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STUDIES OF NUCLEOSIDES AND NUCLEOTIDES—XLV[1]

PURINE CYCLONUCLEOSIDES.-12. SYNTHESIS OF ADENINE CYCLONUCLEOSIDES HAVING 8,5′-O-ANHYDRO LINKAGE[2]

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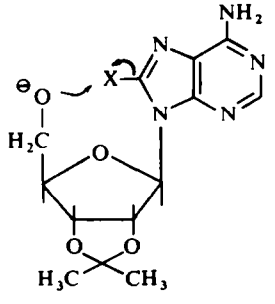
Abstract—A cyclonucleoside having an 8,5′-O-anhydro linkage was first synthesized by treatment of 8-bromo-2′-3′-O-isopropylideneadenosine with sodium hydride in dioxan at room temperature. The cyclonucleoside (III) has UV absorption properties similar to those reported for other O-cyclonucleosides and shows a large positive Cotton curve in ORD and CD.

When compound III was heated in N H_2SO_4, 8-oxyadenosine (IV) and 8,5′-anhydro-8-oxyadenosine (V) were obtained. Heating III in 0·1N H_2SO_4 gave 5-(adenyl-8)-D-ribose (VI). Treatment of III with sodium hydride in DMF gave a nucleoside having an exocyclic methylene (VII).

Compound III was also reacted with potassium thiocyanate, sodium azide and hydrogen sulfide. In each case the nucleophiles attacked at $C^{5'}$ and gave 5′-substituted 8-oxyadenosine.

IT HAS been generally shown,[3,4] that cyclonucleosides are formed by the nucleophilic attack of keto or thioketo groups in heterocyclic bases of nucleosides to the electron-deficient C atom caused by the leaving group such as alkyl or arylsulfonyloxy group. In this respect if we attempted to synthesize cyclonucleosides having O- or S-anhydro linkages between C^8 and $C^{5'}$ position in analogy with 8,2′- or 8,3′-counterparts, a sulfonyloxy group must be introduced into the 5′-OH of the nucleoside. However, as shown in the case of guanosine,[5] conditions for converting an 8-bromo atom to an 8-oxy function by treatment with acetic acid and sodium acetate at an elevated temperature frequently caused cyclization to the undesired N^3,5′-cyclonucleoside (I).[6] In order to avoid this, we attempted an alternate course, in which an activated sugar OH would attack an electron-deficient carbon in position 8 as shown in Fig 1. We chose 8-bromo as the leaving group and the 5′-OH group, which dissociated to $-O^-$, as the attacking species.



8-Bromo-2′,3′-O-isopropylideneadenosine (II) dissolved in dioxan and two equivalents of sodium hydride reacted at room temperature with vigorous evolution of a gas.

After 12 hr, the product (III) was isolated as white crystals, m.p. 226–226·5°. This compound had UV absorption max at 260 nm, which resembled that of 8-methoxyadenosine,[7] and had no halogen when tested with Beilstein test. Accordingly, the formation of an anhydro bond between C^8 and 5′ position was accepted. In the NMR spectra of compound III, a signal appeared at 7·04 δ (assigned to 6-NH_2) which was interchangeable with D_2O. This would also suggest conversion of the 5′-OH to an ether. ORD and CD curves of compound III are shown in Fig 2. In both curves an extremely large Cotton effect around 260 nm was observed. The positive sign of this Cotton band and its magnitude suggested the cyclonucleoside structure in analogy with other purine cyclonucleosides.[8] Elemental analysis also supported the structure of III as 2′,3′-O-isopropylidene-8,5′-anhydro-8-oxyadenosine.

