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Synthises of N-(fructose) tetracycline derivative.

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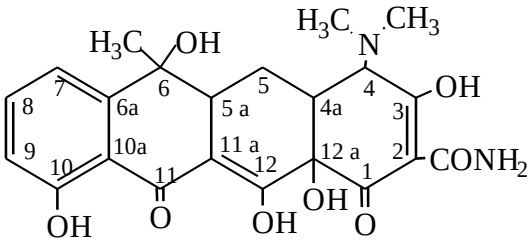
Abstract :

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

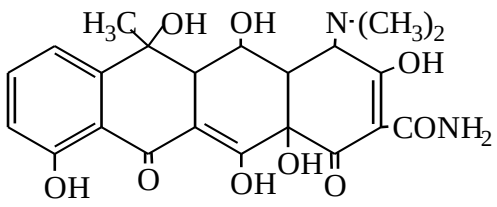
Introduction:-

Tetracycline (I) is one of the most important broad-spectrum antibiotics used in medicine today [1-3].

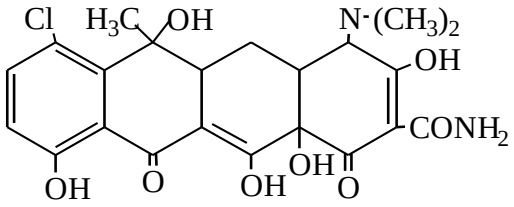


(I)

It hase 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 cosidered to possess characteristic tetracycline activity if it exhibits as much as one -tenth the activity of tetracycline against a number of organisms both in *vitro* and in *vivo*[4] . Among these changes the replacement of 5 - hydrogen by hydroxyl to form oxytetracycline (II) [5] , 7-hydrogen by chlorine to form chlorotetracycline (III)[6], 6- methyl by hydrogen to form demeclocycline (IV)[7],6-hydroxyl by hydrogen to form methacycline (V) [8], 5– hydrogen by hydroxyl and 6-hydroxyl by hydrogen to yield deoxtetracycline (VI) [9,10], 6 –hydroxyl and 6- methyl by hydrogens (VII)[11] .



(II)



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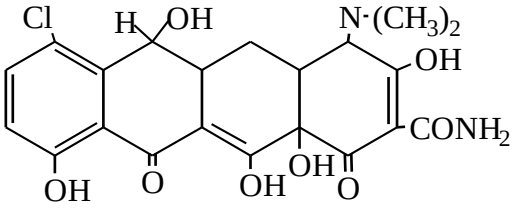

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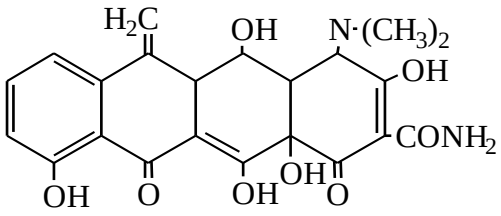

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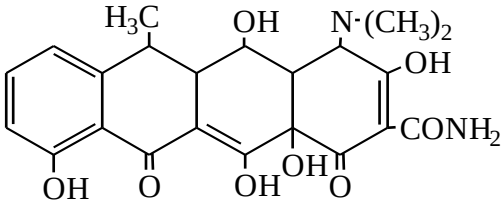

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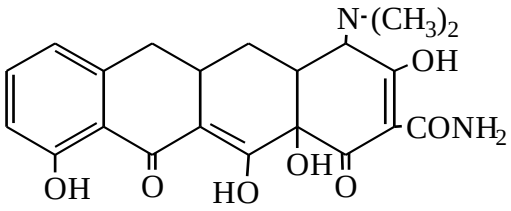
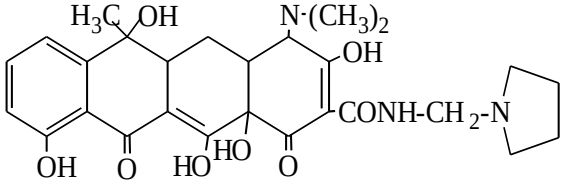


(VII)

All of these derivatives are characterized by there exceptional chemoth- erapeutic efficacy against bacteria, both gram negative , and gram postive . Tetracycline structure has an amide group in postion 2 many reserch found that the interring of (-CH_2- NR_2) group (N –amino mathelation) 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 molcule . 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 with out 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 mean of injecting the antibiotic in a small volume of solution[12,13] .



