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Note

Structure and reactions of aldose semicarbazone and thiosemicarbazone derivatives under acetylating conditions

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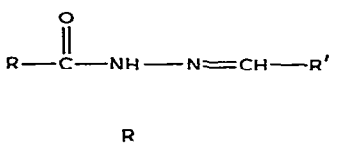
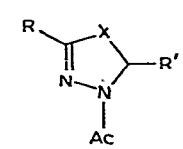
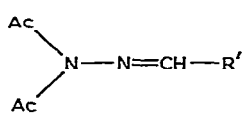
In a preliminary communication, we showed[1] that treatment of penta-*O*-acetyl-*aldehydo*-D-galactose acetylhydrazone (**1**) with acetic anhydride–anhydrous zinc chloride, or with hot acetic anhydride or acetyl chloride, gave the 1,3,4-oxadiazoline derivative **5**. Treatment of the corresponding benzoylhydrazone (**2**) with acetic anhydride, even in the presence of pyridine at room temperature, afforded the oxadiazoline **6**, as a result of the greater tendency of **2** to exist in the tautomeric iminol form.



	R
1	Me
2	Ph
3	H_2N
4	PhHN



	R	X
5	Me	O
6	Ph	O
7	AcHN	S



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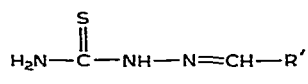

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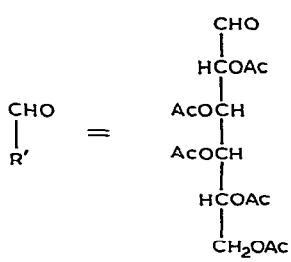

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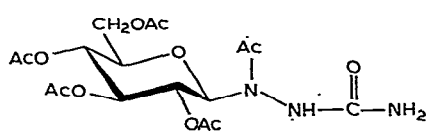

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We now report on the acetylation reactions of some aldose semicarbazone and thiosemicarbazone derivatives.

Several attempts to acetylate D-galactose semicarbazone with acetic anhydride in pyridine at room temperature gave penta-*O*-acetyl-*aldehydo*-D-galactose semicarbazone (**3**) instead of the 4-acetyl derivative of **3** obtained by Galmarini and co-workers[2]. The structure of **3** was proved by its synthesis from penta-*O*-acetyl-*aldehydo*-D-galactose (**10**) and semicarbazide hydrochloride in pyridine. Treatment of **3** with acetic anhydride in pyridine, even at elevated temperature, did not give Galmarini's hexa-acetate, but afforded the corresponding *N*,*N*-diacetylhydrazone **8** with loss of the carbamoyl group. Under similar conditions, compound **8** was obtained from penta-*O*-acetyl-*aldehydo*-D-galactose 4-phenylsemicarbazone (**4**) with loss of the phenylcarbamoyl moiety. Compound **8** was identical in all respects with the product obtained by Helferich and Schirp[3] from D-galactose acetylhydrazone on treatment with hot acetic anhydride–pyridine.

Treatment of D-galactose semicarbazone with acetic anhydride–pyridine was reported by Wolfrom and his co-workers[4,5] to give a mixture containing penta-*O*-acetyl-*aldehydo*-D-galactose semicarbazone (**3**). Without further purification, this mixture was suitable[5] for conversion into penta-*O*-acetyl-*aldehydo*-D-galactose ethyl hemiacetal by treatment with sodium nitrite and hydrochloric acid in aqueous ethanol. We have reinvestigated this acetylation reaction and found that the crude product contained **3** and **8** as major components. Therefore, we supposed that the diacetylhydrazone **8** should undergo a similar degradation reaction. Indeed, with sodium nitrite in aqueous acetic acid, **8** gave **10**, which was isolated as its ethyl hemiacetal in a yield of ~70%. A more detailed study of the degradation of acyl- and diacyl-hydrazones by nitrous acid will be published elsewhere.

Treatment of **3**, **4**, or **8** with acetic anhydride in the presence of anhydrous zinc chloride gave **5**. The formation of **5** from **3** and **4** involves the loss of the carbamoyl and phenylcarbamoyl group, respectively. The reaction **8**→**5**, however, requires a deacetylation–reacetylation reaction or the rearrangement of the Ac_2N-N= residue. The formation of **5** from **8**, even in propionic anhydride at 150°, gave evidence for an N→N acetyl migration.

On treatment with acetic anhydride in the presence of anhydrous zinc chloride, the 1-acetyl-1-(2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl)semicarbazide (**11**) underwent acetolysis and yielded 1,2,3,4,6-penta-*O*-acetyl-*α*-D-glucopyranose. This acetolysis reaction is similar to that[6] for the L-rhamnose benzoylhydrazone tetra-acetate having a pyranoid structure.