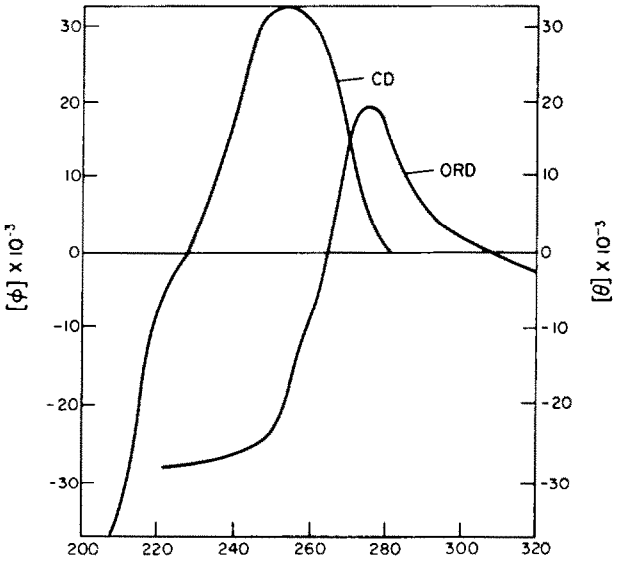


FIG 2. ORD and CD of 8,5′-Anhydro-8-oxyadenosine

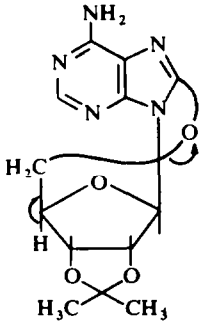
Mild acidic treatment yielded the desired unprotected cyclonucleoside. When compound III was heated at 60° in N H_2SO_4, 8,5′-anhydro-8-oxyadenosine (IV) was obtained after a column chromatography on cellulose powder. The second product 8-oxyadenosine[9] (V) was also obtained as a completely resolved peak. The structure of IV was confirmed by elemental analysis and UV spectrum which closely resembles that of III, as well as periodate-benzidine spray[10] showing the existence of vicinal OH groups. Formation of 8-oxyadenosine suggested that the cleavage of the anhydro linkage occurred prior to the hydrolysis of the nucleosidic linkage.

In contrast to this, if we hydrolysed the compound III in 0·1N H_2SO_4, a compound VI having m.p. 170° was obtained. This compound has a UV spectrum closely resembling that of 8-methoxyadenine.[11] The elemental analysis suggested that VI is 5-(adenyl-8)-D-ribose. Consequently, it appeared that the susceptibility of anhydro and nucleosidic linkages to the acidic hydrolysis depends on the concentration of acid and the reaction temperature. The fact that hydrolysis of the anhydro linkage occurred predominantly in the more concentrated acid may suggest that the protonation of N^7

was preceded by that of N^9. Furthermore, occurrence of 8-oxyadenosine (V) and 5-(adenyl-8)-D-ribose (VI) as the hydrolysis products demonstrates that compounds III and IV have anhydro linkages between C^8 and $C^{5'}$. Therefore, the formation of internucleosidic ether linkages was eliminated. Synthesis of compound III by an analogous procedure has been reported independently.[12]

This type of intramolecular cyclization is not possible with an unprotected 8-bromoadenosine.[13] When the latter compound was treated with sodium hydride in dioxan, products having similar UV absorption properties with those of IV were obtained. However, in spite of many efforts, no one single compound could be isolated. Thin-layer chromatography and the insolubility in water and alcohol, suggested the products were mixtures of oligomers having intermolecular ether linkages between 8 and 2'-3' or 5'-carbons. Although it may be difficult to understand why intramolecular cyclization predominates in compound IV and not in 8-bromoadenosine, different conformations of these two compounds could be an explanation. Quite recently, Tavale and Sobell[14] reported that the structure of 8-bromoadenosine elucidated by X-ray crystallography was in *syn* form. If this conformation is valid in the solution, we could expect different conformation for the isopropylidene derivative, because of an unusually fast cyclization of compound III, which could be very difficult in the *syn* form.[15]

