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Purines. XI.[1] The Synthesis of N-Alkoxyadenosines and Their 2',3'-O-Isopropylidene Derivatives[2]

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Alkylation of adenosine 1-oxide (I) and its 2',3'-O-isopropylidene derivative (V) with alkyl halides in N,N-dimethylacetamide furnished the corresponding 1-alkoxy derivatives (IIa—f). The free bases, obtained from IIa—f, readily underwent rearrangement to give the isomeric N^6-alkoxy derivatives (IVa—f) when heated in water. Treatment of 1-benzyloxyadenosine perchlorate (IIc: X=ClO_4) with water at pH 9.5 and 39—41° for 4 hr afforded the ring-opened intermediate (IIIc) (79% yield), which was recyclized in hot water (pH 7) to IVc. In alternative synthesis of IVa, b, c, condensation of 6-chloro-9-β-D-ribofuranosylpurine (VIa) with the appropriate alkoxyamines proceeded smoothly. Removal of the isopropylidene group from IVe under acid conditions or exchange amination of adenosine with ethoxyamine at pH 5 also yielded N-ethoxyadenosine (IVb).

Previous papers[4-6] in this series described the facile Dimroth rearrangement of 1-alkoxyadenine derivatives (type II: R^1=alkyl or H; R^2=alkyl) to the corresponding N^6-alkoxy isomers (type IV) through readily isolable monocyclic intermediates (type III). The salient feature of those studies was the finding that acceleration of the ring-opening step (II→III) and retardation of the recyclization step (III→IV) could be attributed directly to the alkoxyl group at the 1-position.[6] In view of the potential utility of this rearrangement in chemical modification of adenine derivatives[7] and nucleic acids, it was of interest to extend the scope of the reaction to include nucleoside analogues. The present paper reports the syntheses of N-alkoxyadenosines (IVa, b, c) and of their 2',3'-O-isopropylidene derivatives (IVd, e, f) from 1-alkoxyadenosine derivatives (IIa—f) by the Dimroth rearrangement method; three other syntheses of IVb are also included.

A model starting material selected for the rearrangement route (Chart 1) was 1-benzyloxyadenosine perchlorate (IIc: X=ClO_4)[8] since this salt could be prepared as a nicely crystallizing substance from the corresponding hydrobromide (IIc: X=Br).[7b,8] In a previous rate study[6] of the ring-opening of 1-methoxy-9-methyladenine perchlorate (type II: R^1=R^2=CH_3; X=ClO_4),[9] it has been shown that the maximum yield (91%) of the monocyclic intermediate (type III: R^1=R^2=CH_3)[4b] should be expected from the reaction in water at pH 9.44 and 40° for 4 hr. When IIc (X=ClO_4) was allowed to react under similar reaction

1) Part X: T. Fujii, T. Saito, T. Itaya, and K. Yokoyama, *Chem. Pharm. Bull.* (Tokyo), **21**, 209 (1973).
2) Presented in part at the Symposium on the Chemistry of Heterocyclic Compounds organized by Society of Synthetic Organic Chemistry, Japan, and Chemical Society of Japan, Tokyo, Nov. 28, 1967.
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4) *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*, **27**, 2415 (1971).
5) T. Fujii, T. Sato, and T. Itaya, *Chem. Pharm. Bull.* (Tokyo), **19**, 1731 (1971).
6) T. Itaya, F. Tanaka, and T. Fujii, *Tetrahedron*, **28**, 535 (1972).
7) See, for example, *a*) J.A. Montgomery and H.J. Thomas, *Chem. Commun.*, **1969**, 458; *b*) *Idem*, *J. Med. Chem.*, **15**, 182 (1972).
8) T. Fujii, C.C. Wu, and T. Itaya, *Chem. Pharm. Bull.* (Tokyo), **19**, 1368 (1971).
9) T. Fujii and T. Itaya, *Tetrahedron*, **27**, 351 (1971).

conditions, it was possible to isolate the intermediate (IIIc),[10] mp 158—160° (decomp.), in 79% yield along with a small amount (6% yield) of the rearranged product (IVc). The structure IIIc was assignable, as in the case of the $N_{(1)}$-alkylimidazole analogue (type III: $R^1=R^2=CH_3$ or C_2H_5),[4] by analysis and spectral properties and by conversion in hot water (pH 7) into IVc (81% yield). For convenience of ready preparation of IVc, a crude sample of 1-benzyloxyadenosine hydrobromide (IIc: X=Br),[8] obtained by the reaction of adenosine

