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6-THIO AND -SELENO-β-D-GLUCOSE ESTERS OF DIMETHYLARSINOUS ACID

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ABSTRACT

Syntheses of 2-*Se*-(1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranosyl)-3-*N*,*N*-dimethylselenopseudourea hydroiodide (**3**), 1,2,3,4-tetra-*O*-acetyl-6-*S*-dimethylarsino-6-thio-β-D-glucopyranose (**4**), 1,2,3,4-tetra-*O*-acetyl-6-*Se*-dimethylarsino-6-seleno-β-D-glucopyranose (**7**), 6-*S*-dimethylarsino-6-thio-β-D-glucopyranose (**5**), and 6-*Se*-dimethylarsino-6-seleno-β-D-glucopyranose (**9**) are described. Various spectral properties of the compounds are given. The relative rates of alkaline hydrolysis of **5** and **9** are compared.

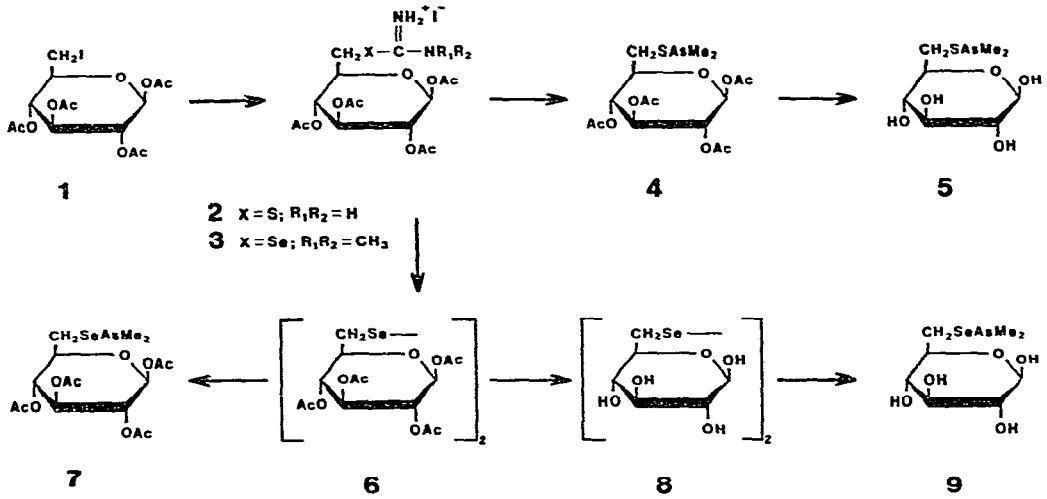
INTRODUCTION

Syntheses of 1-*S*- and 1-*Se*-dimethylarsino and dialkyl- and diaryl-phosphino derivatives of 1-deoxy-β-D-glucopyranose have been recently described[1]. Both 2,3,4,6-tetra-*O*-acetyl-1-*Se*-dimethylarsino-1-seleno-β-D-glucopyranose and 1-*S*-dimethylarsino-1-thio-β-D-glucopyranose have been confirmed to display *in vitro* activity in the KB-9 tissue-culture system (NCI screening data summary reports NSC 163665 and 163666, dated March 30, 1973 and May 11, 1973, respectively). In addition, 1-*S*-dimethylarsino-1-thio-β-D-glucopyranose has been found to be a potent irreversible inhibitor of the muscle glycogen-debranching enzyme[2]. These observations, together with the novel chemistry involved, have prompted us to extend our study of derivatives of this type. In this paper, the syntheses of 6-thio and -seleno sugar esters of dimethylarsinous acid are described.

DISCUSSION

Preparation of the 6-thiopseudourea **2** from the acetylated 6-iodo-β-D-glucopyranose **1** by refluxing[3] with thiourea in pentanol-1 proceeded quantitatively. However, all attempts to prepare the corresponding selenopseudourea by use of selenourea in place of thiourea were unsuccessful. This is to be compared with the case of preparation of the selenopseudourea from the acetylated glucosyl bromide[1]. However, when *N*,*N*-dimethylselenourea[4] was used as the nucleophile, the seleno-

pseudourea **3** was formed in quantitative yield. Conversion of the *N,N*-dimethylselenopseudourea into the diselenide **6** proceeded readily. The use of dimethylselenourea in place of selenourea presents several advantages. It is much more easily prepared and handled and is much more stable than selenourea itself. Also, characterization of the *N,N*-dimethylselenopseudoureido derivative by n.m.r. is also simplified because of the *N*-methyl protons.



