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Reaction of 2,2,6-Trimethyl-1,3-Dioxin-4-One with Isocyanate Derivatives and the Synthesis of 2,3,4,6-Tetra-O-Acetyl-Dglucopyranosyl Phenyl Carbodiimide

Tung Van Le

REACTION OF 2,2,6-TRIMETHYL-1,3-DIOXIN-4-ONE WITH ISOCYANATE DERIVATIVES AND THE SYNTHESIS OF 2,3,4,6-TETRA-O-ACETYL-D-GLUCOPYRANOSYL PHENYL CARBODIIMIDE

by

Tung Van Le

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REACTION OF 2,2,6-TRIMETHYL-1,3-DIOXIN-4-ONE WITH ISOCYANATE DERIVATIVES AND THE SYNTHESIS OF 2,3,4,6,-TETRA-O-ACETYL-D-GLUCOPYRANOSYL PHENYL CARBODIIMIDE

Tung Van Le, M.A.

Western Michigan University, 1987

This research was undertaken to study the synthesis and reactions of isocyanates with diketenes, the synthesis of glycosyl carbodiimide.

The 1,3-oxazine-2,4-dione compounds could be useful in the medicinal chemistry field and the agricultural field, the research using glycosyl carbodiimide as a synthon shows great promise for the medicinal chemistry field.

ACKNOWLEDGEMENTS

To my project advisor, respected professor, Dr. Robert E. Harmon, I owe the greatest thanks. His development and keen insight into the unique problems associated with project have guided it to its successful end.

I would like to thank all the faculty members in the Chemistry Department for their helpful advice.

Tung Van Le

Order Number 1330390

Reaction of 2,2,6-trimethyl-1,3-dioxin-4-one with isocyanate derivatives and the synthesis of 2,3,4,6-tetra-*O*-acetyl-*D*-glucopyranosyl phenyl carbodiimide

Le, Tung Van, M.A.

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To My Parents, My Wife and Our First Child,

My Sisters and Brothers

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CHAPTER I

INTRODUCTION

Our work has involved a study of the synthesis and reactions of isocyanates with diketenes. During the course of an investigation of potential uses of diketene, our interest was focused on the chemistry of the so-called diketene-acetone adduct (2,2,6-trimethyl-1,3-dioxin-4-one), which can be be easily prepared ketene and acetone in the presence of an acidic catylist.[5]

2,2,6-Trimethyl-1,3-dioxin-4-one 1 so-called diketene-acetone adduct, reacts with compounds which possess a C=N or C≡N moiety to give 6-methyl-1,3-oxazin-4-one derivatives.[1] The reaction involves thermal fragmentation of 1 to acetylketene followed by cycloaddition to the 1,2-dipoles. Similar methods have been reported for the formation of the 1,3-oxazin-4-one from α-diazo-β-diketones or furan-2,3-diones as acylketene precursors,[6] but, these methods seem to have limitations as regards substituents on the ketenes.

The method that we propose is based on the reaction given below in Figure 1. Reactions of this general type have been studied by Sato and co-workers who, using substituted alkyl and aryl isocyanates,[1] have demonstrated the utility of this reaction. This reaction involves the

use of one equivalent of diketene-acetone adduct with an excess amount of alkyl or aryl reaction. This reaction involves the use of one equivalent of diketene-aetone adduct with an excess amount of alkyl or aryl isocyanates. The reaction mixture must be heated for approximately one to two hours at 130° - 165°C.

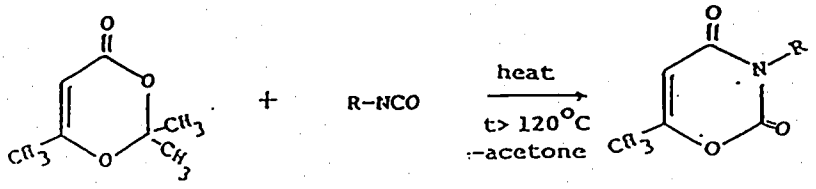


Figure 1. The General Reaction of Diketene-Acetone Adduct with Alkyl Isocyanates.

After the removal of excess alkyl or aryl isocyanates under reduced pressure, the residue was washed with diethyl ether, and the resulting crystals were collected by suction.

Our purpose was to substitude the R group with cyclo-hexyl and glycosyl groups.

For reactions of diketene-acetone adducts with phenyl isocyanate, see Figure 2 and Table 1.

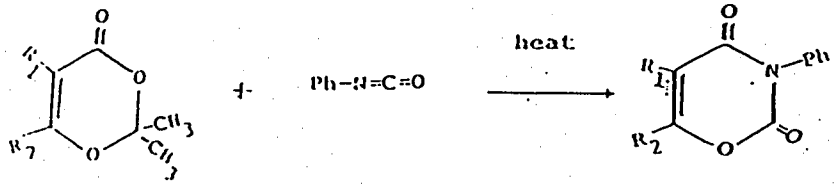


Figure 2. The Reaction of Diketene-Acetone Adducts with Phenyl Isocyanate.

Table 1

The Reactions of Diketene-Acetone Adducts with Phenyl Isocyanate

Substituents		Reaction condition			Appearance
R1	R2	Temp. (℃)	Time (hr.)	Yield (%)	(mp °C)
H	Ph	130	1	21	Needles (237-238)
Me	Me	165	2	42	Needles (143-145)
Me	Ph	165	2	30	Prisms (138-140)

CHAPTER II

EXPERIMENTAL

Instrumentation

General

The compound synthesized during the course of this investigation were identified by infrared spectrometry and elemental analysis. Infrared spectra were run on a Beckman Acculab Spectrophotometer. Thin layer chromatography analysis were carried out on silica gel plates (Merck, 60, F254, precoated, 0.2 mm). Melting points were obtained using a Thomas Hoover Uni-melt Capillary Melting Point apparatus, and are uncorrected. Micro-analysis were carried out by Midwest Microlab, Indianapolis, Indiana.

