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Synthesis and Coronary Vasodilating Activity of 2-Substituted Adenosines

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A large scale preparation of 2-haloadenosines (**1**) was attained by acetylation of 2-haloinosines (**3**), followed by chlorination and amination. 2-Alkoxyadenosines (**5**) were prepared in fairly good yields by protection of both 2'- and 3'-hydroxyl groups of 2-chloroadenosine (**1a**) or 2-chloroinosine (**3a**), followed by substitution of the chlorine atom with alkoxy group. In the reaction of **1a** with sodium alkoxide, there were obtained some oligomers of **5**, of which the structures were elucidated. The reaction of 5-amino-4-cyano-1-β-D-ribofuranosylimidazole with carbon disulfide afforded 2,6-di-mercapto-9-β-D-ribofuranosylpurine (**15**), which was converted to 2-mercaptoadenosine (**14e**) and its S-substituted derivatives. 2-Phenylaminoadenosine (**29e**) was prepared with comparative ease *via* 2-phenylamino-2',3',5'-tri-O-acetylinosine (**32**), the synthesis of which was effected by acetylation of 2-phenylaminoinosine (**30**) with acetylchloride in acetic acid. Many 2-substituted adenosines including O-substituted 2-hydroxyadenosines, S-substituted 2-mercaptoadenosines, N^2-substituted 2-aminoadenosines, 2-alkyl- and -aryl-adenosines were prepared, among which several compounds were found to have a remarkable coronary vasodilating potency. Compound (**29e**) showed not only a strong potency, but also a longer duration of the effect than that of **1a**. The structure-coronary vasodilating activity relationship was also discussed.

The activity of exogenous adenosine on the mammalian cardiovascular system is well documented.[2] The effect is of short duration, however, because of the rapid uptake of adenosine into red blood cells and tissues[3] and its conversion to inosine by adenosine deaminase.[4] Chemical modification of adenosine at the N^6-, 2- or 5'-position increases the duration of coronary vasodilating activity,[5] while it reduces the potency with the exception of 2-chloroadenosine (**1a**).[6] As part of our program to search for useful adenosine derivatives, we have synthesized new 2-substituted adenosines and assessed their coronary dilator potency.[7]

2-Halogenoadenosines (1)

Besides being a potent coronary vasodilator, compound (**1a**) is a key intermediate for the synthesis of various 2-substituted adenosines and is usually prepared by amination of 2,6-dichloro-9-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)purine (**2**).[8] The latter compound is prepared by the following three routes: i) condensation of 2,6-dichloropurine with tetra-O-

1) Location: *Jusohonmachi, Yodogawa-ku, Osaka, 532, Japan.*
2) A.M. Drury and A. Szent-Györgyi, *J. Physiol.* (London), **68**, 213 (1929); M.M. Winbury, D.H. Papierski, M.L. Hemmer, and W.E. Hambourger, *J. Pharmacol. Exp. Ther.*, **109**, 255 (1953).
3) K.E. Pfleger, E. Seifen, and H. Schoendorf, *Biochem. Pharmacol.*, **18**, 43 (1969).
4) H.P. Baer, G.I. Drummond, and E.L. Duncan, *Mol. Pharmacol.*, **2**, 67 (1966); M. Rockwell and M.H. Maguire, *ibid.*, **2**, 574 (1966).
5) W. Jahn, *Arzneim.-Forsch.*, **19**, 701 (1969); D.C. Clark, J. Davoll, F.S. Philips, and G.B. Brown, *J. Pharmacol. Exp. Ther.*, **106**, 291 (1952); M.H. Maguire, D.M. Nobbs, R. Einstein, and J.C. Middleton, *J. Med. Chem.*, **14**, 415 (1971); W. Jahn, *Arch. Exp. Pathol. Pharmakol.*, **251**, 95 (1965).
6) R.H. Thorp and L.B. Cobbin, *Arch. Int. Pharmacodyn. Ther.*, **118**, 95 (1959).
7) K. Kawazoe and K. Kikuchi, unpublished data. Each of the test compounds was administered directly into the coronary artery of anaesthetized, open-chest dog through the polyethylene catheter at doses of 0.1—100 μg/dog. The potency of each compounds was expressed with the potency of adenosine being taken as unity.
8) J.A. Montgomery and K. Hewson, *J. Heterocyclic Chem.*, **1**, 213 (1964).

acetylribofuranose,[8] ii) treatment of tri-O-acetylinosine N^1-oxide with phosphorus oxychloride,[9] and iii) chlorination of 2-amino-6-chloro-9-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)purine with hydrogen chloride and sodium nitrite.[10] All these methods include tedious steps and are not feasible for a large scale preparation of **2**. Our method utilizes 5-amino-4-carbamoyl-1-β-D-ribofuranosylimidazole (AICA-riboside) as starting material which is easily accessible from the culture broth of *Bacillus subtilis* or *Bacillus pumilus*.[11] The synthesis of 2-chloroinosine[12a] (**3a**) or 2-bromoinosine[12b] (**3b**) from AICA-riboside *via* 2-mercaptoinosine has already been reported from our laboratory. Acetylation of **3**, followed by chlorination of the tri-O-acetylated derivative (**4**) with the Vilsmeier reagent afforded **2** in high yields. This provides a very useful route for a large scale preparation of **1**.

O^2-Substituted 2-Hydroxyadenosines (5)

Compounds (**5**) have not been recorded except for 2-methoxyadenosine.[13] The synthesis of the analogous compounds was, therefore, attempted by allowing various alcohols or phenols to react with **1a** in the presence of sodium alkoxide or sodium phenoxide. The yield of 2-ethoxyadenosine (**5a**) was low and the similar synthesis of higher alkoxyadenosines than **5a** was found to be difficult, because of formation of a large amount of oligomers which will be

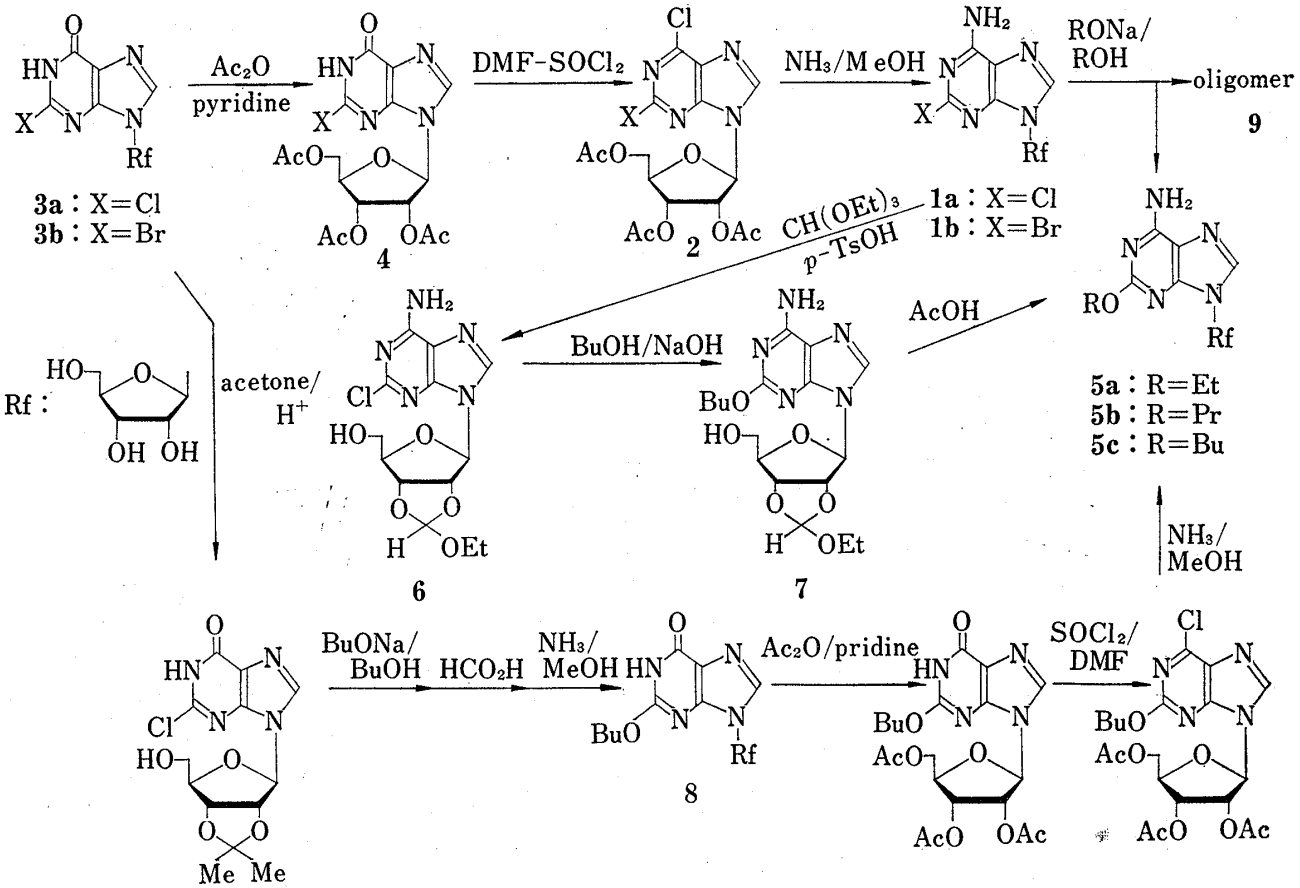


Chart 1

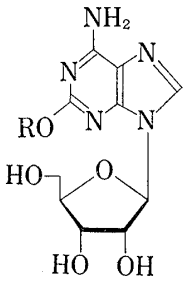
9) Y. Kawashima, I. Kumashiro, and T. Takenishi, Japan Patent 4347 (1967).
10) J.F. Gerster and R.K. Robins, *J. Org. Chem.*, **31**, 3258 (1966).
11) T. Shiro, A. Yamanoi, S. Konishi, S. Okumura, and T. Takenishi, *Agr. Biol. Chem.* (Tokyo), **26**, 785 (1962); H. Shirafuji, A. Imada, S. Yashima, and M. Yoneda, *ibid.*, **32**, 69 (1968).
12) *a*) K. Imai, R. Marumoto, K. Kobayashi, Y. Yoshioka, J. Toda, and M. Honjo, *Chem. Pharm. Bull.* (Tokyo), **19**, 576 (1971); *b*) R. Marumoto, Y. Yoshioka, and M. Honjo, *ibid.*, **22**, 342 (1974).
13) H.J. Schaeffer and H.J. Thomas, *J. Am. Chem. Soc.*, **80**, 3738 (1958).

described later. A slight modification was necessary to effect the synthesis of 2-propoxyadenosine (**5b**) by the reaction of propanol with **1a**. Thus **5b** was prepared by the use of sodium hydroxide in place of sodium metal. Such a modification was not effective for the preparation of 2-butoxyadenosine (**5c**), because of formation of oligomers. This difficulty was overcome by the use of the 2′,3′-O-protected derivatives. Thus, **1a** was converted to the 2′,3′-O-ethoxymethylidene derivative (**6**), which was allowed to react with butanol by the use of sodium hydroxide to yield 2-butoxy-2′,3′-O-ethoxymethylideneadenosine (**7**) in a quantitative yield. Treatment of **7** with acetic acid furnished **5c** in an overall yield of 33% from **1a**. Similarly, reaction of 2′,3′-O-isopropylidene-2-chloroinosine with sodium butoxide followed by removal of the protecting group afforded 2-butoxyinosine (**8**). The latter compound was converted to **5c** by acetylation, followed by chlorination and amination (Chart 1).

