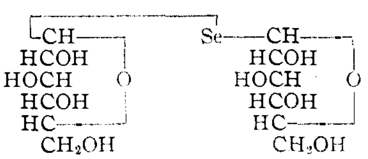
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF STANFORD UNIVERSITY]

The Preparation and Properties of Phenyl β-D-Selenoglucoside and its Tetraacetate

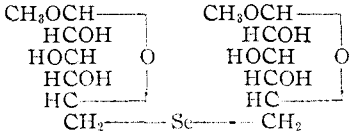
BY WILLIAM A. BONNER* AND ANN ROBINSON

Although naturally occurring thioglycosides have been known for over a hundred years,[1] and the first synthetic thioglycoside was prepared forty years ago,[2] the chemical reactions shown by these substances have only recently begun to receive extensive study,[3] and the selenium analogs of these simple thioglycosides have never been reported.

Relatively few selenium-containing sugars are known. The literature records several compounds related to β-D-glucosyl selenide,[4,5] (I), and methyl 6-seleno-bis-(6-desoxy-β-D-glucoside),[6] (II). The latter compound has been oxidized to the corresponding selenoxide.[7] It has been our purpose herein to prepare and study the physical and chemical properties of phenyl β-D-selenoglucoside, (III), and its tetraacetate as representatives of the unknown simple aryl selenoglycosides.



I



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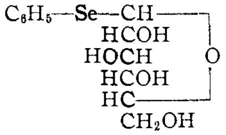

III

After the general method of Schneider[8] and Purves[9] for the synthesis of acetylated thioglycosides, we have treated tetraacetylglucosyl bromide with an alcoholic solution of potassium selenophenylate. Yields of phenyl tetraacetyl-β-D-selenoglucoside ranging from 37–87% were obtained, along with varying amounts of a yellow by-product which was probably diphenyl diselenide. The yield and purity of the product proved rather sensitive to reaction conditions, and best results were obtained when the reaction was conducted in subdued light. It is probable that an inert atmosphere during reaction would further improve the yield, since selenophenol is readily oxidized and colors rapidly on exposure to air.

Pure phenyl tetraacetyl-β-D-selenoglucoside is an odorless, white, crystalline solid, m. p. 99.5–100°, $[\alpha]^{25}\text{D}$ − 27.3° (chloroform). After thorough drying over phosphorus pentoxide it is stable indefinitely. A moist product, or a solution of the substance becomes yellow-brown in a few days. A slightly alkaline solution shows coloration in a few hours.

Phenyl tetraacetyl-β-D-selenoglucoside is readily deacetylated by saturated ammoniacal methanol after the method of Purves.[9] The resulting phenyl β-D-selenoglucoside is an odorless, white solid, m. p. 107.5–108°, $[\alpha]^{20}\text{D}$ − 52.5° (2-propanol). It is stable when stored in an anhydrous atmosphere, but rapidly colors and develops a disagreeable odor when moist or exposed to moist air.

Both phenyl β-D-selenoglucoside and its acetate showed a positive Molisch test, and reacted negatively to Fehling solution and Tollens reagent. Both products gave diphenyl diselenide, however, when the mixtures for the latter tests were permitted to stand for several hours. When attempts were made to subject phenyl β-D-selenoglucoside to periodic acid oxidation, elemental iodine formed in the mixture. The same observation was made when periodic acid acted on the tetraacetate. This behavior, obviously caused by oxidation of the selenium atom, has prevented our experimental verification of the ring size of these compounds. In view of the mode of preparation, however, there is really no question about the presence of the pyranoside structure. It is interesting to note that both phenyl β-D-thioglucoside and its acetate also produce elemental iodine when treated with periodic acid or sodium periodate[10] in precisely the same manner as observed here. This behavior contrasts sharply with the observations of Wolfrom and co-workers,[11] who were able to prove by periodate oxidation that the ethyl tetraacetyl-α-D-thioglucoside of Schneider and Sepp[12] possessed the thiofuranoside structure as previously sus-

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[*] Harvard College B.S. 1941.

[1] Henry and Garot, *J. Chem. Medicale*, **1**, 439, 467 (1825).

[2] Fischer and Delbrück, *Ber.*, **42**, 1476 (1909).

[3] (a) Bonner, THIS JOURNAL, **70**, 770, 3491 (1948); (b) Bonner and Drisko, *ibid.*, **70**, 2435 (1948); (c) Hudson and co-workers, *ibid.*, **70**, 310, 4052 (1948); **69**, 921, 1672 (1947); **65**, 1477 (1943).