Treatment of penta-*O*-acetyl-*aldehydo*-D-galactose thiosemicarbazone (**9**, obtained from **10**) with acetic anhydride in the presence of anhydrous zinc chloride gave (−)-5-acetamido-3-acetyl-2-(D-*galacto*-1,2,3,4,5-penta-acetoxypentyl)-1,3,4-thiadiazoline (**7**), but, in the presence of pyridine, gave the (+)-diastereoisomer of **7**. The cyclisation reaction **9**→(+)-**7** in the presence of pyridine contrasted with the reaction **3**→**8** of the semicarbazone analogue, and may be explained by the more pronounced nucleophilic character of sulphur compared with that of oxygen.

EXPERIMENTAL

General methods. — Melting points (uncorrected) were determined on a Kofler block. U.v. spectra were recorded (for solutions in 95% ethanol) with a Unicam SP 800 spectrophotometer, i.r. spectra (KBr discs) with a Unicam SP 200G spectrophotometer, and p.m.r. spectra (for solutions in $CDCl_3$, internal Me_4Si) with a JEOL JNM-100 spectrometer. Optical rotations were measured with a Schmidt and Haensch polarimeter (1-dm pathlength). Solutions were concentrated *in vacuo* at $\not> 60°$ (bath).

Penta-O-*acetyl*-aldehydo-D-*galactose semicarbazone* (**3**). — A mixture of penta-*O*-acetyl-*aldehydo*-D-galactose (**10**; 1.952 g, 5 mmol) and semicarbazide hydrochloride (0.558 g, 5 mmol) in absolute pyridine (10 ml) was stirred at room temperature until dissolution was complete, and then kept overnight and concentrated. Trituration of the residue with ice and water (10–15 ml) afforded crude product (1.65 g, 73.8%), m.p. 206–208°. Crystallisation from ethyl acetate or ethanol gave **3** (1.56 g, 69.7%), m.p. 211–213°, $[\alpha]_D^{23}$ +87.5° (*c* 1, chloroform); lit.[5] $[\alpha]_D^{25}$ +89° (*c* 2.2, chloroform); λ_{max} 235 nm (log ε 4.15); ν_{max} 3471, 3330 sh, 3230 sh, and 3150 sh (NH), 1696 (Amide I), 1640 (C=N), and 1584 cm^{-1} (Amide II). P.m.r. data: δ 6.88 (d, 1 H, $J_{1,2}$ ~3 Hz, CH=N).

Anal. Calc. for $C_{17}H_{25}N_3O_{11}$: C, 45.64; H, 5.63; N, 9.39. Found: C, 45.80; H, 5.71; N, 9.40.

Penta-O-*acetyl*-aldehydo-D-*galactose 4-phenylsemicarbazone* (**4**). — A solution of **10** (7.806 g, 20 mmol) and 4-phenylsemicarbazide (3.023 g, 20 mmol) in ethyl acetate (30 ml) was boiled for 4 h with azeotropic removal of the water formed, and then concentrated. The syrupy residue was triturated with methanol (8–10 ml), and the crystals that separated were collected by filtration, washed with water, and dried to give crude **4** (9.467 g, 90.4%). A solution of the crude product in chloroform was clarified with Fuller's earth and activated carbon, and then concentrated. The syrupy residue was crystallised from ethanol (20 ml) and recrystallised from 50% aqueous ethanol (50 ml) to give **4** (7.52 g, 71.8%), m.p. 156°, $[\alpha]_D^{23}$ +110.2° (*c* 1, chloroform); λ_{max} 230 (log ε 4.15) and 252 nm (4.28): ν_{max} 3365, 3200, and 3130 (NH), 1705 and 1690 (CON), 1635 (C=N), 1597 (phenyl), and 1540 cm^{-1} ("Amide II"). P.m.r. data: δ 10.32 and 8.12 (2 s, 2 H, both exchangeable with deuterium, 2 NH), 7.00–7.64 (m, 6 H, phenyl and CH=N), 5.20–5.82 (m, 4 H, H-2,3,4,5), 3.78–4.38 (m, 2 H, CH_2), and 2.04–2.18 (5 s, 5 Ac).

Anal. Calc. for $C_{23}H_{29}N_3O_{11}$: C, 52.77; H, 5.58; N, 8.03. Found: C, 52.62; H, 5.63; N, 8.10.

