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STEREOCHEMICAL ASPECTS OF THE FORMATION OF DIASTEREOISOMERIC 3-ACETYL-2-(POLYACETOXYALKYL)-5-PHENYL-2,3-DIHYDRO-1,3,4-OXADIAZOLES

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ABSTRACT

The synthesis of D- and L-3-acetyl-2-[*arabino*-(tetra-acetoxybutyl)]- [(−)- and (+)-**4a**, (−)-**4b**] and 3-acetyl-2-[D-*manno*-(penta-acetoxypentyl)]-5-phenyl-2,3-dihydro-1,3,4-oxadiazoles [(+)-**4d**] *via* cyclisation of the corresponding (*O*-acetylated) aldose benzoylhydrazones (**2a,b,d**) under acetylating conditions is described. The stereochemical aspects of the formation of C-2 epimeric oxadiazolines [*e.g.*, (−)- and (+)-**4a**] are discussed on the basis of optical rotation and n.m.r. data. The acetylation of methylglyoxal bis(benzoylhydrazone) (**8**) was found to give diastereoisomeric 1,3,4-oxadiazolines (**12a** and **12b**) instead of the bis(acetylbenzoylhydrazone) **9** claimed in the literature.

INTRODUCTION

Acetylation of aldose aroylhydrazones (unlike alkanoylhydrazones), even under mild reaction conditions, may afford 5-substituted-3-acetyl-2-(polyacetoxyalkyl)-2,3-dihydro-1,3,4-oxadiazoles, instead of the isomeric *N,N*-diacylhydrazones[1–3]. Further studies were also published from another laboratory[4–6], without optical rotatory data.

Acetylation of D-galactose[1,2] and L-rhamnose (6-deoxy-L-mannose)[3] derivatives gave the levorotatory oxadiazolines [*e.g.*, (−)-**4c**, (−)-**6c**, and (−)-**4e**, respectively]. The chirality of D-galactose and 6-deoxy-L-mannose at C-2 [*i.e.*, C-1′ in (polyacetoxyalkyl)oxadiazolines] is (*R*). The aim of the study now reported was to find a correlation between the C-1′ chirality and the optical rotation of C-2 diastereoisomeric oxadiazolines.

DISCUSSION

Treatment of 2,3,4,5-tetra-*O*-acetyl-D-arabinose benzoylhydrazone [**2a**, with 1′(*S*) chirality] with acetic anhydride–zinc chloride gave a crude 1.5:1 mixture of (+)- and (−)-**4a** diastereoisomers (on the basis of optical rotation and ^{1}H-n.m.r.

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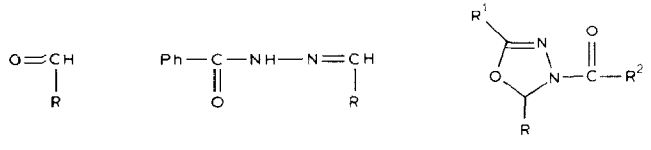
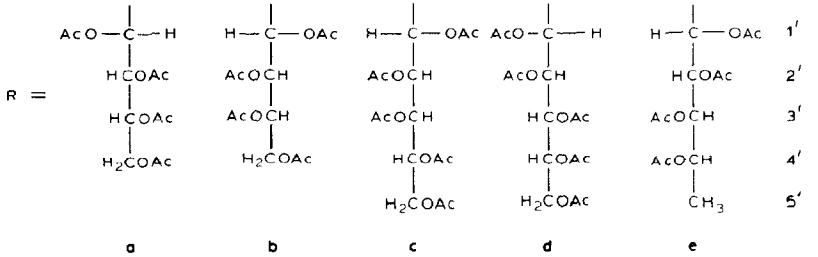


1 2

	R^1	R^2
3	Me	Ph
4	Ph	Me
5	2-HOC_6H_4	Me
6	2-$AcOC_6H_4$	Me
7	2-$MeOC_6H_4$	Me



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data for the O–C*H*R–N unit). The higher melting, less-soluble, pure (+)-D isomer gave m.p., $[\alpha]_D$, and i.r. and ^{1}H-n.m.r. spectral data similar to those of the (−)-**4b** enantiomer, obtained from the L-arabinose derivative **2b** [1′(*R*) chirality] (Table I).

Acetylation of D-mannose benzoylhydrazone in the presence of pyridine gave 2,3,4,5,6-penta-*O*-acetyl-D-mannose benzoylhydrazone [**2d** with 1′(*S*) chirality], treatment of which with acetic anhydride–zinc chloride gave the (+)-**4d** oxadiazoline.

The data in Table I indicate, for the diastereoisomerically pure 2-(polyacetoxyalkyl)-1,3,4-oxadiazolines, that (*a*) the higher melting, less-soluble diastereoisomers of 1′(*R*) chirality are levorotatory and dextrorotatory for 1′(*S*) chirality (the opposite is true for the optical rotation of the lower melting, more-soluble diastereoisomers), (*b*) the ^{1}H-n.m.r. O–C*H*R–N signals of the higher melting [(−)-1′(*R*) and (+)-1′(*S*)] isomers are broad singlets, but doublets ($J_{2,1'} \sim 6$ Hz) for the lower melting [(+)-1′(*R*), or (−)-1′(*S*)] isomers.

