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Note

Pyrazolone and quinoxaline derivatives of triazolyl analogs of L-ascorbic acid*

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Many 2,4-furandione ("tetronic acid") derivatives and ascorbic acid analogs show biological activity as hypnotics[2], antimicrobials[3], or antineoplastic agents[4]. In continuation of our previous work[5], 2-hydroxy-4-(2-phenyltriazol-4-yl)tetronimide (**4**) was prepared by the reaction of 4-formyl-2-phenyl-1,2,3-triazole (**3**) with glyoxal sodium hydrogensulfite and potassium cyanide in alkaline solution under a nitrogen atmosphere for 50 min, followed by acidification. Its infrared (i.r.) spectrum had a band at 3550 cm^{-1}, indicative of an NH group, and a band at 1720–1710 cm^{-1}, characteristic of the lactone carbonyl group. The u.v. spectrum of **4** showed two maxima, at 275 and 206 nm, and a minimum at 225 nm. Oxidation of **4** with nitrous acid gave 2,3-dioxo-4-(2-phenyltriazol-4-yl)butanolactone (**5**), the corresponding analog of dehydro-L-ascorbic acid. Its i.r. spectrum showed two carbonyl bands, at 1795–1780 cm^{-1} and 1720–1710 cm^{-1} and its u.v. spectrum showed two maxima, at 266 and 201 nm, and a minimum at 225 nm.

Acylation of the tetronimide **4** afforded the corresponding 2-acyloxy-3-oxo-4-(2-phenyltriazol-4-yl)butanoiminolactones. Their i.r. spectra had a band at 3420–3300, indicative of an NH group, and at 3100–3050, characteristic of an NH_2^+ group, and two bands in the region of 1750–1715 cm^{-1}, indicative of carbonyl groups.

Compound **5** reacted readily with arylhydrazines, to give the bis(hydrazones) (**6**). These compounds, like the bis(arylhydrazones) of dehydro-L-ascorbic acid, are red in color, and their n.m.r. spectra show two chelated, imino protons in the offset region of the spectrum. Thus, compound **6a** showed the imino protons at δ 10.99 and 11.98, whereas dehydro-L-ascorbic acid bis(phenylhydrazone) shows the imino protons at δ 10.87 and 11.93. The slight difference is probably due to deshielding by the phenyltriazole ring in compounds **6**. The i.r. spectra of these compounds showed a carbonyl lactone band at 1735–1725 cm^{-1}, a frequency lower than that of

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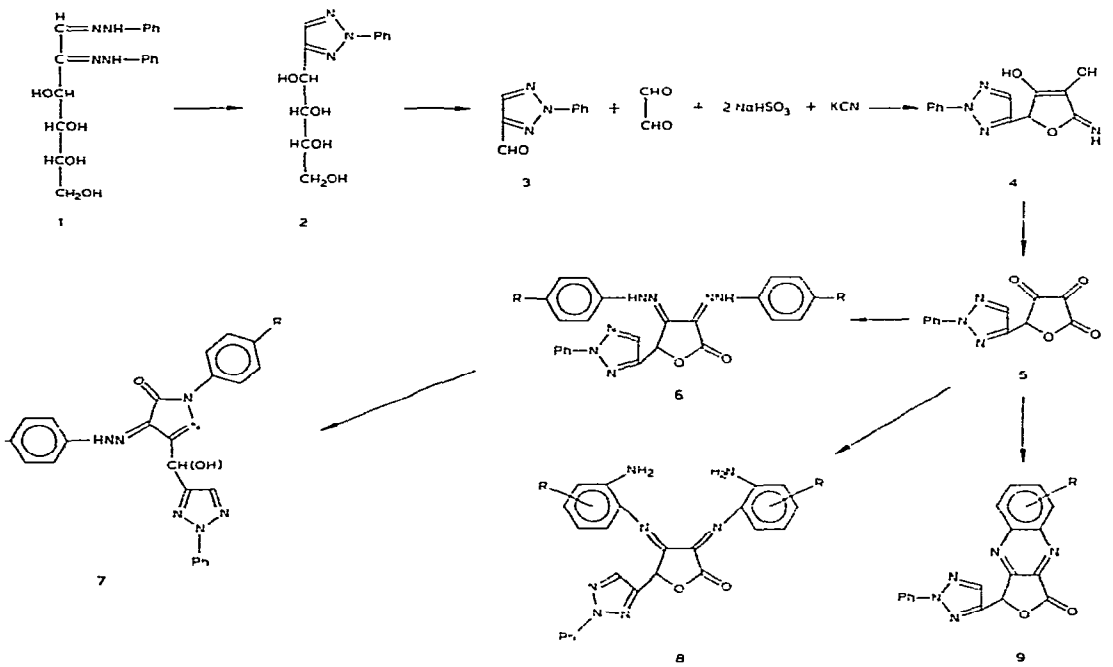
the 1,4-lactone. This low frequency had been observed for analogs[6,7], and is probably due to hydrogen bonding of the lactone carbonyl with the imino proton of the hydrazone residue on C-2. Another broad band was observed at 3300–3100 cm^{-1}, characteristic of an NH group.