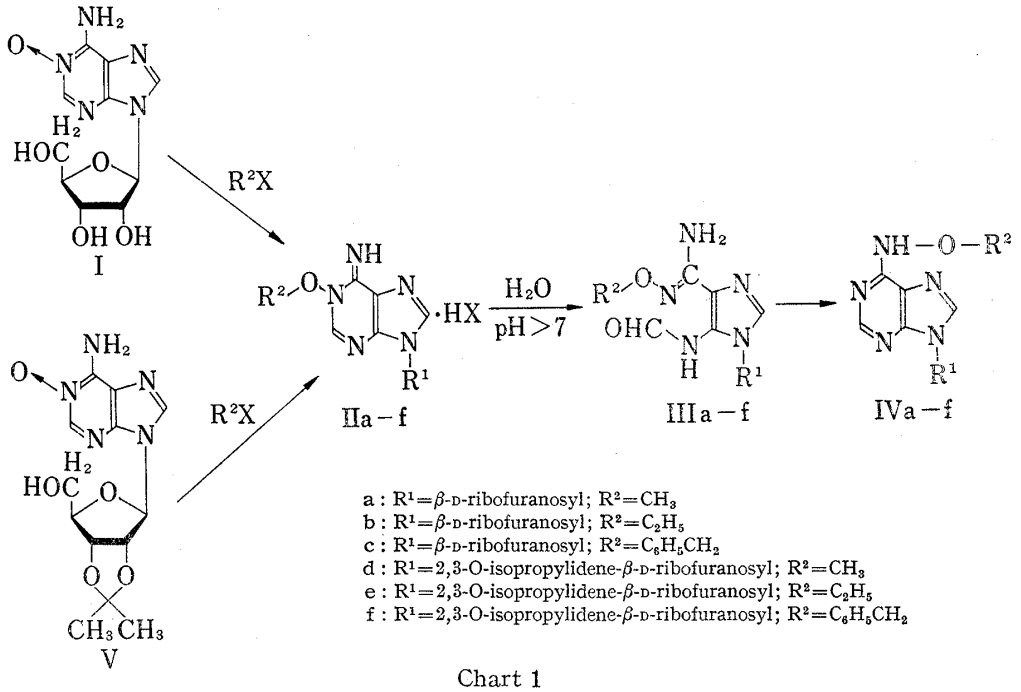

Chart 1

1-oxide (I)[11] and benzyl bromide, could be directly used as a starting material without purification. In this run, the hydrobromide was converted into the corresponding free base, which was then heated in water for 3 hr to produce IVc in an overall yield of 86%.[12] Likewise, alkylation of I with methyl and ethyl iodide and rearrangement of the resulting salts (IIa, b: X=I) furnished the N^6-alkoxy derivatives (IVa[13a] and IVb). Treatment of 2′,3′-O-isopropylideneadenosine 1-oxide (V)[1,11a] with methyl, ethyl iodide, and benzyl bromide in N,N-dimethylacetamide at room temperature gave the corresponding crystalline 1-alkoxy derivatives (IId: X=I, IIe: X=I, and IIf: X=Br) in good yields. These salts were separately converted into the free bases by the use of Amberlite IRA-402 (HCO_3^-), and the rearrangement reactions leading to IVd,[13b] e, f were smoothly effected in hot phosphate buffer solution (pH 7). The results are summarized in Table I. When the rearrangements of the free bases of IId, e, f were carried out in plain water, it was found that the pH of the solutions was lowered (down to pH 4) as the reaction proceeded and this probably caused the 2′,3′-O-isopropylidene group to split off to some extent. In an attempt to obtain IIIa, b, f in a pure form, the free bases of IIa, b, f were treated in a manner similar to that described above for IIIc. However, the desired products failed to crystallize.

10) Preparation of IIIc in a similar manner has recently been outlined by Montgomery and Thomas.[7b]
11) *a*) M.A. Stevens, D.I. Magrath, H.W. Smith, and G.B. Brown, *J. Am. Chem. Soc.*, **80**, 2755 (1958); *b*) See also footnote 8 in Ref. 8.
12) Ref. 7*b* has reported that a similar synthesis afforded IVc in 16% yield.
13) *a*) This compound was recently synthesized in a similar way by T. Ueda, M. Imazawa, K. Miura, R. Iwata, and K. Odajima (*Tetrahedron Letters*, **1971**, 2507); *b*) A. Yamazaki, I. Kumashiro, and T. Takenishi, *Chem. Pharm. Bull.* (Tokyo), **17**, 1128 (1969).

