Food Chemistry **15** (1984) 51–56

Technical Note

Chlorination of Maltose with Triphenylphosphine-*N*-Chlorosuccinimide (TPP–NCS) Reagent

ABSTRACT

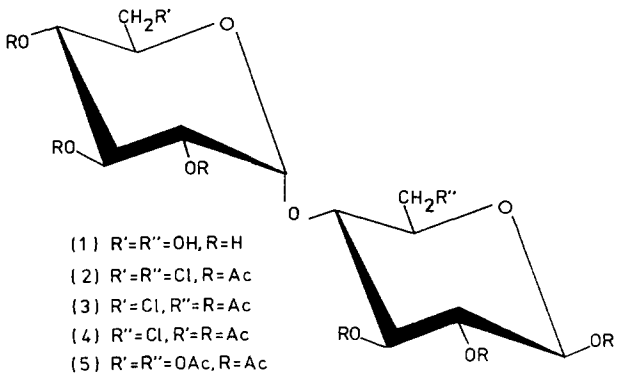
*The triphenylphosphine-*N*-chlorosuccinimide reagent is shown to be effective for direct chlorination of reducing sugars. Under the reaction conditions, on maltose, chlorination shows a preferred selectivity for the primary alcohol grouping at the reducing moiety.*

INTRODUCTION

The similarity of maltose to the glycoside residue of the nucleoside antibiotics amicetamine, biamicetin and plicacetin has been noted (Durette *et al.*, 1978) and its chemistry investigated in view of this (Durette *et al.*, 1974*a*,*b*). Work on halogenated derivatives (Durette *et al.*, 1978) has shown them to be useful intermediates for many reactions in synthetic chemistry (Barnett, 1967; Hanessian, 1968). Our work on structure–activity taste relationships on modified maltose compounds (Dziedzic & Birch, 1981) led us to investigate facile methods for direct chlorination of this unsubstituted glycosyl-hexopyranose type structure.

A mixture of triphenylphosphine and *N*-halosuccinimide reagent (TPP–NCS) has been used for the selective halogenation of primary hydroxyl groups in sugar glycosides, acetals and esters (Hanessian *et al.*, 1972). The possibility of using the TPP–NCS reagent on reducing sugars was noted (Hanessian *et al.*, 1972) but not further investigated.

Food Chemistry 0308-8146/84/$03·00



Scheme 1

This Note describes the preparation of three new maltose derivatives, using the TPP–NCS reagent, that have application to the aforementioned research programmes (see Scheme 1).

Treatment of maltose (1) with TPP–NCS reagent, followed by acetylation with acetic anhydride in pyridine, afforded a mixture of three products, as shown by thin-layer chromatography (dichloromethane:ethyl acetate; 10:1). Column chromatography on silica gel gave the crystalline 6,6′-dichloro-6,6′-dideoxy hexa-*O*-acetate (2) (primed numbers refer to the non-reducing ring) in 35% yield, the 6′-chloro-6′-deoxy hepta-*O*-acetate (3) in 6% yield and the 6-chloro-6-deoxy hepta-*O*-acetate (4) in 15% yield.

Examination of the ^{1}H–nmr parameters (Table 1) clearly identifies the structures of compounds (2), (3) and (4). When compared with the spectrum of maltose octaacetate (5), substitution of OAc by chlorine at C-6 or C-6′ leads to an upfield shift (*ca.* 0·36–0·61 ppm) of the methylene protons situated on the same carbon atom. Chlorination at C-6′ shows a downfield shift for H-5′ (0·15 ppm, compound (2); 0·10 ppm, compound (3)) whereas the H-4′ signal is not affected. On the other hand, chlorination at C-6 shows a relatively large downfield shift (0·2 ppm, compounds (2) and (4)) for the H-4 signal, with slight downfield shifts for the vicinal H-5 signal. Such shielding and deshielding effects are known (Durette *et al.*, 1974*a*) for this type of compound.

Tosylation (Sleeter & Sinclair, 1970) and tritylation (Wolfrom & Koizumi, 1967) of maltose have shown the C-6′ position to be far more reactive than the C-6 position, monosubstituted derivatives being obtained in ratios of 18:1 and 10:1, respectively. The reverse was shown for bimolecular nucleophilic displacement of primary tosyloxy groups, the C-6

TABLE 1
'H–nmr Parameters*

Compound	*(2)*	*(3)*	*(4)*	*(5)*†
H-1	4·23d	4·23d	4·24d	4·26d
H-1′	4·48d	4·54d	4·51d	4·59d
H-2	5·01t	5·00t	5·03t	5·02t
H-2′	5·15dd	5·14dd	5·15dd	5·14dd
H-3	4·67t	4·68t	4·69t	4·71t
H-3′	4·61t	4·61t	4·64t	4·64t
H-4	5·76t	5·92t	5·76t	5·96t
H-4′	4·88t	4·93t	4·94t	4·94t
H-5	6·07m	6·14oc	6·12m	6·16m
H-5′	5·91sx	5·96oc	6·02sx	6·06m
H-6a,6b	6·07m	5·49dd, 5·74dd	6·12m	5·55dd, 5·71dd
H-6′a,6′b	6·24dd, 6·39dd	6·37dd, 6·45dd	5·67dd, 5·87dd	5·76dd, 5·96dd
$J_{1,2}$	7·6	8·0	8·0	8·2
$J_{1',2'}$	3·6	4·0	4·0	4·0
$J_{2,3}$	7·6	8·8	9·0	9·0
$J_{2',3'}$	9·6	10·2	10·4	10·6
$J_{3,4}$	7·6	8·8	9·0	8·8
$J_{3',4'}$	9·2	10·0	9·5	9·7
$J_{4,5}$	7·6	8·8	9·0	8·8
$J_{4',5'}$	9·2	10·0	10·0	10·0
$J_{5,6}$		2·6, 4·2		2·3, 4·1
$J_{5',6'}$	4·0, 3·2	3·0, 4·8	3·4, 2·1	3·7, 2·4
$J_{6,6}$		−12·0		−12·0
$J_{6',6'}$	−12·0	−12·0	−12·8	−12·1

