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STUDIES OF NUCLEOSIDES AND NUCLEOTIDES—LXXIV[1]

PURINE CYCLONUCLEOSIDES—34 A NEW METHOD FOR THE SYNTHESIS OF 2'-SUBSTITUTED 2'-DEOXYADENOSINES[2]

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Abstract—8,2'-O-Cycloadenosine was protected at 3' and 5'-OHs with acetyl groups and cleaved using liq. H_2S. Subsequent dethiolation and mesylation gave 2'-O-mesyl-3',5'-di-O-acetyl-arabinosyladenine (6). When 6 or its deacetylated parent compound (7) was heated with sodium azide in DMF, 3'-azido-3'-deoxyxylofuranosyladenine (9) was the only product. The cyclonucleoside was then protected with tetrahydropyranyl groups and subjected to a similar series of reactions as above to give 2'-O-mesyl-3',5'-di-O-tetrahydropyranylarabinosyladenine (14). The compound 14 was heated with sodium azide after which acidic deprotection afforded 2'-azido-2'-deoxyadenosine (16). Hydrogenation of 16 gave 2'-amino-2'-deoxyadenosine (18). 2'-Chloro-2'-deoxyadenosine (19) was also obtained by treatment of 14 with lithium chloride and subsequent deprotection. UV, IR and NMR spectral data of these compounds are described.

Adenosine is an important compound, because it is a constituent of ribonucleic acids (together with other nucleosides) and is involved as its phosphates in reactions of many enzymes of biological importance. A number of adenosine analogs are also known as antibiotics.[3] Puromycin (1) for example is known to be a strong inhibitor of protein biosynthesis. As the nucleoside component of puromycin is 3'-amino-3'-deoxy-N^6-dimethyladenosine, several methods suitable for the synthesis of 3'-amino-3'-deoxynucleosides have been reported.[4-6] However, 2'-amino-2'-deoxynucleosides were not discovered in nature until 2'-amino-2'-deoxyguanosine (2) was obtained from the culture broth of *Aerobacter* sp KY 3071.[7,8] It seemed worthwhile to investigate methods for obtaining analogous 2'-substituted 2'-deoxyadenosines, which may be interesting for biological studies both as such and in the form of phosphate esters. We attempted to introduce 2'-ribo substituents by opening the 8,2'-O-cyclolinkage[9] and eliminating the resulting 8-C=O group in a number of ways. Although we have succeeded by this pathway in synthesizing 2'-deoxy-2'-aminoinosine and -adenosine,[10] the route is too lengthy to furnish sufficient amounts of products for further biological studies.

We now wish to report a new method for synthesizing 2'-substituted 2'-deoxyadenosine in quantity starting from the 8,2'-O-cyclonucleoside,[11-13] which is easily obtainable from the naturally occurring adenosine. Utilizing these 2'-azido-,[14,15] 2'-amino-[16] and 2'-halogeno-2'-deoxy purine nucleosides[17] a number of polyribonucleotides having interesting biological activities[18] have been obtained. After this work was completed, a method for synthesizing 2'-substituted purine 2'-deoxynucleosides was reported.[19] But isolation of the desired isomer from the anomeric mixture seemed to be labourious.

We first attempted to introduce the 2'-azido group by attack on 2'-O-mesyl-9-β-D-arabinofuranosyladenine (7), which had been synthesized from 8',5'-di-O-acetyl-8,2'-anhydro-8-oxy-9-β-D-arabino-furanosyladenine (3) by cleavage of the anhydro bond with liq. H_2S[20] to give the 8-mercapto compound (4) in a yield of 87%. Raney nickel dethiolation gave 3',5'-di-O-acetylarabinofurabosyladenine (5) in a yield of 55%. Successive mesylation and deacylation of 5 with ammonia gave 7 in 81% overall yield. Characterization of these compounds was achieved by elemental analysis, UV and NMR spectral measurements.

When the 2'-O-mesylarabinosyl compound (7) was heated with sodium azide in DMF at 150°, a crystalline compound (9) was obtained. This compound had m.p. 177–9° and showed an IR band for an azido group at 2120 cm^{-1}. The UV absorpation spectra resembled to those of adenosine. However, in the NMR spectrum H-2' and H-4' signals were shifted to lower field suggesting that an azido group was introduced at the 3'- rather than the 2'-position. This xylo-type azido compound has been described by Robins *et al.*[21] who have obtained 9 by attack of 2',3'-down epoxide with sodium azide. In our case also a down-expoxide might be formed by the neighbouring *trans* 2'-OH group as an intermediate. 3',5'-Di-O-acetylarabinosyl compound (6) was then reacted with sodium azide in DMF. The resulting product was

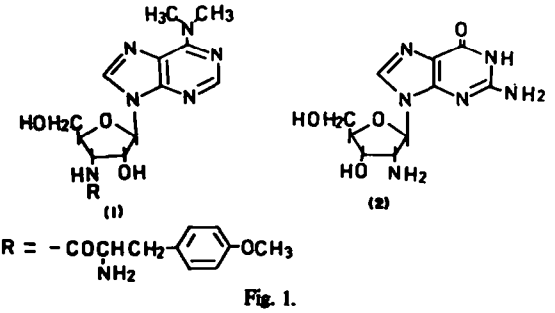

Fig. 1.

