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Note

Hydrazine derivatives of L-ascorbic acid and of its D-*erythro* and phenyl analogs*

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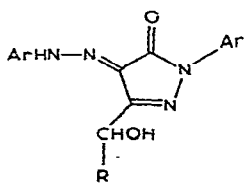
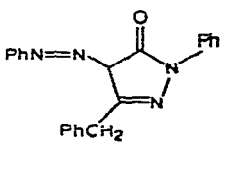
In previous publications[1–6], we have described the rearrangement of bis(arylhydrazones) of L-ascorbic acid, isoascorbic acid, and their simple analog 2,3-dioxobutano-1,4-lactone into pyrazole derivatives (**1**). The rearrangements occur *via* opening of the lactone ring, under the alkaline conditions of the reaction, followed by cyclization of the resulting carboxylic group with the imino proton of the hydrazone residue on C-3.



1



2

The reaction of phenylhydrazine with the hydrolysis product of 2-hydroxy-4-phenyltetronimide was reported by Dahn and Rotzler[7] to give 3-benzyl-2-phenyl-4-phenylazo-3-pyrazolin-5-one (**2**). As compound **2** is a deoxygenated derivative of the pyrazole anticipated from the rearrangement of 2,3-dioxo-4-phenylbutano-1,4-lactone 2,3-bis(2-phenylhydrazone), it became necessary to study the rearrangement of the latter, and to find out whether the phenyl group causes a deoxygenation during the opening of the lactone, to give **7a**, or whether it rearranges normally, to give **9a**. Consequently, the objective of this work was to study the reactions of arylhydrazines with 2,3-dioxo-4-phenylbutanolactone. The bis(acylhydrazones) of the latter, as well as those of isoascorbic and L-ascorbic acids, have been investigated.

DISCUSSION

Dahn and co-workers reported[8] the synthesis of 3-hydroxy-5-phenyltetronimide (**3**), and found[9] that, on boiling with 40% acetic acid or 0.005M sulfuric acid, or

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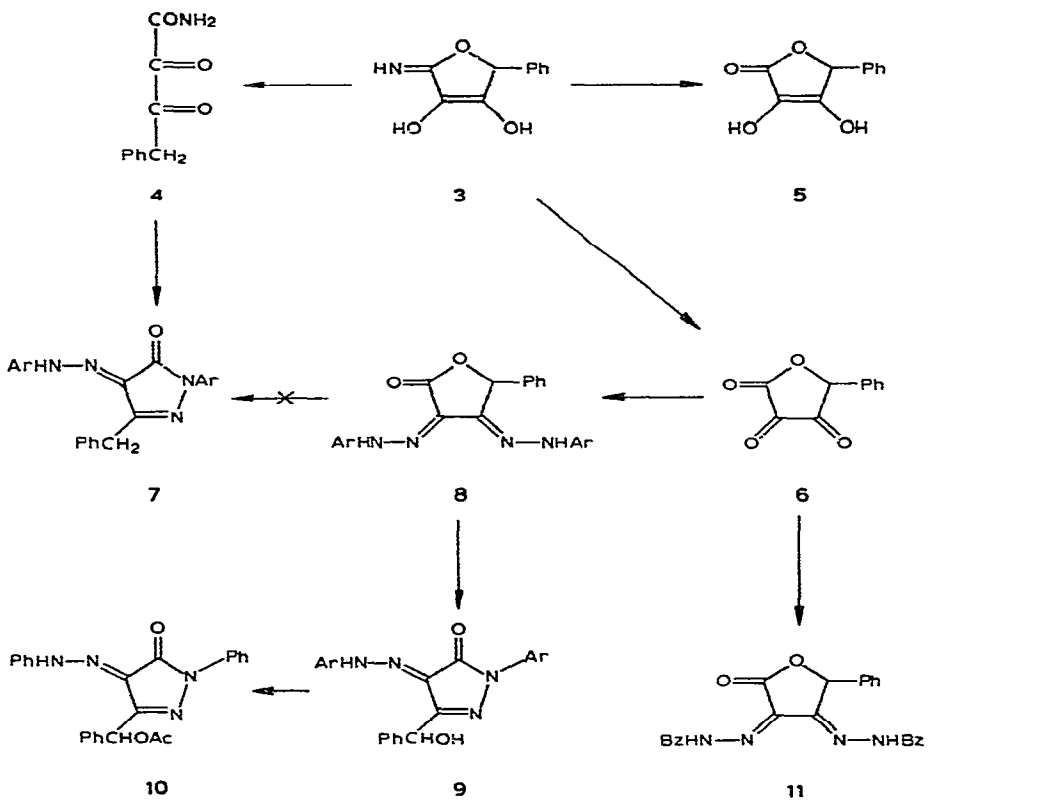
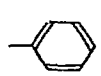
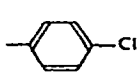
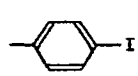
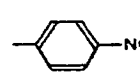
heating with water and Amberlite (H^+) resin, it gave 2,3-dioxo-4-phenylbutanamide (**4**) and 3-hydroxy-5-phenyltetronic acid (**5**). On the other hand, reaction of **3** with nitrous acid gave 2,3-dioxo-4-phenylbutano-1,4-lactone (**6**). Dahn and Rotzler[7] treated **4** with phenylhydrazine, and formulated the product as **2**. In the present work, we have obtained the same compound under conditions similar to those reported by them. Its infrared (i.r.) spectrum showed the presence of a carbonylamide band at 1660 cm^{-1}, and its electronic absorption spectrum showed two maxima, at 250 and 392 nm. These spectral data are similar to those of the related compounds[4,6] **1**, indicating the presence of the same chromophoric groups in both compounds. We therefore consider that this compound has the structure 3-benzyl-1-phenylpyrazole-4,5-dione 4-(phenylhydrazone) (**7a**), instead of the tautomeric structure **2**. It should be noted that compounds **1** were previously[4,10] given a phenylazo structure, and only recently[5,6,11] were they formulated as phenylhydrazones.

