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STUDIES OF NUCLEOSIDES AND NUCLEOTIDES—XLVI[1]

PURINE CYCLONUCLEOSIDES—13. SYNTHESIS AND PROPERTIES OF 8,5′-ANHYDRO-8-MERCAPTOADENOSINE[2]

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Abstract—Starting from 8-bromoadenosine, 2′,3′-O-isopropylidene-(IIa) and 2′,3′-O-ethoxymethylidene-5′-O-tosyl-8-bromoadenosine (IIb) were synthesized. Compounds IIa, b gave 8,5′-anhydronucleosides (IV a and b) on treatment with hydrogen sulfide in pyridine or aqueous sodium hydrogen sulfide in pyridine at − 5– − 15°. The structure of IV was confirmed by UV absorption, NMR and elemental analysis. CD and ORD measurements of IV showed large positive Cotton effects around absorption maxima. Acidic removal of the protecting group in IV gave 8,5′-anhydro-8-mercaptoadenosine (V), which was desulfurized to afford 5′-deoxyadesine (VI).

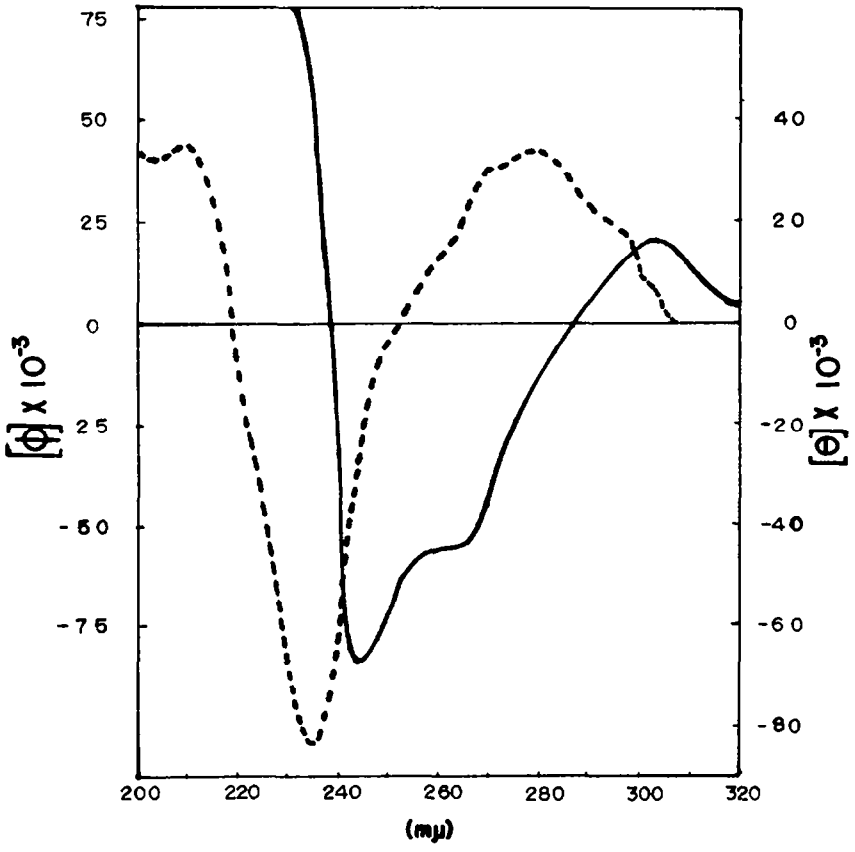
SYNTHESIS of purine cyclonucleosides having O- and S-anhydro linkages between C-8 of the base and C-2′, 3′ or 5′ of the sugar moiety has been reported.[3] Among these compounds 8,2′- and 8,3′-cyclonucleosides were synthesized by cyclization of 8-oxy or -mercapto-2′- or 3′-arylsulfonyl derivatives.[4–7] As in the formation of 8,5′-cyclonucleosides a rapid cyclization of 5′-sulfonylated nucleoside to N^3,5′-cyclonucleoside[8] would be expected, the undesired cyclization was avoided in the synthesis of 8,5′-O-cyclonucleosides by taking an alternate method, in which 8-bromo compounds were cyclized by the attack of 5′-OH dissociated by sodium hydride.[9, 10] This route is difficult in the synthesis of 8,5′-S-cyclonucleoside because a pure sample of 5′-mercapto-5′-deoxyadenosine could not be synthesized easily.

