Synthesis and Coronary Vasodilating Activity of 2-Substituted Adenosines

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A large scale preparation of 2-haloadenosines (I) was attained by acetylation of 2-halo- 
haloinosines (3), followed by chlorination and amination. 2-Alkoxycadenosines (5) were 
prepared in fairly good yields by protection of both 2'- and 3'-hydroxy groups of 2-chloro- 
adenosine (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-cyan- 
1-β-D-ribofuranosylimidazole with carbon disulfide afforded 2,6-di-mercaptop-9-β-D-ribo- 
furanosylpurine (15), which was converted to 2-mercaptopadenosine (14e) and its S- 
substituted derivatives. 2-Phenylnucleoside (29e) was prepared with comparative 
ease via 2-phenylamino-2',3',5'-tri-O-acetylenosine (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-mercaptopadenosines, N-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 ade- 
nosine 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 coro- 

nary vasodilating activity, 5) while it reduces the potency with the exception of 2-chloroadeno- 

sine (1a). 6) As part of our program to search for useful adenosine derivatives, we have syn-
thesized new 2-substituted adenosines and assessed their coronary dilator potency. 7)

2-Halogenoadenosines (I)

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. Dunny and A. Szent-Györgyi, J. Physiol. (London), 68, 213 (1929); M.M. Winbury, D.H. Papierski, 
4) H.F. Bae, C. Drummond, and E.L. Duncan, Mol. Pharmacol., 2, 67 (1966); M. Rockwell and M.H. 
Maguire, ibid., 2, 574 (1966).
Pharmacol. Exp. Ther., 106, 291 (1952); M.H. Maguire, D.M. Nobbs, R. Einstein, and J.C. Middleton, 
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.
acetyrlribofuranose,\(^9\) 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-\(\beta\)-D-ribofuranosyl)purine with hydrogen chloride and sodium nitrite.\(^9\) 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-\(\beta\)-D-ribofuranosylimidazole (AICA-riboside) as starting material which is easily accessible from the culture broth of Bacillus subtilis or Bacillus pumilus.\(^1\) The synthesis of 2-chloro-inosine\(^2\) (3a) or 2-bromoinosine\(^2\) (3b) from AICA-riboside via 2-mercaptopinosine has already been reported from our laboratory. Acetylation of 3, followed by chlorination of the tri-O-acetylated derivative (4) with the Vilsmeyer 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.\(^1\)) 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 phenoxy. 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

\[ 3a : X = \text{Cl} \]
\[ 3b : X = \text{Br} \]

\[ \text{Chart 1} \]

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described later. A slight modification was necessary to effect the synthesis of 2-propoxy-
adenosine (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-ethoxy-
methylidene derivative (6), which was allowed to react with butanol by the use of sodium hydroxide to yield 2-butoxy-2',3'-O-ethoxyethylideneadenosine (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-chlorinosine 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-Alkoxyadenosines Oligomers (9)

The reaction of 1a with sodium propoxide afforded a compound, which scarcely moved on thin-layer chromatography (TLC) [silica gel, MeOH-CHCl₃ (2:3)] and was isolated as a white powder (9a). The ultraviolet (UV) absorption spectra were similar to those of 2-propoxy-

#### Table I. Oβ-Substituted 2-Hydroxyadenosines (5)

<table>
<thead>
<tr>
<th>Compd.</th>
<th>R-</th>
<th>Formula</th>
<th>mp (°)</th>
<th>UV absorption spectra</th>
<th>Coronary dilator potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>5a</td>
<td></td>
<td>C₁₃H₁₇O₅N₄1/2H₂O</td>
<td>amorph.</td>
<td>H₂O: 253 (sh), 268; pH 2: 249, 275</td>
<td>0.63</td>
</tr>
<tr>
<td>5b</td>
<td></td>
<td>C₁₃H₁₇O₅N₄1/2H₂O</td>
<td>amorph.</td>
<td>2.55</td>
<td></td>
</tr>
<tr>
<td>5c</td>
<td></td>
<td>C₁₃H₁₇O₅N₄</td>
<td>155</td>
<td>2.41</td>
<td></td>
</tr>
<tr>
<td>5d</td>
<td></td>
<td>C₁₃H₁₇O₅N₄</td>
<td>amorph.</td>
<td>0.22</td>
<td></td>
</tr>
<tr>
<td>5e</td>
<td></td>
<td>C₁₃H₁₇O₅N₄</td>
<td>177—178</td>
<td>PH 1: 248 (8.0), 273 (11.5); pH 13: 266 (12.1)</td>
<td>0.81</td>
</tr>
<tr>
<td>5f</td>
<td></td>
<td>C₁₃H₁₇O₅N₄</td>
<td>amorph.</td>
<td>1.33</td>
<td></td>
</tr>
<tr>
<td>5g</td>
<td></td>
<td>C₁₃H₁₇O₅N₄</td>
<td>amorph.</td>
<td>0.61</td>
<td></td>
</tr>
<tr>
<td>5h</td>
<td></td>
<td>C₁₃H₁₇O₅N₄</td>
<td>194</td>
<td>0.79</td>
<td></td>
</tr>
<tr>
<td>5i</td>
<td></td>
<td>C₁₃H₁₇O₅N₄</td>
<td>amorph.</td>
<td>0.51</td>
<td></td>
</tr>
<tr>
<td>5j</td>
<td></td>
<td>C₁₃H₁₇O₅N₄</td>
<td>amorph.</td>
<td>H₂O: 266 (11.7)</td>
<td>0.16</td>
</tr>
<tr>
<td>5k</td>
<td></td>
<td>C₁₃H₁₇O₅N₄</td>
<td>amorph</td>
<td>0.81</td>
<td></td>
</tr>
<tr>
<td>5l</td>
<td></td>
<td>C₁₃H₁₇O₅N₄</td>
<td>21/2H₂O</td>
<td>amorph.</td>
<td>2.65</td>
</tr>
<tr>
<td>5m</td>
<td></td>
<td>C₁₃H₁₇O₅N₄</td>
<td>193</td>
<td>0.71</td>
<td></td>
</tr>
<tr>
<td>5n</td>
<td></td>
<td>C₁₃H₁₇O₅N₄</td>
<td>amorph.</td>
<td>0.22</td>
<td></td>
</tr>
<tr>
<td>5o</td>
<td></td>
<td>C₁₃H₁₇O₅N₄</td>
<td>1/2CH₂O</td>
<td>0.74</td>
<td></td>
</tr>
<tr>
<td>5p</td>
<td></td>
<td>C₁₃H₁₇O₅N₄</td>
<td>amorph.</td>
<td>0.72</td>
<td></td>
</tr>
<tr>
<td>5q</td>
<td></td>
<td>C₁₃H₁₇O₅N₄</td>
<td>155—157</td>
<td>MeOH: 252 (sh), 267 (15.3), 277 (sh)</td>
<td>0.55</td>
</tr>
<tr>
<td>5r</td>
<td></td>
<td>C₁₃H₁₇O₅N₄Cl</td>
<td>148—150</td>
<td>0.17</td>
<td></td>
</tr>
</tbody>
</table>
adenosine and the nuclear magnetic resonance (NMR) spectrum \([d_6\text{-dimethyl sulfoxide } (d_6\text{-DMSO})]\) 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-proproxyadenosine. The oligomers thus formed possess a terminal 2-proproxyadenosine 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-proproxy group to the C\(_5\) proton was 1:1. The molecular weight was estimated to be 740 by the polystyrene column chromatography measurement using 2-proproxyadenosine and 2-(5-deoxyinosin-5-yl)-

