glucose and 2-acetamido-2-deoxyglucose,[2] although the values of $2A$ for these differ appreciably from those found in the mannose series. The sensitivity to acid hydrolysis of **3** and **4** is of the correct order of magnitude for pyranosides (48 and 31% liberation of phenol from 0.01 *M* solutions in 0.05 *M* HCl, heated 20 min at 100°), as shown by comparisons with the behavior of the phenyl 2-acetamido-2-deoxy-α- and -β-D-glucopyranosides (15 and 30% liberation of phenol). As reported elsewhere,[6] **3** and **4** are inactive as substrates for α- or β-acetylglucosaminidase or for α-acetylgalactosaminidase.

The crystalline *o*- and *p*-nitrophenyl 2-acetamido-2-deoxy-α-D-galactopyranosides (**5** and **6**) are produced by O-deacetylation of the syrupy product from nitration of the previously characterized phenyl 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-α-D-galactopyranoside (**7**).[2] The two nitrophenyl glycosides, which are separable by adsorption chromatography on Dowex 50,[7] are valuable test substrates for α-acetylgalactosaminidase (to be published).

Experimental Section

Melting points are corrected. A Perkin-Elmer Model 141 polarimeter was used with 1-dm tubes. Microanalyses were done by Spang Microanalytical Laboratories, Ann Arbor, Mich. Acetate esters were O-deacetylated in warm methanol–chloroform with sodium methoxide catalysis.[2] The orientation of nitro groups in pure glycosides and mixtures was determined by acid hydrolysis and chromatography.[2] Phenol was estimated by the method of Folin and Ciocalteau.[6]

Phenyl 2-Acetamido-2-deoxy-α- and -β-D-mannopyranoside (3 and 4).—Pentaacetyl β-mannosamine, 2 g, was allowed to react with 5 g of phenol and 0.5 g of zinc chloride for 2.5 hr at 125° (50 mm).[2] The reaction product was crystallized from ethyl acetate, yielding 1.18 g of the pure tri-O-acetyl α-glycoside **1**, mp 198–198.5°, $[\alpha]^{23}D$ +72.6° (*c* 0.6, chloroform) [lit.[3] mp 192–193°, $[\alpha]^{30}D$ +74° (chloroform)].

A second crop, 0.63 g, mp 165–180°, $[\alpha]^{23}D$ +34.8°, and a third crop, 0.06 g, mp 156–176°, $[\alpha]^{23}D$ +44.6°, were obtained with the aid of ether and hexane. Systematic fractional crystallization of these materials from ethyl acetate–isopropyl ether and absolute ethanol yielded additional quantities of 1 and 59 mg (3%) of pure phenyl 2-acetamido-tri-O-acetyl-2-deoxy-β-D-mannopyranoside (**2**), mp 184.5–185°, $[\alpha]^{23}D$ −70.2° (*c* 0.6, chloroform).

Anal. Calcd for $C_{20}H_{25}NO_9$: C, 56.7; H, 5.95; N, 3.31. Found: C, 56.7; H, 5.96; N, 3.21.

O-Deacetylation of **1** and crystallization of the syrupy product from moist acetone gave the α glycoside **3**, mp 104°, which contained water of hydration not determined with precision. For the monohydrate, a loss of 5.7% was calculated and a loss of 4.1% was found at 110° (0.05 mm). The optical rotation, $[\alpha]^{25}D$ +49.1° (*c* 1.0, ethanol) and +42.9° (*c* 0.8, water), and analyses are reported for the dried substance.

Anal. Calcd for $C_{14}H_{19}NO_6$: C, 56.6; H, 6.44; N, 4.71. Found: C, 56.6; H, 6.49; N, 4.57.

For anhydrous (?) **3**, the following values were reported: mp 98–99°, $[\alpha]D$ +50° (ethanol).[3]

O-Deacetylation of **2** gave a syrup, crystallized from methanol–ether and recrystallized from hot water to yield the pure β glycoside **4**, mp 184–185°, $[\alpha]^{25}D$ −104.4° (*c* 0.8, water).