Preparations

2,3,4,6-Tetra-O-acetyl-α-D-glucopyranosyl bromide

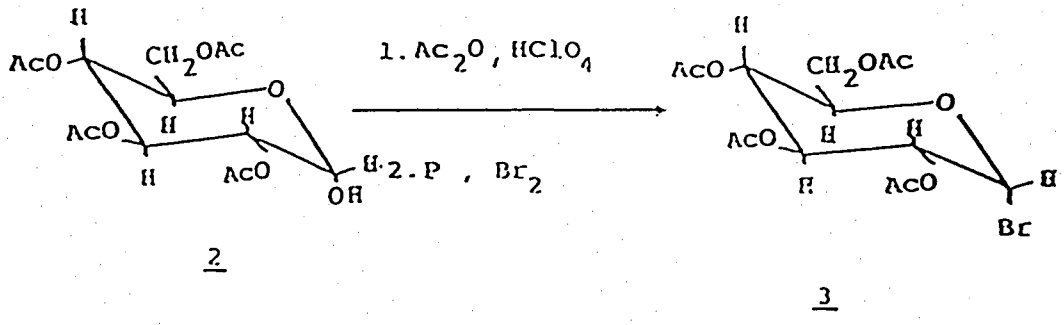
Compound 3 was prepared by a modification of the procedure of Lemieux.[7] See Figure 3.

Two hundred milliliters of acetic anhydrid in a 500 mL, 3-necked flask equipped with an efficient stirrer and a thermometer was cooled in an ice and water mixture, and 1.2 mL (0.014 mol) of 70% perchloric acid was added drop-

wise. The solution was warmed to room temperature, and 50 g (0.28 mol) of anhydrous D-glucose 2 was added to the stirred mixture at such a rate, over a period of about one hour, to keep the reaction temperature between 30° and 40°C. The stirred mixture solution was cooled to 20°C and 15 g (0.48 mol) of red phosphorus was added. Within a few minutes dropwise addition of 29 mL (0.56 mol) of bromine was begun in such a way that the temperature of the mixture was maintained between 15° - 20°C (periodic cooling in an salt-ice bath was necessary). After complete addition of the bromine, 18 mL of water was added slowly, keeping the temperature below 20°C. The reaction mixture was kept two hours at room temperature and then 200 mL of chloroform was added. Once the unreacted phosphorus had settled, the mixture was filtered through a filter-bed of fine glass wool. The reaction flask and the filter funnel were washed with 50 mL of chloroform. The filtrate was poured into 500 mL of crushed ice and water contained in a 2-liter separatory funnel. After the ice melted, the chloroform layer was drawn off into a 2-liter separatory funnel which contained 300 mL of water at 0°C. The operation was repeated and the chloroform extracts combined. After vigorous shaking, the chloroform layer was poured into 300 mL of a stirred saturated aqueous solution of sodium hydrogen carbonate kept in a 2-liter beaker. The mixture was transferred to a 2-liter separatory funnel and shaken vigorously. The chloroform layer was stirred 10 mi-

nute with 7 g of dry silicic acid. The mixture was filtered and the faintly yellow solution was evaporated under reduced pressure below 60 °C in a rotary evaporator.

Addition of 300 mL of a 2:1 (v/v) mixture of petroleum ether (30°-60° range) and diethyl ether yielded crystals which were collected using vacuum filtration, and washed with cold diethyl ether. Crude product was obtained 90 g (80%), mp 79° - 83° C. Recrystallization from diethyl ether and petroleum ether (30°-60° range) afforded the pure product, mp 86°-88°C, $n^{20}D$+ 198° chloroform. The crude 2,3,4, 6-tetra-O-acetyl-α-D-gluco-pyranosyl bromide 3 was dried at reduced pressure over sodium hydroxide and should be used within about 12 hours.



2 3

Figure 3. The Reaction of D-Glucose with Bromine.

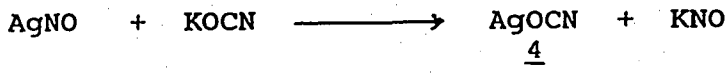


Figure 4. The Reaction of Silver Nitrate and Potassium Cyanate.

Silver cyanate

Compound 4 was prepared by a modification of the procedure of Birkenbach and co-workers.[10] See Figure 4.

Silver nitrate (16.9 g, 0.1 mol) dissoled in 200 mL of water was added to potassium cyanate (8.1 g, 0.1 mol) dissolved in 200 mL of water and stirred for 30 minutes. The mixture was filtered, and the silver cyanate was washed successively with cold water, anhydrous ethyl alcohol and then anhydrous ethyl ether. The silver cyanate was stored in a desiccator under vaccum and over potossium hydroxide.

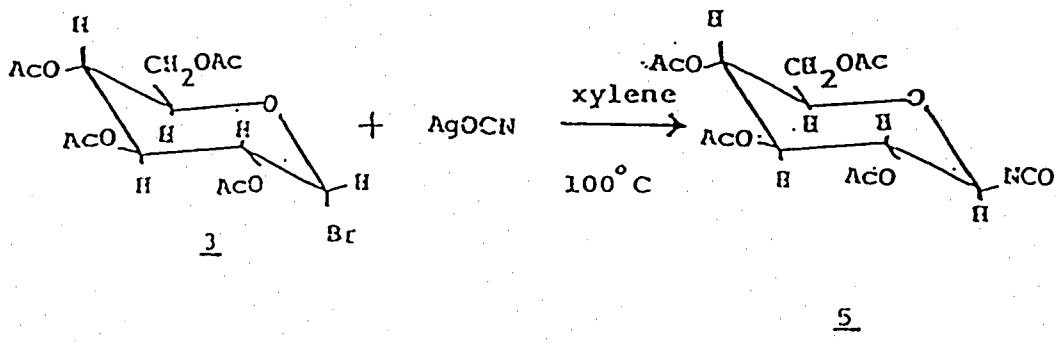


Figure 5. The Reaction of 2,3,4,6-Tetra-O-acetyl-α-D-glucopyranosyl Bromide and Silver Cyanate.

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

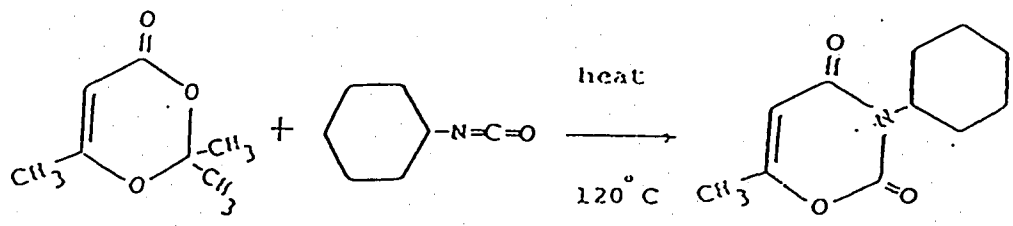
Compound 5 was prepared by a modification of the procedure of Johnson[8] and co-worker, Piskala.[9] See Figure 5.

