cyclohexanone,[13] $[\alpha]^{25}\text{D}$ +12.3° (1 dm, neat) [lit.[9] $[\alpha]^{27}\text{D}$ +12.01 (1 dm, neat)], was treated with a mixture of 26.5 g (0.126 mol) of trifluoroacetic anhydride and 3.63 g of 90% hydrogen peroxide to yield 9.4 g of colorless liquid (bp 83° at 2.5 mm) containing a mixture of δ-methyl-ε-caprolactone and β-methyl-ε-caprolactone. The nmr spectrum (CCl_4) of this mixture showed the low-field methylene signals at 5.84 (t, J = 4 Hz) and 6.0 (m, 4.5 Hz), which were assigned to the chemical shifts of the $-CH_2O-$ groups of β- and δ-methyl-ε-caprolactone, respectively. The δ-methyl-ε-caprolactone was isolated from the mixture by fractional crystallization at 0°, yielding 0.944 g of needles: mp 35.5–36.0°; $[\alpha]^{25}\text{D}$ −37.4° (c 0.855, $CHCl_3$) {lit.[9] $[\alpha]^{25}\text{D}$ −36.11 (c 0.46, $CHCl_3$)}; ir (CCl_4) 5.78 and 8.59 μ; nmr (CCl_4) τ 6.0 (m, 2 H, $-CH_2O-$), 7.47 (m, 2 H, $-CH_2C{=}O$), 8.20 (broad m, 5 H), and 9.08 (d, J = 6.8 Hz, 3 H).

A mixture of (−)-(R)-δ-methyl-ε-caprolactone (415 mg, 3.24 mmol), sodium hydroxide (372 mg), and 5 ml of aqueous ethanol was heated to reflux for 2 hr. Ethanol was removed by vacuum evaporation and the residue was treated with an excess of saturated potassium permanganate (about 1 g) until the pink coloration persisted. The mixture, after storing at room temperature overnight, was treated with a few crystals of sodium bisulfite until the decantation was colorless. The brown precipitate was removed by filtration and the filtrate was extracted twice with 50 ml of methylene chloride. The aqueous layer was separated and adjusted to pH 1 by adding concentrated hydrochloric acid. Continuous extraction with ether yielded 472 mg of crystals, mp 75–78°. Fractional crystallization (thrice) from a mixture of ether and petroleum ether afforded 246 mg of crystals: mp 81–82°; $[\alpha]^{25}\text{D}$ −13.4° (c 2.15 EtOH); ir ($CHCl_3$) 3.80 (br) and 5.85 μ (s) (COOH); nmr ($CDCl_3$) τ −1.6 (s, 2 H, COOH), 7.62 (m, 3 H), 8.33 (m, 4 H), and 8.78 (d, J = 7 Hz, 3 H).

Anal. Calcd for $C_7H_{12}O_4$: C, 52.47; H, 7.55. Found: C, 52.39; H, 7.50.

(+)-S-α-Methyladipic acid had lit.[2] mp 81–83°, $[\alpha]^{25}\text{D}$ +13.8° (c, 1.91 in EtOH). (−)-α-Methyladipic acid had lit.[4b,6] mp 82–83°, $[\alpha]^{28}\text{D}$ −18°.

(−)-**Deoxynupharidine.**—A 200-mg sample of nupharidine ($[\alpha]\text{D}$ +14.8° mp 218–224°, hydrochloride mp 228°; lit.[14] $[\alpha]\text{D}$ +13.0, mp 212°, hydrochloride mp 196°) was dissolved in 100 mg of absolute ethanol, and 100 mg of 10% palladized charcoal was added. The mixture was shaken under 1 atm of hydrogen at room temperature. After 0.5 hr, consumption of hydrogen was complete. The catalyst was filtered and the filtrate evaporated. Chromatography of the 190 mg of oily residue on neutral alumina (activity II), using hexane (95%)–ether (5%) gave 178 mg of deoxynupharidine: $[\alpha]^{25}\text{D}$ −105° (48.6 mg in 2 ml of MeOH), mp (hydrochloride salt) 268°; lit.[15] $[\alpha]^{25}\text{D}$ −112.5°, mp (hydrochloride salt) 262°. The key features of the 100-MHz nmr ($CDCl_3$) spectrum are given in Table I.

