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PREPARATION AND SOME REACTIONS OF D-GLUCOSYL DERIVATIVES OF 2-THIOXO-1,3,4-OXADIAZOLES AND 2-THIOXO-1,3,4-THIADIAZOLES AND THEIR 2-OXO ANALOGUES*

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ABSTRACT

2-Thioxo-1,3,4-oxadiazoles (**1a,b**) and 2-thioxo-1,3,4-thiadiazoles (**1c,d**) reacted with tetra-*O*-acetyl-α-D-glucopyranosyl bromide in the presence of potassium hydroxide to yield thioglucosides (**2a-d**, respectively, in good yield) and *N*-glucosyl derivatives (**3a–d**, respectively, in poor yield). Oxidation of **2a–d** with potassium permanganate yielded the corresponding sulphones (**4a–d**), whereas **3a–d** yielded the corresponding 2-oxo derivatives (**5a–d**). The acetates **2a–d**, **3a–d**, and **5a–d** were deacetylated with ammonia to give the parent D-glucosyl derivatives. The products were characterized by u.v. and i.r. spectroscopy.

INTRODUCTION

1,3,4-Oxadiazoles possess analgesic, antipyretic, and antiphlogistic properties[1,2], and show bactericidal and antitubercular activity[3]. Also, they have anticonvulsive activity[4], and act as hypnotics, sedatives[5,6], and fungicides[7,8]. 1,3,4-Thiadiazoles are effective bactericides, fungicides[9], and herbicides[10], and can depress the central nervous system[11]. Also, they are useful as intermediates in the manufacture of pharmaceuticals[12,13].

Glucosyl derivatives of 1,3,4-oxa- and -thia-diazoles have not previously been described, and we now report on the preparation and some reactions of D-glucosyl derivatives of 5-phenyl-2-thioxo- (**1a**) and 5-(*p*-chlorophenyl)-2-thioxo-1,3,4-oxadiazole (**1b**), 5-phenyl-2-thioxo- (**1c**) and 5-(*p*-chlorophenyl)-2-thioxo-1,3,4-thiadiazole (**1d**), and the corresponding 2-oxo compounds **5a–d**.

DISCUSSION

Compounds **1a–d** reacted with tetra-*O*-acetyl-α-D-glucopyranosyl bromide in the presence of potassium hydroxide, presumably with Walden inversion, to yield

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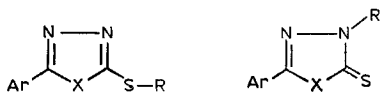
mainly the thioglucosides, 5-aryl-2-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylthio)-1,3,4-oxadiazoles (**2a,b**) and 5-aryl-2-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylthio)-1,3,4-thiadiazoles (**2c,d**), respectively, together with the *N*-glucosyl derivatives 5-aryl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-2-thioxo-1,3,4-oxadiazoles (**3a,b**) and 5-aryl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-2-thioxo-1,3,4-thiadiazoles (**3c,d**), respectively, in poor yields.



2 3

	Ar	X
a	Ph	O
b	*p*-Cl·C_6H_4	O
c	Ph	S
d	*p*-Cl·C_6H_4	S

R = 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl

Compounds **1a–d** will yield ambident anions[14] which will give *S*- and *N*-alkyl derivatives, when treated with alkyl halides[15].

The thioglucosides **2a–d** and the *N*-glucosyl derivatives **3a–d** were charaterized by u.v. (see below, Table I) and i.r. (Table II) spectroscopy, and also by oxidation.

TABLE I

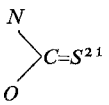
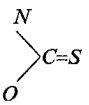
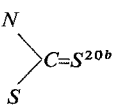
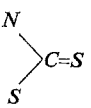
PRINCIPAL U.V.-ABSORPTION BANDS

Compound	λ_{max} (log ε) (*nm*)	*Compound*	λ_{max} (log ε) (*nm*)
2a	265 (4.27)	**3c**	330 (4.17)
2b	270 (4.33)	**3d**	335 (4.21)
4a	268 (4.38)	**7c**	333 (0.88[a])
4b	273 (4.47)	**7d**	340 (1.30[a])
6a	270 (4.13)	**10b**	339 (4.17)
6b	270 (4.30)	**5a**	260 (4.28)
9a	272 (4.27)	**5b**	267 (4.37
2c	294 (4.13)	**11**	270 (4.19)
2d	295 (4.17)	**5c**	275 (4.16)
4c	290 (4.17)	**5d**	280 (4.24)
4d	291 (4.23)	**8c**	277 (1.91[a])
6c	297 (4.25)	**8d**	280 (1.30[a])
6d	302 (4.26)	**12**	280 (4.14)
9b	301 (4.20)	**13**	280 (4.40)
3a	290 (4.21)		
3b	285 (4.24)		
7a	290 (0.94[a])		
7b	297 (0.63[a])		
10a	301 (4.19)		

[a]Absorbance.

