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A CONTRIBUTION TO THE CHEMISTRY OF PYRAZOLE-TYPE DIANHYDROPHENYLOSAZONES

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ABSTRACT

3,4,5,6-Tetra-*O*-acetyl-D-*lyxo*-hexosulose 1-acetylphenylhydrazone 2-phenylhydrazone (**10**) was transformed into 5-(D-*glycero*-1,2-diacetoxyethyl)-3-formyl-1-phenylpyrazole acetylphenylhydrazone (D-**4**, $n = 3$) in boiling acetic anhydride containing anhydrous sodium acetate. Racemic 3,4,6-tri-*O*-acetyl-5-deoxyhex-4-enos-2-ulose 1-acetylphenylhydrazone 2-phenylhydrazone (**11**) was isolated as an intermediate in the reaction performed in the absence of sodium acetate. The cyclisation of **11**, *via* allylic rearrangement, into DL-**4** ($n = 3$) and 5-(DL-*glycero*-1,2-dihydroxyethyl)-3-formyl-1-phenylpyrazole acetylphenylhydrazone (DL-**3**, $n = 3$) in acidic, neutral, and basic media is described.

INTRODUCTION

Sugar osazones and their *O*-acetyl derivatives are transformed[1] into pyrazole-type *O,N*-acetyldianhydrophenylosazones (**4**) by treatment with boiling acetic anhydride for 0.5–1.5 h, and yields of 12–14% have been reported[1d,f]. The reaction conditions employed are suitable not only for the acetylation of the more reactive[2] hydroxyl groups but also for that of the non-chelated NH group[3] of 1,2-bis(arylhydrazone)s. In this cyclisation reaction which gives **4**, dehydration of the osazone is supposed to precede[1d] the acetylation reaction, but, for the osazone acetates, the mechanism **5**→**8** is suggested[4], involving the stepwise elimination of two molecules of acetic acid and formation of the 2-phenylazo-1-phenylhydrazono-2-alkene **6** and the 1,2-bis(phenylhydrazono)-3-alkene **7**. On the other hand, in weakly basic solution, the tri-*O*-acetylpentose phenylosazone (**2**, $n = 2$) is transformed[5] into ~20% of 5-acetoxymethyl-3-formyl-1-phenylpyrazole acetylphenylhydrazone (**4**, $n = 2$). Presumably, an *O*→*N* acetyl migration occurs, involving a secondary acetate and the NH function of the 1-phenylhydrazone moiety.

On the basis of the above data, the effect of an acetyl group on the 1-phenylhydrazono moiety (which precludes *O*→*N* acetyl migration) on the pyrazole ring-closure reaction has been studied.

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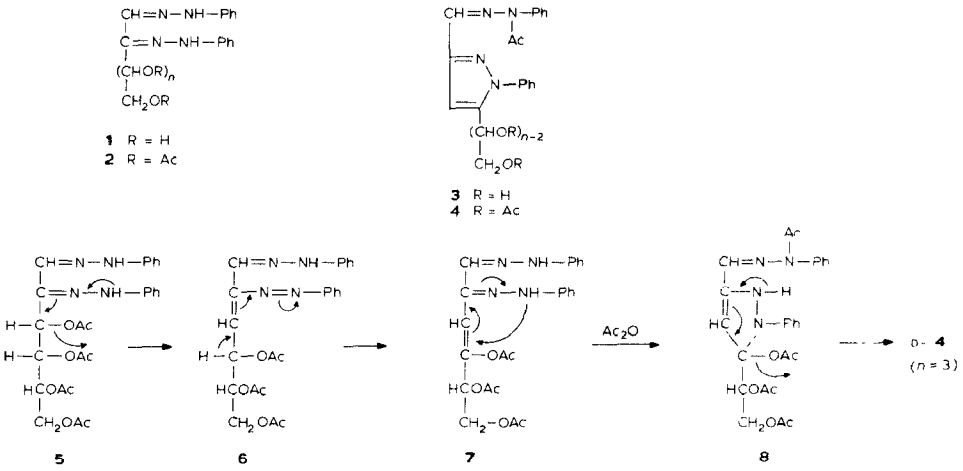
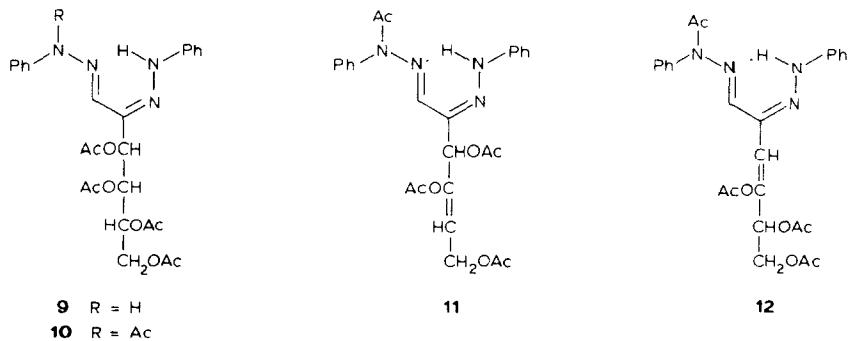


