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The Structure of Dehydromethionine. An Azasulfonium Salt

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Abstract: The crystal and molecular structure of dehydromethionine has been determined by x-ray crystallographic techniques. The compound crystallizes in the monoclinic space group $P2_1/n$ with $a = 5.658$ (6) Å, $b = 8.844$ (6) Å, $c = 13.605$ (9) Å, $\alpha = 90^\circ$, $\beta = 92.54$ (2)°, $\gamma = 90^\circ$, and $Z = 4$. The atoms other than hydrogen were located using direct methods, and the hydrogen atoms were located by Fourier difference maps. Full-matrix least-squares refinement led to a conventional R factor of 0.044. Key features of the molecular structure are an envelope conformation of the five-membered isothiazolidine ring and trivalent sulfur bonded to pyramidal nitrogen. The geometry about the nitrogen atom suggests the absence of p-d π bonding between the sulfur and nitrogen atoms in the azasulfonium linkage. It is suggested that the geometry and bonding in azasulfonium salts is analogous to that in the isoelectronic sulfonium ylides.

Recently, azasulfonium (aminosulfonium, sulfiminium) salts $\text{RR}^1\text{S}^+\text{NR}^2\text{R}^3\text{X}^-$ have been the subject of considerable attention. This is due primarily to their use in organic synthesis. They are intermediates in ortho-alkylation and related reactions of aromatic amines.¹ One of their number, the adduct of *N*-chlorosuccinimide and dimethyl sulfide,² has been advantageously employed in the oxidation of alcohols.³ The adducts of *N*-chloro- or *N*-bromosuccinimide and dimethyl sulfide are selective reagents for the conversion of allylic or benzylic alcohols into the corresponding halides.⁴ Azasulfonium salts, in which the nitrogen atom is bonded to a hydrogen atom, afford the corresponding conjugate bases, sulfilmines (sulfimides, sulfimines, iminosulfuranes) on treatment with base.⁵ The formation of azasulfonium salts by the reaction of sulfilmines with electrophiles has also been studied.^{6,7}

The determination of the structures of azasulfonium salts is of interest to facilitate an understanding of their reactions and to reveal the nature of the bonding of the sulfur atom. This latter concern involves two major considerations: (1) the sulfur atom may be trivalent or tetravalent and (2) there may be p(N)-d(S) π bonding. The detailed structure of one azasulfonium salt has already been reported.⁸ In the present paper, the determination of the structure by x-ray crystallographic techniques of dehydromethionine, an azasulfonium salt that was reported by Lavine⁹ and to which Lavine assigned structure **1** in 1945,^{9b} is presented.

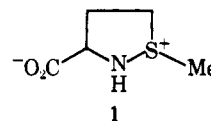


Table I. Crystal Data

Molecular formula	C ₅ H ₉ NO ₂ S
Molecular weight	147.2
<i>d</i> _{obsd}	1.46
<i>d</i> _{calcd}	1.44
Crystal dimension, mm	<i>a</i> = 0.3, <i>b</i> = 0.4, <i>c</i> = 0.7
μ	3.92
Minimum and maximum transmission	0.82–0.89
Space group	<i>P</i> 2 ₁ / <i>n</i>
Cell dimensions	<i>a</i> = 5.658 (6) Å, <i>b</i> = 8.844 (6) Å, <i>c</i> = 13.605 (9) Å, α = 90°, β = 92.54 (2)°, γ = 90°, <i>V</i> = 680.15 Å ³ , <i>Z</i> = 4

In addition to the structural questions, dehydromethionine aroused our interest from another point of view. It would be the product of two-electron oxidation at sulfur of methionine in which the neighboring amino group participates followed by loss of a proton. Indeed, anodic oxidation of methionine at a platinum electrode is reported¹⁰ to afford dehydromethionine. If this process occurs more readily than oxidation of sulfides devoid of neighboring groups, then support is obtained for the hypothesis¹¹ that oxidation at sulfur is facilitated by neighboring group participation. Furthermore, should interaction of dehydromethionine with orthophosphate produce a phosphorylating agent,¹² e.g., a phosphorylated sulfonium salt, then a simple model system for respiratory chain linked oxidative phosphorylation would be in hand. Attempts¹³ to effect phosphorylation of AMP with dehydromethionine and orthophosphate produced no significant ADP or ATP. However, pyrophosphate and compounds tentatively assigned as phosphoramides were produced. These products testify to the intermediacy of a phosphorylating agent.