2-Alkoxyadenosine Oligomers (9)

The reaction of **1a** with sodium propoxide afforded a compound, which scarcely moved on thin-layer chromatography (TLC) [silica gel, MeOH–$CHCl_3$ (2: 3)] and was isolated as a white powder (**9a**). The ultraviolet (UV) absorption spectra were similar to those of 2-propoxy-

Table I. O^2-Substituted 2-Hydroxyadenosines (**5**)



Compd.	R-	Formula	mp (°)	UV absorption spectra λ_{max} nm ($\varepsilon \times 10^{-3}$)	Coronary dilator potency [adenosine= 1.00 dog, ic]
5a	CH_3CH_2-	$C_{12}H_{17}O_5N_5 1/2H_2O$	amorph.	H_2O: 253 (sh), 268; pH 2: 249, 275	0.63
5b	$CH_3(CH_2)_2-$	$C_{13}H_{19}O_5N_5 \cdot 1/2H_2O$	amorph.		2.55
5c	$CH_3(CH_2)_3-$	$C_{14}H_{21}O_5N_5$	155		2.41
5d	$CH_3(CH_2)_4-$	$C_{15}H_{23}O_5N_5$	amorph.		0.22
5e	$CH_3O(CH_2)_2-$	$C_{13}H_{19}O_6N_5$	177—178	PH1: 248 (8.0), 273 (11.5); pH 13: 266 (12.1)	0.81
5f	$CH_3CH_2O(CH_2)_2-$	$C_{14}H_{21}O_6N_5 \cdot 1/2H_2O$	amorph.		1.33
5g	$CH_3(CH_2)_3O(CH_2)_2-$	$C_{16}H_{25}O_6N_5$	amorph.		0.61
5h	$CH_3O(CH_2)_2O(CH_2)_2-$	$C_{15}H_{23}O_7N_5$	194		0.79
5i	$C_6H_5O(CH_2)_2-$	$C_{18}H_{21}O_6N_5 \cdot 1/4H_2O$	amorph.	EtOH: 269 (13.8)	0.51
5j	$CH_3OCH_2CH(CH_3)-$	$C_{14}H_{21}O_6N_5$	amorph.	H_2O: 266 (11.7)	0.16
5k	$CH_3CH(OCH_3)(CH_2)_2-$	$C_{15}H_{23}O_6N_5$	amorph		0.81
5l	$HO(CH_2)_2-$	$C_{12}H_{17}O_6N_5 \cdot 2\,1/2H_2O$	amorph.		2.65
5m	$CH_2=CHCH_2-$	$C_{13}H_{17}O_5N_5$	193		0.71
5n	$CH_3CH=CHCH_2-$	$C_{14}H_{19}O_5N_5$	amorph.		0.22
5o	C_6H_5-	$C_{16}H_{17}O_5N_5 \cdot 1/2CH_3OH \cdot 1/2H_2O$	amorph.		0.74
5p	m-$CH_3C_6H_4-$	$C_{17}H_{19}O_5N_5 \cdot H_2O$	amorph.		0.72
5q	p-$CH_3OC_6H_4-$	$C_{17}H_{19}O_6N_5 \cdot 1/2\,H_2O$	155—157	MeOH: 252(sh), 267 (15.3), 277 (sh)	0.55
5r	o-ClC_6H_4-	$C_{16}H_{16}O_5N_5Cl$	148—150		0.17

adenosine and the nuclear magnetic resonance (NMR) spectrum [d_6-dimethyl sulfoxide (d_6-DMSO)] showed the presence of the ribose moiety. Accordingly, **9a** was presumed to be an oligomer,[14] which was formed by successive intermolecular reactions between the 2-chlorine atom of **1a** and one of the 2′-, 3′- and 5′-hydroxyl groups of 2-propoxyadenosine. The oligomers thus formed possess a terminal 2-propoxyadenosine residue,[16] of which one hydroxyl group in the ribose moiety was substituted to form an ether linkage. The NMR spectrum demonstrated that the intensity ratio of the triplet methyl protons of the 2-propoxy group to the C_8-proton was 1:1. The molecular weight was estimated to be 740 by the polystylene column chromatography measurement using 2-propoxyadenosine and 2-(5-deoxyinosin-5-yl)-

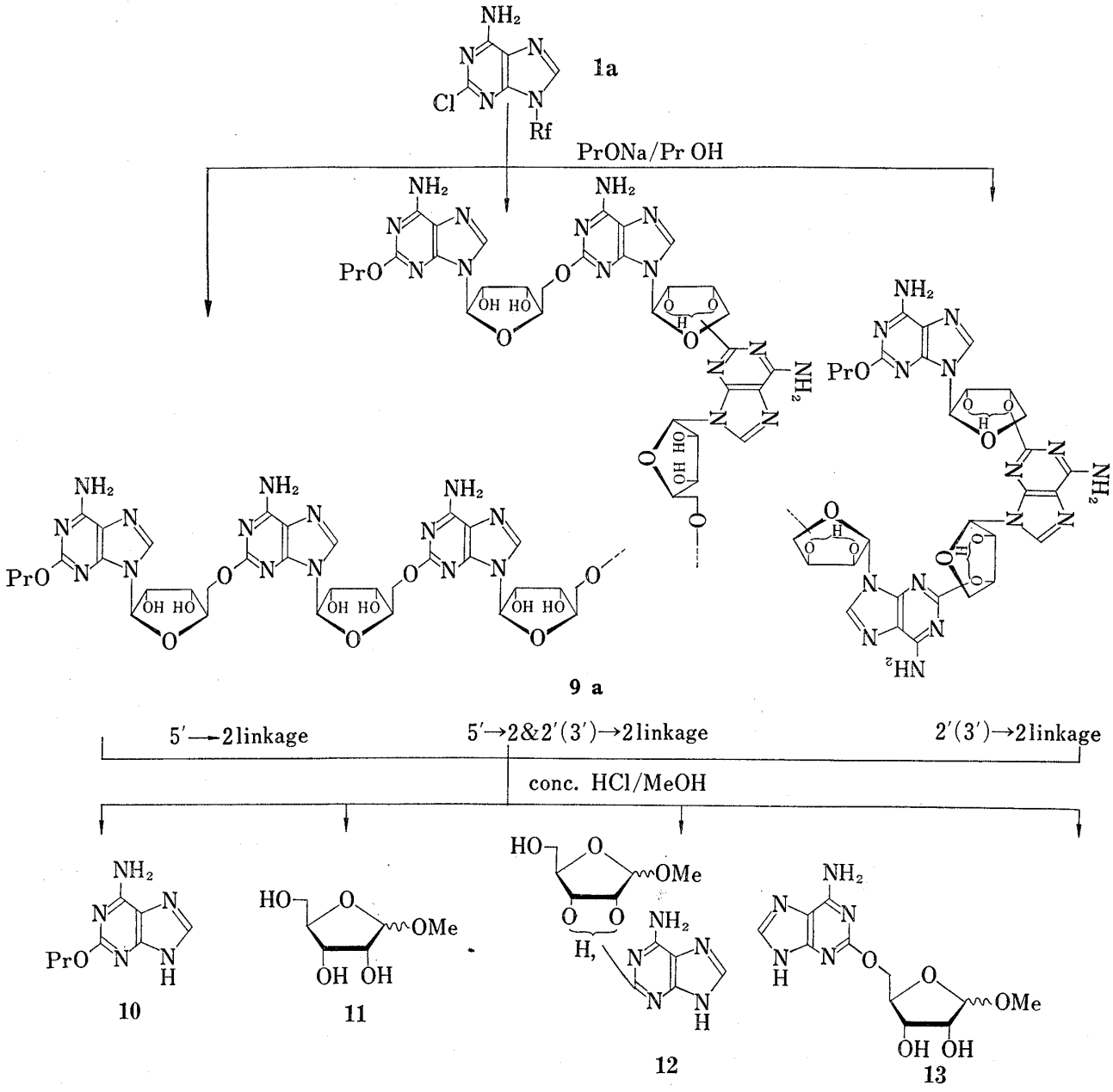


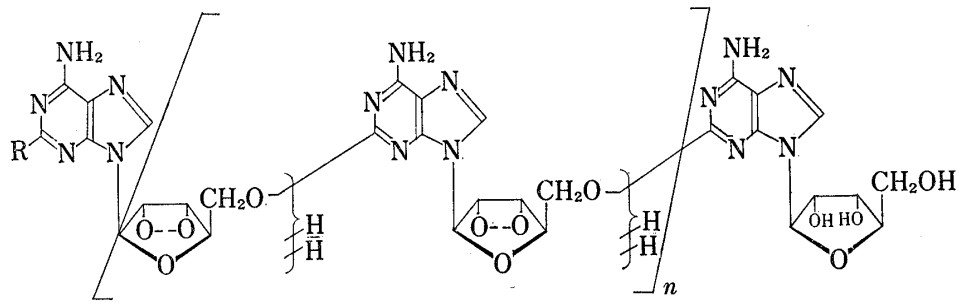
Chart 2

14) It has already been reported that heating of an alkaline solution of 6-chloro-9-β-D-ribofuranosylpurine in water afforded an oligomer.[15]
15) J.A. Montgomery and H.J. Thomas, *J. Org. Chem.*, **36**, 1962 (1971).
16) The elemental analysis of **9a** revealed that the oligomer had no chlorine atom.

thioinosine[17] as standard compounds. Above observations indicate the average polymerization degree of **9a** to be three. Degradation of **9a** with methanolic hydrogen chloride, followed by purification of the products with silica gel column chromatography enabled us to isolate two compounds (**10** and **11**) and a mixture of **12** and **13**, the latter being separated to **12** and **13** by paper electrophoresis (pH 9.2, borate). The structures of these compounds were established to be 2-propoxyadenine (**10**), 1-O-methyl-D-ribofuranose (**11**), 1-O-methyl-2(or 3)-(6-amino-purin-2-yl)-D-ribofuranose (**12**) and 1-O-methyl-5-(6-amino-purin-2-yl)-D-ribofuranose (**13**), on the basis of the UV absorption, NMR spectra, the paper electrophoresis, and the color reaction with a periodate-benzidine test.[18] The yields of **12** and **13** were approximately equal (Chart 2).

The reaction of **1a** with some other sodium alkoxides, *e.g.* sodium iso-propoxide, sodium butoxide, sodium *t*-butoxide and sodium amyloxide afforded the corresponding oligomers. The *t*-butoxyoligomer had a terminal 2-chloroadenosine structure,[19] of which one hydroxyl group in the ribose moiety was also substituted to form an ether linkage.