DISCUSSION

Treatment of 3,4,5,6-tetra-*O*-acetyl-D-*lyxo*-hexosulose 1-acetylphenylhydrazone 2-phenylhydrazone (**10**) with hot acetic anhydride–anhydrous sodium acetate gave 70% of 5-(D-*glycero*-1,2-diacetoxyethyl)-3-formyl-1-phenylpyrazole acetylphenylhydrazone (D-**4**, $n = 3$; the $[\alpha]_D$ value suggests that this compound may be partly racemised). Similarly, the known[1] transformation of hexosazones (**1**) and their *O*-acetyl derivatives (**2**) with hot acetic anhydride affords optically active dianhydro-osazone acetates **4** ($n = 3$). Since the conversion proceeds *via* **6** and **7** as well as their C-1-*N*-acetyl analogues, the chirality of C-5 remains unchanged.



When the penta-acetyl derivative **10** was treated with hot acetic anhydride for 2–3 h, the rate of reaction was relatively slow and a yellow compound was formed with an R_F value (1:1 benzene–ethyl acetate, 9:1 chloroform–acetone) close to that of **10**. Prolonged reaction did not increase the proportion of this product, since the dianhydro-osazone **4** ($n = 3$) appeared in increasing quantity as **10**

disappeared, and racemic 3,4,6-tri-*O*-acetyl-5-deoxyhex-4-enos-2-ulose 1-acetylphenylhydrazone 2-phenylhydrazone (**11**) was isolated and identified on the basis of analytical and spectral data (see Experimental). The ^{13}C-n.m.r. spectrum of this new tetra-acetyl derivative contained only two signals (δ 68.65 and 63.47) in the range of the C-3–6 of **10** [δ ($CDCl_3$) 72.25, 70.12, 68.52, 62.12], whereas a signal (δ 120.02) was observed in the range characteristic of the sp^2 hybridised carbons.

Although C-3 in **11** is chiral, the product is optically inactive and must be a racemate. This phenomenon cannot be explained by the sequence **5**→**8**, because C-3 is achiral and deoxygenated in **6** and **7**. The dianhydrophenylosazone derivative **4** (n = 3) was isolated in addition to **11** after the transformation of **10**, and **4** (n = 3) is optically inactive and considered to be a racemate. In the formation of DL-**4** (n = 3), **11** is an intermediate since it could be converted into DL-**4** (n = 3), in 59% yield, on treatment with hot acetic anhydride–anhydrous sodium acetate. This transformation must be accompanied by a rearrangement including C-5 which is racemised. The observation that **11**, racemised at C-3 and deoxygenated at C-5, is an intermediate in the formation of DL-**4** (n = 3) from **10**, on treatment with hot acetic anhydride, necessitates the assumption that isolated **11** and DL-**12** (the racemic C-1-*N*-acetyl analogue of the previously proposed[4] intermediate form **7**) are in equilibrium by means of an allylic rearrangement prior to formation of the pyrazole ring. Compound **12** can be regarded as a precursor of **11** and DL-**4** (n = 3), thereby explaining their racemic nature. For the rearrangement **11**⇄**12**, involving, presumably "internal return"[6], the acetoxy group involving two atoms with lone pairs of electrons seems to be favourable. When a solution of **11** in $CDCl_3$ was kept at ~50° for 3 h, t.l.c. (9:1 chloroform–acetone) revealed a yellow product less mobile (R_F 0.57) than **11** but of almost equivalent intensity. In the ^{1}H-n.m.r. spectrum of the solution, the signals at δ 5.89 (s) and 5.37 (m), appearing with about the same integrated intensity as that of the respective signals of **11**, could be due to **12**; ~75% of **11** could be recovered by crystallisation and chromatography, further indicating the thermal equilibrium between **11** and **12**.

