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# Addition and cyclisation reactions of sugar phenylhydrazone derivatives via a 1,4-elimination process: preparation of 3-(2-acetamido-1-phenylhydrazonobutyl)-2(1*H*)-quinoxalinone and 3-(1-acetamidopropyl)-pyrazolo[3,4-*b*]quinoxaline (flavazole) derivatives

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ABSTRACT

Acetylation of 3-(L-*threo*-2,3,4-trihydroxy-1-phenylhydrazonobutyl)-2(1*H*)-quinoxalinone derivatives (**1a** and **1c**) and of the D-*erythro* diastereomers (**1b** and **1d**), prepared from L-ascorbic acid and D-isoascorbic acid, respectively, and then treatment of the products (**1h–1k**) with methanolic ammonia gave enantiomeric 3-(2-acetamido-3,4-dihydroxy-1-phenylhydrazonobutyl)-2(1*H*)-quinoxalinone derivatives (**3a–3d**) with unidentified configuration at C-2′ via a stereoselective nucleophilic 1,4-addition reaction to the transiently formed phenylazoene groups. The quinoxalinone derivatives with a free NH-1 group (e.g., **3a** and **3b**) were dehydrocyclised to give the corresponding acetamidodeoxypyrazoloquinoxalines (flavazoles, **4a** and **4b**). The phenyl group of the quinoxaline derivatives **1h–1j** could be nitrated selectively to give the corresponding *p*-nitrophenylhydrazones **1f** and **1g**. Thermolysis of **1h** afforded a pyrazolylquinoxaline derivative (**2b**).

## INTRODUCTION

Polyhydroxycarbonyl compounds carrying an arylhydrazono moiety and their *O*-acylated derivatives can be transformed[1–6] into various types of products by intra- or inter-molecular 1,4-addition reactions to the phenylazoethylene groups formed (usually transiently) during a 1,4-elimination process. The formation of such azoene structures is influenced by electronic (inductive and conjugative) effects and further transformations are determined by the nucleophilicity of the medium and the length of the unprotected side chain. With strong nucleophiles, $\alpha$-alkoxy[7–9], azido[9,10], amino[9,11], and thio[8] derivatives are produced in 1,4-addition

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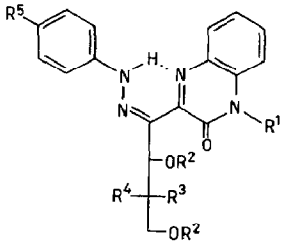
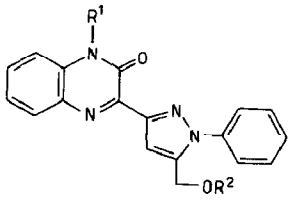




| | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ |
|---|---|---|---|---|---|
| 1a | H | H | H | HO | H |
| b | H | H | OH | H | H |
| c | Me | H | H | HO | H |
| d | Me | H | OH | H | H |
| e | H | H | H | HO | $NO_2$ |
| f | H | Ac | H | AcO | $NO_2$ |
| g | Me | Ac | H | AcO | $NO_2$ |
| h | H | Ac | H | AcO | H |
| i | H | Ac | OAc | H | H |
| j | Me | Ac | H | AcO | H |
| k | Me | Ac | OAc | H | H |

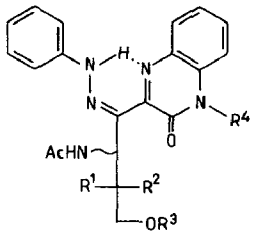
| | $R^1$ | $R^2$ |
|---|---|---|
| 2a | H | H |
| b | H | Ac |
| c | Me | H |
| d | Me | Ac |

reactions. In the presence of a sufficiently long unprotected side chain, intramolecular processes may lead to oxolane ring closure (formation of anhydro-osazones, formazans, etc.) and, when the side chain is shorter, additional elimination steps can result in pyrazole ring closure. Thus, under the conditions required for the development of the phenylazoethylene group, pentosulose 1,2-bis(phenylhydrazones) are transformed into the 3-amino-3-deoxy[9] or epimeric alkoxy compounds, whereas 3-(2,3,4-trihydroxy-1-phenylhydrazonobutyl)-2(1*H*)-quinoxalinones, or their *O*-acetyl analogues (e.g., **1a**, **1c**, or **1j**), which undergo further elimination steps, are converted[12,13] into pyrazole compounds (**2a–2d**).

As the cyclisation of quinoxalyl-poly(acetoxy)alkylketone arylhydrazones (**1**) into pyrazolylquinoxalines (e.g., **2a–2d**) is postulated[14] to involve the transient formation of the respective phenylazoethylene moiety, the synthesis of 2-amino analogues of the L-*threo* and D-*erythro* 3-(2,3,4-trihydroxy-1-phenylhydrazonobutyl)-2(1*H*)-quinoxalinones (**1a–d**) was attempted, based on earlier observations[9] on the reactions of osulose 1,2-bis(phenylhydrazones) with various nucleophiles.

## DISCUSSION

For the synthesis of the 2-acetamido analogues (**3a–d**), the 2,3,4-triacetoxy compounds (**1h–k**) were required. The product isolated after treatment of the L-*threo* compound **1a** with acetic anhydride in pyridine at room temperature was clearly not the reported[12] diacetoxy derivative **5b**, but the triacetoxy derivative **1h** as indicated by the elemental analysis and $^1$H-NMR data. El Ashry and coworkers[15]



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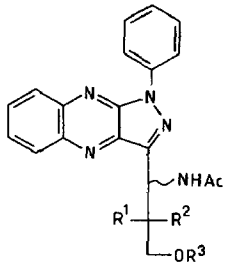