For the C-2 epimers of thiazolidine[7,8] and benzothiazoline[9,10], the levorotatory isomers are 2(*S*) and the dextrorotatory are 2(*R*) at the S–C*H*R–N centre. Since replacement of sulphur by oxygen in this subunit does not change the chirality, it is probable that the levorotatory oxadiazoline derivatives are 2(*S*) and the dextrorotatory isomers are 2(*R*). From the $[\alpha]_D$ and C-1′ chirality data in Table I, it seems that the formation of 1,3,4-oxadiazoline diastereoisomers of C-2 chirality opposite to that of C-1′[(+)-2(*R*)1′(*S*) or (−)-2(*S*)1′(*R*)] is favoured on acetylation.

Space-filling models suggest that, due to steric requirements, the *N*-acetyl

TABLE I

M.P., $[\alpha]_D$, AND SELECTED ^{1}H-N.M.R. (H-2) DATA

Compound		*M.p. (degrees)*	$[\alpha]_D^{23}$[a] *(degrees)*	*Configuration* C-2[b]	C-1'[c]	*δ(CDCl$_3$)(p.p.m.) O-CHR-N ($J_{2,1'}$ in Hz)*
(+)-**3c**[2]	(D-*galacto*)	133–134[d]	+207.5	(*R*)	(*R*)	6.33 (d, ~6)[e]
(−)-**4a**	(D-*arabino*)	95[f]	−213	(*S*)	(*S*)	6.33 (d, 6)[h]
(+)-**4a**	(D-*arabino*)	121[f,g]	+229	(*R*)	(*S*)	6.51 (bs)[h,i]
(−)-**4b**	(L-*arabino*)	121[f,g]	−229	(*S*)	(*R*)	6.51 (bs)[h,i]
(−)-**4c**[1,2]	(D-*galacto*)	148[j]	−209	(*S*)	(*R*)	6.38 (bs)[e]
(+)-**4c**[1,2]	(D-*galacto*)	130[d]	+230	(*R*)	(*R*)	6.20 (d, ~6)[e]
(+)-**4d**	(D-*manno*)	111[g,k]	+233	(*R*)	(*S*)	6.22 (bs)[h,i]
(−)-**4e**[3]	(6-deoxy-L-*manno*)	156[l]	−256	(*S*)	(*R*)	6.23 (bs)[e]
(−)-**5c**[2]	(D-*galacto*)	130–132[d]	−182	(*S*)	(*R*)	6.42 (bs)[e]
(−)-**6c**[2]	(D-*galacto*)	168[d]	−179	(*S*)	(*R*)	6.32 (bs)[e]
(−)-**7c**[2]	(D-*galacto*)	171[d]	−199	(*S*)	(*R*)	6.38 (bs)[e]

[a]In chloroform (*c* 1). [b]Inferred for C-2 of the oxadiazoline ring. [c]Known for C-2 of the aldose. [d]From EtOAc–heptane. [e]100 MHz. [f]From EtOH–water. [g]From EtOH–hexane. [h]200 MHz. [i]From the signal of H-1' ($J_{2,1'} < 1$ Hz). [j]From EtOAc. [k]From EtOH. [l]From di-isopropyl ether.

group and the 2-(polyacetoxyalkyl) side-chain are probably on oppposite sides of the oxadiazoline ring. For the sterically favoured conformation with synclinal H-2 and R′ [R′ is the remainder of the (polyacetoxyalkyl) side-chain which starts with C-2′], the 2(*R*)1′(*S*) or 2(*S*)1′(*R*) configuration and the H-2–H-1′ φ ~90° dihedral angle (see Fig. 1, **A**) are reflected in the broad singlets ($J_{2,1'} \not> 1$ Hz) (Table I and Experimental) for H-2 in the ^{1}H-n.m.r. spectra. For compounds of structure **B** in Fig. 1 [2(*S*)1′(*S*) or 2(*R*)1′(*R*)], this signal is a doublet ($J_{2,1'}$ 6 Hz). In molecules with the 2(*R*)1′(*S*) configuration, the carbonyl group of OAc-1′ is near to the *ortho*-protons of the phenyl group and this results in a 0.08 p.p.m. up-field shift of their signals in the spectrum of the (+)-**4a** D-arabinose derivative compared to that of the (−)-**4a** [2(*S*)1′(*S*)] diastereomer. Similary, for the D-galactose derivatives, the multiplet of the two *ortho*-protons of the phenyl group of (−)-**4c** [2(*S*)1′(*R*)] compound is shifted upfield by 0.15 p.p.m. compared to the signals of the (+)-**4c** [2(*R*)1′(*R*)] isomer. The molecular models, the $J_{2,1'}$ values in the ^{1}H-n.m.r. spectra, and the upfield shift data for the resonances of the *ortho*-protons corroborate the view that the levorotatory oxadiazolines are 2(*S*) and the dextrorotatory compounds are 2(*R*).

