SYNTHESIS OF SOME SULFANILAMIDE-SUBSTITUTED 4,5-PYRAZOLINEDIONE DERIVATIVES FROM DEHYDRO-L-ASCORBIC ACID

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الخلاصة :

يُـنْـتِـجُ تفاعل حمض ديهيدرو-لـ-اسكوربيك ٢ - (باراسالفاميل فينيل هيدرازون) مع الآريل هيدرازوينات عدداً من ثُـنائي الهيدرازونات المختلطة والتي تتحول بالتسخين مع الهيدرازين المائي ثم التحميض إلى (١-أريـل-٣-(لـ-ثـريـوجـليسرول-١-وايـل) - ٤ ، ٥-بـيرازوليـدين ٤- (باراسلفاميل فينيل هيدرازون) . وهذه البيرازولونات وثنائية الهيدرازونات قد أعطت مشتقات ثلاثية وثنائية الأسيتيل على الترتيب . إن جزيء السكر في البيرازولونات قد تكسَّـرَ بواسطة البيرأيودات إلى مشتق ٣-فورميل ثم إختزاله إلى ٣-هيدروكسي ميثيل الذي أعطي بدوره أحادي الأسيتيل . أمّا أستلة أو بنزولة حمض ديهيدرو - إسكوربيك ٢-باراسلفاميل فينيل هيدرازون فقد أعطي أسترات أوليفينية .

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ABSTRACT

Reaction of dehydro-L-ascorbic acid 2-(*p*-sulfamylphenylhydrazone) with arylhydrazines gave a number of mixed *bis*-hydrazones which were rearranged, on heating with hydrazine hydrate followed by acidification, into 1-aryl-3-(L-*threo*-glycerol-1-yl)-4,5-pyrazolinedione-4-*p*-(sulfamylphenylhydrazone)s. These and the *bis*-hydrazones were characterized as the related tri- and di-*O*-acetates respectively. The glycerol side chain of the phenylpyrazolinedione was degraded by a periodate–borohydride sequence to a hydroxymethyl group, the product was further characterized as the monoacetate and monobenzoate. Acetylation or benzoylation of dehydro-L-ascorbic acid 2-(*p*-sulfamylphenylhydrazone) led to olefinic ester.

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INTRODUCTION

Many of the reactions of dehydro-L-ascorbic acid *bis*-hydrazones (L-*threo*-2,3-hexodiulosono-1,4-lactone-2,3-*bis*-hydrazones) differ from those of the sugar osazones (glycosulose 1,2- *bis*-hydrazones). The former readily undergo cyclization involving either nucleophilic attack of the hydrazone nitrogen atom on the 1-carbonyl group, or attack of a hydroxyl group on the hydrazone residue. Thus, for example, oxidation of dehydro-L-ascorbic acid *bis*-hydrazones, yield bicyclic azo compounds [1, 2], where the glycosulose osazones yield triazoles [3], other differences has been discussed [4]. The triazole derivatives of dehydro-L-ascorbic acid and its analogs have been prepared through dehydrative cyclization of the 2-arylhydrazone 3-oximes [5–7].

