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CYCLIZATION OF ALDONIC ACID AROYLHYDRAZIDES TO 1,3,4-OXADIAZOLINE DERIVATIVES*

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ABSTRACT

D-Glucono-1,5-lactone reacts with aroylhydrazines to give the corresponding 1-aroyl-2-D-gluconylhydrazines. Condensative cyclization of these compounds using triethyl orthoformate gave the corresponding 5-aryl-2-ethoxy-3-D-gluconyl-2,3-dihydro-1,3,4-oxadiazoles.

INTRODUCTION

In previous reports[1–8], the preparation and reactions of sugar aroylhydrazides and hydrazones have been described. Continuing our work along this line, we now describe the synthesis of 1-aroyl-D-gluconylhydrazines (D-gluconic acid aroylhydrazides) and their conversion, by condensative cyclization, into the corresponding 3-D-gluconyl-2,3-dihydro-1,3,4-oxadiazole derivatives.

DISCUSSION

Condensation of D-glucono-1,5-lactone (**1**) with one molar equivalent of benzoylhydrazine gave a colorless, highly crystalline compound, m.p. 190°, whose elemental analysis was in conformity with the molecular formula $C_{13}H_{18}N_2O_7$. The infrared spectrum of this product showed two Amide-I absorption bands, at 1680 and 1650 cm^{-1}, in addition to a broad band at 3300 cm^{-1} due to the superimposed hydrazido NH and saccharide hydroxyl-group absorptions (NH, OH).

The ^{1}H-n.m.r. spectrum of this product in pyridine-d_5 showed the two hydrazido protons as two deuteratable, one-proton signals, at δ 10.9–12.3, five aromatic protons as a multiplet at δ 7.15 8.4, and the rest of the protons between δ 4.15 and 5.9 (11 H, multiplet). The proton signals of the hydroxyl groups were superimposed on that of pyridine-d_5 (as an impurity) at δ 4.95–5.7. From these data, the condensation product was formulated as 1-benzoyl-2-D-gluconylhydrazine (**2**).

A solution of **2** in pyridine gave a violet color with 3% methanolic ferric

*Sugar 1,3,4-Oxadiazoles, Part V. For Part IV, see ref. 1.
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chloride solution, indicating that at least one of the two hydrazido groups was engaged in hydrazide ⇌ hydrazidic acid (or amide ⇌ imidic acid) tautomerism, which is in harmony with similar results documenting[9,10] the existence of such a type of tautomerism in the case of aroylhydrazones.

Similarly, condensation of **1** with substituted benzoylhydrazines afforded the corresponding 1-aroyl-2-D-gluconylhydrazines (**3**–**11**), all of which gave correct elemental analyses, had ^{1}H-n.m.r. patterns similar to that of **2**, and gave characteristic colorations with ferric chloride.

Condensative cyclization of aromatic acid hydrazides with triethyl orthoformate is known[11] to yield 2,4-diaryl-5-ethoxy-4,5-dihydro-1,3,4-oxadiazoles (Δ^2-oxadiazolines). During this reaction, a three-carbon fragment is introduced, one carbon atom of which is involved in formation of the 1,3,4-oxadiazole ring-system. We have now explored the application of this condensative cyclization to the 1-aroyl-2-D-gluconylhydrazines.

When a solution of **2** and an excess of triethyl orthoformate in 1,4-dioxane was boiled under reflux, a colorless, crystalline product, m.p. 175–178°, was obtained. Unlike the starting hydrazide, this product lacked the previously mentioned hydrazide–hydrazidic acid tautomerism, as it gave no coloration with ferric chloride. Its elemental analysis data agreed with the molecular formula $C_{16}H_{22}N_2O_8 \cdot H_2O$, showing that the molecule contained three carbon atoms more than the parent hydrazide **2**. The infrared absorption spectrum of the product showed CON and C=N bands at 1690 and 1600 cm^{-1}, respectively, in addition to bands at 1090 (C–O–C), 1040 (C–O), and 790 cm^{-1} (Ph). The fingerprint region of the infrared spectrum of this product showed pronounced differences from that of the parent compound (**2**).