Since acetic anhydride–zinc chloride transforms (−)-**4a** to an ~4:1 mixture of (+)-**4a** and (−)-**4a** (on the basis of ^{1}H-n.m.r. O–C*H*R–N signals), it can be concluded that the formation of diastereoisomeric 1,3,4-oxadiazolines takes place under thermodynamic control.

The reaction of methylglyoxal bis(benzoylhydrazone) [**8**, ν_{max}^{KBr} 1673 cm^{-1} (CON)] with hot acetic anhydride was claimed[11] to yield methylglyoxal bis(acetylbenzoylhydrazone) [**9**, ν_{max}^{KBr} 1680 cm^{-1} (CON)]. However, the reported[11] low ν_{CON} value for **9** (only 7 cm^{-1} higher than that of the starting **8**) and findings[1–3,12] for the ready formation of oxadiazoline derivatives starting both from aldehyde and ketone aroylhydrazones raise doubts about structure **9**.

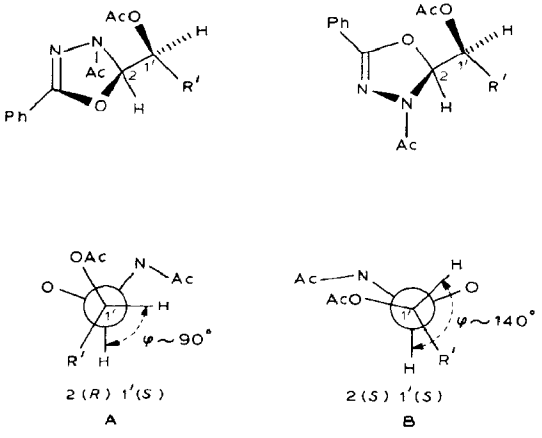
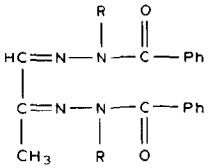


Fig. 1. Steric representation of 2(*R*)1′(*S*) and 2(*S*)1′(*S*) 3-acetyl-2-(polyacetoxyalkyl)-2,3-dihydro-1,3,4-oxadiazole diastereoisomers.

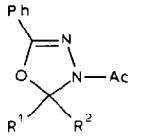
Since it is possible that acylation of 1,2-bis(acylhydrazones) may also yield 1,3,4-oxadiazoline derivatives (*e.g.*, **12**), the acetylation of methylglyoxal 1,2-bis-(benzoylhydrazone) (**8**) was re-investigated.

Acetylation of **8** (prepared from methylglyoxal dimethyl acetal) with boiling acetic anhydride gave a crude product which contained (t.l.c.) two major components. Column chromatography afforded two compounds with m.p. 155° and ν_{max}^{KBr} 1679 cm^{-1} (amide) (which are similar to the reported[11] values for **9**), and m.p. 140–141° and ν_{max}^{KBr} 1692 and 1677 cm^{-1} (amide). These products were also formed when **8** was treated with acetic anhydride–trifluoroacetic acid at ambient temperature. Longer reaction time or an increase in the amount of trifluoroacetic acid increased the proportion of the latter product. The u.v. spectra, composition, and molecular weight (the same as those of **9**, see Experimental) of the two products were identical. Structures **12a,b**, were established by the ^{13}C-n.m.r. spectra. The signals for the O–*C*RR′–NAc should appear in the region δ 102–88. In the ^{13}C-n.m.r. spectra of 3-acetyl-2,2-dimethyl-5-phenyl-2,3-dihydro-1,3,4-oxadiazole[13] (**10**) and the 2-methyl-2-(*p*-bromophenyl) analogue **11**, the signals of O–*C*R^1R^2–NAc appeared at δ 100.04[14] and 99.97, respectively. This chemical shift is characteristic of other 2,2-disubstituted 1,3,4-oxadiazoline derivatives[12,15]. Consequently, the signals for **12a** and **12b** at δ 101.60 and 99.97, respectively, are due to a O–*C*RCH_3–N, whereas those at δ 88.72 and 88.01, respectively, are due to O–*C*HR–N. Thus, the above two products of the acetylation of **8** are the racemic (2*R*, 2′*R*)-(2*S*,2′*S*) and (2*R*,2′*S*)-(2*S*,2′*R*) bi-oxadiazoline diastereomers **12.**



