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Note

Cyclization of hydrazides and hydrazones*

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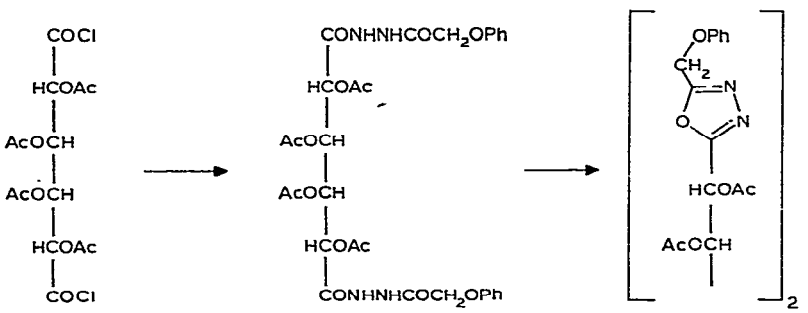
In previous papers[3–6], the preparation and reactions of some new sugar aroylhydrazones have been described. Continuing this interest, we report here their dehydrogenation, and the application of some new cyclizing agents to hydrazides in the carbohydrate series.

Condensation of 2,3,4,5-tetra-*O*-acetylgalactardioyl dichloride (**1**) with two molar equivalents of (phenoxyacetyl)hydrazine gave a colorless product formulated as 2,3,4,5-tetra-*O*-acetylgalactaric acid bis(phenoxyacetyl)hydrazide (**2**). Dehydration of **2** was effected with a solution of thionyl chloride in *N*,*N*-dimethylformamide or pyridine, or with dicyclohexylcarbodiimide in pyridine, to give 1,2,3,4-tetra-*O*-acetyl-1,4-bis[5-(phenoxymethylene)-1,3,4-oxadiazol-2-yl]-*galacto*-tetritol (**3**). A comparative study of reagents for cyclizing such derivatives in the carbohydrate series indicated that $SOCl_2$–$HCONMe_2$ is the reagent of choice, owing to the high yield and purity of the product. A similar dehydration of hydrazides, using phosphoryl chloride, has also been reported[7]. The infrared (i.r.) spectrum of **3** showed, at 1750 cm^{-1},



1 2 3

*Heterocycles from Carbohydrate Precursors, Part XXII. For Part XXI, see ref. 1. The Scope of the Reactions of Hydrazines and Hydrazones, Part XII. For Part XI, see ref. 2.

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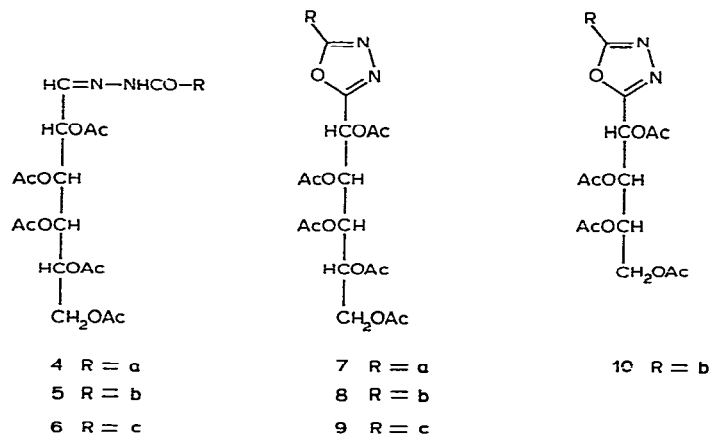
a band corresponding to the acetyl group, whereas bands characteristic for the OCN group [which appeared in the spectrum of its precursor (**2**) at 1675 cm^{-1}] were absent.

