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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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF STANFORD UNIVERSITY]

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

BY WILLIAM A. BONNER* AND ANN ROBINSON

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).

proved optically inactive, suggesting an absence of carbohydrate material in the orange solid intermediate. This absence was further confirmed by the isolation of α-D-glucose pentaacetate on processing the original mother liquors from which the precipitate was isolated. We have made no attempt to purify the intermediate product due to its vile odor and its obvious instability. Bromine analyses on the crude, dried, red crystals above, however, indicated a bromine content of 56.3%. In view of the lack of purity and instability of the sample this figure is in fair agreement with the 60.5% bromine required by the salt $C_6H_5SeBr_2{}^+Br^-$. The suggestion of a salt-like character for the red crystals is made on the basis of their water solubility and the absence of nuclear bromine in the diphenyl diselenide to which they reverted in aqueous solution. The deactivating effect of a positively charged selenium atom linked to the aromatic nucleus would prevent nuclear substitution. A suggestion that the formation of salts like $RSBr_2{}^+ Br^-$ represents the fate of the thio-aglucone in the cleavage of thioglucosides with bromine has already been made,[3] and we find here a rough experimental confirmation of this idea. Unfortunately our bromine analysis on the crude, dried intermediate does not permit an unambiguous distinction between the proposed structure and diphenyl diselenide tetrabromide (50.6% Br), but we prefer the proposed structures for the following reasons, (a) our analytical figures approximate the composition of the proposed structure more closely, and (b) in view of the absence of nuclear bromine in the diphenyl diselenide isolated it is hard to see why the tetrabromide structure should give a high bromine analysis. In any case it is clear that the first step in the mechanism of the cleavage of the selenoglucoside is the addition of bromine to the selenium atom, quite analogous to the first step in the thioglucoside cleavage.

That the second step in the selenoglucoside cleavage is the rupture of the selenium–carbon bond in the adduct with formation of acetobromoglucose has also been determined experimentally. When bromine in carbon tetrachloride acted on phenyl tetraacetyl-β-D-selenoglucoside, the same orange precipitate formed immediately. This was filtered, and from the filtrate acetobromoglucose could be isolated. The second step in the selenoglucoside cleavage thus parallels that of the thioglucoside cleavage, and since the conversion of acetobromoglucose to α-D-glucose pentaacetate by action of bromine in acetic acid has already been demonstrated,[3] it seems safe to say that the cleavage of phenyl tetraacetyl-β-D-selenoglucoside with bromine in acetic acid proceeds through a mechanism identical with that involved in the cleavage of thioglucosides.

Experimental Part

Phenyl Tetraacetyl-β-D-selenoglucoside and Bromine in Acetic Acid.—Phenyl tetraacetyl-β-D-selenoglucoside (3.6 g. 0.0074 mole) was dissolved in acetic acid (40 ml.) and bromine (11 g., 0.0688 mole) was added, causing copious precipitation of an orange colored solid. The mixture stood for three hours and was thrown into an excess of ice-water, whereupon the orange precipitate dissolved. The excess bromine was destroyed by the addition of sufficient sodium bisulfite. The clear solution resulting gradually became yellow and developed an obnoxious odor. The solution was extracted several times with ether, and the extract washed twice with water, twice with saturated sodium bicarbonate solution, once with 10% sodium hydroxide solution, and twice with water. At this point the disagreeable odor was absent. The yellowish ethereal solution was filtered twice through Norit to effect decolorization, was dried over anhydrous sodium sulfate, and the solvent was distilled. There remained 1.13 g. (39%) of crude α-D-glucose pentaacetate, m. p. 97–110°. Three recrystallizations from 2-propanol gave the pure product, m. p. 112–112.5°, $[\alpha]^{28}\text{D}$ 102° (*c*, 0.900; chloroform), mixed m. p. with an authentic sample 112°. The aqueous layer from the original ether extraction deposited yellow crystals (0.73 g.) on standing. Four recrystallizations from a mixture of 2-propanol and water gave pure diphenyl diselenide, as shown by its melting point (61–61.5°) and analysis.

Anal.[5] Calcd. for $C_{12}H_{10}Se_2$: C, 46.16; H, 3.24; Se, 50.60. Found: C, 46.29, 46.21; H, 3.33, 3.36; Se, 50.24, 50.51.

