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THIO AND SELENO SUGAR ESTERS OF DIALKYLARSINOUS ACIDS

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ABSTRACT

The syntheses of 2,3,4,6-tetra-*O*-acetyl-1-*S*-dimethylarsino-1-thio-β-D-glucopyranose (**3**), 2,3,4,6-tetra-*O*-acetyl-1-*Se*-dimethylarsino-1-seleno-β-D-glucopyranose (**4**), 1-*S*-dimethylarsino-1-thio-β-D-glucopyranose (**5**), and 1-*Se*-dimethylarsino-1-seleno-β-D-glucopyranose (**7**) are described. The n.m.r., Raman, and mass-spectral properties of the compounds are given. 3-*O*-Diethylarsino-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose has also been prepared, but characterized only by n.m.r. spectroscopy.

INTRODUCTION

Selenium is now accepted as an essential nutrient[1]. The levels at which selenium is required are exceedingly small and when it is present in plant materials at levels of 400–800 p.p.m., it can be fatal, but it also presents toxicity problems at lower levels. One interesting and unusual aspect of selenium poisoning involves the ability of arsenite to counteract its toxic effects[2,3]. Ganther[4] has recently presented a review of this subject.

Although one of the organism's detoxifying mechanisms involves the elimination of selenium as dimethyl selenide, the respiratory excretion of this compound is almost totally blocked by the administration of arsenite[5]. There has also been reported[5,6] a greatly increased gastrointestinal secretion of injected selenium upon the administration of arsenic. This has been shown[7] to result from an increased clearance of selenium from the liver into the bile. Biochemically, selenium has been associated almost exclusively with proteins[4], and its potential role in carbohydrates has been almost totally ignored. Also, recent chemical observations[8] have revealed that the C–Se–AsR_2 bond possesses remarkable hydrolytic stability. In view of these considerations, we have initiated a program of study concerned with the study of the preparation and properties, both chemical, and biochemical, of dialkylarsenites of thio and seleno sugars.

Sugars containing a free SeH group undergo very rapid aerial oxidation to the diselenides. Sugars having an unblocked SH group are readily available, however. Synthetic procedures are described herein that make sugars containing Se–As and S–As bonds readily available.

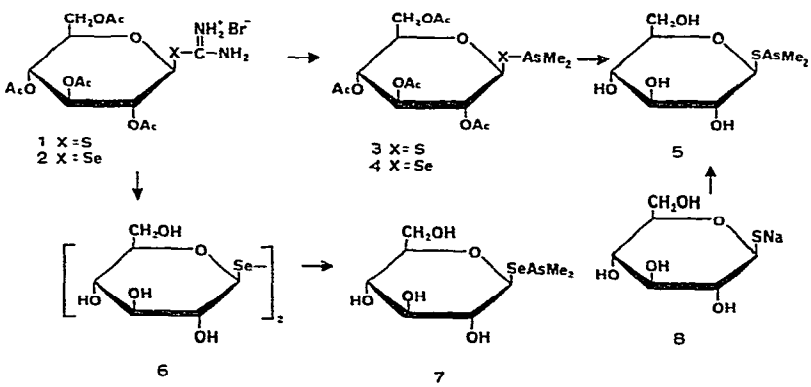
DISCUSSION

The initial approach to this problem was to utilize the method reported by Sagan, *et al.*[8], which involves the reaction between an –SH or –SeH group and a diethylaminodialkylarsine.

$$R\text{–}SeH + Et_2NAsR'_2 \longrightarrow R\text{–}Se\text{–}AsR'_2$$

This procedure was used successfully (see last part of experimental section). However, because of the extreme oxidative instability of –SeH groups in sugars (specifically, their conversion into diselenides) it became necessary to utilize alternative synthetic routes. Furthermore, the dialkylaminoarsines, because of their sensitivity to hydrolysis must be used under rigorously anhydrous conditions. The procedures described here furnish efficient methods for the preparation of the desired compounds.

