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The Preparation and Reaction of Novel Glycosyl Ureas and Thioureas

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THE PREPARATION AND REACTION OF NOVEL GLYCOSYL UREAS AND THIOUREAS

by

Robert Scott Johnson

A Thesis
Submitted to the
Faculty of The Graduate College
in partial fulfillment of the
requirement for the
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THE PREPARATION AND REACTION OF NOVEL GLY COSYL UREAS AND THIOUREAS

Robert Scott Johnson, M.A.
Western Michigan University, 1987

The first phase of this research was to synthesize novel glycosyl propynyl ureas and glycosyl propynyl thioureas. The second phase involved the reactions of these compounds.

It was hoped that 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(2-propynyl) urea would undergo a ring closure when treated with PCl₅ to produce 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-1H-5-methyl-2-imidazolone. However, this was not the case. It is believed that the 3N position of the glycosyl propynyl ureas and glycosyl propynyl thioureas must be disubstituted for the reaction to occur and yield a 2-imidazolone product.

A glycosyl propynyl thiourea was reacted with dibenzylazodicarboxylate to produce N¹-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-N²-(2-propynyl)-S-(N³,N⁴-biscarbobenzoxy)hydrazinolthiourea. Further investigation with this compound may lead to a novel glycosyl carbodiimide.
ACKNOWLEDGEMENTS

I would like to express my gratitude to Robert Nagler and Robert Harmon for all the support, encouragement, and chemical insight they have given me during this project.

Robert Scott Johnson
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Johnson, Robert Scott, M.A.
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CHAPTER I

INTRODUCTION

The objective of this research project has been the construction of a nucleoside antagonist that contains a five membered heterocyclic moiety which is novel. The reaction theme was to design a compound which is similar to the pyrimidine and purine bases that are found in deoxyribonucleic acids (DNA) and ribonucleic acids (RNA). These molecules are known to transmit genetic information and mediate the synthesis of proteins in the cell. The chemical properties and exact structures of the pyrimidine and purine bases dictate the interactions possible between the respective DNA strands and between molecules of DNA and RNA. These interactions not only store but also transmit the genetic information in the cell. Hence, pyrimidine and purine bases play a key role in the metabolic processes of the cell.

The target compound was 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-1H-5-methyl-2-imidazolone. There are at least two different approaches on paper to synthesize 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(2-propynyl)urea which is a key precursor to the target compound. Figures 5 and 6 illustrate the two schemes that yield 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-1H-5-methyl-2-imidazolone.

The purine ring system contains an imidazole ring fused to a pyrimidine ring. It is hoped that 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-1H-5-methyl-2-imidazolone will mimic the structure of the bases found in DNA and
RNA thereby blocking the synthesis of the natural base nucleotides. This may disrupt the metabolic process in cancer cells.

It is well known that cancer cells reproduce in an uncontrolled manner compared with normal cells and are usually more susceptible to drugs. It must be noted that every drug which is used for the treatment of cancer is also toxic to the entire human body.
CHAPTER II

HISTORICAL

Throughout the history of medicinal chemistry the imidazole nucleus has proven itself to be an active source of medicinal agents. Nitroimidazoles are frequently linked with antimicrobial activity. These compounds are synthesized in order to combat infections by trichomonas, a protozoan. Protozoal infections are not usually serious yet they can be annoying. Therefore, these types of agents are important to medicinal chemists. Azomycin (Figure 1) is one such agent that was isolated from a culture broth from a Streptomyces strain.1 Two other antitrichomonal agents (Figure 2) are dimetridazole, which is used in veterinary practice and metronidazole, a compound that is used to combat vaginal trichomoniasis.2

Figure 1. Azomycin

![Azomycin](image1)

from a Streptomyces strain.1 Two other antitrichomonal agents (Figure 2) are dimetridazole, which is used in veterinary practice and metronidazole, a compound that is used to combat vaginal trichomoniasis.2

![Dimetridazole and Metronidazole](image2)

Figure 2. Antitrichomonal Agents
There are numerous nucleoside derivatives that contain a five member heterocyclic moiety which exhibit biological activity. One such compound is 1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide (Figure 3). Ribavirin is very effective against influenza virus in mice.