The cleavage of the 8,5'-anhydro bond in compound III was next investigated. When compound III was treated with sodium hydride in DMF, a compound (VII) having UV absorption properties resembling those of 8-oxyadenosine was obtained. The NMR of this compound shows a broad peak as a doublet at 4·30 δ, which could be assigned to an exocyclic methylene.[16] The existence of a double bond in VII was further confirmed by the addition of bromine. From the elemental analysis, the structure of VII was considered to be 8-oxy-9-(2,3-O-isopropylidene-5-deoxy-β-D-erythropento-4-enofuranosyl)adenine. Robins *et al.*[16] reported that 5'-tosyl-isopropylidene-adenosine gave an exocyclic methylene compound by treatment with t-butoxide in t-butanol. If we assume analogous β-elimination of a 4'-proton caused by sodium hydride, the scheme of the reaction could be represented as in Fig 3. Compound VII is interesting also as an analog of the antibiotic angustmycin A,[17] which has a similar exocyclic double bond in the ketofuranosyl moiety. An attempt to remove the isopropylidene group from VII failed because its nucleosidic linkage is extremely labile to acidic hydrolysis.



When the sodium hydride/DMF treatment was performed under anhydrous conditions, followed by the work-up procedures without using water, a compound (VIII) having a negative charge was obtained. Compound VIII has UV absorption properties resembling those of 4,5-diamino-6-ribosylaminopyrimidine[18] and migration on a paper electrophoreogram was as fast as a cyclic phosphate. This compound (VIII) converted to an 8-oxyadenine exocyclic methylene compound (VII) in an alkaline aqeous solution. The IR spectrum of VIII shows a band at 1750 cm^{-1}, which could be assigned to an —COOH group. IR bands at 1650 and 1750 cm^{-1}, as well as addition of bromine suggested the existence of an exocyclic methylene group. From these results, VII was tentatively assigned the structure of 4-amino-5-carboxylamino-6-(2,3-isopropylidene-5-deoxy-D-erythro-4-eno-pento-furanosyl)aminopyrimidine (VIII). The fast recyclization to 8-oxyadenine would be expected by dissociation of the carboxyl and attack by the 6-amino group.

As has been reported for an 8,5'-anhydro derivative of guanosine,[5] III was subjected to cleavage with various nucleophiles. When III was heated with potassium thiocyanate in acetic acid at 100–105°, 8-oxy-2',3'-O-isopropylidene-5'-deoxy-5'-thiocyanato-adenosine (IX) was obtained as the major product. The structure of IX was confirmed by the UV spectrum, which resembles that of 8-oxyadenosine, and an IR band at 2190 cm^{-1} was assigned to the —SCN group.

When sodium azide was used as the nucleophile, III gave 2',3'-O-isopropylidene-5'-deoxy-5'-azido-8-oxyadenosine (X). The existence of an azide group was confirmed by an IR band at 2137 cm^{-1}. This reaction showed the possibility of introducing an N-function to the sugar moiety by the cleavage of the anhydro linkage.

Compound III on heating with hydrogen sulfide in acetic acid at 100–105° gave a compound (XI), which has an 8-oxyadenosine chromophore and was revealed by periodate-benzidine spray on the paper chromatogram. From the elemental analytical data a structure of 2',3'-O-isopropylidene-5'-deoxy-5'-mercapto-8-oxyadenosine was suggested for XI. Compound III also gave the same product (XI) by the treatment with sodium hydrogen sulfide in DMF-water solution.

From these cleavage reactions of the 8,5'-anhydro linkage of III, it was shown that the 8,5'-O-anhydro linkage is more labile in acetic acid than in the neutral solution and the scission occurred predominantly in C5' position rather than in C^8. Therefore the cleavage of 8,5'-O-anhydro linkage of adenine cyclonucleoside was found to proceed in the same fashion as in the case of guanine 8,5'-O-cyclonucleosides.[19]