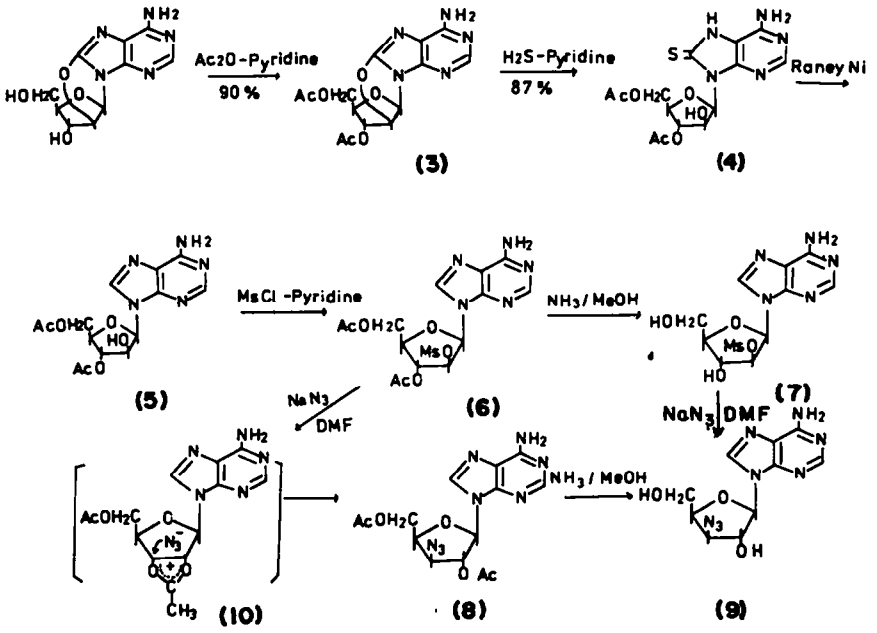

Chart 1.

found to be 2',5'-di-O-acetyl-3'-deoxy-3'-azido-β-D-xylofuranosyladenine (8) which was deacetylated to give the compound 9. The formation of 8 from the compound 1 may be rationalized by invoking a carboxonium type intermediate[22] (10) which could be attacked from the upper side at the C-3' atom to give a xylosyl compound.

In order to avoid this type of neighbouring group participation, we derivatized the 8,2'-O-cyclonucleoside to the 3',5'-tetrahydropyranyl compound (11). This compound was obtained easily by treating the cyclonucleoside with 2,3-dihydropyran under catalysis of *p*-toluenesulfonic acid at 4° in a yield of 59%. The compound 11 was then heated with liq. H_2S in pyridine at 110° for 10 hr. The reaction was checked by the UV shift from 260 to 305 nm and TLC and the product (12) was subjected to dethiolation with Raney Ni to give di-tetrahydropyranyl arabinosyladenine (13). The yield from 12 was 95%. The compound 13 was then allowed to react with methanesulfonyl chloride in pyridine at −20°. 2'-O-Mesyl-3,5'-di-O-tetrahydropropyranyl-9-β-D-arabinofuranosyladenine (14) was obtained in a yield of 71%. The structure was confirmed by a mass fragment of *m/e* 513, an IR band at 1180 cm^{-1} and UV absorption showing λ_{max} around 260 nm. This compound was alternatively synthesized from 2' - O - mesylarabinofuranosyladenine (7) by reaction with di-hydropyran under acid catalysis. The yield was 72%. The compound 14 was then heated with sodium azide in DMF at 150° for 7.5 hr. After the usual work up, the crude product was purified through a silica gel column to give the 2'-azido compound (15) in a yield of 47%. The presence of the azido group was confirmed by an IR band at 2100 cm^{-1}. Treatment of the compound 15 in 80% acetic acid at 50° for 2 hr gave 2'-azido-2'-deoxyadenosine (16), m.p. 221–2.5°, in a yield of 57%. The structure of 16 was confirmed by elemental analysis, UV absorption resembling to that of adenosine, IR bands at 2110 cm^{-1} and 2130 cm^{-1} and migration in paper chromatography. These properties were the same as those reported by others.[19,24] H^1-NMR spectrum of 16 (Fig. 2) showed that the H-3', OH-3' and H-1' signals were shifted towards low field relative to adenosine

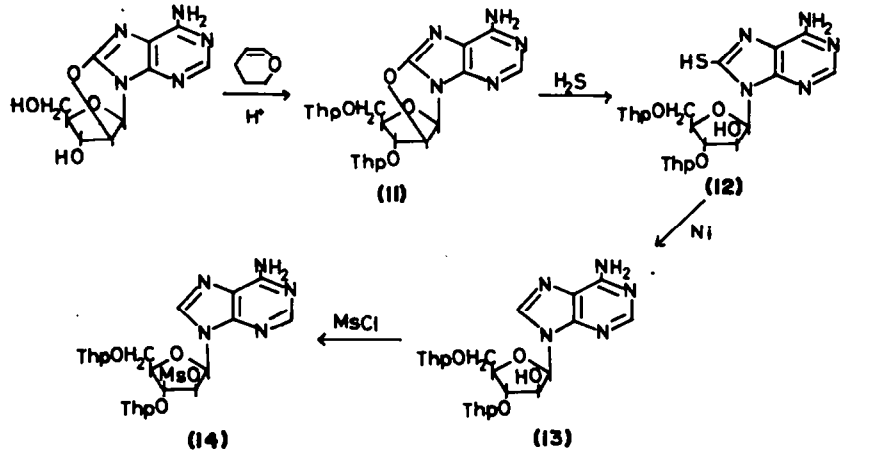

Chart 2.