TABLE II. 2-Alkoxyadenosine Oligomers (**9**)



Compd.	R–	Formula	$[\alpha]^{25}_{D}$ (°) $c=0.5$, DMSO	UV absorption spectra λ_{max} nm ($\varepsilon \times 10^{-3}$)	Coronary dilator potency
9a	$CH_3(CH_2)_2O$–	$C_{33}H_{41}O_{13}N_{15}\cdot H_2O$	−78.6	pH 1: 250 (sh), 271 (31.0); pH 13: 266 (31.0)	0.66
9b	$(H_3C)_2CHO$–	$C_{163}H_{184}O_{65}N_{80}\cdot 3H_2O$	−89.3	pH 1: 270 (120.0); pH 13: 265 (155.0)	0.30
9c	Cl	$C_{120}H_{139}O_{51}N_{60}Cl\cdot 5H_2O$	−82.1	pH 1: 271 (100.0); pH 13: 266 (122.0)	—

S-Substituted 2-Mercaptoadenosine (14) and Its Analogs

Treatment of 5-amino-4-cyano-1-β-D-ribofuranosylimidazole[20] (AICN-riboside) with carbon disulfide in pyridine afforded 2,6-dimercapto-9-β-D-ribofuranosylpurine (**15**) and yellow needles ($C_{10}H_{12}O_4N_4S_2$) (**16**). The structure of **15** was confirmed by its conversion to 2,6-dimethylthio-9-β-D-ribofuranosylpurine[21] (**17**). Compound (**16**) was assigned the 7-imino-5-mercapto-3-(β-D-ribofuranosyl)imidazolo[4,5-*d*][1,3]thiazine structure by analogy with

17) This compound was prepared by reaction of 2-mercaptoinosine with 5′-deoxy-5′-iodoinosine. UV $\lambda^{pH\ 1}_{max}$ nm: 254, 262 (sh), 280 (sh); $\lambda^{pH\ 12}_{max}$ nm: 226, 262. NMR (d_6-DMSO) δ: 5.80 (2H, m, $2H_1'$), 8.05, 8.20, 8.30 (3H, 3s, $2H_8$, H_2).
18) M. Viscontini, D. Hoch, and P. Karrer, *Helv. Chim. Acta*, **38**, 642 (1955).
19) The elemental analysis of the oligomer showed the presence of chlorine atom (1.05%).
20) K. Suzuki and I. Kumashiro, Japan Patent, 5225 (1969).
21) *a*) M. Ikehara, E. Ohtsuka, H. Uno, K. Imamura, and Y. Tonomura, *Biochim. Biophys. Acta*, **100**, 471 (1965); *b*) M. Honjo, Y. Furukawa, Y. Yoshioka, A. Imada, S. Fuji-i, K. Ohtsu, T. Kimura, T. Komeda, and T. Matsumoto, *Takeda Kenkyusho Nempo*, **27**, 1 (1968).

the reaction of 3-amino-4-cyanopyrazole with carbon disulfide.[22] Heating of **16** with methanolic ammonia brought about isomerization to **15**. Treatment of **16** with methyl iodide in dimethylformamide (DMF) afforded pale yellow crystals ($C_{11}H_{15}O_4N_4S_2I$) (**18**), which was presumed to be the hydrogen iodide salt of the 5-S-methyl derivative of **16**. The reaction of **16** with methyl iodide in an aqueous sodium hydroxide yielded a mixture of two UV absorbing compounds in addition to **18** (free type[23]). Compound (**17**) and colorless needles ($C_{11}H_{14}O_4N_4S_2$) (**19**) were isolated by silica gel column chromatography. Treatment of **19** with methanolic ammonia yielded 2-methylthioadenosine[13] and 2-methoxyadenosine. Compound (**19**) was thus assigned the 6-mercapto-2-methylthio-9-β-D-ribofuranosylpurine structure. Formation of three compounds (**17**, **18** and **19**) by methylation of **16** can be explained as follows: The compound (**16**) is methylated to **18**, while **16** is converted to **15** by ring inversion and then

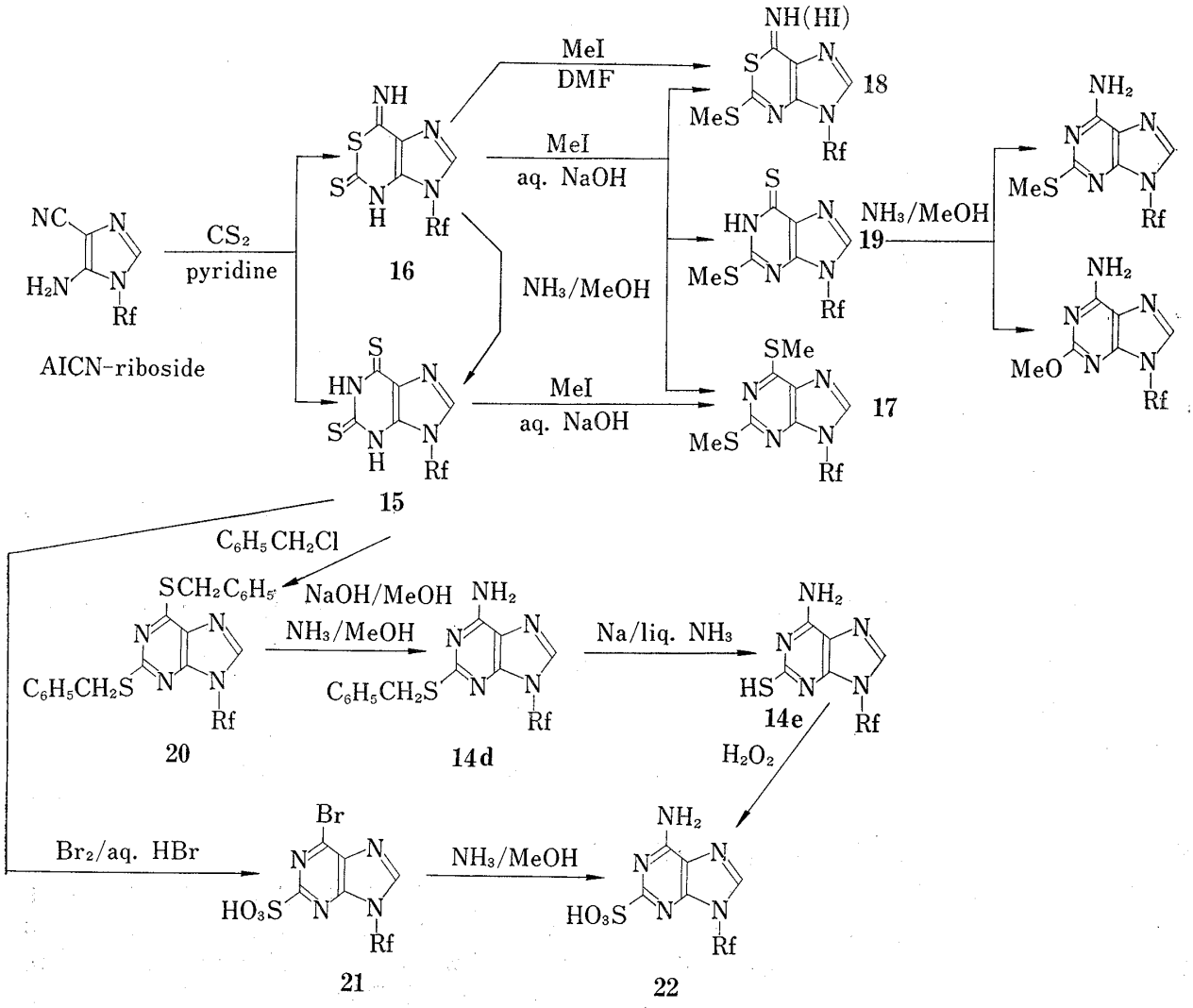


Chart 3

22) E.C. Taylor, R.N. Warrener, and A. McKillop, *Angew. Chem.*, **78**, 333 (1966).

23) The free type of **18** might be assigned the 4-cyano-5-methyldithiocarbamido-1-β-D-ribofuranosylimidazole structure.

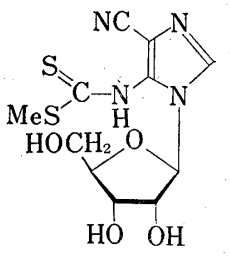
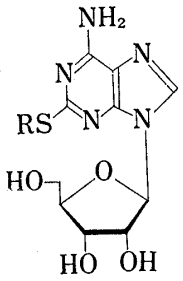


Table III. S-Substituted 2-Mercaptoadenosines (**14**)



Compd.	R-	Formula	mp (°)	UV absorption spectra λ_{max} nm	Coronary dilator potency
14a	$HO(CH_2)_2$–	$C_{12}H_{17}O_5N_5S$	207—208		0.11
14b	$CH_3O(CH_2)_2$–	$C_{13}H_{19}O_5N_5S$	amorph.		0.53
14c	C_6H_5–	$C_{16}H_{17}O_4N_5S \cdot H_2O$	125—126	MeOH: 235, 279	0.59
14d	$C_6H_5CH_2$–	$C_{17}H_{19}O_4N_5S$	158		0.06
14e	H–	$C_{10}H_{13}O_4N_5S \cdot H_2O$	190—191 (decomp.)	pH 1: 240, 245(sh), 293; pH 13: 243, 281, 300 (sh)	0.51

methylated to **17**. The pH value of the reaction mixture decreases gradually by hydrolysis of methyl iodide. The mercapto group at the 2-position of **15** is dissociated easier than that at the 6-position and its preferential methylation leads to **19**.

The reaction of **15** with benzyl chloride in methanolic sodium hydroxide afforded 2,6-dibenzylthio-9-β-D-ribofuranosylpurine (**20**). Treatment of **20** with methanolic ammonia gave 2-benzylthioadenosine (**14d**). Hydrogenation of **14d** with sodium metal in liquid ammonia and treatment of the reaction mixture afforded 2-mercaptoadenosine[24] (**14e**) as pale yellow needles. The reaction of **15** with bromine in hydrobromic acid yielded 6-bromo-2-sulfo-9-β-D-ribofuranosylpurine (**21**), whose structure was confirmed by its conversion to 2-sulfoadenosine[24] (**22**) by the reaction with methanolic ammonia and the positive Beilstein test (Chart 3). The reaction of AICN-riboside with carbon disulfide in methanolic ammonia and with phenyl-(or methyl-)isothiocyanate in pyridine afforded 5-amino-4-thiocarbamoyl-1-β-D-ribofuranosylimidazole[25] (**23**) and N^1-phenyl-(or methyl-)2-mercaptoadenosine (**24a, b**). Hydrogenation of the latter compound with Raney nickel gave N^1-phenyl(or methyl-[26])-adenosine (**25a, b**). The reaction of 2′,3′,5′-tri-O-acetyl-2-bromoadenosine (**26**), with thioacetic acid in pyridine yielded 2-mercapto-N^6,S,$O^{2'}$,$O^{3'}$,$O^{5'}$-pentaacetyladenosine (**27**). Treatment of **27** with methanolic ammonia led to formation of **14e**, which was difficult to be isolated, because the compound was readily oxidized to the disulfide[24] (**28**) (Chart 4). Some S-substituted 2-thioadenosines (**14a—c**) were prepared by reaction of **14e** with appropriate halides or by the analogous route to **14d**.

N^2-Substituted 2-Aminoadenosines (**29**)

The reaction of 2-chloroadenosine (**1a**) with various amines gave the corresponding N^2-substituted 2-aminoadenosines (**29**). No reaction took place, when **1a** was allowed to react with aniline or ring-substituted anilines. Prolonged heating of the reaction mixture of 2-bromoadenosine (**1b**) and aniline yielded 2-phenylaminoadenosine (**29e**) in very low yields, because of fission of the nucleosidic linkage. On the contrary, heating of 2-bromoinosine

24) The synthesis of this compound was recently reported by another group: K. Kikugawa, H. Suehiro, and M. Ichino, *J. Med. Chem.*, **16**, 1381 (1973).
25) A. Yamazaki, I. Kumashiro, T. Takenishi, and M. Ikehara, *Chem. Pharm. Bull.* (Tokyo), **16**, 2172 (1968).
26) J.W. Jones and R.K. Robins, *J. Am. Chem. Soc.*, **85**, 193 (1963).

