SYNTHESIS OF SOME 1-PHENYL-3-SUBSTITUTED-4,5-PYRAZOLE-DIONE-4-ARYL AND AROYL-HYDRAZONES

Mohamed Ali El-Sekily, Sohila Mancy*, and Kamal Atta

Department of Chemistry, Faculty of Science, Alexandria University, Egypt

1. INTRODUCTION

It is known that some of the 4,5-pyrazolinediones and their derivatives showed various biological activities [1–5] as potential drugs for central nervous system, and also as antidiabetic, antiviral, and anticancer agents. This attracted our attention [6, 7] to the synthesis of some pyrazolinediones having varied substituents on the ring and a carbohydrate moiety on C-3 [6–8]. In this paper we describe the synthesis of some pyrazolinediones having different aryl- and aroyl-hydrazones on C-4 and a carbohydrate moiety on C-3.

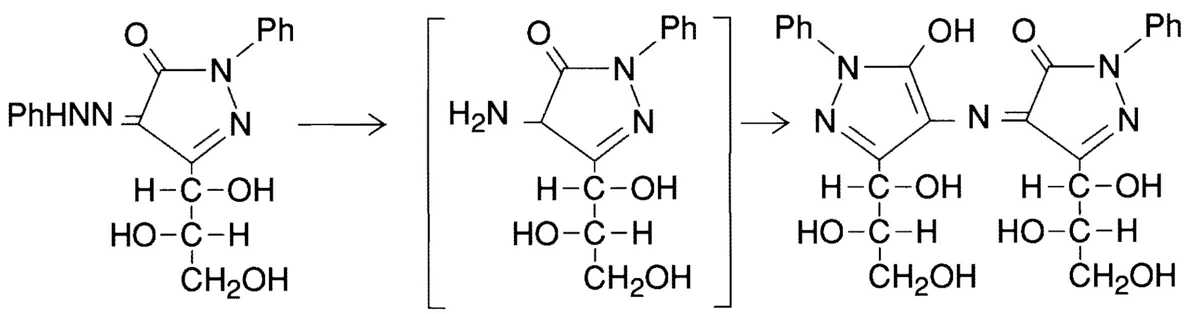
2. SYNTHESIS OF THE COMPOUNDS

In previous publication [9] we dealt with the reduction of 3-hydroxypropyl-1-phenyl-4,5-pyrazolinedione 4-phenylhydrazone [10] with zinc and acetic acid, which afforded the substituted L-*threo*- and D-*erythro* rubazonic acid. Similarly, hydrogenation of the pyrazole (**1**) in presence of palladium on carbon, afforded the intermediate 4-amino-3-hydroxyalkyl-1-phenylpyrazolin-5-one (**2**) that afforded [9] the dimeric reduction product (**3**) upon treatment with hydrochloric acid (yield > 90%).

Treatment of compound (**3**) with the desired aryl- or aroyl-hydrazines afforded the corresponding pyrazolinediones (**4**) (Table 1). Compounds (**4**) are characterized by their orange color and showed in the infrared region an amide band at 1660–1680 cm^{-1} in addition to the hydroxyl absorption at 3450–3500 cm^{-1} (Table 2). Acetylation of the pyrazolinediones (**4**) with boiling acetic anhydride or with acetic anhydride and pyridine, afforded peracetylated pyrazolinediones (**5**) (Table 1), which now showed an ester band at 1740–1750 cm^{-1} and an amide band at 1660–1680 cm^{-1}.

