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PREPARATION OF ACETYLATED *C*-(1-BROMO-D-GLYCOSYL) HETEROCYCLES AND 1-BROMO-D-GLYCOSYL CYANIDES*†

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ABSTRACT

The reaction of acetylated *C*-(D-glycosyl) heterocycles and D-glycosyl cyanides with either *N*-bromosuccinimide in hot carbon tetrachloride or bromine under irradiation resulted in bromination at the anomeric carbon atom. The location of the bromine substituent and the conformations of these products were determined by n.m.r. spectroscopy. Absolute configurations of the bromo compounds were established.

INTRODUCTION

During our experiments directed to the preparation of 2-bromomethyl-5-β-D-glycosyl-1,3,4-oxadiazoles[1], as potential biological alkylating agents, the appropriate 2-methyl-1,3,4-oxadiazoles were treated with *N*-bromosuccinimide in the presence of benzoyl peroxide. However, the bromine substituent of the products was located in the sugar moiety.

Recently, several brominated sugars have been synthesised by the application of radical-mediated bromination of acylated hexo- and pento-pyranosides[2–5], glucopyranuronic acid derivatives[6], 1-thioglycopyranosides[7], glycopyranosides[8], benzoylated anhydrofructose derivatives, other keto sugars and enones, and 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl cyanide[9].

We have reported[10] that radical-mediated bromination of 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl cyanide and 2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl cyanide resulted in 1-bromo derivatives. In each of the above reactions, bromination occurred at C-1 or C-5 of the sugar moiety. Usually, the carbon involved in the reaction was substituted by an electron-acceptor group and the ring oxygen, thereby facilitating the radical reactions[11].

*C-Nucleosides, Part VI. For Part V, see ref. 1.
†Dedicated to Professor Rezső Bognár on the occasion of his 70th birthday.

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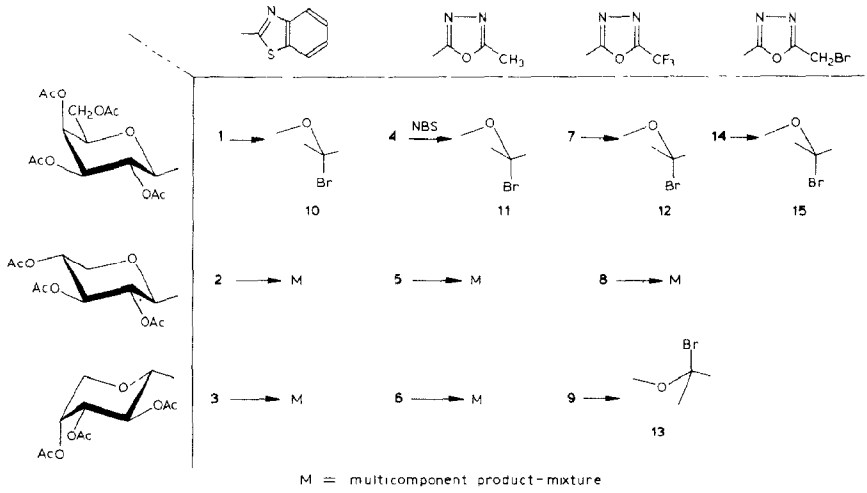
RESULTS AND DISCUSSION

The results of the bromination of the *C*-glycosyl derivatives of benzothiazole, 2-methyloxadiazole, 2-trifluoromethyloxadiazole, and 2-bromomethyloxadiazole are summarised in Scheme 1.



Scheme 1

The reactions were performed using either *N*-bromosuccinimide in hot carbon tetrachloride in the presence of benzoyl peroxide, or bromine and irradiation which usually gave the same product(s).