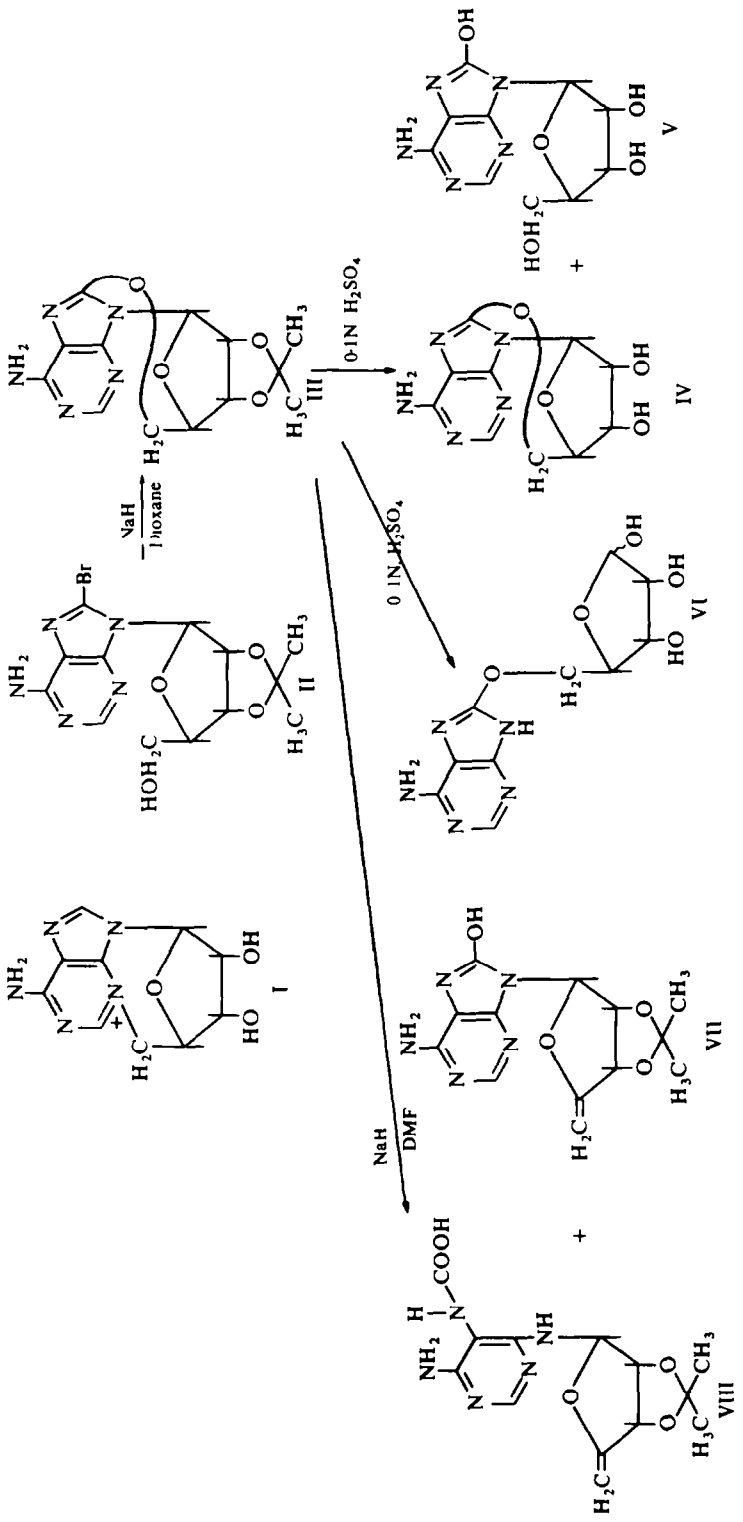
EXPERIMENTAL*

Paper chromatography. Ascending chromatographies were performed on Toyo Roshi No. 51A paper in the following solvent: solvent A, water adjusted to pH 10 with conc ammonia; solvent B, n-butanol–water, 86:14; solvent C, isopropanol–ammonia–water, 7:1:2; solvent D, n-butanol–acetic acid–water, 5:2:3; solvent E, n-propanol–water, 3:1.