The mass spectrum of **7** showed a molecular-ion peak at *m/e* 354, which agreed with the molecular weight expected. This was followed by a small peak at *m/e* 277 due



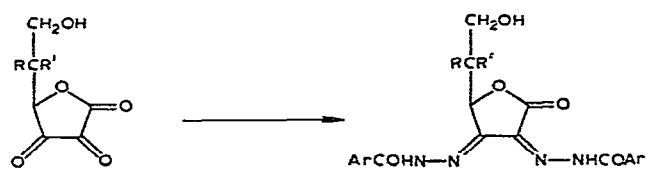
a, Ar =  ; b, Ar =  ; c, Ar =  ; d, Ar = 

to the loss of Ph, and then the second largest peak, at *m/e* 262, due to the loss of PhNH. Further loss of CO and hydrogen gave ions at *m/e* 234 and 233, in addition to other fragments that appeared at *m/e* 119, 105, 93, 92, 91, 77, and 65, all of which support formulation as structure **7**.

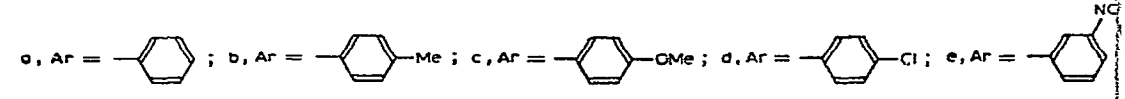
When 2,3-dioxo-4-phenylbutano-1,4-lactone (**6**) was allowed to react with phenylhydrazine, it gave the corresponding bis(hydrazone), namely, 4-phenylbutano-1,4-lactone 2,3-bis(2-phenylhydrazone) (**8a**), characterized by its red color, similar to that of the related, 4-substituted 2,3-dioxobutano-1,4-lactone. Its i.r. spectrum showed a carbonyl lactone band at 1730 cm^{-1} at a frequency lower than that expected for the 1,4-lactone. This low frequency has been observed previously[6,11–14] for other analogs, and is probably due to hydrogen bonding of the lactone carbonyl with the imino proton of the hydrazone residue on C-2. As **8** cannot form a 1,5-lactone, this adds a new example confirming the 1,4-lactone structure for the bis-(arylhydrazones) of dehydro-L-ascorbic acid. The reaction of **6** was similarly conducted with *p*-substituted phenylhydrazines, to give the corresponding bis(arylhydrazones) **8**.

When 4-phenylbutano-1,4-lactone 2,3-bis(2-phenylhydrazone) (**8a**) was heated with sodium hydroxide, and the mixture acidified with acetic acid, it rearranged to 3-(α-hydroxy-α-tolyl)-1-phenylpyrazole-4,5-dione 4-(2-phenylhydrazone) (**9a**). Acetylation of the latter with acetic anhydride in pyridine afforded the monoacetyl derivative **10**, confirming the presence in **9** of a free hydroxyl group resulting from the opening of the lactone group in **8**, *i.e.*, the rearrangement of **8** into **9** occurred similarly to that for the other analogs[1–6], and no deoxygenation took place. This indicates that **7** is formed from the deoxygenated precursor **4**, and that the deoxygenation process occurs during the transformation of **3** into **4**.

Condensation of **6** with benzoylhydrazine gave the corresponding bis(benzoylhydrazone) **11**. Similarly, the oxidized forms of L-ascorbic acid and isoascorbic acid were condensed with a number of aroylhydrazines, to give the corresponding bis(aroylhydrazones) **12** and **13**, respectively.

