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BIOMOLECULES BEARING THE $SAsMe_2$ GROUP: NUCLEOSIDE DERIVATIVES

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ABSTRACT

A number of compounds of the type GS- and $GSeAsR_2$, where G is a monosaccharide, a thio amino acid, a thiol-containing di- or tripeptide or cholesterol display carcinostatic activity in in vivo mouse test systems.
The synthesis and characterization of derivatives in which G is a nucleoside and the synthesis of an arsenic-containing precursor of 5-thioglucose are described. Of the nucleoside derivatives thus far screened, none displays carcinostatic activity.

INTRODUCTION

Biomolecules having the general formula $GXAsR_2$ have been the subject of a number of studies during the past seven years. In these compounds, X is S or Se and derivatives have been prepared in which G is a monosaccharide[1a] or an amino acid or di- or tripeptide[1b]. At the present, 22 of these derivatives have been found to be active (% T/C - 125) against mouse leukemias in in vivo testing (PS388 and L1210 test systems). These observations have caused us to investigate the effect of varying the biomolecular moiety, G. This paper describes the synthesis and characterization of derivatives in which G is a nucleoside. The synthesis of an arsenic-containing precursor of 5-thioglucose is also described.

RESULTS AND DISCUSSION

Synthetic aspects

The molecules which are the subject of this study are shown in Figure 1. Compound 2, 5-deoxy-1,2-O-isopropylidene-5-thio-α-D-glucofuranose was synthesized from 1 according to Nayak and Whistler[2]. Reaction of 1 with dimethyliodoarsine and chromatographic purification, afforded 3.
5'-Deoxy-5'-iodothymidine[3] was a convenient starting material for the synthesis of 4a. Prolonged reflux in n-propanol with thiourea was required for its conversion to the thioureide. In the lower boiling solvents, acetone or ethanol, the nucleophilic displacement proceeds too slowly and remains incomplete. Treatment of the thiopseudoureide with Na_2SO_3 and concurrent reaction with dimethyliodoarsine gave 4a in 60 % yield.

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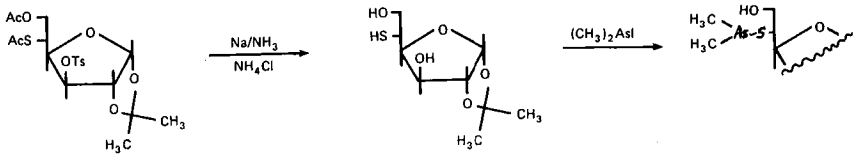

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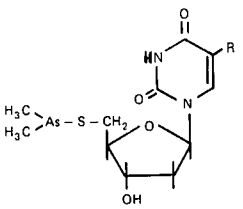

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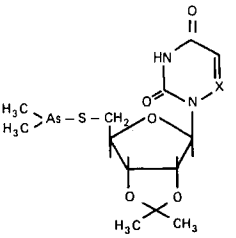
b: = H



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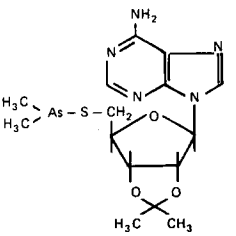
b: = N



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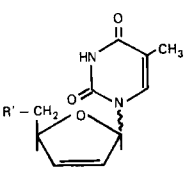
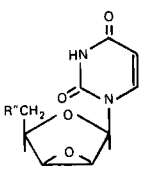


