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SYNTHESIS OF SOME DERIVATIVES OF 1-(2',3',4',6'-TETRA-O-ACETYL-β-D-GLUCOPYRANOSYL)--3-(4",6"-DIARYLPYRIMIDINE-2"-YL)-THIOUREAS

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SUMMARY

Some compounds of 1-(2',3',4',6'-tetra-O-acetyl-β-D-glucopyranosyl)-3-(4□,6□-diarylpyrimidine-2□-yl)thioureas have been synthesized from corresponding isothiocyanates and 2-amino-4,6-diarylpyrimidines using two different synthetic methods. The hydrolysis of these acetated thioureas leads to form the corresponding deacetyled thioureas. Their spectroscopic properties have been studied.

I - INTRODUCTION

Carbohydrates can serve as structural components of natural products, energy sources or key elements in various biomolecular recognition phenomena. Carbohydrate-mediated signaling is especially important during bacterial and viral infections, cell□cell adhesion in inflammation and metastases implantation, tissue differentiation, development and the regulation of many other inter- and intracellular communication and signal transduction events [1]. The molecules involved are characterized by a wide complexity, which contributes to their diversity and biological activity. In other hand, sugar isothiocyanates are among the most versatile synthetic intermediates in carbohydrate chemistry. They play a pivotal role in the preparation of a broad series of functional groups such as amide, isonitrile, carbodiimide, and N-thiocarbonyl derivatives allowing, simultaneously, the covalent coupling of a quite unrestricted variety of structures to the saccharide part [2, 3]. Moreover, isothiocyanates are important reagents in heterocyclic chemistry, which may be exploited in the synthesis of nucleosides and other N-glycosyl structures [4, 5].

In the present study, we report the synthesis of various glucosyl thioureas containing pyrimidine nucleus, together with some of their spectroscopic properties.

II - EXPERIMENT

Melting point of the synthesized compound was measured by using Thiele's apparatus in capillary and uncorrected. The FTIR-spectra were recorded on Magna 760 FT-IR Spectrometer (NICOLET, USA) in form of mixing with KBr and using reflex-measure method. The ^{1}H-NMR was recorded on an AVANCE Spectrometer (BRUKER, German) at 500 MHz, using DMSO-d6 as solvent and TMS as an internal reference. The high-resolution mass (HR-MS) spectra were recorded in instrument AutoSpec Premier (WATERS, USA).

2,3,4,6-Tetra-O-acetyl-β-D-glucopiranosyl isothiocyanate was synthesized by known method [2, 3].

Synthesis of 1-(2□,3□,4□,6□-tetra-O-acetyl-(β-D-glucopiranosyl)-3-(4□,6□-diarylpyrimidine-2□-yl)-thioureas

General Procedure 1 (Refluxing Method)

In a 50-ml round-bottomed flask were placed 0.494 g (0.002 moles) of 2-amino-4,6-diphenylpyrimidine and 0.778 g (0.002 moles) of 2,3,4,6-tetra-O-acetyl-β-D-glucopiranosyl isothiocyanate. Added 20 ml absolute dioxane in the mixture. Then the mixture was heated in refluxing about 10 hrs. Solvent was removed under reduced pressure to obtained ivory-white or white products. Recrystallized from a mixture of ethanol and toluene (1:1 in volume) obtained ivory-white crystals.

General Procedure 2 (using Microwave Oven)

Mixed 0.494 g (0.002 moles) of 2-amino-4,6-diphenylpyrimidine and 0.778 g (0.002 moles) of 2,3,4,6-tetra-O-acetyl-β-D-glucopiranosyl isothiocyanate. Then this mixture was irradiated about 2-3 min. at 750 Watts. The mixture had become dark-yellow. Cooled it to room temperature, recrystallized from a mixture of ethanol and toluene (1:1 in volume) obtained ivory-white crystals.

Results of these above syntheses were represented in table 1.

