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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF *N*-LACTOSYLATED DITHIAZOLIDINE (HYDROCHLORIDES)

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ABSTRACT

A series, 4-aryl-5-hepta-*O*-acetyl-β-D-lactosylimino-3-hepta-*O*-acetyl-β-D-lactosylimino-1, 2, 4-dithiazolidine (hydrochlorides) have been synthesized by the interaction of 1-hepta-*O*-acetyl-β-D-lactosyl-3-aryl thiocarbamides and *N*-hepta-*O*-acetyl-β-D-lactosyl-*S*-chloro isothiocarbamoyl chloride. The title compounds were characterized on the basis of elemental analysis and IR, NMR and Mass spectral studies. The title compounds exhibited comparable antimicrobial activities against different pathogens.

Key words: Thiocarbamides, Isothiocarbamoyl chloride, Dithiazolidine (hydrochlorides).

INTRODUCTION

Very few compounds containing thioamido group and having lactosyl substituent on nitrogen are known, which have been studied for their biological activity. Such *N*-lactosylated derivatives[1-3] exhibit a wide range of medicinal activities such as antiviral, antidiabetic, analgesic, antitumor and other significant activities[4-8]. In view of growing interest in synthetic nucleosides in general and our interest in lactosyl nucleoside in particular, a direct synthetic method has been evolved for the synthesis of lactosyl nucleoside having 1,2,4-dithiazolidine ring.

Several 4-aryl-5-hepta-*O*-acetyl-β-D-lactosylimino-3-hepta-*O*-acetyl-β-D-lactosylimino-1, 2, 4-dithiazolidine (hydrochlorides) have been prepared for the first time by the interaction of 1-hepta-*O*-acetyl-β-D-lactosyl-3-aryl thiocarbamides (**1**) and *N*-hepta-*O*-acetyl-β-D-lactosyl-*S*-chloro isothiocarbamoyl chloride (**2**).

EXPERIMENTAL

Melting points are uncorrected. All the products were crystallized from ethanol-

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water before recording the physical data. Optical rotations were measured at 31°C. IR spectra[9-11] were recorded in the range 4000-450 cm^{-1}. ^1H NMR spectra[12,13] were obtained at 300 MHz for solutions in $CDCl_3$ (reference to TMS). The FAB mass spectra[14,15] were recorded on a Jeol SX-102 /Da-600 mass spectrometer/data system using argon/xenon (6 kV, 10 mA) as the FAB gas. The accelerating voltage was 10 kV, and the spectra were recorded at room temperature. *m*-Nitrobenzyl alcohol (NBA) was used as the matrix unless specified otherwise. Thin layer chromatography was conducted on E. Merck TLC aluminium sheet silica gel 60 F_{254}.

Satisfactory C, H analyses were obtained for all the compounds.

The required 1-hepta-*O*-acetyl-β-D-lactosyl-3-aryl thiocarbamides were prepared by already known method[16].

Preparation of 4-phenyl-5-hepta-O-acetyl-β-D-lactosylimino-3-hepta-O-acetyl-β-D-lactosylimino-1, 2, 4-dithiazolidine (hydrochloride) (3a)

A chloroform solution of *N*-hepta-*O*-acetyl-β-D-lactosyl-*S*-chloro isothiocarb-amoyl chloride (1.86 g, 0.0025 M in 5 mL) was added to a chloroform solution of 1-hepta-*O*-acetyl-β-D-lactosyl-3-phenyl thiocarbamides (1.92 g, 0.0025 *M*, in 25 mL). The reaction mixture was refluxed over a boiling water bath for 3 hrs. A brisk reaction with evolution of HCl was noticed. The excess of $CHCl_3$ was distilled off and the resultant syrupy mass was triturated several times with petroleum ether (60-80°) to afford pale yellow solid **(3a)** (3.48 g, 92.36%). The solid was crystallized from ethanol-water, m.p.135-140°C.

IR (KBr) : ν 2963.5 (C-H aliphatic), 1752.2 (C = O), 1546.9 (C = N), 1373.0 (C - N), 1228.7 (C-O), 757.9 (C-S), 696.3 (monosubstituted phenyl ring), characteristic of lactose at 1051.8 and 901.9 cm^{-1}; ^1H NMR δ 7.25 (5H, s, Ar - H), δ 5.35 - 3.77 (28H, m, lactose ring protons), δ 2.18 - 1.96 ppm (42H, m, acetyl protons); Mass spectrum (*m/z*) 1518 (M^+), 898, 648, 620, 560, 331, 279, 169, 109. (Found: C, 47.42; H, 4.88; N, 2.71; S, 4.28, Calcd for $C_{60}H_{75}O_{34}N_3S_2.2HCl$, : C, 47.46; H, 4.94; N, 2.76; S, 4.21 %).

