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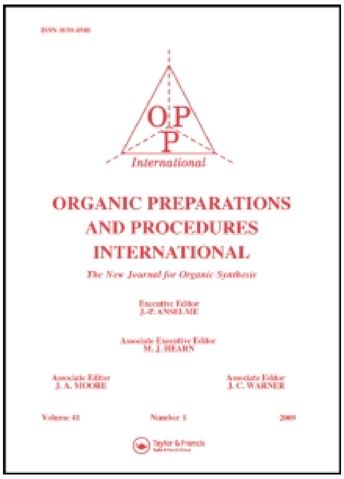

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# SUGAR 1,3,4-OXADIAZOLES. III. THE SYNTHESIS OF 1,2,3,4-TETRA-O-ACETYL-1,4-BIS(5-ARYL-1,3,4-OXADIAZOL-2-YL)-GALACTO-TETRITOLS

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ORGANIC PREPARATIONS AND PROCEDURES INT. 8(3), 113-118 (1976)

# SUGAR 1,3,4-OXADIAZOLES. III[1]. THE SYNTHESIS OF 1,2,3,4-TETRA-O-ACETYL-1,4-BIS(5-ARYL-1,3,4-OXADIAZOL-2-YL)-GALACTOTETRITOLS

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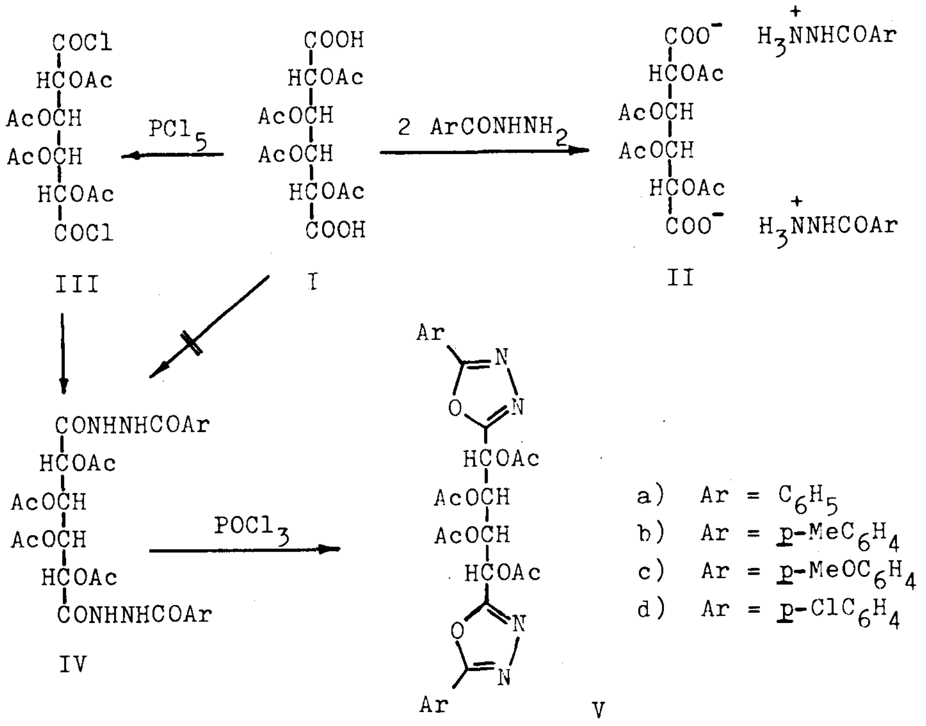
Recently,[1,2] we have described the oxidative cyclization of acetates of aldehydo sugar aroylhydrazones to a new type of carbohydrate heterocyclic derivatives namely 5-aryl-2-(polyacetoxyalkyl)-1,3,4-oxadiazoles.