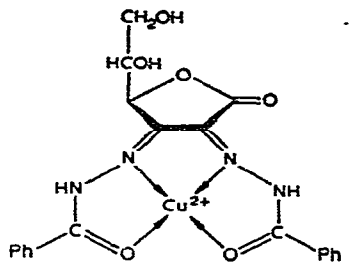


12 R = H, R' = OH
13 R = OH, R' = H



It has been shown that, when dehydro-L-ascorbic acid bis(phenylhydrazone) is treated with cupric chloride, it gives a yellow, bicyclic product[14–16]. When **12a** was

treated with an ethanolic solution of cupric chloride at room temperature, it gave a complex that, as in the case of saccharide bis(benzoylhydrazones) or bis(semicarbazones)[17], is probably formed from the contribution of the two benzoylhydrazone residues to form a tetradentate ligand, as in **14**. This complex decomposed readily upon heating, or standing for two days at room temperature, with the formation of benzoic acid. Probably, dehydro-L-ascorbic acid or its degradation products are also formed in the solution.



14

EXPERIMENTAL

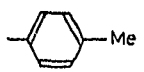
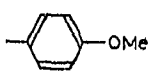
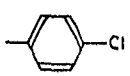
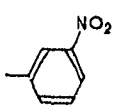
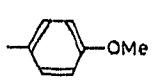
General methods. — Melting points were determined with a Kofler-block apparatus, and are uncorrected. I.r. spectra were recorded with a Unicam SP 200 spectrometer, and u.v. and visible spectra, with a Unicam SP 800 spectrometer. Mass spectra were recorded with an M-66 instrument; intensities are given in parentheses, as percentages of the base peak. Microanalyses were performed in the Microanalytical Laboratory, Cairo University, Cairo.

3-Benzyl-1-phenylpyrazole-4,5-dione 4-(2-phenylhydrazone) (**7a**). — Compound **4** was prepared by the method of Dahn and Rotzler[7], by refluxing 2-hydroxy-4-phenyltetronimide with 40% acetic acid, followed by treatment of the resulting 2,3-dioxo-4-phenylbutanamide with an excess of phenylhydrazine in acetic acid. The mixture was boiled under reflux for 90 min, cooled, and diluted with alcohol and water, to give a crystalline product, m.p. 155–156° (lit.[7] m.p. 153–154°); ν_{max}^{Nujol} 1660 cm^{-1} (CON); λ_{max}^{EtOH} 209, 250, 261 (sh), and 392 nm (log ε 3.42, 3.88, 3.84, and 3.91); mass-spectral data: *m/e* 356 (3, M+2), 355 (57, M+1), 354 (100, M), 323, 277 (1, M−Ph), 262 (27, M−PhN), 261 (1), 234 (5, M−PhN−CO), 233 (11, M−PhN−CO−H), (232 (2), 182 (1), 180, 178, 177, 143 (1), 142 (10), 128 (1), 119 (2, PhNCO), 116 (2), 115 (1), 105 (6, PhNN), 93 (27, $PhNH_2$), 92 (5, PhNH), 91 (15, PhN), 77 (29, Ph), and 65 (2).

2,3-Dioxo-4-phenylbutanolactone (**6**). — A suspension of 3-hydroxy-5-phenyltetronimide (1.9 g) in acetone (10 ml) and M sulfuric acid (25 ml) was cooled, and then a 10% solution of sodium nitrite in water (15 ml) was gradually added. The mixture was kept for 5 min at room temperature and then warmed to 50° and left to cool, whereby colorless needles separated, m.p. 124° (lit.[9] m.p. 125–126°).

TABLE I

MELTING POINTS AND MICROANALYTICAL DATA

Compound No.	*Ar*	*M.p. (degrees)*	*Molecular formula*	*Calculated (%)*			*Found (%)*		
				C	*H*	*N*	*C*	*H*	*N*
11		215	$C_{24}H_{18}N_4O_4$	67.6	4.3		68.0	4.4	
12b		195–197	$C_{22}H_{22}N_4O_6$	60.3	5.1	12.8	60.1	5.0	12.7
12c		254–256	$C_{22}H_{22}N_4O_8$	56.2	4.7	11.9	55.9	4.6	12.0
12d		229–230	$C_{20}H_{16}Cl_2N_4O_6$	50.1	3.4	11.7	50.2	4.0	11.4
12e		209–210	$C_{20}H_{18}N_6O_{10}$	47.8	3.6	16.7	47.6	3.8	16.6
13a		201–202	$C_{20}H_{18}N_4O_6$	58.5	4.4	13.7	58.4	4.8	14.0
13c		229–230	$C_{22}H_{22}N_4O_8$	56.2	4.7		56.3	5.0	

4-Phenylbutano-1,4-lactone 2,3-bis(2-phenylhydrazone) (**8a**). — A solution of **6** (0.01 mole) in ethanol (20 ml) was treated with phenylhydrazine (0.02 mole) and a few drops of acetic acid. The mixture was boiled under reflux for 30 min, cooled, and filtered, and the filtrate was concentrated to give red needles of **8a**, m.p. 217°; ν_{max}^{Nujol} 1730 cm^{-1} (COO).

