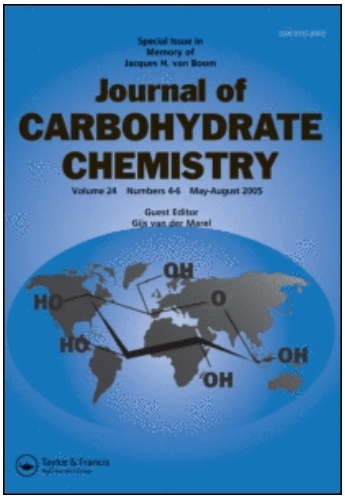

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DEHYDRATIVE CYCLIZATION OF HYDRAZONES:SYNTHESIS OF PYRAZOLO AND PYRAZOLYL QUINOXALINES[1]

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ABSTRACT

A number of 3-(1-arylhydrazono-D-erythro-2,3,4-trihydroxybutyl)-6,7-dimethyl-1H-quinoxalin-2-ones (**6-8**) as well as the semi-and thiosemicarbazones have been prepared. Their periodate oxidation afforded the corresponding 3-(1-arylhydrazono-glyoxal-1-yl)-6,7-dimethyl-1H-quinoxalin-2-ones (**11-13**), and their methylation gave 3-(1-arylhydrazono-D-erythro-2,3,4-trihydroxybutyl)-1,6,7-trimethyl-quinoxalin-2-ones (**15-17**). The action of alkali on the starting hydrazones (**6-8**) caused a loss of one mole of water to give 1-aryl-6,7-dimethyl-3-(D-erythro-glycerol-1-yl)-flavazoles (**18-20**) while the action of acetic anhydride afforded 3-(5-acetoxymethyl-1-arylpyrazol-3-yl)-6,7-dimethyl-1H-quinoxalin-2-ones (**21-23**).

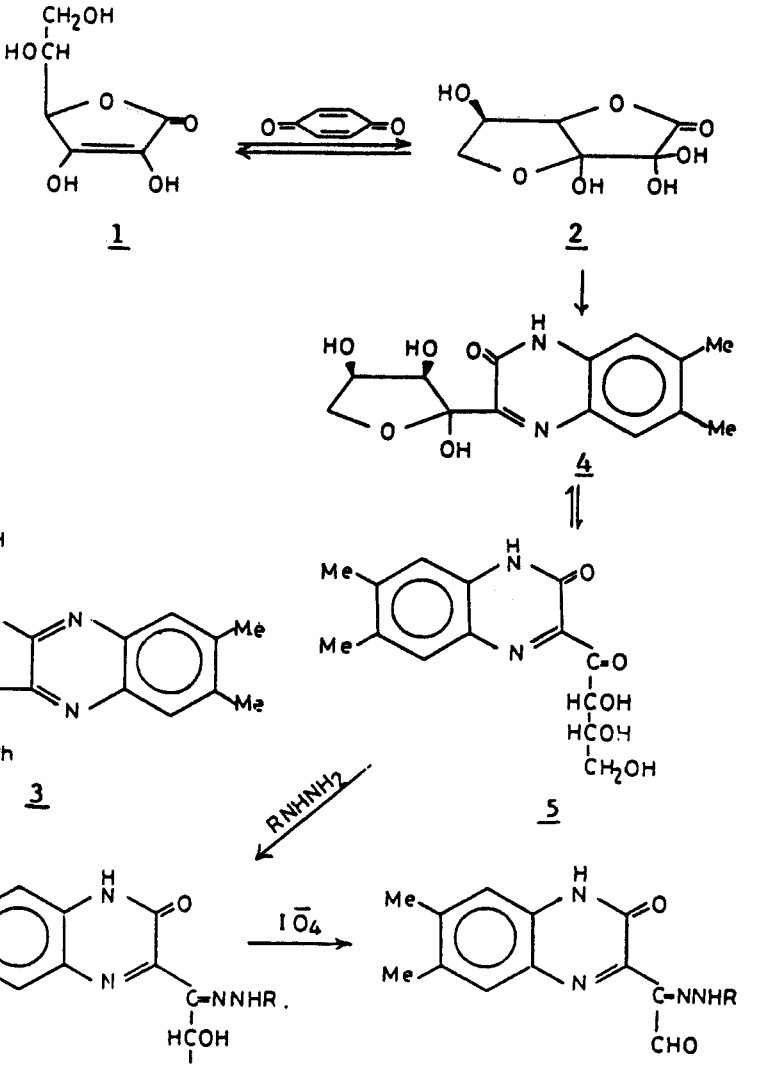
INTRODUCTION

Intensive research has been devoted to the chemical modification of carbohydrates. Advantage has been taken of their many chiral centers in the synthesis of natural

