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FOUR ISOMERIC ETHYL 1-THIOGLYCOSIDES FROM 2-AMINO-2-DEOXY-D-ARABINOSE*

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ABSTRACT

Ethyl 2-amino-2-deoxy-1-thio-α- and -β-D-arabinopyranoside (**2** and **4**) were obtained by direct ethanethiolation of 2-amino-2-deoxy-D-arabinose (**1**), and their structures were determined by mass and p.m.r. spectrometry. Ethyl 2-amino-2-deoxy-1-thio-α- and -β-D-arabinofuranoside (**11** and **13**) were prepared by partial demercaptalation of 2-amino-2-deoxy-D-arabinose diethyl dithioacetal (**6**) with mercuric chloride (or, preferably, with bromine), with or without protection of the 5-hydroxyl group. Demercaptalation with mercuric chloride gave the β-D anomer almost exclusively, and treatment with bromine gave a mixture of the α and β anomers in the ratio of ~1:1. Alternatively, direct ethanethiolation of **1** in trifluoroacetic acid yielded the α-D anomer. The structures of **11** and **13** were determined by mass spectrometry, by direct comparison of their *N*-acetyl derivatives with an authentic enantiomorph (**15b**), and by p.m.r. spectroscopy. The physicochemical properties of the four 1-thioglycosides (**2**, **4**, **11**, and **13**) were compared with those of the *O*-glycosides of D-arabinose.

INTRODUCTION

In the course of synthetic work on the nucleosides of 2-amino-2-deoxy-D-pentoses, 1-thioglycosides from 2-amino-2-deoxy-D-arabinose were needed. This communication describes the preparation of the anomeric ethyl 1-thiopyranosides and ethyl 1-thiofuranosides of 2-amino-2-deoxy-D-arabinose, starting from the reducing sugar.

2-Amino-2-deoxy-D-arabinose (**1**) is not readily available, and its chemistry has been little explored. Among the several known routes[1–3] for the preparation of **1**, we found the cyanohydrin synthesis from 2,4-*O*-ethylidene-D-erythrose reported by Kuhn and Baschang[1] the most convenient for large-scale preparation.

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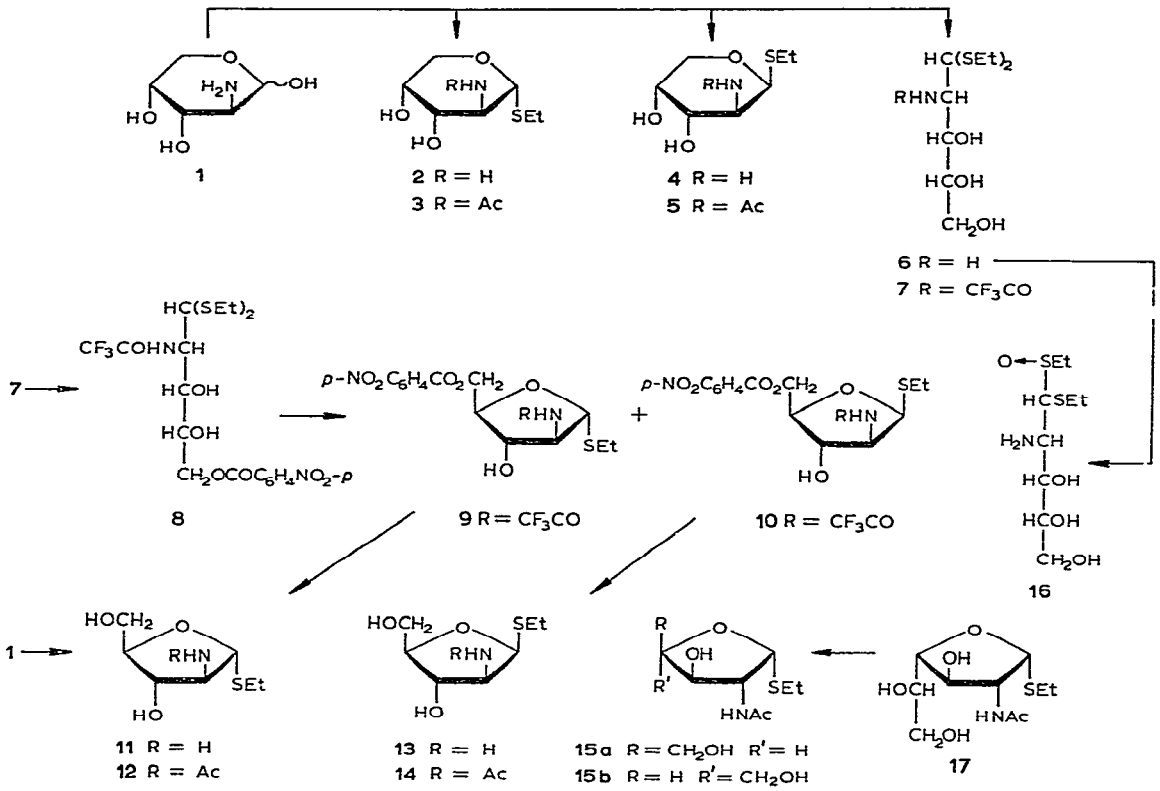
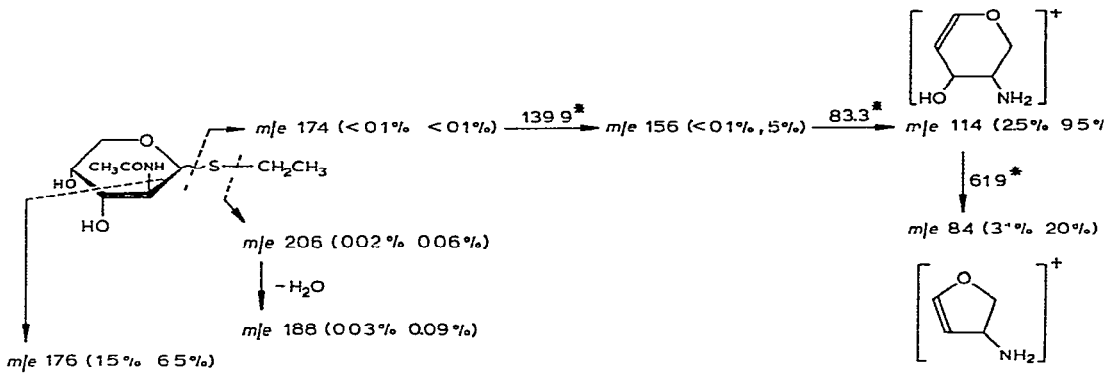


DISCUSSION

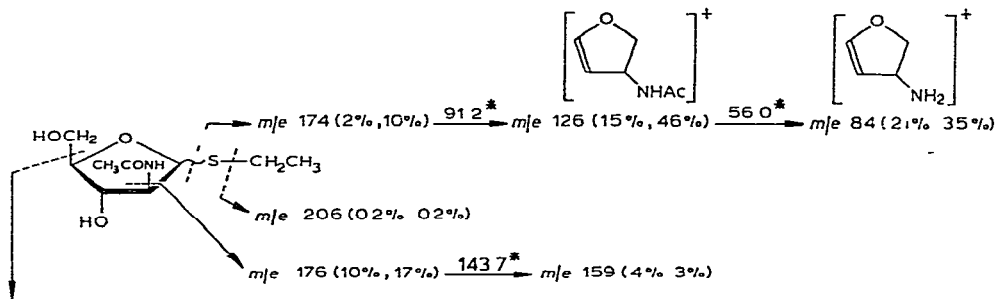
Ethanethiolation of **1** with concentrated hydrochloric acid and ethanethiol for 7 h at room temperature gave a mixture of the diethyl dithioacetal (**6**) and the ethyl 1-thio-α- and -β-D-pyranosides (**2** and **4**), which were separated by chromatography on a column of AG-1 X2 (OH^-) ion-exchange resin[4] that was developed with water The dithioacetal (**6**) was the major product, and no furanosides were obtained under these conditions