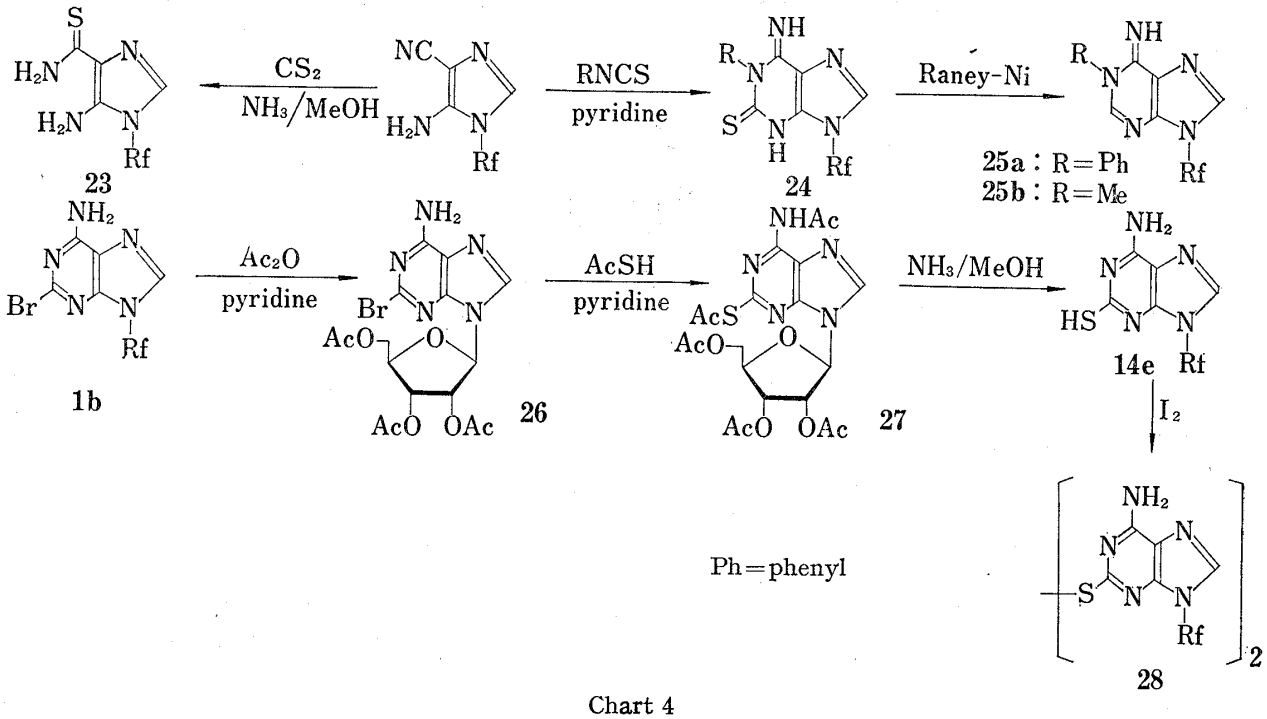
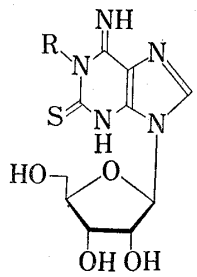


Chart 4

TABLE IV. N^1-Substituted 2-Mercaptoadenosines (24)



Compd.	R–	Formula	mp (°)	UV absorption spectra λ_{max} nm ($\varepsilon \times 10^{-3}$)	Coronary dilator potency
24a	C_6H_5–	$C_{16}H_{16}O_4N_5S \cdot 1/2H_2O$	amorph.	EtOH: 258 (11.1), 301 (22.9)	0.06
24b	CH_3–	$C_{11}H_{15}O_4N_5S$	234—235	pH 1: 239 (15.1), 293 (17.5); pH 13: 244 (13.0), 284 (14.6)	0.08

(**3b**) with aniline in methanol gave 2-phenylaminoinosine (**30**) in high yield. Acetylation of **30** with acetic anhydride in pyridine or in the presence of catalytic amount of sulfuric acid afforded the tetraacetate (**31**) as a main product and the aimed triacetate (**32**) in low yield. When **30** was acetylated with acetyl chloride in acetic acid, **32** was obtained in high yield. Treatment of **31** with methanolic ammonia yielded **30**. Comparison of the NMR spectrum ($CDCl_3$) of **31** with that of **32** revealed that one-proton signal (s, –N<u>H</u>–C_6H_5) at δ 8.8 of **32** had disappeared and that a low-field shift of the signal (1H, s, –N^1H) at δ 10.7 of **32** to δ 13.1 of **31** had occurred. Compound (**31**) was thus assigned the N^2-phenyl-N^2,$O^{2'}$,$O^{3'}$,$O^{5'}$-tetraacetylguanosine structure. The low-field shift can be accounted for by the presence of hydrogen bonding between the N^2-acetyl and the N^1-hydrogen. An attempt to chlorinate **31** with the Vilsmeier reagent was unsuccessful and the starting material was recovered. This can be explained in terms of the fixation of N^1-hydrogen with the hydrogen bonding and therefore may support the validity of the structure (**31**). A high-field shift of the 5′-protons

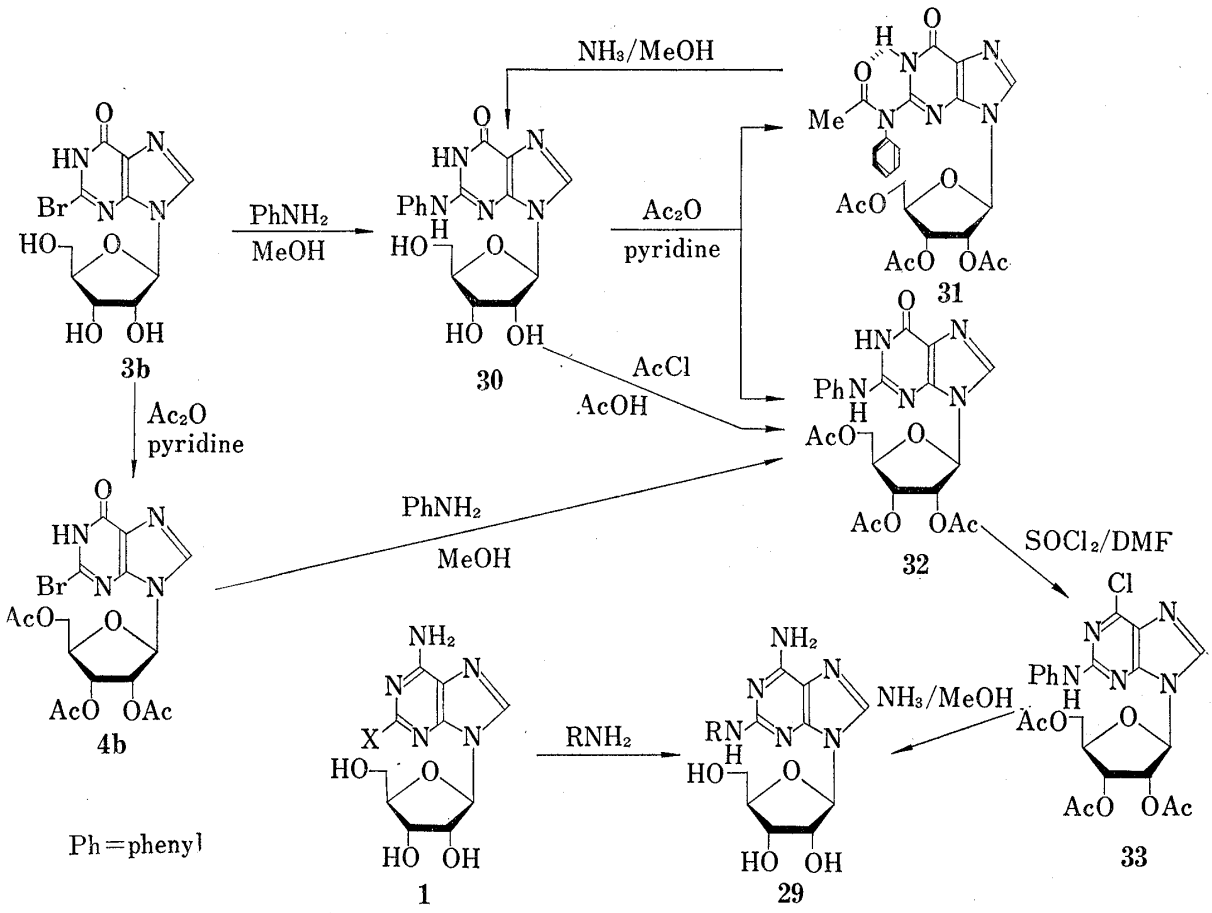


Chart 5

from δ 4.30 of **32** to δ 3.75 of **31** can also be understood in terms of the shielding effect by the benzene ring, which occupies the fixed position by the above-mentioned hydrogen bonding.

An alternative synthesis of **32** was achieved in high yields by treatment of 2-bromo-2′,3′,5′-tri-O-acetylinosine (**4b**) with aniline in methanol. The reaction of **32** with the Vilsmeier reagent gave 6-chloro-2-phenylamino-9-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)purine (**33**), which was converted with methanolic ammonia to 2-phenylaminoadenosine (**29e**) (Chart 5).

2-Alkyl- and-Aryl-adenosines (34)

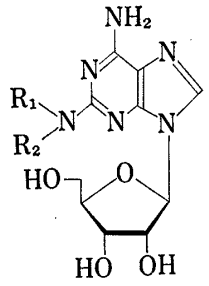
Neither 2-alkyl- nor aryladenosines have so far been reported except 2-methyladenosine.[27] Therefore, we synthesized various analogs by a new route, allowing AICN-riboside to react with alkyl- and aryl-nitriles in methanolic ammonia (Chart 6) or by the analogous route[27] to 2-methyladenosine.

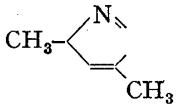
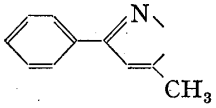
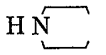
The Structure-Coronary Vasodilating Activity Relationship

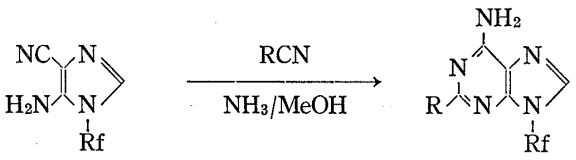
We have synthesized many new 2-substituted adenosines, among which some analogs possessed a comparable or superior vasodilating potency to that of adenosine; these include **5b—f, h, k—m, o, p, 29d, e** and **34b**.[7] It should be noted that **29e** had not only a strong potency, but also manifested a longer duration of the effect than that of 2-chloroadenosine,[5] a potent vasodilator. Replacement of the O-atom in the 2-alkoxyadenosines with the NH-group or S-atom led to decrease of the potency: RO–>RNH–>RS– (*e.g.* **5b**>**29a**>2-propylthioadenosine;[28] **5l**>**29c**>**14a**). Replacement of the O-atom in the 2-aryloxyadenosines, however, led to increase or decrease of the potency: RNH–>RO–>RS– (*e.g.* **29e**>**5o**>**14c**).

27) A. Yamazaki, I. Kumashiro, and T. Takenishi, *J. Org. Chem.*, 33, 2583 (1968).
28) M.H. Maguire, D.M. Nobbs, R. Einstein, and J.C. Middleton, *J. Med. Chem.*, 14, 415 (1971).

TABLE V. N^2-Substituted 2-Aminoadenosines (**29**)



Compd.	R_1–	R_2–	Formula	mp (°)	UV absorption spectra λ_{max} nm ($\varepsilon \times 10^{-3}$)	Coronary dilator potency
29a	$CH_3(CH_2)_2$–	H–	$C_{13}H_{20}O_4N_6$	140		0.65
29b	$CH_3O(CH_2)_2$–	H–	$C_{13}H_{20}O_5N_6 \cdot 1/2H_2O$	128—129		—
29c	$HO(CH_2)_2$–	H–	$C_{12}H_{18}O_5N_6$	190—191	pH5: 221, 259, 288	0.42
29d		H–	$C_{16}H_{24}O_4N_6 \cdot 1/2H_2O$	148—150		2.20
29e	C_6H_5–	H–	$C_{16}H_{18}O_4N_6$	244—245	pH 2: 230 (sh), 272 (16.8); pH 12: 242 (16.5), 277 (19.7)	6.75
29f	*p*-$CH_3C_6H_5$–	H–	$C_{17}H_{20}O_4N_6$	164—165	MeOH: 211, 250, 279, 289	1.75
29g	*p*-$CH_3OC_6H_5$–	H–	$C_{17}H_{20}O_5N_6$	195—197	MeOH: 252, 276, 291 (sh)	2.37
29h	$C_6H_5CH_2$–	H–	$C_{17}H_{20}O_4N_6 \cdot H_2O$	100—105		0.17
29i	C_6H_5–$(CH_2)_2$–	H–	$C_{18}H_{22}O_4N_6 \cdot H_2O$	125—128		0.60
29j			$C_{15}H_{19}O_4N_7$	288		0
29k			$C_{20}H_{21}O_4N_7$	241—242		0.13
29l			$C_{14}H_{21}O_4N_7$	240(decomp.)	pH 1: 225, 260, 297; pH 7: 262, 283	0



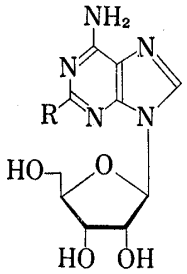
34

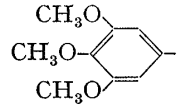
Chart 6

In both cases, the S-substituted analogs showed the weakest potency. The 2-alkoxy-[29] and alkylthio-adenosines[28] showed the maximal potency, when their carbon number of the straight chain was three. No definite structure activity relationship is seen in the alkyladenosine series. Introduction of the double bond or branched chain to the 2-alkoxy group brought about a significant decrease of the potency (*e.g.* **5b** *vs.* **5m**; **5c** *vs.* **5n**; **5e** *vs.* **5j**; **5c** *vs.* **5k**), while introduction of the methoxyl, ethoxyl or hydroxyl group to the terminal of 2-alkoxy chain led to increase of the potency, among which the hydroxyl group had the strongest effect (**5a** *vs.* **5e**, **5f**, **5l**).