TABLE I

100-MHz NMR SPECTRUM OF DEOXYNUPHARIDINE

Chemical shift rel to TMS, (τ 10)	No. of protons	Splitting pattern, J, Hz	Assignment[b]
9.01	6	Doublet, 7.0	C_7 CH_3 (ax)
9.08		Doublet, 5.6	C_1 CH_3 (eq)
8.12	$^1/_2$[a]	Quartet, 12.5, 2.5	$C_{6\beta}$ H (ax)
7.30	1	Quartet, 12.5, 2.5	$C_{6\alpha}$ H (eq)
7.12	1	Quartet, 8.0, 6.2	$C_{4\beta}$ H (ax)

[a] Only the lower field half of the 8.12 quartet is clearly observed. The high-field portion is superimposed on the envelope of the remaining methinyl and methylene protons. [b] ax = axial, eq = equatorial.

Registry No.—4, 1143-54-0; (−)-(R)-α-methyladipic acid, 16200-25-2.

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Anomeric Methyl 4-Thio-D-arabinofuranosides[1]

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Since some nucleosides of D-arabinose possess antitumor activity,[3] and a number of thio and amino sugars and their derivatives have been shown to have biological activity, it is of interest to prepare nucleosides of 4-thio-D-arabinose. The conversion of 9-(4′-thio-β-D-xylofuranosyl)adenine into 9-(4′-thio-β-D-arabinofuranosyl)adenine has been reported,[4] but the synthesis is not applicable to other nucleosides. This paper describes the synthesis of the anomeric methyl 4-thio-D-arabinofuranosides, making the sugar analog available for incorporation into a variety of nucleosides.

The starting material used in the synthesis is 5-S-acetyl-3,6-di-O-benzyl-1,2-O-isopropylidene-α-D-glucofuranose,[5] an intermediate prepared earlier in this laboratory for the synthesis of 5-thio-D-glucopyranose. Selective hydrolysis of the isopropylidene group in the presence of the thiolacetate group of 5-S-acetyl-3,6-di-O-benzyl-1,2-O-isopropylidene-5-thio-α-D-glucofuranose (I) in 50% aqueous acetic acid at 70° gives a 78% yield of crystalline 5-S-acetyl-3,6-di-O-benzyl-5-thio-D-glucofuranose (II) and a 16.2% yield of 3,6-di-O-benzyl-5-thio-D-glucopyranose (III) Scheme (I).

The structure of compound III is confirmed by the absence of absorptions at 1685 (S-acetyl) and 2550 cm^{-1} (SH). Also, the absence of resonance signals at τ 7–7.2 (SH), 7.76 (S-acetyl), and 8.5–8.7 (isopropylidene) indicates that in compound III sulfur has replaced oxygen as the heteroatom in a stable pyranose ring. The strong dextrorotation of compound III (+97.5°) compared with the dextrorotations of compounds I and II (−64.3[5] and −40°) having furanose structures suggests that compound III has a stable pyranose structure in which sulfur has entered the ring. The presence of the S-acetyl group in compound II is confirmed by an absorption at 1685 cm^{-1} and by a resonance signal in the nmr spectrum at τ 7.76. The absence of a signal in the region of τ 8.5–8.7 confirms the absence of the isopropylidene group. Compound II is further characterized by acetylation to obtain 1,2-di-O-acetyl-5-S-acetyl-3,6-di-O-benzyl-5-thio-D-glucofuranose (IX) for which both the ir and nmr spectra showed the presence of S-acetyl and O-acetyl groups.

The structure of compound III is confirmed by the absence of an absorption at 1685 cm^{-1}. Also, the absence of a resonance signal at τ 7.76 (S-acetyl protons) and τ 8.5–8.7 (isopropylidene protons) further indicates that in compound III sulfur has replaced the oxygen as the heteroatom in a stable pyranose ring.

