Syntheses of 1- and 6-*S*- and 1- and 6-*Se*-Derivatives of 2-Amino-2-deoxy-α/β-D-glucopyranose

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The syntheses of 1,1'-dithiobis-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranose) (6), 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-1-*S*-dimethylarsino-1-thio-β-D-glucopyranose (7), 2-acetamido-2-deoxy-1-*S*-dimethylarsino-1-thio-β-D-glucopyranose (8), 2-acetamido-1,3,4-tri-*O*-acetyl-6-*S*-acetyl-2-deoxy-6-thio-α-D-glucopyranose (11), 6,6'-dithiobis-(2-acetamido-1,3,4-tri-*O*-acetyl-2-deoxy-α-D-glucopyranose) (12), 2-acetamido-1,3,4-tri-*O*-acetyl-2-deoxy-6-*S*-dimethylarsino-6-thio-α-D-glucopyranose (13), 1,1'-diseleno-bis-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranose) (17), 2-*Se*-(2-acetamido-1,3,4-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl)-3-(*NN*-dimethyl)selenoisourea hydroiodide (19), and 6,6'-diselenobis-(2-acetamido-1,3,4-tri-*O*-acetyl-2-deoxy-α-D-glucopyranose) (20) are discussed. N.m.r. and mass spectral properties of the compounds are described. The rearrangement of 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucosyl chloride in acetone to 1,3,4,6-tetra-*O*-acetyl-α-D-glucosamine hydrochloride is reported. The α- and β-anomers of the basic amino-sugar compounds have been characterized and discrepancies with previous reports have been noted.

In recent years molecules containing sulphur and selenium have attracted considerable interest from chemists and biologists. Our interest in the chemistry of the arsinous acid esters of seleno- and thio-sugars originated in 1973, with the synthesis of the arsinous acid ester of 1-thio-β-D-glucose. This study describes the syntheses and chemical characterization of the 1- and 6-*S*- and 1- and 6-*Se*-arsinous acid esters. These compounds were submitted for biological testing to the National Cancer Institute and the results are presented. A number of compounds display carcinostatic activity *in vivo* in the PS test system and *in vitro* in the KB test system.

DISCUSSION

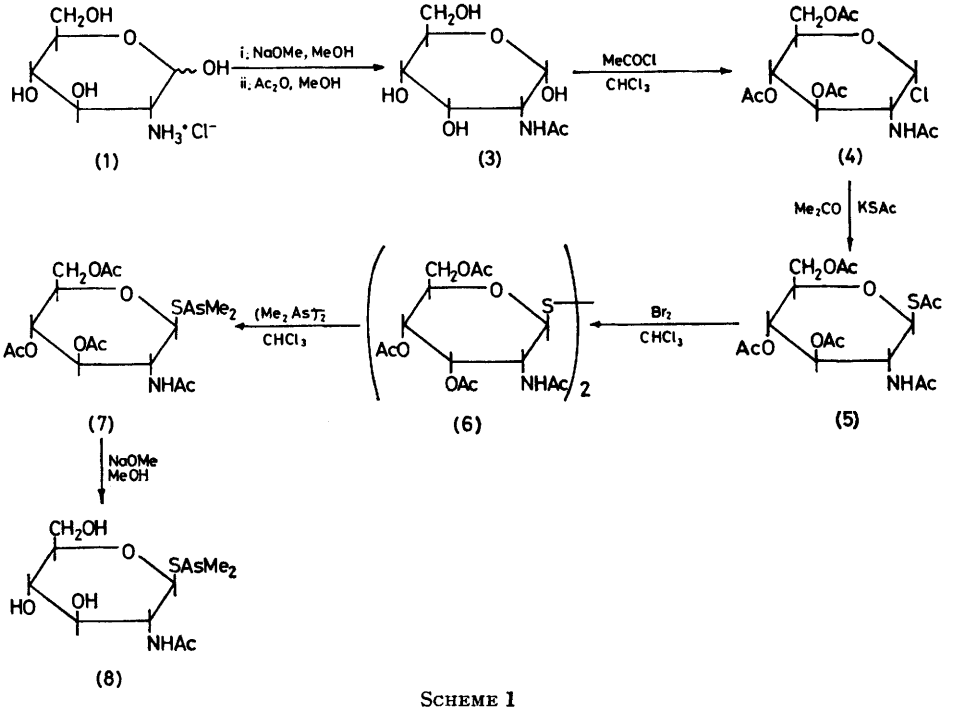
The starting material, 2-acetamido-2-deoxy-α-D-glucopyranose (3),[1] was prepared by liberation of 2-amino-2-deoxy-α-D-glucopyranose (2) [2] from 2-amino-2-deoxy-α-D-glucopyranose hydrochloride (1) with one equivalent of sodium methoxide and subsequent selective acetylation of the amino-group. The n.m.r. coupling constant and chemical shift of compound (2) indicates the presence of the α-anomeric configuration. However, the melting point (111—112 °C) disagrees with the literature value of 88 °C (decomp.) [2] reported for the α-anomer. The β-anomer is reported to have a m.p. of 110—111 °C (decomp.).[2] Attempts to prepare 2-acetamido-2-deoxy-β-D-glucopyranose by the method of Westphal *et al.*[2] gave only 2-acetamido-2-deoxy-α-D-glucopyranose ($J_{1,2}$ 2.8 Hz, τ 4.25).[3,4] Acetylation of compound (2) using the procedure of Westphal *et al.* gave 2-acetamido-2-deoxy-α-D-glucopyranose (3).[1] The reaction of compound (3) with acetyl chloride followed by the *in situ* replacement of the anomeric acetoxy-group by chloride,[5] gave 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl chloride (4).[6] Nucleophilic substitution of the chloride (4) by thioacetate yielded 2-acetamido-3,4,6-tri-*O*-acetyl-1-*S*-thioacetate (5).[5] Subsequent oxidation of the thioacetate (5) with bromine [7] gave the disulphide (6) in good yield (91%). The procedure involves the use of one equivalent of bromine rather than an excess. The coupling constant and the chemical shift of the anomeric proton ($J_{1,2}$ 9.5 Hz, τ 4.58) of the disulphide (6) were indicative of the β-anomeric configuration. The NH proton of the disulphide (6) (J 8.5 Hz, τ 1.63) was distinguished from the anomeric proton by the disappearance of the NH proton signal following exchange with deuterium oxide.

