Carbohydrate Research, 39 (1975) 147–150

Note

The synthesis of *N*-glycosylphthalimides*

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(Received April 16th, 1974; accepted for publication, June 25th, 1974)

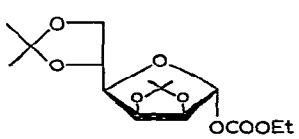
The reaction of alcohols with an equimolar mixture of phthalimide, diethyl azodicarboxylate, and triphenylphosphine leads in one step to substituted phthalimides[1]:

$$R\text{–}OH + HN(CO)_2C_6H_4 + R'O_2C\text{–}N{=}N\text{–}CO_2R' + Ph_3P \rightarrow R\text{–}N(CO_2)C_6H_4 + R'O_2C\text{–}NH\text{–}NH\text{–}CO_2R' + Ph_3PO$$

Free amines can be obtained from the latter compounds by an exchange reaction with, for example, butylamine[2]. Thus, the reaction provides an easy and useful method of conversion of alcohols into amines. Recently, certain *N*-phthalimidodeoxy sugars have been obtained in this way[3].

We have examined the amination reaction of monosaccharide derivatives having a free anomeric hydroxyl group. The synthesis should provide an access to *N*-glycosylphthalimides of which *N*-D-ribosylphthalimide[4] is the only reported example.

Treatment of 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose (**1**), 2,3,4,6-tetra-*O*-methyl-D-glucopyranose (**2**), 3,6-di-*O*-acetyl-2,4-dideoxy-DL-*erythro*- (**3**) and *threo*-hexopyranoses (**4**), and 2,3-dideoxy-DL-pent-2-enopyranos-4-ulose (**5**) in tetrahydrofuran solution at room temperature with phthalimide, diethyl azodicarboxylate, and triphenylphosphine afforded, after ~24 hours, 5–43% of the corresponding *N*-glycosylphthalimides. From **1**, **2**, and **4**, both anomeric *N*-glycosides were formed. The identification of the products was based on analytical and spectral data (see Experimental). For 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose (**1**), two additional products were isolated, each in ~2% yield, and identified as 1-*O*-ethoxycarbonyl-



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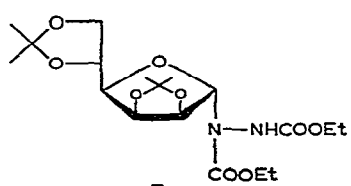

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*Dedicated to Professor Osman Achmatowicz on the occasion of his 75th birthday.

2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose (**6**) and *N*-(2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranosyl)-1,2-diethoxycarbonylhydrazine (**7**). It is noteworthy that **6** and **7** are the main products from the reaction of **1** with diethyl azodicarboxylate and tris(dimethylamino)phosphine[5].

N-Glycosylphthalimides are stable compounds, melting without decomposition. Those obtained from **1** and **2** change immediately to strongly polar compounds (t.l.c.) when dissolved in a ~5% solution of sodium hydroxide in water–tetrahydrofuran. *N*-(Tetra-*O*-methyl-β-D-glucopyranosyl)phthalimide is stable in dilute, aqueous sulphuric acid.

The above synthesis of *N*-glycosylphthalimides is very simple and mild, as exemplified by the conversion of the alkali- and acid-sensitive compound **5**[6] into the *N*-phthalimido derivative. The only disadvantage of the method is the necessity for chromatographic separation of the products.

EXPERIMENTAL

Melting points are not corrected. P.m.r. spectra were recorded on Jeol JMN-4H-100 (100 MHz) and Varian HA-60/IL (60 MHz) spectrometers for solutions in deuterochloroform with tetramethylsilane as internal standard. I.r. spectra were recorded on a Unicam SP-200 spectrophotometer. Optical rotations were measured at 18 ±2° (*c* 1, ethanol) with a Perkin–Elmer 141 automatic polarimeter.

