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Reactions of Some *N*-Phenylcarbamates of Glycosides under Hydrolytic Conditions

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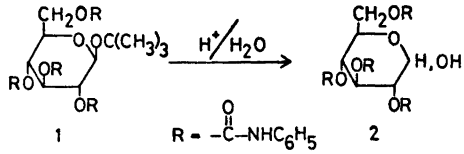
Syntheses and acid hydrolysis studies of *N*-phenylcarbamates of some glycosides are reported. *tert*-Butyl 2,3,4,6-tetra-*O*-(*N*-phenylcarbamoyl)-β-D-glucopyranoside was easily hydrolysed, yielding 2,3,4,6-tetra-*O*-(*N*-phenylcarbamoyl)-D-glucose. The 2-*O*-(*N*-phenylcarbamoyl) derivatives of methyl-α-D-glucopyranoside and methyl β-D-mannopyranoside on hydrolysis reacted further, giving bicyclic oxazolidin-2-one derivatives. The glucose derivative yielded an α-furanosidic oxazolidin-2-one, the mannose derivative a mixture of β-furanosidic and β-pyranosidic oxazolidin-2-ones.

DISCUSSION

The condensation of *N*-phenylcarbamates of sugars to give oligo- and polysaccharides seemed, from the results reported by Husemann and Müller,[1] to be a promising method. Recent results by Eby and Schuerch,[2,3] however, indicate that the value of this approach is limited. We have obtained similar results and arrived at the same conclusion. We now report the syntheses of *N*-phenylcarbamates of some glycosides and their reactions under hydrolytic conditions.

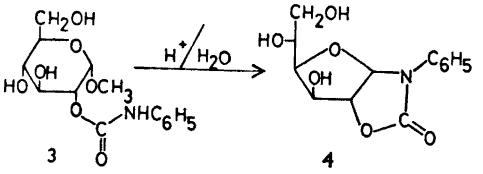
Introduction of the slightly basic *N*-phenylcarbamate group into glycosides renders them more resistant to acid hydrolysis. Thus the methyl 2,3,6- and 2,3,4-tri-*O*-(*N*-phenylcarbamoyl)-α-D-glucopyranosides could not be hydrolysed.[3] Eby and Schuerch [2] prepared 2,3,4-tri-*O*-(*N*-phenylcarbamoyl)-D-glucose by hydrolysis of the corresponding 1,6-anhydro-D-glucopyranose derivative. We have now prepared 2,3,4,6-tetra-*O*-(*N*-phenylcarbamoyl)-D-glucose (*2*) by acid hydrolysis of the fully carbanilated *tert*-butyl β-D-glucopyranoside (*1*).



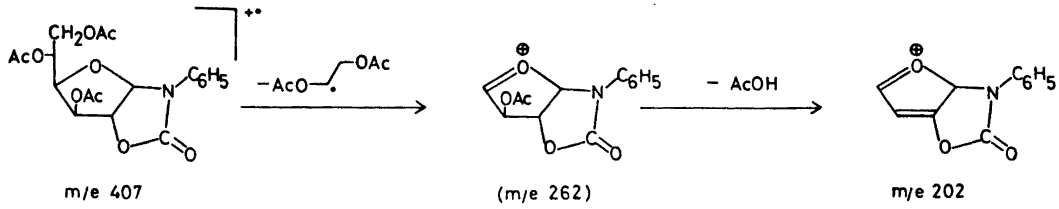
1 2

Methanolysis of *2* yielded a mixture of fully carbanilated methyl α- and β-D-glucopyranosides in the approximate proportion 2:3. The β-anomer predominated but the stereoselectivity of the reaction was not very high.