Thin-layer chromatography. Performed on Merck Kieselgel HF 254 and in a solvent of $CHCl_3$-EtOH,

8,5-Anhydro-2',3'-O-isopropylidene-8-oxyadenosine. 8-Bromo-2',3'-O-isopropylideneadenosine[20] (11·6 g, 30 mmoles) was dissolved in dioxan (180 ml, dried over Na metal). Into this soln was added NaH (3·0 g,

* UV absorption spectra were measured with a Hitachi EPS-3T recording spectrophotometer, IR spectra were with a Hitachi EPI-L spectrophotometer, and NMR spectra with a Hitachi H-6013 high resolution spectrometer operated at 60 mc with TMS as internal standard. M.ps were measured by a Yanagimoto hot stage and are not corrected.


NaH
DMF
NaH
Dioxane
0·1N H2SO4
0·1N H2SO4
I
II
III
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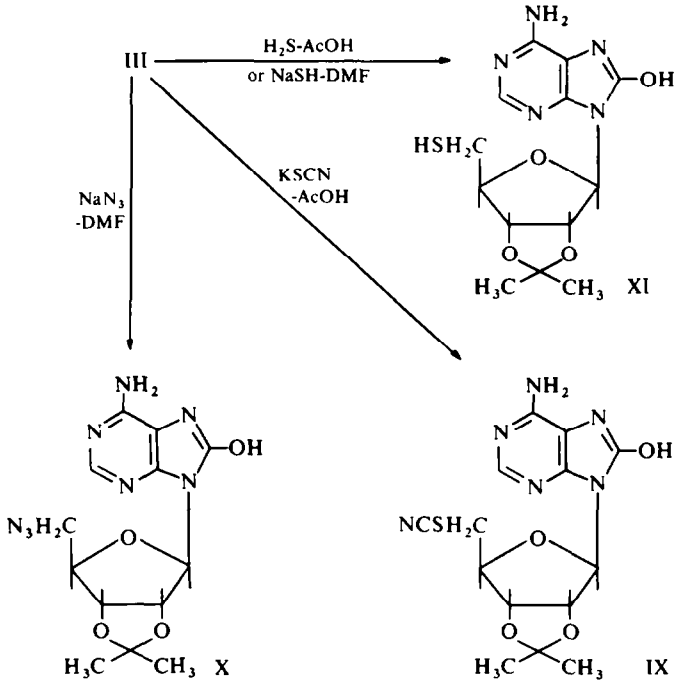
V
VI
VII
VIII



60 mmoles, containing 50% mineral oil), which was washed with dry benzene, with cooling in an ice-salt bath. The mixture was kept at room temp for 12 hr. Unreacted NaH was decomposed with a small amount of EtOH, water (100 ml) was added, and the soln was kept at −5° for 1 hr. White crystals were collected by filtration (5·8 g). The filtrate was neutralized with dil HCl and evaporated to a white solid. This was recrystallized from EtOH to give 2',3'-O-isopropylidene-8,5'-anhydro-8-oxyadenosine (1·5 g, total yield was 80%). A sample for elemental analysis was further recrystallized from EtOH, m.p. 226–226·5° (Found: C, 51·10; H, 4·99; N, 22·94. Calcd. for $C_{13}H_{15}O_4N_5$: C, 51·14; H, 4·96; N, 22·94%); UV: pH 1, 260 nm (ε 15400); pH 7, 259 nm (ε 15100); pH 13, 259 nm (ε 14900); PPC*: RF(A) 0·45, RF(C) 0·83, RF(D) 0·85; NMR: 8·10 δ (s, C^2—H), 7·04 δ (s, NH_2), 6·05 δ (s, $H^{1'}$), 5·0 δ (d, $H^{2'}$, $J_{2'-3'}$ = 6·0 cs), 4·87 δ (d, $H^{3'}$), 1·30, 1·46 δ (CH_3). ORD and CD curves were shown in Fig 2.