The pyranoside structure was first assigned to **2** and **4** on the basis of mass spectrometry As shown in Chart 1, the *N*-acetyl derivatives (**3** and **5**) showed no $(M-31)^+$ peak at *m/e* 204, which is considered to be diagnostic for the furanoside[5] In contrast, the *N*-acetyl derivatives of the furanosides showed the $(M-31)^+$ peak in their mass spectra, as described later The mass spectra, including metastable ions of **3** and **5**, were strikingly similar, suggesting the same framework for **3** and **5** Thus, they both showed a peak at *m/e* 206 arising from the rupture of the sulfur–ethyl bond, and a peak at *m/e* 176 (formed by the elimination of the 2-acetamido group, as has been demonstrated in the mass spectra of 2-acetamido-2-deoxyaldose diethyl dithioacetals[6]) Loss of an ethylthio group from the molecular ion gave rise to a weak peak at *m/e* 174 which underwent loss of water to give the *m/e* 156 peak Release of ketene

from the *m/e* 156 ion gave the *m/e* 114 peak, which was further degraded to give a strong ion at *m/e* 84 These fragmentations were supported by metastable ions, and possible structures for the *m/e* 114 and 84 ions are shown in Chart 1



Fragmentations of compounds 3 and 4 (M^+ at *m/e* 235 not observed)



Fragmentations of compounds 12 and 14 (M^+, *m/e* 235 01% 02%)

Chart 1

The configuration at the anomeric center was established by p m r spectroscopy, utilizing the deshielding effect upon H-1 of an ammonium cation at C-2 It has been shown that a ring proton *cis* to an ammonium group is deshielded more than a proton *trans*-related to a cationic center[7] As summarized in Table I, when the free bases were converted into their trifluoroacetic acid salts, the anomeric proton of the α-D anomer (**2**), which is *cis* to the amino group, showed a larger downfield shift than that of the β-D anomer (**4**), in which H-1 is *trans* to the amino group A similar result was obtained for the anomeric ethyl 2-amino-2-deoxy-1-thio-D-glucopyranosides used as model compounds (see Table I)

Detailed analysis of the p m r spectra in deuterium oxide established the conformation of **2** and **4** The α-D anomer (**2**) as the free base (see Fig 1) showed a doublet at δ 4 30 (H-1), a triplet at 2 90 (H-2), a quartet at 3 50 (H-3), a broad singlet

TABLE I

THE CHEMICAL-SHIFT DIFFERENCE (ΔH-1 VALUE) BETWEEN H-1 OF THE FREE BASE (HIGHER-FIELD) AND H-1 OF THE TRIFLUOROACETIC ACID SALT (LOWER-FIELD) OF SOME 1-THIOGLYCOSIDES IN DEUTERIUM OXIDE

Ethyl 2-amino-2-deoxy-1-thio-D-	ΔH-1	
	α	β
arabinopyranoside	0 40	0 26
arabinofuranoside	0 46	0 13
glucopyranoside	0 25	0 37
xylofuranoside	0 15	

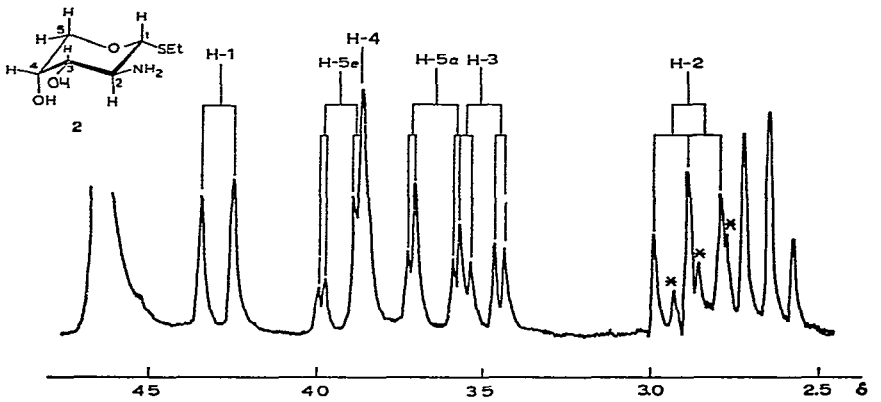


Fig 1 P m r spectrum, at 100 MHz, of ethyl 2-amino-2-deoxy-1-thio-α-D-arabinopyranoside (**2**) in deuterium oxide Signals of the internal standard are indicated by asterisks

(H-4), and two quartets at 3 65 and 3 93 (H-5*a*, H-5*e*) By irradiating at δ 2 90, the H-1 signal collapsed almost to a singlet, and H-3 to a doublet, thus confirming the assignment The large values of $J_{1,2}$ (10 0 Hz) and $J_{2\ 3}$ (10 0 Hz) indicated that the $^1C_4$(D) conformation is preponderant for 2 A similar argument is valid for the p m r spectrum of **4** (see Fig 2), again indicating the $^1C_4$(D) conformation to be preponderant These results are consistent with findings for the α- and β-arabinopyranosides[8].

The thiofuranosides of 2-amino-2-deoxy-D-arabinose (**1**) were first prepared by partial demercaptalation of the dithioacetal (**6**) Treatment of **6** with *S*-ethyl trifluorothioacetate[9] in ethanol gave the *N*-trifluoroacetyl derivative (**7**), which was then treated with one molar equivalent of *p*-nitrobenzoyl chloride in pyridine at -10 to $-20°$, under the conditions used by Zinner and co-workers[10] for terminal *p*-nitrobenzoylation of dithioacetals.

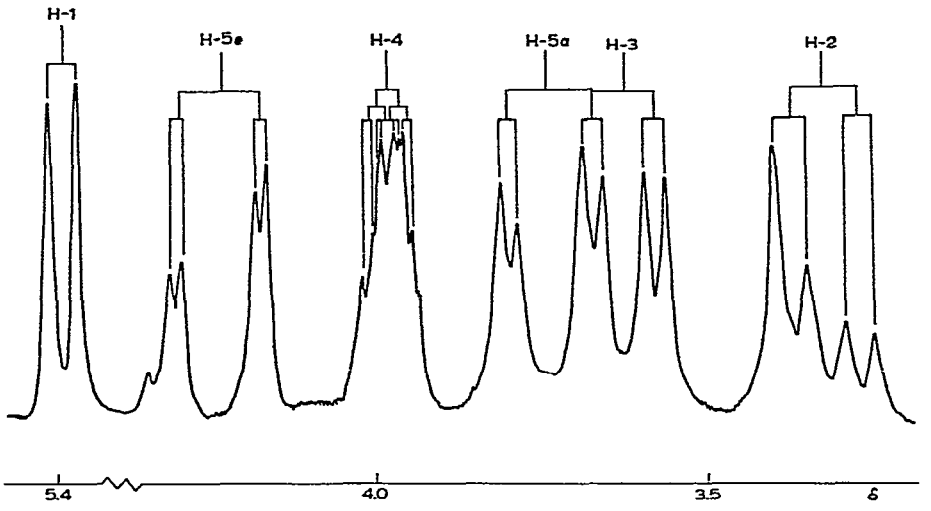


Fig 2 P m r spectrum, at 100 MHz, of ethyl 2-amino-2-deoxy-1-thio-β-D-arabinopyranoside (**4**) in deuterium oxide

