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Note

Acetylation of chelated hydrazone derivatives

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The presence of two phenylhydrazone groups causes osazones[1] to behave differently from monohydrazones in most of their reactions[1b]. The chelated[2] structure **1** (R = R′ = H) explains the spectroscopic[1,3–5] and chemical properties of these compounds. With acetic anhydride in pyridine, *O*-acetyl derivatives (**1**, R = Ac, R′ = H) are produced[6]. Under more vigorous conditions (acetyl chloride in pyridine or *N,N*-dimethylaniline, hot acetic anhydride), only the non-chelated NH function of 1,2-bis(arylhydrazones), *e.g.*, **6**, **12**, and **15**, is acetylated[7–9], although **6** and **15** were not considered[4b,8,10] as chelated or were supposed[5,10] to be chelated systems with low stability. On the other hand, only the diacetate (**5**) of **3** (which contains only aldehyde phenylhydrazone moieties) is known[9a]. Hot acetic anhydride is unsuitable for the *N*-acetylation of osazones and their *O*-acetylated derivatives, since transformation into pyrazole-type *O,N*-acetyldianhydrophenylosazones[11,12] occurs. The *O*-acetylated mono-*N*-acetylated derivatives (**1**, R = R′ = Ac), prepared[12] by using acetyl chloride in pyridine, have been regarded hitherto[1c] as fully acetylated sugar phenylosazones.

The chelated[8,13–15] monoarylhydrazones (**2**) of 1,2-diketones remain unchanged[8,13] on treatment with either refluxing acetic anhydride or acetyl chloride in *N,N*-dimethylaniline. The stability of these chelates may be dependent on temperature, the polarity of the solvent[10a,16], and the alkaline[17] or acidic[18] character of the medium. Their transformation may be initiated photochemically[15,19–21] or by the complex-forming effect[22] of metal ions.

The acetylation reactions now reported were accomplished by disrupting chelation with the acetylium ion (Bronsted-acid catalysis) or by metal–complex formation.

Treatment of glyoxal bis(phenylhydrazone) (**3**) with acetic anhydride in pyridine at room temperature (conditions suitable for selective *O*-acetylation of saccharide osazones) afforded the monoacetate **4**. For the preparation of the simplest *ketone* analogue (**13**) of **4**, treatment of biacetyl bis(phenylhydrazone) (**12**) with boiling acetic anhydride was necessary. Similarly, **7**, supposed to be non-

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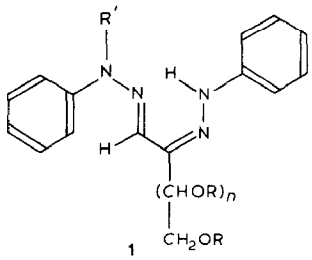

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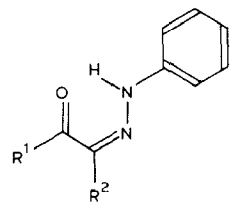

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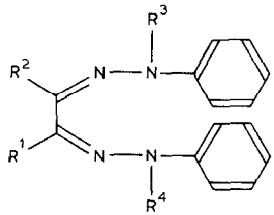

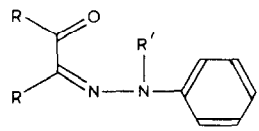

	R^1	R^2	R^3	R^4
3	H	H	H	H
4	H	H	Ac	H
5	H	H	Ac	Ac
6	Me	H	H	H
7	Me	H	Ac	H
8	Me	H	Ac	Ac
9	$(CHOAc)_3$ CH_2OAc	H	H	H
10	"	H	Ac	H
11	"	H	Ac	Ac
12	Me	Me	H	H
13	Me	Me	Ac	H
14	Me	Me	Ac	Ac
15	Ph	Ph	H	H
16	Ph	Ph	Ac	H
17	Ph	Ph	Ac	Ac

	R	R′
18	Me	H
19	Me	Ac
20	Ph	H
21	Ph	Ac

chelated [δ (Me_2SO-d_6) 9.68 (NH)][7], did not react with hot acetic anhydride. Thus, the NH group of the *ketone*-phenylhydrazone unit appears to be resistant towards acetylation, in agreement with structure **1** (R = R′ = Ac). However, methylglyoxal bis(acetylphenylhydrazone) (**8**) was obtained by treatment of **6** or **7** with acetic anhydride–zinc chloride.

