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Note

Synthesis of mixed osazone derivatives by regioselective electrophilic substitution

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It is well known that treatment of sugar osazones (**1**) with nitrous acid results[1] in the formation of osone hydrazones (**2**) by splitting of the C-2–N bond and that the corresponding osotriazoles (**8**, R = H) are formed only as by-products in low yield[2]. Under similar conditions, the reaction of the *O*-acetylated derivatives (**3**) leads[3] to 2-phenyl-4-polyacetoxyalkyl-2*H*-1,2,3-triazoles (**8**, R = Ac) by splitting of the N–N bond of the C-1 hydrazono moiety. In an analogous manner, benzil bis(phenylhydrazone) can be transformed[4] into 2,4,5-triphenyl-1,2,3-triazole in 60% yield.

On the other hand, on treatment with nitrous acid, *O*-acetylated aldose semicarbazones[5] (**10**) and also the corresponding diacetylhydrazones (**11**) could be degraded[6] into the acetylated acyclic aldoses (**9**).

On the basis of the above findings, the effect of an acetyl group on the 1-phenylhydrazone moiety of the acetylated osulose 1,2-bis(phenylhydrazones) in their reactions with nitrous acid has been studied.

Treatment of 3,4,5,6-tetra-*O*-acetyl-D-*lyxo*-hexosulose 1-acetylphenylhydrazone 2-phenylhydrazone (**4a**) with sodium nitrite in dilute, aqueous ethanolic hydrochloric acid at ~50°, as reported[3] for the transformation **3**→**8** (R = Ac), gave a complex mixture containing a large amount of **4a** and only traces (t.l.c.) of the corresponding osotriazole derivative **8a** even after prolonged reaction.

Treatment of **4a** with sodium nitrite in aqueous acetic acid, or, more advantageously, with isopentyl nitrite in benzene, afforded 80% of 3,4,5,6-tetra-*O*-acetyl-D-*lyxo*-hexosulose 1-acetylphenylhydrazone 2-(4-nitrophenylhydrazone) (**6a**) *via* oxidation of the transiently formed nitroso derivative by the excess of reagent or, to obtain higher yields, by treatment with a stream of oxygen. The formation of the *C*-nitro derivative was proved by elemental analysis and by the presence of a peak at *m/z* 613 for the molecular ion in the mass spectrum. Also, ^{1}H-n.m.r. spectroscopy revealed only nine aromatic protons, and **6a** could be transformed into its hexa-acetate (**7a**) under the conditions used[7,8] for the acetylation of chelated hydrazone derivatives. The fragments with *m/z* 135 (AcHNPh) and 406

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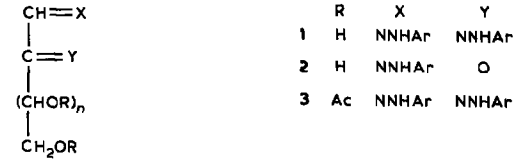
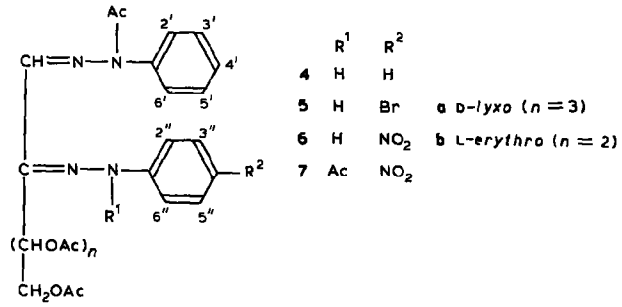
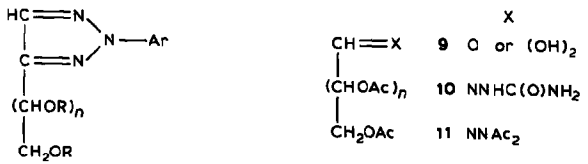


	R	X	Y
1	H	NNHAr	NNHAr
2	H	NNHAr	O
3	Ac	NNHAr	NNHAr



	R^1	R^2	
4	H	H	
5	H	Br	a D-*lyxo* ($n = 3$)
6	H	NO_2	b L-*erythro* ($n = 2$)
7	Ac	NO_2	



	X	
9	O or $(OH)_2$	
10	$NNHC(O)NH_2$	
11	NAc_2	

8

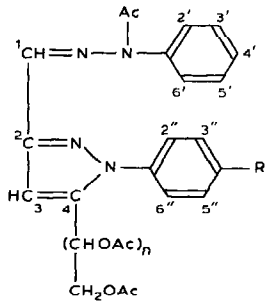
a D-*lyxo* ($n = 3$, Ar = Ph, R = Ac)

($M^+ - CH{=}NNAcPh$) in the mass spectrum of **6a** indicated that nitration of the benzene ring of the phenylhydrazono group attached to position 2 had occurred. In an analogous manner, treatment of 3,4,5-tri-*O*-acetyl-L-*erythro*-pentosulose 1-acetylphenylhydrazone 2-phenylhydrazone (**4b**) with isopentyl nitrite afforded 80% of the 2-(4-nitrophenylhydrazono) derivative **6b**.

