Note

Derivatives of dehydro-L-ascorbic acid bis(hydrazones)

H. EL KHADEM*, M. H. MESHREKI, S. H. EL ASHRY, AND M. EL SEKEILI
Faculty of Science, Alexandria University, Alexandria, Egypt (U. A. R.)
(Received August 26th, 1971)

Continuing our work[1–5] on the bis(hydrazones) of dehydro-L-ascorbic acid and its analogs, we now describe a number of new aryl and aroyl bis(hydrazones) of C_6 and C_7 dehydroascorbic acids [2,3-glycodiulosono-1,4-lactone bis(hydrazones)], together with some of their derivatives.

By starting with dehydro-L-ascorbic acid (L-*threo*-hexodiulosono-1,4-lactone), its D-*erythro* analog, and also D-*arabino*- and L-*xylo*-heptodiulosono-1,4-lactones, and treating them with the required hydrazine, the bis(hydrazones) (**2**) listed in Table I were obtained.

As with the analogs, previously prepared, this reaction was accompanied by formation of the corresponding 1-aryl-3-(hydroxyalkyl)-4,5-pyrazoledione 4-(aryl-hydrazones) (**5**). The formation of compounds of type **5** during the interaction of dehydro-L-ascorbic acid and its homologs with hydrazines is attributed to the fact that, in solution, dehydroascorbic acids (**3**) exist[6] in equilibrium with their lactones (**1**). When the acid **3** reacts with the substituted hydrazine, it forms a bis(hydrazone) (**4**) that cyclizes preferentially to the pyrazole **3** instead of to the lactone **2**. This behavior of the acid explains why, when treated with alkali, the bis(hydrazone) of the lactone **2** is converted into the salt of the 2,3-diulosonic acid (**4**), which yields the pyrazole **3** in almost quantitative yield on acidification. The latter method was used to prepare the pyrazoles (**5**) shown in Table II. The bis(hydrazones) (**2**) that were used needed no purification, as they were already contaminated with the desired product **5**. The bis(hydrazones) (**2**) and the pyrazoles (**5**) are readily recognized visually, the former being dark red, whereas the latter are orange-yellow.

Oxidation of the lactone **6** with cupric chloride or iodine led to a bicyclic compound (**8**); this reaction is characteristic of dehydroascorbic acid 2,3-bis(hydrazones) (**2**). When similarly oxidized, aldosulose 1,2-bis(hydrazones) (sugar osazones) give the 2-aryl-1,2,3-triazoles (sugar osotriazoles)[7]. This difference in behavior can be attributed to chelation of the second hydrazone residue in osazones, which prevents their rearrangement to the cyclic hydrazino-hydrazone forms. On the other hand,

*Present address: Department of Chemistry and Chemical Engineering, Michigan Technological University, Houghton, Michigan 49931, U. S. A.

TABLE I

2,3-GLYCODIULOSONO-1,4-LACTONE BIS(HYDRAZONES) (2)