We have prepared some new types of sugar aroylhydrazones and have found that their acetylation with acetic anhydride in pyridine at room temperature affords the corresponding per-*O*-acetylated derivatives which, on boiling with acetic anhydride, give compounds having an oxadiazoline ring[5]; the corresponding arylhydrazones[3] behave differently. On attempting dehydrogenation of sugar aroylhydrazones with mercuric oxide, no change was noted, whereas iodine–mercuric oxide, a known reagent, effected the reaction[10]. Thus, on applying this reagent to the (*p*-acetamidobenzoyl)hydrazone (**4**), [*p*-(methoxycarbonyl)benzoyl]hydrazone (**5**), and the (phenylacetyl)hydrazone (**6**) of penta-*O*-acetyl-*aldehydo*-D-galactose, colorless, crystalline products were afforded that showed, in the carbonyl-frequency region of their i.r. spectra, only a band at 1735 cm^{-1}, due to acetic ester; the amide absorption band at 1670–1660 cm^{-1}, present in the spectra of their precursors **4**–**6**, as well as in that of their parent, unacetylated hydrazone, was absent. This observation, as well as the elemental analysis, indicated that the oxidation products could be assigned the structures of 5-substituted 2-(1,2,3,4,5-penta-*O*-acetyl-D-*galacto*-pentitol-1-yl)-1,3,4-oxadiazoles (**7**–**9**), two hydrogen atoms being lost during the cyclization. Similar dehydrogenation of tetra-*O*-acetyl-*aldehydo*-L-arabinose (phenylacetyl)-hydrazone afforded **10**.



4 R = a
5 R = b
6 R = c

7 R = a
8 R = b
9 R = c

10 R = b

a,-C_6H_4NHAc-*p* ; b, -$C_6H_4CO_2Me$-*p* ; c, -CH_2Ph.

Deacetylation of 5-benzyl-2-(1,2,3,4,5-penta-*O*-acetyl-D-*galacto*-pentitol-1-yl)-1,3,4-oxadiazole (**9**) with methanolic ammonia afforded a product that showed in its i.r. spectrum an amide band at 1640 cm^{-1} (absent from the spectrum of the oxadiazole acetate **9** and present in that of the hydrazone), and that gave an elemental analysis agreeing (tentatively) with $C_{14}H_{18}N_2O_6$. It should be noted that the difference between this compound and the starting, unacetylated hydrazone corresponding

to **6** is only a matter of two hydrogen atoms, and that its acetylation reafforded the oxadiazole acetate **9**, although the deacetylated derivative could not be assigned the structure of the unacetylated oxadiazole, as the latter might not show a band at 1640 cm^{-1} in its i.r. spectrum. An iminolactone structure was reported by El Khadem and co-workers for the product resulting from similar treatment of 5-phenyl-2-(polyacetoxy)alkyl-1,3,4-oxadiazole. The preparation and reactions of the various (aryloxyacetyl)hydrazones have been investigated[11] and will be published.

EXPERIMENTAL

General methods. — Melting points were determined on a Kofler-block apparatus and are uncorrected. I.r. spectra were recorded with a Unicam SP 200 spectrophotometer. Microanalyses were performed in the Chemistry Department, Faculty of Science, Cairo University, Cairo, Egypt.

2,3,4,5-Tetra-O-acetyl galactaric acid bis(phenoxyacetyl)hydrazide (**2**). — A solution of compound **1** (1 g) in benzene (150 mL) was treated with phenoxyacetylhydrazine (0.9 g) in benzene (30 mL) at room temperature. The product that immediately separated out was filtered off, washed with benzene, and dried (yield 80%). It was recrystallized from ethanol to give colorless needles, m.p. 225–226°; ν_{max}^{Nujol} 1715 (OAc) and 1675 cm^{-1} (OCN).

Anal. Calc. for $C_{30}H_{34}N_4O_{14}$: C, 53.4; H, 5.1; N, 8.3. Found: C, 53.6; H, 5.2; N, 8.6.

1,2,3,4-Tetra-O-acetyl-1,4-bis[5-(phenoxymethylene)-1,3,4-oxadiazol-2-yl]-galacto-tetritol (**3**). — (*a*) A solution of compound **2** (1 g) in *N,N*-dimethylformamide (8 mL) was treated with thionyl chloride (4 mL). The mixture was heated for 10–15 min on a boiling-water bath, cooled, and then diluted with a cold, saturated solution of sodium hydrogencarbonate (200 mL); the product that separated out solidified on washing with water. It was filtered off (yield 75%), and recrystallized from ethanol giving colorless needles, m.p. 202–203°; ν_{max}^{Nujol} 1750 cm^{-1} (OAc).

Anal. Calc. for $C_{30}H_{30}N_4O_{14}$: C, 53.7; H, 4.5; N, 8.4. Found: C, 53.9; H, 4.7; N, 8.5.

(*b*) A solution of compound **2** (1 g) in dry pyridine (15 mL) was treated with thionyl chloride (4 mL). The mixture was processed as in (*a*); the product (yield 55%) was identical with that obtained by method (*a*).