RESULTS AND DISCUSSION

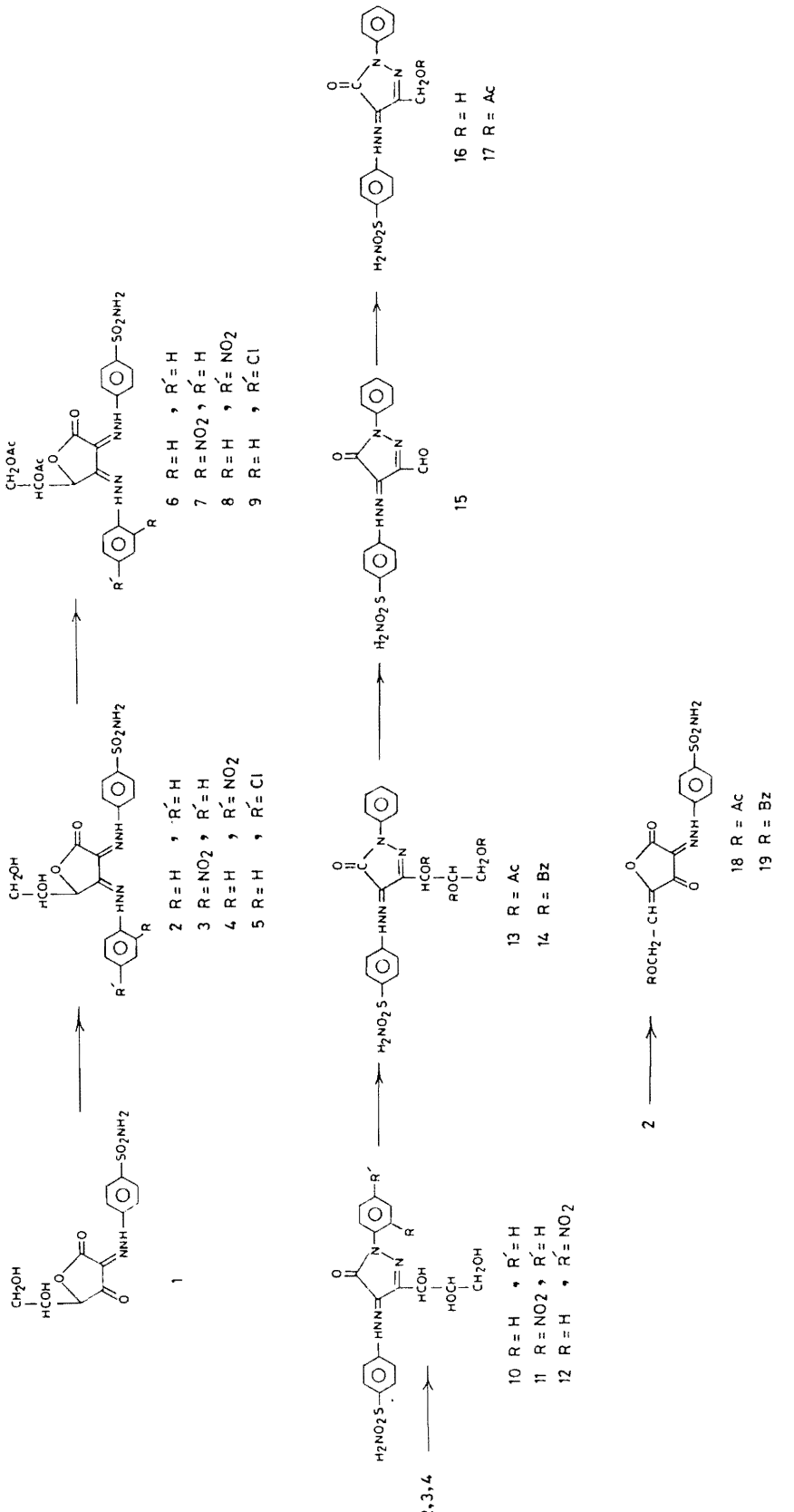
The present work deals with the synthetic application of the 2-(*p*-sulfamylphenylhydrazone) of dehydro-L-ascorbic acid in the synthesis of some pyrazole derivatives. The 4,5-pyrazolinediones showed biological activities [8–12] and this attracted the attention to the synthesis of some pyrazoles attached to the sugar moiety and the active part of sulfanilamide drug. Thus, unimolecular condensation of dehydro-L-ascorbic acid with *p*-sulfamylphenylhydrazine, gave the 2-hydrazone (**1**), from which, upon treatment with phenyl-, *o*-nitrophenyl-, *p*-nitrophenyl-, or with *p*-chlorophenylhydrazine, the corresponding mixed *bis*(hydrazones) (**2–5**) are obtained in red needles; they revealed the lactone bands between 1745–1780 cm^{-1} in addition to the hydroxyl bands between 3400–3490 cm^{-1}. Acetylation of compounds (**2–5**), with acetic anhydride and pyridine, gave the di-*O*-acetyl derivatives (**6–9**), the IR spectra of which showed unresolved bands between 1740–1760 cm^{-1} due to the lactone and ester groups. The ^{1}H-NMR spectrum of (**7**) showed two acetyl groups, appearing at δ 1.90 and 2.1 ppm as two singlets each of three proton intensity; the C-6 methylene protons appeared as a multiplet centered at δ 4.25 ppm followed by a multiplet at δ 4.50 (H-5). A doublet at δ 5.62 was assigned to the C-4 methine proton, and the aromatic protons appeared at δ 7.1–7.72.

Treatment of the mixed *bis*(arylhydrazones) (**2–4**) with hydrazine hydrate in methanol followed by acidification, afforded the corresponding 1-aryl-3-(L-*threo*-glycerol-1-yl)-4,5-pyrazolinedione 4-(*p*-sulfamylphenylhydrazone) (**10–12**). Their IR spectra revealed the amide bands at 1660–1680 cm^{-1} in addition to the hydroxyl bands at 3400–3500 cm^{-1}.