7a: R' = OH
b: = OTs
c: = SAc
d: = $SAs(CH_3)_2$



8a: R'' = I
b: = $SAs(CH_3)_2$

In general, it was found that the group of nucleosides which were the subject of this study, were more easily converted to the thio derivatives by the use of thiolacetate. The reaction of 5'-O-p-toluenesulfonyl thymidine[4] with KSAc in refluxing acetone is complete after 2 hours. Basic hydrolysis (KOH) yields the thiol in the form of the potassium salt. The latter smoothly undergoes reaction with dimethyliodoarsine to give the S-dimethylarsino derivative. The latter method resulted in a decreased reaction time and an increase in yield from 60 to 77 %. The same procedure was utilized for the synthesis of 5'-S-dimethylarsino-5'-thio-2'-deoxyuridine (4b) from 5'-O-p-toluenesulfonyl-2'-deoxyuridine[5]. Both 2',3'-O-isopropylidene-5'-O-toluenesulfonyl uridine[6] and 2',3'-O-isopropylidene-5'-O-toluenesulfonyl adenosine[7] were found to react smoothly with KSAc. The corresponding S-dimethylarsino compounds, 5a and 6, were easily obtained. The tosyl group of 6-aza-2',3'-O-isopropylidene-5'-O-p-toluenesulfonyl uridine, prepared from 6-aza-2',3'-O-isopropylidene uridine[8] was more difficult to displace and a mixture of 5b and the tosyl derivative was obtained. It was necessary to utilize preparative TLC to obtain 5b in pure form.

The synthesis of 3'-deoxy-2'-thymidinene (7a) was carried out according to Horwitz, et al.[9]. Tosylation of this compound at the 5'-position gave 7b. Its reaction with KSAc gave 7c in good yield which was subsequently used to synthesize the S-dimethylarsino derivative, 7d, in the manner described.

The reaction of 1-(2',3'-epoxy-5'-deoxy-5'-iodo-ß-D-lyxosyl) uracil[10] (8a) with KSAc, in contrast with that of the compounds previously discussed, gave only poor yields. This is probably due to side reactions arising from the presence of the epoxy group. The S-dimethylarsino derivative was consequently obtained in poor yields following chromatographic purification.

Nuclear Magnetic Resonance Spectra

The ^{1}H NMR data are listed in the experimental part and they are in agreement with the patterns expected for the individual structures. The most apparent change observed in the spectra of the S-dimethylarsino derivatives compared with those of the starting materials is in the upfield shift of the methylene protons in the 5'-position to which the S-$AsMe_2$ group is attached. The change is of the order of 1 ppm and the chemical shift of the protons located at the 5'-position is invariably between 2.8-3.0 ppm.

The ^{1}H NMR spectra of the thymidinene derivatives 7c and 7d indicate that they are mixtures of the α- and ß-anomers. In the case of 7d, two distinct $AsCH_3$ resonances are observed and the signal from $H_{1'}$, which should appear as a quartet, consistent with the values of the coupling constants (this has been reported in the case of several unsaturated sugars[11]), is observed instead, as a quintet. The latter multiplicity can only be explained in terms two distinct $H_{1'\alpha}$ and $H_{1'\beta}$ signals separated by $J_{H_{1'}-H_{2'}}$.

Anomerisation probably occurred during the synthesis of 7a[9].

The ^{13}C NMR spectra of compounds 4a and -b, 5a and -b, 6, and 7c and -d were recorded and they are given in Table 1.

TABLE I

^{13}C NMR Chemical Shifts

	1'	2'	3'	4'	5'	2	4	5
4a	84.8	40.2	73.4	86.4	34.2	150.3	163.8	111.2
4b	86.4	40.4	73.4	85.2	34.2	150.0	163.0	102.5
5a	94.3	82.9	84.3	88.0	33.8	150.1	164.0	102.3
5b	92.1	83.7	83.7	89.1	34.4	147.7	156.0	135.9
6	90.9	83.5	84.0	88.2	33.7	152.9	149.0	120.0
7c	91.0	137.3	127.8	85.6	31.8	152.4	165.6	112.3
7d	89.7	136.1	126.2	86.4	36.1	151.1	164.3	110.7