Table I. Synthesis and Rearrangement of 1-Alkoxyadenosine Derivatives (IIa—f)

Product	Alkylating reagent	Reaction conditions: Temp.[a] (°C)	Reaction conditions: Time (hr)	Yield (%)	Appearance and recrystn. solvent[b]	mp[c] (°C)	Formula	Analysis (%) Calcd. (Found): C	H	N
1-Methoxyadenosine hydriodide (IIa: X=I)	CH_3I	r.t.	24	—	—	—	$C_{11}H_{16}O_5N_5I$	—	—	—
1-Ethoxyadenosine hydriodide (IIb: X=I)	C_2H_5I	r.t.	24	—	—	—	$C_{12}H_{18}O_5N_5I$	—	—	—
1-Benzyloxyadenosine hydrobromide (IIc: X=Br)	$C_6H_5CH_2Br$	r.t.	24	—	—	—	$C_{17}H_{20}O_5N_5Br$	—	—	—
1-Methoxy-2′,3′-O-isopropylideneadenosine hydriodide (IId: X=I)	CH_3I	r.t.	22	74	colorless prisms (A)	158—160	$C_{14}H_{20}O_5N_5I$	36.14 (36.31)	4.33 (4.31)	15.05 (14.82)
1-Ethoxy-2′,3′-O-isopropylideneadenosine hydriodide (IIe: X=I)[d]	C_2H_5I	r.t.	4	89	colorless leaflets (A)	158—159	$C_{15}H_{22}O_5N_5I \cdot 1/2C_2H_5OH$	38.25 (38.11)	5.02 (4.82)	13.94 (14.04)
1-Benzyloxy-2′,3′-O-isopropylideneadenosine hydrobromide (IIf: X=Br)	$C_6H_5CH_2Br$	r.t.	2.5	93	colorless needles (A)	137—146[e]	$C_{20}H_{24}O_5N_5Br$	48.59 (48.19)	4.89 (5.22)	14.17 (13.94)
N-Methoxyadenosine (IVa)[f]	—	80— 85	3	66[g]	colorless needles (D)	182—183	$C_{11}H_{15}O_5N_5 \cdot 1/2H_2O$	43.13 (43.18)	5.27 (5.44)	22.87 (22.73)
N-Ethoxyadenosine (IVb)[f]	—	80— 85	3	64[g]	colorless needles (D)	146—147	$C_{12}H_{17}O_5N_5 \cdot 1/2H_2O$	45.00 (44.89)	5.66 (5.88)	21.87 (21.77)
N-Benzyloxyadenosine (IVc)[h]	—	95—100	3	86[g]	colorless prisms (B)	111—112	$C_{17}H_{19}O_5N_5 \cdot H_2O$	52.17 (52.04)	5.41 (5.41)	17.90 (18.17)
N-Methoxy-2′,3′-O-isopropylideneadenosine (IVd)	—	95—100	8	74	colorless needles (D)	183—184[i]	$C_{14}H_{19}O_5N_5$	49.84 (49.63)	5.68 (5.66)	20.76 (20.55)
N-Ethoxy-2′,3′-O-isopropylideneadenosine (IVe)	—	95—100	5	84	colorless needles (C)	191—192	$C_{15}H_{21}O_5N_5$	51.27 (51.16)	6.02 (6.03)	19.93 (20.33)
N-Benzyloxy-2′,3′-O-isopropylideneadenosine (IVf)	—	95—100	4	68	colorless needles (A)	223—225	$C_{20}H_{23}O_5N_5$	58.10 (58.06)	5.61 (5.71)	16.94 (17.12)

a) Unless otherwise stated, bath temperature is recorded; r.t., room temperature.
b) The letter in parentheses refers to the recrystallization solvent with A, abs. ethanol; B, 50% (v/v) aq. ethanol; C, 30% (v/v) aq. ethanol; D, H_2O.
c) with decomposition
d) Contained ethanol of crystallization.
e) Gradually decomposed in this range.
f) as a hemihydrate
g) Based on the adenosine 1-oxide monohydrate ($I \cdot H_2O$)[8] used for the preparation of the starting 1-alkoxy derivative.
h) as a monohydrate
i) Yamazaki *et al.*[13b] reported mp 179° (decomp.).