We therefore attempted to obtain 2′,3′-O-isopropylidene-8-bromo-5′-*p*-toluenesulfonyladenosine (IIa) as starting material for 8,5′-S-cyclonucleosides. The tosylation of 2′,3′-O-isopropylidene-8-bromoadenosine (Ia) was performed at − 5°– − 10° in order to avoid N^3,5′-cyclization. Compound IIa was obtained in a yield of 65% and its structure was confirmed by IR absorption band at 1175–1185 cm^{-1} (tosylate), UV absorption which resembled that of 8-bromoadenosine,[11] and elemental analyses.

The tosylated nucleoside IIa was then treated with hydrogen sulfide in pyridine. In contrast to our expectation that at low temperature only conversion of the 8-bromo to a mercapto group might be performed, a compound IVa having UV absorption maximum at 286 nm was obtained. This compound had no covalent tosylate band in the IR and only a signal at 7·32 δ in the NMR spectra was interchangeable with deuterium. These properties as well as elemental analysis suggested the structure of IVa to be 8,5′-anhydro-2′,3′-O-isopropylidene-8-mercaptoadenosine. Therefore, replacement of the 8-bromo by a mercapto group in IIa led to rapid cyclization to IVa even under low temperature conditions. This fact showed that activity of the

8-mercapto function as a nucleophile was compatible to the 2-thio group of uridine derivatives.[12]

As shown in Fig 1, ORD and CD curves of IVa had large positive Cotton effects around major absorption bands, which exist at around 260 nm. This fact suggests that IVa has a cyclonucleoside structure as deduced from comparison with the optical



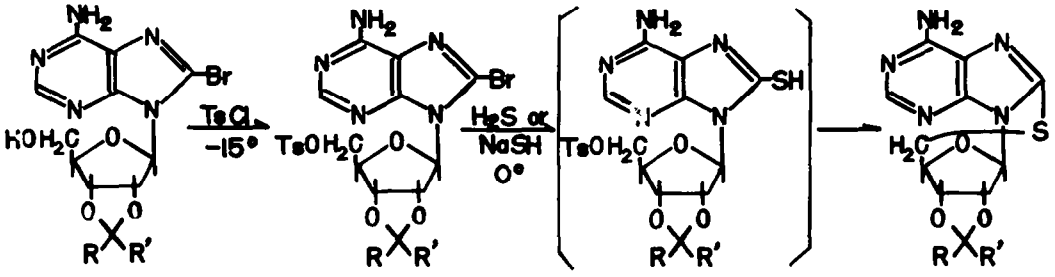
Optical Rotatory Dispersion and Circular Dichroism of 8,5'-Anhydro-8-mercaptoadenosine

FIG. 1. The magnitude of Cotton effect was represented as $[\phi] \times 10^{-3}$ in ORD (bold line) and $[\theta] \times 10^{-3}$ in CD (dotted line). 2',3'-O-Isopropylidene derivative was used.