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(2) National Institutes of Health predoctoral fellow, 1965–1968.

(3) For a review see S. S. Cohen in "Progress in Nucleic Acid Research and Molecular Biology," Vol. 5, J. N. Davidson and W. E. Cohn Ed., Academic Press Inc., New York, N. Y., 1965, p 1.

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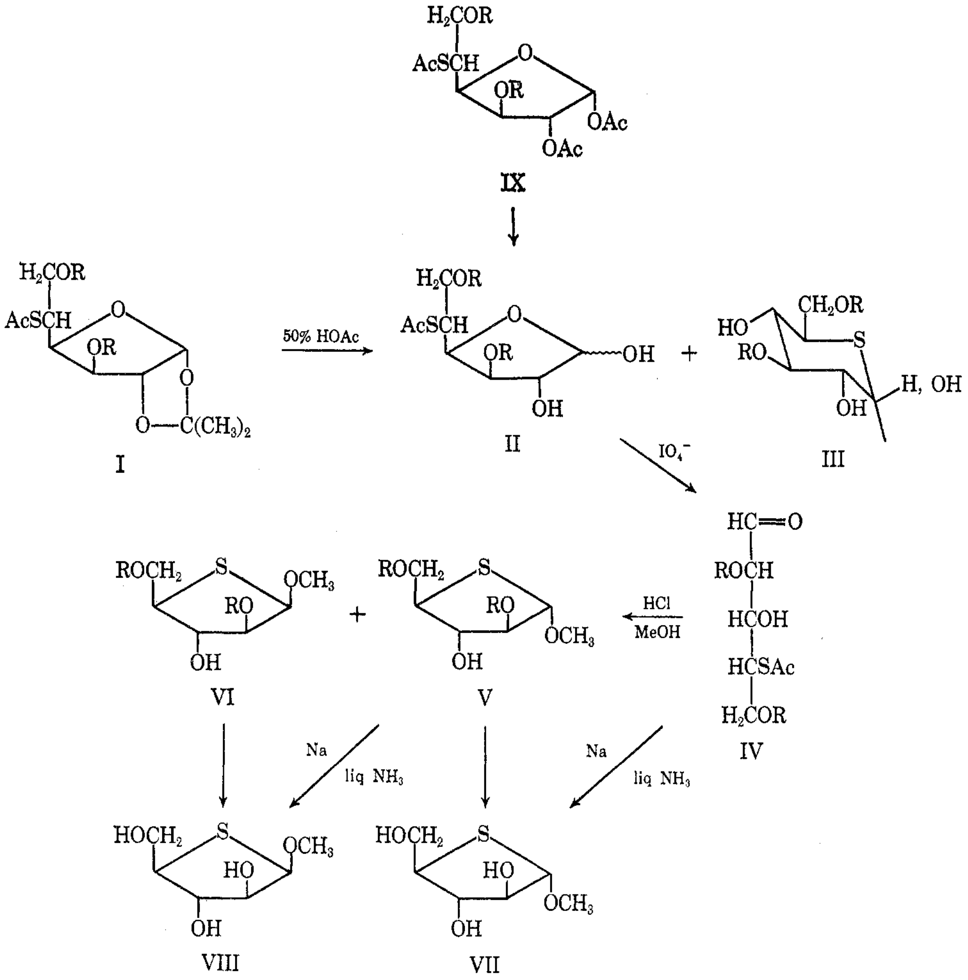
Scheme I



R = $-CH_2C_6H_5$; Ac = $-COCH_3$

Oxidation of sulfides to sulfoxides by metaperiodate has been described[6] as a rather general reaction and has been applied to the synthesis of sulfoxides of thio sugars.[7,8] However, the divalent sulfur of compound II is resistant to oxidation by neutral sodium metaperiodate, possibly owing to the inductive effect of the acetyl substituent. Thus, oxidation of compound II with neutral sodium metaperiodate in 50% aqueous ethanol gives a rapid and quantitative yield of 4-*S*-acetyl-2,5-di-*O*-benzyl-4-thio-*aldehydo*-D-arabinose (IV), which exhibits absorptions at 1730 (aldehyde) and 1685 cm^{-1} (*S*-acetyl). Compound IV is directly converted to the anomeric 2,5-di-*O*-benzyl-4-thio-D-arabinofuranosides (V and VI) by refluxing in 0.5% methanolic hydrogen chloride. The anomers V and VI are separated readily on a silica gel column to give pure, crystalline compounds.