Anal. Calcd for $C_{14}H_{19}NO_6$: C, 56.6; H, 6.44; N, 4.71. Found: C, 56.6; H, 6.32; N, 4.58.

***o*- and *p*-Nitrophenyl 2-Acetamido-2-deoxy-α-D-galactopyranoside (5 and 6).**—A nitration mixture prepared from 2.25 ml of nitric acid (90%) and 7.5 ml of acetic anhydride was added at one time to a stirred solution of 10 g of **7** in 25 ml of acetic acid, and the reaction[2] was allowed to proceed for 2 hr at 37°. After dilution with 60 ml of ice-cold 2 *M* potassium acetate solution and storage for 3 hr at room temperature, the reaction mixture was extracted with chloroform. Washing of the extract with 2 *M* sodium carbonate and water, drying with sodium sulfate, clarification by passage through a small pad of silicic acid, and removal of solvent under reduced pressure left a syrupy mixture of *o*- and *p*-nitrophenyl derivatives, not successfully resolved. O-Deacetylation of the syrup yielded a solid product, recrystallized from absolute ethanol to give 6.1 g of colorless, seemingly homogeneous needles and a second crop, 0.6 g, both shown to be gross mixtures of the *o*- and *p*-nitrophenyl glycosides (**5** and **6**). These were not separated by repeated recrystallizations from absolute ethanol, acetone, or water. The mixture was applied as a 1% solution in 0.001 *M* acetic acid to a column of Dowex 50 × 4-H^+ (200–400 mesh) of bed volume 3.2 l. Development with the same solvent completely resolved two peaks (11.8 and 17.4 l.), as revealed by absorbance measurements at 265 mμ. Concentration *in vacuo* of the pooled fractions of the first peak and recrystallization of the solid residue from absolute ethanol gave the pure *o*-nitrophenyl glycoside **5**: yield 3.6 g; mp 208–209°; $[\alpha]^{25}D$ +244° (*c* 0.5, water); uv max (water) 265 mμ (ε 3640) and 322 (2000); solubility in water at 25°, 0.70%.

Anal. Calcd for $C_{14}H_{18}N_2O_8$: C, 49.1; H, 5.30; N, 8.19. Found: C, 49.0; H, 5.36; N, 8.07.

Similarly, the pooled fractions of the second chromatographic peak gave the pure *p*-nitrophenyl glycoside **6**: yield 2.2 g; mp 266° dec; $[\alpha]^{25}D$ +310° (*c* 0.2, water); uv max 222 mμ (ε 6930) and 305 (10,760); solubility in water at 25°, 0.23%.

Anal. Calcd for $C_{14}H_{18}N_2O_8$: C, 49.1; H, 5.30; N, 8.19. Found: C, 49.3; H, 5.29; N, 8.03.

Registry No.—**2**, 23646-65-3; **3**, 4366-43-2; **4**, 23646-66-4; **5**, 23646-67-5; **6**, 23646-68-6.

(6) B. Weissmann, G. Rowin, J. Marshall, and D. Friederici, *Biochemistry*, **6**, 207 (1967).

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Phosphonic Acids and Esters. XXI.[1] Dimerization and Diels–Alder Reactions of Dialkyl 1-(1,3-Butadienyl)phosphonates

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Previous studies have shown that vinylic[3] and acetylenic[4] phosphonates function as moderately reactive dienophiles in Diels–Alder reactions. Aromatization of the adducts provides a useful synthesis of substituted phenylphosphonates.[3,4] Pudovik and coworkers[5,6] have shown that diethyl 1-(1,3-butadienyl)phosphonate (**1a**) is a comparably effective diene. On heating, **1a** forms

$$CH_2{=}CHCH{=}CHP(O)(OR)_2$$
1a, R = C_2H_5
b, R = CH_3

a dimer, and the reaction of **1a** with acrylonitrile yields a Diels–Alder adduct.[6] Both reactions were apparently directionally specific to yield a single isomer; structures

(1) Part XX: C. E. Griffin and S. K. Kundu, *J. Org. Chem.*, **34**, 1532 (1969).