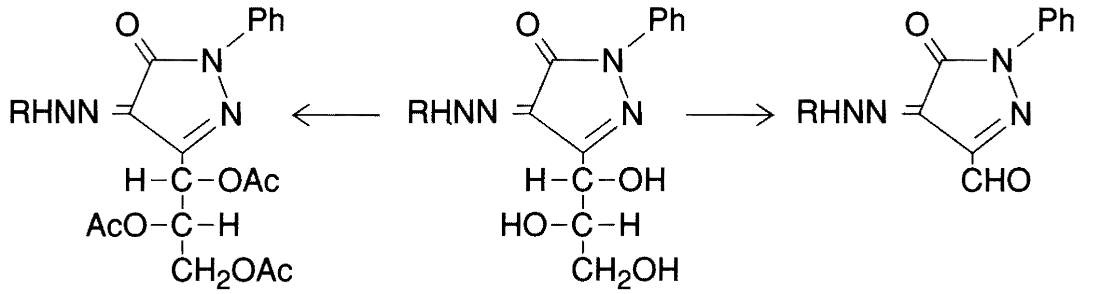
Periodate oxidation of one mole of the pyrazolinediones (**4**) resulted in the consumption of two moles of the oxidant and the formation of the corresponding 3-formyl-1-phenyl-4,5-pyrazolinedione 4-aryl and aroylhydrazones (**6**), the infrared spectra of which showed an aldehyde band at 1690–1700 cm^{-1} in addition to an amide band at 1660–1680 cm^{-1}.

Reduction of compound (**6**) with sodium borohydride, afforded 3-hydroxymethyl-1-phenyl-4,5-pyrazolinedione 4-aryl- and aroylhydrazones (**7**) characterized as its acetate (**8**). On condensation of (**6a**) and (**6c**) with phenyl- or *p*-nitrophenylhydrazine, it yielded the hydrazones (**9–12**). Similarly, reaction of (**6a**) and (**6c**) with *o*-phenylenediamine, afforded compounds (**13**) and (**14**), respectively.

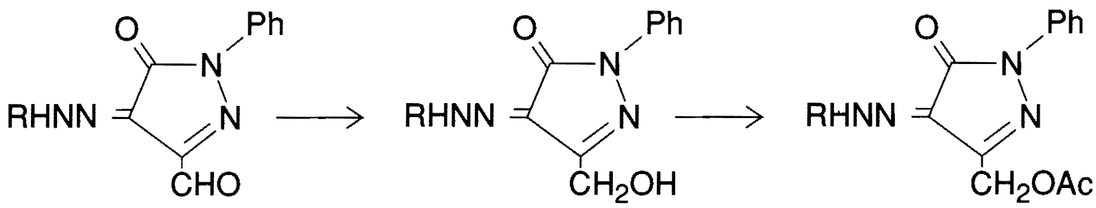


(**1**) (**2**) (**3**)

*To whom crrespondence should be addressed

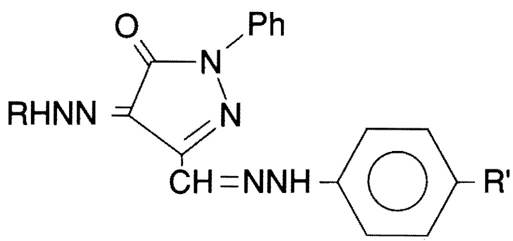


(**5**) (**4**) (**6**)

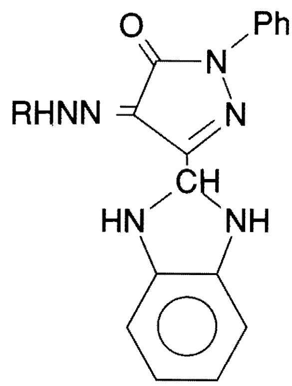


(**6**) (**7**) (**8**)

a R = C_6H_4Cl–*p*
b R = $C_6H_4CH_3$–*p*
c R = $C_6H_4NO_2$–*p*
d R = $C_6H_3(NO_2)_2$–*o,p*
e R = COC_6H_5
f R = COC_6H_4Cl–*p*
g R = $COC_6H_4NO_2$–*p*
h R = $COC_6H_4CH_3$–*p*
i R = $COC_6H_4NO_2$–*o*
j R = $COC_6H_4OCH_3$–*p*



(**9**) R = C_6H_4Cl–*p*, R' = H
(**10**) R = C_6H_4Cl–*p*, R' = NO_2
(**11**) R = $C_6H_4NO_2$–*p*, R' = H
(**12**) R = $C_6H_4NO_2$–*p*, R' = NO_2



(**13**) R = C_6H_4Cl–*p*
(**14**) R = $C_6H_4NO_2$–*p*

Table 1. Microanalytical Data for the Compounds Prepared.

