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The phthalation of 2-amino-2-deoxy-D-glucose and *N*-methyl-1-amino-1-deoxy-D-glucitol; conversion of the products to organotin derivatives. A ready migration of acetyl from oxygen to nitrogen under neutral conditions#

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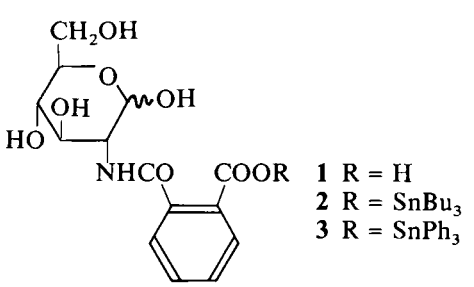
Abstract. *N*-Phthalation of 2-amino-2-deoxy-D-glucose was followed by replacement of the acidic proton by tributyl- and triphenylstannyl groups. A similar reaction with 1-(methylamino)-1-deoxy-D--glucitol failed and successive treatment with benzyl chloroformate and acetic anhydride followed by catalytic hydrogenation showed that a 1,4 O → N acetyl migration had occurred. Phthalation and stannylation succeeded under different conditions.

Introduction

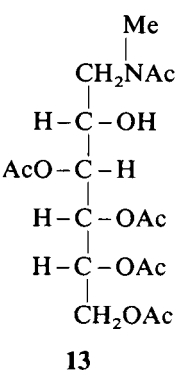
Phthalation of sugars gives derivatives with free carboxyl groups which can be utilised to attach organotin groups giving products with high biological activities[1,2]. For example, the tributylstannyl derivative of phthalated sucrose has enhanced fungicidal and algicidal properties compared with bis(tributyltin) oxide[1]. Free sugars give mixtures of phthalates (though substitution at primary hydroxyl groups is favoured) and these are difficult to separate[3] though pure esters have been obtained by the use of protected sugars[4]. Phthalation of amino sugars should occur regioselectively at nitrogen and it was of interest to examine the biological properties of the corresponding organotin derivatives. This paper describes the synthetic work and a brief summary of some preliminary biological tests on one of the products is included in the Experimental Section.

Results and discussion

Treatment of 2-amino-2-deoxy-D-glucose with phthalic anhydride in methanol gave the expected *N*-phthalyl derivative **1** as mixed anomers, which were converted to the tributyltin and triphenyltin compounds (**2** and **3** respectively) by standrard procedures. The Mössbauer parameters of **2** (IS



1 R = H
2 R = $SnBu_3$
3 R = $SnPh_3$



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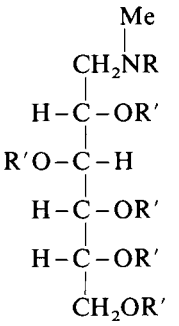

4 R = R′ = H
5 R = *o*-COC_6H_4COOH, R′ = H
6 R = *o*-COC_6H_4COOMe, R′ = H
7 R = *o*-COC_6H_4COOMe, R′ = Ac
8 R = *o*-$COC_6H_4COOSnPh_3$, R′ = H
9 R = *o*-$COC_6H_4COOSnBu_3$, R′ = H
10 R = $PhCH_2OCO$, R′ = H
11 R = $PhCH_2OCO$, R′ = Ac
12 R = H, R′ = Ac

Dedicated to Prof. *G. J. M. van der Kerk* on the occasion of his 75th birthday.

1.50, QS 3.41 mm·s^{-1}) are similar to those of tributyltin acetate[5] indicating a normal trialkyltin carboxylate structure.

Attempted phthalation of 1-(methylamino)-1-deoxy-D-glucitol (**4**) under the same conditions gave an intractable mixture which, from spectroscopic measurements, appeared to contain only small amounts of the desired product. When the solvent was changed to DMF, 1-(*N*-methylphthalamido)-1-deoxy-D-glucitol (**5**) was formed in high yield. The ^{13}C NMR spectrum (Table I) was as expected and a derivative useful as a ^1H NMR reference compound (Table II) was obtained by conversion to the methyl ester **6** followed by acetylation to give **7**. The required triphenyl- and tributyltin derivatives (**8** and **9** respectively) were obtained by standard methods.