With the *N*-bromosuccinimide reagent, the 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl derivatives **1**[12], **4**[13], **7**[14], and **14**[1] gave good yields (53–80%) of the axial bromides **10**–**12** and **15**, respectively (see Table I). Similar results were obtained with the bromine reagent, except for **4** which gave a mixture of **11**, **14**, **15**, and some unidentified components (t.l.c.). The 2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl derivatives **2**[12], **5**[13], and **8**[14], and the 2,3,4-tri-*O*-acetyl-α-D-arabinopyranosyl derivatives **3**[15] and **6**[15], gave complex mixtures of products with each reagent. The 2,3,4-tri-*O*-acetyl-α-D-arabinopyranosyl derivative **9**[15] gave the axial bromide **13**.

In addition to bromination, such processes as dehydrobromination (which would extend the conjugated system) and subsequent addition of bromine to the newly formed double-bond may have contributed to the formation of the complex product-mixtures noted above.

In a parallel series of experiments, the bromination of several glycosyl cyanides was also examined (Scheme 2, Table I). 2,3,4,6-Tetra-*O*-acetyl-α-[16] (**17**) and -β-D-galactopyranosyl cyanide[17] (**16**) gave an excellent yield of the crystalline axial bromide[10] **22**. Likewise, 2,3,4-tri-*O*-acetyl-α-[18] (**18**) and -β-D-arabinopyranosyl cyanide[16] (**19**) gave the axial bromide **23**. Bromination of 2,3,4-tri-*O*-

TABLE I

ACETYLATED C-(1-BROMO-D-GLYCOSYL) HETEROCYCLES AND 1-BROMO-D-GLYCOSYL CYANIDES

Compound	*Yield (%)*	*M.p. (degrees) (solvent)*	R_F[b]	$[\alpha]_D^{20}$[c] *(degrees)*	*Formula*	*Analytical data (%)*	
						Calc.	*Found*
10	67	130–131 (dec.) (ether–light petroleum)	0.35	+134.5[d]	$C_{21}H_{22}BrNO_9S$	N 2.57 Br 14.67 S 5.89	2.54 14.47 5.76
11	75	127–129 (ethanol)	0.26	+176.5	$C_{17}H_{21}BrN_2O_{10}$	N 5.66 Br 16.19	5.61 15.95
12	53	112–113 (ethanol)	0.48	+158	$C_{17}H_{18}BrF_3N_2O_{10}$	N 5.11 Br 14.60 F 10.41	5.22 14.90 10.13
13	50	syrup	0.57	−114	$C_{14}H_{14}BrF_3N_2O_8$	N 5.89 Br 16.81 F 11.99	6.02 17.03 11.75
15	80	syrup	0.39	+146	$C_{17}H_{20}Br_2N_2O_{10}$	N 4.89 Br 27.93	4.58 28.32
22	88	117–118 (ethanol)	0.42	+184	$C_{15}H_{19}BrNO_9$	N 3.21 Br 18.34	3.17 18.14
23	85	103–104 (ethanol)	0.54	−250	$C_{12}H_{14}BrNO_7$	N 3.84 Br 21.94	3.74 22.05
24	45 (56[a])	182–184 (ethanol)	0.52	+148	$C_{12}H_{14}BrNO_7$	N 3.84 Br 21.94	3.94 21.76
25	28[a]		0.46		$C_{12}H_{14}BrNO_7$		
26	50[a]	127–129 (ether)	0.50	+179	$C_{12}H_{14}BrNO_7$	N 3.94 Br 21.94	3.91 22.10
27	33[a]		0.43		$C_{12}H_{14}BrNO_7$		

[a]Based on n.m.r. data. [b]Benzene–ether–light petroleum (6:3:1). [c]In chloroform. [d]In acetone.