Compound No.	R	R′	n.p. (degrees)	Yield (%)	Molecular formula	Calculated (%) C	Calculated (%) H	Calculated (%) N	Found (%) C	Found (%) H	Found (%) N
4a	C_6H_4CL-*p*		224–226	(Lit. [11]	232-232)						
4b	$C_6H_4CH_3$-*p*		222–223	70	$C_{19}H_{20}N_4O_4$	61.95	5.47	15.20	61.76	5.21	15.63
4c	$C_6H_4NO_2$-*p*		199–201	66	$C_{18}H_{17}N_5O_6$	54.14	4.29	17.53	54.36	4.54	17.26
4d	$C_6H_3(NO_2)_2$-*o,p*		242–244	54	$C_{18}H_{16}N_6O_8$	48.66	3.63	18.90	48.42	3.46	18.70
4e	COC_6H_5		216–218	(Lit. [9]	218)						
4f	COC_6H_4Cl-*p*		203–204	68	$C_{19}H_{17}ClN_4O_5$	54.75	4.11	13.44	54.53	4.00	13.36
4g	$COC_6H_4NO_2$-*p*		220–222	68	$C_{19}H_{17}N_5O_7$	53.40	4.00	16.38	53.26	4.32	16.14
4h	$COC_6H_4CH_3$-*p*		206–208	58	$C_{20}H_{20}N_4O_5$	60.60	5.08	14.12	60.42	5.24	14.33
4i	$COC_6H_4CH_3$-*o*		208–209	47	$C_{20}H_{20}N_4O_5$	60.60	5.08	14.122	60.51	5.32	14.36
4j	$COC_6H_4OCH_3$-*p*		213–214	62	$C_{20}H_{20}N_4O_6$	58.25	4.88	13.58	58.04	4.62	13.21
5a	C_6H_4Cl-*p*		146–147	88	$C_{24}H_{23}ClN_4O_7$	55.98	4.50	10.87	55.62	4.41	10.60
5b	$C_6H_4CH_3$-*p*		144–145	86	$C_{25}H_{26}N_4O_7$	60.72	5.30	11.32	60.46	5.03	11.12
5c	$C_6H_4NO_2$-*p*		135–137	76	$C_{24}H_{23}N_5O_9$	54.86	4.41	13.32	54.66	4.12	13.10
5d	$C_6H_3(NO_2)_2$-*o,p*		169–171	82	$C_{24}H_{22}N_6O_{11}$	50.53	3.88	14.72	50.31	3.53	14.34
5g	$COC_6H_4NO_2$-*p*		191–192	67	$C_{25}H_{23}N_5O_{10}$	54.25	4.19	12.64	54.02	4.37	12.48
5h	$COC_6H_4CH_3$-*p*		127–128	64	$C_{26}H_{26}N_4O_8$	59.80	5.01	10.72	59.51	5.36	10.72
5i	$COC_6H_4CH_3$-*o*		111–112	53	$C_{26}H_{26}N_4O_8$	59.80	5.01	10.72	59.64	5.36	10.42
5j	$COC_6H_4OCH_3$-*p*		138–139	64	$C_{26}H_{26}N_4O_9$	57.99	4.86	10.36	57.62	4.70	10.12
6a	C_6H_4Cl-*p*		160–162	86	$C_{16}H_{11}ClN_4O_2$	58.82	3.40	17.14	58.52	3.23	17.42