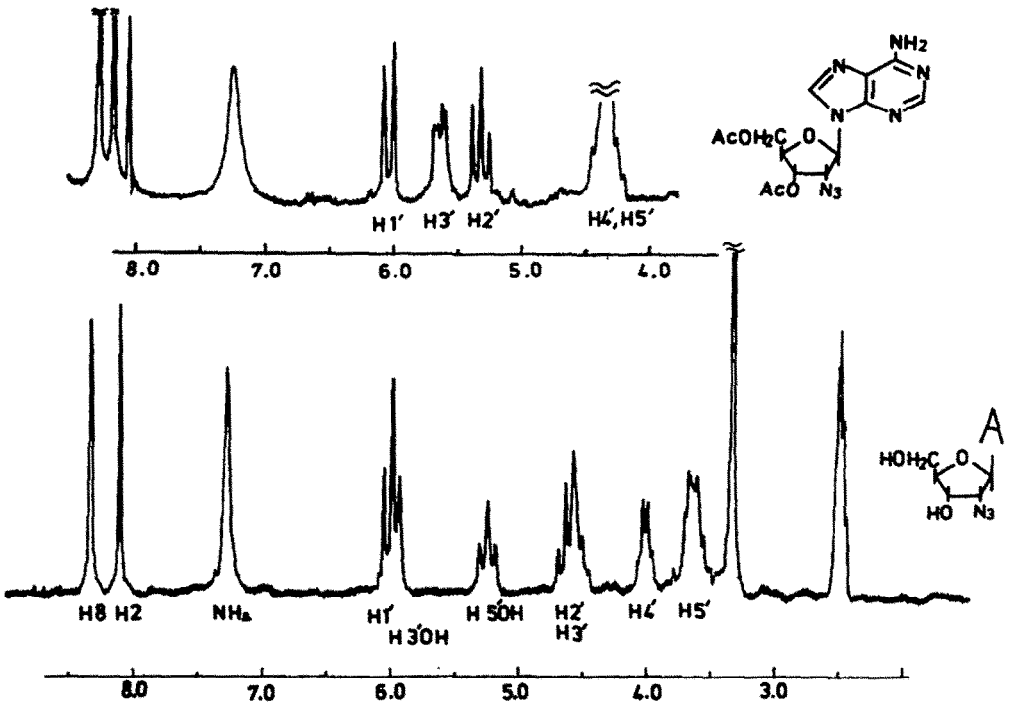

Fig. 2.

presumably because of the magnetic anisotropy of the 2'-azido group. The signals of H-3' and H-5' were shifted towards lower field relative to those of the 3',5'-diacetyl compound (17), (which was synthesized from compound 16) by 1 ppm and 0.7 ppm, respectively. In the ^{13}C-NMR spectrum[25] the C-2' signal of 16 was shifted upfield by 9 ppm relative to adenosine. These facts confirmed the structure of 16 to be 2'-azido-2'-deoxyadenosine.

When the compound 16 was hydrogenated over palladium catalyst, 2'-amino-2'-deoxyadenosine (18) was isolated as the dihydrochloride, m.p. 195–197°, in a yield of 76%. This salt was passed through a column of Dowex 1×2 (OH^- form) and the 2'-amino-2'-deoxyadenosine, m.p. 197–198°,[26] was obtained in a yield of 68%. Elemental analysis and the ninhydrin spray-test suggested the aminonucleoside structure of 18. The UV absorption spectra of 18 closely resembled those of adenosine and the NMR spectrum showed the H-2' signal shifted by 0.6 ppm to higher field relative to adenosine. This sample showed the same *Rf* value in paper chromatography as a sample[23] kindly donated by Dr. R. Mengel.

In order to introduce a Cl atom to the 2'-position, the 2'-O-mesyl-3',5'-tetrahydropyranylarabinosyladenine (14) was heated with lithium chloride in DMF at 150°. The reaction took place rather slowly and after 20 hr heating a byproduct was concomitantly produced in equal amounts to the desired chloro compound. Separation by TLC gave a chlorinated compound (19, R=Thp) in a yield of 31%. Deprotection with 80% acetic acid gave 2'-chloro-2'-deoxyadenosine (14, R=H), m.p. 221–222°, in a

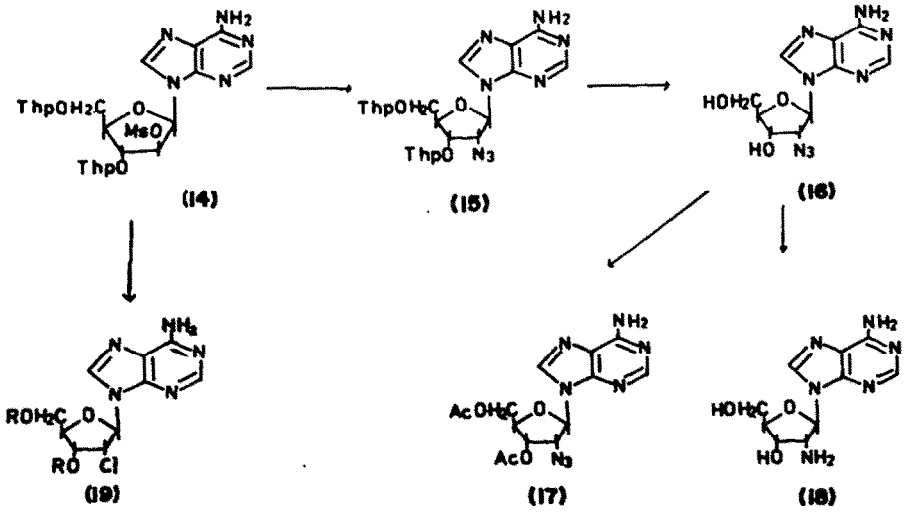

Chart 3.