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(3) W. M. Daniewski and C. E. Griffin, *J. Org. Chem.*, **31**, 3236 (1966).

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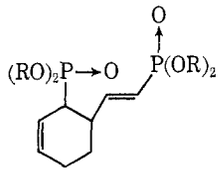
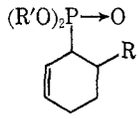
2a and 3a were proposed for these products, but the structures were not substantiated.[6] Since little or no



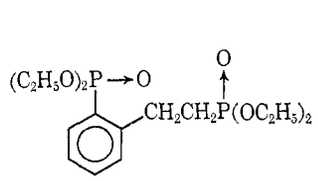
2a, R = C_2H_5
b, R = CH_3



3a, R = CN; R′ = C_2H_5
b, R = $P(O)(OC_2H_5)_2$; R′ = C_2H_5
c, R = $COOC_2H_5$; R′ = C_2H_5
d, R = CHO; R′ = C_2H_5
e, R = CN; R′ = CH_3

orientational selectivity was observed in reactions of vinylic phosphonates with unsymmetrically substituted dienes,[3] these observations suggested that the Diels–Alder reactions of 1 might provide a more effective and selective entry to substituted phenylphosphonates. Accordingly, we have investigated the dimerization of 1, as well as its Diels–Alder reactions with a number of simple dienophiles.

There are four possible orientations for the dimerization of 1. If the less highly substituted (3,4) vinyl group of 1 were the more dienophilic, dimer 2 or its 1,3 isomer 4 would result. Alternatively, a higher dienophilic reactivity for the 1,2 double bond would result in the formation of 5-vinyl-3,4-bis(diethoxyphosphono)-cyclohexene or the corresponding 4-vinyl-3,5-bisphosphono isomer. Dimerization of 1a by the published procedure[6] yielded a single (glpc, tlc) product. The integrated intensities of the vinylic protons of the product established it to be either 2a or 4, but the level of analysis of the pmr spectrum did not allow a differentiation between the two structures. However, structure 2a was confirmed for the adduct by an aromatization–oxidation sequence. Treatment of 2a with 1 equiv of N-bromosuccinimide gave a monobromide, which was dehydrobrominated with triethylamine to yield the phenethylbisphosphonate 5, while a similar sequence employing 2 equiv of N-bromosuccinimide gave the *trans*-styrylbisphosphonate 6. The aromatic proton multiplets of 5 and 6 were similar in appearance



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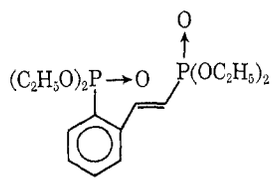
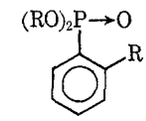


6

to those of other *ortho*-substituted phosphonobenzenes.[7,8] Confirmation of the *ortho* relationship of the substituents in 5 and 6 and, consequently, in 2a was provided by hydrolytic oxidation of both 5 and 6 to the known[9] *o*-carboxyphenylphosphonic acid (7a) with aqueous potassium permanganate. Similar results were obtained with the dimer 2b formed from the dimethyl ester 1b.

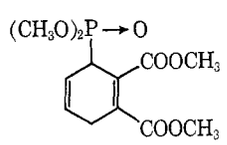
Reactions of 1a with diethyl vinylphosphonate,[3] ethyl acrylate, and acrolein, and of 1b with acrylonitrile, led to the formation of adducts 3b–3d and 3e, respectively. Both 3b and 3e were isolated in a pure state, but 3c and 3d could not be separated from the dimer 2a which is formed during the reaction.[10] Aromatization of 3b, 3c, and 3d to the phenylphosphonates 7b,[4,11] 7c,[9] and 7d[8] was achieved by Pd–C–nitrobenzene



