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SELECTIVE BENZOYLATION OF SOME *N*-ACETYL-*N*-ARYL-β-D-XYLOPYRANOSYLAMINES*

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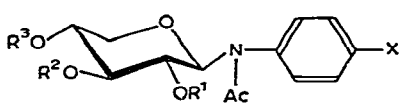
ABSTRACT

Selectivity in the benzoylation of *N*-acetyl-*N*-*p*-methoxyphenyl-, -*p*-bromophenyl-, and -*p*-chlorophenyl-β-D-xylopyranosylamines has been demonstrated. The structures of the products was shown by using periodate oxidation and n.m.r. spectroscopy. The relative reactivity of the hydroxyl groups was HO-3 ≈ HO-4 > HO-2. The β-D-xylopyranosylamine derivatives were shown to possess the $^4C_1$ conformation.

INTRODUCTION

Although the selective esterification of the hydroxyl groups of methyl and benzyl α- and β-D-xylopyranosides has been investigated[1–3], there have been no analogous investigations of D-xylopyranosylamines.

We have reported[4] on the selective benzoylation of some *N*-acetyl-*N*-aryl-α-L-arabinopyranosylamines and, in a continuation of these studies, the selective benzoylation of *N*-acetyl-*N*-*p*-methoxyphenyl-, -*p*-bromophenyl-, and -*p*-chlorophenyl-β-D-xylopyranosylamines is now described.



1 X = OMe, 2 X = Br, 3 X = Cl: $R^1 = H, R^2 = R^3 = Bz$

4 X = Cl: $R^1 = R^3 = H, R^2 = Bz$

5 X = Cl: $R^1 = R^2 = H, R^3 = Bz$

6 X = OMe, 7 X = Br, 8 X = Cl: $R^1 = Ac, R^2 = R^3 = Bz$

9 X = OMe, 10 X = Br, 11 X = Cl: $R^1 = NO_2, R^2 = R^3 = Bz$

12 X = Br, $R^1 = Me, R^2 = R^3 = Bz$

13 X = Br, $R^1 = Me, R^2 = R^3 = H$

14 X = Br, $R^1 = Me, R^2 = R^3 = Ac$

15 X = Cl, $R^1 = R^3 = Ac, R^2 = Bz$

16 X = Cl, $R^1 = R^2 = Ac, R^3 = Bz$

17 X = Cl, $R^1 = R^3 = NO_2, R^2 = Bz$

18 X = Cl, $R^1 = R^2 = NO_2, R^3 = Bz$

*Ester and Ether Derivatives of Glycopyranosylamines: Part VI.

TABLE I

PRODUCTS OF SELECTIVE BENZOYLATION OF β-D-XYLOPYRANOSYLAMINES AND THEIR DERIVATIVES

Compound	Yield (%)	M.p. (degrees)	Rotation (c ≃ 0.5)		ν_{max} (cm^{-1})[a]					
			$[\alpha]_D^{20}$	[M]	OH	C=O (ester)	C=O (amide)	N–O (asym.)	Ring vibrations: Asymmetric	Ring vibrations: Symmetric
1	60	195–196	−45[b]	−227	3270s	1720vs 1730vs	1640vs	—	910s	785m
2	65	85–88	−26[b]	−144	3340s	1720vs 1715vs	1660vs	—	910m	775m
3	60	72–75	−16[b]	−81	3360m	1725vs	1660vs	—	912m	785s
4	35	90–95	+8[c] 0[d]	+32	3360m	1725vs	1760vs	—	905w	785s
5	25	165–166	0[c] +26[d]	+105	3350s	1718vs	1655vs	—	905w	785s
6	90	94–96	−12[b]	−65	—	1760s 1725vs 1715vs	1680vs	—	905w	785m
7	90	85–88	−19[b]	−113	—	1755vs 1720vs	1680vs	—	915m	780m
8	90	Syrup	−6[e] 0[b]	−33	—	1755vs 1725vs	1680vs	—	910w	785m
9	80	122–125	−28[b]	−156	—	1725vs	1685vs	1648vs	915m	770m
10	85	128–130	+14[b]	+84	—	1740vs	1680vs	1645vs	915m	782m
11	85	132–134	+21[b]	+116	—	1730vs	1675vs	1645vs	915m	770m
12	60	70–73	+5[b]	+28	—	1725vs	1680vs	—	905m	782s
13	50	Syrup	+69[e]	+248	3400s	—	1665vs	—	920w	783m
14	85	115–117	+63[b]	+280	—	1745vs	1678vs	—	905w	780m
15	80	120–123	+22[b]	+107	—	1748vs 1718vs	1680vs	—	—	788w
16	80	155	−16[b]	−78	—	1760vs 1750vs 1720vs	1690vs	—	900m	785m
17	75	Amorphous	+38[b]	+188	—	1725s	1680s	1650s	915m	785m
18	70	Amorphous	+7[b]	+35	—	1725s	1675s	1650s	915m	790m

[a]Only important bands are given. [b]In $CHCl_3$. [c]In pyridine. [d]In acetone. [e]In ethanol. [f]Solvent *A*. [g]Solvent *B*.