29) The 2-alkoxyadenosines possessed the following potencies:[7] MeO (0.31), EtO (0.63), PrO (2.55), BuO (2.41), AmO (0.22) and H (1.00).

TABLE VI. 2-Alkyl- and -Aryl-adenosines (**34**)



Compd.	R–	Formula	mp (°)	UV absorption spectra λ_{max} nm ($\varepsilon \times 10^{-3}$)	Coronary dilator potency
34a	CH_3CH_2–	$C_{12}H_{17}O_4N_5 \cdot 1/4H_2O$	amorph.		0.12
34b	$CH_3(CH_2)_3$–	$C_{14}H_{21}O_4N_5 \cdot H_2O$	amorph.	pH 2: 259;pH 7: 264; pH 12: 264	1.10
34c	*p*-ClC_6H_5–	$C_{16}H_{16}O_4N_5Cl$	258	EtOH: 251, 245 (sh)	<0.01
34d	*p*-$CH_3C_6H_5$–	$C_{17}H_{19}O_4N_5 \cdot 1/2H_2O$	153—154		0.07
34e	*p*-$CH_3OC_6H_5$–	$C_{17}H_{19}O_5N_5$	250—251		0.47
34f		$C_{19}H_{23}O_7N_5 \cdot 1/2H_2O$	99—101	H_2O: 221, 260, 294	0.09
34g	C_6H_5–CH_2–	$C_{17}H_{21}O_4N_5$	amorph.		0.11
34h		$C_{14}H_{15}O_5N_5 \cdot 1/2H_2O$	135—140	0.1N HCl: 214 (19.0), 284 (14.8), 317 (20.5); H_2O: 252 (sh), 258 (18.8), 286(sh), 299 (19.4); 0.1N NaOH: 252 (sh), 258 (18.8), 286 (sh), 299 (19.2)	0.05—0.13
34i		$C_{14}H_{15}O_4N_5S$	250	0.1N HCl: 212 (20.9), 273 (12.7), 323 (15.9); H_2O: 253 (16.6), 306 (15.4); 0.1NNaOH: 252 (17.2), 307 (15.5)	0.23
34j	C_6H_5–	$C_{16}H_{17}O_4N_5$	228—229	0.1N HCl: 270 (16.2), 294 (sh); H_2O: 238.5 (23.4), 268 (14.3); 0.1N NaOH: 238.5(24.1), 268(14.3)	0.24
34k	*p*-$NO_2C_6H_5$–	$C_{16}H_{16}O_6N_6$	265	0.1N HCl: 264 (15.5), 315 (13.2); H_2O: 217.5 (22.4), 262(17.4), 318 (11.2); 0.1N NaOH: 220.5 (20.7), 263 (16.9), 320 (10.2)	—
34l		$C_{15}H_{16}O_4N_6 \cdot 1/2\ H_2O$	148—150	0.1N HCl: 233 (15.2), 263 (13.5), 328 (8.3); H_2O: 231.5 (20.9), 262 (13.8), 290 (9.9); 0.1N NaOH: 231.5 (20.8), 262 (13.7), 289 (9.8)	0.12
34m		$C_{15}H_{16}O_4N_6$	265—270	0.1N HCl: 238 (18.9), 260 (14.7), 303 (7.6); H_2O: 233 (24.0), 263 (14.0), 292 (sh); 0.1N NaOH: 233 (23.9), 263 (13.8), 292 (sh)	—
34n		$C_{15}H_{16}O_4N_6$	300	0.1N HCl: 246 (18.9), 270 (12.7), 332 (6.9); H_2O: 233.5 (23.8), 268 (13.5), 305 (sh); 0.1N NaOH: 234 (24.2), 268 (14.0), 305 (sh)	0.25

Experimental[30]

2-Bromoadenosine (1b)——A solution of **2b** (22 g) in 20% methanolic ammonia (180 ml) was heated in an autoclave at 60° for 6 hr and the reaction mixture was evaporated to dryness. The residue was triturated

30) All melting points were uncorrected. Paper electrophoresis (PE) was carried out on Whatman No. 1 filter paper at 22 v/cm for 1 hr using 0.05 M borate buffer (pH 9.2). The following silica gels (E. Merck) were used: "DC Alufolien Kieselgel F 254" for TLC and "Kieselgel 0.05—0.2 mm" for column chromatography.

with AcOEt (200 ml) to give a powder, which was recrystallized from EtOH yielding pale brown crystals (12.2 g). mp 138—139°. UV λ_{max}^{MeOH} nm: 265, Beilstein test (+). NMR (d_6-DMSO) δ: 3.73 (2H, m, $2H_{5'}$), 4.10 (1H, m, $H_{4'}$), 4.24 (1H, m, $H_{3'}$), 4.54 (1H, t, $H_{2'}$), 5.94 (1H, d, $J=5$ Hz, $H_{1'}$), 7.53 (2H, brond s, NH_2), 8.50 (1H, s, H_8).

2,6-Dichloro-9-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)purine (**2a**)——A mixture of 2-chloroinosine (**3a**) (NH_4 salt,[12a] 50 g), Ac_2O (200 ml) and pyridine (200 ml) was stirred vigorously at 0° for 4 hr. After addition of EtOH (100 ml), the reaction mixture was concentrated *in vacuo* (100 ml) and added with $CHCl_3$ (total volume 550 ml). The solution was washed with water (500 ml×4) and 0.1% $NaHCO_3$ (500 ml), and dried over Na_2SO_4. To the $CHCl_3$ layer were added $SOCl_2$ (41 ml) and DMF (10 ml). The mixture was refluxed for 2 hr, cooled to room temperature and poured portionwise into a stirred mixture of ice (250 ml) and water (250 ml). The emulsion, after addition of $CHCl_3$ (100 ml), was shaken and then kept until the clear $CHCl_3$ layer was obtained. The layer was washed with water (500 ml), 3% $NaHCO_3$ (500 ml) and water (500 ml) successively, and dried over Na_2SO_4. The $CHCl_3$ solution was evaporated to dryness *in vacuo*. Addition of MeOH (120 ml) to the residue afforded crude yellow crystals (40 g). TLC [silica gel, $CHCl_3$·MeOH (19: 1)]: *Rf* 0.90: 2-chloro-9-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)inosine *Rf* 0.75. UV λ_{max}^{MeOH} nm: 253, 273 (lit.[8] $\lambda_{max}^{pH\ 1\ and\ 7}$ nm: 252, 273); λ_{max}^{MeOH} nm: 232.

2-Bromo-6-chloro-9-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)purine (**2b**)——To a solution of **4b** (30 g) in $CHCl_3$ (300 ml) were added DMF (9 ml) and $SOCl_2$ (40 ml). The mixture was refluxed for 3 hr and evaporated to dryness. The residue was dissolved in $CHCl_3$ (700 ml) and the solution was washed with ice-water (300 ml×5), dried over Na_2SO_4 and evaporated to dryness. Recrystallization of the residue from EtOH (100 ml) gave colorless crystals (24.5 g). mp 153—154°. UV λ_{max}^{MeOH} nm: 253, 274; λ_{min}^{MeOH} nm: 234, 258. *Anal.* Calcd. for $C_{16}H_{16}O_7N_4BrCl$: C, 39.08; H, 3.28; N, 11.40. Found: C, 39.68; H, 3.31; N, 11.66.

2-Bromo-2′,3′,5′-tri-O-acetylinosine (**4b**)——To a stirred suspension of 2-bromoinosine (**3b**) (NH_4 salt,[12b] 31 g) in an ice-cooled mixture of $CHCl_3$ (400 ml) and Ac_2O (150 ml) was added dropwise pyridine (150 ml). The stirring was continued at 0° for 1 hr and at room temperature for an additional 1 hr. The pale yellow solution was concentrated *in vacuo* below 45° (bath temperature). The residue was dried by coevaporation with added toluene or EtOH to deposit crystals. Recrystallization from EtOH afforded pale yellow crystals (33 g). mp 178—180°. UV $\lambda_{max}^{pH\ 2}$ nm: 254; $\lambda_{max}^{pH\ 12}$ nm: 258.5. *Anal.* Calcd. for $C_{16}H_{17}O_8N_4Br$: C, 40.61; H, 3.62; N, 11.84; Br, 16.89. Found: C, 40.70; H, 3.65; N, 11.89; Br, 17.09.

2-Propoxyadenosine (**5b**)——To a hot solution of NaOH (400 mg) in PrOH (10 ml) was added **1a** (450 mg). The mixture was refluxed with stirring for 3 hr and evaporated to dryness *in vacuo*. The residue was dissolved in water (5 ml) and the solution was adjusted with 1 N HCl to pH 7 to deposit **9a**. Compound (**9a**) was filtered off and the filtrate was evaporated to dryness *in vacuo*. The residue was dissolved in EtOH and to the solution was added silica gel (1 g) with shaking. After evaporation of EtOH, the silica gel was placed on top of a fresh prepared silica gel (4 g) column. The column was eluted with MeOH·$CHCl_3$ (1: 9).[31] Fractions containing **5b** were collected and evaporated to dryness. The residue was washed with ether to give a white powder (250 mg, 50%). UV $\lambda_{max}^{H_2O}$ nm: 252 (sh), 268; $\lambda_{max}^{0.1N\ HCl}$ nm: 248, 275.

2-Butoxyadenosine (**5c**)——a) A mixture of **7** (3.7 g) and 40% AcOH (80 ml) was kept at 35° for 2 days. The solution was shaken with $CHCl_3$ (45 ml×3) and the aqueous layer was evaporated to dryness *in vacuo*. Recrystallization of the residue from water gave colorless needles (2.4 g). mp 155°. UV $\lambda_{max}^{H_2O}$ nm: 254 (sh), 268; $\lambda_{max}^{pH\ 1}$ nm: 248, 276; $\lambda_{max}^{pH\ 13}$ nm: 254, 268. b) A mixture of **8** (4.8 g), Ac_2O (30 ml) and pyridine (40 ml) was stirred at room temperature for 30 min. The solution was evaporated to dryness and the residue was dissolved in $CHCl_3$ (300 ml). The $CHCl_3$ solution was washed with water and dried over Na_2SO_4. To the solution containing 2-butoxy-2′,3′,5′-tri-O-acetylinosine [TLC (silica gel, MeOH–$CHCl_3$ 1: 9): *Rf* 0.60. Compound (**8**) *Rf* 0.09] were added $SOCl_2$ (12 ml) and DMF (5.7 ml). The mixture was heated for 2.5 hr and the solution (*Rf* 0.95) was poured into ice-water (500 ml). The organic solvent layer was washed with water several times, dried over Na_2SO_4 and evaporated to dryness to afford a resin [2-butoxy-6-chloro-9-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)purine]. The resin was treated with 20% methanolic ammonia (120 ml) in an autoclave at 170° for 4 hr. The reaction mixture was evaporated to dryness *in vacuo*. Recrystallization of the residue from MeOH and then from water gave colorless needles (2.0 g). mp 155°.