Although methyl tri- and tetra-*O*-(*N*-phenylcarbamoyl)-glucopyranosides are resistant to acid hydrolysis, the corresponding monoesterified products should be more labile. Methyl 2-*O*-(*N*-phenylcarbamoyl)-α-D-glucopyranoside (*3*) was therefore prepared by carbanilation of methyl 3-*O*-acetyl-4,6-*O*-benzylidene-α-D-glucopyranoside,[4] followed by mild acid hydrolysis. Under stronger hydrolytic conditions, the glucoside was hydrolysed but the product reacted further, yielding the bicyclic α-furanosidic oxazolidin-2-one derivative (*4*). A first order analysis of the NMR spectra of the acetate of *4*, using spin decoupling in order to identify the individual protons, was in agreement with the postulated structure (Table 1). The mass spectrum of the acetate also agreed with this structure. The



3 4



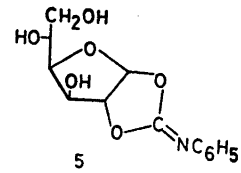
Scheme 1.

Table 1. NMR spectra of the acetylated oxazolidin-2-one derivatives.

	Compound 4	7	8
Chemical shifts (δ-values)			
H-1	6.05	5.87	5.61
H-2	4.88	5.12	4.84
H-3	5.60	5.47	5.29
H-4	4.37	4.29	5.29
H-5	5.30	5.33	3.83
H-6	4.15	4.10	4.09
H-6′	4.55	4.51	4.28
-OAc	1.97	2.01	2.00
	2.03	2.04	2.04
	2.11	2.10	2.09
Coupling constants (Hz)			
$J_{1,2}$	5.5	6.2	3.7
$J_{2,3}$	0	5.7	3.5
$J_{3,4}$	3.0	4.0	–
$J_{4,5}$	9.1	9.0	6.0
$J_{5,6}$	5.0	5.0	3.0
$J_{5,6'}$	2.5	2.5	5.0
$J_{6,6'}$	12.0	12.1	12.3

origin of the main fragment is indicated in Scheme 1.

The results of these analyses do not preclude the cyclic imidocarbonate (*5*) structure. Imidocarbonates are, however, easily hydrolysed whilst *4* is resistant to acid hydrolysis. The observed IR absorption at 1755 cm^{-1} also favours the oxazolidin-2-one structure. Substance *4* was recovered unchanged after treatment with methanolic hydrogen chloride.



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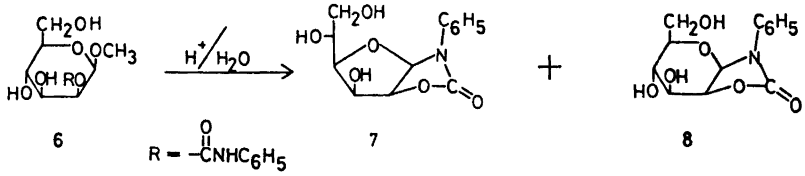
Methyl 2-*O*-(*N*-phenylcarbamoyl)-β-D-mannopyranoside (*6*) was prepared by carbanilation of methyl 3-*O*-benzyl-4,6-*O*-benzylidene-β-D-mannopyranoside,[5] followed by catalytic hydrogenation. Acid hydrolysis of *6* yielded two products, identified by NMR, MS, and optical rotation of their acetates as the β-furanosidic (*7*) and β-pyranosidic (*8*) oxazolidin-2-one derivatives. The results of the NMR analyses are given in Table 1 and the pathways leading to the main fragments in the mass spectrum of *8* are indicated in Scheme 2. The mass spectrum of *7* was similar to that of *4*. From the spectrochemical analyses cyclic imidocarbonate structures cannot be precluded but are considered most unlikely.