The method previously described[1] for preparing the 1-thio derivative was successfully utilized for synthesis of the dimethylarsinous acid esters of the derivative substituted in the 6-position. This synthesis involves reduction of the 6-thiopseudorea to the thiol. The latter was extracted into an organic phase containing dimethylchloroarsine[5] where, in the presence of a base (diethylamine), condensation readily occurs. The only modifications necessary, because of the lesser reactivity of the 6-position, were the use of toluene in place of dichloromethane to allow for a higher reaction temperature, and the use of a nitrogen atmosphere so that the –SH group is not oxidized to the disulfide by atmospheric oxygen at the higher temperature. The foregoing approach failed to yield the seleno analogue, probably because of the stability of the diselenide. It is possible that the disulfide and the diselenide are intermediates formed prior to further reduction. Compound **4** is a colorless crystalline solid, quite stable towards air and water. The coupling constant of the anomeric proton ($J_{1,2}$ 7 Hz) is close to that of 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose ($J_{1,2}$ 6.7 Hz)[6]; this large coupling constant indicates the β-anomeric configuration. The chemical shift of the anomeric proton (τ 4.2) is also in agreement with that observed for β-D-glucose pentaacetate[6].

Compound **7** was prepared in quantitative yield by the homolytic addition of tetramethyldiarsine to the acetylated diselenide **6** in dichloromethane. Although the colorless, crystalline solid was quite stable under ordinary atmospheric conditions,

attempts to recrystallize it from organic solvents were unsuccessful. The coupling constant of the anomeric proton ($J_{1,2}$ 7 Hz) and its chemical shift (τ 4.2), were clearly indicative of the β-anomeric configuration.

Deacetylation of **4** by sodium methoxide gave 6-*S*-dimethylarsino-6-thio-β-D-glucopyranose (**5**). However, no reaction took place between tetramethyldiarsine and 6,6′-dithiobis(β-D-glucopyranose)[7]. This behavior reflects the decreased reactivity of the 6-disulfide, as compared with the 1-derivative[1]. The β-anomeric configuration of **5** is again indicated by the coupling constant of the anomeric proton ($J_{1,2}$ 6.0 Hz) and its chemical shift (τ 4.3).

Although tetramethyldiarsine did not add to 6,6′-dithiobis(β-D-glucopyranose, it did add to 6,6′-diselenobis-(β-D-glucopyranose) (**8**). The latter was an extremely hygroscopic, pale-yellow solid. The coupling constant of the anomeric proton ($J_{1,2}$ 6 Hz) and the chemical shift (τ 4.2) again indicate the β-anomeric configuration.

Hydrolytic considerations. — The greater susceptibility of the D-glucose-Se-$AsMe_2$ bond to alkaline hydrolysis, as compared with the thio derivatives, explains why the attempted deacetylation of **7** was unsuccessful in both the present and previous[1] investigations.

The order of hydrolytic stability in alkaline media, namely, D-glucose-S-$AsMe_2$ > D-glucose-Se-$AsMe_2$ ≫ D-glucose-O-$AsMe_2$, can be explained in terms of a transition state involving a structure that would achieve maximum stability in the case of the sulfur derivative via $p\pi_{As} \rightarrow d\pi_S$ back-bonding. The $d\pi$ levels in selenium are higher in energy and hence, less stable, and *d* orbitals are not available in the case of oxygen. Nucleophilic attack by OH^- at the carbon atom of the C–S bond*, followed by release of $^-SAsMe_2$, could give SH^- and $AsMe_2O\bar{H}$; the latter, because of its extreme oxidative instability, would be rapidly converted into dimethylarsinic acid.

EXPERIMENTAL

General methods. — Evaporations were conducted under diminished pressure in a rotary evaporator or on a vacuum pump. Melting points were determined with a Thiele tube. N.m.r. spectra were recorded at 60 MHz with a Varian T-60 n.m.r. spectrometer. Chemical shifts are given on the τ scale with tetramethylsilane ($\tau = 10.00$) as an internal standard for organic solutions and an external standard for aqueous solutions. Microanalyses were determined by Galbraith Laboratories, Inc.

