A NOVEL CONSTRUCTION FOR 2,3-DIHYDROFURO[2,3-*b*]-QUINOXALINE SKELETON+

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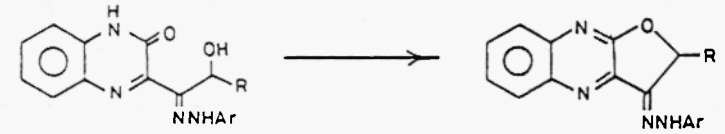
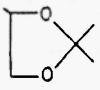
Abstract: The construction of the 2,3-dihydrofuro[2,3-*b*]quinoxaline skeleton has been achieved by the reaction of 3-[1-arylhydrazono)glyoxal-1-yl]quinoxalin-2(1*H*)-one with acetic anhydride in pyridine to give 2-acetoxy-3-(2-acetyl-2-arylhydrazono)-2,3-dihydrofuro[2,3-*b*]quinoxaline. The structures were confirmed.

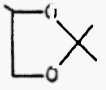
INTRODUCTION

2,3,4-Furantriones have proved to be excellent precursors for the synthesis of nitrogen heterocyclic compounds with different complexities (1) The 2,3-dihydrofuro[2,3-*b*]quinoxaline skeleton constitute one of these heterocycles which has been recently reported[2,3] from our laboratory by two methods. Both methods involved a dehydration process either by the action of acid during the acid catalyzed isopropylidenation (2) of **1** to give **3** or by the action of acetic anhydride during the acetylation (3) of **2** to give **4**. It should be noted that the deisopropylidenated analogue of **3** was reported (4) earlier for the reaction product from the respective 2,3,4-furantrione with *o*-phenylenediamine and phenylhydrazine,



1 R = 

2 R = Ph

3 R = 

4 R = Ph

SCHEME 1

+ Prelimenary results of this work were presented at 2nd Chemistry Conference Fac. of Sci., Alex. Univ., Alexandria, A 10, 94 (1988), XVIIth Int. Carbohydr. Symp., Ottawa, Canada, B1.3, 165 (1994), as well as in reference 1. It was abstracted from the Ph. D. thesis (Alex. Univ., 1986) of **H. Abdel Hamid.**

but it was later proved (1,2,5,6) that the product has the acyclic structure **1**. In the present work, a novel cyclization to this ring system has taken place during the acetylation of 3-[1-(2-arylhydrazono)-glyoxal-1-yl]quinoxalin-2(1*H*)-one **5-7**.