[4] Schneider and Wrede, *Ber.*, **50**, 793 (1917).

[5] Wrede, *Biochem. Z.*, **83**, 96 (1917); *Ber.*, **52**, 1756 (1919); *Z. physiol. Chem.*, **112**, 1 (1920); Schneider and Beuther, *Ber.*, **52**, 2135 (1919).

[6] Wrede, *Z. physiol. Chem.*, **115**, 284 (1921).

[7] Wrede and Zimmermann, *ibid.*, **148**, 65 (1925).

[8] Schneider, Sepp and Stiehler, *Ber.*, **51**, 270 (1918).

[9] Purves, THIS JOURNAL, **51**, 3619 (1929).

[10] Bonner and Drisko, unpublished observations.

[11] Wolfrom, Waisbrot, Weisblat and Thompson, THIS JOURNAL, **66**, 2063 (1944).

[12] Schneider and Sepp, *Ber.*, **49**, 2054 (1916).

pected. Our observations in this connection will be reported more fully at a later date.

A number of attempts were made to oxidize the selenium atom in phenyl tetraacetyl-β-D-selenoglucoside to the selenoxide state. Both peroxide and permanganate were employed, in the manner used successfully[3b] in the oxidation of thioglycosides to the sulfone state. In no case, however, were we able to obtain a selenium-containing carbohydrate product. From both oxidations impure sirups resulted. Since these were occasionally water-soluble, and since partial deacylation seemed[3b] to accompany the oxidation of thioglycosides, these sirups were reacetylated. Such crystalline material as could be isolated after reacetylation proved to be α-D-glucose pentaacetate. Also, during the peroxide oxidations yellow or orange colors developed, and diphenyl diselenide was isolated from one of the permanganate oxidations. These facts seem to point to a cleavage of the selenium–oxygen bond under oxidizing conditions. This behavior of the selenium atom in the number one position contrasts to its behavior in the number six position, where permanganate oxidation produces a true selenoxide.[7]

Experimental

Phenyl Tetraacetyl-β-D-selenoglucoside.—A mixture of selenophenol[13] (3.3 ml., 0.031 mole) and potassium hydroxide (1.28 g., 0.0229 mole) in ethanol (50 ml.) was added to a solution of tetraacetyl-α-D-glucopyranosyl bromide (9.4 g., 0.0229 mole) in dry chloroform (50 ml.). The solution was refluxed for forty minutes, cooled, washed twice with water, thrice with saturated sodium bicarbonate, once with five per cent. sodium hydroxide, and twice with water. The solution became orange during refluxing and reddish during washing. It was dried over anhydrous sodium sulfate, and the chloroform distilled at diminished pressure. The crude product (10.5 g., 97%) was recrystallized several times from 2-propanol to give 9.8 g. (87.6%) of pure product, m. p. 99.5–100° (cor.), $[\alpha]^{25}\text{D}$ −27.2° (*c*, 1.652; chloroform).

Anal. Calcd. for $C_{12}H_{12}O_5Se(COCH_3)_4$: C, 49.4; H, 4.77; acetyl, 35.9. Found: C, 49.2; H, 4.93; acetyl,[14] 35.9.

In subsequent preparation on a larger scale difficulties sometimes arose in the purification of the product, especially when the solutions were unduly exposed to heat. Thus in one preparation on twice the previous scale a reddish oil was obtained, causing a low yield and very impure product. Customary methods of decolorization of these solutions, *i. e.*, boiling the solutions in various solvents with Norit, proved ineffective for purification. Permitting a solution of the impure product in ethanol to traverse an eight-inch column of alternate half-inch layers of Norit and Celite achieved purification, but led to low yields. In later experiments dealing with the separation of α-D-glucose pentaacetate from diphenyl diselenide it was found that the latter was soluble in cold hexane whereas the former was not. As was hoped, this solvent proved very effective in removing the colored impurity in some of the present preparations, and permitted the recovery of good yields of pure product from malodorous, colored samples or from impure second crops in the mother liquors. In all of these cases, solution in hot hexane followed by seeding and cooling resulted in pure products.

