[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY OF PRINCETON UNIVERSITY]

# Glycofuranosides and Thioglycofuranosides. V. The Hydrolysis of α-Ethylthioglucofuranoside

BY EUGENE PACSU AND E. JUSTIN WILSON, JR.

In 1937 Green and Pacsu[1] prepared α-ethylthioglucoside under experimental conditions which are known to yield only furanosides. This substance was found to be identical with Schneider's compound[2] which he described as the diastereomer of the β-ethylthioglucoside.[3] Since the latter thioglycoside was prepared from acetobromoglucose, which is known to give rise to pyranosides only, it became necessary to provide evidence which would show definitely the ring system present in α-ethylthioglucoside. By application of Hudson's rules of isorotation, Green and Pacsu calculated the specific rotation of α-ethylthioglucofuranoside to be 120.7° and that of α-ethylthioglucopyranoside to be 167°. The excellent agreement between the former value and the actually observed rotation (121°) indicated that Schneider's α-ethylthioglucoside possessed furanoid structure and was not the diastereomer of the β-ethylthioglucopyranoside. Confirmatory evidence was offered by the results of hydrolysis experiments, which showed that α-ethylthioglucoside hydrolyzed in 0.01 *N* hydrochloric acid at 98–100° very rapidly, the velocity constant, $K \times 10^5 = 6250$, being of the order given by furanosides. However, a curious effect noted by the authors during the process of hydrolysis led them to the following statement: "It is interesting to note that the final calculated rotation has never been reached. After the last reading, the rotation started slowly to rise, undoubtedly due to the recombination of the liberated mercaptan with the free sugar. After three hours of heating at 100° in a closed vessel, the observed rotation passed the initial value. . . . . This effect might be due to the formation of the α-thioglucopyranoside and will be investigated further." The assumption was made that the following reactions were taking place

$$\underset{(121°)}{\alpha\text{-ethylthioglucofuranoside}} \xrightarrow{0.01\ N\ \text{acid}}$$

$$\underset{(52.2°)}{\text{glucose}} + C_2H_5SH \xrightarrow{0.01\ N\ \text{acid}} \alpha\text{-ethylthioglucopyranoside}\ \underset{(\text{calcd. } 167°)}{}$$

evidently after a sufficient concentration of mercaptan and glucose was obtained. Since α-ethylthioglucopyranoside was shown to have a calculated rotation of 167°, the scheme was entirely plausible and the secondary formation in aqueous solution of the hitherto unknown thiopyranoside from the hydrolysis products of the thiofuranoside, although an unprecedented reaction, seemed quite probable. However, in our recent reinvestigation of this problem a few experiments sufficed to show that the true mechanism of the process must be much more complex than the changes assumed in the above scheme would indicate.

The first step in our work was to repeat the original hydrolysis experiment of Green and Pacsu. As is seen from Table I, the results were substantially the same except that the final rotation did not quite reach the original value.

TABLE I

CHANGE IN ROTATION DURING THE HYDROLYSIS OF 0.5297 G. OF α-ETHYLTHIOGLUCOFURANOSIDE IN 100 CC. OF 0.01 *N* HYDROCHLORIC ACID AT 100°

| Time, min. | Observed rotation 2-dm. tube | Specific rotation |
|---|---|---|
| 0 | 1.23° | 116.1° |
| 3.5 | 1.18 | |
| 6 | 1.10 | |
| 8.5 | 0.92 | |
| 12 | .76 | |
| 15.5 | .65 | |
| 25 | .54 | 63.4° (calcd. as glucose) |
| .. | .. | |
| 45 | .66 | |
| 90 | .95 | |
| 150 | 1.15 | |
| 180 | 1.18 | |
| 210 | 1.18 | 111.4° (calcd. as thioglucoside) |

The next step was to determine whether glucose and ethyl mercaptan would react in 0.01 *N* hydrochloric acid solution. A sample of glucose weighing 0.3690 g. was dissolved in 100 cc. of a saturated solution of ethyl mercaptan in 0.01 *N* hydrochloric acid containing approximately 1.5 g. of the mercaptan, an ample excess. The solution rotated 0.53°, but upon heating it at 100° the rotation dropped quickly, due to the mutarotation of glucose, reaching the value of 0.39° after twenty minutes. There was no fur-

(1) Green and Pacsu, THIS JOURNAL, **59**, 1205 (1937).

