Syntheses of N-( fructose ) tetracycline derivative.

Maha K. Mahmod *

* University of Kerbala, College of Science, Unite of Chemistry.

Abstract :

N-( fructose) tetracycline was synthesized by alkylation of the 1-chloro di-acetone fructose with the hydrogen of 2-carboxamide group of tetracycline to obtain a new derivative that may have more water–solubility than tetracycline.

Introduction:--

Tetracycline (I) is one of the most important broad-spectrum antibiotics used in medicine today\textsuperscript{1-3}. It has been shown that several changes can be made in the fundamental structure of this compound with retention of its characteristic antimicrobial activity, for purposes of this study a compound is considered to possess characteristic tetracycline activity if it exhibits as much as one -tenth the activity of tetracycline against a number of organisms both in \textit{vitro} and in \textit{vivo}\textsuperscript{4}. Among these changes the replacement of 5 - hydrogen by hydroxyl to form oxytetracycline (II)\textsuperscript{5}, 7-hydrogen by chlorine to form chlorotetracycline (III )\textsuperscript{6}, 6- methyl by hydrogen to form demeclocycline (IV)\textsuperscript{7}, 6-hydroxyl by hydrogen to form methacycline (V)\textsuperscript{8}, 5- hydrogen by hydroxyl and 6-hydroxyl by hydrogen to yield deoxtetracycline (VI)\textsuperscript{9,10}, 6 - hydroxyl and 6- methyl by hydrogens (VII)\textsuperscript{11}. 

\begin{center}
\includegraphics[width=0.7\textwidth]{tetracycline.png}
\end{center}
All of these derivatives are characterized by their exceptional chemothapeutic efficacy against bacteria, both gram negative, and gram positive. Tetracycline structure has an amide group in position 2. Many research found that the introduction of \((-\text{CH}_2-\text{NR}_2\) group (N \(-\) amino methylation) through its amino group, will give tetracycline derivative which has good medical property. The 2-carboxamide group apparently is relatively free from steric hindrance in the tetracycline molecule. It has shown that substitution of bulky groups for one of the hydrogens on the amide nitrogen not cause any appreciable loss in the activity. In fact substitution of a pyrolidino methyl group increases the water–solubility of tetracycline about 2,500 times without appreciable change in activity by condensing tetracycline with pyrolidine and formaldehyde in the presence of t-butyl alcohol, this derivative is very soluble in water and provides a means of injecting the antibiotic in a small volume of solution.\textsuperscript{12,13}
In the last few years, carbohydrate mimetics have become an emerging area in drug design. Several applications of carbohydrate mimetics are currently on clinical trial to increase the activity, bioavailability and the selectivity of drugs \(^ {14,15}\).

**Results and Discussion**

**The context of the research:**

Synthesis of N-(fructose) tetracycline.

This study deals with the synthesis of a new tetracycline derivative (X) by replacement of one hydrogen of 2–carboxamide nitrogen by sugar (fructose) group, this may increase the water–solubility since the fructose molecule has many free –OH groups. It is hoped that the new synthesized derivative may possess biological activity with high solubility in water.

![Chemistry Diagram](attachment:chemistry_diagram.png)

**Chemistry :-**

Synthesis of 2,3:4,5-di-O-isopropylidene-\(\beta\)-D-fructopyranose(XI) and 1-chloro 2,3:4,5-di-O-isopropylidene-\(\beta\)-D-fructopyranose(XII) scheme -1-

Reaction of unhydrours–D-fructose with dry acetone in the presence of unhydrours ferric chloride (\(\text{FeCl}_3\)) at 36\(^0\)C afforded 2,3:4,5-di-O-isopropylidene-\(\beta\)-D-fructopyranose (XI) in 66% yield\(^ {14}\) then reacted with unhydrours carbon tetrachloride (\(\text{CCl}_4\)) in the presence of tri phenyl pho- sphen (\(\text{Ph}_3\text{P}\)) at 66\(^0\)C for 90 hours yield compound (XII) in 85 % yield.

![Scheme 1](attachment:scheme1.png)

**Scheme 1- Reagents and conditions:**

(a) 1/ (\(\text{CH}_3\)\(_2\)CO, \(\text{FeCl}_3\), 36\(^0\)C, 10 h  2/ \(\text{Na}_2\text{CO}_3\)

(b) \(\text{CCl}_4\),\(\text{Ph}_3\text{P}\)

**Synthesis of N-(fructose) tetracycline (XIII) Scheme -2-**
Compound (XIII) was synthesized in one step, treated 1-chloro-2,3 : 4, 5-di-O-isopropylidene fructopyranose (XII) was treated with tetracycline in the presence of Et₃N in CH₃CN at 25°C to produce tetracycline derivative (XIII) in 23% yield, then stirring with SnCl₂ for 5 h to produce N-(fructose) tetracycline (XIII) 50% yield.

