Carbohydrate Research, 98 (1981) 148–153
Eisevier Scientific Publishing Company' Amsterdam – Printed in The Netherlands

Note

Reaction of dehydro-D-*erythro*-ascorbic acid 2-(phenylhydrazone) with methylhydrazine

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(Received January 16th, 1981; accepted for publication in revised form, June 1st, 1981)

Continuing our work on the synthesis of nitrogen heterocycles from dehydroascorbic acid bis(hydrazones)[1–5], we now describe the reaction of methylhydrazine with dehydro-D-*erythro*-ascorbic acid 2-(phenylhydrazone)[6] (**1**) (which showed great synthetic potential[7,8]). The reaction of dehydro-L-ascorbic acid 2-(phenylhydrazone)[9,10] with methylhydrazine gives 3-(L-*threo*-glycerol-1-yl)-1-methyl-4,5-pyrazolinedione 4-(phenylhydrazone)[11,12]. Similarly, treatment of **1** with methylhydrazine afforded the orange 3-(D-*erythro*-glycerol-1-yl)-1-methyl-4,5-pyrazolinedione 4-(phenylhydrazone) (**5**). It seems that methylhydrazine reacts more rapidly with the acyclic acid **2**, giving the intermediate, mixed bis(hydrazone) **4** (that would preferentially cyclize to the pyrazolinedione derivative **5**), instead of the lactone (**3**). The mass spectrum of **5** showed a molecular-ion peak at *m/z* 292, followed by a peak at *m/z* 274 resulting from the elimination of a molecule of water from the side chain. The spectrum also showed a fragment at *m/z* 201 due to the loss of the side chain, and at *m/z* 124 due to the loss of the side chain together with the phenyl group. The spectrum showed fragments at *m/z* 119 $(PhNCO)^+$, 105 $(PhNN)^+$, 77 $(Ph)^+$, 43 $(CH_3NN)^+$, and 29 (CH_3N).

Acetylation of **5** with boiling acetic anhydride or with cold acetic anhydride, gave the tri-*O*-acetyl derivative (**6**).

Periodate oxidation of one mole of **5**, or of the L-*threo* analog[11,12], resulted in the consumption of two moles of the oxidant, and the separation of 3-formyl-1-methyl-4,5-pyrazolinedione 4-(phenylhydrazone) (**7**); its i.r. spectrum showed a band at 1700 cm^{-1} due to the aldehyde group, in addition to the amide band at 1660 cm^{-1}, and there was no hydroxyl absorption.

Reduction of **7** with sodium borohydride afforded 3-(hydroxymethyl)-1-methyl-4,5-pyrazolinedione 4-(phenylhydrazone) (**8**), characterized as its acetate (**9**).

On condensation of **7** with hydroxylamine, 3-formyl-1-methyl-4,5-pyrazolinedione 4-(phenylhydrazone) 3-oxime (**10**) was obtained. Acetylation of **10** with cold