To a solution of 33 g (0.08 mol) of 2,3,4,6-tetra-O-acetyl-D-glycopyranosyl bromide in 120 mL xylene, dried over sodium, was added 12 g (0.08 mol) of freshly prepared, dried and pulverized silver cyanate. The reaction flask was connected with a rubber stopper fitted with a calcium chloride tube, and heated with frequent shaking, at 100°C. The silver cyanate soon turned yellow due to the formation of silver bromide. After one-half hour, silver cyanate was added in two (6 g, 0.04 mol) portion at 30 minutes intervals, and the mixture was heated for one hour more liquid was then filtered by suction and the insoluble silver salts were once more extracted with 80 mL of xylene. The combined solutions were then poured into 200 mL of petroleum ether (30° - 60° range), and a slightly yellow resinous solid was precipitated. The mother liquor was at once decanted from the yellow material, mixed with 100 mL petroleum ether and allowed to stand overnight. Crystalline products were obtained which consisted of two distinctly different crystal forms, needles and blocks.

The yield of crystalline material was about 17 g (58%). The melting point of the material fluctuates between 80° - 100°C, according to the proportion of needles or

blocks which were obtained. Concentration of the mother liquors followed by crystallization from a 1:2 (v/v) ethyl acetate-light petroleum solvent mixture afforded an additional 2.5 g of the product. The total yield of pure product was 19.5 g (67%). The infrared spectrum (chloroform): (N=C=O) : 2253 cm^{-1} ; (C=O) : 1710 cm^{-1}.

Anal. Calcd. for $C_{15}H_{19}NO_{10}$: C, 48.24; H, 5.13; N, 3.75. Found: C, 48.37; H, 5.19; N, 3.72.



1 6

Figure 6. The Reaction of 3,4-Dihydro-3-cyclohexyl-6-methyl-2-H-1,3-oxazine-2,4-dione and Cyclohexyl Isocyanate.

3,4-Dihydro-3-cyclohexyl-6-methyl-2-H-1,3-oxazine-2,4-dione

A mixture of 2.84 g (0.02 mol) of 2,2,6-trimethyl-4H-1,3-dioxin-4-one and 6 g (0.04 mol) of cyclohexyl isocyanate was heated at 120°C for two hours. After the removal of excess cyclohexyl isocyanate under reduced pressure, the residue was washed with diethyl ether, and the resulting

crystals were collected by suction. Pure product 6 was obtained by recrystallization from methanol. The yield was 2.1 g (50%) mp 175°C. The infrared spectrum (chloroform) (C=O): 1764, 1690 cm^{-1}; (C=C) 1620 cm^{-1}. Anal. Calcd. for $C_{11}H_{15}NO_3$: C, 63.15; H, 7.17; N, 6.69. Found: C, 62.97; H, 7.27; N, 6.84.

2,2,6-Trimethyl-4H-1,3-dioxin-4-one

A facile and general synthesis of this compound is reported. Treatment of diketene with acetone in the presence of an acidic catalyst.[5] In our research, this compound was supplied by Eastman Kodak Company.

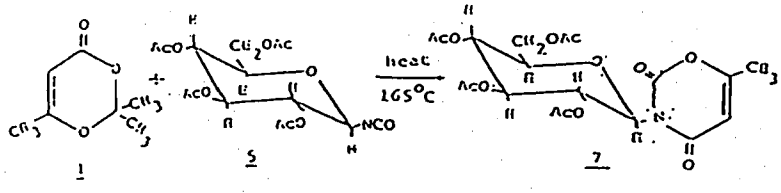


Figure 7. The Reaction of 1,3-Oxazine-2,4-dione and Glycosyl Isocyanate.

3,4-Dihydro-3-glycosyl-6-methyl-2-H-1,3-oxazine-2,4-dione

A mixture of 0.75 g (0.002 mol) glycosyl isocyanate and 0.6 g (0.004 mol) of 2,2,6-trimethyl-4H-1,3-dioxin-4-one was heated with stirring at 165°C for two hours. After the removal of excess 2,2,6-trimethyl-4H-1,3-dioxin-4-one, the residue was washed with a small amount of cold petroleum ether (30°-60° range) and the resulting crystals

were collected by suction. The product 7 was purified by thin layer chromatography with ethyl acetate and hexane 1:1 (v/v) to remove the residual diketene-acetone adduct left. Melting point 94 °C.

The infrared spectrum (chloroform): 1764, 1690 cm^{-1} (C=O), 1620 cm^{-1} (C=C). Anal. Calcd. for $C_{19}H_{23}NO_{12}$: C, 49.89; H, 5.06; N,3.08. Found: C, 50.73; H, 5.71; N, 3.66. See Figure 7.

CHAPTER III

RESULTS AND DISCUSSION

Acetylketene 9 was first mentioned in the literature in 1907,[23] but only in recent years has evidence for the existence of this species appeared. Previous work has indicated that acetylketene may be generated by pyrolysis of the title dioxinone.

The dimer of ketene (diketene 8) has an unusual history.[27] This four-carbon compound, which has been known for more than forty years, was widely used in both laboratory research and in industrial production before its structure was unequivocally established and accepted by the scientific community.

After isolating diketene in 1907, Wilsmore observed that it reacted with nucleophiles to give derivatives of acetoacetic acid, he concluded that the acetylketene structure 9 was consistent with the reactivity observed for diketene.[24]

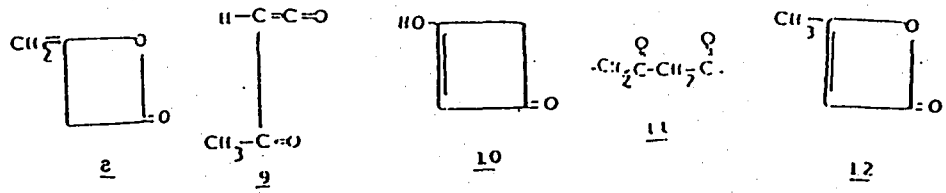


Figure 8. The Forms of Ketenes.