Compound (7) was prepared in quantitative yield by the homolytic addition of tetramethyldiarsine to the disulphide (6). The coupling constant and chemical shift of the anomeric proton ($J_{1,2}$ 10 Hz, τ 5.18) and the NH proton (J 9 Hz, τ 4.10) are close to those of 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-β-D-glucopyranose.[9,21] Deacetylation of (7) by sodium methoxide gave 2-acetamido-2-deoxy-1-*S*-dimethylarsino-1-thio-β-D-glucopyranose (8). The coupling constant and the chemical shift of the anomeric proton ($J_{1,2}$ 9 Hz, τ 5.07) were indicative of the β-anomeric configuration.[3,4] The synthetic procedure is shown in Scheme 1.

2-Acetamido-1,3,4-tri-*O*-acetyl-2-deoxy-6-*O*-toluene-*p*-sulphonyl-α-D-glucopyranose (9) [10] was prepared by an adaptation of the method of Hudson and Dale.[11] This tosylate is used in the preparation of the C-6 derivatives as shown in Scheme 2. The tosylation is carried out at 0 °C with the solution then kept at room temperature for 6 h. After subsequent acetylation at 0 °C, the solution was stirred at room temperature for 24 h before isolation of (9). Nucleophilic displacement of the tosylate (9) by iodide gave 2-acetamido-1,3,4-tri-*O*-acetyl-2,6-dideoxy-6-iodo-α-D-glucopyranose (10).[10] Displacement of the iodide of compound (10) by thioacetate gave the thioacetate (11). The coupling constant and chemical shift of the anomeric and NH protons are similar to those of the α-D-glucopyranose.[2,9]

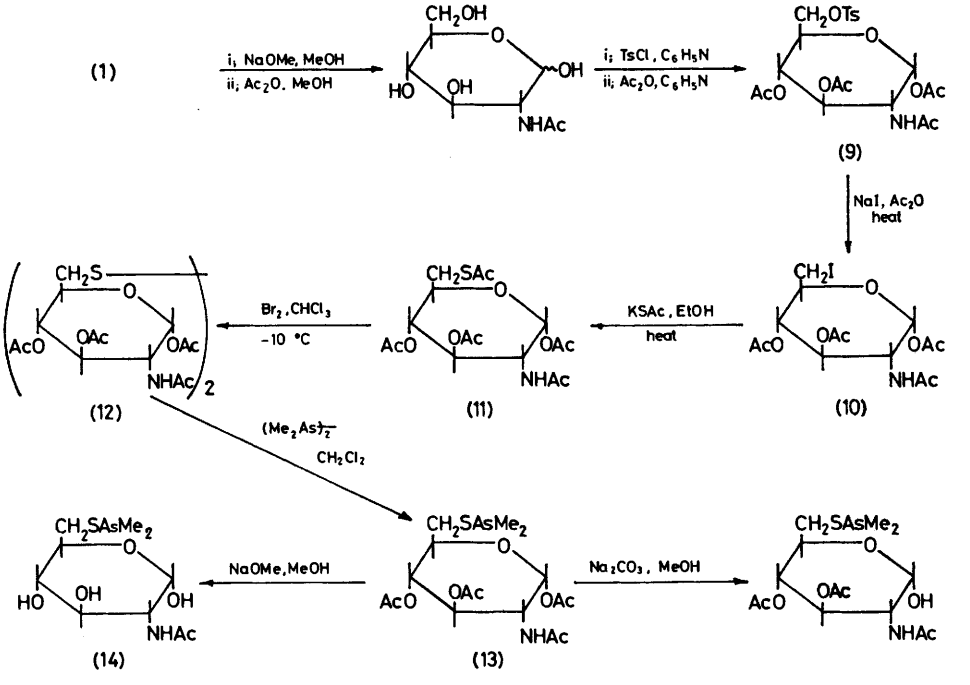
Oxidation of the thioacetate (11) with one equivalent of bromine gave the disulphide (12) in near quantitative yield (98%). The previously prepared acetylated 1-

thioacetate (5) is more stable towards oxidation by bromine than is the acetylated 6-thioacetate (11). The 1-thioacetate (5) was oxidized with one equivalent of pyranose. If the HBr generated during the oxidation was neutralized by pyridine, the yields of disulphides (6) and (12) were higher. The coupling constant and