\[\text{Chart 2}\]

\(^{14}\) It has already been reported that heating of an alkaline solution of 6-chloro-9-\(\beta\)-d-ribofuranosylpurine in water afforded an oligomer.\(^{15}\)


\(^{16}\) The elemental analysis of 9a revealed that the oligomer had no chlorine atom.
thionosine\textsuperscript{(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.\textsuperscript{(18)} The yields of 12 and 13 were approximately equal (Chart 2).

The reaction of 1a with some other sodium alkoxides, e.g., sodium isopropoxide, sodium butoxide, sodium t-butoxide, and sodium amyloxide afforded the corresponding oligomers. The t-butoxyoligomer had a terminal 2-chloroadenosine structure,\textsuperscript{(19)} of which one hydroxyl group in the ribose moiety was also substituted to form an ether linkage.

\textbf{Table II. 2-Alkoxadenosine Oligomers (9)}

<table>
<thead>
<tr>
<th>Compd.</th>
<th>R–</th>
<th>Formula</th>
<th>[(\alpha)]\textsubscript{D} (c=0.05), DMSO</th>
<th>UV absorption spectra (\lambda_{max} \text{ nm} (e \times 10^4))</th>
<th>Coronary dilator potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>9a</td>
<td>CH(_3)(CH(_2))(_2)O–</td>
<td>C(<em>{28})H(</em>{41})O(<em>{11})N(</em>{14})•H(_2)O</td>
<td>–78.6</td>
<td>pH 1: 250 (sh), 271 (31.0); pH 13: 266 (31.0)</td>
<td>0.66</td>
</tr>
<tr>
<td>9b</td>
<td>H(_2)C(\bigtriangledown)CHO–</td>
<td>C(<em>{145})H(</em>{288})O(<em>{56})N(</em>{88})• 3H(_2)O</td>
<td>–89.3</td>
<td>pH 1: 270 (120.0); pH 13: 265 (155.0)</td>
<td>0.30</td>
</tr>
<tr>
<td>9c</td>
<td>Cl</td>
<td>C(<em>{180})H(</em>{219})O(<em>{21})N(</em>{40})Cl•5H(_2)O</td>
<td>–82.1</td>
<td>pH 1: 271 (100.0); pH 13: 266 (122.0)</td>
<td>—</td>
</tr>
</tbody>
</table>

\textbf{S-Substituted 2-Mercaptoadenosine (14) and Its Analogs}

Treatment of 5-amino-4-cyano-1-β-d-ribofuranosylimidazole\textsuperscript{(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\(_4\)N\(_{4}\)S\(_2\)) (16). The structure of 15 was confirmed by its conversion to 2,6-dimethylthio-9-β-d-ribofuranosylpurine\textsuperscript{(21)} (17). Compound (16) was assigned the 7-imino-5-mercaptopo-3-(β-d-ribofuranosyl)imidazo[4,5-a][1,3]thiazine structure by analogy with

\textsuperscript{17} This compound was prepared by reaction of 2-mercaptoinosine with 5′-deoxy-5′-iodoinosine. UV \(\lambda_{max} \text{ nm}: 254, 262 \text{ (sh), 280 (sh)}; \lambda_{max} \text{ nm}: 226, 262. \text{ NMR} (d_6-DMSO) \delta: 5.80 \text{ (2H, m, 2H_1)}, 8.05, 8.20, 8.30 \text{ (3H, 8s, 2H_3, 2H_5).}


\textsuperscript{19} The elemental analysis of the oligomer showed the presence of chlorine atom (1.05%).


the reaction of 3-amino-4-cyanopyrazole with carbon disulfide. 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$_4$N$_4$S$_2$I) (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). Compound (17) and colorless needles (C$_{11}$H$_{14}$O$_4$N$_4$S$_2$) (19) were isolated by silica gel column chromatography. Treatment of 19 with methanolic ammonia yielded 2-methylthioadenosine 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