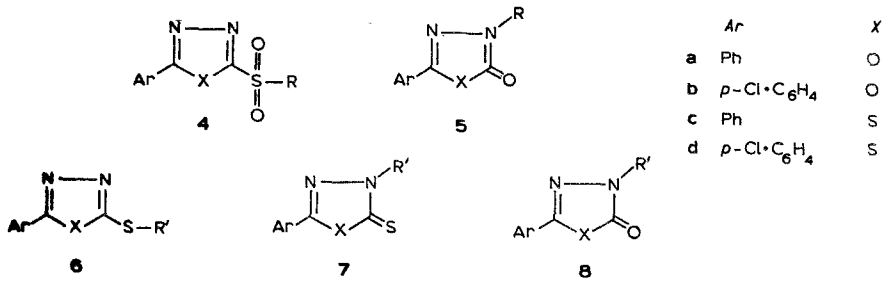
TABLE II

SELECTED I.R. BANDS (CM^{-1}) FOR **2–8**

Compound	*Acetyl*	*C–S–C*[20a]	*Compound*	*OH*	*C–S–C*
2a	1760	695	**6a**	3500–3200	700
2b	1760	690	**6b**	3500–3300	695
2c	1770	690	**6c**	4100–3280	690
2d	1775	690	**6d**	3450–3200	700
					
3a	1755	1375	**7a**	3560–3380	1380
3b	1760	1370	**7b**	3600–3200	1340
					
3c	1755	1275	**7c**	3520–3380	1270
3d	1785	1250	**7d**	3530–3300	1270
		O=S=O[20c]			*C=O*
4a	1755	1200 & 1365	**8a**	3500–3300	1735
4b	1755	1150 & 1370	**8b**	3520–3400	1755
4c	1750	1155 & 1370	**8c**	3520–3340	1695
4d	1750	1160 & 1370	**8d**	3600–3360	1695
		C=O			
5a	1800	1755			
5b	1810	1760			
5c	1755	1690			
5d	1755	1690			

Oxidation of the thioglucosides **2a–d** with potassium permanganate in acetic acid at room temperature yielded the sulphones 5-aryl-2-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylsulphonyl)-1,3,4-oxadiazoles (**4a,b**) and 5-aryl-2-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylsulphonyl)-1,3,4-thiadiazoles (**4c,d**), respectively. Oxidation of the *N*-glucosyl derivatives **3a–d**, under the same conditions, gave 5-aryl-2-oxo-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1,3,4-oxadiazoles (**5a,b**) and 5-aryl-2-oxo-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1,3,4-thiadiazoles (**5c,d**), respectively.

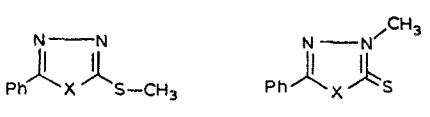
Saponification of the thioglucosides **2a–d** with ammonia yielded 5-aryl-2-β-D-glucopyranosylthio-1,3,4-oxadiazoles (**6a,b**) and 5-aryl-2-β-D-glucopyranosylthio-1,3,4-thiadiazoles (**6c,d**), respectively. Similar treatment of the *N*-glucosyl derivatives **3a–d** and the 2-oxo analogues **5a–d**, followed by paper chromatography, gave 5-aryl-3-



R = 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl
R' = β-D-glucopyranosyl

β-D-glucopyranosyl-2-thioxo-1,3,4-oxadiazoles (**7a,b**), 5-aryl-3-β-D-glucopyranosyl-2-thioxo-1,3,4-thiadiazoles (**7c,d**), 5-aryl-3-β-D-glucopyranosyl-2-oxo-1,3,4-oxadiazoles (**8a,b**), and 5-aryl-3-β-D-glucopyranosyl-2-oxo-1,3,4-thiadiazoles (**8c,d**), respectively, which were characterized by spot tests (see Experimental) and by u.v. and i.r. spectroscopy (see Tables I and II).