After repeated chromatography by t l c on silica gel, the 5-*p*-nitrobenzoate (**8**) was isolated as the main product, together with a small proportion of a di-*p*-nitrobenzoate Although compound **8** was a syrup, it gave an acceptable analysis and showed two absorption bands in its i r spectrum, at 5 81 and 5 83 μm, respectively assignable to an ester-carbonyl stretching mode of the *p*-nitrobenzoyl group and to an amide-carbonyl mode of the trifluoroacetamido group Comparison of the p m r spectrum of **8** with that of **7** in pyridine revealed that a multiplet at δ 4 2, corresponding to two protons in **7**, was shifted downfield by ~0 8 p p m in **8**, supporting the terminal *p*-nitrobenzoylation anticipated The p m r spectrum of the di-*p*-nitrobenzoate showed a downfield shift for three protons, as a result of substitutions at O-6 and one other oxygen atom

A standard method for partial demercaptalation of a sugar dithioacetal consists in treating a dithioacetal with one equivalent of mercuric chloride in the presence of such acid acceptors as mercuric oxide[11] or cadmium carbonate[12] When this method was applied to compound **8** on a small scale, the ethyl 1-thiofuranoside, almost exclusively the β-D anomer (**10**), was obtained in 50% yield The favored formation of the β-D anomer is analogous to the behavior of 5-*O*-benzoyl-D-arabinose diethyl dithioacetal[12] However, when the preparation was scaled up, the reaction did not terminate at the thiofuranoside, but proceeded to the completely demercaptalated product, even though a considerable proportion of the dithioacetal (**8**) remained unchanged It was necessary, therefore, to devise a procedure that would be suitable for large-scale preparation of **10**

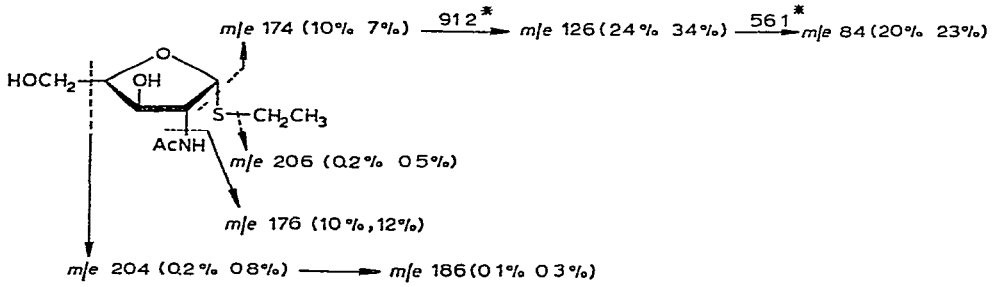
The reaction of alkylthio derivatives of sugars with bromine was initially studied by Bonner[13], and extensively applied in the sugar field by Weygand and

co-workers[14] and Wolfrom and co-workers[15] When a fully acylated aldose dithioacetal is treated with the stoichiometric proportion of bromine, the product is a 1-(alkylthio)-1-bromoalditol If this reaction is applied to a dithioacetal containing an unprotected hydroxyl group at C-4, formation of the thiofuranoside may be expected, as a result of intramolecular, nucleophilic attack of the 4-hydroxyl group on C-1, even if a bromo derivative is formed first This anticipated result was observed in this investigation

Treatment of the 5-*p*-nitrobenzoate (**8**) in dichloromethane with one molar equivalent of bromine in the presence of an excess of lead carbonate gave two ethyl 1-thiofuranosides (**9** and **10**), together with the unreacted dithioacetal (**8**) and the free aldose The products were separated by t l c on silica gel, and each was treated with a strongly basic, ion-exchange resin to remove the *O*- and *N*-protecting groups Treatment with sodium methoxide then readily removed the *p*-nitrobenzoyl groups, but complete removal of the *N*-trifluoroacetyl groups was difficult

The free bases (**11** and **13**) obtained were syrups, but were characterized by converting them into their crystalline *N*-acetyl derivatives (**12** and **14**) The furanoside nature of **12** and **14** was first indicated by mass spectrometry The spectra of both compounds exhibited the $(M-31)^+$ peak at *m/e* 204, formed by the rupture of the C-4 to C-5 bond of a furanoside as shown in Chart 1 Dehydration of *m/e* 204 yielded a peak at *m/e* 186

Ethyl 2-acetamido-2-deoxy-1-thio-α-D-xylofuranoside[16] (**15a**) and ethyl 2-acetamido-2-deoxy-1-thio-β-L-arabinofuranoside[17] (**15b**), used as model compounds,



Fragmentations of compounds 15a (D-*xylo*) and 15b (L-*arabino*) (M^+, *m/e* 235, 0.4%, 0.2%)

Chart 2

indicated the same $(M-31)^+$ peak in their mass spectra (see Chart 2) As already mentioned, the *m/e* 204 peak was absent from the spectrum of the pyranosides Ions at *m/e* 206, 176, and 174 appeared in both the furanoside and pyranoside series, although the *m/e* 174 peak produced by elimination of an ethylthio group was extremely weak for the pyranosides Another fragment-ion characteristic of the furanosides was the peak at *m/e* 126, presumably formed from *m/e* 174 by simul-

taneous release of a hydroxymethyl and a hydroxyl group Loss of ketene from *m/e* 126 yielded a fragment-ion at *m/e* 84 Possible structures of these ions are shown in Chart 1 This pathway was supported by the presence of metastable ions It was shown again that the fragmentation patterns of all furanosides (**12, 14, 15a,** and **15b**) examined were very similar, despite their stereochemical differences

The structures of **12** and **14** were established chemically by direct comparison of their physical properties with those of **15b**, prepared by Wolfrom and Yosizawa[17] from the corresponding β-L-galactofuranoside (**17**) The melting point, i r spectrum, and X-ray powder diffraction pattern of **14**, but not **12**, completely coincided with those of the β-L anomer **15b** Furthermore, as shown in Fig 3, the o r d curve of **14** was superposable on that of **15b**, except for the sign of rotation, whereas **12** exhibited a completely different o r d curve These results clearly indicated that **14** is the enantiomer of the β-L isomer (**15b**) Hence, **14** must be ethyl 2-acetamido-2-deoxy-β-D-arabinofuranoside, and thus, **12** is ethyl 2-acetamido-2-deoxy-α-D-arabino-furanoside