8 R = H

9 R = Ac

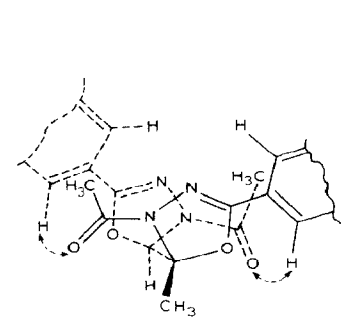


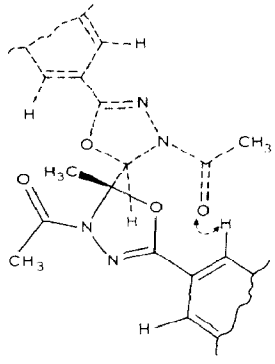
	R^1	R^2
10	Me	Me
11	Me	4-BrC_6H_4

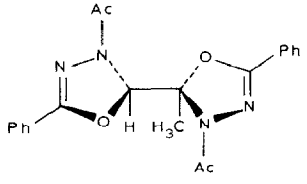
Molecular models were used to study the possibility of placing the aromatic *ortho*-protons in the proximity of one or both NAc carbonyl groups. The *ortho*-protons can come into close proximity to the shielding cones of *both* Ac groups in the 2(*R*)2′(*R*) structure with H-2 and CH_3-2′ synclinal [**12a**, and the corresponding 2(*S*)2′(*S*) compound]. Although the *cis*-orientation of the hetero rings involves a higher energy state, this conformation would allow the oxadiazoline rings to be formed from opposite directions with the acetyl groups on opposite sides of the molecule, thus making it the favoured structure. For the 2(*R*)2′(*S*) configuration [**12b**, or the 2(*S*)2′(*R*) compound] and the conformers with N-3 and N-3′ antiperiplanar or anticlinal (synclinal O-1 and CH_3-2′), only the N-3 acetyl group can come into close proximity to the aromatic *ortho*-protons. Thus, the compound of higher

R_F and melting point, for which the resonances of the *ortho*-protons were shifted upfield, is probably the racemate with the 2(*R*)2′(*R*) (**12a**) and 2(*S*)2′(*S*) configurations. The lower-melting product with the resonances of 2 aromatic protons shifted upfield could be the racemate with the 2(*R*)2′(*S*) (**12b**) and 2(*S*)2′(*R*) configurations.

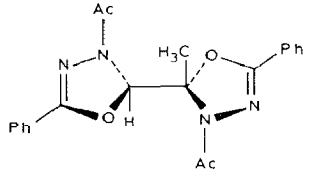
Thus, the acetylation of **8** affords 1,3,4-oxadiazolines **12a,b** and *not* the reported bis(acetylbenzoylhydrazone) **9**. This possibility must be taken into account also in the acylation reaction of aldosulose bis(acylhydrazones), when the formation of 1,3,4-oxadiazolines may replace the diacylhydrazone-forming reaction.







2(*R*) 2′(*R*)
12a



2(*R*) 2′(*S*)
12b

EXPERIMENTAL

General methods. — Melting points are uncorrected and were determined on a Kofler block. Solutions were concentrated at $\gtrless 40°$ (bath) under diminished pressure. T.l.c. was performed on Alurolle-Kieselgel $60F_{254}$ (Merck), using benzene–ethyl acetate mixtures (*A*, 3:1; *B*, 2:1), chloroform–acetone mixtures (*C*, 95:5; *D*, 9:1), and chloroform–ether mixtures (*E*, 95:5; *F*, 9:1). Optical rotations were measured with a Schmidt–Haensch visual polarimeter (1-dm pathlength). I.r. spectra (KBr discs) were recorded with a Perkin–Elmer 283 B spectrophotometer, and 200-MHz ^{1}H- and 50.3-MHz ^{13}C-n.m.r. spectra with a Bruker WP 200 SY spectrometer 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).

*2,3,4,5-Tetra-*O*-acetyl-*D*-arabinose benzoylhydrazone* (**2a**). — Benzoylhydrazine (3.404 g, 25 mmol) was added to a solution of 2,3,4,5-tetra-*O*-acetyl-D-arabi-

nose[16] (**1a**; 7.96 g, 25 mmol) in hot ethyl acetate (10 mL). The mixture was heated on a steam bath for 30 min and then cooled. The product was collected and washed with 1:2 and 1:4 mixtures of ethyl acetate–heptane, to give **2a** (10.35 g, 94.9%), m.p. 157°; lit.[17] L enantiomer, m.p. 153° (from methanol–water).

*2,3,4,5-Tetra-*O*-acetyl-*L*-arabinose benzoylhydrazone* (**2b**). — As described above for the D enantiomer, 2,3,4,5-tetra-*O*-acetyl-L-arabinose (**1b**; 7.96 g, 25 mmol; prepared according to ref. 16) was condensed with benzoylhydrazine to give **2b** (10.60 g, 97%), m.p. 155°; lit.[17] m.p. 153° (from methanol–water).

*2,3,4,5,6-Penta-*O*-acetyl-*D*-mannose benzoylhydrazone* (**2d**). — D-Mannose benzoylhydrazone[17] (5.15 g, 17.26 mmol) in anhydrous *N,N*-dimethylformamide (52 mL) was treated with acetic anhydride (14 mL) and anhydrous pyridine (17 mL) according to ref. 17, to give crude (6.46 g, 73.6%) or pure **2d** (6.01 g, 68.5%), m.p. 135–136° (from aqueous methanol), $[\alpha]_D^{23}$ +24.5° (*c* 1, chloroform) [prepared from 2,3,4,5,6-penta-*O*-acetyl-D-mannose (**1d**), amorphous **2d** had[3] $[\alpha]_D^{23}$ +24° (*c* 1, chloroform)]; ν_{max}^{KBr} 3303 (NH), 1745 and 1730 (OAc), 1668 (Amide-I), 1601 (C=N), 1580 (Ar), and 1530 cm^{-1} (Amide-II). 200-MHz ^{1}H-n.m.r. data ($CDCl_3$): δ 7.81–7.78 (m, 2 H, H-Ar), 7.58–7.40 (m, 4 H, 3 H-Ar and CH=N), 5.50–5.45 (m, 3 H, H-2,3,4), 5.22–5.13 (m, 1 H, H-5), 4.29–4.06 (m, 2 H, CH_2), 2.14–2.06 (15 H, 5 Ac). Mass spectrum: *m/z* 509 ($M^+ + 1$), 508 (M^+), 147 (CH=N–NH–Bz), 105 ($\overset{+}{O}\equiv$C–Ph).

