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(2-QUINOXALINON-3-YL)GLYOXAL DERIVATIVES FROM L-ASCORBIC ACID*

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ABSTRACT

Reaction of dehydro-L-ascorbic acid with *o*-phenylenediamine, followed by aroylhydrazines, gave 3-[1-(aroylhydrazono)-L-*threo*-2,3,4-trihydroxybutyl]-2-quinoxalinones which, upon periodate oxidation, gave 3-[1-(aroylhydrazono)glyoxal-1-yl]-2-quinoxalinones. Various derivatives having substituents on the phenyl ring were also prepared. Reaction of 3-[1-(benzoylhydrazono)glyoxal-1-yl]-2-quinoxalinone with benzoylhydrazine gave 3-[1,2-bis(benzoylhydrazono)glyoxal-1-yl]-2-quinoxalinone, and its reduction gave 3-[1-(benzoylhydrazono)-2-hydroxyethyl]-2-quinoxalinone.

INTRODUCTION

The synthesis of heterocycles from carbohydrate precursors, a subject of interest in our laboratory as a consequence of the widespread use of heterocycles, may be achieved to afford heterocycles having or lacking carbohydrate substituents. In previous papers of this series, we achieved[1–10] the synthesis of various heterocycles by using L-ascorbic acid mono- or bis-(hydrazones). L-Ascorbic acid is known to give, upon oxidation, L-*threo*-2,3-hexodiulosono-1,4-lactone (**1**), which is capable of reacting with *o*-phenylenediamine to afford 3-(L-*threo*-2,3,4-trihydroxy-1-oxobutyl)-2-quinoxalinone (**3**); upon further reaction with arylhydrazines[11–13], compound **3** gives the corresponding mono(arylhydrazones), and these proved to be of excellent value in the synthesis of various types of heterocycles. We now describe the condensation of **3** with various aroylhydrazines, and a study of the reactions of the products.

RESULTS AND DISCUSSION

The work described here was started by constructing the quinoxalinonyl ring from dehydro-L-ascorbic acid by using *o*-phenylenediamine, and then producing

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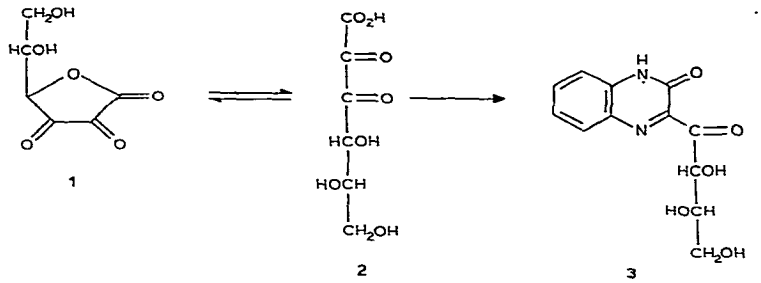
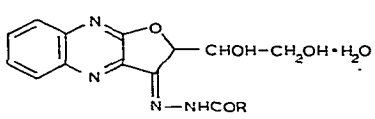
from the polyhydroxyalkyl side-chain a glyoxalyl functionality which is of potential value in the synthesis of various types of heterocycles. Thus, oxidation of L-ascorbic acid with an equimolecular amount of *p*-benzoquinone in aqueous solution at room temperature, followed by reaction with an equivalent amount of *o*-phenylenediamine and benzoylhydrazine, gave a yellow, crystalline product **5**. The same compound could also be prepared unambiguously by pre-forming the intermediate **3**, and treating it with benzoylhydrazine. The elemental analysis of **5** agreed with the molecular formula $C_{19}H_{18}N_4O_5$, which was in harmony with the structure 3-[1-(benzoylhydrazono)-L-*threo*-2,3,4-trihydroxybutyl]-2-quinoxalinone or its hydrated, anhydro derivative **4**.