products.[2,3] The synthesis of heterocyclic,[4] carbocyclic, and aromatic[5] compounds from carbohydrates also has been achieved. Formation of heterocycles from carbohydrate precursors is one of the main objectives in our laboratory. Various types of heterocyclic compounds containing nitrogen, oxygen, or sulfur atoms have been prepared.[5,6] In this paper the cyclization of some hydrazones under acidic and basic conditions to produce carbohydrate substituted heterocycles is described.

RESULTS AND DISCUSSION

The starting materials for this study were the 3-(1-arylhydrazono-D-erythro-2,3,4-trihydroxybutyl)-6,7-dimethyl-1H-quinoxalin-2-ones (**6-8**). These compounds (**6-8**) were prepared from dehydro-D-isoascorbic acid (**2**) by oxidation of **2** and condensation with 1,2-diamino-4,5-dimethylbenzene to give **4**, which exists in equilibrium with **5**. Subsequent reaction with hydrazines, semicarbazide or thiosemicarbazide afforded the required compounds **6-10**. Their infrared spectra showed bands in the carbonyl frequency region at 1648-1665 cm^{-1} indicating the presence of the OCN group. This observation was in agreement with the acyclic structures **6-10** rather than the cyclic structure **3**. To confirm this conclusion, the hydrazones were subjected to the action of sodium periodate to give the corresponding aldehydes, 3-(1-arylhydrazono-glyoxal-1-yl)-6,7-dimethyl-1H-quinoxalin-2-ones (**11-13**). Since under the conditions of the periodate oxidation, there is no reason for the



