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Note

Isopropylidenation of L-*threo*- and D-*erythro*-trihydroxybutylquinoxalinones. A novel approach to the synthesis of furo[2,3-*b*]quinoxalines

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Recently a novel method for the construction of the furo[2,3-*b*]quinoxaline ring system was achieved[1,2] by the dehydrative cyclisation of analogues of **2** during the acylation reactions under which condition **2** itself undergoes dehydration to give **8** or **9** depending upon the reagent used[1]. On the other hand, the structure **4** was reported[3–14] for the product from the reaction of **1** with *o*-phenylenediamine and phenylhydrazine. The structure was based on the formation of a di-*O*-acetyl derivative[4]. However, the structure **2** was given for that product based on the results of periodate oxidation studies[9,14], and its acetyl derivative was revised[2] to be a hemihydrate of its tri-*O*-acetyl derivative whose structure was confirmed by X-ray crystallography[2].

In the present work, it seemed feasible that partial protection of the hydroxyl groups of **2** may afford derivatives such as **6**, whose acylation would form the furo[2,3-*b*]quinoxaline ring system. Consequently, the isopropylidenation of **2** and its D-*erythro* analogue **10** has been studied whereby a novel approach for constructing the furo[2,3-*b*]quinoxaline was achieved.

The isopropylidenation of 3-[1-(phenylhydrazono)-L-*threo*-2,3,4-trihydroxybutyl]quinoxalin-2-one (**2**) had been expected to form either the corresponding *α-threo*-1,3-dioxolane, the *α*-terminal-1,3-dioxolane, or the *β*-terminal-1,3-dioxane ring system. However, isopropylidenation of **2** with acetone and a catalytic amount of sulfuric acid did not afford any of the three anticipated products, but instead gave 2,2′-anhydro-[3-(1-(phenylhydrazono)-L-*threo*-3,4-*O*-isopropylidene-2,3,4-trihydroxybutyl]quinoxaline (**5**). This result indicated that a novel dehydrative cyclisation had taken place in addition to the terminal isopropylidenation. The structure of **5** was confirmed by a combination of chemical and physical methods. Compound **5** resisted acetylation with acetic anhydride in pyridine, indicating the absence of hydroxyl groups. Aqueous acetic acid caused hydrolysis of the isopropylidene ring to give 2-2′-anhydro-[3-(1-(phenylhydrazono)-L-*threo*-2,3,4-trihy-

droxybutyl]quinoxaline (**4**). However, when excess of acetic acid was used, 3-[5-(hydroxymethyl)-1-phenyl-pyrazol-3-yl]quinoxalin-2-one[11] (**8**) was obtained. The IR spectrum of **5** did not show any absorption band in the carbonyl frequency region, indicating the absence of the lactam carbonyl group. Its ^{1}H NMR spectrum showed the isopropylidene (δ 1.33), H-4,4′ (δ 4.05), H-3 (δ 4.60), H-2 (δ 5.50), aromatic (δ 7.12), and NH (δ 12.03) proton signals. The location of H-2 confirmed the size of the furan ring.

When the isopropylidenation of **2** was carried out with acetone in the presence of phosphorus pentoxide, the 3,4-*O*-isopropylidene derivative **6** could be isolated. Acetylation of **6** afforded the mono-*O*-acetyl derivative **7**. The ^{1}H NMR spectrum of **7** showed that the acetylation of **6** caused a downfield shift of the doublet of H-2 (from δ 5.36 to 7.51), whereas the chemical shifts of H-3 (δ 4.54) and H-4,4′ (δ 3.90) were not affected. This indicated that the acetylation occurred at position-2 and consequently the isopropylidene ring would occupy positions-3 and -4.

When the conditions of isopropylidenation were changed and the progress of the reaction was monitored by thin-layer chromatography using 3:2 ethyl acetate–hexane as the developing solvent, it was found that the products of the reactions depended upon the catalysts and reaction time, as well as the extent of dissolution of **2** (Table I). In addition to **5** and **6**, the pyrazole **8** was also formed. An additional two products were also detected by TLC, but attempts to improve their yields were futile and most of the experiments led to the isolation of **8**. Attempts to separate these minor products by chromatography were unsuccessful.

