyl)-NADPH to N^6-(carboxymethyl)-NADPH [H_2O (pH 11.0), 70°C, 1 h];[117] N(1)-(3-sulfonatopropyl)-NADH to the N^6-isomer [H_2O (pH 11.5), 70°C, 1 h];[77] bis[N(1)-(carboxymethyl)-CoA] to bis[N^6-(carboxymethyl)-CoA] [0.1 M $NaHCO_3$ (pH 9.0), 50–60°C, 12 h];[118] 1-(3-methyl-2-butenyl)-ADP to N^6-(3-methyl-2-butenyl)-ADP (in dilute aqueous NH_3, heating on a steam bath, 3 h, 43% yield);[119] 2',3'-cyclic N(1)-(2-carboxyethyl)-NADPH to a mixture of the isomers of N^6-(2-carboxyethyl)-NADPH with their phosphate groups at the 2'- or 3'-position [H_2O (pH 11), 70°C];[120] N(1)-(2-hydroxy-3-trimethylammoniopropyl)-NADH to the N^6-isomer [H_2O (pH 11), 70°C, 1 h];[121] N(1)-(3-carboxy-2-hydroxypropyl)-NADH to the N^6-isomer [H_2O (pH 11.2),75°C, 1 h];[122] N(1)-(3-carboxy-2-hydroxypropyl)-NADPH to the N^6-isomer [H_2O (pH 11.2), 70°C, 1.5 h];[123]

N(1)-(3-carboxy-2-hydroxypropyl)-FAD to the N^6-isomer [H_2O (pH 10), 80°C, 2 h, 58% yield];[124] NADH, bound at N(1) to a methacrylyl choline copolymer or to a methacrylyl glucosamine copolymer, to the corresponding N^6-isomer [H_2O (pH 12), 70°C, 90 min; or H_2O (pH 10), 25°C];[125] the N(1)-(3-acryloyloxy-2-hydroxypropyl) derivatives of ADP, NAD, and an SH-protected CoA to the corresponding polymerized N^6-isomers;[126] N(1)-(2-aminoethyl)-NADH, coupled at the side-chain nitrogen to carboxylated dextran, to the N^6-isomer;[127] N(1)-(2-aminoethyl)-NADH, coupled at the side-chain nitrogen to carboxylated polyethylene glycol, to the N^6-isomer.[127d,128]

The Dimroth rearrangements at the ATP level have also been reported: N(1)-(carboxymethyl)-ATP to the N^6-isomer [in H_2O (pH 8.5) at 90°C for 1.5 h in 52% yield][71] [H_2O, Dowex 1X2 (OH^-), rt for 2 d or 50°C for 240 min or 75°C for 10 min or 100°C for 5 min (84% yield)[129]]; N(1)-(3-acryloyloxy-2-hydroxypropyl)-ATP to the corresponding polymerized N^6-isomer;[126b] N(1)-(5'-phospho-β-D-ribofuranosyl)-ATP to the N^6-isomer [H_2O (pH 10.2);[130] H_2O (pH 10.07) at 45°C;[131] H_2O (pH 10.0) at 45°C for 10 h[132]].

At the polynucleotide level, Lawley and Brookes[53] observed the slow transformation of the 1-methyladenine moieties in methylated denatured DNA to the N^6-methyladenine moieties at neutral pH and 37°C, as with RNA. Michelson and Grundberg-Manago[133] converted methylated polyadenylic acid containing 70% 1-methyladenylic acid and 30% adenylic acid into a polymer containing 70% N^6-methyladenylic acid and 30% adenylic acid by treating the former in H_2O at pH 11 at rt for 24 h. Chang *et al.*[60] reported the conversion of the 1-methyladenine moieties in methylated DNA into the N^6-methyladenine moieties on treatment in D_2O at pD 8.6 and rt for 80 h.

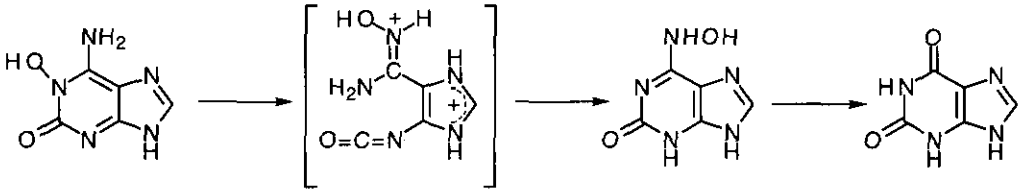
In the 1-alkoxyadenine series, it is of interest that Gulyaev *et al.*[101] reported the anomalous feasibility of the Dimroth rearrangement of 1-(2-aminoethoxy)adenosine 3',5'-phosphate [with or without C(8)-Br] and rationalized it in terms of probable intramolecular catalysis mediated by the aliphatic amino group of the N(1)-substituent. Knowing the rate constants at various pH's for all three reactions in the system that produces **17** and **18** from **15** through **16** (Scheme 5), we were finally able to select optimum conditions under which the maximum concentration of each component should be obtained.[19,102] Indeed, this was quite useful for the preparation of these products, in a practical fashion on meaningful scales, and allowed us and others to synthesize a number of elaborate target molecules from them.[9b–d,134] For isolation of the ring-opened intermediate (type **16**), the use of the 4-nitrobenzyloxy group was superior to the use of other practically applicable alkoxy groups, producing the desired compound in excellent yield at near neutrality and 40°C in the shortest reaction time.[102]

VII. EXAMPLES IN OTHER ADENINE DERIVATIVES

1,8-Disubstituted and 1,8,9-trisubstituted adenines are also known to rearrange to the corresponding N^6,8-disubstituted and N^6,8,9-trisubstituted adenines, respectively: 8-

azido-1-benzyladenine to 8-azido-N^6-benzyladenine (by heating in 0.1 N NaOH on a steam bath for 1.5 h);[25] 1-methyl-8-oxoadenine to N^6-methyl-8-oxoadenine (1 N NaOH, reflux, 30 min, 90% yield);[135] 8-bromo-1,9-dimethyladenine to 8-bromo-N^6,9-dimethyladenine [1 N NaOH, 55°C, 35 min, 88%;[136] H_2O (various pH's), 40°C (a kinetic study)[137]]; 1,9-dimethyl-8-oxoadenine to N^6,9-dimethyl-8-oxoadenine [1 N NaOH, reflux, 1 h, 90%;[136] H_2O (various pH's), 40°C (a kinetic study)[137]]; 1-methyl-8-oxoadenosine to N^6-methyl-8-oxoadenosine (1 N NaOH, reflux, 1 h, 83%);[138] 8-(benzylthio)-1-methyladenosine 3',5'-phosphate to the N^6-methyl isomer (by heating on a steam bath in aqueous $NaHCO_3$/aqueous Na_2CO_3/DMSO for 3 h, 28%);[78] 8-azido-1-benzyladenosine to 8-azido-N^6-benzyladenosine (0.2 N NaOH/DMF, 85°C, 45 min, 44%);[139] 1-benzyl-9-methyl-8-oxoadenine to N^6-benzyl-9-methyl-8-oxoadenine (1 N NaOH, reflux, 1 h, 99%);[140] 1-benzyl-8-bromoadenosine 3',5'-phosphate to the N^6-benzyl isomer (by heating on a steam bath in aqueous $NaHCO_3$/aqueous Na_2CO_3/DMSO for 2 h, 9%);[141] 1-benzyl-8-(methylthio)adenosine 3',5'-phosphate to the N^6-benzyl isomer (by heating in aqueous $NaHCO_3$/aqueous Na_2CO_3/DMSO on a steam bath for 2.5 h, 29%);[141] 1-benzyl-8-(benzylthio)adenosine 3',5'-phosphate to the N^6-benzyl isomer (by heating on a steam bath in aqueous $NaHCO_3$/aqueous Na_2CO_3/DMSO for 2 h, 66%);[78] 1-(2-aminoethoxy)-8-bromoadenosine 3',5'-phosphate to the N^6-(2-aminoethoxy) isomer.[101]

Parham *et al.*[142] reported that hydrolysis of 1-hydroxyisoguanine (**44**) in dilute acid yielded a mixture of xanthine (**47**) and 1-hydroxyxanthine (Scheme 13). They have considered the formation of **47** as a result of a competitive acid-catalyzed Dimroth-type rearrangement of **44** to give 6-hydroxyamino-2-hydroxypurine (**46**) through the dication (**45**) and subsequent ready hydrolysis of **46**.