These data agree with those expected for formation of a 1,3,4-oxadiazole ring, and the product may be assigned the structure of either 2-ethoxy-3-D-gluconyl-2,3-dihydro-5-phenyl-1,3,4-oxadiazole (**12**) or 3-benzoyl-2-ethoxy-2,3-dihydro-5-(D-*gluco*-pentitol-1-yl)-1,3,4-oxadiazole (**22**). The cyclization product could not be definitely assigned eiher structure **12** or **22**. However, structure **12** may be tentatively selected as that of the product, on the basis of those definitely assigned, on the basis of mass-spectral data, to the products of similar condensative cyclization of 2,3,4,5-tetra-*O*-acetylgalactaric acid bis(aroylhydrazides)[1].

Various 5-aryl-2-ethoxy-3-D-gluconyl-2,3-dihydro-1,3,4-oxadiazoles (**13**–**21**) were also prepared by condensative cyclization of the corresponding 1-aroyl-2-D-gluconylhydrazines with triethyl orthoformate.

In an attempt to achieve dehydrative cyclization of the 1-aroyl-2-D-gluconylhydrazines with phosphoryl chloride, we first tried to protect the hydroxyl groups of the D-gluconyl group by acetylation, but attempts made under various conditions (of time, temperature, and sequence of addition of the reactants) failed; the crystalline products obtained were devoid of any sugar moieties, and were proved, by direct comparison, to be 1-acetyl-2-aroylhydrazines, indicating that, under the reaction conditions used, trans-acylation (replacement of the D-gluconyl by an acetyl group) had occurred.

EXPERIMENTAL

Melting points were determined with a Kofler block and are uncorrected. The i.r. spectra were recorded, for potassium bromide discs, with a Unicam SP 1025 spectrophotometer. ^{1}H-N.m.r. spectra were recorded at 90 MHz with a Varian EM 390 spectrometer, for solutions in pyridine-d_5 containing tetramethylsilane as the internal standard. Microanalyses were made in the Microanalysis Unit, Faculty of Science, Cairo University, Cairo, Egypt. Homogeneity of products was checked by thin-layer chromatography on plates of Silica Gel G (layer thickness, 0.25 mm); spots were detected with iodine, or by spraying with 20% sulfuric acid, followed by heating the chromatograms on a hot plate for a few minutes.

*1-Benzoyl-2-*D-*gluconylhydrazine* (**2**). — A solution of D-glucono-1,5-lactone (**1**; 1 g, 5.6 mmol) in distilled water (2 mL) was filtered through a fritted-glass funnel, the filtrate was treated with a filtered solution of benzoylhydrazine (0.76 g, 5.6 mmol) in ethanol (30 mL), and the mixture was boiled under reflux for 30 min, cooled, concentrated by evaporating most of the solvent, and the concentrate kept overnight at room temperature. The crystalline product that separated was filtered off, and washed several times with filtered ethanol, to give 1.5 g (85%) of **2**; m.p. 190°; insoluble in most of the common organic solvents; ν_{max}^{KBr} 3300 (broad, NH + OH), 1680, 1650 (Amide I), and 700 cm^{-1} (Ph); ^{1}H-n.m.r.: δ 4.95–5.7 (5 H, 5 OH), 10.9–12.3 (2 H, 2 NH), and 7.15–8.4 (5 H, Ph). A solution of **2** in pyridine gave a violet color with a 3% solution of ferric chloride in methanol.

Anal. Calc. for $C_{13}H_{18}N_2O_7$: C, 49.6; H, 5.7; N, 8.9. Found: C, 49.1; H, 5.7; N, 8.3.

1-D-*Gluconyl-2*-p-*toluoylhydrazine* (**3**). — This compound was prepared (as for **2**) in 82% yield from **1** and *p*-toluoylhydrazine; m.p. 183–186°, ν_{max}^{KBr} 3400 (broad NH + OH), 1700, 1650 (Amide I), and 730 cm^{-1} (Ar); ^{1}H-n.m.r.: δ 5.25–6.3 (5 H, 5 OH), 11.5 (2 H, 2 NH), 7.0–8.3 (4 H, C_6H_4), and 2.22 (3 H, CH_3).