SCHEME 1

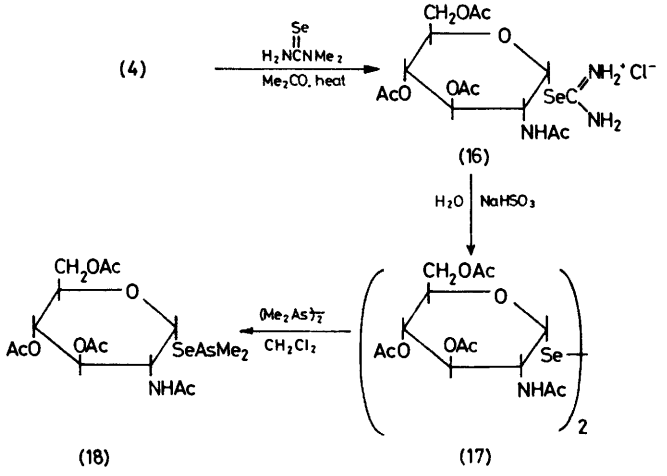
bromine at room temperature for 30 min while (11) required lower temperature (−10 °C) and a much shorter reaction time (2 min). Similar results were noted for 1,2,3,4-tetra-*O*-acetyl-6-*S*-acetyl-6-thio-α-D-glucopyranose. If the HBr generated during the oxidation was neutralized by pyridine, the yields of disulphides (6) and (12) were higher. The coupling constant and chemical shift of the anomeric proton of (12) ($J_{1,2}$ 3 Hz, τ 3.8) are consistent with those of 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-α-D-glucopyranose ($J_{1,2}$ 3.5 Hz, τ 3.82).[2,9]



SCHEME 2

The thioarsine (13) was prepared in quantitative yield by addition of tetramethyldiarsine to the disulphide (12). The coupling constant and chemical shift of the anomeric proton of (13) are similar to those of the α-D-glucopyranose.[2,9] Treatment of (13) with sodium methoxide gave the deacetylated thioarsine (14) as the major product (82%) with the disulphide (12) as a by-product (4%), formed by rupture of the S–As bond of (13) during deacetylation. Attempts to purify (14) were unsuccessful. The coupling constant and chemical shift of the anomeric proton are consistent with the α-anomeric configuration.

The 1- and 6-selenodimethylarsino-derivatives were also prepared (Schemes **3** and **4**). Reaction of the

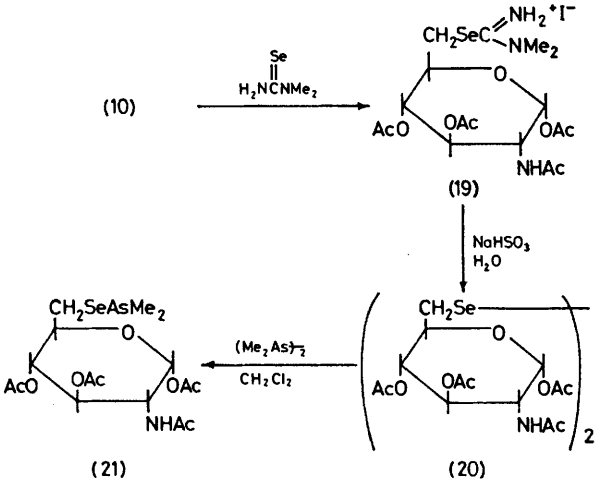


SCHEME 3

chloride (4) [6] with *NN*-dimethylselenourea [12] in acetone led to rearrangement of the *N*-acetal group to give 1,3,4,6-tetra-*O*-acetyl-α-D-glucosamine hydrochloride (15) [3,6] as the major product. Acetyl migration in the 2-amino-2-deoxy-sugar is well known,[13,14] and its migration from the glycosidic centre to the amino-group has been reported.[15] Migration of the methyl group at the glycosidic centre to the 2-amino-group leads to unusual properties and reactions for this compound. The electrostatic shielding effect of the amino-group has been postulated as the cause of the abnormalities in the reactions of 2-amino-2-deoxyglucopyranose,[13] *viz.*, (1) the resistance of the glycosidic methyl group towards acid-hydrolytic reagents, (2) the inability of methanolic hydrogen chloride to effect glycosidation of glucosamine hydrochloride, (3) the conversion of 2-acetamido-1,3,4,6-tetra-*O*-acetyl-*N*-acetyl-2-deoxy-D-glucopyranose into methyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-D-glucopyranose under conditions that will not convert 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-D-glucopyranose into its methyl derivative. The rearrangement of 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl bromide into 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-α-D-glucopyranose hydrobromide has been reported.[15,16] 2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl chloride in polar solvents such as acetone, was found to rearrange readily to 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-α-D-glucopyranose hydrochloride.[17] The rearranged product (15), following its reaction with *NN*-dimethylselenourea, showed no selenium ion in the mass spectrum. The melting point (180 °C) and n.m.r. spectrum (showing the disappearance of NAc and appearance of 1-OAc) were in agreement with those previously reported.[3,6] The filtrate from the reaction of the chloride (4) with *NN*-dimethylselenourea [12] contained the *NN*-dimethylselenoisoureide (16) and the hydrochloride (15). Compound (16) was not isolated. The filtrate was reduced immediately with sodium hydrogen sulphite to give the diselenide (17). The coupling constant and chemical shift of the anomeric proton ($J_{1,2}$ 4 Hz, τ 4.62) of compound (17) are indicative of the α-anomeric configuration. The diselenide (17) was also prepared from the isoureide by reaction between the chloride (4) and selenourea. This procecure is reported in the Experimental section, and yields a more stable intermediate isoureide.