R_F	*Molecular formula*	*Analysis (%)*					
		C		*H*		*N*	
		Calc.	*Found*	*Calc.*	*Found*	*Calc.*	*Found*
0.40[f] 0.18[g]	$C_{28}H_{27}NO_8$	66.53	66.30	5.34	5.20	2.77	2.80
0.54[f] 0.27[g]	$C_{27}H_{24}BrNO_7$	58.48	58.23	4.33	4.38	2.52	2.65
0.45[f] 0.23[g]	$C_{27}H_{24}ClNO_7$	63.59	63.42	4.71	4.62	2.77	2.70
0.25[f] 0.045[g]	$C_{20}H_{20}ClNO_6$	59.18	59.02	4.93	4.81	3.45	3.40
0.23[f] 0.040[g]	$C_{20}H_{20}ClNO_6$	59.18	58.95	4.93	4.95	3.45	3.50
0.72[f] 0.29[g]	$C_{30}H_{29}NO_9$	65.81	65.70	5.30	5.25	2.55	2.60
0.75[f] 0.36[g]	$C_{29}H_{26}BrNO_8$	58.38	58.32	4.36	4.18	2.34	2.40
0.81[f]	$C_{29}H_{26}ClNO_8$	63.10	63.00	4.71	4.68	2.54	2.60
0.55[f] 0.23[g]	$C_{28}H_{26}N_2O_{10}$	61.09	60.90	4.72	4.58	5.09	5.17
0.72[f]	$C_{27}H_{23}BrN_2O_9$	54.09	53.89	3.83	3.80	4.67	4.70
0.77[f] 0.61[g]	$C_{27}H_{23}ClN_2O_9$	58.43	58.31	4.14	4.07	5.05	5.15
0.65[f]	$C_{28}H_{26}BrNO_7$	59.15	59.05	4.57	4.50	2.46	2.40
0.54[h]	$C_{14}H_{18}BrNO_5$	46.66	46.51	5.00	4.85	3.89	3.80
0.60[f]	$C_{18}H_{22}BrNO_7$	48.64	48.40	4.95	4.75	3.15	3.20
0.74[f]	$C_{24}H_{24}ClNO_8$	58.83	58.70	4.90	4.82	2.86	2.95
0.74[f]	$C_{24}H_{24}ClNO_8$	58.83	58.62	4.90	4.78	2.86	2.90
0.81[f] 0.63[g]	$C_{20}H_{18}ClN_3O_{10}$	48.43	48.21	3.63	3.48	8.47	8.56
0.81[f] 0.61[g]	$C_{20}H_{18}ClN_3O_{10}$	48.43	48.35	3.63	3.52	8.47	8.63

RESULTS AND DISCUSSION

N-Acetyl-*N*-*p*-methoxyphenyl-, -*p*-bromophenyl-, and -*p*-chlorophenyl-β-D-xylopyranosylamine, each of which has a $^4C_1$ conformation[5], were separately treated with 2.5 equivalents of benzoyl chloride in a manner analogous to that reported for *N*-acetyl-*N*-aryl-α-L-arabinopyranosylamines[4]. Each xylopyranosylamine gave two products, which could be isolated by chromatography, in contrast to the *N*-acetyl-*N*-aryl-α-L-arabinopyranosylamines which afforded three compounds[4].

The products having the higher R_F values were the known tribenzoates of the *N*-acetyl-*N*-aryl-D-xylopyranosylamines[6]. The other products (**1–3**) were incompletely benzoylated *N*-acetyl-*N*-aryl-β-D-xylopyranosylamines (Table I).

Compounds **1–3** were characterised as the acetates (**6–8**) and nitrates (**9–11**). Compound **2** was converted into a methyl ether (**12**), which was debenzoylated to give an *N*-acetyl-*N*-*p*-bromophenyl-*O*-methyl-β-D-xylopyranosylamine (**13**) which gave a diacetate **14**. Compound **13** reduced ~1 mol. of sodium metaperiodate, which confirmed the presence of one methoxyl group and indicated HO-2 or HO-4 to be unsubstituted.