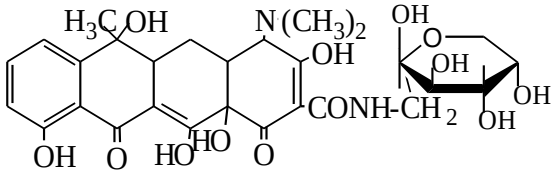
(VIII)

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, bioavilability and the selectivety of drugs [14,15] .

Results and Disccusion

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 increas the water–solubility since the fructose molcule has many free –OH groups . It is hoped that the new synthesized derivative may possess bilogical activity with high solubility in water.



(X)

Chemistry :-

Synthesis of 2,3:4,5-di-o-isopropylidine-*β-D*-fructopyranose(XI) and 1-chloro 2,3:4,5-di-O-isopropylidine-*β-D*-fructopyranose(XII) scheme -1-

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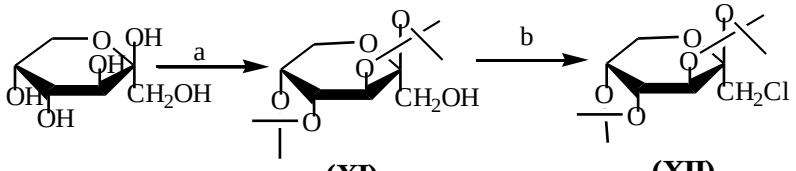
Reaction of unhydrous–D-fructose with dry acetone in the presence of unhydrous ferric chloride ($FeCl_3$) at 36^0 C afforded 2,3:4,5-di-O-isopropylidine-*β-D*-fructopyranose (XI) in 66% yilde[14] then reacted with unhydrous carbon tetrachloride (CCl_4) in the presence of tri phnyl pho- sphen (Ph_3P) at 66^0C for 90 hours yield compound (XII) in 85 % yield.



(XI) **(XII)**

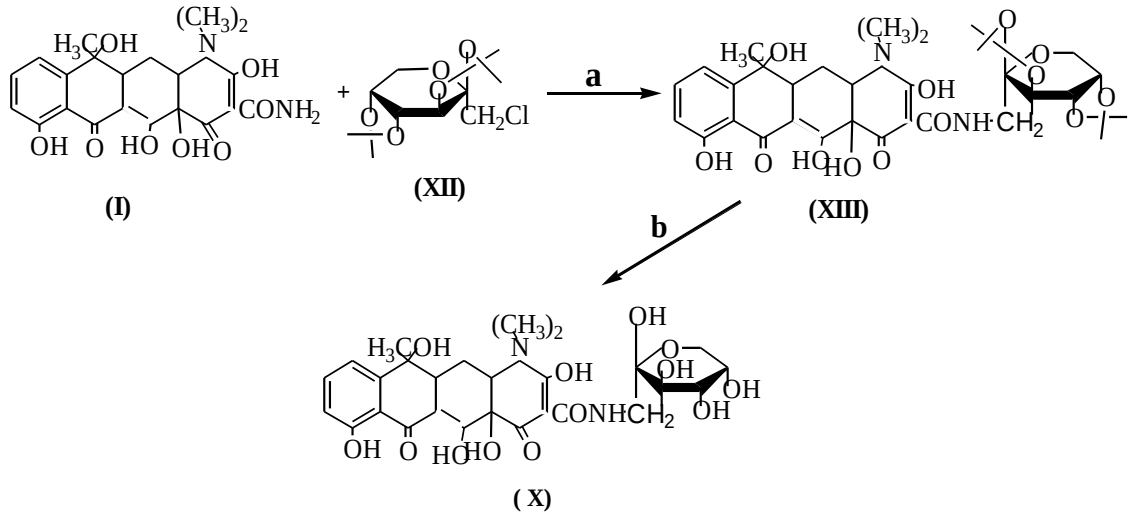
Scheme 1- Reagents and conditions:

(a) 1/ $(CH_3)_2CO$, $FeCl_3$, 36^0 C, 10 h 2/ Na_2CO_3

(b) CCl_4 ,Ph_3P

Synthesis of N-(fructose) tetracycline (XIII) Scheme -2-

Compound (XIII) was synthesized in one step, treated 1-chloro –2 ,3 : 4, 5–di–O-isopropylidine fructopyranose (XII) was treated with tetracycline in the presence of Et_3N in CH_3CN at 25^0C to produce tetracycline derivative (XIII) in 23% yield,then stirring with $SnCl_2$ for 5h. to produce N-(fructose) tetracycline (XIII) 50 % yield .



