cooled through the transition temperature. Ôno and Ito[36] reported a broadening of the Mössbauer peaks as the transition temperature was reached due to the simultaneous existence of both antiferromagnetic phases and the predicted change in sign and doubling in magnitude of the quadrupole splitting.

The effect of pressure on the quadrupole splitting is shown in Figure 10; the splitting passes through zero near 30 kbars, changes sign, and then grows with increasing pressure to about the original magnitude by 200 kbars. Measurements have indicated that the temperature of the Morin transition does increase with pressure,[37,38] and Worlton, *et al.*,[39] have recently reported that it reaches room temperature near 30 kbars. This agrees well with the point where the quadrupole splitting goes through zero, but if the explanation of the quadrupole splitting data were simply the occurrence of the Morin transition with increasing pressure, the peak broadening reported by Ôno and Ito should be detectable and the observed quadrupole splitting should have grown to nearly twice the original size.

The absence of these phenomena indicates that a reduction has occurred in the electric-field gradient before or during the Morin transition. One can interpret this reduction in the electric-field gradient in terms of local movement of ions within the unit cell using a point dipole model for the α-Fe_2O_3 structure. A calculation of this effect[34] indicates that a movement of the iron ion of only 0.04 Å along the body diagonal of the rhombohedral unit cell is sufficient to account for the abnormalities noted in the Mössbauer spectra.

Worlton and Decker[40] have, however, shown that these Mössbauer results, as well as neutron diffraction studies to 40 kbars, can be more plausibly explained by assuming a continuous change in the angle of the antiferromagnetic axis with respect to the (111) axis of the crystal with increasing pressure.

This relatively brief presentation illustrates the power of high-pressure Mössbauer resonance as a tool for uncovering new generalizations about electronic behavior in solids as well as for investigating the electronic structure of specific systems.

The authors express their appreciation to C. P. Slichter, G. K. Lewis, Jr., S. C. Fung, and W. H. Flygare for very helpful discussions and collaboration in many aspects of this work.

(36) K. Ôno and A. Ito, *J. Phys. Soc. Japan*, **17**, 1012 (1962).
(37) R. C. Wayne and D. H. Anderson, *Phys. Rev.*, **155**, 496 (1967).
(38) H. Umebayoshi, B. C. Frayer, G. Shirane, and W. B. Daniels, *Phys. Letters*, **22**, 407 (1966).
(39) T. G. Worlton, R. B. Bennion, and R. M. Brugger, *ibid.*, **A24**, 653 (1967).
(40) T. G. Worlton and D. L. Decker, *Phys. Rev.*, **171**, 596 (1968).

Purine 8-Cyclonucleosides

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Although nucleosides, as essential components of nucleic acids, have been widely studied, the somewhat more elaborate *cyclonucleosides* have received relatively little attention. The first cyclonucleoside was discovered by Lord Todd and his colleagues in 1951.[1] Subsequently, these compounds have become of interest in connection with nucleoside configurational studies. Also, their rigid structures facilitate interpretation of physical properties with respect to structural characteristics, and they are key intermediates in the synthesis of many biologically active substances. Their synthesis has been a considerable challenge in its own right.

To date, no cyclonucleoside has been found to occur naturally, either free or in bound form.

A few words about nomenclature are in order. Certain purine and pyrimidine bases are prominent in the biochemistry of nucleic acids in which these bases are covalently bound to sugar residues, either ribose or 2-deoxyribose, *via* glycosidic linkages. Compounds having one purine or pyrimidine base bound to one sugar residue are called *nucleosides*. For example, guanosine (**1**) is a nucleoside containing guanine and ribose moieties, and thymidine (**2**) contains thymine and 2-deoxyribose moieties. *Nucleotides* are phosphoric acid esters of nucleosides, at the 2′, 3′, or 5′ positions. Thus, in a nucleotide, the 5′ substituent may be OPO_3H_2 instead of OH as in the nucleoside. *Nucleic acids* are polymeric, and can be thought to represent esterification, many times repeated, between the 3′-hydroxyl group of one nucleotide molecule and the 5′-PPO_3H_2 group of another. *Cyclonucleosides* differ from ordinary nucleosides in that they have a covalent linkage, either directly or *via* bridging oxygen atoms, etc., between the 2′, 3′, or 5′ carbon of the sugar moiety and a carbon or nitrogen atom of the purine or pyrimidine moiety (other than the nitrogen

(1) V. M. Clark, A. R. Todd, and J. Zussman, *J. Chem. Soc.*, 2952 (1951).