In the decades that followed, other workers proposed that diketene was enolized 1,3-cyclobutanedione 10,[25] diradical 11, and β-crotonolactone 12.[27] The currently accepted 3-methylene-2-oxetanone structure 8 was proposed in 1940,[26] but it was generally accepted until 1950.[6]

The acetylketene structure for the ketene dimer was still used in the 1940,[26] but after the close of the diketene controversy, this interesting acylketene was not investigated for several decades.

In 1976, Jager and Wenzelburger reported the formation of 1,3-oxazine derivatives from reaction of 2,2,6-trimethyl-4H-1,3-dioxin-4-one 1 with cyanates, cyanamides, and isocyanates.[2] It was suggested that these reactions might proceed via acetylketene 9 generated by retro-Diels-Alder fragmentation of 1. In 1982, Kato et al[1] used diketene-acetone adduct 1 to prepare N-acylacetoacetamides, and in 1983 these workers reported the observation of a weak IR absorption band at 2150 cm^{-1} during the gas-phase pyrolysis of adduct 1. This IR absorption was assigned to acetylketene 9. Other groups have recently implicated acetylketene in amine-catalyzed reactions of diketene and in base-catalyzed decomposition of 6-methyl-4-oxo-2-thio-2,3-dihydro-4H-1,3-oxazine.

In general, we must carry out these reactions at the temperature greater than 120 °C to eliminate acetone. The acetylketene intermediate will react with isocyanate deri-

vatives by cycloaddition to form 6-methyl-1,3-oxazine-2,4-dione derivatives.

On heating, the adduct usually shows behavior similar to that diketene itself. Such diketene-like reactivity of the adduct can be rationalized in terms of thermal fragmentation of the adduct to an acetylketene intermediate. We recently obtained evidence that strongly supports the formation of the acetylketene intermediate in the reaction of the adduct.

Thus, 5-and 6-substituted 1,3-dioxin-4-ones, by analogy with adduct 1, may generate acylketenes 9, which can be regarded as equivalent to mixed diketenes 14. In the literature such mixed diketenes 14 are not easily accessible. Though several references are available concerning synthesis of 1,3-dioxin-4-ones, most of the previous methods utilize 1,4-cycloaddition of ketones to acylketenes 9 prepared from acid halides, furanones, or diazoketones.

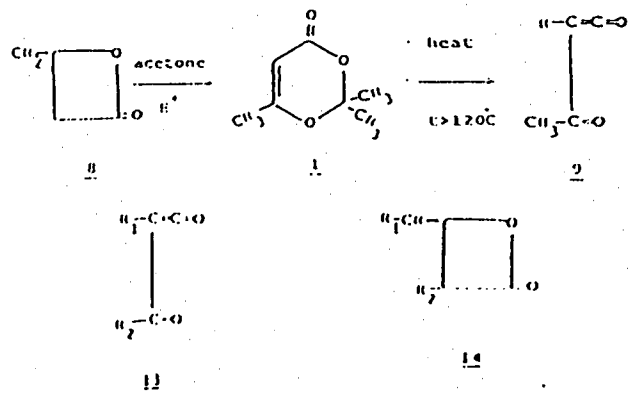


Figure 9. The Formation and the Decomposition of Diketene.

Mechanism

A possible mechanism of the reaction of the isocyanates with the adduct (diketene) is illustrated as in Figure 10. We have proposed that the formation of 1,3-oxazin-4-ones from diketene involves initial isomerization of diketene to acetylketene by heating. The cycloaddition of isocyanate to this intermediate 9 produces the 1,3-oxazin-4-ones.

The reactions of 2,2,6-trimethyl-1,3-dioxin-4-one 1 with cyclohexyl and glycosyl isocyanates have the same mechanism.

The IR spectra of compound 7 exhibited bands at:

1. 1764, 1690 cm^{-1} (C=O): The introduction of a C=C bond adjacent to a carbonyl group results in delocalization of the electrons in the carbonyl and double bonds. This conjugation increases the single bond character of the C=O bond and, hence, lowers its force constant, resulting in a lowering of the frequency of carbonyl absorption. This effect results in a shift about 20 - 30 cm^{-1} to lower frequency from the expected value of 1790, 1715 cm^{-1}.

2. 1620 cm^{-1} (C=C): The conjugation moves C=C stretch to lower frequency from the expected value of 1640 cm^{-1}.

3. 1220 cm^{-1} (C-O): The asymmetric C-O-C stretching vibration leads to a single absorption appearing at about 1220 cm^{-1}. The shift in the asymmetric stretching frequency to a higher value than was found in dialkyl ethers (1200

cm^{-1}) can be explained by using resonane. The C-O band in compound 7 is shifted to a higher frequency (1220 cm^{-1}) because of the increased double bond character, which strengthens the bond.

$$\left[CH_2=CH-\ddot{O}-R \longleftrightarrow \ddot{C}H-CH=\overset{+}{O}-R\right]$$

4. 1350 cm^{-1}(C-N): The C-N stretching absorbtion occurs at 1350 cm^{-1} as a medium band.

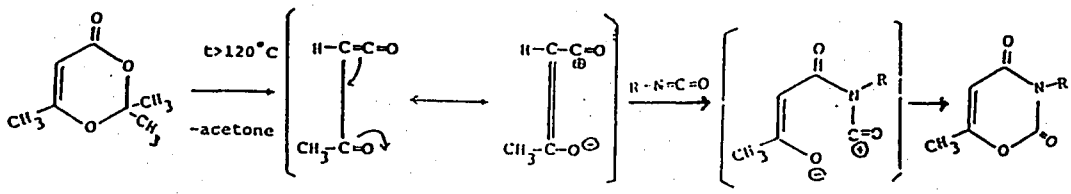


Figure 10. The Mechanism of the Reaction of Diketene-Acetone Adduct with Alkyl Isocyanate.

Interest in 1,3-oxazin-4-ones has been growing recently because of the potential biological properties of this class of heterocycle. The ring transformation of the masked acylketene provides a good method for preparing 1,3-oxazine-4-ones.

In the agricultural area, scientists of Nippon Soda company and Mitsui Toatsu Chemical company synthesized oxazine derivatives. These compounds are very useful as agricultural fungicides, nematocides, and viricides.