Proof of the correctness of structures IVa, b, c was further provided by a second synthesis as shown in Chart 2. The condensation of 6-chloro-9-β-D-ribofuranosylpurine (VIa)[14] with methoxy-, ethoxy-, and benzyloxyamine was conducted in a large excess of the requisite amine, with or without an additional solvent, at reflux. Yields of the resulting N^6-alkoxy derivatives (IVa, b, c) were 75 to 98%. Since completion of this part of our work,[2] similar metathesis of VIa with methoxyamine was reported in the literature.[15]

We next synthesized IVg and IVh, a set of two isomers, by the reaction of the adequate 6-chloro-9-alkylpurines (VIb, c) with benzyloxy- and ethoxyamine in order to catalogue the ultraviolet (UV) spectra of compounds of a IV-type. Table II assembles the UV spectral data on IId, e, f and IVa—h.

The third synthesis of IVb involved removal of the isopropylidene group from IVe and the reaction was carried out in water at pH 1.5 and 70° for 40 min, giving the desired product (IVb) in 74% yield. Thus, the N^6-alkoxy structure of IVd, e, f was confirmed by this conversion together with similarity of the UV spectra of IVd, e, f to those of IVa, b, c and of IVg, h (Table II).

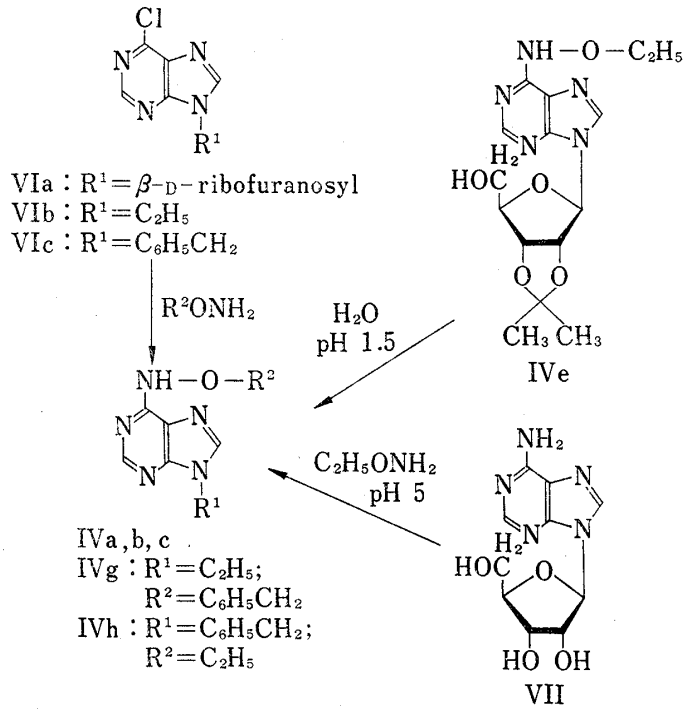

Chart 2

TABLE II. Ultraviolet Spectra of 9-Substituted 1-Alkoxy- (IId, e, f) and N-Alkoxyadenine Derivatives (IVa—h)

Compound	UV spectra							
	Solvent E[a]		Solvent A[b]		Solvent N[c]		Solvent B[d]	
	λ_{max}(mμ)	$\varepsilon\times10^{-3}$	λ_{max}(mμ)	$\varepsilon\times10^{-3}$	λ_{max}(mμ)	$\varepsilon\times10^{-3}$	λ_{max}(mμ)	$\varepsilon\times10^{-3}$
IId (X=I)	260	12.4	259	12.7	259	13.0	257	11.6
IIe (X=I)	260	12.9	259	13.4	259	13.5	258	12.4
IIf (X=Br)	261	11.9	260	12.3	260	12.4	259	11.8
IVa	267	13.4	266	15.8	268	14.6	283	11.7
IVb	267	14.0	267	16.7	268	14.6	283	11.2
IVc	268	15.8	269	16.7	269	16.1	285	12.5
IVd	268	14.0	267	16.1	268	14.8	284	11.8
IVe	269	13.7	268	17.7	270	15.0	284	11.3
IVf	269	16.0	269	17.5	269	16.8	285	12.3
IVg	270	15.2	272	13.7	270	15.8	286	12.2
IVh	268	14.1	268	16.7	269	15.6	285	11.6

a) 95% (v/v) aq. ethanol *b*) 0.1N aq. HCl (pH 1) *c*) 0.005M phosphate buffer (pH 7) *d*) 0.1N aq. NaOH (pH 13)

14) J. Žemlička and F. Šorm, *Collection Czech. Chem. Commun.*, **30**, 1880 (1965).
15) A. Giner-Sorolla, S.A. O'Bryant, C. Nanos, M.R. Dollinger, A. Bendich, and J.H. Burchenal, *J. Med. Chem.*, **11**, 521 (1968).