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23) The free type of 18 might be assigned the 4-cyano-5-methylthiotetrahydrocarbamido-1-β-D-ribofuranosylimidazole structure.
<table>
<thead>
<tr>
<th>Compd.</th>
<th>R-</th>
<th>Formula</th>
<th>mp (°)</th>
<th>UV absorption spectra (\lambda_{max}) nm</th>
<th>Coronary dilator potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>14a</td>
<td>HO(CH(_2))(_2)-</td>
<td>C(<em>{12})H(</em>{14})O(_2)N(_2)S</td>
<td>207—208</td>
<td></td>
<td>0.11</td>
</tr>
<tr>
<td>14b</td>
<td>CH(_3)O(CH(_2))(_3)-</td>
<td>C(<em>{12})H(</em>{15})O(_3)N(_2)S</td>
<td>amorph.</td>
<td></td>
<td>0.53</td>
</tr>
<tr>
<td>14c</td>
<td>C(_6)H(_5)-</td>
<td>C(<em>{12})H(</em>{14})O(_2)N(_2)S•H(_2)O</td>
<td>125—126</td>
<td>MeOH: 235, 279</td>
<td>0.59</td>
</tr>
<tr>
<td>14d</td>
<td>C(_6)H(_5)CH(_2)-</td>
<td>C(<em>{12})H(</em>{13})O(_2)N(_2)S</td>
<td>158</td>
<td></td>
<td>0.06</td>
</tr>
<tr>
<td>14e</td>
<td>H-</td>
<td>C(<em>{12})H(</em>{15})O(_2)N(_2)S•H(_2)O (decomp.)</td>
<td>190—191</td>
<td>pH 1: 240, 245 (sh), 293; pH 13: 243, 281, 300 (sh)</td>
<td>0.51</td>
</tr>
</tbody>
</table>

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\(^{24}\) (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)-\(^{25}\)-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\(^2\),O\(^3\),O\(^9\),O\(^9\)'-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

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(3b) with aniline in methanol gave 2-phenylamininosine (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 (CDCl₃) of 31 with that of 32 revealed that one-proton signal (s, -NH-C₆H₅) at δ 8.8 of 32 had disappeared and that a low-field shift of the signal (1H, s, -N¹H) at δ 10.7 of 32 to δ 13.1 of 31 had occurred. Compound (31) was thus assigned the N²-phenyl-N⁵,O²⁵,O⁶⁵,O⁵⁵-tetra-acetylguanosine structure. The low-field shift can be accounted for by the presence of hydrogen bonding between the N²-acetyl and the N¹-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 N¹-hydrogen with the hydrogen bonding and therefore may support the validity of the structure (31). A high-field shift of the 5⁵'-protons
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-acetylthymidine (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-ribosyl)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. 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 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. 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, 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, 5f>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).

### Table V. N³-Substituted 2-Aminoadenosines (29)

<table>
<thead>
<tr>
<th>Compd.</th>
<th>R₁⁻</th>
<th>R₂⁻</th>
<th>Formula</th>
<th>mp (°)</th>
<th>UV absorption spectra λ_max nm (ε × 10⁻³)</th>
<th>Coronary dilator potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>29a</td>
<td>CH₅(CH₂)₃⁻</td>
<td>H⁻</td>
<td>C₁₃H₂₀O₄N₆</td>
<td>140</td>
<td>pH 5: 221, 259, 288</td>
<td>0.65</td>
</tr>
<tr>
<td>29b</td>
<td>CH₂O(CH₂)₃⁻</td>
<td>H⁻</td>
<td>C₁₃H₂₀O₄N₆•1/2H₂O</td>
<td>128-129</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>29c</td>
<td>HO(CH₂)₃⁻</td>
<td>H⁻</td>
<td>C₁₂H₁₈O₄N₆</td>
<td>190-191</td>
<td>pH 5: 22, 16, 27; pH 12: 224 (16.5), 277 (19.7)</td>
<td>0.42</td>
</tr>
<tr>
<td>29d</td>
<td>H⁻</td>
<td>H⁻</td>
<td>C₁₈H₂₄O₄N₆•1/2H₂O</td>
<td>148-150</td>
<td>2.20</td>
<td></td>
</tr>
<tr>
<td>29e</td>
<td>C₆H₅⁻</td>
<td>H⁻</td>
<td>C₁₉H₂₅O₄N₆</td>
<td>244-245</td>
<td>pH 2: 230 (sh), 272 (16.8); pH 12: 224 (16.5), 277 (19.7)</td>
<td>6.75</td>
</tr>
<tr>
<td>29f</td>
<td>p-CH₃C₆H₄⁻</td>
<td>H⁻</td>
<td>C₁₉H₂₉O₄N₆</td>
<td>164-165</td>
<td>MeOH: 211, 250, 279, 289</td>
<td>1.75</td>
</tr>
<tr>
<td>29g</td>
<td>p-CH₂OC₆H₄⁻</td>
<td>H⁻</td>
<td>C₁₉H₂₉O₄N₆</td>
<td>195-197</td>
<td>MeOH: 252, 276, 291 (sh)</td>
<td>2.37</td>
</tr>
<tr>
<td>29h</td>
<td>C₆H₅CH₃⁻</td>
<td>H⁻</td>
<td>C₁₉H₂₉O₄N₆•H₂O</td>
<td>100-105</td>
<td>0.17</td>
<td></td>
</tr>
<tr>
<td>29i</td>
<td>C₆H₅-(CH₂)₂⁻</td>
<td>H⁻</td>
<td>C₂₁H₂₅O₄N₆•H₂O</td>
<td>125-128</td>
<td>0.60</td>
<td></td>
</tr>
<tr>
<td>29j</td>
<td>CH₂⁻</td>
<td></td>
<td>C₂₅H₁₅O₂N₇</td>
<td>288</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>29k</td>
<td></td>
<td></td>
<td>C₂₅H₁₅O₂N₇</td>
<td>241-242</td>
<td>0.13</td>
<td></td>
</tr>
<tr>
<td>29l</td>
<td></td>
<td></td>
<td>C₂₅H₁₅O₂N₇</td>
<td>240 (decomp.)</td>
<td>pH 1: 225, 280, 297; pH 7: 262, 283</td>
<td>0</td>
</tr>
</tbody>
</table>

In both cases, the S-substituted analogs showed the weakest potency. The 2-alkoxy-²⁹ and alkylthio-adenosines²⁹ 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, 5I).