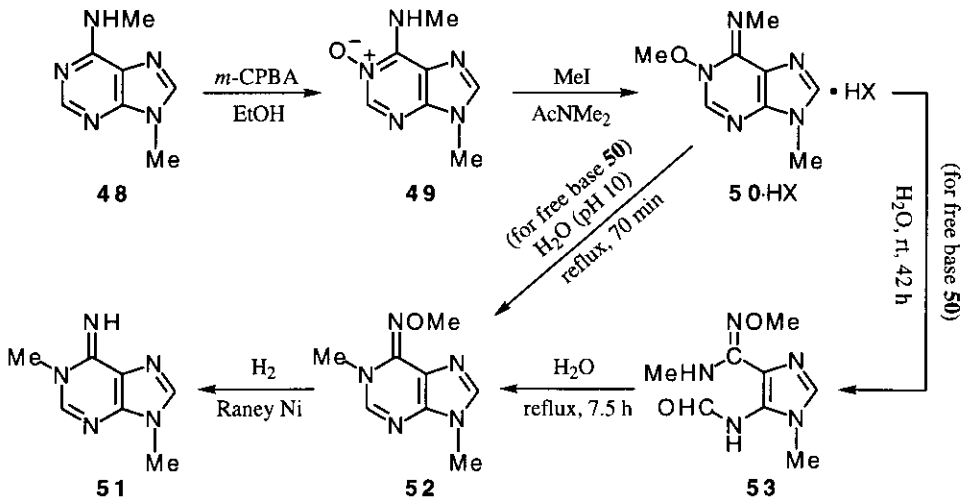


44 **45** **46** **47**

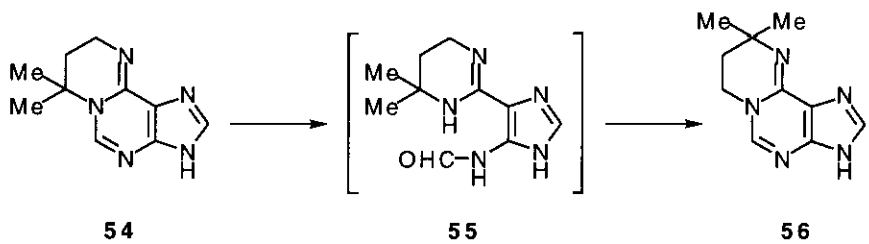
Scheme 13

In the case of 1-methoxy-N^6,9-dimethyladenine (**50**), obtained from N^6,9-dimethyladenine (**48**) through the 1-oxide (**49**) and the *O*-methyl derivative (**50**·HX) (Scheme 14), treatment with H_2O at rt afforded the monocycle (**53**), which was then cyclized to the N^6-methoxy-1-methyl isomer (**52**) in boiling H_2O.[6] Treatment of **50** with H_2O (pH 10) under reflux for 70 min also gave **52** (71% yield). Alternatively, this rearrangement was feasible by treatment with boiling H_2O (pH 9) for 3 h.[42] Reductive demethoxylation of **52** furnished 1,9-dimethyladenine (**51**). Interestingly, this conversion of **48** into **51** utilizing the 1-methoxy group made possible the structural transformation reverse to that

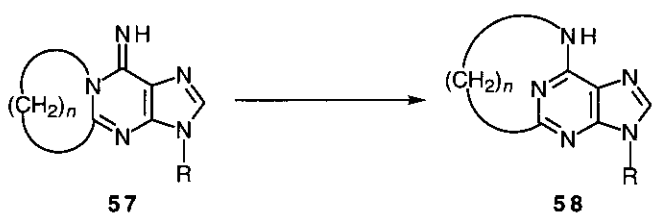
(**51**→**48**) which occurs in the usual Dimroth rearrangement.[6] A similar rearrangement of 1-methoxy-N^6-methyladenosine to N^6-methoxy-1-methyladenosine (in H_2O at 90°C for 5 h, 58% yield)[143] and of N^6-benzyl-1-methoxyadenine to 1-benzyl-N^6-methoxyadenine (H_2O, reflux, 18 h, 56%)[144] has been reported.



Scheme 14



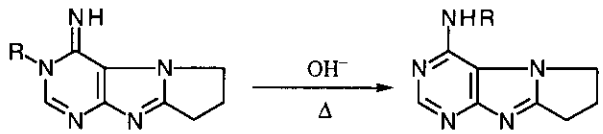
Scheme 15



a: R = β-D-ribofuranosyl; n = 7, 9, or 11
b: R = H; n = 7, 9, or 11

Scheme 16

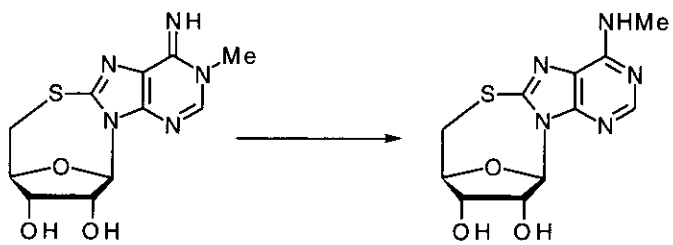
Some examples of Dimroth rearrangement in several tricyclic variants of di- and trisubstituted adenines are known: the tricycle (**54**) to the isomer (**56**) *via* the monocycle (**55**) (2 N aqueous NH_3, 85°C, 36 h) (Scheme 15);[23e] the tricycle (**57a**) to the isomeric tricycle (**58a**) (BuOH, reflux, 1–3 d, 42–94% yield) (Scheme 16);[145] the aglycon (**57b**) to **58b** (BuOH, reflux, 4 d, 63–91%);[146] the tricycle (**59**) to the isomer (**60**) (Scheme 17);[147] 8,5'-anhydro-8-mercapto-1-methyladenosine (**61**) and its 2',3'-*O*-isopropylidene derivative to 8,5'-anhydro-8-mercapto-N^6-methyladenosine (**62**) and its 2',3'-*O*-isopropylidene derivative, respectively [H_2O (pH 8–9), reflux, 5 h] (Scheme 18).[148]



59 **60**

R = $PhCH_2$, $Ph(CH_2)_2$, or 2,4-$(MeO)_2C_6H_3(CH_2)_2$

Scheme 17



61 **62**

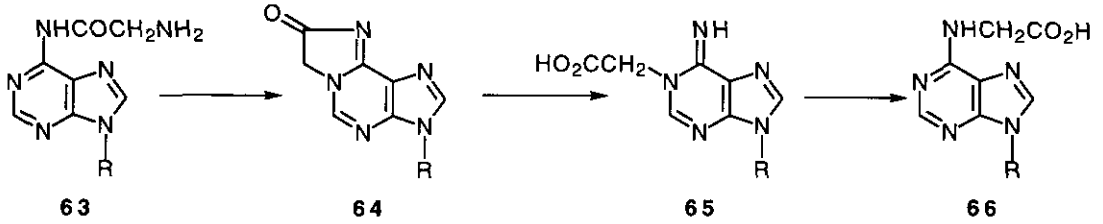
Scheme 18

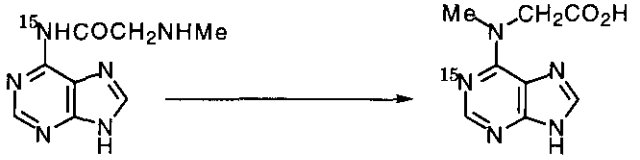
VIII. SOME RELATED REARRANGEMENTS

A certain number of intramolecular rearrangements in the adenine series are closely related to the Dimroth rearrangement but do not fall within its original scope. This section includes some of these, but it is not intended to be exhaustive.