yield of 39%. This compound showed a positive Beilstein test and UV absorption having λ_{max} around 270 nm. Elemental analysis supported the structure as given. Comparison of these properties with those in the literature[23] showed a complete agreement.

The present method provides a way for synthesizing various 2'-substituted 2'-deoxyadenosine derivatives in large quantities. The behaviour of these nucleosides as such or in the form of nucleotides in a variety of biological systems is currently under investigation.

EXPERIMENTAL[27]

3',5' - Di - O - acetyl - 8,2' - anhydro - 8 - oxy - 9 - β - D - arabinofuranosyladenine (3)

8,2'-O-Cycloadenosine (970 mg, 3.66 mmoles) was dissolved in a mixture of pyridine (10 ml) and Ac_2O (5 ml). After stirring form 5 min at room temp., the mixture was cooled to 0° and kept at this temp. for 2 hr. The solvent was evaporated *in vacuo* and H_2O (30 ml) was added to the residue. The diacetyl compound was obtained as tiny priams, m.p. 215–218°, in a yield of 1.137 g (3.26 mmole, 90%). Calc. for $C_{14}H_{15}N_5O_6$: C, 48.14; H, 4.33; N, 20.05%. (Found: C, 47.92; H, 4.16; N, 20.24 UV and Mass spectral data are asummarized in Tables 1 and 2. Mass spectrum: *m/e* 349 (M^+). TLC($CHCl_3$–EtOH, 10:1): R_f 0.23.

3',5'-Di-O-acetyl-8-mercapto-9-β-D-arabinofuranosyladenine (4)

Compound 3 (970 mg, 2.77 mmoles) was dissolved in pyridine (20 ml), N_2 gas was bubbled through the soln and it was cooled to −70°. Liquid H_2S (35 ml) was added to the mixture and it was heated at 100° for 18 hr in a sealed tube. The tube was opened after it was cooled to −70° and the soln was kept at room temp. for 3 hr. N_2 gas was bubbled through the soln, the solvent was evaporated with toluene, and the residue was taken up in $CHCl_3$. Upon addition of toluene the product was obtained as white powder, m.p. 120° in a yield of 927 mg (2.42 mmoles, 87%). (Found : C, 44.36; H, 4.47; N, 18.02; S, 8.23. Calc. for $C_{14}H_{17}N_6O_5S$: C, 43.86; H, 4.47; N, 18.27; S, 8.36). UV absorption data are in Table 1. TLC($CHCl_3$ – EtOH, 10:1) *Rf* 0.31.

3',5'-Di-O-acetyl-9-β-D-arabinofuranosyladenine (5)

(i) Compound 4 (484 mg, 1.26 mmole) was dissolved in EtOH (20 ml) and H_2O (5 ml) and refluxed in the presence of Raney Ni (1 ml) for 1 hr with vigorous stirring. Raney Ni (1 ml) was added again and the mixture was refluxed for another hour. The catalyst was filtered off and washed with hot EtOH. The filtrate and washings were combined and evaporated. To the residue $CHCl_3$ (30 ml) was added and insoluble material was filtered off. The filtrate was evaporated *in vacuo* to give a glass, which was recrystallized from EtOH to give colorless needles, m.p. 173–175°, in a yield of 243 mg (0.692 mmoles, 58%). (Found: C, 47.85; H, 4.64; N, 19.76. Calc. for $C_{14}H_{17}N_5O_6$: C, 47.86; H, 4.88; N, 19.94). UV and NMR spectral data are summarized in Tables 1 and 2. TLC($CHCl_3$–EtOH, 7:1): R_f 0.21.

(ii) *One step procedure from 8,2'-O-cycloadenosine.* 8,2'-O-Cycloadenosine (8.04 g, 30.3 moles) was dissolved in pyridine (100 ml) and Ac_2O (50 ml) wgs added. After heating the mixture at 80° for 5 hr, the solvent was evaporated *in vacuo*. The residue was taken up in H_2O and slight concentration gave crystals, which were collected by filtration. The filtrate was evaporated and the residue was recrystallized from EtOH and combined with the first crop to give 7.9 g (67%) of N^6,3',5'-triacetylcycloadenosine as colorless needles of m.p. 97–100°. UV: $\lambda_{max}^{50\%EtOH}$ 276 nm, $\lambda_{max}^{H^+}$ 276 nm, $\lambda_{max}^{OH^-}$ 287 nm. TLC($CHCl_3$ EtOH, 9:1): R_f 0.69. The triacetyl-cyclonuceoside (4.0 g) was dissolved in

