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Synthesis, Characterization and Microbial assay of some novel *S*-hepta-*O*-acetyl maltosyl-1-aryl dithiocarbamates

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ABSTRACT

Carbohydrate science has been extensively studied and many excellent reviews are available. *N* and *S*-linked derivatives of various sugars have received a great attention because of their vital role in several biological processes. Ureas, thioureas and their derivatives have strong antibacterial, antitumor activities. They also play an important role in organic synthesis as intermediates. This considerable attention has been directed towards the synthesis of various thiomaltosides. A series of *S*-hepta-*O*-acetyl maltosyl-1-aryl dithiocarbamates have been synthesized by the interaction of hepta-*O*-acetyl maltosyl bromide and various ammonium aryl dithiocarbamates in isopropanolic medium. The newly synthesized compounds have been characterized by analytical and IR, ^{1}H NMR and Mass spectral analysis. The polarimetric study of the compounds has been carried out. Antibacterial and antifungal activities of these compounds were determined on *E. coli, S. aureus, Ps. aeruginosa, S. typhi, R. oligosporus* and *A. niger*. These compounds show appreciable activity towards these microorganisms.

Keywords: Maltosyl bromide, ammonium aryl dithiocarbamates, maltosyl aryl dithiocarbamates, Microbial assay.

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INTRODUCTION

Anomeric blocking groups are widely used in carbohydrate synthesis[1]. Per-*O*-acetyl protected glycosyl bromide is in general use[2]. Derivatives of thiourea, dialkyl dithiocarbamates, thiols are found useful in the synthesis of compounds containing *S*-glycosidic bond. These compounds have attracted attention because of their known fungicidal, insecticidal and anticarcinogenic properties[3]. Various reports of synthesis of glucosyl[4], lactosyl[5] and galactosyl[6] aryldithiocarbamates are on record. In view of applications of these compounds some efforts are done to synthesize maltosyl aryl dithiocarbamates.

In this communication, we report the synthesis of *S*-hepta-*O*-acetyl maltosyl-1-aryl dithiocarbamates (IIIa-f) by the interaction of hepta-*O*-acetyl maltosyl bromide (I) and ammonium aryl dithiocarbamates (IIa-f).

MATERIALS AND METHODS:

Experimental:

All the melting points recorded using open capillary tube on Mac digital melting point apparatus and were found to be uncorrected. The structures of newly synthesized compounds were confirmed on the basis of elemental and spectral analysis. The IR spectra of the compounds were recorded in KBr Disks on SHIMADZU IR affinity-1-FTIR spectrometer. ^{1}H NMR spectra are run on Brucker DRX-300 instrument operating at 300 MHz using $CDCl_3$ solution with TMS at internal standard. The mass spectra were recorded on a WATERS, Q-T OF Micromass (LC-MS) having an ESI source in positive mode Mass Spectrometer. Specific rotations were measured on Equip-Tronics EQ-801 Digital Polarimeter in $CHCl_3$. To check purity thin layer chromatography was performed on E. Merck pre-coated silica gel plates and spot were visualized by iodine vapours.

General Procedure:

The reagents required for the synthesis of *S*-maltosides were synthesized as follows:

1. Synthesis of Hepta-*O*-acetyl maltosyl bromide (I)

Hepta-*O*-acetyl maltosyl bromide was prepared by the interaction of maltose octa acetate with brominating reagent. **(Scheme 1)**

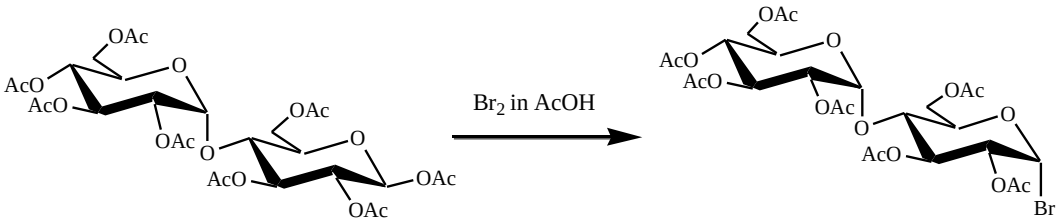
2. Ammonium aryl dithiocarbamates[7] (IIa-f)

Ammonium aryl dithiocarbamates were prepared by the interaction of ammonia, carbon disulphide and aryl amines.