	6	8	a	b	c	d	e	f
4a	135.6	-	-	-	$\frac{14.3}{14.5}$	12.6	-	-
4b	139.8	-	-	-	14.3	-	-	-
5a	143.0	-	114.2	$\frac{25.2}{27.0}$	$\frac{14.0}{14.4}$	-	-	-
5b	-	-	113.6	$\frac{25.3}{26.9}$	$\frac{13.9}{14.6}$	-	-	-
6	156.0	139.9	114.0	$\frac{25.3}{27.0}$	$\frac{14.0}{14.4}$	-	-	-
7c	136.6	-	-	-	-	13.8	196.0	22.9
7d	135.6	-	-	-	$\frac{14.1}{14.5}$	12.5	-	-

a.  ; b. isopropylidene methyl carbons;

c. arsenic-bonded methyl carbons; d.  ;

e. $S\text{-}C^{+}(O)$; f. $S\text{-}C(O)C^{+}H_3$

These values differ from those of the parent nucleosides (in DMSO)[12] by less than 3 ppm, except for $\delta_{C\text{-}5'}$, in which a shielding effect brings about a shift of 27-28 ppm in all cases. The tabulated coupling constants as shown in Table 2, differ by less than 5 Hz from those previously reported[13] for the starting hydroxyl derivatives. The chemical shift observed for the methyl groups attached to the arsenic atom is between 13.9 and 14.6 ppm. Except in the case of 4b, two proton resonances are observed for the arsenic-bonded methyl groups. This indicates a hindered rotation of the $-SAsMe_2$ group. The existence of this magnetic non-equivalence made it possible to measure the coupling constants between the methyl groups bonded to the same arsenic atom. This value, $|J|$, is about 4 Hz.

TABLE II

^{13}C-^{1}H Coupling Constants

	$J_{1'-H}$	$J_{2'-H}$	$J_{3'-H}$	$J_{4'-H}$	$J_{5'-H}$	J_{2-H}	J_{5-H}	J_{6-H}	J_{8-H}
4a	169	133	149	149	140	-	-	181	-
5a	166	156	158	149	138	-	177	181	-
5b	168	156	156	149	138	-	197	-	-
6	166	153	162	153	140	200	-	-	209
7d	171	182	175	151	140	-	-	210	-

	a	b	c	d
4a	-	132	135	-
5a	126	133	-	4
5b	126	133	-	-
6	126	133	-	4
7d	-	131	127	-

a. $J_{O \quad O \quad CH_3}$; b. J_{As-CH_3} ; c. $J_{\quad CH_3}$; d. J_{As-CH_3} CH_3

Mass Spectra

In the case of the uridine (5a and 5b) and adenosine (6) derivatives, the mass spectral fragmentation patterns are characterized by the initial loss of a methyl radical from $(CH_3)_2AsS$-. This is characteristic of dimethylarsinous acid esters. This is followed by the loss of $AsCH_3$ and acetone, but not necessarily in that order. The loss of the base, or a portion of it, before the loss of arsenic is observed in some cases, but it always represents a very minor pathway. Peaks corresponding to $As(CH_3)_2^+$ (m/e = 105), $SAs(CH_3)_2^+$ (m/e = 137) and $SAs_2(CH_3)_4^{\cdot+}$ (m/e = 242) appeared in all of the spectra.

The molecular ion was not observed for the thymidine derivative, 4a. Instead, a peak at m/e = 361 (10 %) corresponding to $C_{12}H_{18}O_4N_2SAs^+$ (M-1) is observed. The major fragmentation pathway involves the frequently observed loss of a methyl radical from $As(CH_3)_2$ [m/e = 347 (20 %)] followed by elimination of $AsCH_3$ to give the cation $C_{10}H_{13}O_4N_2S^+$ [m/e = 257 (19 %)]. Another fragmentation pattern involves the loss of the base to form the cation, $C_7H_{14}O_2SAs^+$ [m/e = 237 (14 %)]. Elimination of water leads to formation of the cation $C_7H_{12}OSAs^+$ [m/e = 219 (10 %)]. Loss of $CH_3\cdot$ and H· leads to formation of the furan fragment, $C_6H_8OSAs^+$ [m/e = 203 (12 %)]. The most intense peak is due to $C_4H_{12}SAs_2^{\cdot+}$ [m/e = 242 (100 %)]. This probably results from the thermal decomposition of 4a. Deuteration of both labile protons, NH and OH shows an increase in mass consistent with the deuteration of the labile protons. The cation, $C_{12}H_{18}O_4N_2SAs^+$ is found to contain only a single labile hydrogen which

indicates that the initial H· loss can be attributed to a labile hydrogen. The mass spectrum of 4a generated by chemical ionization shows the expected molecular ion at m/e = 363 (M+1). The behavior of the 2'-deoxy-uridine derivative (4b) is similar to that of 4a.