Table 1. UV absorption properties of synthesized compounds

	λ max nm (ε)					
	neutral		0.1N HCl		0.1N NaOH	
DiAc-8,2'-O-cycloA	255	(15,800)	257	(15,000)		
			280	(sh 7,600)		
8-SH-diAc-araA	230	(15,800)	243	(10,900)		
	298	(23,900)	298	(sh,19,400)	298	(20,900)
	305	(24,600)	307	(22,500)		
DiAc-araA	258.5	(15,500)	256.5	(15,400)	259	(15.400)
2'-Ms-diAc-araA	258.5	(15,600)	256	(15,400)	258.5	(15,200)
2'-Ms-araA	258.5	(15,100)	256	(15,100)	259	(15,300)
2'-d-2'-N_3-A	259	(15,100)	257	(15,100)	259	(15,200)

Table 2. NMR signals of synthesized compounds

	H-8	H-2	NH-H	H-1'	H-2'	H-3'	H-4'	H-5'	2'-OH	3'-OH	5'-OH
DiAc-8,2'-O-cycloA	8.09	8.09	6.92	6.65	6.02	5.45	4.62	4.05		Ac 2.19	s,3
		s,1	br,2	d,1	d,1	d,1	m,1	d,2		1.98	s,3
				J1'2'=6	J2'3'=0	J3'4'=2					
DiAc-araA	8.10		7.23	6.29	4.40	5.24	4.10–4.50		6.14	Ac 2.16	s,3
	s,2		br,2	d,1		t,1			d,1	2.07	s,3
				J1'2'=4		J2'3'=J3'4'=3			J2'-2'-OH=5		
2'-Ms-diAc - araA	8.23	8.13	7.24	6.48	5.58	5.80	4.15–4.50		Ms-CH3	Ac 2.10	s,3
	s,1	s,1	br,2	d,1	t,1	t,1	m,3		s,3	2.02	s,3
				J1'2'=6	J2'3'=5.5	J3'4'=5.5			3.06		
2'-Ms-araA	8.26	8.17	7.28	6.48	5.27	4.63	3.90	3.74	Ms-CH3	6.01	5.10
	s,1	s,1	br,2	d,1	t,1	q,1	m,1	m,2	3.09	d,1	t,1
				J1'2'=6	J2'3'=6	J3'4'=6				J3'-3'OH=6	J5'-5'OH=5.5

pyridine (40 ml) and N_2 gas was bubbled through the soln for 15 min. The soln was cooled to −50° and after H_2S gas was bubbled for 30 min it was heated at 65° for 18 hr in a sealed tube. After the work up a described above N⁶,3',5'-triacetyl-8-mercaptoarabinosyladenine was obtained in a yield of 4.13 g. UV: $\lambda_{max}^{50\%EtOH}$ 245, 321; $\lambda_{max}^{H^+}$ 251, 324 nm; $\lambda_{max}^{OH^-}$ 245(sh), 317 nm.

This material (4.13 g) was dissolved in a mixture of EtOH (100 ml) and H_2O (20 ml). Insoluble material was filtered off and Raney Ni (5 ml) was added to the filtrate. The mixture was heated at 100° for 45 min with stirring. Raney Ni (3 ml) was added again and the refluxing was continued for 45 min. The catalyst was filtered off and washed with hot EtOH. The filtrate and washings were combined and evaporated *in vacuo*. After drying *in vacuo*, $CHCl_3$ (50 ml) was added to the residue, insoluble material was filtered, and the filtrate was evaporated. Recrystallization of the residue from EtOH gave **5** in a yield of 2.22 g, 6.32 mmoles, 20.9% from 8,2,-cycloadenosine).

3',5'-Di-O-acetyl-2'-O-mesylarabinosyladenine (**6**)

Compound **5** (2.74 g, 7.81 mmoles) was dissolved in pyridine (42 ml) and cooled to 0°. Mesylchloride (4.6 ml, 3 equiv) was added to the soln, which was kept at −20° for 18 hr under exclusion of moisture. The mixture was poured into ice-water (300 ml), extracted with $CHCl_3$ (200 ml + 100 ml), washed with H_2O (100 ml) and dried over $MgSO_4$. The residue obtained by evaporation of $CHCl_3$ was recrystallized from EtOH to give pale yellow crystals, m.p., 170–172°, in a yield of 5.80 mmoles (74%). (Found: C, 41.81; H, 4.19; N, 16.26; S, 7.36; Calc. for $C_{15}H_{19}N_5O_8S$: C, 41.96; H, 4.46; N, 16.31; S, 7.49%) UV and NMR spectral data are summarized in Tables 1 and 2. Mass spectrum *m/e* 429 (M^+). IR: ν_{max}^{KBr} 1180 cm^{-1} ($MeSO_2O$). TLC($CHCl_3$–EtOH 7:1): R_f 0.45.

2'-O-Mesylarabinosyladenine (**7**)

Compound **6** (2.961 g, 6.9 mmoles) was dissolved in MeOH (30 ml). Dry NH_3 gas was bubbled through the soln at 0° for 1 hr. The mixture was sealed and heated at 40° for 18 hr. The solvent was evaporated and the residue was recrystallized from EtOH to give white needles, m.p., 217–220°, in a yield of 2.136 g (6.19 mmoles, 90%). (Found: C, 38.17; H, 4.30; N, 20.17; S, 9.10; Calc. for $C_{11}H_{15}N_5O_6S$: C, 38.26; H, 4.38; N, 20.28; S, 9.28). UV and NMR spectral data are summarized in Tables 1 and 2. I.R.: ν_{max}^{KBr} 1180 cm^{-1} ($MeSO_2O$–). PPC: R_f(B) 0.69, R_f(C) 0.69.