6b	$C_6H_4CH_3$-*p*		161–163	83	$C_{17}H_{14}N_4O_2$	66.65	4.62	18.28	66.32	4.28	18.61
6c	$C_6H_4NO_2$-*p*		244–246	72	$C_{16}H_{11}N_5O_4$	65.98	3.28	20.77	56.76	3.04	20.41
6d	$C_6H_3(NO_2)_2$-*O,P*		259–261	62	$C_{16}H_{10}N_6O_6$	50.22	2.63	21.97	50.00	2.41	21.63
6e	COC_6H_5		199–201	43	$C_{17}H_{12}N_4O_3$	63.75	3.77	47.48	63.30	3.34	17.80
6f	COC_6H_4Cl-*P*		195–197	48	$C_{17}H_{11}ClN_4O_3$	57.56	3.15	15.78	57.74	3.50	15.36
6g	$COC_6H_4NO_2$-*P*		176–178	65	$C_{17}H_{11}N_5O_5$	55.90	3.03	19.16	55.62	3.36	19.48
6h	$COC_6H_4CH_3$-*P*		208–209	54	$C_{18}H_{14}N_4O_3$	64.66	4.22	16.75	64.85	4.00	16.30
6i	$COC_6H_4CH_3$-*O*		174–176	67	$C_{18}H_{14}N_4O_3$	64.66	4.22	16.75	64.44	4.20	16.54
7a	C_6H_4Cl-*P*		180–181	76	$C_{16}H_{13}ClN_4O_2$	58.46	3.98	17.03	58.32	3.67	16.83
7b	$C_6H_4CH_3$-*P*		169–170	64	$C_{17}H_{16}N_4O_2$	66.22	5.23	18.16	66.54	5.62	18.00
7e	COC_6H_5		186–189	52	$C_{17}H_{14}N_4O_3$	63.35	4.38	17.37	63.22	4.16	17.14
7i	$COC_6H_4CH_3$-*O*		135–137	64	$C_{18}H_{16}N_4O_3$	64.28	4.79	16.65	64.42	4.59	16.26
8a	C_6H_4Cl-*P*		170–171	54	$C_{18}H_{15}ClN_4O_3$	58.31	4.07	15.10	58.12	4.21	15.32
8b	$C_6H_4CH_3$-*P*		137–138	53	$C_{19}H_{18}N_4O_3$	65.13	5.18	15.98	65.48	5.32	15.71
8e	COC_6H_5		145–146	43	$C_{19}H_{16}N_4O_4$	62.63	4.43	15.37	65.42	4.17	15.21
9	C_6H_4Cl-*P*	H	200–201		$C_{22}H_{17}ClN_6O$	63.39	4.11	20.15	63.13	4.00	20.46
10	C_6H_4Cl-*P*	NO_2	268–270		$C_{22}H_{16}ClN_7O_3$	57.21	3.49	21.22	57.36	3.64	21.02
11	$C_6H_4NO_2$-*P*	H	253–255		$C_{22}H_{17}N_7O_3$	61.82	4.00	22.95	61.95	4.35	22.74
12	$C_6H_4NO_2$-*P*	NO_2	> 270		$C_{22}H_{16}N_8O_5$	55.93	3.41	23.72	55.72	3.22	23.41
13	C_6H_4Cl-*P*		236–237		$C_{22}H_{17}ClN_6O$	63.39	4.11	20.15	63.64	4.43	20.35
14	$C_6H_4NO_2$-*P*		> 280		$C_{22}H_{17}N_7O$	61.82	4.00	22.94	61.65	3.86	22.62

