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FACILE SYNTHESIS AND REARRANGEMENT OF L-*threo*-2,3-HEXODIULOSONO-1,4-LACTONE 2-(2-ARYLHYDRAZONES)*

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ABSTRACT

Controlled reaction of L-*threo*-2,3-hexodiulosono-1,4-lactone with substituted phenylhydrazines gave the 2-(monoarylhydrazones) (**2**), which underwent dehydrative acetylation to 4-(2-acetoxyethylidene)-4-hydroxy-2,3-dioxobutyro-1,4-lactone 2-(2-arylhydrazones) (**3**). The latter reacted with methylhydrazine to give 1-methyl-3-(1-methylpyrazolin-3-yl)-4,5-pyrazoledione 4-(2-arylhydrazones) (**4**). Reaction of the monoarylhydrazones (**2**) with phenylhydrazine gave the mixed bishydrazones (**5**), which were rearranged by alkali and acidification to the pyrazolediones (**6**). Compounds **6** gave triacetyl (**7**) and tribenzoyl derivatives (**8**), and, on periodate oxidation, the aldehydes (**9**), which afforded the monohydrazones (**10**). The i.r., n.m.r., and mass-spectral data of some of the compounds were investigated.

INTRODUCTION

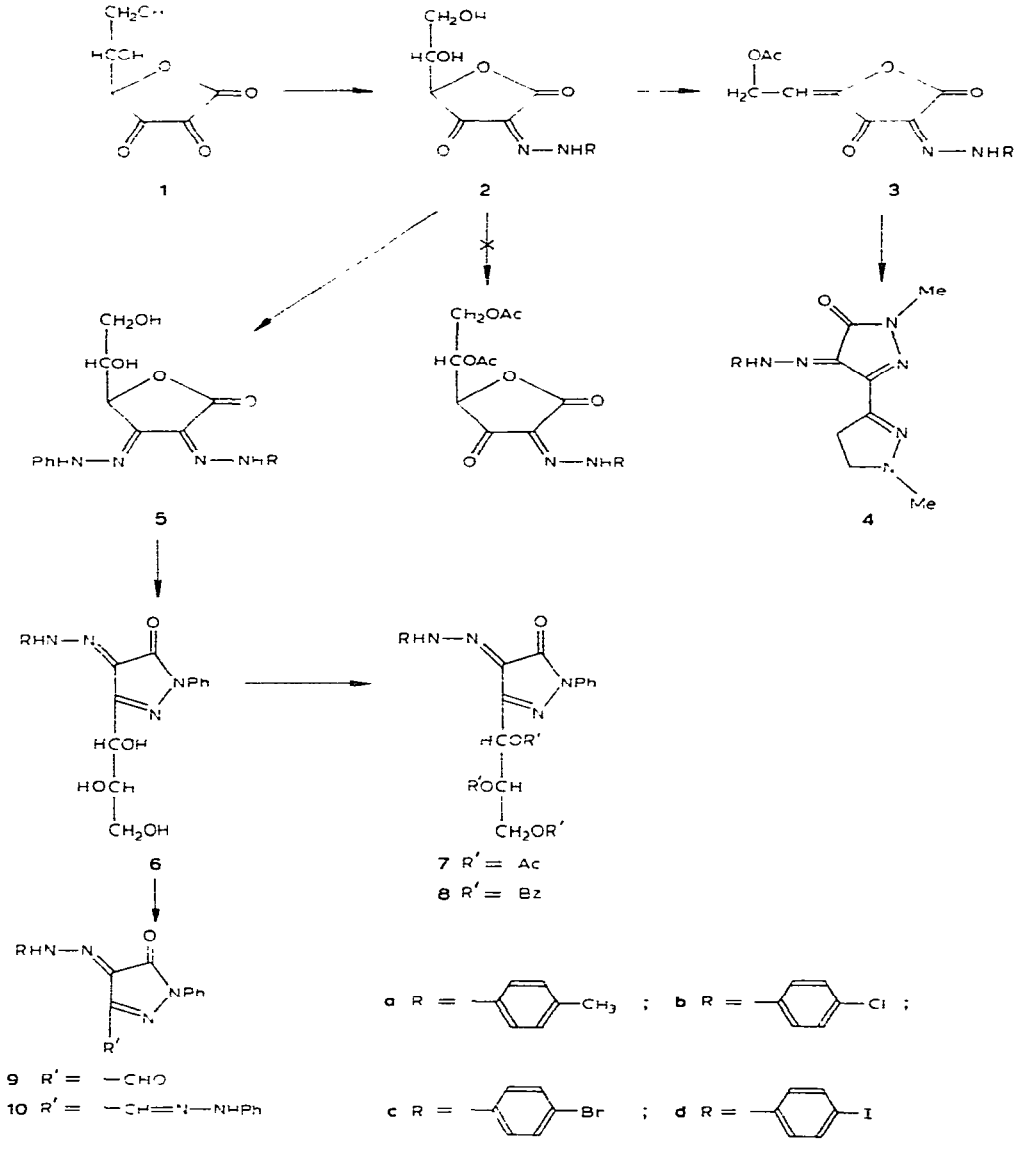
L-*threo*-2,3-Hexodiulosono-1,4-lactone (**1**), obtained by the oxidation of vitamin C, is interesting as a precursor for nitrogen heterocycles or carbohydrate-containing heterocycles. Reaction of **1** with *o*-phenylenediamine or its substituted derivatives gave quinoxaline compounds[1,2] which reacted with a variety of arylhydrazines, affording an excellent synthetic route to different types of nitrogen heterocycles[1,3]. On the other hand, the mono- or bis-phenylhydrazones of **1** provide a good route[4–11] to nitrogen heterocyclic compounds; the rationale of their synthesis has been given in the previous papers in this series. In this report, synthesis of the title compounds, and their rearrangement into a variety of nitrogen heterocycles, were achieved.