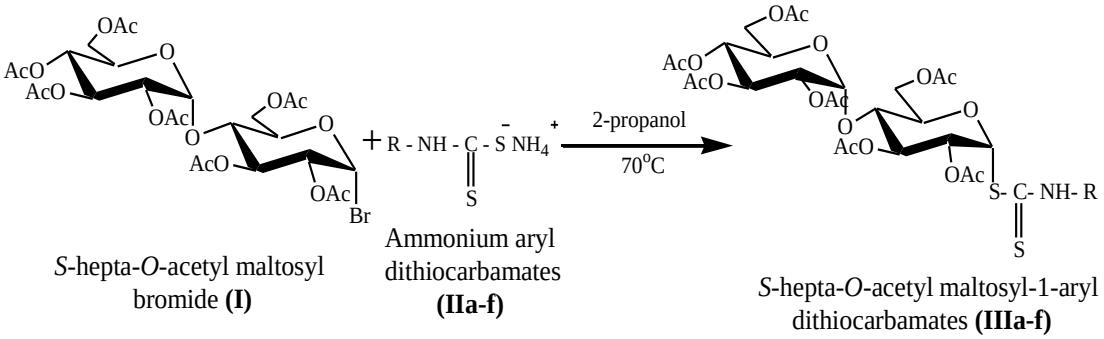
3. Synthesis of Hepta-*O*-acetyl maltosyl-1-aryl dithiocarbamates (IIIa-f)

Isopropanolic suspension of hepta-*O*-acetyl maltosyl bromide (0.005M, 3.5 gm, 20 ml) was mixed with an isopropanolic suspension of ammonium aryl dithiocarbamates (0.005M, 0.93 gm, 10 ml). This mixture was heated on water bath at about 70°C, until the suspension gets cleared. The clear solution was then kept at room temperature for 18 h. It was then mixed with 100 ml distilled water. The aqueous solution was basified with ammonium hydroxide afforded a sticky mass which was not solidified on standing for several hours. The sticky mass was purified by ethanol-water and solid was obtained. **(Scheme 2)**

Scheme for synthesis shown as follows:



Scheme 1



Scheme 2

Where,

R = a) Phenyl, b) *o*-tolyl, c) *p*-totyl, d) *o*-Cl-phenyl, e) *m*-Cl-phenyl, f) *p*-Cl-phenyl

Ac = -$COCH_3$.

RESULTS AND DISCUSSION:

Herein, we report the synthesis of various Hepta-*O*-acetyl maltosyl-1-aryl dithiocarbamates (IIIa-f) by the interaction of hepta-*O*-acetyl maltosyl bromide (I) and ammonium aryl dithiocarbamates (IIa-f) in isopropanol medium. All products were crystallized from ethanol-water before recording the physical data (Table 1). The purity of compounds was checked by TLC. Optical rotation of the product was also recorded. The IR, ^{1}H NMR, Mass spectral analysis[8-12] clearly indicated the product and assign the structure as *S*-hepta-*O*-acetyl maltosyl-1- aryl dithiocarbamate (IIIa-f)

Table 1: **Physical characterization of *S*-hepta-*O*-acetyl maltosyl-1-aryl dithiocarbamates (IIIa-f)**

Reactants: -

1. Hepta-*O*-acetyl maltosyl bromide (I)
2. Ammonium aryl dithiocarbamates (IIa-f

Sr.No.	*S*-hepta-*O*-acetyl maltosyl-1-aryl-dithiocarbamates	Yield (%)	M.P.(°C)	R_f Value 6:4 EtO Ac :Pet. Ether	$[\alpha]_D^{30}$ (c, in $CHCl_3$)	Elemental analysis (%) Found(Required)	
						N	S
1.	IIIa	59.23	130-136	0.86	+130.43° (c, 0.092)	1.73 (1.77)	8.08 (8.13)
2.	IIIb	43.58	148-150	0.93	+142.85° (c, 0.098)	1.70 (1.74)	7.94 (7.99)
3.	IIIc	51.05	157-160	0.92	+113.40° (c, 0.097)	1.69 (1.74)	7.96 (7.99)
4.	IIId	54.73	156-158	0.96	-145.83° (c, 0.096)	1.66 (1.70)	7.75 (7.79)
5.	IIIe	52.21	122-125	0.82	+204.08° (c, 0.098)	1.67 (1.70)	7.74 (7.79)
6.	IIIf	49.81	145-147	0.93	-161.29° (c, 0.098)	1.65 (1.70)	7.76 (7.79)