Deacetylation of derivatives 1-(2',3',4',6'-tetra-o-acetyl-(β-D-glucopiranosyl)-3-(4",6"-diarylpyrimidine-2"-yl)thioureas

To the solution of 0.138 g of sodium metal in 10 ml of absolute methanol in round-bottomed flask was added 1.00 g of 1-(2',3',4',6'-tetra-O-acetyl-β-D-glucopiranosyl)-3-(4",6"-diphenylpyrimidine-2"-yl)thiourea.
The reaction mixture was stirred until the solid was dissolved. After 24 hrs the obtained solution was neutralized using Wofatit KPS (z.A.) resin (H+-type). Filtered, and the filtrate was distilled under reduced pressure to remove completely the solvent. Obtained porous white powder was recrystallized from ethanol or methanol.

Results of this above synthesis were represented in table 2.

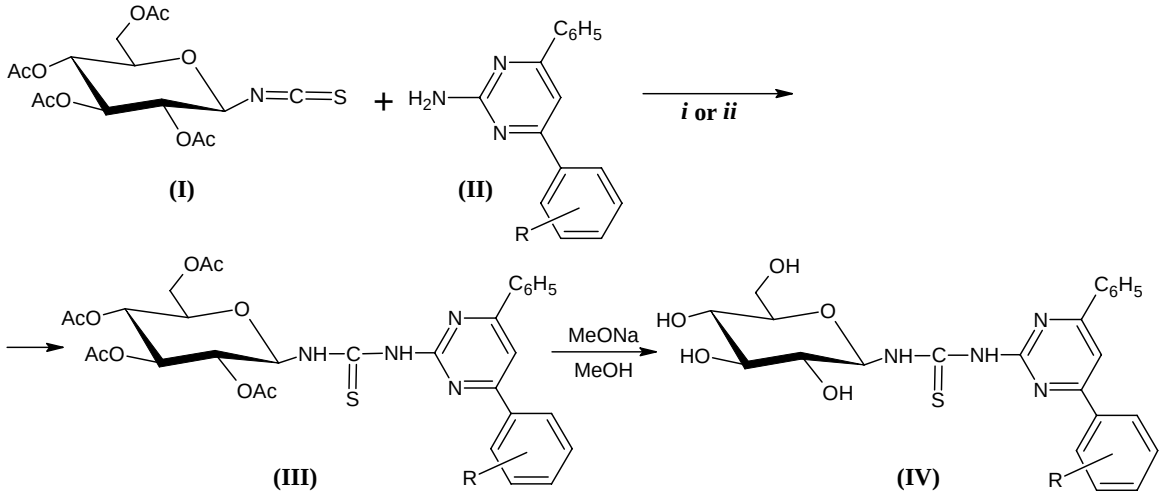
III - RESULTS AND DISCUSSION

1. Synthesis of acetated glucosyl thioureas

The derivatives of 1-(2',3',4',6'-tetra-O-acetyl-β-D-glucopyranosyl)-3-(4",6"-diarylpyrimidine-2"-yl)thioureas (III) could be easily synthesized by the addition of corresponding amino compounds (II) on isothiocyanate derivatives (I). We performed this reaction by using two methods, by refluxing in dried toluene in about 10 hrs [6] or by executing in microwave oven in several minutes [7]. Then obtained acetated glucopyranosyl thioureas have been undergone hydrolysis in the present of natrium methylate into corresponding β-D-glucopyranosyl-3-(4',6'-diarylpyrimidine-2'-yl)thioureas (IV). The synthetic processes could be represented in scheme 1.

We have found that nucleophile addition of 2-amino-4,6-diarylpyrimidine [8] to 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl isothiocyanate has taken place fairly easily. Reaction yields were high in both the methods (refluxing and using MW oven), in 60 - 68% and 72 - 77%, respectively. All these obtained thioureas could be dissolved in common organic solvents (such as ethanol, methanol, toluene, benzene, DMF,…) and couldn't be dissolved in water. Their structures have been affirmed by spectroscopic data (such as IR-, NMR- and mass-spectra).

