



SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 4-ARYL-5-HEPTA-O-BENZOYL- β -D-LACTOSYLIMINO-3-THIO-1,2,4-DITHIAZOLIDINES [HYDROCHLORIDE]

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ABSTRACT

4-Aryl-5-hepta-O-benzoyl- β -D-lactosylimino-3-thio-1,2,4-dithiazolidines [Hydrochloride] have been prepared by the interaction of N-hepta-O-benzoyl- β -D-lactosyl-S-chloro-isothiocarbamoyl chloride and ammonium aryl dithiocarbamates. These newly synthesized compounds were also screened for their antimicrobial and antifungal activities against-*Escherichia coli*, *Proteus vulgaris*, *Staphylococcus aureus*, *Salmonella typhi*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Aspergillus niger* and *Candida albicans*. The newly synthesized compounds have been characterized by IR, ^1H NMR and mass spectral studies. The purity of these compounds was confirmed by TLC.

Key words: Lactosyl isothiocyanate, Isothiocarbamoyl chloride, Dithiocarbamates, 1,2,4-Dithiazolidine hydrochloride, Antimicrobial activity.

INTRODUCTION

Very few compounds containing thioamido group and having lactosyl substituents on nitrogen are known, which have been studied for their biological activity¹⁻³. The drug containing 1,2,4-dithiazolidines^{4,5} show a diverse range of physiological activities such as plant growth promoting activity, antituberculosis⁶ antibacterial, anticancer, and antidiabetic⁷. The above applications of 1,2,4-dithiazolidines and our interest in the carbohydrate chemistry prompts us to combine them in a single entity.

Several 4-aryl-5-hepta-O-benzoyl- β -D-lactosylimino-3-thio-1, 2, 4-dithiazolidines. Hydrochloride have been prepared for the first time by the interaction of N-hepta-O-benzoyl- β -D-lactosyl-S-chloro-isothiocarbamoyl chloride (**1**)⁸ and various ammonium-aryl-dithiocarbamate (**2a-f**)⁹.

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EXPERIMENTAL

Melting points were taken in open capillary tubes and are uncorrected. Specific rotations were measured on Equip Tronics Digital Polarimeter at 31°C in CHCl₃, IR spectra were recorded on Perkin-Elmer Spectrum RXI – FTIR spectrophotometer (4000-450 cm⁻¹). ¹H NMR spectra were recorded in CHCl₃ on Bruker DRX spectrometer operating at 300 MHz (reference to TMS). The mass spectra were recorded on Joel – SX 102 (FAB) instrument. Thin layer chromatography was conducted on E. Merck TLC aluminium sheet silica gel 60F₂₅₄.

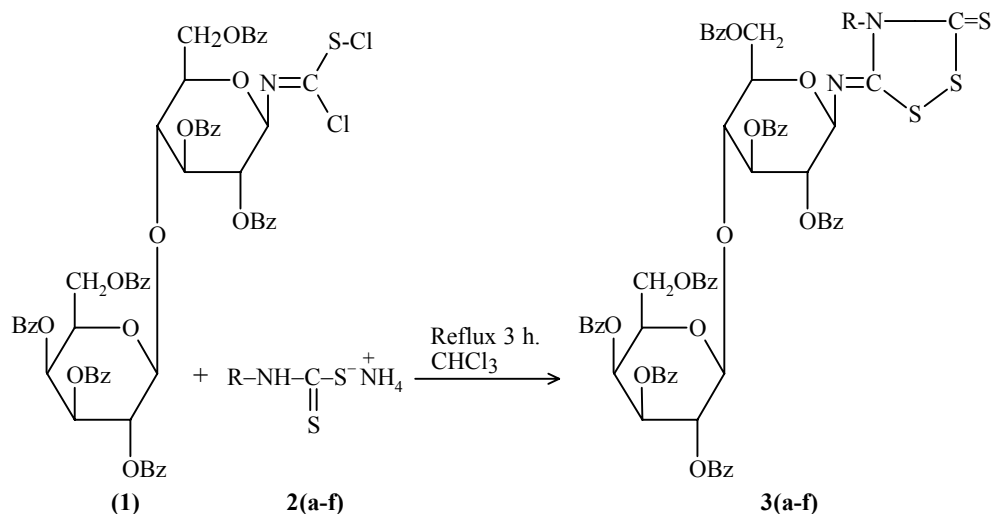
The required N-hepta-O-benzoyl-β-D-lactosyl-S-chloro-isothiocarbamoyl chloride (**1**) and ammonium-aryl-dithiocarbamate (**2a-f**) were prepared by the method described earlier.