Compound (18) was prepared by addition of tetramethyldiarsine to the diselenide (17), and identified from its n.m.r. spectrum. However, attempts to purify this compound by washing, recrystallization, or column chromatography always led to cleavage of the Se–As bond.

The *NN*-dimethylselenoisoureide (19) was prepared from the iodide (10) and *NN*-dimethylselenourea.[12] The coupling constant and the chemical shift of the anomeric proton ($J_{1.2}$ **3** Hz, τ **3.7**) indicates the glucopyranose form.[2,9] Reduction of (19) with sodium



SCHEME 4

hydrogen sulphide and subsequent aerial oxidation gave the diselenide (20) as stable yellow needles. The coupling constant and chemical shift of the anomeric proton are consistent with the α-anomeric configuration. Addition of tetramethyldiarsine to the diselenide (20) afforded the selenoarsine (21), which, although seen from its n.m.r. spectrum to have been formed, was not,

however, isolated due to the instability of the Se–As bond.

The mass spectra of all the thio- and seleno-sugars and their arsinous acid esters were obtained and found to be consistent with the splitting patterns anticipated. The molecular ion was present in all cases and the loss of Me_2As was always observed. The sugar follows the fragmentation pathways delineated by Chizhov *et al.*[18a] Since the fragmentation is a standard one, no further discussion will be offered.

In the preparation of all of the arsinous acid esters, tetramethyldiarsine was used. The preparation of this compound followed the procedure of Auger [20] with some important modifications. These involved the use of HCl in a smaller mole ratio than previously reported. The desired mole ratio of dimethylarsinic acid : hypophosphoric acid : hydrochloric acid is 1 : 2 : 0.2. This procedure gives a high yield (86%) of the diarsine. Attempts to prepare tetramethyldiarsine by Auger's method (0.6 mole ratio of HCl) gave only dimethylchloroarsine. If a 0.33 mole ratio was used a mixture of tetramethyldiarsine and dimethylchloroarsine was collected.

Several factors were found to affect the yield of the diarsine. Continual stirring of the mixture after the reaction begins to produce cacodyl oxide, and the passage of a stream of nitrogen during distillation of the product, results in reaction of the residual water with the tetramethyldiarsine to give cacodyl oxide as the only product. The entire apparatus must be first flushed with nitrogen and the nitrogen stream must then be *turned off*, the distillation being carried out in the resulting nitrogen atmosphere.

Biological Testing.—The compounds that were prepared in this study were screened by the National Cancer Institute for carcinostatic activity. The results are summarized in the Table.

Carcinostatic activity of synthesized arsine compounds

Compound	Toxicity (mg kg^{-1})	*T*/C (mg kg^{-1}) [a]	ED_{50} in μg ml^{-1} [b]
(7)	200	136 (50)	
(8)	200	125 (100)	
(18)	50	129 (12.5)	1.4×10^1
(13)	200	136 (100)	
(14)		125 (100)	
(21)	200	110 (100)	4.3×10^0

[a] Ratio of test *vs.* control animals using P 388 lymphocytic leukemia. [b] The dose that inhibits 50% of control growth. The test used human epidermoid carcinoma as a cell culture.

Two test systems were used, but not all compounds were tested in both systems. These were the P388 lymphocytic leukemia (*in vivo*) and human epidermoid carcinoma of the nasopharynx (KB system) as an *in vitro* cell culture. It can be seen that the toxicity of these compounds is not high. Relatively large doses of the monosaccharides are tolerated quite well by the test animals. Using the established NIH criterion for carcinostatic activity, *viz.*, that the average survival time of a group of animals exceeds that of the control group by at least 25%, *i.e.*, %T/C $\geqslant$ 125 it can be seen that five of the six dimethylarsino-derivatives are active in the *in vivo* test system. Only compound (21), which is a selenium derivative, showed no activity, but also no toxicity.

The selenium derivatives (18) and (21) were tested for activity *in vitro* using the previously mentioned cell culture. The criterion for activity in this system is that a dosage of 4 μg ml^{-1} inhibits 50% of the growth shown by the control culture. Of the two compounds tested in this system, compound (21) displayed minimal activity. It is interesting to note that this monosaccharide was not active in the *in vivo* test system.

The compounds which contain sulphur display a greater activity than the selenium analogues. This has been observed not only in the compounds which are the subject of this study, but in all our studies to date. This could be due either to the lesser chemical stability of the selenium-containing compounds, or in some cases to their greater toxicity.

EXPERIMENTAL

M.p.s were determined with a Büchi SMP-20 melting point apparatus. N.m.r. spectra were measured at 60 MHz with a Varian T-60 n.m.r. spectrometer. Chemical shifts are given on the τ scale with tetramethylsilane as an internal or, when necessary, external standard. Microanalyses were performed by the Galbraith Laboratories, Inc., Knoxville, Tenn. Mass spectra were recorded by Dr. Ronald Grigsby, Department of Biochemistry, Texas A&M University, with a CEC 21-110 high resolution spectrometer operating at an ionizing potential of 70 eV and an iron current of 200 μA. The accelerating potential was 6 KeV and the source temperature ranged from 200 °C to 240 °C. T.l.c. was performed on Baker-flex silica-gel 1B t.l.c. plates and compounds were detected in an iodine chamber. Column chromatography was performed on a 1.1 × 30 cm column using Merck silica gel 60 (70—230 mesh). All solvents were dried according to standard methods before use.

