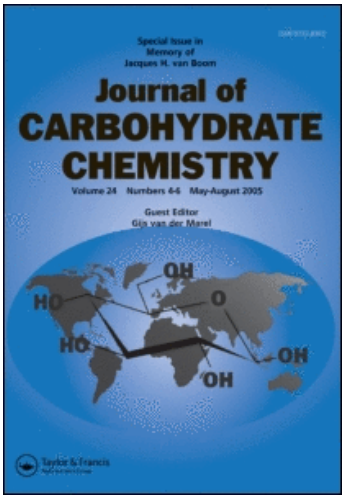

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Synthesis of 3-(L-*Threo*-Glycerol-l-YL)-6,7-Dimethyl-Pyrazolo[3,4-*b*]Quinoxalines

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SYNTHESIS OF 3-(L-THREO-GLYCEROL-1-YL)-6,7-DIMETHYL-PYRAZOLO[3,4-b]QUINOXALINES

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ABSTRACT

Reaction of dehydro-L-ascorbic acid with 1,2-diamino-4,5-dimethylbenzene and arylhydrazines afforded 3-[1-(aryl)hydrazono-L-threo-2,3,4-trihydroxybutyl]-6,7-dimethyl-1H-quinoxalin-2-ones. Their dehydrative cyclization gave 1-aryl-3-(L-threo-glycerol-1-yl)-6,7-dimethylpyrazolo[3,4-b]quinoxalines, whose acetylation and periodate oxidation were studied.

INTRODUCTION

The syntheses of nitrogen heterocycles from carbohydrate precursors via their reaction with hydrazines or diamines have been extensively investigated by El-Ashry and coworkers. L-Ascorbic acid, upon oxidation and subsequent reaction with o-phenylenediamine, followed by reaction with arylhydrazines, gave 3-[1-(aryl)hydrazono-L-threo-2,3,4-trihydroxybutyl]-1H-quinoxalin-2-ones, which have proved to be of great value in the synthesis of various types of heterocycles.[2-7] In this report,

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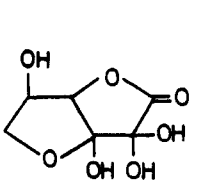
these reactions were extended to use 1,2-diamino-4,5-dimethylbenzene, which upon reaction with dehydro-L-ascorbic acid, would afford 6,7-dimethylquinoxalinone derivatives. Such a ring is an integral part of vitamin B_2 and lumichrome. Moreover, their heterocyclisation would afford pyrazolo[3,4-b]quinoxaline derivatives, which could be of potential value as antibacterial, anti-inflammatory, and analgesic agents.[8]

RESULTS AND DISCUSSION

Oxidation of L-ascorbic acid with p-benzoquinone gave dehydro-L-ascorbic acid, whose structure has been studied by various authors.[9-12] It has been proposed that its major form in aqueous solution is the hydrated hemiketal, 3,6-anhydro-L-xylo-hexulono-1,4-lactone (**1**), whose ring opening probably occurs with time to give **2**. Treatment of the solution of dehydro-L-ascorbic acid with 1,2-diamino-4,5-dimethylbenzene (**3**), followed by reaction with arylhydrazines, afforded orange crystalline products **4** - **8**, whose infrared (IR) spectra showed bands at 1665 - 1660 cm^{-1} indicating the presence of amide groups, which are in agreement with the acyclic structures, 3-[1-(aryl)-hydrazono-L-threo-2,3,4-trihydroxybutyl]-6,7-dimethyl-1H-quinoxalin-2-ones (**4** - **8**).

Heating **4** - **8** in a dilute solution of sodium hydroxide caused a dehydrative ring closure of the hydrazone residue with the quinoxalinone ring giving 1-aryl-3-(L-threo-glycerol-1-yl)-6,7-dimethyl-pyrazolo[3,4-b]quinoxalines (**9** - **13**) that have a bright yellow color that distinguishes them from their starting quinoxalinone derivatives. Their IR spectra showed the absence of the amide bands.