Figure 3. Ribavirin, 1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide

Nucleoside analogs differ greatly from each other with respect to the biological systems they can affect. These nucleosides can undergo a great deal of metabolic conversions and, therefore, they can affect a variety of metabolic targets. It is not possible to predict the potential activity of the nucleoside. Structural change in the heterocycle as well as in the carbohydrate moiety has produced biologically active compounds. It must be pointed out that the correlation between structure and activity cannot be determined with any kind of certainty.

Stoffel and Speziale discovered a novel ring closure of propynylureas using phosphorus pentachloride to produce 2-imidazolones. The 2-imidazolone is produced via an imidazolium chloride (Figure 4). A 2-imidazolone was the target heterocyclic moiety for this project.
Figure 4. 2-Imidazolone
\begin{align*}
\beta-D\text{-glucose pentaacetate} & \xrightarrow{Br_2, \text{P}} 2,3,4,6\text{-tetra-O-acetyl-}\alpha-D\text{-glucopyranosyl bromide} \\
& \xrightarrow{AgOCN, 100^\circC} 2,3,4,6\text{-tetra-O-acetyl-}\beta-D\text{-glucopyranosyl isocyanate} \\
& \xrightarrow{H_2NCH_2C\equiv C-H} 1\text{-}(2,3,4,6\text{-tetra-O-acetyl-}\beta-D\text{-glucopyranosyl})\text{-3-(2-propynyl)urea (1)} \\
& \xrightarrow{PCl_5, CH_2Cl_2, \text{heat, 3 hours}} 1\text{-}(2,3,4,6\text{-tetra-O-acetyl-}\beta-D\text{-glucopyranosyl})\text{-1H-5-methyl-2-imidazolone (2)}
\end{align*}

Figure 5. Approaching the problem on paper

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\[
\begin{align*}
\text{CH}_2\text{OAc} & \quad \xrightarrow{\text{TiCl}_4, \text{CHCl}_3} \quad \text{OAc} \\
\text{H} & \quad \xrightarrow{100^\circ C, \text{3 hours}} \quad \text{C} \\
\text{H} & \quad \text{OAc} \\
\text{H} & \quad \text{OAc} \\
\text{H} & \quad \text{OAc} \\
& \quad \beta\text{-D-glucose pentaacetate} \\
\text{CH}_2\text{OAc} & \quad \xrightarrow{\text{NaN}_3, \text{DMF}} \quad \text{OAc} \\
\text{H} & \quad \xrightarrow{100^\circ C, \text{2.5 hours}} \quad \text{N} \\
\text{H} & \quad \text{OAc} \\
\text{H} & \quad \text{OAc} \\
\text{H} & \quad \text{OAc} \\
& \quad 2,3,4,6\text{-tetra-O-acetyl-}\beta\text{-D-glucopyranosyl azide} \\
\end{align*}
\]

\[
\begin{align*}
\text{CH}_2\text{OAc} & \quad \xrightarrow{\text{Raney Nickel}} \quad \text{NH}_2 \\
\text{H} & \quad \xrightarrow{\text{NiAl}_2+6\text{NaOH}} \quad \text{Ni}+2\text{Na}_3\text{AlO}_3+3\text{H}_2 \\
\text{H} & \quad \text{OAc} \\
\text{H} & \quad \text{OAc} \\
\text{H} & \quad \text{OAc} \\
& \quad 2,3,4,6\text{-tetra-O-acetyl-}\beta\text{-D-glucopyranosyl amine} \\
\text{Br}–\text{CH}_2–\text{C} & \quad \xrightarrow{\text{KOCN, DMF}} \quad \text{H}–\text{C} & \quad \text{propargyl isocyanate} \\
\text{C} & \quad \text{C–CH}_2–\text{N} & \quad \text{C}=\text{O} \\
& \quad \text{propargyl bromide} \\
& \quad (3) + (4) \xrightarrow{\text{CH}_2\text{Cl}_2} \xrightarrow{\Delta, \text{1 hour}} \text{PCl}_5, \text{CH}_2\text{Cl}_2, \text{heat, \text{3 hours}} \xrightarrow{5\%\text{NaHCO}_3} (1) \xrightarrow{(2)}
\end{align*}
\]