In the case of 7d, the initial loss of a methyl radical followed by loss of $AsCH_3$, although of importance, does not represent the principal pathway. Rather, the loss of pyrimidine to yield $C_7H_{12}OSAs^+$ [m/e = 219 (100 %)] is favored. This is followed by loss of either H· or $\cdot CH_2SAs(CH_3)_2$ to form $C_7H_{11}OSAs^{\cdot+}$ [m/e = 218 (64 %)] and $C_7H_4O^{\cdot+}$ [m/e = 68 (10 %)], respectively. Another prominent fragment is $CH_2\text{-}S\text{-}As(CH_3)_2^+$ [m/e = 151 (100 %)].

The common fragmentation pathway is displayed by 8b, i.e., formation of $M^{\cdot+}$, $M^{\cdot+}\text{-}CH_3^{\cdot}$, and $M^{\cdot+}\text{-}^{\cdot}As(CH_3)_2$ (100 %). A minor pathway exists in which an atom of oxygen is lost from $M^{\cdot+}\text{-}CH_3^{\cdot}$ to form $M^{\cdot+}\text{-}CH_3^{\cdot}\text{-}O$ (4 %).

Biological testing

To date, none of these derivatives has been found to be active against mouse leukemias in vivo. This is rather interesting because among this group of compounds, derivatives of monosaccharides, amino acids, di- and tripeptides, and steroids, all have yielded derivatives which are active in the test system. No speculation concerning the reason for this lack of activity is offered at the present time.

EXPERIMENTAL

General Procedures

Melting points were determined using a Büchi-SMP-20 melting point apparatus (capillary method) and are uncorrected. The ^1H NMR spectra were measured on a Varian T-60 spectrometer and the ^{13}C NMR were measured on a JEOL-PFT-100 using either CD_3OD or $CDCl_3$ as the solvent and TMS as an internal standard. Chemical shifts are reported in ppm (δ) and the multiplicity is expressed as s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). The mass spectra were recorded by Dr. R. Grigsby, Department of Biochemistry and Biophysics, Texas A&M University. A Du Pont CEC21-110B spectrometer was used operating at an ionizing potential of 70 eV and an ion current of 200 μA. The accelerating potential was 8 kV and the source temperature ranged from 120-200°. Thin layer chromatography was performed on silica gel PF_{254} (Merck) and spots were observed with ultraviolet light. Solvent evaporations were performed at reduced pressures using a Büchi rotary evaporator. Microanalyses were performed by the Galbraith Laboratories, Inc., Knoxville, Tennessee.

5-S-dimethylarsino-1,2-O-isopropylidene-5-thio-α-D-glucofuranose (3). Compound 2, 5-deoxy-1,2-O-isopropylidene-5-thio-α-D-glucofuranose was prepared from 3.1 g (8.66 mmols) of 1 according to Nayak and Whistler[2]. The syrup obtained by this reaction, red-orange in color, was dissolved in 50 ml of CH_2Cl_2. Then, 2.1 g (9.05 mmols) of dimethyliodoarsine dissolved in 10 ml of CH_2Cl_2 was added followed by the addition of 2 ml of diethylamine. Following 10 min of stirring at room temperature, 10 ml of water was added. The organic layer was separated and dried over anhydrous magnesium sulfate. The solvent was re-

moved by evaporation under reduced pressure. The residue was chromatographically separated using a $CHCl_3$:acetone mixture of composition 9:4. The band at R_f = 0.63 was collected to yield 1.1 g (33 % overall yield) of 3 in the form of a homogeneous syrup.