1 2 3 4 5

6 R = $-C_6H_5$

7 R = $-C_6H_4$-Br-p

8 R = $-C_6H_4$-Cl-p

9 R = $-CONH_2$

10 R = $-CSNH_2$

11 R = $-C_6H_5$

12 R = $-C_6H_4$-Br-p

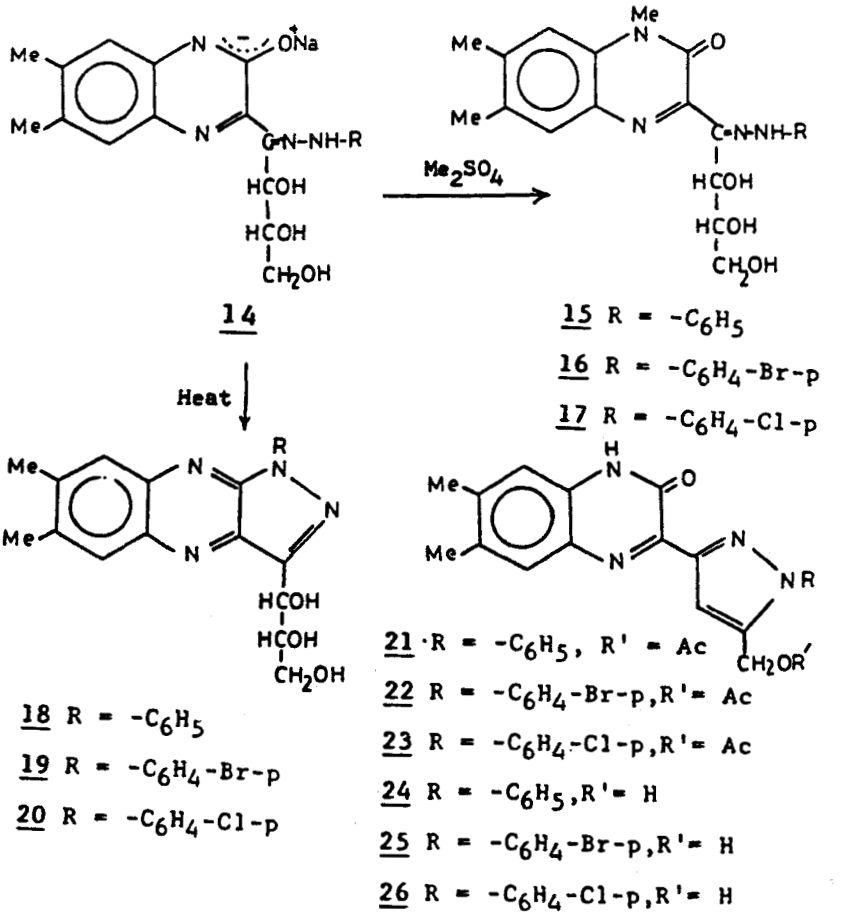
13 R = $-C_6H_4$-Cl-p

aldehyde derived from **3** to rearrange with further oxidation to give **11-13**, the isolation of these aldehydes (**11-13**) should be from a direct oxidation of the acyclic compounds **6-8**. In addition to the role of these aldehydes in structural determination, they are potential precursors to other heterocyclic compounds.

When the hydrazones **6-8** were dissolved in alkali followed by acidification of the solution, the starting materials were regenerated. When their alkaline solutions were heated, however, yellow crystalline products, identified as the flavazoles (pyrazolo[3,4-b]quinoxalines) **18-20** were formed. Formation of these compounds is a result of dehydrative cyclization of the hydrazone residue with the amide carbonyl group. The structures of the flavazoles were confirmed by the absence of absorption in the carbonyl region of their infrared spectra. The ^{1}H NMR spectra of **18-20** showed signals agreeing with the assigned structures.

When solutions of **6-8** in alkali were treated with dimethyl sulfate, 3-(1-aryl-D-*erythro*-2,3,4-trihydroxybutyl)-1,6,7-trimethyl-quinoxalin-2-ones (**15-17**) were obtained. Their infrared spectra showed the presence of a band due to the OCN group, confirming that the methylation product is an N-methyl and not an O-methyl (on the heterocyclic ring) derivative. Moreover, the location of the methyl group was confirmed by subjecting **15** to the action of acetic anhydride to give the N-methyl derivative of **21** which was identical with that prepared from the L-*threo* analog.[7]

Boiling compound 6 in acetic anhydride did not give the corresponding tri-O-acetyl derivative, but the colorless product 21 was obtained. Similarly, 22 and 23 were prepared. Deacetylation of 21-23 gave 24-26. Their structures (21-26) were confirmed by the presence of infrared spectral bands due to the anticipated groups. The ^{1}H NMR spectrum of 21 showed singlets due to the acetyl (δ 2.10) and the two methyl (δ 2.35 and 2.37) groups, followed by a singlet at δ 5.15 corresponding to a methylene group. In addition, an exchangeable, broad singlet at δ 11.72, due to one NH proton,



was observed. The above described data for the reaction products of acetic anhydride with **6-8** confirmed that during the reaction, closure of the pyrazole ring takes place to afford 3-(5-acetoxymethyl-1-aryl-pyrazol-3-yl)-6,7-dimethyl-1H-quinoxalin-2-one. Moreover, the involvement of the glycerolyl residue could also be concluded from the similarity of the products with those obtained upon subjecting the L-threo-analogs of **6-8** to acetic anhydride.

EXPERIMENTAL

General methods. Melting points were determined with a "Meltemp apparatus" using a 76 mm immersion thermometer and are uncorrected. Infrared spectra were recorded with a Pye Unicam SP 1025 spectrometer. ^{1}H NMR spectra were determined with a Varian EM-390 spectrometer for solutions in chloroform-d or dimethylsulfoxide-d_6 with tetramethylsilane (Me_4Si) as standard (δ = 0.0). Microanalyses were made in the Unit of Microanalysis, Cairo University. TLC was performed on "Baker-Flex" silica gel B-F plates.

3-(1-Arylhydrazono-D-erythro-2,3,4-trihydroxybutyl)-6,7-dimethyl-1H-quinoxalin-2-ones (6-8). A solution of compound **4**[7] (1 mmol) in ethanol (15 mL) was treated, while hot, with the respective arylhydrazine (1 mmol). The reaction mixture was allowed to cool, whereupon, the hydrazones crystallized. They were recrystallized from ethanol to form red-orange needles, see Table 1.

6,7-Dimethyl-3-(1-semicarbazono-D-erythro-2,3,4-trihydroxybutyl)-1H-quinoxalin-2-one (9). A solution of comp-

ound 4[7] (10 mmol) in water (100 mL) and a few drops of acetic acid was treated, while hot, with semicarbazide hydrochloride (10 mmol) and sodium acetate (10 mmol). The semicarbazone crystallized upon cooling. It was recrystallized from ethanol, see Table 1.