In the IR-spectrum of these above glucopyranosylthioureas, stretching band of C=S bond in thiourea linkage have appeared in region of 1362 - 1364 cm^{-1}, furthermore, N—H bonds in thioureas have absorption band in region of 3622 - 3410 cm^{-1}, specified for stretching vibration of those bonds. These bands, maybe, have been superimposed each other, hence one absorption band was sometimes appeared in their IR-spectra. These bands were specified for N,N'-substituted thioureas [2, 3]. The characteristic of pentaacetated glucopyranose ring was the present of absorption band in region of 1754-1748 cm^{-1} for stretching vibration of C=O bond in ester function (acetyl group in these cases).



Where, II, III and IV: a R=H, b R=*p*-Cl, c R=*m*-Cl, d R=*p*-Br, d R=*p*-OMe. (**i**) Method A, by refluxing in dried toluene in 10 hrs; (**ii**) Method B, by using microwave oven, 2-3 minutes

Scheme 1: Reaction transformations of tetra-O-acetyl-β-D-glucopyranosyl isothiocyanate

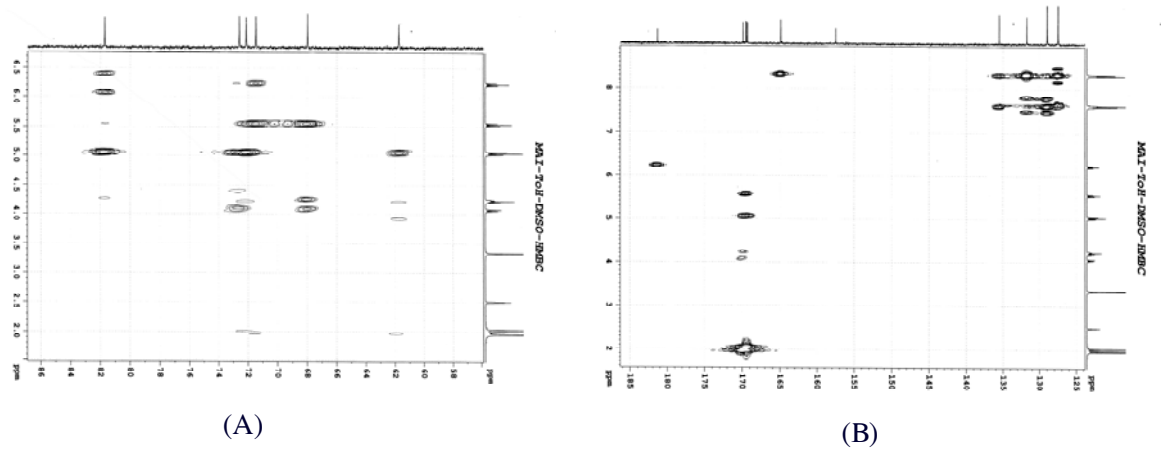
Table 1: Some derivatives of 1-(2',3',4',6'-tetra-O-acetyl-β-D-glucopyranosyl)-3-(4",6"-diarylpyrimidine-2"-yl)thioureas

N°	R	Melting point, °C		Yield, %		IR spectrum, cm^{-1}					
						A			B		
		A	B	A	B	ν_{N-H}	$\nu_{C=Oest}$ ν_{C-O-C}	$\nu_{C=S}$	ν_{N-H}	$\nu_{C=Oest}$ ν_{C-O-C}	$\nu_{C=S}$
IIIa	H	229-230	229-230	60	75	3622; 3531	1754; 1231	1362	3622; 3529	1754; 1231	1362
IIIb	p-Cl	218-219	218-219	68	76	3410	1750; 1222	1364	3410	1750; 1222	1364
IIIc	m-Cl	190-191	190-191	67	72	3410	1750; 1223	1364	3410	1750; 1223	1364
IIId	p-Br	223-224	223-224	66	76	3410	1748; 1223	1363	3410	1748; 1223	1363
IIIe	p-OMe	213-214	213-214	68	77	3434	1750; 1223	1364	3434	1750; 1223	1364

(A): by refluxing; (B): by using microwave oven.