a) Ar = $C_6H_5$
b) Ar = p-$MeC_6H_4$
c) Ar = p-$MeOC_6H_4$
d) Ar = p-$ClC_6H_4$

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The resistance of 2,3,4,5-tetra-O-acetyl aldehydo-L-rhamnose benzoylhydrazone to this oxidation was discussed and attributed to the probable unfavorable geometry of the molecule.[1] Because of the increasing biological and industrial uses of 1,3,4-oxadiazole derivatives,[3] we became interested in the preparation of new types of sugar 1,3,4-oxadiazoles. This article describes the synthesis of sugar di-1,3,4-oxadiazoles (V) by the dehydrative cyclization[4,5] of the newly prepared galactaric acid bis(aroylhydrazide) acetates (IV). Preparation of 2,3,4,5-tetra-O-acetyl galactaric acid bis(aroylhydrazides) (IV) was first attempted by direct condensation of 2,3,4,5-tetra-O-acetylgalactaric acid (I)[6] with the corresponding aroylhydrazine. The products, however, were the unstable salts (II) which decomposed during crystallization to a sugar derivative (unidentified) and 1,2-diaroylhydrazines. When the condensation was made with 2,3,4,5-tetra-O-acetylgalactaroyl dichloride (III)[6], however, the required bis(hydrazides) (IV) were obtained in crystalline form and high yield (78-83%). Compounds IVa-IVd showed four carbonyl absorption bands at 1760-1750 (OAc), 1740-1730 (OAc), 1700-1695 (CONH) and 1680-1670 $cm^{-1}$ (CONH) in addition to the NH absorption at 3500-3350 $cm^{-1}$. The nmr spectrum of IVa showed signals for the two phenyl groups as 10-proton multiplet at $\delta$ 8.1-7.4 and the four O-acetyl groups as two 6-proton singlets at $\delta$ 2.18 and 2.15 ppm. The mass spectrum of IVa did not show a molecular ion fragment, due to its decomposition on the probe, but showed fragments at m/e 136 $(C_6H_5CONHNH_2)^+$, 121

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$(C_6H_5CONH_2)^+$, 105 $(C_6H_5CO)^+$ and 43 $(CH_3CO)^+$.

Dehydrative cyclization of IV by heating with phosphoryl chloride gave products the elemental analyses of which showed the loss of two molecules of water per molecule of the parent bis(hydrazide). The products showed carbonyl ester absorption at 1755-1750 $cm^{-1}$, new bands at 1385 and 980 $cm^{-1}$ due to the oxadiazole rings[7,8] and no amide or NH bands. The cyclization products were thus assigned the structure of 1,2,3,4-tetra-O-acetyl-1,4-bis(5-aryl-1,3,4-oxadiazol-2-yl)-*galacto*-tetritols V. In conformity with this assignment is the mass spectral fragmentation pattern of 1,2,3,4-tetra-O-acetyl-1,4-bis(5-phenyl-1,3,4-oxadiazol-2-yl)-*galacto*-tetritol Va (FIG. 1) which revealed peaks at *m*/*e* 145 due to the 1,3,4-oxadiazole ring, 217, 289 and 433 due to the sequential fragmentation of the polyacetoxyalkyl chain and the molecular ion peak at *m*/*e* 578.

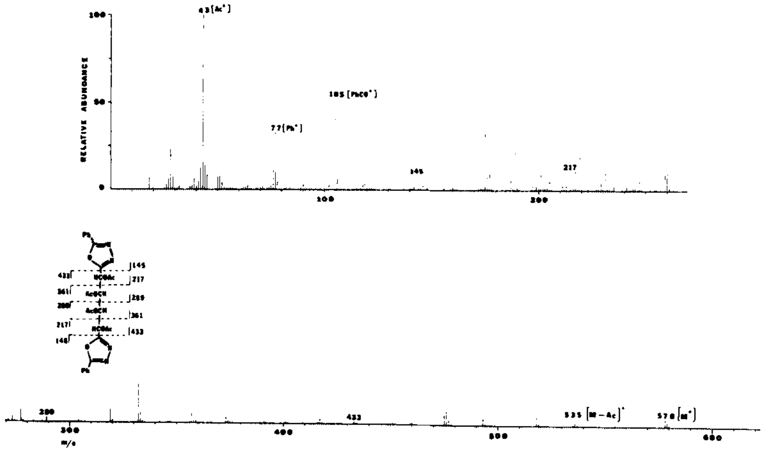

FIG. 1: Mass spectrum of 1,2,3,4-tetra-O-acetyl-1,4-bis(5-phenyl-1,3,4-oxadiazol-2-yl)-*galacto*-tetritol Va

The formation of the oxadiazole rings should have taken place through the elimination of one molecule of water from the enolized hydrazide functions at each terminus of the bis(hydrazide) V. That these hydrazide functions are enolizable was confirmed by the formation of greenish-brown colorations with neutral ferric chloride solution.