Phenyl β-D-Selenoglucoside.—Phenyl tetraacetyl-β-D-selenoglucoside (2.0 g.) was dissolved in methanol (30 ml.) which had been saturated with ammonia from a tank. The solution was permitted to stand overnight, then evaporated in an air stream to yield 1.61 g. of a semicrystalline paste. This was triturated five times with hot absolute ether to leach out acetamide. The undissolved sirupy residue weighed 1.47 g. This was dissolved in 2-propanol and hexane added. Chilling to dry-ice temperature and scratching produced a solid which redissolved on warming to room temperature. The solid remaining on the stirring rod provided seed. On inoculation of the solution and permitting it to stand for several days at room temperature 1.10 g. (83%) of crude product, m. p. 60–90°, was obtained. This was recrystallized several times from a mixture of 2-propanol and hexane to give the pure product, m. p. 107.5–108°, $[\alpha]^{20}\text{D}$ −52.5° (*c*, 3.41; 2-propanol).

Anal. Calcd. for $C_{12}H_{16}O_5Se$: C, 45.18; H, 5.04. Found: C, 45.10; H, 5.22.

Tests on Phenyl β-D-Selenoglucoside and Its Acetate: Fehling Solution.—Both phenyl β-D-selenoglucoside and its acetate were non-reducing when boiled with Fehling solution for short periods. When the reaction mixtures were permitted to stand overnight, however, a yellowish solid formed. This was filtered and dried, and proved to be diphenyl diselenide, m. p. 60–61°.

Tollens Reagent.—Again both the acetylated and deacetylated selenoglucoside gave negative reactions under standard conditions, no silver mirror being formed. Upon standing overnight, however, diphenyl diselenide, m. p. 60–61°, was again obtained.

Periodic Acid.—When phenyl β-D-selenoglucoside was dissolved in water and treated with approximately 0.5 *N* periodic acid, a dark brown solution was immediately obtained. Extraction of a portion of this solution with carbon tetrachloride imparted the characteristic violet color of iodine in organic solvents to the carbon tetrachloride layer. Treatment of another portion of the dark brown solution with starch solution gave the characteristic starch–iodine color. An acetylated sample of the selenoglucoside showed similar behavior. Aqueous solutions of iodic acid also formed iodine when allowed to act upon phenyl β-D-selenoglucoside or its acetate.

Oxidations of Phenyl Tetraacetyl-β-D-selenoglucoside.—A number of attempts were made to oxidize the selenium atom in the selenoglucoside to the selenoxide state. Typical results for oxidations employing both hydrogen peroxide and potassium permanganate are recorded below.

Phenyl tetraacetyl-β-D-selenoglucoside (1 g.) was dissolved in acetic acid (5 ml.) and treated with 30% hydrogen peroxide (2 g.). The solution rapidly became yellow, after which the color faded. After standing two hours the mixture was treated with excess formaldehyde to reduce the remaining peroxide, then evaporated to dryness in an air stream at room temperature. A clear, colorless sirup resulted which proved soluble in water, ethanol, and dioxane but insoluble in ether or hexane. Upon drying *in vacuo* small amounts of crystals formed in the sirup, but the quantity could not be increased by treatment with solvents. The water-solubility of the sirup suggested that deacetylation accompanied the oxidation, and the sirup was therefore reacetylated with acetic anhydride (10 ml.) and pyridine (10 ml.). After twenty-four hours the yellow solution was poured into ice water and extracted with ether. The extract was washed with water, 10% hydrochloric acid, water, saturated bicarbonate solution, and water. After drying over sodium sulfate the solvent was evaporated leaving a white solid, m. p. 80–95°. This was recrystallized several times from 2-propanol and water to give pure α-D-glucose pentaacetate, m. p. 111–112°, mixed m. p. unchanged.

Phenyl tetraacetyl-β-D-selenoglucoside (1 g.) was dissolved in acetic acid (10 ml.) and potassium permanganate (0.3 g.) was added. The mixture was heated for thirty minutes on the steam-bath, then treated with sodium

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[13] Prepared by the method of Foster in "Organic Syntheses," Vol. XXIV, John Wiley & Sons, New York, N. Y., 1944, p. 89. This material was stored under nitrogen in a sealed ampule until used.

[14] Analyzed by the method of Kunz and Hudson, THIS JOURNAL, **48**, 1978 (1926).

bisulfite and additional acetic acid (15 ml.) to reduce the remaining permanganate and manganese dioxide. Half of the resulting yellow solution was saturated with sodium chloride and extracted with ether. The extract was washed with water and bicarbonate solution, then dried over sodium sulfate. Evaporation of the solvent gave an orange paste which was crystallized from 2-propanol to give yellow crystals, m. p. 56–58°. The second half of the original solution deposited white crystals on standing, but these proved to be inorganic. The mother liquors from the second half were then treated as the original first half, yellow crystals again resulting. Both crops of crystals were recrystallized from a mixture of 2-propanol and water to give pure diphenyl diselenide, m. p. 61–61.5° (uncor.), mixed m. p. with an authentic sample 61–61.5°.