In the ^{1}H-NMR spectra of these thioureas there are the resonance signals which are specified for protons in thiourea-NH groups at δ = 11.157 - 12.036 ppm. Some resonance signals are in region δ = 7.625 - 8.350 ppm belonging to some aromatic protons in amino component. Protons C—H in pyranose ring of monosaccharide have some resonance peaks with chemical shifts from 6.212 ppm to 4.208 ppm as observed in ^{1}H-NMR spectra of monosaccharide compounds [9]. Proton H_1 has chemical shift in region δ = 6.188 - 6.212 ppm (in triplet) with

couple constant J_{12} = 9.0 - 9.5 Hz. Resonance signal of proton H_2 appears in triplet in region δ = 5.020 - 5.064 ppm with J_{21} = 9.0 - 9.5 Hz. The values of couple constant are correlative with *trans*-H—H couple interaction and indicate β-anome configuration of NH-thiourea group [9]. Another protons such as H_3, H_4 have triplet resonance signals in regions δ = 5.516 - 5.531 ppm and δ = 5.020 - 5.036 ppm with couple constants $J_{4,3}$ = 9.5 Hz and $J_{4,5}$ = 9.5 Hz, respectively.



(A) (B)

Figure 1: NMR spectrum of compound IIIa (R=H) using HMBC experiment. (A) aliphatic regions; (B) aromatic regions

In the ^{13}C-NMR spectrum, it could be noticed that number of carbon atoms in spectra and this one in molecular formulas of each thiourea were identical each other. It could be parted the spectra of these thioureas into four regions as follows: 169.297 - 169.930 ppm, 157.549 - 106.736 ppm, 81.730 - 61.718 ppm and 20.479 - 20.174 ppm. The magnetic resonance signals of the carbonyl bonds C=O in acetyl groups have appeared in the low-field region of δ = 169.297 - 169.930 ppm. In addition, there were some resonance peaks in high-field region of 20.479 - 20.174 ppm that is indicated the present of methyl groups on acetyl functions. In HMBC spectra, these peaks had some long-range and short-range C—H interactions with the protons in methyl groups. This aspect was agreed with common resonance position of acetyl group. The aromatic and hetero-aromatic carbon atoms had chemical shifts in region of 157.549 - 106.736 ppm. Six carbon atoms in pyranose ring had clearly resonance signals in region of 81.730 - 61.718 ppm and these peaks also had several C—H interaction types with proton on these carbon atoms or adjacent ones.

In NMR spectra using HMBC and HSQC experiments the long-range and the short-range C—H interactions could be determined (see figure 1). For example, carbon atom C_1 had long-range interaction with proton H_2 and proton H_b; carbon atom C_2 interacted with protons H_1 and H_3, ect... Other long-range interactions in thiourea molecules could show in figure 2.

The mass spectra of tetra-O-acetyl-β-D-glucopyranosylthioureas containing pyrimidine ring had some features that are similar with ones of typical hexopyranose pentaacetates. As expected of such a highly substituted molecule, the molecular ion $M^{+\bullet}$ was of very low intensity and could be hardly detected on the spectra. The only observable peaks in the higher mass range were due to loss of the substituents and fall, therefore, at position of fragment ions such as $[M\text{-AcOH}]^+$, $[M\text{-AcOH,-AcO}]^+$ and $[M\text{-2AcOH,-AcO}]^+$, and some peaks such as $[M\text{-2AcOH,-}C_2H_2O]^+$, $[M\text{-3AcOH,-AcO}]^+$ with intensity of 1 - 3% could be specified for