Heteroconjugated dienes are known to react with nucleophiles; when **11** was treated with hydrazoic acid (sodium azide–aqueous acetic acid) at room temperature, t.l.c. (Kieselgel F_{254}, Merck; 9:1 chloroform–acetone) showed the disappearance of **11** (R_F 0.72) and the yellow colour, and the formation of a product with R_F 0.33 detectable by u.v. light (254 and also 366 nm). Upon working-up, this substance was transformed into a compound absorbing only at 254 nm and having a mobility similar to that of **4** (n = 3). After reaction for 20 h at room temperature, instead of an addition product of hydrazoic acid, 71% of DL-**4** (n = 3) could be isolated. In the absence of sodium azide, DL-**4** (n = 3) was formed together with two products (R_F values 0.33 and 0.57), and much unchanged **11** was detected even after reaction for 8 days.

The ring closure of **11** to give a pyrazole derivative can also be induced under alkaline conditions. On attempted *O*-deacetylation of racemic **11** with methanolic

dimethylamine, ~80% of crude 5-(DL-*glycero*-1,2-dihydroxyethyl)-3-formyl-1-phenylpyrazole acetylphenylhydrazone (DL-**3**, $n = 3$) was isolated, which was identical with the compound obtained by the partial deacetylation of DL-**4** ($n = 3$).

EXPERIMENTAL

General methods. — Melting points are uncorrected and were determined on a Kofler block. Solutions were concentrated at ~17 mmHg. I.r. spectra (KBr discs) were recorded with a Perkin–Elmer 283 B spectrophotometer. Mass spectra (70 eV) were obtained by using a VG-7035 GC/MS/DS instrument (ion current, 0.1 mA; direct-insertion technique).

*5-(*DL-glycero-*1,2-Dihydroxyethyl)-3-formyl-1-phenylpyrazole acetylphenylhydrazone* (**3**, $n = 3$). — (*a*) Racemic 3,4,6-tri-*O*-acetyl-5-deoxyhex-4-enos-2-ulose 1-acetylphenylhydrazone 2-phenylhydrazone (**11**; 5.086 g, 10 mmol) was stirred in methanolic 0.445M dimethylamine (160 mL, 71 mmol) until dissolution was complete (~12 min). The solution was kept for 6-7 h at room temperature and then concentrated, and the syrupy residue was crystallised from anhydrous ethanol (15 mL) and hexane (15 mL) to give crude **3** (2.976 g, 81.7%). A solution of the crude product in chloroform was treated with fuller's earth and activated carbon, and then concentrated. Recrystallisation of the residue afforded DL-**3** (2.57 g, 70.5%), m.p. 185–185.5°; ν_{max}^{KBr} 3410 (OH), 1690 (sh) and 1658 (amide), and 1617 cm^{-1} (C=N); lit[1a] for D-**3** ($n = 3$): ν_{max}^{KBr} 3350 (OH) and 1640 cm^{-1} (amide).

Anal. Calc. for $C_{20}H_{20}N_4O_3$: C, 65.92; H, 5.53; N, 15.38. Found: C, 65.44; H, 5.83; N, 15.01.

(*b*) Compound DL-**4** (0.224 g, 0.5 mmol, m.p. 143°, obtained from **11** by reaction with acetic anhydride–sodium acetate) was stirred with methanolic 0.445M dimethylamine (4.5 mL, 2 mmol) until dissolution was complete (~1 h). The solution was kept for 6 h at room temperature, and then processed as in (*a*) to yield DL-**3** (0.188 g, 83.8%), m.p. 185°; lit.[1a] m.p. 175°.

(*c*) A solution of DL-**4** (0.448 g, 1 mmol, modification m.p. 115°, see the preparation of **4**) in methanolic 0.445M dimethylamine (5 mL, 2.2 mmol) was kept for 20 h at room temperature and then processed as in (*a*) to give DL-**3** (0.30 g, 82%), m.p. 186°.