2-Chloro-2′,3′-O-ethoxymethylideneadenosine (**6**)——A mixture of **1a** (6.6 g), $HC(OEt)_3$ (55 ml), *p*-TsOH (0.8 g) and DMF (110 ml) was stirred at 30° for 30 min and poured into a solution of $NaHCO_3$ (0.4 g) in ice-water (600 ml). The mixture was extracted with $CHCl_3$ (100 ml×5). The $CHCl_3$ layer was washed with water (50 ml×4) and chromatographed over silica gel (20+80 g) by using $CHCl_3$ (1 liter) and 2% MeOH·$CHCl_3$ (2.6 liters) successively as eluents. Fractions containing **6** were collected and evaporated to dryness *in vacuo*. Recrystallization of the residue from MeOH afforded colorless needles (5.7 g), mp 191°. NMR (d_6-DMSO) δ: 1.26 (3H, t, $-C\underline{H}_3$), 3.62 (4H, m, $-OC\underline{H}_2CH_3$, $2H_{5'}$), 4.34 (1H, m, $H_{4'}$), 4.8—5.4 (3H, m, $H_{2'}$, $H_{3'}$, –OH), 6.16 (1H, s, $>C\underline{H}$), 6.26 (1H, d, $H_{1'}$), 7.8 (2H, s, NH_2), 8.4 (1H, s, H_8).

31) These procedures were hereafter described for short as follows: the residue was chromatographed over silica gel (1+4 g) by using MeOH·$CHCl_3$ (1: 9) as eluent.

2-Butoxy-2′,3′-O-ethoxymethylideneadenosine (7)——A mixture of **6** (5.6 g), BuOH (62 ml) and NaOH (3.1 g) was stirred at 90° for 1 hr, neutralized with conc. HCl and evaporated to dryness *in vacuo*. The residue was extracted with $CHCl_3$ (200 ml). The $CHCl_3$ layer was washed with water three times and chromatographed over silica gel (11+45 g) by using $CHCl_3$ (600 ml) and then 2% MeOH·$CHCl_3$ (800 ml) as eluents. Fractions containing **7** were combined and evaporated to dryness *in vacuo* to afford a resin (3.7 g). NMR ($CDCl_3$) δ: 0.7—2.0 (10H, m, $-OCH_2\underline{CH_2}\underline{CH_2}\underline{CH_3}$, $-CH_3$), 3.4—4.0 (4H, m, $2H_{5'}$, $-O\underline{CH_2}CH_3$), 4.0—4.8 (3H, m, $H_{4'}$, $O\underline{CH_2}CH_2CH_2CH_3$), 5.0—5.6 (3H, $H_{2'}$, $H_{3'}$, -OH), 5.7—6.3 (2H, $H_{1'}$, $>\underline{CH}$), 6.6 (2H, s, NH_2), 7.7 (1H, s, H_8).

2-Butoxyinosine (8)——To an ice-cooled and stirred suspension of **3a** (NH_4 salt,[12c] 9 g) in acetone (500 ml) was added dropwise pyrophosphoryl chloride (30 ml) and the stirring was continued for 1.5 hr. The pale yellow solution was poured into a mixture of 28% NH_4OH (150 ml) and ice-water (1 liter). The mixture was stirred for 1 hr and concentrated *in vacuo* to distill off excess NH_3 and acetone. The concentrate was chromatographed over activated charcoal (90 g) by using H_2O·EtOH·BuOH·conc. NH_4OH (48: 45: 5: 2) as eluent. The eluate was evaporated to dryness *in vacuo* to yield a resin (2-chloro-2′,3′-O-isopropylideneinosine, 12 g). A suspension of the resin in 1 N BuONa (800 ml) was refluxed for 2 hr. The reaction mixture was poured into an ice-water (600 ml) and adjusted with acid to pH 7.0. The solution was evaporated to dryness and the residue was extracted with $CHCl_3$. The $CHCl_3$ layer was dried over Na_2SO_4 and evaporated to dryness *in vacuo* to afford a resin (2-butoxy-2′,3′-O-isopropylideneinosine, 11 g). A mixture of the resin and 80% HCO_2H (100 ml), after stirring overnight at room temperature, was evaporated to dryness *in vacuo* to give 2-butoxy-5′-formylinosine. To this compound was added 20% NH_3·MeOH (60 ml) and the mixture, after stirring for 1 hr, was evaporated to dryness *in vacuo*. The residue was recrystallized from MeOH to afford colorless crystals (5.8 g), mp 214—216°.

2-Propoxyadenosine Oligomer (9a)——Sodium (100 mg) was dissolved in a mixture of PrOH (3 ml) and dioxane (3 ml) and to the solution was added **1a** (453 mg). The mixture, after stirring at 130° for 16 hr, was evaporated to dryness *in vacuo*. The residue was dissolved in water (3 ml) and the solution was adjusted with AcOH to pH 7 to deposit a white powder (400 mg). NMR (d_6-DMSO) δ: 1.0 (1H, t, $-CH_3$), 5.7—6.4 (1H, m, $H_{1'}$), 7.1—7.7 (2H, broad s, NH_2), 8.2 (1H, broad s, H_8).

Methanolysis of 9a——A mixture of **9a** (300 mg), MeOH (30 ml) and conc. HCl (3 ml) was refluxed at 110° for 6 hr and evaporated to dryness *in vacuo*. Addition of MeOH to the residue, followed by evaporation *in vacuo* was repeated to remove a trace of HCl. The residue was dissolved in a small amount of MeOH and the solution was chromatographed over silica gel (2+30 g) by using $CHCl_3$·MeOH (10: 1, 200 ml) as eluent. The eluate was concentrated and kept to afford crystals, 2-propoxyadenine (**10a**, 30 mg). TLC [silica gel, $CHCl_3$·MeOH (4: 1)]: *Rf* 0.42. $\lambda_{max}^{0.1N\ HCl}$ nm: 240, 273; $\lambda_{max}^{H_2O}$ nm: 250 (sh), 267; $\lambda_{max}^{0.1N\ NaOH}$ nm: 275. NMR (d_6-DMSO) δ: 0.75 (3H, t, $-CH_3$), 1.5 (2H, m, $-C\underline{H_2}CH_3$), 4.0 (2H, t, $-C\underline{H_2}-O-$), 6.9 (2H, broad s, NH_2), 7.8 (1H, broad s, H_8), 12.3 (1H, broad s, >NH). The silica gel column was next eluted with $CHCl_3$·MeOH (5: 1, 200 ml) and the eluate was evaporated to dryness. The residue was dissolved in water and the solution was passed through a column of activated charcoal (0.5 g). The effluent was evaporated to dryness giving a white resin, 1-O-methylribofuranose (**11**, 30 mg), which showed a positive color reaction with HIO_4–benzidine.[18] TLC: *Rf* 0.32. NMR ($CDCl_3$) δ: 3.5 (3H, s, $-OCH_3$), 3.9 (2H, s, $2H_{5'}$), 4.0—4.5 (3H, m, $H_{2',3',4'}$), 4.9 (1H, s, $H_{1'}$). The silica gel column was further eluted with $CHCl_3$·MeOH (5: 1, 300 ml) and the eluate was adsorbed on a column of activated charcoal (1 g). The column was eluted with H_2O·EtOH·BuOH·conc. NH_4OH (48: 45: 5: 2, 100 ml) and the eluate was evaporated to dryness yielding a crystalline substance (30 mg). The compound showed the same UV absorption spectra as those of 2-propoxyadenine and gave a single UV absorbing spot (*Rf* 0.17) on TLC, but was found to be a mixture on the basis of the NMR spectrum (d_6-DMSO $+D_2O$), which showed the presence of three CH_3O- signals (δ: 3.1, 3.2, 3.25). PE revealed the presence of two compounds in a ratio of 1: 1. One (**12**) remained at the original point and the other (**13**) migrated as far as adenosine. The mixture (20 mg) was adsorbed on a column (1.3×7.5 cm) of Dowex-1 (100—200 mesh, borate). The column was washed with water and eluted with 0.05 M borate buffer (400 ml). The eluate was desalted with activated charcoal (500 mg) and evaporated to dryness to give **12**. NMR (d_6-DMSO $+D_2O$) δ: 3.3, 3.35 (6H, 2s, 2-OCH_3), 5.1 (1H, s, $H_{1'}$), 7.9 (1H, s, H_8). The compound **12** was assigned the 1-O-methyl-2 (or 3)-(6-amino-2-purinyl)-D-ribofuranose structure and **13**, the 1-O-methyl-5-(6-amino-2-purinyl)-D-ribofuranose structure.

2-Benzylthioadenosine (14d)——A solution of **20** (350 mg) in 20% methanolic ammonia (5 ml) was heated in an autoclave at 180° for 16 hr. The reaction mixture was evaporated to dryness *in vacuo* and the residue was recrystallized from aq. MeOH giving colorless needles (250 mg), mp 158°.

2-Mercaptoadenosine (14e)——Sodium (115 mg) was added portionwise to a solution of **14d** (389 mg) in liq. NH_3 (5 ml), which was previously cooled with dry-ice·acetone. After 1 hr, NH_4Cl (300 mg) was added and the mixture was kept at room temperature to evaporate liq. NH_3. The slurry, after addition of MeOH, was evaporated to dryness *in vacuo* and this procedure was repeated several times. Addition of water (2 ml) and AcOH (0.1 ml) to the residue deposited crystals which were filtered by suction and dissolved in water (5 ml) containing conc. NH_4OH (a few drops). The solution was concentrated *in vacuo* to 2 ml, to which was added AcOH (0.1 ml) giving pale yellow needles (150 mg). mp 190—191° (decomp.). NMR (d_6-DMSO) δ: 3.36 (2H, m, $2H_{5'}$), 3.7—4.2 (2H, $H_{3'}$, $H_{4'}$), 4.46 (1H, t, $H_{2'}$), 5.76 (1H, d, J=6.0 Hz, $H_{1'}$), 8.16 (1H, s, H_8).

2,6-Dimercapto-9-β-D-ribofuranosylpurine (15) and 7-Imino-5-mercapto-3-β-D-ribofuranosylimidazol-[4,5-d][1,3]thiazine (16)——To a solution of 5-amino-4-cyano-1-β-D-ribofuranosylimidazole[20] (AICN-riboside, 1 g) in pyridine (70 ml) was added CS_2 (10 ml). The mixture was refluxed for 6 hr and evaporated to dryness giving a yellow brown powder. Recrystallization of the powder from water (80 ml) yielded yellow needles, **16** (0.35 g). mp 240°. TLC (silica gel, BuOH saturated with water): *Rf* 0.56. UV $\lambda_{max}^{pH\ 1}$ nm (ε): 233 (21000), 247.5 (17000), 305 (13600), 386 (8500); $\lambda_{max}^{pH\ 12}$ nm (ε): 222 (14800), 283.5 (23000), 332 (10000). *Anal.* Calcd. for $C_{10}H_{12}O_4N_4S_2$: C, 37.96; H, 3.82; N, 17.71; S, 20.27. Found: C, 37.64; H, 3.74; N, 17.73; S, 20.24. Concentration of the mother liquor deposited pale yellow needles, **15** (0.6 g). mp 240°. TLC: *Rf* 0.22. UV $\lambda_{max}^{pH\ 1}$ nm (ε): 254 (7700), 298.5 (26700), 344 (15200), $\lambda_{max}^{pH\ 12}$ nm (ε): 225.5 (15400), 280 (25500), 324 (12200). *Anal.* Calcd. for $C_{10}H_{12}O_4N_4S_2 \cdot H_2O$: C, 35.91; H, 4.21; N, 16.75; S, 19.17. Found: C, 36.07; H, 3.87; N, 16.45; S, 19.64.