Table 2. UV- and IR Spectral Data for the Compounds Prepared.

Compound	λ (nm)	log ε	ν (cm^{-1})			
			ONC	CHO	OH	OAc
4b	max 208, 254, 426	4.27, 4.29, 4.29	1660		3450	
	min 224 304	3.87, 3.44				
4c	max 206, 248, 408, 456	4.45, 4.28, 4.43, 4.21	1670		3450	
	min 220 298	4.03, 3.47				
4d	max 206, 248, 408, 460	4.63, 4.56, 4.61, 4.21	1670		3450	
	min 220 305	4.33, 3.70				
4f	max 206, 244, 328	4.60, 4.49, 4.56	1670	1700	3450	
	min 218 274	4.18, 4.21				
4g	max 204, 262, 350, 384	4.72, 4.63, 4.35 4.16	1660	1690	3450	
	min 220, 320	4.28, 4.12				
4h	max 204, 244, 330	4.68, 4.35, 4.46	1660	1690	3430	
	min 220, 274	4.03, 3.90				
4i	max 206, 248, 366	4.46, 4.23, 4.16	1660	1960	3430	
	min 222, 284	4.00, 3.68				
4j	max 206, 246, 340	4.42, 4.47, 4.34	1670	1690	3430	
	min 220, 276	3.78, 3.71				
5a	max 208, 254, 404	4.46, 4.40, 4.43	1655			1740
	min 223, 306	4.11, 3.85				
5b	max 206, 254, 410	4.80, 4.71, 4.74	1660			1740
	min 218, 310	4.17, 3.19				
5c	max 208, 248, 406, 471	4.62, 4.41, 4.54, 4.14	1660			1750
	min 220, 294	4.18, 3.74				
5d	max 206, 246, 412, 510	4.62, 4.66, 4.53, 4.51	1670			1750
	min 220, 320 442	4.43, 3.73 4.12				
5g	max 204, 256, 436	4.62, 4.55, 4.50	1660	1700		1750
	min 223, 318	4.19, 4.03				
5h	max 204, 244, 336	4.77, 4.69, 4.04	1655	1700		1740
	min 218, 300	4.34, 3.85				
5i	max 204, 244, 322	4.58, 4.39, 4.34	1665	1690		1750
	max 218, 280	4.10, 3.85				
5j	max 206, 248, 338	4.45, 4.44, 4.31	1660	1700		1740
	min 220, 280	3.94, 3.73				
6a	max 207, 252, 430	4.27, 4.27, 4.32	1655		1700	
	min 222, 300	3.89, 3.52				
6b	max 204, 265, 430	4.33, 4.15, 4.11	1660		1700	
	min 226, 320	3.95, 3.69				
6c	max 208, 250, 480	4.61, 4.49, 4.61	1655		1705	
	min 224, 320	4.32, 4.06				
6d	max 206, 246, 508	4.72, 4.63, 4.85	1680		1700	
	min 222, 320	4.47, 3.76				
6e	max 204, 232, 320, 384	4.55, 4.42, 4.18, 4.13	1670		1700	
	min 216, 284 356	4.35, 4.12, 4.08				
6f	max 208, 244, 380	4.32, 4.28, 4.27	1670		1700	
	min 218, 308	4.08, 3.79,				
6g	max 206, 262, 352, 444	4.46, 4.50, 4.24, 4.43	1665		1695	
	min 222, 320 386	4.19, 4.03 4.11				

Table 2: (Cont'd).