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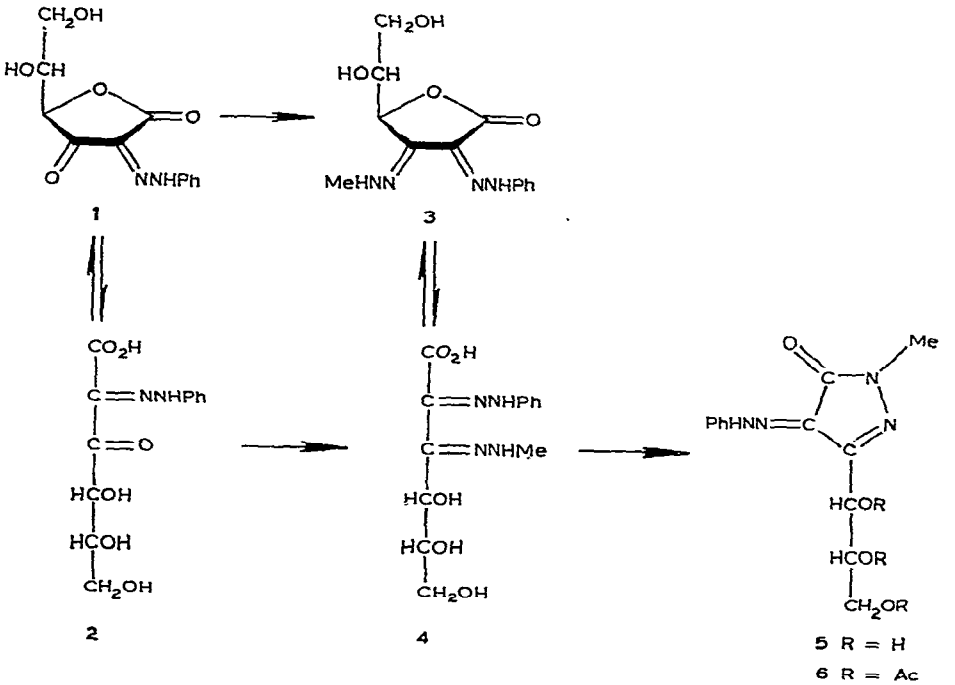
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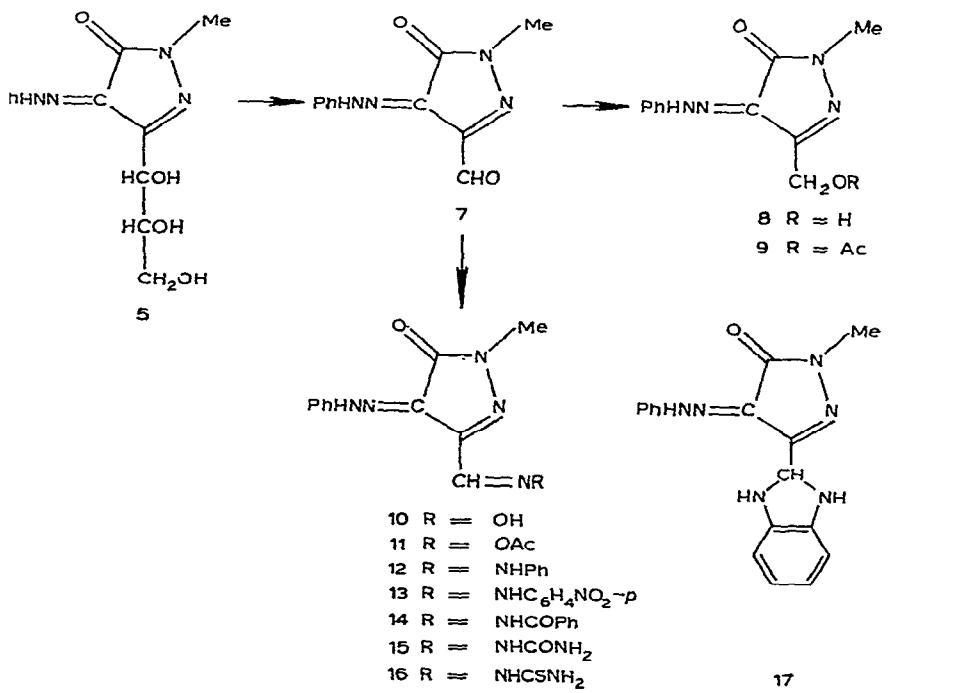
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13 R = NHC6H4NO2-p
14 R = NHCOPh
15 R = NHCONH2
16 R = NHCSNH2
CH
HN
NH
17

acetic anhydride–pyridine afforded the acetyl derivative (**11**); its i.r. spectrum showed the acetyl absorption at 1760 cm^{-1}, in addition to the amide absorption at 1660 cm^{-1}.

When the methylpyrazolinedione aldehyde **7** was treated with phenyl- and with (*p*-nitrophenyl)-hydrazine, it yielded the hydrazone derivatives **12** and **13**, respectively (see Table I). Similarly, it condensed with benzoylhydrazine, semicarbazide, and thiosemicarbazide, to give compounds **14**, **15**, and **16**, respectively (see Table I).