Anal. Calc. for $C_{23}H_{28}N_2O_{11}$: C, 54.33; H, 5.55; N, 5.51. Found: C, 54.27; H, 5.71; N, 5.42.

*3-Acetyl-5-phenyl-2-(*D*-arabino-tetra-acetoxybutyl)-2,3-dihydro-1,3,4-oxadiazoles* [(−)- *and* (+)-**4a**]. — Compound **2a** (8.00 g, 18.33 mmol) was stirred with a solution of anhydrous zinc chloride (16.00 g) in acetic anhydride (160 mL) until dissolution was complete. The solution was kept for 16 h at room temperature, then concentrated. The residue was triturated with ice and water, and dissolved in chloroform. The chloroform solution was washed with aqueous sodium hydrogencarbonate and water, dried ($MgSO_4$), treated with fuller's earth and charcoal, and then concentrated to a solid glass, $[\alpha]_D^{23}$ +74.5° (*c* 1, chloroform). On the basis of optical rotation and ^{1}H-n.m.r. data, this was an ~1.5:1 mixture of the title compounds, together with two minor components (t.l.c.). After column chromatography (silica gel, solvent *A*), the fraction that was homogeneous in t.l.c. (solvents *B* or *D*) but contained (^{1}H-n.m.r.) both diastereoisomers was evaporated and the residue treated with ether to give crude (+)-**4a** (4.46 g, 50.9%), m.p. 102–111°. From the mother liquor, the crude (−)-**4a** (0.96 g, 10.9%), m.p. 92–93°, was obtained. Recrystallisation of the crude (+)-isomer from acetone and aqueous ethanol afforded (+)-**4a** (3.77 g, 43%), m.p. 121°, $[\alpha]_D^{23}$ +229° (*c* 1, chloroform); ν_{max}^{KBr} 1759, 1753, and 1739 (OAc), 1685 (NAc), 1624 (C=N), 1576 cm^{-1} (Ar). The 200-MHz ^{1}H-n.m.r. spectrum ($CDCl_3$) is identical with that of the enantiomer (−)-**4b** (see below).

Anal. Calc. for $C_{22}H_{26}N_2O_{10}$: C, 55.22; H, 5.48; N, 5.86. Found: C, 55.40; H, 5.46; N, 5.89.

Recrystallisation of the crude (−)-isomer from ethanol–water afforded (−)-**4a** (0.66 g, 7.53%), m.p. 94.5–95°, $[\alpha]_D^{23}$ −213° (*c* 1, chloroform); ν_{max}^{KBr} 1755 and

1748 (OAc), 1677 (NAc), 1631 (C=N), 1575 cm^{-1} (Ar). 200-MHz ^{1}H-N.m.r. data ($CDCl_3$): δ 7.88–7.83 (m, 2 H, *o,o*-H-Ar), 7.57–7.42 (m, 3 H, H-Ar), 6.33 (d, 1 H, $J_{2,1'}$ 6 Hz, O-CHR-N), 5.64 (dd, 1 H, $J_{1',2'}$ 3, $J_{2',3'}$ 8.5 Hz, H-2'), 5.49 (dd, 1 H, $J_{2,1'}$ 6, $J_{1',2'}$ 3 Hz, H-1'), 5.29–5.21 (m, 1 H, H-3'), 4.27–4.02 (m, 2 H, CH_2), 2.30 (s, 3 H, NAc), 2.11, 2.08, 2.05, 2.03 (4 s, each 3 H, 4 AcO). Mass spectrum: *m/z* 478 (M^+), 437 ($M^+ + 1 - CH_2CO$), 376 ($M^+ - CH_2CO - AcOH$), 316 ($M^+ - CH_2CO - 2\ AcOH$), 189 (3-acetyl-5-phenyl-1,3,4-oxadiazole$^+$), 147 (base peak, 2-phenyl-1,3,4-oxadiazole$^+ + 1$).

Anal. Found; C, 55.20; H, 5.43; N, 5.81.

*Transformation of (−)-***4a** *into (+)-***4a**. — Compound (−)-**4a** (0.101 g) was added to a solution of anhydrous zinc chloride (0.20 g) in acetic anhydride (2 mL). The solution was kept for 22 h at 41 ± 1° (bath), then cooled, and poured onto ice and water. The mixture was neutralized with sodium hydrogencarbonate and partitioned with chloroform. The organic layer was washed with water, dried ($MgSO_4$), treated with fuller's earth and charcoal, and then concentrated. The amorphous, strongly dextrorotatory, crude product (0.094 g) was an ~ 4:1 mixture of (+)- and (−)-**4a** on the basis of the integrals of O–C*H*R–N signals at δ 6.50 (bs) and 6.33 (d, $J_{2,1'}$ 6 Hz), respectively.