In another experiment phenyl tetraacetyl-β-D-selenglucoside (0.5 g.) in acetic acid (10 ml.) was treated with potassium permanganate (0.6 g.) and the mixture allowed to stand overnight. It was then diluted with water (50 ml.) and decolorized by addition of bisulfite. The colorless solution was extracted thrice with ether, and the extract washed and dried as before. Evaporation of the solvent yielded a clear sirup. Failing to crystallize from a mixture of dioxane and hexane, this was reacetylated with acetic anhydride (15 ml.) and pyridine (15 ml.). After standing the acetylation mixture was thrown into water and the product isolated as described under the peroxide oxidation. A small quantity of white solid, m. p. 80–99°, was recovered. Several recrystallizations from a mixture of 2-propanol and water gave pure α-D-glucose pentaacetate, m. p. 111–112°, mixed m. p. unchanged.

Summary

Phenyl tetraacetyl-β-D-selenoglucoside, the first example of a simple aryl glucoside containing a selenium atom in the number one position, has been synthesized by the action of selenophenol on tetraacetylglucosyl bromide under alkaline conditions.

Phenyl β-D-selenoglucoside has been readily prepared by the action of ammoniacal methanol on phenyl tetraacetyl-β-D-selenoglucoside.

Both phenyl β-D-selenoglucoside and its acetate are attacked by periodic acid with the formation of iodine, the selenium atom being oxidized. Both compounds are initially stable to Fehling solution and Tollens reagent, but form diphenyl diselenide on prolonged contact.

Attempts to oxidize the selenide linkage in phenyl tetraacetyl-β-D-selenoglucoside to the selenoxide state with either peroxide or permanganate resulted in cleavage with the formation of diphenyl diselenide and (after reacetylation) α-D-glucose pentaacetate.

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The Action of Bromine on Phenyl Tetraacetyl-β-D-selenoglucoside

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The bromination of phenyl tetraacetyl-D-glucosides and phenyl tetraacetyl-β-D-thioglucoside follow different courses. Nuclear bromination occurs in the first process,[1] while cleavage of the thiophenyl group with formation of α-D-glucose pentaacetate is observed in the second.[2] The mechanism of the latter reaction has recently been investigated.[3] In view of the unexpected behavior of the thioglucoside, we have extended bromination studies to the recently reported[4] selenium analog.

When phenyl tetraacetyl-β-D-selenoglucoside in acetic acid was treated with seven or more molecular equivalents of bromine, a bright orange precipitate instantly formed. After standing several hours the mixture was diluted with water, whereupon the precipitate dissolved. From an ether extract of the diluted mixture it was possible to isolate α-D-glucose pentaacetate in fair yield. Upon standing, the aqueous solution from the ether extraction deposited substantial amounts of diphenyl diselenide.

The action of bromine in acetic acid on phenyl tetraacetyl-β-D-selenoglucoside thus follows the same pattern observed for the corresponding thioglucoside, namely, cleavage of the bond between the number one carbon and the selenium atoms with simultaneous formation of α-D-glucose pentaacetate from the carbohydrate moiety. In some cases, however, there seems to be a difference in the fate of the cleaved aglucone. Thus with molecular ratios of bromine to phenyl tetraacetyl-β-D-selenoglucoside as high as 9.3:1 we invariably noted the formation of diphenyl diselenide from the selenium moiety, whereas diphenyl disulfide could be isolated as such from the thioglucoside reaction only when the molecular ratio of bromine to phenyl tetraacetyl-β-D-thioglucoside was on the order of 1:1.[3] It is interesting to note that nuclear bromine was absent in both the diselenide and the disulfide. The significance of this is discussed below.

In another series of experiments the orange precipitate instantly observed on addition of bromine to the acetic acid solution of pheny tetraacetyl-β-D-selenoglucoside was filtered, washed, and dried. On standing in a desiccator it changed from an amorphous orange powder to dark red crystals having a metallic appearance. On treatment with water these readily dissolved, and diphenyl diselenide slowly precipitated from the aqueous solution. The mother liquors from the precipitation of the diphenyl diselenide

* Harvard College B.S., 1941.

[1] Hurd and Bonner, THIS JOURNAL, **67**, 1764 (1945).

[2] Bonner, *ibid.*, **70**, 770 (1948).

[3] Bonner, *ibid.*, **70**, 3491 (1948).

[4] Bonner and Robinson, *ibid.*, **72**, 354 (1950).