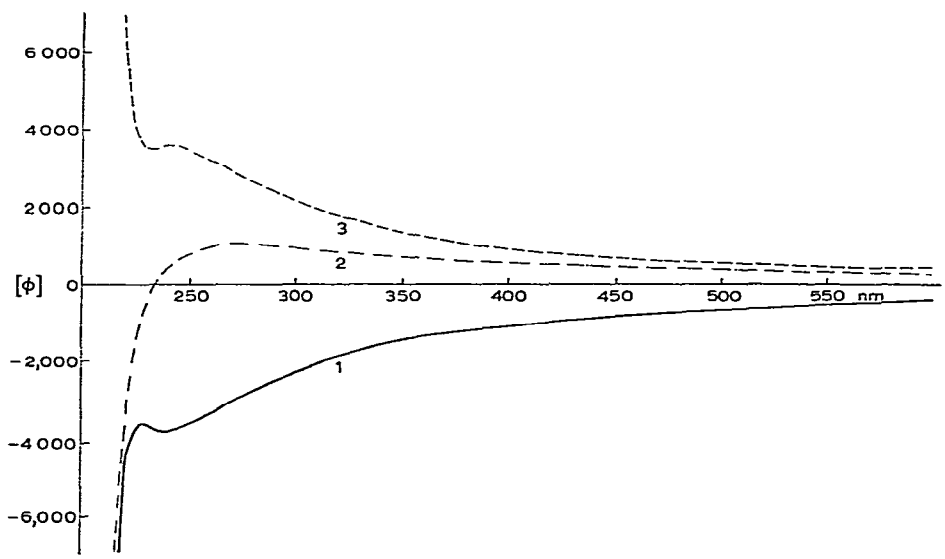
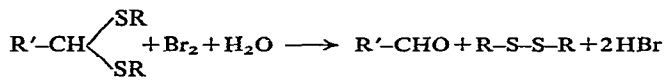


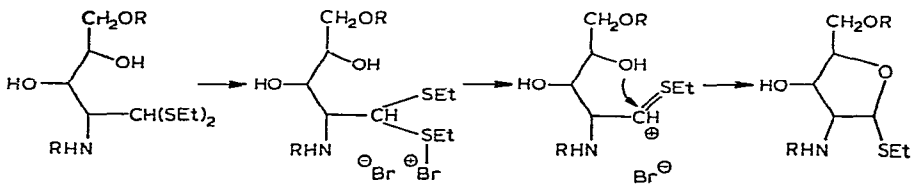
Fig 3 O r d curves of the ethyl 2-acetamido-2-deoxy-1-thio-arabinofuranosides in water [1, β-D anomer (**14**), 2, α-D anomer (**12**), and 3, β-L anomer (**15b**)]

The configuration at the anomeric center of **11** and **13** could be assigned independently by p m r spectroscopy As mentioned earlier, an anomeric proton *cis* to an amino group at C-2 should be much more deshielded than a *trans* proton when the free base is converted into an acid salt In agreement with this, the α-D anomer (**11**) showed a larger downfield shift than the β-D anomer (**13**) (see Table I) Ethyl 2-amino-2-deoxy-α-D-xylofuranoside, used as a model compound, showed only a moderate, downfield shift of H-1, as a result of the *trans* relationship to the amino group at C-2

As the partial demercaptalation by bromine is a rapid reaction, the products may be formed under kinetic control If so, the thiofuranosides (**11** and **13**) might be obtainable directly from **6**, without prior protection of the hydroxyl group at C-5, as HO-4 is statistically closer than HO-5 to C-1. Based on this assumption, the reaction of 2-amino-2-deoxy-D-arabinose diethyl dithioacetal (**6**) with bromine in a variety of solvents was examined Formation of the thiofuranosides was observed in *N,N*-dimethylformamide, or (better) in water Thus, by treating an aqueous solution of the hydrobromide of **6** with one equivalent of bromine in the presence of an excess of lead carbonate, the α and β anomers (**11** and **13**) were obtained in 12 and 23% yields, respectively, in addition to the unreacted dithioacetal (**6**, 15%) and dithioacetal sulfoxide (**16**, 33%) The p m r spectrum of **16** in a mixture of pyridine-d_5 and deuterium oxide showed the H-1 signal at δ 4 22, which is comparable to the chemical shift of **6** (4 34) The *S*-ethyl protons of **16** showed the complicated signal-pattern of an ABX_3 system, as the two methylene protons adjacent to the sulfoxide group are magnetically nonequivalent Formation of the sulfoxide was not unexpected, as Kuhn and co-workers[18] reported the formation of a sulfoxide by oxidation of an aldose diethyl dithioacetal with bromine in water. They further reported that the main reaction between a dithioacetal and one molar equivalent of bromine or chlorine in water is formation of the aldose according to the following equation



When the reaction was conducted in methanol instead of water, they obtained a methyl glycoside[18] It should be noted, however, that these reactions were conducted under strongly acidic conditions, in which an ethyl 1-thiofuranoside would be readily hydrolyzed As far as 2-amino-2-deoxy-D-arabinose is concerned, formation of the ethyl 1-thiofuranosides from the dithioacetal could be explained by postulating a cation (**19**) formed upon heterolysis of the C-1–S bond of an intermediate, bromosulfonium bromide (**18**)



18 **19**

Such a sulfonium ion (**18**), as postulated by Hughes and co-workers[19,20] for neutral solution, could give the thiofuranosides by intramolecular attack from the hydroxyl group at C-4 Attack by a bromide anion at the cationic center may be kinetically less favorable than intramolecular attack Therefore, the formation of a bromo derivative in the intermediate step is improbable

The steric course of the demercaptalation by bromine is of interest In contrast to the demercaptalation by mercuric chloride, where a product having an alkylthio group *cis* to the substituent at C-2 is mainly formed[21], demercaptalation by bromine gave a mixture of the α and β anomers in the ratio of ~1 1 These products are most probably formed in a kinetically controlled reaction, because bromine reacts much more rapidly than mercuric chloride.

An alternative route to the ethyl 1-thio-α-D-furanoside (**11**) involved direct ethanethiolation of 2-amino-2-deoxy-D-arabinose (**1**) Overend and co-workers[22] reported the direct preparation of ethyl 1-thio-D-xylofuranoside by ethanethiolation of D-xylose in *N,N*-dimethylformamide Detailed examination by paper chromatography and monitoring of the course of ethanethiolation of 2-amino-2-deoxy-D-arabinose (**1**) by t l.c revealed that the first product formed is a 1-thiofuranoside, which is then converted into a dithioacetal, suggesting the possibility that a 1-thiofuranoside might be prepared directly from **1** Thus, when **1** was treated with ethanethiol in concentrated hydrochloric acid at room temperature, the only new component after 30 min was revealed by a spot corresponding to a 1-thiofuranoside Upon continuing the reaction, a spot corresponding to the dithioacetal (**6**) appeared after 1 h, it increased in intensity in proportion to the reaction time, whereas the 1-thiofuranoside decreased gradually, and disappeared completely after 7 h The 1-thiopyranoside appeared only after 15 h Unfortunately, the use of concentrated hydrochloric acid did not always give a reproducible yield of the 1-thiofuranosides, because the concentrations of acid and solute, and the temperature, were too critical for control of the reaction After several unsuccessful trials, a reproducible result was obtained by conducting the ethanethiolation at low temperature in trifluoroacetic acid, which was used not only as the solvent but also as the catalyst Thus, a solution of 2-amino-2-deoxy-D-arabinose (**1**) hydrochloride in trifluoroacetic acid was allowed to react with ethanethiol for 2 days at 0°, and the 1-thio-α-D-furanoside (**11**) and the dithioacetal (**6**) were obtained in equal amounts after chromatography on AG-1