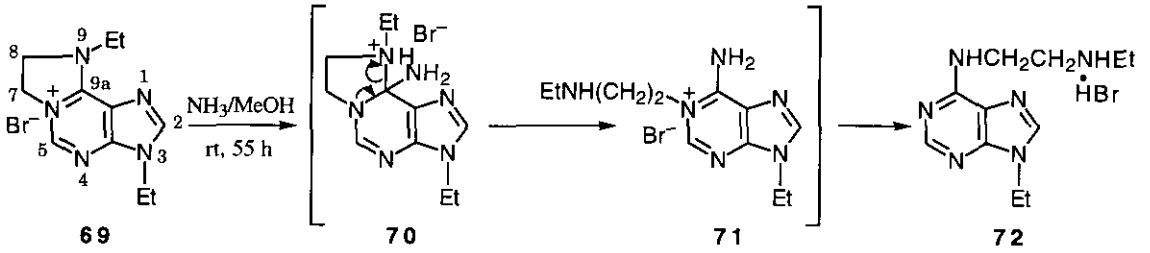
Chheda and Hall[149] reported that treatment of N^6-glycyladenine (**63a**) in H_2O at rt for several hours or at 100°C for a few minutes gave the tricyclic intermediate (**64a**) and that **64a**, on treatment with refluxing H_2O for 24 h, rearranged to form *N*-(6-purinyl)-glycine (**66a**) through 1-(carboxymethyl)adenine (**65a**) (Scheme 19). N^6-Glycyl-9-methyladenine (**63b**) and [6-^{15}N]-labeled N^6-sarcosyladenine (**67**) underwent a similar con-

version to give *N*-(9-methyl-6-purinyl)glycine (**66b**)[70,150] and **68**, respectively, and the mechanism of these rearrangements has been proposed.[70,149,151]





Scheme 19

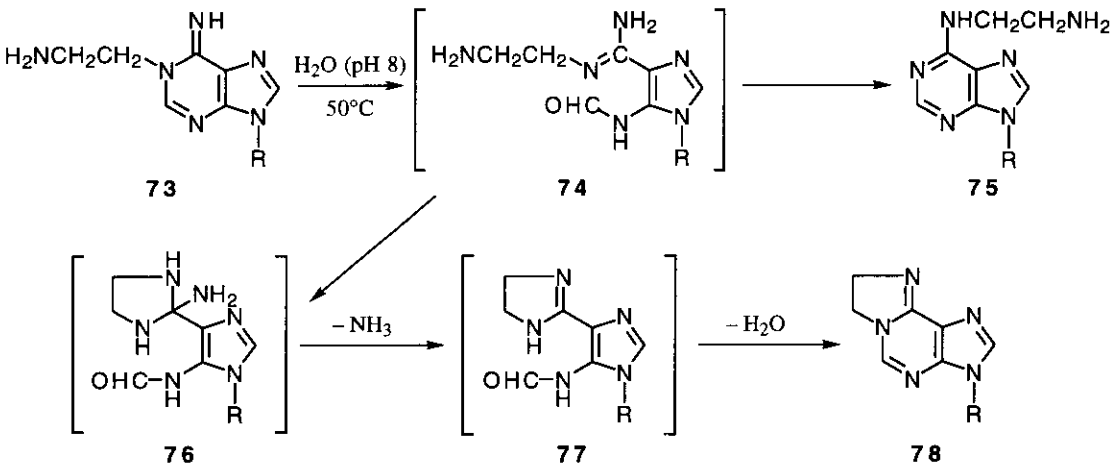


Scheme 20

As shown in Scheme 20, the tricycle (**69**) furnished the N^6,9-disubstituted adenine (**72**) on treatment with methanolic NH_3 at rt for 55 h.[64] This conversion has been interpreted in terms of an initial NH_3 attack at C(9a) of **69** to form **70**, subsequent ring opening of **70** in the imidazolidine moiety, and Dimroth rearrangement of the resulting 1,9-disubstituted adenine derivative (**71**).[64] Bückmann *et al.*[65] reported that treatment of 1-(2-aminoethyl)adenosine (**73**) in H_2O at pH 8.0 and 50°C for 8 h afforded the normal Dimroth rearrangement product (**75**) and the tricycle (**78**) in 11.7% and 9.1% yields, respectively (Scheme 21). They have proposed a reaction pathway for **78**, which involves the intermediates (**74**), (**76**), and (**77**).[65]

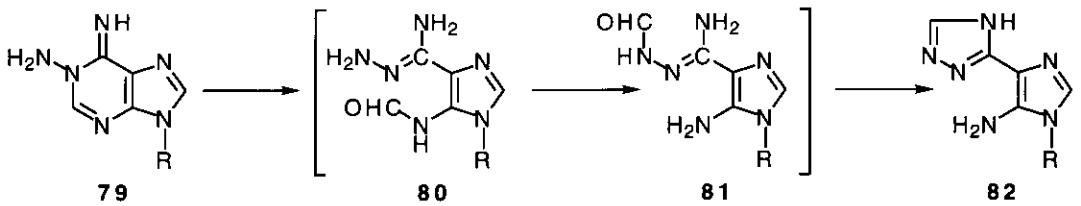
On heating in H_2O (pH 11–12) at 60°C for 2 h, 1-amino derivatives (**79**) rearranged to give the monocycles (**82**) in good yields (Scheme 22),[152] and a mechanism for this rearrangement involving the intermediates (**80** and **81**) has been presented.[152a,b] Hosmane *et al.*[153] reported that treatment of 1-amino-9-benzyladenine (**79c**) with an excess of $NH_2NH_2 \cdot H_2O$ in MeOH at rt for 12 h provided 9-benzyl-6-hydrazinopurine (**83c**) in

79.9% yield (Scheme 23). However, Kohda and co-workers[41] recently found that treatment of the hydrochlorides of **79a–c** with $NH_2NH_2 \cdot H_2O$ in the absence of the solvent MeOH at 50°C for 1–2 d gave the monocycles (**84a–c**) as the major products and the rearranged isomers (**83b,c**) as the minor products. In the case of **79b**·HCl (in MeOH at rt for 36 h), the product ratio of **83b** to **84b** arose with increasing amounts of the solvent MeOH, and a possible mechanism for formation of **83** and **84** has been presented.[41]