T.l.c. was performed with Silica Gel G Merck, and column chromatography with Macherey–Nagel Silica Gel (100–200 mesh).

Reaction of phthalimide, diethyl azodicarboxylate, and triphenylphosphine with monosaccharide derivatives. — The sugar derivative (**1**–**5**, 1 mmole), phthalimide (147 mg, 1 mmole), and triphenylphosphine (262 mg, 1 mmole) were dissolved in 5 ml of tetrahydrofuran and treated with diethyl azodicarboxylate (190 mg, 1.1 mmole). A slight exothermic reaction was observed. The reaction mixture was left at room temperature for 24 h and then concentrated under diminished pressure to dryness. The residue was fractionated on a column of silica gel, using benzene–ether (9:1, solvent *A*) or light petroleum (b.p. 60–80°)–ethyl acetate (9:1, solvent *B*).

The following compounds were thus prepared.

(*a*) *From* **1**. *N*-(2,3:5,6-Di-*O*-isopropylidene-α-D-mannofuranosyl)phthalimide (19 mg, 4.9%), m.p. 125°, $[\alpha]_D$ +19°; ν_{max}^{KBr} 1780, 1720 (phthalimide C=O), 1610, and 725 cm^{-1} (*o*-disubstituted Ph). P.m.r. data: δ 7.90 (4-proton m, aromatic H), 5.96 (s, H-1).

Anal. Calc. for $C_{20}H_{23}NO_7$: C, 61.7; H, 6.0; N, 3.6. Found: C, 61.8; H, 5.9; N, 3.5.

N-(2,3:5,6-Di-*O*-isopropylidene-β-D-mannofuranosyl)phthalimide (98 mg, 25.2%), m.p. 133–134°, $[\alpha]_D$ +37°; ν_{max}^{KBr} 1790, 1730, 1620, and 725 cm^{-1}. P.m.r. data: δ 7.88 (phthalimide H), 5.82 (d, $J_{1,2}$ 3.7 Hz, H-1).

Anal. Calc. for $C_{20}H_{23}NO_7$: C, 61.7; H, 6.0; N, 3.6. Found: C, 61.5; H, 6.0; N, 3.6.

The mass spectra (70 eV, LKB 9000 mass spectrometer) of the foregoing anomers were almost identical: the more important peaks were *m/e* 374 (100%), 316 (40), 288 (5), 273 (6), 256(14), 230(20), 214 (5), 202 (16), 172 (17), 160(27), 101 (94). The fragmentation pattern deduced is in agreement with that described for 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose[7] and confirms the assigned constitution.

1-*O*-Ethoxycarbonyl-2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose (**6**; 6 mg, 1.8%), b.p. 130°/0.001 mmHg, $[\alpha]_D$ +68°; ν_{max} ($CHCl_3$) 1750 (C=O), 1390, and 1260 cm^{-1} (C–O–C). The compound was identical (i.r., t.l.c.) with that obtained earlier[5].

N-(2,3:5,6-D-*O*-isopropylidene-α-D-mannofuranosyl)-1,2-diethoxycarbonylhydrazine, (**7**; 8 mg, 1.9%), b.p. 170°/0.001 mmHg, $[\alpha]_D$ +46°; ν_{max}^{film} 3360 (NH) and 1740 cm^{-1} (C=O). The compound was identical (i.r., t.l.c.) with that described earlier[5].

(*b*) *From* **2**. *N*-(2,3,4,6-Tetra-*O*-methyl-β-D-glucopyranosyl)phthalimide (134 mg, 36.7%), m.p. 111°, $[\alpha]_D$ −55°, ν_{max}^{KBr} 1780, 1730, 1630, and 730 cm^{-1}. P.m.r. data: δ 8.0 (phthalimide H), 5.19 (d, $J_{1,2}$ 9.8 Hz, H-1).

Anal. Calc. for $C_{18}H_{23}NO_7$: C, 59.2; H, 6.3; N, 3.8. Found: C, 59.3; H, 6.5; N, 3.7.