RESULTS AND DISCUSSION

During our investigation on the transformations of **1** into nitrogen heterocycles, the 2-(monoarylhydrazones) (**2**) were required as starting materials. The mono-

*Heterocycles from Carbohydrate Precursors. Part V. For Part IV, see ref. 6.

phenylhydrazones were prepared by two methods: either by multistep synthesis[12] from not readily accessible starting-materials, or by the direct reaction[8] of 1-acetyl-2-phenylhydrazine with **1**. Neither of these methods is suitable for the large-scale preparation of substituted phenylhydrazones, prompting us to attempt to control the reaction of substituted phenylhydrazines with **1**. Thus, the reaction of an aqueous solution of **1** with one equivalent of a substituted phenylhydrazine at room tem-



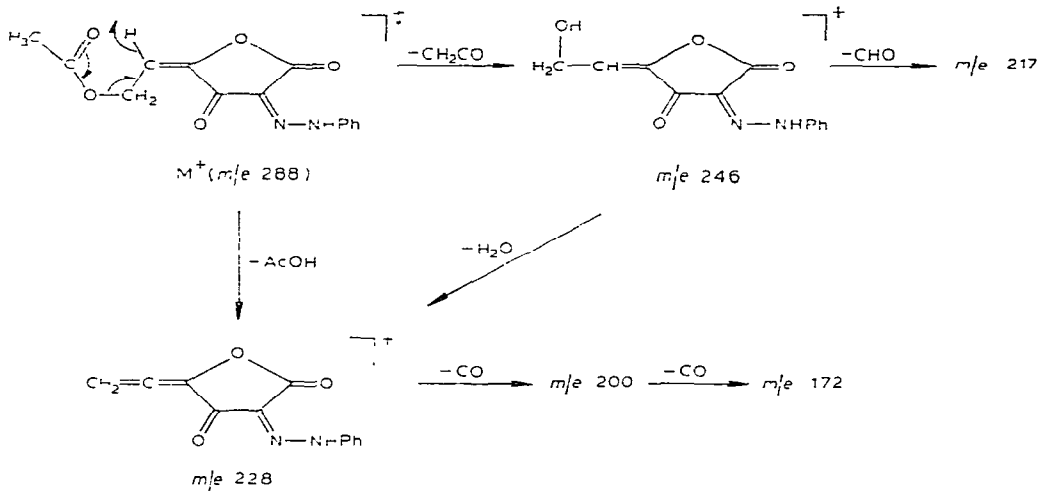
Scheme 1

perature afforded a 65–87% yield of an L-*threo*-2,3-hexodiulosono-1,4-lactone 2-(2-arylhydrazone) (**2**). Although this synthesis could not be satisfactorily applied for the preparation of the phenyl derivative, it provides a facile synthesis for the substituted analogs. The infrared spectra of these hydrazones (**2**) showed two bands in the carbonyl region: one at 1760–1745 cm^{-1} due to the lactone carbonyl, and the other at a longer wavelength, 1665 cm^{-1}, attributed to the 3-carbonyl group. In addition, the hydroxyl absorption appeared at 3450 cm^{-1}. The n.m.r. spectrum of L-*threo*-2,3-hexodiulosono-1,4-lactone 2-(2-*p*-bromophenylhydrazone) (**2c**) showed a doublet of two-proton intensity at δ 4.36 assigned to the C-6 methylene group, followed by a triplet of one-proton intensity at δ 4.92 due to the proton on C-5, and then a singlet (unresolved doublet, due to the small J value and the sweep width) at δ 5.6, due to the proton on C-4. The multiplet centered at δ 7.54 due to the aromatic protons, and the exchangeable singlet at δ 8.64 due to the imino proton.

Acetylation of the 2-(2-*p*-bromophenylhydrazone) (**2c**) and 2-(2-*p*-iodophenylhydrazone) (**2d**) of L-*threo*-2,3-hexodiulosono-1,4-lactone with acetic anhydride in pyridine afforded optically inactive, monoacetyl compounds (**3**), instead of the expected di-*O*-acetyl derivatives, which are optically active. In addition, the i.r. spectra of compounds **3** showed a characteristic pattern in the carbonyl-frequency region, consisting of three bands, at 1775–1770, 1725–1720, and 1665 cm^{-1}, similar to those for the acetylation product of the phenyl analog and respectively due to the carbonyl frequency of the acetyl group (which is shifted to a higher frequency), the carbonyl frequency of the lactone ring (which is shifted towards a lower frequency than that for their precursors), and the 3-carbonyl group, in addition to a band for the double bond. This indicated that, during the acetylation of **2**, dehydration had taken place, to give the alkenic derivatives, namely, 4-(2-acetoxyethylidene)-4-hydroxy-2,3-dioxobutyro-1,4-lactone 