Isomerization of 16——A solution of **16** (100 mg) in 20% methanolic ammonia (10 ml) was heated in an autoclave at 100° for 2 hr. The reaction mixture was evaporated to dryness and the residue was recrystallized from water to give pale yellow crystals, of which the UV absorption spectra and *Rf* value (TLC) were in accord with those of **15**.

2,6-Dimethylthio-9-β-D-ribofuranosylpurine (17)——To a solution of **15** (0.1 g) in 0.1 N NaOH (5 ml) was added CH_3I (0.2 ml). The mixture, after stirring at room temperature for 2 hr, was evaporated to dryness. The residue was dissolved in water, and the solution was adjusted to pH 3 and adsorbed on a column of activated charcoal (1 g). The column was washed with water and eluted with EtOH·H_2O·BuOH·conc. NH_4OH (45: 48: 5: 2, 100 ml). The eluate was evaporated to dryness and the pale yellow residue (90 mg) was dissolved in a small amount of EtOH. The soluinon was kept to deposite crystals. mp 150—155° (lit.[21b] 115—120°). UV λ_{max}^{EtOH} nm: 231, 260, 306; λ_{min}^{EtOH} nm: 244, 285.[21b] *Anal.* Calcd. for $C_{12}H_{16}O_4N_4S_2$: C, 41.84; H, 4.68; N, 16.27. Found: C, 41.63; H, 4.75; N, 15.87.

7-Imino-5-methylthio-3-β-D-ribofuranosylimidazolo[4,5-d][1,3]thiazine (HI salt) (18)——To a suspension of **16** (300 mg) in DMF (2 ml) was added dropwise CH_3I (0.3 ml). The mixture, after stirring at room temperature for 2 hr, was added with $CHCl_3$ (10 ml) to deposit a solid. The solid was filtered by suction and washed with $CHCl_3$ giving pale yellow crystals (250 mg). Beilstein reaction (+). UV $\lambda_{max}^{pH\ 7}$ nm: 227, 272 (sh). NMR (d_6-DMSO) δ: 2.90 (3H, s, $-SCH_3$), 3.83 (2H, q, $2H_{5'}$), 3.90—4.16 (2H, $H_{3'}$, $H_{4'}$), 4.50 (1H, $H_{2'}$), 6.03 (1H, d, J=5.0 Hz, $H_{1'}$), 8.76 (1H, s, H_8). *Anal.* Calcd. for $C_{11}H_{14}O_4N_4S_2 \cdot HI$: C, 28.83; H, 3.30; N, 12.23; S, 13.99. Found: C, 28.85; H, 2.99; N, 12.81; S, 14.03.

6-Mercapto-2-methylthio-9-β-D-ribofuranosylpurine (19)——To a suspension of **16** (0.5 g) in water (20 ml) were added 1N NaOH (3 ml) and MeI (1 ml). The resulting solution, after stirring at room temperature for 5 hr, was evaporated to dryness *in vacuo*. The residue[32] was dissolved in $CHCl_3$ and the solution was chromatographed over silica gel (4+16 g) by using $CHCl_3$·MeOH (9: 1) as eluent. The eluate was concentrated to deposit crystals, **17** (50 mg). The filtrate was evaporated to dryness to afford a pale yellow resin (100 mg), which was triturated with ether giving a white crystalline powder, **19** (80 mg). From the filtrate there was further obtained colorless needles, **19** (20 mg). mp 134—135°. NMR (d_6-DMSO) δ: 2.7 (3H, s, $-SCH_3$), 3.6 (2H, m, $2H_{5'}$), 3.7—4.5 (3H, m, $H_{2'}$,$_{3'}$,$_{4'}$), 5.4 (1H, d, J=4 Hz, $H_{1'}$), 8.0 (1H, s, H_8). UV $\lambda_{max}^{pH\ 2}$ nm: 248, 300; $\lambda_{max}^{pH\ 12}$ nm: 232, 297; $\lambda_{min}^{pH\ 2}$ nm: 284: $\lambda_{min}^{pH\ 12}$ nm: 267. *Anal.* Calcd. for $C_{11}H_{14}O_4N_4S_2$: C, 39.98; H, 4.27; N, 16.96. Found: C, 39.77; H, 4.27; N, 17.95.

Ammonolysis of 19——A solution of **19** (50 mg) in 20% methanolic ammonia (5 ml) was heated at 150° for 6 hr. PE of the reaction mixture showed the presence of two UV absorbing compounds (*ca.* 1: 1), M_{19} 0.90 [UV $\lambda_{max}^{pH\ 2}$ nm: 248: 274; $\lambda_{min}^{pH\ 12}$ nm: 254 (sh), 268; $\lambda_{min}^{pH\ 2}$ nm: 258] and M_{19} 0.68 [UV $\lambda_{max}^{pH\ 2}$ nm: 266, 280 (sh); $\lambda_{max}^{pH\ 12}$ nm: 235, 275; $\lambda_{min}^{pH\ 2}$ nm: 239; $\lambda_{min}^{pH\ 12}$ nm: 250], corresponding to 2-methoxyadenosine[13] and 2-methylthioadenosine,[13] respectively.

2,6-Dibenzylthio-9-β-D-ribofuranosylpurine (20)——To a solution of **15** (316 mg) in a mixture of 1 N NaOH (2.5 ml) and MeOH (2 ml) was added $C_6H_5CH_2Cl$ (300 mg). The mixture, after stirring at room temperature for 5 hr, was concentrated *in vacuo* and chromatographed over silica gel (1+4 g) by using $CHCl_3$–MeOH (39: 1) as eluent. Fractions containing **20** were evaporated to dryness to give a resin (350 mg). TLC [silica gel, $CHCl_3$·MeOH (19: 1)]: *Rf* 0.8. NMR (d_6-DMSO+D_2O) δ: 4.50 (2H, s, $-C\underline{H}_2C_6H_5$), 4.60 (2H, s, $-C\underline{H}_2C_6H_5$).

6-Bromo-2-sulfo-9-β-D-ribofuranosylpurine (21)——To an ice-cooled and stirred mixture of 47% HBr (5 ml) and MeOH (5 ml) were added **15** (0.5 g) and then dropwise Br_2 (1 ml). After 3 hr, the resulting solution was poured into an ice-water (100 ml), neutralized with 28% NH_4OH and desalted with a column of activated charcoal (6 g), using EtOH·H_2O·BuOH·28% NH_4OH (45: 48: 5: 2) as eluent. The eluate (300 ml) was evaporated to dryness *in vacuo* and the residue was triturated with EtOH to give a pale yellow crystalline powder (200 mg). The compound showed a single UV absorbing spot on PE and a positive Beilstein test. UV λ_{max}^{MeOH} nm: 270.

32) It was characterized by TLC [silica gel, $CHCl_3$·MeOH (5: 1)] to be a mixture of **17**, **18** (a minute amount) and **19**.

2-Sulfoadenosine (22)——a) To an ice-cooled and stirred solution of **14e** (300 mg) in 0.5 N NaOH (2 ml) was added dropwise 30% H_2O_2 (1.2 ml) and the mixture was kept in a refrigerator overnight. Addition of EtOH (10 ml) to the solution deposit a solid. The solid was washed with EtOH giving a white crystalline powder (250 mg). The compound showed a signle UV absorbing spot ($M_{\mathbf{14e}}$ 1.17) on PE. UV $\lambda_{max}^{0.1N\ HCl}$ nm: 258 (sh), 263; $\lambda_{min}^{0.1N\ HCl}$ nm: 235; $\lambda_{min}^{H_2O}$ nm: $\lambda_{min}^{H_2O}$ nm: 262; 233; $\lambda_{max}^{0.1N\ NaOH}$ nm: 262; $\lambda_{min}^{0.1N\ NaOH}$ nm: 236. *Anal.* Calcd. for $C_{10}H_{12}O_7N_5SNa \cdot 1/2H_2O$: C, 31.88; H, 3.46; N, 18.51. Found: C, 31.74; H, 3.50; N, 18.20. b) A solution of **21** (10 mg) in 20% methanolic ammonia (1 ml) was heated at 110° for 5 hr. PE of the reaction mixture revealed the presence of two UV absorbing compounds corresponding to **22** (a major compound, $\lambda_{max}^{pH\ 1\ and\ 5.}$ nm: 260) and 2-aminoadenosine (a minor compound; $\lambda_{max}^{H_2O}$ nm: 255, 281), respectively.

5-Amino-4-thiocarbamoyl-1-β-D-ribofuranosylimidazole (23)——A mixture of AICN-riboside (240 mg), CS_2 (76 mg) and 20% methanolic ammonia (4 ml) was heated in an autoclave at 180° for 6 hr. The reaction mixture was evaporated to dryness *in vacuo*, and the residue was recrysrtallized from MeOH giving colorless needle s(200 mg). PE: $M_{\text{AICN-riboside}}$ 0.85. UV $\lambda_{max}^{0.1N\ HCl}$ nm: 257 (sh), 280, 328; $\lambda_{min}^{0.1N\ HCl}$ nm: 235, 297; $\lambda_{max}^{pH\ 9}$ nm: 218, 245 (sh), 270, 330; $\lambda_{min}^{pH\ 9}$ nm: 234, 290. NMR (d_6-DMSO) δ: 5.55 (1H, d, J=5.0 Hz, $H_{1'}$), 7.35 (1H, s, H_2). *Anal.* Calcd. for $C_9H_{14}O_4N_4S \cdot 1/2\text{-}CH_3OH$: C, 39.30; H, 5.56; N, 19.30; S, 11.04. Found: C, 39.45; H, 5.52; N, 19.40; S, 11.19.

2-Mercapto-N¹-phenyladenosine (24a)——To a solution of AICN-riboside (1 g) in pyridine (80 ml) was added C_6H_5NCS (4 ml) and the mixture was refluxed for 6 hr. The pale yellow solution was evaporated to dryness *in vacuo* and the residue was shaken with a mixture of $CHCl_3$ (200 ml) and water (100 ml). The water layer was evaporated to dryness *in vacuo* giving a pale yellow powder (0.25 g). The $CHCl_3$ layer was chromatographed over silica gel (5+25 g) by using $CHCl_3$–MeOH (19: 1) as eluent to give an additional amount (100 mg) of **24a**. The compound gave a single UV absorbing spot on PE ($M_{\text{AICN-riboside}}$ 1.2). NMR (d_6-DMSO) δ: 5.9 (1H, d, J=6 Hz, $H_{1'}$), 7.1—7.9 (5H, m, =N–C_6H_5), 8.22 (1H, s, H_8), 8.47 (1H, broad s, H_{N^6}), 9.98 (1H, broad s, –SH).

2-Mercapto-N¹-methyladenosine (24b)——To a solution of AICN-riboside (1 g) in pyridine (80 ml) was added MeNCS (4 ml). The mixture was refluxed for 6 hr and evaporated to dryness. The residue was dissolved in MeOH and the solution was chromatographed over silica gel (4+40 g) by using $CHCl_3$·MeOH (9: 1) as eluent. Fractions No. 6 to 26 (one fraction 20 ml) were combined and evaporated to dryness. The residue was recrystallized from MeOH giving colorless needles, mp 196—198° (decomp.). The compound was assigned the 2′(3′)-O-N-methylthiocarbamoyl derivative, because its UV absorption spectra agreed very closely with those of **24b**. The similar treatment of fractions No. 27 to 34 afforded colorless needles, **24b** (90 mg). mp 234—235° (decomp.). NMR (d_5-DMSO) δ: 3.95 (3H, s, N^1-CH_3), 5.78 (1H, d, J=6 Hz, $H_{1'}$), 8.02 (1H, s, H_8), 8.47 (2H, broad s, =N^6H, =N^3H).

N¹-Phenyladenosine (25a)——A suspension of **24a** (40 mg) and Raney-Ni (0.1 ml) in EtOH was refluxed for 6 hr. TLC [silica gel, $CHCl_3$·MeOH (4: 1)] and PC [Whatman No. 1, BuOH·AcOH·H_2O (5: 2: 3), ascending method] showed the presence of a single UV absorbing compound, which migrated the same distance as that of N^6-phenyladenosine,[33] but possessed the different UV absorption spectrum (λ_{max}^{EtOH} nm: 267) from that (λ_{max}^{EtOH} nm: 299) of N^6-phenyladenosine.