Finally, the fourth synthesis of IVb was based on the recently reported exchange amination of adenosine (VII) with methoxyamine.[16] On treatment with an excess of ethoxyamine in water at pH 5 and 40° for 10 days, VII could produce N-ethoxyadenosine (IVb), but in a poor yield.

The ready Dimroth rearrangement of 1-alkoxyadenosines (IIa, b, c) and their 2′,3′-O-isopropylidene derivatives (IId, e, f) described above has established the generality of the reaction. It is hoped that this finding and characterization of the intermediate (type III) and the rearranged product (type IV) in the nucleoside series will be useful for a study of chemical modification of adenine nucleotides and nucleic acids.

Experimental[17]

Alkylation of Adenosine 1-Oxide (I)——All alkylations were carried out by the procedure employed for the reaction of I with methyl iodide using the reaction conditions specified in Table I. In the case of benzylation of I, IIc (X=Br) was isolated as described previously.[8] The crude 1-alkoxyadenosine salts (IIa, b, c) thus produced were directly used in the next step without purification.

1-Methoxyadenosine Hydriodide (IIa: X=I)——A mixture of the monohydrate[11b] (3.01 g, 10 mmoles) of I[11a] and methyl iodide (7.10 g, 50 mmoles) in N,N-dimethylacetamide (10 ml) was stirred at room temp. for 24 hr. The resulting solution was evaporated *in vacuo* to leave a brown oil. Trituration of the oil with a mixture of isopropyl alcohol and isopropyl ether induced crystallization. However, the solid failed to give an analytically pure sample because of its hygroscopic nature.

Alkylation of 2′,3′-O-Isopropylideneadenosine 1-Oxide (V)——The procedure used for ethylation of V will be described below in detail. Other alkylations were accomplished similarly (see Table I).

1-Ethoxy-2′,3′-O-isopropylideneadenosine Hydriodide (IIe: X=I)——A stirred mixture of V[1,11a] (1.00 g, 3.1 mmoles), ethyl iodide (2.50 g, 16 mmoles), and N,N-dimethylacetamide (3 ml) was kept at room temp. for 4 hr. The precipitates that resulted were filtered off, washed with a little abs. ethanol, and dried to give a colorless solid (680 mg), shown to be homogeneous by paper chromatography. The filtrate and washings were combined and evaporated *in vacuo* to give a crystalline residue, which was triturated with a little abs. ethanol, filtered off, and dried, affording an almost colorless solid (700 mg) as a second crop, total yield 1.38 g (89%). For analysis the hydriodide (IIe: X=I) was recrystallized from abs. ethanol and dried over P_2O_5 at 50° and 3 mm Hg for 15 hr (see Tables I and II).

Rearrangement of 1-Alkoxy-2′,3′-O-isopropylideneadenosine Salt (IId, e, f) to N-Alkoxy-2′,3′-O-isopropylideneadenosine (IVd, e, f)——The experiment with IIe (X=I) is described in detail as a typical example. Other salts (IId and IIf) were handled similarly.

A solution of IIe·1/2 C_2H_5OH (X=I: 1.00 g, 1.99 mmoles) in H_2O (40 ml) was passed through a column of Amberlite IRA-402 (HCO_3^-) (8 ml) and the column was eluted with H_2O. The eluate (500 ml) was concentrated *in vacuo* to a volume of 20 ml and 0.2M phosphate buffer (pH 7) (10 ml) was added. The mixture was heated in a boiling water bath for 5 hr, concentrated to a small volume (*ca.* 20 ml), and cooled. The precipitates that formed were collected by filtration, washed with a little H_2O, and dried to furnish IVe (590 mg, 84%) as an almost colorless solid, mp 190—191° (decomp.). Recrystallization from 30% (v/v) aq. ethanol yielded an analytical sample (see Tables I and II).