1,1′-*Dithiobis*-(2-*acetamido*-3,4,6-*tri*-O-*acetyl*-2-*deoxy*-1-*thio*-β-D-*glucopyranose*) (6).—To 2-acetamido-3,4,6-tri-*O*-acetyl-1-*S*-acetyl-2-deoxy-1-thio-β-D-glucopyranose (5) (24.32 g, 60 mmol) in chloroform (400 ml) was added bromine (3.08 ml, 60 mmol) at room temperature with stirring for 30 min. The solution then was neutralized with pyridine to pH6 at −10 °C. The solvent was evaporated off to give a dark brown solid. This solid was redissolved in chloroform, and the solution was extracted twice with water, decolourized twice with activated carbon, and dried ($MgSO_4$). Isolation and evaporation of the solvent gave a brown waxy solid (23.6 g). Attempts to crystallize crude (6) from organic solvents were unsuccessful. A portion of the crude material (2 g) was dissolved in methanol, and the solution was decolourized twice with activated carbon to give a colourless solid (6) (1.82 g, 91%), m.p. 212—215 °C (decomp.). Some of the product (0.104 6 g) was passed through a silica gel column (10 g; packing length of 27 cm × 1.1 cm; eluant, $CHCl_3$–MeOH 1 : 1) to give (6) as a white powder (0.086 g, 82%) m.p. 214—216° (decomp.), R_F 0.59 (silica gel; $CHCl_3$–MeOH 1 : 1); τ([$^2H_6$]DMSO) 1.63 (d, 1 H, NH, $J_{-.2}$ 8.5 Hz), 6.2—5.0 (m, 3 H, H-1, -2, and -5), 5.1—6.0 (m, 4 H, H-3,

-4, -6, and -6), 7.60 (s, 3 H, 3-OAc), 7.61 (s, 3 H, 4-OAc), 7.63 (s, 3 H, 6-OAc), and 7.8 (s, 3 H, NAc).

2-*Acetamido*-3,4,6-*tri*-O-*acetyl*-2-*deoxy*-1-S-*dimethylarsino*-1-*thio*-β-D-*glucopyranose* (7).—To the disulphide (6) (8.34 g, 11.5 mmol) in chloroform (250 ml) was added tetramethyldiarsine (6 ml, 19.8 mmol) in a dry-box (with P_2O_5) under nitrogen at room temperature for 3 days. The solution was evaporated to give crude (7) which was then redissolved in chloroform (100 ml), and the solution extracted with water, decolourized twice with activated carbon, dried ($MgSO_4$), and filtered. The filtrate was evaporated to give a pale yellow solid (10.02 g, 93%). The crude product was crystallized from hot ethanol to give (7) as colourless *needles* (7.00 g, 65%), m.p. 182—183.5 °C. Additional crystals (1.26 g, 11.7%) m.p. 179—180 °C were recovered by concentration of the mother-liquor; τ([$^2H_6$]DMSO) 1.75 (d, 1 H, NH, $J_{NH,2}$ 9 Hz), 4.30—5.07 (m, 2 H, H-3, 4), 4.87 (d, 1 H, H-1, $J_{1,2}$ 10 Hz), 5.36—6.13 (m, 4 H, H-2, -5, -6, and -6), 7.63 (s, 3 H, 3-OAc), 7.76 (s, 3 H, 4-OAc), 7.73 (s, 3 H, 6-OAc), 7.87 (s, 3 H, NAc), and 8.35 (s, 6 H, $AsMe_2$); τ($CDCl_3$) 4.1 (d, 1 H, NH, $J_{NH,2}$ 9 Hz), 4.53—5.18 (m, 2 H, H-3 and -4), 5.18 (d, 1 H, H-1, $J_{1,2}$ 10 Hz), 5.5—6.0 (m, 3 H, H-2, -6, and -6), 6.0—6.5 (m, 1 H, H-5), 7.9 (s, 3 H, 3-OAc), 7.95 (s, 6 H, 4- and 6-OAc), 8.02 (s, 3 H, NAc), and 8.61 (d, 6 H, $AsMe_2$); *m/e* 467 (M^+), 452, 362, 330, 210, 168, 150, 138, 126, 108, 96, 83, and 60 (Found: C, 41.15; H, 5.85. $C_{10}H_{20}AsNO_5S$ requires C, 41.12; H, 5.6%).

2-*Acetamido*-2-*deoxy*-1-S-*dimethylarsino*-1-*thio*-β-D-*glucopyranose* (8).—To a suspension of (7) (9.0 g, 19.3 mmol) in methanol (90 ml) was added sodium methoxide [freshly prepared from Na (0.2 g) and methanol (40 ml)] dropwise at room temperature with stirring until pH 9 was reached. The solution was stirred for 1 h, then neutralized with Dowex 50-X8 (H^+ form) resin, and filtered. The solvent was evaporated off to give crude (8) (6.98 g), m.p. 165—168 °C. Since the product could not be crystallized from any of the standard solvents, it was triturated with acetone (50 ml). The product was recovered by filtration and dried to give a white solid (6.32 g, 96%), m.p. 166—167.5 °C. T.l.c. (silica gel, MeOH) showed a single spot. The mother-liquor was evaporated to dryness to give an additional quantity of (8) which was triturated with $CHCl_3$ to give purified (8) (0.16 g, 2.44%), τ([$^2H_6$]-DMSO) 1.92 (d, 1 H, NH, $J_{NH,2}$ 8 Hz), 5.07 (d, 1 H, H-1, $J_{1,2}$ 9 Hz), 5.67—6.67 (m, 6 H, H-2, -3, -4, -5, -6, and -6), 7.77 (s, 3 H, NAc), 8.30 (s, 6 H, $AsMe_2$). The product was contaminated with dimethylarsinic acid and an acceptable elemental analysis was not obtained. Further attempts to purify the compound resulted in its decomposition.