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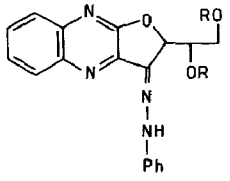
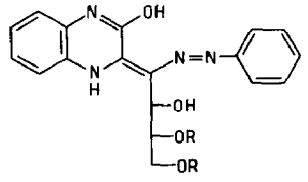
| | $R^1$ | $R^2$ | $R^3$ | $R^4$ |
|---|---|---|---|---|
| a | HO | H | H | H |
| b | H | OH | H | H |
| c | HO | H | H | Me |
| d | H | OH | H | Me |
| e | AcO | H | Ac | H |
| f | H | OAc | Ac | H |
| g | AcO | H | Ac | Me |
| h | H | OAc | Ac | Me |

identified the product of this reaction as the hemihydrate of **1h**. They assigned the $^1H$ signal at $\delta$ 14.42 (s) to NHCO and that at $\delta$ 12.31 (s) to =NNH; the reverse assignments are given in the Experimental because chelation of the 2-phenylhydrazono moiety involves[12] N-4, and the downfield shift of ~ 14 ppm for the NH resonance appeared in the spectra of the 1-methyl derivative **1j** and of the D-*erythro* diastereoisomer **1k** (see Experimental), whereas the signal at ~ 12 ppm was absent.

The phenyl group attached to the chelated system in *O*-acetylated osulose 1-acetylphenylhydrazone 2-phenylhydrazones can be nitrated regioselectively[16] via the *C*-nitroso compound at the *para* position with nitrous acid or with isopentyl nitrite. A similar reactivity was observed for the 3-(L-*threo*-2,3,4-triacetoxy-1-phenylhydrazonobutyl)-2(1*H*)-quinoxalinone derivatives (**1h** and **1j**), which gave the corresponding *p*-nitro analogues (**1f** and **1g**) with isopentyl nitrite as indicated by the $^1H$-NMR and mass spectral data (see Experimental) and proved by acetylation of the authentic *p*-nitrophenylhydrazone **1e**.



5a R = H
b R = Ac



6a R = H
b R = Ac

In contrast to data in the literature, treatment of each of the quinoxalinone derivatives **1a–1e** with acetic anhydride in pyridine at room temperature gave the corresponding triacetoxy derivatives (**1f** and **1h–1k**, but not the diacetoxy compounds **5b**[12] or **6b**[17]) irrespective of the relative configuration at C-2′ and C-3′. The triacetoxy derivative **1h** showed unusual melting behaviour (see Experimental) and, in the solid state, was converted extensively into the pyrazolylquinoxalinone **2b** on drying at 100°/0.1 mmHg (see Experimental). Based on this finding, **1h** could be transformed reproducibly into **2b** (~ 50%) by boiling a solution in xylene. The deep-red, unstable, syrupy intermediate of the thermolysis (possibly a 1-phenylazo-1-ene derivative), which could be isolated by column chromatography, was not identified.

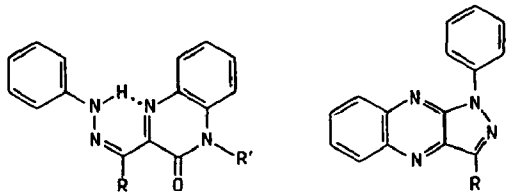
The chelated NHPh group of *O*-acetylated osulose 1,2-bis(phenylhydrazones) and 1-acetylphenylhydrazone-2-phenylhydrazones cannot be acetylated even with hot acetic anhydride, since, under such conditions, pyrazole-type dianhydrophenylosazones are produced[18] by 1,4-elimination of acetic acid via enosulose intermediates[5,6]. However, the chelated 2-phenylhydrazono moiety could be acetylated at room temperature in the presence of Lewis or Bronsted acid catalysts[19]. For the quinoxalinone derivatives **1**, acetylation of the chelated phenylhydrazono group failed and complex mixtures were obtained (see Experimental).

When the 2,3,4-triacetoxybutyl derivatives **1h–1k** were treated with methanolic ammonia, the corresponding 2-acetamido-3,4-dihydroxybutyl derivatives (**3a–3d**) were produced with high regio- and diastereo-selectivity. The transformation of the 1-*N*-methyl derivatives **1j** and **1k** were the most successful. For the non-*N*-methylated analogues (**1h** and **1i**), in addition to the desired 2-acetamido analogues (**3a** and **3b**), deacetylation products (**1a** and **1b**) and the pyrazolyl derivative **2a** were also formed. The formation of **2a** was due most probably to the stronger electron-withdrawing character of the 2-quinoxalinone moiety in **1h** and **1i**. In these reactions, the yield of the required acetamido analogues could be increased by acetylation of the crude product and repeated treatment with methanolic ammonia (see Experimental).

Based on studies of the chiral properties of C-2 of 2-acetamido-2-deoxyformazans[11], produced upon treatment of *O*-acetylated sugar formazans with ammonia in aqueous ethanol [and that of C-3 of 3-acetamido-3-deoxyosazones obtainable from *O*-acetylated osulose 1,2-bis(phenylhydrazones)], it was suggested[9] that the chirality of the *C*-NHAc carbon is determined by the chirality of the neighbouring carbon, with the formation of *threo* products being preferred. In accordance with this view, the L-*threo* (**1h** and **1j**) and D-*erythro* (**1i** and **1k**) triacetoxy compounds afforded the corresponding enantiomeric 2-acetamido-3,4-dihydroxy analogues (**3a** and **3c**, and **3b** and **3d**, respectively) as indicated by the mp's, $R_F$ and $[\alpha]_D$ values, the IR and $^1$H-NMR spectral data, and also the data for 2-acetamido-3,4-diacetoxy analogues (**3e** and **3g**, and **3f** and **3h**) (see Tables I and II, and Experimental). As the NHAc function is a poorer leaving group than the OAc, as observed[9] with the 3-acetamido-3-deoxyosazones, formation of **3e–3h** in the *O*-acetylation reactions of

TABLE I

Optical rotation data of phenylhydrazonobutyl-2-quinoxalinones (**A**) and the corresponding pyrazoloquinoxalines (**B**)