²⁹ The 2-alkoxyadenosines possessed the following potencies:²⁹ 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)

<table>
<thead>
<tr>
<th>Compd.</th>
<th>R-</th>
<th>Formula</th>
<th>mp (°)</th>
<th>UV absorption spectra</th>
<th>Coronary dilator potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>34a</td>
<td>CH₂CH₃</td>
<td>C₁₂H₁₅O₄N₄·1/4H₂O</td>
<td>amorph.</td>
<td>pH 2: 259; pH 7: 264;</td>
<td>0.12</td>
</tr>
<tr>
<td>34b</td>
<td>CH₃(CH₂)₃</td>
<td>C₁₄H₂₁O₄N₄·H₂O</td>
<td>amorph.</td>
<td>pH 12: 264</td>
<td>1.10</td>
</tr>
<tr>
<td>34c</td>
<td>ρ-ClC₆H₅</td>
<td>C₁₆H₁₉O₄N₄Cl</td>
<td>258</td>
<td>EtOH: 251, 245 (sh)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>34d</td>
<td>ρ-CH₂C₆H₅</td>
<td>C₁₇H₂₃O₄N₄·1/2H₂O</td>
<td>153-154</td>
<td></td>
<td>0.07</td>
</tr>
<tr>
<td>34e</td>
<td>ρ-CHOC₆H₅</td>
<td>C₁₈H₂₉O₄N₄</td>
<td>250-251</td>
<td></td>
<td>0.47</td>
</tr>
<tr>
<td>34f</td>
<td>CH₂O</td>
<td>C₁₉H₂₂O₅N₄·1/2H₂O</td>
<td>99-101</td>
<td>H₂O: 221, 260, 294</td>
<td>0.09</td>
</tr>
<tr>
<td>34g</td>
<td>C₆H₅-CH₃</td>
<td>C₁₇H₂₃O₄N₄</td>
<td>amorph.</td>
<td></td>
<td>0.11</td>
</tr>
<tr>
<td>34h</td>
<td></td>
<td>C₁₅H₁₇O₄N₃·1/2H₂O</td>
<td>135-140</td>
<td>0.1HCl: 214 (19.0), 284 (14.8), 0.05-0.13</td>
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<tr>
<td>34i</td>
<td></td>
<td>C₁₄H₂₉O₄N₃</td>
<td>250</td>
<td>0.1HCl: 212 (20.9), 273 (12.7), 323 (15.9); H₂O: 253 (16.6), 306 (15.4); 0.1NaOH: 252 (17.2), 307 (15.5)</td>
<td>0.23</td>
</tr>
<tr>
<td>34j</td>
<td>C₆H₅</td>
<td>C₁₆H₇O₂N₅</td>
<td>228-229</td>
<td>0.1HCl: 270 (16.2), 294 (sh); H₂O: 238.5 (23.4), 268 (14.3); 0.1NaOH: 238.5 (24.1), 268 (14.3)</td>
<td>0.24</td>
</tr>
<tr>
<td>34k</td>
<td>ρ-NO₂C₆H₅</td>
<td>C₁₆H₁₈O₄N₆</td>
<td>265</td>
<td>0.1HCl: 264 (15.5), 315 (13.2); H₂O: 217.5 (22.4), 262 (17.4), 318 (11.2); 0.1NaOH: 220.5 (20.7), 263 (16.9), 320 (10.2)</td>
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<tr>
<td>34l</td>
<td></td>
<td>C₁₈H₂₉O₄N₄·1/2H₂O</td>
<td>148-150</td>
<td>0.1HCl: 233 (15.2), 263 (13.5), 328 (8.3); H₂O: 231.5 (20.9), 262 (13.8), 290 (9.9); 0.1NaOH: 231.5 (20.8), 262 (13.7), 289 (9.8)</td>
<td>0.12</td>
</tr>
<tr>
<td>34m</td>
<td></td>
<td>C₁₅H₂₄O₄N₆</td>
<td>265-270</td>
<td>0.1HCl: 238 (18.9), 260 (14.7), 303 (7.6); H₂O: 233 (24.0), 263 (14.0), 292 (sh); 0.1NaOH: 233 (23.9), 263 (13.5), 292 (sh)</td>
<td></td>
</tr>
<tr>
<td>34n</td>
<td></td>
<td>C₁₅H₁₈O₄N₆</td>
<td>300</td>
<td>0.1HCl: 246 (18.9), 270 (12.7), 332 (6.9); H₂O: 233.5 (23.8), 268 (13.5), 305 (sh); 0.1NaOH: 234 (24.2), 268 (14.0), 305 (sh)</td>
<td>0.25</td>
</tr>
</tbody>
</table>

**Experimental**

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

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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 $\lambda_{\text{max}}$ nm: 265, Beilstein test (+). NMR (d$_2$-DMSO) $\delta$: 3.73 (2H, m, 2H$_2$), 4.10 (1H, m, H$_7$), 4.24 (1H, m, H$_8$), 4.54 (1H, t, H$_4$), 5.94 (1H, d, $i$ = 5 Hz, H$_7$), 7.53 (2H, brd s, NH$_2$), 8.50 (1H, s, H$_6$).

2,6-Dichloro-9-(2,3,5-tri-O-acetyl-$\beta$-D-ribofuranosyl)purine (2a)—A mixture of 2-chlorinosine (3a) (NH$_4$ salt, $^{32}$p 50 g), Ac$_2$O (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 x 4) and 0.1% NaHCO$_3$ (500 ml), and dried over Na$_2$SO$_4$. 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$_2$SO$_4$. 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)]; $R_f$ 0.90: 2-chloro-9-(2,3,5-tri-O-acetyl-$\beta$-D-ribofuranosyl)inosine $R_f$ 0.75. UV $\lambda_{\text{max}}$ nm: 253, 273 (lit. $^{32}$ $\lambda_{\text{max}}$ nm: 252, 273).