TABLE II

A COMPARISON OF SOME PHYSICAL PROPERTIES OF THE FOUR ISOMERIC ETHYL 1-THIOGLYCOSIDES FROM 2-AMINO-2-DEOXY-D-ARABINOSE AND OF THE METHYL D-ARABINOSIDES

Arabinoside	*Property*	*Furanoside*		*Pyranoside*	
		α-D	β-D	α-D	β-D
Ethyl 2-amino-2-deoxy-1-thio-	R_F[a]	0 66	0 70	0 78	0 785
	$[\alpha]_D$ (degrees)	+155	−152	+22	−370
	$J_{1,2}$ (Hz)	6 5	5 5	10 0	4 5
Methyl	$[\alpha]_D$ (degrees)	+123	−119	−17	−244
	$J_{1,2}$ (Hz)	1 0	4 0	8 0	2 5

[a]Relative, paper-chromatographic R_F values 2-amino-2-deoxy-D-arabinose diethyl dithioacetal (**6**) = 1 00, ascending development with 4 1 5 butyl alcohol–acetic acid–water on Whatman No 1 paper

X2 (OH^-) resin. P.m r. spectra of the crude sample of **11** showed no evidence for formation of the β-D anomer (**13**) The favored formation of the α-D anomer, which is considered[23] to be thermodynamically more stable than the β-D anomer, (*a*) suggests that the reaction is thermodynamically controlled, and (*b*) is in sharp contrast to the partial demercaptalation reaction with mercuric chloride, which gave mainly the β-D anomer.

Table II summarizes some of the properties of the four isomeric 1-thioglycosides of 2-amino-2-deoxy-D-arabinose Comparison of the first-order coupling constants ($J_{1,2}$) of the 1-thioglycosides with those of the corresponding *O*-glycosides[24] indicated that the $J_{1,2}$ value for the 1-thio-α-D-furanoside (**11**) is considerably larger than that of the *O*-glycoside It may further be noted that the $J_{1,2}$ value for **11** and its derivatives varies from 1 8 to 6 9 Hz, according to the substituents present, whereas the $J_{1,2}$ value for the β-D anomers remains almost constant One of the most reasonable explanations for this abnormality is that of conformational mobility of the α-D anomer, which can be expected to have two favored conformations [$^3T_2$ (D) and $^2T_3$ (D)], in contrast to the β-D anomer, whose favored conformation[21] is E_2 (D). This matter is discussed in more detail in a separate paper[25].

Comparison of the optical rotations of the 1-thioglycosides with those of the *O*-glycosides[2,26] revealed that Hudson's Isorotation Rule is also valid for the 1-thio sugars, but a difference in magnitude was observed between two β-D-pyranosides

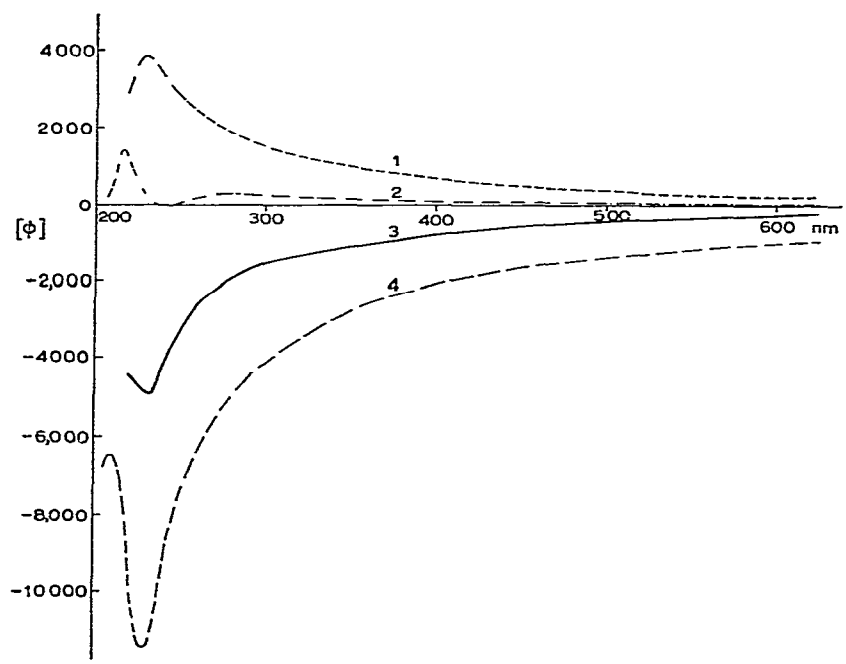


Fig 4 O.r d curves of the ethyl 1-thioglycosides of 2-amino-2-deoxy-D-arabinose in methanol [1, α-D-furanoside (**11**), 2, α-D-pyranoside (**2**), 3, β-D-furanoside (**13**), and 4, β-D-pyranoside (**4**)]

This difference may be attributable, at least partly, to the large, negative, Cotton effect at 220 nm of the 1-thioglycoside, as shown in Fig 4.

EXPERIMENTAL

General methods. — Melting points were determined with a Thomas–Hoover apparatus Specific rotations were measured in a 2-dm polarimeter tube I r spectra were recorded with a Perkin–Elmer Infracord spectrometer, unless otherwise stated O r d , c d , and u v spectra were recorded with a Jasco ORD/UV-5 spectrophotometer. N m r data were obtained, in part, by J Morton and K Christensen, with Varian A-60A and Varian HA-100 spectrometers, and the spectra were recorded, unless otherwise noted, for solutions in deuterium oxide or chloroform-*d*, with an internal standard of sodium 4,4-dimethyl-4-silapentane-1-sulfonate or tetramethylsilane, respectively. Mass spectra were determined by C. R Weisenberger with an AEI MS-9 mass spectrometer, at an ionizing potential of 70 eV and an ion-source temperature of 250° Microanalytical determinations were made by W N. Rond X-Ray powder diffraction data give interplanar spacings, Å, for CuKα radiation Relative intensities were estimated visually m, medium, s, strong, w, weak The strongest lines are numbered (1, strongest), multiple numbers indicate approximately equal intensities T l c was performed by the ascending method with Silica Gel G (E Merck, Darmstadt, Germany) admixed with 0 5% of a 1 1 mixture of zinc orthosilicate and zinc sulfide Spots were detected with ninhydrin for free amino sugars, with potassium permanganate for thio sugars, or with u v light for u v-absorbing products The proportions of developers indicated are by volume Unless otherwise noted, evaporations were performed under diminished pressure below 40°

*Ethanethiolation of 2-amino-2-deoxy-*D*-arabinose* (**1**) *in concentrated hydrochloric acid* — To a solution of 2-amino-2-deoxy-D-arabinose (**1**) hydrochloride (2 0 g) in concentrated hydrochloric acid (9 ml) was added ethanethiol (9 ml) at 4° The mixture was stirred for 1 h at 4°, and then for 7 h at room temperature The resulting, homogeneous solution was made neutral by pouring it gradually onto a suspension of lead carbonate (150 g) in 20% ethanol–water (500 ml). The precipitate was filtered off and the filtrate, which was brought to pH 8 by addition of ammonium hydroxide, was evaporated to dryness The residue (2 93 g) was dissolved in water (40 ml), and chromatographed on a column (3 × 26 cm) of AG-1 X2 (OH^-) resin which was eluted with water The effluent was collected in 6-ml fractions Evaporation of fractions 31–35 gave a syrup that crystallized from ethyl acetate to give **2** (120 mg, 5 7%), m p 88–89°, $[\alpha]_D^{22}$ +22° (*c* 0 625, methanol), λ_{max}^{Nujol} 3 09, 3 16 (OH, NH), and 6 34 μm (NH), c d data (MeOH) 225 nm ([θ] −1,070), p m r data (D_2O) δ 4 30 (H-1), 3 93 (H-5*e*), 3 86 (H-4), 3 65 (H-5*a*), 3 50 (H-3), 2 90 (H-2), 2 70 (CH_2–CH_3), 1 22 (CH_2–CH_3), $J_{1,2}$ 10 0, $J_{2,3}$ 10 0, and $J_{3,4}$ 3 2 Hz; (D_2O–trifluoroacetic acid) δ 4.77 (H-1), $J_{1,2}$ 10 4 Hz, X-ray powder diffraction data 12 90s (2), 7 19s (3), 6 55w, 5 73m, 5 43m, 4 42s (1), 4 20m, and 1 99s