2-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-2-thiopseudourea hydrobromide[9] (**1**) was converted into 2,3,4,6-tetra-*O*-acetyl-1-*S*-dimethylarsino-1-thio-β-D-glucopyranose (**3**) in 88.5% yield. The conversion was accomplished in a two-phase mixture (water and dichloromethane). Compound **1** and sodium hydrogen suifite were dissolved in the aqueous layer to convert **1** into 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranose, which is extracted into the dichloromethane layer, where it reacts with dimethylchloroarsine[10]. The hydrogen chloride given off in the condensation is taken up by diethylamine. The organic layer was then separated, dried, and evaporated to a syrup that crystallizes very readily. The white, crystalline product **3** was stable to air and water. Its n.m.r. spectrum showed the expected signals for the four acetates, the ring protons, and the dimethyl group on the arsenic atom. The Raman spectrum showed strong absorptions for the arsenic–carbon bond at 580 and 570 cm^{-1} and for the sulfur–arsenic bond at 390 cm^{-1}.



Similar treatment of 2-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-2-seleno-pseudourea hydrobromide[11] (**2**) gave the seleno derivative **4** as a white, crystalline product stable to air and water. The n.m.r. spectrum of **4** showed signals for the ring protons, the acetate groups, and the methyl groups. The Raman spectrum showed

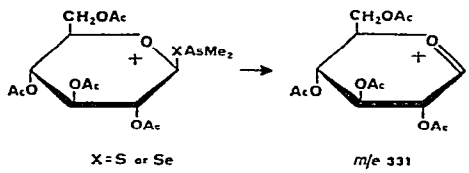
absorptions at 580 and 570 cm^{-1} for the arsenic–carbon bond and at 280 cm^{-1} for the arsenic–selenium bond.

Deacetylation of **3** readily gave 1-*S*-dimethylarsino-1-thio-β-D-glucopyranose (**5**). Compound **5** could also be prepared by treatment of 1-thio-β-D-glucose sodium salt dihydrate (**8**) with dimethylchloroarsine.

All attempts to deacetylate the selenium compound **4** to give compound **7** failed. In order to prepare **7**, compound **2** was converted into bis(β-D-glucopyranosyl) diselenide (**6**) by the method of Wagner and Nuhn[11]. A suspension of the diselenide **6** in dichloromethane was treated with tetramethyldiarsine[12] under nitrogen. Upon being kept, the yellow diselenide **6** was converted quantitatively into the colorless 1-*Se*-dimethylarsino-1-seleno-β-D-glucopyranose (**7**).

Mass spectrometry of the acetylated compounds **3** and **4** revealed no appreciable peak corresponding to the molecular ion. However, a peak (*m/e* 331) corresponding to the M − 137 (loss of $\dot{S}AsMe_2$) and M − 184 (loss of $\dot{S}eAsMe_2$) was observed for **3** and **4**, respectively.

Minor peaks, *m/e* 137, and 185 (the preponderant isotope of selenium has a mass of 80) were observed for $^{+}SAsMe_2$ and $^{+}SeAsMe_2$.



The ion having *m/e* 331 is a well established fragment for acetylated pyranose sugars[13]. The fragmentation of ion *m/e* 331 is well established[13] and gives ions *m/e* 169 and 109 as the major fragments. This fragmentation, however, is a minor pathway with peracetylated pyranose sugars[13]. The lability of the sulfur–carbon bond and the selenium–carbon bond force compounds **3** and **4** to break down almost exclusively through this fragmentation pathway.

EXPERIMENTAL

General Methods. — Evaporations were performed under diminished pressure on a rotary evaporator. Melting points were determined using a Thiele tube. I.r. spectra were measured with a Beckman IR-12 infrared spectrophotometer. Raman spectra were measured with a Cary Model 82 Raman spectrometer by using the 5145 Å line from a Coherent Radiation model 53 argon-ion laser. N.m.r. spectra were measured at 60 MHz with a Varian A-60 n.m.r. spectrometer. Chemical shifts refer to an internal standard of tetramethylsilane ($\tau = 10.00$) for organic solutions and an external standard of tetramethylsilane ($\tau = 10.00$) for aqueous solutions. Microanalyses were determined by Galbraith Laboratories, Inc.

Mass spectra were recorded by Dr. Ronald Grigsby, Dept. of Biochemistry, Texas A&M University with a CEC-21-110 spectrometer operated at an ionizing

potential of 70 eV and an ion current of 100 μA. The accelerating potential was 8 kV and the source temperature was 200°.