Compound	λ (nm)	log ε	ν (cm^{-1})			
			ONC	CHO	OH	OAc
6h	max 206, 244, 310, 380	4.60, 4.44, 4.11, 4.17	1670		1690	
	min 218, 278 340	4.17, 3.94, 4.02				
6i	max 208, 240, 324, 378	4.22, 4.05, 3.93 4.01	1670		1690	
	min 222, 276 346	3.99, 3.76, 3.91				
7a	max 206, 252, 410	4.48, 4.46, 4.48	1660	3430		
	min 220, 300	4.11, 3.64				
7b	max 204, 254, 426	4.61, 4.47, 4.49	1660	3450		
	min 224, 300	4.02, 3.59				
7e	max 207, 244, 380	4.31, 4.36, 4.03	1660	3440		
	min 217, 300	4.14, 3.68				
7i	max 204, 246, 370	4.68, 4.48, 4.17	1660	3480		
	min 220, 284	4.22, 3.74				
8a	max 204, 254, 402	4.44, 4.29, 4.32	1660		1735	
	min 224, 306	4.00, 3.73				
8b	max 202, 254, 404	4.60, 4.53, 4.52	1660		1740	
	min 222, 314	4.12, 3.67				
8e	max 206, 246, 394	4.09, 4.13, 3.69	1660		1745	
	min 216, 310	3.90, 3.41				
9	max 206, 258, 334, 420	4.44, 4.36, 4.41, 4.38	1670			
	min 228, 290 366	4.13 4.14, 4.15				
10	max 204, 254, 296, 436	4.08, 3.84, 3.83, 4.15	1660			
	min 230, 274, 330	3.80, 3.78, 3.68				
11	max 206, 258, 300, 438	4.57, 4.29, 4.40, 4.36	1675			
	min 234, 273, 334	4.14, 4.18, 3.73				
12	max 204, 254, 336, 440	4.82, 4.57, 4.67, 4.63	1670			
	min 230, 288, 380	4.44, 4.38, 4.33				
13	max 206, 248, 288, 450	3.95, 3.78, 3.75, 4.03	1660			
	min 230, 270, 332	3.76, 3.74, 3.66				
14	max 208, 262, 308, 484	4.70, 4.42, 4.51, 4.54	1675			
	min 236, 274, 350	4.37, 4.32, 3.85				

Table 3. ^{1}H-NMR for the Compounds Prepared.

Compound	H-3	H-2	H-1	Aryl	Others	
5a	4.30m	5.80q	6.21d	7.50–8.21m	2.06, 2.08, 2.16	(3s, 3 × 3H, 3OAc)
5b	4.41m	5.86q	6.32d	7.12–8.00m	2.02, 2.08, 2.10	(3s, 3 × 3H, 3OAc); 2.42(Me)
5c	4.38m	5.88q	6.30d	7.24–7.76m	2.06, 2.08, 2.10	(3s, 3 × 3H, 3OAc)
5d	4.40m	5.92q	6.30d	7.10–7.70m	2.08, 2.10, 2.18	(3s, 3 × 3H, 3OAc)
5h	4.40m	5.76q	6.24d	7.20–8.00m	2.04, 2.06, 2.20	(3s, 3 × 3H, 3OAc); 2.52(Me)
5i	4.32	5.64q	6.16d	7.16–7.96m	2.00, 2.06, 2.12	(3s, 3 × 3H, 3OAc); 2.52(Me)
8a			5.18s	7.42–8.16m	2.16 (s, 3H, OAc)	
8b			5.26s	7.15–8.00m	2.16 (s, 3H, OAc)	2.40 (s, 3H, CH_3)
8e			5.28s	7.00–7.92m	2.18 (s, 3H, OAc)	

EXPERIMENTAL

Melting points were determined on a Kofler-block apparatus and are uncorrected. IR spectra were recorded with a Unicam Sp-1025 spectrophotometer for potassium bromide pellets, UV absorption spectra with a Unicam Sp-1750 spectrophotometer for ethanolic solutions. Microanalyses were performed in the Chemistry department, Faculty of Science, Cairo University, Cairo, Egypt. NMR spectres were recorded with a Varian EM-390 spectrometer with Me_4Si as internal standard.

Bis-L-threo-1,2,3-trihydroxypropyl derivatives (3) [9]

A solution of 3-(L-*threo*-glycerol-1-yl)-1-phenyl-4,5-pyrazolinedione (**1**) [10] (3.54 g, 0.01 mole) in absolute ethanol (300 ml) was hydrogenated in the presence of palladium on carbon 10% (1 g) until no more hydrogen was absorbed. The suspension was filtered off, and evaporated under reduced pressure. Water was added (50ml) and the solution was extracted with ether (4 × 30), and then treated with hydrochloric acid and $FeCl_3$, filtered and dried (yield 2.5 g). Compound (**3**) was recrystallized from ethanol in red needles, m.p. 218–220° C. (Lit. [9] m.p. 219° C).