Preparation of 4-phenyl-5-hepta-O-benzoyl-β-D-lactosylimino-3-thio-1,2,4-dithiadiazolidine (Hydrochloride) (**3a**)

The reaction of N-hepta-O-benzoyl-β-D-lactosyl-S-chloro-isothiocarbamoyl chloride (2.426 g, 0.002 M in 10 mL) and ammonium-phenyl-dithiocarbamate (0.37 g, 0.002 M, in 10 mL) was refluxed in chloroform over a boiling water bath for 3 h. The reaction proceeds with evolution of HCl. The excess of CHCl₃ was distilled off and the resultant syrupy mass was triturated several times with petroleum ether (60-80°C) to afford pale yellow solid (**3a**) (2.0 g, 72.04%). The solid was recrystallised by chloroform-petroleum ether, m.p. 145°C.

(3a) IR (KBr) ν (cm⁻¹): 3067.2 (Ar-H), 2966.7 (C-H aliphatic), 1730.2 (C=O), 1655 (C=N), 1270 (C-O), 1176.1 (C=S), 1026.3 (-S-C(=S)-N), 1098.3, 905.5 (characteristic of β-D-lactosyl ring) 769.2 (C-S), 709.2 (monosubstituted benzene ring), 506 (S-S); **¹H NMR** (δ in ppm) CDCl₃; δ 8.2-7.18 (40H, m, 7 COC₆H₅, C₆H₅) δ 6.33-3.59 (14H, m, lactose ring protons); **Mass spectrum** (m/z) 1314 (M⁺), 1203, 1053 (HBL⁺), 931, 948, 579 (TBG⁺), 105; Analytical calculations for C₆₉H₅₄O₁₇N₂S₃, HCl Required: C, 63.01; H, 4.109; N, 2.130; S, 7.305 %; Found C, 64.07; H, 4.45; N, 2.24; S, 7.413 %.

The above chemical evidences established the structure of 4-phenyl-5-hepta-O-benzoyl-β-D-lactosylimino-3-thio-1,2,4-dithiazolidine [Hydrochloride] (**3a**). On extending the above reaction to several other ammonium aryl dithiocarbamates (**2a-f**) have been isolated.



Where, OBz = COC₆H₅

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

Scheme 1

(1) N-Hepta-O-benzoyl-β-D-lactosyl-S-chloro-isothiocarbamoyl chloride

(2a-f) Ammonium Aryl dithiocarbamates.

(3b) IR (KBr) ν (cm⁻¹): 3067.8 (Ar-H), 2965.4 (C-H aliphatic), 1729.2 (C=O), 1654.3 (C=N), 1270.4 (C-O), 1176.2 (C=S), 1026.7 (-S-C(=S)-N), 1069.7, 906.7 (characteristic of β-D-lactose ring), 770.2 (C-S), 709.8 (monosubstituted benzene ring), 518.6 (S-S); **¹H NMR** (δ in ppm) CDCl₃: 8.18-7.09 (39H, m, 7 COC₆H₅, C₆H₄) CDCl₃; 6.53-3.51 (14 H, M, lactose ring protons); **Mass spectrum** (m/z): 1349 (M⁺), 1237, 1053 (HBL⁺), 931, 578.9 (TBG⁺). Analytical calculations for C₆₉H₅₃O₁₇N₂S₃Cl.HCl Required; C, 61.401; H, 4.004; N, 2.076; S, 7.00 %. Found C, 62.83; H, 4.108; N, 2.33; S, 7.23 %

(3e) IR (KBr) ν (cm⁻¹): 3065.8 (Ar-H), 2962.9 (C-H aliphatic), 1727.9 (C=O), 1601.5 (C=N), 1269.2 (C-O), 1157.8 (C=S), 1026.5 (characteristic of lactosyl ring), 758.4 (C-S), 709.9 (monosubstituted benzene ring), 514.5 (S-S); **¹H NMR** (δ in ppm) CDCl₃: 8.19-7.0 (39 H, m, COC₆H₅, C₆H₄), 6.58-3.56 (14H, m, lactose ring protons); **Mass spectrum** (m/z): 1328 (M⁺), 1217, 1053 (HBL⁺), 930, 580 (TBG⁺). Analytical calculations for C₇₀H₅₆O₁₇N₂S₃.HCl Required; C, 63.25; H, 4.22; N, 2.11; S, 7.23 % Found C, 64.33; H, 4.31; N, 2.20; S, 7.34 %