Benzophenone phenylhydrazone reacted with nitrous acid to give the stable *N*-nitroso derivative[9,10]. Presumably, the *C*-nitro derivatives **6a** and **6b** are produced due to the enhanced electron delocalisation in the *N*-phenyl chelate ring[11] and thus to the increased electron density at the *p*-position of this phenyl group. Accordingly, on treatment with the bromine-cation donor[12,13] 2,4,4,6-tetrabromo-2,5-cyclohexadien-1-one[14], the osazone acetate **4a** could be transformed into the 2-(4-bromophenyl) analogue **5a** in high yield.

In accordance with the 1-acetylphenylhydrazone-2-(4-nitrophenylhydrazone) structure, **6b** was transformed into 5-acetoxymethyl-3-formyl-1-(4-nitrophenyl)-pyrazole acetylphenylhydrazone (**14b**) on treatment[15] with hot acetic anhydride–anhydrous sodium acetate.

Similarly to a recently reported[15] reaction, accompanied also by partial racemisation, the acetylated pyrazole-type dianhydroarylosazones **13a** and **14a** were obtained from the hexose derivatives **5a** and **6a**, respectively. The ^{1}H-n.m.r.



	R
12	H
13	Br
14	NO_2

a D-*glycero* ($n = 1$)
b $n = 0$

spectra of **13a, 14a,** and **14b** were indicative of the *p*-substitution of the benzene ring (see Experimental).

Thus, the presence of an acetyl group at the 1-phenylhydrazono moiety strongly inhibits the transformation of acetylated sugar osazones into the corresponding osotriazoles (**8**, R = Ac) by treatment with nitrous acid or its isopentyl ester, and leads to the *p*-nitration of the aromatic ring of the unacetylated C-2 hydrazono unit.

EXPERIMENTAL

General methods. — Melting points are uncorrected and were determined on a Kofler block. Solutions were concentrated at ≯40° (bath) at ~17 mmHg. Column chromatography was performed on silica gel 70–150 mesh (Woelm) and t.l.c. on Alurolle-Kieselgel 60 F_{254} (Merck), with detection by u.v. light at λ 254 nm, using benzene–ethyl acetate mixtures *A*, 1:1, *B*, 8:2, *C*, 9:1; chloroform–acetone mixtures *D*, 95:5; *E*, 9:1; and *F*, light petroleum–acetone (7:3). 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-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).

*3,4,5,6-Tetra-O-acetyl-*D-lyxo-*hexosulose 1-acetylphenylhydrazone 2-(4-bromophenylhydrazone)* (**5a**). — 2,4,4,6-Tetrabromocyclohexadienone[14] (8.195 g, 20 mmol) was stirred with a solution of **4a**[15] (11.371 g, 20 mmol) in anhydrous benzene (100 mL) until dissolution was complete. The solution was kept for 18 h at room temperature, then diluted with benzene, washed with 0.5M sodium hydroxide (2 × 40 mL) and several times with water, treated with $MgSO_4$, fuller's earth, and activated carbon, and then concentrated. The residue (12.87 g, 99%) was crystallised from methanol (10 mL) and water (2 mL) to give **5a** (9.85 g, 76%), m.p. 127°, $[\alpha]_D^{23}$ +63° (*c* 1, chloroform); λ_{max}^{MeOH} 248 (log ε 4.36), 270 (sh) (3.96), and 380 nm (4.39); λ_{min} 315 nm (3.38); ν_{max}^{KBr} 1746 (OAc), 1691 (amide), and 818 cm^{-1} (=CH of

1,4-disubstituted benzene). ^{1}H-N.m.r. data: δ 12.26 (s, ~1 H, NH), 7.67–7.56, 7.45–7.41, and 7.24–7.11 (3 m, 3, 2, and 4 H, aromatic protons), 7.03 (s, 1 H, CH=N), 5.55–5.31 (m, 3 H, H-3,4,5), 4.35–3.96 (m, 2 H, CH_2), 2.63 (bs, 3 H, NAc), 2.06, 2.05, 1.94, and 1.88 (4 s, each 3 H, 4 AcO).