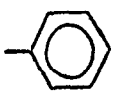
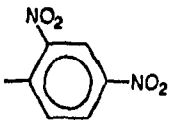
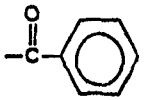
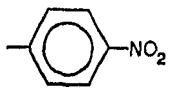
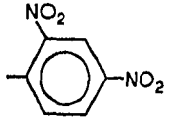
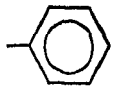
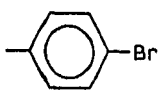
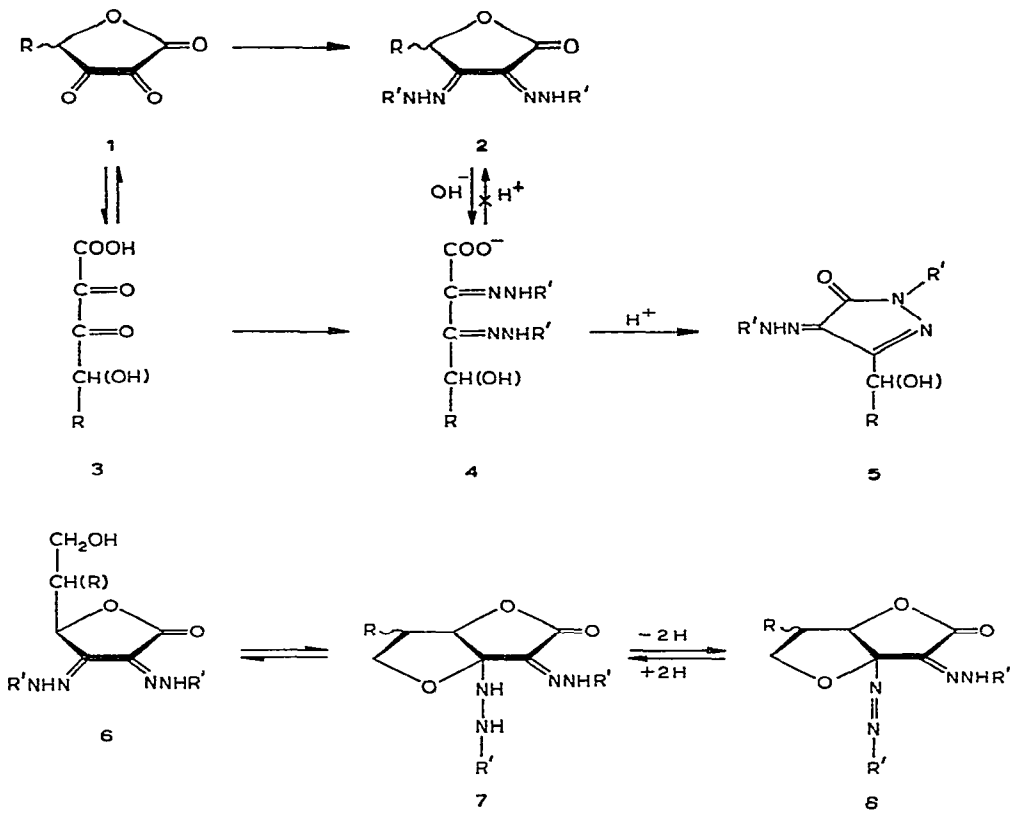
R	*R'*	*M.p.* (*degrees*)	*Yield* (%)	*Formula*	*Calculated* (%)			*Found* (%)		
					C	*H*	*N*	*C*	*H*	*N*
CH_2OH | HOCH |		235	60	$C_{18}H_{16}N_4O_4$	61.2	5.1	15.8	61.0	5.3	15.5
CH_2OH | HOCH |		260	46	$C_{18}H_{14}N_8O_{12}$	40.6	2.6	21.0	40.9	3.0	20.7
HCOH | HCOH | CH_2OH		274	55	$C_{21}H_{20}N_4O_7 \cdot 0.5H_2O$	56.1	4.7	12.2	56.5	4.4	11.7

TABLE II

1-ARYL-3-(HYDROXYALKYL)-4,5-PYRAZOLEDIONE 4-(ARYLHYDRAZONES) (5)

Side chain	*R'*	*M.p.* (*degrees*)	*Yield* (%)	*Formula*	*Calculated* (%)			*Found* (%)		
					C	*H*	*N*	*C*	*H*	*N*
HCOH HOCH CH_2OH		275–277	85	$C_{18}H_{16}N_6O_8 \cdot H_2O$	46.8	3.9	18.2	47.0	4.1	18.0
HCOH HCOH CH_2OH		258	82	$C_{18}H_{14}N_8O_{12}$	40.6	2.6	21.0	41.0	3.0	21.1
HOCH HCOH HOCH CH_2OH		182–184	85	$C_{19}H_{20}N_4O_5$			14.2			14.3
HOCH HCOH HCOH CH_2OH		267–268	84	$C_{19}H_{18}Br_2N_4O_5$			10.3			10.2



dehydroascorbic acid bis(hydrazones) have both of their hydrazone residues unchelated*, and can therefore exist in equilibrium with the bicyclic hydrazino-hydrazone forms (**7**). Upon oxidation, the latter would rapidly yield azo-hydrazones (**8**) rather than undergoing the slower conversion into triazoles. It should be noted that conversion of bis(hydrazones) of type **6** into azo-hydrazones (**8**) takes between 5 and 15 min at 85°, according to the oxidizing agent used, whereas formation of triazoles usually requires several hours of refluxing. Upon reduction with zinc and hydrochloric acid, the azo-hydrazones **8** readily revert to the starting bis(hydrazones) (**6**). *p*-Toluenesulfonylation of compound **8** afforded the expected monosulfonic ester, which was unaffected by treatment with sodium iodide.

Compounds of types **2**, **5**, and **8** were characterized as their acetates and benzoates. It should be noted that the peracetylated products shown in Table IV were obtained by the use either of vigorous conditions (boiling acetic anhydride, or acetyl chloride in dimethylaniline) or of milder ones (acetic anhydride and pyridine). No *N*-acetylation of any these compounds occurred, as verified by microanalysis and by the absence of amide bands in the i.r. spectra of the acetylated derivatives of types **2**

*See the chemical shifts of imino protons given in Ref. 1.