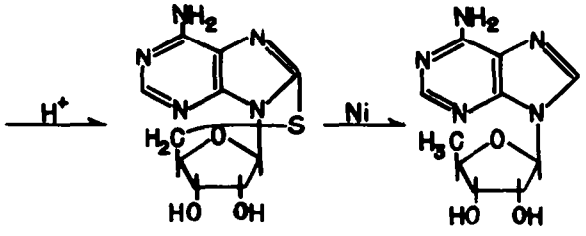
properties of other purine cyclonucleosides.[13] A comparison of amplitudes of the Cotton effects of 8,2'-, 8,3'- and 8,5'-S-cyclonucleoside derived from adenosine, the magnitude increased in the order 8,2'- < 8,3'- < 8,5'-cyclonucleoside as summarized in Table 1. This tendency was also found in O-cyclonucleosides. Therefore, a large Cotton effect of IVa (θ = 10,4400) could safely be ascribed to an anhydro linkage. Previously we postulated an *exo* type conformation for IVa.[2] As deduced from the largest Cotton effect which exceeded that of the 8,3'-cyclonucleoside. However, an X-ray crystallography[14] showed that IVa has an *endo* conformation. This structure was supported also by the NMR spectra of IVa. The compound IVa shows a doublet peak at 3·21 δ and a triplet peak at 4·90 δ. The former peak is assigned to 5'-H_2 and the latter is to 4'-H. Coupling constant $J_{4_s-5_s}$ was 2·8 and 2·6 c/s, respectively. If we

assume an *endo* conformation for IVa, protons of C-4′ and of C-5′ should be in staggered relationship. On the other hand, *exo* conformation led to an eclipsed conformation. Therefore, *endo* conformation could be well interpreted by NMR signals, which suggested a dihedral angle of H—$C^{4'}$—$C^{5'}$—H_2 to be about 60 ± 10° calculated by the Karplus equation.[15] The reason why 8,5′-cyclonucleoside has a extremely large Cotton effect is not clear.

In order to remove the isopropylidene group from IVa several attempts at acidic hydrolysis were made. However, the unprotected nucleoside (V) could not be obtained in reasonable yields. Only in the case of IVa treatment in 98% formic acid at 60–70° gave 8,5′-anhydro-8-mercaptoadenosine (V) in a yield of 10%. This stability of the isopropylidene group was also found in the case of 8,5′-O-cyclonucleoside.[9] The rigidity of the 8,5′-cyclonucleoside may be the cause of this stability because protonation of the base moiety prior to that of the sugar moiety[16] has been proposed. Drastic acidic treatment led to the scission of nucleosidic and anhydro linkages to afford 8-mercaptoadenine.



a: R, R′ = CH_3
b: R = H, R′ = OEt



In order to obtain a suitably protected cyclonucleoside, we synthesized 2′,3′-O-ethoxymethylidene-8-bromoadenosine (Ib) as described in the protection of ordinary nucleosides in oligonucleotide synthesis.[17] Compound Ib was obtained as a powder and its structure was confirmed by optical properties and elemental analysis. Compound Ib was then tosylated at low temperature as in the case of Ia. In this case again no cyclization to N^3,5′-cyclonucleoside occurred and 2′,3′-O-ethoxymethylidene-8-bromo-5′-tosyl-adenosine (IIb) was obtained as a glass. When compound IIb was treated with sodium hydrogen sulfide in aqueous pyridine at 0–5°, 8,5′-anhydro-2′,3′-O-ethoxymethylidene-8-mercaptoadenosine (IVb) was obtained in a yield of 52%. This method is superior to that using hydrogen sulfide in pyridine solution.

The removal of the ethoxymethylene group was achieved smoothly by heating IVb in 50% acetic acid-ethanol mixture. This condition again was stronger in the case of deprotection of the ordinary nucleosides. By this procedure 8,5'-anhydro-8-mercaptoadenosine (V) was obtained in a yield of 60%. Although isolation of the crystalline intermediate was difficult because of sterical isomers,[18] the use of the ethoxymethylidene group for the protection is preferable for the synthesis of 8,5'-cyclonucleosides.

Compound V was then treated with Raney nickel in methanol at reflux temperature. 5'-Deoxyadenosine (VI) was obtained as needles, m.p. 199–200°. The structure of VI was confirmed by UV absorption which closely resembled that of adenosine, a singlet signal at 1·30 δ (assigned to 5'-CH_3 group) in NMR and the elemental analysis. These properties coincide well with those reported for 5-deoxyadenosine.[19] By this desulfurization reaction existence of 8,5'-S-anhydro linkage in compound IV and V was substantially established.

