Bull.Chem.Soc.Ethiop.,3(2), 97-102 (1989).

SYNTHESIS OF 3-[(GLYOXAL-1-YL),(TRIAZOL-4-YL)- AND (PYRAZOL-3-YL)]-6,7-DIMETHYL-1H-QUINOXALIN-2-ONES

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(Received April 4, 1989; revised September 2, 1989)

ABSTRACT. Periodate oxidation of 6,7-dimethyl-3-[1-(phenyl-hydrazono)-L-*threo* -2,3,4-trihydroxybutyl]-1H-quinoxalin-2-one afforded 6,7-dimethyl-3-[1-(phenylhydrazono)-glyoxal-1-yl]-1H-quinoxalin-2-one, which upon reduction gave 3-[2-(hydroxy)-1-(phenylhydrazono)-eth-1-yl]-6,7-dimethyl-1H-quinoxalin-2-one, and upon treatment with phenylhydrazine gave 6,7-dimethyl-3-[1,2-bis(phenylhydrazono)-glyoxal-1-yl]-1H-quinoxalin-2-one, and with hydroxylamine afforded the corresponding oxime which could be cyclised to 6,7-dimethyl-3-[2-(phenyl)-1,2,3-triazol-4-yl]-1H-quinoxalin-2-one. 3-[5-(Acetoxymethyl)-1-aryl-pyrazol-3-yl]-6,7-dimethyl-1H-quinoxalin-2-ones were prepared, and their deacetylation gave 3-[1-aryl-5-(hydroxymethyl)-pyrazol-3-yl]-6,7-dimethyl-1H-quinoxalin-2-ones. The spectral data are discussed.

INTRODUCTION

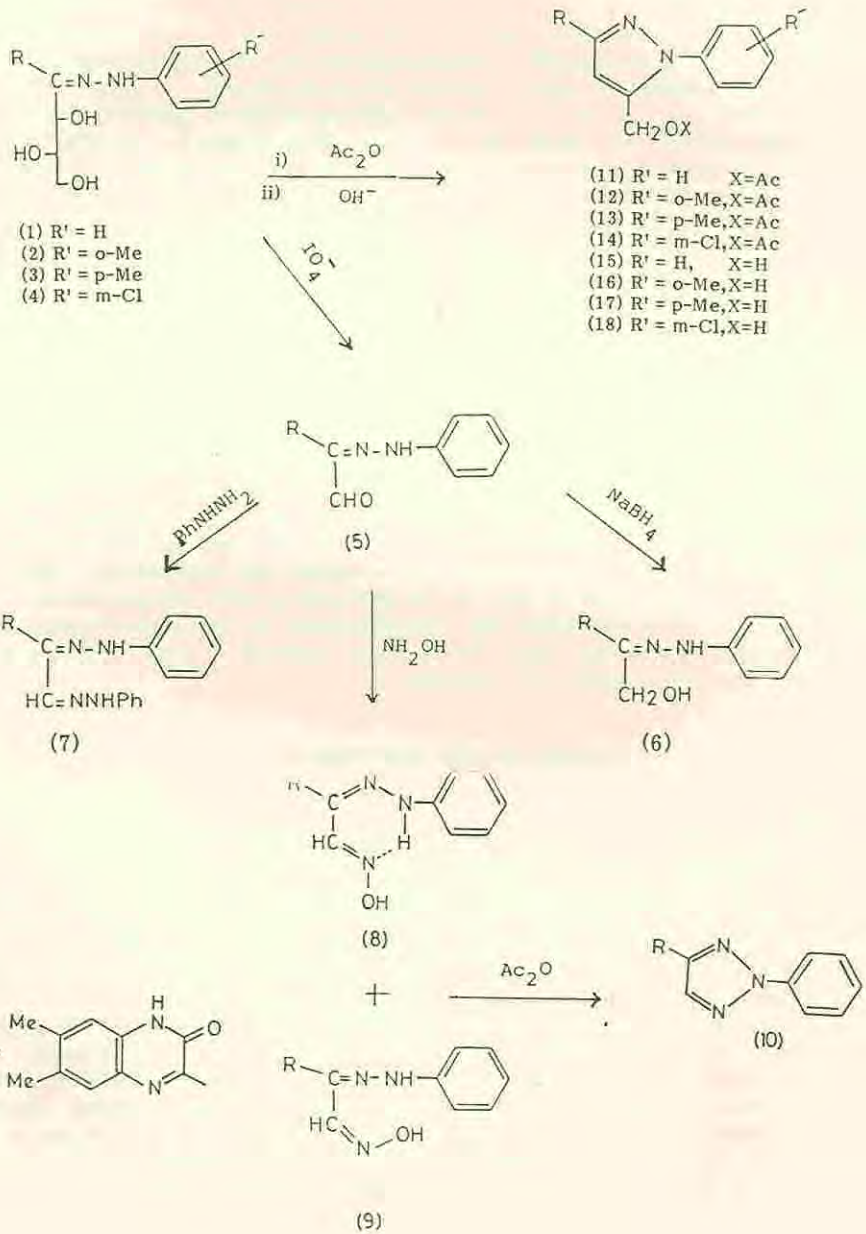
The synthesis of heterocycles from carbohydrate precursors is a subject of interest in our laboratory (1), as a consequence of the widespread use of heterocycles. Dehydro-L-ascorbic acid is one of the excellent precursors in this respect. It could be functionalized for building the heterocyclic rings via its hydrazones, bishydrazones as well as its derivatives with orthodiamines (1-6). In this report we have extended our investigations on some functionalized α-ketoaldehydes (5) synthesised from the reaction products of dehydro-L-ascorbic acid with 4,5-dimethyl-o-phenylenediamine.