Experimental Section

Preparation of Dehydromethionine (1). Dehydromethionine was prepared by a method similar to that of Lavine.⁹ In a dry bag, 0.32 g (14 mmol) of sodium was allowed to react with 20 ml of magnesium-dried methanol. This solution of sodium methoxide was added to 1.04 g (7.01 mmol) of (±)-methionine suspended in 50 ml of dry methanol. This was followed by the addition of 1.78 g (7.01 mmol) of iodine, and the solution was stirred overnight under a dry atmosphere. The decolorized reaction mixture was evaporated to 30 ml and chromatographed on a column of silica gel using reagent-grade methanol as the eluent. Potassium iodide, methionine, methionine sulfoxide, and dehydromethionine eluted in that order. The methanol solution of dehydromethionine was evaporated to dryness, yielding 0.73 g of crude product corresponding to a 70% yield. The crude product was dissolved in 10 ml of methanol and placed in a saturated ether atmosphere so that a vapor diffusion crystallization would take place. Off-white crystals were obtained (0.53 g, 50% yield), and the crystal used in the x-ray diffraction study was selected from these. The product turned to a brown amorphous mass at 167–170° which melts with gas evolution at 194–196° in agreement with the literature.⁹

Collection and Reduction of Intensity Data. Crystals were obtained from a vapor-diffusion crystallization from methanol and ether. Since the material was hygroscopic, the crystal for the x-ray study was selected and mounted in a capillary inside a glove bag filled with dry nitrogen. The observed density of the crystal was 1.46, while the calculated density was 1.44. Weissenberg photographs revealed a monoclinic system. Systematic absences identified the space group as *P*2₁/*n*. The crystal was transferred to a Picker FACS-I diffractometer, and the cell dimensions and orientation matrix were calculated from six accurately centered reflections. The crystal was mounted about the *c* axis. Table I summarizes the pertinent crystal data.

Intensity data were automatically collected on a FACS-I diffractometer to a maximum 2θ of 50° using graphite filtered molybdenum *K* α radiation. No decomposition of the sample during data collection was detected in the standard reflections which were

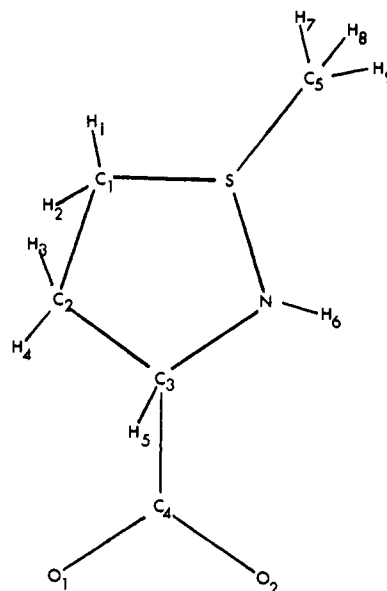


Figure 1. Numbering scheme used for dehydromethionine.

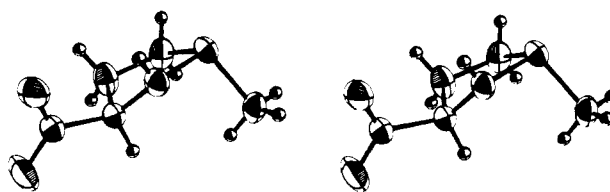


Figure 2. ORTEP¹⁸ stereoscopic view of dehydromethionine.

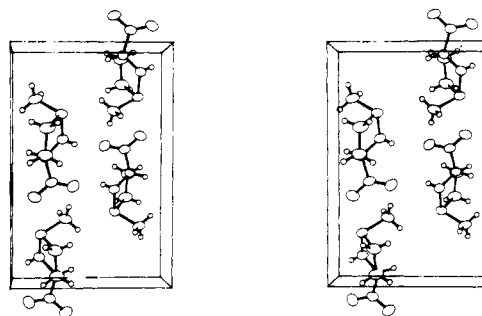


Figure 3. ORTEP¹⁸ stereoscopic view of unit cell.

measured after each block of 50 reflections. In all 1521 diffraction maxima were measured and recorded. A final total of 972 reflections equal to or greater than 3σ were used in the analysis.