Figure 6. Approaching the problem on paper.
CHAPTER III

EXPERIMENTAL

The compounds synthesized during this project were identified by IR and elemental analysis. The IR spectra were obtained by using a Beckman Acculab Spectrophotometer. Microanalyses were carried out by Midwest Microlab of Indianapolis, Indiana and MicAnal of Tucson, Arizona. Melting points were determined with a Thomas Hoover Uni-melt Capillary Melting Point apparatus, and are uncorrected.

Preparations

2,3,4,6-tetra-O-α-D-glucopyranosyl bromide

This compound was synthesized by a modification of the procedure of R. Lemieux.5

β-D-glucose pentacetate, 146 g (.375 mol), was added to 325 mL of acetic anhydride in a 2 L round bottom flask that has three necks. A thermometer was placed in the first neck, a mechanical stirrer in the middle and a pressure equalizing addition funnel in the last. The mixture was stirred and cooled to 15°C then 47.5 g (1.53 mol) of anhydrous red phosphorus was added. Five minutes later 62.5 mL (1.21 mol) of bromine was added dropwise to keep the reactions mixture between 5-20°C. Next 62.5 mL of water was added slowly, keeping the temperature in the 5-20°C range. The reaction mixture was stirred for 2 hrs. Then 375 ml of
chloroform was added and the mixture was filtered. The red phosphorus was discarded and the amber filtrate was poured onto 1000 g of ice in a separatory funnel. The mixture was shaken and the layers separated. The water layer was extracted twice with 150 mL of chloroform. The combined chloroform extracts were washed with 400 mL of an ice cold sodium hydrogen carbonate solution. The chloroform solution was dried with calcium chloride. Next the chloroform was removed by the flash evaporator. A thick yellow syrup remained. This syrup was crystallized by the addition of a 50:50 mixture of light petroleum ether and diethyl ether. Yield of the crude product was 115 g (75% theoretical), m.p. 73-77°C. This compound can be kept in a desiccator over phosphorus pentoxide and potassium hydroxide under reduced pressure and used within forty-eight hours. Recrystallization from diethyl ether, m.p. 88-89°C.

2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl isocyanate

A modified procedure of the procedure of B. Johnson and W. Bergmann was used to prepare this compound.⁶

In a 1 L round bottom, triple necked flask that was fitted with mechanical stirrer was placed 66 g (.17 mol) of 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide, 230 mL of xylene that was dried over sodium, and 24 g (.17 mol) of silver cyanate. The mixture was placed on a steam bath for 30 minutes, the silver cyanate turned yellow due to the formation of silver bromide, then 12 g (.08 mol) more of silver cyanate was added and the mixture was heated for 30 more minutes. Finally 12 g (.08 mol) of silver cyanate was added and the mixture was placed on the steam bath for one more hour. The
solution was then filtered by suction to remove the silver salts. The filtrate was poured into 400 mL of light petroleum ether. The mother liquor was decanted into 200 mL of light petroleum ether. This solution was then poured into a new vessel and was placed in the freezer overnight. The yield was 15 g (23% theoretical), m.p. 95°C. Infrared spectrum (KBr): v (N=C=O), 2250 cm⁻¹.

1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(2-propynyl)urea

In a 100 mL round bottom flask was placed 4.20 g (.011 mol) of 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl isocyanate in 50 mL of chloroform. Then .680 g (.012 mol) of propargyl amine in 10 mL of chloroform was added and the mixture was refluxed for 1 hr. The chloroform was removed with the aid of the flash evaporator and a yellow syrup remained. This syrup was crystallized by adding diethyl ether. The crude product was purified by recrystallization from water. Yield 3.7 g (77% theoretical), m.p. 142-143°C. IR (KBr) cm⁻¹: 3200-3500 (N-H stretch), 2320 (C=CH), 1750 (C=O acetate), 1650 (C=O amide), 1560 (N-H bend). Elemental analysis: found C 49.99, H 5.52, N 6.50; calculated C 50.47, H 5.64, N 6.54.