(2) Schneider and Sepp, *Ber.*, **49**, 2054 (1916).

(3) Schneider, Sepp and Stichler, *ibid.*, **51**, 220 (1918); Schneider, Gilk and Eisfeld, *ibid.*, **61**, 1244 (1928).

ther change in the rotation after two and one-half hours of heating. Since 0.39° corresponds to $[\alpha]_D$ 52.8°, the constant rotation of glucose, it was concluded that either there was no reaction possible, or else the mercaptan boiled off so that its concentration was insufficiently high. That the latter was not the case was shown by repeating the above experiment, this time in a pressure flask fitted with a stopcock for withdrawing samples. Upon heating the mixture at 100° on a water-bath for some hours, the same negative results were obtained. At this point it was of interest to ascertain whether the final rotation (111.4°) shown by the solution of the hydrolyzed furanoside was affected by the concentration of the mercaptan. Two samples of α-ethylthioglucofuranoside were dissolved in saturated ethyl mercaptan solutions in 0.01 *N* hydrochloric acid, the solutions placed in pressure flasks and hydrolyzed at 100° as before. The rotation values obtained were almost identical (110°) and agreed closely with those obtained from the hydrolysis without pressure, indicating that the mercaptan concentration made little difference.

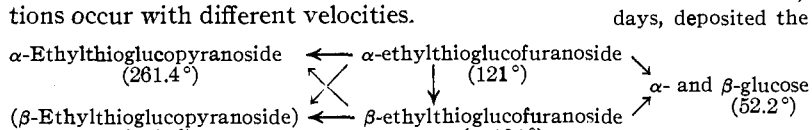
The presence of *d*-glucose in the final hydrolyzed solution was readily shown by a Fehling's test and, hence, it was now of value to determine the amounts of reducing sugar present at various stages of the hydrolysis. The Shaffer–Hartmann method[4] was first applied, but the results were inconsistent and useless, since both the initial thiofuranoside and the liberated mercaptan—as was shown by subsequent tests—reacted with one of the Shaffer–Hartmann solutions. The Bertrand method was next employed. In a preliminary test, α-ethylthioglucofuranoside was found to be non-interfering, but a saturated ethyl mercaptan solution immediately gave a yellow precipitate, which was found to contain copper and to reduce readily ferric sulfate, presumably being a cuprous mercaptide. It became evident, therefore, that the method could be used only after the mercaptan liberated during the hydrolysis had been removed from the samples. Accordingly, a sample of 0.4856 g. of the furanoside in 100 cc. of 0.01 *N* hydrochloric acid was hydrolyzed as before, and 20-cc. portions were withdrawn after twenty minutes, one hour, two hours and three hours; these rotated, respectively, 0.49, 0.82, 1.05, and 1.08°, the initial rotation being 1.16° ($[\alpha]^{20}_D$ 119.3). The samples were neutralized with small amounts of sodium bicarbonate and evaporated to dryness over concentrated sulfuric acid in a vacuum desiccator. Upon application of the Bertrand method to the samples, 37, 100, 153 and 180 mg. of glucose, respectively, were found to be present in the original hydrolyzate as against the calculated amount of 390 mg. of glucose. This result was entirely unexpected and it clearly showed that the change in rotation did not go parallel with the actual progress of the hydrolysis. In the first sample, the rotation of 0.49° indicated an 85% completion of the hydrolysis, whereas the glucose content proved that in reality only 9.5% of the thioglucoside had been hydrolyzed. In the last sample, the glucose content indicated that only 46.1% of the thioglucoside suffered hydrolysis, the non-hydrolyzed portion of the original furanoside having been changed into one or more products resistant to further hydrolysis under the conditions of the experiment. The conclusion is obvious that the previous value for the velocity constant, $K \times 10^5 = 6250$, based on the rotational data, is incorrect. With the present data on the glucose content a mean value of $K \times 10^5 = 590$ is obtained. Since but 46.1% of the theoretical yield of glucose was formed, neither of these constitutes the true value. Moreover, a steady drift in the magnitude of *K*, as shown by the successive values, 500, 587 and 686, is ample indication that the simple hydrolysis is complicated by the formation of other products. Evidently, the two points of interest as regards working up the hydrolyzed solution lay at the twenty-five minute point, or point of lowest rotation, and at the completion of the hydrolysis. A quantity of α-thiofuranoside hydrolyzed for twenty-five minutes under the adopted conditions should yield an easily hydrolyzable, negatively rotating substance, presumably the β-ethylthioglucofuranoside, while three hours' heating should yield a highly positive rotating material, presumably the α-ethylthioglucopyranoside, resistant to acid hydrolysis under the conditions of the experiment. In order to isolate the latter compound, a sample of α-ethylthioglucofuranoside in 0.01 *N* hydrochloric acid was heated for three hours at 100°, then the solution neutralized with silver carbonate and the glucose formed removed by fermentation with yeast. A non-reducing, colorless sirup was obtained which, on acetylation, gave a crystalline compound whose analysis and