Acetylation of (**10**) with acetic anhydride and pyridine, gave 1-phenyl-3-(1,2,3-tri-*O*-acetyl-L-*threo*-glycerol-1-yl)-4,5-pyrazolinedione 4-(*p*-sulfamylphenylhydrazone) (**13**) whose IR spectrum showed the amide band at 1670 cm^{-1} and the ester band at 1750 cm^{-1}. Similarly, benzoylation of (**10**) with benzoyl chloride and pyridine, gave the perbenzoyl derivative (**14**).

Treatment of (**10**) with sodium metaperiodate, gave 1-phenyl-3-formyl-4,5-pyrazolinedione 4-(*p*-sulfamylphenylhydrazone) (**15**) whose IR showed the formyl group at 1720 cm^{-1} and the amide band at 1670 cm^{-1}. Sodium borohydride reduction of (**15**), gave the 3-hydroxymethyl derivative (**16**) which was characterized as its acetyl derivative (**17**).

Acetylation of the monohydrazone (**1**) with acetic anhydride and pyridine, caused simultaneous acetylation of the hydroxy group and formation of an optically inactive olefinic compound (**18**). Its combustion analysis agreed with the molecular formula $C_{14}H_{13}N_3O_7S$, and its IR spectrum showed the lactone band at 1770 cm^{-1}. ^{1}H-NMR of (**18**) showed one acetyl group signals at δ 2.03 in addition to the expected proton signals. Similarly, treatment of (**1**) with benzoyl chloride and pyridine gave (**19**).


1
2 R = H , R′ = H
3 R = NO2 , R′ = H
4 R = H , R′ = NO2
5 R = H , R′ = Cl
6 R = H , R′ = H
7 R = NO2 , R′ = H
8 R = H , R′ = NO2
9 R = H , R′ = Cl
2,3,4
10 R = H , R′ = H
11 R = NO2 , R′ = H
12 R = H , R′ = NO2
13 R = Ac
14 R = Bz
15
16 R = H
17 R = Ac
2
18 R = Ac
19 R = Bz

EXPERIMENTAL

General Methods

Melting points were determined with a Tottoli (Büchi) apparatus and are uncorrected. IR, visible, and ultraviolet spectra were recorded with a 580-B Perkin–Elmer spectrometer and NMR spectra with a Varian EM-390 spectrometer for solutions of $CDCl_3$ and DMSO-d using tetramethylsilane as internal standard. Microanalyses were performed in the Chemistry Department, Faculty of Science, Cairo University, Cairo, and in the Chemistry Department, Faculty of Science, Assiut University, Egypt.

L-*threo*-2,3-Hexodiulosono-1,4-lactone-2-(*p*-sulfamylphenylhydrazone) 3-arylhydrazones (2–5)

A solution of the monohydrazone (**1**) [13, 14] (0.5 g) in ethanol (50 ml) was treated with the desired arylhydrazine (0.5 g) in ethanol (20 ml) and few drops of acetic acid. The mixture was refluxed for 3 h, concentrated and left to cool at room temperature. The solid was filtered off, washed with ethanol and ether, and dried. Each product recrystallized from ethanol in red needles (see Table 1).

5,6-Di-*O*-acetyl-L-*threo*-2,3-hexodiulosono-1,4-lactone-2-(*p*- sulfamylphenylhydrazone) 3-arylhydrazones (6–9)

To a solution of the mixed *bis*(arylhydrazones) (**2**–**5**) (0.1 g) in dry pyridine (10 ml) was added acetic anhydride (10 ml) and the mixture was left overnight at room temperature. The mixture was poured onto crushed ice, and the product was filtered off, washed with water and ethanol, and dried. Each product recrystallized from ethanol in red needles (see Table 1).

1-Aryl-3-(L-*threo*-glycerol-1-yl)-4,5-pyrazolinedione-4-(*p*-sulfamylphenylhydrazone)s (10–12)

A solution of (**2**–**4**) (1 g) in methanol (30 ml) was treated with hydrazine hydrate (2 ml) and refluxed for 30 minutes, and then acidified with acetic acid (4 ml) and left to cool at room temperature. The solid was filtered off, washed with methanol and dried. Each product recrystallized from ethanol as orange needles (see Table 1).