The 1,3-oxazine-2,4-dione compounds 6 and 7 we have made, could be useful in the medicinal chemistry field (cancer researches) and the agricultural field (Insecticide)

CHAPTER IV

INTRODUCTION

The synthesis of carbodiimides was carried out by Zbiral and Schorkhuber in 1982.[16] In their research,the synthesis was carried out via the combination of ribosyl halides and tetrazole anions or aminotetrazole anions, the resultant product was always an isomer mixture. They selected as starting materials the ribosylazide derivatives 15 and 17 shown in Figure 11.

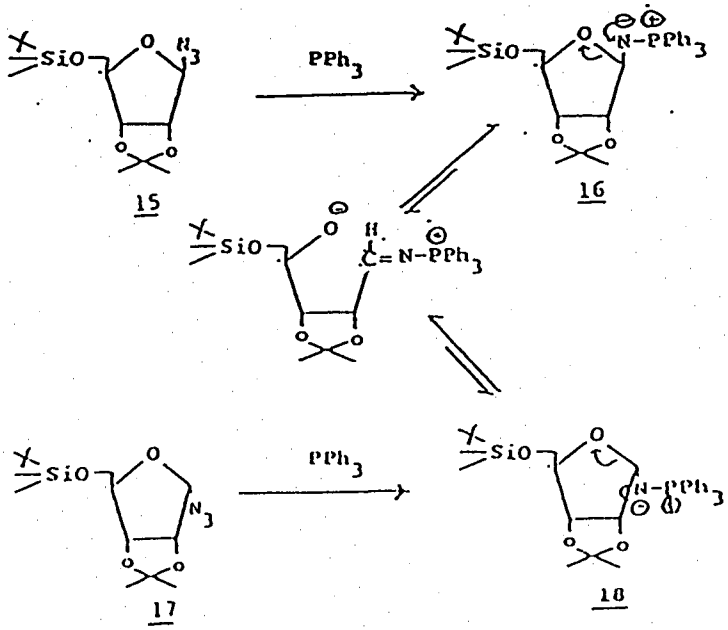


Figure 11. The Reaction of Ribosylazide and Triphenylphosphine.

They had originally planned to use these products to prepare alpha, as well as, beta-tetrazole nucleosides. However, in the course of their studies they made the interesting observation that the Staudinger reaction starting with 15 as well as with 17 produced only the beta-P-N-ylide 16. They studied this reaction with the use of a 250-MHz ^{1}H-NMR spectrum as well as the ^{13}C - and ^{31}P - reasonance spectrum in C_6D_6, and came to the conclusion that the phosphazine contained at least 10% of alpha-P-N-ylide 18. The alpha form disappeared after a few days. They reacted the iminophosphorane 16 with a number of alkylisocyanates, and obtained nonsymmetrical ribosylcarbodiimide derivatives 19, 20. See Figure 12.

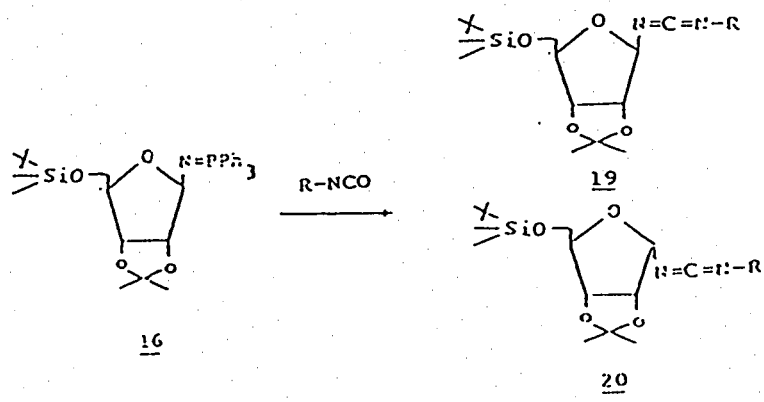


Figure 12. The Reaction of Alkyl Isocyanates and Iminophosphorane.

As shown from thin-layer chromatography examinations, the ribosylcarbodiimide derivatives occur as diastereomer pairs, and usually one of the diastereomer is formed in higher yield. In our research, we selected the glycosyl azide 21 and phenyl isocyanate. There was a mixture of the diastereometric carbodiimides 22, 23 from the reaction (see Figure 13)

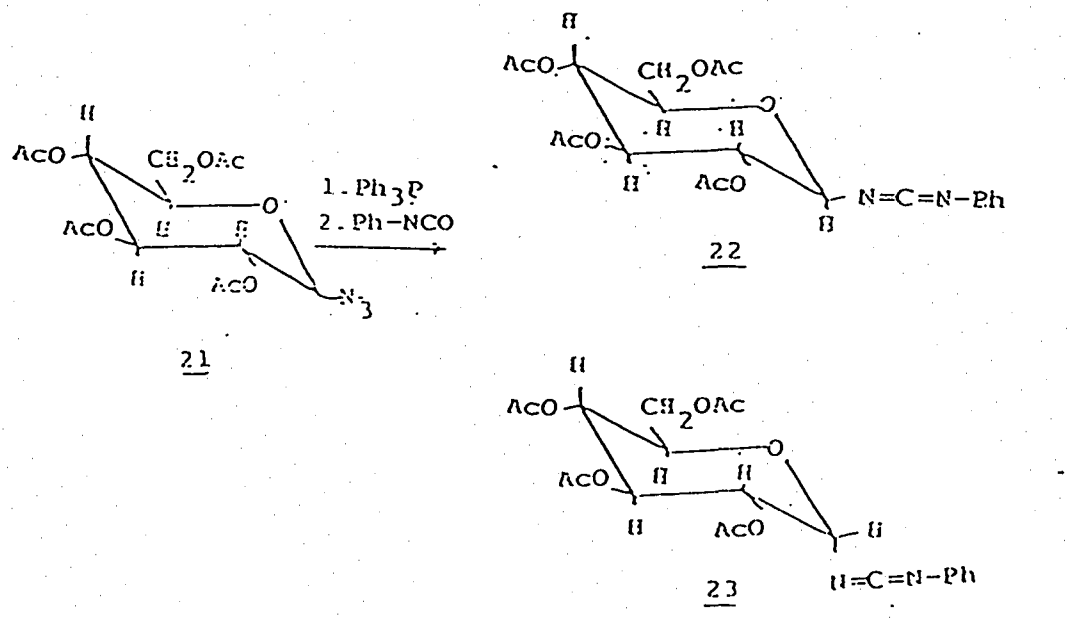


Figure 13. The Reaction of Glycosyl Azide and Phenyl Isocyanate.