glycosides having amino structure. A very important mode of fragmentation of these acetated compounds was the loss of acetic acid (*m*/*z* 60), a process well known for most esters of acetic acid, and the loss of ketene (*m*/*z* 42). In mass spectra of these thioureas, it could be indicated that the fragmentation of peracetate derivatives of glucopyranosylthioureas can be divided some tendencies as follows [11]: (a) Fragmentation enclosing cleavage of bond between pyrimidine ring and thiourea group; (b) Cleavage of substituents and cleavage of pyranose ring starting directly from $M^{+\bullet}$; and (c) Cleavage of NH—Glc and formation of fragment ion F_4 (*m*/*z* 331) which is disintegrated in the next steps specifying for the corresponsive acetated monosaccharides.

2. Hydrolysis of acetated glucosyl thioureas

The compounds of 1-(β-D-glucopiranosyl)-3-(4',6'-diarylpyrimidine-2'-yl)thioureas have been obtained through hydrolysis of corresponding 1-(2',3',4',6'-tetra-O-acetyl-β-D-glucopyranosyl)-3-(4",6"-diarylpyrimidine-2"-yl)thioureas using natrium methylate as reagent. The hydrolysis reactions have carried out overnight in room temperature. Some deacetated glucopyranosyl pyrimidinyl thioureas were listed in table 2. The IR-spectrum of have some new absorption bands in region of ~3400 cm^{-1} that specified for hydroxyl groups in glucopyranose ring. The absorption bands specified for acetyl groups in this ring have been disappeared in IR-spectrum.

Table 2: Some derivates 1-(β-D-glucopiranosyl)-3-(4',6'-diarylpyrimidine-2'-yl)thioureas (IV)

N°	R	m.p., °C	Yield, %	IR spectrum, cm^{-1}		
				ν_{OH}	ν_{NH}	$\nu_{C=S}$
IIIa	H	119 - 120	65	3491	3366	1359
IIIb	*p*-Cl	182 - 183	63	3494	3313, 3193	1361
IIIc	*m*-Cl	182 - 183	62	3382		1358
IIId	*p*-Br	184 - 185	64	3493	3293, 3159	1361
IIIe	*p*-OCH_3	174 - 175	62	3386		1361

The ^{1}H-NMR spectrum of representative compound (IVa, R=H) as follows: δ 12.178 ppm (d), 1H, H_b, $J_{a,1}$ = 8.5 Hz; δ 10.886 ppm (s), 1H, H_a; δ 8.334 - 8.309 (m), 4H, $H_{3''}$; $H_{5''}$; $H_{3'''}$; $H_{5'''}$; δ 7.262 - 7.590 (m), 6H, $H_{2''}$; $H_{4''}$; $H_{6''}$, $H_{2'''}$, $H_{4'''}$; $H_{6'''}$; δ 8.305 (s), 1H, $H_{5'}$; δ 3.498 (q), 1H, H_{6a}, $J_{6a,6b}$ = 14.5 Hz; δ 3.665 (q), 1H, H_{6b}, $J_{6b,6a}$=14.5 Hz; δ 5.426 (t), 1H, H_1, $J_{1,a}$ = 9.5 Hz, $J_{1,2}$ = 9.5 Hz; δ 5.109 (d), 1H, H_2, $J_{5,6}$ = 4.5 Hz; δ 4.948 (d), 1H, H_4, $J_{3,4}$ = 9.5 Hz, $J_{3,2}$ = 9.5 Hz; δ 4.448 (t), 1H, H_5, $J_{2,3}$=9.5 Hz, $J_{2,1}$ = 9.5 Hz; δ 5.347 (d), 1H, H_3, $J_{4,3}$ = 9.5 Hz, $J_{4,5}$ = 9.5 Hz; δ 3.190 - 3.239 (m), 4H, 4xOH). The spectroscopic evidences indicated that the acetyl groups have been completely removed out these above thioureas.

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