The above chemical evidences established the structure as 4-phenyl-5-hepta-*O*-acetyl-β-D-lactosylimino-3-hepta-*O*-acetyl-β-D-lactosylimino-1, 2, 4-dithiazolidine (hydro-chloride) (**3a**).

On extending the above reaction to several other 1-hepta-*O*-acetyl-β-D-lactosyl-3-aryl thiocarbamides (**2b–g**), corrosponding products (**3b-g**) have been isolated.

Table 1: 4-Aryl-5-hepta-*O*-acetyl-β-D-lactosylimino-3-hepta-*O*-acetyl-β-D-lactosylimino-1, 2, 4-dithiazolidine (hydrochlorides)

Lactosyl thiocarbamides	g	Product	Yield (%)	M.P. (°C)	$[\alpha]_D^{31}$ (c, $CHCl_3$)	R_f	Analysis (%)	
							Found	Calcd
-3-Phenyl	1.92	**3a**	92.36	135-140	+70.86	0.80	N, 2.71; S, 4.28	N, 2.76; S, 4.21
-3-*o*-Cl-Phenyl	2.01	**3b**	94.81	128-130	+125.58	0.70	N, 2.68; S, 4.19	N, 2.70; S, 4.12
-3-*m*-Cl-Phenyl	2.01	**3c**	80.95	120-122	+65	0.65	N, 2.64; S, 4.20	N, 2.70; S, 4.12
-3-*p*-Cl-Phenyl	2.01	**3d**	98.44	128-130	+130.9	0.71	N, 2.64; S, 4.08	N, 2.70; S, 4.12
-3-*o*-Tolyl	1.96	**3e**	96.16	132-135	+115.59	0.76	N, 2.69; S, 4.20	N, 2.74; S, 4.18
-3-*m*-Tolyl	1.96	**3f**	92.20	146-150	+99.19	0.78	N, 2.68; S, 4.22	N, 2.74; S, 4.18
-3-*p*-Tolyl	1.96	**3g**	95.80	140-142	+77.17	0.56	N, 2.70; S, 4.20	N, 2.74; S, 4.18

(a) 1-Hepta-*O*-acetyl-β-D-lactosyl-3-aryl thiocarbamides (0.0025 M)

(b) *N*-Hepta-*O*-acetyl-β-D-lactosyl-*S*-chloro isothiocarbamoyl chloride (0.0025 M, 1.86 g)

(3b) : IR (KBr): ν 2964.1 (C-H aliphatic), 1753.6 (C = O), 1541.3 (C = N), 1373.3 (C–N), 1229.5 (C-O), 1053.4 and 903.1 cm^{-1} (characteristic of sugar), 757.8 cm^{-1} (C-S); ^1H NMR δ 7.27 (4H, s, Ar - H), δ 5.35 - 3.87 (28H, m, lactose ring protons), δ 2.18 - 1.70 ppm (42H, m, acetyl protons); Mass spectrum (*m/z*) 1553 $(M+1)^+$, 1479, 932, 842, 620, 331, 211, 109. (Found: C, 46.38; H, 4.72; N, 2.66; S, 4.19, Calcd for $C_{60}H_{74}O_{34}N_3S_2Cl$ .2HCl,: C, 46.42; H, 4.77; N, 2.70; S, 4.12 %).

(3c): ^1H NMR δ 7.26 (4H, s, Ar – H), δ 5.52 - 3.35 (28H, m, lactose ring protons), δ 2.16– 1.97 ppm (42H, m, acetyl protons). (Found: C, 46.38; H, 4.73; N, 2.64; S, 4.20, Calcd for $C_{60}H_{74}O_{34}N_3S_2Cl$ .2HCl, : C, 46.42; H, 4.77; N, 2.70; S, 4.12 %).

(3d): ^1H NMR δ 7.19 (4H, s, Ar – H), δ 5.35 - 3.68 (28H, m, lactose ring protons), δ 2.27 - 1.75 ppm (42H, m, acetyl protons). (Found: C, 46.36; H, 4.73; N, 2.64; S, 4.08, Calcd

for $C_{60}H_{74}O_{34}N_3S_2Cl$ .2HCl, : C, 46.42; H, 4.77; N, 2.70; S, 4.12 %).

(3e): ^{1}H NMR δ 7.19 (4H, s, Ar - H), δ 5.52 - 3.74 (28H, m, lactose ring protons), δ 2.58 (3H, s, Ar - CH_3), 2.23 - 1.97 ppm (42H, m, acetyl protons) (Found: C, 47.78; H, 4.98; N, 2.69; S, 4.20, Calcd for $C_{61}H_{77}O_{34}N_3S_2$ .2HCl, : C, 47.81; H, 5.02; N, 2.74; S, 4.18 %).