Penta-O-*acetyl*-aldehydo-D-*galactose* N,N-*diacetylhydrazone* (**8**). — (*a*) Compound **3** (3.00 g, 6.71 mmol) was treated with pyridine (15 ml) and acetic anhydride (15 ml) at 115° for 2 h after dissolution was complete (20 min), and then cooled and poured into ice and water. A solution of the crude product (2.68 g, 81.7%) in chloroform was decolorised and concentrated. Crystallisation of the residue from ethanol

(20 ml) gave **8** (2.23 g, 68%), m.p. 194°, $[\alpha]_D^{23}$ +45° (*c* 1, chloroform), λ_{max} 224 nm (log ε 3.95); lit.[3] m.p. 193–194° (from propan-2-ol), $[\alpha]_D^{21}$ +53.3° (chloroform).

Anal. Calc. for $C_{20}H_{28}N_2O_{12}$: C, 49.18; H, 5.78; N, 5.74. Found: C, 48.93; H, 5.74; N, 5.62.

(*b*) Treatment of **4** (1.00 g, 1.91 mmol) as in (*a*) gave crude **8** (0.830 g, 89%), m.p. 193–195°. On the basis of the p.m.r. spectra and t.l.c., the products from (*a*) and (*b*) were identical with an authentic specimen obtained by the method of Helferich and Schirp[3].

3-Acetyl-5-methyl-2-(D-galacto-*1,2,3,4,5-penta-acetoxypentyl*)-*1,3,4-oxadiazoline* (**5**). — (*a*) A solution of **8** (1.93 g, 3.95 mmol) in acetic anhydride (40 ml) containing anhydrous zinc chloride (4.0 g) was kept at room temperature for 24 h. The mixture was concentrated, treated with ice and water, and extracted with chloroform. The chloroform solution was washed successively with water, aqueous sodium hydrogen carbonate, and water, dried ($MgSO_4$), clarified, and concentrated. The syrupy residue was crystallised from ethyl acetate (10 ml) to give **5** (1.72 g, 89.2%), m.p. 213–214°, $[\alpha]_D^{23}$ −172° (*c* 1, chloroform). After purification in chloroform and recrystallisation from ethyl acetate, **5** had m.p. 215–216°, $[\alpha]_D^{23}$ −190° (*c* 1, chloroform), λ_{max} 236 nm (log ε 4.03); lit.[1] m.p. 216–217°, $[\alpha]_D^{23}$ −186° (*c* 1, chloroform).

Anal. Calc. for $C_{20}H_{28}N_2O_{12}$: C, 49.18; H, 5.78; N, 5.74. Found: C, 48.69; H, 5.65; N, 5.69.

(*b*) Treatment of **3** (1.00 g, 2.24 mmol) as in (*a*) gave crude **5** (0.39 g, 35.5%), m.p. 214–216°, $[\alpha]_D^{23}$ −178° (*c* 1, chloroform).

(*c*) Treatment of **4** (1.000 g, 1.91 mmol) as in (*a*) gave crude **5** (0.775 g, 83%), m.p. 214–215°.

Anal. Found: N, 5.62.

On the basis of the i.r. and p.m.r. spectra and t.l.c., the products prepared from (*a*), (*b*), and (*c*), were identical with the product obtained[1] from **1**.

Acetolysis of 1-acetyl-1-(*2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranosyl*)*semicarbazide* (**11**). — A solution of **11**[7] (3.000 g, 6.71 mmol) in acetic anhydride (60 ml) containing anhydrous zinc chloride (6.00 g) was kept at 80–85° for 1 h. The mixture was concentrated, treated with ice–water, and extracted with benzene. The benzene solution was washed with aqueous sodium hydrogen carbonate and water, dried ($MgSO_4$), decolorised with Fuller's earth and activated carbon, and concentrated. The residue was crystallised from 20% aqueous methanol to give 1,2,3,4,6-penta-*O*-acetyl-α-D-glucopyranose (1.524 g, 58.2%), m.p. 113–114°, $[\alpha]_D^{23}$ +102° (*c* 1, chloroform); lit.[8] m.p. 112–113°, $[\alpha]_D^{20}$ +102° (chloroform). Its i.r. spectrum and t.l.c. behaviour were identical with those of an authentic[8] compound.