Thus synthesis of 8,5'-S-cyclonucleoside was achieved and the structure was determined by chemical and physical means. The desulfurization of 8,5'-S-cyclonucleoside gave a new route for the synthesis of 5'-deoxyadenosine starting from naturally occurring adenosine.

TABLE 1. OPTICAL ROTATORY DISPERSION OF ADENINE CYCLONUCLEOSIDES

Compound	Peak (nm)	$[\Phi]_{peak}$	Trough (nm)	$[\Phi]_{trough}$	Amplitude ($\times 10^{-2}$)
8,2'-S-Cyclo[a]	295	0	266 (sh)	−14900	149
			235	−24900	249
8,3'-S-Cyclo	295	11900	270 (sh)	−11900	238
			245	−18700	306
8,5'-S-Cyclo[b]	303	22400	260 (sh)	−56000	784
	225	93000	246	−82000	1044
8,2'-O-Cyclo	275	4300	220	−11500	158
8,3'-O-Cyclo	275	2900	220	−26200	291
8,5'-O-Cyclo	274	19000	223	−28000	470

[a] 8,2'-S-Cyclo stands for 8,2'-anhydro-8-mercapto-9-(β-D-arabinofuranosyl)adenine, 8,3'-S-Cyclo for 8,2'-anhydro-8-mercapto-9-(β-D-xylofuranosyl)adenine, etc.

[b] 2',3'-O-Isopropylidene derivative.

EXPERIMENTAL*

Paper chromatography. Performed by ascending technique on Toyo filter paper No. 51A. Solvents used were: A, water adjusted to pH 10 with ammonia; B, n-BuOH-water (86:14); C, isopropanol-conc ammonia-water (7:1:2).

2',3'-O-Isopropylidene-5'-O-p-toluenesulfonyl-8-bromoadenosine.

2',3'-O-Isopropylidene-8-bromoadenosine[7] (3·86 g, 10 mmoles) was dissolved in pyridine (60 ml, distilled in the presence of tosyl chloride and stored over molecular sieves). After the soln was cooled in a refrigerator (−5°–−15°), tosyl chloride (1·90 g, 16 mmoles) was added. The flask was stoppered and the solid material

* UV absorption spectra were measured with a Hitachi EPS-3T spectrophotometer, infrared spectra were with a Hitachi EPI-L spectrophotometer, NMR spectra with a Hitachi H-6013 high resolution spectrometer operated at 60 mc with TMS as internal standard. ORD and CD were measured with a JASCO ORD/UV-5 spectropolarimeter installed with CD attachment.

dissolved by shaking in an ice-salt bath. The mixture was added in a freezer at − 10°– − 15° for 40 hr. Water (100 ml) was added and the soln was stored in a refrigerator at 0–5° for 12 hr. Crystals which separated were collected by filtration. The filtrate was evaporated *in vaco* to *ca* 100 ml and stored again in a refrigerator. Crystals were filtered and combined with the first crop (3·5 g, 65%). 2',3'-O-Isopropylidene-5'-tosyl-8-bromoadenosine, thus obtained, has m.p. 194°. (Found: C, 44·57; H, 4·13; N, 12·74. Calcd. for $C_{20}H_{22}O_6N_5BrS$: C, 44·45; H, 4·11; N, 12·96%); UV: λ_{max}^{pH1} 264 nm (ε 22,000); λ_{max}^{pH7} 214·5 nm (ε 24,100), 265 nm (ε 20,200); λ_{max}^{pH13} 265 nm (ε 19,200); IR: ν_{max}^{Kujol} 1175–1185 cm^{-1} (covalent tosylate). Halogen was detected by Beilstein's test. PPC*: R_f(B) 0·89, R_f(C) 0·94.