*(−)-3-Acetyl-2-(*L-arabino-*tetra-acetoxybutyl)-5-phenyl-2,3-dihydro-1,3,4-oxadiazole* [(−)-**4b**]. — The title compound was synthesised and purified by column chromatography as given above for the D isomer, starting from compound **2b** (6.00 g, 13.75 mmol), to yield (−)-**4b** (2.57 g, 39%), m.p. 121° (from aqueous ethanol), $[\alpha]_D^{23}$ −229° (*c* **1**, chloroform); ν_{max}^{KBr} 1758, 1752, and 1738 (OAc), 1684 (NAc), 1623 (C=N), 1575 cm^{-1} (Ar) [identical with that for (+)-**4a**]. 200-MHz ^{1}H-N.m.r. data ($CDCl_3$): δ 7.80–7.75 (m, 2 H, *o,o*-H-Ar), 7.53–7.42 (m, 3 H, H-Ar), 6.51 (bs, 1 H, O–CHR–N), 5.78 (dd, 1 H, $J_{2,1'}$ 1, $J_{1',2'}$ 2.8 Hz, H-1'), 5.65 (dd, 1 H, $J_{1',2'}$ 2.8, $J_{2',3'}$ 9 Hz, H-2'), 5.21–5.13 (m, 1 H, H-3'), 4.29–4.26 (m, 2 H, CH_2), 2.26, 2.24, 2.11, 2.07, and 1.94 (5 s, each 3 H, NAc and 4 AcO), identical with those of the enantiomer (+)-**4a**. Mass spectrum: *m/z* 478 (M^+), 376 ($M^+ - CH_2CO - AcOH$), 316, 189, and 147 [as assigned for the fragments of (−)-**4a**].

Anal. Calc. for $C_{22}H_{26}N_2O_{10}$: C, 55.22; H, 5.48; N, 5.86. Found: C, 55.37; H, 5.39; N, 5.82

*(+)-3-Acetyl-2-(*D-manno-*penta-acetoxypentyl)-5-phenyl-2,3-dihydro-1,3,4-oxadiazole* [(+)-**4d**]. — (*a*) Powdered D-mannose benzoylhydrazone[17] (2.983 g, 10 mmol) was stirred, under cooling with ice, with a solution of anhydrous zinc chloride (3 g) in acetic anhydride (30 mL) until dissolution was complete. The solution was kept for 18 h at room temperature, then poured onto ice and water. The product was partitioned in chloroform, and the organic layer was washed with aqueous sodium hydrogencarbonate and water, dried ($MgSO_4$), treated with fuller's earth and activated carbon, and then concentrated. Purification of the solid residue { 5.906 g, $[\alpha]_D^{23}$ +82° (*c* 1, chloroform)} by column chromatography (silica gel, solvent *C*), with subsequent crystallisation from anhydrous ethanol–hexane, afforded (+)-**4d** (1.82 g, 33%), m.p. 111°, $[\alpha]_D^{23}$ +233° (*c* 1, chloroform); ν_{max}^{KBr} 1750 and 1735 (OAc), 1664

(NAc), 1628 (C = N), 1575 cm^{-1} (Ar). 200-MHz ^{1}H-N.m.r. data ($CDCl_3$): δ 7.89–7.84 (m, 2 H, *o,o*-H-Ar), 7.55–7.42 (m, 3 H, H-Ar), 6.22 (bs, 1 H, O-CHR-N), 5.66 (dd, 1 H, $J_{1',2'}$ 9.5, $J_{2',3'}$ 2 Hz, H-2'), 5.52 (dd, 1 H, $J_{2,1'}$ 0.8, $J_{1',2'}$ 9.5 Hz, H-1'), 5.44 (dd, 1 H, $J_{2',3'}$ 2, $J_{3',4'}$ 9 Hz, H-3'), 5.16–5.07 (m, 1 H, H-4'), 4.26–4.00 (m, 2 H, CH_2), 2.24, 2.18, 2.11, 2.10, 2.04, and 1.93 (6 s, each 3 H, NAc and 5 AcO). Mass spectrum: *m/z* 550 (M^+), 508 ($M^+ - CH_2CO$), 448 ($M^+ - CH_2CO - AcOH$), 189 and 147 [as assigned for the fragments of (−)-**4a**].

Anal. Calc. for $C_{25}H_{30}N_2O_{12}$: C, 54.54; H, 5.49; N, 5.09. Found: C, 54.75; H, 5.59; N, 5.08.