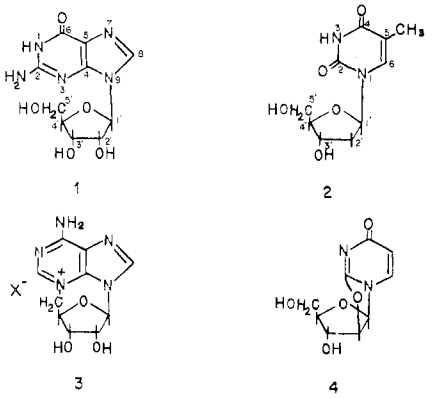
to which the sugar moiety is attached in the related nucleoside).

Before my group undertook research in this area, a certain number of cyclonucleosides had been prepared in other laboratories.[1-4] These involved either bonding of the 5′ carbon of the sugar moiety with N-3 of purine nucleosides, or between the 2′, 3′, or 5′ carbon and the 2 carbon of the pyrimidine ring of pyrimidine nucleosides. An example of the former sort was N^3,5′-cyclo-2′,3′-O-isopropylideneadenosine tosylate (**3**), prepared by Clark, *et al.*[1] A difficulty with this compound, with respect to the use in transformations in the carbohydrate moiety, is the reported instability of the purine ring system when quaternized in this way. However, pyrimidine cyclonucleosides such as **4** had been shown to be useful intermediates in such transformations.[3,4]

Inasmuch as great interest attaches to nucleosides resembling the natural ones but modified in the base or the carbohydrate moiety, we undertook the preparation of previously unknown purine cyclonucleosides involving bonding *via* bridging oxygen or sulfur atoms between C-8 of the purine system and the 2′, 3′, or 5′ carbon of the sugar moiety. It was anticipated that such compounds could easily be transformed into modified nucleosides. The first to be synthesized was 8,2′-anhydro-2-chloro-8-mercapto-9-β-D-arabinofuranosyladenine (**5**). From comparison of the structures of pyrimidine and purine nucleosides, it is evident that position 8 of a purine is analogous to position 2 of a pyrimidine nucleoside in its steric relationship to the sugar moiety.[5] Therefore, if a keto or thioketo function could be introduced into the 8 position of a purine nucleoside, nucleophilic attack by either of these groups on a carbon of the carbohydrate moiety bearing an alkyl- or arylsulfonyloxy group should give rise to a cyclonucleoside.

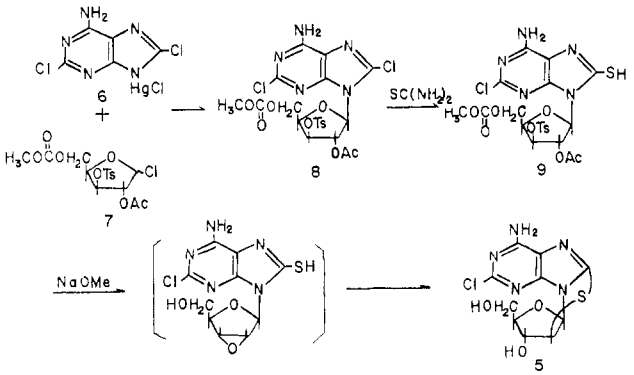
Synthesis of Purine Cyclonucleosides Having S-Anhydro Linkages

Compounds which fall into this category include 8,2′-, 8,3′-, and 8,5′-cyclonucleosides derived from adenosine, guanosine, and inosine. The first purine cyclonucleoside having an 8,2′-anhydro linkage was synthesized[6,7] as shown in Chart I. Base **6** and sugar **7** were synthesized beforehand and were condensed by Davoll's method, as shown. Reaction of **8** with thiourea effected nucleophilic displacement of chlorine and introduction of a thiol group in position 8. Treatment of **9** with $NaOCH_3$ in CH_3OH brought about a sequence of changes which resulted in formation of



cyclonucleoside **5**, the proper name of which is 8,2′-anhydro-2-chloro-8-mercapto-9-β-D-arabinofuranosyladenine. These changes presumably were, first, ester interchange to free the 2′- and 5′-hydroxy groups, then intramolecular base-catalyzed attack of the 2′-hydroxy on C-3′, displacing tosylate and forming an epoxide, and finally nucleophilic attack of the 8-thiolate ion on the epoxidized 2′ carbon, forming the cyclonucleoside sulfur bridge. Support for the structure shown, with its 8,2′-S-anhydro linkage, was provided by its physical properties, elemental analytical data, and chemical reactions as discussed below. One of its most important reactions was desulfurization with Raney nickel which produced a *deoxy*ribonucleoside. The synthesis of compound **5** demonstrated the possibility of forming cyclonucleosides in the purine series analogous to those such as **4** in the pyrimidine series.