2',3'-O-*Isopropylidene*-8,5'-*anhydro*-8-*mercaptoadenosine*. 2',3'-O-Isopropylidene-5'-O-tosyl-8-bromoadenosine (4·30 g, 8 mmoles) was dissolved in anhyd pyridine (100 ml) and H_2S (dried over $CaCl_2$) was bubbled through for 10 min. The mixture was tightly stoppered and stored in a refrigerator at 0–5° for 12 hr. The solvent was evaporated *in vacuo* to afford a glass. The residue was extracted with EtOH (50 ml) by shaking, insoluble materials were removed by filtration, and the filtrate was decolorized with charcoal. The solvent was evaporated *in vacuo* to give a glass. The residue was recrystallized from 70% EtOH to give white crystals, which began to sublime at 190° and melted at 269°. (Found: C, 48·57; H, 4·90; N, 21·70. Calcd. for $C_{13}H_{15}O_3N_5S$: C, 43·59; H, 4·71; N, 21·80%); UV: λ_{max}^{pH1} 235 nm (sh, ε 5100), 275 nm (sh, ε 17800), 284 nm (ε 20700), 294 nm (sh, ε 14800); λ_{max}^{pH7} 238 nm (ε 8000); 278·5 (ε 16700), 268 nm (ε 18000), 295 nm (sh, ε 11900); λ_{max}^{pH13} 217 nm (ε 8200), 238 nm (ε 8000), 278·5 nm (ε 16700), 286 nm (ε 17700), 295 nm (sh, ε 11700). PPC: R_f(A) 0·43, R_f(B) 0·64, R_f(C) 0·85; NMR: 3·21 δ (d, 5'-H_2, $J_{4'-5'}$ = 2·8 cs), 4·90 δ (t, 4'-H, $J_{4'-5'}$ = 2·6 cs), 6·28 δ (s, 1'-H, $J_{1'-2'}$ = 0), 7·32 δ (s, 6-NH_2), 8·12 δ (s, 2-H); ORD: peak 225 nm (φ 93000), 303 nm (φ 22400); trough 246 nm (φ − 82000), 260 nm (shoulder, φ-56000); amplitude = 104400. CD: peak 280 nm (θ 33000), 213 nm (θ 23500); trough 235 nm (θ 87000).

8,5'-*Anhydro*-8-*mercaptoadenosine*

(i) 2',3'-O-Isopropylidene-8,5'-anhydro-8-mercaptoadenosine (1·46g, 4·6 mmoles) was dissolved in 98% formic acid (200 ml) and heated at 60–70° for 24 hr with exclusion of moisture. Formic acid was evaporated *in vacuo* and the odour of formic acid was totally removed by repeated addition and evaporation of EtOH. The residue was recrystallized from EtOH to yield a yellow solid material (500 mg). Recrystallization from MeOH (charcoal decolorization) gave white needles, m.p. 213–215° (130 mg, 10%). (Found: C, 42·51; H, 3·90; N, 24·62. Calcd. for $C_{10}H_{11}O_3N_5S$: C, 42·70; H, 3·95; N, 24·90%); UV: λ_{max}^{pH1} 237 nm (sh, ε 4900), 276 nm (sh, ε 17100), 284 nm (ε 19500), 294 nm (sh, ε 13900); λ_{max}^{pH7} 237 nm (ε 8100), 278 nm (sh, ε 16400), 285·5 nm (ε 17900), 294 nm (sh, ε 12100); λ_{max}^{pH13} 238 nm (ε 8300), 278 nm (sh, ε 16300), 285·5 nm (ε 17800), 295 nm (sh, ε 12100). PPC; R_f(A) 0·21, R_f(B) 0·29, R_f(C) 0·43.

(ii) 2',3'-O-Ethoxymethylidene-8-mercaptoadenosine (674 mg, 2·0 mmoles) was dissolved in 50% AcOH-EtOH (40 ml, 1:1, vol/vol) and heated at reflux temp for 30 min. Total conversion of the starting material to the product was confirmed by TLC. Then the solvent was removed by vacuum distillation. Addition and evaporation of EtOH was repeated until the odour of AcOH was diminished. The crystalline residue was recrystallized from MeOH with charcoal decolorization. 8,5'-Anhydro-8-mercaptoadenosine was obtained as colourless needles, m.p. 213–215° (336 mg, 60%). This sample was identical with the sample obtained in (i).