2-(2-arylhydrazones) (**3**). The n.m.r. spectrum of the 2-(2-*p*-bromophenylhydrazone) (**3c**) showed a singlet of three-proton intensity at δ 2.08 attributed to one acetyl group, a doublet of two-proton intensity centered at δ 4.84 due to the C-6 methylene group, and a triplet of one-proton intensity at δ 6.00 assigned to the contiguous proton on C-5. The coupling constant for the doublet and triplet was the same (J = 6.3). The multiplet at δ 7.52 was due to the aromatic protons, and the exchangeable singlet at δ 12.72 to the imino proton, probably chelated with one of the adjacent carbonyl groups.

The mass spectrum of 4-(2-acetoxyethylidene)-4-hydroxy-2,3-dioxobutyro-1,4-lactone 2-(2-phenylhydrazone), which is the parent compound of the alkenic acetates **3**, showed a molecular-ion peak at *m/e* 288 which underwent a series of losses as shown in Scheme 2. In addition, it showed fragments at *m/e* 105, 91, and 77 due to PhN_2^+, PhN^+, and Ph^+, respectively.

Reaction of **3** with methylhydrazine gave products showing in their i.r. spectra a band at 1660 cm^{-1}, instead of the three-band pattern in the spectra of their precursors, characteristic of an amide, and indicating the absence of the acetyl and lactone groups. Moreover, their elemental analyses agreed with those calculated for 1-methyl-3-(1-methylpyrazolin-3-yl)-4,5-pyrazoledione 4-(2-arylhydrazones) (**4**), result-



Scheme 2

ing from the reaction of **3** with two molar proportions of methylhydrazine, accompanied by simultaneous rearrangement. The mechanism of their formation could be that given for the phenyl analog[5].

The reaction of L-*threo*-2,3-hexodiulosono-1,4-lactone 2-(2-phenylhydrazone) with substituted phenylhydrazines successfully afforded the corresponding, mixed bishydrazones[13], which rearranged into the corresponding pyrazolediones[6] having a phenylhydrazone group at C-4 and an aryl substituent on N-1 of the heterocyclic ring. In the present work, the reaction of **2** with phenylhydrazine gave the corresponding mixed bishydrazones (**5**), which rearranged into 1-phenyl-3-(L-*threo*-glycerol-1-yl)-4,5-pyrazoledione 4-(2-arylhydrazones) (**6**), having the substituents on N-1 and C-4, contrary to that described previously[6]. The mass spectrum of L-*threo*-2,3-hexodiulosono-1,4-lactone 2-(2-*p*-bromophenylhydrazone) 3-(2-phenylhydrazone) (**5c**) showed a molecular-ion peak at *m/e* 434,432 as the base peak which underwent the loss of the dihydroxyalkyl side-chain to give ions at *m/e* 373,371, and the loss of PhNH to give ions at *m/e* 355,353. After the loss of the side chain, a loss of CO_2 occurred, to give ions at *m/e* 329,327, and loss of PhNH, to give ions at *m/e* 282,280. This was in addition to fragments at *m/e* 185,183 ($BrC_6H_4N_2^+$), 173,171 ($BrC_6H_4NH_2^+$), 172,170 ($BrC_6H_4NH^+$), 157,155 ($BrC_6H_4^+$), 119 ($PhNCO^+$), 105 (PhN_2^+), 93 ($PhNH_2^+$), 92 ($PhNH^+$), 91 (PhN^+), and 77 (Ph^+).