N-Methoxyadenosine (IVa)——i) Rearrangement of IIa (X=I): The total amount of the crude IIa (X=I) described above was dissolved in H_2O (10 ml) and the aq. solution was passed through a column packed with Amberlite IRA-402 (HCO_3^-) (30 ml). The column was eluted with H_2O (800 ml). The eluate was concentrated *in vacuo* to a small volume (*ca.* 10 ml) and heated in a water bath kept at 80—85° for 3 hr. On cooling, the reaction mixture deposited colorless needles and a yellow, gelatinous substance. Addition of H_2O (20 ml) and trituration of the mixture transformed all the precipitates into needles, which were filtered off, washed with a little H_2O, and dried. Concentration of the filtrate gave a second crop. Recrystallization from H_2O and drying over P_2O_5 at 60° and 3 mm Hg for 14 hr provided an analytical sample (see Tables I and II), $[\alpha]_D^{15}$ −55.3° (c=0.922, l=0.5, H_2O).

ii) Reaction of VIa with Methoxyamine: A stirred mixture of VIa[14] (570 mg, 2 mmoles) and methoxyamine[18] (4.70 g, 100 mmoles) was heated at reflux for 3 hr. The precipitates that resulted were filtered

16) *a*) E.I. Budowsky, E.D. Sverdlov, and G.S. Monastyrskaya, *J. Mol. Biol.*, **44**, 205 (1969); *b*) *Idem*, *Biochim. Biophys. Acta*, **246**, 320 (1971).

17) All melting points are corrected. Paper chromatographies were developed as described previously.[8] See also Ref. 8 for details of instrumentation and measurement. We are indebted to Dr. E. Kimura and his associates at University of Tokyo and to Mr. Y. Itatani and Misses M. Imai and S. Toyoshima at Kanazawa University for microanalyses and NMR spectral data.

18) T. Fujii, C.C. Wu, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **15**, 345 (1967).

off, washed with abs. ethanol (5 ml), then with ether (3 ml), and dried to yield colorless needles (350 mg), mp 180—182° (decomp.), shown to be pure by paper chromatography. The filtrate and washings were combined and evaporated *in vacuo* to dryness. The residue was dissolved in H_2O (50 ml) and the aq. solution was passed through a column of Amberlite IRA-402 (HCO_3^-) (6 ml). The column was eluted with H_2O (300 ml) and the eluate was concentrated to give a second crop (180 mg), total yield 530 mg (87%). An analytical sample was prepared by recrystallization from H_2O and dried as described in method-(i), mp 182—183° (decomp.) (lit.[15] mp 202°). *Anal.* Calcd. for $C_{11}H_{15}O_5N_5 \cdot 1/2H_2O$: C, 43.13; H, 5.27; N, 22.87. Found: C, 42.90; H, 5.39; N, 22.90. This sample was identical [by mixed melting-point test, paper chromatography, and infrared (IR) spectrum] with the one obtained by method-(i).

N-Ethoxyadenosine (IVb)——i) Rearrangement of IIb (X=I): By treating IIb (X=I) as described above for IVa [method-(i)], a hemihydrate of IVb was obtained in 64% yield (based on the $I \cdot H_2O$ used). Recrystallization from H_2O and drying over P_2O_5 at 60° and 3 mm Hg for 16 hr produced an analytical sample (see Tables I and II), $[\alpha]_D^{12}$ −54.3° (c=0.844, l=0.5, H_2O).

ii) Reaction of VIa with Ethoxyamine: A stirred mixture of VIa[14] (860 mg, 3 mmoles) and ethoxyamine[18] (12.7 g, 208 mmoles) was heated at reflux for 3 hr. The resulting mixture was worked up as described above for IVa [method-(ii)], giving $IVb \cdot 1/2H_2O$ in 98% yield. Recrystallization from H_2O and drying in the same way as in method-(i) afforded an analytical sample, mp 146—147° (decomp.), identical (by mixed melting-point test and IR spectrum) with the specimen prepared by method-(i). *Anal.* Calcd. for $C_{12}H_{17}O_5N_5 \cdot 1/2H_2O$: C, 45.00; H, 5.66; N, 21.87. Found: C, 44.83; H, 5.77; N, 21.80.

iii) From IVe: To a suspension of IVe (230 mg, 0.655 mmole) in H_2O (20 ml) was added 1N aq. HCl until the pH of the mixture became 1.5. The resulting mixture was heated at 70° with stirring for 40 min. After cooling, the reaction solution was passed through a column of Amberlite IRA-402 (HCO_3^-) (6 ml) and the column was eluted with H_2O. The eluate (150 ml) was evaporated *in vacuo* to dryness and the residual solid was recrystallized from H_2O to yield $IVb \cdot 1/2H_2O$ (155 mg, 74%) as colorless needles, mp 146—147° (decomp.). Identity of this sample with the one obtained by method-(i) was established by mixed melting-point test, paper chromatography, and IR spectrum.