Treatment of the bis(hydrazones) **6** with sodium hydroxide solution led to opening of the lactone ring, followed by nucleophilic attack, on the carbonyl group, by the nitrogen atom of the hydrazone residue attached to C-3; this resulted in the formation of the more-stable pyrazolones (**7**), which are analogs of the corresponding dehydro-L-ascorbic acid derivatives. The i.r. spectra of these compounds had a band in the region of 3500–3400 cm^{-1}, indicative of an OH group, and in the region of 1680–1660 cm^{-1}, characteristic of an OCN group.



When **5** was treated with an excess of *o*-phenylenediamine, the Schiff base **8** was obtained. However, when equimolar proportions of *o*-phenylenediamine and lactone **5** interacted, the quinoxaline derivative **9** was obtained. The i.r. spectra of the quinoxalines **9** showed the carbonyl band in the region of 1790–1770 cm^{-1}, whereas the Schiff bases showed this band in the region of 1700–1670 cm^{-1}, besides a broad band in the region of 3400–3200 cm^{-1}, indicative of an NH group.

The elemental analyses and physical properties of the compounds prepared are shown in Tables I–IV.

TABLE I

MICROANALYTICAL AND SPECTRAL DATA FOR 2,3-DIOXO-4-[2-PHENYLTRIAZOL-4-YL]-BUTANO-1,4-LACTONE BIS(HYDRAZONES) (6)

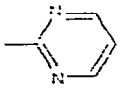
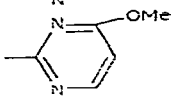
R	*Yield* (%)	*M.p.* (degrees)	*Molecular formula*	*Calculated* (%)			*Found* (%)			ν_{max}^{Nujol} (cm^{-1})
				C	*H*	*N*	*C*	*H*	*N*	
H	50	167–168	$C_{24}H_{19}N_7O_2$	65.9	4.3	22.4	66.2	3.9	22.6	1725
CO_2H	45	244–245	$C_{26}H_{19}N_7O_6 \cdot H_2O$	57.5	3.9	18.0	57.4	3.6	17.8	1730
NO_2	40	168–169	$C_{24}H_{17}N_9O_6$	54.6	3.2	23.9	54.1	3.6	23.7	1735
$2,4\text{-}(NO_2)_2$	45	165–166	$C_{24}H_{15}N_{11}O_{10}$	46.7	2.4	25.0	47.0	2.7	25.2	1730
SO_2NH_2	50	170–171	$C_{24}H_{21}N_9O_6S_2$	48.2	3.5	21.1	48.4	3.5	21.0	1730
	40	225–226	$C_{32}H_{25}N_{13}O_6S_2 \cdot H_2O$	49.9	3.5	23.7	49.5	3.6	23.8	1725
	45	190–191	$C_{31}H_{29}N_{13}O_8S_2$	50.3	3.6	22.4	49.5	3.2	22.6	1735