Acetylation of **9**, **12**, and **13** with acetic anhydride in pyridine afforded 1-aryl-3-(1,2,3-tri-O-acetyl-L-threo-glycerol-1-yl-6,7-dimethyl-pyrazolo[3,4-b]quinoxalines (**14** - **16**). Their IR spectra showed the carbonyl frequency of the acetyl groups at 1750 cm^{-1}. The ^1H NMR spectrum of **14** showed the presence of the three acetyl groups as two singlets at 1.99 and 2.15 ppm, and the two methyl groups as a singlet at 2.45 ppm. The H-3' and H-3 of the glycerolyl residue appeared as two quartets at 4.25 and 4.56



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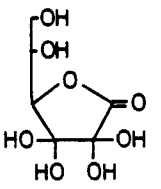

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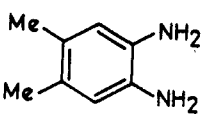

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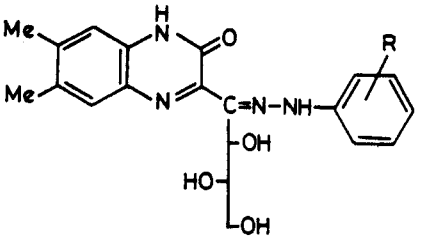
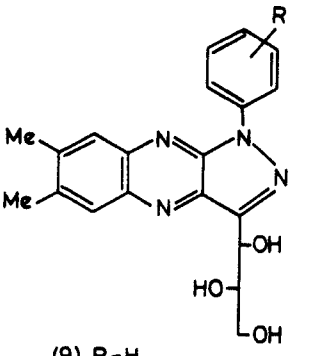
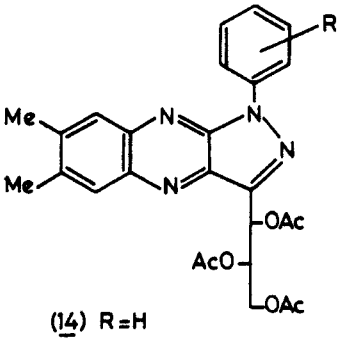


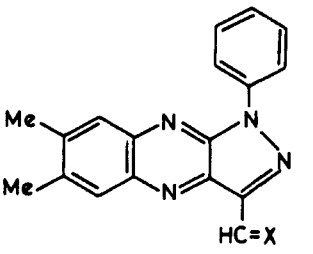
(4) R=H
(5) R=o-Me
(6) R=p-Me
(7) R=m-Cl
(8) R=p-Cl



(9) R=H
(10) R=o-Me
(11) R=p-Me
(12) R=m-Cl
(13) R=p-Cl



(14) R=H
(15) R=m-Cl
(16) R=p-Cl



(17) X=O
(18) X=NHN

SCHEME 1

ppm, respectively. Both protons were split by H-2 with a small coupling constant ($J_{2,3}$ 4.0 Hz and $J_{2,3'}$ 6.0 Hz), whereas their geminal coupling gave larger coupling constant ($J_{3,3'}$ 12.0 Hz). The multiplet at 6.15 ppm was assigned for H-2, and the doublet at 6.90 ppm was assigned for H-1. The ^{1}H NMR spectra of **15** and **16** showed similar patterns (Table 1).

Table 1. ^{1}H NMR Spectral Data for Compounds 14-16.

Compound. No.	Chemical Shifts (ppm) H-1 ($J_{1,2}$Hz)	H-2	H-3 ($J_{2,3}$Hz)	($J_{3,3'}$Hz)	H-3' ($J_{2,3'}$Hz)	CMe_2	3OAc	aromatic
14	6.90 (d, 6.0)	6.15 (m)	4.56 (d, 4.0)	(12.0)	4.25 (q, 6.0)	(s)	1.99 (2s)	8.38m 7.37d 7.37s 7.37s
15	6.78 (d, 6.0)	6.04 (m)	4.49 (q, 4.0)	(12.0)	4.15 (q, 6.0)	(s)	2.25 2.09 (2s)	7.41m 8.42m 8.00s 7.95s
16	6.74 (d, 5.0)	6.04 (m)	4.49 (q, 4.0)	(12.0)	4.14 (q, 6.0)	(s)	2.24 2.01 (2s)	8.36d 7.44d 7.95s 7.87s