The failure of the phthalation of **4** in methanol was surprising and it was thought that interference by the hydroxyl groups may have been the reason. It was therefore decided to protect the nitrogen with a benzyloxycarbonyl group, acetylate the hydroxyl functions and then remove the benzyloxycarbonyl group. This should leave a free NH group for phthalation without interference from hydroxyl groups. Preparation of the benzyloxycarbonyl derivative **10** and conversion to the penta-acetate **11** occurred smoothly but hydrogenation over palladized carbon failed to give the expected penta-acetate with a free NH group (**12**). Instead, 3,4,5,6-tetra-O-acetyl-1-(*N*-methylacetamido)-1-deoxy-D--glucitol **13** was obtained. The ^1H NMR spectrum of **13** showed that the singlet at δ3.08 due to N–CH_3 was shifted downfield from its position in unreacted **4** (δ2.15) indicating *N*-acetylation. Comparison of the spectrum of **13** with that of hexa-acetyl-1-(methylamino)-1-deoxy-D-glucitol (Table II) showed that a complex multiplet at δ5.32 due to H-2 in the latter had moved 1.33 ppm upfield to 3.99 in **13** because of the free 2-OH group[6]. The presence of 5 acetyl groups in **13** was confirmed by integration of the singlets at δ2.06–2.14 due to acetyl methyl groups. Addition of trichloroacetyl isocyanate to **13** (Table II) removed the H-2 signal at δ3.99 shifting it to δ5.34 and a I-proton signal appeared at δ8.97 due to $Cl_3CCONHCOOR$ supporting the absence of an acetyl group at the 2-OH in **13**. The mass and IR spectra of **13** (see Experimental Section) also supported the assigned structure. Finally, acetylation of **13** gave a product which was identical with hexa-acetyl-1-(methylamino)-1-deoxy-D-glucitol.

All attempts to obtain **12** by carrying out the hydrogenation at lower temperatures or in different solvents were unsuccessful. It thus appears that migration of acetyl from O-2 to N, presumably by an intramolecular aminolysis occurs very readily under neutral conditions, even at −20°C. Although examples of migration of an acyl group from oxygen to nitrogen on a neighbouring carbon in sugar derivatives have been reported these have been under basic conditions[6,7].

Table I ^{13}C *NMR chemical-shift values, measured in water, of 1-(methylamino)-1-deoxy-*D*-glucitol* (**4**) *and its* N*-phthalyl derivative* (**5**).

Assignment[a]	**4**	**5**
C-1	53.48	53.41 54.24
C-2	72.14	70.23 70.49
C-3		70.68 71.53
C-4		72.42 72.29
C-5		70.88
C-6	64.00	63.31 63.17
N–Me	35.84	38.66
OMe	–	50.78
N–CO–R	–	174.28 174.18
–CO–OMe	–	168.03

[a] Except for C-1, C-6, N–Me and O–Me, these assignments are tentative.

Table II ^1H *NMR chemical shifts (δ values) and coupling constants (Hz) measured at* 250 *MHz in* $CDCl_3$ *for derivatives of* 1*-(methylamino)-*1*-deoxy-*D*-glucitol* (**4**).

Assignment	Hexa-acetyl derivative of **4**	**11**	**13**	**13** + $Cl_3CCOCNO$	**7**
(a) *Chemical shifts (ppm)*[a]					
H-1a	3.58	3.46 dd	3.20 dd	3.13 dd	3.90
H-1b		3.56 dd	3.72 dd	3.50 dd	
H-2	5.32 m	5.14	3.99 m	5.34	5.48
H-3			5.10 dd		
H-4	5.48 dd	5.48 dd	5.49 dd	5.46 dd	5.56 dd
H-5	5.04 m	5.04 m	5.18 m	5.10 m	5.10 m
H-6a	4.28 dd	4.28 dd	4.30 dd	4.34 dd	4.34 dd
H-6b	4.10 dd	4.10 dd	4.16 dd	4.10 dd	4.16 dd
N–CH_3	3.0 s	2.93 s	3.08 s	3.04 s	2.80 s
(b) *Coupling constants (Hz)*					
$J_{1a,2}$			9.0		
$J_{1b,2}$			2.0	2.0	
$J_{1a,1b}$			13.57	14.5	
$J_{2,3}$			8.0		
$J_{3,4}$	4.0		4.0	4.0	5.0
$J_{4,5}$	7.0		8.0	7.0	7.0
$J_{5,6a}$	3.0		2.0	2.0	3.0
$J_{5,6b}$	6.0		6.0	6.0	6.0
$J_{6a,6b}$	12.5		12.5	12.5	12.5

[a] s = singlet; d = doublet; dd = double doublet; t = triplet; m = multiplet.