*5-(*D- *and* DL-glycero-*1,2-Diacetoxyethyl)-3-formyl-1-phenylpyrazole acetylphenylhydrazone* (**4**, $n = 3$). — (*a*) A mixture of **10** (1.000 g, 1.76 mmol), acetic anhydride (5 mL), and anhydrous sodium acetate (1 g) was boiled gently under reflux for 2 h, and then poured onto crushed ice. A solution of the crude product (0.795 g) in chloroform was treated with fuller's earth and activated carbon, and then concentrated. Crystallisation of the residue from methanol–water afforded D-**4** (0.550 g, 70%), m.p. 127°, $[\alpha]_D^{23}$ +56° (*c* 1, chloroform); ν_{max}^{KBr} 1753 (OAc), 1686 (amide), 1612 (C=N), and 1596 cm^{-1} (Ph). ^{1}H-N.m.r. data (200 MHz, $CDCl_3$): δ 7.55–7.14 (m, 11 H, 2 Ph and H-4), 6.93 (s, 1 H, CH=N), 6.03 (t, 1 H, C*H*-OAc), 4.35 and 4.32 (2 s, each 1 H, CH_2), 2.63 (bs, 2.7 H) and 2.18 (s, 0.3 H, NAc), 2.05

and 2.03 (2 s, each 3 H, 2 Ac). Lit.[1a] m.p. 131° (from aqueous ethanol), $[\alpha]_D$ +68° (chloroform); ν_{max} 1725 (OAc) and 1670 cm^{-1} (amide). ^{1}H-N.m.r. data ($CDCl_3$)[1c]: δ 6.92 (s, 1 H, CH=N), 6.05 (t, 1 H, C*H*-OAc), 4.30 (d, 2 H, *J* 6 Hz, CH_2OAc), 2.58 (s, 3 H, NAc) and 1.99 (s, 2 Ac).

(*b*) Column chromatography (Kieselgel 40; benzene–ethyl acetate, 6:1) of the product from the mother liquor of crude **11**, with repeated recrystallisation from ethyl acetate and aqueous methanol, gave DL-**4** in various yields; m.p. 143°, ν_{max}^{KBr} 1754 and 1745 (OAc), 1683 (amide), 1608 cm^{-1} (C=N).

(*c*) Treatment of DL-**3** (m.p. 185°, 0.20 g) with acetic anhydride–pyridine for 17 h at room temperature gave DL-**4** (93%), m.p. 143°; ν_{max}^{KBr} 1755 and 1747 (OAc), 1687 (amide), and 1610 cm^{-1} (C=N).

(*d*) Compound **11** (0.50 g, 0.98 mmol) was added to a suspension of anhydrous sodium acetate (0.5 g) in acetic anhydride (10 mL) at ~100°. The mixture was boiled gently under reflux for 1 h and then processed as in (*a*) to give DL-**4** (0.26 g, 59%), m.p. 142°. In some experiments, the product prepared in this way had m.p. 114–115°, and ν_{max}^{KBr} 1750 (OAc) and 1686 cm^{-1} (amide). Both modifications could be deacetylated to give DL-**3**.

(*e*) To a solution of **11** (0.175 g, 0.344 mmol) in acetone (9 mL) were added 5M acetic acid (0.35 mL, 1.75 mmol), powdered sodium azide (0.1 g, 1.54 mmol), and water (2 mL). The mixture was stirred until dissolution was complete (1–2 min), stored for 20 h at room temperature, and then concentrated. A solution of the residue in benzene was washed successively with aqueous sodium hydrogencarbonate and water, dried ($MgSO_4$), treated with fuller's earth and activated carbon, and then concentrated. The residue was crystallised from methanol–water to yield DL-**4** (0.11 g, 71%), m.p. 143°.

Compounds D-**4** and DL-**4** (both the samples m.p. 114–115° and 143°) described at (*a*)–(*e*) had R_F 0.67 (t.l.c., chloroform–acetone, 9:1) and gave the same ^{1}H-n.m.r. spectrum.