^{1}H NMR ($CDCl_3$): δ 5.97 (1H, d, H_1, J_{1-2} = 4.4 Hz); δ 4.53 (1H, d,H_2); δ 4.4-3.2 (7H, m, H_3-H_6, OH); δ 1.52 and 1.33 (3H-3H, s-s, isopropylidene methyls); δ 1.40 [6H, s, $As(CH_3)_2$].

5'-S-Dimethylarsino-5'-thio-5'-deoxythymidine (4a).

Method A. - The thiopseudoureide of 5'-deoxy-5'-iodothymidine was prepared by refluxing 2 g (5.68 mmols) of the latter with 0.4 g or thiourea in n-propanol for 48 h. The solvent was removed and the residual thiopseudoureide hydroiodide was hydrolyzed to the thiol by stirring with a solution of 1.2 g of $NaHSO_3$ in 50 ml of water at 40° for 10 min. To the aqueous solution containing the thiol was added 50 ml of CH_2Cl_2 in which was dissolved 1.4 g (6.0 mmols) of dimethyliodoarsine. Diethylamine was added to the stirred solution until it was basic to litmus and stirring was continued for 15 min. The phases were separated and the organic layer was dried ($MgSO_4$) and subsequently taken to dryness. The solid, recrystallized from ethanol, yielded 1.25 g (60 % yield) of 4a.

Method B. - A mixture of 2.4 g (6.06 mmols) of 5'-O-tosyl thymidine and 0.7 g (6.14 mmols) of KSAc was refluxed for 2 h in 150 ml of acetone. The cooled solution deposited a solid which was removed by filtration and the filtrate was distilled to remove the acetone. The residue was found to be homogeneous by TLC. It was treated with a solution of 1 g of KOH in 40 ml of water and 20 ml of ethanol. The mixture was stirred at room temperature for 1 h after which 1.5 g (6.46 mmols) of dimethyliodoarsine was added dropwise. After 5 min, acetic acid was added to just turn the mixture acidic. The product was extracted into CH_2Cl_2, the organic solution dried ($MgSO_4$) and the solvent removed by evaporation. This gave 1.7 g (77 %) of 4a which was recrystallized from ethanol, m.p. 143-144°. Anal.: Calcd for $C_{12}H_{19}N_2O_4SAs$: C, 39.77; H, 5.25; N, 7.73; found: C, 39.98; H, 5.33; N, 7.81.

^{1}H NMR data (CD_3OD): δ 7.60 (1H, q, H_6, J_{6-CH_3} = 1.2 Hz); δ 6.23 (1H, t, $H_{1'}$, $J_{1'-2'}$ = 6.8 Hz); δ 4.36 (1H, m, $H_{3'}$, $J_{3'-4'}$ = 3.2 Hz); δ 4.00 (1H, m, $H_{4'}$, $J_{4'-5'}$ = 5.6 Hz); δ 2.98 (2H, d, $H_{5'}$); δ 2.27 (2H, m, $H_{2'}$, $J_{2'-3'}$ = 4.8 Hz); δ 1.90 (3H, d, CH_3); δ 1.35 [6H, s, $As(CH_3)_2$].

Mass spectrum (mol. ion-$H_3C^{\cdot}$), exp., 347.006119; calcd, 347.004762, Δ = 3.9ppm.

5'-S-Dimethylarsino-5'-thio-2',5'-dideoxyuridine (4b).

5-Acetylthio-2',5'-dideoxyuridine (1.1 g) was prepared from 1.9 g (5 mmols) of 5'-O-tosyl-2'-deoxyuridine, as described[5]. Recrystallization from ethanol gave 1 g of product, m.p. 150-152°. The 5'-acetylthio-compound was treated with 40 ml of 0.5 N KOH and 20 ml of ethanol. Following the procedure just described, 0.85 g of compound 4b was obtained (70 % yield). Recrystallization from ethanol yielded crystals m.p. 140-141°. Anal.: Calcd for $C_{11}H_{17}N_2O_4SAs$: C, 37.93; H, 4.88; N, 8.04; found: C, 39.10; H, 4.99; N, 7.95.