The structures of the thioglycosides and the *N*-glycosyl derivatives (compounds **2**, **3**, **4**, **6**, and 7) were confirmed by a study of their u.v. spectra and comparing their principal absorption bands with those reported[16] for 2-methylthio-5-phenyl-1,3,4-oxadiazole (**9a**), 2-methylthio-5-phenyl-1,3,4-thiadiazole (**9b**), 3-methyl-5-phenyl-2-thioxo-1,3,4-oxadiazole (**10a**), and 3-methyl-5-phenyl-2-thioxo-1,3,4-thiadiazole (**10b**) (see Table I). Also, the structures of the 2-oxo analogues (compounds **5** and **8**) were confirmed by comparing their principal absorption bands with those of 3-methyl-2-oxo-5-phenyl-1,3,4-oxadiazole (**11**; which was prepared[17], and for which we determined the u.v.-absorption spectrum), 2-oxo-5-phenyl-1,3,4-thiadiazole (**12**; which is known to exist in the keto form[18]), and *N*-Mannich bases of 2-oxo-5-phenyl-1,3,4-thiadiazole[19], *e.g.*, 3-(diethylaminomethyl)-2-oxo-5-phenyl-1,3,4-thiadiazole (**13**).



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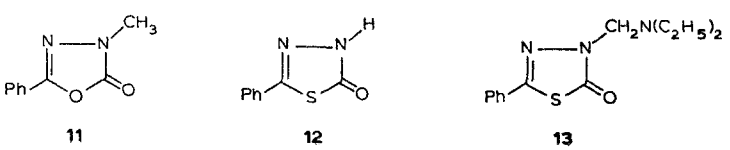
a, X = O; b, X = S



11 **12** **13**

EXPERIMENTAL

Melting points are uncorrected. Microanalyses were performed by the Microanalytical Lab., N.R.C., Cairo. U.v. spectra were determined for solutions in ethanol with a Carl Zeiss Spectrophotometer Type PM QII, and i.r. spectra for KBr discs with a Carl Zeiss Jena Spectrophotometer Model UR 10.

*Reaction of 2,3,4,6-tetra-*O*-acetyl-α-*D*-glucopyranosyl bromide with* **1a–d**. — A solution of the glucosyl bromide (4.1 g, 0.01 mol) in acetone (50 ml) was added to solutions of **1a**, **1b**, **1c**, or **1d** (0.01 mol) in water (6 ml) containing potassium hydroxide (0.6 g, 0.01 mol). The mixture was shaken for 5 h at room temperature, and then concentrated under reduced pressure at room temperature. The residue was washed with water to remove the potassium bromide, and then continuously extracted with cyclohexane. The solid which precipitated from the extract was collected, and recrystallized from cyclohexane to yield colourless needles of the thioglucosides **2a–d** (Table III).

The solid remaining in the extraction thimble was recrystallized from ethanol to give colourless needles of the *N*-glucosyl derivatives **3a–d** in poor yield (Table III).

Oxidation of **2a–d** *and* **3a–d** *with potassium permanganate.* — To a solution of substrate (2 mmol) in glacial acetic acid (25 ml), a solution of potassium permanganate (0.6 g, 4 mmol) in water (10 ml) was added gradually with stirring during 30 min. Stirring was continued for 3 h at room temperature, and the mixture was then poured onto crushed ice. The solid was collected, and a solution in ethanol was filtered to remove manganese salts, and then concentrated. Compounds **2a–d** yielded the corresponding sulphones **4a,b** (recrystallized from cyclohexane) and **4c,d** (recrystallized from ethanol), respectively. Compounds **3a–d** yielded the corresponding 2-oxo derivatives **5a,b** (recrystallized from ethanol) and **5c,d** (recrystallized from cyclohexane), respectively (see Table IV).

Action of ammonia on **2a–d**, **3a–d**, *and* **5a–d**. — To a suspension of **2a–d** (2 mmol) in methanol (25 ml), methanol (25 ml) saturated with ammonia was added. The reaction mixture was kept at $\sim -10°$ for 2 days, then filtered, and concentrated under reduced pressure at room temperature. The residue was triturated several times with chloroform to remove the impurities, and then dissolved in the minimal amount of ethanol, and the solution was filtered and concentrated. Recrystallization of the residue from water gave the deacetylated products **6a–d** (see Table IV).

