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Note

Substituent effects in the acetylation of acylhydrazones of penta-*O*-acetyl-*aldehydo*-D-galactose

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Acetylation of aldose acylhydrazones may yield 3-acyl-5-alkyl/aryl-2,3-dihydro-2-polyacetoxyalkyl-1,3,4-oxadiazoles instead of diacylhydrazones[1]. Aroylhydrazones give 1,3,4-oxadiazolines because of the formation of the iminol tautomer before the cyclisation[2,3]. More recently, syntheses of other carbohydrate-containing oxadiazolines have been reported[4–7]. The acylation of acylhydrazones is influenced by the substitution pattern of the starting compounds. Thus, isoindoline derivatives[8] are formed from the acylhydrazones of 6-formyl-2,3-dimethoxybenzoic acid (opianic acid). The formation of the iminol tautomer of benzoylhydrazones is influenced by electronic effects, O–O and N–O chelate-formation[9] (for 2-hydroxy derivatives), and by the substituents of the aromatic ring. Although there are known (*p*-acetamido)salicyloylhydrazones of some aldoses[5], their acylation has not been described. The effect of an *o*-hydroxyl group on the acylation of benzoylhydrazones is now reported.

Treatment of 2,3,4,5,6-penta-*O*-acetyl-D-galactose benzoylhydrazone (**2a**) with acetic anhydride in pyridine gave[1] (−)- and (+)-3-acetyl-2-(D-*galacto*-pentaacetoxypentyl)-5-phenyl-1,3,4-oxadiazolines (**3a**). However, under similar conditions, the corresponding *o*-hydroxy compound **2c** gave the bisacylhydrazone **5**. The (−)-diastereoisomer of the oxadiazoline derivative **3e**, the isomer of **5**, was obtained from **2c** either by treatment with acetic anhydride–zinc chloride or with hot acetic anhydride, and the benzoylhydrazone **2a** afforded[1] the (−)- and (+)-diastereoisomers of **3a**. Treatment of **2c** with hot acetyl chloride gave a hexa-acetate which was not the diacylhydrazone **4** but the oxadiazoline (−)-**3c**. Although, unlike **2c**, (−)-**3c** gave a negative reaction with ferric chloride, the presence of a phenolic hydroxyl group was proved by further transformations; negative ferric chloride reactions of 2-hydroxyphenyl derivatives of O,N-[10,11] and N,S-heterocycles[12] have been reported. Thus, with acetic anhydride–pyridine at room temperature, (−)-**3c** gave (−)-**3e**, and dimethyl sulphate transformed it into the 5-(2-methoxyphenyl)-1,3,4-oxadiazoline derivative (−)-**3d**. Compound (−)-**3d** was identical with the

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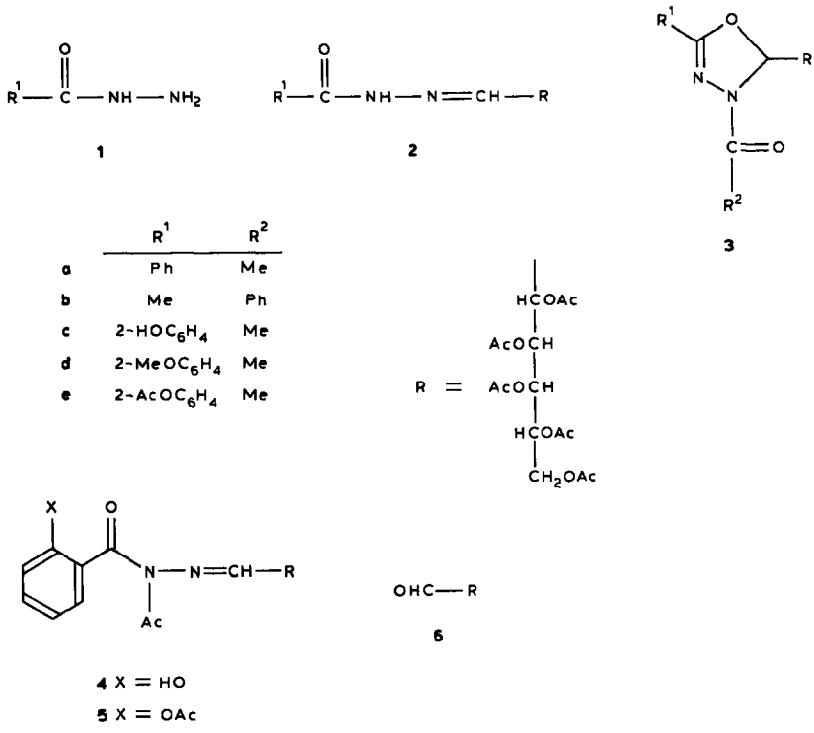