Further experiments conducted at low temperature (5°), at high temperature (100°) and for a shorter reaction time (10 minutes) led to no differences in the products or improvements in the yields.

The Orange Intermediate.—Phenyl tetraacetyl-β-D-selenoglucoside (1.0 g.) in acetic acid (20 ml.) was treated with bromine (2.5 g.). After fifteen minutes the mixture was filtered through sintered glass and the orange precipitate rinsed several times with acetic acid. The red filtrate was diluted, treated with bisulfite, extracted with ether, and processed as before. There resulted 0.14 g. of crude α-D-glucose pentaacetate, m. p. 111–113° after two recrystallizations from 2-propanol and water. The diluted filtrate deposited a small quantity of diphenyl diselenide, m. p. 60.5–61.5°, on standing.

The orange precipitate was transferred to a vacuum desiccator and dried over phosphorus pentoxide, occasional re-evacuation being employed to flush out bromine vapor. On standing *in vacuo* the amorphous red precipitate changed to extremely vile-smelling, red-grey crystals with a metallic appearance. A portion of the dried crystals (0.105 g.) was dissolved in water (25 ml.). The clear solution became slightly pink, then colorless, and a yellow-white precipitate (0.04 g.) of diphenyl diselenide settled, m. p. 60–61° after recrystallization.

Quantitative bromine analyses were run on the crude, dried intermediate. Tenth gram samples were dissolved in water (10 ml.) and acidified with nitric acid (0.5 ml.). The precipitated diphenyl diselenide was filtered, and the filtrate treated with tenth normal silver nitrate. Duplicate runs gave silver bromide corresponding to 56.3% bromine in the intermediate. The theoretical bromine content of $C_6H_5SeBr_3$ is 60.5%.

Phenyl Tetraacetyl-β-D-selenoglucoside and Bromine in Carbon Tetrachloride.—Phenyl tetraacetyl-β-D-selenoglucoside (0.22 g.) in carbon tetrachloride (3 ml.) was treated with a solution of bromine (0.24 ml.) in the same solvent (2 ml.). The orange precipitate immediately formed, and after ten minutes was filtered and rinsed. The filtrate and rinsings were washed with bisulfite solution and bicarbonate solution as before, then dried and evaporated to yield 0.1 g. of amber sirup. This was crystallized from hexane to give a white solid shown to be impure acetobromoglucose by its m. p. (84–85°), a mixed m. p. with an authentic sample (85–88°), and its positive bromine analysis.

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(5) Performed by Huffman Microanalytical Laboratories, Denver, Colo.

Summary

Bromine in acetic acid reacts instantly with phenyl tetraacetyl-β-D-selenoglucoside to give an orange precipitate. From the filtrate of this orange precipitate α-D-glucose pentaacetate is recoverable in fair yield. The precipitate, which is probably a salt of the composition $C_6H_5SeBr_2^+Br^-$, reverts to diphenyl diselenide on treatment with water.

Bromine in carbon tetrachloride reacts with phenyl tetraacetyl-β-D-selenoglucoside to give the orange precipitate and acetobromoglucose.

A similarity in mechanisms of these reactions and the analogous cleavage of phenyl tetraacetyl-β-D-thioglucoside with bromine is pointed out.

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Diphenylethylamines. I. The Preparation of Tertiary Amines by the Grignard Reaction[1,2]

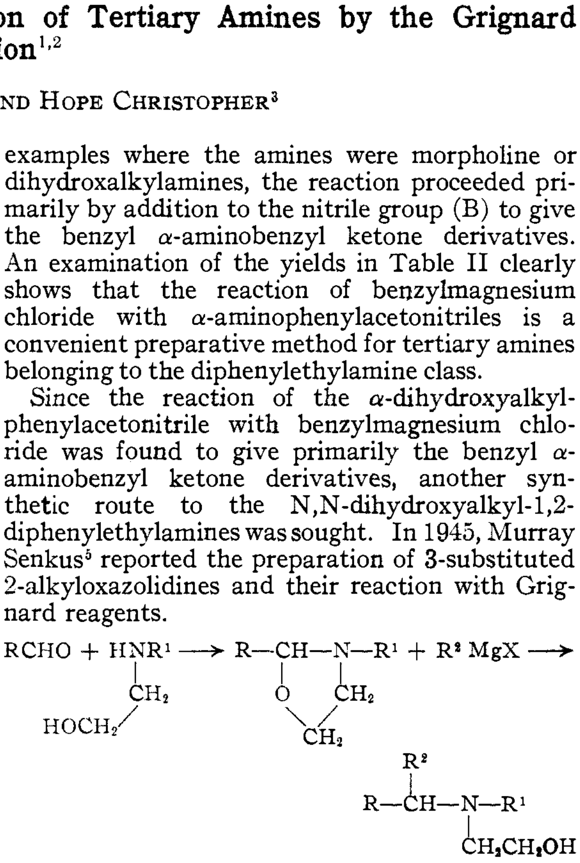
BY LOUIS H. GOODSON* AND HOPE CHRISTOPHER[3]