The products (**7a–d**, **8a–d**) from **3a–d** and **5a–d**, respectively, were isolated by chromatography on Whatman No. 1 paper with (*A*) 1-butanol–pyridine–water (3:2:1) or (*B*) 1-butanol–acetic acid–water (4:1:5), and detection with silver nitrate[22]. The deacetylated products, which were extracted from the chromatogram with ethanol, had the following R_{Glc} values:

	7a	**7b**	**7c**	**7d**	**8a**	**8b**	**8c**	**8d**
Solvent *A*	2.21	2.29	2.27	2.31	2.74	2.72	2.23	2.33
Solvent *B*	4.64	4.81	4.70	4.84	4.27	4.25	3.85	3.98

TABLE III

ANALYTICAL AND OTHER DATA FOR **2a–d** AND **3a–d**

Product (*yield*, %)	*M.p.* (*degrees*)	$[\alpha]^{25}$ ($CHCl_3$) (*degrees*)	*Formula*	*Analysis*									
				Calc.					*Found*				
				C	*H*	*Cl*	*N*	*S*	*C*	*H*	*Cl*	*N*	*S*
2a (55)	120	+88	$C_{22}H_{24}N_2O_{10}S$	52.0	4.7	—	5.5	6.3	52.4	4.6	—	4.8	6.8
3a (6)	229	+45		52.0	4.7	—	5.5	6.3	52.5	5.0	—	4.7	6.5
2b (57)	123	+39	$C_{22}H_{23}ClN_2O_{10}S$	48.7	4.2	6.5	5.2	5.9	49.0	4.4	6.8	5.3	6.1
3b (7)	230	+24		48.7	4.2	6.5	5.2	5.9	49.1	4.3	5.8	5.0	5.8
2c (57)	139	+123	$C_{22}H_{24}N_2O_9S_2$	50.4	4.6	—	5.3	12.2	50.7	4.7	—	5.2	12.5
3c (8)	218	+59		50.4	4.6	—	5.3	12.2	50.3	4.9	—	4.8	12.5
2d (60)	137	+23.5	$C_{22}H_{23}ClN_2O_9S_2$	47.3	4.1	6.4	5.0	11.5	46.8	4.1	6.3	4.8	11.7
3d (7)	220	+32		47.3	4.1	6.4	5.0	11.5	47.1	4.0	6.2	5.5	11.6

TABLE IV

ANALYTICAL AND OTHER DATA FOR **4a–d**, **5a–d**, AND **6a–d**

Product (*yield*, %)	*M.p.* (*degrees*)	$[\alpha]_D^{25}$ ($CHCl_3$) (*degrees*)	*Formula*	*Analysis*									
				Calc.					*Found*				
				C	*H*	*Cl*	*N*	*S*	*C*	*H*	*Cl*	*N*	*S*
4a (53)	135	−61	$C_{22}H_{24}N_2O_{12}S$	48.9	4.4	—	5.2	5.9			—	5.1	6.2
4b (63)	137	−67	$C_{22}H_{23}ClN_2O_{12}S$	46.0	4.0	6.2	4.9	5.6			5.8	5.0	5.7
4c (72)	172	+67	$C_{22}H_{24}N_2O_{11}S_2$	47.5	4.3	—	5.0	11.5	47.8	4.2	—	5.0	11.0
4d (63)	165	−22	$C_{22}H_{23}ClN_2O_{11}S_2$	44.7	3.9	6.0	4.7	10.8	44.6	4.1	6.4	4.0	10.5
5a (61)	192	−87	$C_{22}H_{24}N_2O_{11}$	53.7	4.9	—	5.7	—	53.2	5.3	—	5.1	—
5b (54)	182	−48	$C_{22}H_{23}ClN_2O_{11}$	50.1	4.4	6.7	5.3	—	50.1	4.1	6.7	5.0	—
5c (60)	193	−20.5	$C_{22}H_{24}N_2O_{10}S$	52.2	4.7	—	5.5	6.3	52.2	4.8	—	5.6	6.3
5d (45)	196	−59	$C_{22}H_{23}ClN_2O_{10}S$	48.7	4.2	6.5	5.2	5.9	49.1	4.0	6.9	4.6	5.8
6a (43)	167	−36	$C_{14}H_{16}N_2O_6S$	49.4	4.7	—	8.2	9.4	50.0	4.7	—	7.9	10.1
6b (37)	180	−29.5	$C_{14}H_{15}ClN_2O_6S$	44.9	4.0	9.5	7.5	8.5	45.0	4.6	9.3	7.9	8.2
6c (43)	173	−86	$C_{14}H_{16}N_2O_5S_2$	47.2	4.5	—	7.9	18.2	46.9	4.5	—	7.6	18.2
6d (50)	176	−74	$C_{14}H_{15}ClN_2O_5S_2$	43.0	3.8	9.1	7.2	16.4	43.3	3.9	9.4	7.2	16.4

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