iv) Reaction of VII with Ethoxyamine: To 3M aq. ethoxyamine hydrochloride[18] (34 ml) was added VII (510 mg, 1.91 mmoles) and the pH of the solution was adjusted to 5 by adding KOH pellets. After the mixture had been kept at 40° with stirring in an incubator for 10 days, cyclohexanone (30 ml) was added. After 15 min, the mixture was extracted with three 50-ml portions of ether in order to remove the excess of ethoxyamine and cyclohexanone. The aq. solution was neutralized with aq. KOH and evaporated *in vacuo* to dryness. The residual solid was dried and extracted with ethyl acetate by using a Soxhlet extractor. The ethyl acetate solution thus obtained was evaporated *in vacuo* to leave a slightly brownish solid. The solid was triturated with hot abs. ethanol (5 ml) and the mixture, after cooling, was filtered in order to remove an insoluble material (VII). The filtrate was evaporated *in vacuo* to leave a solid, which was subjected to preparative thin-layer chromatography [Merck silica gel PF_{254}, chloroform–ethanol (3: 1, v/v)]. The crude IVb thus isolated was recrystallized from H_2O to give $IVb \cdot 1/2H_2O$ (12 mg, 2%) as colorless needles, mp 146—147° (decomp.), identical (by mixed melting-point test, paper chromatography, and IR spectrum) to an authentic sample.

N-Benzyloxyadenosine (IVc)——i) Rearrangement of IIc (X=Br): Carried out in the manner described above for IVa [method-(i)]. Recrystallization from 50% (v/v) aq. ethanol and drying over P_2O_5 at room temp. and 3 mm Hg for 24 hr provided an analytical sample ($IVc \cdot H_2O$) (see Tables I and II), mp 111—112° (decomp.) [lit.[7b] mp 129—130° (an anhydrous sample)], $[\alpha]_D^{13}$ −57.1° (c=0.550, l=0.5, abs. ethanol).

ii) Reaction of VIa with Benzyloxyamine: A stirred mixture of VIa[14] (860 mg, 3 mmoles), benzyloxyamine[18] (2.09 g, 17 mmoles), and 1-butanol (85 ml) was kept at 80° for 6 hr. To the resulting mixture was added ether (400 ml) and colorless scales (benzyloxyamine hydrochloride) that separated out were removed by filtration. The filtrate was evaporated *in vacuo* to leave a yellowish semicrystalline mixture, which was triturated with ether (500 ml). Colorless prisms that deposited were filtered off and triturated with H_2O (20 ml) to give $IVc \cdot H_2O$ (880 mg, 75%), mp 111—112° (decomp.). It was recrystallized from 50% (v/v) aq. ethanol and dried as described in method-(i) to furnish an analytical sample as colorless prisms, mp 111—112° (decomp.), undepressed in melting point on admixture with the sample obtained by method-(i). The IR spectra of both samples were also identical. *Anal.* Calcd. for $C_{17}H_{19}O_5N_5 \cdot H_2O$: C, 52.17; H, 5.41; N, 17.90. Found: C, 52.43; H, 5.52; N, 17.66.

iii) Cyclization of IIIc: A solution of IIIc (391 mg, 1 mmole) in 1/15M phosphate buffer (pH 7) (15 ml) was heated in a boiling water bath for 4 hr. The reaction mixture was concentrated *in vacuo* to a small volume (*ca.* 3 ml) and allowed to stand at room temp. for 2 days. The precipitates that resulted were filtered off, washed with H_2O (1 ml), and dried to give $IVc \cdot H_2O$ (317 mg, 81%) as slightly brownish, minute crystals, mp 108—112° (decomp.). Recrystallization from 50% (v/v) aq. ethanol afforded colorless prisms, mp 111—112° (decomp.), identical with an authentic sample of $IVc \cdot H_2O$.