When this reaction was carried out with glycosyl isocyanate and p- chlorophenyl phosphine, only one kind of carbodiimine 24 was formed (see Figure 14).

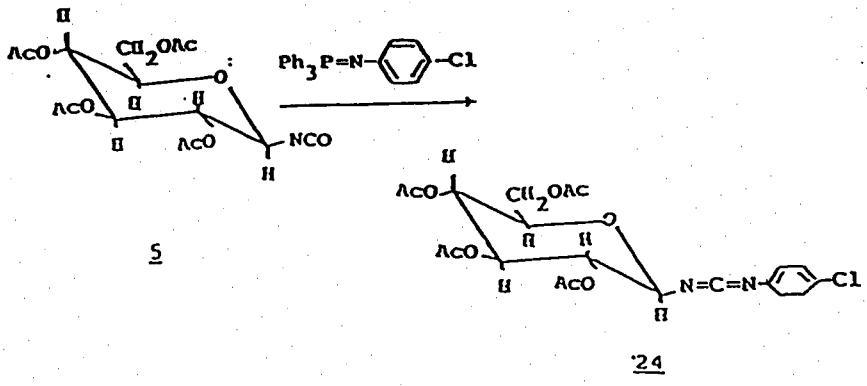


Figure 14. The Reaction of Glycosyl Isocyanate and Triphenylphosphine-p-chlorophenylimine.

The mechanism of this reaction will be discussed in the Results and Discussion chapter.

CHAPTER V

EXPERIMENTAL

Instrumentation

The compounds synthesized during the course of this investigation were identified by infrared spectrometry and elemental analysis. Infrared spectra were run on a Beckman Acculab spectrophotometer. Thin layer Chromatography analysis were carried out on silica gel plates (Merck, 60, F254, precoated, 0.2 mm). Melting points were obtained using a Thomas Hoover Uni-melt Capillary Melting Point apparatus, and are uncorrected. Microanalysis were carried out by Midwest Microlab, Indianapolis Indiana.

Preparations

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

Compound 26 was prepared by a modification of the procedure of Lemieux.[12] See Figure 14.

Twenty grams (0.05 mol) of dry β-D-glucopyranose pentaacetate 25 was dissolved in 100 mL of pure, dry chloroform contained in a 250-mL flask equipped with a water-cooled condenser and protected from the atmosphere by a tube filled with calcium chloride. A solution of 5.8 mL

(0.05 mol) of titanium tetrachloride in 35 mL of purified chloroform was added with shaking. The yellow precipitate which formed soon dissolved. The solution was refluxed 3 hours on a steam bath and then poured into 200 mL of an ice and water mixture kept in a 1-liter separatory funnel. The chloroform layer was washed twice with 100 mL amounts of water, dried with calcium chloride, and evaporated to to a thick colorless sirup under reduced pressure. The sirup was dissolved in 50 mL of anhydrous diethyl ether, and petroleum ether (30^{c} - 60^{c} range) was added to near turbidity. After the introduction of seed crystals, which were obtained readily by rubbing a little of the sirup with ethanol, crystallization took place. After cooling the crystals were collected, washed with a little cold diethyl ether, and dried under reduced pressure over sodium hydroxide pellets; yield about 16 g (85%), mp 72^{c} - 74^{c}. After recrystallization in the same manner, the pure compound melted at 75^{o} - $76\ ^{o}C$.

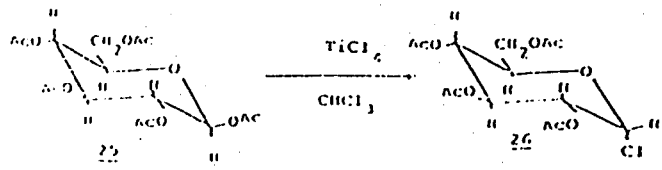


Figure 15. The Reaction of β-D-Glucopyranose Pentaacetate with Titanium Tetrachloride.

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

Compound 21 was prepared by a modification of the procedure of Yamamoto,[11] and co-workers. See Figure 16.

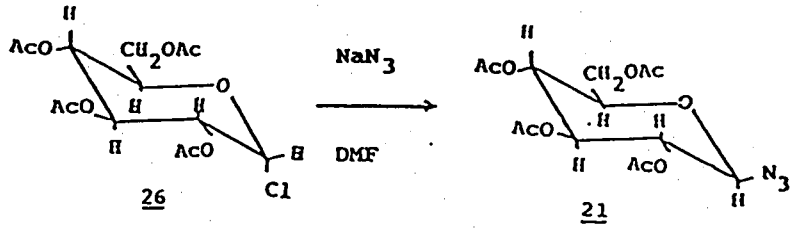


Figure 16. The Reaction of Glycosyl Chloride with Sodium Azide.

In a 250-mL flask equipped with a water cooled condenser and protected from the atmosphere by a tube filled with calcium chloride, was dissolved 6.5 g (0.0177 mol) of O-acetyl-α-D-glucopyranosyl chloride in 50 mL. of dimenformamide and added 1.3 g (0.02 mole) of sodium azide. The solution was refluxed 30 minutes and then 40 mL of acetone was added. The solution was headed under reflux for two hours. The reaction mixture was filtered. The sodium chloride precipitate was discarded and the filtrate was evaporated under reduced pressure. The mixture was allowed to cool 10 minutes in the refrigerator. Addition of 100 mL of prechilled mixture of a 2:1 (v/v) ethyl ether and petroleum ether (30° - 60° range) yielded light yellow crystals which are suction filtered. Yield about 3.97 g (60%), melting point 90° - 92°C. The infrared spectrum (chloroform) : (N=N=N) 2230 cm^{-1}; (C=O) 1710 cm^{-1}.

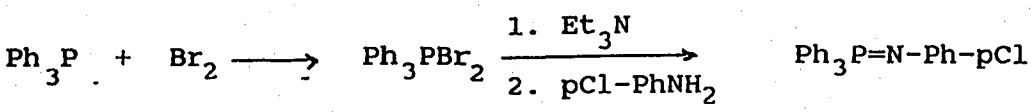


Figure 17. The Synthesis of Triphenylphosphine-p-chlorophenylimine.