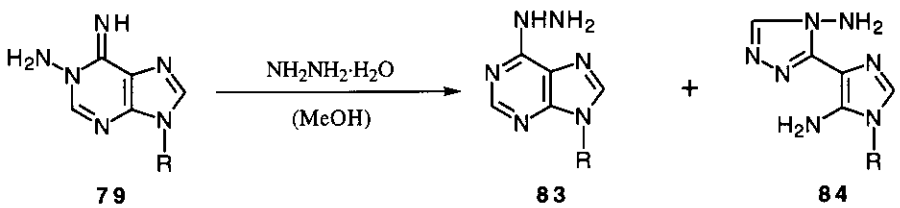
R = β-D-ribofuranosyl

Scheme 21



R = Me, β-D-ribofuranosyl, or 2-deoxy-β-D-ribofuranosyl

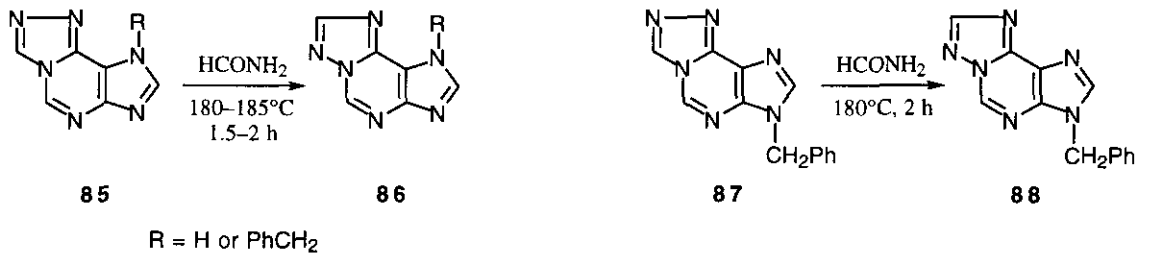
Scheme 22



a: R = H **b**: R = Me **c**: R = $PhCH_2$

Scheme 23

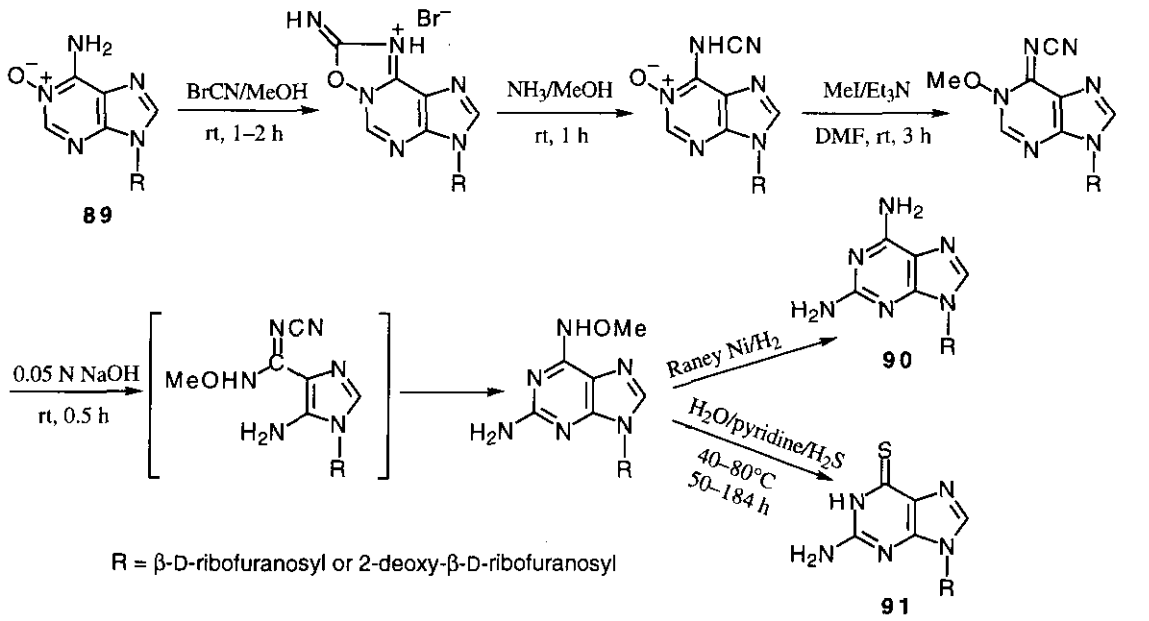
Rearrangements of the tricycles (**85** and **87**) were effected in hot formamide to give the corresponding isomeric tricycles (**86** and **88**) in 58–69% yields (Scheme 24).[154]



85 **86** **87** **88**

R = H or $PhCH_2$

Scheme 24



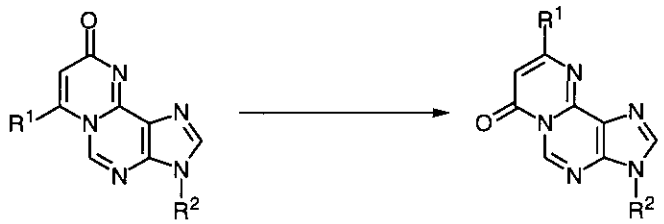
89 **90** **91**

R = β-D-ribofuranosyl or 2-deoxy-β-D-ribofuranosyl

Scheme 25

As illustrated in Scheme 25, Ueda's group[155] prepared the nucleosides (**90** and **91**) of 2,6-diaminopurine and 6-thioguanine from adenine nucleosides *via* reaction of the N(1)-oxides (**89**) with cyanogen bromide followed by a series of reactions involving a near Dimroth rearrangement utilizing the N(1)-methoxy group. Starting from the N(1)-oxides of AMP, 2'-deoxy-AMP, and 9-β-D-arabinofuranosyladenine 5'-phosphate, the corresponding 6-thioguanine nucleotides were likewise prepared.[155b] This method has been successfully applied to the syntheses of [1-^{15}N]- and [2-^{15}N]-labeled 2'-deoxyguanosines;[156] carbocyclic 9-(2'-deoxy-2'-fluoro-β-D-arabinofuranosyl)guanine from aristeromycin;[157] (–)-carbovir triphosphate from aristeromycin;[158] chiral 4'-substituted carbocyclic nucleosides from aristeromycin;[159] and the griseolic acid analogues bearing the guanine, isoguanine, and xanthine rings instead of the adenine ring.[160]

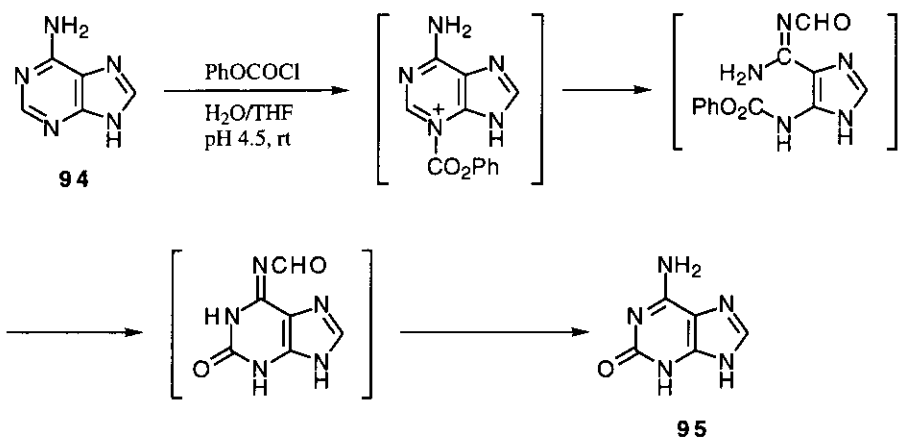
Olomucki and co-workers[161] reported that the tricycle (**92a**) underwent a complete rearrangement to give the isomer (**93a**) in DMSO at rt (half-life 24 h) in the presence of 1.5 equivalents of NaOH (Scheme 26); but in the case of the benzylthiomethyl derivative (**92b**), an equilibrium of *ca.* 65% **92b** and 35% **93b** was reached after 24 h and remained unchanged for over 10 d in the presence of an excess of NaOH. Koomen and co-workers[162] reported that treatment of **92c** with Ac_2O in pyridine at rt for 3 h and then at 55°C for 1 h gave a 4:6 mixture of **93d** and the 2',3',5'-tri-*O*-acetyl derivative (**92d**) of **92c** in 92% yield.



92 **93**

a: R^1 = $ClCH_2$; R^2 = β-D-ribofuranosyl
b: R^1 = $PhCH_2SCH_2$; R^2 = β-D-ribofuranosyl
c: R^1 = MeO_2C; R^2 = β-D-ribofuranosyl
d: R^1 = MeO_2C; R^2 = 2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl

Scheme 26



94 **95**

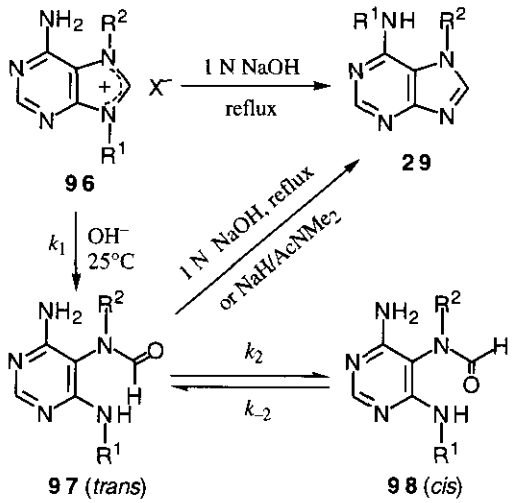
Scheme 27

Leonard and Henderson[85] reported the low-yield conversion of 3-benzyladenine into N^6-benzyladenine (**20**: R = $PhCH_2$) under 2 atm of steam at 120°C at pH 5.8 and have proposed possible pathways for this rearrangement, some of which involve the Dimroth rearrangement of 1-benzyladenine (**19**: R = $PhCH_2$) that is assumed to occur *via* ring opening–reclosure sequences. N^6,7-Dialkyladenine (**29**) was among several products

from the reaction of 3,7-dialkyladenine in boiling 1 N aqueous NaOH for 2 h, and the formation of this rearranged product has been interpreted in terms of a ring opening–reclosure sequence involving the Dimroth rearrangement of the putative intermediate 1,7-dialkyladenine (**28**).[163]

Pratt and Kraus[164] reported that treatment of adenine (**94**) in 50% aqueous THF with phenyl chloroformate at pH 4.5 and rt for 1 h yielded isoguanine (**95**) (Scheme 27). This conversion has been assumed to proceed *via* the initial acylation of **94** at N(3) followed by a near Dimroth rearrangement.[164] Similar treatment of N^6-methyladenine (**6**) with phenyl chloroformate yielded 1-methylisoguanine.[164]