(*c*) A solution of compound **2** (0.7 g) in pyridine (10 mL) was treated with dicyclohexylcarbodiimide (0.5 g), and the mixture was heated under reflux for 1 h on a boiling-water bath, cooled, and poured onto crushed ice; the product that separated out was washed repeatedly with water by decantation, whereby the product solidified. It was filtered off, dried (yield 60%), and recrystallized from ethanol to give colorless needles, identical with the product obtained by method (*a*).

5-(p-Acetamidophenyl)-2-(1,2,3,4,5-penta-O-acetyl-D-galacto-pentitol-1-yl)-1,3,4-oxadiazole (**7**). — A suspension of **4** (2 g) in ether (300 mL) was treated with yellow mercuric oxide (2.4 g), magnesium oxide (0.4 g), and iodine (2 g), and the

mixture was stirred for 2 days at room temperature. The suspension was filtered, and the filtrate was washed successively with potassium iodide solution, sodium thiosulfate solution, and water, dried, and evaporated, giving a syrup that crystallized from ethanol to afford a colorless product (yield 58%), m.p. 99–101°; ν_{max}^{Nujol} 1735 (OAc) and 1690 (sh) cm^{-1} (NAc).

Anal. Calc. for $C_{25}H_{29}N_3O_{12}$: C, 53.3; H, 5.2; N, 7.5. Found: C, 53.6; H, 5.4; N, 7.4.

*5-[p-(Methoxycarbonyl)phenyl]-2-(1,2,3,4,5-penta-*O*-acetyl-*D*-galacto-pentitol-1-yl)-1,3,4-oxadiazole* (**8**). — To a suspension of compound **5** (1 g) in dry ether (100 mL) were successively added yellow mercuric oxide (1.2 g), magnesium oxide (0.2 g), and iodine (1 g), and the mixture was stirred for 2 days at room temperature. The suspension was filtered, and the filtrate was processed as for compound **7**, to give **8** (yield 70%); it was recrystallized from ethanol–water to give colorless needles, m.p. 158–159°; ν_{max}^{Nujol} 1735 (OAc) and 1720 cm^{-1} (CO_2Me).

Anal. Calc. for $C_{25}H_{28}N_2O_{13}$: C, 53.2; H, 5.0; N, 5.0. Found: C, 53.2; H, 4.9; N, 5.0.

*5-Benzyl-2-(1,2,3,4,5-penta-*O*-acetyl-*D*-galacto-pentitol-1-yl)-1,3,4-oxadiazole* (**9**). — A solution of compound **6** (0.5 g) in dry ether (50 mL) was treated with mercuric oxide (0.75 g), magnesium oxide (0.1 g), and iodine (0.4 g). The mixture was stirred overnight in a dry system, and then filtered; the filtrate was treated as before, to give a syrup that crystallized from ethanol in colorless needles, m.p. 82°; ν_{max}^{Nujol} 1735 cm^{-1} (OAc).

Anal. Calc. for $C_{24}H_{28}N_2O_{11}$: C, 55.4; H, 5.4; N, 5.4. Found: C, 55.2; H, 5.1; N, 5.2.

*5-Benzyl-2-(1,2,3,4-tetra-*O*-acetyl-*D*-arabino-tetritol-1-yl)-1,3,4-oxadiazole* (**10**). — This was prepared from tetra-O-acetyl-*aldehydo*-L-arabinose (phenylacetyl)hydrazone as described for **7**, to give crystals that, upon recrystallization from ethanol, gave a colorless product, m.p. 75°; ν_{max}^{Nujol} 1740 cm^{-1} (OAc).

Anal. Calc. for $C_{21}H_{24}N_2O_9$: C, 56.2; H, 5.4; N, 6.2. Found: C, 56.0; H, 5.4; N, 6.0.

Deacetylation of **9**. — A solution of compound **9** (1 g) in methanol (20 mL) was treated with 20% ammonium hydroxide solution (10 mL), and kept for 24 h at room temperature. The resulting solution was evaporated under vacuum, the residue was triturated with a small volume of water, and the solid was filtered off, washed with alcohol, and dried (yield 77%). It was recrystallized from ethanol, giving colorless needles, m.p. 218–220°; ν_{max}^{Nujol} 3220 (OH) and 1640 cm^{-1} (OCN).

Anal. Calc. for $C_{14}H_{18}N_2O_6$: C, 54.2; H, 5.8; N, 9.0. Found: C, 54.0; H, 5.9; N, 8.8.

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