* First-order chemical shifts (τ-values) and coupling constants (J) at 220 MHz for solutions in $CDCl_3$. Key: s, singlet; d, doublet; t, triplet; dd, double doublet; sx, sextet; oc, octet; m, multiplet.
† Durette *et al.* (1974*a*).

monosubstituted compound being isolated as the major product (Sleeter & Sinclair, 1970). The formation of an intermediate alkoxyphosphonium salt (Hanessian *et al.*, 1978) [RCH_2—O—$P^+Ph_3Cl^-$] from the reaction of TPP–NCS with a primary alcohol followed by SN_2 displacement by the chloride ion, rationalises the reaction of maltose with TPP–NCS. Although the C-6 position is sterically more hindered, it is more favourably disposed to SN_2 displacement reactions by providing a preferred electronic environment for the transition state. The reason for this is not clear, although more favourable dipole–dipole interactions

involving the approaching nucleophile have been suggested (Tarelli, 1980).

Previously, modification of maltose at the primary alcohol group of the reducing moiety has been carried out by lengthy multi-step procedures via 1,6-anhydromaltose (Asp & Lindberg, 1952; Durette *et al.*, 1974*a*) or the 4′,6′-acetal of 6-*O*-tritylmaltose (Aspinall *et al.*, 1975). Use of the TPP–NCS reagent under the conditions reported here has shown it to have a certain degree of selectivity towards the primary hydroxyl group of the reducing moiety. Use of milder chlorinating conditions (Hanessian & Lavallee, 1973) could lead to a facile one-step preparation of 6-chloro-6-deoxymaltose as the major product.

EXPERIMENTAL

General

Optical rotations were measured on a Bellingham and Stanley P.70-2 automatic polarimeter. ^{1}H–nmr spectra were recorded for solutions in chloroform-d at 220 MHz with tetramethylsilane as the internal standard. Column chromatography was performed on Merck silica gel 7734 (70–230 mesh). Thin-layer chromatography was performed on plates coated with silica gel GF_{254} and detected with a 10% sulphuric acid in ethanol spray at 110 °C.

Reaction of maltose with (TPP–NCS) reagent

To a solution of maltose (1) (1·368 g, 4 mmoles) and triphenylphosphine (4·32 g, 16 mmoles) in *N*,*N*-dimethylformamide (100 ml) at 0 °C, *N*-chlorosuccinimide (2·14 g, 16 mmoles) was added slowly with stirring. After 1 h the temperature was raised to 60 °C and the mixture was stirred for a further 6 h. The solution was cooled, methanol (100 ml) was added and the solution was evaporated to dryness. Ice-cold saturated sodium bicarbonate (300 ml) was added and the mixture was stirred for half-an-hour. After extraction with chloroform (3 × 50 ml), the aqueous layer was evaporated and acetylated with acetic anhydride (10 ml) in pyridine (20 ml) at 0 °C for 36 h. After conventional work-up, dry column

chromatography with dichloromethane–ethyl acetate (10:1) as eluant afforded the following products:

(i) *1,2,3-Tri*-O-*acetyl-6-chloro-6-deoxy-4*-O-(*2,3,4-tri*-O-*acetyl-6-chloro-6-deoxy-α*-D-*glucopyranosyl*)-*β*-D-*glucopyranose* (2) (917 mg, 35%), recrystallised from propan-2-ol; melting point, 190°, $[\alpha]_D^{20} + 62{\cdot}6°$ (*c.* 1·0, chloroform).

Anal. Found: C, 45·8; H, 5·1; Cl, 11·3. Calc. for $C_{24}H_{32}Cl_2O_{15}$: C, 45·7; H, 5·1; Cl, 11·3%.

(ii) *1,2,3,6-Tetra*-O-*acetyl-4*-O-(*2,3,4-tri*-O-*acetyl-6-chloro-6-deoxy-α*-D-*glucopyranosyl*)-*β*-D-*glucopyranose* (3) (151 mg, 6%), recrystallised from ethanol, melting point, 178–180°, $[\alpha]_D^{20} + 60{\cdot}3°$ (*c.* 0·3, chloroform).

Anal. Found: C, 47·7; H, 5·6; Cl, 5·9. Calc. for $C_{26}H_{35}ClO_{17}$: C, 47·6; H, 5·4; Cl, 5·4%.

(iii) *1,2,3-Tri*-O-*acetyl-6-chloro-6-deoxy-4*-O-(*2,3,4,6-tetra*-O-*acetyl-α*-D-*glucopyranosyl*)-*β*-D-*glucopyranose* (4) (379 mg, 15%). recrystallised from ethanol, melting point, 155–157°, $[\alpha]_D^{20} + 57{\cdot}6°$ (*c.* 1·1, chloroform).

Anal. Found: C, 48·1; H, 5·4: Cl, 5·7; Calc. for $C_{26}H_{35}ClO_{17}$: C, 47·6; G, 5·4; Cl, 5·4%.

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Stanley Z. Dziedzic,
Department of Food Science,
University of Reading, London Road,
Reading, Berks, Great Britain

Elner B. Rathbone* & G. G. Birch,
National College of Food Technology,
University of Reading, Food Studies Building,
Whiteknights, Reading, Berks, Great Britain

(Received: 5 March, 1984)

* Present address: Tate & Lyle Ltd, Group R&D, Philip Lyle Memorial Research Laboratory, University of Reading, Reading, Berks, Great Britain.