The nmr spectra of both compounds V and VI integrated for 24 protons. The absence of a resonance signal in the τ 7.6–7.8 region and that of an absorption in the region of 1690 cm^{-1} confirms the absence of the *S*-acetyl group in both V and VI. The presence of a resonance signal at τ 2.7 integrating for 10 aromatic protons substantiates that both the benzyl groups are intact.

Debenzylation of V and VI with sodium in liquid ammonia separately has afforded crystalline methyl 4-thio-α-D-arabinofuranoside (VII) and methyl 4-thio-β-D-arabinofuranoside (VIII), respectively. Assignment of the anomeric configurations have been made by analogy to the known methyl D-arabinofuranoside.[9] The nmr spectra of compounds VII and VIII in D_2O show the anomeric proton as a doublet centered at τ 5.01 ($J_{1,2}$ = 4.5 Hz) and 5.3 ($J_{1,2}$ = 3.8 Hz), respectively. In compound VII the H-1 and H-2 protons are *trans* to each other and hence will have a larger coupling constant, thus confirming VII as the α anomer and VIII as the β anomer.

Experimental Section

Analytical Methods.—Purity of products was determined by thin layer chromatography (tlc) with silica gel G[10] coated on 5.0 × 12.5 cm glass slides according to published procedure.[11] Components were located by spraying with 5% sulfuric acid in ethanol and heating until permanent char spots were visible. Column chromatography was carried out on silica gel.[12] Solvents (in parts by volume) were A, chloroform–acetone (9:1); B, hexane–ethyl acetate (6:1); C, benzene–ethyl acetate (10:1); D, chloroform–methanol (10:1); and E, chloroform–methanol (6:1). Melting points are corrected and were determined with a calibrated Fisher-Johns apparatus. Nuclear Magnetic resonance (nmr) spectra were obtained with a Varian Associates A-60

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[12] J. T. Baker Chemical Co., Phillipsburg, N. J.

instrument. Infrared (ir) spectra were obtained with a Perkin-Elmer Model 337 spectrophotometer. Evaporations were done under reduced pressure with a bath temperature below 40°. Optical rotations were measured on a Perkin-Elmer Model 141 polarimeter.

5-*S*-Acetyl-3,6-di-*O*-benzyl-1,2-*O*-isopropylidene-5-thio-α-D-glucofuranose (I).—Compound I was prepared according to published directions.[5]

5-*S*-Acetyl-3,6-di-*O*-benzyl-5-thio-D-glucofuranose (II).—Compound I (30 g) was dissolved in 750 ml of glacial acetic acid at 25° and to this solution 750 ml of water was added with stirring. The stirred mixture was heated at 70° under nitrogen for 36 hr. The reaction mixture was concentrated on a rotatory evaporator to a solid mass which was taken in 750 ml of chloroform. The chloroform solution was washed sequentially with 10% aqueous sodium chloride, dilute aqueous sodium bicarbonate, and water until the washings were neutral. The washed chloroform solution was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated to dryness, whereupon the residue solidified. The solid was recrystallized by dissolving it in 100 ml of ether. To this was added 300 ml of hexane and the solution was set aside at 25° to obtain compound II as flocculent needles: yield 20 g; mp 104–105°; $[\alpha]^{25}\text{D}$ −40° (*c* 1.2, $CHCl_3$). The supernatant from the recrystallization, on being examined by tlc in solvent A, showed the presence of some more of compound II (R_f 0.34) and compound III (major component having R_f 0.24); and hence was concentrated and chromatographed over a silica gel column using solvent A as eluent, to give an additional 1.25 g of compound II. Total yield of compound II was 21.25 g (78%): ir λ_{max} (Nujol) 3450 (OH) and 1685 (S-acetyl); nmr ($CDCl_3$) τ 2.71 (s, 10, aromatic) and 7.76 (s, 3, *S*-acetyl). The nmr spectrum of compound II in $CDCl_3$ integrated for 26 protons with assignable resonances at τ 2.71 (10 H, aromatic) and 7.76 (3 H, S-acetyl), and none for the isopropylidene protons in the region of 8.5–8.7.