product obtained by treatment of the 2-methoxybenzoylhydrazone **2d** with acetic anhydride–pyridine. Thus, in contrast to 2-hydroxy derivatives, the 2-methoxybenzoylhydrazones give oxadiazolines under mild acetylation conditions.

The oxadiazoline derivative (+)-**3b** can be obtained by treatment of the acetylhydrazone **2b** with benzoyl chloride–pyridine. The differences in structure of the two isomeric oxadiazolines are indicated by the ~30-nm bathochromic shift of the longer wavelength λ_{max} of **3a**, and the higher-field location of the ^{13}C-n.m.r. signal of the methyl group of (+)-**3b** [11.21 p.p.m., characteristic[13] for [O–C(CH_3)=N–] than that of the acetyl groups (~20 p.p.m.).

The effects of thiol and amino groups on the above transformations are being studied.

EXPERIMENTAL

General methods. — Melting points are uncorrected and were determined on a Kofler block. Solutions were concentrated at ⩽40° (bath) at ~17 mmHg. T.l.c. was performed on Alurolle-Kieselgel 60F_{254} (Merck) with 2:1 benzene–ethyl acetate. Optical rotations were measured with a Schmidt–Haensch visual polarimeter (1-dm pathlength). I.r. spectra (KBr discs) were recorded with a Unicam SP-200 spectrophotometer, 100-MHz ^{1}H-n.m.r. spectra with a JEOL JNM-100 spectrometer, and 50.3-MHz ^{13}C-n.m.r. spectra with a Bruker WP-200 SY spectro-

meter for solutions in $CDCl_3$ (internal Me_4Si). Mass spectra (70 eV) were obtained by using a VG-7035 GC/MS/DS instrument (ion current, 0.1 mA; direct-insertion technique).

Methods of acetylation (cf. *Table I*). — (*a*) A solution of the substrate in acetic anhydride and anhydrous pyridine was kept at the temperature stated and then concentrated. The residue was triturated with ice and water. A solution of the crude product in chloroform was treated with fuller's earth and activated carbon, and then concentrated. The residue was crystallised.

(*b*) A solution of the substrate in acetic anhydride was boiled gently for the time stated, then cooled, and poured into ice and water. The crude product was purified as in (*a*).

(*c*) A solution of the substrate in acetyl chloride was boiled for the time stated, then cooled, and concentrated to dryness. A solution of the residue in chloroform was purified as in (*a*).

(*d*) A solution of the substrate and anhydrous zinc chloride in acetic anhydride was kept at room temperature for the time stated and then concentrated. The residue was triturated with ice and water, and purified as in (*a*).

(*e*) A solution of the substrate in benzoyl chloride and pyridine was kept for 2 h at room temperature and for 4 h at 45°, and then concentrated. The residue was poured into ice and excess of aqueous sodium acetate. The product was extracted with chloroform, and the extract was washed successively with cold aqueous $KHSO_4$, water, aqueous $NaHCO_3$, and water, treated with $MgSO_4$, fuller's earth, and activated carbon, and then concentrated. The residue was purified by column chromatography on silica gel, using 9:1 chloroform–acetone, and then recrystallised.