Anal. Calc. for $C_{22}H_{18}N_4O_2$: C, 71.3; H, 4.9. Found: C, 71.4; H, 4.9.

*4-Phenylbutano-1,4-lactone 2,3-bis[2-(p-chlorophenyl)hydrazone]** (**8b**). — This was prepared similarly to **8a**; m.p. 245°.

Anal. Calc. for $C_{22}H_{16}Cl_2N_4O_2$: C, 60.3; H, 3.7. Found: C, 60.4; H, 4.2.

*4-Phenylbutano-1,4-lactone 2,3-bis[2-(p-iodophenyl)hydrazone]** (**8c**). — This was prepared similarly; m.p. 247°.

Anal. Calc. for $C_{22}H_{16}I_2N_4O_2$: C, 42.4; H, 2.6. Found: C, 42.1; H, 3.1.

*4-Phenylbutano-1,4-lactone 2,3-bis[2-(p-nitrophenyl)hydrazone]** (**8d**). — This was prepared similarly; m.p. 252°.

Anal. Calc. for $C_{22}H_{16}N_6O_6$: C, 57.4; H, 3.5. Found: C, 57.7; H, 3.8.

3-(α-Hydroxy-α-tolyl)-1-phenylpyrazole-4,5-dione 4-(2-phenylhydrazone) (**9**). — A suspension of the bis(hydrazone) **8** (0.5 g) in water (25 ml) and ethanol (5 ml) was heated with 2M sodium hydroxide (30 ml) at 70–80° until the bis(hydrazone) had dissolved. The base was then neutralized with acetic acid, and the product was filtered off, washed several times with water, and recrystallized from ethanol, to give orange needles of **9**; m.p. 188–190°; ν_{max}^{Nujol} 1660 (CON) and 3400 cm^{-1} (OH).

Anal. Calc. for $C_{22}H_{18}N_4O_2$: C, 71.3; H, 4.9; N, 15.1. Found: C, 71.7; H, 4.7; N, 14.7.

3-(α-Acetoxy-α-tolyl)-1-phenylpyrazole-4,5-dione 4-(2-phenylhydrazone) (**10**). — A solution of the pyrazole **9** (0.1 g) in dry pyridine (2 ml) was treated with acetic anhydride (1 ml); the mixture was kept overnight at room temperature, and poured onto crushed ice, and the acetate that separated was filtered off, and recrystallized from ethanol, to give yellow-orange needles of **10**, m.p. 169°; ν_{max}^{Nujol} 1660 (CON) and 1740 cm^{-1} (OAc).

Anal. Calc. for $C_{24}H_{20}N_4O_3$: C, 69.9; H, 4.9. Found: C, 69.5; H, 4.7.

Bis(aroylhydrazones) **11**, **12**, *and* **13**. — A solution of the appropriate dioxo compound (0.01 mole) in water (20 ml) was treated with benzoylhydrazine (0.02 mole), and heated on a boiling-water bath for 30 min. The mixture was cooled, and the product was recrystallized from ethanol in pale-yellow needles (see Table I). Compound **12a** was reported by R. Fischer[18] as showing the following spectral data: ν_{max}^{Nujol} 1610 (C=N), 1675, 1710 (CONH), 1740 (CO), and 3350 cm^{-1} (OH); λ_{max}^{EtOH} 204, 220, 268, 285 (sh), 340 (sh), and 380 nm (log ε 4.31, 4.19, 4.26, 4.17, 3.77, and 4.10), λ_{min}^{EtOH} 214, 235, and 319 nm (log ε 4.18, 4.05, and 3.53).

Absorption spectrum of the copper complex of **12a**. — An ethanolic solution of L-*threo*-2,3-hexodiulosono-1,4-lactone 2,3-bis(benzoylhydrazone) (0.8 mg in 2 ml) was treated with cupric chloride (13 mg) in ethanol (2 ml), and the volume was

*Compounds **8b**, **8c**, and **8d** were prepared by H. Mokhtar.

brought to 10 ml with ethanol. The absorbance of the solution, λ_{max}^{EtOH} 458 nm (log ε 47.4), remained constant for 24 h.

Action of boiling cupric chloride solution on **12a**. — A suspension of **12a** (1 g) in a 5% ethanolic solution of cupric chloride (50 ml) was boiled under reflux for 15 min. The mixture was concentrated, whereupon benzoic acid crystallized out.

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