## EXPERIMENTAL

Melting points were determined with a Kofler block and are uncorrected. The ir spectra were recorded as KBr pellets on a Unicam SP200 spectrophotometer. The nmr spectra were determined at 60 MHz with a Varian T-60 spectrometer in $CDCl_3$ containing 1% tetramethylsilane as the internal standard. The mass spectra were performed on a Hitachi-Perkin-Elmer RMU-6 mass spectrometer. The homogeneity of the products was checked by tlc on Silica Gel G plates (layer thickness 0.25 mm) and the spots were detected by spraying with anisaldehyde-sulfuric acid-ethanol (1:1:18 v/v) (ref. 9) followed by heating the chromatograms on a hot plate for a few minutes.

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2,3,4,5-Tetra-O-acetylgalactaric acid bis(aroylhydrazides) (IVa-IVd) (TABLE 1).– A solution of 2,3,4,5-tetra-O-acetylgalactaroyl dichloride[6] (III, 1 g) in dry benzene (150 ml) was treated with a solution of the corresponding aroylhydrazine (2.2 equivalent) in the same solvent (50 ml) and the mixture was heated at 100° for 15 min. The reaction mixture was cooled to room temperature and the bis(hydrazide) was collected, washed with ethanol and crystallized from dioxane.

TABLE 1. 2,3,4,5-Tetra-O-acetylgalactaric acid bis(aroylhydrazides) (IVa-IVd).

| Cpd No. | Yield % | mp. °C | Found C | Found H | Found N | Formula | Calcd C | Calcd H | Calcd N |
|---|---|---|---|---|---|---|---|---|---|
| IVa | 76 | 275 | 55.0 | 4.8 | 9.0 | $C_{28}H_{30}N_4O_{12}$ | 54.7 | 5.2 | 9.1 |
| IVb | 78 | 305 | 56.0 | 5.2 | 8.5 | $C_{30}H_{34}N_4O_{12}$ | 56.1 | 5.3 | 8.7 |
| IVc | 82 | 280 | 53.2 | 4.9 | 8.4 | $C_{30}H_{34}N_4O_{14}$ | 53.4 | 5.1 | 8.3 |
| IVd | 83 | 265 | 49.3 | 4.2 | 8.2 | $C_{28}H_{28}N_4Cl_4O_{12}$ | 49.2 | 4.1 | 8.2 |

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*1,2,3,4-Tetra*-O-*acetyl-1,4-bis(5-aryl-1,3,4-oxadiazol-2-yl)*-galacto-*tetritols* (Va-Vd) (*TABLE 2*).– A suspension of 2,3,4,5-tetra-O-acetylgalactaric acid bis(aroylhydrazide) (IV, 0.5 g) in phosphoryl chloride (10 ml) was heated under reflux until complete dissolution occurred (10-20 min.). The mixture was cooled to room temperature, poured into a cold saturated solution of sodium hydrogencarbonate (200 ml) and extracted with chloroform (4 x 50 ml). The chloroform extract was washed with water (3 x 50 ml), dried (sodium sulfate) and evaporated. The products were crystallized from methanol.

*TABLE 2*. *1,2,3,4-Tetra*-O-*acetyl-1,4-bis(5-aryl-1,3,4-oxadiazol-2-yl)*-galacto-*tetritols* (Va-Vd).

| Cpd No. | Yield % | mp. °C | Found C | Found H | Found N | Formula | Calcd C | Calcd H | Calcd N |
|---|---|---|---|---|---|---|---|---|---|
| Va | 71 | 217 | 57.9 | 4.3 | 9.9 | $C_{28}H_{26}N_4O_{10}$ | 58.1 | 4.5 | 9.7 |
| Vb | 74 | 215 | 59.3 | 5.0 | 9.4 | $C_{30}H_{30}N_4O_{10}$ | 59.4 | 5.0 | 9.2 |
| Vc | 70 | 212 | 56.1 | 4.4 | 8.7 | $C_{30}H_{30}N_4O_{12}$ | 56.4 | 4.7 | 8.8 |
| Vd | 75 | 245 | 52.1 | 3.8 | 9.0 | $C_{28}H_{24}N_4Cl_2O_{10}$ | 51.9 | 3.7 | 8.7 |

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