(*b*) A solution of **2d** (2.7 g, 5.31 mmol) and anhydrous zinc chloride (2.7 g) in acetic anhydride (27 mL) was kept for 20 h at room temperature, and then processed as in (*a*). Purification of the amorphous crude product {2.875 g, 98%; $[\alpha]_D^{23}$ +120.5° (*c* 1, chloroform)} by column chromatography and subsequent crystallisation from ethanol–hexane, as in (*a*), afforded (+)-**4d** (1.4 g, 47.9%), m.p. 111°.

Methylglyoxal bis(benzoylhydrazone) (**8**). A mixture of methylglyoxal dimethyl acetal (5.91 g, 50 mmol), benzoylhydrazine (13.62 g, 100 mmol), and acetic acid (30 mL) was heated until dissolution was complete; after a vigorous reaction, the crystalline product separated. Subsequently, the mixture was gently boiled for an additional ~2 h and then cooled. The crystals were collected, washed with conc. and 50% acetic acid, and finally washed with water, to give **8** (13.70 g, 88.8%), m.p. 278°. Recrystallisation from 2-methoxyethanol–water gave material with m.p. 283° (dec.) [when prepared from methylglyoxal, lit.[11] m.p. 253° (from 1:1 benzene–ethanol)]; Σ_{max}^{EtOH}(log ε) 240 (4.17), 314 nm (4.50); λ_{min} 221 (4.07), 268 nm (4.11); ν_{max}^{KBr} 3210 (NH), 3050 and 3020 (Me and Ar), 1655 (Amide I), 1600 and 1578 (Ar), 1521 (Amide II), 1364 (Me), 1270 cm^{-1} (C-O). ^{1}H-N.m.r. data [$(CD_3)_2SO$]: δ 11.99 and 10.95 (2 s, each 1 H, exchangeable with deuterium, 2 NH), 8.12 (s, 1 H, CH = N), 7.91–7.84 (m, 4 H, H-Ar), 7.62–7.48 (m, 6 H, H-Ar), 2.26 (s, 3 H, CH_3). Mass spectrum: *m/z* 308 (M^+), 203 (base peak, 1-benzoylamino-4-methyl-1,2,3-triazole$^+$ + 1).

Anal. Calc. for $C_{17}H_{16}N_4O_2$: C, 66.22; H, 5.23; N, 18.17. Found: C, 65.93; H, 5.41; N, 18.10.

3-Acetyl-2-(4-bromophenyl)-2-methyl-5-phenyl-2,3-dihydro-1,3,4-oxadiazole (**11**). — A solution of 4-bromoacetophenone benzoylhydrazone (1.00 g, 3.15 mmol) in warm acetic anhydride (5 mL) was gently boiled under reflux for 75 min, then cooled, and poured onto ice and water to give crude (1.11 g, 97%) or pure **11** (0.940 g, 83%) m.p. 108° (from methanol–water); ν_{max}^{KBr} 1665 (NAc), 1638 (C = N), 1598 and 1579 cm^{-1} (Ar), $\nu_{max}^{CCl_4}$ 1676 (NAc), 1637 (C = N), 1595 and 1578 cm^{-1} (Ar). N.m.r. data ($CDCl_3$): ^{1}H, δ 7.90–7.85 (m, 2 H, H-Ar), 7.54–7.43 (m, 7 H, H-Ar), 2.35 (s, 3 H, NAc), 2.27 (s, 3 H, Me-2); ^{13}C, δ 166.78 (C = O), 153.51 (O-*C*Ph = N), 138.37, 131.38, 128.50, 127.45, 126.66, 124.50, and 123.21 (Ar), 99.97 [O-*C*(C_6H_4Br)-Me-N], 22.93 (CH_3-2), 22.24 (*C*H_3–CO). Mass spectrum: *m/z* 360 and 358 (M^+), 318 and 316 ($M^+ - CH_2CO$), 303 and 301 [2-(4-bromophenyl)-5-phenyl-1,3,4-oxadiazole$^+$ + 1], 161 (2-methyl-5-phenyl-1,3,4-oxadiazole$^+$ + 1). In some experiments, the pure product, recrystallised as above, had m.p. 81–82°; ν_{max}^{KBr} 1675 (NAc), 1632

(C=N), 1596 and 1580 cm^{-1} (Ar); but practically the same $\nu_{max}^{CCl_4}$, ^1H-, ^{13}C-n.m.r., and mass-spectral data, and R_F (7:3 hexane–acetone) as **11** melting at 108°.

Anal. Calc. for $C_{17}H_{15}BrN_2O_2$: C, 56.84; H, 4.21; Br, 22.25; N, 7.80. Found: C, 56.40; H, 4.41; Br, 22.31; N, 7.81.