RESULTS AND DISCUSSION

The synthesis of 3-(1-arylhydrazono-L-*threo*-2,3,4-trihdroxybutyl)6,7-dimethyl-1H-quinoxalin-2-one (**1-4**) have been described in another paper (5). The acyclic nature of the parent compound **1** was apparent from the results of its periodate oxidation. The resulting aldehyde 6,7-dimethyl-3-[1-(phenylhydrazono)-glyoxal-1-yl]-1H-quinoxalin-2-one (**5**), was identical with that prepared from the D-*erythro* analog. The ^{1}H NMR spectrum of **5** showed two NH protons (δ 11.20 and 12.50) and an aldehydic proton (δ 9.58).

Reduction of **5** with sodium borohydride afforded 3-[2-(hydroxy)-1-(phenyl hydrazono)-eth-1-yl]-6,7-dimethyl-1H-quinoxalin-2-one (**6**). Treatment of **5** with phenylhydrazine afforded orange crystals of 6,7-dimethyl-3-[1,2-bis-(phenylhydrazono)-glyoxal-1-yl]-1H-quinoxalin-2-one (**7**). The infrared spectra of **6** and **7** showed the absence of the aldehydic absorption of their precursor **5**, whereas both compounds still retain bands for the OCN groups. The ^{1}H NMR spectrum (DMSO-d_6) of **7** showed the three NH protons (δ 10.40, 12.45 and 13.00.

Reaction of **5** with hydroxylamine afforded the corresponding two isomeric oximes **8** and **9.** Boiling the mixture with acetic anhydride, gave 6,7-dimethyl-3-[2-(phenyl)-1,2,3-triazol-4-yl]-1H-quinoxalin-2-one (**10**), whose IR spectrum showed an amide band at 1660 cm^{-1}. Its ^1H NMR spectrum showed the presence of only one exchangeable proton at δ 12.60 due to the proton of NHCO, and a singlet at δ 8.75 due to the H-5 of the triazolyl ring in addition to the expected signals of the aromatic protons.



When compounds **1-4** were subjected to the action of acetic anhydride, acetylation with simultaneous dehydrative cyclisation had taken place to afford the corresponding products **11-14.** Their IR specta showed bands at 1750-1740 and 1675-1650 cm^{-1} due to the acetyl and amide carbonyl groups respectively. Their ^1H NMR spectra (Table 1) confirmed the presence of an $-CH_2OAc$ moiety (two singlets at δ 2.10-1.95 and 5.20-4.95) and a one N-H (δ 12.5-12.3) which indicated that a cyclisation process had taken place between the nydrazone residue and the glycerolyl side chain. This cyclisation may have occurred after the acetylation of the glycerolyl residue followed by the elimination of two molecules of acetic acid to form the pyrazole ring. The spectral data also confirm the structures of the products to be 3-[5-(acetoxymethyl)l-pyrazol-3-yl]-6,7-dimethyl-lH-quinoxalin-2-ones (**11-14**). Moreover, compound **11** and the product obtained under the same condition from the D-*erythro* analog of **1**, (6) confirm the involvement of the glycerolyl residue in the cyclisation process.

Deacetylation of compounds **11-14** with dilute sodium hydroxide afforded 3-[1-aryl-5-(hydroxymethyl)pyrazol-3-yl]-6,7-dimethyl-1H-quinoxalin-2-ones **15-18**). Their IR spectra showed the absence of the acetyl carbonyl band and the presence of the hydroxy and amide bands at 3500-3350 and 1670-1650 cm^{-1}, respectively.