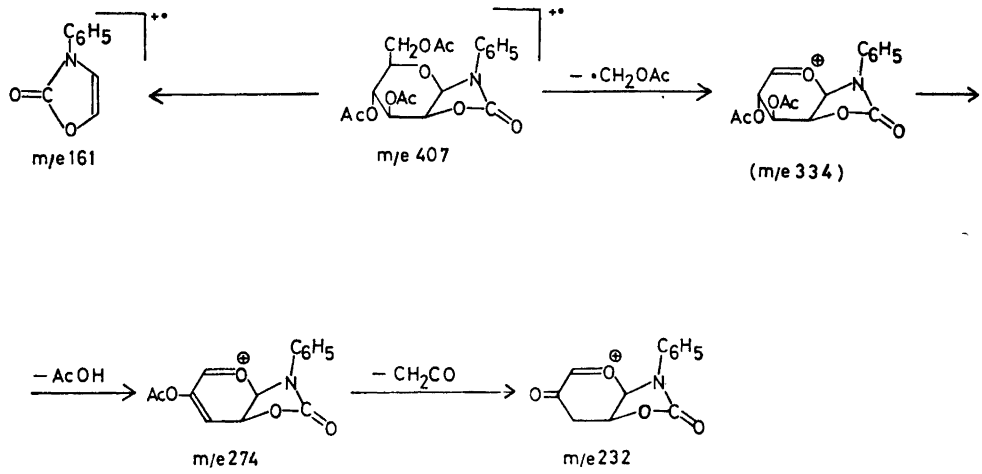
On treatment of either *7* or *8* with strong acid in water or methanol, the equilibrium between them was reestablished but no other products were formed. At equilibrium, the ratio between furanoside and pyranoside was approximately 1:3.

The α-D-glucofuranosidic oxazolidin-2-one derivative (*4*) should be considerably more stable than the corresponding α-D-glucopyranosidic derivative, in agreement with the findings. In the mannose series, however, the



6 7 8

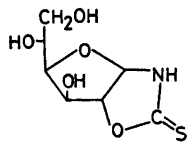
R = $-\overset{O}{\overset{\|}{C}}NHC_6H_5$



Scheme 2.

steric compression from the substituents in the β-furanoside (*7*) is much greater than that in the β-pyranoside (*8*), which may explain the somewhat greater relative stability of the latter.

A number of bicyclic oxazolidin-2-ones, imidazolidin-2-ones, and corresponding 2-thione derivatives of carbohydrates have been prepared (compare Ref. 6). For several of these, in which the anomeric carbon atom is part of both rings, the ring structure (pyranoside or furanoside) has not been convincingly established. The furanosidic nature of the oxazolidin-2-thione (*9*) which is similar to the D-glucose derivative (*4*) above, has been demonstrated by Schwarz.[7] It seems probable, at least in the glucose series, that several of these derivatives are furanosidic.



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EXPERIMENTAL

Concentrations were performed at reduced pressure at bath temperatures not exceeding 40°. Melting points are corrected. TLC was performed on Silica Gel F_{254} (Merck). Optical rotations were determined with a Perkin-Elmer 141 polarimeter. NMR spectra were recorded with a Varian XL-100 spectrometer, using tetramethylsilane as internal reference Chemical shifts (δ) are given as ppm downfield from tetramethylsilane. NMR spectra were determined for all new substances and were in agreement with the postulated structures. For GLC-MS the compounds were injected into a glass column (190 × 0.15 cm) containing 3 % UCW-98 on Gas Chrom Q fitted in a Perkin-Elmer 270 gas chromatograph-mass spectrometer.

*tert-Butyl 2,3,4,6-tetra-*O-(N-*phenylcarbamoyl*)-β-D-*glucopyranoside* (*1*). Phenyl isocyanate (1.6 ml) was added to a solution of *tert*-butyl β-D-glucopyranoside [8] (0.8 g) in anhydrous pyridine (4.0 ml). The mixture was heated 1 h at 100°, cooled, diluted with methanol (1.5 ml) to destroy excess phenyl isocyanate, and heated for another 10 min. The reaction mixture was concentrated, dissolved in acetone (20 ml) and applied to a Sephadex LH-20 column (5 × 40 cm) which was irrigated with acetone. The first fraction to be eluted (*tert*-butyl 2,3,4,6-tetra-*O*-(*N*-phenylcarbamoyl)-β-D-glucopyranoside) was concentrated, yielding crystals (2.10 g), m.p. 214–217°, $[\alpha]_D$ +2° (*c* 1.01, acetone). (Found: C 63.9; H 5.60; N 8.03. $C_{38}H_{40}N_4O_{10}$ requires: C 64.0; H 5.66; N 7.86).