All nonhydrogen atoms were located using direct methods.¹⁴ Two cycles of full-matrix least-squares refinement¹⁵ of nine atomic positions using isotropic temperature factors gave an unweighted *R* of 0.139. Further refinement using anisotropic temperature factors reduced *R* to 0.069. All hydrogen atoms were located by Fourier difference maps¹⁶ and were included in the least-squares refinement. Anomalous scattering by sulfur was taken into account using scattering factor tables by Cromer and Mann.¹⁷ After several cycles of least-squares refinement, a final *R* of 0.044 was obtained. The maximum shift of parameters, with respect to the standard deviation in the final cycle, was 0.09 for the nonhydrogen atoms and 0.34 for the hydrogens. The standard deviation of an observation of unit weight was 2.248.

Results

The numbering scheme used in this x-ray diffraction study is given in Figure 1, and a stereoscopic view of the molecule is shown in Figure 2. The packing of the molecules in the unit cell is illustrated in Figure 3. Final atomic positional and thermal parameters are given in Tables II and

Table II. Atomic Positional and Thermal Parameters

	X	Y	Z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
S	0.94047 (12)	0.68815 (8)	0.70807 (5)	0.02654 (27)	0.01171 (12)	0.00307 (4)	-0.00066 (12)	0.00256 (7)	0.00036 (5)
N	1.1017 (4)	0.6786 (3)	0.60757 (16)	0.0250 (8)	0.0109 (4)	0.00321 (13)	0.0006 (5)	0.00218 (24)	-0.00058 (19)
O(1)	1.1006 (5)	0.85089 (27)	0.36984 (16)	0.0754 (15)	0.0146 (4)	0.00381 (12)	-0.0004 (5)	0.0071 (3)	0.00145 (17)
O(2)	1.1242 (4)	0.61024 (23)	0.41348 (15)	0.0535 (11)	0.0120 (3)	0.00480 (14)	-0.0041 (4)	0.0084 (3)	-0.00163 (15)
C(1)	0.6784 (5)	0.7758 (5)	0.64797 (22)	0.0189 (9)	0.0193 (6)	0.00418 (17)	0.0003 (6)	0.0007 (3)	-0.00091 (26)
C(2)	0.7377 (6)	0.7886 (5)	0.54032 (22)	0.0247 (10)	0.0183 (5)	0.00385 (16)	0.0031 (6)	0.0010 (3)	0.00022 (25)
C(3)	1.0098 (5)	0.7885 (3)	0.53377 (18)	0.0245 (9)	0.0098 (4)	0.00309 (14)	-0.0013 (5)	0.00152 (28)	-0.00031 (18)
C(4)	1.0875 (5)	0.7455 (3)	0.42994 (18)	0.0278 (10)	0.0125 (4)	0.00323 (15)	-0.0034 (5)	0.00254 (29)	-0.00064 (21)
C(5)	1.0710 (6)	0.8484 (4)	0.77051 (23)	0.0287 (11)	0.0160 (5)	0.00332 (16)	-0.0014 (6)	0.0007 (3)	-0.00155 (24)

Table III. Hydrogen Atom Positional and Thermal Parameters

	X	Y	Z	Atomic β
H(1)	0.651 (7)	0.868 (4)	0.6712 (27)	5.5 (9)
H(2)	0.541 (7)	0.715 (4)	0.6644 (24)	5.6 (9)
H(3)	0.666 (6)	0.876 (4)	0.5106 (25)	5.8 (9)
H(4)	0.673 (6)	0.702 (4)	0.5058 (23)	4.2 (7)
H(5)	1.072 (4)	0.8865 (27)	0.5527 (17)	1.9 (5)
H(6)	1.081 (5)	0.606 (3)	0.5859 (20)	2.2 (7)
H(7)	0.968 (5)	0.868 (3)	0.8220 (23)	3.6 (6)
H(8)	1.054 (6)	0.926 (4)	0.7250 (27)	5.2 (8)
H(9)	1.232 (7)	0.812 (3)	0.7945 (24)	5.0 (8)

Table IV. Bond Distances (Å) for Dehydromethionine

S-N	1.6791 (26)	C(1)-H(2)	0.98 (4)
S-C(1)	1.834 (4)	C(2)-C(3)	1.546 (4)
S-C(5) ^a	1.802 (3)	C(2)-H(3)	0.96 (3)
O(1)-C(4) ^a	1.283 (4)	C(2)-H(4)	0.96 (3)
O(2)-C(4) ^a	1.259 (4)	C(3)-C(4) ^a	1.551 (4)
N-C(3)	1.475 (4)	C(3)-H(5)	0.966 (23)
N-H(6)	0.716 (25)	C(5)-H(7)	0.95 (3)
C(1)-C(2)	1.521 (4)	C(5)-H(8)	0.93 (4)
C(1)-H(1)	0.89 (4)	C(5)-H(9)	1.01 (3)

^a Corrected for thermal motion.