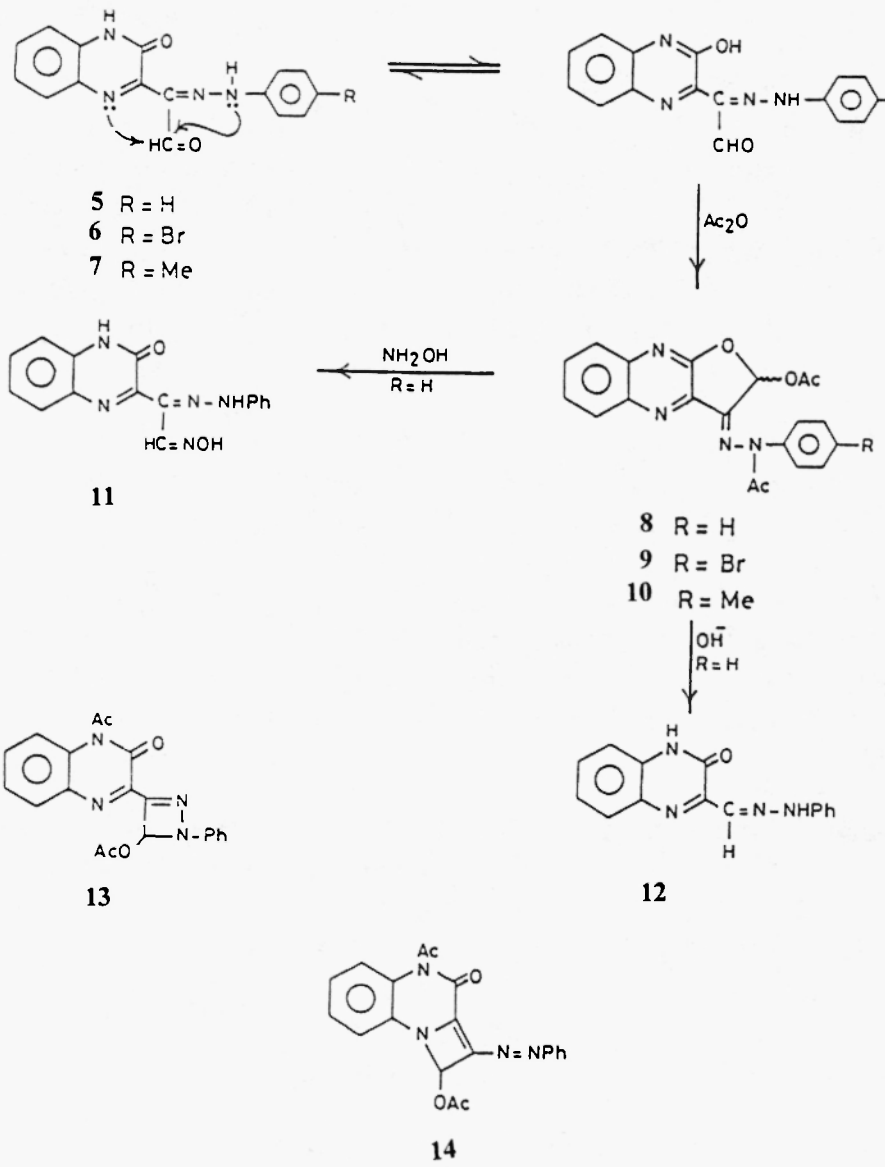
RESULTS AND DISCUSSION

Reaction of **5** with acetic anhydride in pyridine did not afford any of the anticipated acetyl derivatives, but a yellow product was isolated whose structure was deduced to be **8** from the following data. Its elemental analysis agreed with the molecular formula $C_{20}H_{16}N_4O_4$, compatible with a structure of a diacetylated derivative of **5**. The infrared spectrum of the product showed a band at 1775 cm^{-1} due to the presence of an OAc, in addition to a band at 1705 cm^{-1} which may be attributed to the presence of NAc group and a band at 1630 cm^{-1} due to a C=N. The absence of a strong absorption band at 1585-1570 cm^{-1} indicated the absence of conjugation of the phenyl group with unsaturated group, and more specifically with an azo group, which intensifies the aromatic ring vibration.

The ^1H NMR spectrum of the product indicated the absence of the resonances of the two NH (at δ/ ppm 11.23 and 12.63) as well as the singlet of the CHO (δ/ ppm 9.60) which appeared in that of its precursor **5**. On the other hand, the spectrum showed the presence of two singlets at δ 1.99 and 2.76 due to the OAc and NAc respectively. A minor singlet appeared at δ 1.98 due to the presence of a minor anomer. The deshielding nature of the singlet at δ 6.12 could be attributed to the attachment of this proton to a carbon bearing two heteroatoms. The ^{13}C NMR spectrum showed two singlets (appeared as two quartets in the coupled spectrum) at δ_c 20.65 and 22.38 accompanied by two singlets at δ_c 160.21 and 167.67 due to the OAc and NAc respectively. The singlet at δ_c 89.70 (J_{C-H} 186.05) appeared as a doublet in the coupled spectrum. Its chemical shift indicated its attachment to a two heteroatoms. Although the structure could probably be assigned as **8**, **13** or **14**, the later structures **13** and **14** could be ruled out based on the aforementioned discussions of the spectral data as well as the following chemical evidences. The reaction could be extended to compounds having, on the phenylhydrazono group, different substituents such as bromine and methyl groups. The infrared and ^1H NMR spectra of the product in each case showed a similar pattern with that of the phenyl analog. When the reaction was tried with the *N*-methyl derivative of **5**, it afforded unchanged material and did not afford the anticipated *N*-methyl analog of the product. This indirectly agreed with **8** rather than with **13** or **14**.