Reaction of **7** with *o*-phenylenediamine afforded the pyrazole imidazole (**17**); its i.r. spectrum showed an NH band at 3150 cm^{-1}, and the amide band at 1660 cm^{-1}.

TABLE I

MICROANALYTICAL DATA FOR SOME CONDENSATION PRODUCTS (**12–16**) OF 3-FORMYL-1-METHYL-4,5-PYRAZOLINEDIONE 4-(PHENYLHYDRAZONE)

Compound No.	*R*	*M.p. (°C)*	*Molecular formula*	*Calculated (%)*			*Found (%)*		
				C	*H*	*N*	*C*	*H*	*N*
12	HNPh	192–193	$C_{17}H_{16}N_6O$	63.73	5.04	26.24	63.91	5.34	26.36
13	$HNC_6H_4NO_2$-*p*	246–248	$C_{17}H_{15}N_7O_3$	55.86	4.13	26.83	55.68	4.01	26.70
14	NHCOPh	260–261	$C_{18}H_{16}N_6O_2$	62.06	4.63	24.13	62.30	4.91	24.32
15	$NHCONH_2$	238–240	$C_{12}H_{13}N_7O_2$	50.16	4.56	34.13	50.42	4.72	34.40
16	$NHCSNH_2$	272–273	$C_{12}H_{13}N_7OS$	47.52	4.32	32.33	47.33	4.47	32.06

EXPERIMENTAL

General methods. — Melting points were determined on a Kofler-block apparatus and are uncorrected. I.r. spectra were recorded with a Unicam Sp-1025 spectrophotometer for potassium bromide pellets, and u.v. 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, N.m.r. and mass spectra were recorded with a Varian EM-390 and M 60 spectrometer, respectively.

3-(D-erythro-*Glycerol-1-yl*)*-1-methyl-4,5-pyrazolinedione 4-(phenylhydrazone)* (**5**). — A solution of D-*erythro*-2,3-hexodiulosono-1,4-lactone 2-(phenylhydrazone)[6,8] (**1**) (2 g) in ethanol (20 mL) was treated with methylhydrazine (2 mL) in ethanol (20 mL) containing a few drops of acetic acid. The mixture was boiled under reflux for 2 h, and then allowed to cool to room temperature. The product was filtered off, successively washed with ethanol and ether, and dried (yield 1.0 g). Compound **5** was recrystallized from ethanol, to give orange needles, m.p. 190–191°; ν_{max}^{KBr} 3450 (OH) and 1660 cm^{-1} (CON); λ_{max}^{EtOH} 216, 262, and 418 nm (log ε 4.14, 4.19, and 4.46); λ_{min}^{EtOH} 241 and 292 nm (log ε 4.08 and 3.69). It is soluble in acetone or chloroform, sparingly soluble in methanol or ethanol, and insoluble in water.

Anal. Calc. for $C_{13}H_{16}N_4O_4$: C, 53.42; H, 5.52; N, 19.17. Found: C, 53.62; H, 5.76; N, 19.36.

*1-Methyl-3-(1,2,3-tri-O-acetyl-*D*-erythro-glycerol-1-yl)-4,5-pyrazolinedione 4-(phenylhydrazone)* (**6**). — A solution of compound **5** (0.1 g) in dry pyridine (10 mL) was treated with acetic anhydride (5 mL), kept overnight at room temperature, and the mixture poured onto crushed ice. Compound **6** was obtained as a syrup; ^{1}H-n.m.r. data ($CDCl_3$): δ 6.11 (d, 1 H, $J_{1,2}$ 2.5 Hz, H-1), 5.71 (m, 1 H, H-2), 4.18 (m, 2 H, H-3), 3.40 (s, 3 H, NCH_3), 2.00, 2.11, and 2.15 (9 H, $OCOCH_3$), 7.00–8.0 (m, 5 H, phenyl); ν_{max}^{KBr} 1730 (OAc), 1660 (CON), and 1600 cm^{-1} (C=N); λ_{max}^{EtOH} 217, 236, and 409 nm (log ε 4.00, 4.12, and 3.76); λ_{min}^{EtOH} 224 and 298 nm (log ε 3.88 and 3.21).