^{1}H NMR data (CD_3OD): δ 7.73 (1H, d, H_6, J_{5-6} = 8.0 Hz); δ 6.20 (1H, t, $H_{1'}$, $J_{1'-2'}$ = 6.8 Hz); δ 5.70 (1H, d, H_5); δ 4.33 (1H, m, $H_{3'}$, $J_{3'-2'}$ = 4.8 Hz; $J_{3'-4'}$ = 3.2 Hz); δ 4.00 (1H, m, $H_{4'}$, $J_{4'-5'}$ = 5.8 Hz); δ 2.95 (2H, d, $H_{5'}$); δ 2.27 (2H, m, $H_{2'}$).

5'-S-Dimethylarsino-5'-thio- 2',3'-O-isopropylidene-5'-deoxyuridine (5a). The conversion of 5'-O-tosyl-2',3'-O-isopropylideneuridine[6] (4.0 g, 9.13 mmols) into 5a was performed in the manner just described. The yield of 5a was 3.2 g (87 %). Recrystallization from ethanol gave a product m.p. 136-137°. Anal.: Calcd for $C_{14}H_{21}N_2O_5SAs$: C, 41.59; H, 5.20; N, 6.93; found: C, 41.44; H, 5.29; N, 6.93. ^{1}H NMR data ($CDCl_3$): δ 9.0 (1H, broad s, NH); δ 7.40 (1H,d, H_6, J_{6-5} = 8.2 Hz); δ 5.75 (1H, d, H_5); δ 5.70 (1H, d, $H_{1'}$, $J_{1'-2'}$ = 2.0 Hz); δ 5.00 (1H, m, $H_{2'}$, $J_{2'-3'}$ = 6.4 Hz); δ 4.80 (1H, m, $H_{3'}$, $J_{3'-4'}$ = 3.6 Hz); δ 4.25 (1H, m, $H_{4'}$, $J_{4'-5'}$ = 6.4 Hz); δ 2.98 (2H, d, $H_{5'}$); δ 1.57 and 1.37 (3H-3H, s-s, isopropylidene methyl protons); δ 1.37 [6H, s, $As(CH_3)_2$]. Mass spectrum: mol. ion: exp. 404.037824, Calcd 404.038818, Δ = 2.4 ppm.

6-Aza-5'-S-dimethylarsino-5'-thio-2',3'-O-isopropylidene-5'-deoxyuridine (5b). From 9 g of 6-aza-2',3'-O-isopropylideneuridine[14] was prepared, in the manner described for the preparation of 5'-O-tosyl-2',3'-O-isopropylideneuridine[6], 10.1 g (m.p. 152-153°, 73 % yield) of the 5'-O-tosyl derivative. A mixture of 3.5 g (7.95 mmols) of 6-aza-5'-O-tosyl-2',3'-O-isopropylideneuridine and 1.4 g (12.3 mmols) of KSAc was refluxed in 200 ml of acetone for 24 h. Thin layer chromatography using $CHCl_3$-EtOH, 9:1, showed the presence of the thioacetate (R_f = 0.76) with 10-20 % of the starting material (R_f = 0.42) remaining (as determined by ^{1}H NMR). Neither a longer reaction time nor the use of a higher ratio of KSAc was found to take the reaction to completion. The mixture was therefore treated with 1 g of KOH in 40 ml of water and 20 ml of ethanol for a period of 30 min. Dimethyliodoarsine (1.85 g, 8 mmols) was added dropwise and after 5 min the solution was made just acidic with acetic acid. Extraction of the reaction mixture with chloroform left, after drying and removal of the solvent, 2.5 g of a syrup containing about 20 % of the starting material and 80 % of 5b as determined by ^{1}H NMR spectroscopy. The yield of crude product was 62 %. The mixture was separated by preparative TLC using $CHCl_3$/EtOH, 9:1, as the eluent. A large band (R_f = 0.5-0.6) contained both the starting tosyl derivative and the product. Collecting between R_f = 0.55 and 0.6 gave 1 g of 5b in the form of an oil as determined by elemental analysis and ^{1}H NMR. The oil, subjected to drying at reduced pressure for 24 h converted to a solid which reverted to an oil upon exposure to the atmosphere. Anal.: Calcd for $C_{13}H_{20}N_3O_5SAs$: C, 38.52; H, 4.94; N, 10.37; found: C, 38.26; H, 5.01; N, 10.08. ^{1}H NMR data ($CDCl_3$): δ 8.0 (1H, broad s, NH); δ 7.43 (1H, s, H_5); δ 6.29 (1H, d, $H_{1'}$, $J_{1'-2'}$ = 1.2 Hz); δ 5.06 (1H, m, $H_{2'}$, $J_{2'-3'}$ = 6.0 Hz); δ 4.80 (1H, m, $H_{3'}$, $J_{3'-4'}$ = 2.8 Hz); δ 4.27 (1H, m, $H_{4'}$, $J_{4'-5'}$ = 7.4 Hz); δ 2.82 (2H, d, $H_{5'}$); δ 1.57 and 1.33 (3H-3H, s-s, isopropylidene methyl protons); δ 1.37 [6H, s, $As(CH_3)_2$].