![Scheme 2](image)

Scheme 2- Reagents and conditions:
(a) Et₃N, CH₃CN, 25°C, 6 h  (b) 1/ SnCl₂, 25°C, 5 h . 2/ Na₂CO₃

**Experimental:-**

**General methods:-**

For anhydrous reaction, glassware was dried overnight in an oven at 120°C and cooled in a desicator over anhydrous CaSO₄ or silicagel. Reagents were purchased from fluca (switzerland) or sigma (Louis.USA) Solvents, including dry ether and (CH₃CN), were obtained by distillation from the sodium ketyl of benzophenone under nitrogen. Other solvent including chloroform ethyl acetate, carbon tetrachlorid and hexane were distilled over CaH₂ under nitrogen. Absolute methanol and ethanol were purchased from Merck (Germany). Melting points were obtained with Buch, 510 melting point apparatus. Infrared (FTIR) spectra were recorded on a Beckman I. R-8 spectrophotometer. The wave numbers reported are referenced to the 200 Cm⁻¹ of chloroform. Tetracycline unhydrous was supplied from Samarra drug industries. Samarra, Iraq. The purity of this compound is checked according to m.p and Meric index. UV spectra were carried out using an Hp 8452A diode array spectrophotometer. Purification on silicagel refers to gravity column chromatography on Merck silicagel 60 (particle size 230-400 mesh). Analytical TLC was performed on precoated plates purchased from Merck (Silica gel 60 F 254). Compounds were visualized by using U.V light, I₂ vapor or 2.5% phospho molybic
acid in ethanol with heating.

2,3:4,5-di-O-isopropylidene-β-D-fructopyranose(XI).

To the solution of anhydrous–D-fructose (10 gm, 0.05 mol) in dry acetone (133 mL) was added unhydrous ferric chloride (3 gm), the reaction mixture was stirred at 36°C for 10 h., the solution was concentrated under reduced pressure, and 10% of potassium carbonate was added, then extracted with chloroform (30 *3 mL) the chloroform solution was washed with water (2 * 50 mL), dried over MgSO₄ and filtered, then evaporated under reduced pressure to yield (XI) which was recrystalized from a mixture of chloroform and hexan (1:2) then from petroleum ether to give (XI) [9.3 gm, 0.03 mol] as yellow crystal in 66% yield, m.p 190–191°C, Rf [CH₂Cl₂: CH₃OH] (0.84), FTIR (KBr disk), 3311 cm⁻¹ (O-H str.), 2983 cm⁻¹ (C-H aliphatic) 1250 – 1050 of the acetal (C-O-C). UV (λ max) 291 nm.

1-chloro2,3:4,5-di-O-isopropylidene -β-D- fructopyranose (XII).

To the solution of 2,3:4,5-di-O-isopropylidene -β - D – fructopyranose (XI) (1gm, 3.8 mmol) in dry carbon tetrachloride CCl₄ (30 mL), was added Ph₃P (1.5 gm) the reaction mixture was heated under reflux, with exclusion of water for 90 h. at 70°C. Triphynl phosphine oxide was separated from the mixture after all 10 h., the cold solution was filtered through kieselguhr evaporation under reduced pressure and purification of the residue by use of column chromatography (EtOAC) afforded (XII) [0.9 gm, 3.2 mmol] in 85% yield m.p 140–141°C, Rf (CH₂Cl₂ : CH₃OH 1:0.5) 0.7, FTIR (film) 2900 cm⁻¹ (C-H aliphatic), 696 cm⁻¹ for (C-Cl) UV (chloroform) λ max at 249 nm.

N-(acetyl fructose) tetracycline (XIII).

To (1.1 gm, 2.5 mmol) tetracycline in (50 mL) of CH₃CN and (2.9 mL) Et₃N was added (0.7 gm, 2.5 mmol) 1-chloro 2,3: 4, 5-di- O– isopropylidene-β-D-fructopyranose (XII), the reaction mixture was stirred at 25°C for 10 h., the solution was concentrated under reduced pressure, purification of the residue by using column chromatography (EtOAC/CH₃OH 8.5:1.5) afforded (XIII) (0.37, 0.5 mmol) in 23% yield as sime solid, Rf (CH₂Cl₂ : CH₃OH ,1:0.5) (0.6) FTIR (film) (cm⁻¹) 3320 (N-H aliphatic), 1650 (C=O ketone) 1600 (C=C).

N-(fructose) tetracycline (X).
Compound (XIII)(1gm, 1.4 mmol) was dissolved in 10 mL of chloroform, then adding (0.2 gm) ZnCl₂, with stirring for 3 h. at 25 °C, and 50% KHCO₃ The reaction mixture was poured onto cooled water (50 ml) and extracted with chloroform, washed with water dried over MgSO₄ and filtered, the solution was concentrated then added to a column of silicagel, the column was eluted with chloroform, The major fraction was evaporated to afford (X) in 50% yield as syrup; Rₜ (EtOA : CH₃OH 5:1 ) (0.65); FTIR (film) (cm⁻¹) 3380 (O-H), 3320 (N-H aliphatic) and 1739 (C=O).

![FTIR Spectra](image)

**Fig. 1.** Comparison of FTIR spectra of: a) D-fructose, b) diacetone fructose(XI) and c) Compound (XII).
Fig. 2. Comparison of FTIR spectra of: a) Tetracycline, b) Compound (XIII) and Compound (X).

Acknowledgements

For financial support, thanks give to chemistry department college of science baghdad university for offering requirement to facilitate this work, also compound thanks for Samarra drug industries for supplying me the tetracycline.

References