EXPERIMENTAL

General Methods. Melting points were determined on a Kofler block and are uncorrected. IR spectra were recorded with a Unicam SP 1025 spectrometer. ^1H NMR spectra were determined with a Varian EM 390 spectrometer using TMS as internal and external references in $CDCl_3$ and DMSO-d_6 solutions respectively. Microanlyses were made in the unit of microanalysis, Faculty of Science, Cairo University, Cairo, Egypt.

6,7-Dimethyl-3-[l-(phenylhydrazono)-glyoxal-l-yl]-lH-quinoxalin-2-one **(5).** To a stirred suspension of **1** (3.8 g, 0.01 mol) in distilled water (50 ml), a solution of sodium metaperiodate (5.3 g, 0.025 mol) in 50 ml distilled water was added. The reaction mixture was stirred for 2 h and then left for 24 h at room temperature. The product was filtered, washed with water, dried, (87 % yield) and crystallized from dimethylformamide-ethanol; m.p. 260-262° (lit. (6) m.p. 266°C); IR ν_{max} cm^{-1} (KBr) 1650 (OCN), 1700 (CHO) and 3245 (NH). ^1H NMR (DMSO-d_6), δ 2.20 and 2.30(2s, 6H, 2Me), 7.20-7.00, 7.35 and 7.62 (m, d and s, 7H, Ar-H), 9.58 (s, 1H, HC=O), 11.2 and 12.5 (2s, 2H, 2NH). Found: C, 68.0; H, 4.9; N, 17.8. $C_{18}H_{16}N_4O_2$ requires: C, 67.5; H, 5.0; N, 17.5.

3-[2-(Hydroxy)-1-(phenylhydrazono)-eth-1-yl]-6,7-di-methyl-1H-quinoxalin-2-one **(6).** To a stirred solution of **5** (0.2 g, 6.2 mmol) in a mixture of methanol (15 ml) and dimethylformamide (15 ml), sodium borohydride (0.3 g) was added. Stirring was continued for 1 h, then left for 24 h at room temperature. The mixture was diluted with water and the product was filtered, washed with water and ethanol, dried and recrystallized from ethanol (75% yield); m.p. 240-242°; IR ν_{max} cm^{-1} (KBr) 1660 (OCN), 3050 (NH) and 3300 (OH). Found; C, 67.2; H, 5.3; N, 17.8. $C_{18}H_{18}N_4O_2$ requires: C, 67.1; H, 5.6; N, 17.4.

6,7-Dimethyl-3-[1,2-bis(phenylhydrazono)-glyoxal-l-yl]-lH-quinoxalin-2-one **(7).** A mixture of **5** (0.1 g, 0.3 mmol) and phenylhydrazine (0.03 g, 0.3 mmol) in ethanol (25 ml) was refluxed for 30 min. The product (90% yield) was filtered, washed with ethanol, dried and recrystallized from ethanol; m.p. 242-244; IR ν_{max} cm^{-1} (KBr), 1660 (OCN), 3100 (NH); ^1H NMR (DMSO-d_6): δ 2.48 (s, 6H, 2Me), 7.75-6.80 (m, 12H, Ar-H), 9.8 (s, 1H H-C=N), 10.40, 12.45 and 13.00 (3 s, 3H, 3NH). Found: C, 70.4; H, 5.6; N, 20.2. $C_{24}H_{22}N_6O$ requires: C, 70.2; H, 5.4; N, 20.5.

6,7-Dimethyl-3-[2-(oximo)-1-(phenyldrazono)-glyoxal-1-yl]-1H-quinoxalin-2-one (8 and 9). To a solution of **5** (0.1 g, 0.3 mmol) in ethanol (25 ml) and few drops of dimethylformamide, hydroxylamine hydrochloride (0.04 g, 0.5 mmol) and sodium acetate (0.03 g, 0.5 mmol) were added. The reaction mixture was boiled for 10 min and left to cool. The product (60% yield) was filtered, washed with water, dried and recrystallized from ethanol. The mixture of the isomeric oximes could not be separated due to their solubility in various solvents. M.p. 173-175; IR ν_{max} cm^{-1} (KBr) 1650 (OCN), 3100 (NH) and 3480 (OH); ^1H NMR (DMSO-d_6) δ 2.30 (2 s, 6H, 2Me), 7.17 (m, 5H Ar-H), 7.52 and 7.85 (2 s, 2H, H-5 and H-8 of the quinoxaline ring), 8.43 and 10.00 (2 s, 1H, HC=N) 11.08 (s, 1H, OH), 11.88 and 12.00 (2 s, 1H, NH), 12.29 (bd, 1H, NH). Found: C, 64.0; H, 5.6: N, 21.3. $C_{18}H_{17}N_5O_2$ requires: C, 64.5; H, 5.1; N, 20.9.