Acylation of **6** with acetic anhydride or benzoyl chloride in pyridine gave 1-phenyl-3-(tri-*O*-acetyl-L-*threo*-glycerol-1-yl)-4,5-pyrazoledione 4-(2-arylhydrazones) (**7**) and 1-phenyl-3-(tri-*O*-benzoyl-L-*threo*-glycerol-1-yl)-4,5-pyrazoledione 4-(2-arylhydrazones) (**8**), respectively. The i.r. spectra of **7** and **8** showed, in addition to the amide band (which appeared at 1660 cm^{-1}) present in the spectra of their precursors, an ester band, at 1740 and 1720 cm^{-1}, respectively. Periodate oxidation of **6** gave 3-formyl-1-phenyl-4,5-pyrazoledione 4-(2-arylhydrazones) (**9**), which showed in

their i.r. spectra the aldehydic group at 1690 cm^{-1}, in addition to the amide at 1660 cm^{-1}. The aldehydes **9** gave monohydrazones on reaction with hydrazine.

EXPERIMENTAL

General methods. — Melting points were determined with a Kofler-block apparatus and are uncorrected. I.r. spectra were recorded with a Unicam SP200 spectrometer, and n.m.r. spectra (for solutions in pyridine-d_5 or chloroform-d), with a Joel-100 spectrometer, with tetramethylsilane as the standard. Chemical shifts are given on the δ scale. Mass spectra were recorded with an A.E.I. MS902 instrument; intensities are given in parentheses, as percentages of the base peak. Microanalyses were performed in the Chemistry Department, Faculty of Science, Cairo University, Cairo, Egypt.

L-threo-*2,3-Hexodiulosono-1,4-lactone 2-(2-arylhydrazones)* (**2**). — A solution of dehydro-L-ascorbic acid (**1**) (0.01 mole) in water (20 ml) was treated with the arylhydrazine (0.01 mole). The mixture was kept for 20 h at room temperature, whereby the monohydrazones separated out. They were filtered off, washed with a little alcohol and then ether, and recrystallized from ethanol (see Table I). N.m.r. data for compound **2c** in pyridine-d_5: δ 4.36 (d, 6-H_2), 4.92 (t, H-5), 5.6 (s, H-4), 7.54 (m, Ar), and 8.64 (s, N-H).

4-(2-Acetoxyethylidene)-4-hydroxy-2,3-dioxobutyro-1,4-lactone 2-(2-arylhydrazones) (**3**). — A solution of **2** (1 g) in pyridine (10 ml) was cooled and treated with acetic anhydride (8 ml), and the solution was kept for 2 h in an ice box and then overnight at room temperature. The mixture was poured onto crushed ice, and the product crystallized from chloroform–ethanol (see Table II). N.m.r. data for compound **3c** in $CDCl_3$: δ 2.08 (s, CH_3), 4.84 (d, 6-H_2), 6.00 (t, H-5), 7.52 (m,Ar), and 12.72 (s, N-H); mass-spectral data for compound **3** (R = Ph): 290 (1), 289 (2), 288 (37), 247 (11), 246 (100), 230 (10), 229 (54), 228 (96), 217 (11), 201 (3), 200 (64), 172 (60), 150 (2), 117 (7), 104 (8), 93 (32), 92 (47), 91 (73), 77 (99), 71 (7), 65 (31), 64 (4), 63 (5), and 54 (37).

1-Methyl-3-(1-methylpyrazolin-3-yl)-4,5-pyrazoledione 4-(2-arylhydrazones) (**4**). — A solution of compound **3** (0.2 g) in ethanol (20 ml) was treated with methylhydrazine (0.2 ml), and the mixture was boiled for 15 min, concentrated, and cooled: the product (**4**) crystallized in dark-orange plates (see Table II).