2-Se-(2-*Acetamido*-3,4,6-*tri*-O-*acetyl*-α-D-*glucopyranosyl*)-*selenoisourea Hydrochloride*.—2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl chloride (4) (14.64 g, 40 mmol) and selenourea (4.9 g, 40 mmol) in acetone (300 ml) were refluxed for 15 min under a dry atmosphere. The solution was then refrigerated for 1 h and a white precipitate was obtained. The precipitate was recovered by filtration, and dried to give the isoureide as a colourless solid (7.06 g, 35.8%). The product then was dissolved in methanol, and the solution was decolourized twice with activated carbon, and filtered. Evaporation of the solvent gave a solid which was recrystallized twice from cold methanol to give colourless needles, m.p. 153—154 °C (decomp.); τ([$^2H_6$]DMSO) 0.54br (4 s, 4 H, 2 × NH_2), 4.03 (d, 1 H, H-1), 5.8—6.3 (m, 2 H, H-2 and -4), 5.6—6.3 (m, 4 H, H-2, -5, -6, and -6), and 7.97, 8.00, 8.03, and 817 (4s, 12 H, 3-, 4-, and 6-OAc, and NAc).

1,1′-*Diselenobis*-(2-*acetamido*-3,4,6-*tri*-O-*acetyl*-2-*deoxy*-α-D-*glucopyranose*) (17).—The preceding hydrochloride (1.55 g, 3.0 mmol) and sodium hydrogen sulphite (0.347 g, 3.3 mmol) were dissolved in 30 ml of water and refluxed for 10 min. The solution was evaporated to a syrup. The syrup was dried to a white solid which was triturated with chloroform (100 ml). The solution was then dried ($MgSO_4$) and filtered. The solution was evaporated to dryness to give (17) as a white solid (1.064 g, 82%). The solid turned to a syrup upon standing. The impure (17) (0.149 7 g) was purified by column chromatography [Merck silica gel 60 (70—230 mesh); 10 g, packing length 27 × 1.1 cm; eluant, $CHCl_3$–MeOH 1 : 1] to give a colourless *syrup* (0.143 9 g, 96%; R_F 0.55); τ([$^2H_6$] DMSO) 1.87 (d, 1 H, NH, $J_{NH,2}$ 9 Hz), 4.18—5.20 (m, 2 H, H-3 and -4), 4.62 (d, 1 H, H-1, $J_{1,2}$ 4 Hz), 5.20—6.40 (m, 4 H, H-2, -5, -6, and -6), 7.57 (s, 3 H, 3-OAc), 7.60 (s, 3 H, 4-OAc), 7.68 (s, 3 H, 6-OAc), 7.78 (s, 3 H, NAc) Found: C, 41.05; H, 5.1. $C_{28}H_{40}N_2O_{16}Se_2$ requires C, 41.08; H, 4.92%).

Attempted Preparation of 2-*Acetamido*-3,4,6-*tri*-O-*acetyl*-2-*deoxy*-1-Se-*dimethylarsino*-1-*seleno*-α-D-*glucopyranose* (18).—To a solution of the diselenide (17) (0.73 g, 89.1 mmol) in chloroform (60 ml) in a dry-box (with P_2O_5) under nitrogen at room temperature was added tetramethyldiarsine (0.70 ml). The mixture was allowed to stand for 3 days and, after removal from the dry-box, the excess of tetramethyldiarsine was oxidized in the air. The solvent was removed to give a colourless solid which was dissolved in chloroform (30 ml). The solution was extracted once with distilled water, and the organic layer was separated, dried ($MgSO_4$), and filtered. The filtrate was evaporated to dryness to give a colourless solid (0.37 g, 40%); the n.m.r. spectrum ($CDCl_3$) was consistent with that expected for the product (18) which was not isolated in analytically pure form.

2-*Acetamido*-1,3,4-*tri*-O-*acetyl*-6-S-*acetyl*-2-*deoxy*-6-*thio*-α-D-*glucopyranose* (11).—2-Acetamido-1,3,4-tri-*O*-acetyl-2-deoxy-6-iodo-α-D-glucopyranose (10) (9.14 g, 20 mmol) and potassium thioacetate (3.42 g, 30 mmol) in absolute ethanol (60 ml) were refluxed for 30 min. The precipitate was filtered off, and the solution decolourized twice with activated carbon and dried to give a brown solid. The solid was triturated with distilled water (80 ml) and dried to again give a brown solid. The solid was dissolved in chloroform, decolourized with activated carbon, and extracted with water. The chloroform layer then was separated, dried, and evaporated to yield (11) as a yellow solid (6.40 g, 79%). After crystallization from ethanol colourless *crystals* were obtained, m.p. 186—170 °C; τ(CD-Cl_3) 5.97 (d, 1 H, H-1, $J_{1,2}$ 4 Hz), 6.15 (d, 1 H, NH, $J_{NH,2}$ 9 Hz), 4.52—5.20 (m, 2 H, H-3 and -4), 5.33—5.87 (m, 1 H, H-2), 5.87—6.40 (m, 1 H, H-5), 6.93 (d, 2 H, $J_{6,6}$ 4.2 Hz), 7.72 (s, 3 H, SAc), 7.82 (s, 3 H, 1-OAc), 7.95 (s, 3 H, 3-OAc), 7.97 (s, 3 H, 4-OAc), and 8.08 (s, 3 H, NAc) (Found: C, 48.05; H, 5.9. $C_{19}H_{23}NO_9S$ requires C, 47.40; H, 5.72%).