From the structure of the products as well as the profile shown in Table I, it is possible to conclude that the formation of the intermediate **3**, whose cyclisation may give products having dioxolane and dioxane rings, is a feasable initial process. On the other hand, a competing process may be the dehydrative cyclisation to **4** which is readily isopropylidenated to **5**.

When the isopropylidenation was performed on the D-*erythro* analogue **10**, TLC showed the presence of two products. The major product was found to be **11**, and the minor product was **12**. The structures were deduced by a combination of chemical and spectroscopic methods. The IR spectrum of **11** showed the absence of the lactam group. The structure of **12** was confirmed by acetylation whereby 3-[2-*O*-acetyl-3,4-*O*-isopropylidene-1-(phenylhydrazono)-D-*erythro*-2,3,4-trihydroxybutyl]quinoxalin-2-one (**13**) was formed. Its IR spectrum showed the lactam carbonyl absorption band at 1663 cm^{-1}, in addition to the *O*-acetyl absorption band at 1743 cm^{-1}. Its ^{1}H NMR spectrum showed a downfield shift of the H-2 proton signal from δ 4.30 to 7.54 upon acetylation, indicating that isopropylidenation of **10** afforded the corresponding 3,4-acetal **12** in a similar manner to that of the L-*threo* analogue. When the amount of sulfuric acid was increased, a dehydrative heterocyclisation similar to that found in the L-*threo* analogue to give **8** had taken place. It should be noted that the rearrangement of the dioxolane ring in **12** to the α-*erythro* dioxolane ring is not favored. This is due to the fact that the recovery from the generated unsymmetrical substitution around the dioxolane ring will be

TABLE I

Results of isopropylidenation of **2**

Reaction condition	Time	Products/(R_f)				
		5 (0.86)	**6** (0.34)	x [a] (0.26)	y [a] (0.40)	**8** (0.14)
10 drops H_2SO_4	4 h	+				
5 drops H_2SO_4 / 1 mL DMF	10 min	+	+	+	+	+
	4 h	+				+
3 drops H_2SO_4 / 1 mL DMSO	1 h	+				
3 drops H_2SO_4 / 1 mL DMF	1 h/Δ	+				+
2 drops H_2SO_4 / 1 mL DMF	15 min		+	+		+
	2days		+	+	+	+
	7 days	+	+	+	+	+
0.1 g PTSA/ 1 mL DMF	30 min		+	+	+	+
	1 h/Δ	+				+
0.1 g P_2O_5 1 mL DMF	30 min		+	+	+	+
	2 h		+	+	+	+
	24 h	+	+	+	+	+
	2 days		+			+
HCl gas 1 mL DMF	1 min					+

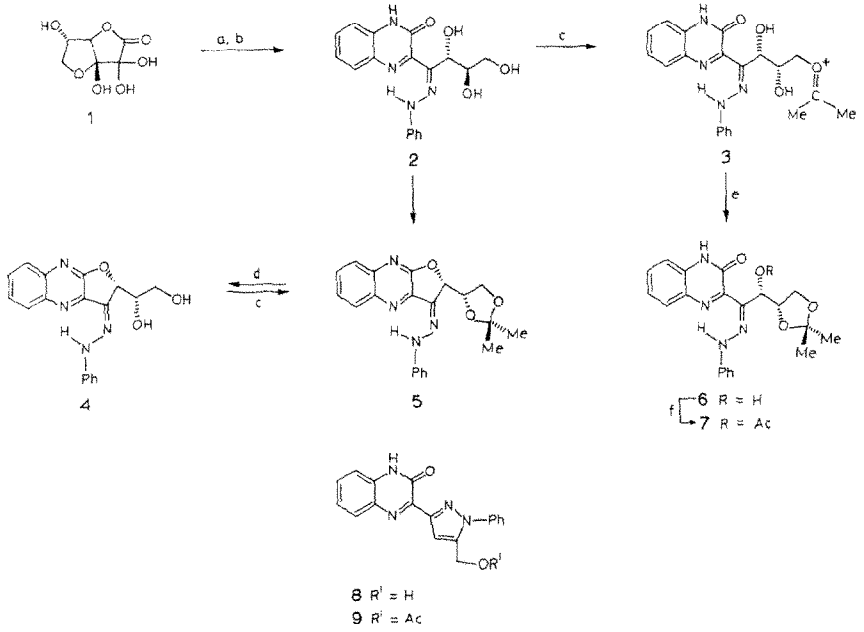
[a] x and y indicate the two unidentified derivatives of **2**.

accompanied by a *cis* disposition of substituents around the new ring[17]. On the other hand, in the case of the *α-threo* dioxolane ring, a *trans* disposition of substituents will be a promoting factor towards the rearrangement of the α-terminal ring[17].