1-Phenyl-3-(1,2,3-tri-*O*-acetyl-L-*threo*-glycerol-1-yl)-4,5-pyrazolinedione 4-(*p*-sulfamylphenylhydrazone) (13)

To a solution of (**10**) [13] (0.4 g) in pyridine (10 ml) was added acetic anhydride (10 ml) and left overnight at room temperature. The mixture was poured onto crushed ice, and the product was filtered off, washed with water and ethanol, and dried (yield 0.4 g; 80%). It recrystallized from methanol as orange needles, m.p. 180–181°C; ν_{max}^{KBr} 1770 (ester) and 1660 cm^{-1} (OCN); λ_{max}^{EtOH} 248, 394 nm (log ε 4.93, 4.56); λ_{min} 220, 300 nm (log ε 4.18, 3.05); ^1H NMR data ($CDCl_3$): δ 2.0, 2.09, 2.12 (3s, 9H, 3 $OCOCH_3$), 4.21 (m, 2H, H-3), 5.71 (m, 1H, H-2), 6.17 (d, 1H, H-1), 7.6–8.0 (m, 9H, aromatic protons).

Analysis: *Calc.:* for $C_{24}H_{25}N_5O_9S$: C, 51.52; H, 4.47; N, 12.52.

Found: C, 51.30; H, 4.51; N, 12.60.

1-Phenyl-3-(1,2,3-tri-*O*-benzoyl-L-*threo*-glycerol-1-yl)-4,5-pyrazolinedione 4-(*p*-sulfamylphenylhydrazone) (14)

A solution of (**10**) (0.4 g) in pyridine (10 ml) was treated with benzoyl chloride (1 ml) and left overnight at room temperature. The mixture was poured onto crushed ice, and the solid was filtered off, washed with water and ethanol, and dried (yield 0.4 g; 60%). It recrystallized from methanol as orange needles, m.p. 200–201°C; ν_{max}^{KBr} 1730 (ester) and 1680 cm^{-1} (OCN).

Analysis: *Calc.:* for $C_{39}H_{31}N_5O_9S$: C, 62.82; H, 4.16; N, 9.4.

Found: C, 62.63; H, 3.91; N, 9.0.

Table 1. Microanalytical and Spectral Data for Compounds (2–12).

Compound No.	R	R′	Melting points (degrees)	Yield (%)	Molecular Formula	Analyses			ν (cm^{-1})						
						C	H	N	OH	Lectone C=O	Lectone + ester	OCN	λ (nm)		log ε
2	H	H	240–241	50	$C_{18}H_{19}N_5O_6S$	Calc. : 49.90	4.38	16.16	3400	1750			max	272, 350, 446	4.27, 4.05, 4.25
						Found : 50.30	4.18	15.92					min	246, 316, 384	4.10, 3.76, 3.80
3	NO_2	H	243–244	56	$C_{18}H_{18}N_6O_8S$	Calc. : 45.18	3.78	17.57	3450	1780					
						Found : 44.90	3.80	17.90							
4	H	NO_2	> 270	66	$C_{18}H_{18}N_6O_8S$	Calc. : 45.18	3.78	17.57	3450	1780			max	252, 350, 464	3.53, 3.85, 3.84
						Found : 44.90	3.90	17.60					min	300, 394	3.25, 3.23
5	H	Cl	235–236	79	$C_{18}H_{18}ClN_5O_6S$	Calc. : 46.20	3.85	14.97	3400	1770			max	269, 351, 450	4.43, 4.24, 4.42
						Found : 45.90	3.40	15.30					min	240, 316	4.24, 3.94
6	H	H	205–206	67	$C_{22}H_{23}N_5O_8S$	Calc. : 51.06	4.44	13.53			1750		max	276, 350, 442	4.14, 3.83, 4.02
						Found : 50.70	4.60	13.10					min	216, 314	3.67, 3.61
7	NO_2	H	185–186	68	$C_{22}H_{22}N_6O_{10}S$	Calc. : 46.97	3.91	14.94			1780		max	266, 370, 480	3.60, 3.48, 3.43
						Found : 46.40	3.90	14.50					min	239, 312, 436	3.45, 3.10, 3.26
8	H	NO_2	120–122	79	$C_{22}H_{22}N_6O_{10}S$	Calc. : 46.97	3.91	14.94			1770				
						Found : 46.60	4.20	15.00							
9	H	Cl	190–191	72	$C_{22}H_{22}ClN_5O_8S$	Calc. : 47.86	4.00	12.69			1775				
						Found : 47.90	4.32	12.20							
10	H	H	> 280	(11t. [13])	300 (dec.)										
11	NO_2	H	266–267		$C_{18}H_{18}N_6SO_8S$	Calc. : 45.18	3.78	17.57	3450			1680			
						Found : 45.60	3.90	17.72							
12	H	NO_2	273–274		$C_{18}H_{18}N_6SO_8S$	Calc. : 45.18	3.76	17.57	3450			1680			
						Found : 45.12	3.81	17.36							

3-Formyl-1-phenyl-4,5-pyrazolinedione 4-(*p*-sulfamylphenylhydrazone) (15)

A suspension of (**10**) (0.1 g) in water (10 ml) was treated with a solution of sodium metaperiodate (0.5 g) in water (10 ml), and the mixture was shaken for 6 h. The solid was filtered, washed with water and ethanol, and dried (yield 0.3 g; 82%). It recrystallized from methanol as needles, m.p. 170–171°C; ν_{max}^{KBr} 1710 (CHO) and 1670 cm^{-1} (OCN).