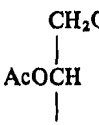
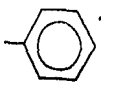
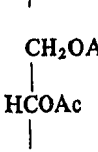
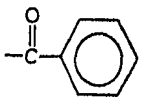
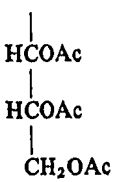
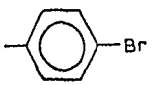
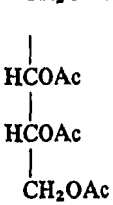
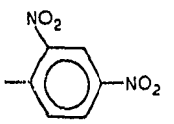
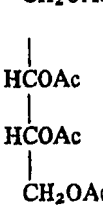
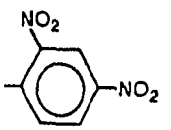
TABLE III

3,6-ANHYDRO-3-(ARYLAZO)-GLYCULOSONO-1,4-LACTONE ARYLHYDRAZONES (8)

R	R'	M.p. (degrees)	Yield (%)	Formula	Calculated (%)			Found (%)		
					C	H	N	C	H	N
OH		241–242	67	$C_{18}H_{14}N_6O_8$	48.9	3.2	19.0	49.2	3.5	18.5
OH		195	72	$C_{18}H_{12}N_8O_{12}$	40.6	2.3	21.1	40.8	2.7	21.5

TABLE IV

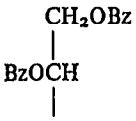
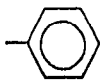
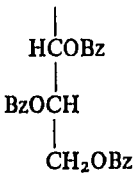
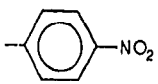
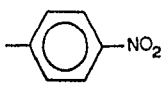
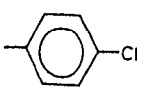
O-ACETYL DERIVATIVES

Compound	*R'*	*M.p.* (*degrees*)	*Formula*	*Calculated* (%)			*Found* (%)		
				C	*H*	*N*	*C*	*H*	*N*
2, R = 		159	$C_{22}H_{22}N_4O_6$	60.3	5.0	12.8	60.3	5.0	12.4
2, R = 		163	$C_{24}H_{22}N_4O_8$	58.2	4.5	11.3	58.3	4.8	11.0
2, R = 		182–184	$C_{25}H_{24}Br_2N_4O_8$	44.9	3.6	8.4	44.8	3.6	8.4
2, R = 		240–242	$C_{25}H_{22}N_8O_{16}$			16.2			15.7
5, chain = 		214	$C_{24}H_{20}N_8O_{10}$	43.6	3.3	17.0	44.0	3.7	17.2

5,	chain = HCOAc, AcOCH, CH_2OAc		181–182	$C_{24}H_{32}N_6O_{11}$	50.5	3.9	14.7	50.2	4.3	14.9
5,	chain = AcOCH, HCOAc, HCOAc, CH_2OAc		138	$C_{27}H_{26}Br_2N_4O_9$	45.7	3.7	7.9	45.9	3.8	7.8
8	R = OAc		225–226	$C_{20}H_{16}N_6O_9$	49.6	3.3	17.4	50.1	3.8	16.9

TABLE V

O-BENZOYL DERIVATIVES

Compound		*R'*	*M.p.* (*degrees*)	*Formula*	*Calculated* (%)			*Found* (%)		
					C	*H*	*N*	*C*	*H*	*N*
2,	R = 		185	$C_{39}H_{30}N_4O_7$	70.2	4.5	8.5	69.7	4.4	8.5
5,	chain = 		183–185	$C_{39}H_{28}N_6O_{11}$	61.9	3.7	11.1	61.4	3.8	10.9
8,	R = 		218–219	$C_{25}H_{18}N_6O_9$	54.9	3.3	15.4	54.7	3.7	15.4
8,	R = 		160–161	$C_{25}H_{18}Cl_2N_4O_5$	57.2	3.5	10.7	56.9	3.8	10.9

and **8**. Similarly, benzoylation overnight at room temperature, or prolonged benzoylation with benzoyl chloride and pyridine, afforded the per-*O*-benzoylated products listed in Table V, with no *N*-benzoylation.

EXPERIMENTAL

2,3-Glycodiulosono-1,4-lactone bis(hydrazones) (**2**). — A solution of the 2,3-glycodiulosono-1,4-lactone, obtained by air oxidation of dehydro-L-ascorbic acid or one of its homologs (2 g), in water (100 ml) was treated with an aryl- or benzoyl-hydrazine (2 molar proportions) and a few drops of acetic acid. The mixture was heated for 20–60 min on a steam bath, and cooled. The bis(hydrazone) that separated was filtered off, successively washed with water, ethanol, and ether, and recrystallized from ethanol or acetone–ethanol (see Table I).

1-Aryl-3-(hydroxyalkyl)-4,5-pyrazoledione 4-(arylhydrazones) (**5**). — A suspension of the bis(hydrazone) (**2**, 1 g) in water (50 ml) was heated with 2M sodium hydroxide (25 ml) at 70–80° until the osazone had dissolved (5 min). The pH was then brought to 6 with acetic acid, and the product was filtered off, washed several times with water, and recrystallized from ethanol or acetone–ethanol, to give orange needles (see Table II).