L-threo-*2,3-Hexodiulosono-1,4-lactone 2-arylhydrazone 3-phenylhydrazones* (**5**). — A solution of compound **2** (0.5 g) in ethanol (20 ml) was treated with the calculated amount of the required hydrazine and two drops of acetic acid. The mixture was heated for 5 min, and then concentrated, and cooled. The product crystallized in red needles from ethanol (see Table III).

3-(L-threo-Glycerol-1-yl)-1-phenyl-4,5-pyrazoledione 4-(2-arylhydrazones) (**6**). — A suspension of the bishydrazone **5** (0.5 g) in water (25 ml) was heated with 2M sodium hydroxide (25 ml) until the bishydrazone had dissolved. The solution was

TABLE I

MICROANALYTICAL AND INFRARED ABSORPTION DATA FOR L-*threo*-2,3-HEXODIULOSONO-1,4-LACTONE 2-(2-ARYLHYDRAZONES) (2)

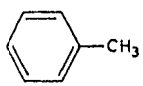
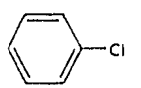
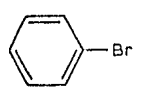
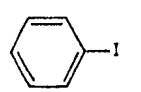
Compound No.	*R*	*M.p. (degrees)*	*Yield (%)*	*Molecular formula*	*Calculated (%)*			*Found (%)*			ν_{max}^{Nujol}		
					C	*H*	*N*	*C*	*H*	*N*	CO	COO	OH
2a		170–172	87	$C_{13}H_{14}N_2O_5$	56.1	5.1	10.1	56.1	5.5	10.4	1665	1760	3450
2b		203–204	65	$C_{12}H_{11}ClN_2O_5$	48.3	3.7	9.4	48.2	3.4	9.0	1665	1750	3450
2c		220–221	80	$C_{12}H_{11}BrN_2O_5$	42.0	3.2	8.2	42.4	3.5	8.6	1665	1750	3450
2d		232–235	79	$C_{12}H_{11}IN_2O_5$	36.9	2.8	7.2	37.0	3.1	7.6	1665	1755	3450

TABLE II

MICROANALYTICAL AND INFRARED ABSORPTION DATA FOR 4-(2-ACETOXYETHYLIDENE)-4-HYDROXY-2,3-DIOXOBUTYRO-1,4-LACTONE 2-(2-ARYLHYDRAZONES) (3) AND 1-METHYL-3-(1-METHYLPYRAZOLIN-3-YL)-4,5-PYRAZOLEDIONE 4-(2-ARYLHYDRAZONES) (4)

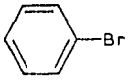
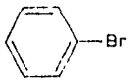
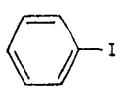
Compound No.	*R*	*M.p. (degrees)*	*Yield (%)*	*Molecular formula*	*Calculated (%)*			*Found (%)*			ν_{max}^{Nujol}		
					C	*H*	*N*	*C*	*H*	*N*			
3c		186–187	75	$C_{14}H_{11}BrN_2O_5$	45.8	3.0	7.6	46.1	2.8	7.9	1655	1720	1775
3d		212–213	70	$C_{14}H_{11}IN_2O_5$	40.6	2.7	6.8	40.9	2.8	6.4	1665	1725	1770
4c		240	67	$C_{14}H_{15}BrN_6O$	46.3	4.2	23.1	46.0	4.1	23.0	1660		
4d		231–232	58	$C_{14}H_{15}IN_6O$	41.0	3.7	20.5	41.1	3.8	20.2	1660		

TABLE III

MICROANALYTICAL AND INFRARED ABSORPTION DATA FOR L-*threo*-2,3-HEXODIULOSONO-1,4-LACTONE 2-(2-ARYLHYDRAZONE) 3-(2-PHENYLHYDRAZONES) (5) AND THEIR REARRANGEMENT PRODUCTS (6)

