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Note

A novel route to terminal chlorodeoxy sugars*

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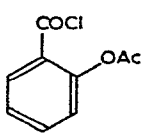
Several new methods for the synthesis of chloro-, bromo-, and iodo-deoxy sugars *via* direct substitution of hydroxyl groups by halogen have been proposed recently. Interest[1] in this class of compounds is largely due to their being convenient precursors for the synthesis of deoxy sugars and various sugar derivatives, including aminodeoxy[2] and unsaturated sugars[3].

We now report on the scope of a new reaction of acetylsalicyloyl chloride[4] (**1**), whereby diol groups of sugars are transformed into chlorodeoxy acetyl groupings.

The action of **1** on 3-*O*-acetyl-1,2-*O*-isopropylidene-α-D-glucofuranose (**2**) in anhydrous *p*-dioxane at room temperature for 24 h yielded salicylic acid and two carbohydrate products. One of these products, isolated in crystalline form (75% yield) after chromatography on alumina, was identified as 3,5-di-*O*-acetyl-6-chloro-6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose (**9**) on the basis of elemental analysis, and i.r., p.m.r., and mass-spectral data. Compound **9** had no i.r. absorption for hydroxyl, but showed strong carbonyl absorption (1745 cm^{-1}) characteristic of an acetyl group. The signals for H-6,6′ in the p.m.r. spectrum of **9** were shifted upfield



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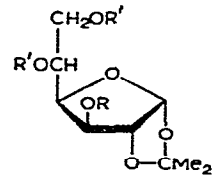
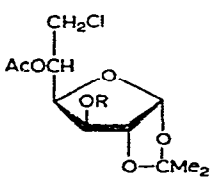
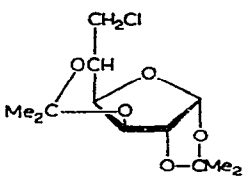


2 R = Ac, R′ = H
3 R = Ts, R′ = H
4 R = CONHPh, R′ = H
5 R = R′ = Ac
6 R = Ts, R′ = Ac
7 R = CONHPh, R′(5) = H, R(6) = Ac
8 R = CONHPh, R′ = Ac



9 R = Ac
10 R = Ts
11 R = CONHPh



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*For a preliminary communication, see Ref. 5.

TABLE I

P.M.R. DATA FOR COMPOUNDS **15–18**

Compound	*Chemical shift (δ p.p.m.)*							*Coupling constants (Hz)*					
	H-1	*H-2*	*H-3*	*H-4*	*H-5*	*H-5′*	*Others*	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{4,5'}$	$J_{5,5'}$
16	5.86d	4.45d	5.19d	~4.35m[a]	~4.07q[a]	~4.23q	2.00, 2.03 (2Ac); 1.0–1.8 (cyclohexyl)	3.50	<0.4	3.00	~7.00[a]	~5.0[a]	[11.5][a]
18	5.73d	4.44d	5.23d	~4.20m	[b]	[b]	2.06 (Ac); 1.0–1.8 (cyclohexyl)	3.50	<0.4	3.00			
15	5.87d	4.44d	5.28d	~4.40m[a]	~4.10[a]	~4.25[a]	1.26, 1.46 (CMe_2); 2.00, 2.03 (2Ac)	3.75	<0.4	3.00	~7.50[a]	~5.0[a]	[11.5][a]
17	5.75d	4.41d	5.19d	~4.35m	[b]	[b]	1.28, 1.50 (CMe_2); 2.08 (Ac)	3.00	<0.4	2.50			

[a]Taken directly from the spectrum; the protons form an ABX system. [b]The signals of H-5 and H-5′ are visible in the form of three lines at 360, 352, and 350 Hz (for **17**, 358, 349, and 352 Hz), with intensities in the ratios 2:1:1.