Analysis: *Calc.:* for $C_{16}H_{13}N_5O_4S$: C, 51.75; H, 3.50; N, 18.87.

Found: C, 51.40; H, 4.0; N, 18.70.

3-Hydroxylmethyl-1-phenyl-4,5-pyrazolinedione 4-(*p*-sulfamylphenylhydrazone) (16)

A solution of (**15**) (0.37 g) in methanol (30 ml) was treated with a solution of sodium borohydride (0.2 g) in water (10 ml) with occasional shaking and the mixture was left for 6 h at room temperature. The mixture was acidified with acetic acid and the solid was filtered off, washed with water and methanol, and dried (yield 0.28 g; 75%). It recrystallized from ethanol as yellow needles, m.p. 207–208°C; ν_{max}^{KBr} 3420 (OH) and 1660 cm^{-1} (OCN).

Analysis: *Calc.:* for $C_{16}H_{15}N_5O_4S$: C, 51.47; H, 4.02; N, 18.76.

Found: C, 51.42; H, 4.00; N, 18.50.

3-Acetoxymethyl-1-phenyl-4,5-pyrazolinedione-4-(*p*-sulfamylphenylhydrazone) (17)

A solution of (**16**) (0.1 g) in pyridine (10 ml) was treated with acetic anhydride (15 ml) and the mixture was left overnight at room temperature. The mixture was poured onto crushed ice, and the solid was filtered off, washed with water and ethanol, and dried (yield 80 mg; 70%). It recrystallized from methanol as yellow needles, m.p. 190–191°C; ν_{max}^{KBr} 1740 (ester) and 1670 cm^{-1} (OCN).

Analysis: *Calc.:* for $C_{18}H_{17}N_5O_5S$: C, 52.05; H, 4.09; N, 16.86.

Found: C, 52.30; H, 4.20; N, 16.60.

4-(2-Acetoxyethylidene)-4-hydroxy-2,3-dioxobutano-1,4-lactone-2-(*p*-sulfamylphenylhydrazone) (18)

A solution of (**1**) (0.34 g) in pyridine (10 ml) was treated with acetic anhydride (5 ml) and the mixture was left overnight at room temperature. The mixture was poured onto crushed ice, and the solid was filtered off, washed with water and ethanol, and dried (yield 0.3 g; 87%). It recrystallized from ethanol as yellow needles, m.p. 201–202°C; ν_{max}^{KBr} 1770 (lactone C=O), 1730 (ester) and 1680 cm^{-1} (C=O); λ_{max}^{EtOH} 235, 282 nm (log ε 4.15, 4.39); λ_{min} 216, 298 nm (log ε 4.04, 3.78); ^{1}H NMR data ($CDCl_3$): δ 2.03 (s, 3H, $OCOCH_3$), 4.79 (d, 2H, H-6), 5.86 (t, 1H, H-5), 7.40–7.87 (m, 4H, aromatic protons).

Analysis: *Calc.:* for $C_{14}H_{13}N_3O_7S$: C, 45.77; H, 3.54; N, 11.44.

Found: C, 46.20; H, 3.50; N, 11.20.

4-(2-Benzoyloxyethylidene)-4-hydroxy-2,3-dioxobutano-1,4-lactone 2-(*p*-sulfamylphenylhydrazone) (19)

A solution of (**1**) (0.37 g) in dry pyridine (10 ml) was treated with benzoyl chloride (0.5 ml) and the mixture was kept overnight at room temperature. The mixture was poured onto crushed ice, and the solid was filtered off, washed with water and ethanol, and dried (yield 0.3 g; 75%). It recrystallized from ethanol as yellow needles, m.p. 190–191°C; ν_{max}^{KBr} 1760 (lactone C=O and ester) and 1680 cm^{-1} (C=O).

Analysis: *Calc.:* for $C_{19}H_{15}N_3O_7S$: C, 53.14; H, 3.50; N, 9.79.

Found: C, 53.10; H, 3.80; N, 10.00.

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Paper Received 12 June 1993; Revised 28 September 1993; Accepted 11 January 1994.