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Synthesis and Antimicrobial Properties of Bis-Thiocarbamides

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ABSTRACT

Several per-*O*-acetyl and per-*O*-benzoyl glycosylbis-thiocarbamides were synthesized by the interaction of glycosylisothiocyanates and o-phenylenediamine. The identities of these newly synthesized compounds were established on the basis of usual chemical transformations, IR, ^{1}H NMR and Mass spectral studies. All the synthesized compounds have been evaluated for their antibacterial and antifungal activity against different bacteria and fungi by agar diffusion method.

Keywords: Glycosylbis-thiocarbamides, glycosylisothiocyanate, antimicrobial analysis.

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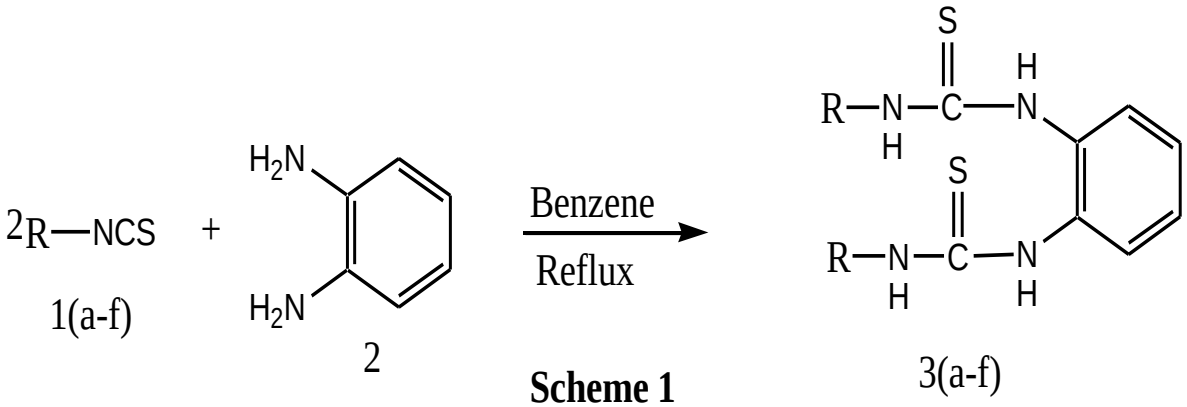
INTRODUCTION

The chemistry of thiourea and their derivatives of saccharides are extensively elaborated and documented for their biological properties. Literature survey reveals that urea and thiourea derivatives showed a broad spectrum of biological activities as antioxidant, antibacterial, antimicrobial, anti HlV activity, anti malarial and anticancer [1]. Some derivatives are biologically active, such as antifungal[2-3], antitumour[4-6], antiviral, herbicidal, insecticidal[7-9] and pharmacological[10] properties.

In view of the advantage conferred by glycosylthiourea, it was interesting to carry out synthesis of various per-*O*-acetyl and per-*O*-benzoyl glycosylthiocarbamides by the interaction of per-*O*-acetyl and per-*O*-benzoyl glycosylisothiocyanate with o-phenylenediamine in 2:1 ratio (Scheme 1).

MATERIALS AND METHOD

All melting points were uncorrected and obtained in capillary using paraffin bath. Specific rotations of the newly synthesized compounds were measured on Equip-Tronic digital polarimeter model No. EQ 801 at 30^{O}C in $CHCl_3$. IR spectra were recorded on Shimatzu FTIR spectrophotometer, ^{1}H NMR were obtained on a Bruker DRX-300 (300 MHz FT NMR) NMR spectrophotometer in $CDCl_3$ solution with TMS as an internal reference. The Mass spectra were recorded on a Jeol SX-102 FAB mass spectrometer. Purity of the compound was checked by thin layer chromatography using Merck silica gel coated aluminium plates and petroleum ether : ethyl acetate as eluent and iodine vapours as a visualizing agent.