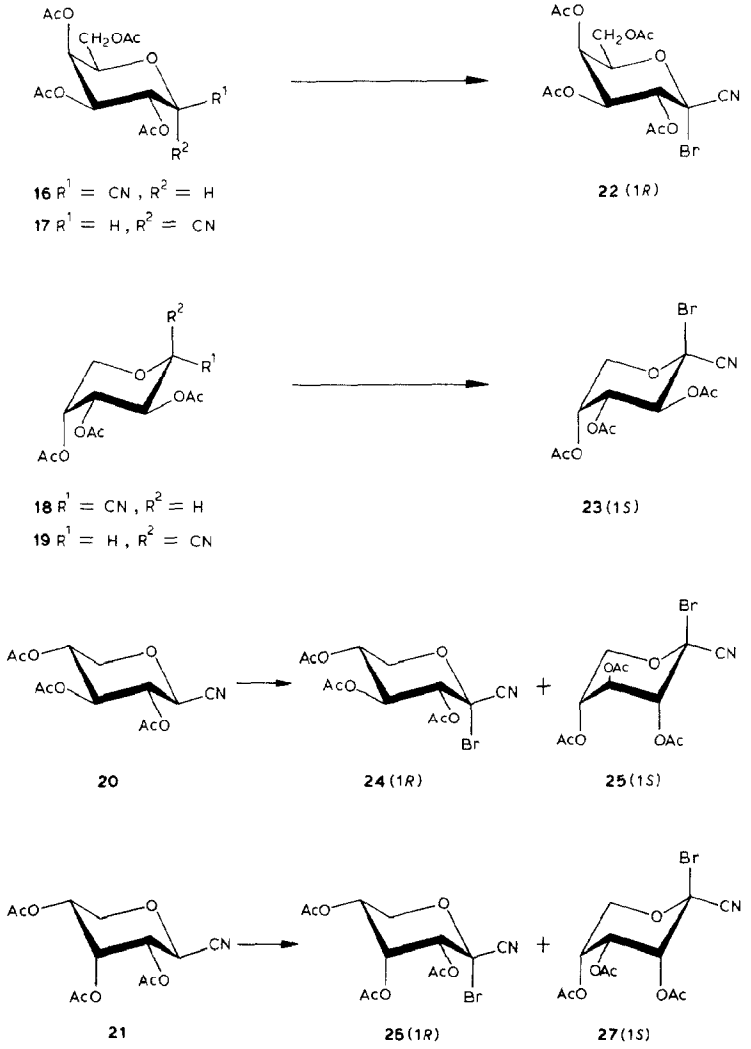
acetyl-β-D-xylopyranosyl cyanide[19] (**20**) gave the axial bromides[10] **24** (isolated by crystallisation) and **25** (not isolated homogeneous). Likewise, 2,3,4-tri-*O*-acetyl-β-D-ribopyranosyl cyanide[18] (**21**) gave the axial bromides **26** and **27**, of which only the former was isolated homogeneous by column chromatography; the corresponding tribenzoate[20] did not react. Compounds **25** and **27** were detected and characterised by ^{1}H-n.m.r. spectroscopy (Tables II and III).

The main products formed on bromination of the glycosyl cyanides (Scheme 2) are those which have the least adverse 1,3-*syn*-diaxial interactions.

On mass spectrometry of the bromo derivatives, only **24** gave a molecular ion; **11**, **12**, **23**, and **24** gave ($M^+ - Br$) ions, and **22** gave an ($M^+ - HBr$) ion.

The ^{1}H-n.m.r. data in Table II showed that bromination had occurred on the sugar moieties. The loss of the signals for H-1 and the simplification of the signals for H-2 indicated unequivocally that C-1 had been brominated. The conformations shown in Schemes 1 and 2 were assigned on the basis of the coupling constants given in Table III.

The downfield shifts (0.1–0.5 p.p.m., Table II, Δ values) of the signals for H-



Scheme 2

3 and H-5 of the bromides, as compared to those of the starting materials, indicated that these protons were in *syn*-axial relationship with the bromine attached to C-1. Because of the anomeric effect, conformations containing an equatorial bromine would be destabilised. The operation of the anomeric effect is apparent for the pairs of epimers **24** and **25**, and **26** and **27**. For each compound, the bromine substituent is axial.

The assignment of the ^{13}C-n.m.r. resonances was based on the ^{1}H-n.m.r. spectra and off-resonance decoupling experiments[21] (Table IV). In accordance with the well-known α-shift[22], bromination resulted in a downfield shift of 15–20 p.p.m. of the C-1 signal.