5'-S-Dimethylarsino-5'-thio-2',3'-O-isopropylidene-5'-deoxyadenosine (6). 5'-Acetylthio-2',3'-O-isopropylidene-5'-deoxyadenosine (4 g, 11 mmols) was prepared from the tosyl derivative[7] and treated with 40 ml of 0.5 N KOH and 20 ml of ethanol. Reaction with dimethyliodoarsine in the manner previously described yielded 3 g of an oil which appeared homogeneous by TLC. Drying for 24 h under reduced pressure caused the oil to solidify, but it slowly reverted to an oil on exposure to the atmosphere. Anal.: Calcd for $C_{15}H_{22}N_5O_3SAs$: C, 42.16; H, 5.15; N, 16.34; found: C, 42.34; H, 5.24; N, 16.11.

^{1}H NMR data ($CDCl_3$): δ 8.23 (1H, s, H_8); δ 7.90 (1H, s, H_2); δ 6.8 (2H, broad s, NH_2); δ 6.07 (1H, d, $H_{1'}$, $J_{1'-2'}$ = 2.0 Hz); δ 5.50 (1H, m, $H_{2'}$, $J_{2'-3'}$ = 6.4 Hz); δ 5.07 (1H, m, $H_{3'}$, $J_{3'-4'}$ = 2.8 Hz); δ 4.36 (1H, m, $H_{4'}$, $J_{4'-5'}$ = 7.4 Hz); δ 1.60-1.40 (3H-3H, s-s, isopropylidene methyl protons); δ 1.30 [6H, s, $As(CH_3)_2$].

5'-O-Tosyl-3'-deoxy-2'-thymidinene (7b).
A solution containing 6.72 g (30 mmols) of 7a[9] in 100 ml of dry pyridine was taken to ice-bath temperature. To the cooled solution was added dropwise, with stirring, 6.0 g (31.5 mmols) of p-toluenesulfonyl chloride. The stirring was continued for 1 h and the mixture was kept in the refrigerator overnight. Following the addition of 1 ml of water the solution was poured slowly, with vigorous stirring, into 1 l of ice water. The precipitate was separated by filtration and dried. The yield was 8.9 g (78 %). The product, recrystallized from ethanol, melted at 128° (dec.).