6,6′-*Dithiobis*-2-*acetamido*-1,3,4-*tri*-O-*acetyl*-2-*deoxy*-α-D-*glucopyranose* (12).—The thioacetate (11) (2.03 g, 5.0 mmol) was dissolved in chloroform (16 ml) at −10 °C. Bromine (0.258 ml, 5.0 mmol) in chloroform (7.5 ml) was cooled to −10 °C and added with stirring to the solution containing (11). After 2 min, the solvent was quickly

evaporated at reduced pressure and room temperature to leave a sticky yellow solid. Trituration with water, and neutralization at 0 °C with sodium hydrogen carbonate gave crude (12) as a white solid. The crude product was dissolved in chloroform and extracted once with a saturated aqueous sodium hydrogen carbonate. The chloroform layer was separated, dried ($MgSO_4$), and filtered. After evaporation, a white solid (1.77 g, 97.79%), m.p. 211—215 °C (decomp.) was obtained. The solid was crystallized from boiling methanol to give (12) as *needles* (1.14 g, 62.98%), m.p.226—227 °C (decomp.). Additional crystals (0.25 g, 13.18%), m.p. 220—227 °C (decomp.), were recovered from the mother-liquor; τ($CDCl_3$) 3.82 (d, 1 H, H-1, $J_{1,2}$ 3 Hz), 4.3 (d, 2 H, NH, $J_{NH,2}$ 9 Hz), 4.47—5.20 (m, 4 H, H-3 and -4), 5.3—5.67 (d, 2 H, H-2), 5.67—6.23 (m, 2 H, H-5), 7.00—7.30 (m, 4 H, H-6 and -6), 7.8 (s, 6 H, 1-OAc), 7.95 (s, 6 H, 3-OAc), 7.97 (s, 6 H, 4-OAc), and 8.07 (s, 6 H, NAc) (Found: C, 46.45; H, 5.3. $C_{28}H_{40}N_2O_{16}S_2$ requires C, 46.40; H, 5.56%).

2-*Acetamido*-1,3,4-*tri*-O-*acetyl*-2-*deoxy*-6-S-*dimethylarsino*-6-*thio*-α-D-*glucopyranose* (13).—To a solution of the disulphide (12) (4.0 g, 5.5 mmol) in dichloromethane (80 ml), tetramethyldiarsine (4.0 ml, 27.6 mmol) was added in a dry-box (with P_2O_5) under nitrogen at room temperature. After standing overnight, the solution was removed from the dry-box and the excess of tetramethyldiarsine was oxidized in the air while the solution was cooled with solid CO_2. A colourless precipitate formed which was isolated and washed with dichloromethane. The filtrate and washings were combined and evaporated to give a solid which was dissolved in chloroform, and the solution extracted (×2) with water, dried ($MgSO_4$), and filtered. The solvent was evaporated off to give crude (13) (5.23 g, 101%), m.p. 120—122 °C. A portion (2.14 g) was crystallized from ethanol to give (13) as *crystals* (1.74 g, 81%), m.p. 125—126 °C; τ($CDCl_3$) 3.50—4.10 (m, 2 H, H-1 and NH), 4.50—5.2 (m, 2 H, H-3 and -4), 5.20—5.80 (m, 1 H, H-2), 5.80—6.40 (m, 1 H, H-5), 6.87—7.47 (m, 2 H, H-6 and -6), 7.82 (s, 3 H, 1-OAc), 7.97 (s, 6 H, 3- and 4-OAc), 8.07 (s, 3 H, NAc), and 8.70 (s, 6 H, $AsMe_2$) [after addition of D_2O the anomeric proton was found to absorb at τ 3.92 (d, 1 H, H-1, $J_{1,2}$ 3.8 Hz)]; *m/e* 467 (M^+), 452, 408, 348, 330, 288, 244, 202, 168, 126, 101, and 98 (Found: C, 41.55; H, 5.8. $C_{10}H_{20}AsNO_5S$ requires C, 41. 12; H, 5.61%).

2-*Acetamido*-2-*deoxy*-6-S-*dimethylarsino*-6-*thio*-α-D-*glucopyranose* (14).—To a solution of the thioarsine (13) (0.5 g, 1.06 mmol) in methanol (30 ml) freshly prepared sodium ethoxide (from 0.1 g of sodium, 2.0 ml of methanol) was added dropwise with stirring at room temperature until the reaction mixture was at pH 9. After stirring for 1 h, the solution was neutralized with Dowex 50-X8 (H^+ form) resin, and filtered. The filtrate was dried to give crude (14) as a white solid (0.3 g, 82%), containing (n.m.r., t.l.c.) 6,6′-dithiobis-(2-acetamido-2-deoxy-α-D-glucopyranose) as a minor product (3.8%); m.p. 146—152 °C. The crude product was dissolved in MeOH, decolourized twice with activated carbon, and then precipitated by addition of diethyl ether. The product (0.28 g) then was further purified by column chromatography [Merck silica gel 60 (70—230 mesh), 10 g, packing length 27 × 1.1 cm; eluant $CHCl_3$–MeOH 9 : 1, R_F 0.15]. The impure compound was triturated with methylene chloride to remove the final traces of the disulphide, and (14) was obtained as a colourless *powder*, m.p. 161—162 °C (decomp.); n.m.r. (D_2O): τ 4.2 (s, 1 H, H-1), 5.8—7.2 (m, 6 H, H-2, -3, -4, -5, -6, and -6), 7.96 (s, 3 H, NAc), and 8.6 (s, 6 H, $AsMe_2$). The compound decomposed on standing.