Inspection of the n.m.r. data (Table II) reveals changes in the chemical shifts of H-3 and H-4 for the sequence of compounds **12**→**13**→**14**. These data coupled with the results of periodate-oxidation data for **12** indicate **1–3** to have HO-2 unsubstituted and to be the 3,4-dibenzoates of *N*-acetyl-*N*-*p*-methoxyphenyl-, -*N*-*p*-bromophenyl-, and -*N*-*p*-chlorophenyl-β-D-xylopyranosylamine.

For compounds **1–3**, the signal for H-2 occurs at δ ~3.3 p.p.m. After substitution of the OH group by OAc (**6–8**), ONO_2 (**9–11**), or OMe (**12**), the signal appears at δ 4.80, 4.85, and 3.12 p.p.m., respectively.

The above evidence shows that, as for the *N*-acetyl-*N*-aryl-α-L-arabinopyranosylamines[4], HO-2 in the *N*-acetyl-*N*-aryl-β-D-xylopyranosylamines is the most difficult to benzoylate. However, for the *N*-acetyl-*N*-aryl-α-L-arabinopyranosylamines, there are differences in the reactivity of HO-3 and HO-4. Such differences were not observed for the *N*-acetyl-*N*-aryl-β-D-xylopyranosylamines.

When different conditions of benzoylation were used (2 mol. of benzoyl chloride, ~50°), *N*-acetyl-*N*-*p*-chlorophenyl-β-D-xylopyranosylamine gave four products which were isolated by chromatography. Two of these compounds were identified as the tribenzoate and the 3,4-dibenzoate (**3**). The two remaining compounds (**4** and **5**, Table I) were monobenzoates.

On acetylation or nitration of **4** (to give **15** and **17**, respectively), the n.m.r. signals (Table II) for H-2 and H-4 were shifted downfield (**4** δ 3.10, 3.92; **15** δ 4.72, 4.90; **17** δ 4.78, 5.05). On the other hand, the signals for H-2 and H-3 were shifted to lower field in the acetate (**16**) and nitrate (**18**) of **5** (**5** δ 3.05, 3.90; **16** δ 4.57, 5.40; **18** δ 4.62, 5.56).

Thus, **4** and **5** are the 3- and 4-benzoates, respectively, of *N*-acetyl-*N*-*p*-chlorophenyl-β-D-xylopyranosylamine. The assignment was confirmed by the fact that **5** reduced ~1 mol. of periodate, whereas **4** was not oxidised.