2-Bromo-6-chloro-9-(2,3,5-tri-O-acetyl-$\beta$-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 x 5), dried over Na$_2$SO$_4$ and evaporated to dryness. Recrystallization of the residue from EtOH (100 ml) gave colorless crystals (24.5 g). mp 155–154°. UV $\lambda_{\text{max}}$ nm: 253, 274; $\lambda_{\text{max}}$ nm: 254, 238. Anal. Calcd. for C$_{14}$H$_{13}$O$_5$N$_2$BrCl: 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-acetylenosine (4b)—To a stirred suspension of 2-bromenosine (3b) (NH$_4$ salt, $^{32}$p 31 g) in an ice-cooled mixture of CHCl$_3$ (400 ml) and Ac$_2$O (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 $\lambda_{\text{max}}$ nm: 254; $\lambda_{\text{max}}$ nm: 258.5. Anal. Calcd. for C$_{14}$H$_{12}$O$_5$N$_2$: C, 40.61; H, 3.62; N, 11.84; Br, 16.89. Found: C, 40.70; H, 3.65; N, 11.89; Br, 17.99.

2-Propanoyladenosine (5b)—To a solution of 2-chloroacetamide (40 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 (0.3 g) was filtered off an, 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). Fractions containing 5b were collected and evaporated to dryness. The residue was washed with ether to give a white powder (250 mg, 50%). UV $\lambda_{\text{max}}$ nm: 252 (sh), 268; $\lambda_{\text{max}}$ nm: 248, 275.

2-Butyroyladenosine (5c)—A mixture of 7 (3.7 g) and 40% AcOH (80 ml) was kept at 35° for 2 days. The crystallization of the residue from water gave colorless needles (2.4 g). mp 153°. UV $\lambda_{\text{max}}$ nm: 254 (sh), 268; $\lambda_{\text{max}}$ nm: 248, 276; $\lambda_{\text{max}}$ nm: 254, 268. b) A mixture of 8 (4.8 g), Ac$_2$O (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$_2$SO$_4$. To the solution containing 2-butoxy-2',3',5'-tri-O-acetylenosine [TLC (silica gel, MeOH-CHCl$_3$ 1:9); $R_f$ 0.60]. Compound (8) $R_f$ 0.09 were added SOCl$_2$ (12 ml) and DMF (5.7 ml). The mixture was heated for 2.5 hr and the solution (8) 0.95 was poured into ice-water (500 ml). The organic solvent was layer was washed with water several times, dried over Na$_2$SO$_4$ and evaporated to dryness to afford a resin [2-butoxy-6-chloro-9-(2,3,5-tri-O-acetyl-$\beta$-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(O)Et$_2$ (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 x 5). The CHCl$_3$ layer was washed with water (50 ml x 4) and chromatographed over silica gel (20 x 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$_2$-DMSO) $\delta$: 1.26 (3H, t, -CH$_3$), 3.62 (4H, m, -OCH$_2$CH$_2$H, 2H$_2$), 4.34 (1H, m, H$_7$), 4.8–5.4 (3H, m, H$_7$, H$_8$, -OH), 6.16 (1H, s, $\gamma$CH), 6.26 (1H, d, H$_4$), 7.8 (2H, s, NH$_2$), 8.4 (1H, s, H$_6$).

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 CHCl₃ (200 ml). The CHCl₃ layer was washed with water three times and chromatographed over silica gel (11 + 45 g) by using CHCl₃ (600 ml) and then 2% MeOH-CHCl₃ (800 ml) as eluents. Fractions containing 7 were combined and evaporated to dryness in vacuo to afford a resin (3.7 g). NMR (CDCl₃) δ: 0.7–2.0 (10H, m, -OCH₂CH₂CH₂CH₂–), 3.4–4.0 (4H, m, 2H₄, -OCH₂CH₂), 4.0–4.8 (3H, m, H₄', OCH₂CH₂CH₂CH₂–), 5.0–5.6 (3H, H₅', H₆', -OH), 5.7–6.3 (2H, H₅, 3CH₃), 6.6 (2H, s, NH₂), 7.7 (1H, s, H₆).

2-Butoxynosine (8) — To an ice-cooled and stirred suspension of 3a (NH₄ salt) 9 g) in acetone (500 ml) was added dropwise pyrophosphoryl chloride (20 ml) and the stirring was continued for 1 hr. The pale yellow solution was poured into a mixture of 28% NH₄OH (150 ml) and ice-water (1 liter). The mixture was stirred for 1 hr and concentrated in vacuo to distill off excess NH₄ and acetone. The concentrate was chromatographed over activated charcoal (80 g) by using H₂O-EtOH-BuOH-conc. NH₄OH (48: 45: 3: 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 CHCl₃. The CHCl₃ layer was dried over Na₂SO₄ 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% HCO₂H (100 ml), after stirring overnight at room temperature, was evaporated to dryness in vacuo to give 2-butoxy-5'-formylnosine. To this compound was added 20% NH₄, 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 2-butoxyadenosine (0.5 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 (d₆-DMSO) δ: 1.0 (1H, t, -CH₃), 5.7–6.4 (1H, m, H₅), 7.1–7.2 (2H, broad s, NH₂), 8.2 (1H, broad s, H₆).

Methanalysis 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 CHCl₃-MeOH (10: 1, 200 ml) as eluent. The eluate was concentrated and kept to afford crystals, 2-propoxyadenine (10a, 30 mg). TLC [silica gel, CHCl₃-MeOH (4: 1)]: Rf/0.42. [a]D₂O 20°: 240, 273; [α]D₂O 25°: 267; βmax 241 (characteristic nm: 275). NMR (d₆-DMSO) δ: 0.75 (3H, t, -CH₃), 1.5 (2H, m, -CH₂CH₂), 4.0 (2H, t, -CH₂O–), 6.9 (2H, broad s, NH₂), 7.8 (1H, broad s, H₆), 12.3 (1H, broad s, >NH). The silica gel column was next eluted with CHCl₃-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-methylribonafuranosine (11, 30 mg), which showed a positive color reaction with HIO₂-benzidine. TLC: Rf 0.32. NMR (CDCl₃) δ: 3.9 (3H, s, -OCH₃), 3.9 (2H, s, 2H₅), 4.0–4.5 (3H, m, H₅/s', s'), 4.9 (1H, s, H₆). The silica gel column was further eluted with CHCl₃-MeOH (5: 1, 300 ml) and the eluate was adsorbed on a column of activated charcoal (1 g). The column was eluted with H₂O-EtOH-BuOH-conc. NH₄OH (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 (d₆-DMSO + D₂O), which showed the presence of three CH₃O- 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 x 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 (d₆-DMSO + D₂O) δ: 3.3, 3.35 (6H, 2s, 2-OCH₃), 5.1 (1H, s, H₅), 7.9 (1H, s, H₆). The compound 12 was assigned the 1-O-methyl-2 (or 3)-[6-amino-2-purinyl]-p-ribonafuranoside structure and 13, the 1-O-methyl-5-[6-amino-2-purinyl]-ribonafuranoside structure.