In conclusion, a novel approach for the synthesis of furo[2,3-*b*]quinoxalines has been achieved from suitably substituted quinoxalinones by selecting the conditions of the reactions.

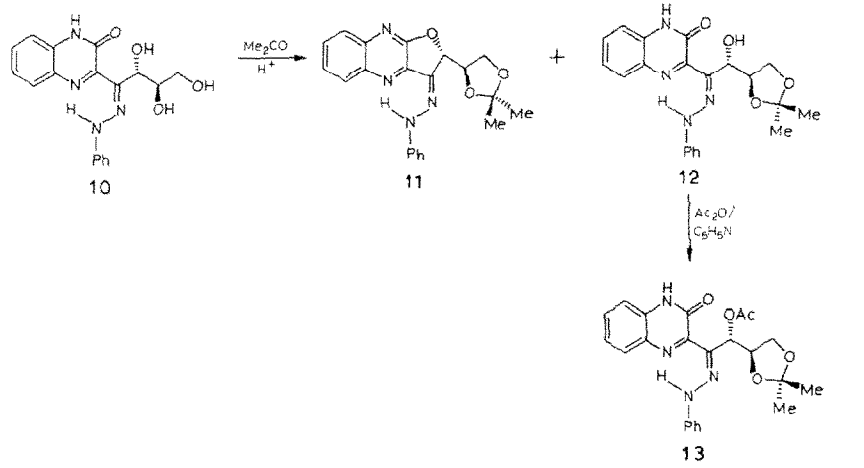
EXPERIMENTAL

General methods.—Melting points were determined on a Mel-Temp apparatus and are uncorrected. IR spectra were recorded with a Unicam SP 1025 spectrophotometer. ^1H NMR spectra were determined with a Varian EM-390 spectrometer using Me_4Si as the internal standard. Chemical shifts are given on the δ scale. TLC was performed on Baker-Flex Silica Gel 1B-F (2.5–7.5 cm) plates using, as the developing solvent, 3:2 EtOAc–hexane. Elemental analyses were performed at the microanalytical laboratory, Cairo University.



a, OPDA b, $PhNHNH_2$ c, Me_2CO/H^+
d, $AcOH/H_2O$ e, Me_2CO/P_2O_5 f, Ac_2O/C_5H_5N

2,2'-Anhydro-[3-(1-phenylhydrazono)-L-threo-*3,4*-O-iso*propylidene-2,3,4-trihydroxybutyl]quinoxaline* (**5**).—Compound **2** (0.5 g, 1.4 mmol) was vigorously stirred with dry acetone (60 mL) and 96% H_2SO_4 (10 drops) for 4 h, and then kept



overnight at room temperature. The resulting mixture was neutralized by the addition of solid anhyd Na_2CO_3, filtered, and the inorganic salts were well washed with dry acetone. The acetone solution was evaporated in vacuo at 30–40°C, and the resulting product was dissolved in EtOH, decolorized with charcoal, and concentrated. The product (0.36 g, 68%) that separated out was filtered off and recrystallized from EtOH to give orange needles: mp 221–223°C; R_f 0.86; ν_{max} 1600 cm^{-1} (C=N). ^1H NMR ($CDCl_3$): δ 1.33 (s, 6 H, 2 Me), 4.05 (d, 2 H, H-4,4'), 4.60 (m, 1 H, H-3), 5.50 (d, 1 H, $J_{1,2}$ 3.0 Hz, H-2), 7.12 (m, 9 H, ArH) and 12.03 (bs, 1 H, NH); the latter singlet disappeared upon deuteration. Anal. Calcd for $C_{21}H_{20}N_4O_3$: C, 67.0; H, 5.4; N, 14.9. Found: C, 67.1; H, 5.6; N, 15.2.