Another example of a near Dimroth rearrangement may be drawn from the following study by Fujii's group. On treatment with boiling 1 N aqueous NaOH for 60 min, 7,9-dialkyladeninium salts (**96**) rearranged to isomeric N^6,7-dialkyladenines (**29**) in 50–91% yields (Scheme 28).[165] Treatment of **96** with 0.5 N aqueous Na_2CO_3 at rt for 30–90 min or with Amberlite CG-400 (OH^-) in H_2O at rt gave the ring-opened derivatives (**97**) (in the *trans*-formamide form) in 56–83% yields, and rate constants (k_1) for **96**→**97** were determined in H_2O at pH 9.84 and 25°C.[165] Cyclization of **97a** in boiling 1 N aqueous NaOH or with NaH in $AcNMe_2$ at rt afforded **29a** in 72% or 84% yield, respectively.[165] In solution, the *trans*-formamides (**97**) seemed to transform slowly into the *cis*-formamides (**98**), attaining equilibria. The existence of such an equilibrium in D_2O or DMSO-d_6 at 25°C or in H_2O at pH 9.84 and 25°C was kinetically confirmed in the case of **97a**.[165]



a: $R^1 = R^2 = Me$
b: $R^1 = Me$; $R^2 = Et$
c: $R^1 = Me$; $R^2 = PhCH_2$
d: $R^1 = Et$; $R^2 = Me$
e: $R^1 = R^2 = Et$
f: $R^1 = Et$; $R^2 = PhCH_2$
g: $R^1 = PhCH_2$; $R^2 = Et$

Scheme 28

ACKNOWLEDGMENT

We gratefully acknowledge the assistance of Tae Kanai in gathering references by an on-line computer search of *Chemical Abstracts*.

REFERENCES AND NOTES

1. For comprehensive reviews, see (a) D. J. Brown, 'Mechanisms of Molecular Migrations,' Vol. 1, ed. by B. S. Thyagarajan, Interscience, New York, 1968, pp. 209–245; (b) M. Wahren, *Z. Chem.*, 1969, **9**, 241.
2. D. J. Brown and J. S. Harper, *J. Chem. Soc.*, 1963, 1276.
3. The alias "amidine rearrangement"[1a] has scarcely been used for such a process. For a recent review on rearrangements in ordinary amidines and related compounds of both acyclic and heterocyclic types, see V. I. Minkin and I. E. Mikhailov, 'The Chemistry of Amidines and Imidates,' Vol. 2, ed. by S. Patai and Z. Rappoport, Wiley, Chichester, 1991, pp. 527–621.
4. B. Rathke, *Ber. Dtsch. Chem. Ges.*, 1888, **21**, 867.
5. (a) O. Dimroth, *Justus Liebigs Ann. Chem.*, 1909, **364**, 183; (b) *Idem*, *ibid.*, 1910, **377**, 127.
6. T. Fujii, F. Tanaka, K. Mohri, and T. Itaya, *Chem. Pharm. Bull.*, 1974, **22**, 2211, and references cited therein.
7. J. B. Macon and R. Wolfenden, *Biochemistry*, 1968, **7**, 3453.
8. T. Itaya, F. Tanaka, and T. Fujii, *Tetrahedron*, 1972, **28**, 535.
9. (a) T. Fujii, T. Itaya, and T. Saito, 'Symposium on Heterocycles,' ed. by T. Kametani, Sendai Institute of Heterocyclic Chemistry, Sendai, Japan, 1977, pp. 129–134; (b) *Idem*, *Yuki Gosei Kagaku Kyokai Shi*, 1983, **41**, 1193; (c) T. Fujii, *Yakugaku Zasshi*, 1996, **116**, 355; (d) T. Fujii and T. Itaya, *Rev. Heteroat. Chem.*, 1997, **16**, 257. (In that paper, pages 274 and 275 were mistakenly interchanged owing to a printing error.)
10. (a) G. B. Elion, 'The Chemistry and Biology of Purines,' ed. by G. E. W. Wolstenholme and C. M. O'Connor, Little, Brown and Co., Boston, 1957, pp. 39–49 and p. 57; (b) *Idem*, *J. Org. Chem.*, 1962, **27**, 2478.
11. P. Brookes and P. D. Lawley, *J. Chem. Soc.*, 1960, 539.
12. E. C. Taylor and P. K. Loeffler, *J. Am. Chem. Soc.*, 1960, **82**, 3147.
13. H. G. Windmueller and N. O. Kaplan, *J. Biol. Chem.*, 1961, **236**, 2716.
14. M. H. Wilson and J. A. McCloskey, *J. Org. Chem.*, 1973, **38**, 2247.
15. J. D. Engel, *Biochem. Biophys. Res. Commun.*, 1975, **64**, 581.
16. G. Grenner and H.-L. Schmidt, *Chem. Ber.*, 1977, **110**, 373.
17. (a) T. Fujii, T. Itaya, and T. Saito, *Chem. Pharm. Bull.*, 1975, **23**, 54; (b) T. Fujii and T. Saito, *ibid.*, 1985, **33**, 3635; (c) T. Fujii, T. Saito, and N. Terahara, *ibid.*, 1986, **34**, 1094.

18. (a) T. Fujii, T. Itaya, C. C. Wu, and S. Yamada, *Chem. Ind. (London)*, 1966, 1967; (b) T. Fujii, T. Itaya, C. C. Wu, and F. Tanaka, *Tetrahedron*, 1971, **27**, 2415; (c) T. Fujii, C. C. Wu, T. Itaya, S. Moro, and T. Saito, *Chem. Pharm. Bull.*, 1973, **21**, 1676.
19. T. Itaya, T. Saito, S. Kawakatsu, and T. Fujii, *Chem. Pharm. Bull.*, 1975, **23**, 2643.
20. A. Segal, U. Maté, and J. J. Solomon, *Chem.-Biol. Interact.*, 1979, **28**, 333.
21. T. Fujii, T. Saito, and T. Muramoto, *Chem. Pharm. Bull.*, 1983, **31**, 4270.
22. T. Fujii, T. Saito, H. Hisata, and K. Shinbo, *Chem. Pharm. Bull.*, 1990, **38**, 3326.
23. (a) N. J. Leonard and T. Fujii, *Proc. Natl. Acad. Sci. U. S. A.*, 1964, **51**, 73; (b) H. Q. Hamzi and F. Skoog, *ibid.*, 1964, **51**, 76; (c) N. J. Leonard, S. Achmatowicz, R. N. Loeppky, K. L. Carraway, W. A. H. Grimm, A. Szweykowska, H. Q. Hamzi, and F. Skoog, *ibid.*, 1966, **56**, 709; (d) W. A. H. Grimm and N. J. Leonard, *Biochemistry*, 1967, **6**, 3625; (e) D. M. G. Martin and C. B. Reese, *J. Chem. Soc. (C)*, 1968, 1731.
24. N. Tretyakova, Y. Lin, R. Sangaiah, P. B. Upton, and J. A. Swenberg, *Carcinogenesis*, 1997, **18**, 137.
25. R. Mornet, N. J. Leonard, J. B. Theiler, and M. Doree, *J. Chem. Soc., Perkin Trans. 1*, 1984, 879.
26. H. Matsumoto, S. Hara, N. Nagata, K. Ikeda, and Y. Mizuno, *Heterocycles*, 1995, **41**, 47.
27. N. J. Leonard and K. L. Carraway, *J. Heterocycl. Chem.*, 1966, **3**, 485.
28. D.-H. Kim, W. G. Humphreys, and F. P. Guengerich, *Chem. Res. Toxicol.*, 1990, **3**, 587.
29. T. Fujii, T. Sato, and T. Itaya, *Chem. Pharm. Bull.*, 1971, **19**, 1731.
30. K. Plna, D. Segerbäck, and E. K. H. Schweda, *Carcinogenesis*, 1996, **17**, 1465.
31. A. D. Broom, L. B. Townsend, J. W. Jones, and R. K. Robins, *Biochemistry*, 1964, **3**, 494.
32. T. Fujii, T. Saito, and T. Nakasaka, *Chem. Pharm. Bull.*, 1983, **31**, 3521.
33. J. Béres, Y.-C. Lee, D. I. Brixner, J. I. Olsen, and M. P. Schweizer, *Nucleosides Nucleotides*, 1986, **5**, 1.
34. (a) T. Fujii, T. Saito, and M. Kawanishi, *Tetrahedron Lett.*, 1978, 5007; (b) T. Fujii, T. Saito, and T. Nakasaka, *Heterocycles*, 1981, **15**, 195; (c) T. Fujii, T. Itaya, T. Saito, K. Mohri, M. Kawanishi, and T. Nakasaka, *Chem. Pharm. Bull.*, 1989, **37**, 1504; (d) T. Fujii, T. Saito, and T. Nakasaka, *ibid.*, 1989, **37**, 3243; (e) T. Saito and T. Fujii, *J. Chem. Soc., Chem. Commun.*, 1979, 135; (f) T. Fujii, T. Saito, and T. Nakasaka, *ibid.*, 1980, 758; (g) *Idem*, *Chem. Pharm. Bull.*, 1989, **37**, 2601.
35. T. Fujii, T. Saito, R. Ii, and T. Suzuki, *Chem. Pharm. Bull.*, 1994, **42**, 382.
36. D. E. Cowley, C. C. Duke, A. J. Liepa, J. K. MacLeod, and D. S. Letham, *Aust. J. Chem.*, 1978, **31**, 1095.
37. N. J. Leonard, K. L. Carraway, and J. P. Helgeson, *J. Heterocycl. Chem.*, 1965, **2**, 291.
38. T. Itaya, N. Ito, T. Kanai, and T. Fujii, *Chem. Pharm. Bull.*, 1997, **45**, 832.