Table V. Bond Angles (deg) for Dehydromethionine

N-S-C(5)	101.4 (1)	S-C(1)-C(2)	104.6 (2)
N-S-C(1)	96.6 (1)	H(6)-N-C(3)	105 (2)
C(5)-S-C(1)	100.6 (2)	H(6)-N-S	107 (2)
C(3)-N-S	109.5 (2)	H(3)-C(2)-H(4)	107 (3)
O(1)-C(4)-O(2)	126.2 (3)	H(1)-C(1)-H(2)	106 (3)
O(1)-C(4)-C(3)	116.4 (3)	H(5)-C(3)-N	107 (2)
O(2)-C(4)-C(3)	117.4 (2)	H(5)-C(3)-C(2)	110 (2)
N-C(3)-C(2)	106.4 (2)	H(7)-C(5)-H(8)	108 (3)
N-C(3)-C(4)	110.7 (2)	H(7)-C(5)-H(9)	121 (3)
C(1)-C(2)-C(3)	108.5 (2)	H(8)-C(5)-H(9)	113 (2)

Table VI. Selected Torsion Angles (deg) in Dehydromethionine

N-S-C(1)-C(2)	2.1	C(4)-C(3)-C(2)-C(1)	160.1
C(1)-S-N-C(3)	20.9	C(5)-S-C(1)-C(2)	105.0
N-C(3)-C(4)-O(2)	27.9	H(6)-N-C(3)-C(4)	-44

III. Bond length, bond angle, and selected torsion angle data are collected in Tables IV-VI, respectively.

The structure **1** assigned to dehydromethionine by Lavine is correct. The carboxylate group and N-hydrogen atom are cis to each other and trans to the S-methyl group. The isothiazolidine ring of dehydromethionine is in the envelope conformation. Atoms C(1), C(2), S, and N are coplanar to within $\epsilon = 0.012$ Å. Atom C(3) is puckered toward the S-methyl group and is 0.53 Å from the ring plane. In crystalline proline, the pyrrolidine ring is also in an envelope conformation in which C(2), C(3), C(5), and N are coplanar, and C(4) is puckered toward the carboxylate group and 0.60 Å out of the ring plane.¹⁹ NMR studies on 1,3-thiazolidines suggest that the ring is in an envelope conformation.²⁰

Dehydromethionine shows intermolecular hydrogen bonding. Two identical hydrogen bonds join the molecules in pairs. In each pair the N-H of one molecule is hydrogen bonded to O(2) of the other, and O(2) of the first molecule is hydrogen bonded to N-H of the second molecule. The N-O distance in these hydrogen bonds is 2.86 Å and the N-H...O bond angle is 147°. It is of interest to note that the intramolecular N-O distance is 2.72 Å and the N-H...O angle is 111°. ²¹

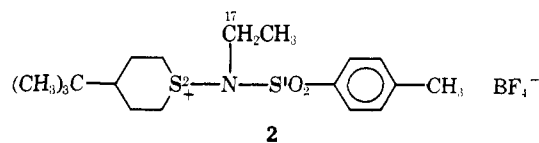
The closest S...O contacts are intermolecular. These distances are S...O(1') = 3.006 (3) Å and S...O(2') = 3.826 (3) Å.

Discussion

The sulfur atom in dehydromethionine is trivalent. The closest contact of the sulfur atom and an oxygen atom is 3 Å. The sum of the covalent radii²² of sulfur and oxygen is 1.70 Å. Clearly there is no covalent bond between an oxygen and sulfur atoms. However, the S...O(1') contact is less than the sum of the van der Waals radii²³ of sulfur and oxygen which is 3.25 Å. Furthermore, there is a small difference in O(1)-C(4) and O(2)-C(4) bond lengths, with the former slightly longer than the latter. These data are consistent with a weak electrostatic attraction between S and O(1').