3,4,5,6-Tetra-O-*acetyl*-D-lyxo-*hexosulose 1-acetylphenylhydrazone 2-phenylhydrazone* (**10**). — A solution of **9**[2b] (10.531 g, 20 mmol) in anhydrous *N,N*-dimethylaniline (6.50 mL, 51.3 mmol) and acetyl chloride (4.00 mL, 56.3 mmol) was kept for 16 h at room temperature and then poured on to crushed ice. The crystalline material was collected, washed successively with water, aqueous sodium hydrogencarbonate, water, and then with light petroleum, and dried in a vacuum desiccator to give crude **10** (10.909 g, 96%), m.p. 143–144°. Recrystallisation from methanol (50 mL) afforded **10** (10.2 g, 90%), m.p. 148° (lit.[1d] m.p. 139–141°); λ_{max}^{MeOH} 242 (log ε 4.33), 273 (sh, 3.88), and 377 nm (4.29), λ_{min} 310 nm (3.45); ν_{max}^{KBr} 3190 (b, NH), 1750 and 1742 (OAc), 1690 (NAc), 1600 (C=N), and 1580 cm^{-1} (Ph). N.m.r. data ($CDCl_3$): ^{1}H, δ 12.30 (bs, NH), 7.63–7.04 (m, 11 H, 2 Ph and CH=N), 5.49–5.36 (m, 3 H, H-3,4,5), 4.36–3.98 (m, 2 H, CH_2), 2.67 (bs, 1 H, ~0.33 Ac), 2.10 (s, 3 H, Ac), 2.08 (s, 3 H, Ac), 1.96 (s, 2 H, ~0.66 Ac), 1.89 (s, 3 H, Ac), and 1.62 (s, 3 H, Ac); ^{13}C (50.3 MHz), δ 170.22, 169.80, 169.25, and 169.00 (C=O), 143.26 (C=N), 137.72 (CH=N), 130.41, 130.17, 129.93, 129.32, and 129.16 (Ar), 127.11

(quaternary Ar), 122.46, 114.06, and 113.85 (Ar), 72.25, 70.12, and 68.52 (C-3,4,5), 62.16 (CH_2), 22.63, 20.51, and 20.35 (CH_3-CO).

Racemic 3,4,6-tri-O-acetyl-5-deoxyhex-4-enos-2-ulose 1-acetylphenylhydrazone 2-phenylhydrazone (**11**). — A solution of **10** (10 g, 17.59 mmol, m.p. 148–149°) in warm acetic anhydride (50 mL) was gently boiled for 3 h under nitrogen, cooled, and poured into ice and water. A chloroform solution of the separated gum was washed with aqueous $NaHCO_3$ and water, treated with $MgSO_4$, fuller's earth, and activated carbon, and then concentrated. A solution of the syrupy residue in methanol (45 mL) was diluted with water (~25 mL) in small portions at ~40° to give a crystalline mixture (5.54 g) of **11** and **10**. Extraction of **10** with hot methanol (10 mL) left **11** (3.14 g, 35%), m.p. 175–176°. Recrystallisation from aqueous acetone afforded **11** (2.45 g, 36% of the **10** transformed), m.p. 180–181°, $[\alpha]_D^{23}$ ~0° (*c* 1, chloroform); λ_{max}^{MeOH} 260 (log ε 4.24), 269 (sh, 4.22), 359 (4.01), 402 nm (3.97), λ_{min} 312 (3.60), 382 nm (3.96); ν_{max}^{KBr} 3440 (NH), 1757, 1743, and 1732 (OAc), 1686 (NAc), 1640 (C=N), 1592 (Ar). ^{1}H-N.m.r. data ($CDCl_3$): δ 12.7 (bs, 1 H, NH), 7.59–6.97 (m, 10 H, 2 Ph), 6.84 (s, 1 H, CH=N), 6.57 (X part of the ABX system, 1 H, H-5), 5.73 (s, 1 H, H-3), 4.49 and 4.35 (AB part of the ABX system, J_{AB} 11.8, J_{AX} 8.3, and J_{BX} 3.3 Hz, H-6,6), 2.67 (bs, 3 H, NAc), 2.15, 2.09, and 2.03 (3 s, each 3 H, 3 AcO). Mass spectrum: *m/z* 508 (M^+).

Anal. Calc. for $C_{26}H_{28}N_4O_7$: C, 61.41; H, 5.55; N, 11.02. Found: C, 61.66; H, 5.58; N, 11.11.

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