2-Se-(2-*Acetamido*-1,3,4-*tri*-O-*acetyl*-2-*deoxy*-α-D-*glucopyranosyl*)-3(-NN-*dimethyl*)*selenoisourea Hydroiodide* (19.)—The iodide (10) (8.8 g, 19.2 mmol) and *NN*-dimethylselenourea (3.3 g, 22 mmol) in pentan-1-ol (90 ml) were refluxed under a dry atmosphere for 15 min. A colourless precipitate appeared at reflux temperature. The solution then was stirred at room temperature overnight. The white precipitate was recovered by filtration and dried to give crude (19) as a solid (10.67 g, 91%), m.p. 216.5—217 °C (decomp.). The product was twice recrystallized from cold methanol to give the *hydroiodide* as crystals, m.p. 217.5—218 °C (decomp.); τ([$^2H_6$]DMSO) 0.68 (s, 2 H, NH_2), 1.67 (d, 1 H, NH, $J_{NH,2}$ 7 Hz), 3.68 (d, 1 H, H-1, $J_{1,2}$ 3 Hz), 4.18—5.00 (m, 2 H, H-3 and -4), 5.00—5.80 (m, 2 H, H-2 and -5), 5.8—6.40 (m, 2 H, H-6 and -6), 6.38 (s, 6 H, NMe_2), 7.62 (s, 3 H, 1-OAc), 7.58 (s, 3 H, 3-OAc), 7.66 (s, 3 H, 4-OAc), and 7.8 (s, 3 H, NAc) (Found: C, 33.05; H, 4.75. $C_{17}H_{28}N_3O_8Se$ requires C, 33.57; H, 4.5%).

6,6′-*Diselenobis*-(2-*acetamido*-1,3,4-*tri*-O-*acetyl*-2-*deoxy*-α-D-*glucopyranose*) (20).—A suspension of the hydroiodide (19, 3.04 g, 5.0 mmol) and sodium hydrogen sulphite (2.6 g, 25 mmol) in distilled water (45 ml) was refluxed for 3 min. As the mixture was heated the reactants dissolved to give a clear solution, and then a pale yellow precipitate was formed. After reflux, the solution was cooled, and the yellow precipitate was isolated, washed with water, and dried to give (20) as a pale yellow powder (1.47 g, 71%), m.p. 236—237 °C. The product was crystallized from methanol to give yellow *needles*, m.p. 236.5—237.5 °C (decomp.); τ([$^2H_6$]DMSO) 1.60 (d, 2 H, NH, $J_{NH,2}$ 8 Hz), 3.67 (d, 2 H, H-1, $J_{1\ 2}$ 3 Hz), 4.17—5.0 (m, 4 H, H-3 and -4), 5.00—5.82 (m, 4 H, H-2 and -5), 6.00—6.70 (m, 4 H, H-6 and -6), 7.42 (s, 6 H, 1-OAc), 7.58 (s, 6 H, 3-OAc), 7.65 (s, 6 H, 4-OAc), and 7.78 (s, 6 H, NAc) (Found: C, 40.7; H, 4.95. $C_{28}H_{40}N_2O_{16}Se_2$ requires C, 41.08; H, 4.92%).

2-*Acetamido*-1,3,4-*tri*-O-*acetyl*-2-*deoxy*-6-Se-*dimethylarsino*-6-*seleno*-α-D-*glucopyranose* (21).—Attempts to prepare and purify compound (21) by oxidative addition of tetramethyldiarsine to the diselenide (20) were unsuccessful. Although n.m.r. showed the product to have been formed, purification procedures resulted in the cleavage of the Se–As bond. Despite repeated attempts, the compound appeared to be too unstable to isolate.

Formation of 1,3,4,6-*Tetra*-O-*acetyl*-2-*amino*-2-*deoxy*-α-D-*glucopyranose Hydrochloride* (22).—Rearrangement of the chloride (4) (64 g, 40 mmol) occurred upon refluxing with *NN*-dimethylselenourea (6.0 g, 40 mmol) in previously dried acetone (300 ml) for 15 min under a dry atmosphere. The solution was refrigerated to give a colourless precipitate which was filtered off (8.20 g, 41.84%), m.p. 176—178 °C (decomp.). The mother-liquor was refluxed for a further 75 min to give additional product (4.50 g, 23.3%), m.p. 170—176 °C (decomp.). The solid which became coloured (pink) upon standing, was dissolved in methanol and decolourized twice with activated carbon. Evaporation gave a white solid. Crystallization from cold methanol gave white *needles*, m.p. 187.5—188 °C (decomp.); τ([$^2H_6$]-DMSO) 0.57 (s, 3 H, NH_3), 3.27 (d, 1 H, H-1, $J_{1,2}$ 3 Hz), 4.00—4.80 (m, 2 H, H-3 and -4), 5.13—6.30 (m, 4 H, H-2, -5, -6, and -6), 7.40 (s, 3 H, 1-OAc), 7.55 (s, 3 H, 6-OAc), and 7.65 (s, 6 H, 3, 4-OAc) (Found: C, 43.85; H, 6.0. $C_{14}H_{22}O_9NCl$ requires C, 43.80; H, 5.73%).

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