6,7-Dimethyl-3-(1-thiosemicarbazono-D-erythro-2,3,4-trihydroxybutyl)-1H-quinoxalin-2-one (10). Compound **10** was prepared as described for compound **9**, but using thiosemicarbazide, see Table 1.

3-(1-Arylhydrazono-glyoxal-1-yl)-6,7-dimethyl-1H-quinoxalin-2-ones (11-13). A typical experiment is described. To a stirred solution of sodium periodate (2 mmol) in distilled water (10 mL), compound **6** (1 mmol) was added and the reaction mixture was left overnight in the dark at room temperature. The suspension was filtered and the products were recrystallized from 1-butanol to give orange needles, see Table 1.

3-(1-Arylhydrazono-D-erythro-2,3,4-trihydroxybutyl)-1,6,7-trimethyl-quinoxalin-2-ones (15-17). A typical experiment is described. To a solution of sodium hydroxide (2 g) in 40% aqueous ethanol (250 mL), compound **6** (1 mmol) was added. The reaction mixture was heated on a water bath till dissolution. Dimethyl sulfate (3.5 mL) was then added and the mixture was left at room temperature for 10 h. The product that separated was washed with water and recrystallized from ethanol to give orange needles, see Table 2.

1-Aryl-3-(D-erythro-glycerol-1-yl)-6,7-dimethyl-flavazoles (18-20). A typical experiment is described. A

Table 1. Microanalytical and IR Spectral Data for Compounds 6-13.

Comp. No.	mp (°C)	Yield (%)	Molecular formula	Calculated (%) C	H	N	Found (%) C	H	N	IR (KBr) cm^{-1} OCN	CO	OH
6[a]	230	63	$C_{20}H_{22}N_4O_4$	62.8	5.8	14.6	62.7	6.1	14.9	1653		3306
7	239	68	$C_{20}H_{21}BrN_4O_4$	52.1	4.6	12.1	52.0	4.7	12.1	1663		3440
8	230	72	$C_{20}H_{21}ClN_4O_4$	57.6	5.1	13.4	57.5	5.4	13.6	1665		3380
9	226	50	$C_{15}H_{19}N_5O_5$	51.6	5.5	20.1	51.4	5.3	20.2	1665		3340
10[b]	225	55	$C_{15}H_{19}N_5O_4S$	49.3	5.2	19.2	49.0	5.2	19.4	1648		3320
11	266	85	$C_{18}H_{16}N_4O_2$	67.5	5.0	17.5	67.3	5.1	17.2	1658	1710	
12	243	88	$C_{18}H_{15}BrN_4O_2$	54.2	3.8	14.0	54.4	4.0	13.8	1655	1710	
13	265	90	$C_{18}H_{15}ClN_4O_2$	60.9	4.3	15.8	61.3	4.5	15.6	1656	1710	

[a] ^1H NMR (DMSO-d_6): δ 2.35 and 2.30 (2 s, 2 Me), 3.00,3.30 and 5.20 (2 m, and d,3 OH), 3.00 and 3.30 (2 m, H-3,3'), 3.98 (m, H-2), 4.69 (d,H-1), 6.80-7.60, (m, Ar-H).

[b] ^1H NMR (C_5D_5N): δ 2.16 and 2.23 (2 s, 2 Me), 4.38 (q, H-3,3'), 4.62 (m, H-2), 4.92,5.75, (m and d 3 OH),6.27 (d, H-1), 7.16,7.63, 8.7 (d and 2 s, Ar-H), 8.86, 9.63, 9.78, 12.66 (4 bs,4 NH).

Table 2. Microanalytical and Spectral Data for Compounds 15-20.