TABLE II

DATA FOR COMPOUNDS **7–11, 17,** AND **18**

Compound	*Yield (%)*	*M.p. (degrees)*	*Solvent*[a]	$[\alpha]_D^{20}$[b] *(degrees)*	*Formula*	*Calc. (%)*				*Found (%)*			
						C	*H*	*N*	*Cl*	*C*	*H*	*N*	*Cl*
7	35	135–137	C	+45 (*c* 7.4)	$C_{18}H_{23}NO_8$	56.60	6.06	3.68		56.73	6.16	3.60	
8	68	136–137	D	−18 (*c* 7.5)	$C_{20}H_{25}NO_9$	56.80	5.92	3.30		57.02	5.69	3.31	
9	75	121–122	A	+4 (*c* 7.7)	$C_{13}H_{19}ClO_7$	48.40	5.89		11.00	48.23	5.95		10.90
10	76	75–76	B	−43 (*c* 0.6)	$C_{18}H_{23}ClO_8S$	49.90	5.31		8.20	49.90	5.73		8.37
11	70	138–139	C	−47 (*c* 6.5)	$C_{18}H_{22}ClNO_7$	54.20	5.51	3.50	8.90	54.49	6.00	3.61	8.63
17	59	32–33	B	−42 (*c* 10.4)	$C_{10}H_{15}ClO_5$	47.80	6.00		14.28	47.78	5.93		14.28
18	82	oil	—	−29 (*c* 9.6)	$C_{13}H_{19}ClO_5$	53.90	6.53		12.20	54.16	6.58		12.30

[a]Crystallized from: A, ethanol; B, aqueous ethanol; C, heptane–benzene; D, hexane–benzene. [b]Chloroform.

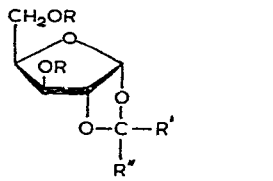
as compared with those of the corresponding protons in 3,5,6-tri-*O*-acetyl-1,2-*O*-isopropylidene-α-D-glucofuranose[6] (**5**), thereby indicating[7] the chlorine substituent to be at position 6. The structure of **9** was proved by its synthesis from 6-chloro-6-deoxy-1,2:3,5-di-*O*-isopropylidene-α-D-glucofuranose[8] (**12**) *via* selective hydrolysis of the 3,5-*O*-isopropylidene group followed by treatment with acetic anhydride in anhydrous pyridine.

Under conditions similar to those used in the synthesis of **9**, the action of **1** on 3-*O*-toluene-*p*-sulphonyl (**3**) and 3-*O*-phenylcarbamoyl (**4**) derivatives of 1,2-*O*-isopropylidene-α-D-glucofuranose afforded 5-*O*-acetyl-6-chloro-6-deoxy-1,2-*O*-isopropylidene-3-*O*-toluene-*p*-sulphonyl-α-D-glucofuranose (**10**) and 5-*O*-acetyl-6-chloro-6-deoxy-1,2-*O*-isopropylidene-3-*O*-phenylcarbamoyl-α-D-glucofuranose (**11**), respectively, the structures of which were established on the basis of spectral data. Small proportions of **6** and **8** were also present (t.l.c.) in the respective reaction mixtures; the authentic compounds were synthesized by the action of acetic anhydride–pyridine on **3** and **4**.

Reaction of **1** with **4**, carefully dried by azeotropic distillation, gave 70% of the chlorine-containing product **11** together with a small amount (0.6%) of 6-*O*-acetyl-1,2-*O*-isopropylidene-3-*O*-phenylcarbamoyl-α-D-glucofuranose (**7**) which was isolated by column chromatography. The p.m.r. spectrum[9] of **7** contained a signal at δ 2.0 for OAc protons, and the signal for H-5 was shifted upfield by 1.27 p.p.m. in comparison with that of the corresponding proton in the 5,6-di-*O*-acetyl derivative of **8**. The reaction of **1** with **4**, dried *in vacuo* over P_2O_5, afforded 50% of **11** together with 30% of **4**. The formation of **7** probably involves hydrolysis of the intermediate cyclic chloroacetate (*cf.* Ref. 10), but partial hydrolysis of **1** to acetylsalicylic acid and subsequent acetyl exchange cannot be ruled out.

The compounds studied gave well-resolved, first-order p.m.r. spectra, with the exception of H-5 and H-6 which form an ABX system. The analysis of the i.r. and p.m.r. data of **5**–**11** is published elsewhere[9].

The response of a 1,3-diol grouping to **1** was investigated by using 1,2-*O*-isopropylidene (**13**) and 1,2-*O*-cyclohexylidene (**14**) derivatives of α-D-xylofuranose, and 6-*O*-acetyl-1,2-*O*-isopropylidene-α-D-glucofuranose (**15**).