A B

| R | $[\alpha]_D$ ($CHCl_3$) | | | Ref. |
|---|---|---|---|---|
| | **A** | | **B** | |
| AcO, OAc, OAc | −527° | (**1h**, R′ = H) | +37.8° | 23 |
| | −641° | (**1j**, R′ = Me) | | 12 |
| OAc, OAc, OAc | −625° | (**1i**, R′ = H) | +64.4° | 22 |
| | −716° | (**1k**, R′ = Me) | +60.7° | 20 |
| AcO, NHAc, OAc | −246° | (**3e**, R′ = H) | +53° (**4e**) | |
| | −350° | (**3g**, R′ = Me) | | |
| NHAc, OAc, OAc | +242° | (**3f**, R′ = H) | −53° (**4f**) | |
| | +350° | (**3h**, R′ = Me) | | |

the acetamido derivatives **3a–3d** is not accompanied by the formation of pyrazolyl derivatives (**2b** and **2d**) even at higher temperature (see Experimental). Since it is not known which of the diastereoisomers undergoes AcO-2 → AcHN-2 transformation with retention or inversion of configuration, the C-2 chirality of the products could not be determined because of the medium $J_{1,2}$ values.

When heated in dilute alkali, the **1a**-type 3-(1-phenylhydrazonoalkyl)-2-quinoxalinones could be readily dehydrocyclised[12] into 3-polyhydroxyalkyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]quinoxalines (flavazoles). Analogous treatment of the 2-acetamido derivatives **3a** and **3b** results in the enantiomeric 3-(1-acetamido-2,3-dihydroxypropyl)pyrazoloquinoxalines **4a** and **4b**. The $^1$H-NMR data for these compounds and also for the corresponding diacetoxy derivatives **4e** and **4f** did not allow determination of the chirality of the *C*-NHAc centre.

3-Poly(acetoxy)alkyl-1-phenylpyrazolo[3,4-*b*]quinoxalines with (1′*S*) and (1′*R*) chirality possess[20] positive and negative optical rotations, respectively. As shown in Table I, the 3-(2,3,4-triacetoxy-1-phenylhydrazonobutyl)-2(1*H*)-quinoxalinones [**A** L-*threo* (**1h**), D-*erythro* (**1i**)] and their 1-*N*-methyl derivatives [**A** L-*threo* (**1j**),

D-*erythro* (**1k**)] have optical rotations of the opposite sign, as compared to the 3-triacetoxypropyl-1-phenylpyrazolo[3,4-*b*]quinoxalines [**B**, R = $-(CHOAc)_2CH_2$-OAc] carrying the same chiral side chain.

Such a correlation is valid also for the corresponding 2-acetamido analogues (**3e–3h** and **4e** and **4f**, respectively). The configuration of C-2′ in the quinoxalinones **1** and **3** (**A**) and C-1′ in the corresponding flavazoles **4** (**B**) makes the largest contribution to the optical rotation. But since there is no unambiguous correlation between the sign of the optical rotatory contribution of a given chiral centre with OAc and NHAc substituents, the *threo* configurations suggested for the acetamido analogues **3e–3h** (**A**) and **4e** and **4f** (**B**) are tentative.

## EXPERIMENTAL

*General methods.*—Melting points are uncorrected and were determined on a Kofler block. Solutions were concentrated under reduced pressure by using a rotatory evaporator. TLC was performed on Alurolle-Kieselgel $60F_{254}$ (Merck), using 1:1 benzene–EtOAc (*A*), $CHCl_3$–$Me_2CO$ mixtures (*B*, 95:5; *D*, 9:1), 95:5 $CHCl_3$–MeOH (*E*), and EtOAc–MeOH mixtures (*F*, 9:1; *G*, 8:2). Optical rotations were measured with a Schmidt–Haensch visual polarimeter (1-dm pathlength). IR spectra (KBr discs) were recorded with a Perkin–Elmer 283 B spectrophotometer, and 200-MHz $^1$H- and 50.3-MHz $^{13}$C-NMR spectra (internal $Me_4Si$) with a Bruker WP 200 SY spectrometer (in the compounds described below, the atoms of the hydroxylated alkyl substituents are designated by single primes). Mass spectra (70 eV) were obtained by using a VG-7035 GC/MS/DS instrument (ion current, 0.1 mA; direct insertion technique).

*3-(*D-erythro-*2,3,4-Trihydroxy-1-phenylhydrazonobutyl)-2(1*H*)-quinoxalinone* (**1b**).—As for the preparation of the L-*threo* diastereomer[12], D-isoascorbic acid (3.520 g, 19.6 mmol; Aldrich, 98%) was added to a stirred suspension of *p*-benzoquinone (2.160 g, 20 mmol) in MeOH (30 mL). The mixture was stirred until dissolution was complete (~ 10 min), then kept for 90 min at room temperature. A solution of *o*-phenylenediamine (2.160 g, 20 mmol) in MeOH (20 mL) was added, the solution was diluted with water (100 mL) and heated on a steam bath to ~ 100°, and phenylhydrazine (2.2 mL, 20 mmol) was added. The mixture was boiled under reflux for 30 min, then cooled to give **1b** (4.940 g, 71.1%), mp 205–206°, $[\alpha]_D^{23}$ −76° (*c* 0.9, pyridine); lit.[21] mp 203°, $[\alpha]_D^{16}$ −84.6° (pyridine).

*1-Methyl-3-(*D-erythro-*2,3,4-trihydroxy-1-phenylhydrazonobutyl)-2(1*H*)-quinoxalinone* (**1d**).—As for the preparation of the L-*threo* isomer[12], to a vigorously stirred solution of NaOH (4.60 g, 115 mmol) in water (300 mL) were added EtOH (200 mL), **1b** (20.00 g, 56.44 mmol), and, when the dissolution was practically complete, dimethyl sulfate (30 mL, ~ 316 mmol). The mixture was stirred for 5–10 min, then kept for 5 h at room temperature, and for 1 h in the refrigerator. The solid (19.12 g) was collected, washed with water, aq $NaHCO_3$, water, ether, and hexane, and extracted with hot MeOH (100 mL), to leave **1d** (16.10 g, 77.4%), mp 181–183°, $R_F$

0.48 (solvent *F*). Recrystallisation of the product (1.20 g) from MeOH (140 mL) afforded **1d** (1.00 g), mp 182.5–183°.