C and H analysis were found satisfactory in all cases.

Spectral Analysis:

IIIa) Hepta-*O*-acetyl maltosyl-1-phenyl dithiocarbamates:

IR(KBr, cm^{-1}): ν 3420 (N-H), 3118 (Aromatic C-H), 2902 (Aliphatic C-H), 1745 (C=O), 1313 (C-N), 1228 (C-O), 1039 (Characteristics of maltose), 758 (C-S); ^1H NMR ($CDCl_3$, ppm): δ 7.8-7.2 (5H, m, aromatic protons), 6.25-6.23 (1H, s, NH), 5.4-3.7 (14H, m, maltosyl protons), 2.2-2.0 (21H,m, acetyl protons); Mass (*m/z*): 787 ($M^{+\cdot}$), 683 ($M^{+\cdot}$- $C_4H_8O_3$), 619 ($M^{+\cdot}$-$C_7H_6NS_2$), 559 (HAM-$C_2H_4O_2$), 331 (HAM-$C_{10}H_{12}O_6$), 229 $(C_{10}H_{12}O_6)^+$, 169 $(C_8H_9O_4)^+$,126 $(C_6H_6O_3)^+$, 109 $(C_6H_5O_2)^+$. Anal. Calcd. for $C_{33}H_{41}O_{17}NS_2$: C, 50.31; H, 5.20; N, 1.77; S, 8.13%. Found: C, 50.27; H, 5.16; N, 1.73; S, 8.08%.

IIIc) Hepta-*O*-acetyl maltosyl-1-*p*-tolyl dithiocarbamates:

IR(KBr, cm^{-1}): ν 3398 (N-H), 3024 (Aromatic C-H), 2949 (Aliphatic C-H), 1745 (C=O), 1375 (C-N), 1230 (C-O), 1039 (Characteristics of maltose), 702 (C-S); ^1H NMR ($CDCl_3$, ppm): δ 7.265-7.225 (4H, m, aromatic protons), 6.592 (2H,s,NH), 5.4-3.7 (14H, m, maltosyl protons), 2.3-2.0 (21H, m, acetyl protons), 1.254 (3H, s, methyl protons); Mass (*m/z*): 801 ($M^{+\cdot}$), 619 ($M^{+\cdot}$-$C_8H_8NS_2$), 559 (HAM-$C_2H_4O_2$), 331 (HAM-$C_{10}H_{12}O_6$), 169 $(C_8H_9O_4)^+$,108 $(C_6H_4O_2)^+$. Anal. Calcd. for $C_{34}H_{43}O_{17}NS_2$: C, 50.93; H, 5.36; N, 1.74; S, 7.99%. Found: C, 50.89; H, 5.31; N, 1.69; S, 7.96%.

IIIf) Hepta-*O*-acetyl maltosyl-1-*p*-Cl-phenyl dithiocarbamates:

IR(KBr cm^{-1}): ν 3411 (N-H), 3176 (Aromatic C-H), 2978 (Aliphatic C-H), 1745 (C=O), 1377 (C-N), 1234 (C-O), 1043 (Characteristics of maltose), 713 (C-S);); ^{1}H NMR ($CDCl_3$, ppm): δ 7.4-6.9 (4H, m, aromatic protons), 6.15-6.0 (2H, s, NH), 5.3-3.9 (14H, m, maltosyl protons), 2.1-2.0 (21H, m,7-acetyl protons); Mass (*m/z*): 821 ($M^{+\cdot}$), 619 ($M^{+\cdot}$-$C_7H_5NS_2Cl$), 559 (HAM-$C_2H_4O_2$), 331 (HAM-$C_{10}H_{12}O_6$), 169 $(C_8H_9O_4)^+$, 126 $(C_6H_6O_3)^+$, 102 $(C_4H_5O_3)^+$. Anal. Calcd. for $C_{33}H_{40}O_{17}NS_2Cl$: C, 48.23; H, 4.87; N, 1.70; S, 7.79%. Found: C, 48.19; H, 4.83; N, 1.65; S, 7.76%.