*2,3,4,6-Tetra-*O-*(*N-*phenylcarbamoyl)-*D-*glucose* (*2*). *tert*-Butyl 2,3,4,6-tetra-*O*-(*N*-phenylcarbamoyl)-β-D-glucopyranoside (250 mg) was hydrolysed with 5.0 M sulphuric acid (2.0 ml) in dioxane (8.0 ml) for 2 h at 100°. The reaction mixture was neutralised with barium carbonate, filtered, and concentrated to dryness. The crude product was purified by preparative TLC (acetone-chloroform, 1:4) yielding crystals (190 mg), m.p. 244–247° (decomp.), $[\alpha]_D$ +30° (*c* 0.60, acetone). (Found: C 62.1; H 4.84;

N 8.45. $C_{34}H_{32}N_4O_{10}$ requires: C 62.2; H 4.91; N 8.53).

*Methanolysis of 2,3,4,6-tetra-*O*-(N-phenylcarbamoyl)-*D*-glucose.* 2,3,4,6-Tetra-*O*-(*N*-phenylcarbamoyl)-D-glucopyranose (20 mg) was refluxed in 3 % (w/v) methanolic hydrogen chloride (5 ml) for 16 h. The reaction mixture was neutralised with silver carbonate, filtered and concentrated to dryness. TLC of the products (acetone-chloroform, 1:4) showed the presence of two compounds in the approximate proportions 2:3, with the same mobility as fully carbanilated methyl α- and β-D-glucopyranoside,[9] respectively.

*Methyl 3-*O*-acetyl-4,6-*O*-benzylidene-2-*O*-(N-phenylcarbamoyl)-α-D-glucopyranoside.* Phenyl isocyanate (1.2 ml) was added to a solution of methyl 3-*O*-acetyl-4,6-*O*-benzylidene-α-D-glucopyranoside[4] (2.2 g) in anhydrous pyridine (3.0 ml). The mixture was heated for 1 h at 100°, cooled, diluted with methanol (1.5 ml) and heated for another 10 min. The reaction mixture was concentrated, and the product crystallised from methanol (2.4 g), m.p. 198–199°, $[\alpha]_D$ +69° (*c* 0.63, chloroform). (Found: C 62.0; H 5.60; N 3.00. $C_{23}H_{25}O_8N$ requires: C 62.3; H 5.69; N 3.15).

*Methyl 2-*O*-(N-phenylcarbamoyl)-α-D-glucopyranoside (3).* Methyl 3-*O*-acetyl-4,6-*O*-benzylidene-2-*O*-(*N*-phenylcarbamoyl)-α-D-glucopyranoside (2.3 g) was treated with 2 % hydrogen chloride in methanol (60 ml) for 36 h. The reaction mixture was neutralised with silver carbonate, filtered, and concentrated to dryness. The crude product was purified by preparative TLC (ethyl acetate) giving a chromatographically pure syrup (1.3 g), $[\alpha]_D$ +103° (*c* 0.95, ethanol).

*Acid hydrolysis of methyl 2-*O*-(N-phenylcarbamoyl)-α-D-glucopyranoside. 3* (1.0 g) was hydrolysed with 1.0 M sulphuric acid (20 ml) for 14 h at 100°. The reaction mixture was neutralised with barium carbonate, filtered, and concentrated to dryness. The product was acetylated with acetic anhydride (2.5 ml) in pyridine (2.5 ml) for 20 min at 100°. The reaction product (*4*) (1.0 g) gave one spot on TLC (ethyl acetate–light petroleum, 1:2) and crystallised from ethyl ether, m.p. 129–130°, $[\alpha]_D$ +138° (*c* 0.55, chloroform). (Found: C 56.2; H 5.20; N 3.49. $C_{19}H_{21}O_9N$ requires: C 56.0; H 5.21; N 3.44). The NMR spectrum is given in Table 1. The mass spectrum showed, *inter alia*, the following peaks (relative intensities in brackets): 43(100), 77(16), 91(6), 104(13), 119(12), 130(8), 147(12), 161(7), 162(16), 174(9), 201(10), 202(29), 203(5), 217(5), 245(3), 305(1), 347(1), and 407(14).