2',3'-O-*Ethoxymethylidene*-8-*bromoadenosine*

8-Bromoadenosine[11] (13·8 g, 40 mmoles) was dissolved in anhyd DMF (200 ml, distilled over P_2O_5 and stored over molecular sieves) by a slight heating. After cooling to the room temp, ortho ethyl formate (13·6 ml, 80 mmoles) and HCl [4 ml, 80 mmoles, prepared by the absorption of dry HCl gas (32·4 g) in DMF (50 ml)] was added into the mixture. The mixture was tightly stoppered and kept at room temp for 40 hr. The progress of the reaction was examined by TLC and triethylamine (30 ml) was added into the mixture. The resulting ppt was removed by filtration and the filtrate was evaporated *in vacuo* at 40° to give a glass. To this glass was added EtOH (50 ml) and the soln evaporated. After repeating this procedure twice, benzene (100 ml) was added and the soln was shaken on a water bath at 60 until a white solid appeared. The mixture was set aside at room temp overnight, the ppt was collected by filtration, and dried over P_2O_5 in a desiccator. 2',3'-O-Ethoxymethylidene-8-bromoadenosine was obtained as a white powder (7·29 g). A sample for the elemental analysis was obtained by further recrystallization from EtOH, which gave colorless crystals having m.p. 131·5–132·5°. (Found: C, 38·67; H, 4·23; N, 17·13. Calcd. for $C_{13}H_{16}O_5N_5Br$: C, 38·82; H, 4·01; N, 17·41%); UV: λ_{max}^{pH1} 262 nm (ε 18400); (ε 18400); λ_{max}^{pH7} 212 nm (ε 22700), 263 nm (ε 17000); λ_{max}^{pH13} 214 nm (ε 18500), 263 nm (ε 17000). PPC: R_f(A) 0·61, R_f(B) 0·87, R_f(C) 0·96.

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

2',3'-O-Ethoxymethylidene-5'-O-p-toluenesulfonyl-8-bromoadenosine

2',3'-O-Ethoxymethylidene-8-bromoadenosine (3·03 g, 7·5 mmoles) was dissolved in anhyd pyridine (50 ml) and tosyl chloride (2·83 g × 3) was added every 1 hr with cooling in an ice–salt bath. The mixture was stored in a refrigerator overnight. Tosyl chloride (1·42 g) was added again into the mixture, which was set aside at room temp for 2 hr. The mixture was poured in ice–water (300 mg) with stirring. After keeping at room temp for 30 min, the soln was extracted with chloroform (150 ml + 50 ml). The chloroform layer was washed with water (150 ml × 2) and dried over $MgSO_4$. The solvent was evaporated to give a red–brown glass (4·49 g). This material was used for the next step without further purification; UV: λ_{max}^{pH1} 264 nm; λ_{max}^{pH7} 215 nm, 265 nm; λ_{max}^{pH13} 265 nm; IR: ν_{max}^{Kujol} 1175–1185 cm^{-1} (covalent tosylate); PPC: R_f(B) 0·85, R_f(C) 0·92.

8,5'-Anhydro-2',3'-O-ethoxymethylidene-8-mercaptoadenosine

(i) 2',3'-O-Ethoxymethylidene-5-tosyl-8-bromoadenosine (2·0 g, 3·5 mmoles) was dissolved in pyridine (30 ml), followed by the bubbling N_2 through for 10 min. H_2S was bubbled through the soln for 20 min with cooling in an ice–salt bath. After 6 days, N_2 was bubbled through to remove the remainder of H_2S. The mixture was evaporated *in vacuo* to afford a yellow glass. Addition and evaporation of EtOH were repeated until the odour of H_2S was diminished and the residue was dissolved in MeOH. Insoluble materials were removed by filtration. The MeOH solution was heated at reflux temp for 2 hr. The MeOH was evaporated *in vacuo*, the residue was taken up in chloroform (50 ml) and washed with water (10 ml × 2). Drying over $MgSO_4$ and evaporation of the solvent gave a glass (630 mg). Recrystallization of the glass from MeOH afforded pale-yellow crystals (230 mg, 19·5%). This sample was identical with the sample obtained in (ii).