*Anal.* Calcd for $C_{19}H_{20}N_4O_4$: C, 61.94; H, 5.47; N, 15.21. Found: C, 62.40; H, 5.51; N, 15.02.

*3-(*L-threo-*2,3,4-Trihydroxy-1-*p-*nitrophenylhydrazonobutyl)-2(1*H*)-quinoxalinone* (**1e**).—With slight modifications of the literature methods[12,14], L-ascorbic acid (7.045 g, 40 mmol) was added to a suspension of *p*-benzoquinone (4.324 g, 40 mmol) in MeOH (60 mL). The mixture was stirred at room temperature until dissolution was complete, then stored for 1.5 h. *o*-Phenylenediamine (4.326 g, 40 mmol) was added, the mixture was boiled for 15 min, *p*-nitrophenylhydrazine (6.126 g, 40 mmol) and AcOH (1 mL) were added, and boiling was continued for 90 min. The mixture was then cooled, and the precipitate was collected, washed with MeOH, 50% MeOH, and then water to give **1e** (12.953 g, 81%), mp 216°; lit.[14] mp 217°.

*3-(*L-threo-*2,3,4-Triacetoxy-1-*p-*nitrophenylhydrazonobutyl)-2(1*H*)-quinoxalinone* (**1f**).—(*a*) A mixture of $Ac_2O$ (22 mL), anhydrous pyridine (86 mL), and **1e** (8.600 g, 21.53 mmol) was shaken and cooled until dissolution was complete, then kept for 28 h at room temperature, and concentrated at $\not> 36°$ (bath), and the residue was treated with ice and water. Crystallisation of the product (11.480 g) from EtOH (230 mL) and water (80 mL) afforded **1f** (3.770 g, 33.3%), mp 192–193°, $R_F$ 0.38 (solvent *A*), $[\alpha]_D^{23}$ −444° (*c* 0.4, chloroform); $\nu_{max}^{KBr}$ 3200 (NH), 1745 (OAc), 1675 (NHCO), 1599 $cm^{-1}$ (Ar). $^1$H-NMR data ($CDCl_3$): δ 14.11 (s, 1 H, slowly exchangeable with $D_2O$, =NN*H*–), 11.89 (s, 1 H, exchangeable with $D_2O$, N*H*CO), 8.24 (d, 2 H, H-3,5 of the benzene ring), 7.79–7.74 (m, 1 H, aromatic H), 7.62–7.54 (m, 1 H, aromatic H), 7.44–7.29 (m, 5 H, aromatic H), 6.90 (d, 1 H, $J_{2',3'}$ 5 Hz, H-2′), 6.09–5.98 (m, 1 H, H-3′), 4.60–4.41 (m, 2 H, H-4′,4′), 2.15, 2.07, and 2.05 (3 s, each 3 H, 3 Ac).

*Anal.* Calcd for $C_{24}H_{23}N_5O_9$: C, 54.85; H, 4.41; N, 13.33. Found: C, 54.89; H, 4.80; N, 13.38.

(*b*) A mixture of **1h** (0.7207 g, 1.5 mmol), anhydrous benzene (20 mL), and isopentyl nitrite (0.60 mL, 4.4 mmol) was stirred for 20 h at room temperature, then more isopentyl nitrite (0.60 mL, 4.4 mmol) was added. The mixture was kept for 70 h at room temperature, then filtered to give **1f** (0.3734 g, 47.3%), mp 192–194°. From the mother liquor, a second crop of **1f** (0.0766 g, 9.7%), mp 191–192°, was obtained.

*1-Methyl-3-(*L-threo-*2,3,4-triacetoxy-1-*p-*nitrophenylhydrazonobutyl)-2(1*H*)-quinoxalinone* (**1g**).—A mixture of **1j** (1.4835 g, 3.0 mmol), anhydrous benzene (30 mL), and isopentyl nitrite (1.80 mL, 13.2 mmol) was stirred for 1 day, then more isopentyl nitrite (2.0 mL, 14.6 mmol) was added. The mixture was kept for 2 days at room temperature, then filtered to give **1g** (1.006 g, 62%), mp 191°, $[\alpha]_D^{23}$ −500° (*c* 0.4, chloroform). The mother liquor was treated with a stream of oxygen for 7 h, stored for 2.5 days, then filtered to give more **1g** (0.210 g, 13%), mp 190–192°. A solution of the crude products in $CHCl_3$ was treated with fuller's earth and

charcoal, then concentrated, and the residue was crystallised from MeOH (5 mL) to give **1g** (1.178 g, 72.8%), $R_F$ 0.52 (solvent *A*), mp 187–188°; $\nu_{max}^{KBr}$ 1742 (OAc), 1657 (amide), 1597 $cm^{-1}$ (Ar). $^1$H-NMR data ($CDCl_3$): $\delta$ 13.89 (s, 1 H, exchangeable with $D_2O$, –N*H*N=), 8.26–8.21 (m, 2 H, H-3,5 of the benzene ring), 7.86–7.30 (m, aromatic H), 6.76 (d, 1 H, $J_{2',3'}$ 5.5 Hz, H-2'), 6.03–5.95 (m, 1 H, H-3'), 4.51–4.38 (m, 2 H, $CH_2$), 3.77 (s, 3 H, NMe), 2.10, 2.09, and 2.04 (3 s, each 3 H, 3 Ac). Mass spectrum: *m/z* 421 ($M^+$ – AcOH – Ac – Me), 378 (base peak, $M^+$ – 2 Ac – AcOH – Me), 138 (nitroaniline$^+$).