TABLE II

^{1}H-N.M.R. DATA[a] (δ, P.P.M.) FOR ACETYLATED *C*-(D-GLYCOSYL) HETEROCYCLES AND D-GLYCOSYL CYANIDES, AND THEIR 1-BROMIDES

Compound	*H-1*	*H-2*	*H-3*	Δ^b	*H-4*	*H-5*	Δ^b	*H-6,6'*	*Sugar moiety*
10	—	5.62d	5.52dd	+0.27	5.63dd	4.75m	+0.5	4.32 2dd	2,3,4,6-Tetra-*O*-
1	4.89d	5.50dd	5.25dd		5.56dd	4.33–4.10m			acetyl-D-
11	—	5.65d	5.46dd	+0.25	5.60dd	4.67m	+0.5	4.25 2dd	galactopyranosyl
4	4.77d	5.49dd	5.21dd		5.54dd	4.24–4.05m			
12	—	5.61d	5.47dd	+0.23	5.62dd	4.68m	+0.5	4.27 2dd	
7	4.85d	5.44dd	5.24dd		5.55dd	4.27–4.06m			
15	—	5.63d	5.46dd	+0.26	5.61dd	4.68m	+0.5	4.30, 4.22 2dd	
14	4.79d	5.49dd	5.20dd		5.54dd	4.22–4.04m			
22[d]	—	5.47d	5.33dd	+0.10	5.61dd	4.73m	+0.39	4.30, 4.23 2dd	
16[d]	4.89d	5.46dd	5.23dd		5.47dd	4.34m		4.17m	

						H-5e	Δ^b	*H-5a*	Δ^b	
13	—	5.63d	5.48dd	+0.24	5.51m	4.44dd[c]	+0.23	4.28dd[c]	+0.40	2,3,4-Tri-*O*-
9	4.79d	5.48dd	5.24dd		5.43m	4.21dd		3.88dd		acetyl-D-
23	—	5.52d	5.31dd	+0.23	5.41m	4.20dd[c]	+0.19	4.11dd[c]	+0.36	arabinopyranosyl
18	4.42d	5.28dd	5.08dd		5.21m	4.01dd		3.75dd		
8	4.81d	5.24dd	5.40dd		5.13m	4.32dd		3.52dd		2,3,4-Tri-*O*-
24	—	5.23d	5.45dd	+0.34	5.08m	4.24dd	0	3.80dd	+0.22	acetyl-D-
20	4.50	5.11	5.11		4.92m	4.24dd		3.58dd		xylopyranosyl
25	—	5.44d	5.11dd		4.93m	4.32dd[c]		4.01dd[c]		
26	—	5.24d	5.68dd	+0.03	5.17m	4.03dd	+0.03	4.12dd	+0.39	2,3,4-Tri-*O*-
21	4.59d	5.16dd	5.65dd		5.07m	4.00dd		3.73dd		acetyl-D-
27	—	5.57d	5.63dd		5.27m	4.24dd[c]		4.17dd[c]		ribopyranosyl

[a]First-order analysis, 200 MHz, $CDCl_3$, Me_4Si. [b]The difference between the corresponding chemical-shift values for H-3 and H-5 of the bromo compounds and the starting materials. [c]The assignments may be interchanged. [d]Acetone-d_6.

Further evidence for the stereochemistry of the products was obtained from the $^1H,^{13}C$ couplings for the cyanide resonances and the signals of the carbon atoms (C-1') of the heterocycles attached to the sugar moiety. Due to coupling with both H-1 and H-2, these signals are double doublets for the starting materials, but are simplified to doublets for the bromo derivatives. According to the values of the three-bond couplings[23,24] $J_{C\text{-}1',H\text{-}2}$ (Table IV), it was established that H-2 and C-1' were *gauche,* thereby further indicating that the bromine substituent is axial. On the basis of these results, the absolute configurations of the bromo compounds could be established (Scheme 2).