2-Se-(1,2,3,4-Tetra-O-acetyl-β-D-glucopyranosyl)-3-N,N-dimethylselenopseudourea hydroiodide (**3**). — 1,2,3,4-Tetra-*O*-acetyl-6-deoxy-6-iodo-β-D-glucopyranose[3] (45.8 g) and *N,N*-dimethylselenourea[4] (15.3 g) in pentanol-1 (300 ml) were refluxed for 30 min[3]. The mixture dissolved upon warming and a greyish precipitate formed on

*The formation of D-glucose in aqueous solutions of 1-*S*-dimethylarsino-1-thio-β-D-glucopyranose has been observed; Dr. T. E. Nelson, Dept. of Biochemistry, Baylor College of Medicine, personal communication. However, the formation of D-glucose by hydrolysis of the 6-derivative is by no means unequivocally established in this study, and other hydrolytic products may well be involved.

boiling for 5 min. After cooling to room temperature, the precipitate was recovered by filtration and dried; yield, 59.4 g (97.5%). The product was recrystallized from methanol to give a white, crystalline compound, m.p. 217–218° (dec.); n.m.r. (dimethyl sulfoxide-d_6): τ 0.9 (2-proton singlet, NH_2), 4.6 (1-proton doublet, $J_{1,2}$ 8 Hz, H-1), 4.3–5.4 (3-proton multiplets, H-2,3,4), 5.7 (1-proton multiplet, H-5), 6.5 (2-proton multiplets, H-6,6′), 6.8 (6-proton singlet, NMe_2), 7.94, 7.97, 8.00, and 8.03 (3-proton singlets, OAc).

Anal. Calc. for $C_{17}H_{27}IN_2O_9Se$: C, 33.51; H, 4.47; N, 4.60. Found: C, 33.63; H, 4.36; N, 4.59.

1,2,3,4-Tetra-O-*acetyl-6*-S-*dimethylarsino-6-thio-β*-D-*glucopyranose* (**4**). — To a suspension containing 2-*S*-(1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranosyl)-2-thiopseudourea hydroiodide[3] (**2**, 9 g) in water (90 ml) was added aqueous sodium hydrogen sulfite (9 g of sodium hydrogen sulfite in 30 ml of water) under a nitrogen atmosphere. The mixture was stirred and boiled under reflux (~2 min) until an oily layer appeared[8]. Toluene (60 ml) and chlorodimethylarsine[5] (1.5 ml) were added and the two-phase mixture was stirred. Diethylamine (10.5 ml) was then added until the mixture became basic. After stirring for 1 h, the organic phase was separated, dried (magnesium sulfate), and evaporated to give a syrup that solidified after refrigeration; yield 7.2 g (91.2%). After recrystallization from 95% ethanol, the product had m.p. 99–101°; n.m.r. (chloroform-*d*) τ 4.2 (1-proton doublet, H-1, $J_{1,2}$ 7.0 Hz), 4.5–5.3 (3-proton multiplets, H-2,3,4), 6.2 (1-proton multiplet, H-5), 7.1 (2-proton multiplets, H-6,6′), 7.89, 7.92, 7.97, 8.02 (3-proton singlets, OAc), and 8.7 (6-proton singlet, NMe_2).

Anal. Calc. for $C_{16}H_{25}AsO_9S$: C, 41.03; H, 5.38. Found: C, 40.79; H, 5.34.

1,2,3,4-Tetra-O-*acetyl-6*-Se-*dimethylarsino-6-seleno-β*-D-*glucopyranose* (**7**). — An attempt to prepare **7** in the manner just described for the thio analog was unsuccessful. The following synthesis, which involves the homolytic addition of a diarsine to a diselenide, worked well.

6,6′-Diselenobis(1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranose) (**6**, 3 g) was dissolved with stirring in dichloromethane (15 ml) under a nitrogen atmosphere. Tetramethyldiarsine[9] (0.53 ml) was added slowly to the yellow solution. The yellow color disappeared upon addition of the diarsine. The solution was stirred overnight at room temperature, and then evaporated to dryness, yielding a white solid (3.75 g, 99.2%), m.p. 93–95°; n.m.r. (chloroform-*d*) τ 4.2 (1-proton doublet, H-1, $J_{1,2}$ 7.0 Hz), 4.4–5.1 (3-proton multiplets, H-2,3,4), 6.1 (1-proton multiplet, H-5), 7.1 (2-proton multiplets, H-6,6′), 7.82, 7.90, 7.92, 8.00 (3-proton singlets, OAc), and 8.5 (6-proton singlet, Me_2). Attempts to recrystallize the product were unsuccessful.