7a, R = COOH; R′ = H
b, R = $P(O)(OC_2H_5)_2$; R′ = C_2H_5
c, R = $COOC_2H_5$; R′ = C_2H_5
d, R = CHO; R′ = C_2H_5
e, R = CN; R′ = CH_3

treatment. Separations of 7c and 7d from the contaminating 2a were readily achieved. Attempted aromatization of 3e with Pd–C–nitrobenzene was unsuccessful, but 7e was formed by the reaction sequence used in the preparation of 6. The cyanophenylphosphonate 7e could not be purified satisfactorily, but was identified by hydrolysis to 7a.[9] In all of these Diels–Alder reactions, orientation was specific. Glpc examinations of reaction mixtures indicated the absence of the 1,3 isomers of 3b–3e. However, the low yields (11–23%) of the adducts severely limits this approach for the synthesis of 7.

Adducts were also obtained from the reactions of 1b with two symmetrical dienophiles. Reaction of the diene with dimethyl acetylenedicarboxylate gave a 32% yield of a 1:1 adduct. The pmr spectrum of this adduct indicated structure 8, but integrated intensities indicated some degree of disproportionation or rearrangement to the conjugated cyclohexadiene. Aromatization of 8 with Pd–C–nitrobenzene gave 9. Similarly, reaction of 1b with dimethyl maleate gave a low yield of adduct,[10] which was not isolated but aromatized



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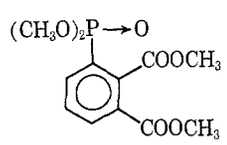

9

directly to 9 with Pd–C–nitrobenzene. Attempted reactions of 1a with benzoquinone and maleic anhydride were unsuccessful.

Experimental Section[12]

Diethyl 1-(1,3-butadienyl)phosphonate (1a), bp 82–83° (0.5 mm) [lit.[5] bp 122–123° (13 mm)], and dimethyl 1-(1,3-butadienyl)phosphonate (1b), bp 60–63° (0.3 mm) [lit.[13] bp 77–78.5° (3 mm)], were prepared by the published[5] procedure.

Formation of Dimers 2a and 2b.—A mixture of 0.1 mol of the butadienylphosphonates 1a or 1b and 0.1 mol of anhydrous cuprous chloride was held under a nitrogen atmosphere with constant stirring at 120–130° for 12 hr. After cooling to room temperature, the reaction mixture was diluted with 200 ml of

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(8) R. Obrycki and C. E. Griffin, *J. Org. Chem.*, **33**, 632 (1968).
(9) M. Gordon, V. A. Notaro, and C. E. Griffin, *J. Amer. Chem. Soc.*, **86**, 1898 (1964).
(10) Pudovik and coworkers[6] reported successful Diels–Alder reactions of 1a with methyl methacrylate, acrolein, and dialkyl maleates, but were also unable to separate the dimer contaminant.
(11) R. Obrycki and C. E. Griffin, *Tetrahedron Lett.*, 5049 (1966).
(12) Details of experimental procedures are given in ref 3.
(13) K. N. Anisimov and N. E. Kolobova, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 923 (1956).

carbon tetrachloride and filtered. The solvent was removed under reduced pressure to give an oil which was distilled to give **2a** (63%), bp 185–190° (0.05 mm) [lit.[6] bp 182° (0.04 mm)], and **2b** (57%), bp 195° (0.1 mm).

Aromatization of Dimers 2a and 2b.—N-Bromosuccinimide (2.6 g, 14.5 mmol) was added in portions to a refluxing solution of 5.0 g (13 mmol) of **2a** and 0.1 g of azoisobutyronitrile in 40 ml of carbon tetrachloride. When dissolution of N-bromosuccinimide was complete, the reaction mixture was refluxed for an additional 0.5 hr, cooled to room temperature, and kept at 5° overnight. Succinimide (1.2 g, 84%) separated, was removed by filtration, and was washed with carbon tetrachloride. The combined carbon tetrachloride solutions were concentrated under reduced pressure to yield an oil which was dissolved in 40 ml of benzene. A solution of 10.0 g (100 mmol) of triethylamine in 20 ml of benzene was added slowly with stirring to this solution. After the addition was completed, the reaction mixture was refluxed with stirring for 1 hr, cooled, and held at 5° overnight. Triethylammonium bromide (2.3 g, 96%) was removed by filtration and the filtrate was concentrated under reduced pressure to give an oil which was distilled to yield 2.5 g of an oil, bp 198–210° (0.08 mm). This product was further purified by chromatography on neutral alumina using successive elutions with hexane, benzene, and chloroform. The combined chloroform eluents were dried over sodium sulfate, concentrated, and distilled to give 2.0 g (40%) of **diethyl *o*-(2-diethoxyphosphonoethyl)-phenylphosphonate** (**5**), bp 181° (0.03 mm).