Anal Calc for $C_7H_{15}NO_3S$ C, 43 50, H, 7 82, N, 7 25, S, 16 59 Found. C, 44.15, H, 8.06, N, 7 10, S, 16 56

Evaporation of fractions 36–37 gave a mixture of α- and β-D-pyranosides (110 mg) Crystallization from ethanol of the syrup obtained from fractions 38–43 gave **4** (55 mg, 2 0%) After recrystallization from ethanol, it had m p 122–123°, $[\alpha]_D^{22}$ −370° (*c* 0 14, methanol), λ_{max}^{Nujol} 3 09, 3 17 (OH, NH), and 6 33 μm (NH), c d data (MeOH) 222 nm ([θ] −6,500), p m r. (D_2O) δ 5 40 (H-1), 4 24 (H-5*e*), 3 98 (H-4), 3.74 (H-5*a*), 3 62 (H-3), 3 32 (H-2), 2 70 (CH_2–CH_3), 1 27 (CH_2–CH_3), $J_{1\ 2}$ 4 5, $J_{2\ 3}$ 10 0, $J_{3\ 4}$ 3 1, $J_{4,5a}$ 2 8, $J_{4,5e}$ 1 6, and $J_{5a\ 5e}$ 12 8 Hz, (D_2O–trifluoroacetic acid)· δ 5 65 (H-1), X-ray powder diffraction data 8 38w, 6 21s (2), 5 29w, 4 68s (1), 4 21s (3), 3 64m, and 3 13m

Anal Calc for $C_7H_{15}NO_3S$ C, 43 50, H, 7 82, N, 7 25, S, 16 59 Found C, 43 30, H, 7 87, N, 7 64, S, 16 34

Fractions 44–72 were concentrated, to deposit crystals of compound **6**, which were filtered off, and washed with water, yield, 2 0 g The mother liquors were concentrated, and further crystals of **6** (0 48 g) were obtained, total yield, 2 48 g (90%) Recrystallization from ethyl acetate gave an analytical sample, m p 131–132°, $[\alpha]_D^{22}$ −23 4° (*c* 0 87, methanol), λ_{max}^{Nujol} 3 00, 3 13 (OH, NH), and 6 26 μm (NH), p m r data (1 1 pyridine-d_5–D_2O) δ 4 34 (H-1), 3 54 (H-2), 2 83 (CH_2–CH_3), 1 31 (CH_2–CH_3), $J_{1\ 2}$ 8 4, and $J_{2\ 3}$ 2 0 Hz, X-ray powder diffraction data 12 62s (2), 8 75s (1), 4 79m, 4 47s (3), 4 06m, 3.35w, and 3 21w

Anal Calc for $C_9H_{21}NO_3S_2$ C, 42 32, H, 8 29, N, 5 48, S, 25 11. Found C, 42 50, H, 7 90, N, 5 60, S, 24 96

Ethyl 2-acetamido-2-deoxy-1-thio-α-D-arabinopyranoside (**3**) — The *N*-acetyl derivative **3** was prepared by treating **2** with acetic anhydride in methanol, and recrystallizing the product from ethanol, m p 237–238° (with partial sublimation above 200°), $[\alpha]_D^{22}$ −38 5° (*c* 0 26, water), λ_{max}^{Nujol} 3 13 (OH, NH), 3 34 (NH), 6 07, and 6 50 μm (CO–NH), p m r data (D_2O) δ 4.51 (H-1), 2 00 ($COCH_3$), and $J_{1\ 2}$ 9 7 Hz, (1 1 pyridine-d_5–D_2O) δ 4 94 (H-1) and 2 24 ($COCH_3$), X-ray powder diffraction data 14 78w, 7 62s (1), 6 84w, 4 87m, 4 43s (3), 4.10s (2), 3 85m, 3 62w, 3 03w, 2 81w, and 2 54w

Anal Calc for $C_9H_{17}NO_4S$ C, 45 94, H, 7 28, N, 5 95 Found· C, 46 18; H, 7 43, N, 5 99.

Ethyl 2-acetamido-2-deoxy-1-thio-β-D-arabinopyranoside (**5**) — The *N*-acetyl derivative **5** was prepared by treating the free base **4** with acetic anhydride in methanol, and recrystallizing the product from acetone, m p 206–209° (with partial sublimation above 200°), $[\alpha]_D^{21}$ −270° (*c* 0 16, water), λ_{max}^{Nujol} 3 10 (OH, NH), 3 35 (NH), 6 07, and 6 50 μm (CO–NH), p m r data (1 1 pyridine-d_5–D_2O) δ 5 74 (H-1), 4 89 (H-2), 2 26 (CO–CH_3), $J_{1,2}$ 4 5, and $J_{2,3}$ 8.9 Hz, X-ray powder diffraction data 14 13m, 7 43s, 6 55m, 4 82s (1), 4 37s (2), 4 07s (3), 3 79w, and 3 58w

Anal Calc for $C_9H_{17}NO_4S$ C, 45 94; H, 7 28, N, 5 95 Found C, 46 30, H, 7 38, N, 6 12

A mixture of the anomers obtained from fractions 36–37 from the resin column was *N*-acetylated, and resolved on 3 plates (each 20 × 20 × 0 15 cm) of silica gel by developing first with butyl alcohol saturated with water and then with ethyl acetate

Crystals of **4** (60 mg) and **5** (40 mg) were recovered from the faster-moving and the slower-moving band, respectively.