8,5'-*Anhydro*-8-*oxyadenosine*. 2',3'-O-Isopropylidene-8,5'-anhydro-8-oxyadenosine (1·0 g, 3·3 mmoles) was dissolved in N H_2SO_4 (30 ml) and heated at 60° for 3 hr. The soln was neutralized with Dowex 1X8 (OH^- form), the residue was filtered, and evaporated *in vacuo* to a glass. The glass was applied to a column (3 × 75 cm) of cellulose powder, which was previously equilibrated with water adjusted to pH 10 with ammonia. Fractions (5 ml) No. 76–84 were pooled and evaporated *in vacuo*. Crystallization from water gave 8-oxyadenosine (133 mg), m.p. > 220°. (Found: C, 41·38; H, 4·66; N, 24·43. Calcd. for $C_{10}H_{13}O_5N_5 \cdot 1/3H_2O$: C, 41·52; H, 4·76; N, 24·21%); UV: pH 1 265 nm, 283 nm; pH7 260 nm (shr), 270 nm; pH13 280 nm; IR (KBr): 1740 cm^{-1} (5-membered ureide); PPC: R_f(A) 0·47, R_f(B) 0·17, R_f(C) 0·44, R_f(D) 0·29. This sample was identical with an authentic specimen.[9]

Fractions No. 93–100 were pooled and evaporated *in vacuo* to give the starting material (79 mg). Fractions No. 102–103 were pooled and evaporated. Recrystallization of the residue from water gave 8,5'-anhydro-8-oxyadenosine (365 mg), m.p. 209–210°. (Found: C, 44·57; H, 4·58; N, 25·74. Calcd. for $C_{10}H_{11}O_4N_5 \cdot 1/4H_2O$: C, 44·57; H, 4·38; N, 25·97%). UV: pH1 260 nm (ε 15000), pH7, 260·5 nm (ε 16200), pH13, 261 nm (ε 16400); PPC: R_f(A) 0·28, R_f(B) 0·20, R_f(C) 0·34, R_f(D) 0·43; NMR: 8·2 (s, C^2—H), 6·07 (s, $H^{1'}$) taken in DMSO-d_6-D_2O mixture.

5-*Adenyl*-8)-D-*ribose*. 8,5'-Anhydro-2',3'-O-isopropylidene-8-oxyadenosine (1·5 g) was suspended in 0·1N

* PPC stands for paper partition chromatography and R_f(A) for R_f observed in the solvent A.

H_2SO_4 and the mixture was refluxed in an oil-bath for 3·5 hr. After concentration of the mixture, the acidity was adjusted to 0·3N by the addition of N H_2SO_4 and the soln was refluxed further for 1·5 hr. Decomposition of the starting material was confirmed by TLC. The mixture was neutralized with Dowex 1X8 (OH^- form), the resin was filtered and washed with water. Filtrate and washings were combined and evaporated to dryness. The glass thus obtained was dissolved in 50% EtOH and stored in a refrigerator overnight. A white powder was collected by filtration and recrystallized from water to give 5-(adenyl-8)-D-ribose (300 mg). This compound darkened at 157° and decomposed at 170°. (Found: C, 42·30; H, 4·89; N, 24·46. Calcd. for $C_{10}H_{13}O_5N_5$: C, 42·40; H, 4·63; N, 24·73%); UV: pH1 220 nm (shoulder, ε 8700), 260 nm (shoulder, ε 10100), 272 nm (ε 12400); pH7, 265 nm (ε 12100); pH13 272 nm (ε 13900); IR (Nujol): 1740 cm^{-1} (CHO). This sample reduced Fehling's soln.