Reaction of **8** with hydroxylamine gave the oxime **11** through the deacetylation of the product. The oxime **11** was identical in every respect with the product obtained by the reaction of the aldehyde **5** with hydroxylamine.

Attempted deacetylation of **8** by alkali gave the hydrazone **12**, which could be explained as a result of the initial formation of the aldehyde **5** that underwent splitting of the aldehydic group by the action of alkali.



SCHEME 2

The above data led to the conclusion that the product has the structure **8** rather than the alternative structures **13** and **14**. The mechanism of formation of the product could based on the possible interaction of either of the two nitrogens or the oxygen on the aldehydic carbonyl group which followed by acetylation. The formation of two isomers is thus expected, however the spectra showed the presence of a major one. This may be explained by the presence of rotameric forms which energitically favoured a conformer whose carbonyl group not in a cisoid face with the C=N of the hydrazone residue.

In conclusion a preparative method for the construction of 2,3-dihydrofuro[2,3-*b*]quinoxaline ring has been achieved.

EXPERIMENTAL SECTION

Melting points (Meltemp apparatus) are uncorrected. IR spectra were recorded with a Unicam SP 1025 spectrophotometer. ^{1}H NMR spectra were determined with an EM-390 spectrometer. ^{1}H NMR and ^{13}C NMR spectra of **8** were recorded with a Brucker 400 MHz spectrometer. Tetramethylsilane (TMS) was used as standard and chemical shifts are given on δ Scale. TLC was performed on Baker-flex silica gel 1B-F (2.5-7.5 cm) plates. Microanalyses were performed in the unit of Microanalysis at the University of Cairo.

3-[1-(2-Phenylhydrazono)glyoxal-1-yl]quinoxalin-2(1*H*)-one 5

Mp 245°C (lit. (7) mp 243°C); ^{1}H NMR (DMSO-d_6, δ/ppm) 7.10 and 7.30 (2 m, 5 H, Ph), 7.4-7.8 (m, 4 H, quinoxaline-H), 9.60 (s, 1 H, CHO), 11.23 (bs, 1 H, NH), 12.63 (bs, 1 H, NH).

General method for 2,3-dihydro[2,3-*b*]quinoxaline 8-12

A solution of **1** (1.7 mmol) in dry pyridine (5 ml) was cooled and treated with acetic anhydride (5 ml). The mixture was kept for 2 hours at 0° and then left overnight at room temperature. It was poured onto crushed ice, and the product that separated out was filtered off, washed repeatedly with water, dried and recrystallized from ethanol in pale-yellow needles.

2-Acetoxy-3-(2-acetyl-2-phenylhydrazono)-2,3-dihydrofuro[2,3-*b*]quinoxaline 8

(90% Yield): mp 200-202°C; IR (KBr, $\tilde{\nu}$/cm^{-1}):1615 and 1630 (C=N), 1705 (NAc); 1775 cm^{-1} (OAc); ^{1}H NMR ($CDCl_3$, δ/ppm) 1.98 and 1.99 (2 s, 3 H, OAc), 2.76 (s, 3 H, NAc), 6.12 (s, 1 H, CH), 7.29 and 7.50 (2 m, 5 H, Ph), 7.65 (dt, 1 H, H-6), 7.71 (dt, 1 H, H-7), 7.88 (dd, 1 H, H-5), 8.17 (dd, 1 H, H-8); ^{13}C NMR ($CDCl_3$, δ_c/ppm) 20.65 (OAc), 22.38 (NAc), 89.70 (C-2), 128.00, 128.09, 128.42 and 138.20 (C_6H_5), 129.79, 130.03, 130.34, and 131.30 (C_6H_4), 140.10 (C-3), 141.13 (C-3a), 141.50 (C-9a); Anal. calcd for $C_{20}H_{16}N_4O_4$; C, 63.8; H, 4.3; N, 14.9; found: C, 63.7; H, 4.1; N, 14.6.