Periodate oxidation of 9 afforded 6,7-dimethyl-1-phenyl-pyrazolo-[3,4-b]quinoxaline-3-carbaldehyde (17). Its IR spectrum showed the presence of a carbonyl frequency absorption band at 1700 cm^{-1} (due to CHO). The reaction of 17 with phenylhydrazine afforded 6,7-dimethyl-1-phenyl-pyrazolo[3,4-b]quinoxaline-3-carbaldehyde phenylhydrazone (18), whose IR spectrum showed the absence of the carbonyl frequency absorption, and its ^{1}H NMR spectrum agreed with the assigned structure.

EXPERIMENTAL

General Methods. Melting points were determined on a Kofler-block apparatus and are uncorrected. Infrared (IR) absorption spectra were recorded with a 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 internal and external reference, respectively. The spectra are reported with chemical shifts downfield from Me_4Si. Microanalyses were carried out in the unit of microanalysis, Faculty of Science, Cairo University.

3-[1-(Aryl)hydrazono-L-threo-2,3,4-trihydroxybutyl)]-6,7-dimethyl-1H-quinoxalin-2-ones (4 - 8). A mixture of L-ascorbic

acid (17.6 g, 0.1 mol) and p-benzoquinone (10.8 g, 0.1 mol) in ethanol (150 mL) was stirred for 90 min at room temperature. The resulting solution was then treated with a solution of 1,2-diamino-4,5-dimethylbenzene (13.6 g, 0.1 mol) in ethanol (100 mL) and water (500 mL). The mixture was heated until boiling, and the arylhydrazine (0.1 mol) in ethanol (50 mL) or a mixture of the arylhydrazine hydrochloride (0.1 mol) and sodium acetate (0.1 mol) in water (100 mL) was then added. The mixture was boiled for an additional 5 - 10 min, whereby orange crystalline products separated out. The title compounds were crystallized from ethanol as orange needles (Table 2).

1-Aryl-3-(L-threo-glycerol-1-yl)-6,7-dimethyl-pyrazolo[3,4-b]quinoxalines (9 - 13). Solutions of compounds **4 - 8** (0.03 mmol) in ethanol (30 mL) were treated with 0.1 M sodium hydroxide (50 mL). The mixtures were heated under reflux for 5 - 7 h. The resulting solutions were then concentrated, and the products were collected by filtration and recrystallized from ethanol to give yellow crystals (Table 3).

1-Aryl-3-(1,2,3-tri-O-acetyl-L-threo-glycerol-1-yl)-6,7-dimethyl-pyrazolo[3,4-b]quinoxalines (14 - 16). Solutions of compounds **1**, **12**, and **13** (0.03 mmol) in pyridine (5 mL) were treated with acetic anhydride (2 mL), and the mixtures were left for 24 h at room temperature. They were then poured onto crushed ice, and the yellow products that precipitated were filtered, washed with water, and recrystallized from ethanol to give yellow needles (Table 3).

6,7-Dimethyl-1-phenyl-pyrazolo[3,4-b]quinoxaline-3-carbaldehyde (17). A suspension of **9** (0.1 mmol) in water (25 mL) was treated with a solution of sodium metaperiodate (0.25 mmol) in water (25 mL). The mixture was stirred for 24 h at room temperature, filtered, and the product was washed with water and crystallized from ethanol (80% yield): mp 200 - 202 °C; IR (KBr) 1700 cm^{-1} (C=O).

Anal. Calcd for $C_{18}H_{14}N_4O$: C, 71.5; H, 4.7; N, 18.5. Found: C, 71.2; H, 4.6; N, 18.1.

6,7-Dimethyl-1-phenyl-pyrazolo[3,4-b]quinoxaline-3-carbaldehyde phenylhydrazone (18). A solution of **17** (0.05 mmol) in

Table 2. Microanalyses and Spectral Data for 3-[1-(Aryl)hydrazono-L-threo-2,3,4-trihydroxybutyl]-6,7-dimethyl-1H-quinoxalin-2-ones (4 - 8).