Anal. Calcd for $C_{16}H_{28}O_6P_2$: C, 50.80; H, 7.47; P, 16.37. Found: C, 50.99; H, 7.51; P, 16.51.

The reaction of **2a** with 2 equiv of N-bromosuccinimide was carried out in the same manner. The crude product was not distilled, but was purified by chromatography on neutral alumina. Two purifications gave analytically pure **diethyl *o*-(2-diethoxyphosphonovinyl)phenylphosphonate** (**6**, 13%).

Anal. Calcd for $C_{16}H_{26}O_6P_2$: C, 51.18; H, 6.88; P, 16.44. Found: C, 51.31; H, 7.08; P, 16.59.

The same procedure was employed for the aromatization of **2b**. A 30% yield of **dimethyl *o*-(2-dimethoxyphosphonovinyl)-phenylphosphonate** was obtained: pmr (CCl_4) τ 6.25 (d, J_{PH} = 11 Hz, CH_3), 3.78 [2 × 2, $J_{HH} \cong J_{PH} \cong 17$ Hz, H(P)C=], 2.0–3.0 (m, C_6H_4), and 1.88 ppm (2 × 2, $J_{HH} \cong J_{PH} \cong 17$ Hz).

Anal. Calcd for $C_{12}H_{18}O_6P_2$: C, 45.10; H, 5.64; P, 19.32. Found: C, 45.20; H, 5.74; P, 19.21.

Diels–Alder Reactions of Dienes 1a and 1b. A. With Diethyl Vinylphosphonate.—A mixture of 7.0 g (37 mmol) of **1a**, 30.0 g (183 mmol) of diethyl vinylphosphonate, and 0.1 g of hydroquinone was placed in an autoclave which was then evacuated and heated at 150° for 12 hr. Distillation of the reaction mixture gave 26.1 g of diethyl vinylphosphonate, bp 48–55° (0.1 mm), 1.0 g (11%) of **3,4-bis(diethoxyphosphono)cyclohexene** (**3b**), bp 200–205° (0.1 mm), and polymeric residue (7.1 g).

B. With Acrylonitrile.—A mixture of 16.0 g (100 mmol) of **1b**, 15.9 g (300 mmol) of acrylonitrile, and 0.1 g of hydroquinone was heated in an autoclave under an atmosphere of nitrogen at 125° for 12 hr. The reaction mixture was concentrated under reduced pressure in a rotary evaporator and the residue was distilled to give 4.5 g of **1b**, 4.5 g of crude **3e**, bp 130–137° (0.2 mm), 1.0 g of a mixture of **3e** and **2b**, bp 137–175° (0.2 mm), and 8 g of a rubbery residue. The two higher boiling fractions were combined and redistilled to give 3.5 g (23%) of **3-dimethoxyphosphono-4-cyanocyclohexene** (**3e**), bp 134–135° (0.2 mm). The same conditions were employed for the reactions of **1a** with ethyl acrylate and acrolein and of **1b** with dimethyl maleate. In each of these cases, the mixture of adduct and dimer could not be separated by distillation.