Anal. Calc. for $C_{28}H_{31}BrN_4O_9$: C, 51.94; H, 4.83; Br, 12.34; N, 8.65. Found: C, 51.95; H, 4.97; Br, 11.68; N, 8.70.

*3,4,5,6-Tetra-*O*-acetyl-*D-lyxo*-hexosulose 1-acetylphenylhydrazone 2-(4-nitrophenylhydrazone)* (**6a**). — (*a*) Isopentyl nitrite (5.75 mL, 17.3 mmol; Merck) was added during 5 h in five equal portions to a stirred suspension of **4a**[15] (8.529 g, 15 mmol) in anhydrous benzene (50 mL). After storage at room temperature for 19 h, the solution was treated with a stream of oxygen for 8 h, then kept again at room temperature for 15 h, and concentrated at <1 mmHg. A solution of the residue in benzene was washed with aqueous $NaHCO_3$ and water, treated with $MgSO_4$, fuller's earth, and activated carbon, and then concentrated. The residue was crystallised from methanol to give **6a** (5.470 g, 59.4%), m.p. 109–112°. Column chromatography (solvent *D*) of the material in the mother liquor afforded more (1.90 g, 20.6%) **6a** of the same purity, $[\alpha]_D^{23}$ +84° (*c* 1, chloroform); λ_{max}^{MeOH} 225 (log ε 4.23), 280 (3.88), and 402 nm (4.55); λ_{min} 264 (3.84) and 327 nm (3.59); ν_{max}^{KBr} 1752 (OAc), 1703 and 1699 (NAc), 1603 (C=N), 1587 (Ar), 1506 (NO_2), 1330 (NO_2), and 846 cm^{-1} (=CH of 1,4-disubstituted benzene). ^{1}H-N.m.r. data: δ 8.25–8.21 (m, 2 H, H-3″,5″), 7.68–7.64 and 7.36–7.22 (2 m, 3 and 4 H, aromatic protons), 7.02 (s, 1 H, CH=N), 5.49–5.37 (m, 3 H, H-3,4,5), 4.36–3.95 (m, 2 H, CH_2), 2.75–2.12 (bs, 3 H, NAc), 2.05, 2.04, 1.94, and 1.88 (4 s, each 3 H, 4 AcO). Mass spectrum: *m/z* 613 (M^+), 451 (M^+ – CH=NNAcPh – H), 135 (AcNHPh), and 122 ($C_6H_4NO_2$).

Anal. Calc. for $C_{28}H_{31}N_5O_{11}$: C, 54.81; H, 5.09; N, 11.42. Found: C, 54.52; H, 5.09; N, 11.39.

(*b*) A solution of sodium nitrite (0.280 g, 4.06 mmol) in water (1 mL) was added in small portions to a stirred suspension of **4a**[15] (2.274 g, 4.0 mmol) in acetic acid (10 mL) during 5 h. The solution was kept for 1.5 h at room temperature and then poured into ice and water. Several recrystallisations of the crude product (2.147 g) from methanol afforded **6a** (0.640 g, 26%), m.p. 109–111°.

The products obtained in (*a*) and (*b*) were homogeneous and identical (t.l.c., solvents *B* and *E*).

*3,4,5-Tri-*O*-acetyl-*L-erythro*-pentosulose 1-acetylphenylhydrazone 2-(4-nitrophenylhydrazone)* (**6b**). — Isopentyl nitrite (5.75 mL, 17.3 mmol) was added to a solution of **4b**[8] (7.448 g, 15 mmol) in anhydrous benzene (35 mL). The mixture was kept for 21 h at room temperature, then treated with a stream of oxygen for 8 h, stored for 17 h at room temperature, and worked-up as described above for the preparation of **6a**, to give **6b** (3.98 g, 49%), m.p. 96–97°, $[\alpha]_D^{23}$ +6.5° (*c* 1, chloroform); λ_{max}^{MeOH} 277 (log ε 3.92) and 404 nm (4.63); λ_{min} 264 (3.90) and 324 nm (3.64); ν_{max}^{KBr} 3196 (NH), 1745 (OAc), 1695 (amide), 1583 (Ar), 1500 (NO_2), 1326 (NO_2), and 841 cm^{-1} (=CH of 1,4-disubstituted benzene). ^{1}H-N.m.r. data: δ 8.24–

8.19 (m, 2 H, H-3″,5″), 7.69–7.60 and 7.35–7.23 (2 m, 3 and 4 H, aromatic protons), 7.00 (s, 1 H, CH=N), 5.54–5.52 (m, 2 H, H-3,4), 4.40–4.14 (m, 2 H, CH_2), 2.60 (bs, 3 H, NAc), 2.04, 1.97, and 1.89 (3 s, each 3 H, 3 AcO). Mass spectrum: *m/z* 541 (M^+), 379 (M^+ − CH=NNAcPh − H), 135 (AcNHPh).