Comparison of the chemical shifts of the signals for the galactopyranoside derivatives shows the value of the γ-*gauche* effect ($\delta_{C\text{-}3\text{-}C\text{-}C\text{-}Br} - \delta_{C\text{-}3\text{-}C\text{-}C\text{-}H}$, Table IV) to be − 1–2 p.p.m. Since insufficient data are available in the literature[25], no reliable stereochemical correlation could be made.

TABLE IV

^{13}C-N M R DATA[a] FOR ACETYLATED *C*-(D-GLYCOSYL) HETEROCYCLES AND D-GLYCOSYL CYANIDES, AND THEIR 1-BROMIDES

Compound	*C-1*	*α-Shift*	*C-2*	*C-3*	*γ-Shift*	*C-4*	*C-5*	*C-6*	*C-1'*	$J_{C-1',H-1}$	$J_{C-1',H-2}$	*Others*
10	98.03	19.97	69.15	70.3	−1.3	66.84	73.75	60.65	168.58	—	<3 Hz	C=O 170.15, 3 CH_3 20.47 169.88 CH_3 20.98 169.79 169.30 Aromatic: 135.24, 152.41, 121.65, 126.22, 126.40, 124.28
1	78.06		68.73	71.6		67.45	75.08	61.51	166.89	~4	~4	C=O 170.17, 4 CH_3 20.49 170.03 169.87 169.25 Aromatic: 152.67, 134.98, 121.76, 125.41, 126.04, 123.25
11	91.79	19.98	67.87	69.65	−1.51	66.53	73.49	60.41	162.65	—	2	C=O 169.97; CH_3 20.56 169.68 20.29 169.56 2 CH_3 20.34 168.71 OD-CH_3 10.82 (C(CH_3) 164.79
4	71.81		66.83	71.16		67.22	75.18	61.41	161.37	3.5	3.5	C=O 170.03 2 CH_3 20.37 169.86 20.26 169.59 20.17 169.06 OD-CH_3 10.77 C(CH_3) 164.91
12	90.44	18.81	67.93	69.37	−1.44	66.44	73.91	60.33	164.25	—	2.1	C=O 169.95 3 CH_3 20.40 169.62 CH_3 20.33 169.45 168.81 CF_3 115.90 C(CF_3) 155.74

7	71.63		69.99	70.81		67.06	75.52	61.37	163.49	3.6	3.6	C=O 169.28 2 CH_3 20.35 169.58 20.24 169.87 20.05 170.07 CF_3 116.05 C(CF_3) 156.16
22[b]	81.85	15.31	67.55	68.26	−2.36	65.94	73.44	60.07	113.36	—	2.7	C=O 169.73 CH_3 20.18 169.35 20.12 169.08 20.07 168.21 20.01
16[b]	66.54		65.94	70.62		66.69	75.21	61.11	114.31	7.2	3.9	C=O 170.08 CH_3 20.38 169.78 20.31 169.61 2CH_3 20.24 168.62
23	83.23	14.90	67.96[c]	67.80[c]		66.59	66.59	—	113.61	—	2.7	C=O 169.49 CH_3 20.38 169.17 2 CH_3 20.07 168.29
18	68.33		66.85	65.99		65.15	65.15	—	114.40	7.8	2.6	C=O 169.41 CH_3 20.18 169.16 20.08 168.50 19.98
24[b]	81.81	16.11	67.08	70.18		71.23	64.22	—	113.69	—	2.2	C=O 169.29 2 CH_3 20.26 168.26 20.14
20[b]	65.70		68.15[c]	69.38[c]		67.15	65.41	—	114.31	8.1	2.0	C=O 169.23 2 CH_3 20.33 169.15 20.17 168.64

[a]50.3 MHz, $CDCl_3$, internal Me_4Si, 40°. [b]Room temperature. [c]Interchangeable assignments.