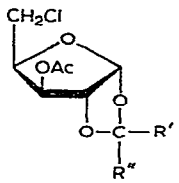


13 R = H, R' = R" = Me

14 R = H, R'—C—R" = 

15 R = Ac, R' = R" = Me

16 R = Ac, R'—C—R" = 



17 R' = R" = Me

18 R'—C—R" = 

Reaction of **1** with **13** or **14** gave four products (t.l.c.); the 3-*O*-acetyl-5-chloro-5-deoxy derivatives **17** and **18** were the main products, and small proportions of the 3,5-di-*O*-acetyl derivatives **15** and **16** were detected (t.l.c.).The p.m.r. data for **15–18** are given in Table I.

6-*O*-Acetyl-1,2-*O*-isopropylidene-α-D-glucofuranose, prepared[11,12] by treatment of 1,2-*O*-isopropylidene-α-D-glucofuranose in sequence with benzeneboronic acid, acetic anhydride–pyridine, and propane-1,3-diol, reacted slowly with **1**. After 15 days, a significant proportion of the starting compound remained (t.l.c.), and although four products were formed only 3,5,6-tri-*O*-acetyl-1,2-*O*-isopropylidene-α-D-glucofuranose (**5**) was identified (t.l.c.). The reaction of **1** with 6-*O*-acetyl-1,2-*O*-isopropylidene-α-D-glucofuranose may be sterically hindered by the CH_2OAc group.

The action of **1** on methyl 4,6-*O*-benzylidene-α-D-glucopyranoside gave a complex mixture of products which was not studied further. Evidently, vicinal *trans*-hydroxyl groups do not permit the formation of an intermediate cyclic product[4].

EXPERIMENTAL

I.r. spectra were recorded on a UR-20 spectrophotometer (Carl Zeiss, DDR). P.m.r. spectra were measured with HD-100 (Varian Associates, USA) and JNM PS-100 (Jeol, Japan) spectrometers with Me_4Si as internal standard.

Concentrations *in vacuo* were carried out at 35–40° on a rotary evaporator.

All melting points were determined in a capillary and are uncorrected.

T.l.c. was performed on unfixed alumina (Brockmann II–III) or silica gel (Silufol Czechoslovakia), with acetone–hexane mixtures (1:1 and 1:2).

1,2-O-Isopropylidene-3-O-phenylcarbamoyl-α-D-glucofuranose (**4**). — Phenyl isocyanate (2.4 ml, 0.03 mol) was added to a solution of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (5 g, 0.02 mol) in dry pyridine (25 ml). The mixture was boiled for 13 h, and then concentrated *in vacuo* with successive additions of methanol and toluene. The oily residue was treated with chloroform, *N*,*N*-diphenylurea was removed, and the filtrate was added to a column of alumina (Brockmann II, 300 ml). Elution with chloroform gave 1,2:5,6-di-*O*-isopropylidene-3-*O*-phenylcarbamoyl-α-D-glucofuranose (6.5 g, 88%) as an oil; ν_{max}^{KBr} 1752 (CONH), 1605 (Ph), 3340, 3450, 1525 (NH), 1372, and 1382 cm^{-1} (CMe_2). 0.1M Sulphuric acid (2.5 ml) was added to a solution of the diacetal (4.5 g) in methanol (75 ml). After 2 days at room temperature, the acid was neutralized ($BaCO_3$), and the filtered solution was concentrated to dryness. The oily residue crystallized from benzene to give **4** (1.5 g, 37%), m.p. 87–88°, $[\alpha]_D^{20}$ −15° (*c* 13.2, methanol); ν_{max}^{KBr} 1540 (NH), 1720 (C=O), 1605 (Ph), and 3380 cm^{-1} (OH, NH) (Found: C, 54.16; H, 6.60; N, 3.92. $C_{16}H_{21}NO_7 \cdot H_2O$ calc.: C, 53.80; H, 6.44; N, 3.93%).

Standard procedure for transformation of sugar diol groups into chloroacetyl groupings. — A mixture of diol (0.01 mol) and **1** (0.01 mol) in anhydrous *p*-dioxane (20 ml) was kept for 24 h at room temperature under anhydrous conditions, and then concentrated *in vacuo*. A solution of the oily residue in benzene was added to a

column of anhydrous alumina (50 ml). The column was eluted with benzene. The products are listed in Table II.

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