(ii) 2',3'-O-Ethoxymethylidene-5'-O-tosyl-8-bromoadenosine (4·49 g, 8 mmoles) was dissolved in pyridine (40 ml)-water (10 ml) mixture and N_2 gas was bubbled through for 10 min. 40% NaHS (1·26 ml, 9 mmoles) was added and the mixture was stored in a refrigerator overnight. NaHS soln (1·26 ml, 9 mmoles) was added and the mixture was again stored in a refrigerator overnight. The mixture was rapidly neutralized with N HCl with cooling, N_2 gas was bubbled through for 20 min, and the solvent was evaporated *in vacuo*. The residue was treated with EtOH and evaporated to dryness. This procedure was repeated until the odour of H_2S was totally removed. The residue was dissolved in chloroform (100 ml) and washed with water (100 ml × 2). Drying over $MgSO_4$ and evaporation of the solvent afforded a glass, which crystallized on storing in a refrigerator in a MeOH soln. The crystals were collected by filtration and the mother liquor was concentrated to obtain a second crop. The total yield was 1·42 g (52%). A sample for the elemental analysis was obtained by recrystallization of this specimen twice from isopropanol. The sample effervesed at 236° and decomposed at 255°. (Found: C, 46·11; H, 4·40; N, 20·51. Calcd. for $C_{13}H_{15}O_4N_5S$: C, 46·27; H, 4·48; N, 20·70%); UV: λ_{max}^{pH1} 235 nm (sh, ε 4600), 275 nm (sh, ε 19200), 283 nm (ε 22100), 293 nm (sh, ε 4400); λ_{max}^{pH7} 237 nm (ε 9600), 278 nm (ε 18000), 285·5 nm (ε 19300), 295 nm (sh, ε 12800); λ_{max}^{pH13} 217 nm (ε 9000), 237 nm (ε 8900). IR: ν_{max}^{KBr}. No band at 1175–1185 cm^{-1} region. (covalent tosylate); PPC: R_f(A) 0·24, R_f(B) 0·68, R_f(C) 0·85.

5'-Deoxyadenosine

8,5'-Anhydro-8-mercaptoadenosine (100 mg) was dissolved in MeOH (10 ml). The soln was heated under reflux in the presence of Raney nickel[2b] (*ca* 1 ml, wet volume) for 2 hr. The catalyst was removed by filtration and washed with hot MeOH (5 ml). Filtrate and washings were combined and evaporated to afford a glass (51 mg). The glass was dissolved in EtOH-water (2 ml, 1:1, v/v), treated with charcoal, and stored in a refrigerator. 5'-Deoxyadenosine was obtained as colorless needles, m.p. 199–200° (21 mg, 23·6%). (Found: C, 48·22; H, 5·52; N, 26·84. Calcd. for $C_{10}H_{13}O_3N_5 \cdot 1/4C_2H_6O$: C, 47·98; H, 5·56; N, 26·65%); UV: λ_{max}^{pH1} 258 nm (ε 14,100); λ_{max}^{pH7} 260 nm (ε 14,500); λ_{max}^{pH13} 260 nm (ε 14,300). NMR: 5·90 δ (d, H^{1a}, J_{1a-2a} = 5·1 cps), 1·30 (d, 5'-CH_3, J_{4a-5a} = 6·0 cs); PPC: R_f(A) 0·55 ($R_{adenosine}$* 1·10), R_f(B) 0·36 ($R_{adenosine}$ 1·70), R_f(C) 0·71 ($R_{adenosine\ 1\cdot10}$).

* $R_{adenosine}$ stands for relative migration distance compared with adenosine.

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