2,2'-Anhydro-[3-(1-phenylhydrazono)-L-threo-*2,3,4-trihydroxybutyl]quinoxaline* (**4**).—A solution of compound **5** (0.1 g, 0.27 mmol) in 60% aq acetic acid (10 mL) was heated for 15 min until dissolution occurred, and then it was kept overnight at room temperature, when an orange crystalline product separated out. The product was filtered off and recrystallized from EtOH to afford orange crystals (0.05 g, 56%): mp 215°C; ν_{max} 3354 (OH), 1602 cm^{-1} (C=N). Anal. Calcd for $C_{18}H_{16}N_4O_3$: C, 64.3; H, 4.8; N, 16.7. Found: C, 64.1; H, 4.8; N, 16.6.

If the amount of aq acetic acid and/or the reaction time were increased, 3-[5-(hydroxymethyl)-1-phenylpyrazol-3-yl]quinoxalin-2-one (**8**) formed.

3-[3,4-O-Isopropylidene-1-(phenylhydrazono)-L-threo-*2,3,4-trihydroxybutyl]quinoxalin-2-one* (**6**).—A solution of compound **2** (0.5 g, 1.4 mmol) in DMF (1 mL) was vigorously stirred with dry acetone (60 mL) and phosphorus pentoxide (0.1 g) for 30 min. TLC of the mixture showed the presence of four products, R_f 0.14, 0.26, 0.34, and 0.40. After 2 h, the mixture showed the same products, but after 24 h, five products, R_f 0.14, 0.26, 0.34, 0.40, and 0.86, were detected. The resulting mixture was neutralized by addition of solid anhyd Na_2CO_3, followed by filtration, and the inorganic salts were washed well with dry acetone. The acetone solution was evaporated in vacuo at 30–40°C, and the resulting product was dissolved in ethanol. Fractional crystallisation from ethanol led to the isolation of the slower-migrating component **8** (0.19 g, 42%): mp 259°C (lit.[10] 250–252°C). The fast-migrating component **6** was obtained by evaporating the mother liquor in vacuo at 30–40°C and dissolving the residue in $CHCl_3$ to give orange needles of compound **6** (0.22 g, 40%); R_f 0.34; mp 182–184°C; ν_{max} 3433 (OH), 1663 (OCN), and 1597 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 1.39 and 1.50 (2 s, 6 H, 2 Me), 3.90 (m, 2 H, H-4,4'), 4.54 (q, 1 H, H-3), 5.36 (d, 1 H, H-2), 7.13 (m, 9 H, ArH), 11.51 (bs, 1 H, NH), and 13.48 (s, 1 H, NH). Anal. Calcd for $C_{21}H_{22}N_4O_4$: C, 63.9; H, 5.6; N, 14.2. Found: C, 63.9; H, 5.7; N, 14.1.

3-[2-O-Acetyl-3,4-O-isopropylidene-1-(phenylhydrazono)-L-threo-*2,3,4-trihydroxybutyl]quinoxalin-2-one* (**7**).—A cold solution of **6** (0.1 g, 0.13 mmol) in dry pyridine (1 mL) was treated with Ac_2O (1 mL) and kept overnight at room temperature. The mixture was poured onto crushed ice, and the product that separated out was filtered off, washed with water, and then dried (0.09 g, 82%). Recrystallization from EtOH gave orange crystals; mp 154°C; ν_{max} 1730 (OAc) and 1660 cm^{-1}

(OCN). ^{1}H NMR ($CDCl_3$): δ 1.38 and 1.50 (2 s, 6 H, 2 Me), 1.99 (s, 3 H, MeCO), 4.10 (d, 2 H, H-4,4′), 5.84 (m, 1 H, H-3), 6.69-7.30 (m, 9 H, ArH), 7.51 (d, 1 H, H-2), 12.46 (bs, 1 H, NH), and 13.60 (s, 1 H, NH). Anal. Calcd for $C_{23}H_{24}N_4O_5$: C, 63.3; H, 5.5; N, 12.8. Found: C, 63.4; H, 5.2; N, 13.3.

Isopropylidenation of **2** *under various conditions.*—Compound **2** (0.5 g, 1.4 mmol) was dissolved in DMF (1 mL) and acetone (60 mL). The catalyst was added, and the progress of the reaction was monitored by TLC. The results are shown in Table I.