The most surprising result of this study is that the nitrogen atom in dehydromethionine is apparently pyramidal, i.e., sp³ hybridized.²⁴ The bond angles around nitrogen (C(3)-N-S, H(6)-N-S, and H(6)-N-C(3)) are close to the tetrahedral angle. The sum of these bond angles is 321.5°. The expected values for sp³- and sp²-hybridized nitrogen are 328.5 and 360°, respectively. Furthermore, the nitrogen is 0.40 Å out of the S-H(6)-C(3) plane. Clearly the nitrogen atom is sp³ hybridized. The S-N bond length (1.68 Å) is significantly shorter than the sum of the covalent radii of S and N (1.74 Å).²² This shortening is surprising because S-N multiple bonding is not expected for sp³-hybridized nitrogen. Factors which may affect the S-N bond length are the oxidation state and hybridization of sulfur and the electronegativity difference. Alternatively, there may be some additional bonding as a result of sp³ (N)-d(S) overlap despite expectations.

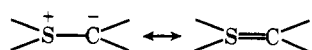
In contrast to these results, the only other azasulfonium salt, *trans*-4-*tert*-butyl-1-(*N*-ethyl-*N*-*p*-toluenesulfonylamino)-1-thioniacyclohexane fluoroborate (**2**), whose detailed



structure has been reported,⁸ has sp²-hybridized nitrogen bonded to sulfur.²⁵ The S(1)-N-S(2), S(1)-N-C(17), and S(2)-N-C(17) bond angles are 114.5, 119.6, and 121.9°, respectively, and the nitrogen atom lies 0.19 Å out of the C(17)-S(1)-S(2) plane. It should be pointed out that the

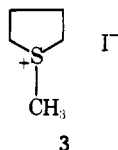
nitrogen atom in **2** is part of a sulfonamide group. The nitrogen atom in sulfonamides such as $\text{Me}_2\text{NSO}_2\text{NMe}_2^{26}$ have hybridization intermediate between sp^3 and sp^2 . Thus the average S-N-C and C-N-C bond angles are 119 and 112.9° , respectively. The nitrogen atom is 0.27 Å away from the plane of the three atoms bonded to it. Therefore, the planarity of the nitrogen atom in **2** may be due in large part to its participation in a sulfonamide linkage. Whether the nitrogen atom will, in general, be sp^2 or sp^3 hybridized in azasulfonium salts in which the nitrogen atom is bonded to alkyl groups or hydrogen atoms must await further structural studies.²⁷

If the nitrogen atom is tetrahedral in azasulfonium salts with hydrogen or alkyl groups attached to nitrogen, then one expects a similar geometry for the carbon bearing the negative charge in sulfonium ylides²⁸ since the two systems are isoelectronic.²⁹ This is contrary to the expectations based on the usual explanation given for stabilization of a carbanion by sulfonium sulfur. Such stabilization is alleged to be due to p-d π conjugation,³⁰ as shown below, in which



one expects the carbon bearing the negative charge to be planar and sp^2 hybridized. If the carbon atom is indeed pyramidal,³¹ then the sulfur atom in sulfonium ylides stabilizes the negative charge by a mechanism other than p-d π conjugation, perhaps by polarization.³²

Dehydromethionine is a model (save for a carboxylate group) for the sulfonium ylide obtained from 1-methylthiolanium iodide (**3**). Interestingly, the diastereotopic α hydrogens in **3** undergo base-catalyzed H-D exchange at differ-



ent rates.³³ The α hydrogens cis to the methyl group exchange faster than those trans. The explanation offered for this phenomenon is that the ylide obtained by removal of a proton cis to the methyl group is thermodynamically more stable than the alternative. In support of this suggestion it will be observed that the structure of dehydromethionine corresponds to this ylide.³⁴ Since the stability of this ylide has been related to the gauche effect,^{31,33} it should be noted that the angle between the major axis of the sp^3 orbital containing the lone pair of electrons on nitrogen and that containing the lone pair of electrons on sulfur in dehydromethionine is approximately 90° .³⁵

Acknowledgment. The authors gratefully acknowledge support of this work by the U.S. Public Health Service Grant No. HL 15104. The authors thank Drs. Paul Johnson and Satish Arora for technical assistance in the x-ray studies.

Supplementary Material Available. A listing of structure factor amplitudes (4 pp). Ordering information is given on any current masthead page.