2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl chloride

This compound was made using a modification of the procedure of R. Lemieux.⁷

Forty grams of β-D-glucose pentaacetate (.102 mol) was dissolved in 200 mL of chloroform which was contained in a 500 mL round bottom flask equipped with a condenser that was fitted with a calcium chloride tube. A
solution of 11.6 mL (20.0 g) of titanium tetrachloride in 80 mL of chloroform was added. The mixture was shaken and the yellow precipitate dissolved. This solution was refluxed 3 hrs on a steam bath and then was added to a 400 mL ice water mixture that was in a 2 L separatory funnel. The chloroform layer was washed twice with 200 mL of water, dried with calcium chloride and evaporated to a syrup using the flash evaporator. The syrup was added to 100 mL of anhydrous ether. Light petroleum ether was then added to the mixture to make the solution turbid. Crystallization soon took place. The crude product was washed with 40 mL of cold diethyl ether. The yield was 32 g (85% theoretical), m.p. 72-74°C. After recrystallization from diethyl ether the substance melted at 75-76°C.

2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl azide

This compound was synthesized by a modification of the procedure of A. Yamamoto, C. Miyashita, and H. Tsukamoto.8

In a 250 mL round bottom flask was placed 3.2 g (.05 mol) of sodium azide in 100 mL of DMF. Then 16.1 g (.044 mol) of 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl chloride was added. The mixture was heated on a steam bath for 30 minutes and 80 mL of acetone was added through the top of the condenser. The mixture was refluxed for 2 hrs and then filtered to remove the sodium chloride. Vaporization of the solvent using the flash evaporator left a brown oil. A 50:50 mixture of diethyl and light petroleum ether was added to induce crystallization. Yield 13.3 g (81% theoretical), m.p. 123-124°C.
2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl isothiocyanate

This compound was synthesized by a modification of the procedure of B. Johnson and W. Bergmann. In a 1 L flask equipped with a condenser and a mechanical stirrer was placed 61.6 g (.150 mol) of 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl bromide that was dissolved in 375 mL of water-free toluene. This mixture was stirred while 49.8 g (.301 mol) of AgSCN was added. The reaction mixture was refluxed for 1 hr. Yellow silver bromide precipitated as the reaction went to completion. The silver bromide was filtered and the filtrate was concentrated. This solution was put in the refrigerator overnight. The product was obtained in almost quantitative yield. This yellow compound had a m.p. of 100-103°C.

1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(2-propynyl)thiourea

In 25 mL of CH₂Cl₂ 7.20 g (.018 mol) of 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl isothiocyanate was dissolved. Then one gram (.018 mol) of propargyl amine in 10 mL of CH₂Cl₂ was added to the reaction vessel. The mixture was refluxed for 1 hr and then the solvent was removed. The resulting syrup was dissolved in absolute ethanol and eluted through a column of silica gel. The ethanol was removed. Every attempt to crystallize the syrup failed. Yield 6.5 g (79% theoretical). IR (neat) cm⁻¹: 3200-3400 (N-H stretch), 2320 (C=C-), 1750 (C=O acetate), 1545 (N-H bend), 1340 (C=S). Elemental analysis: found C 48.55, H 5.84, N 6.02, S 6.39; calculated C 48.65, H 5.43, N 6.30, S 7.20.
1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-1H-5-methyl-2-imidazolone

In a 100 mL round bottom flask was placed 3.700 g (0.0086 mol) of 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(2-propynyl)urea in 45 mL of methylene chloride. Then 1.750 g (0.0086 mol) of PCl₅ was added and the mixture was refluxed for 3 hrs. After 1 hr the mixture turned black. A 5% sodium bicarbonate solution was added to the reaction mixture. The organic layer was washed and then separated from the aqueous layer. CaCl₂ was added to the solvent layer and was removed by filtration after 15 minutes. The methylene chloride was removed. This black residue had an identical IR spectra as the starting material.¹⁰ An elemental analysis was not taken on this substance.