3'-Azido-3'-deoxy-9-β-D-xylofuranosyladenine (**9**)

(i) 2'-O-Mesylarabinosyladenine (82 mg, 0.24 mmole) was dissolved in DMF (12 ml) and anhyds NaN_3 (80 mg) was added. The mixture was heated at 150° for 1 hr with stirring under exclusion of moisture. The salt was filtered off and the filtrate was evaporated *in vacuo*. The residue was recrystallized from H_2O to give pale yellow needles, m.p., 177–179°, in a yield of 42 mg (0.14 mmole 60%). (Found: C, 40.25; H, 3.99; N, 37.87. Calc. for $C_{10}H_{12}N_8O_3 \cdot 1/3\ H_2O$: C, 40.27; H, 4.17; N, 37.57). NMR (δ): 8.23 (s, 1H, H-8), 8.13 (s, 1H, H-2), 7.24(br, 2H, N^6-H), 6.13(d, 1H, 2'-OH, $J_{2'H\text{-}2'OH}$=5HZ), 5.82(d, 1H, H-1', $J_{1'H\text{-}2'H}$=5Hz), 5.32(t, 1H, 5'-OH, $J_{5'H\text{-}5'OH}$=5Hz), 4.77(q, 1H, H-2'), 4.32(m, 2H, H-3' and 4'), 5.67(m, 2H, H-5'). PPC: R_f(A) 0.67, R_f(B) 0.83.

(ii) Compound **6** (586 mg, 1.37 mmoles) was dissolved in DMF (40 ml) and heated with anhyd NaN_3 (1.2 g) at 150° for 1 hr with stirring under exclusion of moisture. The salt was filtered off and the solvent was evaporated *in vacuo*. To the residue $CHCl_3$ (50 ml) was added, the $CHCl_3$ layer was washed with H_2O (20 ml × 2), and dried over $MgSO_4$. Evaporation of $CHCl_3$ *in vacuo* gave a glass, which was dissolved in MeOH (25 ml). After addition of cone NH_3aq (25 ml), the soln was kept at room temp overnight. Evaporation of the solvent gave a residue, which was recrystallized from EtOH to give **9** in a yield of 167 mg(0.57 mmole, 42%). This sample is identical to that obtained in (i) in all respects.

2',5' - Di - O - acetyl - 3' - azido - 3' - deoxy - 9 - β - D - xylofuranosyladenine (**8**)

Compound **6** (30 mg) was dissolved in DMF (2 ml) and anhyd NaN_3 (60 mg) was added. The mixture was heated at 150° for 1 hr with stirring under exclusion of moisture. The salt was removed by filtration, the solvent was evaporated *in vacuo*, and the residue was dissolved in $CHCl_3$. Application of the $CHCl_3$ soln to TLC and separation of the material migrating in a band at *Rf* 0.50 gave white crystals, m.p., 172–175° by recrystallization from benzene. (Found: C, 45.09; H, 4.02; N, 29.25. Calc. for $C_{14}H_{16}N_8O_5$: C, 44.68; H, 4.29; N, 29.77%). Mass spectrum: *m/e* 376 (M^+). TLC($CHCl_3$–EtOH, 7:1): R_f 0.55. This compound gave the compound **9** by deprotection with ammonia as described above.

3',5'-Di-O-tetrahydropyranyl-8,2'-O-cycloadenosine (**11**)

8,2'-O-C-Cycloadenosine (1.01 g, 3.8 mmoles) was dissolved in DMF 20 ml) and the soln was slightly conc. by evaporation with added benzene to remove traces of H_2O. To this soln 2,3-dihydropyran (5 ml) was added and the soln was cooled to 0°. After *p*-toluenesulfonic acid (1.32 g, 7.6 mmoles, dried over P_2O_5 at 60° for 2 hr) was added, the mixture was kept at 4° overnight. The reaction was stopped by adding NH_4OH, the solvent was removed by vacuum distillation, and the residue was taken up in $CHCl_3$–H_2O. The $CHCl_3$-layer was dried over $MgSO_4$ and evaporated to give a residue, which was recrystallized from EtOH to give the crystalline product in a yield of 0.96 g (2.2 mmoles, 59%). (Found: C, 55.23; H, 6.48; N, 16.02. Calc. for $C_{20}H_{27}O_6N_5$: C, 55.41; H, 6.28; N, 16.16%). TLC($CHCl_3$–EtOH, 10:1) R_f 0.32.

3',5'-Di-O-tetrahydropyranyl-8-mercaptoarabinofuranosyladenine (**12**)

Compound **11** (0.96 g, 2.2 mmole) was dissolved in pyridine (30 ml) and N_2 gas was bubbled through the soln. After cooling the soln to −50°, H_2S gas was bubbled for 30 min. The sealed mixture was heated at 110° for 10 hr. The solvent was evaporated and the residue was coevaporated with toluene. The residue showed UV: $\lambda_{max}^{75\%EtOH}$ 239, 298, 305 nm and was used as such in the next step.