(4) Shaffer and Hartmann, *J. Biol. Chem.*, **45**, 349, 365 (1921); Shaffer and Somogyi, *ibid.*, **100**, 695 (1933).

properties indicated that it was the α-ethylthioglucopyranoside tetraacetate, with m. p. 95° and $[\alpha]^{20}D$ 194.1° in chloroform solution. The deacetylated product, the α-ethylthioglucopyranoside, could not be secured in definite crystalline state, since it readily gelatinized in the organic solvents and was obtained in the form of small globules from ethyl acetate. Its high specific rotation, $[\alpha]^{20}D$ 261.4° in water solution instead of the calculated value of 167°, indicates that for some reason, as yet unknown, the principle of optical superposition does not apply even approximately to this thioglycoside.

For the isolation of the easily hydrolyzable, negative rotating substance, a sample of α-ethylthioglucofuranoside was treated as before, but after twenty-five minutes the reaction was stopped by cooling the solution and neutralizing it with silver carbonate. From the solution a good portion of unchanged starting material was recovered. The residue, on systematic extraction with ethyl acetate, finally yielded a small quantity of a colorless, non-reducing liquid ($[\alpha]^{20}D$ −104°, in water solution) representing the β-ethylthioglucofuranoside. This substance, just like the α-form from which it originated, but unlike the α- and β-ethylthioglucopyranoside, was very sensitive to acid and hydrolyzed rapidly, although incompletely, in dilute hydrochloric acid into glucose and ethyl mercaptan. Judging from the final rotation of the acid solution, a small portion of the substance changed into the acid resistant α- and perhaps also the β-ethylthioglucopyranoside.

The results of all these experiments indicate that about one-half of the α-ethylthioglucofuranoside hydrolyzes partly directly, and partly indirectly, through the β-isomer, into glucose and ethyl mercaptan. The other half of the starting material suffers a shift in its ring system and changes into the stable pyranosides, thereby escaping the hydrolyzing effect of the dilute acid used in the experiment. The whole process is of a very unusual nature for a glycoside and its mechanism can probably be expressed by the following diagram, where the single transformations occur with different velocities.




It appears to be noteworthy that while both the α- and β-ethylthioglucofuranoside and the β-ethylthioglucopyranoside display the normal relationship to each other in their optical behavior, no such claim can be made for the α-ethylthioglucopyranoside. Whether the *cis*-position of the $-SC_2H_5$ and the adjacent —OH group in the latter compound, causing one particular conformation of the mobile six-membered ring to prevail, would lead to such constitutional dissimilarity as to render the principle of optical superposition invalid, remains, at present, conjectural.

## Experimental

**Improved Preparation of α-Ethylthioglucofuranoside.**—To 16 g. of sodium hydroxide in 300 cc. of water, a solution of 54.3 g. of mercuric chloride in 800 cc. of water was added slowly at room temperature, under mechanical stirring. The yellow mercuric oxide formed was washed twice by decantation, then suspended in 500 cc. of water. In this suspension 57.2 g. of finely powdered glucose ethylmercaptal was dissolved at room temperature under vigorous mechanical stirring, then 500 cc. of a cold aqueous solution of 27.2 g. of mercuric chloride was introduced and the stirring maintained for one hour. After this time 5 cc. of pyridine was added to the mixture, which subsequently was filtered and the filtrate concentrated *in vacuo* at 40° to about 300 cc. Addition of a few cc. of *n*-octyl alcohol during the latter operation prevented foaming of the solution. From the concentrated solution, on cooling at 0°, about 23 g. of α-ethylthioglucofuranoside separated. From the mother liquor of the crystals, on evaporation *in vacuo* to dryness and recrystallization of the residue from alcohol, 7 g. of the same material was isolated. The united products were recrystallized from 200 cc. of hot water; yield 28 g., or 63% of the theoretical. The m. p., 153–157°, and specific rotation, 120.7°, in water solution, agreed closely with the values found previously.