*Penta-*O*-acetyl-*aldehydo-D-*galactose benzoylhydrazone* (**2a**). — Benzoylhydrazine (**1a**; 1.36 g, 10 mmol) was added to a solution of 2,3,4,5,6-penta-*O*-acetyl-D-galactose[14] (**6**; 3.90 g, 10 mmol) in hot ethyl acetate (15 mL). The mixture was heated on a steam bath for 2 h and then cooled. The product was collected, and washed with ethyl acetate and light petroleum. A solution of the crude product (4.42 g, 87%) in hot chloroform was treated with fuller's earth and activated carbon, and then concentrated. The residue was crystallised from ethyl acetate (20 mL) to give **2a** (4.32 g, 85%), m.p. 192° (lit.[15] m.p. 183–184°), $\lambda_{max}^{95\%\ EtOH}$ 254 nm (log ε 4.20); ν_{max}^{KBr} 1658 cm^{-1} (Amide I). ^{1}H-N.m.r. data ($CDCl_3$): δ 9.50 (s, 1 H, NH), 7.76–7.32 (m, 6 H, Ph and CH=N).

*Penta-*O*-acetyl-*aldehydo-D-*galactose acetylhydrazone* (**2b**). — Acetylhydrazine (**1b**; 2.30 g, 31 mmol) was added to a solution of **6** (ref. 14) (11.71 g, 30 mmol) in hot ethyl acetate (50 mL). The mixture was heated on a steam bath for 4 h and then processed as described above, to give **2b** (10.52 g, 78.6%), m.p. 200° (from ethyl acetate) (lit.[16] m.p. 190°), $[\alpha]_D^{23}$ +50.5° (*c* 1, chloroform); $\lambda_{max}^{95\%\ EtOH}$ 233 nm (log ε 4.28); ν_{max}^{KBr} 1687 and 1681 (sh) cm^{-1} (Amide I). ^{1}H-N.m.r. data ($CDCl_3$): δ 6.94 (d, 1 H, J ~5 Hz, CH=N).

*Penta-*O*-acetyl-*aldehydo-D-*galactose 2-hydroxybenzoylhydrazone* (**2c**). —

Salicyloylhydrazine (**1c**; 3.044 g, 20 mmol) was added to a solution of **6** (ref. 14) (7.806 g, 20 mmol) in hot ethyl acetate (30 mL). The mixture was heated on a steam bath for 1 h, then cooled, and processed as described above, to yield **2c** (9.55 g, 91%), m.p. 195–197° (from ethyl acetate), which gave an intense violet colour with ethanolic ferric chloride; $\lambda_{max}^{95\%\ EtOH}$ (log ε) 210 (4.27), 227 (4.19), 242 (4.15), 259 (4.15), 312 (3.62), and 345 (sh) nm (3.56); ν_{max}^{KBr} 3420 (OH), 3240 (NH), 1750 (OAc), 1650 (Amide I), 1602 (Ar), and 1550 cm^{-1} (Amide II). ^{1}H-N.m.r. data (200 MHz, $CDCl_3$): δ 9.26 (s, 1 H, exchangeable with D_2O, OH, or NH), 7.54–7.40 (m, 3 H, CH=N and 2 H–Ar), 7.02–6.81 (m, 2 H, H–Ar), 5.63–5.30 (m, 4 H, H-2,3,4,5 of galactose), 4.33–3.85 (m, 2 H, CH_2), 2.19, 2.15, 2.12, 2.10, and 2.05 (5 s, 15 H, 5 Ac). Mass spectrum: *m/z* 524 (M^+).

Anal. Calc. for $C_{23}H_{28}N_2O_{12}$: C, 52.67; H, 5.38; N, 5.34. Found: C, 52.78; H, 5.43; N, 5.28.

*Penta-*O*-acetyl-*aldehydo-D-*galactose 2-methoxybenzoylhydrazone* (**2d**). — 2-Methoxybenzoylhydrazine (**1d**; 1.66 g, 10 mmol) was added to a solution of **6** (ref. 14) (3.90 g, 10 mmol) in hot ethyl acetate (20 mL). The mixture was heated on a steam bath for 1.5 h and then processed as described above, to give **2d** (3.83 g, 71%), m.p. 169° (from ethyl acetate), $[\alpha]_D^{23}$ +33° (*c* 1, chloroform); $\lambda_{max}^{95\%\ EtOH}$ (log ε); 209 (4.36), 250 (4.14), 300 (sh) nm (3.60); ν_{max}^{KBr} 3295 (NH), 2840 (OMe), 1762–1740 (OAc), 1680–1660 (Amide I), 1602 (Ar), and 1533 cm^{-1} (Amide II). ^{1}H-N.m.r. data ($CDCl_3$): δ 10.61 (s, 1 H, exchangeable with D_2O, NH), 8.16–6.89 (m, 5 H, CH=N and H–Ar), 5.64–5.25 (m, 4 H, H-2,3,4,5 of galactose), 4.36–3.76 (m, 2 H, CH_2), 3.94 (s, 3 H, OMe), 2.14–2.02 (5 Ac). Mass spectrum: *m/z* 539 ($M^+ + 1$).

