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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-*Escherichi coli*, *Proteus vulgaris*, *Staphylococcus aureus*, *Salmonella typhi*, *Klebsiella pneumonie*, *Psudomonas aeruginosa*, *Aspergillus niger and Candida albicance*. The newly synthesized compounds have been characterized by IR, ^{1}H NMR and mass spectral studies. The purity of these compounds was confirmed by TLC.

Key words: Lactosyl isothiocynate, 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 activity[1-3]. The drug containing 1,2,4-dithiazolidines[4,5] show a diverse range of physiological activities such as plant growth promoting activity, antituberculosis[6] antibacterial, anticancer, and antidibetic[7]. 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 $CHCl_3$, IR spectra were recorded on Perkin-Elmer Spectrum RXI – FTIR spectrophotometer (4000-450 cm^{-1}). ^1H NMR spectra were recorded in $CHCl_3$ 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 $60F_{254}$.

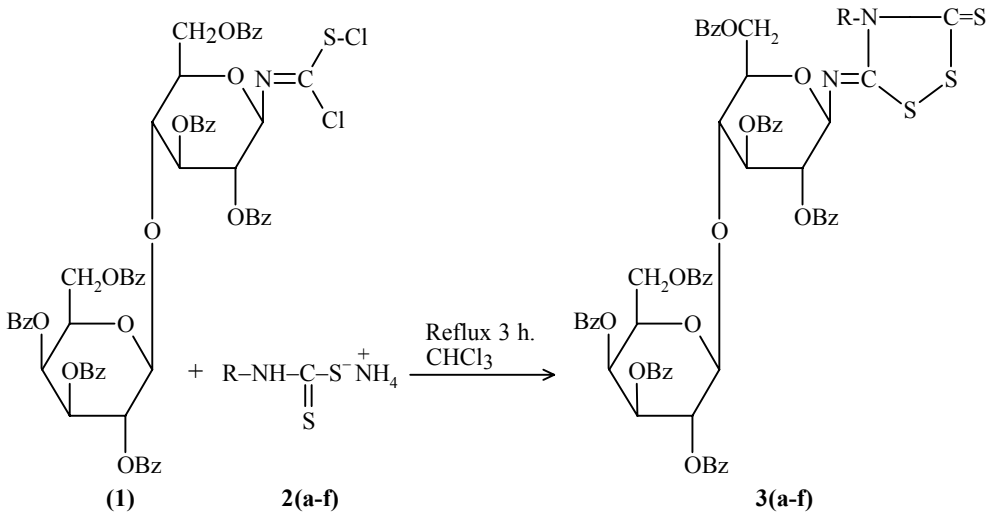
The required N-hepta-O-benzoyl-β-D-lactosyl-S-chloro-isothiocarbamoyl chloride **(1)** and ammonium-aryl-dithiocarbamate **(2a-f)** were prepared by the method described earlier.

Preparation of 4-phenyl-5-hepta-O-benzoyl-β-D-lactosylimino-3-thio-1,2,4-dithiadithiazolidine (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 escess of $CHCl_3$ 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) *v* (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); **^{1}H NMR** (δ in ppm) $CDCl_3$; δ 8.2-718 (40H, m, 7 COC_6H_5, C_6H_5,) 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 $C_{69}H_{54}O_{17}N_2S_3$, 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.



(1) **2(a-f)** **3(a-f)**

Where, OBz = COC_6H_5

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 dithiacarbamates.

(3b) IR (KBr) *v* (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); **^{1}H NMR** (δ in ppm) $CDCl_3$: 8.18-7.09 (39H, m, 7 COC_6H_5, C_6H_4) $CDCl_3$; 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 $C_{69}H_{53}O_{17}N_2S_3Cl.HCl$ 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) *v* (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 (charectristic of lactosyl ring), 758.4 (C-S), 709.9 (monosubstituted benzene ring), 514.5 (S-S); **^{1}H NMR** (δ in ppm) $CDCl_3$; 8.19-7.0 (39 H, m, COC_6H_5,C_6H_4), 6.58-3.56 (14H, m, lactose ring protons); **Mass spectrum** (m/z); 1328 (M^+), 1217, 1053 (HBL^+), 930, 580 (TBG^+). Analytical calculations for $C_{70}H_{56}O_{17}N_2S_3$. 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 dithiacarbamates	g	Product	Yield (%)	m.p. (^oC)	$[\alpha]_D^{31}$ $CHCl_3$	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 $CHCl_3$. After condensation, the solvent was distilled off to obtain a sticky residue. This residue was triturated with petroleum ether (60-80^{o}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	***E.c***	***S.a***	***P.v***	***P.a***	***S.t***	***K.p***	***A.n***	***C.a***
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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