**Preparation of α-Ethylthioglucopyranoside and its Tetraacetate from α-Ethylthioglucofuranoside.**—A 3-g. sample of α-ethylthioglucofuranoside was dissolved in 200 cc. of hot 0.01 *N* hydrochloric acid and the solution heated at 100° for three hours. The solution was then cooled and neutralized with silver carbonate, filtered and the filtrate treated with hydrogen sulfide to remove any dissolved silver salt. The solution rotating 110° was evaporated *in vacuo* to a sirup which was dissolved repeatedly in 30 cc. of water, each time the solutions being filtered and evaporated to a thin sirup. Finally, the solution of the residue was kept with yeast at 40° for two days to ensure removal of all glucose. After filtration of the yeast with carbon, the solution was again evaporated to a colorless, non-reducing sirup with $(\alpha)^{20}D$ 151°. The ethyl acetate solution of the residue, on standing in the ice-box for several days, deposited the α-pyranoside contaminated probably with the β-isomer in the form of small, glassy buttons rotating $(\alpha)^{20}D$ 170.5° in water solution. Since no further purification could be attained by recrystallization, the substance was converted into its acetate. For this purpose 1 g. of the sirup was heated at 100° for one hour with 0.1 g.

of fused sodium acetate in 10 cc. of acetic anhydride in a distilling flask. After this time the solution was evaporated *in vacuo* to a half solid mass which was shaken with a cold solution of sodium bicarbonate. By extraction with chloroform and after evaporation of the latter solvent, a partly crystalline solid was obtained, which was recrystallized first from pure methyl alcohol, then from methyl alcohol containing a little water. About 1 g. of small, colorless, prismatic needles was obtained, m. p. 95°, specific rotation 194.1° (0.1612 g. substance, 10 cc. of chloroform, 2-dm. tube, rotation 6.26° to the right). The acid equivalent was found by saponifying at 0° 0.2127 g. of substance with 30 cc. of 0.1 *N* sodium hydroxide aqueous solution for two hours; the alkali used up was 21.7 cc. as compared with the calculated value 21.67 cc. The substance was very soluble in most of the organic solvents.

On deacetylation according to the method of Zemplén and Pacsu,[5] the acetate gave rise to pure α-ethylthioglucopyranoside with $(\alpha)^{20}D$ 261.5° (0.2 g. of substance, 10 cc. of water solution, 2-dm. tube, rotation 10.46° to the right). The substance could not be obtained in definite crystalline state, since it gelatinized readily on cooling its alcoholic or acetone solution. From ethyl acetate solution, on keeping it at low temperature, the substance separated in the form of small globules of amorphous character. For analysis, a 0.15-g. sample of the finely powdered and dried substance in 5 cc. of water was mixed with 1 cc. of a hot, saturated solution of mercuric chloride and the mixture was kept immersed in boiling water for twenty minutes. After this time the precipitate was filtered, washed with a little water and dried at 100°; calcd. $C_2H_5S\cdot HgCl$, 0.2115 g.; found, 0.1988 g. The filtrate, containing a calculated quantity of 0.1204 g. of *d*-glucose, showed $(\alpha)^{20}D$ 52.7° (10 cc. of solution, 2-dm. tube, rotation 1.27° to the right), which agrees closely with the constant rotation of that sugar in pure water.