3',5'-Di-O-tetrahydropyranylarabinosyladenine (**13**)

The crude **12** obtained as above was dissolved in a mixture of dioxane (50 ml) and H_2O (14 ml). The mixture was refluxed with Raney Ni (2 ml) for 1 hr. Raney Ni (1 ml) was added again and the refluxing was continued for 30 min. The catalyst was removed by filtration and the filtrate was evaporated to give a hard syrup. The yield was 0.91 g (2.1 mmoles, 95%). UV: $\lambda_{max}^{95\%EtOH}$ 258 nm. TLC($CHCl_3$–EtOH, 7:1): R_f 0.51.

3',5'-Di-O-tetrahydropyranyl-2'-O-mesylarabinosyladenine (**14**)

(i) Compound **7** (667 mg, 1.94 mmole) was dissolved in DMF (5.8 ml). To the soln freshly distilled dihydropyran (5.8 ml) and toluenesulfonic acid (606 mg, 3.88 mmoles) were added. The mixture was kept at 4° for 17 hr. The reaction was stopped by the addition of triethylamine (3 ml) and the solvent was removed by vacuum distillation. The residue was dissolved in $CHCl_3$ (60 ml), washed with H_2O (20 ml × 2), and dried over $MgSO_4$. The $CHCl_3$ soln was applied to a column (3.0 × 28 cm) of silica gel. Elution with $CHCl_3$ (300 ml) and $CHCl_3$ containing 3% EtOH (11) gave the desired product in a yield of 862 mg (1.39 mmoles, 72%). UV: $\lambda_{max}^{50\%EtOH}$ 259 nm, $\lambda_{max}^{H^+}$ 256 nm, $\lambda_{max}^{OH^-}$ 258 nm. IR: ν_{max}^{KBr} 1180 cm^{-1} ($MeSO_2O-$). Mass spectrum: *m/e* 513 (M^+). TLC($CHCl_3$–EtOH, 7:1): R_f 0.38.

(ii) Compound **13** (0.91 g, 2.1 mmoles) was dissolved in pyridine (10 ml) and mesyl chloride (1.3 ml) was added. The mixture was kept at −20° for 10 hr and poured onto ice. Extraction of the product with $CHCl_3$, washing with H_2O, drying over $MgSO_4$, and evaporation of $CHCl_3$ *in vacuo* gave a hard syrup in a yield of 0.75 g (1.5 mmole, 71%). This sample was identical to that obtained in (i).

3',5'-Di-O-tetrahydropyranyl-2'-azido-2'-deoxyadenosine (**15**)

Compound **14** (2.73 g, 5.3 mmoles) was dissolved in anhyd DMF (240 ml). Well-dried NaN_3 (2.73 g) was added and the mixture was heated at 150° for 7.5 hr. The salt was filtered off, the filtrate was evaporated *in vacuo*, and the residue was taken up in $CHCl_3$ (200 ml). Insoluble material was filtered off, the $CHCl_3$ soln was dried over $MgSO_4$, and evaporated to a small volume. The soln

was applied to a column (3.0 × 45.0 cm) of silica gel and eluted with $CHCl_3$ containing 2% EtOH. The fractions showing R_f 0.46 in TLC($CHCl_3$–EtOH, 10:1) were collected and evaporated *in vacuo*. The produce **15** was obtained as a hard syrup in a yield of 1.14 g (2.5 mmoles, 47%); UV: $\lambda_{Max}^{95\%EtOH}$ 259 nm, IR: $\nu_{max}^{CHCl_3}$ 2100 cm^{-1} (N_3).

2'-Azido-2'-deoxyadenosine (**16**)

Compound **15** (1.39 g, 3.0 mmoles) was dissolved in a mixture of AcOH (100 ml) and H_2O (15 ml) and heated at 50–55° for 6 hr. Checking by TLC($CHCl_3$–EtOH, 5:11) showed four spots at R_f 0.71 (sugar), 0.61 (starting material), 0.30 (product) and 0.10 (adenine) in a ratio of 3:10:72:15. The solvent was evaporated *in vacuo* and the residue was extracted with $CHCl_3$ and H_2O. The H_2O-layer was separated and evaporated *in vacuo* to give a residue. The residue was recrystallized from H_2O to give **16** as colorless needles, m.p. 221–222.5° in a yield of 496 mg, (1.7 mmole, 57%). (Found: C, 41.37; H, 3.87; N, 38.04. Calc. for $C_{10}H_{12}N_8O_3$: C, 41.09; H, 4.14; N, 38.34%). IR: ν_{max}^{KBr} 2110, 2130 cm^{-1} (N_3). UV data are in Table 1. NMR (Fig. 2) (δ): 8.33 (s, 1H, H-8), 8.11 (s, 1H, H-2), 7.28(br, 2H, N^6-H), 6.04(d, 1H, H-1, $J_{H1'-H2'}$ = 5.5 Hz), 5.97(d, 1H, 3'-OH), 5.24(t, 1H, 5'-OH, $J_{H5'-OH5'}$ = 6H), 4.60(m, 2H, H-5'). PPC: R_f (A) 0.60, R_f(B) 0.77. R_f(C) 0.71. These values are in good agreement with those reported by Mengel.