*2,3,4,6-Tetra-*O*-acetyl-1-S-dimethylarsino-1-thio-β-*D*-glucopyranose* (**3**). — An aqueous solution (90 ml) of sodium hydrogen sulfite (5.6 g) was heated to ~40° and 2-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-2-thiopseudourea hydrobromide[9] [**1**, 20 g (0.04 mole)] was added. Dichloromethane (75 ml) and dimethylchloroarsine[10] [6 g (0.04 mole)] were added and the two-phase mixture was stirred. Diethylamine (~7 ml) was added until the mixture was basic. After stirring for ~15 min the organic phase was separated, dried (magnesium sulfate), and evaporated to give a syrup. The syrup solidified when scratched to give **3** as a white, crystalline compound, yield 17 g (88.5%). The product was recrystallized from 95% ethanol; m.p. 103–105°, Raman: 580 cm^{-1}, 570 ($AsMe_2$), 390 cm^{-1} (As–S); n.m.r. (60 MHz, chloroform-*d*): τ 4.8–5.6 4-proton multiplets, H-1,2,3,4), 5.8 (2-proton multiplets, H-6,6'), 6.3 (1-proton multiplet, H-5), 7.98, 8.02, 8.04, 8.06 (3-proton singlets, OAc), 8.63 (6-proton singlet, Me_2).

Anal. Calc. for $C_{16}H_{25}AsO_9S$: C, 41.02; H, 5.39. Found: C, 40.82; H, 5.24.

*2,3,4,6-Tetra-*O*-acetyl-1-*Se*-dimethylarsino-1-seleno-β-*D*-glucopyranose* (**4**). — Compound **4** was prepared from 2-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-2-selenopseudourea hydrobromide[11] [**2**, 21 g (0.04 moles)] in the manner just described for the thio analog; yield 19.5 g (96%). The product was recrystallized from 95% ethanol; m.p. 96–98°, Raman: 580 cm^{-1}, 570 ($AsMe_2$), 280 cm^{-1} (As–Se); n.m.r. (60 MHz, chloroform-*d*): τ 4.6–5.2 (4-proton multiplets, H-1, 2, 3, 4), 5.8 (2-proton multiplets H-6,6'), 6.2 (1-proton multiplet, H-5), 7.92. 7.95, 7.98, 8.01 (3-proton singlets, OAc), 8.52 (6-proton singlet, Me_2).

Anal. Calc. for $C_{16}H_{25}AsO_9Se$: C, 37.29; H, 4.90. Found: C, 37.40; H, 5.07.

*1-*S*-Dimethylarsino-1-thio-β-*D*-glucopyranose* (**5**). — 2,3,4,6-Tetra-*O*-acetyl-1-*S*-dimethylarsino-1-thio-β-D-glucopyranose [**3**, 6.0 g (0.013 moles)] was added to anhydrous methanol (50 ml) and a small amount of sodium metal. The resulting solution was kept overnight at room temperature. The solution was neutralized with Dry Ice and evaporated to a syrup that solidified upon scratching; yield 3.0 g (79%). Compound **5** was recrystallized from dichloromethane to give a white solid having a very poorly defined m.p. N.m.r. (60 MHz, deuterium oxide): τ 4.92 (1-proton multiplet, H-1), 5.6–6.2 (6-proton multiplet, H-2, 3, 4, 5, 6, 6'), 8.12 (6-proton singlet, (Me_2).

Anal. Calc. for $C_8H_{17}AsO_5S$: C, 32.00; H, 5.72. Found: C, 31.96; H, 5.81.

A suspension of 1-thio-β-D-glucose, sodium salt dihydrate [**8**, 1.0 g (0.0039 mole) Sigma Chemical Co., St. Louis Mo.] in acetone (20 ml) was treated with dimethylchloroarsine[10] (0.5 ml). The mixture was stirred for 5 min and filtered. Evaporation of the filtrate gave a syrup that crystallized upon the addition of a small amount of chloroform; yield 0.95 g (79%). The product was recrystallized to give **5**, identical with **5** prepared by deacetylation of **3**.

*1-*Se*-Dimethylarsino-1-seleno-β-*D*-glucopyranose* (**7**). — All attempts to prepare **7** by deacetylation of **4**, by analogy with the conversion of **3** into **5**, were unsuccessful.