**Preparation of β-Ethylthioglucofuranoside from α-Ethylthioglucofuranoside.**—Thirteen grams of α-ethylthioglucofuranoside was dissolved in 495 cc. of boiling water ($\alpha^{20}D$ 6.25°, 2-dm. tube), then 5 cc. of *N* hydrochloric acid was added to the solution, which was subsequently kept at 100° for twenty-five minutes, when the rotation was found to be 2.67°. The acid solution then was neutralized immediately with 5 cc. of *N* alkali and evaporated *in vacuo* to dryness. About 3 g. of unchanged crystalline starting material was recovered by recrystallization of the residue from water. The filtrate was evaporated *in vacuo* to a thin sirup which was extracted in small portions with about 100 cc. of boiling ethyl acetate. The united solutions on cooling at 0° deposited a thin sirup which was discarded and the clear ethyl acetate solution was evaporated *in vacuo* to a thin liquid with $(\alpha)^{20}D$ − 41° in water solution. This substance was now extracted at room temperature with about 80 cc. of ethyl acetate and the solution, after treatment with decolorizing carbon, was kept at 0° for several days. The sirup which separated during this time was again rejected and the supernatant solution evaporated to a liquid with $(\alpha)^{22}D$ −70°. The procedure was repeated but this time the substance was extracted with ice-cold ethyl acetate. The residue obtained from the solution had a specific rotation −92°. Further purification was attained by the extraction of the liquid with a mixture of cold ethyl acetate and absolute ether yielding a residue rotating −101° in water solution. A final extraction with about 300 cc. of absolute ether gave a small quantity (about 0.4 g.) of a colorless, non-reducing, thin liquid with $(\alpha)^{20}D$ −104° (0.0685 g. of substance; 1.5 cc. of water solution; 1-dm. tube; rotation 4.75° to the left). For analysis 0.1643 g. of the β-ethylthioglucofuranoside in 5 cc. of water was treated with 1 cc. of a hot, saturated solution of mercuric chloride in the manner described for the α-pyranoside. Calcd. $C_2H_5SHgCl$: 0.2207 g.; found, 0.2183 g. The filtrate containing a calculated amount of 0.1320 g. of glucose had $(\alpha)^{20}D$ 53° (10 cc. of solution, 1-dm. tube, rotation 0.70° to the right) in good agreement with the constant rotation of *d*-glucose. The new thiofuranoside was found to be very sensitive to acid and it hydrolyzed rapidly at elevated temperature, but more slowly at room temperature, into its components. To a 0.0317-g. sample of the substance in 1.5 cc. of water two drops of hydrochloric acid was added and the solution was kept at room temperature for about two weeks. During this time the initial rotation of −2.2° changed to +1.25°, corresponding to a final rotation of $(\alpha)^{20}D$ 73.5 calculated on the assumption that complete hydrolysis took place yielding 0.0255 g. of *d*-glucose. This experiment showed that during the hydrolysis a small portion of the furanoside must have changed into a higher rotating substance, presumably into the α-pyranoside.

On acetylation with sodium acetate and acetic anhydride, the β-ethylthioglucofuranoside gave a sirupy tetraacetate with $(\alpha)^{20}D$ −53.1° (0.2367 g. of substance, 10 cc. of chloroform solution, 2-dm. tube; rotation 2.51° to the left). In an acetyl estimation 0.2000 g. of the substance required 20.3 cc. of decinormal alkali; calcd. for four acetyls, 20.7 cc.

**The Rotations of the Tetraacetates of α-Ethylthioglucofuranoside and β-Ethylthioglucopyranoside in Chloroform Solutions.**—Both compounds have been described in previous publications by Schneider and co-workers,[1,2] but the rotations were not recorded in chloroform solutions. Their procedure was repeated and the substances were obtained in good yields. The specific rotation of α-ethylthioglucofuranoside tetraacetate was found to be 150.0° (0.2526 g. of substance, 10 cc. of chloroform solution, 2-dm. tube, rotation 7.58° to the right). The specific rotation of β-ethylthioglucopyranoside tetraacetate was found to be −25.6° (0.1464 g. of substance, 10 cc. of chloroform solution, 2-dm. tube, rotation 0.75° to the left).

**The Rotation of Glucose Ethylmercaptal in Water Solution.**—Green and Pacsu[1] reported that from the combined mother liquors of several α-ethylthioglucofuranoside preparations a small amount of an unidentified material with $(\alpha)^{20}D$ −37° in water solution was obtained. On closer investigation the substance turned out to be unchanged glucose ethylmercaptal, whose specific rotation was given by Emil Fischer[6] to be −29.8°. Since Fischer's measurement was carried out at 50°, it became evident that the deviation in the rotations was due to a temperature effect. An authentic sample of glucose ethylmercaptal showed $(\alpha)^{20}D$ −37.4° (0.2870 g. of substance, 25 cc. of water solution, 2-dm. tube, rotation 0.86° to the left).