8-*Oxy*-9-(2,3-O-*isopropylidene*-5-*deoxy*-β-D-*erythropent*-4-*enofuranosyl*)*adenine*. 8,5'-Anhydro-2',3'-O-isopropylidene-8-oxyadenosine (3·71 g, 10·8 mmoles) was dissolved in DMF with slight heating. Into this soln was added NaH (2·0 g, 40 mmoles, containing 50% mineral oil), which was washed with dry benzene and suspended in DMF (20 ml). After the mixture had been kept at room temp for 20 hr, EtOH (2 ml) was added to decompose unreacted NaH. The solvent was evaporated *in vacuo* and EtOH (100 ml) and water (50 ml) were added to the residue. Na ions were removed with IRC-50 (H^+ form) and the soln was evaporated to give a brown glass. The glass was dissolved in benzene, insoluble material was removed by filtration, and the filtrate was evaporated to give a glass (3·134 g). The glass was dissolved in $CHCl_3$ (50 ml) and applied to a column (3 × 8 cm) of alumina. The column was eluted with $CHCl_3$, $CHCl_3$-EtOH (5:1) and finally with $CHCl_3$-EtOH (1:1). A glass (1·6 g) having one spot in TLC was obtained. The glass was dissolved in water-EtOH and stored in a refrigerator. A bundle of needles was collected by filtration and dried over P_2O_5. 8-Oxy-9-(2,3-O-isopropylidene-5-deoxy-β-D-erythropent-4-enofuranosyl)adenine was obtained as white-yellow crystals (770 mg, 23·4%). A well-dried sample was further recrystallized for elemental analysis to give colorless needles, m.p. 240° (dec). (Found: C, 51·10; H, 4·99; N, 22·94. Calcd. for $C_{13}H_{15}O_4N_5$: C, 51·14; H, 4·96; N, 22·94%); UV: pH1, 267·5 nm (ε 8800), 290 nm (ε 7300, shr); pH7, 257 nm (ε 9600, sh), 269 nm (ε 10600); pH13, 282·5 nm (ε 14100). NMR: 8·05 δ (s, C^2—H), 6·54 δ (s, NH_2), 6·06 δ (s, $H^{1'}$), 5·50 δ (d, $H^{2'}$, $J_{2'-3'}$ = 6·0 cs), 5·25 δ (d, $H^{3'}$), 4·30 δ (d, $CH_2^{5'}$), 1·45, 1·35 δ (s, CH_3); PPC: R_f(A) 0·64, R_f(B) 0·87, R_f(C) 0·92

4-*Amino*-5-*carboxylamino*-6-(2,3-O-*isopropylidene*-5-*deoxy*-D-*erythropent*-4-*enofuranosyl*)*pyrimidine*. 8,5'-Anhydro-isopropylidene-8-oxyadenosine (457 mg, 1·5 mmole) was dissolved in DMF (25 ml). To this soln was added NaH (200 mg, 4 mmoles, containing 50% mineral oil), which was washed with n-hexane. The mixture was kept at room temp for 21 hr. NaH was decomposed by the addition of EtOH (10 ml) and the Na ions were removed with IRC-50 (H^+ form, 20 ml). The residue was separated from the insoluble material by filtration and the filtrate was evaporated to a glass. The glass was recrystallized from water-EtOH to give a slightly brown solid (239 mg). Recrystallization of this solid from EtOH-water gave a colorless crystal, m.p. 180° (dec). (Found: C, 48·86; H, 4·85; N, 21·50. Calcd. for $C_{13}H_{17}O_5N_5$: C, 48·34; H, 5·31; N, 21·68%); UV: pH1 and 7, 288 nm; pH13, 260, 283 (sh). IR: (KBr) 1155 cm^{-1} (isopropylidene); 884, 1650, 1750 cm^{-1} (terminal methylene); 1750 (—COOH); paper electrophoresis (pH 7·5, 1 hr): $R_{A-2',3'-cyclic\ P}$ 0·93,(8-oxyadenosine: $R_{A-2',3'-cyclic\ P}$ 0·68); PPC: R_f(C) 0·86, R_f(G) 0·91. The sample consumed bromine rapidly.