Comp. No.	mp (°C)	Yield (%)	Molecular formula	Calculated (%) C	H	N	Found (%) C	H	N	IR (KBr) cm^{-1} OCN	OH
15	247	55	$C_{21}H_{24}N_4O_4$	63.6	6.1	14.1	63.2	6.0	13.7	1635	3490
16	210	62	$C_{21}H_{23}BrN_4O_4$	53.0	4.9	11.8	52.5	4.8	11.6	1652	3370
17	207	58	$C_{21}H_{23}ClN_4O_4$	58.5	5.4	13.0	59.0	5.4	13.2	1652	3260
18[a]	213	75	$C_{20}H_{20}N_4O_3$	65.9	5.5	15.4	65.5	5.1	15.2		3425
19[b]	234	85	$C_{20}H_{19}BrN_4O_3$	54.2	4.3	12.6	54.0	4.4	12.7		3380
20[c]	236	80	$C_{20}H_{19}ClN_4O_3$	60.2	4.8	14.0	60.0	4.5	14.2		3360

[a] ^{1}H NMR (DMSO-d_6): δ 2.53 (s, 2Me), 3.76 (m, H-3,3'), 4.57 (m, H-2 and 2 OH), 5.03 (dd, H-1), 5.76 (d, OH), 7.46, 7.97, 8.03 and 8.42 (m, 2 s and d, Ar-H).

[b] ^{1}H NMR (DMSO-d_6): δ 2.53 (s, 2Me), 3.83 (m, H-3,3'), 4.48 (m, H-2 and 2 OH), 5.00 (dd, $J_{1,2}$ 8.0 Hz, H-1), 8.78 (d, OH), 7.78, 7.96, 8.02 and 8.38 (d, 2 s and d, Ar-H).

[c] ^{1}H NMR (DMSO-d_6): δ 2.53 (s, 2Me), 3.69 (m, H-3,3'), 4.49 (m, H-2 and 2 OH), 5.04 (dd, $J_{1,2}$ 8.0 Hz, H-1), 5.73 (d, OH), 7.66, 7.97, 8.03 and 8.45 (d, 2 s and d, Ar-H).

Table 3. Microanalytical and Spectral Data for Compounds 21-26.

Comp. No.	mp (°C)	Yield (%)	Molecular formula	Calculated (%) C	H	N	Found (%) C	H	N	IR (KBr) cm^{-1} OCN	CO	OH
21[a]	268	75	$C_{22}H_{20}N_4O_3$	68.0	5.2	14.4	68.2	5.7	14.8	1675	1755	
22	290	82	$C_{22}H_{19}BrN_4O_3$	56.5	4.1	12.0	56.3	4.2	11.7	1668	1755	
23[b]	280	70	$C_{22}H_{19}ClN_4O_3$	62.5	4.5	13.2	62.3	4.7	13.0	1670	1745	
24	265	62	$C_{20}H_{18}N_4O_2$	69.3	5.2	16.2	69.0	5.5	16.2	1655		3370
25	266	77	$C_{20}H_{17}BrN_4O_2$	56.5	4.0	13.2	56.6	4.2	12.9	1658		3390
26	308	71	$C_{20}H_{17}ClN_4O_2$	63.1	4.5	14.7	63.3	4.6	14.9	1650		3340

[a] ^1H NMR ($CDCl_3$): δ 2.10 (s, COMe), 2.35 and 2.37 (2 s, 2 Me), 5.15 (s, $-CH_2O-$), 7.49 (m, Ar-H), 11.72 (bs, NH).

[b] ^1H NMR ($CDCl_3$): δ 2.07 (s, COMe), 2.37 and 2.43 (2 s, 2 Me), 5.10 (s, $-CH_2O-$), 7.43 (m, Ar-H), 11.93 (bs, NH).

suspension of compound **6** (1 mmol) in 0.01 N sodium hydroxide (120 mL) and 1-butanol (2 mL) was heated under reflux for 2 h. The solution was cooled to allow the flavazole derivatives to crystallize. They were recrystallized from ethanol to give yellow needles, see Table 2.

3-(5-Acetoxymethyl-1-aryl-pyrazol-3-yl)-6,7-dimethyl-1H-quinoxalin-2-ones (21-23). A typical experiment is described. A solution of compound **6** (0.5 mmol) in acetic anhydride (10 mL) was heated under reflux for 15 min and the reaction mixture was cooled and poured onto crushed ice. The products were recrystallized from ethanol to give colorless needles, see Table 3.

3-(1-Aryl-5-hydroxymethyl-pyrazol-3-yl)-6,7-dimethyl-1H-quinoxalin-2-ones (24-26). A typical experiment is described. A solution of compound **21** (1 mmol) and sodium hydroxide (0.1 g) in 1:1 water-ethanol (10 mL) was boiled under reflux for 4 h. The mixture was cooled, acidified with acetic acid and the product, which crystallized on cooling, was washed with water. The product was recrystallized from ethanol to give colorless needles, see Table 3.

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