Anal. Calc. for $C_{19}H_{22}N_4O_7$: C, 54.54; H, 5.30; N, 13.39. Found: C, 54.71; H, 5.54; N, 13.41.

3-Formyl-1-methyl-4,5-pyrazolinedione 4-(phenylhydrazone) (**7**). — A suspension of compound **5** (0.5 g) in water (20 mL) was treated with a solution of sodium metaperiodate (1.5 g) in water (10 mL), and the mixture was kept overnight at room temperature, with shaking. The resulting solid was filtered off, successively washed with water, ethanol, and ether, and dried (yield 0.2 g). Recrystallization from ethanol gave compound **7** as orange prisms, m.p. 136–138°; ν_{max}^{KBr} 1700 (CHO), 1660 (CON), and 1600 cm^{-1} (C=N); λ_{max}^{EtOH} 214, 257, and 430 nm (log ε 4.06, 3.90, and 4.12); λ_{min}^{EtOH} 234 and 292 nm (log ε 3.81 and 3.36).

Anal. Calc. for $C_{11}H_{10}N_4O_2$: C, 57.38; H, 4.38; N, 24.34. Found: C, 57.52; H, 4.21; N, 24.67.

3-(Hydroxymethyl)-1-methyl-4,5-pyrazolinedione 4-(phenylhydrazone) (**8**). — A solution of **7** (0.1 g) in methanol (10 mL) was treated with a solution of sodium borohydride (0.1 g) in water (10 mL), added in small portions with occasional shaking. The solution was acidified with acetic acid, and the solid that separated was filtered off, successively washed with water, ethanol, and ether, and dried (yield 50 mg). It was recrystallized from ethanol, to give yellow needles, m.p. 118–120°; ν_{max}^{KBr} 3450 (OH) and 1670 cm^{-1} (CON); λ_{max}^{EtOH} 215, 255, and 425 nm (log ε 3.92, 3.87, and 3.99); λ_{min}^{EtOH} 235 and 287 (log ε 3.68 and 3.25).

Anal. Calc. for $C_{11}H_{12}N_4O_2$: C, 56.89; H, 5.21; N, 24.13. Found: C, 57.00; H, 5.46; N, 24.40.

3-(Acetoxymethyl)-1-methyl-4,5-pyrazolinedione 4-(phenylhydrazone) (**9**). — This compound was prepared from **8** as described for the preparation of **6**; m.p. 91–92°; ^{1}H-n.m.r. data ($CDCl_3$): δ 5.10 (s, 2 H, H-1), 3.43 (s, 3 H, NCH_3), 2.12 (s, 3 H, $OCOCH_3$), 7.26–7.90 (m, 5 H, phenyl); ν_{max}^{KBr} 1740 (OAc) and 1660 cm^{-1} (CON); λ_{max}^{EtOH} 216, 254, and 418 nm (log ε 4.00, 3.87, and 4.06); λ_{min}^{EtOH} 236 and 286 nm (log ε 3.80 and 3.31). It is soluble in acetone or chloroform, sparingly soluble in methanol or ethanol, and insoluble in water.

Anal. Calc. for $C_{13}H_{14}N_4O_3$: C, 56.93; H, 5.15; N, 20.43. Found: C, 56.71; H, 5.00; N, 20.64.

3-Formyl-1-methyl-4,5-pyrazolinedione 3-oxime 4-(phenylhydrazone) (**10**). — A solution of compound **7** (0.5 g) in ethanol (20 mL) was treated with hydroxylamine

hydrochloride (1 g) and sodium acetate (1 g), and the mixture was boiled under reflux for 3 h. It was concentrated, water (10 mL) was added, and the solid that separated was filtered off, successively washed with water, ethanol, and ether, and dried (yield 0.4 g). Compound **10** was recrystallized from ethanol, to give yellow needles, m.p. 265–266°; ν_{max}^{KBr} 3200 (OH) and 1660 cm^{-1} (CON); λ_{max}^{EtOH} 214, 248, and 412 nm (log ε 4.10, 4.20, and 4.09); λ_{min}^{EtOH} 225 and 315 nm (log ε 3.94 and 3.88).