Scheme 2- Reagents and conditions:

(a) Et_3N, CH_3CN, 25^OC, 6h (b) 1/ $SnCl_2$, 25^0 C,5 h . 2/ Na_2CO_3

Experimental:-

General methods:-

For anhydrous reaction, glassware was dried overnight in an oven at 120^0C and colled in a desicator over anhydrous $CaSO_4$ or silicagel . Reagents were purchased from fluca (switzerland) or sigma (Louis.USA) Solvents, incuding dry ether and (CH_3CN), were obtained by distillation from the sodium ketyl of benzophenone under nitrogen .Other solvent including chloroform ethyl acetate , carbon tetrchlorid and hexane were distilled over CaH_2 under nitrogen . Absolute methanol and ethanol were purchased from Merck (Germany). Melting points were obtained with Buch, 510 melting point appartus. 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 carrid 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 purched from Merck (Silica gel 60 F 254). Compounds were visualized by using U.V light , I_2 vapor or 2.5 % phospho molybic

acid in ethanol with heating .

2,3:4,5-di-O-isopropylidine-*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 36^0C for 10 h ., the solution was concentrated under reduced pressure, and 10% of potassum carbonate was added, then extracted with chloroform (30 *3 mL) the chloroform solution was washed with water (2 * 50 mL), dried over $MgSO_4$ and filtered, then evaporated under reduced pressure to yield (XI) which was recrystalized from a mixture of chloroform and hexan (1:2) then from petrolumether to give (XI) [9.3 gm , 0.03 mol] as yellow crystal in 66 % yield, m.p 190-191^{0}C , R_f [CH_2Cl_2: CH_3OH] (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}) 291nm.

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

To the solution of 2,3:4,5-di-O-isopropylidine - *β* - *D* – fructopyranose (XI) (1gm, 3.8 mmol) in dry carbon tetrachloride CCl_4 (30 mL), was added Ph_3P (1.5 gm) the reaction mixture was heated under reflux, with exclusion of water for 90 h. at 70 ^{0} C. Triphnyl phosphen 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 ^{0}C, R_f (CH_2Cl_2 : CH_3OH 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 CH_3CN and (2.9 mL) Et_3N was added (0.7 gm, 2.5 mmol) 1-chloro 2,3: 4, 5–di– O– isopropylidine-*β*-D-fructopyranose (XII),the reaction mixture was stirred at 25^0 C for 10 h., the solution was concentrated under reduced pressure , purification of the residue by using column chromatography (EtOAC/ CH_3 OH 8.5:1.5) afforded (XIII) (0.37, 0.5 mmol) in 23% yield as sime solid , R_f (CH_2Cl_2 : CH_3OH ,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) $ZnCl_2$, with stirring for 3 h. at 25 ^{0}C , and 50% $KHCO_3$ The reaction mixture was poured onto cooled water (50 ml) and extracted with chloroform,washed with water dried over $MgSO_4$ 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 afforde (X) in 50% yield as syrup ; R_f (EtOA : CH_3OH 5:1) (0.65); FTIR (film) (cm^{-1}) 3380 (O-H), 3320 (N-H aliphatic) and 1739 (C=O).