Triphenylphosphine-p-chlorophenylimine

Compound 27 was prepared by a modification of the procedure of Honer[13] et al., Aimmer[14] et al., Zimmer[15] et al. See Figure 17.

To a solution of 6.5 g (25 mmol) of triphenylphosphine in 70 mL of dry benzene in a 500-mL 3-necked flask equipped with an efficient stirrer and a thermometer, was added slowly bromine in 15 mL of dry benzene over a period of about 30 minutes, and the reaction temperature was kept between 0°C and 6°C.

To an ice-cooled suspension of the above mixture, was added 5.05 g (50 mmol) of triethylamine and 3.18 g (25 mmol) of p-chloroaniline. The reaction was stirred for 30 minutes at 60°C. The reaction mixture was filtered and the precipitate was discarded, the filtrate was evaporated. Addition of 100 mL low boiling-point petroleum ether yielded crystals which were collected by vaccuum filtration. Recrystallization from hexane afforded 6.5 g pure product. Yield is 70%. Melting point 120°C. Anal. Calcd. for $C_{24}H_{19}NClP$: C, 74.32; H, 4.90; N, 3.61. Found:

C, 74.28; H, 4.97; N, 3.84.

2,3,4,6-Tetra-O-acetyl-D-glucopyranosyl phenyl carbodiimide

General Comment

All reactions were carried out in the presence of the molecular sieve (3A).

Process A

Glycosyl azide 21, 11.19 g (0.03 mol) and 7.86 g (0.03 mol) of triphenylphosphine were dissolved in 300 mL of absolute toluene and heated at 110 °C in a two necked flask fitted with reflux condense, drying tube, and a septum. After the nitrogen evolution had subsided, the solution was kept for another hour at 110°C. The solution was allowed to cool then 2.85 g (0.024mol) of phenyl isocyanate was added via the septum at room temperature and the reaction mixture was allowed to stand for one hour. At which time the formation of the carbodiimide was completed. The mixture was evaporated under reduced pressure. Addition of 100 mL of anhydrous ether yielded crystals of triphenylphosphine oxide (mp 165°C). The filtrate was evaporated and an oily product was obtained which was a mixture of the alpha- and beta-diastereometric carbodiimides. The infrared spectrum (chloroform) (N=C=N): 2160 cm^{-1}, (C=O): 1710 cm^{-1}

Anal. Calcd. for $C_{21}H_{24}N_2O_9$: C, 56.25; H, 5.35; N,

6.25. Found: C, 56.67; H, 5.62; N, 5.81.

Process B

Tetraacetate glycosyl isocyanate 5, 3.73 g (0.01 mol) and 3.87 g (0.01 mol) of triphenylphosphine-p-chlorophenylimine were dissolved in 100 mL of absolute toluene and heated in a 250-mL two necked flask with reflux condenser drying tube and septum at 110 $^{\circ}$ C for two hours. The mixture was evaporated under reduced pressure. Addition of 50 mL of anhydrous diethyl ether yields crystals of triphenylphophine oxide (mp 165°C). The filtrate was evaporated under reduced pressure. The residue was dissolved in 30 mL of anhydrous diethyl ether and petroleum ether (30° - 60° range) was added until the solution became turbid. The solution was allowed to stand overnight at room temperature and then put in the refrigerator. The resulting crytals were collected by vacuum filtration. Melting point 109° - 112°C. The infrared spectrum (chloroform) (N=C=N): 2160 cm^{-1}; (C=O) : 1710 cm^{-1}.

CHAPTER VI

RESULTS AND DISCUSSION

The isolation of a number of natural nucleosides with unconventional bases, occasionally also with sugar component is the starting point of a large number of syntheses of nucleoside analogs[17] as potential inhibitors of the replication wide range of pathogenic viruses. Of particular importance among the synthetic nucleoside analogs are ribavirin and virazole prepared by Sidwell.[28] A summary was recently published which takes into account the chemical, biologic, and therapeutic aspects of nucleoside analogs.

Zbiral and Schorkhuber[19,21] used glycosylazides for the regioselective synthesis of a number of 1,3,3-triazole-nucleosides by exploiting the principle of the 1,3-dipolar cycloaddition to beta-oxophosphorylene.

In 1982, Zbiral and Schorkhuber were dealing with the possibilities of the regioselective synthesis of tetrazole nucleosides.[16] Thus far, there have been few articles published on this subject.[17,19] As we mentioned in the introduction, Zbiral and Schorkhuber found that after the evaporation of the N_2 to form 16 and 18 (see Figure 11), there can be at most 10% of alpha-P-N-ylide 18. Even this small amount disappeared after a few days. The ^{31}P resonance spec-

trum was used to determine whether it might be possible to obtain from the open ribosyl derivative a entacovalent phosphoran structure with a five-member ring.[16] The answer was clearly in favor of the ylide structure. The fact that it is 16 which is present, and not 18, is demonstrated not only by usual slight $1'H$, $2'H$ coupling (< 0.5 Hz) and by the analogous signal position of the two germinal methyl groups[18] (compared to a large number of other 2,3-O-isopropylide-beta-ribosyl derivatives), but is demonstrated also by a markedly strong movement separating the signals for the ABX system from $5\text{-}H_a$ and $5\text{-}H_b$.[20] The emphasis (center of gravity) is on δ = 3.77 and 4.33.

Schmidt observed in 1-ribosylhydrazines a basically comparable anomerization phenomenon. As can be seen from Figure 18, we changed iminophosphorane 16, together with a number of alkyl isocyanates, into the corresponding nonsymmetrical ribosyl carbodiimide derivatives 19, 20 and then reacted it with HN_3 in benzene.[22]

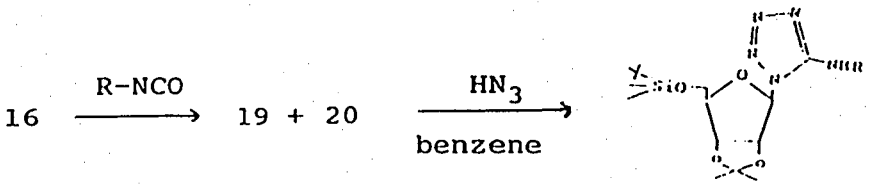
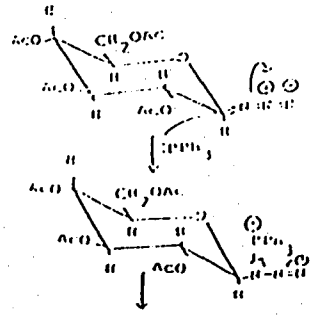