(3f): ^{1}H NMR δ 7.26 (4H, s, Ar - H), δ 5.53 - 3.53 (28H, m, lactose ring protons), δ 2.46 (3H, s, Ar – CH_3), 2.43 – 1.86 ppm (42H, m, acetyl protons) (Found: C, 47.76; H, 4.97; N, 2.68; S, 4.22, Calcd for $C_{61}H_{77}O_{34}N_3S_2$. 2HCl, C, 47.81; H, 5.02; N, 2.74; S, 4.18 %).

(3g) : IR (KBr): ν 2961.5 (C-H aliphatic), 1751.5 (C = O), 1545.5 (C = N), 1374.3 (C–N), 1230.7 (C-O), 1051.5 and 905.2 cm^{-1} (characteristic of sugar), 772.4 cm^{-1} (C-S); ^{1}H NMR δ 7.27 (4H, s, Ar - H), δ 5.35 - 3.76 (28H, m, lactose ring protons), δ 2.44 (3H, s, Ar-CH_3), 2.29 - 1.97 ppm (42H, m, acetyl protons); Mass spectrum (*m/z*) 1531 (M^+), 782, 619, 560, 331, 169, 109. (Found: C, 47.76; H, 4.96; N, 2.70; S, 4.20, Calcd for $C_{61}H_{77}O_{34}N_3S_2$ .2HCl, : C, 47.81; H, 5.02; N, 2.74; S, 4.18 %).

RESULTS AND DISCUSSION

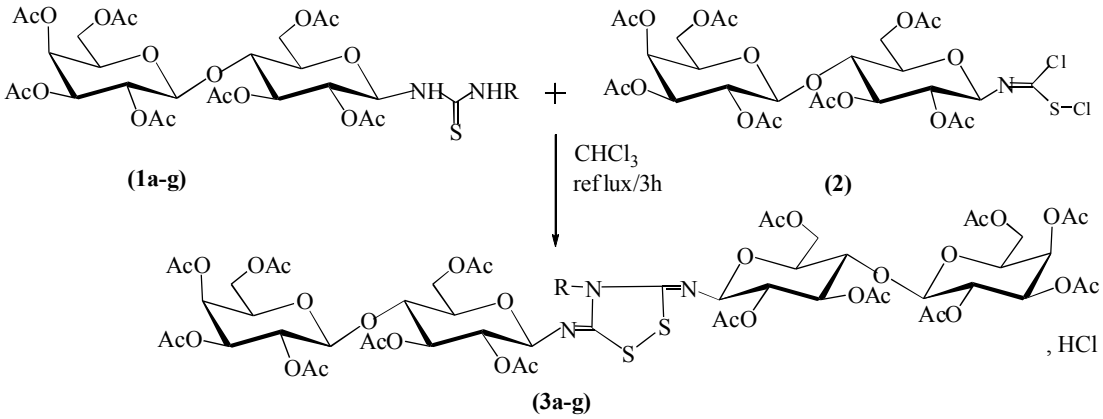
The reagent 1-hepta-*O*-acetyl-β-D-lactosyl-*S*-chloro isothiocarbamoyl chloride[17] was prepared by passing calculated quantity of gaseous chlorine into the chloroform solution of hepta-*O*-acetyl-β-D-lactosyl isothiocyanate, when a resultant yellow colour solution was obtained. When the interaction of this reagent with 1-hepta-O-acetyl- β-D-lactosyl-3-aryl thiocarbamides was carried out in $CHCl_3$ medium (refluxed for 3 hrs), evolution of HCl was noticed. On distilling off the solvent, the resultant viscous oily mass was triturated with petroleum ether (60-80°) to give pale yellow solid (**3**). This solid was crystallized from ethanol-water. It was found non-desulphurisable, when boiled with alkaline lead acetate solution. The specific rotation was measured in chloroform[18] and R_f value[19] was recorded.

Microbial activity

Antibacterial activity

The compounds were screened for their antibacterial activities against various pathogenic bacteria such as *Escherichia coli, Staphylococcus aureus, Salmonella typhi, Proteus vulgaris* and *Pseudomonas* by cup plate method[20] at a concentration 10 μgmL^{-1} in DMSO by using the standard cotrimazine. All the compounds showed higher activity against *Salmonella typhi, Proteus vulgaris* and *Pseudomonas.* The compounds **(3a)**, **(3e)** and **(3f)**

showed moderate activity against *Staphylococcus aureus* whereas all the compounds were found resistant against *Escherichia coli*.



Where R = (a) Phenyl, (b) *o*-Cl-Phenyl, (c) *m*-Cl-Phenyl, (d) *p*-Cl-Phenyl, (e) *o*-Tolyl, (f) *m*-Tolyl and (g) *p*-Tolyl

Ac = -$COCH_3$ (acetyl)

Antifungal activity

All the compounds were also screened for their antifungal activities by cup plate method at a concentration 10 μgmL^{-1} in DMSO by using the standard griseofulvin against *Aspergillus niger* and *Fusarium riazoctomia*. All the compounds showed good activity against both the fungi.

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