5'-S-Acetyl-5'-thio-3',5'-dideoxy-2'-thymidinene (7c).
A mixture consisting of 4.5 g (11.4 mmols) of 7b, 1.7 g (15.0 mmols) of KSAc and 300 ml of acetone was refluxed for 2 h. The solution was cooled, filtered, and the filtrate evaporated under reduced pressure to remove the acetone. The yield of crude 7c was 3.3 g (97 %). Recrystallization from ethanol yielded a product m.p. 155-156°. Anal.: Calcd for $C_{12}H_{14}N_2O_5S$: C, 51.06; H, 4.94; N, 9.92; found: C, 50.19; H, 5.08; N, 9.31.
^{1}H NMR data ($CDCl_3$): δ 9.80 (1H, s, NH); δ 7.26 (1H, q, H_6, J_{6-CH_3} = 1.2 Hz); δ 6.93 (center of multiplet) (1H, m, $H_{1'}$, $J_{1'-2'}$ = 1.6 Hz, $|J_{1'-3'}|$ = 1.6 Hz, $J_{1'-4'}$ = 1.6 Hz); δ 6.26 (1H, m, $H_{2'}$, $J_{2'-3'}$ = 6.0 Hz, $|J_{2'-4'}|$ = 1.6 Hz); δ 5.87 (1H, m, $H_{3'}$, $J_{3'-4'}$ = 2.0 Hz, $J_{3'-5'} \simeq 0$); δ 5.00 (1H, m, $H_{4'}$, $J_{4'-5'}$ = 5.8 Hz); δ 3.25 (2H, d, $H_{5'}$); δ 2.39 (3H, s, acetyl methyl protons); δ 1.96 (3H, d, CH_3).

5'-S-Dimethylarsino-5'-thio-3',5'-dideoxy-2'-thymidinene (7d).
In 50 ml of water were dissolved 2 g (7.1 mmols) of 7c and 10 ml of ethanol containing 1 g of KOH. The resulting solution was stirred at room temperature for 30 min. Dimethyliodoarsine (1.7 g, 7.3 mmols) was added dropwise and after 5 min, acetic acid was added to just turn the solution acidic. The solution was extracted with chloroform and the latter, following drying and evaporation of the solvent gave 1.75 g (71 %) of 7d. Recrystallization from ethanol gave a solid m.p. 126-128°. Anal.: Calcd for $C_{12}H_{17}N_2O_3SAs$: C, 41.87; H, 4.94; N, 8.14; found: C, 42.02; H, 5.03; N, 8.24.
^{1}H NMR data ($CDCl_3$): δ 8.60 (H, s, NH); δ 7.35 (1H, q, H_6, J_{6-CH_3} = 1.2 Hz); δ 6.95 (center of multiplet) (1H, m, $H_{1'}$, $J_{1'-2'}$ = 1.6 Hz, $|J_{1'-3'}|$ = 1.6 Hz, $J_{1'-4'}$ = 1.6 Hz); δ 6.40 (1H, m, $H_{2'}$, $J_{2'-3'}$ = 6.0 Hz, $|J_{2'-4'}|$ = 1.6 Hz); δ 5.90 (1H, m, $H_{3'}$, $J_{3'-4'}$ = 2.0 Hz, $J_{3'-5'} \simeq 0$); δ 4.97 (1H, m, $H_{4'}$, $J_{4'-5'}$ = 5.8 Hz); δ 2.98 (2H, d, $H_{5'}$); δ 1.93 (3H, d, CH_3); δ 1.36 and 1.38 [6H, s-s, $As(CH_3)_2$]. Mass spectrum, mol. ion: exp. 344.017055, Calcd 344.017677, $\triangle$ = 1.8 ppm.

1-(2',3'-Epoxy-5'-S-dimethylarsino-5'-thio-5'-deoxy-ß-D-lyxosyl)-uracil (8b).
A mixture of 0.5 g (1.5 mmols) of 8a[10] and 0.2 g (1.7 mmols) of KSAc were refluxed in 30 ml of acetonylacetone for 4 h. The solvent was removed by evaporation and the residue was treated with 20 ml of 0.5 N KOH and 10 ml of etha-

nol. After 30 min of stirring at room temp the mixture was made just acidic by the addition of acetic acid. The mixture was extracted with chloroform, the organic layer dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was separated by preparative chromatography on silica gel using $CHCl_3$/EtOH, 95:5 as the eluent. A small quantity of 8b, R_f = 0.65, was obtained. Anal.: Calcd for $C_{11}H_{15}O_4N_2SAs$: C, 38.16; H, 4.33; N, 8.09; found: C, 37.18; H, 4.53; N, 7.56. Mass spectrum: mol. ion, exp. 345.997760, Calcd 345.996956, $\triangle$= 2.0 ppm.

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