Experimental

NMR spectra were measured using either Bruker WM 250 or Bruker WH 400 ULIRS instruments at King's College and Queen Mary College respectively. Chemical shift values refer to either TMS or DSS as internal standards. Optical rotations were measured with a Perkin-Elmer 141 polarimeter. Mössbauer spectra were measured on the ULIRS instrument at Birkbeck College, isomer shifts refer to barium stannate.

*2-Phthalamido-2-deoxy-*D*-glucopyranose* **1**

Sodium (1.24 g, 54 mmole) was dissolved in methanol (50 ml) cooled in an ice bath, after warming to room temperature, 2-amino-2-deoxy-α-D-glucose hydrochloride (11.0 g, 51 mmole) was added with stirring. The mixture was filtered, cooled in ice, and treated with phthalic anhydride (7.56 g, 51 mmole). The mixture was allowed to warm to room temperature and stirred for 90 min. The white product (10.0 g, 60%) was filtered and recrystallised (water/ethanol/ether) to give the pure phthalamide (**1**), m.p. 200°C, $[\alpha]_D$ +62.5 → +36.5° (*c* 2.0, H_2O). Anal. $C_{14}H_{17}O_8$ calcd.: C 51.4, H 5.2, N, 4.2; found: C 52.0, H 5.2, N 4.2%.

A mixture of the phthalamide **1** (0.19 g, 0.58 mmole), bis(tributyltin) oxide (0.14 g, 0.24 mmole) and benzene was boiled under reflux with azeotropic removal of water for 8h. The solvent was removed and the product extracted from the resulting syrup with dichloromethane; drying ($MgSO_4$) and evaporation gave the tributylstannyl derivative **2** as a glassy solid (0.19 g, 52%). IR spectrum (Nujol) showed $\nu(C{=}O)_{COOSn}$ 1650 and $\nu(C{=}O)_{CONH}$

1620 cm^{-1}. Mössbauer spectrum showed a doublet IS 1.50, quadrupole splitting 3.41 $mm \cdot s^{-1}$.
Anal. $C_{26}H_{44}O_8NSn$ (617.3); calcd.: C 50.6, H 7.1; found: C 50.2, H 8.6%.
The corresponding triphenylstannyl derivative **3** was prepared similarly from **1** and triphenyltin hydroxide in 54% yield. IR spectrum showed $\nu(C=O)_{COOSn}$ 1650 and $\nu(C=O)_{CONH}$ 1620 cm^{-1}. Anal. $C_{32}H_{31}O_8NSn$ (676.27) calcd.: C 56.8, H 4.6, N 2.1; found: C 51.3, H 5.1, N 1.8%. We are unable to explain the low value for carbon.