Chart I



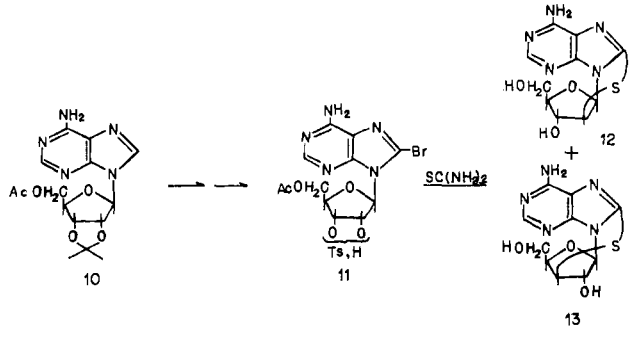
The next problem was formation of a cyclonucleoside directly from a naturally occurring purine nucleoside, such as adenosine, guanosine, or inosine. If this were possible, chemical transformation of a purine ribonucleoside to a deoxyribonucleoside could be accomplished. This transformation is known to occur in living organisms, but it has not been accomplished by the organic chemist.

The first goal in this study was introduction of a bromine atom in position 8 of purine nucleosides. After many attempts, it was found that direct bromination of adenosine, guanosine, inosine, and the related nucleosides can be performed in high yield using bro-

(2) B. R. Baker and J. P. Joseph, *J. Am. Chem. Soc.*, **77**, 15 (1955).
(3) A. M. Michelson and A. R. Todd, *J. Chem. Soc.*, 816 (1955), and following papers; J. F. Codington, R. Fecher, and J. J. Fox, *J. Am. Chem. Soc.*, **82**, 2794 (1960), and following papers.
(4) J. J. Fox and I. Wempen, *Advan. Carbohydrate Chem.*, **14**, 283 (1959); A. M. Michelson, "The Chemistry of Nucleosides and Nucleotides," Academic Press, New York, N. Y., 1963 pp 15, 68.
(5) M. Wilkins, "Nucleoproteins," R. Stoops, Ed., Interscience Publishers, New York, N. Y., p 48.
(6) M. Ikehara and H. Tada, *J. Am. Chem. Soc.*, **85**, 2344 (1963).
(7) M. Ikehara and H. Tada, *ibid.*, **87**, 606 (1965).

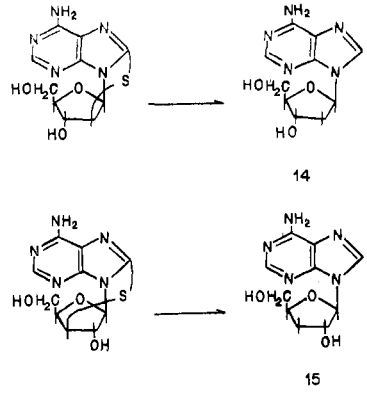
mine water with an acetate buffer.[8,9] This method is superior to those employed previously.[10] Starting from 2′,3′-O-isopropylidene-5′-O-acetyladenosine (**10**), introduction of a bromine atom in the 8 position and tosylation of the 2′- or 3′-hydroxy gave 5′-O-acetyl-2′(or 3′)-tosyl-8-bromoadenosine (**11**). Compound **11** was refluxed in 1-butanol with thiourea to afford a cyclonucleoside mixture, which was separated by recrystallization and chromatography to give 8,2′-anhydro-8-mercapto-9-β-D-arabinofuranosyladenine (**12**) and 8,3′-anhydro-8-mercapto-9-β-D-xylofuranosyladenine (**13**) (Chart II).[11]

Chart II



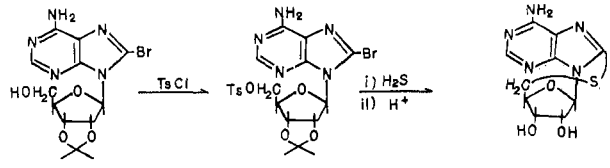
Although the yields of these cyclonucleosides were rather low, recent experiments[12] involving specific arylsulfonylation by means of NaH and the bulky reagent, 2,4,6-triisopropylbenzenesulfonyl chloride, gave 8,2′-S-cyclonucleoside **12** in satisfactory yield (60%). By desulfurization of compounds **12** and **13**, 2′-deoxyadenosine (**14**) and 3′-deoxyadenosine (**15**) were obtained. The latter is the antibiotic Cordycepin. This constitutes the first chemical transformation of naturally occurring adenosine into 2′-deoxyadenosine. The reaction was further extended to inosine; 2′-deoxyinosine was synthesized in good over-all yield.[13] Similarly, 8,3′-anhydro-8-mercapto-9-(2-deoxy-*threo*-pentofuranosyl)adenine was synthesized from 2′-deoxyadenosine.[14] Because 5′-tosyladenosine is prone to cyclize to a N^3,5′-cyclonucleoside salt[1] (**3**), an 8,5′-S-cyclonucleoside was first synthesized in the guanosine series.[15,16] This reaction was later applied to adenosine; 8,5′-anhydro-8-mercaptoadenosine (**16**)

Chart III



was obtained by the use of low-temperature tosylation and thiolation procedures (Chart IV).[17]

Chart IV



Thus the formation of 8,2′-, 8,3′-, and 8,5′-cyclonucleosides with S-anhydro linkages from purine nucleosides has been accomplished.