Scheme 1

Where, R = a) Tetra-*O*-acetyl-β-D-glucopyranosyl b) Hepta-*O*-acetyl-β-D-lactosyl
c) Hepta-*O*-acetyl-β-D-maltosyl d) Tetra-*O*-benzoyl-β-D-glucopyranosyl
e) Hepta-*O*-benzoyl-β-D-lactosyl f) Hepta-*O*-benzoyl-β-D-maltosyl

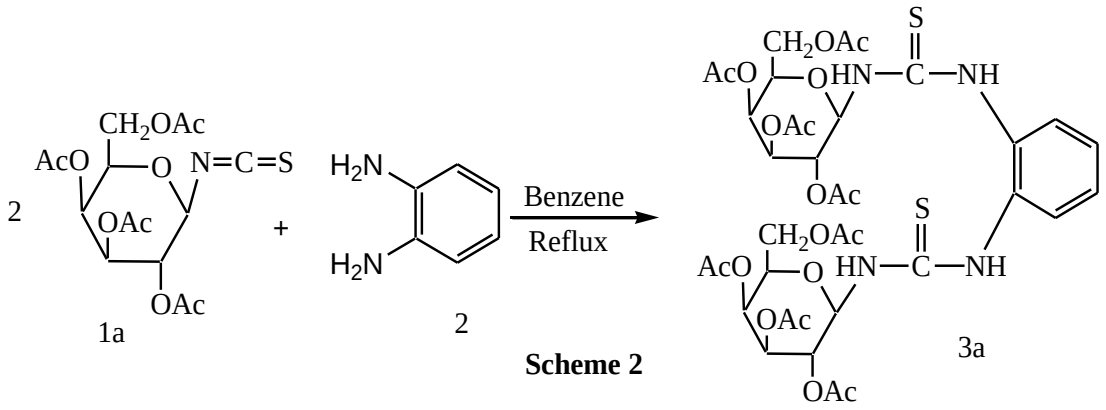
Synthesis of per-*O*-acetyl and per-*O*-benzoyl glycosylisothiocyanates :

The required glycosyl isothiocyanates[11] were prepared by earlier known method by the interaction of glycosyl bromide and lead thiocyanate, while o-phenylenediamine was purchased from S. D. fine-chem. limited company (SDFCL). All the chemicals used were of high purity.

RESULTS AND DISSCUSSION

N^1N^2Bis[(Tetra-*O*-acetyl-β-D-glycosyl) thiocarbamide]-1,2-diaminobenzene (3a):

N^1N^2Bis[(Tetra-*O*-acetyl-β-D-glycosyl) thiocarbamide]-1,2-diaminobenzene **(3a)** was synthesized by interaction of Tetra-*O*-acetyl-β-D-glucosylisothiocyanate (0.006M , 4.062g) **(1a)** and *O*-phenylenediamine (0.003M, 0.324g) **(2)** in benzene, was refluxed for 12 h while monitoring the reaction by TLC. After the completion of reaction benzene was distilled off and resultant syrupy mass was triturated several times with petroleum ether (60-80 ^{O}C), to afford white granular solid **(3a)** purified from chloroform-petroleum ether (**Scheme 2**). The characterization of product **(3a)** was established by usual chemical transformation, IR[12],^{1}H NMR[13-17],^{13}CNMR and Mass[18] spectral studies.



Scheme 2

N^1N^2Bis[(Tetra-*O*-acetyl-β-D-glycosyl) thiocarbamide]-1,2-diaminobenzene (3a):

$C_{38}H_{46}O_{18}N_4S_2$; **IR (KBr)** ν cm^{-1} : 3387 (N-H str.), 1745 (C=O str.), 1629 (N-H bend.), 1498,1473 (Ar. C=C str.), 1377 (C=S str.), 1226 (C-O str.);**^{1}H NMR** ($CDCl_3$) δ ppm : 2.18-2.02 (24H, s, 8 x $COCH_3$), 3.79-5.75 (14H, m, glucosyl-H), 7.70 (1H, s, N-H), 6.55 (1H, s, N-H), 6.33 (1H, s, N-H), 2.13 (1H, s, N-H) 7.27-6.70 (4H, m, Ar-H) **Mass** : 886 (M^+) not located, 791, 520, 413, 353, 109

All other thiocarbamides**(3b-f)** were prepared in a similar manner.

N^1N^2Bis[(Hepta-*O*-acetyl-β-D-lactosyl) thiocarbamide]-1,2-diaminobenzene (3b):

$C_{60}H_{78}O_{34}N_4S_2$; **IR (KBr)** ν cm^{-1} : 3356 (N-H str.), 1747 (C=O str.), 1633 (N-H bend.), 1504,1454 (Ar. C=C str.), 1373 (C=S str.), 1224 (C-O str.);**^{1}H NMR** ($CDCl_3$) δ ppm : 2.18-1.96 (42H, s, 14 x $COCH_3$), 5.66-3.75 (28H, m, lactosyl-H), 7.65 (1H, s, N-H), 6.25 (1H, s, N-H),

2.10 (1H, s, N-H), 0.89 (1H, s, N-H) 7.27-6.71 (4H, m, Ar-H); **Mass** : 1462(M^+), 808, 701, 659, 559, 331, 109.