39. T. Fujii, Y. Takada, K. Ogawa, T. Itaya, and S. Matsubara, *Chem. Pharm. Bull.*, 1995, **43**, 325.
40. K. Yamauchi, T. Tanabe, and M. Kinoshita, *J. Org. Chem.*, 1976, **41**, 3691.
41. S. Asano, K. Itano, Y. Yamagata, and K. Kohda, *J. Heterocycl. Chem.*, 1996, **33**, 1115.
42. T. Fujii, T. Saito, T. Itaya, K. Kizu, Y. Kumazawa, and S. Nakajima, *Chem. Pharm. Bull.*, 1987, **35**, 4482.
43. S.-B. Fang, Y. Inaki, and K. Takemoto, *Polym. J. (Tokyo)*, 1985, **17**, 433.
44. J. L. Kelley and E. W. McLean, *J. Heterocycl. Chem.*, 1986, **23**, 1189.
45. K. Imai and T. Seo, *Eur. J. Med. Chem.-Chim. Ther.*, 1980, **15**, 207.
46. E. F. Rogers and R. W. Graham, **Brit. 1,534,163** (29 Nov 1978) (*Chem. Abstr.*, 1979, **91**, 74653r).
47. C. L. Leese and G. M. Timmis, Abstr. of 7th Internat. Cancer Congress, London, 1958, p. 144.
48. (a) J. W. Jones and R. K. Robins, *J. Am. Chem. Soc.*, 1963, **85**, 193; (b) B. Zagalak and J. Pawelkiewicz, *Acta Biochim. Polon.*, 1965, **12**, 103 (*Chem. Abstr.*, 1965, **63**, 5726*h*).
49. E. R. Garrett and P. J. Mehta, *J. Am. Chem. Soc.*, 1972, **94**, 8542.
50. B. Singer, L. Sun, and H. Fraenkel-Conrat, *Biochemistry*, 1974, **13**, 1913.
51. K. Yamauchi, K. Hattori, and M. Kinoshita, *J. Chem. Soc., Perkin Trans. 1*, 1985, 1327.
52. (a) F. G. Ott and E. Schlimme, *Kiel. Milchwirtsch. Forschungsber.*,1991, **43**, 213 (*Chem. Abstr.*, 1992, **116**, 127266k); (b) E. Schlimme, F. G. Ott, C. Kiesner, and H. G. Biewendt, *Chem. Abstr.*, 1994, **121**, 7707m; (c) E. Schlimme, F. G. Ott, and C. Kiesner, *Int. Diary J.*, 1994, **4**, 617 (*Chem. Abstr.*, 1994, **121**, 299581d); (d) E. Schlimme, F. G. Ott, K. P. Raezke, and C. Kiesner, *Chem. Abstr.*, 1995, **122**, 289146x; (e) D. Martin, C. Kiesner, and E. Schlimme, *Kiel. Milchwirtsch. Forschungsber.*, 1995, **47**, 75 (*Chem. Abstr.*, 1995, **123**, 226409k).
53. P. D. Lawley and P. Brookes, *Biochem. J.*, 1963, **89**, 127.
54. B. E. Griffin and C. B. Reese, *Biochim. Biophys. Acta*, 1963, **68**, 185.
55. S. Mansy, W. L. Peticolas, and R. S. Tobias, *Spectrochim. Acta, Part A*, 1979, **35A**, 315.
56. S. Shibuya, A. Kuninaka, and H. Yoshino, **Japan. Kokai 74 100,100** (20 Sep 1974) (*Chem. Abstr.*, 1975, **82**, 73416t).
57. J. Béres, P. Sándor, A. Kálmán, T. Koritsánszky, and L. Ötvös, *Tetrahedron*, 1984, **40**, 2405.
58. A. Coddington, *Biochim. Biophys. Acta*, 1962, **59**, 472.
59. A. Guy, D. Molko, L. Wagrez, and R. Téoule, *Helv. Chim. Acta*, 1986, **69**, 1034.
60. C.-j. Chang, J. D. Gomes, and S. R. Byrn, *J. Org. Chem.*, 1983, **48**, 5151.
61. T. Tanabe, K. Yamauchi, and M. Kinoshita, *Bull. Chem. Soc. Jpn.*, 1983, **56**, 1826.

62. Yamasa Shoyu Co., Ltd., **Jpn. Kokai Tokkyo Koho 80,160,796** (13 Dec 1980) (*Chem. Abstr.*, 1981, **95**, 115943p).
63. T. Fujii, K. Sakamoto, S. Kawakatsu, and T. Itaya, *Chem. Pharm. Bull.*, 1976, **24**, 655.
64. T. Saito, M. Murakami, T. Inada, H. Hayashibara, and T. Fujii, *Chem. Pharm. Bull.*, 1993, **41**, 453.
65. A. F. Bückmann, V. Wray, and H. C. van der Plas, *Heterocycles*, 1995, **41**, 1399.
66. S. Sicsic, J. Leonil, and F. Le Goffic, *Eur. J. Biochem.*, 1989, **179**, 435.
67. T. Saito, M. Murakami, T. Inada, H. Hayashibara, and T. Fujii, *Chem. Pharm. Bull.*, 1992, **40**, 3201.
68. J. Béres, E. Moravcsik, and L. Radics, *Heterocycles*, 1981, **16**, 1951.
69. G. H. Sack, Jr., C. Fenselau, M.-N. N. Kan, and L. S. Kan, *J. Org. Chem.*, 1978, **43**, 3932.
70. G. B. Chheda and R. H. Hall, *J. Org. Chem.*, 1969, **34**, 3492.
71. M. Lindberg and K. Mosbach, *Eur. J. Biochem.*, 1975, **53**, 481. See also ref. 129b.
72. N. Platzer, H. Galons, Y. Bensaid, M. Miocque, and G. Bram, *Tetrahedron*, 1987, **43**, 2101.
73. K. Kikugawa, K. Iizuka, and M. Ichino, *J. Med. Chem.*, 1973, **16**, 358.
74. J. E. Reimann, P. G. Grant, R. W. Colman, and R. F. Colman, *J. Protein Chem.*, 1983, **2**, 113.
75. J. J. Solomon, I. L. Cote, M. Wortman, K. Decker, and A. Segal, *Chem.-Biol. Interact.*, 1984, **51**, 167.
76. J. J. Solomon, J. Fedyk, F. Mukai, and A. Segal, *Cancer Res.*, 1985, **45**, 3465.
77. G. Carrea, G. Ottolina, S. Riva, B. Danieli, G. Lesma, and G. Palmisano, *Helv. Chim. Acta*, 1988, **71**, 762; *ibid.*, 1989, **72**, 1169.
78. J. P. Miller, K. H. Boswell, R. B. Meyer, Jr., L. F. Christensen, and R. K. Robins, *J. Med. Chem.*, 1980, **23**, 242.
79. R. R. Selzer and A. A. Elfarra, *Chem. Res. Toxicol.*, 1996, **9**, 875.
80. M. H. Fleysher, A. Bloch, M. T. Hakala, and C. A. Nichol, *J. Med. Chem.*, 1969, **12**, 1056.
81. (a) F. Skoog, H. Q. Hamzi, A. M. Szweykowska, N. J. Leonard, K. L. Carraway, T. Fujii, J. P. Helgeson, and R. N. Loeppky, *Phytochemistry*, 1967, **6**, 1169; (b) W. Grimm, T. Fujii, and N. J. Leonard, 'Synthetic Procedures in Nucleic Acid Chemistry,' Vol. 1, ed. by W. W. Zorbach and R. S. Tipson, Interscience, New York, 1968, pp. 212–214.
82. M. J. Robins and E. M. Trip, *Biochemistry*, 1973, **12**, 2179.
83. M. H. Fleysher, *J. Labelled Compd.*, 1972, **8**, 455.
84. H. Rosemeyer and F. Seela, *Angew. Chem., Int. Ed. Engl.*, 1984, **23**, 385.
85. N. J. Leonard and T. R. Henderson, *J. Am. Chem. Soc.*, 1975, **97**, 4990.
86. J. A. Montgomery and H. J. Thomas, *J. Med. Chem.*, 1972, **15**, 182.