1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-methyl-3-(2-propynyl)-thiourea

In a 250 mL round bottomed flask was placed 20.00 g (0.0154 mol) of 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl isothiocyanate in 75 mL of CH₂Cl₂. Next 3.500 g (0.0154 mol) of N-methyl propargyl amine was added to the reaction flask. The contents were refluxed for 1 hr and the solvent was removed. This syrup was crystallized by adding a 50:50 mixture of 30/60 pet. ether and diethyl ether. It took eight days for the syrup to crystallize. Yield 19.6 g (83% theoretical). Melting point 105-107°C. IR (KBr) cm⁻¹: 2320 (C=H=C–), 1750 (C=O), 1430 (C=S). Elemental analysis: found C 49.37, H 5.85, N 6.02, S 6.71; calculated C 49.78, H 5.70, N 6.13, S 6.98.
1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3,5-dimethyl-2-imidazolone

In a 100 mL round bottom flask was placed 2.000 g (.0043 mol) of 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-methyl-3-(2-propynyl)-thiourea in 30 mL of CH₂Cl₂. Next .8900 g (.0043 mol) of PCl₅ was added and the solution was refluxed for 3 hrs. The reaction mixture was washed with a 5% sodium bicarbonate solution. The organic layer was separated from the water layer and was dried with CaCl₂. The drying agent was removed by filtration and then the solvent was taken away leaving a yellow syrup that could not be crystallized. TLC indicated one compound but the elemental analysis did not agree with the calculated value for the target compound.¹¹ Elemental analysis: found C 44.05, H 4.83, N 4.74; calculated C 51.58, H 5.88, N 6.33.

N¹-[2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl]-N²-(2-propynyl)-S-(N³,N⁴-biscarbobenzoxy)hydrazinolisothiourea

A modified procedure of De, Shiau, and Harmon was used to prepare this compound.¹²

Four grams (.009 mol) of 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(2-propynyl)thiourea was dissolved in 35 mL of CH₂Cl₂. This mixture was cooled to 10°C and 2.68 g (.009 mol) of dibenzylazodicarboxylate was added dropwise to the reaction mixture while it was being stirred. The reaction was allowed to mix for 24 hrs. at room temperature. The methylene chloride was removed. The syrup did not crystallize. Yield 5.1 g (74% theoretical). Elemental analysis: found C 53.75, H 4.43, N 6.60, S 4.41; calculated C 53.54, H 4.98, N 7.30, S 4.19.
CHAPTER IV

RESULTS AND DISCUSSION

The target compound 1-(2,3,4,6-tetra-0-acetyl-β-D-glucopyranosyl)-1H-5-methyl-2-imidazolone was not obtained in this project. The chemical rational used to design this compound can be summarized by the following reaction mechanisms:
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I believe that position three of the urea or thiourea must be disubstituted as in the compound 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-methyl-3-(2-propynyl)thiourea for a ring closure to occur with PCl₅. In the case where position N-3 was monosubstituted with a 2-propargyl group the black residue was actually the starting material 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(2-propynyl)-urea. The IR spectra of both substances were identical. However, when the N-3 position was disubstituted as was the
case when 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-methyl-3-(2-propynyl)thiourea was used as the starting material the IR spectra of reactant and product were not the same. The elemental analysis was not in an acceptable range for the expected product. TLC only indicated one compound present and the NMR was not available to use so the structure was undetermined at this time.

Scheme 1 of Figure 5 was the actual model used in this project because 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(2-propynyl)urea was synthesized before 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl amine. Therefore, Scheme 2 of Figure 5 was abandoned. If more time were available it is believed that 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-methyl-3-(2-propynyl)thiourea could undergo a ring closure to produce a 2-imidazolone. This project was not a failure because four novel compounds were synthesized. They are 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(2-propynyl)urea, 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(2-propynyl)thiourea, 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-methyl-3-(2-propynyl)thiourea, and N1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-N2-(2-propynyl)-S-(N3,N4-bis-carbobenzoxy)hydrazinoisothiourea. All of these compounds are hygroscopic.
REFERENCES


2. Ibid., p. 240.


7. Ref. 5, pp. 223-224.


9. Ref. 6.

10. Ref. 4.

11. Ref. 4.