Anal. Calc. for $C_{24}H_{30}N_2O_{12}$: C, 53.53; H, 5.62; N, 5.20. Found: C, 53.56; H, 5.61; N, 5.14.

*(−)-3-Acetyl-2,3-dihydro-5-(2-methoxyphenyl)-2-(*D-galacto-*penta-acetoxypentyl)-1,3,4-oxadiazole* [(−)-**3d**]. — A mixture of (−)-**3c** (0.113 g, 0.2 mmol), acetone (2.5 mL), dimethyl sulphate (0.052 g, 0.4 mmol), and powdered anhydrous K_2CO_3 (0.055 g, 0.4 mmol) was boiled under reflux for 8 h, and then kept for 20 h at room temperature. The solids were collected and washed with chloroform, and the combined filtrate and washings were diluted with chloroform, washed with aqueous $KHCO_3$ and water, dried ($MgSO_4$), treated with fuller's earth and activated carbon, and concentrated to dryness. Recrystallisation of the residue from ethyl acetate (1 mL)–heptane (4 mL) afforded (−)-**3d** (0.097 g, 84%), m.p. 170°, $[\alpha]_D^{23}$ −199° (*c* 0.96, chloroform), which was identical with the product obtained by treatment of **2d** with acetic anhydride–anhydrous zinc chloride (see Tables I and II).

TABLE I

PREPARATION AND PHYSICAL DATA OF **3a–e** AND **5**

Product	*Starting material (mmol)*	*Acylation agent (mL)*	*Solvent (mL)*	*Reaction time Temp.)*[a]	*Method of prepa-ration*[b]	*Yield (%) [crude (pure)]*	*M.p.*[h] *(degrees)*	$[\alpha]_D^{23}$ *(c 1, chloroform) (degrees)*	*Formula*	*Anal.: found (calc.) Mass spectra*
3a	**2a** (39.3)	Ac_2O (200) $ZnCl_2$ (40 g)	—	18 h	(*d*)	87[c]	148 (from EtOAc)	−209	$C_{25}H_{30}N_2O_{12}$	N, 5.18 (5.09) *m/z* 550 (M^+)
	2a (3.93)	Ac_2O (20)	Pyridine (10)	18 h	(*a*)	92[d]	130	+230		N, 5.12 (5.09)
3b	**2b** (10)	PhCOCl (5)	Pyridine (25)	2 h and 4 h (45°)	(*e*)	(35)	133–134	+207.5	$C_{25}H_{30}N_2O_{12}$	C, 54.76 (54.54) H, 5.50 (5.49) N, 5.09 (5.09)
3c	**2c** (38.13)	AcCl (60)	—	5 h (b.p.)	(*c*)	78	130–132	−182	$C_{25}H_{30}N_2O_{13}$	N, 5.01 (4.95) *m/z* 567 (M^++1)
3d[e]	**2d** (0.93)	Ac_2O (10) $ZnCl_2$ (1 g)	—	18 h	(*d*)	92 (57)	171	−199	$C_{26}H_{32}N_2O_{13}$	C, 54.06 (53.79) H, 5.62 (5.56) N, 4.81 (4.83)
	2d (3.7)	Ac_2O (40)	Pyridine (15)	2 h[f] (b.p.)	(*a*)	62 (50)	171 (from EtOAc)	−194		
3e[g]	**2c** (0.95)	Ac_2O (5)	—	2 h (b.p.)	(*b*)	68 (37)	167.5		$C_{27}H_{32}N_2O_{14}$	N, 4.68 (4.60)
	2c (19.1)	Ac_2O (200) $ZnCl_2$ (20 g)	—	24 h	(*d*)	84 (52)	167–168	−179		*m/z* 608 (M^+)
	(−)-**3c** (0.53)	Ac_2O (1.5)	Pyridine (1.5)	48 h	(*a*)	96 (88)	168	−179		
5	**2c** (11.44)	Ac_2O (30)	Pyridine (18)	20 h	(*a*)	80 (58)	143 (from EtOAc)	+26	$C_{27}H_{32}N_2O_{14}$	N, 4.62 (4.60) *m/z* 608 (M^+)