*3,3'-Diacetyl-2'-methyl-5,5'-diphenyl-2,2'-bi-2*H*-1,3,4-oxadiazolines* (**12a** *and* **12b**). — (*a*) A mixture of **8** (0.500 g, 1.62 mmol), acetic anhydride (5 mL), anhydrous pyridine (0.5 mL), and anhydrous 2-methoxyethyl ether (1 mL) was boiled until dissolution was complete (~20 min) and then for an additional 75 min, and concentrated. The residue was triturated with ice and water, and partitioned between chloroform and water. The organic layer was washed successively with aqueous $KHSO_4$, water, aqueous $NaHCO_3$, and water, dried ($MgSO_4$), and concentrated to a foam. Purification of the residue by column chromatography (solvent *E*) afforded, first, **12a** (0.184 g, 29%), m.p. 155° (from ethyl acetate–hexane) [R_F 0.39 (solvent *F*) or 0.60 (solvent *D*); ν_{max}^{KBr} 1679 (amide), 1638 (C=N), 1603 and 1578 cm^{-1} (Ar)]; and then **12b** (0.102 g, 16%), m.p. 139–140° (from ethyl acetate–hexane) [R_F 0.24 (solvent *F*) or 0.45 (solvent *D*); ν_{max}^{KBr} 1692 and 1677 (amide), 1645 and 1635 (C=N), 1604 and 1579 cm^{-1} (Ar)].

(*b*) A mixture of acetic anhydride (50 mL) and trifluoroacetic acid (>98%, 4.5 mL) was kept for 5 h at room temperature, then **8** (6.167 g, 20 mmol) was added. The mixture was stirred until dissolution was complete, kept for an additional 60–65 h at room temperature, and then processed as described in (*a*), to give a crystalline crude product (1.442 g) which consisted (t.l.c) of two components with R_F values the same as those of **12a** and **12b** in (*a*). Column chromatography (solvent *E*) of the crude product and of the material in the mother liquor afforded **12a** (3.15 g, 40%), m.p. 155°, and **12b** (1.49 g, 19%), m.p. 141°.

Compound **12a** had λ_{max}^{MeOH}(log ϵ) 225 (4.33), 290 nm (4.38), λ_{min} 251 nm (4.10); ν_{max}^{KBr} 1677 (amide), 1636 (C=N), 1575 cm^{-1} (Ar). N.m.r. data ($CDCl_3$): ^1H, δ 7.67–7.56 (m, 4 H, H-Ar), 7.32–7.21 (m, 6 H, H-Ar), 7.13 (s, 1 H, O-C*H*R-N), 2.44 and 2.43 (each s, each 3 H, 2 Ac), 1.99 (s, 3 H, O-CRCH_3-N); ^{13}C, δ 169.93 and 167.72 (CH_3-*C*=O), 156.76 and 154.18 (O-*C*Ph=N), 131.52, 131.22, 128.34, 128.28, 126.82, and 126.51 (aromatic -CH=), 123.88 and 123.64 (aromatic -*C*R=), 101.60 (O-*C*RCH$_3$-N), 88.72 (O-*C*HR-N), 22.18 and 21.48 (*C*H$_3$-CO), 19.39 (O-CR*C*H$_3$-N). Mass spectrum: *m/z* 392 (M^+).

Anal. Calc. for $C_{21}H_{20}N_4O_4$: C, 64.27; H, 5.14; N, 14.28. Found: C, 64.70; H, 5.43; N, 14.31.

Compound **12b** had λ_{max}^{MeOH} (log ϵ) 225 (4.35), 292 nm (4.32), λ_{min} 261 nm (4.12); ν_{max}^{KBr} 1688 and 1676 (amide), 1643 and 1632 (C=N), 1602 and 1577 cm^{-1} (Ar). N.m.r. data ($CDCl_3$): ^1H, δ 7.91–7.87 (m, 2 H, H-Ar), 7.71–7.66 (m, 2 H, H-Ar), 7.56–7.32 (m, 6 H, H-Ar), 6.96 (s, 1 H, O-C*H*R-N), 2.32 and 2.18 (each s, each 3 H, 2 Ac), 2.14 (s, 3 H, O-CRCH_3-N); ^{13}C, δ 169.90 and 168.57 (CH_3-*C*=O), 156.34 and 154.07 (O-*C*Ph=N), 131.74, 131.31, 128.72, 128.52, 126.94, and 126.71 (aromatic -CH=), 124.20 and 124.10 (aromatic -*C*R=), 99.77 (O-*C*RCH$_3$-N), 88.01 (O-*C*HR-N), 22.14 and 21.41 (*C*H$_3$-C=O), 19.12 (O-CR*C*H$_3$-N). The mass spectrum was identi-

cal with that of **12a**.

Anal. Found; C, 64.20; H, 5.31; N, 14.25.

4-Bromoacetophenone benzoylhydrazone. — A mixture of 4-bromoacetophenone (1.99 g, 10 mmol) and benzoylhydrazine (1.361 g, 10 mmol) in ethyl acetate (2 mL) was boiled for 2 h to give the title compound (3.11 g, 98%), m.p. 219°. Recrystallisation from 2-propanol gave material with m.p. 222°; ν_{max}^{KBr} 3256 (NH), 1653 and 1646 (Amide I), 1605 (C=N), 1582 (Ar), 1527 cm^{-1} (Amide II). Mass spectrum: *m/z* 318 and 316 ($M^{\pm}$), 303 and 301 (M^{+} − Me).

Anal. Calc. for $C_{15}H_{13}BrN_2O$: C, 56.80; H, 4.13; Br, 25.20; N, 8.83. Found: C, 57.05; H, 4.20; Br, 25.55; N, 8.59.

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