The reaction of 3,4,5,6-tetra-*O*-acetyl-D-*lyxo*-hexosulose 1,2-bis(phenylhydrazone) (D-*lyxo*-**9**) with acetic anhydride–zinc chloride gave the crystalline D-*lyxo*-hexa-acetate **11**. The same product was obtained by the reaction of the D-*lyxo*-**9** or D-*lyxo*-**10** penta-acetate with acetic anhydride and trifluoroacetic acid. The change of the chelated NH group is reflected by the u.v. spectrum; the intense λ_{max}

in the spectrum of **9** or **10** at 380–390 nm disappeared upon acetylation, indicating the decreased electron-delocalisation in the phenylhydrazone moiety at C-2, which is responsible[4b] for this spectral band. Similar changes in the u.v. spectra were observed when the acetic anhydride–zinc chloride reagent was applied to other 1,2-bis(phenylhydrazones) and α-oxo-phenylhydrazones. In an analogous manner, acetylation of biacetyl bis(phenylhydrazone) (**12**) and benzil bis(phenylhydrazone) (**15**) [or its known[8] monoacetate **16**] afforded the bis(acetylphenylhydrazones) **14** and **17**, respectively. Under analogous conditions, biacetyl phenylhydrazone (**18**) gave the *N*-acetyl derivative **19**, and benzil phenylhydrazone (**20**) gave two stereoisomeric acetylated products of which the lower-melting isomer could be transformed into the higher-melting form.

The acetylation of other *O*-acetylated osulose-1-acetylphenylhydrazone-2-phenylhydrazones is being studied.

EXPERIMENTAL

Methods of acetylation. — (*a*) The starting material (2–5 mmol) was stirred with acetic anhydride (10 mL) containing anhydrous zinc chloride (1 g) until dissolution was complete. The solution was kept for 16–48 h at room temperature, and then poured into ice and water, the crude product was collected, and a solution in chloroform was treated with Fuller's earth and activated carbon, and then concentrated under diminished pressure. The residue was recrystallised from the solvents given.

(*b*) A solution of the starting material (1–1.1 mmol) in acetic anhydride (10 mL) and trifluoroacetic acid (0.9 mL) was kept for 24 h at room temperature, then concentrated under diminished pressure, and poured into ice and water. After the addition of sodium hydrogencarbonate, the solidified material was collected, and a warm solution of the crude product in benzene was processed as described in (*a*).

Glyoxal acetylphenylhydrazone phenylhydrazone (**4**). — Acetic anhydride (70 mL) was added to a solution of **3** (10.00 g, 42 mmol) in anhydrous pyridine (50 mL). The mixture was kept for 48 h at room temperature, and then poured into ice and water. The crude product (11.76 g, 100%) was extracted with hot methanol (30 mL), and the residue (7.62 g, m.p. 234–237°) was recrystallised from pyridine (40 mL) and water (15 mL) to yield **4** (7.36 g, 62.6%), m.p. 241–242° (dec.); λ_{max}^{MeOH} 240 (log ε 4.18), 302 (4.02), and 350 nm (4.71); λ_{min} 280 (3.89) and 308 nm (4.00); ν_{max}^{KBr} 3250 (NH), 1668 and 1661 (amide), 1603 cm^{-1} (Ar). ^{1}H-N.m.r. data (200 MHz): pyridine-d_5, δ 11.64 (s, 1 H, NH), 8.1–6.9 (m, 12 H, 2 Ph and 2 CH=N), and 2.50 (s, 3 H, Ac); Me_2SO-d_6, δ 10.75 (s, 1 H, NH), 2.40 (s, 3 H, Ac); CF_3CO_2H (the solvent as the internal standard), δ 12.5 (s, 1 H, exchangeable with deuterium by CF_3CO_2D, NH), 3.00 (s, 1 H, 1/3 Ac), and 2.93 (s, 2 H, 2/3 Ac). Mass spectrum: *m/z* 280 (M^+).

Anal. Calc. for $C_{16}H_{16}N_4O$: N, 19.99. Found: N, 19.90.