2-Benzylthioadenosine (14a) — 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 aqueous MeOH giving colorless needles (250 mg), mp 158°.

2-Mercaptadenosine (14c) — Sodium (115 mg) was added portionwise to a solution of 14d (389 mg) in liq. NH₄ (5 ml), which was previously cooled with dry-ice-acetone. After 1 hr, NH₄Cl (300 mg) was added and the mixture was kept at room temperature to evaporate liq. NH₄. 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. NH₄OH (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 (d₆-DMSO) δ: 3.36 (2H, m, 2H₄), 3.7–4.2 (2H, H₅, H₆), 4.46 (1H, t, H₇), 5.76 (1H, d, J = 6.0 Hz, H₈), 8.16 (1H, s, H₉).
2.6-Dimercapto-9-β-n-ribofuranosylpurine (15) and 7-Imino-5-mercapto-3-β-n-ribofuranosylimidazole-4,5-dione (I3) thiazine (16) — To a solution of 5-amino-4-cyano-1-β-n-ribofuranosylimidazole98 (AICN-ribose, 1 g) in pyridine (70 ml) was added Cs₂ (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 0.58. UV λ_max nm (e): 233 (21000), 247.5 (17000), 305 (15600), 386 (8500); λ_min nm (e): 222 (14800), 283.5 (23000), 332 (10000). Anal. Calcd. for C₉H₁₅O₇N₅S₂: C, 37.96; H, 3.82; N, 17.71; S, 20.27. Found: C, 37.84; 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 λ_max nm (e): 254 (7700), 298.5 (26700), 344 (15200), 395 (11200). Anal. Calcd. for C₉H₁₅O₇N₅S₂·H₂O: C, 35.91; H, 4.21; N, 16.75; S, 19.17. Found: C, 38.07; H, 5.87; 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-n-ribofuranosylpurine (17) — To a solution of 15 (0.1 g) in 0.1 M NaOH (5 ml) was added CH₃S (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-H₂O-BuOH-conc. NH₄OH (4: 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 solution was kept to deposit crystals. mp 150–155° (lit. 115–120°). UV λ_max nm: 231, 260, 306; λ_min nm: 244, 285. Anal. Calcd. for C₁₁H₁₅O₇N₅S₂: C, 41.84; H, 4.68; N, 16.27. Found: C, 41.65; H, 4.75; N, 15.87.

7-Imino-5-methylthio-3-β-n-ribofuranosylimidazole[4,5-d][1,3]thiazine (H salt) (18) — To a suspension of 16 (300 mg) in DMF (2 ml) was added dropwise CH₃S (0.3 ml). The mixture, after stirring at room temperature for 2 hr, was added with CHCl₃ (10 ml) to deposit a solid. The solid was filtered under suction and washed with CHCl₃ giving pale yellow crystals (250 mg). Beilstein reaction (+). UV λ_max nm: 227, 272 (sh). NMR (δ-DMSO): δ: 2.90 (3H, s, -SCH₃), 3.83 (2H, q, 2H₂), 3.90–4.16 (2H, H₂t, H₂t'), 4.50 (1H, H₂), 6.03 (1H, d, J = 5.0 Hz, H₂), 8.76 (1H, s, H₂). Anal. Calcd. for C₁₁H₁₅O₇N₅S₂·H₂O: C, 38.53; H, 3.30; N, 12.23; S, 13.99. Found: C, 38.85; H, 2.99; N, 12.61; S, 14.03.

6-Mercapto-2-methylthio-9-β-n-ribofuranosylpurine (19) — To a suspension of 16 (0.5 g) in water (20 ml) were added 1× 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 residue99 was dissolved in CHCl₃ and the solution was chromatographed over silica gel (4+16 g) using CHCl₃-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 (δ-DMSO): δ: 2.7 (3H, s, -SCH₃), 3.6 (2H, m, 2H₂), 3.7–4.5 (3H, m, H₁′, H₁′, H₂′), 5.4 (1H, d, J = 4 Hz, H₂), 8.0 (1H, s, H₂). UV λ_max nm: 248, 300; λ_min nm: 232, 297; λ_max nm: 284; λ_min nm: 267. Anal. Calcd. for C₁₁H₁₅O₇N₅S₂: 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, M₁ 0.90 (UV λ_max nm: 248: 274; λ_min nm: 254 (sh), 268; λ_min nm: 258) and M₂ 0.68 (UV λ_max nm: 266, 280 (sh); λ_min nm: 235, 275; λ_min nm: 239; λ_min nm: 250], corresponding to 2-methoxyadenosine10 and 2-methylthioadenosine,10 respectively.

2.6-Diethylthio-9-β-n-ribofuranosylpurine (20) — To a solution of 15 (316 mg) in a mixture of 1 M NaOH (2.5 ml) and MeOH (2 ml) was added C₅H₅N₂Cl (300 mg). The mixture, after stirring at room temperature for 5 hr, was concentrated in vacuo and chromatographed over silica gel (1+4 g) using CHCl₃-MeOH (39: 1) as eluent. Fractions containing 20 were evaporated to dryness to give a resin (350 mg). TLC [silica gel, CHCl₃-MeOH (19: 1)]: Rf 0.8. NMR (δ-DMSO+D₂O) δ: 4.50 (2H, s, -CH₂CH₂H), 4.60 (2H, s, -CH₂CH₂H).