Microbial assay:

All the compounds have been screened for both antimicrobial and antifungal activity using cup plate agar diffusion method[13-14] by measuring the inhibition zone in mm. the compounds were taken at a concentration of 1 mg/ml using dimethyl sulphoxide (DMSO) as solvent.

Amikasin (100 µg/ml) was used as standard for antibacterial activity. The compounds were screen for antibacterial activity against *Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa* and *Salmonella typhi species* by using Nutrient Agar medium. The compounds were screen for antifungal activity against *Rhizopus oligosporus* and *Aspergillus niger species* was determined by using Potato Dextrose Agar medium. Fluconazole (100 µg/ml) was used as standard for antifungal activity. These sterilized agar media were poured into Petri dishes and allowed to solidify. On the surface of the media microbial suspensions were spread with the help of sterilized cotton swab. After inoculation the well was punched by using sterile stainless steel cork borer of 6mm diameter. In to these wells were added 0.1 ml portion of the test compounds in solvent. The drug solution was allowed to diffuse for an hour into the medium. The plate was incubated at 37°C for 24 hours and 30°C for 48 hours for antibacterial and for antifungal activities respectively. The zone of inhibition observed around the cups after respective incubation was measured.

Table 2: **Antimicrobial activity of *S*-hepta-*O*-acetyl maltosyl-1-aryl dithiocarbamates (IIIa-f)**

Compounds	**Antibacterial****				**Antifungal****	
	E. coli	*S. aureus*	*S.typhi*	*Ps. aeruginosa*	*R. oligosporus*	*A. niger*
IIIa	23	19	18	16	21	14
IIIb	16	24	22	16	18	13
IIIc	17	20	15	17	17	17
IIId	14	23	22	17	20	14
IIIe	28	22	19	18	22	18
IIIf	25	19	13	21	20	19
Amikacin	29	25	23	22	-	-
Fluconazole	-	-	-	-	24	21

**zone of inhibition in mm (15 or less) resistance, (16-20mm) moderate and (more than 20mm) sensitive. *Escherichia coli* (*E.* coli), *Staphalococcus aureus* (*S.* aureus), *Salmonella typhi* (*S. typhi*), *Psudomonas aeruginosa* (*Ps. aeruginosa*), *Rhizopus oligosporus (R. oligosporus)* and Aspergillus *niger* (*A. niger*).

Antibacterial studies of these compounds indicated that all compounds exhibited most significant activity against *S. aureus* and *Ps. aeruginosa*. IIIa, IIIb, IIIc, IIIe and IIIf show appreciable activity towards *E. coli*. All compounds show good activity against *S. typhi* except IIIc and IIIf. All the other compounds exhibited low to moderate activity. The results are presented in Table-2.

The compounds were screen for antifungal activity against *Rhizopus oligosporus* and *Aspergillus niger species* was determined by using Potato Dextrose Agar medium. Fluconazole (100 µg/ml) as standard for antifungal activity

The results of antifungal activities are also tabulated in Table 2. All compounds displayed promising activity against *R. oligosporus*. IIIc, IIIe and IIIf are effective towards *A. niger*. While other compounds inhibited moderate to low activity.

CONCLUSION:

A series of *S*-hepta-*O*-acetyl maltosyl-1-aryl dithiocarbamates have been synthesized and assign the structures of compounds on the basis of chemical transformations and IR, ^{1}H NMR, and Mass spectral studies. These compounds were screened for their antibacterial and antifungal activities. Thus, the newly synthesized thiomaltosides, exhibits comparable antibacterial and antifungal activities against the organisms tested. The method adopted in this investigation is simple, efficient and inexpensive and is useful in synthesizing pharmacologically important molecules.

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