References and Notes

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Polynucleotides. XXX.¹ Synthesis and Properties of Oligonucleotides of Cyclouridine Phosphate. Hybridization with the Oligomer of *S*-Cycloadenosine Phosphate to Form Left-Handed Helical Complexes²

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Abstract: Oligonucleotides containing 6,2'-anhydro-1-(β -D-arabinofuranosyl)-6-hydroxyuracil (U°) were synthesized by chemical polymerization of its 5'-phosphate with dicyclohexylcarbodiimide in pyridine. After separation by chromatography on a DEAE-cellulose column and purification by paper chromatography, a series of linear oligonucleotides and some cyclic oligonucleotides were obtained. Chain lengths of the linear oligomers were determined by phosphorus analyses of the oligomers and their corresponding dephosphorylated products. The linear oligomers of chain length up to 10, cyclic dinucleotide, and cyclic trinucleotide were characterized by paper chromatography and paper electrophoresis. Uv absorption and CD spectra for these oligomers are reported. From these data, it was concluded that these oligomers do not adopt stacked helical conformation in aqueous solution. Although the linear octamer did not form a complex with poly(A), it did hybridize with the octamer of 8,2'-*S*-cycloadenosine phosphate, which is assumed to have a left-handed helical conformation, forming a double- or a triple-stranded complex depending on the conditions. On the basis of their CD spectra, a left-handed multistranded helical structure was proposed for these complexes.

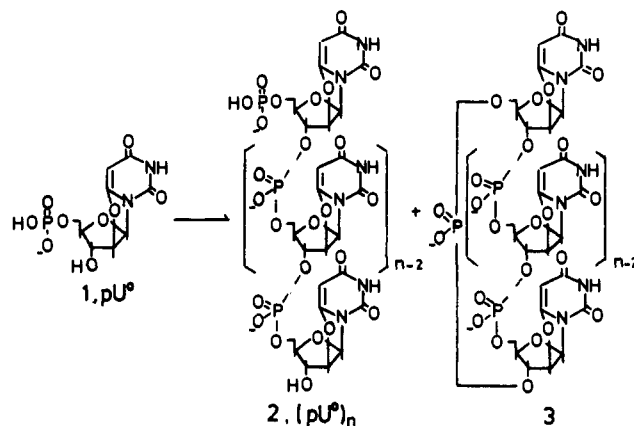
Introduction

As part of our continuing study on the effect of the torsion angle about the glycosidic linkage on the conformation of polynucleotides, various oligomers of cycloadenosine phosphates were synthesized and their properties examined.²⁻⁶ The dinucleoside monophosphate ($A^s p A^s$) of 8,2'-*S*-cycloadenosine was fully examined by uv absorption, CD and NMR spectroscopy and proved to have a highly stacked conformation with a left-handed screw axis.^{3,4} The oligonucleotides, $(pA^s)_n$,^{5,6} and the dinucleotide monophosphate ($A^o p A^o$)^{6,7} of 8,2'-*O*-cycloadenosine gave similar CD spectra to that of $A^s p A^s$, suggesting that they have the same kind of left-handed helical conformation. None of these compounds hybridized with poly(U), which is assumed to form a right-handed helix, but $(pA^s)_8$ formed a complex with poly(formycin phosphate) in which the torsion angle about the glycosidic linkage is assumed to be easily rotatable.⁸ It may be concluded that oligomers of cycloadenosine phosphate, in which the torsion angle, χ ,⁹ is fixed at around 120°, can form hydrogen-bonded complexes with oligo- and polynucleotides which can have similar torsion angles. In this respect, we were interested in the hybridization of $(pA^s)_n$ with oligomers of cyclouridine phosphate which is the complementary pyrimidine counterpart of cycloadenosine phosphate. The synthesis and properties of the dinucleoside monophosphate, $U^o p U^o$, have been reported.¹¹ In this paper we report the synthesis and properties of the oligonucleotides of 6,2'-*O*-cyclouridine (U^o), which is assumed to have nearly the same torsion angle as 8,2'-cycloadenosines.¹² From uv absorption and CD studies, these oligomers, $(pU^o)_n$, have almost no stacked or helical confor-

mation in aqueous solution. The octamer, $(pU^o)_8$, did not form a complex with poly(A), but did hybridize with $(pA^s)_8$. The resulting complexes are assumed to have left-handed multistranded helical structures.

Synthesis of Oligonucleotides

Oligonucleotides (**2** and **3**) were synthesized by chemical



polymerization of pU^o (**1**). As the pyridinium salt pU^o was not soluble in pyridine, the polymerization reaction was carried out with dicyclohexylcarbodiimide in DMF in the presence of pyridinium Dowex 50 resin. The reaction mixture containing pU^o (0.7 mmol) was kept at 30° for 2 weeks. After the reaction was stopped by addition of 50% aqueous pyridine, acetic anhydride-pyridine treatment was carried out to cleave any pyrophosphate linkages. After deacetylation with 9 N ammonium hydroxide, the products were sep-