N^1N^2Bis[(Hepta-*O*-acetyl-β-D-maltosyl) thiocarbamide]-1,2-diaminobenzene (3c):

$C_{60}H_{78}O_{34}N_4S_2$; **^{1}H NMR** ($CDCl_3$) δ ppm : 2.19-1.95 (42H, s, 14 x $COCH_3$), 5.75-3.82 (28H, m, maltosyl-H), 7.53 (1H, s, N-H), 6.80 (1H, s, N-H), 6.71 (1H, s, N-H), 2.22 (1H, s, N-H) 7.36-6.99 (4H, m, Ar-H) **Mass** : 1462(M^+), 1427, 808, 752, 701, 331, 109.

N^1N^2Bis[(Tetra-*O*-benzoyl-β-D-glucopyranosyl) thiocarbamide]-1,2-diaminobenzene (3d):

$C_{76}H_{62}O_{18}N_4S_2$; **IR (KBr)** ν cm^{-1} : 3329 (N-H str.), 1732 (C=O str.), 1629 (N-H bend.), 1531,1450 (Ar. C=C str.), 1371 (C=S str.), 1267 (C-O str.);**^{1}H NMR** ($CDCl_3$) δ ppm : 6.32-4.28(14H, m, glucosyl-H), 3.64 (2H, hump, 2 x N-H), 2.16 (1H, s, N-H), 2.23 (1H, s, N-H) 8.09-6.74 (44H, m, Ar-H)**Mass** : 1382(M^+), 768, 746, 520, 413, 353, 177.

Table 1: Characterization data of compounds 3(a-f)

Compound	% yield	M.P. (^{O}C)	Required (Found)	
			%N	%S
3a	66%	117-125	6.32 (6.30)	7.22 (7.25)
3b	58%	96	3.83 (3.79)	4.37 (4.39)
3c	61%	128	3.83 (3.81)	4.37 (4.34)
3d	74%	123	4.05 (4.01)	4.63 (4.66)
3e	56%	146	2.40 (2.42)	2.74 (2.76)
3f	52%	138-142	2.40 (2.38)	2.74 (2.77)

Antimicrobial activity:

These newly synthesized glycosyl bis-thiocarbamides were screened against different pathogenic microbes for their antibacterial and antifungal activities using standard method[19], using Gentamycine and Nystatine as standard compounds for antibacterial and antifungal screening respectively.

Procedure for antimicrobial screening:

Media used (Nutrient broth): Peptone – 10 g, NaCl – 10 g and yeast extract 5 g, Agar 20 g in 1000 ml of distilled water. Initially, the stock culture of bacteria were revived by inoculating in broth media and grown at 37 ^{0}C for 18 h. The agar plates of the above media were prepared and wells were made in the plate. Each plate was inoculated with 18 h old culture and spread evenly on the plate. After 20 min. the wells were filled with different samples of concentration 0.01 g in 1ml DMSO. All the plates were incubated at 37 ^{O}C for 24 h and the diameter of inhibition zones were noted in mm.

Table-2: Antimicrobial activity of glycosylbis-thiocarbamides (3a-f)

Compounds	Inhibition Zone in mm				
	E. coli	S. aureus	Ps. aeruginosa	Niger	Trichoderma
3a	14	16	14	14	13
3b	13	15	R	12	12.5
3c	11	18	14	11	12
3d	11	18	23	10	11
3e	14	19	20	12	14
3f	12	17	21	13	13

R- Resistant

Antibacterial study of synthesized compounds indicate that compound 3f shows significant activity while 3c, 3d, 3e were found to be active against S. aureus. 3d, 3e, and 3f shows most significant activity against *Ps. aeruginosa* while all other compounds exhibited low to moderate activity against *S. aureus, Pseudomonas, E. coli, A. niger and Tricoderma.*

CONCLUSION

N-Substituted glycosylbis-thiocarbamides were synthesized and characterized. Various chemical and spectral data supported the structures. The method adopted in this investigation is simple, efficient and inexpensive. Thus, the newly synthesized title compounds, exhibits comparable antibacterial activities against the organisms tested. So these compounds due to their appreciable activity towards these micro-organisms are biologically active and useful in the future for the preparation of pharmacologically important derivatives.

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