This reaction was found to be a general one whereby such aroylhydrazines as *m*-toluoyl, *p*-toluoyl-, *p*-chlorobenzoyl-, *p*-iodobenzoyl-, *p*-methoxybenzoyl-, *p*-nitrobenzoyl-, and -isonicotinoyl-hydrazine can be used, affording the corresponding, yellow, crystalline derivatives **6–12**. The infrared (i.r.) spectra of these hydrazones showed two bands in the carbonyl-frequency region, at 1680–1660 and 1645–1640 cm^{-1}, due to the OCN groups, in addition to the hydroxyl absorption bands at 3425–3325 cm^{-1}. The structure assigned to similar compounds having arylhydrazone residues, namely, 3-[1-(arylhydrazono)-L-*threo*-2,3,4-trihydroxybutyl]-2-quinoxalinones, as having an acyclic side-chain (rather than the hydrated, anhydro structure), was favored by the presence of a band in the i.r. spectra at 1660 cm^{-1} (due to the OCN group) and by the results of periodate oxidation. In the case of the aroylhydrazones herein described, the i.r. data did not favor either of the structures, as a result of the presence of an OCN group in the hydrazone residue. However, the results of periodate oxidation favored the acyclic structure. The n.m.r. spectrum of 3-[1-(benzoylhydrazono)-L-*threo*-2,3,4-trihydroxybutyl]-2-quinoxalinone showed a multiplet of two-proton intensity at δ 4.6 due to the methylene protons of the C-4 butyl side-chain; this was followed by a multiplet and a doublet, at δ 5.8 and 6.7, due, respectively, to H-3 and H-2. The aromatic protons appeared as two multiplets, at δ 7.5 and 8.0.

Periodate oxidation of 3-[1-(aroylhydrazono)-L-*threo*-2,3,4-trihydroxybutyl]-2-quinoxalinones, either dissolved in 1,4-dioxane, or as a suspension in water, afforded 3-[1-(aroylhydrazono)glyoxal-1-yl]-2-quinoxalinones (as shown from their combustion analysis), favoring the acyclic structure of their precursors, as, otherwise, they would have consumed one molar proportion of the oxidant, to give the aldehydes predicted as being formed from the anhydro derivative **4**. The i.r. spectra of the aldehydes showed, in addition to amide bands at 1680–1660 cm^{-1}, a carbonyl band at 1710–1690 cm^{-1}, and NH absorption bands at 3240–3170 cm^{-1}. It is of interest that the periodate-oxidation products, the 3-[1-(aroylhydrazono)glyoxal-1-yl)]-2-quinoxalinones (**15–20**), are monosubstituted glyoxal mono(arylhydrazones) which it would be difficult to obtain if theoretically we started with the possible, but unknown, precursor 3-(glyoxal-1-yl)-2-quinoxalinone (**21**) and allowed it to react with aroylhydrazines. The only possible mono(aroylhydrazone) expected upon such direct condensation is **13**, and not **15–20**. The route now described provides a simple and



1 2 3



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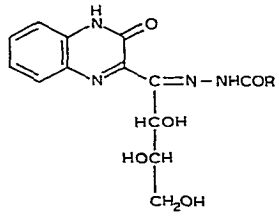
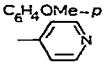
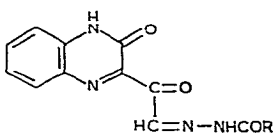


5 R = Ph
6 R = C_6H_4Me-m
7 R = C_6H_4Me-p
8 R = C_6H_4Cl-p
9 R = C_6H_4I-p
10 R = C_6H_4OMe-p
11 R = $C_6H_4NO_2-p$
12 R = 



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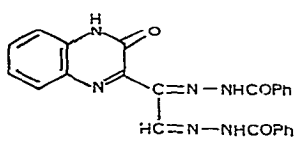

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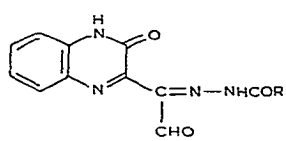
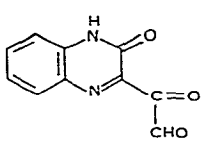


15 R = Ph
16 R = C_6H_4Me-m
17 R = C_6H_4Me-p
18 R = C_6H_4Cl-p
19 R = C_6H_4I-p
20 R = C_6H_4OMe-p



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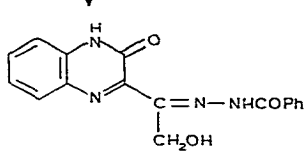

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convenient method for the preparation of members of such a class of compounds.