(5) Zemplén and Pacsu, *Ber.*, **62**, 1613 (1929).

(6) Fischer, *Ber.*, **27**, 673 (1894).

## Summary

Based on the rotational data, the velocity constant of the hydrolysis of α-ethylthioglucofuranoside in 0.01 N hydrochloric acid at 100° was found by Green and Pacsu to be $K \times 10^5 = 6250$. It has now been shown that the change in rotation does not go parallel with the actual progress of the hydrolysis. Quantitative estimation of the glucose formed during the reaction indicates that only 9.5% of the thioglucofuranoside is hydrolyzed when the drop in rotation shows an 85% completion of the hydrolysis.

Working up the solutions after twenty-five minutes and three hours of hydrolysis, two new thioglycosides, β-ethylthioglucofuranoside and α-ethylthioglucopyranoside, respectively, have been isolated. From the latter compound a crystalline tetraacetate has been prepared. A possible mechanism is suggested for this unprecedented hydrolysis, in which about one-half of the α-ethylthioglucofuranoside changes into glucose and mercaptan whereas the other half escapes the hydrolyzing effect of the acid by shifting the furanoid ring into the acid resistant pyranoid ring.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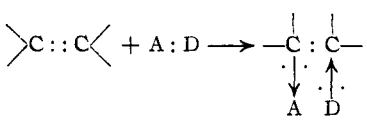
[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF NOTRE DAME]

# Solvent Effects in Addition Reactions. I. Addition of Hydrogen Bromide and Chloride to Cyclohexene and 3-Hexene

BY S. FIDELIS O'CONNOR, L. H. BALDINGER, R. R. VOGT AND G. F. HENNION

## Introduction

In many additions to unsaturated carbon compounds it is commonly believed that an electron-seeking reagent (A) accepts a pair of electrons from one of the unsaturated carbon atoms while a nucleus-seeking reagent (D) donates a pair of electrons to the other unsaturated carbon atom. The two addenda apparently may exist as separate molecules, ions or fragments or originally may be united in the same molecule.



Opinions differ as to the order of these steps. Ingold[1] cited evidence to show that the electron-seeking or positive addendum is attached first and a similar mechanism has been employed by Whitmore[2] to explain the rearrangement of intermediate positive organic fragments. On the other hand, Ogg[3] advanced the theory that addition of the nucleus-seeking or negative addendum is the first step.

Regardless of which addendum is attached first, or if both are attached simultaneously, it is reasonably evident that the presence of a strong electron-seeking addendum is essential to the occurrence of many addition reactions. Proof of this lies in the fact that all substances which add spontaneously to unsaturated carbon compounds appear to be electron-seeking reagents, as Ingold has pointed out, and in the further fact that all catalysts for these addition reactions, such as strong acids, halides of boron and aluminum, etc., seem to fall within the same category. If this is a true picture, it follows that the presence of any substance, such as a solvent, which tends to combine with the electron-seeking reagent, and thus reduce its effectiveness, should retard or prevent addition. This should be particularly true of substances containing electron-donor atoms, such as oxygen and nitrogen.

To test this hypothesis, we have studied the addition of hydrogen bromide and hydrogen chloride to two olefins in various solvents. The reactions were carried out in dilute homogeneous solution and relative rates determined. In order to avoid directional influences and the formation of isomers, cyclohexene and 3-hexene only were employed. The results of these studies are given in Tables I–IV. The initial hydrogen halide concentrations are given in normality. It is evident that the reactions are remarkably rapid in non-donor solvents, such as xylene and heptane, and extremely slow in strong donor solvents, like ether and dioxane.

(1) Ingold, *Chem. Rev.*, **15**, 268–272 (1934).
(2) Whitmore, "Organic Chemistry," D. Van Nostrand Co., New York, 1937, pp. 665, 670–672.
(3) Ogg, THIS JOURNAL, **57**, 2727 (1935).