C. With Dimethyl Acetylenedicarboxylate.—A mixture of 5.0 g (31 mmol) of **1b**, 4.4 g (31 mmol) of dimethyl acetylenedicarboxylate, and 0.1 g of hydroquinone was heated under a nitrogen atmosphere for 12 hr at 100°. The reaction mixture was concentrated under reduced pressure in a rotary evaporator (bath temperature 130°) to give a 6.0-g residue, which was chromatographed on silicic acid (100 g). Elution with *n*-hexane gave small amounts of the acetylene dicarboxylate. **1,2-Dicarbomethoxy-3-dimethoxyphosphonocyclohexa-1,4-diene** (**8**, 3.0 g, 32%) was eluted with 1:1 benzene–*n*-hexane.

Aromatization of Diels–Alder Adducts.—The general procedure[3] is exemplified by the aromatization of **3b**. A mixture of 0.75 g (3 mmol) of **3b**, 1.0 g (8 mmol) of nitrobenzene, 1.5 g of 5% palladium on charcoal, and 80 ml of anhydrous ethanol was held at reflux temperature for 100 hr. The catalyst was removed by filtration and, after concentration under reduced pressure, the reaction mixture was distilled to give 0.4 g (80%) of **tetraethyl *o*-phenylenebisphosphonate** (**7b**), bp 180–185° (0.1 mm). The aromatizations of **3c** and **3d** to **7c** and **7d** were carried out in the same manner. Products **7b–7d** were identified by comparisons with authentic samples.[8,9,11]

Dimethyl 2,3-dicarbomethoxyphenylphosphonate (**9**) was prepared by refluxing a mixture of 3.0 g (10 mmol) of **8**, 6.0 g (49 mmol) of nitrobenzene, 3.0 g of 5% palladium on charcoal, and 60 ml of anhydrous methanol for 72 hr. The catalyst was removed by filtration and, after concentration under reduced pressure in a rotary evaporator (bath temperature 100°), the reaction mixture was chromatographed on silicic acid (100 g). Initial elution with *n*-hexane gave small amounts of nitrobenzene. Elution with benzene gave 1.5 g (50%) of **9**.

Anal. Calcd for $C_{12}H_{15}O_7P$: C, 47.71; H, 5.04; P, 10.25. Found: C, 47.33, 47.41; H, 4.87, 4.91; P, 10.03, 9.98.

Aromatization of the adduct of dimethyl maleate and **1b** and isolation of **9** was carried out in the same manner.

Adduct **3e** was aromatized by the bromination–elimination sequence used for the preparation of **6**. **Dimethyl *o*-cyanophenylphosphonate** (**7e**) was isolated by distillation, but was contaminated by **2b** and its aromatization products. Neither redistillation nor silicic acid chromatography achieved satisfactory purification, and the product was hydrolyzed with refluxing 2 *N* hydrochloric acid to yield **7a**. Identity was established by comparisons with an authentic sample.[9]

Registry No.—**1a**, 7158-35-2; **1b**, 4037-11-0; **5**, 23293-54-1; **6**, 23293-55-2; **9**, 23293-56-3; dimethyl *o*-(2-dimethoxyphosphonovinyl)phenylphosphonate, 23293-57-4.

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A Novel Acylation of Amino Acids with S-Carboxymethyl Dialkyldithiocarbamates

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In an attempt to thioacylate[1,2] 7-aminocephalosporanic acid (**2**) with S-carboxymethyl N,N-diethyldithiocarbamate (**1**) in the presence of iodine–sodium iodide complex, we have unexpectedly isolated N,N-diethylcarbamoylmercaptomethylcephalosporin (**3**). This compound was identified by its ir and nmr spectra and by synthesis through the direct acylation of **2** with S-carboxymethyl N,N-diethylthiocarbamate mixed anhydride.

This acylation is not confined to **2**[3] but works equally well with other amino acids such as 6-aminopenicillanic acid and 2-phenylglycine. The reaction also proceeds readily with other S-carboxymethyl dialkyldithiocarbamates. However, in the absence of iodine, the reaction fails.

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(3) W. J. Gottstein and A. H. Eachus, U. S. Patent 3,391,141 (1968); *Chem. Abstr.*, **69**, 86992 (1968).