Anal. Calc. for $C_{25}H_{27}N_5O_9$: C, 55.45; H, 5.03; N, 12.93. Found: C, 55.38; H, 5.07; N, 12.92.

Column chromatography (solvent *D*) of the material in the mother liquor afforded more **6b** (2.480 g, 30.5%), m.p. 95–96°.

*3,4,5,6-Tetra-*O*-acetyl-*D*-lyxo-hexosulose 1-acetylphenylhydrazone 2-[acetyl-(4-nitrophenyl)hydrazone]* (**7a**). — (*a*) A solution of **6a** (1.227 g, 2 mmol) in acetic anhydride (20 mL)and trifluoroacetic acid (1.8 mL) was kept for 6 days at room temperature, then concentrated, and poured into ice and water. After the addition of sodium hydrogencarbonate, the product was collected and a solution in chloroform was washed with water, dried ($MgSO_4$), and then concentrated. Column chromatography (solvent *D*) of the residue afforded a homogeneous (t.l.c.) fraction, which was concentrated to dryness. A filtered solution of the residue in acetone was concentrated to give **7a** as a foam (0.740 g, 56%), $[\alpha]_D^{23}$ +77.5° (*c* 1, chloroform); λ_{max}^{MeOH} 288 (log ε 4.35) and 349 nm (3.86); λ_{min} 249 nm (4.09). ^{1}H-N.m.r. data: δ 8.04–8.00, 7.45–7.33, 7.03–6.95, and 6.68–6.63 (4 m, 2, 3, 2, and 2 H, aromatic protons), 6.49 (s, 1 H, CH=N), 6.15 (d, 1 H, $J_{3,4}$ 8 Hz, H-3), 5.76 (dd, 1 H, $J_{4,5}$ 2 Hz, H-4), 5.61 (cm, 1 H, H-5), 4.39–3.98 (m, 2 H, CH_2), 2.54, 2.28, 2.16, 2.12, 2.07, and 2.05 (6 s, each 3 H, 6 Ac).

Anal. Calc. for $C_{30}H_{33}N_5O_{12}$: C, 54.96; H, 5.07; N, 10.68. Found: C, 54.97; H, 5.07; N, 10.52.

(*b*) Compound **6a** (0.300 g, 0.49 mmol) was treated[7] with a solution of anhydrous zinc chloride (0.3 g) in acetic anhydride (3 mL) for 24 h at room temperature. Column chromatography of the crude product as in (*a*) gave amorphous **7a** (0.215 g, 67%) identical (t.l.c., ^{1}H-n.m.r. spectra) with the product in (*a*).

*1-(4-Bromophenyl)-5-(*D*-glycero-1,2-diacetoxyethyl)-3-formylpyrazole acetylphenylhydrazone* (**13a**). — A mixture of **5a** (3.237 g, 5 mmol), acetic anhydride (17.5 mL), and anhydrous sodium acetate (3 g) was boiled gently under reflux for 1.5 h and then poured onto crushed ice. A solution of the crude product in chloroform was washed with aqueous sodium hydrogencarbonate and water, treated with $MgSO_4$, fuller's earth, and activated carbon, and then concentrated. The residue was crystallised from aqueous methanol to give DL-**13a** (0.247 g, 9.4%), m.p. 162°, $[\alpha]_D^{23}$ ~0° (*c* 1, chloroform); ν_{max}^{KBr} 1747 (OAc), 1689 (NAc), 1603 (C=N), 1492 (Ar), and 828 cm^{-1} (=CH of 1,4-disubstituted benzene).

Column chromatography (solvent *F*) of the material in the mother liquor and crystallisation from ethanol–heptane gave partially racemised D-**13a** (1.40 g, 53%), m.p. 134°, $[\alpha]_D^{23}$ +39° (*c* 1, chloroform); λ_{max}^{MeOH} 282 nm (log ε 4.67); λ_{min} 246 nm (4.14); ν_{max}^{KBr} 1744 (OAc), 1686 (NAc), 1606 (C=N), 1490 (Ar), and 833 cm^{-1} (=CH of 1,4-disubstituted benzene). ^{1}H-N.m.r. data: δ 7.64–7.60 (m, 2 H, H-3″,5″), 7.56–7.43 (m, 3 H, H-3′,4′,5′), 7.36–7.32 (m, 2 H, H-2″,6″), 7.33 (s, 1 H, H-3), 7.16–7.13

(m, 2 H, H-2′,6′), 6.91 (s, 1 H, CH=N), 5.90 (t, 1 H, H-5), 4.32 (d, 2 H, *J* 6 Hz, CH_2), 2.60 (s, 3 H, NAc), 2.06 and 2.03 (2 s, each 3 H, 2 AcO). Mass spectrum: *m/z* 528 and 526 (M^+ with Br^{81} and Br^{79}, respectively), 486 and 484 ($M^+ - CH_2CO$).