87. T. Fujii, S. Sakurai, and T. Uematsu, *Chem. Pharm. Bull.*, 1972, **20**, 1334.
88. P. Brookes, A. Dipple, and P. D. Lawley, *J. Chem. Soc.* (*C*), 1968, 2026.
89. R. C. Moschel, W. R. Hudgins, and A. Dipple, *J. Org. Chem.*, 1979, **44**, 3324.
90. S. R. Sarfati and V. K. Kansal, *Tetrahedron*, 1988, **44**, 6367.
91. X. Gao and R. A. Jones, *J. Am. Chem. Soc.*, 1987, **109**, 1275.
92. Yamasa Shoyu Co., Ltd., **Jpn. Kokai Tokkyo Koho 80,160,794** (13 Dec 1980) (*Chem. Abstr.*, 1981, **95**, 7703b).
93. F. Lemière, P. Joos, K. Vanhoutte, E. L. Esmans, A. De Groot, M. Claeys, and E. Van den Eeckhout, *J. Am. Soc. Mass Spectrom.*, 1996, **7**, 682.
94. R. E. Royer, T. A. Lyle, G. G. Moy, G. H. Daub, and D. L. Vander Jagt, *J. Org. Chem.*, 1979, **44**, 3202.
95. (a) T. Saito, H. Hayashibara, Y. Kumazawa, T. Fujisawa, and T. Fujii, *Heterocycles*, 1990, **31**, 1593; (b) T. Fujii, T. Saito, K. Kizu, H. Hayashibara, Y. Kumazawa, S. Nakajima, and T. Fujisawa, *Chem. Pharm. Bull.*, 1991, **39**, 301.
96. K. Miura and T. Ueda, *Chem. Pharm. Bull.*, 1975, **23**, 2064.
97. A. Yamazaki, I. Kumashiro, and T. Takenishi, *Chem. Pharm. Bull.*, 1969, **17**, 1128.
98. R. B. Meyer, Jr., D. A. Shuman, R. K. Robins, J. P. Miller, and L. N. Simon, *J. Med. Chem.*, 1973, **16**, 1319.
99. (a) M. Saneyoshi, S. Nishimura, M. Okabe, and F. Fukuoka, *J. Pharmacobio-Dyn.*, 1980, **3**, 105; (b) H. Nishio, A. Ono, A. Matsuda, and T. Ueda, *Nucleic Acids Res.*, 1992, **20**, 777.
100. T. Fujii, T. Saito, and K. Iguchi, *Chem. Pharm. Bull.*, 1994, **42**, 495.
101. N. N. Gulyaev, V. L. Tunitskaya, L. A. Mazurova, and E. S. Severin, *Bioorg. Khim.*, 1979, **5**, 552 (*Chem. Abstr.*, 1980, **92**, 6852a).
102. T. Fujii, T. Itaya, T. Saito, and S. Kawakatsu, *Chem. Pharm. Bull.*, 1984, **32**, 4842.
103. T. Fujii, T. Saito, T. Sakuma, M. Minami, and I. Inoue, *Chem. Pharm. Bull.*, 1990, **38**, 652.
104. When this reaction was effected in aqueous EtOH at 25°C for 2 d, the ring-opened intermediate (**16**: R^1 = $PhCH_2$; R^2 = cyclopentyl) was obtained in 82% yield,[86] in general agreement with the findings[18] of Fujii's group.
105. T. Fujii, T. Itaya, and S. Moro, *Chem. Pharm. Bull.*, 1972, **20**, 1818.
106. M. Kaneko, M. Kimura, and Y. Murofushi, **Eur. Pat. Appl. EP 200,522** (10 Dec 1986) (*Chem. Abstr.*, 1987, **106**, 214306k).
107. C. Gallo-Rodriguez, X.-d. Ji, N. Melman, B. D. Siegman, L. H. Sanders, J. Orlina, B. Fischer, Q. Pu, M. E. Olah, P. J. M. van Galen, G. L. Stiles, and K. A. Jacobson, *J. Med. Chem.*, 1994, **37**, 636.
108. Ma. Eto, M. Iio, H. Omura, and Mo. Eto, *Agric. Biol. Chem.*, 1991, **55**, 1999.
109. H. F. Deng, Y. Z. Jiang, and Z. Z. Zhao, *Chin. Chem. Lett.*, 1994, **5**, 271 (*Chem. Abstr.*, 1994, **121**, 180087g).
110. J. J. Solomon, U. S. Singh, and A. Segal, *Chem.-Biol. Interact.*, 1993, **88**, 115.

111. T. Toraya and S. Fukui, *J. Biol. Chem.*, 1980, **255**, 3520.
112. K. Ushio, S. Fukui, and T. Toraya, *Biochim. Biophys. Acta*, 1984, **788**, 318.
113. S. Murakami, K. Saito, A. Muromatsu, M. Moriyasu, and A. Kato, *Nippon Kagaku Kaishi*, 1993, 1328.
114. C. Qian and A. Dipple, *Chem. Res. Toxicol.*, 1995, **8**, 389.
115. (a) A. F. Bückmann, *Biocatalysis*, 1987, **1**, 173; (b) *Idem*, **Ger. Offen. DE 3,617,535** (26 Nov 1987) (*Chem. Abstr.*, 1989, **110**, 58011k).
116. J. Salord, C. Tarnus, C. D. Muller, and F. Schuber, *Biochim. Biophys. Acta*, 1986, **886**, 64.
117. (a) C. R. Lowe and K. Mosbach, *Eur. J. Biochem.*, 1974, **49**, 511; (b) K. Mosbach, P. O. Larsson, and M. Lindberg, **Swed. 386,186** (02 Aug 1976) (*Chem. Abstr.*, 1977, **86**, 16910h).
118. E. Rieke, S. Barry, and K. Mosbach, *Eur. J. Biochem.*, 1979, **100**, 203.
119. G. C. Walker and O. C. Uhlenbeck, *Biochemistry*, 1975, **14**, 817.
120. (a) K. Okuda, I. Urabe, and H. Okada, *Eur. J. Biochem.*, 1985, **151**, 33; (b) I. Urabe, K. Okuda, and H. Okada, *Kagaku to Seibutsu*, 1985, **23**, 58.
121. G. Ottolina, G. Carrea, S. Riva, and A. F. Bückmann, *Enzyme Microb. Technol.*, 1990, **12**, 596.
122. (a) P. Zappelli, A. Rossodivita, and L. Re, *Eur. J. Biochem.*, 1975, **54**, 475; (b) L. Re and P. Zappelli, **Ger. Offen. 2,519,063** (20 Nov 1975) (*Chem. Abstr.*, 1976, **84**, 59961b).
123. P. Zappelli, R. Pappa, A. Rossodivita, and L. Re, *Eur. J. Biochem.*, 1977, **72**, 309.
124. P. Zappelli, R. Pappa, A. Rossodivita, and L. Re, *Eur. J. Biochem.*, 1978, **89**, 491.
125. C. W. Fuller, J. R. Rubin, and H. J. Bright, *Eur. J. Biochem.*, 1980, **103**, 421.
126. (a) F. Le Goffic, S. Sicsic, and C. Vincent, *Enzyme Eng.*, 1980, **5**, 127 (*Chem. Abstr.*, 1981, **94**, 79164d); (b) *Idem*, **Fr. Demande FR 2,454,448** (14 Aug 1981) (*Chem. Abstr.*, 1982, **97**, 68553r); (c) S. Sicsic, Y. Mavambu, B. Brémont, and F. Le Goffic, *Eur. J. Biochem.*, 1982, **127**, 513.
127. (a) A. Bückmann, **Ger. 2,841,414** (19 Jul 1979) (*Chem. Abstr.*, 1979, **91**, 136299r); (b) C. Wandrey, R. Wichmann, A. F. Bückmann, and M.-R. Kula, *Prepr.–Eur. Congr. Biotechnol., 1st*, 1978, 44 (*Chem. Abstr.*, 1979, **91**, 104493h); (c) A. Bückmann, **U. S. US 4,443,594** (17 Apr 1984) (*Chem. Abstr.*, 1984, **101**, 146810q); (d) A. F. Bückmann, M.-R. Kula, R. Wichmann, and C. Wandrey, *J. Appl. Biochem.*, 1981, **3**, 301.
128. A. F. Bückmann, M. Morr, and M.-R. Kula, *Biotechnol. Appl. Biochem.*, 1987, **9**, 258.
129. (a) Y. Yamazaki and H. Maeda, *Agric. Biol. Chem.*, 1981, **45**, 2631; (b) Agency of Industrial Sciences and Technology, **Jpn. Kokai Tokkyo Koho JP 57,139,094** (20 Feb 1981) (*Chem. Abstr.*, 1983, **98**, 89817r). N^6-(Carboxymethyl)-ADP has been prepared from the N(1)-isomer in a similar manner.