Anal. Calc. for $C_{14}H_{20}N_2O_7 \cdot H_2O$: C, 48.6; H, 6.4; N, 8.1. Found: C, 48.2; H, 6.3; N, 8.3.

1-D-*Gluconyl-2*-m-*toluoylhydrazine* (**4**). — This compound was prepared (as for **2**) in 76% yield from **1** and *m*-toluoylhydrazine; m.p. 170–174°; ν_{max}^{KBr} 3300 (broad, NH + OH), 1690, 1655 (Amide I), and 720 cm^{-1} (Ar); ^{1}H-n.m.r.: δ 5.3–6.0 (5 H, 5 OH), 11.0–12.2 (2 H, 2NH), 7.1–8.2 (4 H, C_6H_4), and 2.18 (3 H, CH_3).

Anal. Calc. for $C_{14}H_{20}N_2O_7 \cdot 0.5\ H_2O$: C, 49.8; H, 6.2; N, 8.3. Found: C, 49.9; H, 6.4; N, 8.2.

1-D-*Gluconyl-2*-(p-*methoxybenzoyl*)*hydrazine* (**5**). — This compound was prepared in 88% yield from **1** and (*p*-methoxybenzoyl)hydrazine; m.p. 187°; ν_{max}^{KBr} 3400 (broad, NH + OH), 1683, 1640 (Amide I), and 700 cm^{-1} (Ar); ^{1}H-n.m.r.: δ 5.35–6.1 (5 H, 5 OH), 11.17–11.90 (2 H, 2 NH), 6.8–8.4 (4 H, C_6H_3), and 3.68 (3 H, OCH_3).

Anal. Calc. for $C_{14}H_{20}N_2O_8 \cdot 0.5\ H_2O$: C, 47.6; H, 6.9; N, 7.9. Found: C, 48.1; H, 6.6; N, 8.2.

1-(p-*Chlorobenzoyl*)-*2*-D-*gluconylhydrazine* (**6**). — This compound was prepared in 82% yield from **1** and (*p*-chlorobenzoyl)hydrazine; m.p. 203–205°; ν_{max}^{KBr} 3400 (broad, NH + OH), 1685, 1650 (Amide I), and 735 cm^{-1} (Ar); ^{1}H-n.m.r.: δ 4.85–5.5 (5 H, 5 OH), 7.1–8.3 (4 H, C_6H_4), and 10.4–11.5 (2 H, 2 NH).

Anal. Calc. for $C_{13}H_{17}ClN_2O_7$: C, 44.7; H, 4.9; N, 8.0. Found: C, 44.6; H, 4.9; N, 8.2.

1-(m-*Chlorobenzoyl*)-*2*-D-*gluconylhydrazine*(**7**). — This compound was prepared in 77% yield from **1** and (*m*-chlorobenzoyl)hydrazine; m.p. 143–145°; ν_{max}^{KBr} 3300 (broad NH + OH), 1690, 1645 (Amide I), and 715 cm^{-1} (Ar); ^{1}H-n.m.r.: δ 5.25–5.9 (5 H, 5 OH), 7.1–8.35 (4 H, C_6H_4), and 10.3–11.65 (2 H, 2 NH).

Anal. Calc. for $C_{13}H_{17}ClN_2O_7$: C, 44.7; H, 4.9; N, 8.0. Found: C, 44.2; H, 5.1; N, 8.5.

1-(o-*Chlorobenzoyl*)-*2*-D-*gluconylhydrazine* (**8**). — This compound was prepared in 71% yield from **1** and (*o*-chlorobenzoyl)hydrazine; m.p. 183–186°; ν_{max}^{KBr} 3400 (broad, NH + OH), 1685, 1650 (Amide I), and 700 cm^{-1} (Ar).

Anal. Calc. for $C_{13}H_{17}ClN_2O_7$: C, 44.7; H, 4.9; N, 8.0. Found: C, 44.5; H, 4.9; N, 8.3.