3',5'-Di-O-acetyl-2'-azido-2'-deoxyadenosine (**17**)

2'-Azido-2'-deoxyadenosine (30 mg) was dissolved in a mixture of pyridine (2 ml) and Ac_2O (0.5 ml) was added and the soln was kept at room temp. for 30 min. The solvent was evaporated *in vacuo* and trace of Ac_2O was azeotropically distiled off. The residue was dissolved in $CHCl_3$ (5 ml), dried over $MgSO_4$, and evaporated *in vacuo*. The yield was 28 mg (83%). UV: $\lambda_{max}^{50\%EtOH}$ 259 nm. NMR(d_6-DMSO, δ): 8.26. (s, 1H, H-8), 8.18(s, 1H, H-2), 7.22(br, 2H, N^6-H), 6.02(d, 1H, H-1'), 5.62(s, 1H, H-3'), 5.30(t, 1H, H-2'), 4.32(m, 3H, H-4' and 5').

2'-Amino-2'-deoxyadenosine (**18**)

Compound **16** (247 mg, 0.85 mmole) was dissolved in a mixture of H_2O (45 ml) and AcOH (10 ml), H_2-gas was bubbled through the soln in the presence of 10% Pd-C (100 mg) with stirring at room temp. The catalyst was removed by filtration and the filtrate was evaporated *in vacuo* to give a syrup. The syrup was dissolved in EtOH and 1N HCl (1.5 ml) was added. Evaporation of the soln gave a residue, which was recrystallized from EtOH to give the dihydrochloride **18** m.p., 195–197°, in a yield of 219 mg (0.65 mmole, 76%). (Found : C, 35.02; H, 4.74; N, 24.56; Cl, 20.88. Calc. for $C_{10}H_{14}N_6O_3 \cdot 2HCl$: C, 35.41; H, 4.75; N, 24.78; Cl, 20.91). UV: $\lambda_{max}^{H_2O}$ 258.5 nm (ϵ 15,000), λ_{max}^{NHCl} 256.5 (14,900), $\lambda_{max}^{0.1NNaOH}$ 259 (15,100). NMR(d_6-DMSO-D_2O(3:2), pD4): 8.62(s, 1H, H-8), 8.47(s, 1H, H-2), 6.39 (d, 1, H-1', $J_{H1'-H2'}$=6.5 Hz), 4.0–4.8($H_{2'}$,$H_{3'}$,$H_{4'}$,HOD), 3.75(d, 2H, H-5', $J_{H4'-H5'}$ = 3.5 Hz).

The hydrochloride (219 mg) was dissolved in H_2 (5 ml) and passed through a column of Dowex 1×2 (OH^- form, 8 ml). Elution with H_2O (100 ml) and evaporation gave a hard syrup, which was recrystallized from acetonitrile to give 154 mg, (0.56 mmole, 68%, from **16**) of 2'-amino-2'-deoxyadenosine, m.p. 197–198°. (Found: C, 44.80; H, 5.46; N, 31.53. Calc. for $C_{10}H_{14}N_6O_3$: C, 45.10; H, 5.31; N, 31.57%). UV: $\lambda_{max}^{H_2O}$ 259.5 nm (ϵ, 14,800), $\lambda_{max}^{0.1NHCl}$ 256.5 (14,600), $\lambda_{max}^{0.1NNaOH}$ 259.5 (14,900). NMR(D_2O): 8.32(s, 1H, H-8), 8.12(s, 1H, H-2), 5.88(d, 1H, H-1'$J_{H1'-H2'}$ = 8 Hz), 4.25–4.50(m, 2H, H-3' and H-4'), 4.03(q, 1H, H-2', $J_{H2'-H3'}$=5 Hz), 3.91(d, 2H, H-5', $J_{H4'-H5'}$=3.5 Hz). PPC: R_f(A) 0.09, R_f(B) 0.50, R_f(C) 0.37. The e values coincided with those reported earlier.[23–26] Direct comparison of the sample with an authentic sample[23] of 2'-amino-2'-deoxyadenosine showed them to have completely identical properties.

2'-Chloro-2'-deoxyadenosine (**19**, R=H)

Compound **14** (450 mg, 0.88 mmole) wgs heated with LiCl (373 mg, 8.8 mmole) in DMF (50 ml) at 150° for 24 hr. The solvent was evaporated *in vacuo* and the residue was taken up in $CHCl_3$–H_2O. The $CHCl_3$-layer was conc. and applied to a TLC plate of silica gel. Compound **19** (R=Thp) was obtained as a hard glass in a yield of 124.7 mg, (0.28 mmole, 31%).

This material (81.1 mg, 0.18 mmole) was dissolved in 80% AcOH (5 ml) and heated at 50° for 5 hr. The solvent was evaporated *in vacuo* and azeotropically dried until the odor of AcOH was removed. To the residue $CHCl_3$ was added and the soln was washed with H_2O. The water layer was evaporated *in vacuo* to give a residue, which was recrystallized from H_2O to give 2'-chloro-2'-deoxyadenosine, m.p., 221–222°, in a yield of 39%. (Found C, 41.78; H, 4.24; N, 24.30. Calc. for $C_{10}H_{12}N_5O_3Cl$: 42.03; H, 4.24; N, 24.52%). UV: $\lambda_{max}^{H_2O}$ 259.5 nm, $\lambda_{max}^{H^+}$ 256.5, $\lambda_{max}^{OH^-}$ 259.5. PPC: R_f(A) 0.62, R_f(B) 0.83, R_f(C) 0.74. This sample showed a positive Beilstein test and its properties were identical with those reported.[23]

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