*Anal.* Calcd for $C_{25}H_{25}N_5O_9$: C, 55.65; H, 4.67; N, 12.98. Found: C, 55.94; H, 4.68; N, 12.79.

*3-(*L-threo*-2,3,4-Triacetoxy-1-phenylhydrazonobutyl)-2(1*H*)-quinoxalinone* (**1h**). —A mixture of $Ac_2O$ (9.5 mL), anhydrous pyridine (40 mL), and **1a**[12] (3.540 g, 9.99 mmol) was shaken with cooling until dissolution was complete (~ 30 min), kept for 2 days at room temperature, and then concentrated at ≯ 30° (bath). The syrupy residue was triturated with ice and water, and the solid was collected, washed with water, and dried in a vacuum desiccator over $P_2O_5$ to give a homogeneous (TLC) product (4.730 g). Recrystallisation from MeOH (15 mL) and water (5 mL) gave **1h** (4.297 g, 89.5%), $R_F$ 0.42 (solvent *A*), mp 134–135° (upon raising the temperature, the melt solidified at ~ 139°, melted again at 167–168°, and on cooling to ~ 100° resolidified to a crystalline mass with mp 237–245°), $[\alpha]_D^{23}$ –527° (*c* 0.4, chloroform) and –434° (*c* 0.5, pyridine); $\nu_{max}^{KBr}$ 3540 (NH), 3460 (NH), 1745 (OAc), 1667 (NHCO), 1601 $cm^{-1}$ (Ar). $^1$H-NMR data ($CDCl_3$): $\delta$ 14.10 (s, 1 H, slowly exchangeable with $D_2O$, =NN*H*–), 12.0 (bs, 1 H, exchangeable with $D_2O$, H-1, e.g., N*H*CO), 7.69–7.65 (m, 1 H, aromatic H), 7.51–7.27 (m, 7 H, aromatic H), 7.05–6.99 (d, 1 H, $J_{2',3'}$ 6 Hz, H-2'; m, 1 H, aromatic H), 6.09–6.00 (quasi-q, 1 H, $J_{2',3'}$ 6, $J_{3',4'}$ 5 Hz, H-3'), 4.51 (d, 2 H, $J_{3',4'}$ 5 Hz, $CH_2$), 2.10, 2.05, and 2.04 (3 s, each 3 H, 3 Ac). Mass spectrum: *m/z* 420 ($M^+$ – AcOH), 360 (**2b**$^+$).

*Anal.* Calcd for $C_{24}H_{24}N_4O_7$: C, 59.99; H, 5.03; N, 11.66. Calcd for $C_{24}H_{24}N_4O_7 \cdot 0.5H_2O$: C, 58.89; H, 5.15; N, 11.45. Found: C, 59.22; H, 5.14; N, 11.63.

When **1h** was stored at 100°/~ 0.1 mmHg over $P_2O_5$, there was a 12.5% loss in weight to give a solid mixture consisting mainly of the pyrazolyl compound **2b** together with **1h** (TLC).

*Attempted* N-*acetylation of* **1h**.—(*a*) Treatment of **1h** (0.4805 g, 1 mmol) with $Ac_2O$ (10 mL) and > 98% trifluoroacetic acid (1 mL, 13 mmol) at room temperature for 4 days, followed by conventional work-up, gave a wax-like product which contained (TLC) **2b** and seven other components.

(*b*) Treatment of **1h** (2.00 g, 4.16 mmol) with $Ac_2O$ (24 mL) and aq 70% perchloric acid (0.4 mL, 4.64 mmol) for 7 days at room temperature, followed by conventional work-up, gave a syrupy product which contained (TLC, solvents *A* and *D*) **1h**, traces of **2b**, and many other components.

(*c*) Treatment of **1h** (1.00 g, 2.08 mmol) with $Ac_2O$ (20 mL) and anhyd $ZnCl_2$ (2 g, 14.7 mmol) for 5 days at room temperature, followed by conventional work-up

and column chromatography (Kieselgel 60, solvent *B*) of the product, gave **1h** (0.098 g, 9.8%), mp 135–136°, as the sole identified compound.

All of the above reactions were accompanied by intense discolouration of the reaction mixtures.

*3-(*D-erythro-*2,3,4-Triacetoxy-1-phenylhydrazonobutyl)-2(1*H*)-quinoxalinone* (**1i**). —A mixture of **1b** (4.833 g, 13.64 mmol), $Ac_2O$ (15 mL), and anhydrous pyridine (30 mL) was shaken and cooled until dissolution was complete, then kept for 24 h at room temperature, and concentrated at ≯ 34° (bath). The residue was triturated with ice and water to yield a homogeneous product (6.348 g), $R_F$ 0.37 (solvent *A*). Recrystallisation from EtOH gave **1i** (5.358 g, 81.8%), mp 164–165°, $[\alpha]_D^{23}$ −625° (*c* 1, chloroform); $\nu_{max}^{KBr}$ 1750 (OAc), 1671 (NHCO), 1617 (shoulder) and 1607 $cm^{-1}$ (C=N and Ar). $^1$H-NMR data ($CDCl_3$): δ 14.22 (s, 1 H, slowly exchangeable with $D_2O$, =NN*H*–), 12.34 (s, 1 H, exchangeable with $D_2O$, N*H*CO), 7.80–7.31 (m, 8 H, aromatic H), 7.16 (d, 1 H, $J_{2',3'}$ 5.5 Hz, H-2′), 7.08–7.00 (m, 1 H, aromatic H), 5.99–5.92 (m, 1 H, H-3′), 4.82–4.42 (m, 2 H, $CH_2$), 2.09, 2.07, and 2.06 (3 s, each 3 H, 3 Ac).

*Anal.* Calcd for $C_{24}H_{24}N_4O_7$: C, 59.99; H, 5.03; N, 11.66. Found: C, 59.91; H, 5.13; N, 11.86.