N′-Benzyloxy-1-β-D-ribofuranosyl-5-formamidoimidazole-4-carboxamidine (IIIc)——A stirred solution of the monohydrate[8] (3.44 g, 70 mmoles) of IIc (X=ClO_4) in 0.5M carbonate buffer (Na_2CO_3–$NaHCO_3$, pH 9.5) (140 ml) was kept at 39—41° for 4 hr. The resulting solution was evaporated under vacuum to

dryness. The residue was triturated with boiling abs. ethanol (100 ml) and an insoluble material was removed by filtration while hot. The solid was washed with two 50-ml portions of abs. ethanol. The filtrate and washings were combined and cooled to come to room temp. A small amount of precipitates that formed were filtered off and the filtrate was concentrated to give a partially crystallized residue. The solid was collected by filtration, washed with abs. ethanol (1 ml) and H_2O (2 ml) successively, and dried to provide IIIc (2.16 g, 79%) as a crystalline mass, mp *ca.* 130°, shown to be homogeneous by thin-layer chromatography. Recrystallization from abs. ethanol furnished an analytical sample as colorless prisms, mp 158—160° (decomp.); $[\alpha]_D^{28}$ −32.5° (c=0.763, l=1, H_2O); UV $\lambda_{shoulder}^{95\%\ aq.\ ethanol}$ 222 mμ (ε 14700), 256 (6400); $\lambda_{max}^{H_2O}$ (pH 1)[19] 249 (8200); $\lambda_{shoulder}^{H_2O}$ (pH 7)[20] 249 (6400); $\lambda_{max}^{H_2O}$ (pH 13)[21] 249 (12500); NMR (dimethyl sulfoxide-d_6) τ: 6.40 (2H, dull, C<u>H</u>$_2$OH), 6.10 (1H, dull, $C_{(4')}$-H), 5.90 (2H, dull, $C_{(3')}$-H and $C_{(2')}$-H), 5.12 (2H, singlet, C_6H_5-C<u>H</u>$_2$O), 4.90 (2H, dull, OH's), 4.55 (2H, dull, OH and $C_{(1')}$-H), 4.25 (2H, dull, NH_2), 2.68 (5H, multiplet, C_6H_5), 2.02 [*ca.* 1.5H, $C_{(2')}$-H and <u>H</u>CONH (*trans*)], 1.82 [*ca.* 0.5H <u>H</u>CONH (*cis*)], 0.50 (1H, very broad, CO-NH). *Anal.* Calcd. for $C_{17}H_{21}O_6N_5$: C, 52.17; H, 5.41; N, 17.90. Found: C, 52.40; H, 5.67; N, 17.99.

On the other hand, the filtrate and washings, originating from the filtration of the crude IIIc, were combined and the mixture was kept in a refrigerator for 2 days. The precipitates that resulted were collected by filtration, washed successively with H_2O (2 ml) and abs. ethanol (1 ml), and dried to give the rearranged product (IVc) (167 mg, 6.1%) as colorless prisms, mp 107—112° (decomp.), shown to be identical with an authentic specimen by comparison of IR spectrum.

N-Benzyloxy-9-ethyladenine (IVg)——A stirred mixture of 6-chloro-9-ethylpurine (VIb)[22] (280 mg, 1.53 mmoles) and benzyloxyamine[18] (1.88 g, 15.3 mmoles) was heated in an oil bath kept at 85° for 5 hr. The crystals that separated out were filtered off, washed with a little abs. ethanol, and recrystallized from abs. ethanol to give IVg (340 mg, 83%) as colorless prisms, mp 154—155° (decomp.); UV (see Table II). *Anal.* Calcd. for $C_{14}H_{15}ON_5$: C, 62.44; H, 5.61; N, 26.01. Found: C, 62.17; H, 5.76; N, 25.95.

N-Ethoxy-9-benzyladenine (IVh)——A stirred mixture of 6-chloro-9-benzylpurine (VIc)[22] (370 mg, 1.51 mmoles) and ethoxyamine[18] (1.05 ml) was refluxed for 3 hr. The crystals that resulted were treated in a manner similar to that described above for IVg. Yield, 310 mg (76%). An analytical sample was recrystallized from abs. ethanol as colorless scales, mp 227—228° (decomp.); UV (see Table II). *Anal.* Calcd. for $C_{14}H_{15}ON_5$: C, 62.44; H, 5.61; N, 26.01. Found: C, 62.28; H, 5.59; N, 26.19.

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19) Measured in 0.1N aq. HCl.
20) Measured in 0.005M phosphate buffer.
21) Determined in 0.1N aq. NaOH.
22) J.A. Montgomery and C. Temple, Jr., *J. Am. Chem. Soc.*, **83**, 630 (1961).