The above findings, together with the product yields (Table I) show that, on

TABLE II

THE CHEMICAL SHIFTS (δ, p.p.m.) AND COUPLING CONSTANTS (J, ±0.5 Hz) FOR **1–18**

Compound	*H-1*	*H-2*	*H-3*	*H-4*	*H-5e*	*H-5a*	$\Delta H_{5e}H_{5a}$	$J_{1,2}$	$J_{2,3}$ (4,3)	$J_{5e,4}$	$J_{5a,4}$	$J_{5e,5a}$	*OMe*	*OAc*	*NAc*
1	6.00d[a]	3.30t	5.66t	5.06m	4.20q	3.60t	0.60	10	10	4	10	−12	—	—	1.80s
2	6.00d[a]	3.28t	5.65t	5.05m	4.20q	3.62t	0.58	9.5	9.5	3.5	9.5	−12	—	—	1.80s
3	5.96d[a]	3.28t	6.50t	5.05m	4.20q	3.60t	0.60	10	10	3.5	10	−12	—	—	1.80s
4	5.85d[b]	3.10t	5.30t	3.92m	4.22q	3.58t	0.64	9	9	3.5	9	−12	—	—	1.72s
5	5.82d[b]	3.05t	3.90t	4.85m	4.05q	3.40	0.65	9.5	9.5	3.5	10	−12	—	—	1.75s
	6.20d[c]	3.38t	4.20t	5.15m	4.15q	3.50t	0.65	8.5	8.5	3	9	−12	—	—	1.72s
6	6.12d[a]	4.80t	5.68t	5.06m	4.28q	3.60t	0.68	9.5	10	3.5	9.5	−12	—	1.90s	1.80s
7	6.12d[a]	4.78t	5.68t	5.08m	4.28q	3.60t	0.68	9	9	3.5	9.5	−12	—	1.92s	1.82s
8	6.15d[a]	4.82t	5.70t	5.05m	4.30q	3.60t	0.70	9.5	9.5	3	9.5	−12	—	1.90s	1.80s
9	6.00d[a]	4.82t	5.74t	5.08m	4.22q	3.60t	0.62	10	10	4	10	−12	—	—	1.80s
10	6.12d[a]	4.87t	5.85t	5.15m	4.32q	3.62t	0.70	10	10	4	10	−12	—	—	1.82s
11	5.98d[a]	4.80t	5.70t	5.05m	4.22q	3.58t	0.64	10	10	4	10	−12	—	—	1.78s
12	5.92d[a]	3.12t	5.80t	4.98m	4.20q	3.62t	0.58	9.5	9.5	3	9.5	−12	3.20s	—	1.82s
13	5.55d[a]	2.60t	4.3—	—	—	3.00m	—	10	10	—	—	—	3.28s	—	1.80s
14	5.78d[a]	2.92t	5.30t	4.72m	4.00q	3.38t	0.62	10	10	3	10	−12	3.20s	1.95s	1.82s
15	6.07d[a]	4.72t	5.48t	4.90m	4.15q	3.50t	0.65	9	9	3.5	9.5	−12	—	2.00 1.85	1.80
16	6.02d[a]	4.57t	5.40t	4.92m	4.20q	3.45t	0.75	9	9.5	3	9.5	−12	—	1.98 1.78	1.75
17	5.92d[a]	4.78t	5.55t	5.05m	4.22q	3.55t	0.67	10	10	4	10	−12	—	—	1.78s
18	5.93d[a]	4.62t	5.56t	4.98m	4.28q	3.50t	0.78	10	10	4	10	−12.5	—	—	1.78s

[a]In $CDCl_3$. [b]In $CDCl_3+C_5D_5N$. [c]In C_5D_5N. Key: d, doublet; m, multiplet; q, quartet; t, triplet.

benzoylation, the relative reactivity of the hydroxyl groups in *N*-acetyl-*N*-*p*-chlorophenyl-β-D-xylopyranosylamine is 3-OH≈4-OH>2-OH.

It is probable that a similar sequence holds for *N*-acetyl-*N*-*p*-methoxyphenyl- and *N*-acetyl-*N*-*p*-bromophenyl-β-D-xylopyranosylamines.

The reactivity sequence for benzoylation of the hydroxyl groups of *N*-acetyl-*N*-aryl-β-D-xylopyranosylamines is analogous to that for *N*-acetyl-*N*-aryl-α-L-arabinopyranosylamines[4], but it differs from that reported[1] for benzyl α-D-xylopyranoside for which HO-2 was found to be the most reactive.

The configuration and conformation of compounds **1–18** were determined by n.m.r. spectroscopy. The coupling constants for H-1 (*d*, $J_{1,2}$ 10 Hz), H-2 and H-3 (*t*, $J_{2,3} \approx J_{3,4} \approx 10$ Hz, Table II) show that H-1,2,3,4 are oriented axially and indicate the presence of $^4C_1$ conformations. The pyranosidic nature of the sugar ring in these compounds has also been confirmed by the i.r. bands at 910 and 780 cm^{-1} (Table I).

From the δ values for *N*-acetyl-*N*-aryl-β-D-xylopyranosylamines[5] (Table II) and those reported earlier for *N*-acetyl-*N*-aryl-tri-*O*-benzoyl-β-D-xylopyranosylamines[6], the effect of substituents on the magnitude of the chemical shifts of protons in the sugar ring has been determined quantitatively. Substitution of a HO by BzO, ONO_2, or AcO results in a paramagnetic shift of the signal of the proton attached to the appropriate carbon atom by about 1.80, 1.55, and 1.50 p.p.m., respectively. The OMe group increases the resonance frequency of the proton by ~0.18 p.p.m. The deshielding effect of the benzoyl group on protons attached to vicinal carbon atoms is ~0.45 p.p.m. Almost identical values were obtained previously for L-arabinose derivatives[4]. This suggests that the magnitude of the effect of these substituents on the chemical shifts of the protons of the sugar moiety is constant. This finding may prove useful in assigning the signals of protons attached to a pyranoside ring in the $^4C_1$ conformation.