*1-Methyl-3-(*L-threo-*2,3,4-triacetoxy-1-phenylhydrazonobutyl)-2(1*H*)-quinoxalinone* (**1j**).—A mixture of $Ac_2O$ (32 mL), anhydrous pyridine (100 mL), and **1c**[12] (10.264 g, 27.86 mmol) was shaken with cooling until dissolution was complete (3–4 min), then kept for 1 day at room temperature, and concentrated at ≯ 41° (bath). The crystalline residue was triturated with ice and water, and the crude product (13.490 g) was recrystallised from MeOH to give **1j** (10.960 g, 79.5%), $R_F$ 0.60 (solvent *A*), mp 128°; $\nu_{max}^{KBr}$ 1744 (OAc), 1659 [N(Me)CO], 1602 and 1585 $cm^{-1}$ (Ar). NMR data ($CDCl_3$): $^1$H, δ 14.23 (s, ~ 1 H, slowly exchangeable with $D_2O$, N*H*Ph), 7.79–6.97 (m, 9 H, aromatic H), 6.91 (d, 1 H, $J_{2',3'}$ 6 Hz, H-2′), 6.06–5.98 (quasi-q, 1 H, $J_{2',3'}$ 6, $J_{3',4'}$ 5.5 Hz, H-3′), 4.47 (d, 2 H, $J_{3',4'}$ ~ 5.5 Hz, $CH_2$), 3.73 (s, 3 H, NMe), 2.08, 2.07, and 2.05 (3 s, each 3 H, 3 Ac); $^{13}$C, δ 170.61 ($CH_3CO$), 170.37 (2 $CH_3CO$), 29.29 ($NCH_3$), 20.87, 20.80, and 20.63 (3 $CH_3CO$). Mass spectrum: *m/z* 495 ($M^+ + 1$), 435 ($M^+ + 1 - AcOH$).

*Anal.* Calcd for $C_{25}H_{26}N_4O_7$: C, 60.72; H, 5.30; N, 11.33. Found: C, 60.96; H, 5.39; N, 11.20.

*1-Methyl-3-(*D-erythro-*2,3,4-triacetoxy-1-phenylhydrazonobutyl)-2(1*H*)-quinoxalinone* (**1k**).—Acetylation (for 2 days) of **1d** (17.22 g, 46.75 mmol) with $Ac_2O$ (52 mL) in pyridine (100 mL), as described for the preparation of **1j**, and recrystallisation of the product (23.35 g) from MeOH gave **1k** (19.35 g, 83.7%), $R_F$ 0.56 (solvent *A*), mp 123–124° (the crystals formed from the melt on cooling had mp ~ 138°). When **1j** was dried at 100°/ ~ 0.1 mmHg for several hours (loss of weight, 1.1%; $R_F$ unchanged), it had mp 146–147°, $[\alpha]_D^{23}$ −716° (*c* 1, chloroform); $\nu_{max}^{KBr}$ 1749 (OAc), 1666 [N(Me)CO], 1607 and 1588 $cm^{-1}$ (Ar). $^1$H-NMR data ($CDCl_3$): δ 13.98 (s, 1 H, exchangeable with $D_2O$, NN*H*Ph), 7.82–7.24 (m, 8 H, Ph and 3 aromatic H), 7.05–6.95 (m, 1 H, aromatic H), 6.94 (d, 1 H, $J_{2',3'}$ ~ 5 Hz,

H-2′), 5.96–5.88 (m, 1 H, H-3′), 4.77–4.38 (ABX-m, 2 H, $CH_2$), 3.73 (s, 3 H, NMe), 2.08–2.05 (3 s, each 3 H, 3 Ac). Mass spectrum: $m/z$ 495 ($M^+ + 1$); the fragmentation pattern was similar to that of the L-*threo* analogue (**1j**).

*Anal.* Calcd for $C_{25}H_{26}N_4O_7$; C, 60.72; H, 5.30; N, 11.33. Found: C, 60.70; H, 5.25; N, 11.56.

*3-(5-Acetoxymethyl-1-phenylpyrazol-3-yl)-2(1H)-quinoxalinone* (**2b**).—(*a*) A solution of **1h** (2.000 g, 4.16 mmol) in xylene (15 mL) was boiled for ~3 h, then cooled, and diluted with hexane (10 mL). A solution of the crude product (1.144 g, 76.3%, mp 242–244°) in warm $CHCl_3$ was treated with charcoal, then concentrated. The residue was boiled with EtOH (7 mL) for a few minutes to give **2b** (0.779 g, 52%), mp 249–250°, which was identical on the basis of TLC [$R_F$ 0.27 (solvent *A*)], IR, $^1$H-NMR, and mass spectral data with authentic[14] **2b**.

(*b*) A solution of **1h** (1.00 g, 2.08 mmol) in $Ac_2O$ (5 mL) was boiled for 60 min, then concentrated. The residue was triturated with ice and water, and a solution of the product in $CHCl_3$ was washed with aq $NaHCO_3$ and water, dried ($MgSO_4$), decolourised with fuller's earth and charcoal, and then concentrated.

(*c*) A solution of **1h** (1.00 g, 2.08 mmol) in $Ac_2O$ (10 mL) was boiled for 15 min[14], then cooled and poured onto crushed ice.

Column chromatography (Kieselgel 60, solvent *B*) of the amorphous products obtained in (*b*) and (*c*) afforded **2b** (25–30%), mp 249–250°.

*Preparation of 3-(2-acetamido-3,4-dihydroxy-1-phenylhydrazonobutyl)-2(1H)-quinoxalinones and the 1-methyl derivatives* (**3a–d**, see Table II).—(*a*) The triacetate **1** (10 g) was added, with ice-cooling, to MeOH (50–60 mL) saturated with $NH_3$ at 0°. When dissolution was complete, the solution was kept at 0–4° for ~70 h, then concentrated. The residue was treated with ice-cold water, and the crude product was collected and crystallised.