During the course of our work, it became desirable to synthesize a series of 1,2-diphenylethylamines possessing a tertiary nitrogen atom. It was hoped that these compounds would produce tumor necrosis and they were, therefore, to be screened for this activity. Our first approach to this problem was through the alkylation of primary and secondary amines by the usual methods. Some amines reacted well; N-ethyl-1,2-diphenylethylamine, for example, gave a 70% yield of tertiary amine on reaction with ethyl bromide at 120–140°. Others were troublesome as witnessed by the 10% yield of tertiary amine isolated from the reaction mixture of piperidine and 1,2-diphenylethyl bromide. Stilbene was the major product in the latter reaction.

Grignard reagents (RMgX) are known[4] to react in one of three ways with α-amino nitriles $ArCH(CN)NR_2$, as follows: (A) replacement of the cyano group, yielding $ArCHRNR'_2$; (B) addition to the cyano group to form $RCOCHArNR'_2$; (C) removal of cyano groups from two moles of the nitriles giving rise to the coupled product, $[ArCH(NR'_2)\text{-}]_2$.

The type (C) coupling reaction has not been observed in this work. Both of the other two types of reactions (A and B) have been observed but, in each of the fourteen examples described here, one type of reaction (either A or B) predominated. In the examples where the α-aminophenylacetonitrile was prepared from piperidine, alkyl-substituted piperidines, or aliphatic secondary amines, it will be noted that good yields of replacement products (A) were obtained. In the examples where the amines were morpholine or dihydroxalkylamines, the reaction proceeded primarily by addition to the nitrile group (B) to give the benzyl α-aminobenzyl ketone derivatives. An examination of the yields in Table II clearly shows that the reaction of benzylmagnesium chloride with α-aminophenylacetonitriles is a convenient preparative method for tertiary amines belonging to the diphenylethylamine class.

Since the reaction of the α-dihydroxyalkylphenylacetonitrile with benzylmagnesium chloride was found to give primarily the benzyl α-aminobenzyl ketone derivatives, another synthetic route to the N,N-dihydroxyalkyl-1,2-diphenylethylamines was sought. In 1945, Murray Senkus[5] reported the preparation of 3-substituted 2-alkyloxazolidines and their reaction with Grignard reagents.



By the reaction of aromatic aldehydes and hydroxyalkylalkylamines or dihydroxyalkylamines, we have prepared a series of 3-substituted 2-aryloxazolidines (Table III) and treated each of them with benzylmagnesium chloride (Table IV). The aldehyde amine condensations and Grignard reactions proceeded rapidly and in good yields; for example, in the case of 2-phenyl-3-(2-hydroxyethyl)oxazolidine which was obtained in 91% yield from benzaldehyde and diethanolamine, the yield of purified N,N-di-2-hydroxyethyl-1,2-diphenylethylamine was 97%. This product was shown to be identical with the material obtained in 34% yield from the reaction of 1,2-diphenylethyl bromide and diethanolamine. In this particular series of compounds (Table

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* Harvard University Ph.D. 1940.

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[2] Presented befoie the Division of Organic Chemistry, Atlantic City, N. J., September 19, 1949.

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[4] Migrdichian, "The Chemistry of Organic Cyanogen Compounds," A. C. S. Monograph, No. 105, Reinhold Publishing Corp., New York, N. Y., 1947, p. 253.

[5] Senkus, THIS JOURNAL, 67, 1515 (1945).