2',3'-O-*Isopropylidene*-5'-*deoxy*-5'-*thiocyanato*-8-*oxydenosine*. 8,5'-Anhydro-2',3'-O-isopropylidene-8-oxyadenosine (153 mg, 0·5 mmole) was heated in AcOH (2·5 ml) with KCNS (97 mg, 1 mmole) at 100–105° After 4 hr, the solvent was evaporated *in vacuo*. Addition and evaporation of EtOH were repeated until the odour of the AcOH was diminished. The residue was dissolved in $CHCl_3$ and insoluble materials were removed by filtration. $CHCl_3$ was evaporated *in vacuo* and the residue was recrystallized from benzene to give 2',3'-O-isopropylidene-5'-deoxy-5'-thiocyanato-8-oxyadenosine as a white powder, m.p. 129° (yield was 75 mg). (Found: C, 46·63; H, 4·45; N, 17·37. Calcd. for $C_{14}H_{16}O_4N_6S$: C, 46·72; H, 4·48; N, 17·78%); UV: pH1, 263 nm; pH7, 270 nm; pH13, 280 nm; R_f(C) 0·66.

2',3'-O-*Isopropylidene*-5'-*deoxy*-5'-*azido*-8-*oxyadenosine*. 8,5'-Anhydro-2',3'-isopropylidene-8-oxyadenosine (305 mg, 1 mmole) was heated in DMF (20 ml) with sodium azide (260 mg, 4 mmoles) at 70–75° for 7 days. The solvent was evaporated at 40° *in vacuo*. To the residue was added a small amount of water and the insoluble material was collected by filtration. The collected material was dissolved in EtOH and stored in a refrigerator overnight. The resulting ppt was collected by filtration, washed with water, and recrystallized from water. 2',3'-O-Isopropylidene-5'-deoxy-5'-azido-8-oxyadenosine was obtained as needles, m.p. 211–213° (115 mg). (Found: C, 45·29; H, 4·79; N, 31·31. Calcd. for $C_{13}H_{16}N_8O_4 \cdot 1/6C_2H_6O$: C, 44·98; H, 4·81; N, 31·47%); UV: pH1, 264, 283 nm (sh); pH7, 258 (sh), 270 nm; pH13, 280 nm; IR (Nujol): 2137 cm^{-1} (—N_3); PPC: R_f(B) 0·84, R_f(A) 0·66.

2',3'-O-Isopropylidene-5'-deoxy-5'-mercapto-8-oxyadenosine

(i) 8,5'-Anhydro-2',3'-O-isopropylidene-8-oxyadenosine (15·3 mg, 0·05 mmole) was dissolved in AcOH (1 ml). H_2S was bubbled through this soln for 5 min. The mixture was then heated at 100–105° for 15·5 hr in a glass tube; the solvent was evaporated *in vacuo* and the residue dissolved in EtOH and evaporated. This procedure was repeated 2–3 times. After addition of water to the residue and prolonged storage, 2',3'-O-isopropylidene-5'-deoxy-5'-mercapto-8-oxyadenosine, m.p. 173–175° was obtained as a colorless solid. (Found: C, 45·67; H, 5·32; N, 20·21. Calcd. for $C_{13}H_{17}O_4N_5S$: C, 46·09; H, 5·04; N, 20·66%); UV: pH1, 264, 284 nm (sh); pH7, 258 (sh), 270 nm; pH13, 280 nm; PPC: R_f(B) 0·83, R_f(C) 0·29. The spot R_f(C) 0·69 was revealed by IO_4^--benzidine spray.[10]

(ii) 8,5'-Anhydro-2',3'-O-isopropylidene-8-oxyadenosine (305 mg, 1 mmole) was dissolved in DMF (10 ml) at 50°. After the soln was cooled to room temp, N_2 was bubbled through it. NaHS (40% aqeous soln, 280 μl, 2 mmoles) was added. The flask was tightly stoppered and heated at 80° for 20 hr. The solvent was evaporated *in vacuo* and the residue was recrystallized from water. 2',3'-isopropylidene-5'-deoxy-5'-mercapto-8-oxyadenosine was obtained as a slightly yellow crystals, m.p. 173–175° (125 mg). The properties of this sample were identical with those of the sample obtained in (i).

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