Compound	Yield	mp	Molecular	Calculated (%)				Found (%)				IR(KBr)cm^{-1}	
No.	(%)	(°C)	formula	C	H	N	Cl	C	H	N	Cl	OCN	OH
4[a]	90	227-229	$C_{20}H_{22}N_4O_4$	62.8	5.8	14.7		63.2	5.6	15.0		1655	3320
5	90	224-226	$C_{21}H_{24}N_4O_4$	63.6	6.1	14.1		63.2	5.8	14.3		1660	3350
6	95	208-210	$C_{21}H_{24}N_4O_4$	63.6	6.1	14.1		63.3	5.7	14.3		1660	3350
7	91	221-223	$C_{20}H_{21}ClN_4O_4$	57.6	5.1	13.4	8.5	58.0	5.5	13.4	8.7	1665	3350
8	96	234-235	$C_{20}H_{21}ClN_4O_4$	57.6	5.1	13.4	8.5	58.1	5.4	13.6	8.8	1665	3350

[a] ^1H NMR data (DMSO-d_6): δ 2.32, 2.34 (2s, 2Me); 3.44, 3.76, 4.30, and 4.67, 5.10 (2m, t, and 2m, glycerolyl protons); 6.67, 7.10, 7.32, and 7.55 (2m, 2s, Ar-H); and 10.50, 10.60, 12.12, and 12.48 (4s, 2NH).

Table 3. Microanalyses and Spectral Data for 1-Aryl-3-(L-threo-glycerol-1-yl)-6,7-dimethylpyrazolo[3,4-b]quinoxalines (9-13) and Their O-Acetyl Derivatives 14-16.

Compound No.	Yield (%)	mp (°C)	Molecular formula	Calculated (%) C	H	N	Found (%) C	H	N	IR(KBr) cm^{-1} OH	OAc
9	77	190-192	$C_{20}H_{20}N_4O_3$	65.9	5.5	15.4	65.7	5.6	15.0	3360	
10	60	174-175	$C_{21}H_{22}N_4O_3$	66.6	5.9	14.8	66.3	5.5	14.5	3350	
11[a]	60	190-192	$C_{21}H_{22}N_4O_3$	66.6	5.9	14.8	66.4	5.9	14.6	3300	
12	80	207-208	$C_{20}H_{19}ClN_4O_3$	60.2	4.8	14.0	59.8	5.1	13.9	3360	
13	78	220-222	$C_{20}H_{19}ClN_4O_3$	60.2	4.8	14.0	60.4	4.7	14.1	3360	
14	85	107-108	$C_{26}H_{26}N_4O_6$	63.7	5.3	11.4	63.7	5.3	11.2		1750
15	80	153-155	$C_{26}H_{25}ClN_4O_6$	59.5	4.8	10.7	59.6	4.6	10.5		1750
16	90	135-137	$C_{26}H_{25}ClN_4O_6$	59.5	4.8	10.7	59.6	4.5	10.3		1750

[a] ^1H NMR data (DMSO-d_6): δ 2.43, 2.56 (2s, 3Me), 3.54, 4.33, 4.60, 4.83, and 5.31 (2m, t, d, and m, glycerolyl protons), and 7.39, 7.93, 8.00, and 8.25 ppm (d, 2s, and d, Ar-H).

ethanol (50 mL) was treated with phenylhydrazine (0.06 mmol). After 5 min of boiling under reflux, a red crystalline product separated. Heating was continued for 30 min, the mixture was cooled, and the product was collected by filtration, washed with ethanol, and recrystallized from N,N-dimethylformamide - ethanol to give red needles (76% yield): mp 210 - 212 °C; ^{1}H NMR data ($CDCl_3$): δ 7.90 (m, 13H, ArH, and H=C), 2.50 (s, 6H, 2Me), and 12.09 ppm (s, 1H, NH).

Anal. Calcd for $C_{24}H_{20}N_6$: C, 73.4; H, 5.1; N, 21.4. Found: C, 73.0; H, 5.5; N, 20.9.

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