N-(2,3,4,6-Tetra-*O*-methyl-α-D-glucopyranosyl)phthalimide (15 mg, 4.1%), syrup, $[\alpha]_D$ +12°, ν_{max} (Nujol) 1770, 1720, 1610, and 725 cm^{-1}. P.m.r. data: δ 7.91 (phthalimide H), 6.28 (d, $J_{1,2}$ 7.1 Hz, H-1), 3.4 (2 MeO), 3.6 (MeO), and 3.7 (MeO).

(*c*) *From* **3***. *N*-(3,6-Di-*O*-acetyl-2,4-dideoxy-β-DL-*erythro*-hexopyranosyl)-phthalimide (156 mg, 43.3%), m.p. 142°, ν_{max}^{KBr} 1770, 1740, 1620, and 720 cm^{-1}. P.m.r. data: δ 7.92 (phthalimide H), 5.85 (dd, $J_{1,2a}$ 11.7, $J_{1,2e}$ 3.0 Hz, H-1).

Anal. Calc. for $C_{18}H_{19}NO_7$: C, 59.8; H, 5.3; N, 3.9. Found: C, 59.9; H, 5.3; N, 3.6.

(*d*) *From* **4***. *N*-(3,6-Di-*O*-acetyl-2,4-dideoxy-β-DL-*threo*-hexopyranosyl)-phthalimide (30 mg, 8.2%), m.p. 192°, ν_{max}^{KBr} 1790, 1740, 1720, 1620, and 720 cm^{-1}. P.m.r. data: δ 7.90 (phthalimide H), 5.50 (dd, $J_{1,2a}$ 11.7, $J_{1,2e}$ 2.5 Hz, H-1).

Anal. Calc. for $C_{18}H_{19}NO_7$: C, 59.8; H, 5.3; N, 3.9. Found: C, 59.9; H, 5.5; N, 3.6.

N-(3,6-Di-*O*-acetyl-2,4-dideoxy-α-DL-*threo*-hexopyranosyl)phthalimide (118 mg, 32.8%), m.p. 170°, ν_{max}^{KBr} 1775, 1720, 1610, and 715 cm^{-1}. P.m.r. data: δ 7.90 (phthalimide H), 6.09 (t, $J_{1,2a} \approx J_{1,2e} \approx 5.5$ Hz, H-1).

Anal. Calc. for $C_{18}H_{19}NO_7$: C, 59.8; H, 5.3; N, 3.9. Found: C, 59.7; H, 5.3; N, 3.7.

(*e*) *From* **5**[6]. *N*-(2,3-Dideoxy-DL-pent-2-enopyranosyl-4-ulose)phthalimide (104 mg, 42.9%), m.p. 122°, ν_{max}^{KBr} 1770, 1730, 1700, 1610, and 720 cm^{-1}. P.m.r. data: δ 7.93 (phthalimide H), 7.17 (dd, $J_{2,3}$ 10, $J_{1,2}$ 3.0 Hz, H-2), 6.46 (dd, $J_{1,3}$ 2.3 Hz, H-3), 6.36 (1-proton m, partially overlapped with H-3, H-1) 4.57, 4.30 (2-proton AB system, $J_{5,5'}$ 17 Hz, H-5,5').

*Obtained from the corresponding 1,3,6-tri-*O*-acetyl-2,4-dideoxy-αβ-DL-hexopyranose by hydrolysis with water[8].

Anal. Calc. for $C_{13}H_9NO_4$: C, 64.2; H, 3.7; N, 5.8. Found: C, 64.0; H, 3.6; N, 5.9.

The above compound (*cf.* ref. 9) inhibited the growth of *Staphylococcus aureus* 209P, *Enterococcus*, *Escherichia coli*, *Proteus mirabilis*, *Klebsiella pneumoniae*, *Sarcina lutea*, and *Bacillus subtilis* at a concentration of 25 μg/ml.

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