Reaction of 3-[1-(benzoylhydrazono)glyoxal-1-yl]-2-quinoxalinone (**15**) with benzoylhydrazine readily afforded the corresponding bis(benzoylhydrazone), 3-[1,2-bis(benzoylhydrazono)glyoxal-1-yl]-2-quinoxalinone (**14**). The bis(aroylhydrazones) of dicarbonyl compounds undergo oxidation with iodine and yellow mercuric oxide, to give 1,2,3-triazole derivatives. When this reaction was applied to 3-[1,2-bis(benzoylhydrazono)glyoxal-1-yl]-2-quinoxalinone, a product was isolated whose elemental analysis and mass spectrum agreed with the molecular formula $C_{24}H_{16}N_6O_3$, indicating the loss of two protons, as expected, and this was confirmed by the n.m.r. spectrum, which showed the presence of only one imino proton.

Reduction of aldehyde **15** with sodium borohydride afforded 3-[1-(benzoylhydrazono)-2-hydroxyethyl]-2-quinoxalinone (**22**).

EXPERIMENTAL

General methods. — Melting points were determined with a Kofler-block apparatus, and are uncorrected. I.r. spectra were recorded with a Unicam SP-200 spectrometer. Microanalyses were performed in the Chemistry Department, Faculty of Science, Cairo University, Cairo, Egypt.

*3-[1-(Aroylhydrazono)-*L*-threo-2,3,4-trihydroxybutyl]-2-quinoxalinones* (**5–12**). — A solution of L-ascorbic acid (10 mmol) and *p*-benzoquinone (10 mmol) in methanol (15 mL) was stirred for 90 min, and then treated with a solution of *o*-phenylenediamine (10 mmol) in methanol (15 mL) and water (50 mL). The mixture was boiled under reflux for 5 min, and then treated with the appropriate aroylhydrazine (10 mmol), and boiling was continued for a further 10 min. The products that separated on cooling were filtered off, washed with methanol, and dried. They were recrystallized from ethanol, to give yellow crystals (see Table I).

3-[1-(Aroylhydrazono)glyoxal-1-yl]-2-quinoxalinones (**15–20**). — A suspension of each of compounds **5–10** (2 mmol) in distilled water (10 mL) was treated with sodium metaperiodate (4 mmol), and the mixture was stirred overnight at room temperature. The products that separated out were filtered off, washed with water, and dried. They were recrystallized from ethanol as yellow crystals (see Table II).

3-[1,2-Bis(benzoylhydrazono)glyoxal-1-yl]-2-quinoxalinone (**14**). — A solution of compound **15** (1 g) in 1-butanol (50 mL) was treated with a solution of benzoylhydrazine (0.5 g) in 1-butanol (3 mL), and the mixture was boiled under reflux for 1 h. The product that separated on cooling was filtered off, washed with 1-butanol, and dried (yield 1.2 g). It was recrystallized from 1-butanol, giving yellow crystals; m.p. 185°; ν_{max}^{Nujol} 3270 (NH) and 1665 cm^{-1} (OCN).

Anal. Calc. for $C_{24}H_{18}N_6O_3$: C, 65.8; H, 4.1; N, 19.2. Found: C, 66.0; H, 4.6; N, 18.8.

Oxidation of compound **15**. — A suspension of compound **15** (1.59 g) in dry ether (120 mL) was treated successively with mercuric oxide (2.4 g), magnesium oxide (0.3 g), and iodine (2.4 g), and the mixture was kept for 72 h at room tempera-