6-Bromo-2-sulfo-9-β-n-ribofuranosylpurine (21) — An ice-cooled and stirred mixture of 47% HBr (5 ml) and MeOH (5 ml) were added 15 (0.5 g) and then dropwise Br₂ (1 ml). After 3 hr, the resulting solution was poured into an ice-water (100 ml), neutralized with 28% NH₄OH and desalted with a column of activated charcoal (6 g), using EtOH-H₂O-BuOH-28% NH₄OH (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 nm: 270.

32 It was characterized by TLC [silica gel, CHCl₃-MeOH (3: 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% H₂O₂ (1.2 ml) and the mixture was kept in a refrigerator overnight. Addition of EtOH (200 ml) to the solution deposited a solid. The solid was washed with EtOH giving a white crystalline powder (250 mg). The compound showed a single UV absorbance peak at 260 (sh), 263; λ<sub>max</sub><sup>meas</sup> nm: 235; λ<sub>max</sub><sup>nm</sup> nm: 262; 236; 262; λ<sub>max</sub><sup>n</sup> nm: 236. Anal. Calcd. for C₁₆H₁₃O₄N₅Na·1/2H₂O: 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 110º for 5 hr. PE of the reaction mixture revealed the presence of two UV absorbing compounds corresponding to 22 (a major compound, λ<sub>max</sub><sup>n</sup> nm: 260) and 2-aminoadenosine (a minor compound; λ<sub>max</sub><sup>n</sup> nm: 255, 281), respectively.

5-Amino-4-thiocarbamoyl-1-b-0-ribofuranosylimidazole (23)—A mixture of AICN-riboside (240 mg), CS<sub>2</sub> (76 mg) and 20% methanolic ammonia (4 ml) was heated in an autoclave at 180º for 6 hr. The reaction mixture was evaporated to dryness in vacuo, and the residue was recrystallized from MeOH giving colorless needle s(200 mg). PE: MAICN-riboside 0.85. UV λ<sub>max</sub><sup>meas</sup> nm: 257 (sh), 280, 328; λ<sub>max</sub><sup>nm</sup> nm: 235, 297; λ<sub>max</sub><sup>n</sup> nm: 218, 245 (sh), 270, 330; λ<sub>max</sub><sup>n</sup> nm: 234, 290. NMR (d<sub>6</sub>-DMSO) δ: 5.55 (1H, d, J = 5.0 Hz, H₅), 7.35 (1H, s, H₂). Anal. Calcd. for C₆H₄O₂N₅S·1/2-CH₂OH: C, 39.30; H, 5.66; N, 19.30; S, 11.04. Found: C, 39.45; H, 5.52; N, 19.40; S, 11.19.

2-Mercapto-5-phenyladenosine (24a)—To a solution of AICN-riboside (1 g) in pyridine (80 ml) was added C₆H₅NCS (4 ml) and the mixture was refluxed for 6 hr. The pale yellow solution was evaporated to dryness in vacuo and the residual was shaken with a mixture of CHCl₃ (200 ml) and water (100 ml). The water layer was evaporated to dryness in vacuo giving a pale yellow powder (0.25 g). The CHCl₃ layer was chromatographed over silica gel (5+25 g) by using CHCl₃-MeOH (19:1) as eluent to give an additional amount (100 mg) of 24a. The compound gave a single UV absorbing spot on PE (MAICN-riboside 1.2). NMR (d<sub>6</sub>-DMSO) δ: 5.9 (1H, d, J = 6 Hz, H₅), 7.1–7.9 (5H, m, =N-C₆H₄), 8.22 (1H, s, H₀), 8.47 (1H, broad s, H₆), 9.98 (1H, broad s, —SH).

2-Mercapto-5-phenyladenosine (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 CHCl₃-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 196–198º (decomp.). The compound was assigned the 3'·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 234–235º (decomp.), NMR (d<sub>6</sub>-DMSO) δ: 3.95 (3H, s, N<sub>1</sub>·CH₃), 5.78 (1H, d, J = 6 Hz, H₅), 8.02 (1H, s, H₀), 8.47 (2H, broad s, =NH). N<sub>1</sub>-Phenyladenosine (25a)—A solution of 24a (40 mg) and Raney Ni (0.1 ml) in EtOH was refluxed for 6 hr. TLC [silica gel, CHCl₃-MeOH (4:1)] and PC [Whatman No. 1, BuOH·AcOH·H₂O (5:2:3), ascending method] showed the presence of a single UV absorbing compound, which migrated the same distance as that of N<sub>1</sub>-phenyladenosine, but possessed the different UV absorption spectrum (λ<sub>max</sub><sup>meas</sup> nm: 267) from that of λ<sub>max</sub><sup>meas</sup> nm: 299 of N<sub>6</sub>-phenyladenosine.

N<sub>6</sub>-Phenyladenosine (25b)—A solution 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 (Moadenosine 0.5) possessing the same UV absorption spectrum (λ<sub>max</sub><sup>meas</sup> 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 Ac₂O (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 145º. TLC (silica gel, AcOEt): RF 0.5. UV λ<sub>max</sub><sup>meas</sup> nm: 295. NMR (d<sub>6</sub>-DMSO) δ: 2.65 (3H, s, COCH₃), 2.13 (3H, s, COCH₃), 2.63 (3H, s, COCH₃), 4.33 (3H, broad m, H₅, 2H), 5.60 (1H, m, H₅), 5.87 (1H, t, H₆), 6.14 (1H, d, J = 5 Hz, H₅), 7.76 (2H, broad s, NH₂), 8.24 (1H, s, H₆).