*2-Deoxy-2-(trifluoroacetamido)-*D*-arabinose diethyl dithioacetal* (**7**) — A solution of the dithioacetal (**6**, 220 mg) in ethanol (15 ml) was allowed to react with *S*-ethyl trifluorothioacetate (200 mg) at room temperature. The reaction was almost complete after 30 min, as checked by t l c After 2 h, the solution was evaporated to dryness, and the residue was dissolved in a small volume of ethyl acetate Addition of benzene caused deposition of crystals of the *N*-trifluoroacetyl derivative (**7**, 224 mg, 74%) Recrystallization from ethyl acetate–benzene–petroleum ether gave an analytical sample, m p 112 5–114°, $[\alpha]_D^{19}$ +3 65° (*c* 1 66, methanol), λ_{max}^{Nujol} 3.09, 3 19 (OH), 3 36 (NH), 5 90, and 6 40 μm (CO–NH), p m r. data (pyridine-d_5) δ 4 46 (H-1), ~4 2 (H-5), 2 71 (CH_2–CH_3), 1.12 (CH_2–CH_3, sextet), $J_{1,2}$ 9 9 Hz, X-ray powder diffraction data 11 47w, 8 50m, 7 10s (1), 5 69m, 5 34w, 4 18s (2), and 3 77s (3)

Anal. Calc for $C_{11}H_{20}F_3NO_4S_2$ C, 37 60, H, 5 74, N, 3 99, S, 18 25 Found C, 37 59, H, 5 89, N, 4 46, S, 18 33

*2-Deoxy-5-*O*-p-nitrobenzoyl-2-(trifluoroacetamido)-*D*-arabinose diethyl dithioacetal* (**8**) — To a solution of **7** (1 47 g) in dry pyridine (25 ml, dried by distillation from sodium hydride) was added dropwise, at −10 to −20°, a solution of *p*-nitrobenzoyl chloride (770 mg) in dry pyridine (10 ml) After 2 h at −10°, a further 120 mg of *p*-nitrobenzoyl chloride in dry pyridine was added, and the solution was stirred for 2 h at 4°, and then evaporated to dryness The residue was dissolved in ethyl acetate, and the solution was washed with water and evaporated to dryness, to give a crude product (2 59 g) that was purified by t l c on 6 plates of silica gel, each plate being developed three times with 40 1 chloroform–methanol Bands containing the 5-*p*-nitrobenzoate (**8**) were combined, and extracted with a mixture of acetone and methanol Evaporation of the extract gave a syrup (1 75 g, 83%) of **8**, which did not crystallize, $[\alpha]_D^{21}$ −18 3° (*c* 0 90, chloroform), $\lambda_{max}^{CHCl_3}$ (Beckman Model IR-9 spectrometer) 2 94 (OH), 5 81 (CO–O), 5 83 (CO–NH), and 6 22 μm (CO–NH), λ_{max}^{MeOH} 260 nm (ε 15,500), p m r data (pyridine-d_5) δ 8 13 (aromatic C*H*), ~5 0 (H-5), 4 58 (H-1), 2 78 (CH_2–CH_3), 1 17 (CH_2–CH_3), $J_{1,2}$ 10 0 Hz, ($CDCl_3$) δ 4 18 (H-1), $J_{1,2}$ 7 3 Hz

Anal Calc for $C_{18}H_{23}F_3N_2O_7S_2$ C, 43 19, H, 4 63, N, 5 60 Found C, 43 19, H, 4.77, N, 5 70

From a band moving faster than **8**, there was obtained a syrupy di-*p*-nitrobenzoate (69 mg, 2 5%), $[\alpha]_D^{22}$ −13 6° (*c* 0 92, chloroform), λ_{max}^{Nujol} 3 03 (OH), 5 79, and 6 21 μm (CO–O, CO–NH), λ_{max}^{MeOH} 259 nm (ε 25,000)

Anal Calc for $C_{25}H_{26}F_3N_3O_{10}S_2$ N, 6 47 Found N, 6 47

*Ethyl 2-deoxy-5-*O*-p-nitrobenzoyl-1-thio-2-(trifluoroacetamido)-*α*-*D*-arabinofuranoside* (**9**) *and -*β*-*D*-arabinofuranoside* (**10**) — *Method A* To a solution of **8** (509 mg) in dichloromethane (30 ml) were added Drierite and an excess of lead carbonate, and then M bromine in dichloromethane (3 2 ml) was added dropwise, with stirring, at room temperature The reaction, monitored by t l c, was stopped just before the spot for **8** disappeared, the suspension filtered, and the filtrate evaporated to

dryness. The residue (450 mg) was chromatographed on two plates (200 × 200 × 1.5 mm) of silica gel by development with 19:1 chloroform–propyl alcohol and then (twice) with 100:1 chloroform–methanol. Unchanged starting material (**8**; 113 mg, 22%) was recovered from the fastest-moving band. The bands migrating moderately fast were combined, and extracted with acetone. The extract was again chromatographed on silica gel plates with the two solvent-systems previously used. Extraction of the faster-moving band followed by evaporation of the extract gave 1.45 mg (33%) of ethyl 2-deoxy-5-*O*-*p*-nitrobenzoyl-1-thio-2-(trifluoroacetamido)-β-D-arabinofuranoside (**10**), which was recrystallized from benzene, m.p. 132–133°, $[\alpha]_D^{23}$ −38° (*c* 0.56, chloroform), λ_{max}^{Nujol} 2.84 (OH), 3.03 (OH, NH), 3.24 (NH), 5.78 (CO–O), 5.85, and 6.22 μm (CO–NH), p.m.r. data (pyridine-d_5): δ 8.18 (aromatic C*H*), 6.06 (H-1), 2.72 (CH_2–CH$_3$), 1.19 (CH$_2$–CH_3), $J_{1,2}$ 6.0 Hz, ($CDCl_3$) δ 5.50 (H-1), $J_{1,2}$ 6.0 Hz, X-ray powder diffraction data 9.45m, 6.10w, 5.17w, 4.68s (1), 4.29s (3), 3.93s (2), 3.49m, and 2.69w.

Anal. Calc. for $C_{16}H_{17}F_3N_2O_7S$: C, 43.94; H, 3.91; N, 6.39. Found: C, 43.84; H, 4.00; N, 6.65.

From the slower-moving band, there was obtained ethyl 2-deoxy-5-*O*-*p*-nitrobenzoyl-1-thio-2-(trifluoroacetamido)-α-D-arabinofuranoside (**9**, 125 mg, 28%), which was recrystallized from acetone–benzene, m.p. 179–179.5°, $[\alpha]_D^{23}$ +119° (*c* 0.61, chloroform), λ_{max}^{Nujol} 2.82 (OH), 3.06 (OH, NH), 3.23 (NH), 5.77 (CO–O), 5.86, and 6.22 μm (CO–NH), p.m.r. data (pyridine-d_5): δ 8.16 (aromatic C*H*), 5.80 (H-1), 2.76 (CH_2–CH$_3$), 1.21 (CH$_2$–CH_3), $J_{1,2}$ 5.4 Hz, ($CDCl_3$) δ 5.28 (H-1), $J_{1,2}$ 4.8 Hz, X-ray powder diffraction data 11.26s (2), 9.40w, 6.32s (3), 4.58s (1), 3.64m, 3.13w, and 2.95w.

Anal. Calc. for $C_{16}H_{17}F_3N_2O_7S$: C, 43.84; H, 3.91; N, 6.39. Found: C, 44.16; H, 4.13; N, 6.22.

Method B. To a stirred solution of **8** (50 mg) in acetone (10 ml) were added a suspension of mercuric oxide (freshly prepared according to Pacsu and Wilson[11] from 120 mg of mercuric chloride) followed by 28 mg of mercuric chloride dissolved in acetone. The mixture was stirred for one day, and stirring was continued for 18 h after the addition of further mercuric chloride (14 mg). One drop of pyridine was then added, the solids were filtered off, and the filtrate was evaporated to a syrup which, on preparative t.l.c., gave the ethyl 1-thiofuranoside (22 mg, 50%). P.m.r. spectroscopy revealed that it consisted almost exclusively of the β-D anomer **10**. Compound **10** was also obtained in 35% yield by treating **8** with mercuric chloride and cadmium carbonate.