Anal. Calcd for $C_{22}H_{26}O_6S$: C, 63.14; H, 6.26; S, 7.65. Found: C, 62.95; H, 6.42; S, 7.45.

The fractions having R_f 0.24 were combined and concentrated to give 4 g (16.2%) of pure compound III. An analytical sample prepared by recrystallization from ether–hexane, had mp 102–103°; $[\alpha]^{25}\text{D}$ +97.5° (*c* 1, $CHCl_3$); ir λ_{max} (Nujol) 3500 (OH); nmr ($CDCl_3$) τ 2.71 (s, 10, aromatic), 5.26 and 5.56 (2 s, 4, CH_2 of benzyl).

Anal. Calcd for $C_{20}H_{24}O_5S$: C, 63.8; H, 6.4; S, 8.52. Found: C, 64.0; H, 6.30; S, 8.41.

1,2-Di-*O*-acetyl-5-*S*-acetyl-3,6-di-*O*-benzyl-5-thio-D-glucofuranose (IX).—Compound II (1.046 g) was acetylated using pyridine and acetic anhydride and the reaction mixture was worked up in the usual manner. Compound IX was recrystallized from ether–hexane as needles: mp 85–86°; $[\alpha]^{25}\text{D}$ +1.2° (*c* 1.07, $CHCl_3$); ir λ_{max} (Nujol) 1740 (O-acetyl) and 1685 (S-acetyl).

Anal. Calcd for $C_{26}H_{30}O_8S$: C, 62.13; H, 6.02; S, 6.38. Found: C, 61.96; H, 6.16; S, 6.54.

Methyl 2,5-Di-*O*-benzyl-4-thio-α- and -β-D-arabinofuranoside (V and VI).—To a stirred solution of compound II (24.4 g, 0.058 mol) in 300 ml of ethanol was added a solution of neutral sodium metaperiodate (13.65 g, 0.0638 mol) in 300 ml of water. The mixture was stirred below 30° for 30–40 min, then filtered, using a little ethanol to wash the precipitate. The filtrate was concentrated under diminished pressure at a bath temperature below 30° to remove ethanol and water. The oily residue was then taken in 500 ml of chloroform and washed twice with water to remove the inorganic salts. The washed chloroform solution was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated to give an almost quantitative yield of 4-*S*-acetyl-2,5-di-*O*-benzyl-4-thio-*aldehydro*-D-arabinose (IV) (22 g) which crystallized on standing. Compound IV exhibited λ_{max} (Nujol) 1730 (aldehyde) and 1685 (*S*-acetyl).

Compound IV thus obtained, was dissolved in 400 ml of 0.5% solution of hydrogen chloride in methanol. The solution was refluxed for 3 hr, after which time it was cooled in ice water and neutralized with silver carbonate. The mixture was filtered and the filtrate was concentrated. The syrupy mixture of the anomeric glycosides were readily separated by column chromatography over silica gel using solvent C as eluent. The pure components were crystallized from ether–hexane to give 9.5 g (40.7%) of methyl 2,5-di-*O*-benzyl-4-thio-α-D-arabinofuranoside (V): mp 43–45°, $[\alpha]^{25}\text{D}$ +112° (*c* 1.4, $CHCl_3$), and 11 g (52.2%) of methyl 2,5-di-*O*-benzyl-4-thio-β-D-arabinofuranoside (VI), mp 74–75°, $[\alpha]^{25}\text{D}$ −139° (*c* 1.26, $CHCl_3$). In subsequent preparations, it was possible to achieve fractional crystallization of VI by seeding a solution of the mixture in ether–hexane. The nmr ($CDCl_3$) of compound V was suggestive of α configuration: τ 2.69 (s, 10, aromatic), 5.36 and 5.50 (2 s, 4, CH_2 of benzyl), 6.72 (s, 3, CH_3O–), and 4.93 (broad s, 1, H-1).