TABLE I

MICROANALYTICAL AND SPECTRAL DATA FOR 3-[1-(AROYLHYDRAZONO)-L-*threo*-2,3,4-TRIHYDROXYBUTYL]-2-QUINOXALINONES

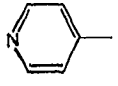
Compound No.	*R*	*Yield (%)*	*M.p. (degrees)*	*Molecular formula*	*Calculated (%)*			*Found (%)*			ν_{max}^{Nujol} *(cm^{-1})*		
					C	*H*	*N*	*C*	*H*	*N*			
5	Ph	60	200	$C_{19}H_{18}N_4O_5$	59.7	4.7	14.7	59.4	4.6	14.5		1670	3425
6	C_6H_4Me-*m*	40	175	$C_{20}H_{20}N_4O_5$	60.6	5.1	14.1	60.8	4.9	13.8	1640	1675	3400
7	C_6H_4Me-*p*	80	175	$C_{20}H_{20}N_4O_5$	60.6	5.1	14.1	60.7	4.8	14.1	1645	1670	3420
8	C_6H_4Cl-*p*	70	155	$C_{19}H_{17}ClN_4O_5$	54.7	4.1	13.4	54.5	4.0	13.2		1675	3325
9	C_6H_4I-*p*	70	210	$C_{19}H_{17}IN_4O_5$	44.9	3.3	11.2	44.6	3.4	11.0	1640	1675	3330
10	C_6H_4OMe-*p*	60	> 300	$C_{20}H_{20}N_4O_6$	58.2	4.9	13.6	58.6	5.1	13.3	1640	1660	3400
11	$C_6H_4NO_2$-*p*	50	210	$C_{19}H_{17}N_5O_7$	53.4	4.0	16.4	53.5	4.0	16.1	1640	1670	3395
12		60	205	$C_{18}H_{17}N_5O_5$	56.4	4.5	18.3	56.7	4.8	18.5	1640	1680	3425

TABLE II

MICROANALYTICAL AND SPECTRAL DATA FOR 3-[1-(AROYLHYDRAZONO)GLYOXAL-1-YL]-2-QUINOXALINONE

Compound No.	*R*	*Yield (%)*	*M.p. (degrees)*	*Molecular formula*	*Calculated (%)*			*Found (%)*			ν_{max}^{Nujol} *(cm^{-1})*		
					C	*H*	*N*	*C*	*H*	*N*			
15	Ph	60	230	$C_{17}H_{12}N_4O_3$	63.7	3.8	17.5	63.6	3.5	17.8	1660	1670	3240
16	C_6H_4Me-*m*	50	200	$C_{18}H_{14}N_4O_3$	64.7	4.2	16.8	64.7	4.2	16.4	1670	1705	3200
17	C_6H_4Me-*p*	60	140	$C_{18}H_{14}N_4O_3$	64.7	4.2	16.8	64.9	4.2	17.1	1665	1710	3200
18	C_6H_4Cl-*p*	65	160	$C_{17}H_{11}ClN_4O_3$	57.5	3.1	15.8	57.8	2.9	16.0	1670	1690	3175
19	C_6H_4I-*p*	60	180	$C_{17}H_{11}IN_4O_3$	45.7	2.5	12.6	45.5	2.8	13.0	1670	1690	3190
20	C_6H_4OMe-*p*	50	210	$C_{18}H_{14}N_4O_4$	61.7	4.0	16.0	61.8	4.3	16.3	1660	1690	3190

ture, with occasional shaking. The suspension was filtered, and the inorganic residue was repeatedly extracted with chloroform. The filtrate and extracts were combined, successively washed with potassium iodide solution, sodium thiosulfate solution, and water, dried (anhydrous sodium sulfate), and evaporated. Crystallization of the residue from ethanol afforded colorless crystals (yield 1.1 g); m.p. 295°.

Anal. Calc. for $C_{24}H_{16}N_6O_3$: C, 66.1; H, 3.7; N, 19.3. Found: C, 65.9; H, 3.5; N, 19.1.

3-[1-(Benzoylhydrazono)-2-hydroxyethyl]-2-quinoxalinone (**22**). — A cooled solution of compound **15** (1 g) in methanol (250 mL) was stirred with sodium borohydride (0.5 g). The mixture was stirred for 1 h, and then acidified with acetic acid, and diluted with water. The product that separated out was successively washed with water and ethanol, and dried (yield 0.7 g). It was recrystallized from ethanol, giving yellow, fine plates; m.p. 212°.

Anal. Calc. for $C_{17}H_{14}N_4O_3$: C, 63.4; H, 4.4; N, 17.4. Found: C, 63.1; H, 4.2; N, 17.4.

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