TABLE III

FIRST-ORDER $^1H,^1H$ COUPLING CONSTANTS (Hz) FOR ACETYLATED *C*-(D-GLYCOSYL) HETEROCYCLES AND D-GLYCOSYL CYANIDES, AND THEIR 1-BROMIDES

Compound	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$	*Sugar moiety*
10	—	10.2	2.8	1.3	6.5	6.5	12.5	2,3,4,6-Tetra-*O*-acetyl-
1	9.8	9.8	3.4					D-galactopyranosyl
11	—	10.5	3	1.5	6.5	6.5	12	
4	10	10	3.5					
12	—	10.5	3	1.5	6.5	6.5	12	
7	10	10	3.5					
15	—	10.2	3	1.3	7	6.5	12	
14	9.5	10	3.2					
22	—	10.4	3.2	1.4	5.4	6.7	11.8	
16	10.2	10.2	3.4	1.2	5.3	7.1	11.6	
					$J_{4,5e}$	$J_{4,5a}$	$J_{5e,5a}$	
13	—	9.5	3.2		4	1.5	13.5	2,3,4-Tri-*O*-acetyl-
9	9.5	10	3.5		2	1.5	13	D-arabinopyranosyl
23	—	10.2	3.2		1.5	1.9	13.4	
18	6.3	7.3	3.1		5.6	2.9	12	
8	9.3	9.3	9.3		5.5	10.5	11.5	2,3,4-Tri-*O*-acetyl-
26	—	9.5	9.5		6	11	12	D-xylopyranosyl
20[a]					4	7	12.5	
25	—	5.4	5.3		5	3.5	12.7	
26	—	3	3		6	11	11	2,3,4-Tri-*O*-acetyl-
21	9	3	3		5	9	11.5	D-ribopyranosyl
27	—	3.5	3.5		3	3	13	

[a]Because of strong couplings, complete first-order analysis was not possible.

EXPERIMENTAL

Melting points are uncorrected. Optical rotations were measured with a Perkin–Elmer 241 polarimeter. N.m.r. spectra were recorded with a Bruker WP-200 SY instrument (^1H, 200 MHz; ^{13}C, 50.3 MHz). G.l.c.–m.s. was performed with a VG-7035 gas chromatograph–mass spectrometer system. T.l.c. was performed on Kieselgel 60 F_{254} (Merck) and column chromatography on Kieselgel 60 (Reanal) and 40 (Merck), using benzene–ether–light petroleum (6:3:1). Spots in t.l.c. were visualised by gentle heating. Solvents were dried over $MgSO_4$. Concentrations were carried out under diminished pressure at 40–50°.

Carbon tetrachloride was distilled from phosphorus pentaoxide, and *N*-bromosuccinimide and benzoyl peroxide were kept in a vacuum desiccator over phosphorus pentaoxide.

Bromination reactions. — (*a*) *With* N-*bromosuccinimide.* To a solution of the

substrate (1 g) in warm carbon tetrachloride (20 mL) were added *N*-bromosuccinimide (1.2 mol) and benzoyl peroxide (0.10–0.15 mol). The mixture was boiled under reflux in the absence of moisture until all of the starting material had disappeared (t.l.c.; 40–60 min for the C-glycosyl heterocycles and 20–40 min for the glycosyl cyanides), and then cooled and filtered. The insoluble material was washed with a little cold carbon tetrachloride, the combined filtrate and washings were concentrated, and the residue was crystallised from the solvent noted in Table I.

(*b*) *With bromine.* To a solution of the substrate (1 g) in warm carbon tetrachloride (20 mL) was added bromine (3–4 mol), and the mixture was boiled in the absence of moisture under irradiation with a domestic quartz lamp until all of the starting material had disappeared (t.l.c.; 40–60 min for the *C*-glycosyl heterocycles, 20–40 min for the glycosyl cyanides). The reaction mixture was then concentrated, and a solution of the syrupy residue in chloroform was washed with aqueous sodium hydrogencarbonate until neutral, dried, and concentrated. The residual syrupy product crystallised from the solvent noted in Table I.

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