EXPERIMENTAL

Melting points are uncorrected. Optical rotations were measured with a Hilger–Watt polarimeter. T.l.c. was carried out on silica gel G, using *A* carbon tetrachloride–acetone (3:1), *B* carbon tetrachloride–acetone (1:1), or *C* light petroleum–ethyl acetate (8:3). Chromatography was performed on columns of Kieselgel (<0.08 mm), using the above solvent systems.

N.m.r. spectra were recorded on a Tesla-BS 487C (80 MHz) spectrometer with Me_4Si as the internal reference. I.r. spectra were obtained with a Perkin–Elmer 257 spectrophotometer.

Benzoylation of N-*acetyl*-N-*aryl*-β-D-*xylopyranosylamines.* — (*a*) Benzoyl chloride (37.5 mmoles) was added dropwise during 30 min to a vigorously stirred mixture of 15 mmoles of each *N*-acetyl-*N*-aryl-β-D-xylopyranosylamine[5] and 35 ml of dry pyridine, at about −30°. The mixtures were left at ~0° for 2 h, and then poured into mixtures of water and ice. Insoluble material was dissolved in chloroform, and the solutions were washed successively with 2–3% sulphuric acid, 5% aqueous sodium carbonate, and water, then dried (Na_2SO_4), and concentrated. The residues

were subjected to chromatography (solvents *A* and *B*) to give *N*-acetyl-3,4-di-*O*-benzoyl-*N*-*p*-methoxyphenyl- (**1**), -*N*-*p*-bromophenyl- (**2**), and -*N*-*p*-chlorophenyl-β-D-xylopyranosylamine (**3**), and the corresponding tribenzoates (Table I).

(*b*) Benzoyl chloride (30 mmoles) was added to a stirred solution of 15 mmoles of *N*-acetyl-*N*-*p*-chlorophenyl-β-D-xylopyranosylamine in 25 ml of dry pyridine at −50°. The mixture was left for 3 h at about −40°, then 20 ml of chloroform was added, and the mixture was poured into water and ice. The chloroform layer was separated and processed as described in (*a*) to give *N*-acetyl-4-*O*-benzoyl-*N*-*p*-chlorophenyl-β-D-xylopyranosylamine (**5**, 90%). Chromatography (solvent *A*) of the residue gave **3**, *N*-acetyl-3-*O*-benzoyl-*N*-*p*-chlorophenyl-β-D-xylopyranosylamine (**4**), **5**, and a small quantity of the tribenzoate. The diacetates (**15** and **16**) of **4** and **5** were conventionally prepared, using pyridine–acetic anhydride, and crystallised from methanol or ethanol (Table I).

Derivatives of N-*acetyl-3,4-di*-O-*benzoyl*-N-p-*methoxyphenyl* (**1**), -N-p-*bromophenyl-* (**2**), *and* -N-p-*chlorophenyl-β*-D-*xylopyranosylamine*. — (*a*) *Acetates*. Conventional treatment of **1**, **2**, or **3** with acetic anhydride–pyridine and crystallisation of the crude products from ethanol afforded chromatographically homogeneous 2-acetates **6**, **7**, and **8** (Table I).

(*b*) *Nitrates*. Compounds **1**, **2**, or **3** (0.5 mmole) were each treated[4] with 7 mmoles of anhydrous nitric acid, and 5 mmoles each of acetic acid and acetic anhydride at about −50° for ~30 min. Crystallization of the crude products from ethanol or methanol gave the 2-nitrates **9**–**11** (Table I).

Likewise, **4** and **5** were converted into the dinitrates **17** and **18** (Table I).

N-*Acetyl-3,4-di*-O-*benzoyl*-N-p-*bromophenyl-2*-O-*methyl-β*-D-*xylopyranosylamine* (**12**). — Compound **2** (4 mmoles) was methylated[4] with *N*,*N*-dimethylformamide (40 ml), 20 mmoles of methyl iodide, and 8 mmoles of silver oxide. Chromatography (solvent *A*) of the crude product gave **12** (Table I).

N-*Acetyl*-N-p-*bromophenyl-2*-O-*methyl-β*-D-*xylopyranosylamine* (**13**). — A solution[7] of **12** (2 mmoles) and 30 mmoles of dimethylamine in 10 ml of dry methanol was stored at room temperature for 140 h. The oily, crude product was subjected to chromatography (solvent *C*) to give **13** (Table I). When oxidised in aqueous methanol (2:1) with sodium metaperiodate[8], **13** reduced 0.95 mol. of oxidant.

The diacetate (**14**) (Table I) of **13** was conventionally prepared by using pyridine–acetic anhydride.

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