Isopropylidenation of compound **2** *using hydrogen chloride.*—To a solution of compound **2** (0.5 g, 1.4 mmol) in a mixture of DMF (1 mL) and acetone (10 mL), HCl was passed through the mixture for 1 min. TLC showed the formation of one product, R_f 0.14. The mixture was neutralized with anhyd Na_2CO_3 and evaporated under reduced pressure to give a product which was recrystallized from EtOH to give compound **8** as colorless needles; mp 259°C (lit[10]. 250–252°C).

*Isopropylidenation of 3-[1-(phenylhydrazono)-*D-erythro-*2,3,4-trihydroxybutyl]-quinoxalin-2-one* (**10**).—A mixture of compound **10** (0.4 g, 1.1 mmol), DMF (1 mL), dry acetone (20 mL), and 2 drops of H_2SO_4 was stirred vigorously for 1–2 h. TLC showed the presence of the starting material, in addition to three products, R_f 0.74, 0.35, and 0.28. The mixture was neutralized by the addition of solid anhyd Na_2CO_3, and the drying agent was filtered off and washed with acetone. The combined filtrate and washings were evaporated in vacuo at 40°C. Petroleum ether was added to the resulting viscous syrup, and the product that separated out was filtered off, washed with EtOH and dried. Fractional crystallisation with EtOH gave **11** as a major product (0.19 g, 45%); R_f 0.74; mp 223–225°C; ν_{max} 1600 cm^{-1} (C=N). ^{1}H NMR ($CDCl_3$): δ 1.30 (s, 6 H, 2 Me), 4.03 (d, 2 H, H-4,4′), 4.54 (m, 1 H, H-3), 5.33 (s, 1 H, H-2), 7.03 (m, 9 H, ArH) and 11.72 (s, 1 H, NH); the latter singlet disappeared upon deuteration. Anal. Calcd for $C_{21}H_{20}N_4O_3$: C, 67.0; H, 5.4; N, 14.9. Found: C, 66.8; H, 5.5; N, 15.0.

Preparative TLC of the mother liquor led to the isolation of **12**, (0.14 g, 30%); R_f 0.35; mp 116–118°C; ν_{max} 3440 (OH), 1658 (OCN), and 1602 cm^{-1} (C=N); ^{1}H NMR ($CDCl_3$): δ 1.33 and 1.45, (2 s, 6 H, 2 Me), 2.69 (t, 1 H, OH), 3.36 and 3.51 (2 m, 2 H, $J_{4,4'}$, 12.0 Hz, H-4,4′), 3.81 (m, 1 H, H-3); 4.30 (d, 1 H, $J_{1,2}$ 4.5 Hz, H-2), 7.18 (m, 9 H, ArH), 7.65 (s, 1 H, NH), and 11.97 (s, 1 H, NH). Anal. Calcd for $C_{21}H_{22}N_4O_4$: C, 63.9; H, 5.6; N, 14.2. Found: C, 63.6; H, 5.8; N, 14.5.

*3-[2-O-Acetyl-3,4-O-isopropylidene-1-(phenylhydrazono)-*D-erythro-*2,3,4-trihydroxybutyl]quinoxalin-2-one* (**13**).—Compound **12** (0.5 g, 1.3 mmol) was treated with Ac_2O (5 mL) as for compound **6** to yield the product **13** (0.38 g, 68%); mp 234–236°C; ν_{max} 1743 (OAc) and 1663 cm^{-1} (OCN). ^{1}H NMR ($CDCl_3$): δ 1.39 and 1.42 (2 s, 6 H, 2 Me), 2.06 (s, 3 H, COMe), 4.24 (m, 2 H, H-4,4′), 4.72 (m, 1 H, H-3), 5.60 (d, 1 H, $J_{1,2}$ 4.5 Hz, H-2), 7.15 (m, 9 H, ArH), 12.57 (bs, 1 H, NH), and 13.90 (s, 1 H, NH). Anal. Calcd for $C_{23}H_{24}N_4O_5$: C, 63.3; H, 5.5; N, 12.8. Found: C, 63.4; H, 5.2; N, 13.0.

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