Anal. Calc. for $C_{24}H_{23}BrN_4O_5$: C, 54.66; H, 4.40; Br, 15.15; N, 10.62. Found: C, 55.12; H, 4.70; Br, 14.59; N, 10.63.

The products having m.p. 162° and 134° had the same R_F value (0.66) in t.l.c. (solvent *E*) and gave identical ^{1}H-n.m.r. and mass spectra.

5-(D-glycero-1,2-Diacetoxyethyl)-3-formyl-1-(4-nitrophenyl)pyrazole acetylphenylhydrazone (**14a**). — Compound **6a** (2.454 g, 4 mmol) was treated with hot acetic anhydride (14 mL) and sodium acetate (2.4 g) for 1.5 h. The mixture was processed as described above for the preparation of **13a**. Column chromatography (solvent *C*) of the product and crystallisation from aqueous ~80% methanol gave **14a** (1.32 g, 66.7%), m.p. 96°, $[\alpha]_D^{23}$ +37.5° (*c* 1, chloroform); λ_{max}^{MeOH} 276 (log ε 4.38) and 307 (sh) nm (4.26); λ_{min} 233 nm (4.08); ν_{max}^{KBr} 1745 (OAc), 1687 (NAc), 1608 (C=N), 1594 (Ar), 1521 (NO_2), 1343 cm^{-1} (NO_2). ^{1}H-N.m.r. data: δ 8.37–8.33 and 7.75–7.70 (2 m, each 2 H, H-3″,5″ and H-2″,6″, respectively), 7.60–7.47 (m, 3 H, H-3′,4′,5′), 7.34 (s, 1 H, H-3), 7.19–7.15 (m, 2 H, H-2′,6′), 6.99 (s, 1 H, CH=N), 6.05–5.99 (X part of an ABX system, 1 H, H-5), 4.44–4.26 (m, 2 H, CH_2), 2.60 (s, 3 H, NAc), 2.09 and 2.05 (2 s, each 3 H, 2 AcO). Mass spectrum: *m/z* 493 (M^+), 451 ($M^+ - CH_2CO$), 136 ($AcNH_2Ph$), 93 (H_2NPh).

Anal. Calc. for $C_{24}H_{23}N_5O_7$: C, 58.41; H, 4.70; N, 14.19. Found: C, 58.24; H, 4.80; N, 14.35.

5-Acetoxymethyl-3-formyl-1-(4-nitrophenyl)pyrazole acetylphenylhydrazone (**14b**). — A mixture of **6b** (1.083 g, 2 mmol), acetic anhydride (7 mL), and anhydrous sodium acetate (1.0 g) was gently boiled for 1.5 h, and then poured into ice and water. The crude product (0.80 g, 95%) was recrystallised from ethanol to give **14b** (0.73 g, 87%), m.p. 202°; λ_{max}^{MeOH} 276 (log ε 4.35) and 313 nm (4.32); λ_{min} 237 (4.09) and 293 nm (4.25); ν_{max}^{KBr} 1747 (OAc), 1691 and 1680 (sh) (NAc), 1608 (C=N), 1594 (Ar), 1516 (NO_2), and 1337 cm^{-1} (NO_2). ^{1}H-N.m.r. data: δ 8.37–8.33 and 7.74–7.70 (2 m, each 2 H, H-3″,5″ and H-2″,6″, respectively), 7.60–7.43 (m, 3 H, H-3′,4′,5′), 7.34 (s, 1 H, H-3), 7.19–7.14 (m, 2 H, H-2′,6′), 7.04 (s, 1 H, CH=N), 5.18 (s, 2 H, CH_2), 2.60 (s, 3 H, NAc), 2.14 (s, 3 H, OAc). Mass spectrum: *m/z* 421 (M^+), 379 ($M^+ - CH_2CO$), 378 ($M^+ - Ac$), 244 ($M^+ - CH_2CO - AcNHPh$), 135 (AcNHPh).

Anal. Calc. for $C_{21}H_{19}N_5O_5$: C, 59.85; H, 4.54; N, 16.62. Found: C, 59.74; H, 4.62; N, 16.80.

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