(*b*) When the crude product obtained in (*a*) contained considerable proportions of deacetylated derivatives, it was treated conventionally with $Ac_2O$ in pyridine. The resulting crude product (mainly a mixture of the tri-*O*-acetyl and 2-acetamido-3,4-di-*O*-acetyl-2-deoxy compounds) was re-treated with $NH_3$–MeOH as in (*a*), and the product was extracted twice with 12–15-fold amounts of hot MeOH to leave a crude product that could be crystallised.

*3-(L-2-Acetamido-3,4-diacetoxy-1-phenylhydrazonobutyl)-2(1H)-quinoxalinone* (**3e**).—A mixture of $Ac_2O$ (10 mL), anhydrous pyridine (5 mL), and **3a** (1.000 g, 2.529 mmol) was stirred until dissolution was complete (~3 h), then kept for 19 h at room temperature, and concentrated at $\not>$ 40° (bath), and the residue was treated with ice and water. Column chromatography (solvent *E*) of the crude product (1.197 g) and crystallisation from ether afforded **3e** (1.064 g, 87.7%), mp 229°, $[\alpha]_D^{23}$ −246° (*c* 0.5, chloroform); $\nu_{max}^{KBr}$ 3420 and 3080 (NH), 1754 (OAc), 1681 (amide), 1608 $cm^{-1}$ (Ar). $^1$H-NMR data ($CDCl_3$): $\delta$ 13.99 (s, 1 H, slowly exchangeable with $D_2O$, N*H*Ph), 12.21 (s, 1 H, exchangeable with $D_2O$, H-1), 7.66–7.00 (m, 9 H, aromatic H), 6.76 (d, 1 H, $J_{NH,2'}$ ~10 Hz, exchangeable with $D_2O$, N*H*Ac), 6.57 (dd, 1 H, $J_{NH,2'}$ ~10, $J_{2',3'}$ ~3.3 Hz, H-2′), 5.90–5.81 (m, 1 H, H-3′),

TABLE II

Preparation and physical data of the 2-acetamido analogues **3a**–**3d**

| Product | Starting material | Method[a] | Reaction time (h) at 0–4° | Yield (%) [crude (pure)] | Mp (degrees) | $[\alpha]_D^{23}$ ($c$ 0.5, $Me_2SO$) | Formula *Anal.*: Found (Calcd) |
|---|---|---|---|---|---|---|---|
| **3a**[b] | **1h** | (*b*) | 65–70 | 77 (42) | 244–245 (from $MeOCH_2CH_2OH$–$H_2O$) | +33° | $C_{20}H_{21}N_5O_4$: C, 60.71 (60.74); H, 5.53 (5.35); N, 17.48 (17.71) |
| **3b**[b] | **1i** | (*b*) | 65–70 | 86 (45) | 243–244 (from $MeOCH_2CH_2OH$–$H_2O$) | −34° | $C_{20}H_{21}N_5O_4$: C, 60.80 (60.74); H, 5.46 (5.35); N, 17.52 (17.71) |
| **3c**[c] | **1j** | (*a*) | 70–80 | 96 (73) | 240–241 (from MeOH) | +33° | $C_{21}H_{23}N_5O_4$: C, 61.76 (61.60); H, 5.93 (5.66); N, 17.16 (17.11) |
| **3d**[c] | **1k** | (*a*) | 70 | 100 (68)[d] | 239–240 (from MeOH) | −31° | $C_{21}H_{23}N_5O_4$: C, 61.75 (61.60); H, 5.72 (5.66); N, 17.23 (17.11) |

[a] See Experimental. [b] The products **3a** and **3b** have $R_F$ 0.45 (solvent *G*) and identical IR spectra [$\nu_{max}^{KBr}$ 1670 (amide), 1605 $cm^{-1}$ (Ar)]. [c] The products **3c** and **3d** have $R_F$ 0.32 (solvent *F*) and identical IR spectra [$\nu_{max}^{KBr}$ 1652 (amide), 1603 $cm^{-1}$ (Ar)]. [d] An impure by-product (~2%; N, 16.99%) with an $R_F$ value similar to that of **3d** was isolated and considered to be the C-2′ epimer.

4.55–4.36 (m, 2 H, $CH_2$), 2.15 (s, 3 H, NHAc), 2.01 and 2.00 (2 s, each 3 H, 2 AcO).

*Anal.* Calcd for $C_{24}H_{25}N_5O_6$: C, 60.12; H, 5.26; N, 14.61. Found: C, 60.37; H, 5.49; N, 14.48.

*3-(D-2-Acetamido-3,4-diacetoxy-1-phenylhydrazonobutyl)-2(1H)-quinoxalinone* (**3f**).—Acetylation of **3b** (1.000 g, 2.529 mmol) and column chromatography of the crude product (1.205 g), as described above for **3e**, afforded **3f** (0.985 g, 81.2%), mp 227° (from ether), $[\alpha]_D^{23}$ +242° (*c* 0.6, chloroform), $R_F$ 0.23 (solvent *E*). The $R_F$ value and the IR and $^1$H-NMR spectral data of **3f** and **3e** were identical.

*Anal.* Calcd for $C_{24}H_{25}N_5O_6$: C, 60.12; H, 5.26; N, 14.61. Found: C, 60.48; H, 5.39; N, 14.35.