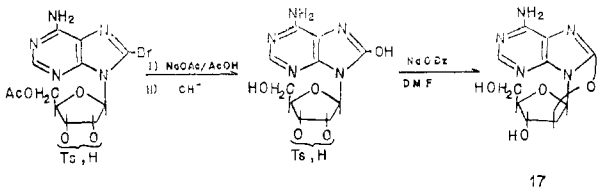
Synthesis of Purine Cyclonucleosides Having O-Anhydro Linkages

Since most of the naturally occurring pyrimidine nucleosides have a C=O group in the 2 position, cyclonucleosides having O-anhydro linkages have been investigated extensively in the pyrimidine nucleoside series. Hydrolytic cleavage of this type of compound affords a nucleoside having an altered carbohydrate moiety. As described in subsequent section on the reaction of purine S-cyclonucleosides, the S-anhydro linkage is resistant to mild hydrolytic cleavage. For comparison purposes in the study of cleavage reactions, synthesis of O-cyclonucleosides of the purine series was required.

Since the introduction of an oxy function in the 8 position of a purine nucleoside is necessary to synthesize O-cyclonucleosides, methods for conversion of an 8-bromo atom to an oxy group were sought. This was achieved by treatment of the bromo compound with sodium acetate either in acetic acid[15] or in acetic anhydride.[18] Utilizing this method, 8,2′-anhydro-8-oxy-9-β-D-arabinofuranosyladenine (**17**) was synthesized as shown in Chart V.[19,20]

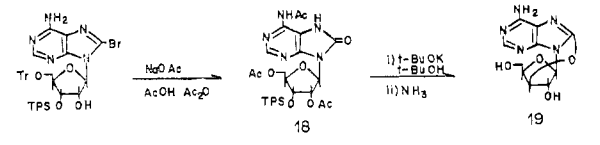
(8) M. Ikehara, S. Uesugi, and M. Kaneko, *Chem. Commun.*, 17 (1967).
(9) M. Ikehara and S. Uesugi, *Chem. Pharm. Bull.* (Tokyo), in press.
(10) R. E. Holmes and R. K. Robins, *J. Am. Chem. Soc.*, **87**, 1772 (1965).
(11) M. Ikehara and H. Tada, *Chem. Pharm. Bull.* (Tokyo), **15**, 94 (1967).
(12) M. Ikehara, M. Kaneko, and K. Tomimoto, reported at the Annual Meeting of Pharmaceutical Society of Japan, Kinki Regional Meeting, 1968.
(13) A. Yamazaki, unpublished experiments.
(14) M. Ikehara and M. Kaneko, Abstracts of Papers, 21st International Congress, IUPAC, Prague, 1967, p N-28.
(15) M. Ikehara, H. Tada, and K. Muneyama, *Chem. Pharm. Bull.* (Tokyo), **13**, 639 (1965).
(16) M. Ikehara and K. Muneyama, *J. Org. Chem.*, **32**, 3042 (1967).
(17) M. Ikehara, M. Kaneko, and M. Sagai, *Chem. Pharm. Bull.* (Tokyo), **16**, 1151 (1968).
(18) M. Ikehara and M. Kaneko, *ibid.*, **15**, 1261 (1967).
(19) M. Ikehara, H. Tada, K. Muneyama, and M. Kaneko, *J. Am. Chem. Soc.*, **88**, 3165 (1966).
(20) M. Ikehara, H. Tada, and M. Kaneko, *Tetrahedron*, **24**, 3489 (1968).

Chart V



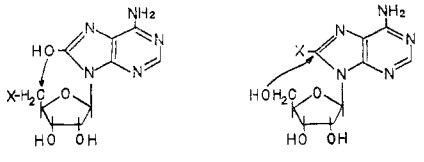
In contrast to our expectation, an 8,3′-O-cyclonucleoside was not formed in this cyclization reaction. The first 8,3′-O-cyclonucleoside was therefore synthesized from 2′-deoxyadenosine;[21] the synthesis was analogous to that shown in Chart V, except for the use of a 5′-trityl group. However, it was eventually possible to obtain an 8,3′-O-cyclonucleoside bearing a 2′-OH group; cyclization of 3′-O-triisopropylbenzenesulfonyl-N^6,2′,3′-O-triacetyl-8-oxyadenosine (**18**) by heating with *t*-butoxide in *t*-butyl alcohol and subsequent treatment with NH_3 afforded 8,3′-anhydro-9-β-D-xylofuranosyladenine (**19**) (Chart VI).[12]