130. B. N. Ames, R. G. Martin, and B. J. Garry, *J. Biol. Chem.*, 1961, **236**, 2019.
131. D. Chelsky and S. M. Parsons, *J. Biol. Chem.*, 1975, **250**, 5669.
132. Q.-M. Gu and C. J. Sih, *J. Am. Chem. Soc.*, 1994, **116**, 7481.
133. A. M. Michelson and M. Grunberg-Manago, *Biochim. Biophys. Acta*, 1964, **91**, 92.
134. (a) J. A. Montgomery and H. J. Thomas, *J. Med. Chem.*, 1972, **15**, 1334; (b) J. A. Montgomery, A. G. Laseter, A. T. Shortnacy, S. J. Clayton, and H. J. Thomas, *ibid.*, 1975, **18**, 564; (c) D. A. Shuman, R. B. Meyer, Jr., and R. K. Robins, **U. S. 3,948,886** (06 Apr 1976) (*Chem. Abstr.*, 1976, **85**, 6012g); (d) S. Sato, I. Mikoshiba, K. Kawai, and K. Hirai, *J. Labelled Compd. Radiopharm.*, 1993, **33**, 195.
135. T. Itaya, Y. Takada, T. Kanai, and T. Fujii, *Chem. Pharm. Bull.*, 1996, **44**, 2318.
136. (a) T. Fujii, T. Saito, and S. Mori, *Heterocycles*, 1988, **27**, 1145; (b) *Idem*, *Chem. Pharm. Bull.*, 1990, **38**, 2146.
137. T. Fujii, T. Saito, and S. Mori, *Chem. Pharm. Bull.*, 1990, **38**, 2591.
138. T. Saito, T. Kanai, and T. Fujii, *Chem. Pharm. Bull.*, 1993, **41**, 1850.
139. M. R. Sussman and H. Kende, *Planta*, 1977, **137**, 91.
140. (a) T. Fujii, T. Saito, S. Mori, and J. Chikazawa, *Tetrahedron Lett.*, 1991, **32**, 97; (b) T. Saito, S. Mori, J. Chikazawa, T. Kanai, and T. Fujii, *Chem. Pharm. Bull.*, 1993, **41**, 1746.
141. K. H. Boswell, L. F. Christensen, D. A. Shuman, and R. K. Robins, *J. Heterocycl. Chem.*, 1975, **12**, 1.
142. J. C. Parham, J. Fissekis, and G. B. Brown, *J. Org. Chem.*, 1967, **32**, 1151.
143. T. Fujii, T. Itaya, F. Tanaka, T. Saito, K. Mohri, and K. Yamamoto, *Chem. Pharm. Bull.*, 1983, **31**, 3149.
144. (a) T. Fujii, K. Ogawa, and T. Itaya, *Heterocycles*, 1994, **37**, 219; (b) T. Itaya, K. Ogawa, Y. Takada, and T. Fujii, *Chem. Pharm. Bull.*, 1996, **44**, 967.
145. K. Ienaga and W. Pfleiderer, *Liebigs Ann. Chem.*, 1979, 1872.
146. K. Ienaga, T. Hasegawa, D. J. Brown, and W. Pfleiderer, *J. Chem. Soc., Perkin Trans. 1*, 1988, 593.
147. E. N. Dozorova, A. V. Kadushkin, G. A. Bogdanova, N. P. Solov'eva, and V. G. Granik, *Khim. Geterotsikl. Soedin.*, 1991, 754 (*Chem. Abstr.*, 1992, **116**, 6334x).
148. M. Ikehara and Y. Matsuda, *Chem. Pharm. Bull.*, 1974, **22**, 1313.
149. G. B. Chheda and R. H. Hall, *Biochemistry*, 1966, **5**, 2082.
150. J. Ohrt, R. Parthasarathy, and G. B. Chheda, *J. Am. Chem. Soc.*, 1970, **92**, 6604.
151. G. B. Chheda, R. H. Hall, and P. M. Tanna, *J. Org. Chem.*, 1969, **34**, 3498.
152. (a) G.-F. Huang, T. Okamoto, M. Maeda, and Y. Kawazoe, *Chem. Pharm. Bull.*, 1974, **22**, 1938; (b) G.-F. Huang, M. Maeda, T. Okamoto, and Y. Kawazoe, *Tetrahedron*, 1975, **31**, 1363; (c) S. Asano, K. Itano, Y. Yamagata, and K. Kohda, *Nucleosides Nucleotides*, 1994, **13**, 1453; (d) 1-Aminoadenine (**79a**) has been reported to give a 1:1 mixture of **83a** and **82** (R = H) under the same alkaline conditions, but

at pH 12 it gave only **83a**: T. Saga, T. Kaiya, S. Asano, and K. Kohda, *Nucleosides Nucleotides*, 1996, **15**, 219.

153. R. S. Hosmane, B. B. Lim, and F. N. Burnett, *J. Org. Chem.*, 1988, **53**, 382.
154. C. Temple, Jr., C. L. Kussner, and J. A. Montgomery, *J. Org. Chem.*, 1965, **30**, 3601.
155. (a) K. Miura, T. Kasai, and T. Ueda, *Chem. Pharm. Bull.*, 1975, **23**, 464; (b) T. Ueda, K. Miura, and T. Kasai, *ibid.*, 1978, **26**, 2122.
156. B. Goswami and R. A. Jones, *J. Am. Chem. Soc.*, 1991, **113**, 644.
157. A. D. Borthwick, K. Biggadike, S. Holman, and C.-L. Mo, *Tetrahedron Lett.*, 1990, **31**, 767.
158. A. M. Exall, M. F. Jones, C.-L. Mo, P. L. Myers, I. L. Paternoster, H. Singh, R. Storer, G. G. Weingarten, C. Williamson, A. C. Brodie, J. Cook, D. E. Lake, C. A. Meerholz, P. J. Turnbull, and R. M. Highcock, *J. Chem. Soc., Perkin Trans. 1*, 1991, 2467.
159. A. D. Borthwick, K. Biggadike, I. L. Paternoster, J. A. V. Coates, and D. J. Knight, *Bioorg. Med. Chem. Lett.*, 1993, **3**, 2577 (*Chem. Abstr.*, 1994, **120**, 315219d).
160. M. Kaneko, M. Kimura, Y. Murofushi, T. Yasumoto, Y. Iijima, and M. Yamazaki, *Nucleosides Nucleotides*, 1992, **11**, 865.
161. P. Roques, J. Y. Le Gall, L. Lacombe, and M. Olomucki, *J. Org. Chem.*, 1992, **57**, 1579.
162. R. F. de Boer, D. G. I. Petra, M. J. Wanner, A. Boesaart, and G.-J. Koomen, *Heterocycles*, 1995, **41**, 1197.
163. T. Fujii, T. Saito, I. Inoue, Y. Kumazawa, and K. Tamura, *Chem. Pharm. Bull.*, 1988, **36**, 107.
164. R. F. Pratt and K. K. Kraus, *Tetrahedron Lett.*, 1981, **22**, 2431.
165. T. Saito, I. Inoue, and T. Fujii, *Chem. Pharm. Bull.*, 1990, **38**, 1536.

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