Figure 18. The Reaction of Ribosyl Carbodiimide with HN

As can be seen from thin-layer chromatography examination, the ribosylcarbodiimide derivatives 19, 20 occur as

diastereomer pairs, where almost always one component 19 is by far the stronger. When the tetrazole nucleotides are further changed, this stereo-chemical differentiation, which is due to the heterocumule arrangement, disappears. It was only in the case of $R=CH_3$ that a rapid accumulation was carried out for characterization by way of a test, based on the intensive frequency at 2100 cm^{-1} in the IR spectrum. In all other instances, the reaction solutions were immediately reacted into tetrazole. The necessary isocyanate can also be produced in situ by Curfius degradation of the appropriate azide.

The reaction of glycosylazide with aryl isocyanate can yield diastereometric carbodiimides. The thin layer chromatography plates (petroleum ether/ethyl acetate 8:1 to 4:1) showed the mixture of the diastereometric carbodiimides usually as two spots that appeared together on the thin layer chromatography plate in the Rf range of 0.4 - 0.7 and could not be distinguished by fluorescence. A possible mechanism for this reaction is shown in Figure 19.



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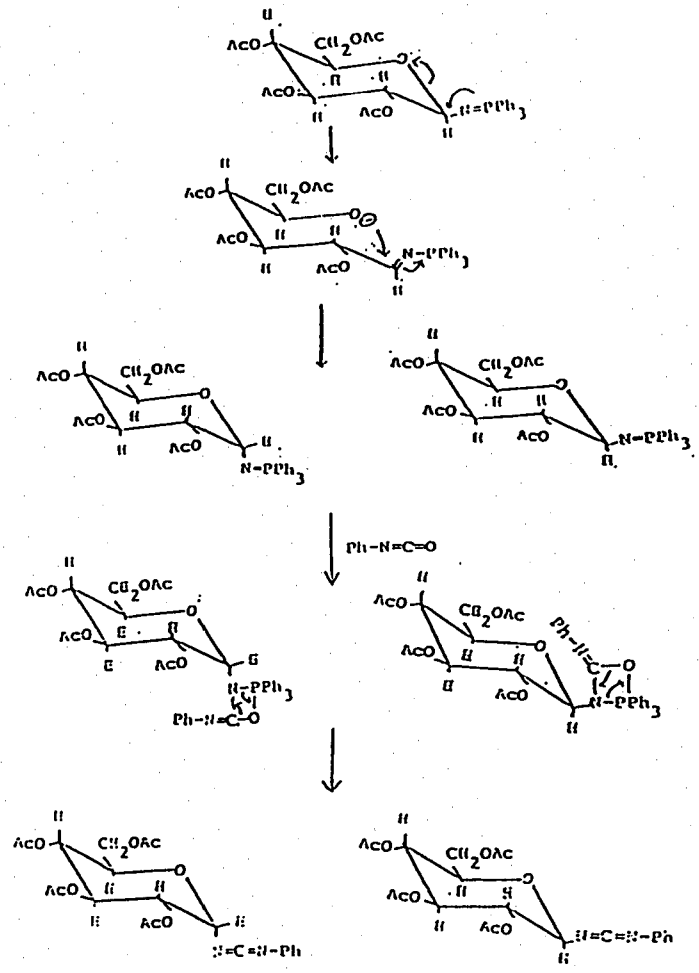

Figure 19. The Mechanism of the Reaction of Glycosyl Azide with Phenyl Isocyanate.

According to this mechanism, the presence of isomer mixtures of alpha-and beta-iminophosphorane led to the presence of a mixture of alpha-and beta-glycosyl carbodiimides.

When glycosyl isocyanate and p-chlorophenyl triphenylphosphine were selected as starting materials, only one isomer was obtained. A possible mechanism for this reaction is shown in Figure 20.

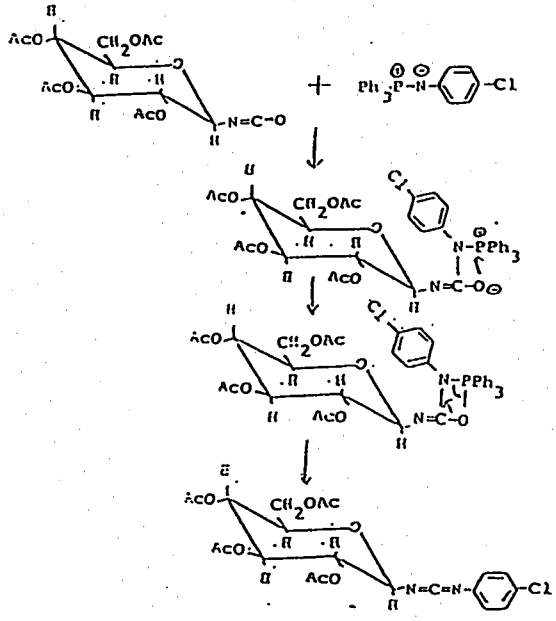

Figure 20. The Mechanism of the Reaction of Glycosyl Isocyanate with Triphenylphosphine-p-chloro-phenylimine.

The IR spectra of compound 24 exhibited bands at:

1. 2160 cm^{-1} (N=C=N): Stretch is a broad and intense absorption.

2. 1730 cm^{-1} (C=O): Stretch is a sharp and intense absoprtion. This can be explained by using electron-withdrawing effect in esters of sugar. This effect results in a shift of about 20 cm^{-1} to higher frequency from the expected value of 1710 cm^{-1}.

3. 1300-1000 cm^{-1} (C-O): Two bands appear for the C-O stretching vibrations in esters of the sugar.

CHAPTER VII

CONCLUSIONS

This research using glycosyl isocyanate as a synthon shows great promise for the medicinal chemistry field. The reactions using glycosyl isocyanates as synthons involves the synthesis of tetrazole nucleosides. The isolation of a number of natural nucleosides which contain unconventional bases and antibiotic activity, has lead to the investigation of a large number of syntheses. These nucleoside act as potential inhibitors of the replication for a wide range of pathogenic viruses and bacterias.

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