Chart VI



In general, the formation of an O-cyclonucleoside might be performed in either of two ways, as shown in Chart VII. An oxy group of the base may attack

Chart VII

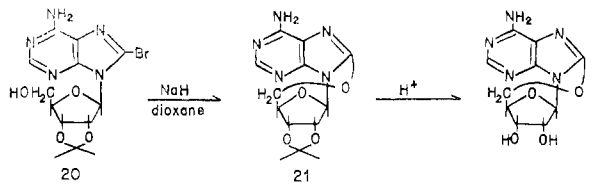


an electrophilic carbon of the sugar moiety, or, a sugar hydroxyl may attack an electrophilic carbon of the base. The formation of purine cyclonucleosides described above falls into the first category.

When 2′,3′-O-isopropylidene-8-bromoadenosine (**20**) was treated with sodium hydride in dioxane at room temperature, 8,5′-anhydro-8-oxyadenosine (**21**) was formed in good yield.[22,23] This reaction is an example of the cyclization of second category. The same type of reaction occurred also in the guanosine series (Chart VIII).[24]

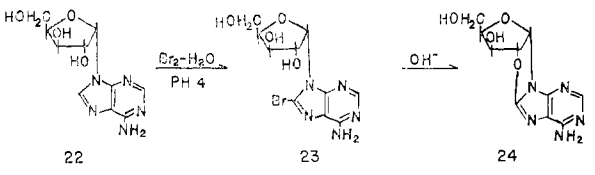
An alternative synthesis of compound **17**, involving as a key step nucleophilic attack on C-8 by the nearby 2′-OH in the *arabino* configuration, was reported.[25]

Chart VIII



Starting from 9-α-D-xylofuranosyladenine (**22**), 8,2′-O-cyclonucleoside (**24**) was formed by the reactions shown in Chart IX.[26] A point of special interest is

Chart IX



that the 2′-OH, being *cis* to the purine moiety, is able to participate in cyclization, but the 3′-OH is not able to do so. This compound is the first purine cyclonucleoside having an α configuration. It is of interest in the ord study discussed below.

A cyclonucleoside having an 8,2′-O-anhydro linkage was also synthesized from guanosine.[27] Thus cyclonucleosides having 8,2′-, 8,3′-, and 8,5′-O-anhydro linkages derived from purine nucleosides have been synthesized.

Reactions of Purine Cyclonucleosides

Variously substituted purine nucleosides can be obtained by cleavage of the purine cyclonucleosides described above.

Cyclonucleosides having S-anhydro linkages are easily desulfurized by treatment with Raney nickel to the corresponding deoxynucleosides.[6,7,11,15,16] This reaction enables chemical conversion of purine ribonucleosides to deoxyribonucleosides as described above.

Purine S-cyclonucleosides in general are resistant toward mild acidic or alkaline hydrolysis.[7] However, there are indications that a favorably located hydroxyl group may provide intramolecular catalysis of hydrolysis, causing cleavage of the anhydro linkage to occur.[28] Hydrolysis with strong acid or alkali at elevated temperatures leads to destruction of the purine ring and to cleavage of the nucleophilic linkage.[7]

In contrast to the S-anhydro linkage, the O-anhydro linkage of purine cyclonucleosides is easily cleaved under mild conditions.[19-22,26] For instance, treatment of 8,2′-anhydro-9-β-D-arabinofuranosyladenine (**17**) with acid gave arabinofuranosyl nucleoside (**25**), and

(21) M. Ikehara and M. Kaneko, *Chem. Pharm. Bull.* (Tokyo), **15**, 1261 (1967).
(22) M. Ikehara and M. Kaneko, *J. Am. Chem. Soc.*, **90**, 497 (1968).
(23) K. L. Nagpal and M. M. Dahr, *Tetrahedron Letters*, 47 (1968).
(24) M. Ikehara and K. Muneyama, in preparation.
(25) E. J. Reist, D. F. Calkins, L. V. Fisher, and L. Goodman, *J. Org. Chem.*, **33**, 1600 (1968).
(26) M. Ikehara, M. Kaneko, and Y. Nakahara, *Tetrahedron Letters*, 4707 (1968).
(27) M. Ikehara and K. Muneyama, *J. Org. Chem.*, **32**, 3039 (1967).
(28) Y. Mizuno and C. Okuda, Abstracts of Papers, Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, 1968, p 155.