[a]Room temperature unless stated otherwise. [b]See Experimental. [c]The $[\alpha]_D$ value indicated a ~7:3 mixture of the (−)- and (+)-diastereoisomers. [d]The $[\alpha]_D$ value indicated a ~2:3 mixture of the (−)- and (+)-diastereoisomers. [e]On the basis of m.p., $[\alpha]_D$, t.l.c., i.r., and ^{1}H-n.m.r. data identical with the product obtained by the methylation of (−)-**3c** (see Experimental). [f]When kept for 16 h at room temperature and processed as in method (*a*), 61% of **2d** was recovered. [g]On the basis of m.p., $[\alpha]_D$, t.l.c., i.r., and ^{1}H-n.m.r. data, the products obtained from **2c** and (−)-**3c** were identical. [h]Recrystallised from EtOAc–heptane unless stated otherwise.

TABLE II

U.V., I.R., AND ^{1}H-N.M.R. DATA FOR **3a–e**, AND **5**

Compound	$\lambda_{max}^{95\%\ EtOH}$ *[nm (log ε)]*	ν_{max}^{KBr} *(cm^{-1})*	*δ (100 MHz, $CDCl_3$) (p.p.m.)*
(−)-**3a**	221 (4.12), 288 (4.18)	1760–1750 (OAc), 1679 and 1653 (amide) 1640 (C=N), 1580 (Ar)	6.38 (s, 1 H, O–C*H*R–N) 2.22–1.91 (6 Ac)
(+)-**3a**		1755–1745 (OAc), 1678 (amide) 1635 (C=N), 1575 (Ar)	6.20 (d, 1 H, *J* ~6 Hz, O–C*H*R–N) 2.22–1.98 (6 Ac)
(+)-**3b**	227 (4.00), 255 (3.91)	1755–1745 (OAc), 1660 and 1653 (amide) 1603 and 1580 (Ar)	6.33 (d, 1 H, *J* ~6 Hz, O–C*H*R–N)[a] 2.15–2.00 (Me–C=N and 5 Ac)
(−)-**3c**	265 (sh) (3.86), 277 (3.97), 289 (3.96), 313 (3.94), 328 (sh) (3.80)	3280 (OH), 1750 (OAc), 1675 (amide) 1630 (C=N), 1610 (Ar)	8.74 (s, 1 H, OH), 6.42 (s, 1 H, O–C*H*R–N) 2.24–1.78 (6 Ac)
(−)-**3d**	277 (4.01), 289 (4.01), 305 (4.00)	1758–1739 (OAc), 1676 (amide) 1624 (C=N), 1603 (Ar)	6.38 (s, 1 H, O–C*H*R–N)[b] 3.90 (s, 3 H, OMe) 2.23–1.98 (6 Ac)
(−)-**3e**	222 (3.53), 288 (3.56)	1755 (OAc), 1675 (amide) 1627 (C=N), 1610 (Ar)	6.32 (s, 1 H, O–C*H*R–N) 2.30–1.95 (7 Ac)
5	239 (3.96) inflexion 250 (sh) (3.93)	1750 (OAc), 1708 (CO–N–CO) 1637 (C=N), 1602 (Ar)	7.81 (d, 1 H, *J* ~4 Hz, CH=N) 2.41–2.00 (7 Ac)

[a] ^{13}C-N.m.r. data (50.3 MHz, $CDCl_3$): δ 88.15 (O–CHR–N), 11.21 (O–C*Me*=N). [b] 200 MHz: δ 6.41 (s, 1 H, O–C*H*R–N), 3.93 (s, 3 H, OMe), 2.27–2.00 (6 Ac).

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