The following reaction, which involves the reaction between a diarsine and a diselenide, was found to work easily and efficiently.

A suspension of bis(β-D-glucopyranosyl) diselenide[11] [6, 1 g (0.0027 mole)] in dichloromethane (10 ml) was treated under nitrogen with tetramethyldiarsine[12] (1 ml). The yellow suspension was kept overnight at room temperature and underwent conversion into a colorless solid. Under nitrogen, the product (7) was filtered, washed with dichloromethane, then ether, and dried; yield 1.9 g (92%). The white solid decomposed on heating. N.m.r. (60 MHz, deuterium oxide): τ 4.9 (1-proton multiplet, H-1), 5.5–6.5 (6-proton multiplet, H-2, 3, 4, 5, 6, 6'), 8.09 (6-proton singlet, Me_2).

Anal. Calc. for $C_8H_{17}O_5AsSe$: C, 27.68; H, 4.95. Found: C, 27.55; H, 5.01.

3-O-Diethylarsino-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose. — 1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose (1 g) was dissolved in CH_2Cl_2 (~10 ml) under an atmosphere of nitrogen. Diethylaminodiethylarsine (1 ml) was added and the solution was stirred for 0.5 h. The solvent was removed and any excess aminoarsine and diethylamine were removed under diminished pressure (~2 mm Hg) at 65°. The resulting syrup was distilled (b.p. 108°/0.005 mm Hg) to give crystals after 48 h. The n.m.r. spectrum of the distilled material was totally consistent, both in the observed chemical shifts and integrated intensities, for the compound. The compound underwent hydrolysis almost immediately upon exposure to the atmosphere, and no further attempts were made to characterize it. However, the extreme hydrolytic instability of the C–O–As bond compared with the C–S–As and C–Se–As bonds is again qualitatively demonstrated.

TABLE I

MASS-SPECTRAL DATA[a] FOR COMPOUNDS 3 AND 4

m/e	*2,3,4,6-Tetra-O-acetyl-1-S-dimethylarsino-1-thio-β-D-glucopyranose* (3)	*2,3,4,6-Tetra-O-acetyl-1-Se-dimethylarsino-1-seleno-β-D-glucopyranose* (4)
43	100	100
81	3	3
97	4	6
103	2	3
105	3	2
109	30	26
110	2	3
115	3	3
127	10	10
137	3	—
139	3	3
145	3	3
169	33	33
170	3	3
185	—	3
331	14	14

[a]Principal fragment-ions given. Numbers denote % of base peak.

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REFERENCES

1 *Selenium in Nutrition*, National Academy of Sciences, Washington, D. C., 1971, p. 4.
2 A. L. MOXON, *Science*, 88 (1938) 81.
3 I. S. PALMER AND C. W. BARNHORST, *J. Agr. Food Chem.*, 5 (1957) 928.
4 H. E. GANTHER, *Biochemistry of Selenium*, chapter in *Selenium*, R. A. ZINGARO AND W. C. COOPER, Eds., Van Nostrand Rheinhold, New York, N. Y., in press.
5 H. E. GANTHER AND C. A. BAUMANN, *J. Nutr.*, 77 (1962) 210.
6 O. A. LEVANDER AND C. A. BAUMANN, *Toxicol. Appl. Pharmacol.*, 9 (1966) 98.
7 O. A. LEVANDER AND C. A. BAUMANN, *Toxicol. Appl. Pharmacol.*, 9 (1966) 106.
8 L. S. SAGAN, R. A. ZINGARO, AND K. J. IRGOLIC, *J. Organometal. Chem.*, 39 (1972) 301.
9 M. ČERNÝ, J. STANĚK, AND J. PAČÁK, *Monatsh. Chem.*, 94 (1963) 290.
10 G. P. VAN DER KELEN, *Bull. Soc. Chim. Belges*, 65 (1956) 343.
11 G. WAGNER AND P. NUHN, *Arch. Pharm.*, 297 (1964) 461.
12 V. AUGER, *Compt. Rend.*, 142 (1906) 1153.
13 H. BUDZIKEWICZ, C. DJERASSI, AND D. H. WILLIAMS, *Structure Elucidation of Natural Products by Mass Spectrometry*, Holden–Day, San Francisco, Calif., Vol. 2, 1964, p. 203.