Anal. Calcd for $C_{20}H_{24}O_4S$: C, 66.64; H, 6.71; S, 8.90. Found: C, 66.38; H, 7.00; S, 8.84.

The nmr ($CDCl_3$) for compound VI showed τ 2.7 (s, 10 H, aromatic), 5.35 and 5.48 (2 s, H, CH_2 of benzyl), and 6.76 (s, 3, CH_3O–).

Anal. Found: C, 66.83; H, 6.86; S, 9.12.

Methyl 4-Thio-α-D-arabinofuranoside (VII).—To a stirred solution of compound V (21.6 g, 0.06 mol) in liquid ammonia (500 ml) contained in a 1-l.. three-necked flask, fitted with mechanical stirrer and Dry Ice–acetone condenser, was added 100 ml of dry 1,2-dimethoxyethane to assist the solubility of V during reduction. Freshly cut sodium was added in small pieces (about 200-mg size), one at a time, until the blue color of the solution persisted for 15 min or more. The reaction mixture was then carefully decomposed with excess solid ammonium chloride and ammonia was allowed to evaporate overnight in a current of nitrogen. Chloroform (500 ml) was added and the solution warmed to 40° to drive off the trace of dissolved ammonia, with a current of nitrogen bubbling through the solution. The reaction mixture was filtered to separate the inorganic salts and the filtrate concentrated under reduced pressure to a yellowish syrup which was chromatographically homogeneous in solvent D but contained some bibenzyl, which was removed by silica gel chromatography using solvent D as eluent. The product (10.6 g, ∼100%) crystallized spontaneously upon removal of the solvent and was recrystallized from either chloroform or ethyl acetate as small needles: mp 71–72°; $[\alpha]^{25}\text{D}$ +299° (*c* 1, CH_3OH). The nmr spectrum of VII in D_2O showed the complete absence of the benzyl groups and showed the anomeric proton as a doublet centered at τ 5.01 ($J_{1,2}$ = 4.5 Hz); the methoxyl resonance occurred at τ 6.80.

Anal. Calcd for $C_6H_{12}O_4S$: C, 39.99; H, 6.71; S, 17.79. Found: C, 39.73; H, 6.88; S, 17.65.

Methyl 4-Thio-β-D-arabinofuranoside (VIII).—In a similar manner described above for the α anomer, compound VI (21.6 g, 0.06 mol) was debenzylated. The resultant syrup was chromatographed using solvent E as eluent. Pure compound VIII (10.5 g, ∼100%) so obtained was recrystallized from hotc hloroform as long needles: mp 98°; $[\alpha]^{25}\text{D}$ −156° (*c* 1.25, CH_3OH). Again, the nmr spectrum of compound VIII in D_2O showed the absence of benzyl groups. Assignable resonance signals for the anomeric proton occurred at τ 5.3 ($J_{1,2}$ = 3.8 Hz), and for the methoxyl protons at τ 6.38.

Anal. Found: S, 17.53.

Registry No.—II, 22538-35-8; III, 22538-36-9; V, 22377-93-1; VI, 22377-94-2; VII, 22377-95-3; VIII, 22377-96-4; IX, 22554-94-5.

The Structure and Conformation of the *cis* and *trans* Isomers of 1-(*p*-Chlorobenzylidene)-2-methyl-5-methoxyindenylacetic Acid

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During the course of a research program on anti-inflammatory agents, 1-(*p*-chlorobenzylidene)-2-methyl-5-methoxyindenylacetic acid was synthesized in a study of indomethacin analogs.[1] The presence of

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