N¹-Methyladenosine (25b)——A suspension of **24b** (10 mg) and Raney Ni (0.2 ml) in EtOH (5 ml) was refluxed for 6 hr. PE revealed the presence of a major UV absorbing compound ($M_{\text{adenosine}}$ 0.5) possessing the same UV absorption spectrum [$\lambda_{max}^{H_2O}$ nm: 258, 265 (sh)] as the reported one.[26]

2-Bromo-2′,3′,5′-tri-O-acetyladenosine (26)——A solution of **1b** (500 mg) in a mixture of Ac_2O (5 ml) and pyridine (10 ml) was stirred at room temperature for 1.5 hr. The reaction mixture was evaporated to dryness *in vacuo*, and the residue was recrystallized from MeOH (5 ml) to afford colorless needles (500 mg), mp 145°. TLC (silica gel, AcOEt): *Rf* 0.5. UV λ_{max}^{MeOH} nm: 265. NMR (d_6-DMSO) δ: 2.05 (3H, s, $COCH_3$), 2.13 (3H, s, $COCH_3$), 2.63 (3H, s, $COCH_3$), 4.33 (3H, broad m, $H_{4'}$, $2H_{5'}$), 5.60 (1H, m, $H_{3'}$), 5.87 (1H, t, $H_{2'}$), 6.14 (1H, d, J=5 Hz, $H_{1'}$), 7.76 (2H, broad s, NH_2), 8.24 (1H, s, H_8).

2-Mercapoto-N⁶,S,O²′,O³′,O⁵′-pentaacetyladenosine (27)——A solution of **26** (500 mg) in a mixture of AcSH (10 ml) and pyridine (30 ml) was refluxed for 2 hr. The reaction mixture was evaporated to dryness *in vacuo*. The residue was chromatographed over silica gel (6+24 g) by using $CHCl_3$·MeOH (19: 1) as eluent. Fractions containing **25** [TLC (silica gel, MeOH·$CHCl_3$ 1: 19): *Rf* 0.6] were evaporated to dryness and the residue was rechromatographed over silica gel (2+8 g) by using AcOEt as eluent. Fractions containing **25** [TLC (silica gel, AcOEt): *Rf* 0.4; **26** *Rf* 0.5] were evaporated to dryness to yield a resin (300 mg). UV λ_{max}^{MeOH} nm: 247, 297; λ_{min}^{MeOH} nm: 283. NMR ($CDCl_3$) δ: 2.10 (6H, s, 2 O·$COCH_3$), 2.15 (3H, s, $OCOCH_3$), 2.33 (3H, s, N·$COCH_3$), 2.67 (3H, s, S·$COCH_3$), 4.40 (3H, m, $H_{4'}$, $2H_{5'}$), 5.49 (1H, m, $H_{3'}$), 5.90 (1H, t, $H_{2'}$), 6.13 1H, d, J=5 Hz, $H_{1'}$), 8.16 (1H, s, H_8), 9.16 (1H, broad s, N<u>H</u>·$COCH_3$).

Di(2-Adenosinyl)disulfide (28)——To an ice-cooled suspension of **14e** (318 mg) in 0.25 M phosphate buffer (pH 7.0, 5.7 ml) was added dropwise 1 M I_2 solution (0.46 ml). The reaction mixture was adjusted

33) It was prepared by the reaction of 6-chloro-9-(β-D-ribofuranosyl)purine with aniline. mp 189—191°. UV λ_{max}^{EtOH} nm: 299. *Anal.* Calcd. for $C_{16}H_{17}O_4N_5$: C, 55.97; H, 4.99; N, 20.40. Found: C, 55.84; H, 4.97; N, 20.07.

with 1 M K_2CO_3 to pH 7.0 and stirred for 30 min to deposit a solid, which was filtered by suction and washed with water giving a pale yellow crystalline powder (250 mg). mp 235° (decomp.). PE: M_{14e} 0.61. UV $\lambda_{max}^{H_2O}$ nm (ε): 232 (38300), 275 (22400); $\lambda_{min}^{H_2O}$ nm: 249. NMR (d_6-DMSO) δ: 5.83 (1H, d, J=5.0 Hz, H_1'), 8.26 (1H, s, H_8). *Anal.* Calcd. for $(C_{10}H_{12}O_4N_5S)_2 \cdot H_2O$: C, 39.18; H, 3.93; N, 22.75; S, 10.42. Found: C, 39.42; H, 4.19; N, 22.31; S, 10.49.

2-Phenylaminoadenosine (29e)——a) To a solution of **1b** (1.2 g) in β-methoxyethanol (20 ml) was added aniline (2.4 ml) and the mixture was heated at 120° for 16 hr. The dark brown solution was evaporated to dryness and the residue was triturated with $CHCl_3$ and filtered. The solid was purified by column chromatography [silica gel (20+80 g), $CHCl_3$·MeOH (9: 1)] giving a white powder (100 mg). Recrystallization from EtOH afforded colorless needles. mp 238—239°. b) A solution of **33** (17.5 g) in 20% methanolic ammonia (280 ml) was heated in an autoclave at 120° for 4 hr. The reaction mixture was concentrated to deposit crystals which were recrystallized from water giving colorless needles (9.4 g). mp 244—245°. NMR (d_6-DMSO) δ: 4.55 (1H, q, H_2'), 5.82 (1H, d, J=6 Hz, H_1'), 6.90 (2H, s, NH_2), 6.5—8.0 (5H, m, phenyl), 8.05 (1H, s, H_8), 8.8 (1H, s, $-N\underline{H}-C_6H_5$).

2-Phenyllaminoinosine (30)——A mixture of **3b** (NH_4 salt, 10 g), aniline (15 ml), 60% MeOH (125 ml) was refluxed for 6 hr to become clear and then turbid. The solid was filtered by suction and washed with 5% MeOH giving fine white crystals (7.7 g, 78%). mp 241—242°. The compound gave a single UV absorbing spot by PE (M_{3b} 0.56). UV $\lambda_{max}^{0.1N\ HCl}$ nm: 275; $\lambda_{max}^{H_2O}$ nm: 276; $\lambda_{max}^{0.1N\ NaOH}$ nm: 283. NMR (d_6-DMSO) δ: 3.63 (2H, m, $2H_5'$), 3.94 (1H, m, H_4'), 4.13 (1H, m, H_3'), 4.50 (1H, m, H_2'), 5.82 (1H, d, H_1'), 6.9—7.9 (5H, m, phenyl), 8.07 (1H, s, H_8), 8.8 (1H, s, $-N\underline{H}-C_6H_5$), 10.8 (1H, broad s, N^1H). *Anal.* Calcd. for $C_{16}H_{17}O_5N_5 \cdot 1/3H_2O$: C, 52.60; H, 4.87; N, 19.17. Found: C, 53.00; H, 4.65; N, 18.92.

N^2-Phenyl-N^2,$O^{2'}$,$O^{3'}$,$O^{5'}$-tetraacetylguanosine (31)——To a stirred mixture of **30** (1.0 g), pyridine (10 ml) and DMF (2 ml) was dropwise added Ac_2O (5 ml) at room temperature. After 3 hr, the reaction mixture was evaporated to dryness *in vacuo*, the residue was dissolved in MeOH (5 ml) to deposite feathery crystals (**32**), which was removed by filtration. The filtrate was evaporated to dryness and the residue was chromatographed over silica gel (2+6 g) by using MeOH·$CHCl_3$ (1: 19) as eluent, giving a resin (800 mg). λ_{max}^{MeOH} nm: 254, 260, 283; λ_{min}^{MeOH} nm: 228, 258, 271. NMR ($CDCl_3$) δ: 2.10, 2.07, 2.03 (12H, 3 $OCOCH_3$, N^2-$COCH_3$), 3.75 (2H, s, H_5'), 4.16 (1H, m, H_4'), 4.66 (1H, m, H_3'), 5.5—5.8 (2H, H_1', H_2'), 7.5—7.8 (6H, m, phenyl, H_8), 12.9 (1H, broad s, N^1H).

2-Phenylamino-2',3',5'-tri-O-acetylinosine (32)——a) The feathery crystals in the preceding section were filtered and washed with MeOH, 200 mg. mp 234—235°. UV λ_{max}^{MeOH} nm: 276. NMR (d_6-DMSO) δ: 1.89 (3H, s, $COCH_3$), 2.05 (3H, s, $COCH_3$), 2.14 (3H, s, $COCH_3$), 4.30 (3H, m, H_4', $2H_5'$), 5.33 (1H, m, H_3'), 6.0 (2H, m, H_1', H_2'), 6.9—7.9 (5H, m, phenyl), 7.93 (1H, s, H_8), 8.80 (1H, s, $-NH-C_6H_5$), 10.08 (1H, broad s, N^1H). *Anal.* Calcd. for $C_{22}H_{23}O_8N_5$: C, 54.43; H, 4.77; N, 14.43. Found: C, 54.40; H, 4.41; N, 13.97. b) To an ice-cooled and stirred suspension of **30** (1.0 g) in AcOH (5 ml) was dropwise added AcCl (2.0 ml). The reaction mixture, after stirring at room temperature for 5 hr, was evaporated to dryness *in vacuo* (bath temperature below 30°). The residue was triturated with ice-water (5 ml) and the mixture was adjusted to pH 7 with conc. aqueous ammonia. The resulting solid was recrystallized from MeOH to give colorless crystals (0.8 g). mp 231—233°. c) To a solution of **4b** (60 g) in MeOH (500 ml) was added aniline (75 ml). The mixture, after heating at 95° for 3 hr, was concentrated and left to deposit colorless crystals (25 g). mp 231—233°.

6-Chloro-2-phenylamino-9-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)purine (33)——DMF (17 ml) and $SOCl_2$ (53 ml) were added to an ice-cooled suspension of **32** (23.5 g) in $CHCl_3$ (600 ml). The resulting solution was kept at 25° for 30 min under protecting from moisture and then refluxed at 90° for 2 hr. The solvent was distilled off and the residue was dissolved in $CHCl_3$ (1 liter). The solution was poured into ice-water (1 liter) and neutralized with $NaHCO_3$. The $CHCl_3$ layer was washed twice with water (500 ml) and evaporated to dryness giving a yellow-brown resin (24 g). The compound was chromatographed over silica gel (100+400 g) by using $CHCl_3$·MeOH (99: 1, 5 liters) as eluent to yield a pale yellow resin (17.5 g). NMR (d_6-DMSO) δ: 3.10, 3.03 (9H, 3 $COCH_3$), 4.3 (3H, m, H_4', $2H_5'$), 4.90 (1H, m, H_3'), 6.0 (2H, m, H_1', H_2'), 7.0—8.0 (5H, m, phenyl), 8.05 (1H, s, H_8), 10.0 (1H, s, $-N\underline{H}-C_6H_5$).

2-Furyladenosine (34h)——A mixture of AICN-riboside (10 g), 2-furonitrile (12.5 g) and 20% methanolic ammonia (100 ml) was heated in an autoclave at 180° for 5 hr, and evaporated to dryness *in vacuo*. The resulting syrup was triturated with EtOH (50 ml) to deposit curde crystals, which were recrystallized from water (160 ml) giving colorless crystals. NMR (d_6-DMSO) δ: 3.74 (2H, broad, $2H_5'$), 4.07 (1H, d, H_4'), 4.29 (1H, H_3'), 4.75 (1H, m, H_2'), 6.01 (1H, d, J=6.0 Hz, H_1'), 6.61 (1H, m, furyl-H_4), 7.18 (1H, d, furyl-H_3), 7.38 (2H, s, NH_2), 7.78 (1H, m, furyl-H_5), 8.38 (1H, s, H_8).

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