Anal. Calc. for $C_{11}H_{11}N_5O_2$: C, 53.87; H, 4.52; N, 28.56. Found: C, 53.62; H, 4.71; N, 28.46.

3-Formyl-1-methyl-4,5-pyrazolinedione 3-acetoxime 4-(phenylhydrazone) (**11**).— A solution of compound **10** (0.1 g) in dry pyridine (5 mL) was treated with acetic anhydride (10 mL) and kept overnight at room temperature. The mixture was poured onto crushed ice, and the solid was filtered off, successively washed with water and ethanol, and dried (yield 60 mg). Compound **11** was recrystallized from ethanol, to give orange needles, m.p. 166–168°; ^{1}H-n.m.r. data ($CDCl_3$): δ 3.69 (s, 1 H, H-1), 3.51 (s, 3 H, $NOCOCH_3$), 2.27 (s, 3 H, $OCOCH_3$), and 7.25–8.20 (m, 5 H, phenyl); ν_{max}^{KBr} 1760 (OAc) and 1690 cm^{-1} (CON); λ_{max}^{EtOH} 214, 253, 313, and 430 nm (log ε 4.20, 4.14, 4.06, and 3.91); λ_{min}^{EtOH} 229, 283, and 351 nm (log ε 4.08, 3.85, and 3.73).

Anal. Calc. for $C_{13}H_{13}N_5O_3$: C, 54.35; H, 4.56; N, 24.38. Found: C, 54.62; H, 4.66; N, 24.06.

Condensation products of 3-formyl-1-methyl-4,5-pyrazolinedione 4-(phenylhydrazone) (**12–16**). — A solution of **7** (0.1 g) in ethanol (20 mL) was treated under reflux with the respective aryl- and aroyl-hydrazines, semicarbazide, and thiosemicarbazide (one molar proportion) and a few drops of acetic acid. Each product crystallized from ethanol in orange crystals (see Table I).

3-(Benzimidazolin-2-yl)-1-methyl-4,5-pyrazolinedione 4-(phenylhydrazone) (**17**). — A solution of compound **7** (0.5 g) in methanol (20 mL) was treated with *o*-phenyl-

TABLE II

U.V.- AND I.R.-SPECTRAL DATA FOR SOME CONDENSATION PRODUCTS (**12–16**) OF 3-FORMYL-1-METHYL-4,5-PYRAZOLINEDIONE 4-(PHENYLHYDRAZONE)

Compound No.	*λ (nm)*	*log ε*	*(cm^{-1})*	
			CON	NH
12	max 214, 259, 326, 430 min 246, 280, 365	4.17, 3.96, 4.08, 4.12 3.88, 3.79, 3.61	1660	3200
13	max 218, 269, 388, 441 min 250, 315	3.99, 3.75, 3.63, 3.95 3.70, 3.53	1660	3200
14	max 218, 273, 292, 430 min 251, 283, 361	4.28, 4.22, 4.16, 4.02 3.96, 4.10, 3.39	1680	3250
15	max 218, 269, 418 min 241, 328	4.04, 4.09, 3.91 3.74, 3.48	1655	3200
16	max 216, 260, 297, 418 min 237, 274, 342	3.87, 3.73, 3.74, 3.76 3.65, 3.67, 2.91	1670	3250

enediamine (0.4 g) in methanol (20 mL) containing a few drops of acetic acid. The mixture was boiled under reflux, and cooled to room temperature, and the solid was filtered off, washed with ether, and dried (yield 0.3 g). Compound **17** crystallized from methanol in reddish-brown prisms, m.p. 296–297°; ν_{max}^{KBr} 3150 (NH) and 1660 cm^{-1} (CON); λ_{max}^{EtOH} 218, 246, and 430 nm (log ε 4.50, 4.32, and 4.26); λ_{min}^{EtOH} 232 and 338 nm (log ε 4.30 and 3.70).

Anal. Calc. for $C_{17}H_{16}N_6O$: C, 63.73; H, 5.04; N, 26.24. Found: C, 64.00; H, 5.20; N, 26.41.

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