2-Acetoxy-3-(2-acetyl-2-(4-bromophenylhydrazono)-2,3-dihydrofuro[2,3-*b*]quinoxaline 9

(87% Yield); mp 210-211°C; IR (KBr, $\tilde{\nu}$/cm^{-1}) 1610 and 1640 (C=N); 1715 (NAc); 1775 cm^{-1} (OAc); ^{1}H NMR ($CDCl_3$, δ/ppm) 1.93 (s, 3 H, OAc); 2.66 (s, 3 H, NAc); 6.17 (s, 1 H, CH); 7.00-8.20 (3 m, 8 H, aromatic-protons); Anal. calcd for $C_{20}H_{15}BrN_4O_4$: C, 52.8; H, 3.3; N, 12.3; found: C, 52.4; H, 3.7; N, 12.2.

2-Acetoxy-3-(2-acetyl-2-(4-tolylhydrazono)-2,3-dihydrofuro[2,3-*b*]quinoxaline 10

(85% Yield): mp 204-206°C; IR (KBr, $\tilde{\nu}$/cm^{-1}) 1625 (C=N); 1700 (NAc); 1775 cm^{-1} (OAc). ^{1}H NMR ($CDCl_3$, δ/ppm) 2.03 (s, 3 H, OAc); 2.47 (s, 3 H, CH_3); 2.80 (s, 3 H, NAc); 6.13 (s, 1 H, CH) and 7.10-8.20 (3 m, 8 H, aromatic-protons). Anal. calcd for $C_{21}H_{18}N_4O_4$: C, 64.6; H, 4.7; N, 14.4; found: C, 64.3; H, 4.8; N, 14.3.

3-[2-Oxime-1-(phenylhydrazono)glyoxal-1-yl]quinoxalin-2-one 11

A solution of **8** (0.4 g) in dry pyridine (10 ml) was treated with hydroxylamine hydrochloride (0.3 g). The mixture was kept overnight at room temperature. It was poured onto crushed ice, and the product that separated out was filtered off, washed repeatedly with water, and dried. The product was recrystallized from ethanol in orange needles (0.24 g, 80% yield): mp 217-218°C; IR (KBr, $\tilde{\nu}$/cm^{-1}) 1600 (C=N);1660 cm^{-1} (OCN); ^{1}H NMR (DMSO-d_6, δ/ppm) 6.80-8.00 (m, 9 H, aromatic-protons), 8.57 (s, 1 H, HC=N), 11.87, 12.20, 11.10 and 12.46 (2 s, and 2 bs, 3 H, OH and 2 NH). Anal. calcd for $C_{16}H_{13}N_5O_2$: C, 62.5; H, 4.3; N, 22.8; found: C, 62.3; H, 4.2; N, 22.6.

3-Formylquinoxalin-2-one-phenylhydrazone 12

A solution of **8** (0.1 g) and sodium hydroxide (0.1 g) in 1:1 water-ethanol (10 ml) was boiled under reflux for 4 hour. The mixture was cooled, acidified with acetic acid, and the product recrystallized from ethanol in bright-red needles (0.06 g, 86% yield): mp 270°C (lit.(7) mp 275°C; IR (KBr, $\tilde{\nu}$/cm^{-1}) 1600 (C=N); 1660 cm^{-1} (OCN); ^{1}H NMR (DMSO-d_6, δ/ppm) 7.00 and 7.30 (2 m, 5 H, Ph), 7.5-8.1 (m, 4 H, quinoxaline-H), 8.37 (s, 1 H, HC=N),11.20 and 12.40 (2 bs, 1 H, NH), 14.4 (bs, 1 H, NH). Anal. calcd for $C_{15}H_{12}N_4O$: C, 68.2; H, 4.6; N, 21.2; found:C, 68.4; H, 4.7; N, 20.9.

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Received May 12, 1996