Methylglyoxal bis(acetylphenylhydrazone) (**8**). — (*a*) Compound **6** (1.00 g,

3.96 mmol) was acetylated by method (*a*) to give crude (0.811 g, 61%), and then recrystallised **8** (0.696 g, 52%), m.p. 135–136° (from dry ethanol–light petroleum); λ_{max}^{MeOH} 270 (log ε 4.13) and 303 (sh) nm (3.91); ν_{max}^{KBr} 1705, 1690 and 1684 (amide), 1590, and 1490 cm^{-1} (Ar). ^{1}H-N.m.r. data (100 MHz): $CDCl_3$, δ 7.44–7.00 (m, 11 H, 2 Ph and CH=N), 2.46 (s, 3 H, Ac), 2.04 (s, 3 H, Ac), 1.96 (s, 3 H, CMe); Me_2SO-d_6, δ 7.12 (s, 1 H, CH=N), 2.80 (s, ~1.3 H, 0.4 Ac), 2.71 (s, 3 H, Ac), 2.27 (s, 3 H, CMe), 2.20 (s, ~2 H, 0.6 Ac).

Anal. Calc. for $C_{19}H_{20}N_4O_2$: C, 67.84; H, 5.99; N, 16.66. Found: C, 68.00; H, 6.00; N, 16.80.

(*b*) Compound **7** (1.00 g, 3.40 mmol) was acetylated by method (*a*) to yield, after recrystallisation, **8** (0.515 g, 45%), m.p. 136°.

*3,4,5,6-Tetra-*O*-acetyl-*D*-lyxo-hexosulose 1,2-bis(acetylphenylhydrazone)* (**11**). — (*a*) Compound **10**[12] (9.00 g, 15.83 mmol) was acetylated by method (*b*) to give crude (9.40 g, 97%) or recrystallised **11** (5.56 g, 58%), m.p. 126.5–127° (from ethanol), $[\alpha]_D^{23}$ +43° (*c* 1, chloroform); λ_{max}^{MeOH} 237 (sh) (log ε 4.08), 286 (4.26), 320 (sh) nm (3.97); λ_{min} 255 (4.08), and 310 (sh) nm (4.04); ν_{max}^{KBr} 1748 and 1733 (OAc), 1702 and 1695 (NAc), 1590, 1578, and 1552 cm^{-1}. ^{1}H-N.m.r. data (200 MHz, $CDCl_3$): δ 7.46–6.76 (m, 10 H, 2 Ph), 6.58 (s, 1 H, CH=N), 6.20 (d, *J* ~9 Hz, H-3), 5.80 (dd, 1 H, *J* ~9 Hz, H-4), 5.57 (m, 1 H, H-5), 4.38–3.96 (m, 2 H, CH_2), 2.57 (s, 3 H, NAc), 2.18 (s, 3 H, NAc), 2.12 (s, 6 H, 2 Ac), 2.06 (s, 3 H, Ac), and 2.02 (s, 3 H, Ac).

Anal. Calc. for $C_{30}H_{34}N_4O_{10}$: C, 59.01; H, 5.61; N, 9.18. Found: C, 59.41; H, 5.59; N, 9.17.

(*b*) Acetylation of **9**[6b] (1.50 g, 2.85 mmol) by method (*b*) gave crude (1.65 g, 95%) or pure **11** (0.73 g, 42%), m.p. 126–126.5°.

(*c*) Compound **9**[6b] (5.00 g, 9.50 mmol) was acetylated by method (*a*) to yield **11** (2.80 g, 48%), m.p. 126°.

Biacetyl acetylphenylhydrazone phenylhydrazone (**13**). — A mixture of **12** (1.00 g, 3.75 mmol) and acetic anhydride (5 mL) was boiled under reflux until dissolution was complete (~12 min) and then for an aditional 30 min, cooled, and poured into ice and water. The resulting gum was triturated with ethanol (5 mL), and then water (3–4 mL) was added in small portions to give a crude product (0.813 g, 70%) which was homogeneous in t.l.c. (benzene–ethyl acetate, 2:1). Recrystallisation from ethanol–hexane gave **13** (0.642 g, 55.4%), m.p. 132°; λ_{max}^{MeOH} 231 (log ε 4.25), 273 (sh) (3.83), 298 (4.02), and 340 nm (4.52); λ_{min} 268 (3.81), 278 (sh) (3.85), and 302 nm (4.00); ν_{max}^{KBr} 3275 (NH), 1665, 1660 and 1652 cm^{-1} (amide). ^{1}H-N.m.r. data (100 MHz, $CDCl_3$): δ 7.80 (s, 1 H, exchangeable with deuterium, NH), 7.28–7.00 (m, 10 H, 2 Ph), 2.15 (s, 6 H, 2 Me), and 2.03 (s, 3 H, Ac).