Ethyl 2-amino-2-deoxy-1-thio-α-D-arabinofuranoside (**11**) — *Method A.* A solution of **9** (53 mg) in 1:1:1 ethanol–water–acetone (15 ml) was stirred for 3 h with 4 ml of Dowex-2 X8 (OH^-) resin at room temperature. The resin was filtered off, and the filtrate evaporated to give completely deprotected **11** (30 mg). Purification of syrupy **11** by chromatography on a column of AG-1 X2 (OH^-) resin (development with water) gave an analytically pure sample. $[\alpha]_D^{21}$ +155° (*c* 0.79, methanol), c.d. data (MeOH): 229 nm ([θ] +440), p.m.r. data (D_2O) δ 5.04 (H-1), 3.19 (H-2),

2 74 (CH_2–CH_3), 1 28 (CH_2–CH_3), $J_{1,2}$ 6 5, $J_{2,3}$ 6 0 Hz, (D_2O–trifluoroacetic acid) δ 5 52 (H-1), $J_{1,2}$ 4 2 Hz

Anal. Calc for $C_7H_{15}NO_3S$ C, 43 50, H, 7 82, N, 7 25 Found C, 43 39, H, 7 62, N, 7 37.

Method B The direct preparation of **11** from 2-amino-2-deoxy-D-arabinose (**1**) is described later in this paper (last experiment)

Ethyl 2-amino-2-deoxy-1-thio-β-D-arabinofuranoside (**13**) — *Method A* Treatment of **10** (100 mg) with Dowex-2 X8 (OH^-) resin, as described for the preparation of the α-D anomer (**11**), gave 57 mg of clear, syrupy ethyl 2-amino-2-deoxy-1-thio-β-D-arabinofuranoside (**13**), which did not crystallize Chromatography of this syrup on a column of AG-1 X2 (OH^-) resin by elution with water gave an analytically pure sample, $[\alpha]_D^{21}$ −152° (*c* 0 55, methanol), c d data (MeOH) 223 nm ([θ] −2,000), p m r. data (D_2O) δ 5.44 (H-1), 3.49 (H-2), 2 75 (CH_2–CH_3), 1 28 (CH_2–CH_3), $J_{1,2}$ 5 5, $J_{2,3}$ 5 5 Hz, (D_2O–trifluoroacetic acid) δ 5 57 (H-1), $J_{1\ 2}$ 5 4 Hz

Anal Calc. for $C_7H_{15}NO_3S$ C, 43 50; H, 7 82, N, 7.25 Found C, 43 70, H, 7 61; N, 7 47

Method B Direct preparation of **13** from 2-amino-2-deoxy-D-arabinose diethyl dithioacetal (**6**) is described later (partial demercaptalation of **6** by bromine)

Ethyl 2-acetamido-2-deoxy-1-thio-α-D-arabinofuranoside (**12**) — The *N*-acetyl derivative **12** (10 mg) was prepared by treating the free base **11** (15 mg) with acetic anhydride in methanol The product was recrystallized from acetone–benzene, yield, 55%, m p 136 5–137 5°, $[\alpha]_D^{21}$ +109° (*c* 0 10, water), c d data (H_2O) 202 nm ([θ] −23,600), X-ray powder diffraction data 17 31m, 9 02s (3), 6 83s (2), 4 21s (1), 3 96m, 3 51m, 3 32w, and 2 58w

Anal Calc for $C_9H_{17}NO_4S$ C, 45 94, H, 7 28, N, 5 95 Found C, 46 01, H, 7.27, N, 5 81.

Ethyl 2-acetamido-2-deoxy-1-thio-β-D-arabinofuranoside (**14**) — The crystalline *N*-acetyl derivative **14** was prepared by treating the syrupy free base (**13**) with acetic anhydride in methanol and recrystallizing from acetone–benzene, m p 130–131 5°, $[\alpha]_D^{21}$ −195° (*c* 0 13, water); c d data (H_2O) 211 nm ([θ] +11,800), X-ray powder diffraction data 13 38m, 8 11s (1), 6 91m, 6 32w, 4 81s (3), 4.11s (2), 3 91m, and 3 17m

Anal Calc for $C_9H_{17}NO_4S$ C, 45 94, H, 7 28, N, 5 95 Found C, 45 86, H, 7 15, N, 5 99

Partial demercaptalation of the diethyl dithioacetal **6** *by bromine.* — To a suspension of 2-amino-2-deoxy-D-arabinose diethyl dithioacetal (**6**) (2 6 g) in water was added one equivalent of dilute hydrobromic acid to afford a clear solution An excess of lead carbonate was added, and, under vigorous stirring, a dilute solution of bromine (1 45 g) in dichloromethane (45 ml) was added dropwise The reaction was monitored by t l c The mixture was filtered to remove insoluble materials, and the filtrate was evaporated to dryness The residue (3 2 g) was dissolved in water, and chromatographed on a column (2 5 × 30 cm) of AG-1 X2 (OH^-) resin by developing with water, 6-ml fractions were collected The results are summarized as follows

Fractions	*Dry wt.* (*mg*)	*Yield* (%)	*Components*
13–17	930	33	Diethyl dithioacetal sulfoxide[a] (16)
18–21	56		Ethyl β-D-pyranoside[a] (4)
22–27	392	15	Diethyldithioacetal[a] (6)
28–30	469	23	Ethyl β-D-furanoside[a] (13)
31–36	235	12	Ethyl α-D-furanoside[a] (11)

[a]Of 2-amino-2-deoxy-D-arabinose

The formation of a small proportion of the β-D-pyranoside **4** was indicated by paper-chromatographic R_F values and p m r spectroscopy No α-D-pyranoside was detected

The sulfoxide (**16**) was recrystallized from ethanol, m p 151–152°, $[\alpha]_D^{21}$ −7 0° (*c* 1 08, methanol); p m r data (1.1 pyridine-d_5–D_2O) δ 4 22 (H-1), $J_{1,2}$ 10 0 Hz No signal was observed below δ 4 7

Anal Calc for $C_9H_{21}NO_4S_2$ C, 39 83, H, 7 80, N, 5 16 Found C, 40 34, H, 7 63, N, 5 39

*Ethanethiolation of 2-amino-2-deoxy-*D*-arabinose* (**1**) *in trifluoroacetic acid* — To a solution of 2-amino-2-deoxy-D-arabinose (**1**) hydrochloride (2 2 g) in trifluoroacetic acid (30 ml) was added ethanethiol (9 ml) under ice-cooling, and the mixture was kept for 2 days at −5° Most of the ethanethiol and trifluoroacetic acid was removed by concentration (concentrated sodium hydroxide was used to trap these vapors), the concentrate was poured into a suspension of AG-1 X2 (OH^-) resin in 80% aqueous methanol, and the solution, which became alkaline, was decanted from the resin and concentrated, whereupon crystals of the dithioacetal **6** (357 mg) were deposited The mother liquor was placed directly on a column (1 5×45 cm) of AG-1 X2 (OH^-) resin and chromatographed, water being used as the developing solvent Effluents were collected in 6-ml fractions Evaporation of the solvent from fractions 23–31 gave further crops of the dithioacetal **6** (153 mg; total yield, 18 5%), whereas, from fractions 32–45, there was recovered syrupy ethyl 2-amino-2-deoxy-1-thio-α-D-arabinofuranoside (**11**, 442 mg, 21 5%). Examination of other fractions by p m r spectroscopy showed no indication of the corresponding β-D anomer (**13**)

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