1-(N-Methylphthalamido)-1-deoxy-D-glucitol **5**

A mixture of **4** (19.5 g, 100 mmole), phthalic anhydride (14.8 g, 100 mmole) and dry *N,N*-dimethylformamide (200 ml) was stirred at room temperature for 15 min. Concentration of the resulting solution and addition of chloroform precipitated the product (30 g, 87%) shown by tlc to be virtually homogeneous, $[\alpha]_D$ −11.76° (*c* 1.0, methanol). Anal. $C_{15}H_{21}O_8N$ (343.38) calcd.: C 52.5, H 6.2, N 4.1; found: C 51.2, H 6.2, N 3.9%. The ^{13}C NMR spectrum was measured in water and the assignments are given in Table I.
Compound **5** (0.26 g, 0.75 mmole) and triphenyltin hydroxide (0.18 g, 0.5 mmole) were boiled under reflux in benzene for 1 h. Unreacted solid was removed by centrifugation and evaporation gave the solid triphenylstannyl derivative **8** (0.31 g, 89%). IR spectrum showed $\nu(C=O)_{COOSn}$ 1650 and $\nu(C=O)_{CONH}$ 1620 cm^{-1}. Anal. $C_{33}H_{35}O_8NSn$ (692.31) calcd.: C 57.2, H 5.1, N 2.0; found: C 57.3, H 5.0, N 1.5%. The corresponding tributylstannyl compound **9** was obtained similarly in 73% yield using bis(tributyltin) oxide, $[\alpha]_D$ −4.65° (*c* 1.0, chloroform). IR spectrum showed $\nu(C=O)_{COOSn}$ 1640 and $\nu(C=O)_{CONH}$ 1620 cm^{-1}. Anal. $C_{27}H_{47}O_8NSn$ (632.35) calcd.: C 51.3, H 7.5, N 2,2; found: C 49.8, H 8.6, N 2.0%. This syrupy product could not be further purified. Preliminary biological evaluation of **9** showed it to have marked insecticidal, fungicidal and herbicidal properties and it exhibited plant growth regulatory activity with some species.
A solution of 1-(*N*-methylphthalamido)-1-deoxy-D-glucitol (**5**) in methanol was methylated with ethereal diazomethane under standard conditions to give the crystalline methyl ester **6** in 67% yield, m.p. 110°C, $[\alpha]_D$ −9.33° (*c* 1.0, methanol). Anal. $C_{16}H_{23}O_8N$ (357.35) calcd.: C 53.8, H 6.4, N 3.9; found: C 53.4, H 6.5, N 3.8%. Conventional acetylation of **6** with acetic anhydride and pyridine gave the corresponding penta-acetate **7** as a syrup (57%), $[\alpha]_D$ +8.08° (*c* 1.0, chloroform). Anal. $C_{26}H_{33}O_{13}N$ (567.53) calcd.: C 55.0, H 5.8, N 2.5; found: C 54.2, H 5.8, N 2.5%. The ^1H NMR spectrum (250 MHz, solvent $CDCl_3$) showed the expected absorptions, see Table II.

[(Benzyloxycarbonyl)methylamino]-1-deoxy-D-glucitol **10**

Benzyl chloroformate (32.0 g, 228 mmole) was added, with vigorous stirring, to a solution of **4** (34.0 g, 170 mmole) and sodium carbonate (25.0 g, 236 mmole) in water (100 ml). The mixture was stirred for 18 h at room temperature when filtration gave the product (48.0 g, 86%), shown by TLC (aq. NH_4OH/MeOH/acetone) to be homogeneous; $[\alpha]_D$ −14.9° (*c* 1.0, methanol). Anal. $C_{15}H_{23}O_7N$ (329.34) calcd.: C 54.7, H 7.0, N 3.9; found: C 54.4, H 7.0, N 3.9%.
Acetylation of **10** with acetic anhydride and pyridine under standard conditions gave 2,3,4,5,6-penta-O-acetyl-1-[(benzyloxycarbonyl)methylamino]-1-deoxy-D-glucitol (**11**) in 85% yield, $[\alpha]_D$ −10.5° (*c* 1.0, chloroform). Anal. $C_{25}H_{33}O_{12}N$ (539.52) calcd.: C 55.7, H 6.1, N 2.6; found: C 55.3, H 5.9, N 2.6%. The ^1H NMR spectrum (250 MHz, solvent $CDCl_3$) showed the expected absorptions, see Table II).

3,4,5,6-Tetra-O-acetyl-1-(N-methylacetamido)-1-deoxy-D-glucitol **13**

A solution of the acetylated benzyloxycarbonyl compound **11** (3.6 g, 6.6 mmole) in a 1:1 mixture of ethyl acetate/methanol was hydrogenated over 10% palladium-on-charcoal (200 mg) at 50 psi when TLC showed that starting material had been consumed. After filtering off the catalyst, evaporation gave the crude product which was crystallised from dichloromethane/ether mixture giving the pure penta-acetate as colourless crystals (2.0 g, 75%), m.p. 124°C, $[\alpha]_D$ −7.46° (*c* 0.75, methanol). Anal. $C_{17}H_{27}O_{10}N$ (405.40) calcd.: C 50.4, H 6.7, N 3.4; found: C 49.7, H 6.7, N 3.0%.

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