Anal. Calc. for $C_{18}H_{20}N_4O$: C, 70.10; H, 6.54; N, 18.20. Found: C, 70.37; H, 6.33; N, 18.29.

Biacetyl bis(acetylphenylhydrazone) (**14**). — Compound **12** (5.00 g, 18.8 mmol) was acetylated by method (*a*) to give crude (4.84 g, 73.6%) and then recrystallised **14** (4.07 g, 62%), m.p. 142° (from dry ethanol–hexane); λ_{max}^{MeOH} 242 (log ε

4.19) and 309 nm (3.86); λ_{min} 227 (4.15) and 283 nm (3.78); ν_{max}^{KBr} 1675, 1668 and 1662 (amide), 1645 cm^{-1} (C=N). ^{1}H-N.m.r. data (100 MHz, $CDCl_3$): δ 7.30 ("s", 5 H, Ph), 7.25 ("s", 5 H, Ph), 2.24 (s, 6 H, 2 Ac), 1.90 (s, 6 H, 2 Me).

Anal. Calc. for $C_{20}H_{22}N_4O_2$: C, 68.55; H, 6.33; N, 15.99. Found: C, 68.75; H, 6.37; N, 16.08.

Biacetyl acetylphenylhydrazone (**19**). — Acetylation of **18** (2.00 g, 11.3 mmol) by method (*a*) afforded crude (1.264 g) or recrystallised **19** (1.02 g, 41%), m.p. 84–84.5° (from dry ethanol–hexane); λ_{max}^{MeOH} 240 (sh) (log ε 3.93), 269 (3.96); ν_{max}^{KBr} 1705 (amide), 1690 (C=O), 1607 cm^{-1} (C=N and Ar?). N.m.r. data ($CDCl_3$): ^{1}H (100 MHz), δ 7.40–7.08 (m, 5 H, Ph), 2.42 (s, 6 H, 2 CH_3CO), and 1.42 (s, 3 H, CH_3C=N); ^{13}C (50.3 MHz), δ 198.18 (C=O), 140.68 (C=N), 25.03 (CH_3C=O), 22.70 (CH_3C=O), and 13.41 (CH_3C=N). Mass spectrum: *m/z* 219 ($M^+ + 1$).

Anal. Calc. for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 65.82; H, 6.36; N, 13.02.

Benzil acetylphenylhydrazone (**21**). — Compound **20** (1.00 g, 3.33 mmol) was acetylated by method (*a*) to yield crude (1.116 g, 98%) or recrystallised **21** (0.506 g, 44%), m.p. 141° (from ethyl acetate–hexane); λ_{max}^{MeOH} 261 (log ε 4.32) and 2.71 (sh) nm (4.29); λ_{min} 230 nm (4.11); ν_{max}^{KBr} 1702 and 1698 (amide), 1665 cm^{-1} (ketone CO). ^{1}H-N.m.r. data (200 MHz, $CDCl_3$): δ 7.71–6.99 (m, 15 H, 3 Ph), 2.67 (bs, 3 H, Ac).

Anal. Calc. for $C_{22}H_{18}N_2O_2$: C, 77.17; H, 5.30; N, 8.18. Found: C, 77.26; H, 5.23; N, 8.09.

Addition of light petroleum to the above mother liquor gave material (0.37 g, 32%) having m.p. 107–108°; ν_{max}^{KBr} 1693 and 1660 cm^{-1} (amide and ketone CO, respectively). ^{1}H-N.m.r. data (200 MHz, $CDCl_3$): δ 8.10 (d, 1 H, J ~10 Hz, H-Ar), 7.64–6.86 (m, 14 H, H-Ar), 2.58 (bs, 0.75 H, ~0.25 Ac), 2.44 (s, ~0.2 H, ~0.06 Ac), and 2.32 (s, 2.1 H, ~0.7 Ac).

Anal. Found: C, 77.20; H, 5.27; N, 8.28.

To a hot solution of **21** (0.33 g), m.p. 107–108°, in ethyl acetate (0.6 mL) was added warm heptane (10 mL). The solution was seeded with crystals having m.p. 141° and kept for 3 h at ~80°. The deposited crystals (0.17 g), collected whilst still warm, had m.p. 141–142°.

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