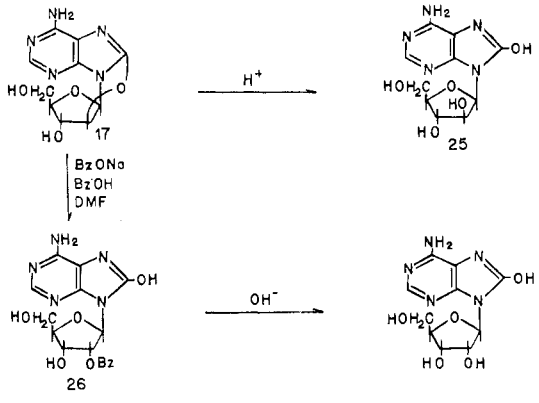
Table I
Physical Constants of Purine Cyclonucleosides

Compound	Mp, °C	λ max, mμ pH 1	λ max, mμ pH 7	λ max, mμ pH 14	[α]D, [c] deg	Nmr δH1′	Nmr J1′,2′, cps
2-Chloro-8,2′-S-cycloadenosine (**5**)	228–229	281	281	282.5	−214	6.82	7.0
8,2′-S-Cycloadenosine (**8**)	191–194	276	276	277	−187	6.51	6.6
		273 sh[a]	274 sh	285 sh			
8,3′-S-Cycloadenosine (**9**)	231–232	283	284	288			
		287 sh	290 sh	291 sh	−32	6.39	2.5
		276 sh	277 sh	277 sh			
8,5′-S-Cycloadenosine (**12**)[b]		284	286	286		6.24	0
		294 sh	294 sh	296 sh			
8,5′-S-Cycloguanosine[b]		273	274	289			
8,2′-O-Cycloadenosine (**15**)	190 dec	259	259	260	−122	6.50	5.4
8,3′-O-Cyclo-2′-deoxyadenosine (**18**)	266.5–267	262	263	263			
8,5′-O-Cycloadenosine (**26**)	209–210	260	260.5	261		6.07	0
8,2′-O-Cyclo-α-adenosine (**24**)	258–261 dec	259.5	257	260	+86.9	6.52	5.0

[a] Shoulder. [b] 2′,3′-O-Isopropylidene derivative. [c] Specific rotations were measured in water, pyridine, or DMSO at 19–23.5° ($c \sim 1.0$).

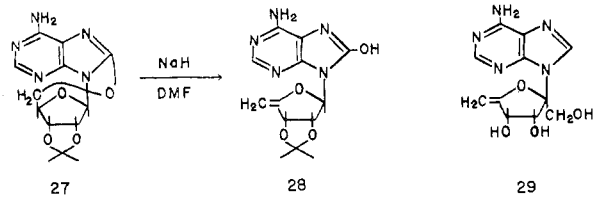
attack of benzoate anion in DMF gave 2′-O-benzoyladenosine (**26**).[19,20] In the acid-catalyzed reaction, the configuration at the 2′ carbon is retained, but in the benzoate reaction it is inverted (Chart X).

Chart X



Treatment of 2′,3′-O-isopropylidene-8,5′-anhydro-8-oxyadenosine (**27**) with excess sodium hydride in DMF gave a compound (**28**) which had an exocyclic double bond at 4′,5′.[29] This structure resembles that of the antibiotic, Angustmycin A (Decoyinine) (Chart XI).[30]

Chart XI



Reactions of 8,5′-anhydro-8-oxyguanosine with various nucleophiles, such as hydroxyl, acetate, thiolacetate, isocyanate, and isothiocyanate, gave only 5′-substituted 8-oxyguanosines,[24] showing the occurrence of aliphatic C–O fission. This is in contrast to the reactions of pyrimidine cyclonucleosides, in which both aryl and alkyl C–O fission occur according to the nature of the reagent used.[31]

Physical Properties of Purine Cyclonucleosides

Since the true conformations of purine nucleosides in solution have not yet been determined, physical studies of structurally rigid cyclonucleosides are of interest. Their physical properties serve, so to speak, to calibrate physical methods for determination of nucleoside conformations.

Constants obtained by the measurement of melting point, ultraviolet absoprtion, nmr, and specific rotation of the cyclonucleosides above are listed in Table I. In general, cyclonucleosides have lower melting points than the parent nucleosides and have larger R_f values in paper chromatography in the solvent systems containing organic solvent. Their ultraviolet absorption resembles that of the analogous 8-SCH_3 or 8-OCH_3 purine nucleosides. However, slight differences between the 8,2′-S-cyclonucleoside and the 8,3′- or 8,5′-S-cyclonucleoside derived from adenosine were observed. In 8,3′-anhydro-8-mercapto-9-β-D-xylofuranosyladenine (**13**), for instance, shoulders before and after 280 mμ due presumably to the splitting of the B_{2u} band appeared.

In nmr studies, the coupling constant H_1′–H_2′ suggested the 2′-*endo* conformation for 8,2′-cyclonucleosides and 3′-*endo* conformation for the 8,3′- and 8,5′-cyclonucleosides. Although for the 8,5′-O- and -S-cyclonucleosides two possible conformations, Figure 1, A and B, are conceivable, conformation A is indicated

(29) M. Ikehara and M. Kaneko, Abstracts of Papers, Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, 1968, p 155.