Table 1: 4-Aryl-5-hepta-O-benzoyl- β -D-lactosylimino-3-thio-1, 2, 4-dithiazolidines [Hydrochloride]

Ammonium aryl dithiocarbamates	g	Product	Yield (%)	m.p. (°C)	$[\alpha]_D^{31}$ CHCl ₃	R _f	Analysis (%)	
							Found	Calcd
-Phenyl	0.37	3a	72.04	145	- 479.9	0.56	N, 2.19 S, 7.30	N, 2.24 S, 7.33
-o-Cl-Phenyl	0.44	3b	69.72	129	+ 22.50	0.83	N, 2.07 S, 7.11	N, 2.11 S, 7.15
-m-Cl-Phenyl	0.44	3c	84.0	140	+ 57.50	0.62	N, 2.07 S, 7.11	N, 2.13 S, 7.18
-p-Cl-Phenyl	0.44	3d	79.03	145	+ 102.5	0.46	N, 2.07 S, 7.11	N, 2.12 S, 7.16
-o-Tolyl	0.49	3e	78.94	118	+ 182.5	0.85	N, 2.10 N, 7.22	N, 2.13 S, 7.26
-p-Tolyl	0.49	3f	73.07	135	+ 67.50	0.86	N, 2.10 S, 7.22	N, 2.15 S, 7.28

(1): N-Hepta-O-benzoyl- β -D-lactosyl-S-chloro isothiocarbamoyl chloride (2.22 g, 0.002 M, 10 mL chloroform)

(2): Ammonium aryl dithiocarbamate (0.002 M, 10 mL chloroform)

RESULTS AND DISCUSSION

4-Aryl-5-hepta-O-benzoyl- β -D-lactosylimino-3-thio-1, 2, 4-dithiazolidines [Hydrochloride] (**3a-f**) were prepared by the reaction of N-hepta-O-benzoyl- β -D-lactosyl-S-chloro-isothiocarbamoyl chloride (**1**) with ammonium-aryl-dithiocarbamate (**2a-f**) in CHCl₃. After condensation, the solvent was distilled off to obtain a sticky residue. This residue was triturated with petroleum ether (60-80°C) to afford a pale yellow solid (**3a-f**). The product was found desulphurisable, when boiled with alkaline lead acetate solution. The specific rotation was measured in chloroform. The reaction can be easily monitored by TLC and R_f values were also recorded.

Antimicrobial activity

All the compounds have been screened for both; antimicrobial and antifungal activity

by using disc diffusion assay. For this, sterial filter paper disc (6 mm) impregnated with fixed doses of compounds was placed on pre-innoculated surface. The disc bearing plates were incubated at 37°C for 24 h. After incubation, zone diameter were measured. The compounds were taken at a concentration or 1 mg/mL using dimethyl sulphoxide as a solvent. Amikacin (100 µg/mL) was used as standard for antibacterial and fluconazole (100 µg/mL) as a standard for antifungal activity. The compound were screened for antibacterial activity against *Eschrichia coli*, *Proteus vulgaris*, *Staphylococcus aureus*, *Salmonella typhi*, *Klebsiella pneumonie* and *Psudomonas aeruginosa* in nutrient agar medium and for, antifungal activity against *Aspergillus niger* and *Candida albicance* in potato dextrose agar medium. It has been observed that all the compounds showed good activity against both; bacteria and fungi.

Compound	<i>E.c</i>	<i>S.a</i>	<i>P.v</i>	<i>P.a</i>	<i>S.t</i>	<i>K.p</i>	<i>A.n</i>	<i>C.a</i>
3a	17	16	20	19	18	21	19	20
3b	10	15	15	12	20	19	20	21
3c	18	14	19	17	15	18	17	19
3d	14	19	18	18	19	20	20	19
3e	16	13	12	10	15	17	24	22
3f	13	14	20	16	17	20	22	20
DMSO	-	-	-	-	-	-	-	-
Amikacin	18	21	23	19	20	21	-	-
Fluconazole	-	-	-	-	-	-	24	24

Zone of inhibition in mm. (15 or less) resistance, (16-20 mm) moderate and more than (20 mm) sensitive

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