3,6-Anhydro-3-(arylazo)-glyculosono-1,4-lactone arylhydrazones (**8**). — *Method A*. A suspension of the bis(hydrazone) **2** (2 g) in a solution of cupric chloride (5 g) in ethanol (80 ml) was boiled for 15 min under reflux. The solution was concentrated to 50 ml, and hot water was added to incipient turbidity. The product that separated on cooling was filtered off, washed with water, and recrystallized from ethanol or *p*-dioxane–ethanol (see Table III).

Method B. A suspension of the bis(hydrazone) **2** (2 g) in a mixture of ethanol (20 ml) and *p*-dioxane (10 ml) was treated with a solution of iodine (1 g) in ethanol (20 ml). The mixture was heated for 5 min, and diluted with water; the product that separated had the same m.p. as that obtained by Method *A*.

O-*Acetyl derivatives*. — Acetylation was performed with 1-g portions, which were dissolved in dry pyridine (10 ml) and treated with acetic anhydride (8 ml) overnight at room temperature. The reaction mixture was poured onto crushed ice, and the acetate was filtered off, washed thoroughly with water, and recrystallized from ethanol or benzene–ethanol as needles (see Table IV). Vigorous conditions, involving boiling with acetic anhydride (25 ml) for 1 h, or overnight treatment with acetyl chloride (10 ml) in dimethylaniline (10 ml), with processing as before, gave rise to the same product, but in slightly lower yield.

O-*Benzoyl derivatives*. — Benzoylation was performed with 1-g portions by using benzoyl chloride (4 ml) and dry pyridine (10 ml). After being kept overnight at room temperature, the mixture was poured onto crushed ice. The benzoate was filtered off, washed repeatedly with water, and recrystallized from ethanol or benzene–ethanol, to give an almost quantitative yield as needles (see Table V). Prolonging the reaction time to one week had no effect on the yield or nature of the product.

p-*Toluenesulfonylation.* — 3,6-Anhydro-3-(phenylazo)-D-*arabino*-hexulosono-1,4-lactone 2-(phenylhydrazone) (1 g) and *p*-toluenesulfonyl chloride (2 g) were dissolved in dry pyridine (20 ml). After being kept for one week at room temperature, the mixture was poured onto crushed ice, and the product that separated (0.85 g; 70%) was filtered off, washed with water, and recrystallized from chloroform–ethanol as needles, m.p. 164–166°.

Anal. Calc. for $C_{25}H_{22}N_4O_6S$: C, 59.3; H, 4.4; N, 11.1. Found: C, 59.5; H, 4.2; N, 11.1.

The *p*-toluenesulfonate (0.1 g) was recovered unchanged after refluxing with sodium iodide (0.1 g) in acetone (10 ml) for 2 h.

*1-Phenyl-3-(1,2:3,4-di-*O*-isopropylidene-*D*-arabino-1,2,3,4-tetrahydroxybutyl)-4,5-pyrazoledione 4-(phenylhydrazone).* — A solution of 1-phenyl-3-(D-*arabino*-1,2,3,4-tetrahydroxybutyl)-4,5-pyrazoledione 4-(phenylhydrazone) (1 g) in dry acetone (10 ml) was treated with concentrated sulfuric acid (0.2 ml) and kept overnight at room temperature. The solution was evaporated under diminished pressure, and the solid residue was washed with water and dried; yield 0.8 g. It was recrystallized from ethanol in orange-yellow needles, m.p. 190–191°.

Anal. Calc. for $C_{25}H_{28}N_4O_5$: C, 64.6; H, 6.1; N, 12.1. Found: C, 64.7; H, 6.1; N, 12.4.

REFERENCES

1 H. El Khadem and S. H. El Ashry, *J. Chem. Soc.* (*C*), (1968) 2247.
2 H. El Khadem and S. H. El Ashry, *J. Chem. Soc.* (*C*), (1968) 2248.
3 H. El Khadem and S. H. El Ashry, *J. Chem. Soc.* (*C*), (1968) 2251.
4 H. El Khadem and S. H. El Ashry, *Carbohyd. Res.*, 13 (1970) 57.
5 H. El Khadem, I. El Kholy, Z. M. El-Shafei, and M. El Sekeili, *Carbohyd. Res.*, 15 (1970) 179.
6 J. Staněk, M. Černý, J. Kocourek and J. Pacák, *The Monosaccharides*, Academic Press, New York, 1963, p. 734.
7 H. El Khadem, *Advan. Carbohyd. Chem.*, 18 (1963) 99; 25 (1970) 351.