(30) H. Yüntsen, H. Yonehara, and H. Ui, *J. Antibiotics* (Tokyo), *Ser. A*, **7**, 113 (1954); H. Hoeksema, G. S. Slomp, and E. E. van Tamelen, *Tetrahedron Letters*, 1787 (1964).

(31) D. M. Brown, D. B. Parihar, A. R. Todd, and S. Varadarajan, *J. Chem. Soc.*, 3028 (1958).

Table II
Optical Rotatory Dispersion of Purine Cyclonucleosides

Compound	λ_{peak}, mμ	$[\phi]_{peak}$	λ trough, mμ	$[\phi]_{trough}$	Amplitude (× 10^{-2})
8,2′-S-Cycloadenosine (**8**)	295	0	266 sh[a]	−14,900	149
			235	−24,900	249
8,3′-S-Cycloadenosine (**9**)	295	+11,900	270 sh	−11,900	238
			245	−18,700	306
8,5′-S-Cycloadenosine (**12**)[b]	303	+22,400	260 sh	−56,000	784
	225	+93,000	246	−82,000	1044
8,5′-S-Cycloguanosine[b]	302	+10,300	276	−18,900	292
	241	+9,400	223		
8,2′-O-Cycloadenosine (**15**)	275	+4,300	220	−11,500	158
8,3′-O-Cyclo-2′-deoxy-adenosine (**18**)	275	+3,800	220	−24,600	284
8,5′-O-Cycloadenosine (**26**)[b]	274	+19,000	223	−28,000	470
8,2′-O-Cyclo-α-adenosine (**24**)	220	+17,400	264	−2,400	198

[a] Shoulder. [b] Isopropylidene derivative.

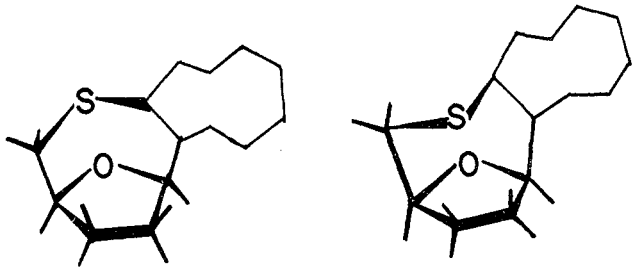


Figure 1. Schematic representation of the conformation of 8,5′-purine cyclonucleosides: A (left), *exo* form; B (right), *endo* form.

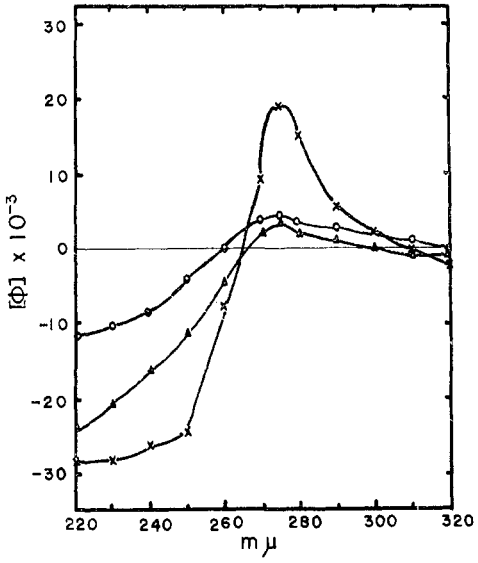


Figure 2. Ord curves of O-cyclonucleosides derived from adenosine: (○) 8,2′-, (△) 8,3′-, and (×), 8,5′-anhydro-8-oxyadenine-cyclonucleosides.

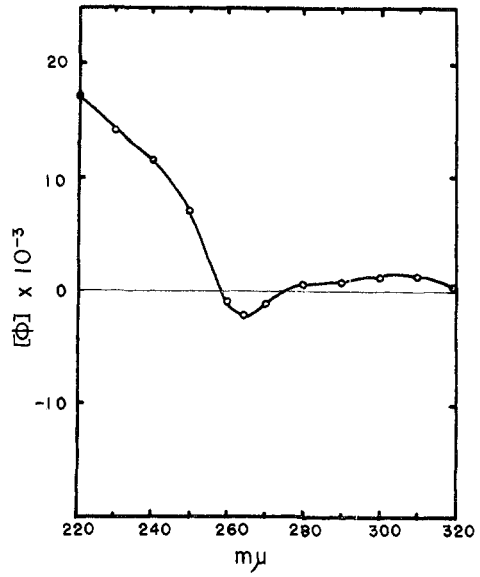


Figure 3. Ord curve of 8,2′-anhydro-8-oxy-α-D-xylofuranosyl-adenine.