2-Mercapto-5',5'-O-O'-pentacetyladenosine (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 (2+8 g) by using Ac₂O as eluent. Fractions containing 25 (TLC [silica gel, MeOH·CHCl₃ 1:1 ]; 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<sub>max</sub><sup>meas</sup> nm: 247, 297; λ<sub>max</sub><sup>nm</sup> nm: 283. NMR (CDCl₃) δ: 2.10 (6H, s, 2-O-COCH₃), 2.15 (3H, s, COCH₃), 2.33 (3H, s, N-COCH₃), 2.67 (3H, s, COCH₃), 4.40 (3H, m, H₅, 2H), 5.49 (1H, m, H₅, 2H), 5.90 (1H, t, H₆), 6.13 1H, d, J = 5 Hz, H₅), 8.16 (1H, s, H₀), 9.16 (1H, broad s, NH·COCH₃).

Dl(2-Adenosinyl)diulvole (28)—To an ice-cooled solution of 14e (318 mg) in 0.25 M phosphate buffer (pH 7.0, 5.7 ml) was added dropwise 1 N I₂ solution (0.46 ml). The reaction mixture was adjusted
with 1 m K₂CO₃ 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; Mf 94.06. UV λ max nm (ε): 232 (38300), 275 (22400); λ max nm: 249. NMR (d₆-DMF) δ: 5.83 (1H, d, d = 5.0 Hz, H₂, 5.86 (1H, s, H₃). Anal. Calcd. for C₁₈H₁₄O₃N₅S₂H₂O: 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-Phenyliaminoadenosine (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 CHCl₃ and filtered. The solid was purified by column chromatography [silica gel (20–80 g), CHCl₃-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 (d₆-DMF) δ: 4.55 (1H, q, H₂, 5.82 (1H, d, d = 6 Hz, H₂), 6.90 (2H, s, NH₂), 6.5–8.0 (5H, m, phenyl), 8.05 (1H, s, H₆, 8.6 (1H, s, =NH-C₃H₃).

2-Phenyliaminosine (30) A mixture of 3b (NH₄ salt, 10 g), aniline (15 ml), 60% MeOH (125 ml) was refluxed for 6 hr to become clear and then turbid. The solution 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 (Mzg, 5.68). UV λ max nm: 275; λ max nm: 276; λ max nm: 283. NMR (d₆-DMF) δ: 3.63 (2H, m, H₂, 3.94 (1H, m, H₃), 4.13 (1H, m, H₄, 4.50 (1H, m, H₅), 5.82 (1H, d, H₆), 6.9–7.9 (5H, m, phenyl), 8.07 (1H, s, H₆), 8.8 (1H, s, =NH-C₃H₃), 10.8 (1H, broad s, NH). Anal. Calcd. for C₁₈H₁₄O₃N₅: 1/3H₂O, C, 52.60; H, 4.87; N, 19.17. Found: C, 53.00; H, 4.65; N, 18.92.

N-Phenyl-N-O₂,N₂O₂'-tetraacetylguanosine (31) To a stirred mixture of 30 (1.0 g), pyridine (10 ml) and DMF (2 ml) was dropwise added Ac₂O (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 deposit feathery crystals (32), which was removed and the residue was recovered by filtration. The filtrate was evaporated to dryness and the residue was chromatographed over silica gel (2 g) by using MeOH-CHCl₃ (1:19) as eluent, giving a resin (860 mg). Anal. C₄₂H₇₀O₃N₅: 254, 260, 283, 300 nm: 228, 258, 271. NMR (CDCl₃) δ: 2.10, 2.07, 2.03 (12H, 3 COOCH₃, N₂COCH₃), 3.75 (2H, s, H₂), 4.16 (1H, m, H₃), 4.66 (1H, m, H₄), 5.5–5.8 (2H, H₂, H₃), 7.5–7.8 (6H, m, phenyl), 12.9 (1H, broad s, NH). 2-Phenyliamino-2',3',5'-tri-O-acytinocylsine (32) a) The feathery crystals in the preceding section were filtered and washed with MeOH, 200 mg. mp 234–235°. UV λ max nm: 276. NMR (d₆-DMF) δ: 1.89 (3H, s, COCH₃), 2.05 (3H, s, COCH₃), 2.14 (3H, s, COCH₃), 4.30 (3H, m, H₂, 2H), 5.33 (1H, m, H₃), 6.0 (2H, m, H₂, H₃), 6.9–7.9 (5H, m, phenyl), 7.03 (1H, s, H₄), 8.80 (1H, s, =NH-C₃H₃), 10.08 (1H, broad s, NH). Anal. Calcd. for C₁₈H₁₄O₃N₅: 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 (30 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-phenylaminono-2-(2,3,5-tri-O-acytin-β-d-ribofuranosyl)purine (33) DMF (17 ml) and SOCl₂ (53 ml) were added to an ice-cooled suspension of 32 (23.5 g) in CHCl₃ (600 ml). The resulting solution was kept at 25° for 30 min under protecting from moisture and then refluxed for 90 min at 200°. The residue was distilled off and the residue was dissolved in CHCl₃ (1 liter). The solution was poured into ice-water (1 liter) and neutralized with NaHCO₃. The CHCl₃ 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 (100–200 g) by using CHCl₃-MeOH (99:1, 5 liters) as eluent to yield a pale yellow resin (17.5 g). NMR (d₆-DMF) δ: 5.10, 3.03 (9H, 3 COCH₃), 4.3 (3H, m, H₂, 2H), 4.90 (1H, m, H₄), 6.0 (2H, m, H₂, H₃), 7.0–8.0 (5H, m, phenyl), 8.05 (1H, s, H₆), 10.0 (1H, s, =NH-C₃H₃).

2-Furyliaminoadenosine (34) A mixture of AICN-ruboside (10 g), 2-furanonitrile (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 crude crystals, which were recrystallized from water (160 ml) giving colorless crystals. NMR (d₆-DMF) δ: 3.74 (2H, broad, 2H), 4.07 (1H, d, H₄), 4.29 (1H, H₅), 4.75 (1H, m, H₃), 6.01 (1H, d, J = 6.0 Hz, H₂), 6.61 (1H, n, furyl-H₄), 7.18 (1H, d, furyl-H₃), 7.38 (2H, s, NH₂), 7.78 (1H, m, furyl-H₃), 8.38 (1H, s, H₆).

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