*Penta-*O*-acetyl-*aldehydo-D-*galactose thiosemicarbazone* (**9**). — A hot solution of thiosemicarbazide (4.00 g, 44 mmol) in water (400 ml) containing glacial acetic acid (3.0 ml) was added to a hot solution of **10** (15.60 g, 40 mmol) in water (1200 ml) and allowed to stand for 1 h. After cooling in ice–water, the crystals were collected by filtration, washed with water, and dried to give **9** (15.63 g, 84.3%), m.p. 210°. A portion (2.00 g) of the product was dissolved in chloroform (30 ml), and the

solution was decolorised and concentrated. The syrupy residue was crystallised from ethanol (10 ml) to give 1.80 g (75.9%) of pure **9**, m.p. 212° (dec.), $[\alpha]_D^{23}$ +112° (*c* 1, chloroform); λ_{max} 235 (log ε 3.87) and 277 nm (4.34); ν_{max} 3450, 3375, 3305, and 3174 (NH), 1600 and 1588 ("$CSNH_2$" I), and 1511 cm^{-1} ("$CSNH_2$" II). P.m.r. data: δ 10.46 (s, 1 H, exchangeable with deuterium, NH), 7.14 (d, broad, 2 H one of which was exchangeable with deuterium, $J_{1,2}$ ~4 Hz, CH=N), 6.66 (s, broad, 1 H, exchangeable with deuterium, NH), 5.22–5.62 (m, 4 H, H-2,3,4,5), 3.76–4.36 (m, 2 H, CH_2), and 2.01–2.14 (5 s, 5 Ac).

Anal. Calc. for $C_{17}H_{25}N_3O_{10}S$: C, 44.06; H, 5.44; N, 9.07; S, 6.92. Found: C, 44.52; H, 5.50; N, 9.16; S, 6.93.

5-Acetamido-3-acetyl-2-(D-galacto-*1,2,3,4,5-penta-acetoxypentyl)-1,3,4-thiadiazoline* (**7**). — (*a*) A solution of **9** (10.00 g, 21.58 mmol) in acetic anhydride (200 ml) containing anhydrous zinc chloride (20 g) was kept at room temperature for 24 h, and then concentrated. The residue was treated with ice and water, and the solid was collected by filtration, washed, and dried *in vacuo* to give diastereoisomeric **7** (11.20 g, 94.8%). A solution of this crude product in chloroform was decolorised and then concentrated. The residue was purified by repeated crystallisation from ethyl acetate to give pure (—)-**7** (5.20 g, 44%), m.p. 234°, $[\alpha]_D^{23}$ −310.5° (*c* 1, chloroform); λ_{max} 215 (log ε 4.02) and 286 nm (4.34); ν_{max} 3281 (NH), 1694 (exo Amide I), 1660 (endo Amide I), 1628 (C=N), and 1496 cm^{-1} (Amide II). P.m.r. data: δ 10.10 (s, 1 H, exchangeable with deuterium, NH), 6.02 (d, 1 H, $J_{1,2}$ 2 Hz, S-C*H*R-N), 5.20–5.65 (m, 4 H, H-2,3,4,5), 3.70–4.30 (m, 2 H, CH_2), 2.02, 2.05, 2.06, 2.08, 2.14, 2.15 and 2.21 (7 s, 7 Ac).

Anal. Calc. for $C_{21}H_{29}N_3O_{12}S$: C, 46.06; H, 5.34; N, 7.67; S, 5.86. Found: C, 46.20; H, 5.30; N, 7.87; S, 5.72.

(*b*) Acetic anhydride (75 ml) was added to a suspension of **9** (15.00 g, 32.36 mmol) in anhydrous pyridine (75 ml). The mixture was heated at 110 ±2° for 1.5 h, cooled, and poured into ice and water. The solid was collected by filtration, washed with water, and dried *in vacuo* to give crude (±)-**7** (15.05 g, 84.9%), $[\alpha]_D^{23}$ +83° (*c* 1, chloroform). The crude product was purified as in (*a*) to give pure (+)-**7** (5.70 g, 32.2%), m.p. 217°, $[\alpha]_D^{23}$ +367° (*c* 1, chloroform); λ_{max} 214 (log ε 3.92), 254 (3.78, sh), and 283 nm (3.93); ν_{max} 3260 and 3180 (NH), 1675 (exo Amide I), 1650 (endo Amide I), 1610 (C=N), and 1485 cm^{-1} (Amide II). P.m.r. data: δ 9.59 (s, 1 H, exchangeable with deuterium, NH), 5.83 (d, 1 H, $J_{1,2}$ ~10 Hz, S-C*H*R-N), 4.98–5.52 (m, 4 H, H-2,3,4,5), 3.72–4.34 (m, 2 H, CH_2), 2.04, 2.05, 2.09, 2.11, 2.14, 2.17, and 2.26 (7 s, 7 Ac).

Anal. Calc. for $C_{21}H_{29}N_3O_{12}S$: C, 46.06; H, 5.34; N, 7.67; S, 5.86. Found: C, 45.93; H, 5.32; N, 7.88; S, 5.76.

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