1-(p-*Bromobenzoyl*)-*2*-D-*gluconylhydrazine* (**9**). — This compound was prepared in 91% yield from **1** and (*p*-bromobenzoyl)hydrazine; m.p. 210–213°; ν_{max}^{KBr} 3300 (broad, NH + OH), 1685, 1645 (Amide I), and 735 cm^{-1} (Ar); ^{1}H-n.m.r.: δ 4.8–6.0 (5 H, 5 OH), 7.4–8.3 (4 H, C_6H_4), and 10.7–11.8 (2 H, 2 NH)

Anal. Calc. for $C_{13}H_{17}BrN_2O_7$: C, 39.7; H, 4.3; N, 7.1. Found: C, 39.4; H, 4.4; N, 6.8.

1-(m-*Bromobenzoyl*)-*2*-D-*gluconylhydrazine* (**10**). — This compound was

prepared in 86% yield from **1** and (*m*-bromobenzoyl)hydrazine; m.p. 175–178°; ν_{max}^{KBr} 3300 (broad, NH + OH), 1680, 1650 (Amide I), and 715 cm^{-1} (Ar); ^{1}H-n.m.r.: δ 4.8–5.6 (5 H, 5 OH), 7.15–8.5 (4 H, C_6H_4), and 11.0–11.8 (2 H, 2 NH).

Anal. Calc. for $C_{13}H_{17}BrN_2O_7 \cdot 1.5\ H_2O$: C, 37.1; H, 4.8; N, 6.7. Found: C, 37.1; H, 4.7; N, 6.9.

*1-*D*-Gluconyl-2-*(p-*nitrobenzoyl)hydrazine* (**11**). — This compound was prepared in 91% yield from **1** and (*p*-nitrobenzoyl)hydrazine; m.p.215°; ν_{max}^{KBr} 3300 (broad, NH + OH), 1685, 1645 (Amide I), and 710 cm^{-1} (Ar).

Anal. Calc. for $C_{13}H_{17}N_3O_9$: C, 43.4; H, 4.7. Found: C, 43.5; H, 4.3.

*2-Ethoxy-3-*D*-gluconyl-2,3-dihydro-5-phenyl-1,3,4-oxadiazole* (**12**). — To a suspension of 1-benzoyl-2-D-gluconylhydrazine (**2**; 1 g, 3,18 mmol) in 1,4-dioxane (10 mL) was added triethyl orthoformate (5 mL), and the mixture was boiled under reflux until complete dissolution had occurred (~20 h). The mixture was evaporated to dryness, and the product crystallized from ethanol to give 0.8 g (68%) of **12**; m.p. 175–178°; ν_{max}^{KBr} 1690 (CON), 1600 (C=N), 1090 (C–O–C), 1040 (C–O), and 790 cm^{-1} (Ar).

Anal. Calc. for $C_{16}H_{22}N_2O_8 \cdot H_2O$: C, 49.4; H, 6.2; N, 7.2. Found: C, 49.0; H, 5.8; N, 7.8.

*2-Ethoxy-3-*D*-gluconyl-2,3-dihydro-5-*p*-tolyl-1,3,4-oxadiazole* (**13**). — Compound **13** was prepared in 69% yield from **3**, as for compound **12**: m.p. 165°; ν_{max}^{KBr} 1685 (CON), 1570 (C=N), 1090 (C–O–C), 1035 (C–O), and 730 cm^{-1} (Ar).

Anal. Calc. for $C_{17}H_{24}N_2O_8$: C, 53.1; H, 6.3; N, 7.3. Found: C, 53.6; H, 6.7; N, 7.1.

*2-Ethoxy-3-*D*-gluconyl-2,3-dihydro-5-*m*-tolyl-1,3,4-oxadiazole* (**14**). — Compound **14** was prepared in 60% yield from **4**, as for compound **12**; m.p. 155°; ν_{max}^{KBr} 1690 (CON), 1600 (C=N), 1100 (C–O–C), 980 (C–O), and 780 cm^{-1} (Ar).

Anal. Calc. for $C_{17}H_{24}N_2O_8$: C, 53.1; H, 6.3; N, 7.3. Found: C, 53.5; H, 6.5; N, 7.3.

*2-Ethoxy-3-*D*-gluconyl-2,3-dihydro-5-*(p-*methoxyphenyl)-1,3,4-oxadiazole* (**15**). — Compound **15** was prepared in 69% yield from **5**, as for compound **12**; m.p. 168–172°; ν_{max}^{KBr} 1640 (CON), 1580 (C=N), 1080 (C–O–C), 1050 (C–O), and 700 cm^{-1} (Ar).