TABLE II

MICROANALYTICAL AND SPECTRAL DATA FOR 1-ARYL-3-[HYDROXY-(2-PHENYLTRIAZOL-4-YL)METHYL]-PYRAZOLE-4,5-DIONE 4-(ARYLHYDRAZONES) (7)

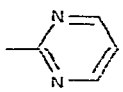
R	*Yield* (%)	*M.p.* (degrees)	*Molecular formula*	*Calculated* (%)			*Found* (%)			ν_{max}^{Nujol} (cm^{-1})
				C	*H*	*N*	*C*	*H*	*N*	
H	40	155–156	$C_{24}H_{19}N_7O_2$	65.9	4.3	22.4	66.1	4.2	22.0	1660
CO_2H	45	290–292	$C_{26}H_{19}N_7O_6$	59.4	3.6	18.7	59.2	3.4	18.9	1670
$2,4\text{-}(NO_2)_2$	35	195–196	$C_{24}H_{15}N_{11}O_{10}$	46.7	2.4	25.0	47.0	2.1	24.7	1665
SO_2NH_2	45	155–156	$C_{24}H_{21}N_9O_6S_2$	48.2	3.5	21.1	48.6	3.3	21.3	1680
	40	285–286	$C_{32}H_{25}N_{13}O_6S_2$	51.1	3.3	24.2	51.1	3.2	24.0	1660

TABLE III

MICROANALYTICAL AND SPECTRAL DATA FOR SCHIFF BASES (8)

R	*Yield* (%)	*M.p.* (degrees)	*Molecular formula*	*Calculated* (%)			*Found* (%)			ν_{max}^{Nujol} (cm^{-1})
				C	*H*	*N*	*C*	*H*	*N*	
H	55	219–220	$C_{24}H_{19}N_7O_2$	65.9	4.3	22.4	66.1	4.7	22.0	1670
3-Cl	50	210–211	$C_{24}H_{17}Cl_2N_7O_2$	56.9	3.4	19.4	57.1	3.2	19.2	1680
$3\text{-}NO_2$	45	265–266	$C_{21}H_{17}N_9O_6$	54.6	3.2	23.9	54.3	3.2	23.5	1690

TABLE IV

MICROANALYTICAL AND SPECTRAL DATA FOR QUINOXALINES (9)

R	*Yield* (%)	*M.p.* (degrees)	*Molecular formula*	*Calculated* (%)			*Found* (%)			ν_{max}^{Nujol} (cm^{-1})
				C	*H*	*N*	*C*	*H*	*N*	
H	45	264–265	$C_{18}H_{11}N_5O_2$	65.7	3.3	21.3	66.1	3.6	21.5	1770
3-Cl	40	216–217	$C_{18}H_{10}ClN_5O_2$	59.4	2.8	19.3	59.0	3.2	19.6	1775
3-NO_2	45	273–274	$C_{18}H_{10}N_6O_4$	57.7	2.7	22.5	57.5	3.0	22.9	1790

EXPERIMENTAL

General methods. — Melting points were determined with a Kofler block and are uncorrected. I.r. spectra were recorded with a Unicam SP 200 spectrophotometer, u.v. spectra with a Unicam SP 800 spectrophotometer, and n.m.r. spectra with a Varian HA 60 instrument. Microanalyses were performed in the Institute of Organic Chemicals Microanalysis, Polish Academy of Science, Warsaw, Poland.

4-Formyl-2-phenyl-1,2,3-triazole (**3**). — A suspension of D-*arabino*-hexose phenylosotriazole (**2**) (0.5 g), prepared from **1**, in a mixture of water (50 mL) and 0.43M aqueous sodium periodate solution (15 mL) was stirred for 25 h at room temperature, and filtered, and the crystals obtained were washed with water; m.p. 68–69° (lit.[8] m.p. 69°), yield 60%.