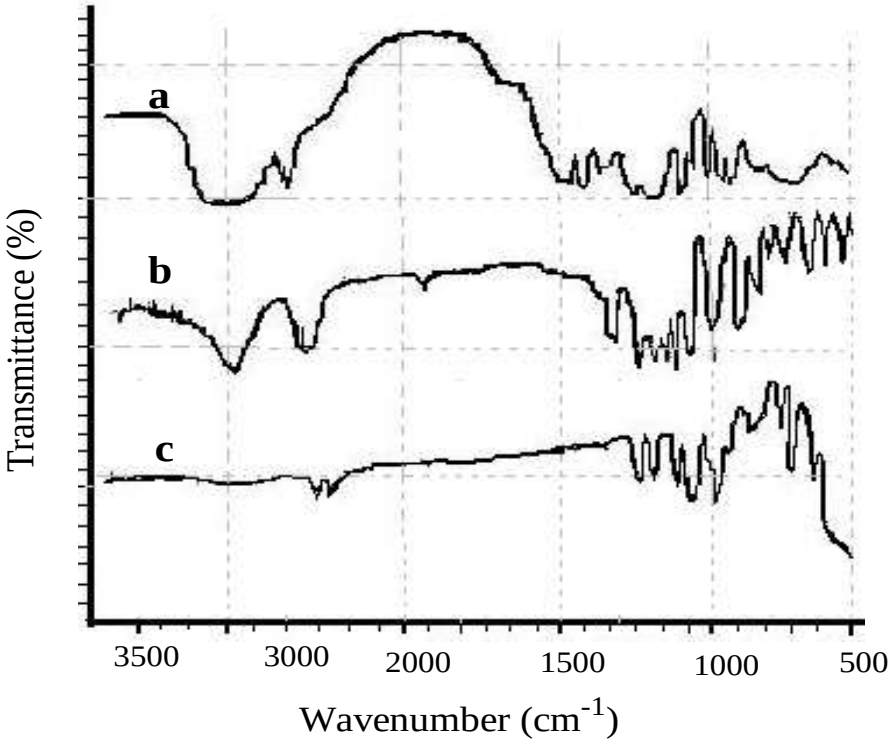


Fig. 1. Comparison of FTIR spectra of : a) D-fructose, b) diacetone fructose(XI) and c) Compound (XII).

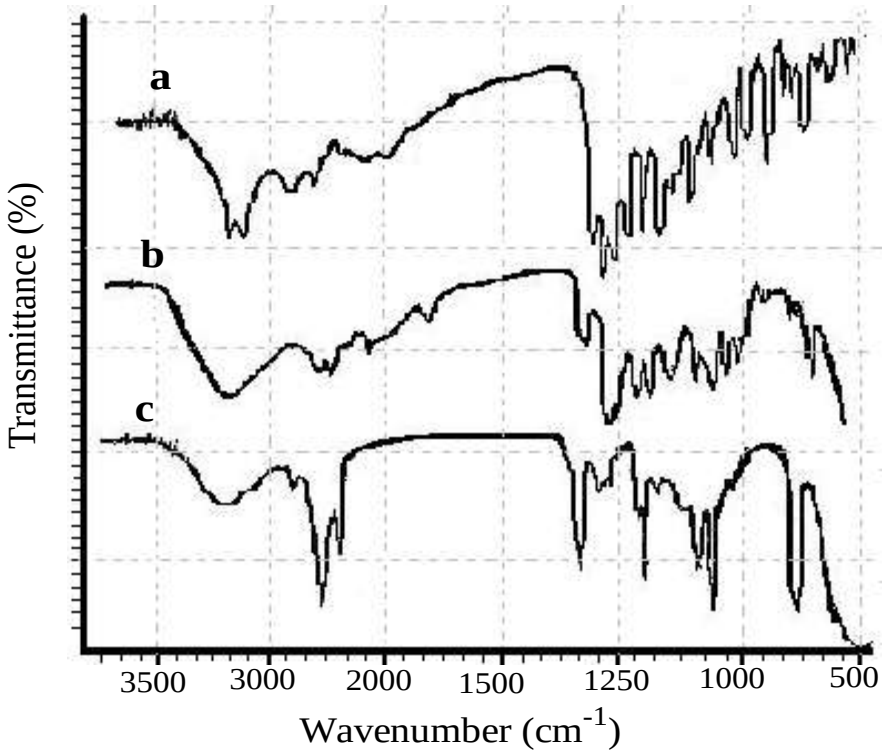


Fig. 2. Comparison of FTIR spectra of : a) Tetracycline, b) Compound (XIII) and Compound (X) .

Acknowledgements

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