Anal. Calc. for $C_{17}H_{24}N_2O_9 \cdot 1.5\ H_2O$: C, 47.7; H, 6.3; N, 6.6. Found: C, 48.2; H, 6.4; N, 6.4.

5-(p-*Chlorophenyl)-2-ethoxy-3-*D*-gluconyl-2,3-dihydro-1,3,4-oxadiazole* (**16**). — Compound **16** was prepared in 68% yield from **6**, as for compound **12**; m.p. 128°; ν_{max}^{KBr} 1710 (CON), 1570 (C=N), 1085 (C–O–C), 1005 (C–O), and 750 cm^{-1} (Ar).

Anal. Calc. for $C_{16}H_{21}ClN_2O_8 \cdot 1.5\ H_2O$: C, 44.5; H, 5.6; N, 6.5. Found: C, 43.9; H, 5.0; N, 6.5.

5-(m-*Chlorophenyl)-2-ethoxy-3-*D*-gluconyl-2,3-dihydro-1,3,4-oxadiazole* (**17**). — Compound **17** was prepared in 60% yield from **7**, as for compound **12**;

m.p. 175°; ν_{max}^{KBr} 1680 (CON), 1600 (C=N), 1065 (C–O–C), 990 (C–O), and 780 cm^{-1} (Ar).

Anal. Calc. for $C_{16}H_{21}ClN_2O_8 \cdot 2\ H_2O$: C, 43.6; H, 5.7; N, 6.4. Found: C, 43.1; H, 5.4; N, 7.0.

5-(o-Chlorophenyl)-2-ethoxy-3-D-gluconyl-2,3-dihydro-1,3,4-oxadiazole (**18**). — Compound **18** was prepared in 51% yield from **8**, as for compound **12**; m.p. 162–166°; ν_{max}^{KBr} 1650 (CON), 1600 (C=N), 1050 (C–O–C), 1005 (C–O), and 760 cm^{-1} (Ar).

Anal. Calc. for $C_{16}H_{21}ClN_2O_8 \cdot H_2O$: C, 45.4; H, 5.4; N, 6.6. Found: C, 45.2; H, 5.0; N, 6.8.

5-(p-Bromophenyl)-2-ethoxy-3-D-gluconyl-2,3-dihydro-1,3,4-oxadiazole (**19**). — Compound **19** was prepared in 70% yield from **9**, as for compound **12**; m.p. 145°; ν_{max}^{KBr} 1720 (CON), 1600 (C=N), 1100 (C–O–C), 1015 (C–O), and 760 cm^{-1} (Ar).

Anal. Calc. for $C_{16}H_{21}BrN_2O_8$: C, 42.8; H, 4.7; N, 6.2. Found: C, 42.3; H, 4.3; N, 6.5.

5-(m-Bromophenyl)-2-ethoxy-3-D-gluconyl-2,3-dihydro-1,3,4-oxadiazole (**20**). — This compound was prepared in 62% yield from **10**, as for compound **12**; m.p. 127–130°; ν_{max}^{KBr} 1680 (CON), 1520 (C=N), 1060 (C–O–C), 970 (C–O), and 790 cm^{-1} (Ar).

Anal. Calc. for $C_{16}H_{21}BrN_2O_8 \cdot 1.5\ H_2O$: C, 40.3; H, 5.0; N, 5.9. Found: C, 40.4; H, 4.7; N, 6.3.

2-Ethoxy-3-D-gluconyl-2,3-dihydro-5-(p-nitrophenyl)-1,3,4-oxadiazole (**21**). —Compound **21** was prepared in 61% yield from **11**, as for compound **12**; m.p. 145°; ν_{max}^{KBr} 1680 (CON), 1590 (C=N), 1085 (C–O–C), 1005 (C–O), and 660 cm^{-1} (Ar).

Anal. Calc. for $C_{16}H_{21}N_3O_{10}$: C, 46.3; H, 5.1; N, 10.1. Found: C, 46.6; H, 5.5; N, 10.6.

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