Methanolysis of acetylated 4. Acetylated *4* (10 mg) was refluxed in 15 % (w/v) methanolic hydrogen chloride (2.5 ml) for 16 h. The reaction mixture was neutralised with silver carbonate, filtered, and concentrated to dryness. The crude product was acetylated with acetic anhydride (1.0 ml) in pyridine (1.0 ml) for 20 min at 100°. GLC-MS gave one product identical with the starting material.

*Methyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*-(N-phenylcarbamoyl)-β-D-mannopyranoside.* Phenyl isocyanate (1.8 ml) was added to a solution of methyl 3-*O*-benzyl-4,6-*O*-benzylidene-β-D-mannopyranoside[5] (3.0 g) in anhydrous pyridine (5.0 ml). The mixture was heated for 1 h at 100°, cooled, diluted with methanol (2.5 ml) and heated for another 10 min. The reaction mixture was concentrated, and the product was purified on a silicic acid column (40 × 4 cm; ethyl acetate–light petroleum, 1:2), yielding a syrup (3.2 g), $[\alpha]_D$ −75° (*c* 0.96, chloroform).

*Methyl 2-*O*-(N-phenylcarbamoyl)-β-D-mannopyranoside (6).* Methyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*-(*N*-phenylcarbamoyl)-β-D-mannopyranoside (2.9 g) in ethanol (40 ml) was hydrogenated over palladium on carbon (10 %, 0.5 g) at room temperature and atmospheric pressure. When the hydrogen consumption had ceased, the catalyst was filtered off. Concentration yielded a syrup (1.8 g), $[\alpha]_D$ −76° (*c* 0.87, ethanol).

*Acid hydrolysis of methyl 2-*O*-(N-phenylcarbamoyl)-β-D-mannopyranoside (6).* Substance *6* (1.0 g) was hydrolysed with 1.0 M sulphuric acid (20 ml) for 14 h at 100°. The reaction mixture was neutralised with barium carbonate, filtered, and concentrated to dryness. The crude product was acetylated with acetic anhydride (2.5 ml) in pyridine (2.5 ml) for 20 min at 100°. The reaction mixture gave two spots on TLC. The mixture was separated on a silicic acid column (40 × 3 cm, acetone–chloroform, 1:19). The separation was followed by polarimetry and TLC. The first fraction to be eluted (acetylated *8*) on concentration yielded a syrup (0.82 g), $[\alpha]_D$ −117° (*c* 0.88, chloroform). The next fraction (acetylated *7*) yielded a syrup which crystallised from ethanol–light petroleum (1:2, v/v) (0.29 g), m.p. 168–170°, $[\alpha]_D$ −161° (*c* 0.56, chloroform). (Found: C 56.0; H 5.22; N 3.22. $C_{19}H_{21}O_9N$ requires: C 56.0; H 5.21; N 3.44). The NMR spectra are given in Table 1. The mass spectrum of acetylated *8* showed, *inter alia*, peaks at *m/e* 43(100), 77(12), 104(13), 119(9), 161(17), 162(6), 190(5), 203(5), 204(6), 232(27), 245(2), 305(1), 347(1) and 407(16). The mass spectrum of acetylated *7* showed peaks at *m/e* 43(100), 77(9), 104(7), 119(7), 130(11), 147(6), 162(12), 190(6), 202(41), 203(6), 217(4), 245(2), 305(1), 347(1) and 407(12).

Methanolysis and acid hydrolysis of acetylated 7 *and* 8. Methanolysis of acetylated *7* and *8* was performed in 3 % (w/v) methanolic hydrogen chloride as described above. Acid hydrolysis of acetylated *7* and *8* was performed with 1.0 M sulphuric acid as described above. The reaction mixtures were acetylated with acetic anhydride in pyridine and analysed on GLC-MS. All reactions produced the same mixture (1:3) of *7* and *8*.

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