2-Hydroxy-4-(2-phenyltriazol-4-yl)tetronimide (**4**). — Glyoxal sodium hydrogensulfite (0.15 mol) was added in one portion to a well-stirred, cold solution of potassium cyanide (0.26 mol) in 2M sodium carbonate (40 mL) under a nitrogen atmosphere. To the resulting solution was added, in one portion, a solution of compound **3** (0.1 mol) in 1,4-dioxane (30 mL). A precipitate appeared after 20 min, and stirring was continued for a further 45 min. The flow of nitrogen was then discontinued, and the mixture was acidified with glacial acetic acid. Stirring was continued for another 3 h, after which, the tetronimide was separated, washed with water, and recrystallized from alcohol; m.p. 184° (lit.[5] m.p. 184°), yield 60%.

2-Acetoxy-3-oxo-4-(2-phenyltriazol-4-yl)butanoiminolactone. — This compound was prepared by heating a mixture of **4** (2 mmol) with acetic anhydride (2 mL) on a steam bath for 15 min, and then keeping for 3 h at room temperature. The mixture was poured into ice-cold, saturated sodium hydrogencarbonate solution, and the solid that separated out was filtered off, washed with water, dried, and recrystallized from benzene–methanol, to give colorless needles, m.p. 235°, yield 60%.

Anal. Calc. for $C_{14}H_{11}N_4O_4$: C, 56.2; H, 3.7; N, 18.7. Found: C, 55.9; H, 3.3; N, 18.5.

2-(Benzoyloxy)-3-oxo-4-(2-phenyltriazol-4-yl)butanoiminolactone. — A solution of **4** (2 mmol) in pyridine (6 mL) was gently warmed with benzoyl chloride (2 mmol) for 15 min, kept for 5 h at room temperature, and poured into cold, 2M sulfuric acid

(25 mL). The crude product thus obtained was treated with saturated sodium hydrogencarbonate solution (25 mL), the suspension filtered, and the solid washed with water, dried, and recrystallized from benzene–methanol, to give colorless needles, m.p. 237°, yield 70%.

Anal. Calc. for $C_{19}H_{13}N_4O_4$: C, 63.2; H, 3.6; N, 15.5. Found: C, 63.0; H, 3.2; N, 15.3.

2,3-Dioxo-4-(2-phenyltriazol-4-yl)butano-1,4-lactone (**5**). — A suspension of **4** (0.01 mol) in acetone (15 mL) and 2M sulfuric acid (25 mL) was cooled to 10°, and treated with a 10% solution of sodium nitrite (15 mL). The mixture was warmed to expel the nitrogen gas, and then allowed to cool. The product was filtered off, washed with water, and recrystallized from water: m.p. 132° (lit.[5] m.p. 132°), yield 20%.

2,3-Dioxo-4-(2-phenyltriazol-4-yl)butano-1,4-lactone bis(hydrazones) (**6**). — A solution of **5** (1 mmol) in 1:1 water–ethanol (15 mL) and a few drops of glacial acetic acid was heated with the desired arylhydrazone (2 mmol) for 2 h on a boiling-water bath. The red bis(arylhydrazones) that separated out were filtered off, washed with water, dried, and recrystallized from ethanol (see Table I).

1-Aryl-3-[hydroxy-(2-phenyltriazol-4-yl)methyl]pyrazole-4,5-dione 4-(arylhydrazones) (**7**). — These compounds were obtained by heating bis(arylhydrazones) **6** (1 g) with 20% aqueous sodium hydroxide solution (40 mL) for 15 min on a boiling water bath, cooling, and acidifying with glacial acetic acid; the desired products separated out, and were recrystallized from aqueous ethanol, to give orange needles (see Table II).

Schiff bases (**8**) *and quinoxalines* (**9**). — A solution of **5** (1 mmol) in ethanol (10 mL) containing two drops of glacial acetic acid was refluxed for 1 h with (*a*) *o*-phenylenediamine (1 mmol) for preparing quinoxalines (see Table IV), or with (*b*) 2 mmoles for preparing Schiff bases (see Table III). On concentrating and cooling, a yellow solid separated out, and this was recrystallized from ethanol, to give yellow needles.

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