*3-(L-2-Acetamido-3,4-diacetoxy-1-phenylhydrazonobutyl)-1-methyl-2(1H)-quinoxalinone* (**3g**).—A mixture of $Ac_2O$ (6 mL), anhydrous pyridine (4 mL), and **3c** (1.242 g, 3.032 mmol) was heated on a steam bath for 2 h, then concentrated. The mainly crystalline residue was triturated with EtOH (2 mL), and the mixture was kept for ~2 h at room temperature, then diluted gradually with water (~25 mL) to give the crude product (1.411 g), a solution of which in $CHCl_3$ was treated with fuller's earth and activated carbon, then concentrated. Crystallisation of the residue from EtOAc (4 mL) and hexane (4 mL) afforded **3g** (1.243 g, 83%), mp 149–150°, $[\alpha]_D^{23}$ −350° (*c* 0.5, chloroform); $\nu_{max}^{KBr}$ 1744 (OAc), 1680 (shoulder) and 1659 (amide), 1601 and 1584 $cm^{-1}$ (Ar). $^1$H-NMR data ($CDCl_3$): δ 14.30 (s, 1 H, slowly exchangeable with $D_2O$, N*H*Ph), 7.80–6.97 (m, 9 H, aromatic H), 6.66 (d, 1 H, $J_{NH,2'}$ 10 Hz, exchangeable with $D_2O$, N*H*Ac), 6.41 (dd, 1 H, $J_{NH,2'}$ 10, $J_{2',3'}$ 3.5 Hz, H-2′), 5.85–5.77 (m, 1 H, H-3′), 4.48–4.32 (m, 2 H, $CH_2$), 3.74 (s, 3 H, NMe), 2.08, 2.04, and 1.99 (3 s, each 3 H, 3 Ac).

*Anal.* Calcd for $C_{25}H_{27}N_5O_6$: C, 60.84; H, 5.52; N, 14.19. Found: C, 60.58; H, 5.54; N, 14.02.

*3-(D-2-Acetamido-3,4-diacetoxy-1-phenylhydrazonobutyl)-1-methyl-2(1H)-quinoxalinone* (**3h**).—Acetylation of **3d** (2.000 g, 4.885 mmol), as described above for **3g**, afforded **3h** (2.076 g, 86.1%), mp 148° (from EtOAc–hexane), $[\alpha]_D^{23}$ +350° (*c* 0.5, chloroform), $R_F$ 0.47 (solvent *E*). The $R_F$ value and the IR and $^1$H-NMR spectral data of **3g** and **3h** were identical.

*Anal.* Calcd for $C_{25}H_{27}N_5O_6$: C, 60.84; H, 5.52; N, 14.19. Found: C, 60.63; H, 5.58; N, 14.27.

*3-(1-Acetamido-1-deoxy-L-glycerol-1-yl)-1-phenyl-1H-pyrazolo[3,4-b]quinoxaline* (**4a**).—A mixture of NaOH (0.800 g, 20 mmol), water (200 mL), **3a** (3.954 g, 10 mmol), and 1-butanol (2–3 drops) was boiled under reflux for 45 min, then cooled. The product was collected and washed with aq 10% AcOH to give a homogeneous crude product (3.541 g), $R_F$ 0.42 (solvent *F*), mp 253–255°, which was recrystallised from aq 50% AcOH to give **4a** (2.041 g, 54.1%), mp 259–260°; $\nu_{max}^{KBr}$ 1651 (amide), 1604 $cm^{-1}$ (Ar). $^1$H-NMR data [$(CD_3)_2SO$]: δ 2.04 (s, 3 H, *N*Ac). Mass spectrum (CI, $NH_4Cl$): *m/z* 359 ($M^+ - H_2O$).

*Anal.* Calcd for $C_{20}H_{19}N_5O_3$: C, 63.65; H, 5.07; N, 18.56. Found: C, 63.90; H, 5.27; N, 18.35.

*3-(1-Acetamido-1-deoxy-D-glycerol-1-yl)-1-phenyl-1H-pyrazolo[3,4-b]quinoxaline* (**4b**).—Compound **3b** (0.395 g, 1 mmol) was treated as described above for **3a**, to yield crude **4b** (0.330 g, 87.4%), mp 252–254°, $R_F$ 0.42 (solvent *F*). The product, which had a contaminant with $R_F$ 0.52, was characterised as the diacetate **4f** as described for **4e**. Compound **4f** had mp 177° (from anhyd EtOH and hexane), $[\alpha]_D^{23}$ −53° (*c* 0.5, chloroform). The $R_F$ value and the IR and $^1$H-NMR spectra were identical with those of **4e**.

*Anal.* Calcd for $C_{24}H_{23}N_5O_5$: N, 15.18. Found: N, 15.14.

*3-(1-Acetamido-2,3-di-O-acetyl-1-deoxy-L-glycerol-1-yl)-1-phenyl-1H-pyrazolo[3,4-b]quinoxaline* (**4e**).—A mixture of **4a** (3.542 g, 9.387 mmol), $Ac_2O$ (33 mL), and anhydrous pyridine (22 mL) was heated on a steam bath for 2.5 h, then concentrated. The residue was triturated with ice and water to give the crude product (4.275 g) which was crystallised from anhyd EtOH–hexane to give **4e** (3.658 g, 84.4%), mp 177°, $R_F$ 0.27 (solvent *D*), $[\alpha]_D^{23}$ +53° (*c* 0.5, chloroform); $\nu_{max}^{KBr}$ 3300 (NH), 1746 (OAc), 1658 (NAc), 1599 $cm^{-1}$ (Ar). $^1$H-NMR data ($CDCl_3$): $\delta$ 8.44–7.30 (m, 9 H, aromatic H), 7.08 (d, 1 H, $J_{1',NH}$ 9.5 Hz, exchangeable with $D_2O$, NH), 6.29 (dd, 1 H, $J_{1',NH}$ 9.5, $J_{1',2'}$ 4.5 Hz, H-1'), 5.90–5.82 (m, 1 H, H-2'), 4.49–4.21 (ABX-m, 2 H, $CH_2$), 2.17, 2.07, and 1.98 (3 s, each 3 H, 3 Ac). Mass spectrum: *m/z* 462 ($M^+ + 1$), 461 ($M^+$), 401 ($M^+ - AcOH$), 316 ($M^+ - HCOAcCH_2OAc$), 274 (base peak, 1-phenyl-1*H*-pyrazolo[3,4-*b*]quinoxaline-3-carboxaldimine$^+ + 1$).

*Anal.* Calcd for $C_{24}H_{23}N_5O_5$: C, 62.46; H, 5.02; N, 15.18. Found: C, 62.45; H, 5.32; N, 15.01.

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