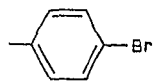
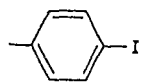
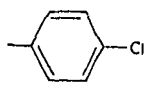
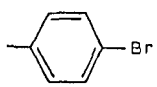
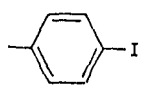
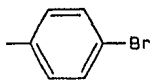
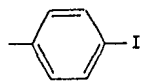
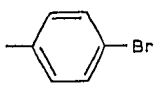
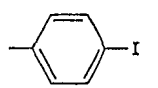
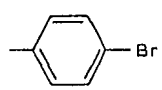
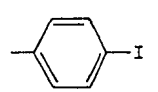
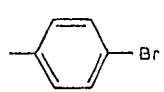
Compound No.	*R*	*M.p. (degrees)*	*Yield (%)*	*Molecular formula*	*Calculated (%)*			*Found (%)*			ν_{max}^{Nujol}	
					C	*H*	*N*	*C*	*H*	*N*		
5c		223–225	70	$C_{18}H_{17}BrN_4O_4$	49.9	4.0	13.4	49.7	3.6	13.5	1740	3300
5d		225–226	65	$C_{18}H_{17}IN_4O_4$	45.0	3.6	11.7	45.2	3.9	12.0	1725(sh)	1730
6b		232–233	90	$C_{18}H_{17}ClN_4O_4$	55.6	4.4	14.4	55.3	4.2	14.7	1660	3400
6c			96	$C_{18}H_{17}BrN_4O_4$	49.9	4.0	13.4	50.1	4.5	13.0	1660	3400
6d		235–236	80	$C_{18}H_{17}IN_4O_4$	45.0	3.6	11.7	45.1	4.0	11.2	1660	3400

TABLE IV

MICROABALYTICAL AND INFRARED ABSORPTION DATA FOR DERIVATIVES OF COMPOUND **6**

Compound No.	*R*	*M.p. (degrees)*	*Yield (%)*	*Molecular formula*	*Calculated (%)*			*Found (%)*			ν_{max}^{Nujol}	
					C	*H*	*N*	*C*	*H*	*N*		
7c		148–150	89	$C_{24}H_{23}BrN_4O_7$	51.5	4.1	10.0	52.0	4.3	10.4	1660	1740
7d		125–127	74	$C_{24}H_{23}IN_4O_7$	47.5	3.8	9.2	47.4	4.0	9.4	1660	1740
8c		176–178	65	$C_{30}H_{29}BrN_4O_7$	62.8	3.9	7.5	62.4	4.1	7.9	1660	1720
8d		178–179	54	$C_{30}H_{29}IN_4O_7$	59.1	3.7	7.1	58.9	4.1	6.8	1660	1720
9c		182–184	80	$C_{16}H_{11}BrN_4O_2$	51.8	3.0	15.1	52.1	3.4	15.5	1660	1690
9d		182–183	78	$C_{16}H_{11}IN_4O_2$	45.9	2.7	13.4	45.5	3.0	13.0	1660	1690
10c		199–200	60	$C_{22}H_{17}BrN_6O$	57.3	3.7		57.7	4.0		1660	

then made neutral with acetic acid, and the product was filtered off, washed with water, and recrystallized from ethanol, to give orange needles (see Table III).

*1-Phenyl-3-(1,2,3-tri-*O*-acetyl-*L*-threo-glycerol-1-yl)-4,5-pyrazoledione 4-(2-arylhydrazones)* (**7**). — A solution of compound **6** (1 g) in dry pyridine (15 ml) was treated with acetic anhydride (8 ml), and kept overnight at room temperature. The mixture was poured onto crushed ice, and the solid that separated was filtered off, washed repeatedly with water, and recrystallized from ethanol in orange needles (see Table IV).

*1-Phenyl-3-(1,2,3-tri-*O*-benzoyl-*L*-threo-glycerol-1-yl)-4,5-pyrazoledione 4-(2-arylhydrazones)* (**8**). — A solution of compound **6** (0.2 g) in dry pyridine (10 ml) was treated with benzoyl chloride (1 ml), and kept overnight at room temperature. The mixture was poured onto crushed ice, and the benzoate that separated was washed repeatedly with water, and recrystallized from ethanol in orange needles (see Table IV).

3-Formyl-1-phenyl-4,5-pyrazoledione 4-(2-arylhydrazones) (**9**). — A solution of compound **6** (0.5 g) in ethanol was treated with a solution of sodium metaperiodate in water, and kept for 30 min at room temperature. The mixture was diluted with water, and the product was filtered off after 1 h, washed with water, and dried. It was recrystallized from ethanol in orange needles (see Table IV).

Hydrazones of **9**. — When a solution of compound **9** (0.01 mole) in ethanol was treated with the calculated amount of phenylhydrazine, and the mixture was heated for 10 min, it afforded the corresponding hydrazones, which were recrystallized from ethanol (see Table IV).

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