Anal. Calc. for $C_{16}H_{25}AsO_9Se$: C, 37.29; H, 4.87; Se, 15.32. Found: C, 36.66; H, 4.89; Se, 14.58.

6-S-*Dimethylarsino-6-thio-β*-D-*glucopyranose* (**5**). — Attempts to prepare compound **5** by the reaction between 6,6′-dithiobis(β-D-glucopyranose) and tetramethyldiarsine were unsuccessful. The following reaction gave high yields and required fewer steps.

To a suspension of 1,2,3,4-tetra-*O*-acetyl-6-*S*-dimethylarsino-6-thio-β-D-glucopyranose (**4**, 6 g) in anhydrous methanol (60 ml) was added methanolic sodium methoxide [prepared from sodium (0.2 g) and methanol (40 ml)] dropwise until the solution became basic (pH ~8). The solution was stirred for 1 h at room temperature and then neutralized with Dowex-50W X8 (H^+ form) resin. The mixture was filtered and the filtrate evaporated to dryness, to yield a white solid (3.65 g, 94.8%). The product, recrystallized from dichloromethane, had a very poorly defined m.p.; n.m.r. (deuterium oxide): τ 4.3 (1-proton doublet, H-1, $J_{1,2}$ 6.0 Hz), 5.4–6.9 (6-proton multiplets, H-2,3,4,5,6,6'), 8.1 (6-proton singlets, Me_2).

Anal. Calc. for $C_8H_{17}AsO_5S$: C, 32.01; H, 5.58. Found, C, 31.77; H, 5.58.

6-Se-Dimethylarsino-6-seleno-β-D-glucopyranose (**9**). — To a suspension of 6,6'-diselenobis(β-D-glucopyranose)[7] (3 g) in 1,2-dichloroethane (30 ml) was added tetramethyldiarsine[9] (3 ml) dropwise, under nitrogen, with stirring. The mixture was kept overnight at room temperature, whereupon a yellow syrup appeared at the bottom of the flask. The supernatant was decanted off and the heavy yellow syrup, after three washings with dichloromethane, gave a yellow solid (3.1 g, 72.1%), having a poorly defined m.p.; n.m.r. (deuterium oxide): τ 4.2 (1-proton doublet, H-1, $J_{1,2}$ 6.0 Hz), 5.3–6.8 (6-proton multiplets, H-2,3,4,5,6,6'), 8.0 (6-proton singlet, Me_2).

Anal. Calc. for $C_8H_{17}AsO_5Se$: C, 27.68; H, 4.94. Found: C, 27.30; H, 4.92.

Rates of alkaline hydrolysis of –C–S–AsMe$_2$ and –C–Se–AsMe$_2$ derivatives. — In this, and in prior work[1], it has been observed that, under alkaline conditions, it is possible to deacetylate the thio sugar ester without disturbing the –C–S–$AsMe_2$ linkage. However, under similar conditions, the –C–Se–$AsMe_2$ linkage is also subject to hydrolysis. For this reason, the rates of hydrolysis of **5** and **9** were measured. The measurements were based upon titration of the dimethylarsinic acid formed by very rapid atmospheric oxidation of the probable hydrolytic intermediate, dimethylhydroxyarsine.

$$R\text{–}X\text{–}AsMe_2 \xrightarrow[H_2O]{OH^-} ROH + HS^- + [HOAsMe_2] \xrightarrow[\text{rapid}]{O_2} HO\text{–}\overset{\overset{O}{\|}}{As}Me_2$$

X = S, Se; R = sugar moiety

Samples of about 0.2 g of **5** and **9** were separately dissolved in 0.1M aqueous potassium chloride and the pH was adjusted to 10.75 with potassium hydroxide. The total volume was adjusted to 100 ml and 0.1M potassium hydroxide was added periodically from a microburette to maintain the pH at its initial value. The volume of titrant needed to maintain the pH was plotted as a function of time. The half lives, namely, the times required for the concentrations of the respective compounds to reach half of the initial values, were readily calculated. For compound **5**, at 25° $t_{1/2}$ = 24 h 30 min, whereas, for compound **9**, the corresponding value is 3 h 54 min. It is apparent that, in an alkaline medium, the –C–Se–As< bonded compound is hydrolyzed about six and a half times faster than the sulfur compound.

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