3-(L-*threo*-glycerol-1-yl)-1-phenyl-4,5-pyrazolinedione 4-hydrazones (4)

Bis-L-*threo*-1,2,3-trihydroxypropyl derivative (**3**) (1 g) in ethanol (30 ml) was treated with the desired aryl- or aroyl-hydrazine (1 g) and acetic acid (16 ml), and the solution was heated under reflux for 6 h, concentrated to a small volume and left to cool at room temperature. The product was filtered off, washed with ethanol and dried. Each product was recrystallized from ethanol in orange needles (except for compound (**4c**) which was red).

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

A suspension of pyrazole (**4**) (0.1 g) in dry pyridine (10 ml) was treated with acetic anhydride (10 ml) and kept overnight at room temperature. The mixture was poured into crushed ice, and the product was filtered off, successively washed with water, ethanol, and ether and dried. Each product was recrystallized from ethanol in orange needles.

3-Formyl-1-phenyl-4,5-pyrazolinedione 4-hydrazone (6)

A suspension of the pyrazoles **4** (0.1 g) in water (20 ml) was treated with a solution of sodium metaperiodate (0.3 g) in water (10 ml) and kept 24 h at room temperature with shaking. The solid was filtered off, washed with water, and dried.

3-Hydroxymethyl-1-phenyl-4,5-pyrazolinedione 4-hydrazone (7)

A solution of compound (**6**) (0.1 g) in methanol (10 ml) was treated with a solution of sodium borohydride (0.1 g) in water (10 ml) in portionwise and with shaking and the solution was kept overnight at room temperature. The solution was acidified with acetic acid, and the solid that separated was filtered off, washed with water and dried. The products were recrystallized from ethanol in orange needles.

3-Acetoxymethyl-1-phenyl-4,5-pyrazolinedione 4-hydrazones (8)

A solution of (**7**) (0.1 g) in dry pyridine (10 ml) was treated with acetic anhydride (5 ml) and left overnight at room temperature. The mixture was poured onto crushed ice and the solid was filtered off, washed with water and dried.

Condensation products of 3-formyl-1-phenyl-4,5-pyrazolinedione 4-hydrazones (9–14)

A solution of compound (**6**) (0.1 g) in methanol (20 ml) was treated under reflux with phenyl-, *p*-nitrophenylhydrazine or with *o*-phenylenediamine (one molar proportion) and a few drops of acetic acid. Each product was recrystallized from ethanol in red needles.

REFERENCES

[1] H. G. Garg, *J. Med. Chem.*, **14** (1971), p. 266.
[2] H. G. Garg, *J. Med. Chem.*, **15** (1972), p. 446.
[3] H. G. Garg and P. P. Singh, *J. Pharm. Sci.*, **59** (1970), p. 876.
[4] R. M. Shafik and F. S. G. Soliman, *Pharmazie*, **29** (1974), p. 290.
[5] F. S. G. Soliman and R. M. Shafik, *Pharmazie*, **30** (1975), p. 436.
[6] M. A. El Sekily, *Pharmazie*, **34** (1979), p. 531.

[7] K. F. Atta, H. Wilde, and S. Hauptman, *Pharmazie*, **43** (1988), p. 77.

[8] M. A. El Sekily, S. Mancy, I. El Kholy, E. S. H. El Ashry, H. S. El Khadem, and D. L. Swartz, *Carbohydr. Res.*, **59** (1977), p. 141.

[9] H. S. El Khadem, Z. M. El Shafei, and M. A. El Sekily, *J. Org. Chem.*, **37** (1972), p. 3523.

[10] H. S. El Khadem and E. S. H. El Ashry, *J. Chem. Soc.*, (*C*) 1968, p. 2248.

[11] E. S. H. El Ashry, I. El Kholy, and Y. El Kilany, *Carbohydr. Res.*, **59** (1977), p. 417.

Paper Received 19 February 1990; Revised 1 December 1990.