6,7-Dimethyl-3-[2-(phenyl)-1,2,3-triazol-4-yl]-1H-quinoxalin-2-one (10). A mixture of **8** and **9** (0.5 g, 1.4 mmol) and acetic anhydride (20 ml) was refluxed for 6 h. It was then cooled and poured onto crushed ice. The product was filtered, washed with water, dried and recrystallized from ethanol as yellow needles (66% yield); m.p. >300°; IR ν_{max} cm^{-1} 1660 (OCN), 2920 (NH); ^1H NMR (DMSO-d_6) δ 2.25 (s, 6H, 2Me), 8.15-7.04 (m, 7H, Ar-H), 8.75 (s, 1H, H-5) and 12.6 (s, 1H, NH). Found: C, 67.7; H, 5.0; N, 22.5. $C_{18}H_{15}N_5O$ requires: C, 68.1; H, 4.8; N, 22.1.

3-[5-(Acetoxymethyl)-1-aryl-pyrazol-3-yl]-6,7-dimethyl-1H-quinoxalin-2-ones (11-14). A mixture of **1-4** (0.2 g) and acetic anhydrice (5 ml) was heated under refluxed for 30 min. The reaction mixture was cooled, and poured onto crushed ice. The products were filtered, washed with water and recrystallized from ethanol to give pale yellow needles. (Table 1)

Table 1. Microanalyses and spectral data of 3-[5-(acetoxymethyl)-1-aryl-pyrazol-3-yl]-6,7-dimethyl-1H-quinoxalin-2-ones (11-14).

Compound No.	R	Yield (%)	m.p.°C	Molecular formula	Anal. Required/Found C	H	N	IR(KBr) ν_{max} cm^{-1} OCN	OAC
11[a]	H	80	267-268	$C_{22}H_{20}N_4O_3$	68.0 68.3	5.2 5.4	14.4 14.1	1670	1750
12[b]	o-CH_3	75	263-265	$C_{23}H_{22}N_4O_3$	68.6 68.7	5.5 5.7	13.9 14.0	1660	1740
13[c]	p-CH_3	80	255-258	$C_{22}H_{22}N_4O_3$	68.6 68.6	5.5 5.7	13.9 13.7	1660	1750
14[d]	m-Cl	87	256-257	$C_{22}H_{19}ClN_4O_3$	62.5 62.5	4.5 4.6	13.3 12.9	1675	1750

[a] lit[6] m.p. 268
[b] ^1H-nmr($CDCl_3$) δ 2.05, (s, 3 H, OAc), 2.10, 2.29, 2.38 (3 s, 9 H, 3 Me), 4.95 (s, 2 H, OCH_2), 12.50 (s, 1 H, N H)
[c] ^1H-nmr($CDCl_3$) δ 2.00, (s, 3 H, OAc), 2.30, 2.40, 2.50 (3 s, 9 H, 3 Me), 5.15 (s, 2 H, OCH_2), 12.4 (s, 1 H, N H)
[d] ^1H-nmr($CDCl_3$) δ 2.00, (s, 3 H, OAc), 2.30 (s, 6 H, 2 Me), 5.20 (s, 2 H, OCH_2), 12.30 (s, 1 H, N H).

Table 2. Microanalyses and spectral data of 3-[1-aryl-5(hydroxymethyl)-pyrazol-3-yl]-6,7-dimethyl-1H-quinoxalin-2-ones (15-18).

Compound No.	R	Yield (%)	m.p°C	Molecular formula	Anal.Required/Found C	H	N	IR(KBr) ν_{max} cm^{-1} OCN	NH	OH
15[a]	H	70	258-260	$C_{20}H_{18}N_4O_2$	69.3 69.0	5.2 5.1	16.2	1670	3200	3500
16	o-CH_3	70	253-255	$C_{21}H_{20}N_4O_2$	70.0 69.7	5.6 5.9	15.5 15.8	1675	3100	3420
17	p-CH_3	65	285-286	$C_{21}H_{20}N_4O_2$	70.0 70.2	5.6 5.8	1665 15.2	3100	3400	
18	m-Cl	78	264-266	$C_{20}H_{17}ClN_4O_2$	63.1 63.0	4.5 4.3	14.7 14.3	1675	2900	3350

[a] lit[6] m.p 265

3-[1-Aryl-5-(hydroxymethyl)-pyrazol-3-yl]-6,7-dimethyl-1H-quinoxalin-2- ones ***15-18***. A suspension of **11-14** (0.2 g) in 50% aqueous ethanol (15 ml) containing sodium hydroxide (2.0 g) was heated under reflux for 4 h, and the resulting clear solution was cooled and acidified with acetic acid. The pale yellow crystals of the title compounds were then filtered washed with water, dried, and recrystallized from ethanol. (Table 2)

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