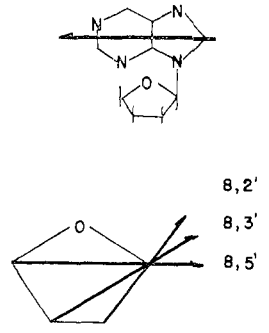


Figure 4. Schematic representation of the position of the base fixed by the anhydro linkages.

by nmr and ord data. The coupling constant $H_{4'}$–$H_{5'}$ suggested an *eclipsed* relationship of C-4 to C-5, which is satisfied only in conformation A.

Ord data for several purine cyclonucleosides are listed in Table II. Typical ord curves showing large positive Cotton effects around the major absorption band are shown in Figure 2. In Figure 3 the negative Cotton curve for an α-cyclonucleoside is shown. In these cyclonucleosides the plane of the base was fixed in the angle indicated by an arrow in Figure 4. The magnitude of Cotton effect around the major absorption band increases regularly according to the rotation of the arrow (base plane) clockwise around the nucleosidic linkage. From this correlation, the true angle of the base plane relative to the furanose ring can be deduced. Therefore, the 8,5′-cyclonucleosides must be in the A

form and not in B form, because the former should have a Cotton effect of far greater magnitude than that of 8,3′-cyclonucleosides. Final clarification of this point awaits analysis by X-ray crystallography.[32]

For a purine α-cyclonucleoside, a negative Cotton effect was observed. This is in contrast to ordinary α-nucleosides, which have small positive Cotton effects.[33] This finding is of extreme interest because in purine cyclonucleosides the small negative Cotton effect in the parent nucleosides is converted to a large positive one. These inversions of Cotton effect in both α- and β-cyclonucleosides suggest that the conformations of purine nucleosides in solution are not similar to those imposed by their structures in purine cyclonucleosides with bonding to C-8.

Investigation of other properties of purine cyclonucleosides by means of physical measurement would be desirable to facilitate understanding of the conformations of purine nucleosides, especially in solution.

Purine 8-cyclonucleosides thus are interesting compounds for the elucidation of the configuration and the conformation of purine nucleosides, and they are useful as intermediates in the synthesis of various biologically interesting compounds.

(32) K. Tomita, unpublished results.
(33) T. R. Emerson, R. J. Swan, and T. L. V. Ulbricht, *Biochemistry*, **6**, 843 (1967).

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Thermodynamic Order in Mesophases[1]

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The melting of a crystalline substance is a familiar phase transition. The highly structured solid melts to the isotropic liquid phase at a well-defined temperature and with a characteristic heat of fusion.

In contrast, a considerable number of organic compounds—more than 3000—do not melt directly from crystalline solid to isotropic liquid.[2,3] Instead, the substance passes through an intermediate phase, a *mesophase*. In such a case, two phase transitions are involved: at a lower temperature, a transition from crystalline solid to mesophase, and at a higher temperature, a transition from mesophase to isotropic liquid.

The mesophase appears as a turbid liquid, and the transitions can be observed visually or by other common techniques. The term *liquid crystal* has been used interchangeably with mesophase. To a lesser extent, this state has been referred to as anisotropic or paracrystalline.[2]

Mesophases are ordered on a molecular level, yet possess some of the mechanical properties of liquids. The ordered domains in mesophases contain typically about 10^5 molecules. However, the sense of arrangement of the molecules is not the same in all mesophases. Three basic types are recognized: nematic, smectic, and cholesteric mesophases. A single compound can exhibit more than one mesophase.

Figure 1 illustrates the general structural features of the three mesophases. The nematic type is the simplest. In pure compounds, *e.g.*, *p*-azoxyanisole, the nematic mesophase is thought to consist of bundles of rodlike structures. The only structural restriction in nematic mesophases is that the molecules are parallel or nearly parallel within a bundle.

In the smectic mesophase, molecules are arranged side by side in a series of stratified layers,[2a] *e.g.*, diethyl *p,p′*-azoxydibenzoate. Molecules in the layers may be arranged in a regular or random side-by-side spacing. The long axes of the molecules are parallel to one another and essentially perpendicular to the base plane of the layer. The layer can be one or more molecules thick. In general, the smectic mesophase has greater order than the nematic.

The third type is the cholesteric mesophase; it is formed principally by derivatives of cholesterol, *e.g.*, cholesteryl benzoate, but not by cholesterol itself.

(1) Part XVI of a series on Order and Flow of Liquid Crystals.
(2) (a) G. H. Brown and W. G. Shaw, *Chem. Rev.*, **57**, 1049 (1957); (b) J. L. Fergason, *Sci. Am.*, **211**, 76 (1964).
(3) G. W. Gray, "Molecular Structure and the Properties of Liquid Crystals," Academic Press, New York, N. Y., 1962.